Organic Chemistry and Chemical Biology for the Students by the Students! (and the Profs...)

ORGANIC CHEMISTRY AND CHEMICAL BIOLOGY FOR THE STUDENTS BY THE STUDENTS! (AND THE PROFS...)

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Hamilton Ontario

CONTENTS

INTRODUCTION

Textbook Introduction

This textbook aims to provide students with an extra resource to supplement their learning by including different examples, practice problems and explanations than what was shown in lecture. This chapter serves as an introduction to help you navigate the textbook and explain the purpose of the various coloured boxes.

Note that throughout the textbook, you will see the words "substrate", "reagent" and "reactant" being used interchangeably. A substrate is a molecule that is targeted by an enzyme. A reagent is a molecule added to a substance or mixture to initiate/cause a chemical reaction. A reactant is a substance that undergoes a change during a chemical reaction and is typically referred to as the starting material. In the literature, you will see a combination of these terms being used, so using these words interchangeably is acceptable.

Learning Objectives

The "Learning Objectives" green boxes list the main ideas and concepts that will be spoken about in the chapter. They also serve as a guide to help you identify the key concepts you should be taking away from the chapter. A picture of the "Learning Objectives" box is included below.

Learning Objectives

Learning objectives will be found in these boxes.

Are You Wondering Boxes

The "Are You Wondering?" purple boxes explain concepts in greater detail, and the information in them will **not** be tested. Examples of information you may find in these boxes include why certain reagents are used, or the importance of reagent conditions. A picture of the "Are you Wondering?" box is included below.

Are You Wondering?

Are You Wondering information will be found in these boxes.

Shaded Box

The light blue shaded box includes **mandatory** information that students should know. These boxes provide notes, tips or relevant information to help explain concepts. The information in these boxes **is** testable. A picture of the shaded box is included below.

Shaded Boxes

Key Takeaways

The "Key Takeaways" orange boxes provide a summary of the concepts discussed in that chapter. These boxes are similar to the "Key Concepts" slide at the end of your CHEM 1AA3 lecture slides. Content in these boxes **is** testable. A picture of the "Key Takeaways" box is included below.

Key Takeaways

Key takeaways will be found in these boxes.

Diversity in Chemistry

The "Diversity in Chemistry" blue boxes highlight talented scientists from diverse backgrounds and the

information in them will **not** be tested. Let us know if there are any other scientists you would like to see included!

Diversity in Chemistry

Diversity in Chemistry will be found in these boxes.

In-Text Questions

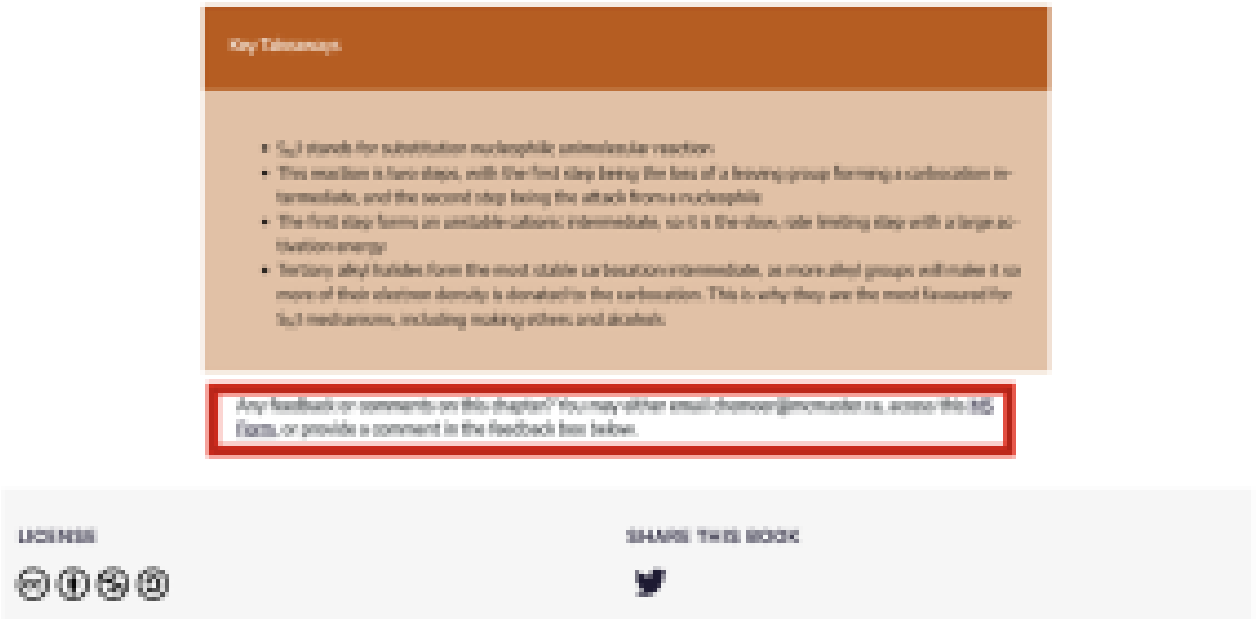
The in-text practice questions are found in various formats, such as multiple choice. These questions are meant to test your knowledge on the concepts explained in the chapter. The questions are not designed to be difficult and should instead be used as a guide for you to assess areas you feel comfortable with or areas you might need to work on. Once you click on an option, you will get instant feedback detailing why the answer is correct or incorrect. It is suggested that you use these questions to prepare for your future midterms and exams, as some of these questions were past CHEM 1AA3 midterm and exam questions. A picture of a multiple-choice question is included below. Note that underneath every question is a "Click here for full solutions" link that will take you directly to the question and answer in the Solutions chapter (Chapter 5).

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/mcmasterchem1aa3/?p=4#h5p-8

Questions and Comments Feature

If you have questions about any of the content in the textbook (the material, the questions, the solutions, etc.,) or suggestions that we can implement for future students, we would like to know! There are 2 ways you can give us feedback: Microsoft Forms or the Pressbooks comment section. There is a link to the Microsoft Form

at the end of each chapter (below the orange "Key Takeaways" box) as pictured below. Note that you must use a McMaster account to access/submit this form.



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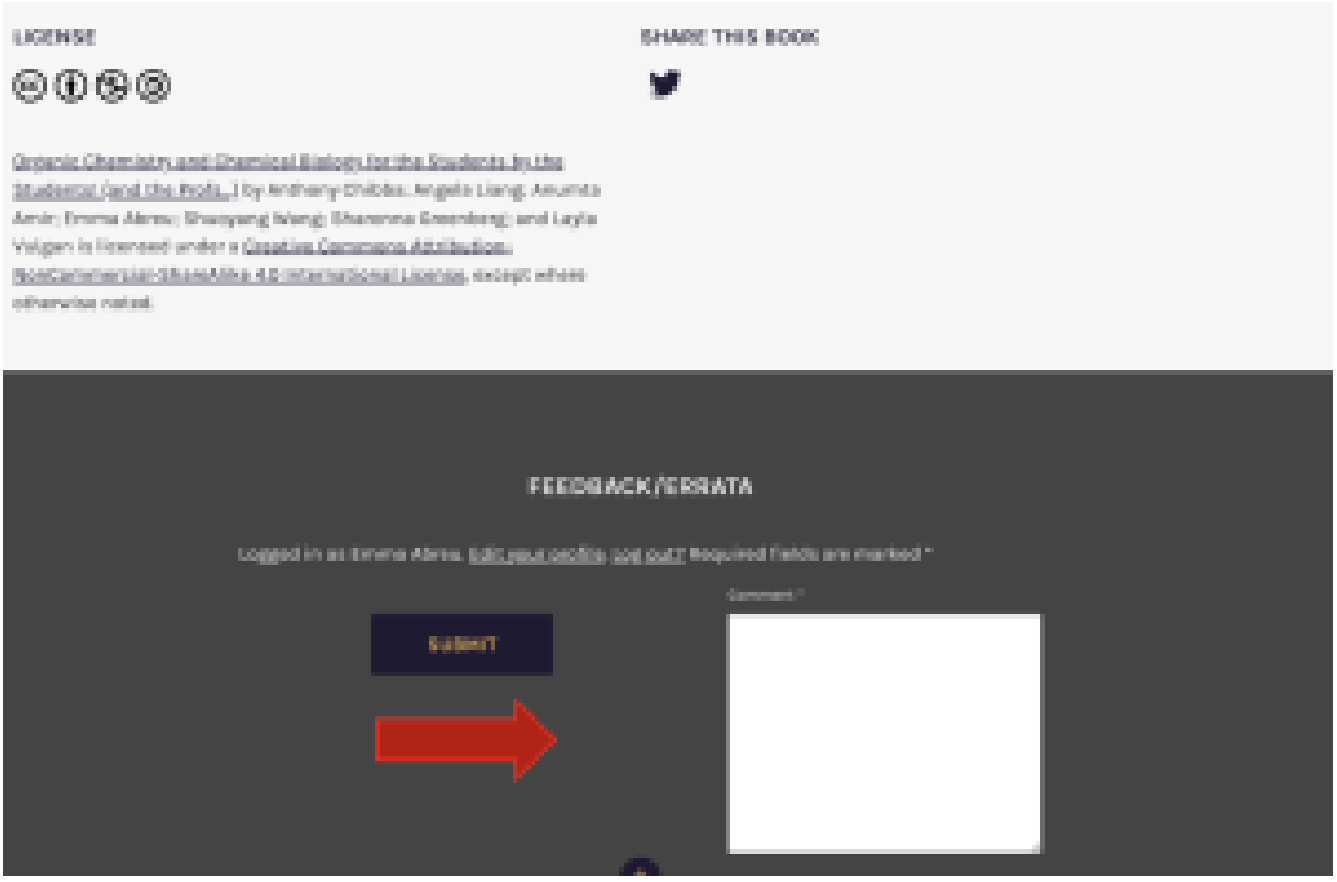
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AUTHOR BIOGRAPHIES

The authors behind ***Organic Chemistry and Chemical Biology for the Students by the Students! (and the Profs...).*** Comprised of two professors and five student partners, the team worked over the summer of 2023 to deliver a effective textbook to (hopefully!) help you ace CHEM 1AA3. Click below to learn more about each member of the team.

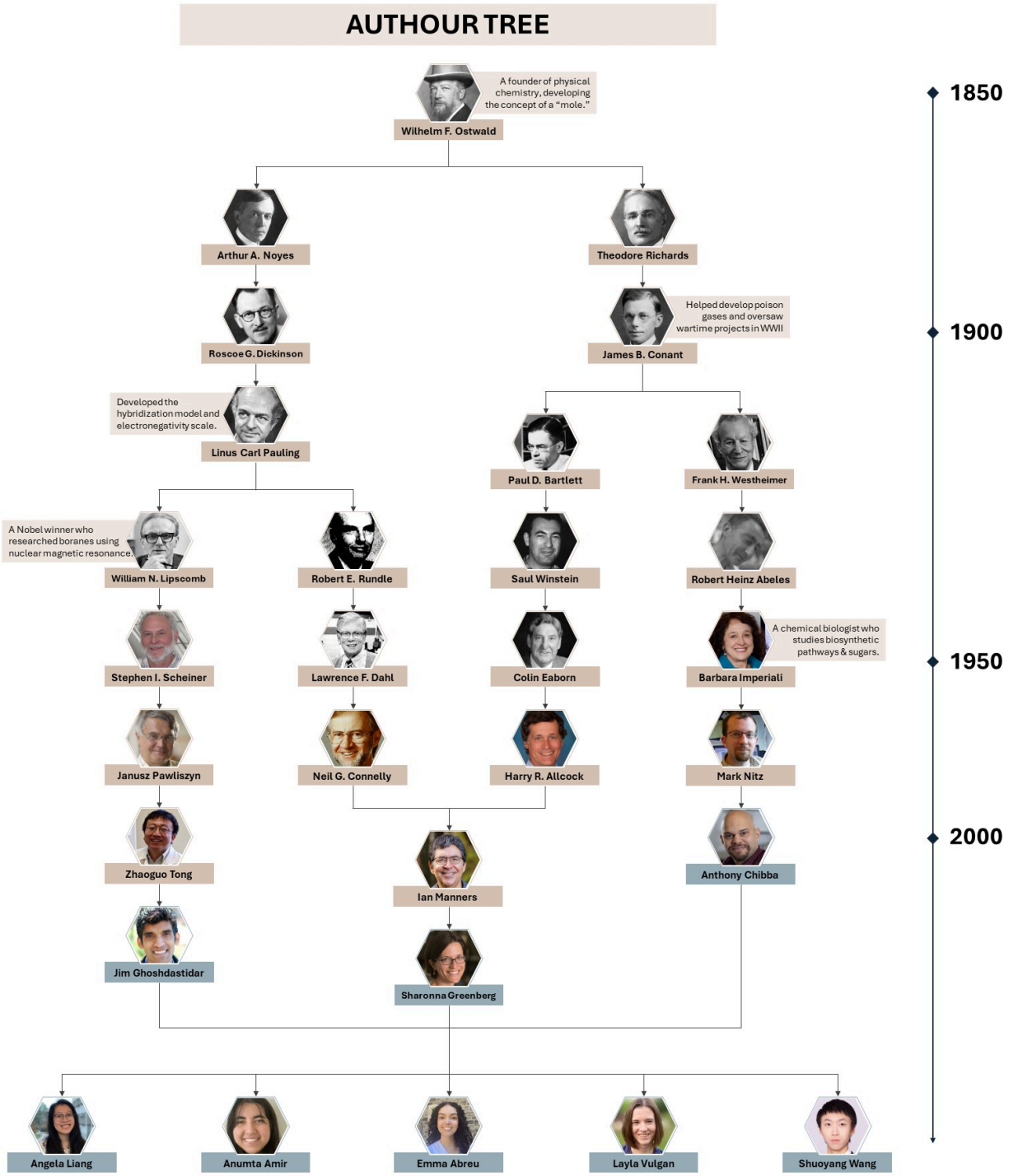
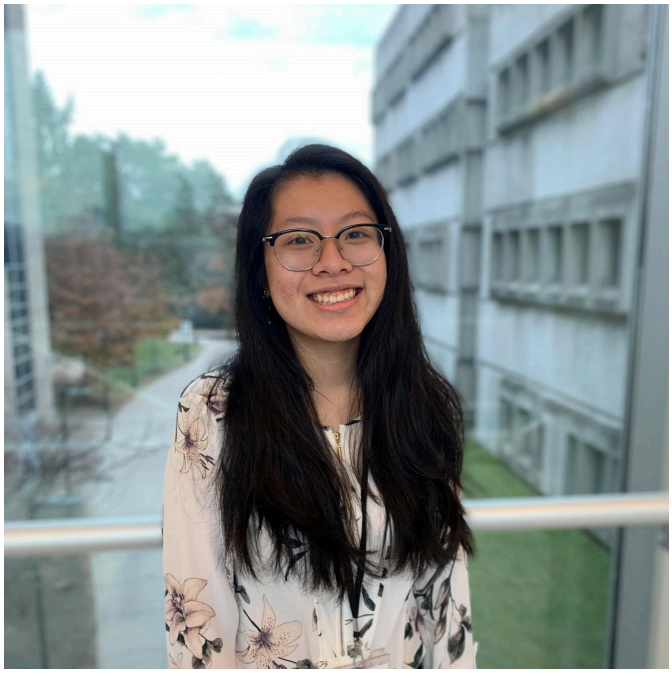


Figure. An academic family tree connecting all eight authours of this textbook, going back to a common ancestor of Wilhelm Ostwald, who worked as a scientist in the late 19th century. In the field of science, mentorship plays a crucial role in the development and fostering of budding scientists to impart the necessary skills and expertise required for scientific advancement. Skilled mentors also foster a culture of curiousity, creativity, and critical thinking, pushing their mentees to reach their full potential.

Dr. Anthony Chibba (He/Him) is the instructor involved in teaching general chemistry, organic chemistry and chemical biology at McMaster University. Anthony joined the Department of Chemistry and Chemical Biology in August 2018 as an Assistant Professor – Teaching Stream after a brief 2 year foray at Trent University. He has been involved in teaching 1st year chem (1A03, 1AA3, 1R03), Organic Chem (2OA3, 2OB3, 2E03) as well as some chemical biology lab courses (CHEMBIO 2L03, 3L03). Outside of writing OER textbooks, some of his research efforts focus on the use of social media to communicate science and enhance student learning outcomes. On his spare time, Anthony likes to play softball, bike long distances, and annoy his cat.

Dr. Sharonna Greenberg (she/her) joined the Department of Chemistry and Chemical Biology at McMaster University in 2017. She has taught several chemistry courses, including general chemistry (CHEM 1A03, CHEM 1AA3, ISCI 1A24), inquiry (CHEM

2Q03), and lab courses (CHEM/CHEMBIO 2OG3, CHEM 2LB3). Sharonna loves everything about assessments. Her research projects focus on how to make assessments better and more predictable for students and instructors alike, and how to help students study effectively and efficiently. In her spare time, she enjoys knitting, cooking (edible chemistry!), bike riding (manageable distances), reading or listening to audiobooks, and playing board games.



Angela Liang (she/her) is a graduate of the Chemical Biology Co-op program at McMaster University, graduating in June 2023 with a minor in Classics. After enjoying the content of first-year chemistry and biology, she joined the Chemical Biology program to learn about the discipline bridging the two subjects in hopes of entering the pharmaceutical field. In her time at McMaster, she worked in the labs of Dr. Bujold and Dr. Rullo to synthesize and investigate nano-sized structures made from DNA. Her co-op work terms also brought her to the University of Calgary all the way in Alberta, as well as the biopharmaceutical company BlueRock Therapeutics in downtown Toronto to play around with stem cells. She is currently pursuing her Master of Science in Pharmaceutical Sciences at the University of Toronto in the Zheng Lab. In her spare time, she enjoys bullet journaling, playing video games, and reading novels.

Emma Abreu (she/her) is in her third year of the Chemical Biology Co-op program at McMaster University. Having enjoyed all of the sciences throughout high school, she was unsure what program to choose when entering university. Through her first-year courses (mainly CHEM 1AA3), she discovered she had an overwhelming interest in chemistry, particularly when applied to biological systems for the purposes of drug delivery and discovery, leading her to join the Chemical Biology program. Over the summer, she worked in the lab of Dr. Katherine Bujold, looking at the synthesis of modified oligonucleotides and spherical nucleic acids for improved cellular uptake and gene knockdown. In her spare time, Emma enjoys reading, travelling and spending time with family and friends.

Shuoyang Wang (he/him) is a third-year student seeking concurrent degrees in both Honours Chemistry and Honours Mathematics and Physics. He is currently working in Dr. Paul Ayers' group, and he is enthusiastic about the theoretical perspective of quantum many-body systems, specifically molecular electron structure theory. As a theorist, he holds a relatively nerdy lifestyle. Besides working, he loves taking long walks and having coffee.

Anumta Amir (she/her) joined McMaster in 2021 and is pursuing her undergraduate degree in Honours Chemical Biology Co-op with minors in Biochemistry and Commerce. She worked in Dr. Alex Adronov's group over the summer of 2023 and is interested in synthetic chemistry with the application to biological systems (think pharmaceuticals, food science, cosmetics). Other than studying somewhere between Thode and ABB, she likes to read books (including graphic novels), cooking/baking, go bike riding with her friends, and making art (including textiles like crocheting/sewing).

Layla Vulgan (she/her) is a third year McMaster University student pursuing a degree in Honour's Chemical Biology Co-Op. She is currently working with Dr. Chen and Dr. Saravanamuttu to improve and evaluate the impact of the Department of Chemistry and Chemical Biology's second year mentorship program. Layla enjoys teaching peers about chemistry and related subjects, and she especially likes finding ways to explain concepts in more accessible ways. When she has spare time, she enjoys tutoring others, playing badminton, and goofing around with her dog.

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CHAPTER 1 - INTRODUCTION TO ORGANIC CHEMISTRY

1.1 - INTRODUCTION TO ORGANIC CHEMISTRY

An Introduction to Organic Chemistry

Organic chemistry is often described as the chemistry of life. The term "organic" originally referred to compounds derived from living organisms, such as plants and animals. More recently, it has been redefined as a branch of chemistry that focuses on the study of carbon-containing compounds, including their structure, properties, and reactions. It is a field of science that has played a pivotal role in shaping our understanding of the natural world and has had a profound impact on various aspects of our lives, from the development of life-saving drugs to the creation of innovative materials.

At the heart of organic chemistry lies the carbon atom, a unique and versatile element that forms the foundation of organic compounds. What makes carbon exceptional is its ability to form strong covalent bonds with other carbon atoms and a wide range of other elements, including hydrogen, oxygen, nitrogen, sulfur, and more. This characteristic enables carbon to create complex and diverse molecules with varying structures and functions.

Carbon atoms can link together to form long chains, branched structures, or intricate three-dimensional networks. These diverse arrangements give rise to the incredible diversity of organic molecules, which range from simple hydrocarbons, such as methane and ethane, to complex biomolecules like DNA, proteins, and carbohydrates. Understanding the structure of organic compounds is the first step in predicting their behavior and reactivity.

Organic chemistry has wide-ranging implications in various fields:

1. **Pharmaceuticals:** Organic chemistry is instrumental in the design and synthesis of pharmaceutical drugs. Medicinal chemists create and modify organic molecules to develop effective treatments for a wide range of diseases and conditions.
2. **Materials Science**: Organic chemistry plays a pivotal role in the development of innovative materials, including plastics, polymers, and composite materials. These materials find applications in everything from electronics to aerospace.
3. **Agriculture:** The synthesis of agrochemicals, such as pesticides and fertilizers, relies on organic chemistry principles. Understanding the chemistry of plant compounds and natural products also contributes to crop improvement.
4. **Environmental Science:** Organic chemistry is crucial in the study of environmental pollutants, the degradation of plastics, and the development of sustainable energy sources. It helps us address pressing

environmental challenges.

To navigate the world of organic chemistry, you'll encounter several fundamental concepts:

1. **Functional Groups**: Organic compounds can be classified into families based on specific structural arrangements known as functional groups. These groups can have an impact on the physical properties and chemical reactivity of the molecule they are a part of.
2. **Nomenclature**: The systematic naming of organic compounds, following the rules established by the International Union of Pure and Applied Chemistry (IUPAC), is essential for effective communication within the field.
3. **Chemical Bonding**: Understanding the types of chemical bonds, including covalent, polar covalent, and ionic bonds, is fundamental to grasp the behavior of organic molecules. We will also delve into the concepts of hybridization, sigma (σ) and pi (π) bonds.
4. **Reaction Mechanisms**: Organic reactions involve the breaking and forming of chemical bonds. Learning reaction mechanisms is critical for predicting and explaining how molecules interact and transform into new compounds.

This textbook will aim to provide a comprehensive and accessible foundation for organic chemistry. Whether you are a student pursuing a degree in chemistry, biology, medicine, or any field related to the natural sciences, a solid understanding of organic chemistry is essential. This text will serve as your guide to mastering the fundamental principles, reactions, and applications of organic chemistry.

1.2 - CHEMISTRY AND ITS INTERDISCIPLINARY FIELDS

Chemistry is the scientific discipline dedicated to understanding the properties, composition, structure, and behavior of matter. It plays a central role in explaining the world around us, from the elements that make up the universe to the chemical reactions that drive biological processes. Chemistry can be divided into several subfields, including organic, inorganic, physical, and analytical chemistry. The study of chemistry is vital for addressing a wide range of global challenges, from developing new medicines to addressing environmental concerns, giving rise to various interdisciplinary subjects.

In regard to the life around us, both biochemistry and chemical biology are two closely related fields that explore the complex world of molecules and their roles within biological systems. While they share a common foundation in chemistry and biology, they exhibit significant differences in their approaches, methodologies, and academic curricula. This discussion aims to highlight these distinctions, with an emphasis on the dynamic realm of chemical biology and explore the unique educational paths students can pursue in university programs.

Biochemistry: The Molecular Basis of Life

Biochemistry is the study of the chemical processes that underpin biological functions. Biochemists investigate the composition, structure, and basic function of biological molecules, such as proteins, nucleic acids, and lipids. They seek to understand fundamental processes like metabolism, replication, and signaling, providing insights into the molecular machinery of life. Biochemistry aims to apply concepts in chemistry to biology at the cellular and tissue level.

University programs in biochemistry offer a comprehensive education that delves deeply into core biochemistry subjects, including enzymology, molecular biology, and cell biology. A strong foundation in chemistry, encompassing organic and inorganic chemistry, is often a prerequisite for this program. This traditional approach equips graduates with a solid understanding of biochemical concepts, preparing them for careers in research, academia, and the pharmaceutical industry.

Chemical Biology: The Intersection of Chemistry and Biology

Chemical biology is an interdisciplinary field that melds the principles of chemistry and biology to explore the chemical basis of life. It focuses on using chemical tools and techniques to probe, manipulate, and understand biological systems at the level of individual biological molecules. Chemical biologists aim to design small

molecules, known as chemical probes, to illuminate the functions of specific biomolecules or pathways and to develop novel therapeutic interventions. Chemical biology ultimately wants to understand the functional importance of small biological molecules through chemistry, with the aim of applying this knowledge to affect larger biological signalling pathways.

Chemical biology programs emphasize the integration of chemical and biological concepts. Students in chemical biology programs typically receive a broader education that includes coursework in organic chemistry, molecular biology, pharmacology, and bioinformatics. These programs encourage students to think creatively and bridge the gap between chemistry and biology, making them well-suited for careers in drug discovery, chemical genetics, and interdisciplinary research.

All in all, the key differences between the two subjects stem from the:

1. **Interdisciplinarity**: Chemical biology places a strong emphasis on interdisciplinary learning and research, enabling students to develop a versatile skill set that can bridge the gap between chemistry and biology.
2. **Tools and Techniques:** While biochemists primarily use classical biochemical methods, chemical biologists employ a broader range of techniques, such as chemical synthesis, high-throughput screening, and molecular modeling.
3. **Career Opportunities:** Biochemistry graduates often find roles in academia, pharmaceuticals, and research institutions. Chemical biology graduates, with their ability to design and use small molecules to modulate biological processes, are well-equipped for careers in drug discovery, biotechnology, and chemical genetics.

The Support for Chemical Biology

Chemical biology is an exciting and dynamic field that offers a unique perspective bridging chemistry and biology. This specialization equips students with versatile skills, making them well-suited for an ever-evolving job market that values interdisciplinary expertise. Chemical biologists have the power to design and use small molecules to modulate biological processes, providing a competitive edge in drug development, target identification, and drug discovery. They stand at the forefront of innovation, driving advancements in biotechnology and personalized medicine.

By choosing chemical biology as a specialization or major, students position themselves to be at the forefront of modern biological research. They become problem solvers, designing novel therapeutic agents, uncovering the molecular mechanisms underlying diseases, and contributing to the development of cutting-edge treatments. The synergy of chemistry and biology in chemical biology offers a unique and powerful platform for addressing some of the most challenging questions in science.

In conclusion, both biochemistry and chemical biology are essential fields for understanding the molecular basis of life. However, chemical biology, with its emphasis on interdisciplinary learning, innovative problem-solving, and the ability to design and utilize small molecules to modulate biological processes, offers students

a dynamic and influential path. This field is ideal for those who want to navigate the complexities of modern biology while harnessing the power of chemistry to shape the future of healthcare and scientific discovery.

Chemistry and Sustainable Chemistry Programs at McMaster University

McMaster University offers a diverse range of undergraduate programs in chemistry, including a specialization focused on sustainable chemistry. These programs provide students with a solid foundation in the principles of chemistry and offer an opportunity to explore the exciting field of sustainable chemistry.

Honours Bachelor of Science in Chemistry (B.Sc.): This program provides a comprehensive education in chemistry, covering the essential topics in organic, inorganic, physical, and analytical chemistry. Students gain a strong theoretical and practical foundation in the field, preparing them for careers in research, industry, or further studies.

Honours Bachelor of Science in Sustainable Chemistry (B.Sc.): Sustainable chemistry is a specialized field that focuses on developing eco-friendly chemical processes, materials, and solutions. It plays a crucial role in addressing environmental challenges, reducing waste, and promoting resource efficiency.

In conclusion, McMaster University offers a dynamic and comprehensive undergraduate education in chemistry, with a specialized focus on sustainable chemistry. Students have the opportunity to explore the fascinating world of matter, from the fundamental principles of chemistry to its practical applications in addressing sustainability challenges. Through coursework, research opportunities, and engagement with like-minded peers, McMaster equips its students to become future leaders in the field of chemistry and sustainable chemistry, prepared to tackle the world's most pressing issues with knowledge and innovative solutions.

CHAPTER 2 - ORGANIC STRUCTURE AND BONDING

2.1 - BONDING

Learning Objectives

1. Draw and interconvert between Lewis structures, structural formulas, and line-angle drawings, using proper drawing conventions.
2. Determine polarity in covalent bonds.
3. Calculate formal charge on an atom.
4. Recognize the normal valency of atoms found in organic chemistry (C, N, O, H, Halides).
5. Identify carbocations and carbanions and determine the number of surrounding hydrogens.

Introduction

In chemistry, we discuss the properties of individual elements on the periodic table, as well as the molecules that are comprised of those elemental building blocks. Bonding allows for the association of individual atoms through the sharing of electrons and allows for the formation of molecules.

What is Bonding?

A chemical bond consists of a pair of electrons that are localized to certain regions of space between two nuclei. A **bond** is the result of the overlap of individual atomic orbitals, with the pair of electrons occupying the overlapping orbital space. Orbitals are regions around the nucleus of an atom where electrons are likely to be found. Chemical reactions result in bonds breaking and bond forming events, creating new molecules. Two atoms sharing one pair of electrons results a single covalent bond, while the sharing of two and three pairs of electrons create covalent double and triple bonds respectively.

Drawing Lewis Structures

This section provides a review of how to draw Lewis structures using a step-by-step approach, followed by an example of how to draw the Lewis structure of the bicarbonate anion, HCO_3^-.

Step-by-step approach to drawing Lewis structures:

1. Count the total number of valence electrons, including charge of structure. Note that you need to add electrons if the species is negatively charged (an anion) and subtract electrons if the species is positively charged (a cation).
2. Draw the skeletal structure, including the central and terminal atoms. Note that the least electronegative atom is usually the central atom, and hydrogen and fluorine are always terminal.
3. Use the remaining electrons to complete the octet of all terminal atoms. Note that hydrogen needs only 2 electrons, not 8.
4. Subtract all electrons used in previous steps and place any remaining electrons on the central atom. Sometimes this can lead to expanded octet where there are more than 8 electrons around an atom.
5. Calculate formal charges (FC) on each atom, using the following formula:

   FC = # of valence e^- − # of bonds − # of nonbonding e^-
6. Minimize formal charges by creating multiple bonds using nonbonding electrons. This typically happens when two neighboring atoms have opposite charges, one positive and the other negative.
7. Ensure all atoms have an allowed electron count. Recall that C, N, O, F must obey octet rule, while others may have an expanded octet.

As an example, we will draw the Lewis structure of the bicarbonate anion, HCO_3^-, where C is the central atom, and H is bonded to O.

Step 1: Count the total number of valence electrons, including charge of structure

- We count 1 for hydrogen, 4 for carbon, 6 for each of the three oxygens, plus an additional 1 for the negative charge.
- Total number of valence electrons = 1 + 4 + 3(6) + 1 = 24 e^-

Step 2: Draw the skeletal structure, including the central and terminal atoms (Figure 2.1.a). Note that C is the central atom, and H is bonded to O.

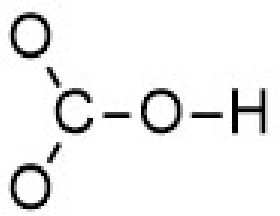

Figure 2.1.a. The skeletal structure of HCO_3^-. Carbon is the central atom, surrounded by three oxygen atoms. The hydrogen atom is terminal, bonded to one of the oxygen atoms.

Step 3: Use the remaining electrons to complete the octet of all terminal atoms, or 2 e^- for hydrogen (Figure 2.1.b). Note we are treating all the oxygen atoms as terminal (although one of the oxygen atoms is also a central atom, being attached to both carbon and hydrogen).

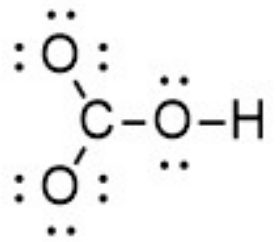

Figure 2.1.b. Skeletal structure of HCO_3^-, including lone pairs on all oxygen atoms.

Step 4: Subtract all electrons used in previous steps and place any remaining electrons on the central atom.

- Number of electrons used so far: 8 lone pairs = 16 e^-; 4 bonds = 8 e^-
- Total = 16 + 8 = 24 e^-
- All electrons have been accounted for, and none are left over for the central atom.

Step 5: Calculate formal charges (FC) on each atom (Figure 2.1.c). More information about formal charge and its utility can be found below in in the "Calculating Formal Charge" section. The formula for calculating formal charge is:

FC = # of valence electrons – # of bonds – # of lone electrons.

NOTE: We are subtracting the number of lone electrons, NOT the number of lone pairs. For example, if there is 1 lone pair, subtract 2 (since a lone pair has 2 electrons).

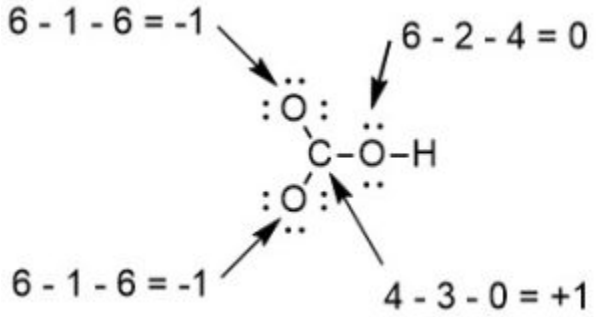

Figure 2.1.c. Sample calculations for the formal charge on the carbon atom and each oxygen atom in HCO_3^-.

This Lewis structure can be drawn with all non-zero formal charges as shown in Figure 2.1.d:

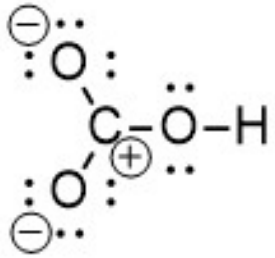

Figure 2.1.d. Skeletal structure of HCO_3^-, with any non-zero formal charges indicated on each atom.

Step 6: Minimize formal charges by creating multiple bonds using nonbonding electrons.

To create a multiple bond, we use two neighbouring atoms, one of which has a positive formal charge while the other has a negative formal charge. A double bond is created when the lone pair of electrons (originally on oxygen) is shared between oxygen and carbon. We can use either one of the oxygen atoms on the left (both of which have a formal charge of -1), and the carbon atom (with a formal charge of +1). There are two choices of where to create a multiple bond, and therefore two resonance structures that can be drawn.

Using a lone pair of electrons from the bottom left oxygen to create a C=O double bond (Figure 2.1.e):

Figure 2.1.e. Minimize non-zero formal charge by sharing a lone pair of electrons between the bottom left oxygen atom and the central carbon atom. This generates a double bond between C and O.

Using a lone pair of electrons from the top left oxygen to create a C=O double bond (Figure 2.1.f):

Figure 2.1.f. Minimize non-zero formal charge by sharing a lone pair of electrons between the top left oxygen atom and the central carbon atom. This generates a double bond between C and O.

Both resonance structures drawn together in one diagram (Figure 2.1.g):

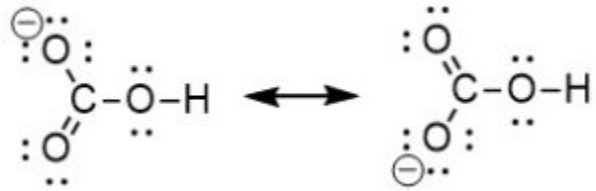

Figure 2.1.g. Two resonance structures can be drawn for HCO_3^-, shown together in one diagram with a double barbed arrow.

Step 7: Ensure all atoms have an allowed electron count. Recall that C, N, O, F must obey octet rule, while others may have an expanded octet.

The carbon and oxygen atoms have a complete octet, while hydrogen has two electrons.

Bond Polarity in Organic Chemistry

A **covalent chemical bond** represents the sharing of a pair of electrons by two nuclei. Although the electron

density in a bond is found between two atoms, the electron density is often will biased towards one atom in the bond over the other. This creates a charge dipole between the 2 atoms in the bond, with one atom becoming electron rich and behaving as if it has a negative charge, and the other becoming electron poor and behaving as if it has a positive charge.

In organic chemistry, a C–C and C–H bond are considered **non-polar**. This is because the electronegativity differences are 0 and 0.4 respectively, so the electrons aren't largely attracted to one atom over the other. This means that electron density resides more equally between these two atoms.

Any other C–X bond is considered **polar**, even if their electronegativities are similar. Here, the halogen (X) is more electronegative, and will pull electrons towards itself. Electron density will therefore reside closer to the halogen than to carbon. C–I is an example of a bond that you would expect to be non-polar due to the electronegativity difference of 0, but is considered polar. Electronegativity can help us predict bonding and reactivity, due to the preference of some atoms to carry electron density over others.

How To Draw Organic Molecules

Simple organic molecules like ethane are quick and straightforward to draw using a Lewis diagram, but for more complex molecules, drawing the Lewis structure will be tedious. Line-angle drawings, as in Figure 2.1.h, were therefore designed to efficiently draw organic molecules.

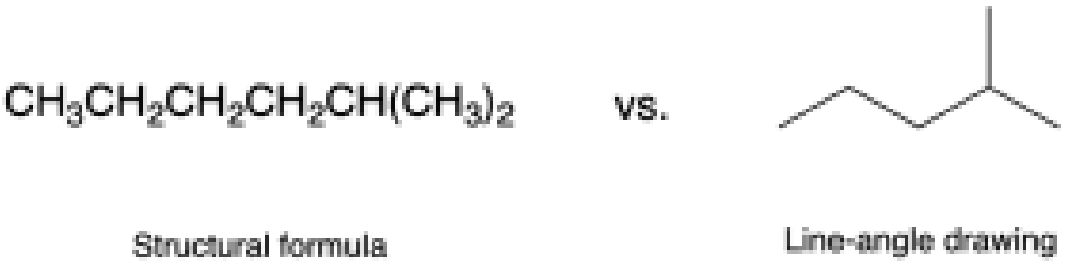

Figure 2.1.h. The drawing on the left is the structural formula of 2–methylpentane, while the structure on the right is the line-angle drawing of 2–methylpentane. The latter will be used from now on to represent organic structures. Each carbon in a line-angle drawing is represented by a vertex or an end point.

Line-angle representations are the most common way to depict organic molecules. There are several rules used to properly represent organic molecules using line-angle convention:

Rule 1: Every point or vertex in a line-angle diagram represents a carbon atom (Figure 2.1.i).

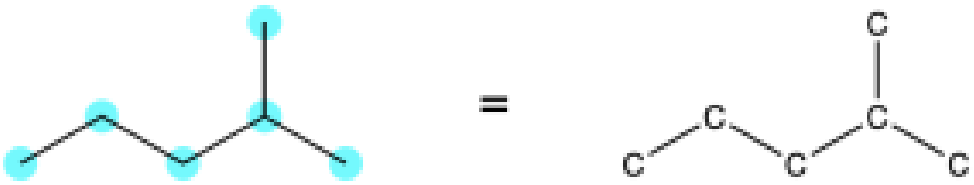

Figure 2.1.i. The highlighted points in blue on the left represent the presence of carbon atoms. In line-angle drawings, every vertex is a carbon atom unless stated otherwise. 2–methylpentane has 6 "points" or vertices, highlighted in blue, representing the 6 carbon atoms.

Rule 2: Assume that there are hydrogen atoms attached to each carbon for a valence of four (Figure 2.1.j).

Any carbon not shown to have four explicit bond has its valency implicitly filled with bonds to hydrogen atoms

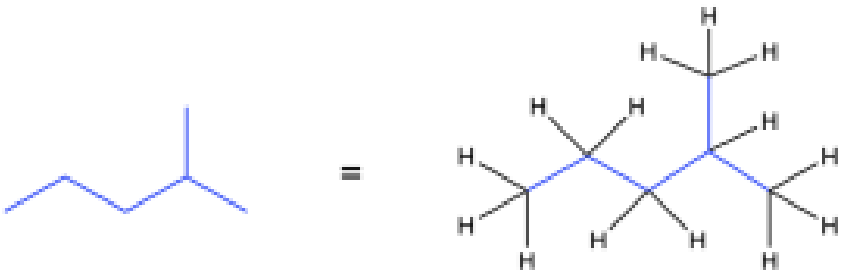

Figure 2.1.j. In line-angle drawings, the hydrogens bonded to carbon atoms are not explicitly drawn (see Rule 4 for the exception). The structure on the right shows the hydrogen atoms of 2–methylpentane, with the line-angle drawing backbone highlighted in blue.

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Rule 3: Draw molecules in a zig-zag shape for single/double blonds, and linear for triple bonds (Figure 2.1.k).

Line-angle convention is that the bonds angles mimic how the molecules are observed in 3 dimensional space. Alkanes and alkenes are observed to have a tetrahedral (109.5º) and trigonal planar (120 º) geometries

respectively, which is closely represented by the zig-zag format. Alkynes are observed to have a liner geometry, and should be drawn in a linear format in line-angle.

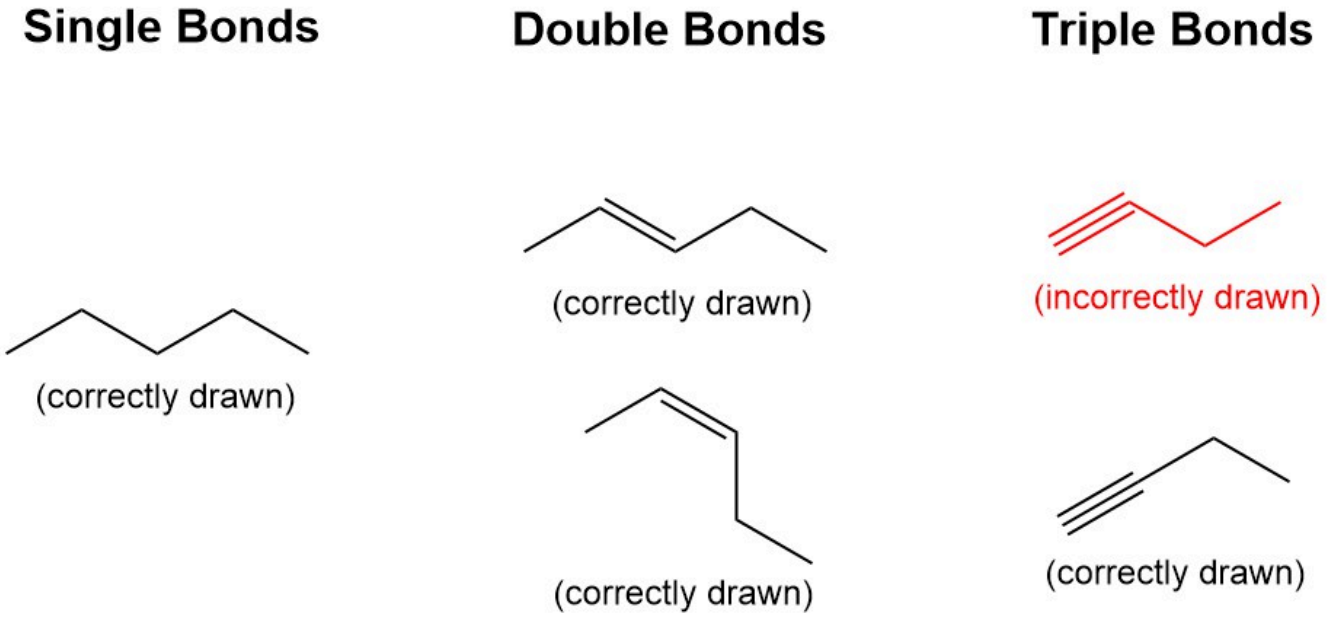

Figure 2.1.k. Single and double bonds should be drawn zig-zag, with each vertex representing a carbon atom. Triple bonds should be drawn in a linear fashion.

Rule 4: Any time you write the symbol for an atom (for heteroatoms and carbon), you MUST also write the hydrogens bound to that atom (Figure 2.1.l). Note: "heteroatom" means any atom that is not carbon or hydrogen.

It is important to remember that you do not need to indicate the hydrogens bonded to carbon if the carbon atom is not explicitly drawn. But if the carbon atom is explicitly drawn, you **must** show the bonded hydrogen atoms.

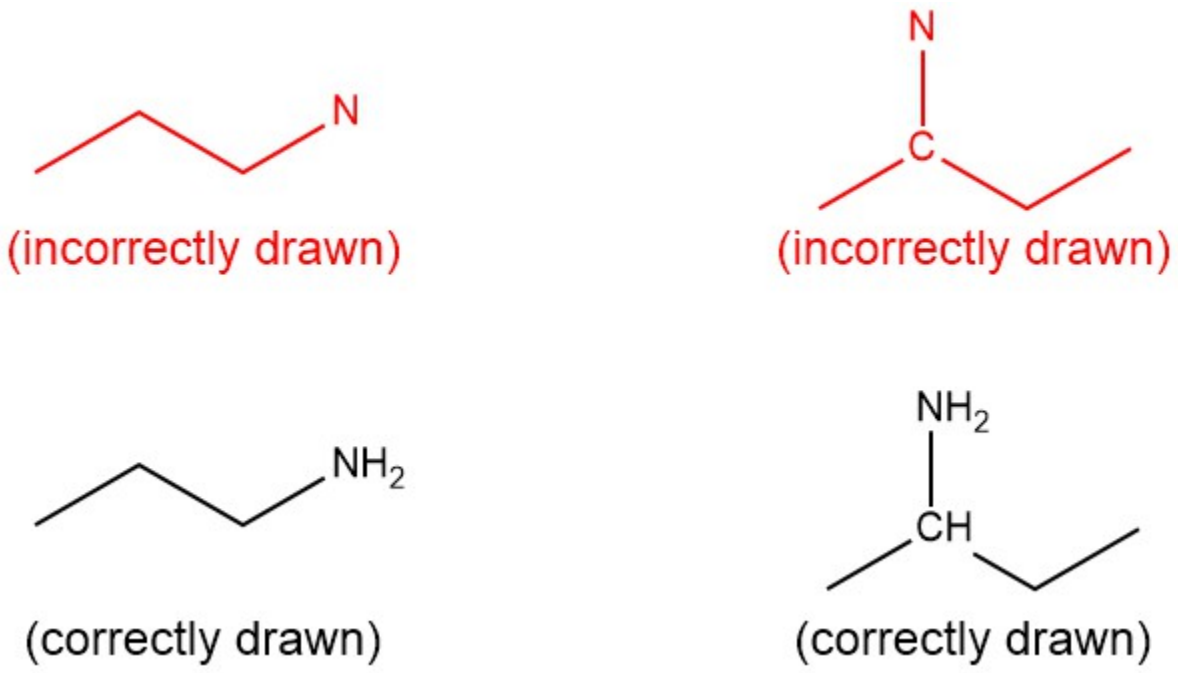

Figure 2.1.l. When the symbol for an atom is explicitly written, the hydrogen must also be shown. Top: the structures in red are drawn incorrectly: the nitrogen atom (a heteroatom) and the explicitly written carbon atom do not show attached hydrogens. Bottom: the structures in black are drawn correctly, where all hydrogens are shown whenever an atom (such as C or N) is explicitly indicated.

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Rule 5: Indicate all non-zero formal charges with a (+) or (-) sign beside the atom carrying that charge (Figure 2.1.m).

A review of how to calculate formal charges is shown above, in the "Review of Lewis Structures" section of this chapter.

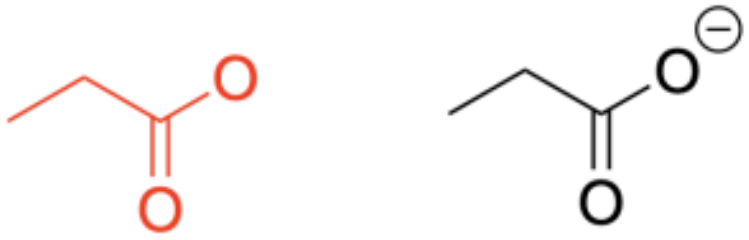


Figure 2.1.m. Non–zero formal charges must be indicated, as this will be useful when discussing reactivity. The structure in red is not properly drawn, as the oxygen on the right does not have the (–) sign to show a formal charge of –1. The structure on the right is the correct way of drawing a carboxylate.

Rule 6: Count the carbon atoms and the substituents on each carbon atom. There are never more than 4 pairs of electrons on any second-row element.

Rule 7: Drawing lone pairs on all explicitly drawn atoms is optional (Figure 2.1.n). You can either draw all the lone pairs, only a select few of the lone pairs, or none of the lone pairs. You will see this come up in Chapter 3 – Reactivity.

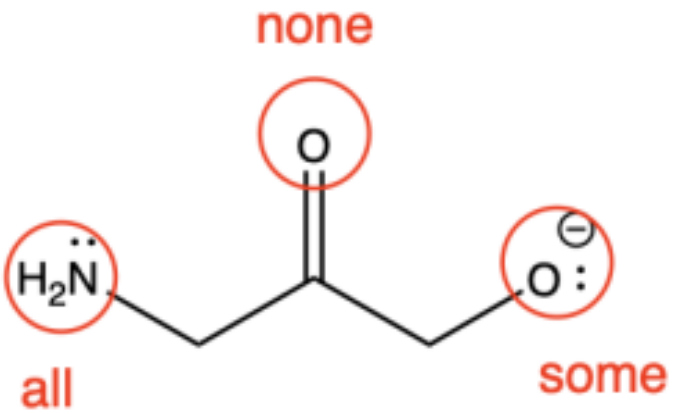
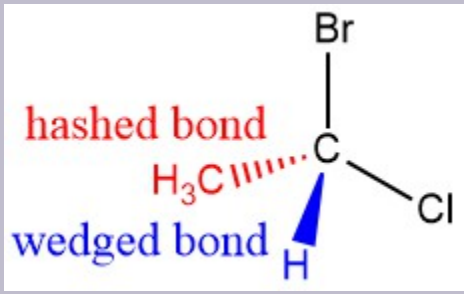


Figure 2.1.n. Drawing lone pairs on explicitly drawn atoms is optional. All lone pairs may be drawn (seen with the $–NH_2$ group), no lone pairs may be drawn (seen with the C=O group), and some may be drawn (seen with the –O group).

Line–angle convention is utilized to emphasize the reactive parts of the molecule. For example, bonds between carbon and a heteroatom in a functional group are polar, and this is often the site of reactivity. In addition, positively or negatively charged species are often reactive. In contrast, bonds between carbon and hydrogen are generally non-polar and unreactive. Line-angle convention helps to de-emphasize the unreactive parts of molecules (by hiding hydrogen atoms and drawing carbon atoms as points or vertices), and emphasize the reactive parts of molecules (by explicitly showing heteroatoms and formal charges).

Are You Wondering? Wedged and Hashed Bonds

Recall that chemists indicate the 3D geometry of a molecule using wedged bonds and hashed bonds. A wedged bond indicates that the atom or group is pointing towards the viewer while a hashed bond indicates that the atom or group is pointing away from the viewer .



Three-dimensional representation of 1-bromo-1-chloroethane. The wedged bond, shown in blue, indicates that the hydrogen atom is projecting out towards the viewer, while the hashed bond, shown in red, indicates that the methyl group is receding away from the viewer.

Formal Charge

A review of formal charge, and formula to calculate formal charge is provided above in the "Drawing Lewis Structures" section of this chapter. **Formal charge** is the charge assigned to atoms in molecules, and is a way of keeping track of electrons. On a line-angle representation of an organic molecule, both positive and negative formal charges must be indicated on the atom that bares the charge (as stated above in Rule 6). Positive and negative formal charges occur in a variety of organic molecules. A few examples are shown below, along with how to calculate the formal charge (Figure 2.1.o).

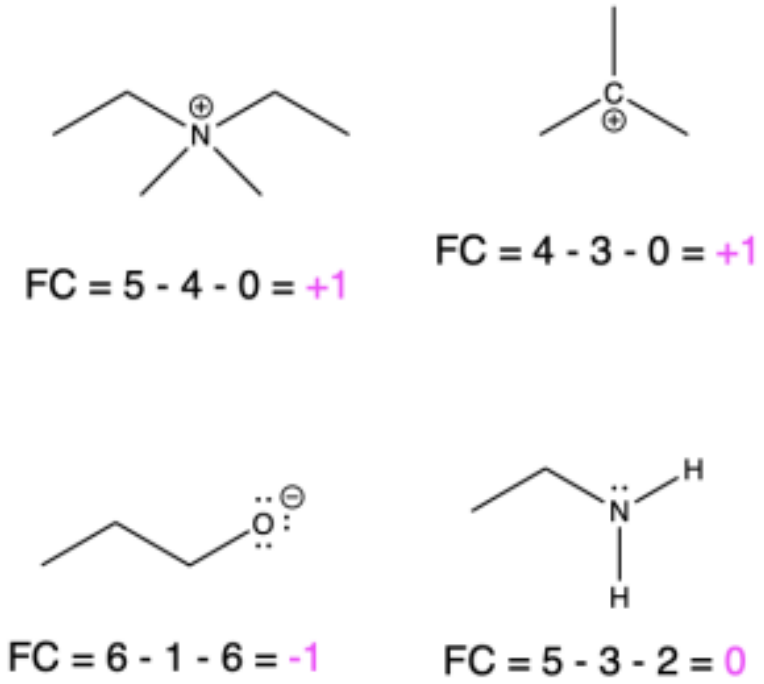


Figure 2.1.o. Sample calculations for formal charge.

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The Octet Rule

A source of stability for atoms is to have a complete shell of electrons in its outer shell. For second row elements like carbon, nitrogen, oxygen, we refer to it as the **octet rule**, since the outer shell can bear 8 electrons maximally. The octet rule will **generally** hold true for carbon, nitrogen, and oxygen. That is, they will typically have a complete octet. Having an atom with a complete octet is a larger stabilizing force than minimizing formal charges when drawing Lewis structures for second-row elements (C, N, O, F), as shown below for carbon monoxide, CO (Figure 2.1.p).

Figure 2.1.p. The Lewis structure for carbon monoxide on the left is the best way to draw it. Despite both the carbon and oxygen atoms having formal charges of –1 and +1 respectively, the octet rule is obeyed, which is favoured over formal charge. The structure on the right is not an accurate representation of carbon monoxide. While the formal charges on both the carbon and oxygen atoms are zero, carbon only has 6 electrons, which is less than a complete octet.

Trends in Formal Charge

To determine the formal charge of any atom, we can use bonding patterns (which includes the number of lone pairs and bonds) for elements commonly found in organic chemistry. Below, we elaborate on bonding patterns and formal charges for oxygen, nitrogen, carbon and hydrogen.

For oxygen, nitrogen, and carbon, notice how the sum of the bonds and lone pairs never exceeds 4. This is due to the octet rule. Similarly, for hydrogen, notice how the sum of the bonds and lone pairs never exceeds 1.

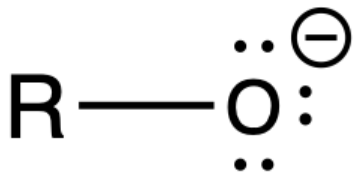
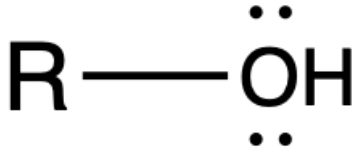
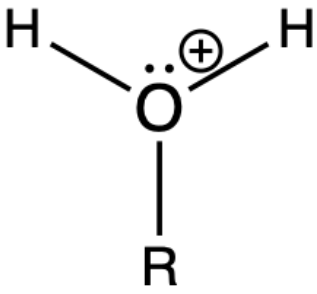
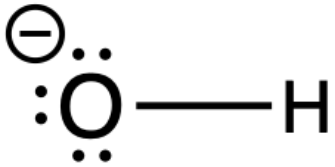
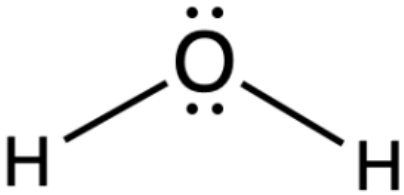
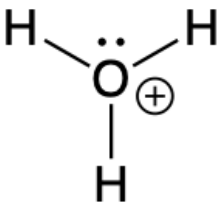
Trends in Formal Charge for Oxygen

If oxygen is bonded to 1 atom and has 3 lone pairs, then it has a formal charge of -1 (Table 1, left). This is called an **alkoxide**, and it is similar to hydroxide, which shares the same bonding pattern.

If oxygen is bonded to 2 atoms and has 2 lone pairs, then it has a formal charge of zero (Table 1, center). An example is seen with the alcohol, ethanol. This is similar to water, which shares the same bonding pattern.

If oxygen is bonded to 3 atoms and has 1 lone pair, then it has a formal charge of +1 (Table 1, right). This is called an **oxonium**, and it is similar to hydronium, which shares the same bonding pattern.

Table 1. *Bonding patterns for oxygen, with formal charge calculations.*

Negative	Neutral	Positive
Alkoxide  FC = 6 - 1 - 6 = -1	Alcohol  FC = 6 - 2 - 4 = 0	Oxonium  FC = 6 - 3 - 2 = +1
Hydroxide  FC = 6 - 1 - 6 = -1	Water  FC = 6 - 2 - 4 = 0	Hydronium  FC = 6 - 3 - 2 = +1

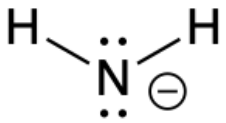
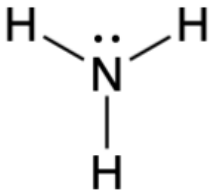
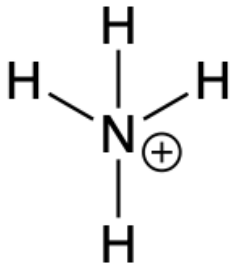
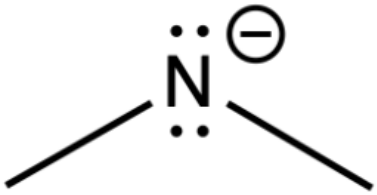
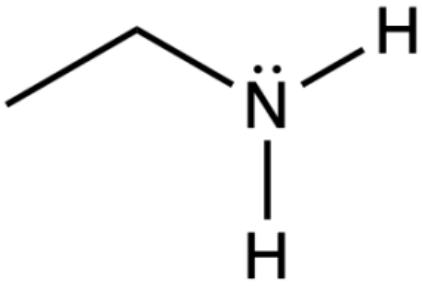
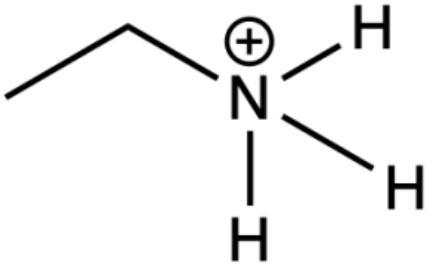
Trends in Formal Charge for Nitrogen

If nitrogen is bonded to 2 atoms and has 2 lone pairs, then it has a formal charge of –1 (Table 2, left). An example is seen with amide.

If nitrogen is bonded to 3 atoms and has 1 lone pair, then it has a formal charge of zero (Table 2, center). An example is seen with ammonia.

If nitrogen is bonded to 4 atoms and has no lone pairs, then it has a formal charge of +1 (Table 2, right). An example is seen with the ammonium ion.

Table 2. *Bonding patterns for nitrogen, with formal charge calculations.*

Negative	Neutral	Positive
Amide  FC = 5 - 2 - 4 = -1	Ammonia  FC = 5 - 3 - 2 = 0	Ammonium  FC = 5 - 4 - 0 = 1
Dimethylamide  FC = 5 - 2 - 4 = -1	Ethanamine  FC = 5 - 3 - 2 = 0	Ethanaminium  FC = 5 - 4 - 0 = +1

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/mcmasterchem1aa3/?p=1323#h5p-108

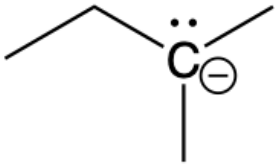
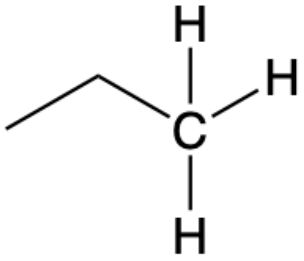
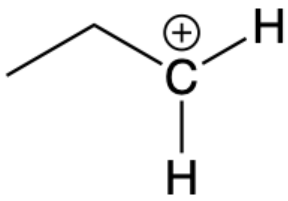
Trends in Formal Charge for Carbon

If carbon is bonded to 3 atoms and 1 lone pair, then it has a formal charge of –1 (Table 3, left). An example is seen with a negatively charged carbanion.

If carbon is bonded to 4 atoms and no lone pairs, then it has a formal charge of zero (Table 3, center). An example is seen with propane.

If carbon is bonded to 3 atoms and no lone pairs, then it has a formal charge of +1 (Table 3, right). An example is seen with a positively charged carbocation.

Table 3. *Bonding patterns for carbon, with formal charge calculations.*

Negative	Neutral	Positive
Carbanion  FC = 4 - 3 - 2 = -1	Propane  FC = 4 - 4 - 0 = 0	Carbocation  FC = 4 - 3 - 0 = +1

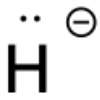
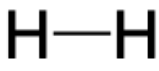
Trends in Formal Charge for Hydrogen

If hydrogen carries a lone pair of electrons, then it has a formal charge of is –1 (Table 4, left). This is called a **hydride**. You will see hydride used as a reactant in Chapter 3.4.

If hydrogen does not carry a lone pair of electrons and instead is covalently bonded to another atom of equal, or higher electronegativity, it is sharing its one electron, and carries a formal charge of 0 (Table 4, center). An example is hydrogen gas (H_2). You will see hydrogen gas used as a reactant in Chapter 3.2.

If hydrogen does not carry any electrons, then the charge of the atom is +1. This is called a proton, because its positive charge comes from the one proton inside the nucleus. You will see a proton used as a reactant (in the form of an acid) in several reactions in Chapter 3.

Table 4. *Bonding patterns for hydrogen, with formal charge calculations.*

Negative	Neutral	Positive
Hydride  FC = 1 p^+ - 2 e^- = -1	Hydrogen  FC = 1 p^+ - 1 e^- = 0	Proton  FC = 1 p^+ - 0 e^- = +1

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Key Takeaways

- Chemistry involves studying elements on the periodic table and how they form molecules through bonding.
- Chemical bonding involves the sharing of electrons between atoms to create molecules.
- Covalent bonds can be single, double, or triple, based on the number of shared electron pairs.
- Bond polarity depends on electronegativity differences, affecting electron distribution.
- Line-angle drawings are used to represent organic molecules efficiently.
- Rules for line-angle drawings include representing carbon atoms at vertices, assuming hydrogen atoms attached to carbon, and drawing bond angles based on geometry.
- Formal charge helps track electrons in molecules and is calculated using valence electrons, bonds, and lone electrons.
- The octet rule states that atoms aim for a complete outer shell with 8 electrons.
- Trends in formal charge are determined for oxygen, nitrogen, carbon, and hydrogen

Diversity in Chemistry: Dorothy Hodgkin

Throughout this chapter, we draw the structures of various compounds using line-angle drawing, but how exactly did scientists deduce these structures? There are many techniques nowadays that can be used to elucidate the structures of both small and large molecules, with one of them being *X-ray crystallography*. This technique involves shooting a beam of x-rays at a solid crystal, which causes the rays to diffract, bending the light in various directions. The angles and extent of diffraction can then be measured to determine the density of electrons around the crystal, which is used to deduce how the atoms are arranged in the crystal. **Dorothy Hodgkin** was a renowned X-ray crystallographer, using the technique to determine the exact structure of many complex, yet significant compounds, such as penicillin and insulin. During her Ph.D experience, Hodgkin was diagnosed with rheumatoid arthritis in her hands, presenting itself as an obstacle in her work; however, she persevered and continued to work despite being unable to operate simple switches, opting to make long levers that she could use instead. In 1964, Hodgkin was recognized for her work, being the sole receiver of the Nobel Prize in Chemistry for her X-ray crystallography studies and continued to travel around the world to give presentations on her work despite her condition. More information on Hodgkin and her scientific career can be found on her page on The Royal Society website.

A portrait of Dorothy Hodgkin.

2.2 - VALENCE BOND THEORY

Learning Objectives

1. Understand how hybridization occurs using an electron configuration.
2. Identify an atom in a molecule as spx-hybridized (where x = 1, 2, or 3) or unhybridized.
3. Identify s, p, and hybridized spx orbitals and the resulting bond angles and geometries.
4. Distinguish between σ and π bonding and explain their significance.

Chapter 2.1.1. introduced the concept of covalent bonding, which involves the sharing of electrons between two atoms. The electronegativity of these atoms determines where the electron density is more closely held and the polarity of the bond. While the exact location of an electron cannot be known, the probability of finding an electron in a particular area can be estimated. This area is called an **orbital**.

Electrons reside in orbitals according to the quantum mechanical model. According to valence bond theory, a chemical bond is formed when two half-filled orbitals overlap to share two electrons.

Hybridization

Hybridization is a concept that was developed to explain the experimentally observed electron geometries around atoms in bonds that could not be explained by atomic orbitals alone.

Hybridization explains the bonding in a wide range of molecules, including simple molecules like methane (CH_4). The **electronic ground state** of carbon ($1s^2 2s^2 2p^2$) has two unpaired valence electrons in p orbitals (Figure 2.2.a). This would suggest that:

1. Carbon should only make two bonds through orbital overlap, since it only has two unpaired electrons in two half-filled shells; and
2. The H–C–H bond angle in methane should be 90º, since the p orbitals are oriented 90º from one

another.

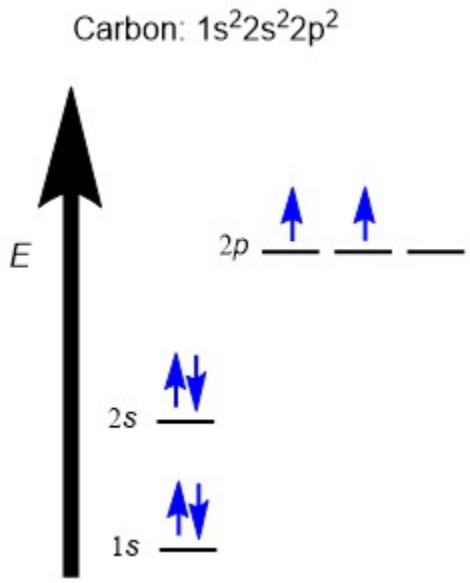

Figure 2.2.a. Energy level diagram for carbon in its ground state.

However, experimental structure determination of methane shows that:

1. There are four hydrogens around the central carbon atom with equal C–H bond lengths, which suggests the same C–H bond energy for all four bonds.
2. There is a tetrahedral geometry with 109.5º bond angles.

Taken together, these experimental results imply that electrons must be occupying orbitals of equal energy, called **degenerate orbitals**, to form bonds with equal bond angles and bond energies.

The bonding in methane can instead be described by mixing the valence orbitals (one 2s and three 2p) to form four degenerate sp^3 hybrid orbitals (Figure 2.2.b). Being degenerate, Hund's Rule states that each orbital will first be filled with a single electron before electrons are paired together. Thus, these orbitals are half-filled, with one electron in each. These four degenerate sp^3 hybridized orbitals are oriented in 3-dimensaional space to minimize electrostatic repulsion of the occupying electrons, resulting in the tetrahedral geometry. Thus, carbon makes four bonds using four half-filled hybrid orbitals, all of equal bond energy and bond length.

The word **hybrid** means something of mixed origin or composition. With respect to atomic systems, hybridization is the mixing of two or more standard atomic orbitals (such as s, p, d, f orbitals) to form new hybrid orbitals (such as sp^3 orbitals). Hybridization explains how the energy levels and orientations of ground

state atomic orbitals (s, p, d, f) could be adjusted in 3 dimensional space to match the experimental observations found in organic molecules.

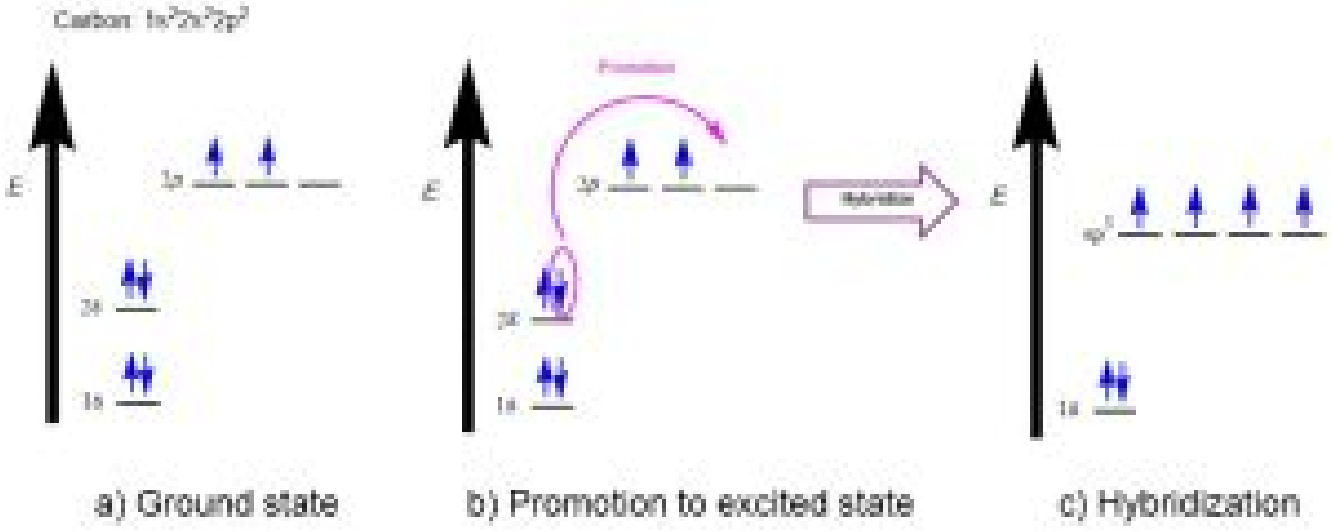

Figure 2.2.b. Electron configuration diagram for carbon. Left: ground-state electron configuration for carbon, showing two electrons in the 2s orbital and two unpaired electrons in the 2p orbitals. Middle: Electron promotion and mixing of orbitals. Right: sp^3 hybridization for carbon, in which all four orbitals (one 2s and three 2p) are mixed together, producing four degenerate sp^3 hybrid orbitals.

Promotion of an electron from the ground state to facilitate the formation of hybrid orbitals requires energy, making it an endothermic process. However, bond formation releases energy, making it an exothermic process. The hybridized carbon atom can now form four covalent bonds with its four unpaired electrons (instead of two in the unhybridized state), resulting in a net release of energy upon bond formation.

There are two key rules in hybridization:

1. The number of standard atomic orbitals mixed together is equal to the number of hybrid orbitals formed. In other words, the total number of orbitals is conserved upon hybridization. For example, mixing **one** 2s and **three** 2p orbitals generates **four** sp^3 hybrid orbitals.
2. The combination of standard atomic orbitals mixed together determines the shapes of the hybrid orbitals formed. For example, mixing one s and three p orbitals of the same energy level generates four sp^3 hybrid orbitals that point towards the corners of a **tetrahedron**, (Figure 2.2.c).

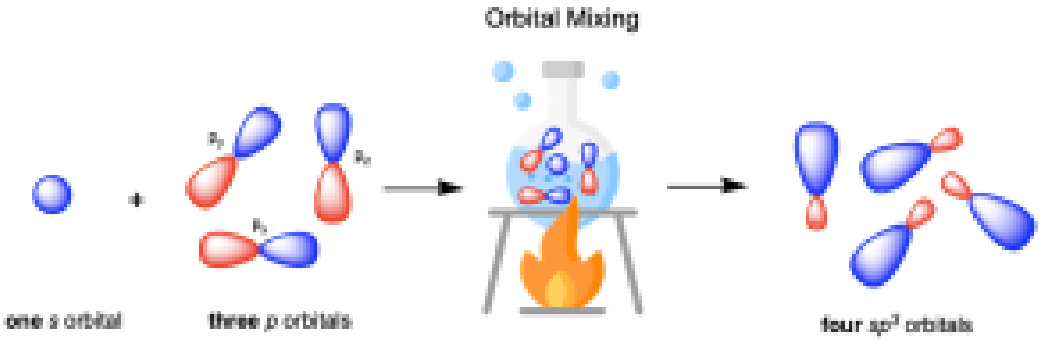

Figure 2.2.c. The mixture of one s orbital and three p orbitals will yield four sp^3 hybridized orbital. Note that four atomic orbitals were mixed together to form four sp^3 hybrid orbitals, illustrating that the total number of orbitals is conserved upon hybridization.

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Sigma and Pi Bonding

Two types of bonds formed by orbital overlap will be considered: sigma (σ) and pi (π) bonds.

σ bonds involve orbitals overlapping end-on, as illustrated in Figure 2.2.d. Exactly one σ bond is possible between two atoms. All single bonds are made through σ bonding.

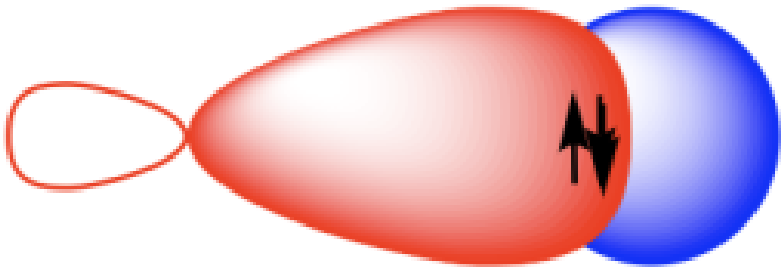

Figure 2.2.d. End-on overlap of a hybrid orbital (red) and an s orbital (blue) to produce a **σ** bond, as seen in a C–H bond.

In contrast, π bonds consist of side-on orbital overlap. π bonds are seen in molecules with double bonds or

triple bonds. Double bonds consist of one σ and one π bond, while triple bonds consist of one σ bond and two π bonds. Up to two π bonds in total are possible between two atoms.

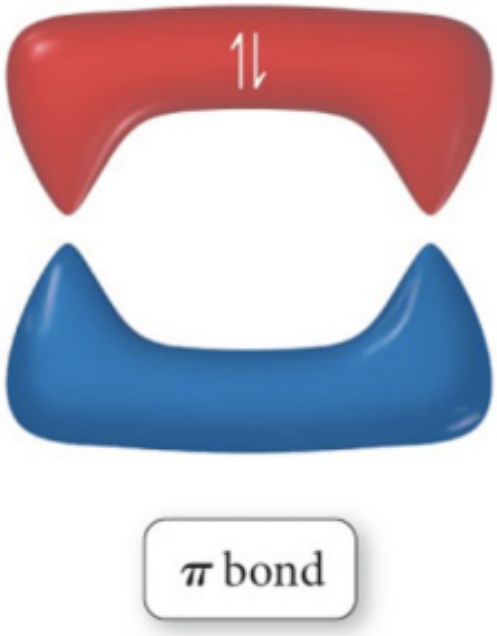

Figure 2.2.e. Side-on overlap of two p orbitals produce a π bond.

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VSEPR vs. Hybrid Orbitals

The **Valence Shell Electron Pair Repulsion** (VSEPR) model and the hybridization model predict the same molecular geometry (Table 2.2.a). This is because the orientation of the hybrid orbitals produces certain bond angles to minimize repulsion, yielding a specific geometry.

Table 2.2.a. *Molecular geometries of molecules predicted based on the number of electron groups. The same result is obtained through the VSEPR model and the hybridization model.*

# of electron groups	Electron–group geometry from VSEPR	Hybridization	Ideal Bond Angle	Examples
2	Linear	sp	180°	CO_2, $BeCl_2$
3	Trigonal planar	sp^2	120°	BH_3, SO_2
4	Tetrahedral	sp^3	109.5°	CH_4, H_2O

NOTE: The hybridization schemes shown in this chart work well for organic compounds, but do not apply to all molecules.

Are You Wondering? A Review of VSEPR Theory

Valence Shell Electron Pair Repulsion (VSEPR) Theory is a model to explain the molecular shapes of molecules based on the idea that electron groups repel one another. An electron group can be a bond (single, double, triple) or a lone pair. A molecule is symbolized a AX_nE_m, where A is the central atom, X represents atoms that are bonded to the central atom, and E represents lone pairs of electrons. There can be any number of bonded atoms (n) or lone pairs (m). The chart below summarizes some of the important VSEPR classes for 2, 3, or 4 groups of electrons. Other VSEPR classes exist for greater numbers of electron groups, but they are largely unnecessary for organic compounds.

	2 e^- groups	3 e^- groups	3 e^- groups	4 e^- groups	4 e^- groups	4 e^- groups
VSEPR Cass	AX_2	AX_3	AX_2E	AX_4	AX_3E	AX_2E_2
Molecular Geometry	Linear	Trigonal planar	Bent	Tetrahedral	Trigonal pyramidal	Bent
Angles	180°	120°	< 120°	109.5°	< 109.5°	< 109.5°
Examples	$BeCl_2$, CO_2	BF_3, CH_3^+	BH_2^-	CH_4	NH_3, CH_3^-	H_2O

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sp^3 Hybridization

As previously mentioned with methane, **sp^3 hybridization** involves four atomic orbitals (one 2s and three 2p) undergoing hybridization to form **four** sp^3 hybrid orbitals. Since these hybrid orbitals are degenerate in energy, the bond length and bond energy of all four bonds are equal. The sp^3 orbitals resemble an asymmetric dumbbell shape, with most electron density residing in the larger lobe.

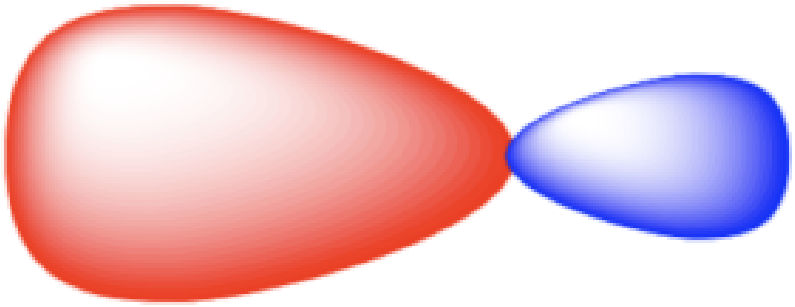

Figure 2.2.f. The sp^3 hybrid orbital resembles an asymmetric dumbbell, with most electron density residing in the larger lobe.

In sp^3 hybridization, the large lobes point to the corners of a tetrahedron. The angle between orbitals is 109.5º. The hybrid orbitals overlap with orbitals on other atoms to form σ bonds.

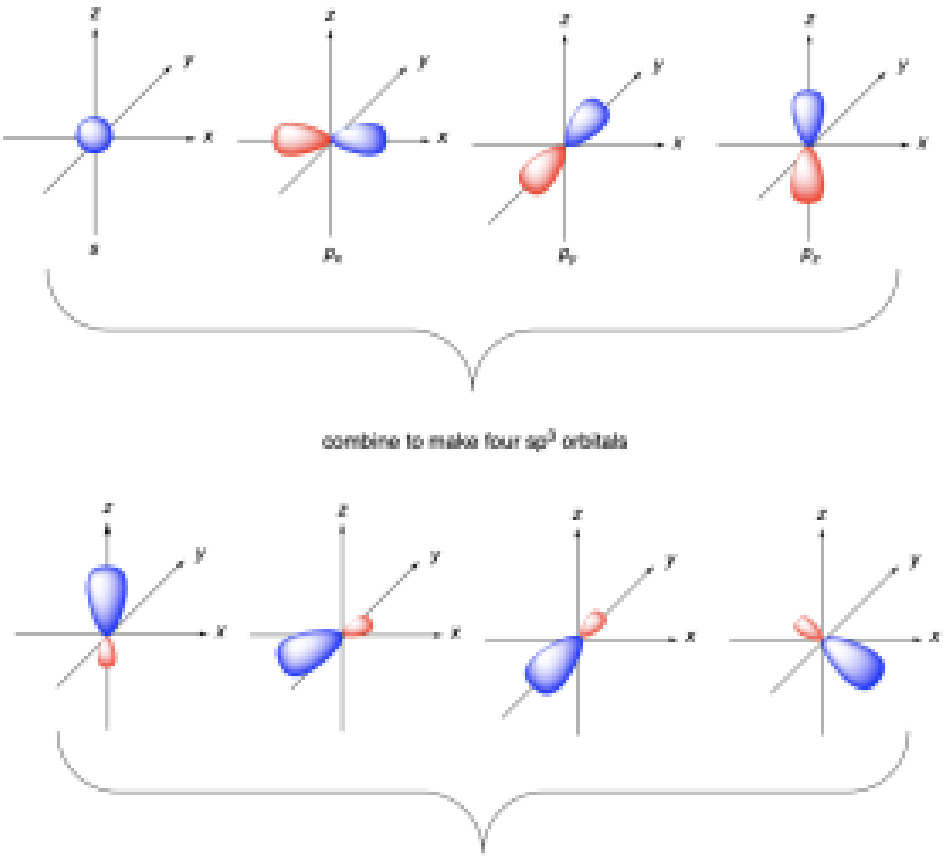

Figure 2.2.g. Four atomic orbitals combine to generate four sp^3 hybrid orbitals. The orbitals point towards the corners of a tetrahedron to minimize repulsion.

Below, the hybridization and bonding in four molecules are discussed: methane (CH_4), methide anion (CH_3^-), ammonia (NH_3), and ethane (C_2H_6).

The sp^3 hybrid orbitals in carbon overlap with atomic s orbitals on hydrogen to produce C–H σ bonds, as seen in methane (Figure 2.2.h.) and methide anion (Figure 2.2.i, left). For methane, all four sp^3 hybrid orbitals form σ bonds to hydrogen; for methide anion, three sp^3 hybrid orbitals form σ bonds to hydrogen, with the fourth sp^3 hybrid orbital containing a lone pair of electrons. Ammonia is isoelectronic to methide anion, which means that they have the same bonding arrangement (Figure 2.2.i, right): three sp^3 hybrid orbitals to form σ bonds to hydrogen, with the fourth sp^3 hybrid orbital containing a lone pair of electrons. This example showcases the fact that hybridization can be invoked not just for carbon but for heteroatoms such as nitrogen as well.

The geometry around the central atom is tetrahedral, with ideal bond angles of 109.5°. For methide anion and ammonia, the H–C–H or H–N–H bond angle will be slightly less than 109.5° due to the electrostatic repulsion by the lone pair of electrons.

Figure 2.2.h. Bonding in methane, CH_4. There are four sp^3 hybrid orbitals, shown in grey, all of which overlap with an atomic 1s orbital on hydrogen, shown in white, resulting in four C–H σ bonds.

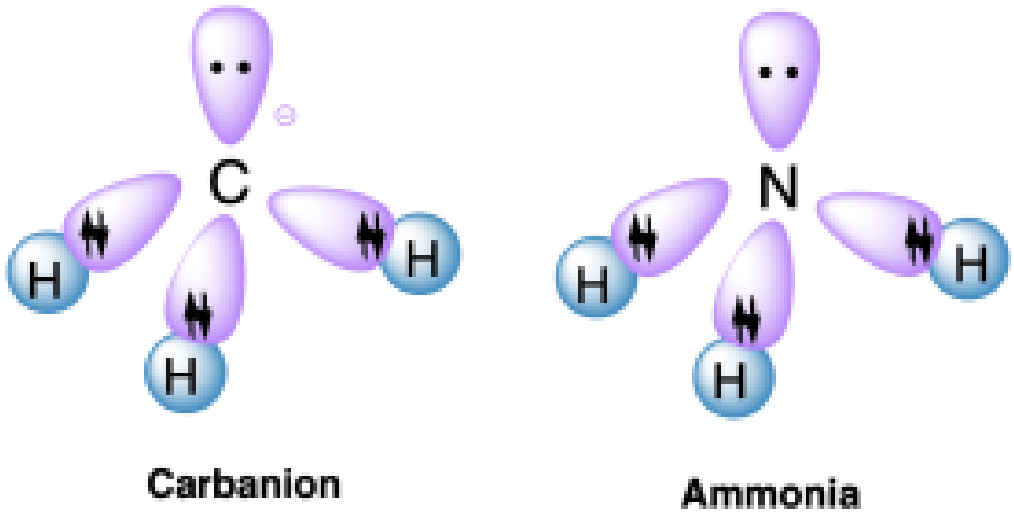

Figure 2.2.i. Bonding in the methide anion (CH_3^-, left) and ammonia (NH_3, right). Both molecules have four sp^3 hybrid orbitals, shown in purple. Three of these sp^3 hybrid orbitals overlap with an atomic 1s orbital on hydrogen, shown in blue, forming three σ bonds, while the fourth sp^3 hybrid orbital contains a lone pair of electrons.

End-on overlap of hybrid orbitals on two atoms can also produce a σ bond. For example, in ethane (C_2H_6), both carbon atoms are sp^3 hybridized, and overlap of these orbitals produces a C–C σ bond (Figure 2.2.j.). There are also six C–H σ bonds, formed from overlap of an sp^3 hybrid orbital on carbon with an atomic s orbital on hydrogen. The geometry around the central carbon atom is tetrahedral, with ideal bond angles of 109.5°.

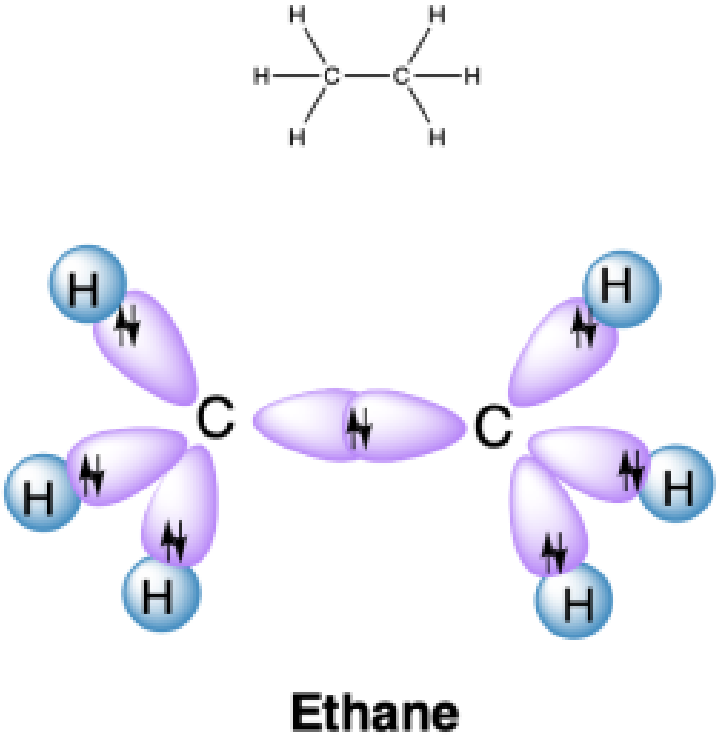

Figure 2.2.j. Bonding in ethane, C_2H_6. Top: line-bond structure of ethane. Bottom: The purple orbitals represent the sp^3 hybrid orbitals on carbon, while the blue orbital represents the atomic s orbital on hydrogen.

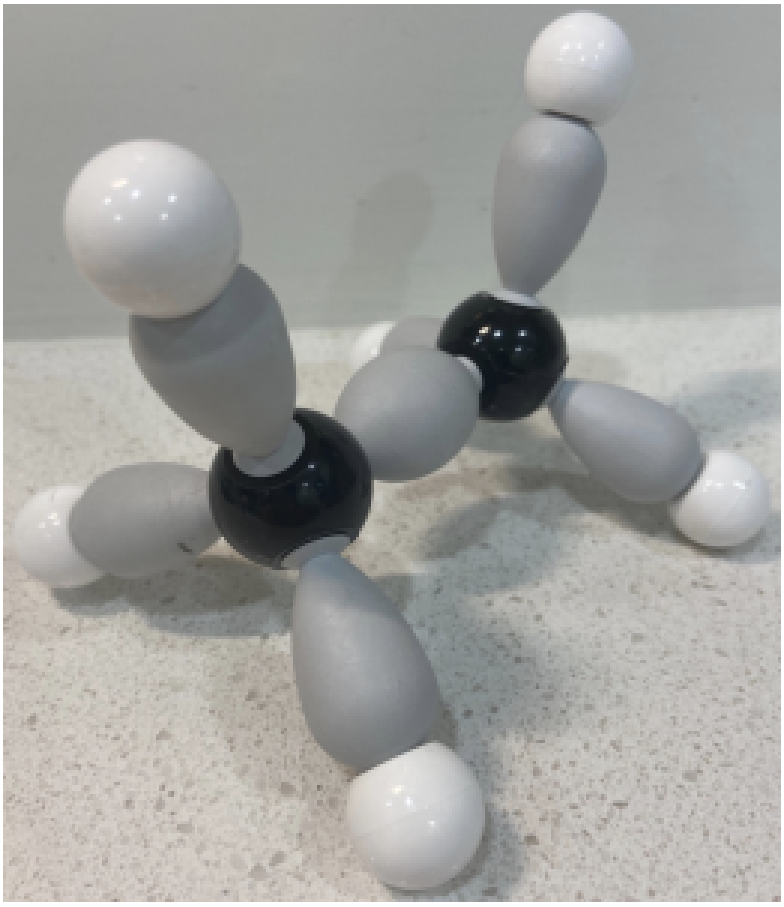

Figure 2.2.k. Orbital model of ethane (C_2H_6). Black represents carbon, white represents hydrogen and grey represents sp^3 hybrid orbitals, which are arranged in a tetrahedral shape. Each carbon atom has four sp^3 hybrid orbitals. Overlap of these orbitals result in C-C or C-H σ bonds.

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sp^2 Hybridization

sp^2 hybridization (Figures 2.2.l-n) involves the mixing of **three** atomic orbitals (one 2s and two 2p orbitals) to form **three** sp^2 hybrid orbitals. One atomic p orbital remains unhybridized.

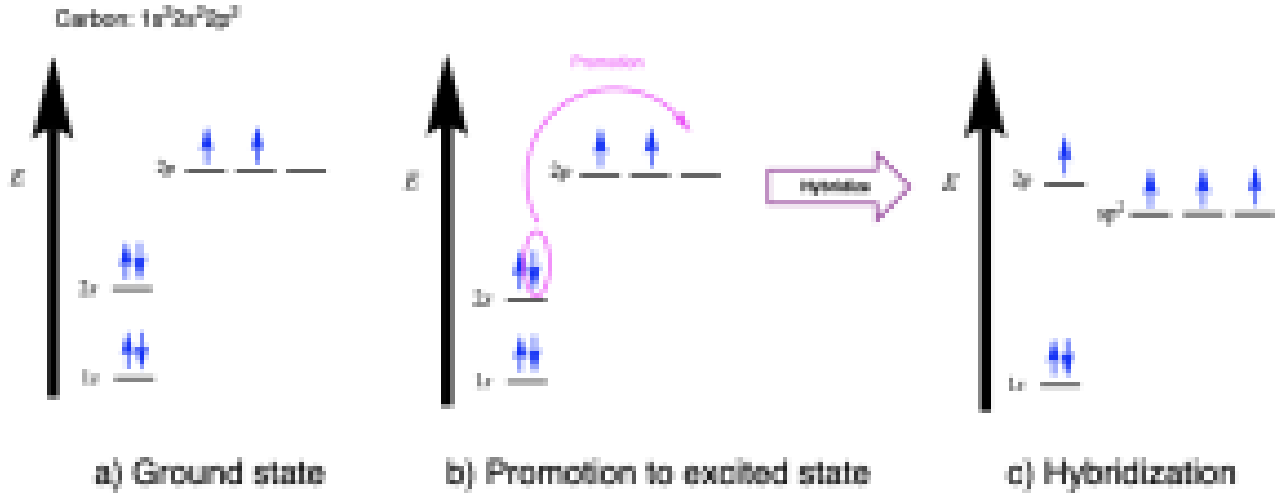

Figure 2.2.1. Electron configuration diagram for carbon. Left: ground-state electron configuration for carbon, showing two electrons in the 2s orbital and two unpaired electrons in the 2p orbitals. Middle: Electron promotion and mixing of orbitals. Right: sp^2 hybridization for carbon, in which three orbitals (one 2s and two 2p) are mixed together, producing three degenerate sp^2 hybrid orbitals, with one remaining unhybridized p orbital.

The three sp^2 hybrid orbitals each contain an unpaired electron and can overlap with other orbitals to form three σ bonds. The three hybrid orbitals point to the corners of an equilateral triangle, resulting in a trigonal planar geometry, with bond angles of 120°. The unhybridized p orbital lies in an orthogonal (perpendicular) plane.

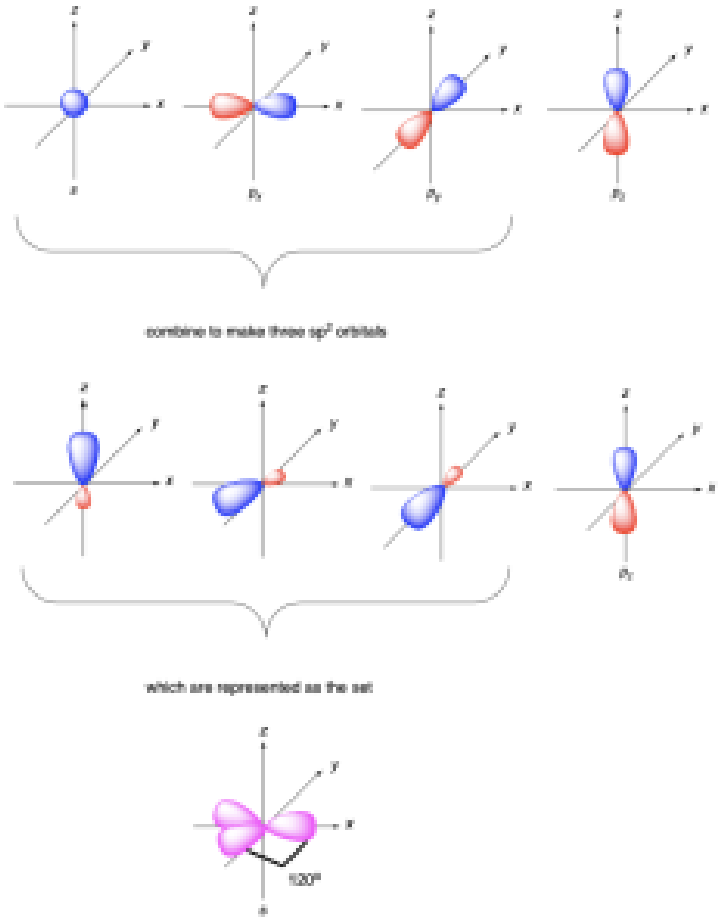

Figure 2.2.m. Three atomic orbitals combine to generate three sp^2 hybrid orbitals. Left: The hybrid orbitals adopt trigonal planar geometry, pointing towards the corners of an equilateral triangle, to minimize repulsion. Right: one unhybridized 2p orbital is left over, which lies perpendicular to the equilateral triangle.

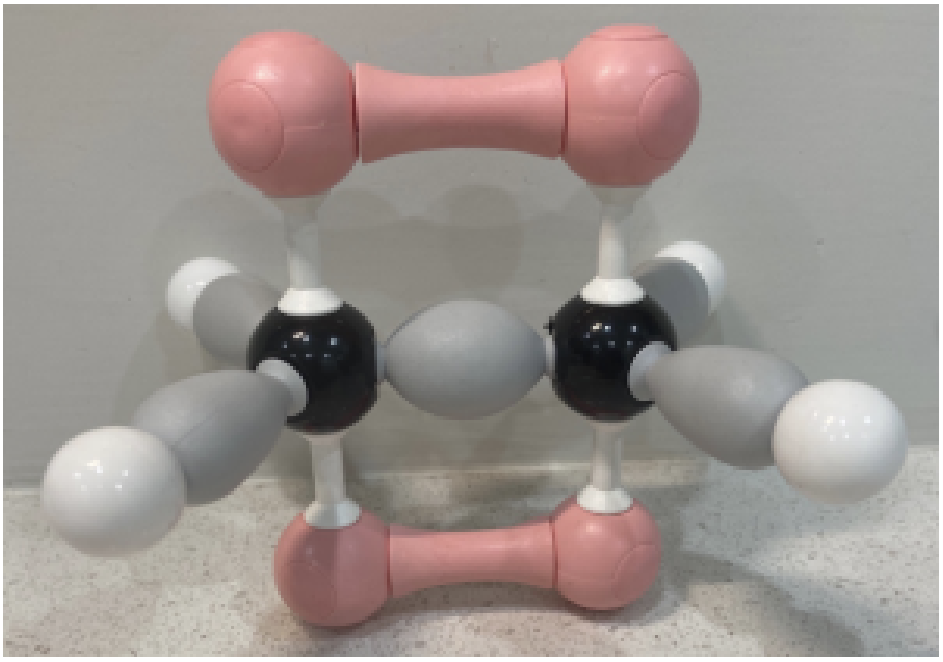

Figure 2.2.n. Orbital model of ethene (C_2H_4). Black represents carbon, white represents hydrogen, grey represents sp^2 hybrid orbitals and pink represents p orbital overlap. The sp^2 hybrid orbitals are arranged in a trigonal planar shape to minimize repulsion, and they will overlap with hydrogen's s–orbital to form σ bonds. The p orbitals on adjacent carbon atoms overlap to form one π bond.

Below, the hybridization and bonding in four molecules will be discussed: borane (BH_3), methyl cation (CH_3^+), and ethene (C_2H_4).

Borane and methyl cation are isoelectronic, with **three** valence electrons on the central atom (boron or carbon). The orbital energy diagram is shown below (Figure 2.2.o.). Three atomic orbitals (one 2s and only **two** of the 2p orbitals) undergo hybridization to form **three** sp^2 hybrid orbitals. One 2p orbital remains unhybridized. Because there are only three valence electrons in this case, the unhybridized p orbital is **empty**.

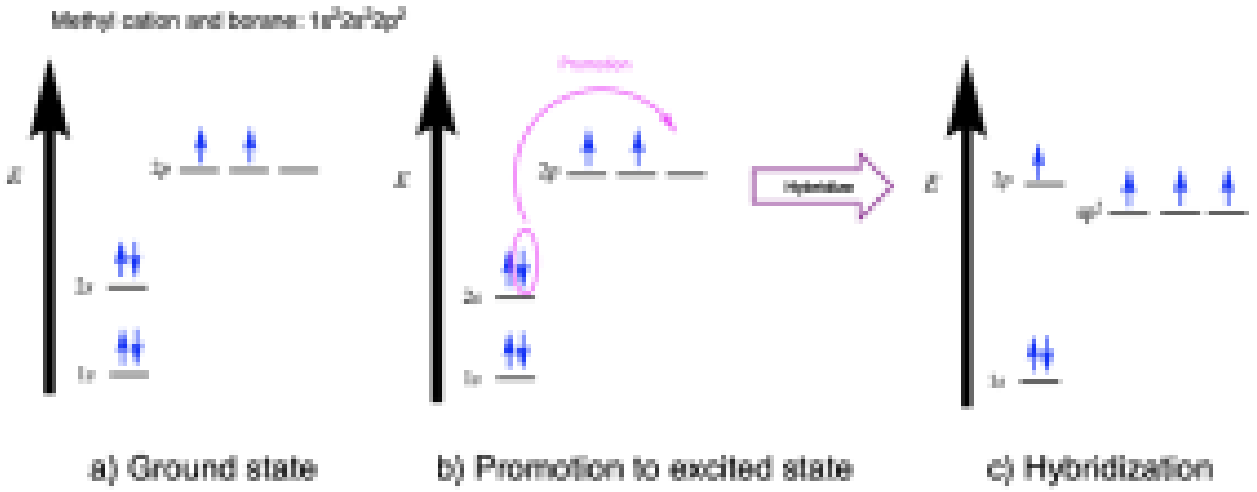

Figure 2.2.o. Electron configuration diagrams for carbon or boron. Left: ground-state electron configuration diagram for borane and methyl cation. Middle: Electron promotion and mixing of orbitals. Right: sp^2 hybridization for carbon or boron, in which three orbitals (one 2s and two 2p) are mixed together, producing three degenerate sp^2 hybrid orbitals, with one remaining unhybridized p orbital.

For borane, the sp^2 hybrid orbitals on boron overlap with an atomic 1s orbital on each hydrogen to produce B–H σ bonds (Figure 2.2.p.). The remaining unhybridized p orbital is not involved in bonding. The positively charged methyl cation is isoelectronic with borane, and therefore has the same bonding arrangement (Figure 2.2.q.): three C–H σ bonds are formed from the overlap of the sp^2 hybrid orbitals on carbon with an atomic 1s orbital on each hydrogen, while the unhybridized p orbital does not participate in bonding.

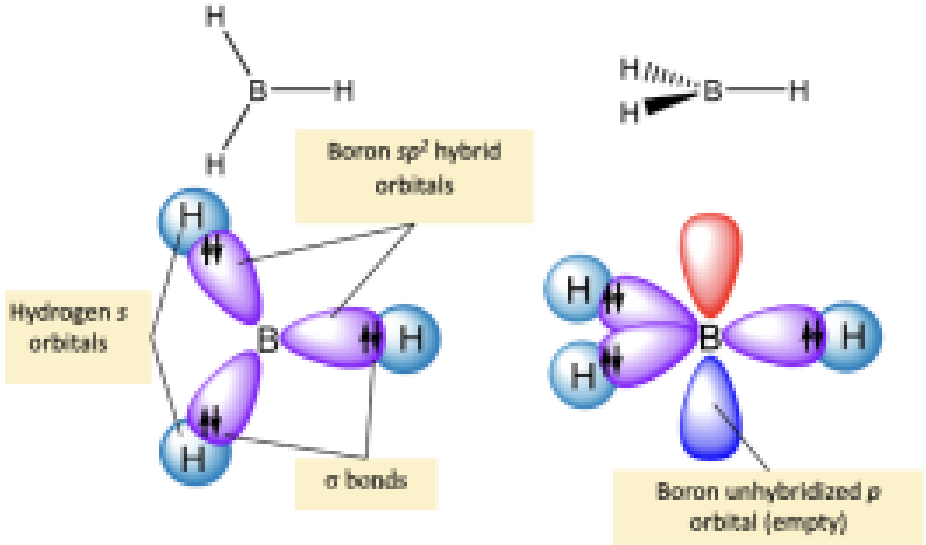

Figure 2.2.p. Bonding in borane. Borane has three sp^2 hybrid orbitals that overlap with the atomic 1s orbital on each hydrogen atom, and one empty p orbital that does not participate in bonding.

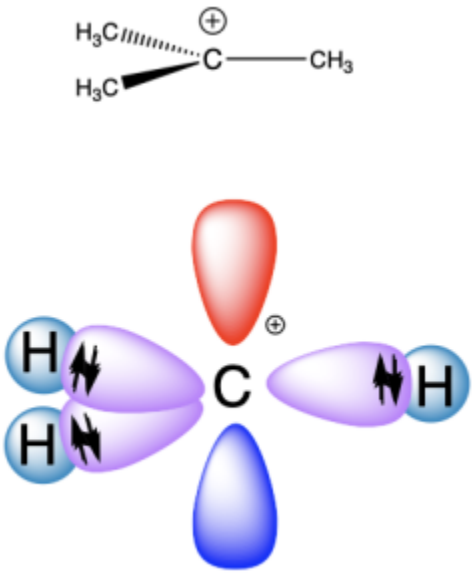

Figure 2.2.q. Bonding in the methyl cation. Carbon has three sp^2 hybrid orbitals that overlap with the atomic 1s orbital on each hydrogen atom, and one empty p orbital that does not participate in bonding.

The empty, unhybridized p orbital in borane or methyl cation is not involved in bonding. However, a half-filled p orbital (Figure 2.2.r.) can also overlap side-on with another half-filled p orbital to form a π-bond. Functional groups with a double bond have sp^2 hybrid orbitals, along with an unhybridized p orbital.

An example of a molecule with a double bond is ethene (CH_2=CH_2) (Figure 2.2.r.). The C=C double bond is formed by: (1) end-on overlap of the two carbon atoms' sp^2 orbitals, creating a σ bond, **and** (2) side-on overlap of the two carbon atoms' half-filled unhybridized p orbital, creating a π bond. Therefore, a double bond is formed from a σ bond and a π bond.

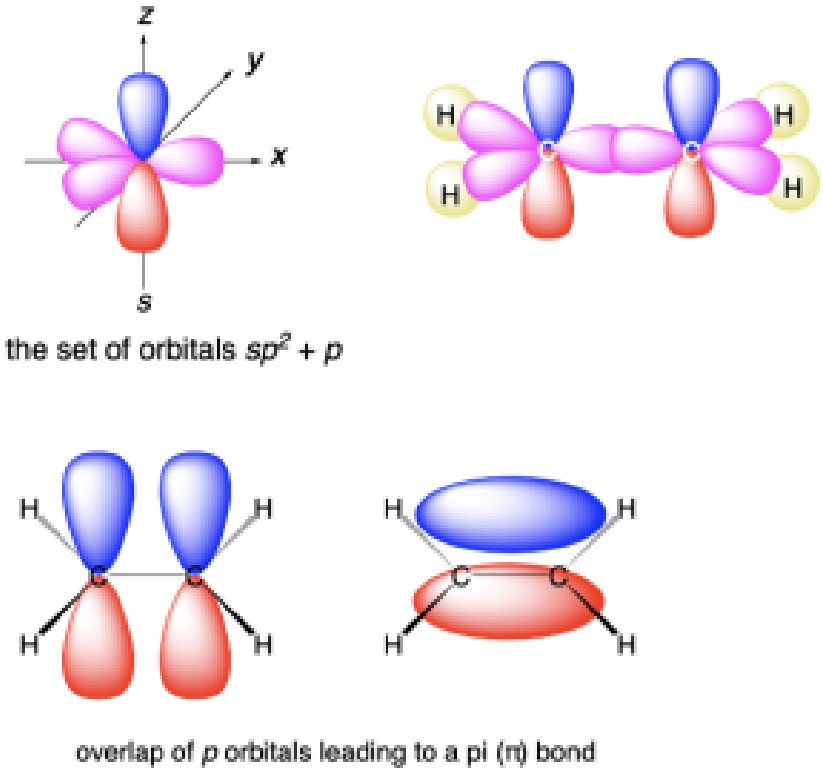

Figure 2.2.r. Bonding in ethene, C_2H_4. Top left: the purple orbitals represent the sp^2 hybrid orbitals, while the blue/red orbital represents the unhybridized 2p orbital perpendicular to the plane of the sp^2 hybrid orbitals. Top right: overlap of sp^2 hybrid orbitals on each carbon creates a C–C σ bond, while overlap of an sp^2 hybrid orbital on carbon with an atomic 1s orbital on each hydrogen creates a C–H σ bond. Bottom: the unhybridized p orbitals on carbon overlap side-on to create a π bond.

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sp Hybridization

sp hybridization (Figure 2.2.s) involves mixing **two** atomic orbitals (one 2s and one 2p) to form **two** sp^2 hybrid orbitals. Two atomic p orbitals remain unhybridized.

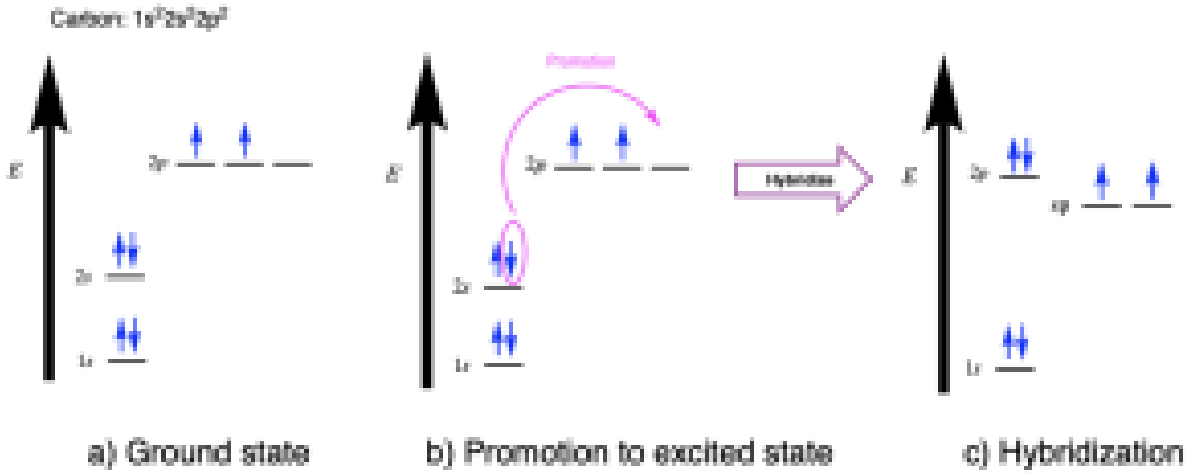

Figure 2.2.s. Electron configuration diagram for carbon. Left: ground state electron configuration diagram for carbon. Middle: Electron promotion and mixing of orbitals. Right: sp hybridization for carbon, in which two orbitals (one 2s and one 2p) are mixed together, producing two degenerate sp hybrid orbitals, with two remaining unhybridized p orbitals.

The two sp hybrid orbitals each contain an unpaired electron and can make two σ bonds. The two hybrid orbitals point along a straight line, resulting in a linear geometry, with a bond angle of 180°. The unhybridized p orbitals lie in orthogonal (perpendicular) planes (Figure 2.2.t.).

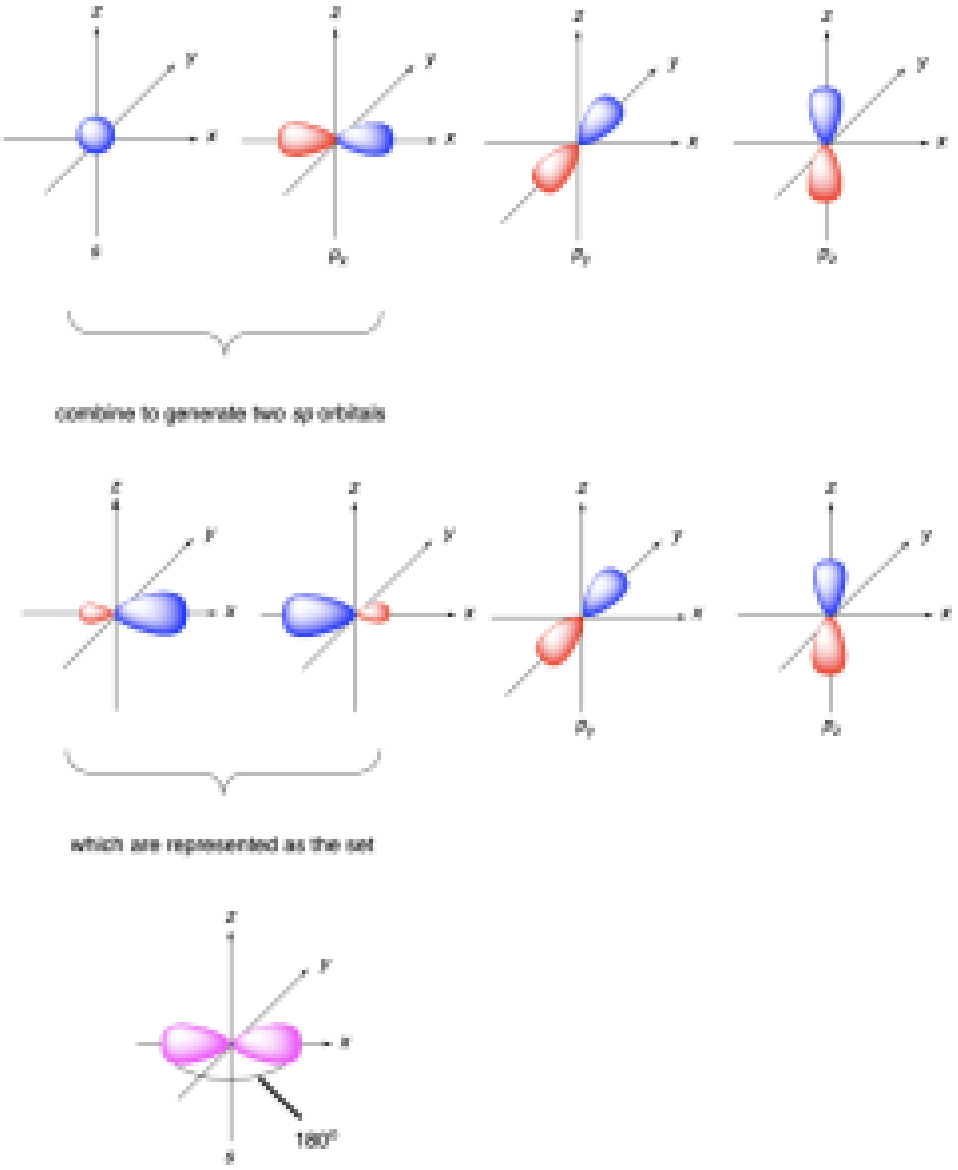

Figure 2.2.t. Two atomic orbitals combine to generate two sp hybrid orbitals. Left: The hybrid orbitals adopt a linear geometry, pointing along a straight line to minimize repulsion. Right: two unhybridized 2p orbitals are left over, both of which lie perpendicular to the linear sp hybrid orbitals.

The half-filled unhybridized p orbitals can overlap side-on with another half-filled p orbital to form a π-bond. Functional groups with a triple bond have sp hybrid orbitals (to form a σ bond), along with two unhybridized p orbitals (to form two π bonds).

An example of a molecule with a triple bond is ethyne (HC≡CH) (Figure 2.2.u.). The C≡C triple bond is formed by: (1) end-on overlap of the two carbon atoms' sp orbitals, creating a σ bond, **and** (2) side-on overlap of the two carbon atoms' half-filled unhybridized p orbitals, creating two π bonds. The two π bonds

are oriented 90º to one another, matching the angle between the p orbitals. Therefore, a triple bond is formed from a σ bond and two π bonds.

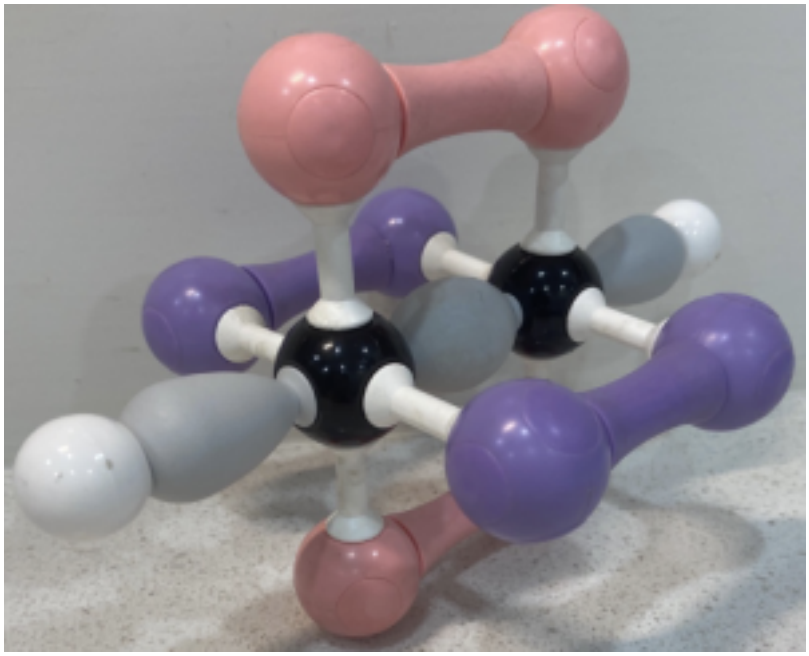

Figure 2.2.u. Orbital model of ethyne (C_2H_2). Black represents carbon, white represents hydrogen, grey represents sp hybrid orbitals and pink and purple represent p–orbital overlap. The sp hybrid orbitals are arranged in a linear shape to minimize repulsion, and they overlap with hydrogen's s–orbital to form σ bonds. The p orbitals on adjacent carbon atoms overlap to form two π bonds.

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The following videos below include examples from previous CHEM 1AA3 tests or exams that students struggled with. Try solving the practice questions on your own before looking at the solution.

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(The full solution to this problem can be found in Chapter 5.1).

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(The full solution to this problem can be found in Chapter 5.1).

Key Takeaways

- According to quantum mechanics, the exact location of an electron cannot be known, thus

electrons reside in general areas called **orbitals**. Orbitals are a probable estimate of where the electrons will be.

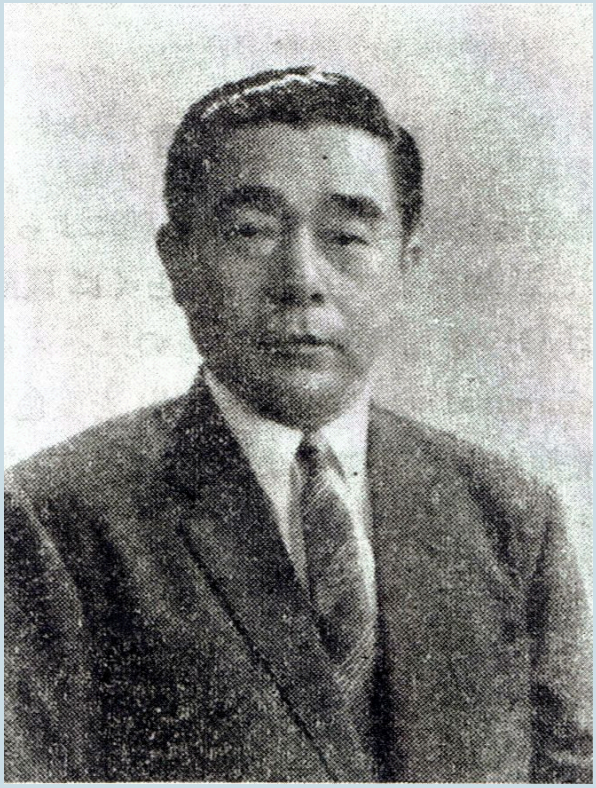
- **Hybridization** in bonding is a better way in which experimentally observed electron geometries around two atoms in a bond can be explained.
    - Hybridization involves the existence of hybrids of s and p orbitals.
- **sp^3hybridization** involves one s orbital and three p orbitals hybridizing to form four new hybrid sp^3 orbitals. This allows for four bonds.
    - Example: methane
    - Geometry: tetrahedral
- **sp^2hybridization i**nvolves one s orbital and two p orbitals hybridizing to form two new hybrid sp^2 orbitals, with one leftover p orbital. This allows for three bonds.
    - Example: Ethene
    - Geometry: trigonal planar
- **sp hybridization** involves one s and one p orbital to hybridize, forming two new sp orbitals, and leaving two unhybridized p orbitals.
    - Example: ethyne
    - Geometry: planar
- In bonding, orbitals of two atoms form bonds from overlapping orbitals.
    - When two orbitals overlap directly head on, for example two neighbouring sp^3 orbitals, it is called a **sigma (σ) bond**.
    - When two orbitals overlap from side-to-side contact, for example two neighbouring p orbitals, they form a **pi (π) bond**.
- Double and triple bonds with carbon utilize sp^2 and sp hybridized carbons respectively.
    - **Double bonds** involve one σ bond and one π bond between two sp^2 hybridized carbons, as there is one available p orbital which can overlap in an sp^2 hybridized carbon.
    - **Triple bonds** involve one σ bond and two π bonds between two sp hybridized carbons, as there are two available p orbitals which can overlap in an sp hybridized carbon.

Key terms in this chapter:

Key Term	Definition
Hybridization	The mixing of two or more standard atomic orbitals (such as s, p, d, f orbitals) to form new hybrid orbitals (such as sp3 orbitals) suitable for bonding.

Diversity in Chemistry: From Fukui to Krylov

Valence bond theory is introduced in this chapter, yet there is another notable theory that is used to explain chemical binding. This theory is called the *Molecular Orbital Theory*, and it was developed years after the original valence bond theory was introduced. **Kenichi Fukui** was the first person of East Asian descent to be awarded the Nobel Prize in Chemistry, winning one-half of the award in 1981 for his work involved with molecular orbital theory. His research specifically focused on the discovery of two molecular orbitals involved in the bonding process: the highest occupied molecular orbital, the HOMO, and the lowest unoccupied molecular orbital, the LUMO. These two molecular orbitals are the entire basis of how organic reactions occur. In short, he discovered that it was possible to approximate reactivity by looking at these two orbitals, as the HOMO and LUMO orbitals interact with each other resulting in attraction.



A portrait of Kenichi Fukui.

When it was first published, his work was deemed a "sleeping beauty — it generally fell under the radar due to Fukui's highly mathematical approach and because his works were published in a more Japanese-oriented journal. However, after being cited by another famous computational chemist working on a similar topic, Roald Hoffman, who was awarded the second half of the same Nobel Prize, Fukui gained worldwide recognition. More information on Fukui can be found on his profile at the Michigan State University.

A portrait of Anna Krylov.

In the present day, the study of chemical structure and reactions has gotten much more advanced, employing new technologies to understand these interactions. *Computational chemistry* is a branch of chemistry that uses computer programs that use theoretical chemistry to calculate molecular structure & properties, as well as model organic reactions. **Anna Krylov** is a current professor at the University of Southern California whose main work focuses on modeling open shell (unfilled valence shells) and electronically excited species. She invented the *spin-flip approach*, which expanded the breadth of a popular quantum chemistry theory to have more applications to biradicals and bond-breaking events. She also uses computational chemistry to investigate the role of radicals and excited state species in events such as combustion, astrochemistry, solar energy and many more diverse fields. Krylov is also very active in the field of science education and outreach, developing labs and tutorials to promote quantum chemistry literacy among chemists. She is also passionate about promoting gender equality in the theoretical chemistry field and is an advocate of freedom of speech and academic freedom.

2.3 - FUNCTIONAL GROUPS

Learning Objectives

1. Recognize and name a variety of functional groups
2. Identify primary, secondary, tertiary, and quaternary carbon centres for saturated carbons (i.e. only single bonds).

What are Functional Groups?

A **functional group** is a group of atoms bonded together in a particular way that impact the molecule's chemical behaviour. Molecules with the same functional group can typically undergo the same chemical reactions. The greater the number of functional groups, the greater the diversity of chemical reactions the molecule can undergo. Being able to recognize a molecule's functional groups will help you to understand and predict its reactivity.

Examples of functional groups are shown in Figure 2.3.a.

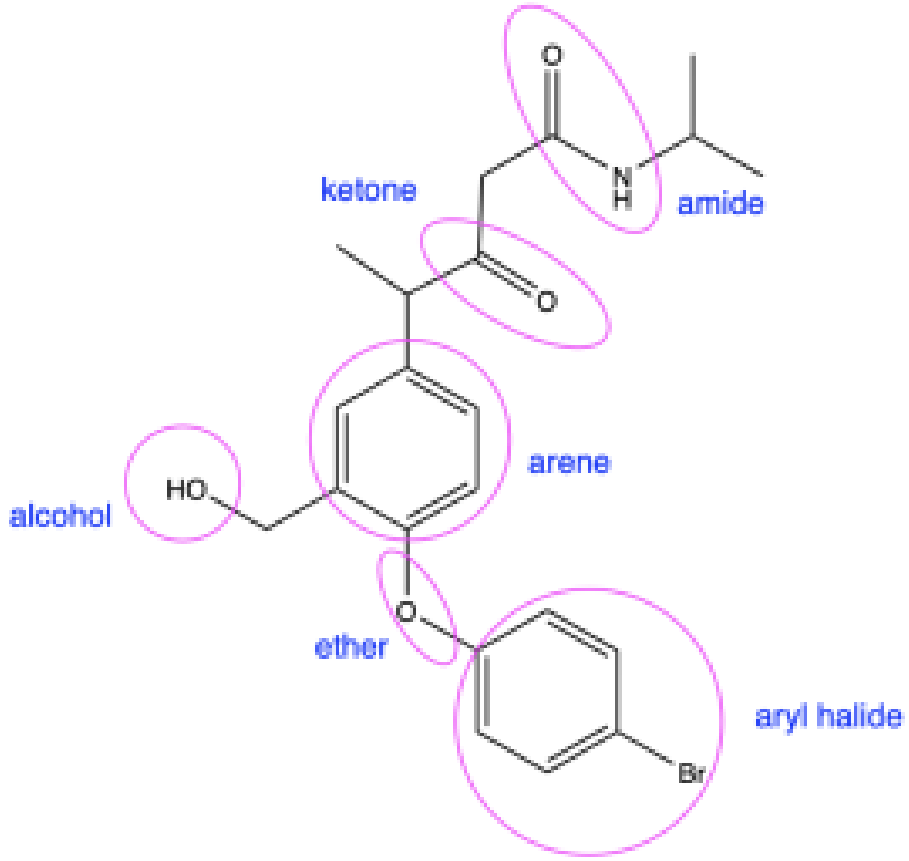
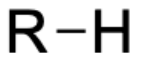
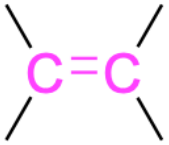
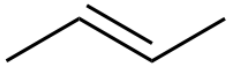
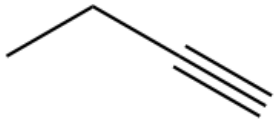
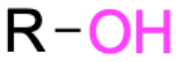
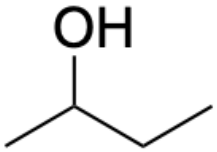
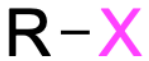
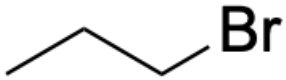
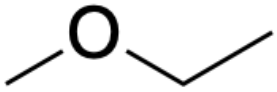
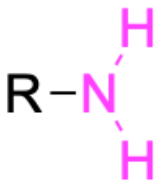
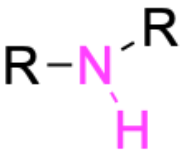
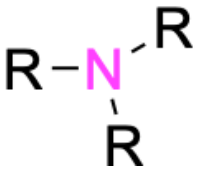
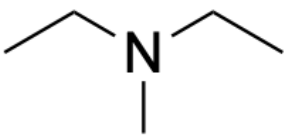


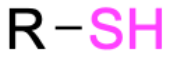
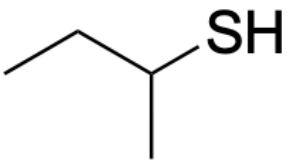
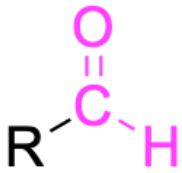
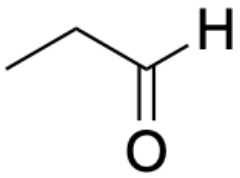
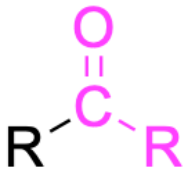
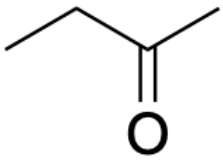
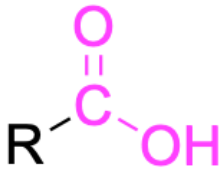
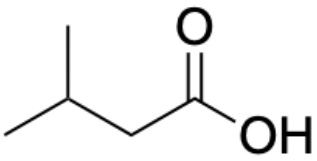
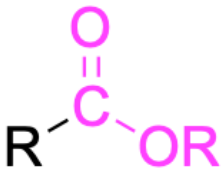
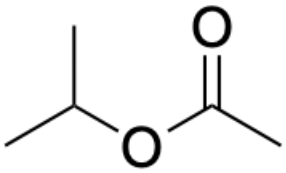
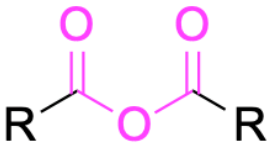
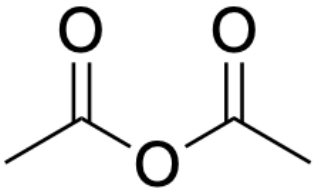
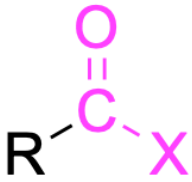
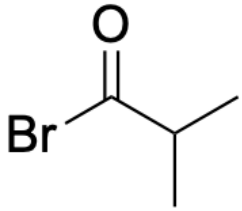
Figure 2.3.a. Structure of 4–(4–(4–bromophenoxy)–3–(hydroxymethyl)phenyl)–*N*–isopropyl–3–oxopentanamide. The various functional groups of this molecule are circled in pink and named in blue.

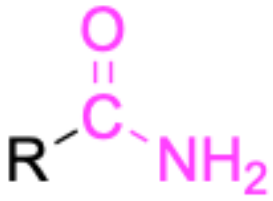
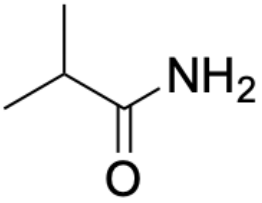
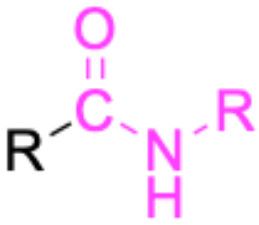
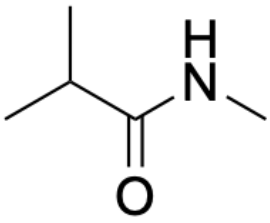
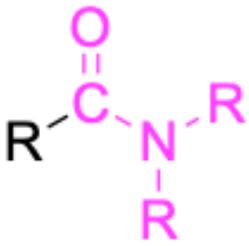
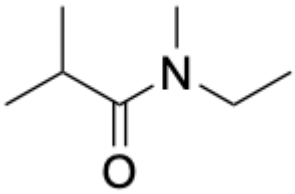
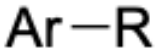
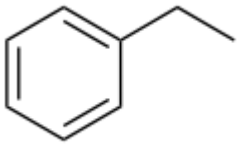
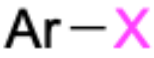
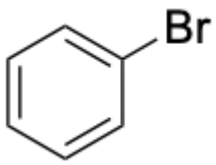
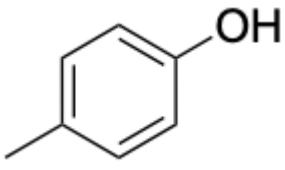
Classes of Organic Compounds and Their Functional Groups

The table below summarizes the structures of various functional groups that you must be able to recognize. Areas highlighted in pink are the functional groups of the molecule.

Table 2.3.a. *Common functional groups in organic chemistry.*

Class	General Structural Formula	Example
Alkane		
Alkene		
Alkyne		
Alcohol		
Alkyl halide		
Ether		
Primary amine*		
Secondary amine*		
Tertiary amine*		

Thiol		
Aldehyde		
Ketone		
Carboxylic acid		
Ester		
Carboxylic acid anhydride		
Acid halide		

Primary amide*		
Secondary amide*		
Tertiary amide*		
Arene		
Aryl halide		
Phenol		

*For more information about how amines and amides can be designated as primary, secondary, and tertiary, see the Are You Wondering box at the end of this chapter.

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An interactive H5P element has been excluded from this version of the text. You can view it online here:
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(The full solution to this problem can be found in Chapter 5.1).

Primary, Secondary, Tertiary and Quaternary Designation

To predict a molecule's reactivity (which we will see in Chapter 3), it is important to identify not only its functional groups but also the number of substituents bonded to a particular atom.

A **saturated carbon** is a carbon atom that is bonded to other atoms through single bonds only. Saturated carbon atoms can be designated as either methyl, 1°, 2°, 3° or 4° depending on how many other *carbon* atoms are bonded to it.

If a carbon atom is bonded to *one* carbon substituent, it is said to be **primary**.

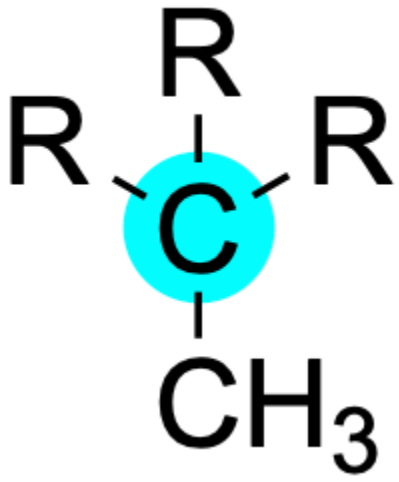

Figure 2.3.b. Structure of a primary carbon. The central carbon atom highlighted in blue is bonded to one carbon substituent.

If a carbon atom is bonded to *two* carbon substituents, it is said to be **secondary**.

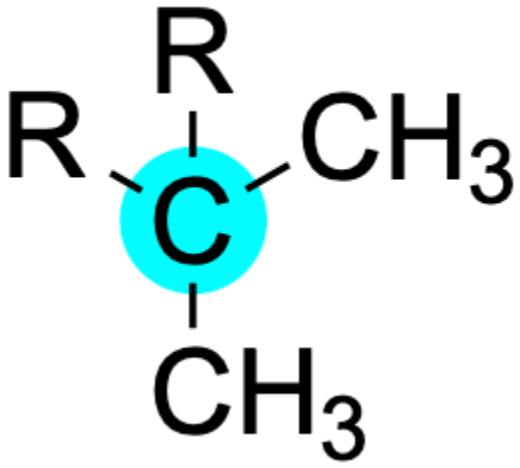

Figure 2.3.c. Structure of a secondary carbon. The central carbon atom highlighted in blue is bonded to two carbon substituents.

If a carbon atom is bonded to *three* carbon substituents, it is said to be **tertiary**.

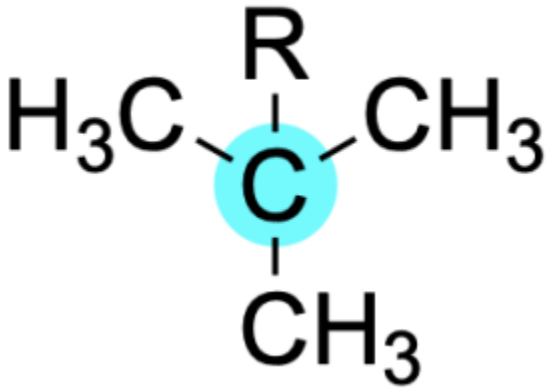

Figure 2.3.d. Structure of a tertiary carbon. The central carbon atom highlighted in blue is bonded to three carbon substituents.

If a carbon atom is bonded to *four* carbon substituents, it is said to be **quaternary**.

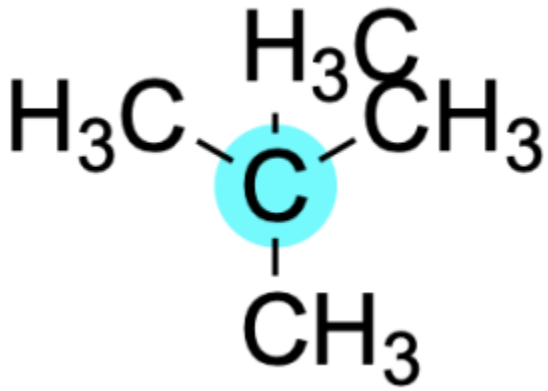

Figure 2.3.e. Structure of a quaternary carbon. The central carbon atom highlighted in blue is bonded to four carbon substituents .

This designation can also be applied to saturated alkyl halides, carbocations, and alcohols. The figure below shows examples of each.

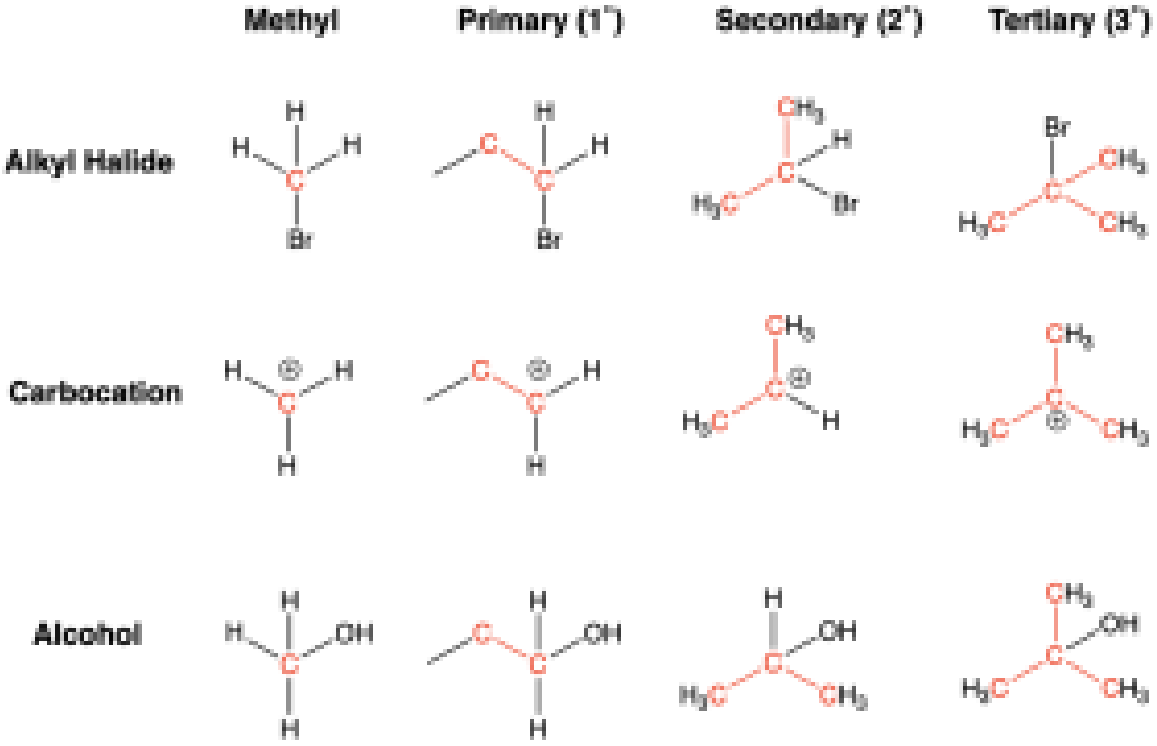

Figure 2.3.f. Methyl, primary, secondary and tertiary designations for alkyl halides, carbocations and alcohols.

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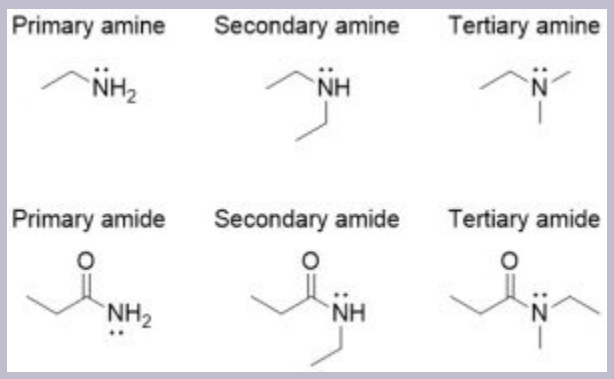
Note that when carbon is bonded to a **heteroatom** (like a halogen or an oxygen shown in the examples above), there is no quaternary designation. This is because carbon cannot have more than 4 bonds.

Are You Wondering? Primary, Secondary, and Tertiary Centres

The designation of primary, secondary, and tertiary also applies to the nitrogen centre in amines and amides (Figure 2.3.g). To determine whether the amine or amide is primary, secondary, or tertiary, count the number of carbon-containing substituents bonded to the nitrogen centre. If there is one carbon-containing substituent, then it is a primary amine. If there are two carbon-containing substituents, then it is a secondary amine. If there are three carbon-containing substituents, then it is a tertiary amine.



Designation of primary, secondary, and tertiary for amines (top) and amides (bottom).

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(The full solution to this problem can be found in Chapter 5.1).

Key Takeaways

- A **functional group** is defined as two or more bonded atoms which affect a molecules reactivity or chemical properties.
    - The same functional group on two different molecules will exhibit similar reactivity
- Carbon bonded to other atoms with single bonds only is called a **saturated carbon**.
- Carbon can be designated primary, secondary, tertiary or quaternary, depending on how many other carbons it is bound to. Carbon can also be referred to as methane if it is not bound to any other carbons.
    - **Primary carbon**: a carbon bound to one other carbon.
    - **Secondary carbon**: a carbon bound to two other carbons.
    - **Tertiary carbon**: a carbon bound to three other carbons.
    - **Quaternary carbon**: a carbon bound to four other carbons.
- This characterization of carbons can be applied to any other carbon bound to functional groups such as alcohols, alkyl halides, etc.

Key terms in this chapter:

Key term	Definition
Heteroatom	An atom other than carbon, such as oxygen, nitrogen, and sulfur.

Diversity in Chemistry: Slayton Evans Jr.

Although a wide variety of the most important functional groups have been introduced in this chapter, this does not even cover half of the known groups. Phosphorus, P, is a common heteroatom found in biology that makes up a number of functional groups, such as the phosphate group. **Slayton Evans Jr**., a professor at the University of North Carolina, was a trailblazer in organophosphorus chemistry, resulting in a deeper understanding of their properties and aiding in the development of novel methods to synthesize them for pharmaceutical use. Raised in Mississippi, Evans lived in a segregated public housing project with his family and became enamoured by science after he received a chemistry lab toy set and miniature microscope.

A portrait of Slayton Evans Jr.

After his postdoctoral fellowship, Evans joined the University of North Carolina as the first African American chemistry professor at the university in 200 years, and quickly became successful due to his excellent work and dedication to teaching. Evans was also known as an outstanding mentor who advocated for recruiting underprivileged and students from underrepresented groups, closely guiding many of his undergraduate and graduate students. More information on Evanscan be found on his page at UNC.

2.4 - IUPAC NOMENCLATURE

Learning Objectives

1. Given systematic (IUPAC) or common names, draw the structure and vice versa.
2. Identify correct names for given structures and identify whether a given name follows IUPAC rule.

Introduction

Chapter 2.1.1. introduced line-angle drawings to draw organic compounds. The ability to draw and recognize these structures is an important skill, as is the ability to name these structures. The International Union of Applied and Pure Chemistry (IUPAC) has standardized the naming of organic compounds by creating a list of rules and regulations to abide by.

This chapter will introduce how to name organic compounds using IUPAC rules.

Prefixes, Parent Chains and Suffixes

When naming an organic structure, or drawing an organic structure based on its name, look for these three key details:

1. The suffix indicates the functional group.
2. The parent chain indicates the number of carbon atoms in the longest chain that contains the highest priority functional group.
3. The prefix indicates the identity and location of substituents on the parent chain. A substituent is an atom or a group of atoms that is attached to the parent chain.

Once these details have been identified, the name of the compound is constructed as follows:

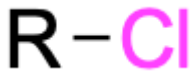
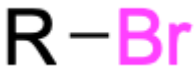
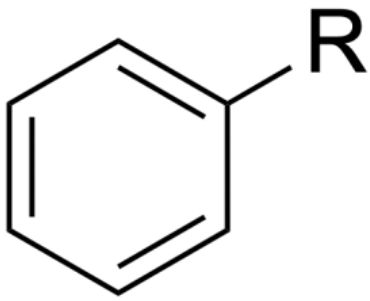
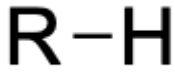
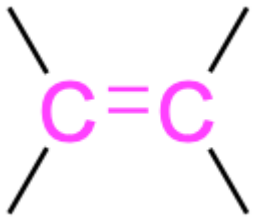
Prefix + parent + suffix

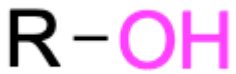
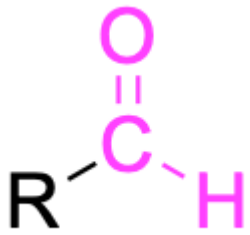
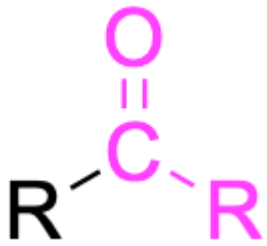
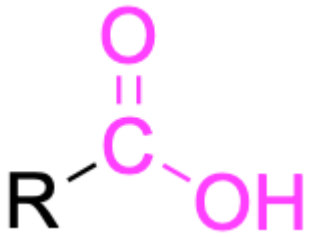
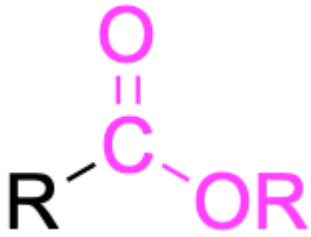
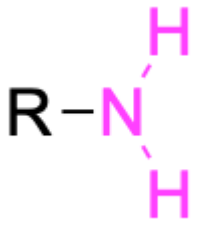
Identifying the functional groups and priority

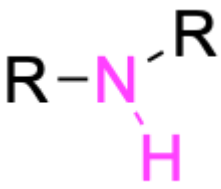
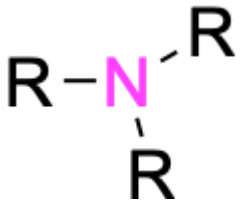
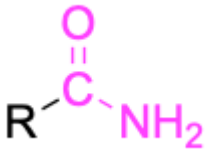
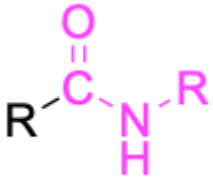
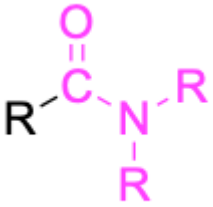
When naming organic molecules, **identify the functional groups** first, as this will aid in determining the parent chain. For compounds with **more than one** functional group, the highest priority functional group defines the final suffix of the parent chain. Lower priority functional groups are considered substituents and are named as prefixes. Figure 2.4.a. shows functional groups listed in priority sequence. Table 2.4.a. shows the name of the functional group when used as a prefix or as a suffix.

Figure 2.4.a. Functional groups in order of priority. Functional groups on the left take priority over those to the right.

Table 2.4.a. *Functional groups and their IUPAC prefixes and suffixes.*

Functional Group	Structure	Prefix	Suffix
fluorine		fluoro–	None
chlorine		chloro–	None
bromine		bromo–	None
iodine		iodo–	None
ether		alkoxy–	–ether
benzene		phenyl–	–benzene
alkane		alkyl–	–ane
alkene		alk–#–en–yl–	–ene
alkyne		alk–#–yn–yl–	–yne

alcohol		hydroxy–	–ol
aldehyde		None	–al
ketone		None	–one
carboxylic acid		None	–oic acid
ester		None	–oate
Primary amine		None	–amine

Secondary amine		None	–amine
Tertiary amine		None	–amine
Primary amide		None	–amide
Secondary amide		None	–amide
Tertiary amide		None	–amide

An example of determining priority is shown below in Figure 2.4.b. There are two functional groups present: alcohol and aldehyde. Figure 2.4.a. shows that aldehydes have a higher priority than alcohols, so the aldehyde will be the final suffix (name will end with "–al"), while the alcohol will be a substituent and use the prefix "hydroxy–".

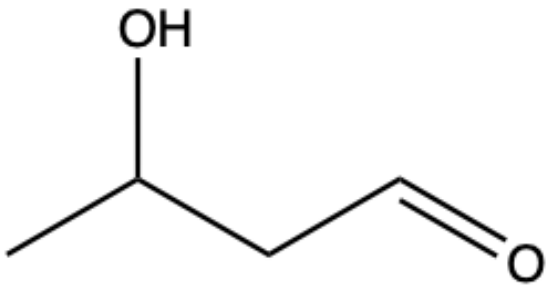


Figure 2.4.b. Structure of 3–hydroxybutanal. The aldehyde functional group has a higher priority than the alcohol functional group, so the aldehyde will determine the final suffix (–al) while the alcohol will be treated as a substituent (hydroxy).

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(The full solution to this problem can be found in Chapter 5.1).

The Parent Chain

Once the functional groups have been identified and priority has been assigned, the next step is to **identify the parent chain**. The parent chain is the carbon chain that contains the highest priority functional group and the greatest number of carbon atoms.

For example, the molecule shown in Figure 2.4.c. is an alkane. To name this molecule, we must identify the chain containing the greatest number of carbon atoms. The parent chain is the path shown in red path, as it contains the most carbon atoms: seven. In comparison, the blue path contains six carbon atoms, and should not be chosen as the parent chain.

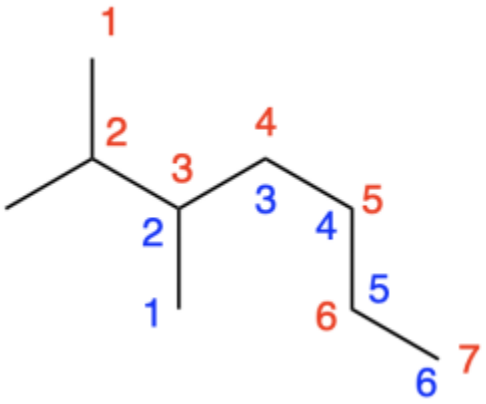

Figure 2.4.c. Identifying the parent chain of the molecule 2,3-dimethylheptane. The red path indicates the parent chain, as this path contains the most carbons (seven). The blue path contains fewer carbons (six) and should not be chosen as the parent chain.

The name of the parent chain depends on the number of carbon atoms. Table 2.4.b below summarizes parent chains containing up to 10 carbons.

Table 2.4.b. *Naming parent chains and alkyl substituents containing 1-10 carbons.*

Parent Alkane Name	**Alkyl Substituents**	**Number of Carbon Atoms**
methane	methyl	1
ethane	ethyl	2
propane	propyl	3
butane	butyl	4
pentane	pentyl	5
hexane	hexyl	6
heptane	heptyl	7
octane	octyl	8
nonane	nonyl	9
decane	decyl	10

Note that there are common propyl and butyl branched substituents named “isopropyl” and “tert–butyl” respectively, which are pictured below. You will see these substituents often in this course and in second year, so it’s important to become familiar with their structure.

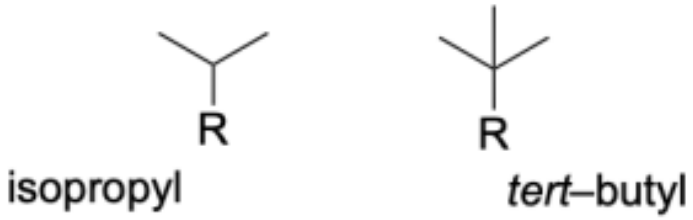

Figure 2.4.d. Structures of the common propyl and butyl substituents, "isopropyl" and "tert–butyl". Note that "R" denotes an alkyl substituent.

The molecule shown below in Figure 2.4.e is named 2,3-dimethylheptane. In the name, *heptane* comes from the fact that there are seven carbon atoms in the parent chain (*hept*) and it is an alkane (suffix *–ane*). We will examine the prefix (2,3-dimethyl–) in the next section.

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An interactive H5P element has been excluded from this version of the text. You can view it online here:
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Branch Points

The parent chain may not include all carbon atoms in the molecule. For example, in Figure 2.4.e, the parent chain (shown in red) contains two **branch points**, at positions 2 and 3 in the chain. A branch point refers to a point where a substituent diverges from the parent chain.

If a compound contains two chains of equal length, the parent chain is designated to be the chain with **more** branch points. For example, for the molecule shown in Figure 2.4.e, the red path and the blue path both have seven carbon atoms, but the red path has three branch points while the blue path has two branch points (shown in green). The red path should therefore be chosen as the parent chain.

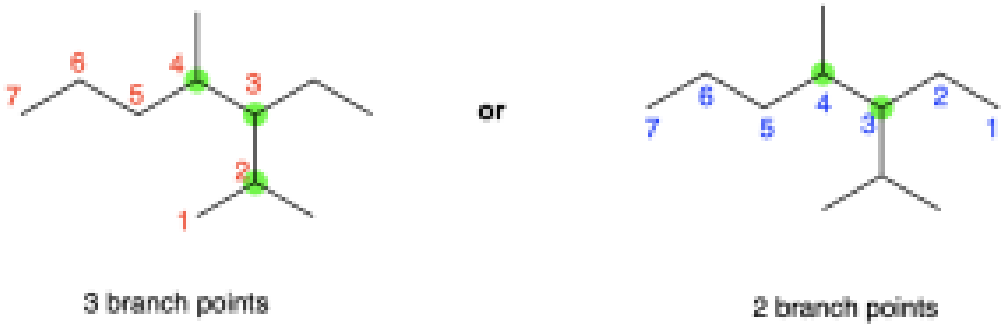

Figure 2.4.e. Identifying the parent chain of a molecule based on the number of branch points, shown in green circles. Two possibilities are shown in red on the left and blue on the right, both of which have seven carbon atoms. The red path on the left should be chosen as the parent chain, because it contains more branch points (3) whereas the blue path contains fewer branch points (2).

When deciding which end of the parent chain to begin numbering, first choose the path that gives the highest priority functional group the lowest number. If both paths give the same numbering to the highest priority functional group, or the priority of all side chains/functional groups are the same, then choose the path that reaches a branch point sooner. For example, for the molecule shown in Figure 2.4.f, the red path and the blue path both have eight carbon atoms and one branching point. To number the parent chain correctly, the blue path should be chosen because the branch point occurs sooner, at position 4. In comparison, the red path has the first branch point at position 5.

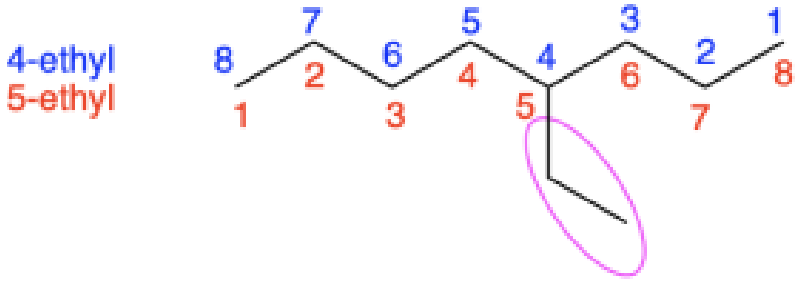

Figure 2.4.f. There are two possibilities to number the parent chain in this molecule, shown in red below the atoms and blue above the atoms, both of which have eight carbon atoms. The blue path should be chosen as the parent chain, because it reaches the branch point sooner (position 4), compared to the red path that reaches the branch point at a later position (position 5).

Naming the Branches

To name alkyl branches attached to the parent chain, use the prefix associated with the carbon length (Table 2.4.b), followed by –yl. The position of the branch should be indicated **before** the branch name with a hyphen separating the number and branch name.

For example, the molecule shown earlier in Figure 2.4.f has one substituent with two carbons. The substituent is named "ethyl", and we specify that it occurs at position 4 in the parent chain by writing "4-ethyl". Therefore, the compound shown in Figure 2.4.f is named 4-ethyloctane.

If there is more than one substituent on the parent chain, then the substituents are listed in alphabetical order. For example, the molecule in Figure 2.4.g has two substituents: a fluoro group at position 2 and an ethyl group at position 4 of the parent chain. The word ethyl comes earlier in the alphabet than the word fluoro, and therefore the ethyl group is listed first in the prefixes. There molecule is an alkane with seven carbon atoms in the parent chain, so it is called heptane. Thus, this compound is named 4-ethyl-2-fluoroheptane.

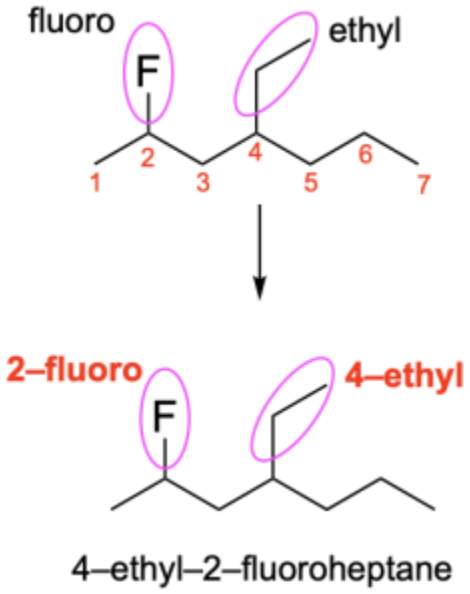

Figure 2.4.g. Naming molecules with more than one substituent. The parent chain is an alkane with seven carbons. There are two substituents in this molecule: a fluoro group at position 2 and an ethyl group at position 4. This molecule is named "4-ethyl-2-fluoroheptane".

If a molecule has more than one identical substituent, then the prefixes di-, tri-, tetra-, etc., are used to indicate how many identical substituents there are, with the locations on the parent chain separated by commas. For example, let's once again consider the molecule shown in Figure 2.4.c.

- The molecule is an alkane (*-ane*).
- There are seven carbon atoms in the parent chain (*hept*).
- There are two branching points at position 2 and 3, both containing methyl substituents (*2,3-dimethyl-*).

Therefore, this molecule is named 2,3-dimethylheptane.

A prefix that indicates the quantity of identical substituents (di-, tri-, tetra-, etc.) is **not** included in alphabetizing the substituents. For example, consider the molecule shown in Figure 2.4.e.

- The molecule is an alkane (*-ane*).
- There are seven carbon atoms in the parent chain (*hept*).
- There are three branching points: positions 2 and 4 contain methyl groups (*2,4-dimethyl-*) while position 3 contains an ethyl group (*3-ethyl-*).
- Note that *ethyl* comes first alphabetically compared to *methyl*; the prefix *di-* in front of *methyl* does not count (*3-ethyl-2,4-dimethyl-*).

Therefore, this molecule is named 3-ethyl-2,4-dimethylheptane.

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Combining the Parent Chain and Substituents

When combining the branches and the parent chain to fully name the molecule, write the name as one word, with hyphens separating prefixes, and commas separating numbers. List all substituents in alphabetical order (without alphabetizing prefixes like di, tri, tetra, etc.).

Figure 2.4.h. below illustrates these conventions using the molecule 5,5-diethyl-3-methyloctane.

- The molecule is an alkane (*-ane*)
- There are eight carbon atoms in the parent chain (*oct*)
- There are three branching points: position 3 contains a methyl group (*3-methyl-*) while position 5 contains two ethyl groups (*5,5-diethyl-*).
- Note that *ethyl* comes first alphabetically compared to *methyl*; the prefix *di-* in front of *ethyl* does not count when alphabetizing (*5,5-diethyl-3-methyl-*).

Therefore, this molecule is named 5,5-diethyl-3-methyloctane.

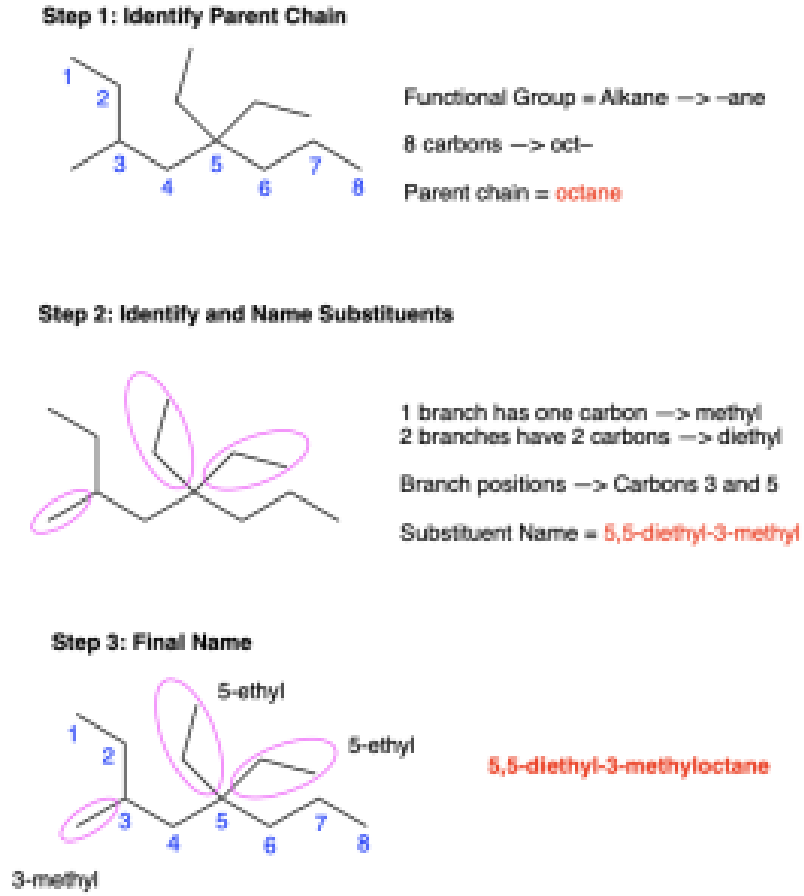

Figure 2.4.h. Steps to name the molecule 5,5-diethyl-3-methyloctane. First, begin with identifying the parent chain. Next, identify and name the substituents. Last, put the parent chain and substituents together to yield the final name.

When determining the direction to begin numbering the parent chain, if both paths contain branches at the same number, alphabetization is used to determine the lowest number.

An example is seen below in Figure 2.4.i. Both the red and blue path contain branch points at the same positions (4 and 6). In the blue path, carbon 4 contains a propyl group while carbon 6 contains an ethyl group. In the red path, carbon 4 contains an ethyl group while carbon 6 contains a propyl group. Since the red path contains an ethyl group on the first branch, the red path should be chosen takes priority, as the letter "E" comes first alphabetically.

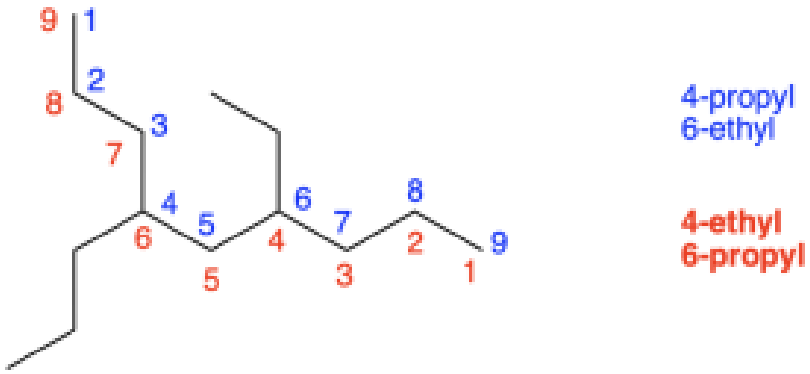

Figure 2.4.i. If the number of carbon atoms in the parent chain and branches present are the same, then alphabetization is used to determine the lowest number.

Table 2.4.a mentioned the suffixes and prefixes used for naming the various functional groups. Esters are a special case of combining the parent chain and substituents using the suffixes and prefixes, as shown in the following example (Figure 2.4.j).

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(The full solution to this problem can be found in Chapter 5.1).

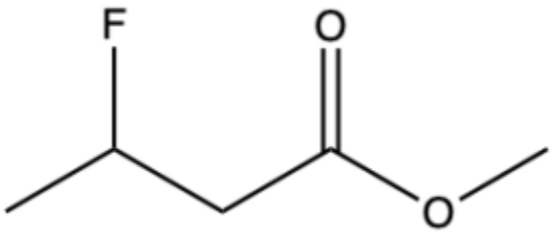

Figure 2.4.j. Structure of the unknown ester that will be named below.

To name esters, split the molecule into two portions (Figure 2.4.k): the portion containing the carbonyl (C=O) group, shown in green, and the substituent that is singly bonded to oxygen, shown in blue. The blue portion is named first, like a prefix, and the green portion is named last.

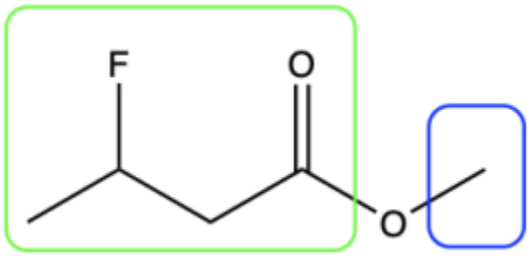

Figure 2.4.k. To name esters, split the molecule into the two groups: the portion containing the carbonyl group (C=O, shown in a green box) and the group singly bonded to oxygen (shown in a blue box).

The first step is to name the group singly bonded to oxygen (in blue). In this example, there is one carbon atom (*methyl*). The next step is to name the portion containing the carbonyl group (in green). Begin numbering this portion starting at the carbonyl carbon atom (this is carbon 1). At carbon 3, there is a fluorine atom (*3-fluoro-* prefix). The parent chain is 4 carbons long, derived from butane, while the suffix for esters is "-oate" (*butanoate*). Note that the two portions that comprise the ester (*methyl* and *3-fluorobutanoate*) are separated by a space rather than a hyphen. Therefore, the final name is methyl 3-fluorobutanoate (Figure 2.4.l).

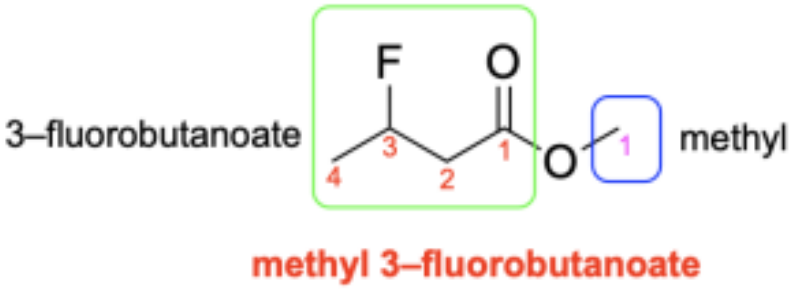

Figure 2.4.l. Structure of the ester methyl 3-fluorobutanoate. When naming esters, the group singly bonded to oxygen is named first (*methyl*), while the portion containing the carbonyl group is named last (*3-fluorobutanoate*).

Naming Rings

To name the parent chain for cyclic compounds, indicate the number of carbon atoms in the ring, and add the prefix "cyclo". If there is more than one substituent attached to the ring, number the ring in such a way that the lowest numbered substituent has the highest priority, and continue numbering the ring so that the

substituents have the lowest possible number. An example is seen in Figure 2.4.m. There are two functional groups on the cyclopentane ring: an alcohol and an alkyl group. Alcohols have a higher priority, so the ring is labeled starting with carbon 1 at the alcohol, while the methyl group is at carbon 2.

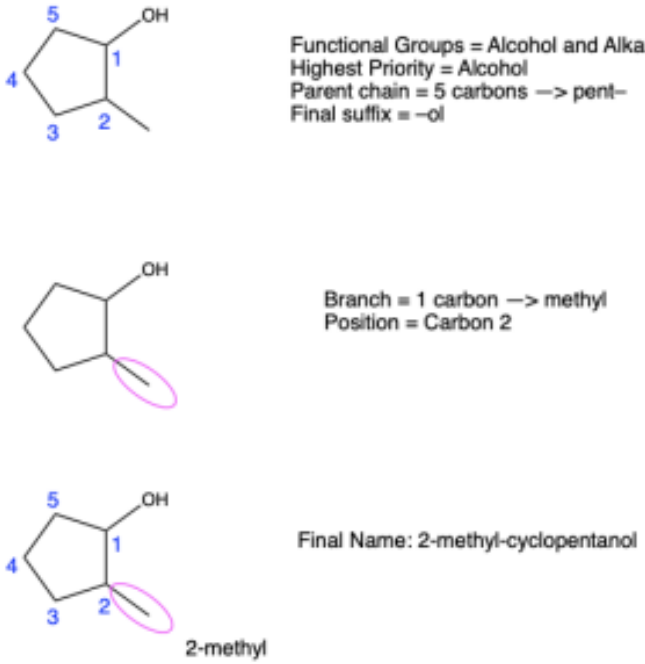

Figure 2.4.m. Steps to name the cyclic compound 2-methylcyclopentanol. First, identify the functional groups to determine priority and name the parent chain. Next, name the branches. Finally, put the branches and parent chain together and add the prefix "cyclo-" before the name of the parent chain.

If the substituents have equal priority, then alphabetization is used to determine the numbering scheme. Note that if a substituent is not numbered, it is implied to be at position 1. Figure 2.4.n shows both conventions. The only functional group present is an alkane, so alphabetization is used to determine numbering. The letter "E" comes before the letter "M" in the alphabet, so the numbering will begin with the ethyl group at position 1. The compound can be named 1-ethyl-3-methylcycloheptane or ethyl-3-methylcycloheptane, as the lack of a number before a substituent suggests that it is at position 1.

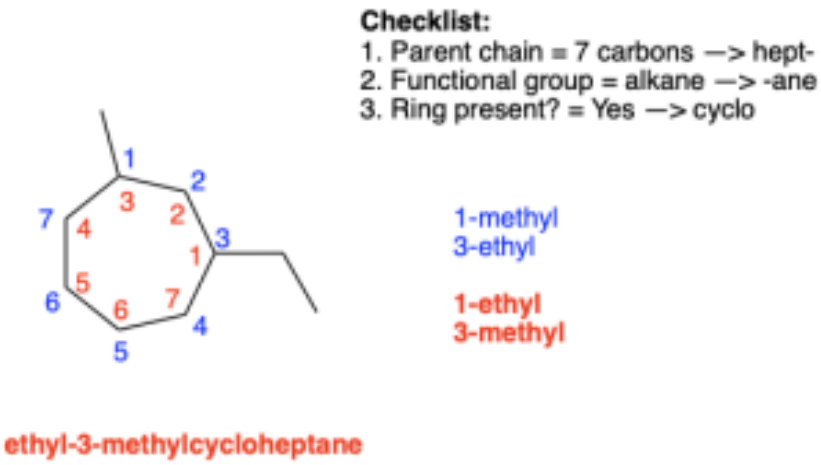

Figure 2.4.n. Steps to name the cyclic compound 1-ethyl-3-methylcycloheptane. The first step is to identify the parent chain and functional groups, adding the prefix "cyclo-" to denote the ring. Next, identify and name any substituents. In this case, the parent chain and functional groups yields cycloheptane, while the substituents are 1-ethyl and 3-methyl, giving 1-ethyl-3-methylcycloheptane.

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Converting from Name to Structure

Throughout this chapter, we've discussed how to name organic molecules based on their structure. It is also important to be able to recognize and draw the organic molecules from their IUPAC name.

One example is to draw the structure that represents the name 5-fluoro-6,7-dimethyloctan-2-one. The first step is to look at the final suffix and identify the functional group, as that indicates the parent chain. In this example, the final suffix is "–one". This corresponds to a ketone being the highest priority functional group in the parent chain.

Next, look for the number of carbons in the parent chain, which is located directly before the final suffix. In this example, "octan", indicates that 8 carbons make up the parent chain. The number 2 in front of "one" denotes the position of that functional group (a ketone) in the parent chain. Therefore, the 8-carbon parent chain has a ketone at position 2 (Figure 2.4.o).

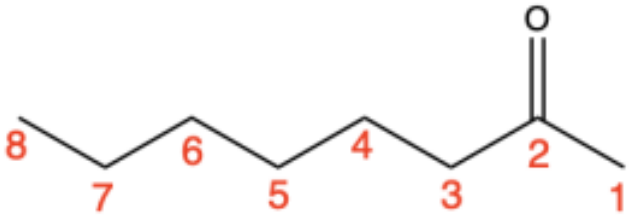

Figure 2.4.o. The first step when converting from the name to the structure of the organic molecule is to identify the parent chain and highest priority functional group. This name ends in "octan-2-one", so the parent chain is 8 carbon atoms long with a ketone at position 2.

Next, identify the remaining substituents. One substituent listed is "5-fluoro", meaning there is a fluorine substituent at position 5 of the parent chain. Other substituents listed are "6,7-dimethyl", so there are 2 methyl groups on positions 6 and 7 of the parent chain (Figure 2.4.p).

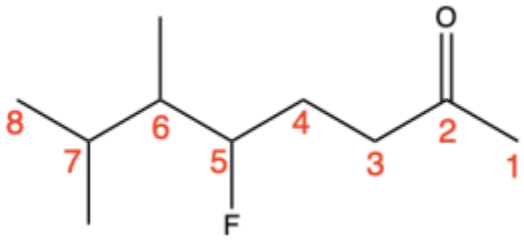

Figure 2.4.p. The next step when converting from the name to the structure of the organic molecule is to identify the substituents, including 5-fluoro and 6,7-dimethyl".

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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(The full solution to this problem can be found in Chapter 5.1).

Challenging Example

Using the rules from this past chapter, we will work through the example below (Figure 2.4.q).

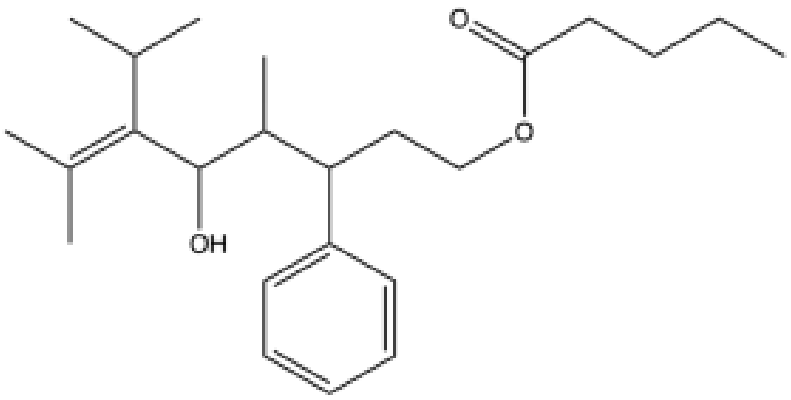

Figure 2.4.q. Unknown molecule to be named.

The first step is to identify the functional groups and parent chain (Figure 2.4.r). This molecule contains an ester, alcohol, phenyl group, and alkene. The ester is the highest priority functional group, so it will determine the final suffix. The portion containing the carbonyl (C=O) group (numbered in blue) contains 5 carbons, so the name of the molecule will end in "pentanoate". The substituent that is singly bonded to oxygen contains 9 carbons in its longest chain (numbered in red), so the prefix will be "non–". Every other substituent present will be treated as a branch, and the position of the alkene will be specified.

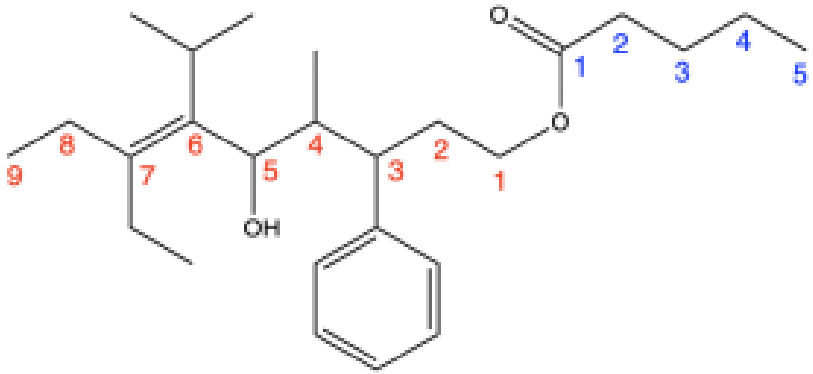

Figure 2.4.r. The first step in naming organic molecules is to identify the functional groups and parent chain. The ester is the highest priority functional group, so it will determine the final suffix. The portion containing the carbonyl group is numbered in blue, while the portion singly bonded to oxygen is numbered in red.

After identifying the parent chain, look for the branches. In this molecule, there are no branches in the carbonyl-containing portion, and five branches in the substituent singly bonded to oxygen: 3-phenyl, 4-methyl, 5-hydroxy, 6-isopropyl and 7-ethyl. In alphabetical order, these prefixes are: 7-ethyl-5-hydroxy-6-isopropyl-4-methyl-3-phenyl.

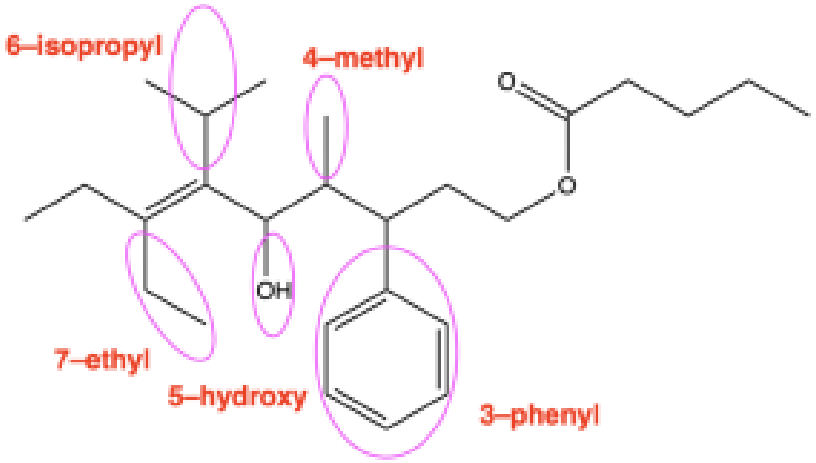

Figure 2.4.s. After identifying the parent chain, identify and name the branches present. In this molecule, there are 5 branches: 3–phenyl, 4–methyl, 5–hydroxy, 6–isopropyl and 7–ethyl.

Also note the alkene present between carbon 6 and 7. Functional groups that involve two carbon atoms (such as alkenes and alkynes) are identified by the lower numbered carbon atom, in this case carbon 6. The chain that is singly bonded to the oxygen group contains 9 carbons (nonane), with an alkene at position 6 (6-ene), and is bonded to the carbonyl group at position 1 of the chain (1-yl). Therefore, it is named "non-6-en-1-yl" (without considering the branches in this chain).

For the substituent singly bonded to oxygen, combining all aspects leads to the name: 7-ethyl-5-hydroxy-6-isopropyl-4-methyl-3-phenylnon-6-en-1-yl.

The final step is putting the name together. Remember that branches are placed as prefixes before the parent chain, and the portion that is singly bonded to oxygen is named before the carbonyl-containing portion, with a space between each portion. Therefore, the final name of the molecule would be: 7-ethyl-5-hydroxy-6-isopropyl-4-methyl-3-phenylnon-6-en-1-yl pentanoate.

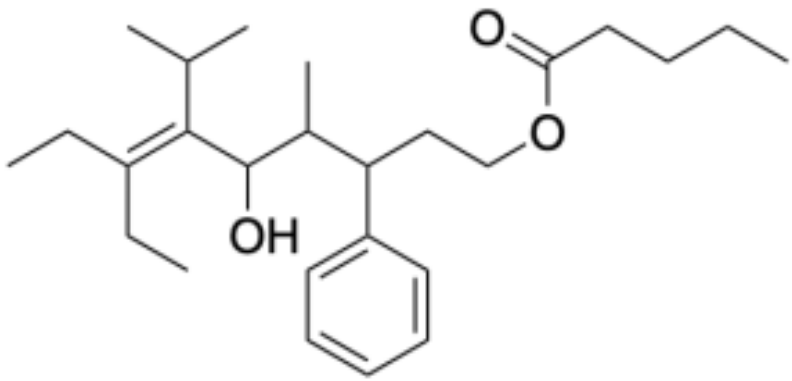

Figure 2.4.t. Structure of 7-ethyl-5-hydroxy-6-isopropyl-4-methyl-3-phenylnon-6-en-1-yl pentanoate.

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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(Click here for full solution).

Key Takeaways

Below is a checklist to ensure you have correctly named the organic molecule:

1. Have you identified all functional groups in the molecule?
2. Have you assigned priority to the functional groups using Figure 2.4.a. as a guide?
3. Have you identified the parent chain?
   ➔ Remember: to identify the parent chain, choose the path that contains more branch points and follows alphabetization if applicable.
4. Have you identified and named the branches?
5. Have you placed the branches in alphabetical order (not including di-, tri-, etc.)?
6. Is the molecule a ring?
   ➔ If so, include the prefix “cyclo–”
7. Have you put the names of the branches and parent chain together to yield the final name, with the branches first and the parent chain last?

2.5.1 - ALKENE STRUCTURE

Learning Objectives

1. Explain why alkenes display restricted rotation about the double bond, as compared to alkanes.
2. Explain the impact of chain structure on the melting point of fatty acids.
3. Identify the stereochemistry of an alkene (cis vs trans, *E* vs *Z*) using Cahn-Ingold-Prelog rules for priority (atomic number, branching).

Chapter 2.3 introduced the various functional groups commonly seen in organic molecules. Each functional group has distinct properties that affects the molecule's reactivity. This chapter will focus on the structure, properties, stereochemistry, and nomenclature of alkenes. Chapter 3.2 will cover the reactivity of alkenes.

Alkene Structure

Molecules are in constant motion, including translation through space, bond vibration, and molecular rotation. Rotation about a carbon-carbon single bond changes the 3-dimensional arrangement of atoms of a molecule. These different arrangement of atoms are called **conformations**. In Figure 2.5.1.a, two different conformations of butane (an alkane) are shown on the left. These conformations represent rotation about the central carbon-carbon single bond. They are the same molecule and are named the same way: butane.

In contrast, two different structures are shown for the alkene but-2-ene (Figure 2.5.1.a, right). They are different **configurations** of the molecule. A configuration is a permanent geometry of a molecule resulting from spatial arrangements of its bonds. The two configurations of but-2-ene are different molecules and are named differently: *trans*–but–2–ene vs *cis*–but–2–ene.

The ***cis* configuration** means that similar substituents are pointing in the same direction on either side of the double bond. For example, in *cis*–but–2–ene, the methyl groups on either side of the double bond are both pointing up and the implied hydrogens on either side of the double bond are both are pointing down. In contrast, the ***trans* configuration** means that similar substituents are pointing in opposite directions on either side of the double bond. For example, in *trans*–but–2–tene, one methyl group is pointing up and the other is pointing down on either side of the double bond. This nomenclature is further explored in Chapter 2.5.2. You will also see *cis* and *trans* terminology in future chemistry and biochemistry courses to designate relationships between different substituents in a molecule.

Although similar, configurations (shown for but-2-ene on the right) and conformations (shown for butane on the left) have different meanings when applied to molecules. This is because molecules with single bonds can rotate freely, but molecules with double bonds (or triple bonds) exhibit **restricted rotation**.

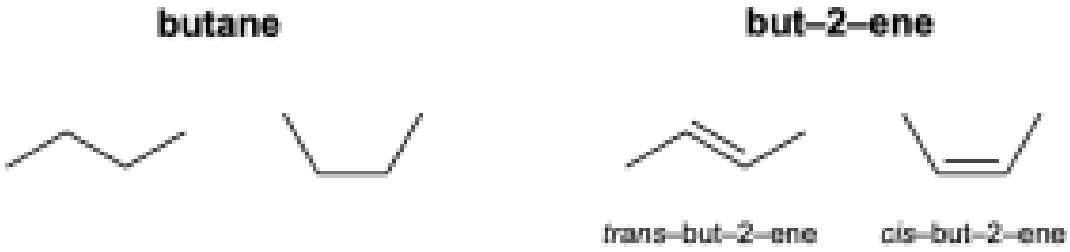

Figure 2.5.1.a. The two structures on the left represent the different conformations of butane, as alkanes experience free rotation. The two structures on the right represent the two configurations of but–2–ene: *trans*–but–2–ene and *cis*–but–2–ene.

The reason for restricted rotation in alkenes relates to the orbitals discussed in Chapter 2.2. Carbon atoms in alkenes are sp^2 hybridized, meaning they contain three hybridized sp^2 orbitals and one unhybridized p-orbital. This unhybridized p-orbital can make a π-bond by overlapping with another p-orbital. The two unhybridized p-orbitals overlap above and below the plane of the molecule (Figure 2.5.1.b). If one of the carbon atoms in the π-bond were to rotate, the p-orbitals would no longer overlap above and below the plane of the molecule, which would break the π-bond. Therefore, alkenes have a restricted rotation.

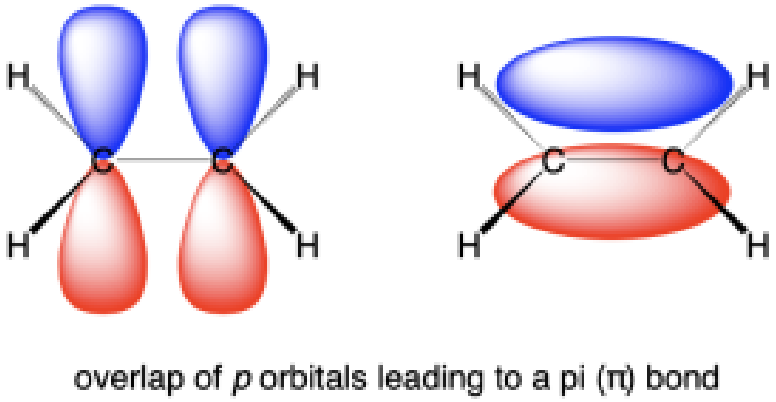

Figure 2.5.1.b. Formation of a π-bond from the overlap of p-orbitals. This creates a large area of electron density above and below the plane of the molecule.

Note the different terminology used for the structural arrangement of alkenes compared to alkanes. Alkenes have different **configurations**, which are permanent geometries due to restricted rotation about the carbon-carbon double bond. This means that two configurations of an alkene cannot be interconverted, and they are different molecules with different properties. Alkanes have different **conformations** due to the free rotation about carbon-carbon single bonds. Two conformations of an alkane can be interconverted, which happens regularly at room temperature as molecules are in constant motion.

Impact of Geometry on Melting Point

The *cis* and *trans* configurations of alkenes are seen in fatty acids such as oleic and elaidic acid pictured below in Figure 2.5.1.c.

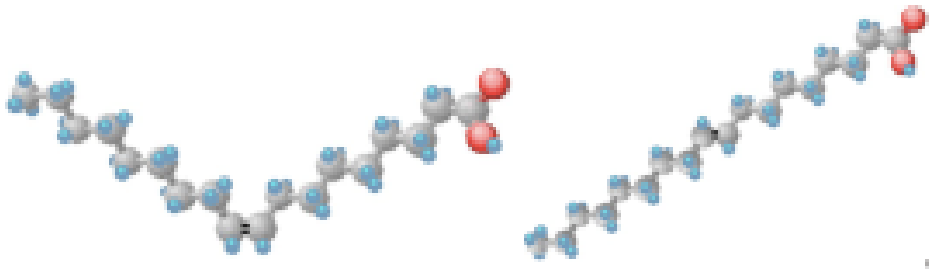

Figure 2.5.1.c. Two configurations of the fatty acid 9-octadecenoic acid. The structure on the left is *cis*-9-octadecenoic acid (oleic acid) and on the right is *trans*-9-octadecenoic acid (elaidic acid).

The *cis* configuration of this molecule (left) creates kinks in the chain, while the *trans* configuration (right) has

a similar zig-zag structure as a saturated hydrocarbon. The kinks in oleic acid prevent molecules from packing tightly together. The lower packing efficiency prevents intermolecular forces of attraction between chains, and thus requires less energy to melt. In contrast, the *trans* configuration will pack together more efficiently. Greater possibilities for intermolecular attractive forces in elaidic acid means that more energy is required to melt it, raising the melting point compared to the *cis* configuration. This can be seen in the melting points, where oleic acid has a melting point of 17^{o}C and elaidic acid has one of 52^{o}C.

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An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/mcmasterchem1aa3/?p=1328#h5p-64

(The full solution to this problem can be found in Chapter 5.1).

Key Takeaways

- **Conformations** of molecules are the different non-permanent orientations in three-dimensional space which a molecule can take. This is possible as bonds can rotate, changing the 3D shape.
    - This is seen in alkanes, which switch between conformations.
- **Configurations** are permanent geometric spatial arrangements that a molecule has, for example in alkenes. Confirmations occur in alkenes with *cis* and *trans* configurations, being permanent spatial arrangements as the double bond cannot rotate.

    - The double bond cannot rotate since the π bond with the p orbitals in alkenes would have to break, requiring energy.

- Alkenes have multiple names for their configurations, such as the *cis/trans* naming convention
- ***Cis* alkenes** have their alkyl chains on the same side of the double bond, while ***trans* alkenes** have their alkyl chains on opposite sides of the double bond.
- The properties of *cis* and *trans* alkenes vary.

    - *Trans* alkenes have a zig-zag structure that can pack closely together, resulting more intermolecular interactions and higher melting points.
    - As *cis* alkenes have kinks in their chain, they cannot pack together as efficiently, resulting in less intermolecular interactions and lower melting points.

2.5.2 - ALKENE STEREOCHEMISTRY AND NOMENCLATURE

Stereochemistry and Nomenclature: *Cis/Trans* vs. *E/Z*

The previous section of this chapter introduced the *cis/trans* designation of alkenes. This refers to the **stereochemistry** of the molecule, or the relative spatial arrangement of groups relative to a carbon-carbon double bond. In the *cis/trans* designation, ***cis*** refers to similar substituents located on the same side of the double bond, and ***trans*** refers to similar substituents on opposite sides of the double bond (Figure 2.5.2.a.). However, *cis/trans* designation can only be used when there are similar groups on each carbon of the alkene. If the groups on the alkene are different, then *cis/trans* designation is not useful to denote the stereochemistry of the molecule.

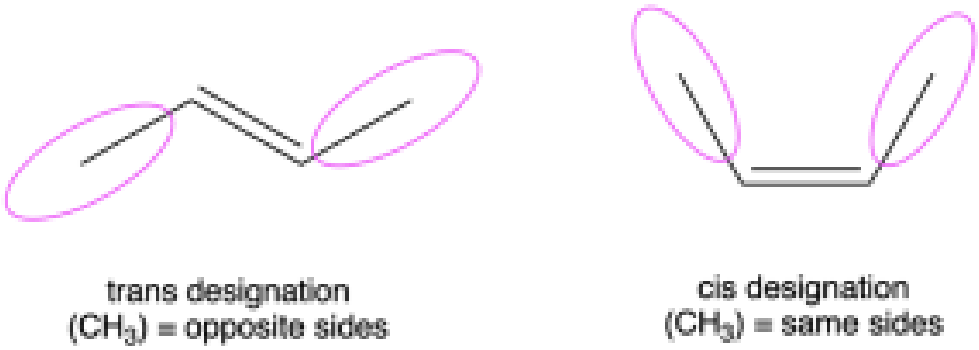

Figure 2.5.2.a. Two designations for the alkene 2-butene. The molecule on the left illustrates *trans*-but-2-ene, as the methyl groups are on opposite sides of the carbon-carbon double bond. The molecule on the right illustrates *cis*-but-2-ene, as the methyl groups are on the same side of the double bond.

The *E/Z* designation provides an alternative and more general nomenclature system. This nomenclature system relies on assigning priority to each group bonded to the carbon atoms of the double bond. A designation of ***E*** denotes higher priority groups on **opposite sides** of the double bond, while ***Z*** denotes higher priority groups on the **same side** of the double bond. The letters *E* and *Z* come from the German words *entgegen* (opposite) and *zusammen* (together).

Because *E/Z* designation relies on priority of groups, rather than similarity, it is a more applicable system to any scenario. The *E/Z* system can be used for any alkene, whether the substituents on either side of the carbon-carbon double bond are similar or different from one another. Therefore, *E/Z* notation has replaced the more traditional *cis/trans* notation.

For example, Figure 2.5.2.b shows a molecule with different groups attached to the C=C double bond. *Cis/trans* designation would not be useful for this molecule because none of the substituents are similar, but *E/Z* designation can be used to denote the stereochemistry of this molecule.

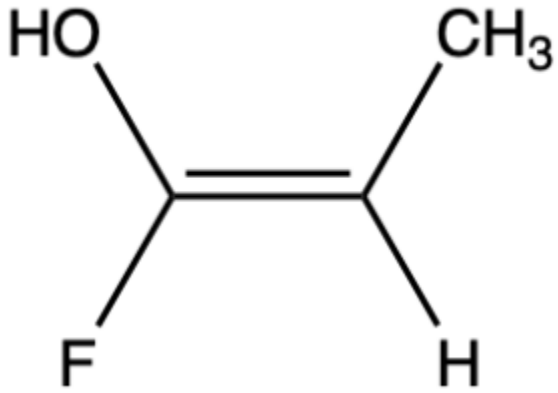

Figure 2.5.2.b. Structure of *E*-1-fluoroprop-1-en-1-ol. The *E* designation at the beginning of the compound's name is used to denote the presence of higher priority groups attached to *opposite* sides of the C=C double bond.

To determine whether a molecule has *E* or *Z* configuration, priority must first be assigned to each group using the **Cahn-Ingold-Prelog** rules.

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/mcmasterchem1aa3/?p=1372#h5p-65

(The full solution to this problem can be found in Chapter 5.1)

Cahn-Ingold-Prelog Rules

The first step is to cut the molecule through the double bond to create two halves, shown in green and blue in Figure 2.5.2.c.

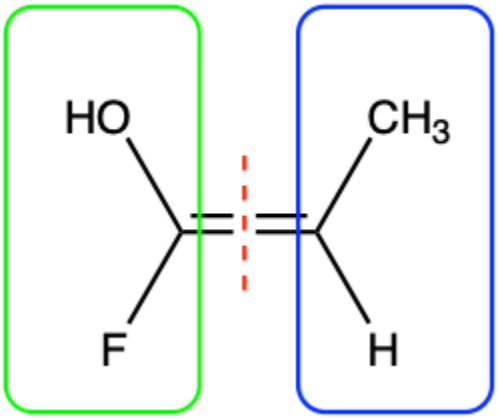

Figure 2.5.2.c. The first step of assigning *E/Z* configuration: cut the molecule in half at the double bond.

Next, consider the substituents on each half of the molecule (green and blue). Compare the substituents in the green (left) box with each other and compare substituents in the blue (right) box with each other.

Use atomic number to define priority for each pair of atoms that is singly bonded to each carbon in the C=C bond. The atom with the higher atomic number is considered the higher priority group. For example, in Figure 2.5.2.c, in the green (left) box, fluorine has an atomic number 9, compared to oxygen with atomic number of 8. This makes fluorine the higher priority group in the green (left) box. In the blue (right) box, carbon has a higher atomic number than hydrogen, meaning that carbon takes priority in the blue (right) box. The results are summarized in Figure 2.5.2.d, with the higher priority groups shown in red font.

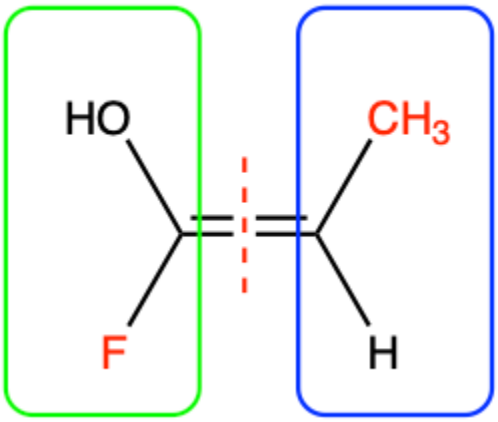

Figure 2.5.2.d. The second step in assigning *E/Z* configuration: use the highest atomic number to assign priority. The higher priority groups are shown in red.

Since the two higher priority groups are on opposite faces, the alkene has the *E* configuration.

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If the groups to be compared are different, but have identical atoms bound to the C=C bond, move on to the next connected atom until a point of difference is found. An example is seen in Figure 2.5.2.e. below.

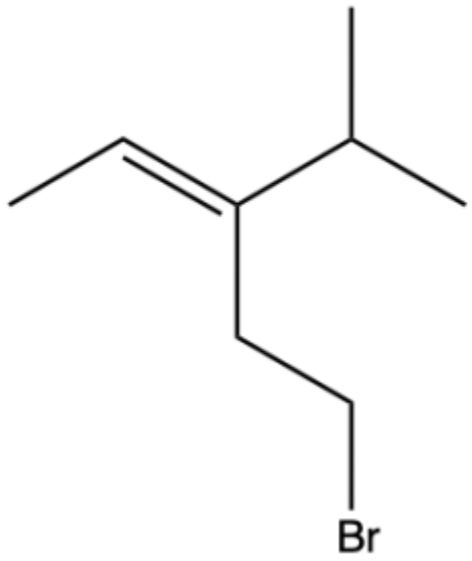

Figure 2.5.2.e. Structure of *E*-5-bromo-3-isopropylpent-2-ene.

We will follow the same procedure, by first splitting the molecule through the double bond (Figure 2.5.2.f). In the green (left) box, the carbon atom takes priority because it has a higher atomic number than hydrogen. Thus, the methyl group is shown in red font to denote that it is the higher priority group.

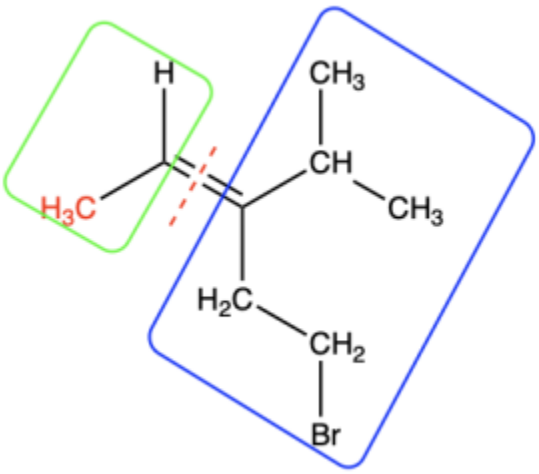

Figure 2.5.2.f. First step in assigning *E/Z* configuration: cut the molecule in half at the double bond.

In the blue (right) box, both atoms bonded to the alkene carbon are carbon atoms. They are identical. We need to move on to the next connected atom until we find a point of difference. We compare the three atoms to which each carbon is bonded, in order of decreasing atomic number. Figure 2.5.2.g. illustrates this comparison.

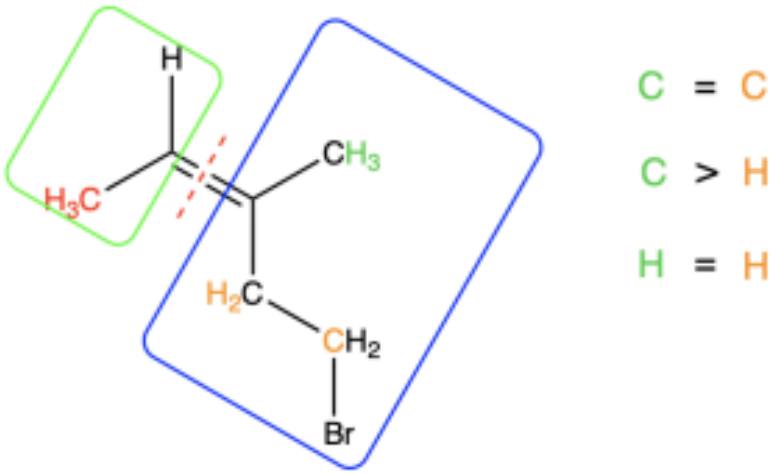

Figure 2.5.2.g. Second step of assigning *E/Z* configuration: when identical atoms are bound to the C=C bond, assign priority by moving on to the next connected atom until a point of difference is found.

On the top carbon, the atoms shown in green include two carbons and one hydrogen. On the bottom carbon, the atoms highlighted in orange include one carbon and two hydrogens. The top carbon contains more atoms

with a higher atomic number than the bottom carbon. Thus, the top carbon takes priority. Since the highest priority groups (highlighted in red on the left and orange on the right) are on opposite sides of the double bond, this alkene has an *E* configuration (Figure 2.5.2.h). Note that, despite bromine having the highest atomic number in this molecule, the bottom carbon does not take priority, because an earlier point of difference is found before the bromine is reached.

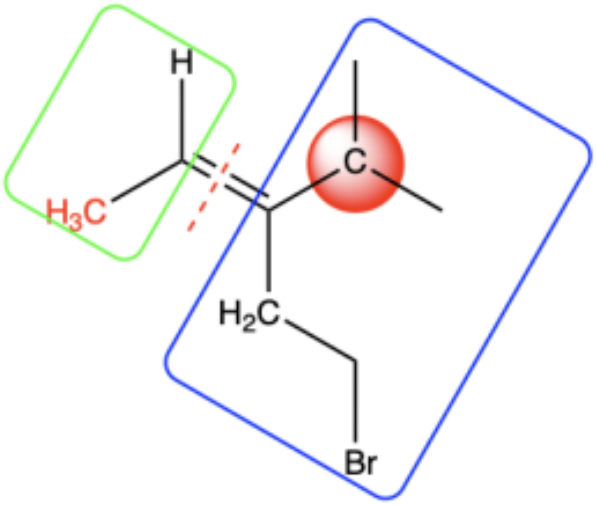

Figure 2.5.2.h. Final step in assigning E/Z configuration: the highest priority groups (shown in red font) are on opposite sides of the double bond, so this molecule has *E* configuration. It is named *E*-5-bromo-3-isopropylpent-2-ene.

If the second layer does not reveal a point of difference, move on to the next connected atoms and compare until a point of difference is discovered. An example is shown below in Figure 2.5.2.i.

In the green (left) box, bromine takes priority over hydrogen due to its greater atomic number, as shown in red font. In the blue (right) box, the first three layers do not reveal a point of difference, with a series of carbon atoms bonded to another carbon atom and two hydrogen atoms. On the third carbon atom, a difference is observed: one carbon atom is bonded to two hydrogen atoms and a fluorine atom, while the other carbon atom is bonded to two hydrogen atoms and a nitrogen atom. Since fluorine has a higher atomic number than nitrogen, the carbon atom bonded to fluorine takes priority, as shown in red font. The two highest priority groups being on the same side of the double bond means this molecule has *Z*– designation.

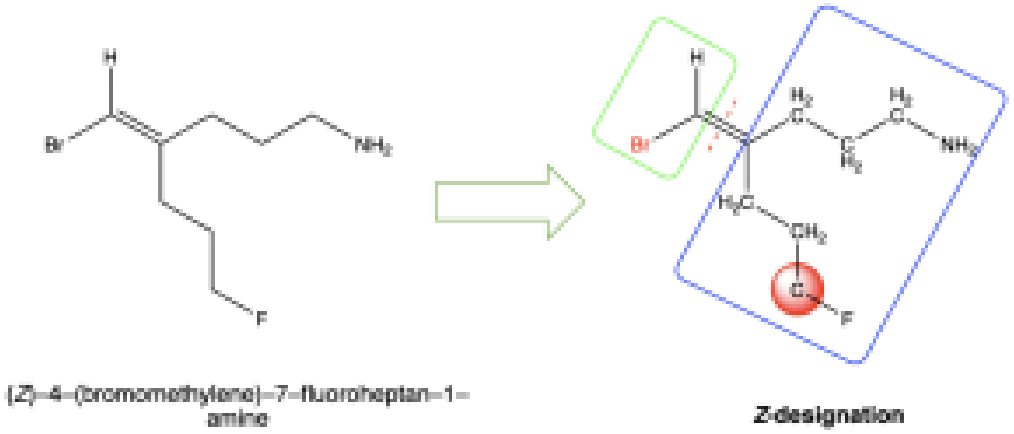

Figure 2.5.2.i. Assigning configuration in *Z*-4-(bromomethylene)-7-fluoroheptan-1-amine. The highest priority groups (shown in red font) are on the same side of the double bond, so this molecule has *Z* configuration.

If there is no point of difference, then there is no *E/Z* designation, because the two stereoisomers (*E* vs *Z*) are identical to one another. An example of this is shown below in Figure 2.5.2.j.

In the green (left) box, oxygen has a higher atomic number than carbon so the oxygen atom will take priority, as shown in red font. In the blue (left) box, there is no point of difference: the two groups bonded to the alkene carbon are identical. Since there is no point of difference, this molecule does **not** have *E/Z* designation.

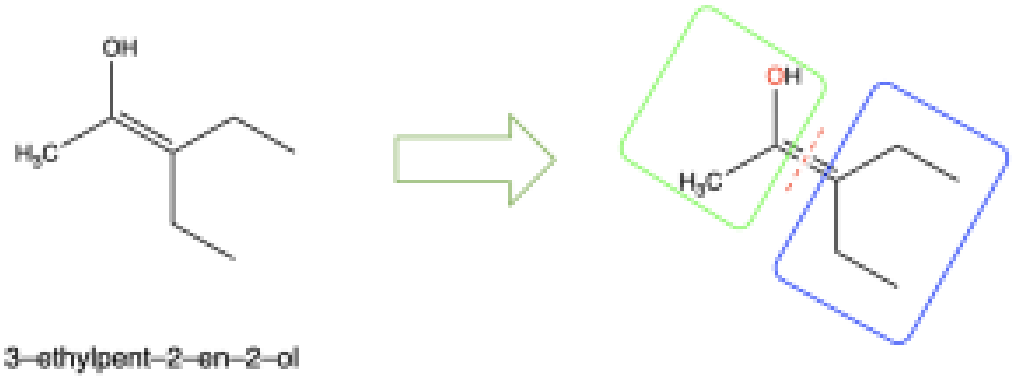

Figure 2.5.2.j. Structure of 3-ethylpent-2-en-2-ol. This molecule does not have *E/Z* configuration because there is no point of difference for the atoms in the blue box.

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(The full solution to this problem can be found in Chapter 5.1)

Stereochemistry and Cahn-Ingold-Prelog Rules: A Quick Summary

- When presented with an alkene with 3 or more unique substituents, *E/Z* conformation must be assigned. To do so, the Cahn-Ingold-Prelog rules need to be followed.
- Step to remember when abiding by these rules are as follows:
  - Draw an imaginary line through the double bond, splitting the alkene in half. Focus on one half at a time.
    - If the two substituents are completely identical on one half, you cannot assign *E/Z*. Otherwise:
    - On the first half of the alkene, there are two substituents. Assign priority to the first substituent atom with the GREATER atomic number. If the substituents bound directly to the double bond are the same atomic number, continue to the next atom of highest priority on both sides of the double bond. Continue until you reach the first point of difference.
    - Assign priority to the side with the higher priority atom, which appears closest to the double bond.
    - Do this process again on the other side of the split alkene.
    - If the two assigned highest priority atoms on each half are on the SAME side, then this is a *Z* configuration. If they are opposite to each other, then this is an *E* configuration.

Are You Wondering? Other Uses of Cahn-Ingold-Prelog Rules

The Cahn-Ingold-Prelog rules are used extensively in organic chemistry, and they will be present if continuing with future organic chemistry courses. They are not only used with alkenes, but also with alkanes when assigning names to groups of isomeric compounds with differing conformations. It is important to differentiate them due to their varying reactivity and properties.

The following video includes a worked example from a previous CHEM 1AA3 test or exam that students struggled with. Try solving it on your own before looking at the solution.

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Key Takeaways

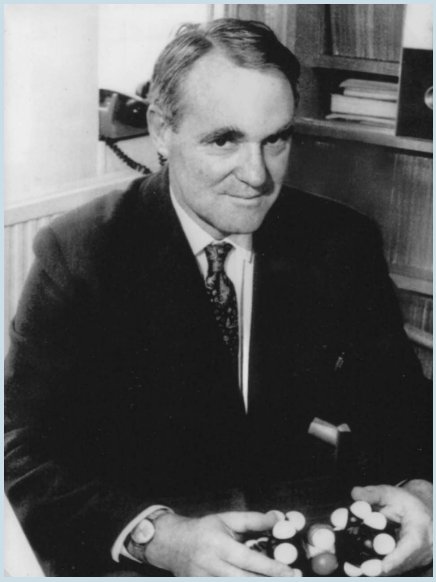
- Previously, *cis/trans* was introduced as a way to designate the stereochemistry of the molecule.
    - If there are two of the same functional groups across a double bond and they are positioned opposite to each other, it is denoted as *trans*
    - If they are positioned on the same side, then it is *cis.*
- However, *cis/trans* designation is not useful if there are different functional groups across a double bond, so we use the *E/Z* designation.
    - ***E*** refers to when higher priority groups are positioned opposite of each other.
    - ***Z*** refers to when higher priority groups are positioned on the same side.

- To determine priority of the functional groups, use the **Cahn-Ingold-Prelog rules** summarized above.

Key terms in this chapter:

Key term	Definition
Stereochemistry	The relative spatial arrangement of groups relative to a carbon-carbon double bond.

Diversity in Chemistry: John Cornforth



The stereochemistry of alkenes is described in this chapter; however, stereochemistry is applicable to other molecules in organic chemistry as well (a concept which is taught in second year!). **John Cornforth** was an Australian-British chemist who won the Nobel Prize in Chemistry in 1975 due to his work in stereochemistry. He was able to deduce exactly which clusters of hydrogens would be replaced in a synthetic reaction that used an enzyme as a catalyst. This ultimately paved the way for the development of cholesterol-lowering drugs that are still used today that target the enzymes he studied. Cornforth was diagnosed with otosclerosis at the young age of 10, a condition which deformed the bones within his ears and resulted in full deafness by age 20. Despite so, he excelled in his undergraduate classes, studying through primary literature, and succeeded greatly in his career as he contributed significantly to pharmaceutical research, and also elucidated the full biosynthetic pathway of cholesterol. More information on Cornforthand his journey can be found on his spotlight profile at The Royal Society website.

CHAPTER 3 - ORGANIC REACTIVITY

3.1.1 - INTRODUCTION TO NUCLEOPHILES, ELECTROPHILES AND CURVED ARROWS

Learning Objectives

1. Use curved arrows to demonstrate electron movement in various chemical processes.
2. Differentiate between nucleophiles and electrophiles.
3. Identify a nucleophile, electrophile, and leaving group in a nucleophilic substitution reactions

In organic chemistry, chemical reactions occur through the breaking and forming of bonds. Since a bond is a pair of electrons associated between nuclei, the flow of electrons in a reaction process can be used to represent the breaking and forming of bonds. Below (Figure 3.1.1.a) is an example of a simple substitution reaction.

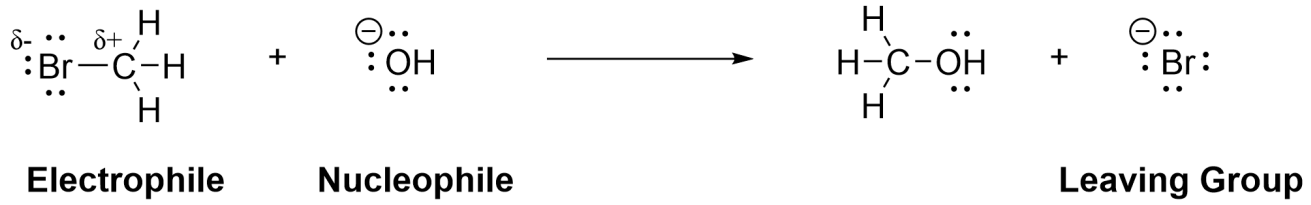
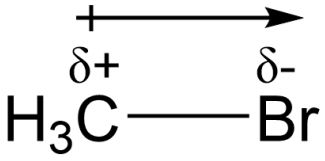


Figure 3.1.1.a. *A substitution reaction between bromomethane (CH_3Br) and hydroxide (OH^-).*

In this reaction, the bromine atom (Br) in the reactant bromomethane (CH_3Br) is replaced by the hydroxyl group (OH), making the products methanol (CH_3OH) and bromide (Br^-). This process involves both the breaking and forming of a sigma bond, and is classified as a substitution reaction. Before we learn the details of this reaction, we must first introduce some key terms that are critical for understanding why and how the reaction proceeds. These terms are **electrophile**, **nucleophile**and **leaving group**.

Electrophile

The reactant CH_3Br is classified as an alkyl halide. The C–X bond represents an alkyl halide, where X is a halogen and C is a carbon. Alkyl halides are polar due to the electronegativity difference of the two atoms in the bond, as halogens behave as more electronegative than carbon. Additionally, the difference in atomic radii also contributes to polarity of the bond as halogens tend to be larger and more electron rich atoms. As a result, a dipole moment exists where carbon has a partial positive charge and Br has a partial negative charge. This can be seen in the following diagram:



Because of the partial positive charge on carbon, the carbon atom in the C–X bond is considered *electron-deficient*. An electron-deficient species, such as an alkyl halide, is called an **electrophile**, also known as a Lewis Acid (introduced in CHEM 1A03), with the carbon being classified as an electrophilic center. As an electron-deficient center, the carbon atom is capable of accepting electrons from electron donors in a chemical reaction. Electrophiles often have a **positive charge**, a **partial positive charge**, and/or **an incomplete octet**. For example, the carbon atom in CH_3Br has a partial positive charge because of the polarity of the carbon-halogen bond. A carbocation is another example of an electrophile, in which the carbon centre has a positive charge and an incomplete octet (6 electrons).

Some common electrophiles are shown below in Figure 3.1.1.b. Notice how all examples contain either a positive or partial positive charge.

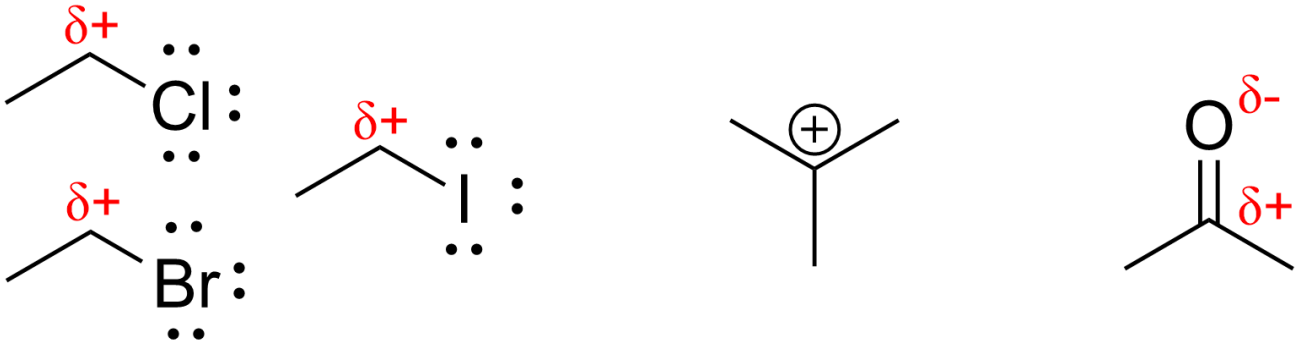


Figure 3.1.1.b. Several common electrophiles in organic chemistry.

For CH_3Br in this reaction, this carbon is referred to as an **electrophilic site** – the atom that will accept a pair of electrons in a bond forming process.

The entire compound CH_3Br that undergoes the substitution is called the **substrate**. It may help to think of a substrate as just another word for a reagent involved in a reaction.

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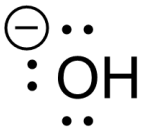
Nucleophile

The hydroxide anion, OH^-, is another reactant in the substitution reaction shown in Figure 3.1.1.a. In the Lewis structure of OH^-, the oxygen atom has three lone pairs of electrons and is negatively charged. Due to these factors, hydroxide can be considered an *electron-rich*species with a high electron density around the oxygen atom.



An electron-rich species, such as hydroxide, is called a **nucleophile**, with oxygen behaving as the nucleophilic center. Nucleophiles can also be referred to as Lewis base, as they behave as electron-pair donors in bond forming reactions. Nucleophiles seek positively charged or electron-deficient species to form bonds with. In this case, hydroxide is considered the nucleophile and the oxygen atom is what acts as an electron pair donor and is referred to as the nucleophilic site.

Generally, any **neutral or anionic** species with a **lone pair of electrons** available to donate can be a nucleophile. Nucleophiles, often written as Nu, can either be negatively charged ($Nu:^-$) or neutral (Nu:). For example, OH^-, OR^-, H_2O, ROH, NH_3, RNH_2, and $RCOO^-$ are all possible nucleophiles due to the presence of at least one pair of electrons. Various nucleophiles are shown below in Figure 3.1.1.c.

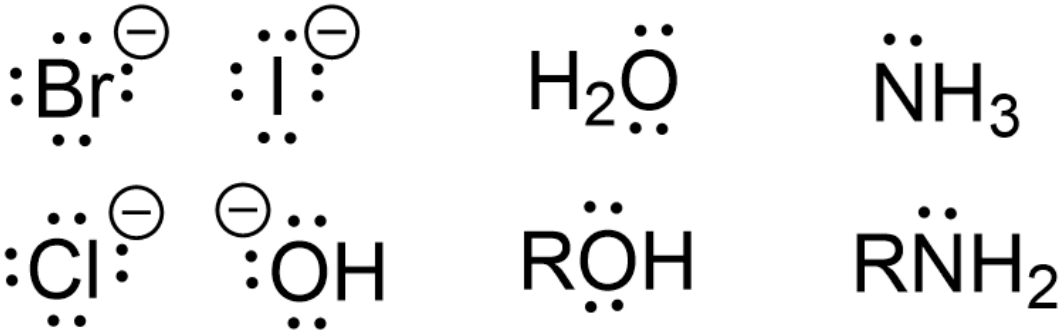


Figure 3.1.1.c. *Some common nucleophiles in organic chemistry.*

Based on this understanding of nucleophiles and electrophiles, it can be said that **when electron-rich nucleophiles meet electron-deficient electrophiles in the correct orientation, bond formation can occur.** For the reaction to proceed, these two molecules must collide in the correct orientation which is dependent on the geometry of both species.

Are You Wondering? The Greek Origins of "Electrophile" and "Nucleophile"

The terminology "electrophile" and "nucleophile" actually have from a Greek origin! These words can be split into two parts, which can be used to help remember the reactivity of these species.

The word **electrophile** is made up of the terms *electro* and *phile*, where *electro* refers to electrons, and *phile* is the Greek suffix meaning love. Together, they make the word electrophile mean "electron-lover." This makes sense with what we know, as they are electron deficient species that want more electrons.

Like electrophile, the word **nucleophile** has two parts: *nucleo*, meaning nucleus, and *phile*, meaning love. This word then means nucleus loving. Since the nucleus is made of positive protons, this means nucleophiles love positively charged species.

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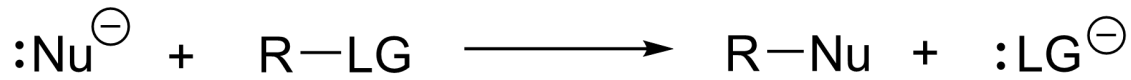
(The full solution to this problem can be found in Chapter 5.2)

Leaving Group

To ensure the substitution reaction shown in Figure 3.1.1.a occurs, another critical factor is that the C–Br bond must break in order for the carbon to accept a bond from the incoming nucleophile (OH^-) without exceeding its octet. The bromide, Br^-, is referred to as the leaving group in this scenario. The leaving group (often written as LG) is an electronegative species that leaves with the pair of electrons from the C–LG bond. Without a proper leaving group, even if a nucleophile is electrostatically attracted to an electrophile, the substitution will not occur. Leaving groups can start as neutral and become negatively charged upon accepting the pair of electrons from the bond breaking process, or they can positively charged and become neutral upon accepting the pair of electrons from the bond breaking process. They are not only seen in substitution reactions, but in a number of reactions in organic chemistry.

Applying the three key terms, the above substitution reaction can be summarized as: the nucleophile displaces the leaving group in a substrate. Such a reaction is called a nucleophilic substitution reaction. A nucleophilic substitution reaction can therefore be shown in a more general way:



Note: The nucleophile and leaving group are not necessarily negatively charged, as they could be neutral as mentioned earlier.

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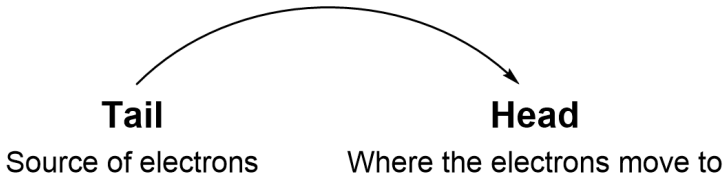
Drawing Curved Arrows

Curved arrows are an essential part of organic chemistry, as they showcase what is happening in these chemical reactions at the subatomic level. Curved arrows show the **flow of electrons**as they move from one region to another. Each curved arrow represents the movement of **a pair of electrons.**



The **tail** of the curved arrow always represents the source of the electrons. This can only come from a bond or a lone pair on an atom. The **head**of the arrow points to where the electrons are going and will also end up either as a lone pairor a new bond. Examples of curved arrows are shown in Figures 3.1.1.d, 3.1.1.e, 3.1.1.f.

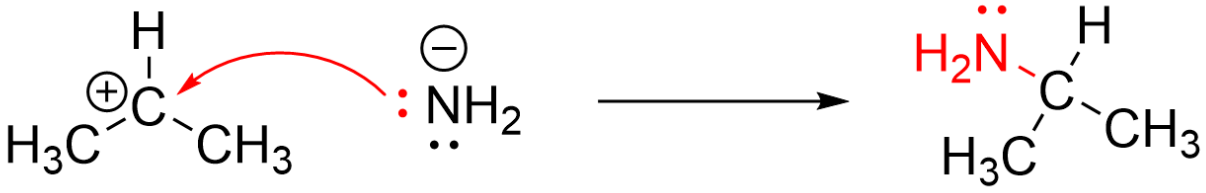


Figure 3.1.1.d. *A bond forming reaction between NH_2^- (the nucleophile), and a carbocation (the electrophile). A curved arrow is drawn starting from the electron-rich nucleophile pointing to the electron-deficient carbon.*

The example shown in Figure 3.1.1.d depicts a bond forming curved arrow. The arrow starts at the NH_2^- anion, which acts as the nucleophile as it has a lone pair that can act as an electron pair donor. It points to the electron-poor electrophile, which contains a positive charge and an incomplete octet. Thus, the arrow shows how the NH_2^- nucleophile donates a lone pair to form a new covalent bond with the carbon. A good way to remember how to draw curved arrows for a bond forming reactionis: the electrons always move from a species with a high electron density to one with a low electron density.

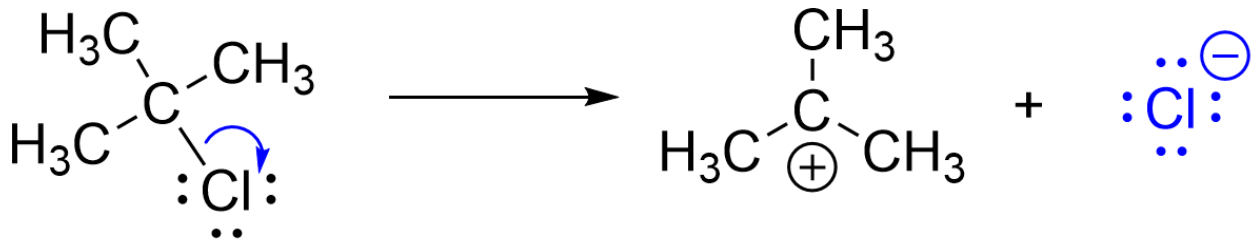


Figure 3.1.1.e. *A bond breaking reaction, where chlorine dissociates from carbon, taking the shared electron pair along with it. A curved arrow is drawn, depicting the movement of electrons from the C–Cl bond to Cl.*

In contrast, the example shown in Figure 3.1.1.e showcases a **bond breaking curved arrow**. Remember: a covalent bond represents the sharing of two electrons between two atoms, and thus, the electrons can move to form new bonds or to become lone pairs. This arrow starts at a bond, which acts as a source of electrons. The arrow points toward chlorine, indicating the movement of the electron pair to the chloride ion, breaking the bond. When looking at electronegativity trends, it is understandable that the more electronegative chlorine accepts the pair of electrons. As carbon loses an electron, it gains a positive charge, whereas chlorine gains an electron to make an anion.

Let's apply this new knowledge of curved arrows to the substitution reaction that was shown in Figure 3.1.1.a.

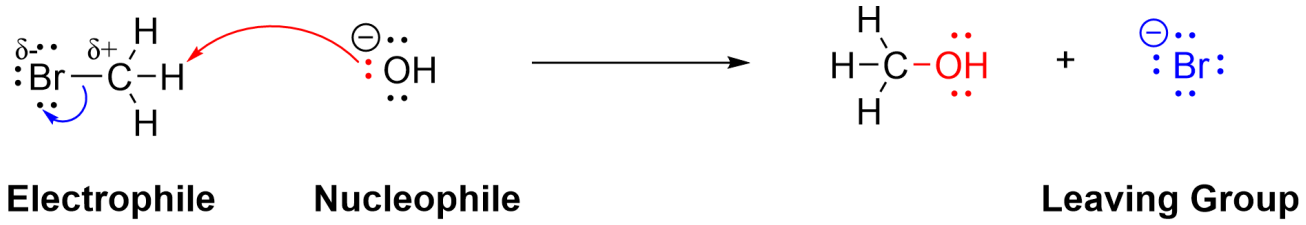


Figure 3.1.1.f. *The mechanism of a substitution reaction showing a bond forming arrow (red) and bond breaking arrow (blue).*

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The first arrow, shown in red, is a bond forming curved arrow that depicts the formation of a new bond between the nucleophilic hydroxide and electrophilic carbon. As carbon cannot have more than 8 electrons in

its valence shell, it is necessary for carbon to lose electrons elsewhere. Thus, a bond breaking curved arrow is also drawn between the polar bond of C–Br, where the electrons move from the bond to the electronegative Br. This results in the final product, methanol, and the leaving group, bromide.

When drawing the mechanism of an organic reaction, it is important to ***never violate the octet rule*** by exceeding 2 electrons around hydrogen or 8 electrons around carbon, nitrogen or oxygen. Incomplete octets around carbon atoms can occur in certain scenarios that we will explore in this text. If a bond is forming that leads to more than 8 electrons residing on C, N, or O, then this atom must lose electrons elsewhere. This is often seen in reaction mechanisms where multiple arrows are drawn in one step.

The reaction mechanism between a Lewis Acid and a Lewis Base drawn below (Figure 3.1.1.g) also strongly parallels that of a reaction between a nucleophile and an electrophile.

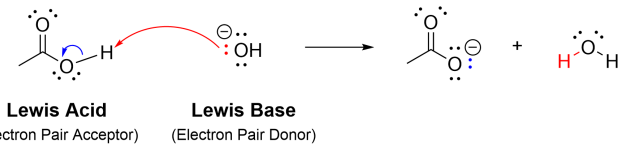
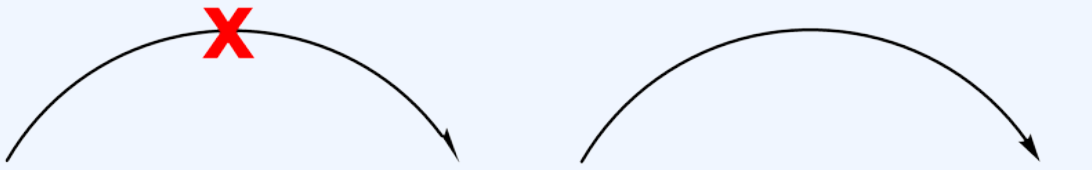


Figure 3.1.1.g. *Acid-base reaction depicting bond forming arrows (red) and bond breaking arrows (blue).*

The Lewis Base, hydroxide, functions similarly to a nucleophile, using its lone pair of electrons to donate to the electron acceptor, the Lewis Acid (or electrophile). This will form a bond between the two species. However, hydrogen can only hold two electrons in its valence shell. Thus, for this bond to form, a bond to hydrogen must also break. The blue arrow demonstrates the movement of the pair of electrons from the O-H bond to the oxygen, giving oxygen a negative charge in the product.

Ensure that the curved arrows you draw are clearly **double-sided arrows**, as these represent the flow of a **pair** of electrons. Single-sided arrows represent something slightly different, which will be further discussed in second year organic chemistry.



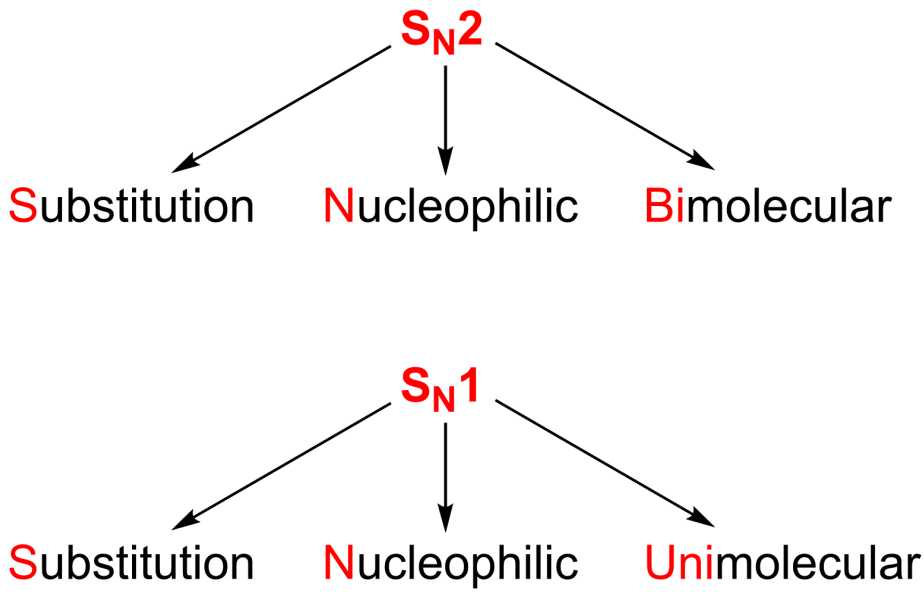
Single-headed Arrow
(Do NOT draw this arrow to show movement of two electrons)

Double-headed Arrow
(Draw this arrow to show movement of two electrons)

Types of Nucleophilic Substitution Reactions

Now that we have discussed some key terminology, it is important to know that there are two types of **nucleophilic substitution reactions**, which will be discussed in detail in Chapter 3.1.2 and Chapter 3.1.3. Although the products of these reactions look the same, they both undergo different reaction mechanisms, which was discussed in the kinetics unit. These are:

- **The S_N2 reaction** (see Chapter 3.1.2 for greater detail):
  - A second-order reaction that goes through the bimolecular reaction mechanism
  - The name S_N2 means **Substitution, Nucleophilic and Bimolecular.**
- **The S_N1 reaction** (see Chapter 3.1.3 for greater detail):
  - A first-order reaction that goes through the unimolecular reaction mechanism
  - The name S_N1 means **Substitution, Nucleophilic and Unimolecular.**



We will have detailed discussions on **S_N2 and S_N1 mechanisms** respectively, and then compare the similarities and differences between them in the upcoming chapters.

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

Key Takeaways

- Electrophiles, nucleophiles and leaving groups are all key components in organic reactions
- Nucleophiles are electron-rich, visible as lone pairs, which attract to electron deficient electrophiles in a reaction; this movement of electrons can be shown using two-headed arrows
- Remember: carbon cannot exceed its octet, so any bond formation to carbon must have the *loss of a leaving group* to take away two electrons
- Nucleophilic substitution reactions can be one of two types, S_N1 or S_N2, each involving a nucleophile, electrophile and a leaving group, but differing kinetics and mechanisms

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Key terms in this chapter:

Key term	Definition
Nucleophilic Substitution Reactions	A reaction type which involves the substitution of a leaving group with a nucleophile. The reactants are a nucleophile and an electrophile bonded to a leaving group. The products are the lone leaving group and an electrophile now bonded to the nucleophile. It can be also viewed as the nucleophile "taking place" of the leaving group.
Electrophile	An electron-deficient species, such as an alkyl halide (C–X). It accepts electrons from nucleophiles (electron donors) in a chemical reaction. These often have a positive charge, partially positive charge, or an incomplete octet. The **electrophilic center** is the specific atom on the electrophile that is electron-deficient and will accept electrons.
Nucleophile	An electron-rich species, such as hydroxide (OH-). Nucleophiles seek positively charged or electron-deficient species to form bonds with. Generally, any species, either neutral or anionic, which contains a lone pair of electrons can behave as a nucleophile in an organic reaction.

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3.1.2 - SN2 MECHANISMS

Learning Objectives

1. For an S_N2 reaction, predict products, write reaction schemes, draw curved arrow mechanisms, and draw energy profile diagrams, including all intermediates and transition states.
2. For an S_N2 reaction, understand the relationship between the energy profile diagram, curved arrow mechanism, and rate law.
3. Rank carbocations in terms of their stability and their propensity to undergo S_N2 mechanisms.

S_N2 Reaction Mechanism

An S_N2 reaction is a nucleophilic substitution reaction that occurs in a single step with both bond breaking and bond forming happening *simultaneously*. In this type of reaction, an electrophile bound to a good leaving group is attacked by a nucleophile, and the bond to the leaving group dissociates from the molecule just as a bond to the nucleophile is formed. This forms the final products.

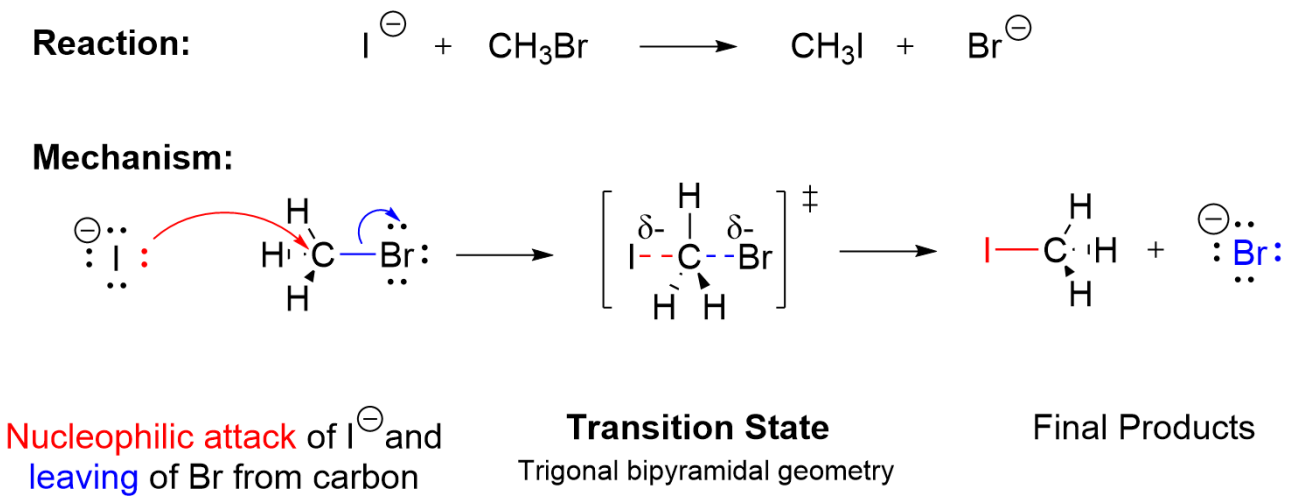

Fig 3.1.2.a. *The reaction mechanism of an SN2 reaction between a halide (the nucleophile) and bromomethane (the electrophile).*

The mechanism is said to be **concerted** , as one bond is breaking and another is forming simultaneously. The nucleophile donates a pair of electrons to attack the carbon center (Figure 3.1.2.a., red arrow), as the leaving group takes a pair of electrons and dissociates from the carbon center (Figure 3.1.2.a., blue arrow). In the example above, the nucleophile (I^-) approaches the electrophilic carbon 180° from the leaving group Br. As the nucleophile I^- approaches, the C–Br bond begins to weaken and break. The C–I bond forming event and the C–Br bond breaking event occur simultaneously. For a transient moment (~0.1 picoseconds at room temperature), the transition state has a carbon atom that is *partially* connected to *both* I^- and Br, which is depicted by the dotted lines. This is the highest energy level state of the whole process. In the transition state of an S_N2 reaction, the carbon is pentavalent in nature in a **trigonal bipyramidal geometry**, with two of the groups only partially bonded. As the I^- continues to approach the carbon, the Br further dissociates, taking both electrons in the old C–Br bond. Eventually, the new bond between C and I is completely formed and the old bond between C and Br is fully broken, which gives the product CH_3I and the anionic leaving group Br^-.

Notes for drawing an S_N2 mechanism:

- **Two** arrows must be shown when drawing the S_N2 mechanism to indicate the proper flow of electrons. The first curved arrow points from the nucleophile towards to the electrophilic carbon that it is attacking to demonstrate the electron flow in bond formation. The second curved arrow points from the bond between the carbon and the

leaving group towards the leaving group itself as it dissociates to demonstrate electron flow in bond breaking.

- When drawing the transition state, ensure that the nucleophile and leaving group are connected to the center carbon by **dotted lines,** as these bonds are in the process of forming or breaking respectively. The nucleophile and leaving group are oriented 180° to one another. The entire molecule is enclosed in **square brackets** with the **double dagger symbol** on the top right to indicate that it is the transition state.

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Because the reaction proceeds in a single step that involves both the nucleophile and the alkyl halide electrophile, increasing the concentration of either species will increase the possibility of a collision occurring between the two. Thus, the S_N2 reaction follows **second-order kinetics**, and the rate law can be written as:

Rate = k_{obs}[Alkyl Halide][Nucleophile].

Due to this, the reaction name **S_N2** stands for: **substitution, nucleophilic, and bimolecular**, as two molecules influence the rate of reaction.

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(The full solution to this problem can be found in Chapter 5.2)

Energy Diagram of the S_N2 Mechanism

The energy profile for the above reaction can be represented in Figure 3.1.2.b. As an S_N2 reaction happens in a single step, the diagram has only a single maximum, which is the point of the high energy transition state. This peak represents the overall activation energy for the entire process. The reactants are indicated on the left side and the products are shown on the right.

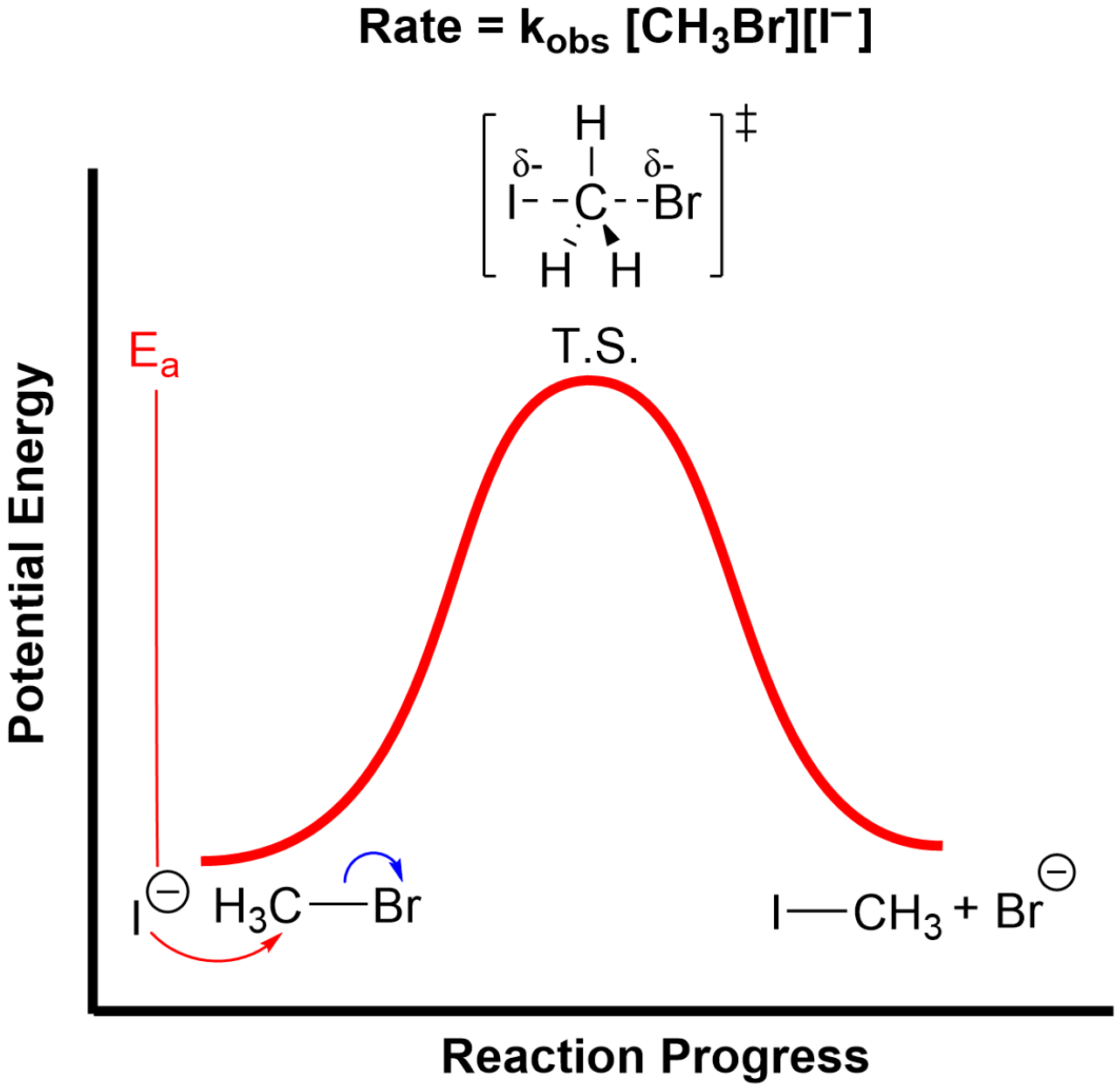


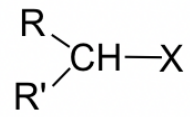
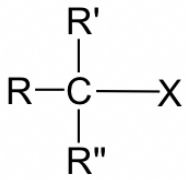
Fig 3.1.2.b. *An energy profile diagram of the reaction between an iodine anion and bromomethane.*

The maximum on the curve corresponds to the **transition state**, which is the highest-energy structure involved in the reaction. A transition state always involves partial bonds; eitherpartially formed bonds

orpartially broken bonds or both, which results in a molecule that is high in energy and unstable. As a transient species, the transition state can never be isolated, and its structure cannot be determined using experimental techniques. Instead, the structure of the transition state is proposed based on the process taking place, and can be predicted using computational techniques.

The Effect of Alkyl Halide Structure on S_N2 the Reaction Rate

Thus far, discussions of the S_N2 mechanism have focused on the reaction of bromomethane (CH_3Br) with a nucleophile. However, other alkyl halides can also undergo S_N2 reactions as well. Studies of the reaction rates for S_N2 reactions indicate that the structure of the electrophilic carbon in the alkyl halide dramatically influences the reaction rate (Table 3.1.2.).

Type of Alkyl Halide	Alkyl Halide Structure	Relative Rate
Methyl	CH_3X	30
Primary (1^o)	R-CH_2X	1
Secondary (2^o)		0.03
Tertiary (3^o)		Negligible (no S_N2 reaction observed)

As shown in Table 3.1.2., methyl and primary alkyl halides react the fastest, the rate decreases dramatically for secondary alkyl halides, and tertiary alkyl halides do not undergo an S_N2 reaction at all because the rate is too slow to be practically measured. In general, as the number of alkyl substituents increase on the electrophilic carbon, the activation energy for the S_N2 reaction increases. A larger activation energy results in a smaller rate constant and a slower rate of reaction. Figure 3.1.2.c.displays how changing the alkyl halide influences the reaction profile diagram and activation energy of the reaction.

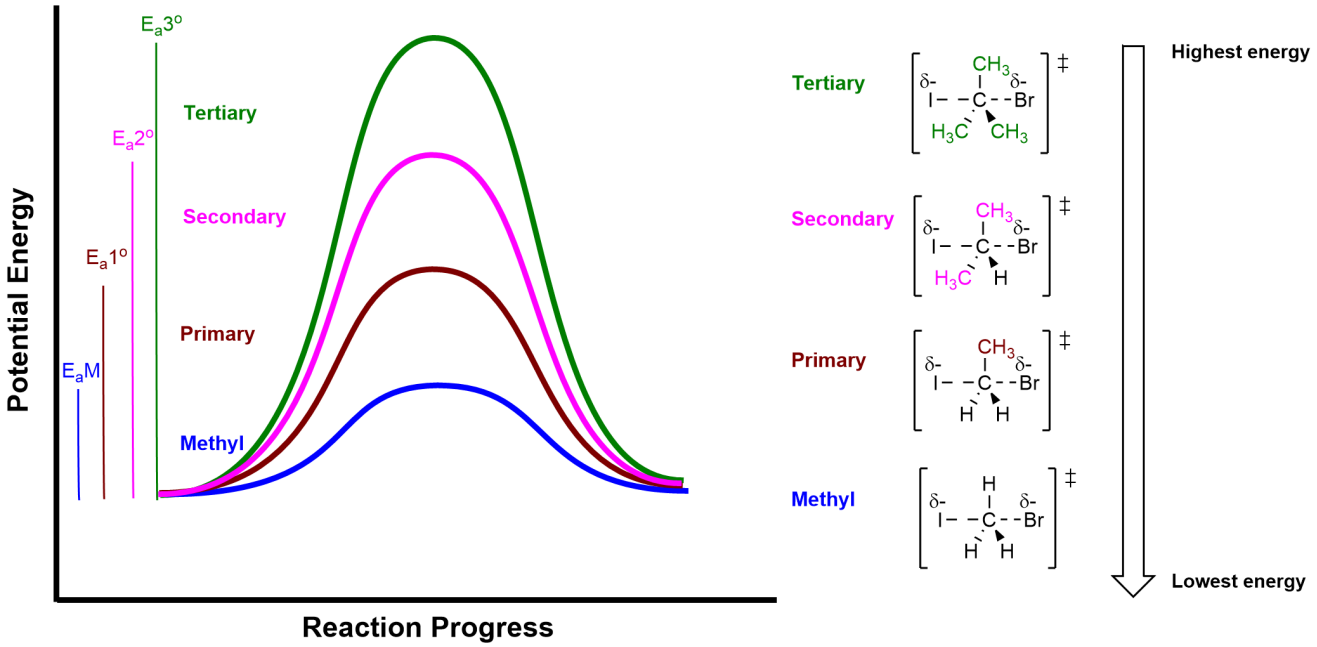


Fig 3.1.2.c. *Energy profile diagrams of S_N2 reactions involving alkyl halides. As the number of carbon groups on the electrophilic carbon increases, the activation energy barrier also rises*

The **relative reactivity of alkyl halides towards an S_N2 reaction** can be summarized as:

Methyl > Primary (1°) > Secondary (2°) >> Tertiary (3°)

Too unreactive to undergo S_N2 reaction

This trend can be explained by the mechanism of the S_N2 reaction. When nucleophiles approach the electrophilic carbon, the carbon is still bonded to three other groups as well as the leaving group. For the methyl electrophile, it is easiest for an electron-rich nucleophile to approach the electrophilic carbon because the surrounding hydrogen atoms are small and there is minimal electrostatic repulsion. If the size of the bonded groups becomes larger, it is more difficult for the nucleophile to access the electrophilic carbon as a result of increasing electrostatic repulsion to the neighbouring groups. For tertiary electrophiles, the electrophilic carbon is effectively inaccessible to the incoming nucleophile, as it has three large alkyl groups connected to it.

This reactivity difference is a result of the steric effect . The **steric effect** describes how the size of the groups (also known as **steric bulk**) around the electrophile can influence the reaction rate. As the groups around the electrophile become more bulky, steric hinderance increases, making the electrophilic carbon less accessible for nucleophiles to attack. Thus, the S_N2 reaction rate of secondary (2°) and tertiary (3°) substrates decreases dramatically. In fact, the 3° substrates almost never undergo S_N2 mechanisms because the reaction rate is too

slow due to the steric effect, and would prefer to undergo a different type of nucleophilic substitution reaction, the S_N1 mechanism, which will be described in Chapter 3.1.3.

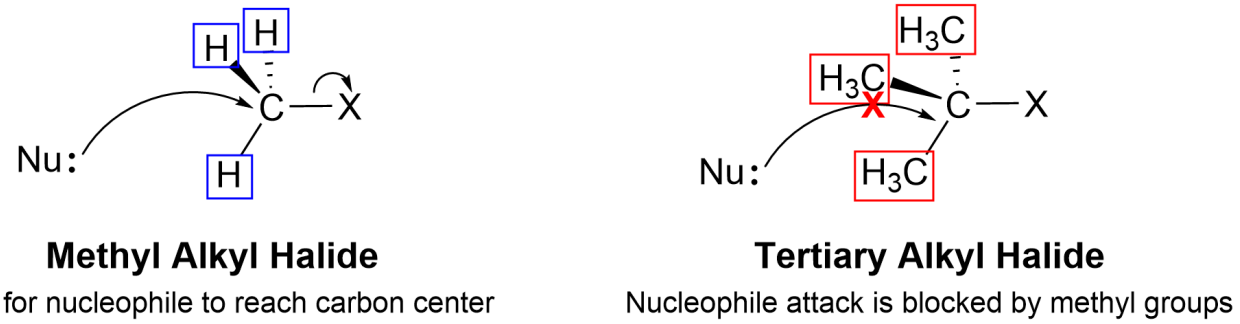


Figure 3.1.2.d. *The steric effect is illustrated, showcasing how the substituents on a tertiary alkyl halides block nucleophilic attack compared to the hydrogen groups on a methyl halide.*

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Adding Other Functional Groups via S_N2 mechanisms

Although the previous section focused on the use of a halide ion as a nucleophile, a variety of other nucleophiles can also be utilized. Hydroxide (OH^-), alkoxides (RO^-) and carboxylates ($RCOO^-$) can also be used as nucleophiles in S_N2 reactions, making it possible to synthesize compounds with a variety of functional groups. For example, the following reaction in Figure 3.1.2.e. can be performed with a primary alkyl halide and a nucleophilic alkoxide, forming an ether product.

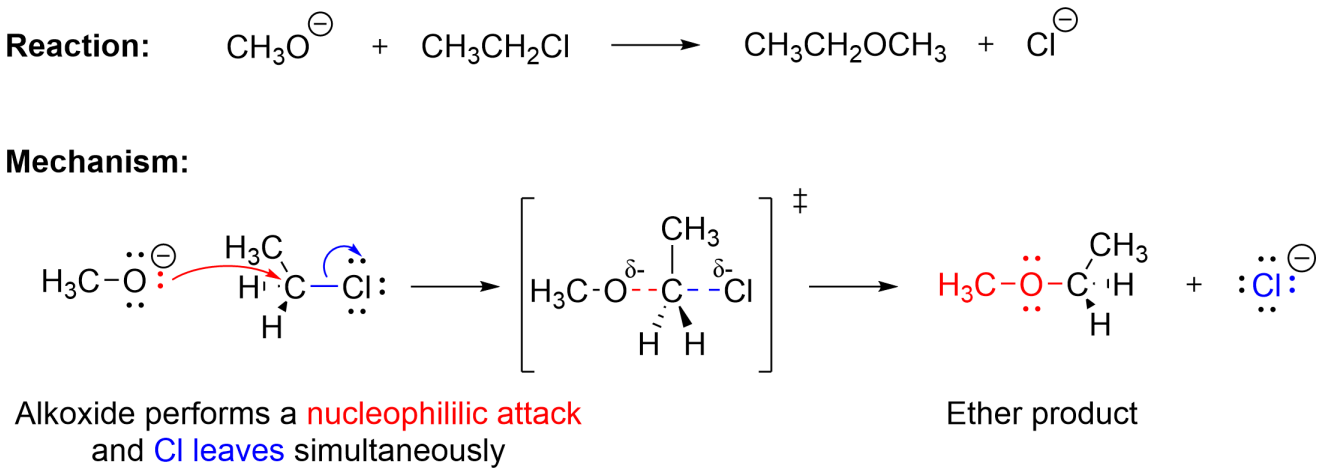

Figure 3.1.2.e. *Reaction mechanism of an S_N2 reaction between an alkoxide and a primary alkyl halide.*

The alkoxide acts as a nucleophile in this reaction, as it is anionic and contains at least one lone pair of electrons that can be used to form a bond, similar to the halide nucleophile discussed in earlier. Thus, the red curved arrow shows the nucleophilic attack of the alkoxide on the electrophilic carbon center, which results in a newly formed C–O bond. Simultaneously, as shown by the blue arrow, the chlorine leaving group takes a pair of electrons and leaves. The arrow represents the movement of the electron pair from the C–Cl bond to the electronegative chlorine, leading to its dissociation. As expected for an S_N2 mechanism, the reaction goes through a pentavalent transition state where two partial bonds exist: the C–O bond which is forming, and the C–Cl bond which is breaking. The final products of this process are an ether and a chloride anion.

Several oxygen-based nucleophiles can used to build a variety of functional groups onto a compound (Figure 3.1.2.f.). A hydroxide nucleophile can be used to form an alcohol (Figure 3.1.2.f., i), an alkoxide can be used to form an ether (Figure 3.1.2.f., ii), and a carboxylate can be used to form an ester (Figure 3.1.2.f., iii). Note that in each case, the nucleophile is anionic, with oxygen bearing the formal negative charge and acting as the nucleophilic atom. S_N2 reactions can also be used to produce thiol products (Figure 3.1.2.f.iv). As sulfur is located directly under oxygen on the periodic table, it has a similar number of valence electrons and reactivity. A hydrosulfide ion (HS^-), like hydroxide, contains a lone pair which can be used to attack the electrophilic carbon, forming a new C-S bond and ejecting the chloride as a leaving group.

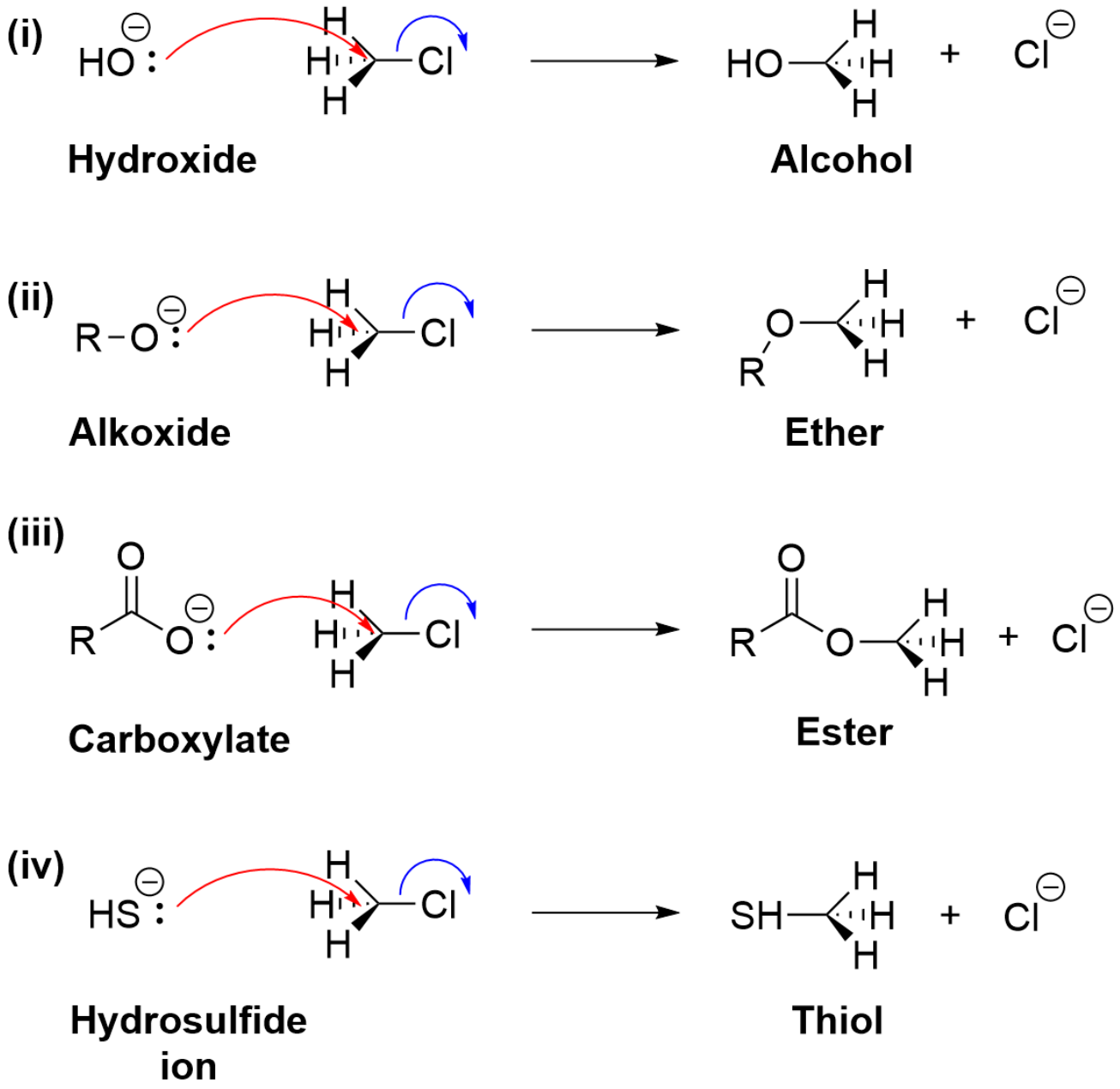

Figure 3.1.2.f. *The interconversion of functional groups using different nucleophiles in an S_N2 reaction.*

An Analogy For S_N2 Reactions:

Imagine an SN2 reaction as the orchestrated motion of a Newton's Cradle, where the nucleophile and leaving group play the roles of the swinging spheres. The reaction, like the Cradle, operates in a seamless, single step, without any transitional pause. In this analogy, the electrophile, represented as the stationary spheres throughout the motion, is equipped with a good leaving group, while the nucleophile represents the incoming sphere in motion. As the nucleophile approaches the electrophilic carbon opposite of the leaving group, it initiates a constant backside attack, mirroring the kinetic energy transfer in the Newton's Cradle. The nucleophile donates a pair of electrons to the carbon center simultaneously as the leaving group dissociates, symbolizing the exchange of energy between the spheres. Unlike the Cradle, however, Sn2 has a partial connection between the carbon/electrophile and leaving group as the nucleophile approaches. The reaction progresses seamlessly, resembling the continuous motion of the spheres in the absence of any pause or hesitation. The concerted nature of the SN2 mechanism, much like the perpetual swing of the Newton's Cradle, exemplifies the simultaneous breaking of one bond and formation of another, culminating in the creation of the final products.

Key Takeaways

- S_N2 stands for substitution nucleophilic bimolecular reaction.
- This reaction occurs in a single, concerted step, with an electrophilic carbon and a nucleophile as reagents.
    - This single step involves a transition state which has the electrophilic carbon forming a bond to the nucleophile and breaking a bond to the leaving group.
- Due to the steric effect, only methyl and primary alkyl halides can only be used as effective electrophiles in S_N2 reactions.

Key terms in this chapter:

Key term	Definition
Steric Effect	The effect that substituents have on a reaction due to the spatial arrangement of the groups. This plays a large part in determining the rate of SN2 reaction for primary, secondary, and tertiary alkyl halides. More sterically hindered compounds, such as the tertiary alkyl halides, have a larger steric effect resulting in a very slow rate for SN2 reactions.

Diversity in Chemistry: Maud Menten

When working with the rate laws of biological reactions, things get a lot more complicated with the introduction of enzyme catalysts. The Michaelis-Menten equation, therefore, is key to understanding simple enzyme kinetics. This equation was in part developed by **Maud Menten**, a female Canadian physician and chemist. Born in Port Lambton, Menten was one of the first women in Canada to obtain a medical doctorate at the University of Toronto, graduating in 1911. As research opportunities for women were quite scarce during this time period, Menten had to travel abroad in order to pursue her interests. The following year, she moved to Germany in order to work with Leonor Michaelis after becoming interested in his early work on enzyme kinetics. She then went on to publish the Michaelis-Menten equation alongside Michaelis in 1913, before pursuing her Ph.D at the University of Chicago and becoming a professor at University of Pittsburgh until her retirement.

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3.1.3 - SN1 REACTION MECHANISMS

Learning Objectives

1. For S_N1 reactions, predict products, write reaction schemes, draw curved arrow mechanisms, and draw energy profile diagrams, including all intermediates and transition states.
2. For S_N1 reactions, understand the relationship between the energy profile diagram, curved arrow mechanism, and rate law.
3. Draw and explain the geometry and orbitals involved in a carbocation.
4. Rank carbocations in terms of their stability and their propensity to undergo S_N1 mechanisms.
5. Explain how carbocations are stabilized based on their degree through electron density.

S_N1 Reaction Mechanism

The previous section established how S_N2 reactions cannot occur with tertiary alkyl halides as substrates due to the steric effect. However, they can undergo another type of nucleophilic substitution reaction called **S_N1**.

S_N1 reactions occur in more than one step by a dissociative mechanism where the leaving group leaves first. This generates a carbocation intermediate, which is a compound with a positively charged carbon atom that has trigonal planar geometry. The second step of an S_N1 reaction involves nucleophilic attack by the electron rich nucleophile at the carbocation centre.

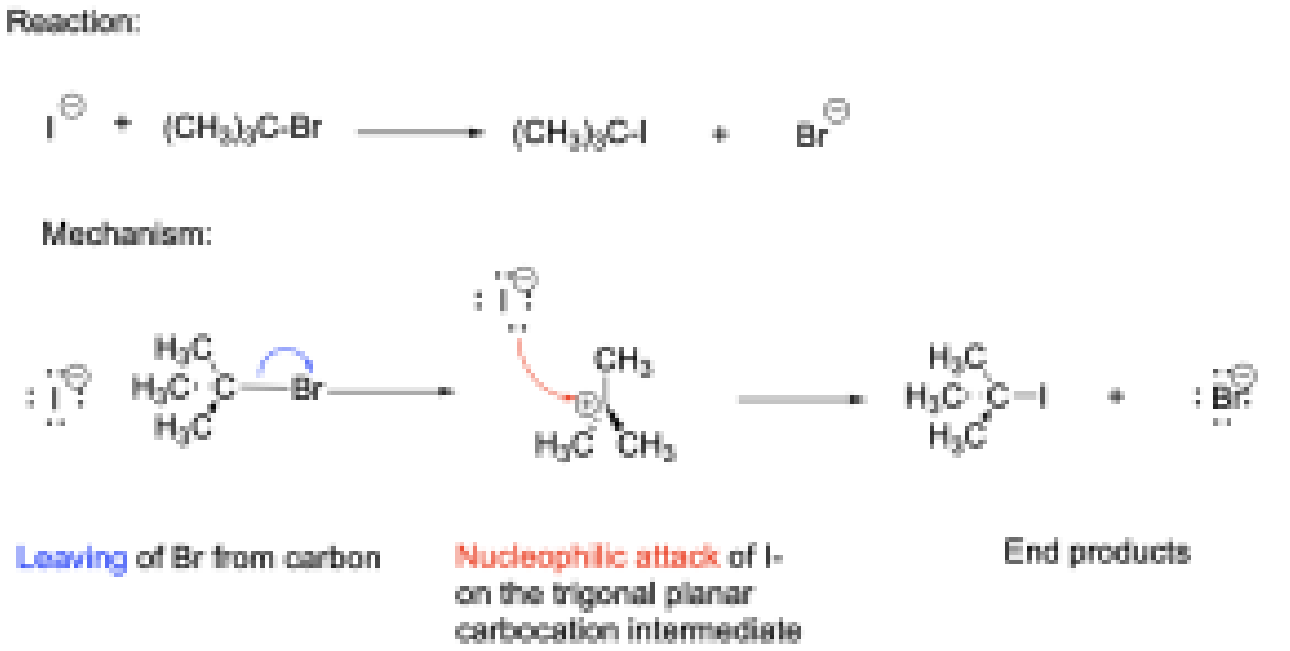

Figure 3.1.3.a. Overall mechanism for an S_N1 reaction. The halide Br^- will first leave generating a positively charged carbocation intermediate. The halide I^- will perform a nucleophilic attack on the trigonal planar carbocation intermediate, generating the final products.

Let's break down each step of the mechanism:

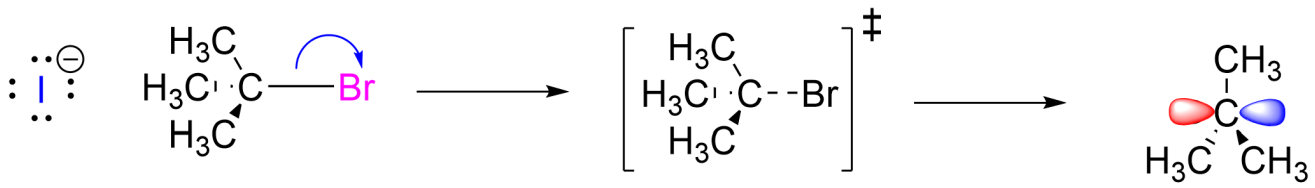

Figure 3.1.3.b. First step of the SN1 mechanism. The C–Br bond breaks with bromine acting as the leaving group and taking a pair of electrons, generating a tetrahedral transition state. An electron deficient carbocation intermediate with an empty p-orbital forms.

Step 1. The C–Br bond breaks with bromine acting as the leaving group. The transition state has tetrahedral geometry, and includes the C–Br bond in the process of breaking (depicted with a dashed line). This generates a positively charged carbocation intermediate, which has an empty p-orbital. The incomplete octet and positively charged carbon centre makes this intermediate highly reactive.

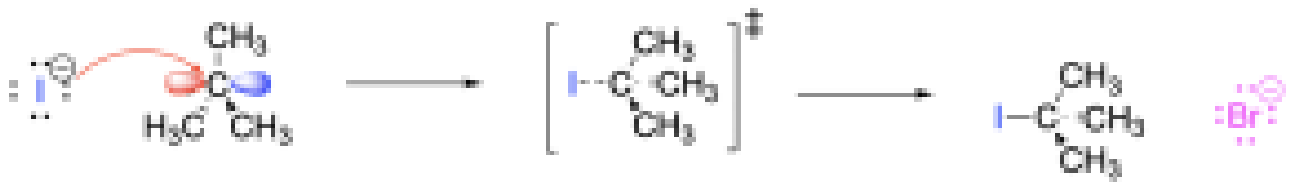

Figure 3.1.3.c. Second step of the S_N1 mechanism. Iodide attacks the electron-deficient carbocation, donating a pair of electrons into the empty p-orbital, forming a new C–I covalent bond. A tetrahedral transition state yields the products tert-butyl iodide and bromide.

Step 2. The carbocation intermediate acts as an electrophile while the electron-rich iodide acts as the nucleophile. The iodide attacks the electron-deficient carbocation, donating its electron density into the empty p-orbital and forming a new C–I bond. The transition state has tetrahedral geometry and includes the C–I bond in the process of forming (depicted with a dashed line). This generates the final products: *tert*–butyl iodide and bromide.

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Rate Law and Energy Diagram of S_N1 Mechanism

The S_N1 reaction proceeds through a two-step mechanism. This is shown in an energy profile diagram with two energy maxima, corresponding to the two transition state species. The local energy minimum represents the carbocation intermediate.

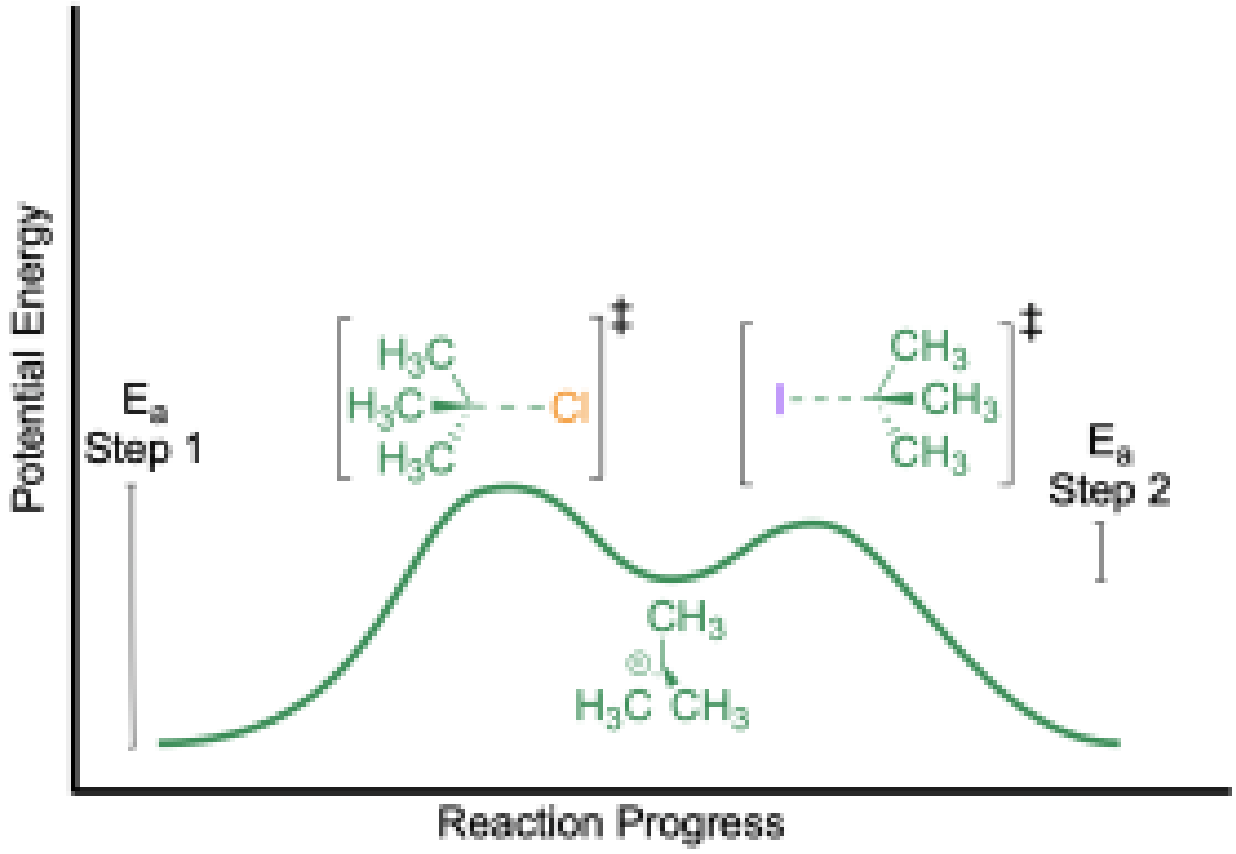

Figure 3.1.3.d. Energy profile diagram for the S_N1 reaction $(CH_3)_3C–Br + I^- \rightarrow (CH_3)_3C–I + Br^-$

The first maximum represents the first step of the reaction: C–Br bond breaking and loss of the halide leaving group. This is the step with the largest activation energy barrier (E_a, step 1) in the mechanism. The activation energy barrier for the first step is largest because the initial reactant is stable as a neutral molecule with a complete octet. Bond breaking of the carbon-halide bond is endothermic, leading to a less stable, more reactive carbocation intermediate. The first step of an S_N1 reaction is therefore the rate-determining step of the reaction.

The second maximum represents the second step of the reaction: nucleophilic attack by iodide to form the final product. This step has a lower activation energy (E_a, step 2) compared to the first step. The carbocation intermediate will readily accept electrons from the electron-rich nucleophile in an exothermic bond forming event. This yields the rate law shown below:

Rate = k_{obs}[Alkyl Halide]

Since the first step is the slow step, the rate of an S_N1 reaction only depends on the rate at which the carbon-halide breaks in the alkyl halide reactant. The reaction rate does not depend on the nucleophile. The overall rate law for an S_N1 reaction is therefore first order, hence the name S_N1 (**S**ubstitution **N**ucleophilic **U**nimolecular).

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(The full solution to this problem can be found in Chapter 5.2)

The Effect of the Substrate Structure on the S_N1 Reaction Rate

The alkyl halide substrate plays a key role in determining the rate of an S_N1 reaction. It is experimentally observed that tertiary substrates most readily undergo an S_N1 reaction, while methyl and primary alkyl halides are rarely observed to undergo an S_N1 reaction.

The relative reactivity of substrates towards the S_N1 reaction can be explained by the activation energy of the first step of the mechanism. This is in turn correlated to the energy of the carbocation intermediate: the more stable the carbocation intermediate, the lower the activation energy barrier to form that intermediate, and the faster it will form. In an S_N1 reaction, tertiary substrates have the lowest activation energy barrier, and will undergo an S_N1 reaction faster than secondary, primary and methyl substrates respectively.

An energy profile diagram of the four differently substituted alkyl halides (methyl, primary, secondary, and tertiary) is shown below:

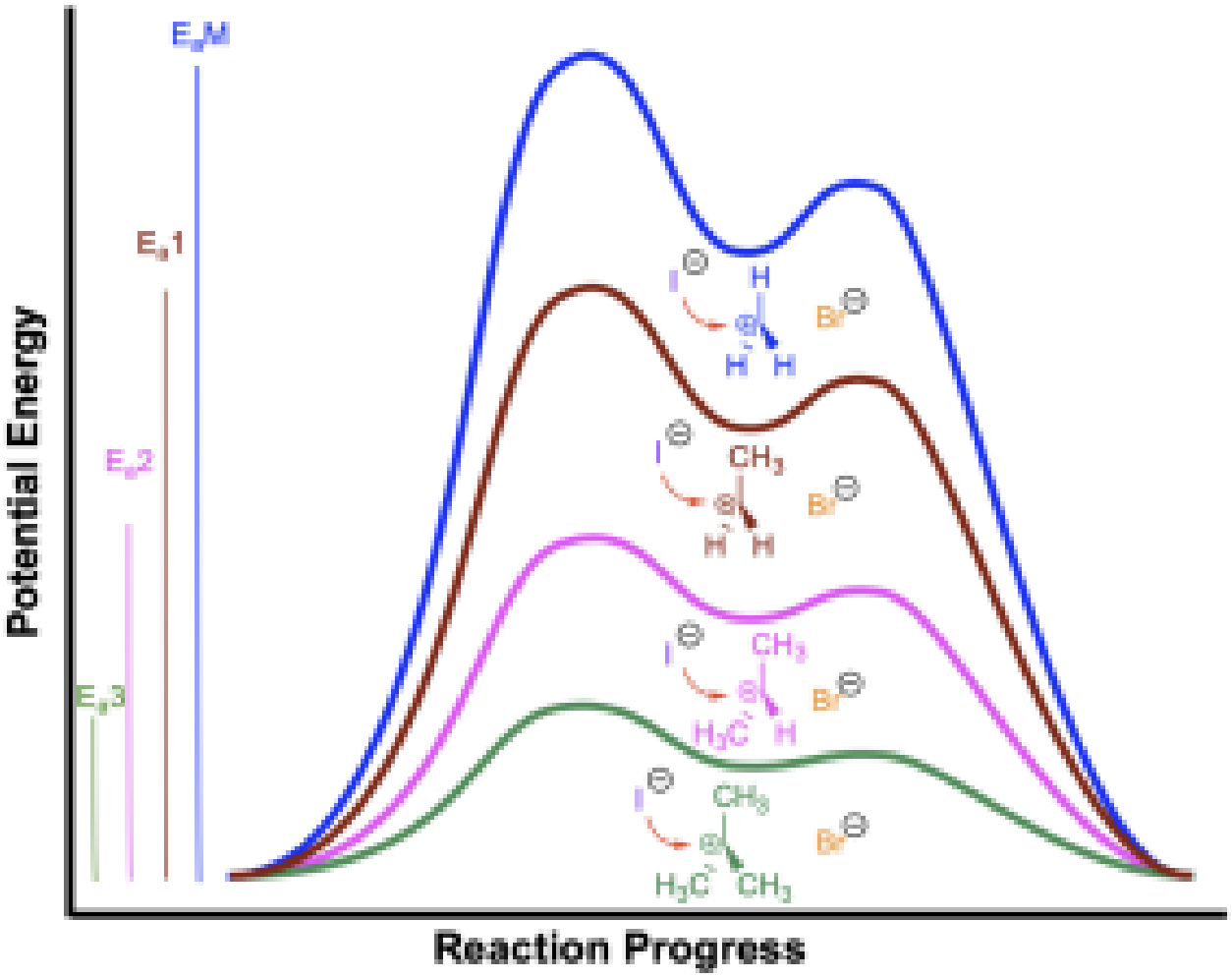

Figure 3.1.3.e. Energy profile diagram for the S_N1 reaction involving four different substrates: tertiary, secondary, primary, and methyl halides. $E_a3$corresponds to the activation energy for a tertiary alkyl halide to form a tertiary carbocation intermediate. $E_a2$corresponds to the activation energy for a secondary alkyl halide to form a secondary carbocation intermediate. E_a1 corresponds to the activation energy for a primary alkyl halide to form a primary carbocation intermediate. $E_aM$corresponds to the activation energy for a methyl halide to form a methyl carbocation intermediate. The methyl carbocation intermediate is the least stable of all the carbocations and will have the highest activation energy barrier.

This trend is explained by the stability of the carbocation intermediates, which is in turn explained by considering the electron densities of surrounding groups. The greater the electron density surrounding the electron-deficient carbocation center, the greater the ability to dissipate the positive charge, and the more stable the carbocation. Alkyl groups possess larger electron clouds than hydrogen atoms and can donate their electron density towards the carbocation, and thereby dissipate the positive charge to a larger degree than hydrogen atoms.

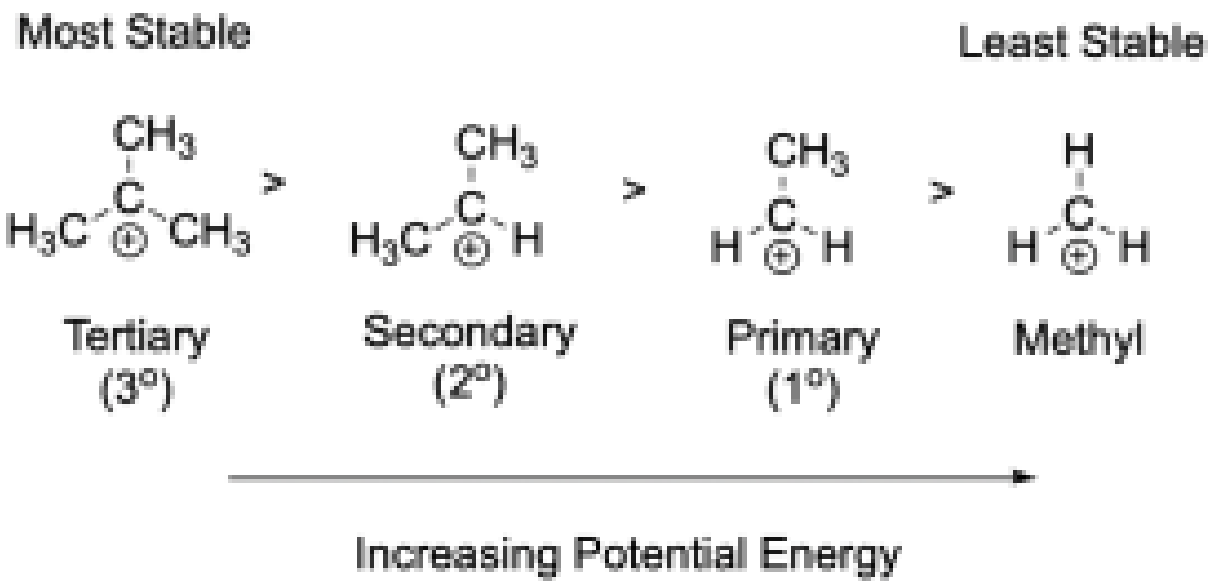

Figure 3.1.3.f. Experimentally observed relative stability of carbocations.

In the tertiary carbocation, the electron-deficient carbon center is surrounded by three alkyl groups, which donate some of their electron density towards the carbocation centre. This allows for dissipation of the positive charge, which stabilizes the carbocation. In the primary and secondary carbocations, there are fewer alkyl groups surrounding the carbocation center. As a result, these intermediates have less electron density surrounding the carbocation, which limits their stabilizing capacity. The methyl carbocation has only hydrogen atoms bound to the carbocation, resulting in limited electron density available to stabilize the carbocation center, making the methyl carbocation the least stable.

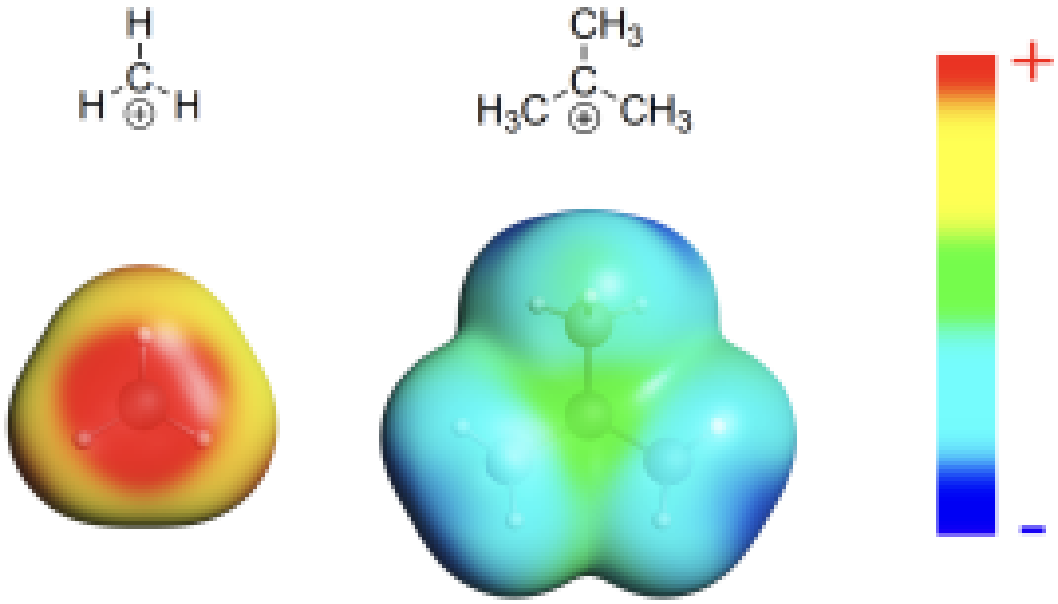

Figure 3.1.3.g. Electrostatic potential maps for methyl, and tertiary carbocation intermediates, respectively, from left to right. As shown in the red and yellow colouring, the methyl carbocation (left) has limited dissipation of positive charge, making this an unstable species. The tertiary carbocation (right) has three methyl groups to donate electron density towards the carbocation (shown in green), allowing the positive charge to be dissipated. The stability of the carbocations increases from left (least stable) to right (most stable).

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Nucleophilic Substitution – Making Alcohols and Ethers

An S_N1 mechanism can also be used to synthesize alcohols and ethers, by reacting a tertiary alkyl halide substrate with either water or an alcohol, respectively, as the nucleophile. This reaction occurs in three steps, these being the two-steps involved in the S_N1 mechanism, followed by a proton transfer step.

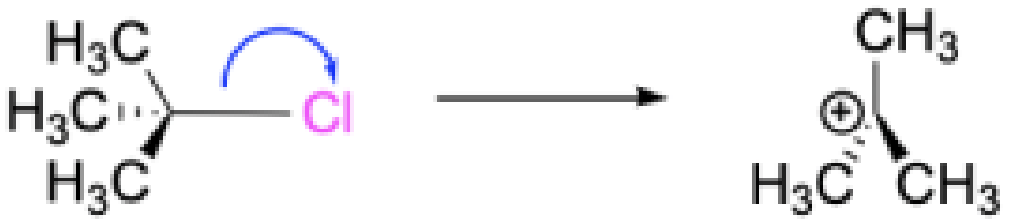

Figure 3.1.3.h. First step of the S_N1 mechanism to generate alcohols and ethers. The C–Cl bond breaks, generating a tertiary carbocation.

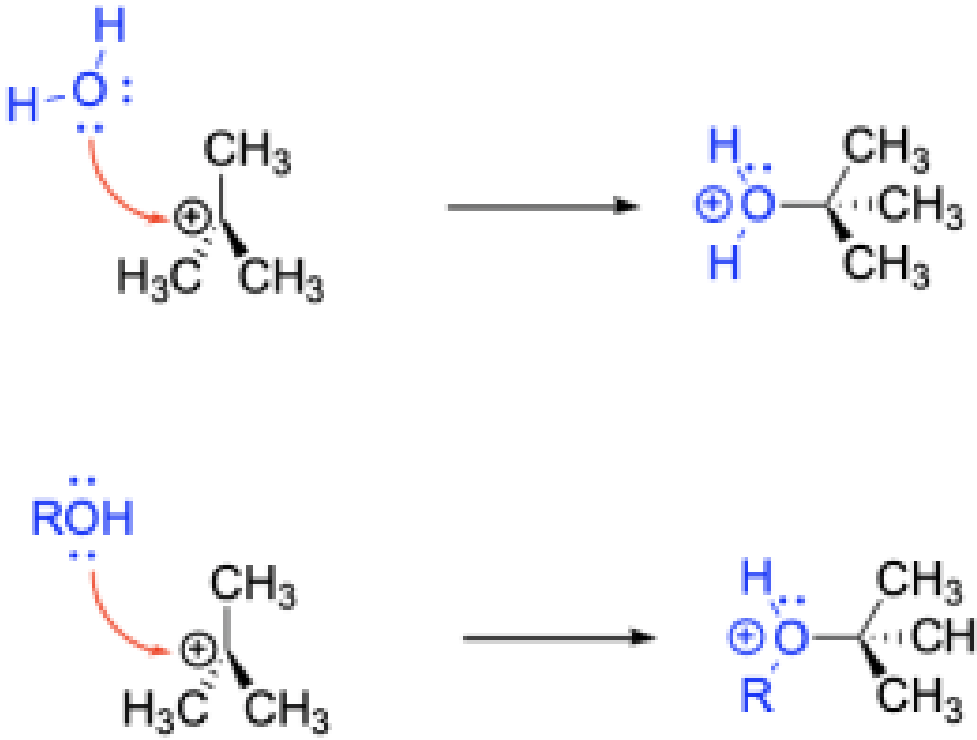

Figure 3.1.3.i. Second step of the S_N1 mechanism to generate alcohols and ethers. On top, water acts as a nucleophile while alcohol acts as a nucleophile in the reaction on the bottom. These nucleophiles will attack the electrophilic carbocation center, generating oxonium cation intermediates.

Step 2, top. Water acts as a nucleophile to attack the electrophilic carbocation center, generating an oxonium cation intermediate.

Step 2, bottom. An alcohol acts as a nucleophile to attack the electrophilic carbocation center, generating an **oxonium** cation intermediate.

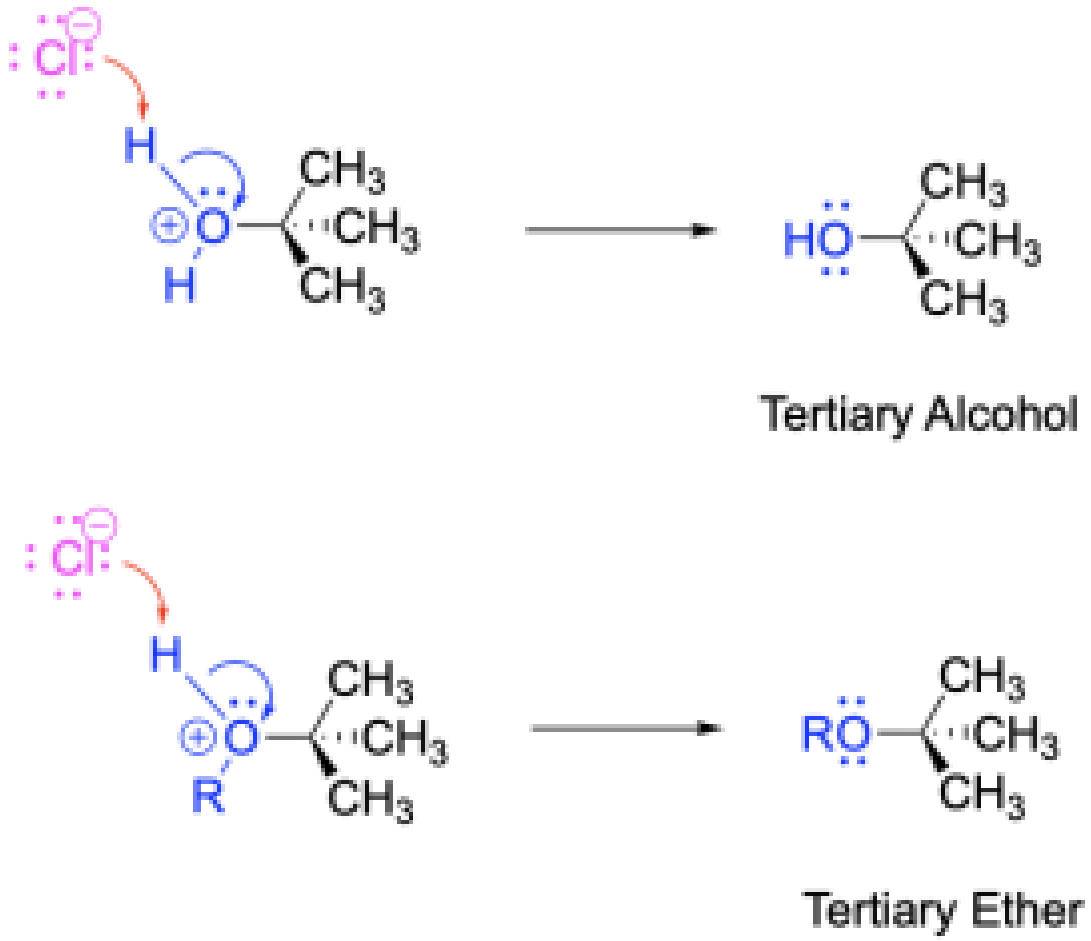

Figure 3.1.3.j. Third step of the S_N1 mechanism to generate alcohols and ethers. The chloride leaving group from step 1 will act as a base and deprotonate the oxonium intermediate, generating a tertiary alcohol and ether.

Step 3, top. Chloride (the halide leaving group from Step 1) acts as a base to deprotonate the oxonium intermediate resulting in HCl and a tertiary alcohol.

Step 3, bottom. Chloride (the halide leaving group from Step 1) acts as a base to deprotonate the oxonium intermediate, resulting in HCl and a tertiary ether.

The mechanism above in which the tertiary alkyl halide reacts with water or an alcohol, requires *three*steps. In comparison, the S_N1 reaction examined earlier, in which the tertiary alkyl halide reacts with a halide such

as iodide, requires two steps. This is because reaction with a neutral nucleophile (water or an alcohol) requires an extra deprotonation step (Step 3 in Figure 3.4.1.j.) to generate a final product; this step is not needed when using an anionic nucleophile (such as I^-).

This reaction yields the energy profile diagram shown below:

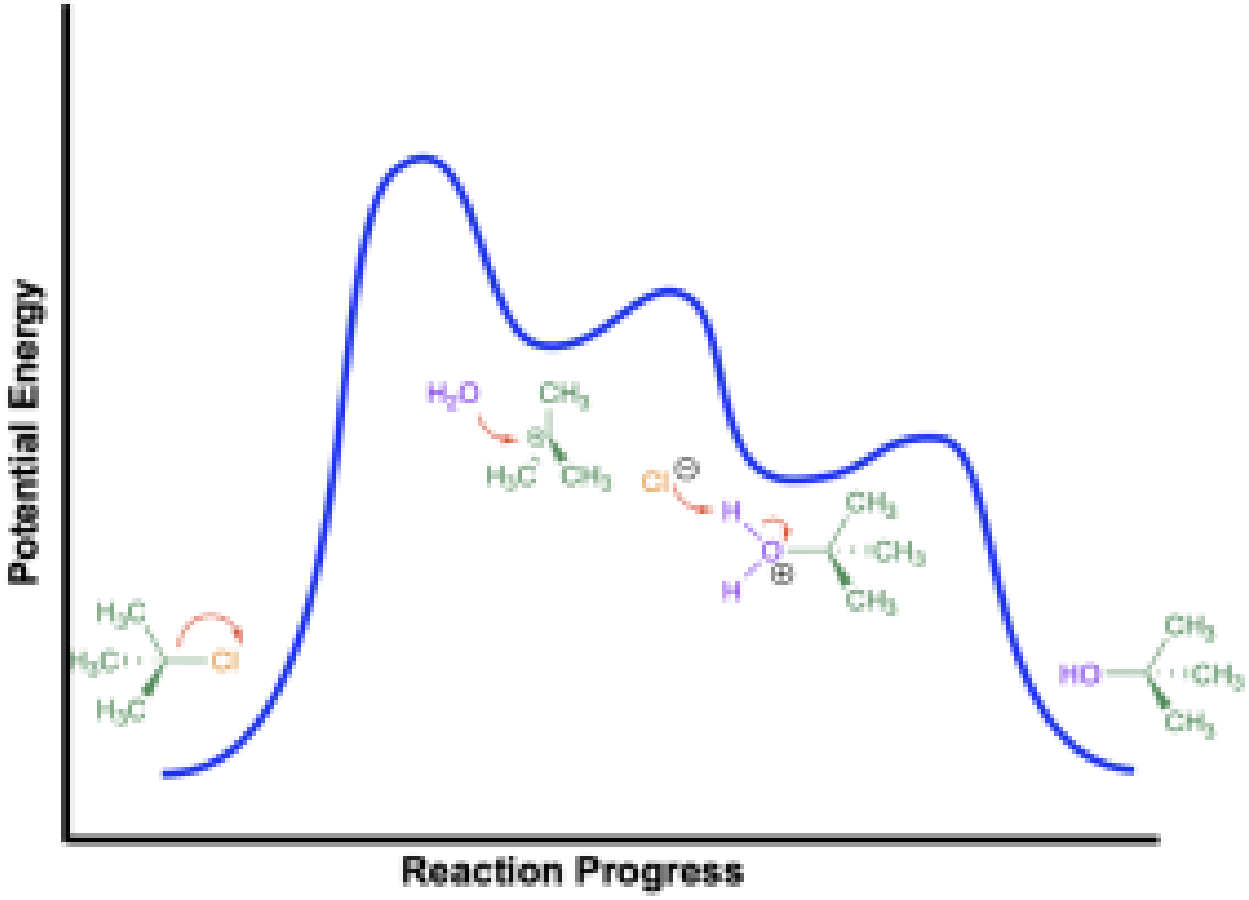

Figure 3.4.1.k. Energy profile diagram for the S_N1 reaction $(CH_3)_3C–Cl + H_2O \rightarrow (CH_3)_3C–OH + HCl$. This energy profile diagram also illustrates the formation of ethers, but instead of water acting as a nucleophile, an alcohol acts as the nucleophile.

The first step of the reaction (loss of the halide leaving group) is the slow step and requires the greatest amount of energy. This will generate a carbocation intermediate. Then, water or an alcohol attacks the carbocation to form the corresponding oxonium intermediate. The second step has a lower activation energy than the first step because forming a full octet at carbon is favourable and will lead to stabilization. The third step involves deprotonation of the oxonium intermediate, yielding the neutral alcohol or ether.

The following video includes a worked example from a previous CHEM 1AA3 test or exam that students struggled with. Try solving it on your own before looking at the solution.

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Key Takeaways

- S_N1 stands for substitution nucleophilic unimolecular reaction
- This reaction is two steps, with the first step being the loss of a leaving group forming a carbocation intermediate, and the second step being the attack from a nucleophile
- The first step forms an unstable cationic intermediate, so it is the slow, rate limiting step with a large activation energy
- Tertiary alkyl halides form the most stable carbocation intermediate, as more alkyl groups will make it so more of their electron density is donated to the carbocation. This is why they are the most favoured for S_N1 mechanisms, including making ethers and alcohols

Key terms in this chapter:

Key term	Definition
Oxonium	A cation intermediate that is typically formed when water performs a nucleophilic attack on an electrophilic substrate. The oxygen atom will have a formal charge of +1.

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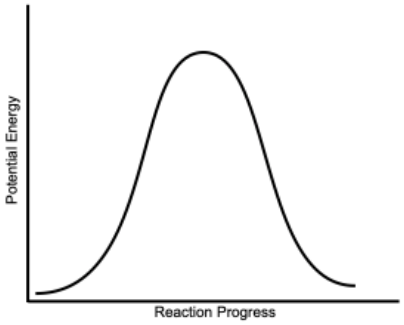
3.1.4 - SN1 VS SN2

Comparison Between S_N1 and S_N2 Reactions

This past chapter has taught us the basic concepts about S_N1 and S_N2 reactions. There are some similarities between the two reactions. For example, both S_N1 and S_N2 are substitution reactions where an electrophile is subject to nucleophilic attack. The electrophile contains a carbon centre with a positive or partial positive charge, such as a carbocation or an alkyl halide. Another similarity between S_N1 and S_N2 reactions is the nucleophile, which has a lone pair of electrons to donate to the electrophilic carbon atom. The nucleophile could be a halide, a hydroxide or alkoxide, water or an alcohol, among others. Another similarity between S_N1 and S_N2 is the leaving group, which must leave to allow for the nucleophile and electrophile to react. This will result in a functional group "switch" or substitution.

Despite those similarities, there are many differences between the two. Below is a table summarizing the key differences. Try making your own table or summary to help with your understanding.

	S_N1	S_N2
Rate Law	Rate = k[Alkyl Halide]	Rate = k[Nucleophile]x[Alkyl Halide]
Mechanism	Multiple steps; **dissociative**	One step; **concerted**
Presence of an Intermediate?	Yes (Carbocation)	No
Reaction Diagram		
Electrophilic Substrate	tertiary 3° > secondary 2° > primary 1° and methyl	primary 1° and methyl > secondary 2° > tertiary 3°
Reason for Preference	Electron density stabilization	Steric effect
Alternative Reactions	• Alcohol formation (water nucleophile) • Ether formation (alcohol nucleophile)	• Alcohol formation (hydroxide nucleophile) • Ether formation (alkoxide nucleophile) • Ester formation (carboxylate nucleophile)
Nucleophile	Typically involves *neutral* nucleophiles such as water	Typically involves *anionic* nucleophiles like hydroxide

Note: While an S_N1 reaction involving alkyl halides is a two-step process, the formation of alcohols and ethers requires an extra-step, since the nucleophiles used are neutral, and deprotonation is required. Therefore, depending on the nucleophile used, an S_N1 reaction can be a two or three-step process.

The best way to determine the order of reactivity based on electrophilic substrate is whether the carbon bonded to the halogen is **more substituted**, or **less substituted**. If a carbon atom is said to be more substituted, it is bonded to less hydrogen atoms, and more substituents, such as other carbon chains. S_N1 reactions favour

more substituted carbons due to electron density stabilization. If a carbon atom is said to be less substituted, it is bonded to more hydrogen atoms, and less substituents. S_N2 reactions favour less substituted carbons due to sterics.

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The Choice of Reaction Pathway: S_N1 or S_N2?

The reaction pathway predominantly depends on the nature of the substrate (primary, secondary, or tertiary), as shown in Figure 3.1.4.a.

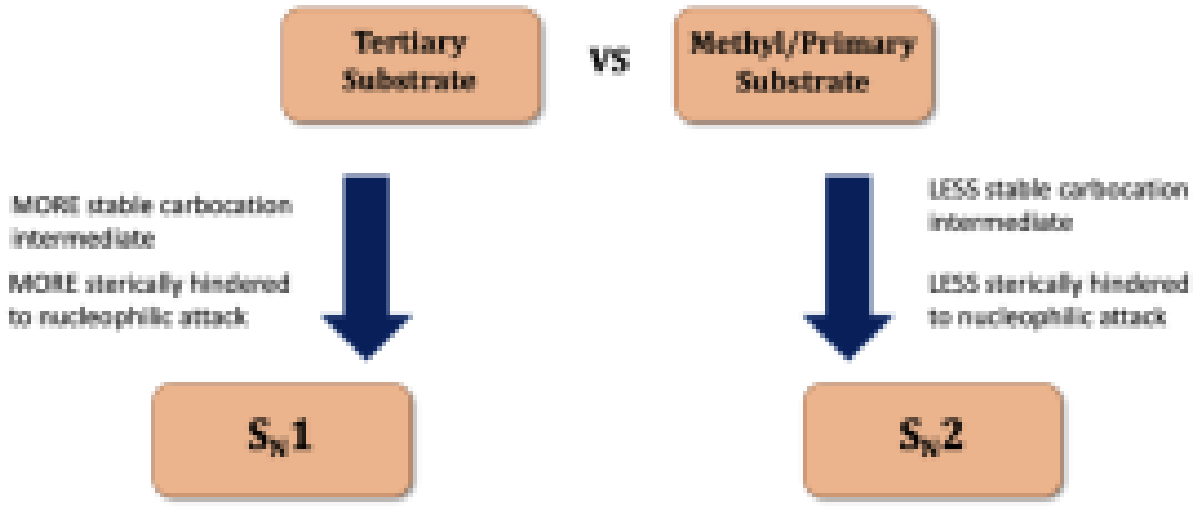

Figure 3.1.4.a. *S_N1 and S_N2 prevalence based on the nature of the substrate.*

- Primary and methyl substrates predominantly undergo S_N2 reactions.
- Tertiary substrates will undergo an S_N1 process.
- The reaction of secondary substrates mainly relies on the conditions applied (which will be further discussed in year 2 organic chemistry).

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(The full solution to this problem can be found in Chapter 5.2)

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Key terms in this chapter:

Key term	Definition
Dissociative	A mechanism where bonds are broken and formed in multiple steps. This is typically seen when a neutral nucleophile attacks a sterically hindered electrophile, with the first step being the loss of a leaving group followed by a nucleophilic attack (SN1 reaction).
Concerted	A mechanism in which bonds are broken and formed simultaneously, occurring all in one step. This is typically seen when an anionic nucleophile attacks an electrophile that is not sterically hindered (such as in SN2 reactions).
More substituted	Refers to a carbon atom that is bonded to less hydrogen atoms and more substituents, such as other carbon atoms. SN1 reactions favour more substituted carbons.
Less substituted	Refers to a carbon atom that is bonded to more hydrogen atoms and less substituents. SN2 reactions favour less substituted carbons.

Study Notes

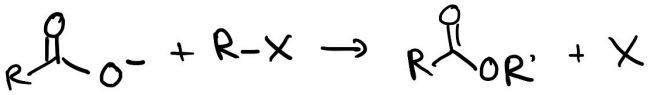
Reactions

Substitutions: Break a bond, form a bond

Sn2: 1 step, unless neutral nucleophiles are used, prefers 1° C concerted. (Rate depends on both concentrations)

e.g: $I^{\ominus} + (CH_3)_3C\text{-}Cl \rightarrow I\text{-}C(CH_3)_3 + Cl^-$

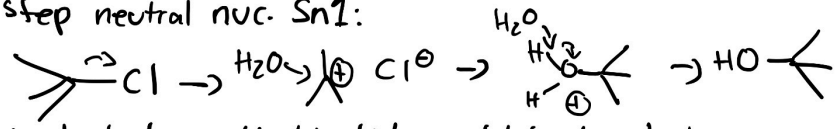
alcohol $R\text{-}X + NaOH$ or $H_2O \rightarrow R\text{-}OH + X$

esters 

Sn1: 2 step, unless neutral nucleophiles/elec. used, prefers 3° C, dissociative: carbocation intermediate (Rate depends on first step)

Stability: 3° C to 1° C (least)

3-step neutral nuc. Sn1:



neutral electro: alkyl halides, aldehydes, ketones

neutral nucleophiles: alcohols, alkenes, amines, H_2O, $NaBH_4$, R-MgX

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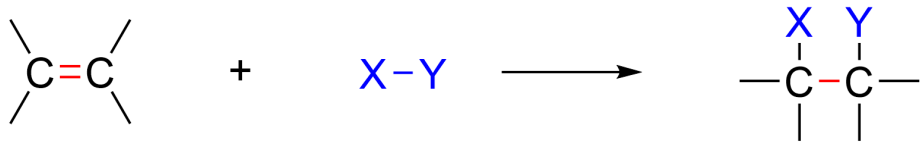
3.2 - ALKENE ADDITION REACTIONS

Learning Objectives: Chapters 3.2.1 – 3.2.4 (Alkene Addition Reactions)

1. Predict products and write reaction schemes for the following reactions (no curved arrow mechanisms or energy profile diagrams required):
    1. Hydrogenation of an alkene or alkyne
    2. Halogenation of an alkene
2. Predict products, write reaction schemes, draw curved arrow mechanisms, and draw energy profile diagrams, including all intermediates and transition states, for the following reactions:
    1. Hydrohalogenation of an alkene
    2. Acid-catalyzed hydration of an alkene
3. Understand the relationship between the curved arrow mechanism, energy profile diagram, and rate law for the addition reactions to alkenes.
4. Explain trends in carbocation stability (primary, secondary, tertiary) and why carbocation stability would favour certain products (i.e., the chemical basis for Markovnikov's rule).

Alkene Reactivity

Alkenes undergo a wide variety of reactions that share some common features due to the electron dense carbon-carbon double bond. This reactivity makes alkenes an important type of organic compound because they can be used to synthesize a wide variety of other compounds. The most common type of reaction for alkenes is the addition reaction to a C=C double bond. In **addition reactions**, a small molecule is added across a π bond. As a result, one π bond and one σ bond are broken, and two σ bonds are formed. This also means that the hybridization of the atoms in the molecule changes – for addition reactions of alkenes, the carbon atoms in the C=C double bond of reactants are sp^2 hybridized, and they become sp^3 hybridized in the products.



General equation for the addition reaction of alkenes across a π bond

Figure 3.2.a. General equation for addition reaction of alkene.

This chapter will focus on the various addition reactions that alkenes undergo, and the chapter is divided based on which molecule is added across the π bond.

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Key terms in this chapter:

Key term	Definition
Addition reactions	A small molecule (such as water) is added to a multiple bond (a double or a triple bond). This results in one π–bond and one σ–bond being broken and two new σ–bonds being formed.

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3.2.1 - HYDROHALOGENATION OF ALKENES

Hydrohalogenation of Alkenes

The addition reaction of a hydrogen halide molecule, such as HCl or HBr, to an alkene produces an alkyl halide as a product. This process is known as a **Hydrohalogenation reaction**.

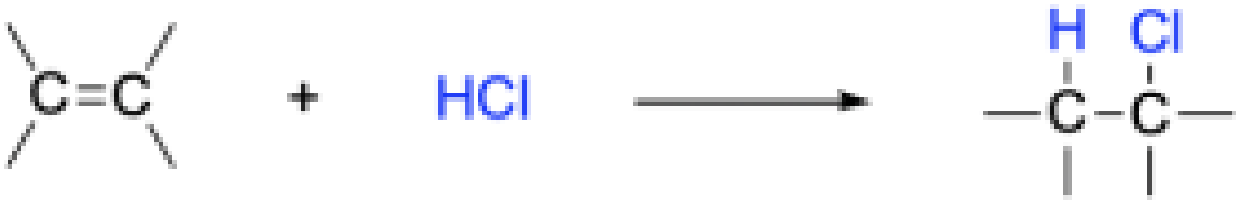

Figure 3.2.1.a. *Addition reaction of the hydrogen halide HCl to an alkene*

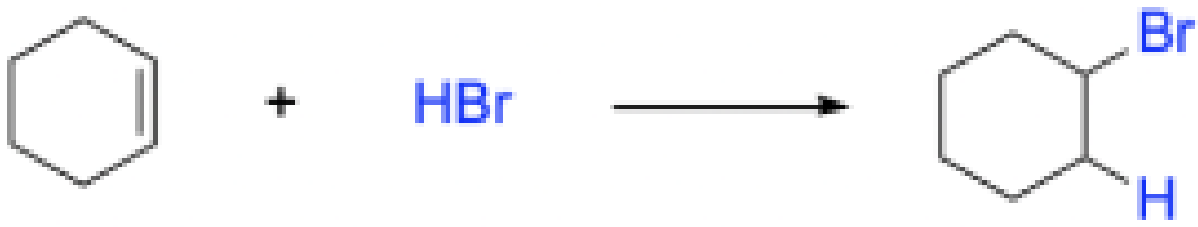

Figure 3.2.1.b. *Addition reaction of the hydrogen halide HBr to an alkene*

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The mechanism (Figure 3.2.1.c.) for hydrohalogenation is a two-step process. In the first step, the alkene is protonated by HBr, resulting in a carbocation intermediate and a halide anion (such as Br^-). In this protonation step, the π bond is broken to allow for formation of a sigma bond to the proton. This results in a carbon that loses π electron density and becomes cationic. In the second step, the halide ion formed in the first step acts as a nucleophile to attack the electrophilic carbocation intermediate. The result of the second step is that a new C–Br σ bond is formed.

Recall that in addition reactions, one π bond and one σ bond are broken, and two σ bonds are formed. In this mechanism, the first step involves breaking the H–Br σ-bond and the C=C π-bond and forming a new C–H σ-bond, while the second step involves forming a new C–Br σ bond. In addition, the hybridization at carbon changes: the C=C double bond of reactants have sp^2 hybridized carbon atoms, which become sp^3 hybridized in the products.

This reaction mechanism has some similarities with the S_N1 mechanism discussed in Chapter 3.1.3. For example, hydrohalogenation and unimolecular nucleophilic substitution (S_N1) are similar in that both mechanisms occur in two steps and involve a carbocation intermediate. In addition, the second step of both mechanisms is identical: the electrophilic carbocation is attacked by the nucleophilic halide to form a new C–X bond. S_N1 reactions and hydrohalogenation differ in the first step of the reaction: an S_N1 mechanism involves loss of a leaving group, whereas an alkene has no leaving group and instead is protonated in the first step.

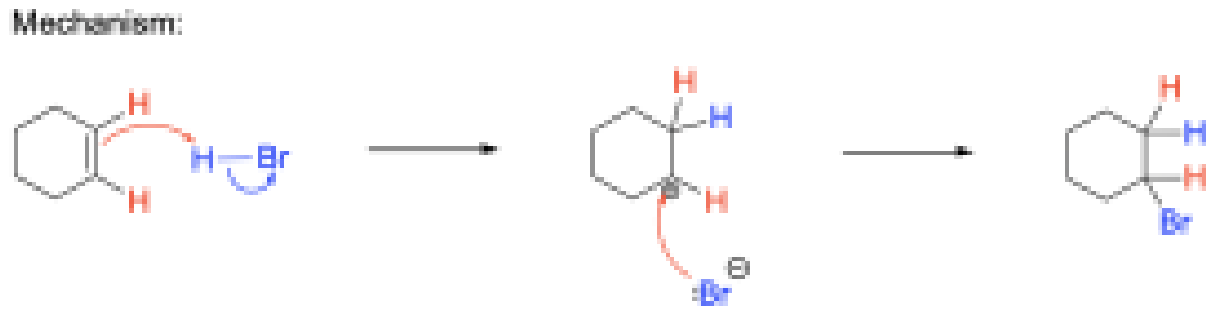

Figure 3.2.1.c. *Mechanism of hydrohalogenation addition reaction to a symmetric alkene. The nucleophilic π electrons in the alkene attack the electrophilic proton, breaking the H–Br bond and forming a new C–H bond, resulting in a carbocation intermediate. After the breaking of the π bond, one of the carbon atoms has only 3 bonds and becomes cationic. The anionic, nucleophilic bromide can then attack the carbocation and form a new C–Br bond.*

In the above examples, the alkenes are symmetrical in structure, with each alkene carbon existing in identical bonding environments. As a result. it is observed that there is no preference between which atom the halide or hydrogen atom are added to This is because the reaction pathway will proceed via an identical carbocation intermediate, so there is no preference on which side the C–H vs. C–X bond is formed, and the final product will be the same.

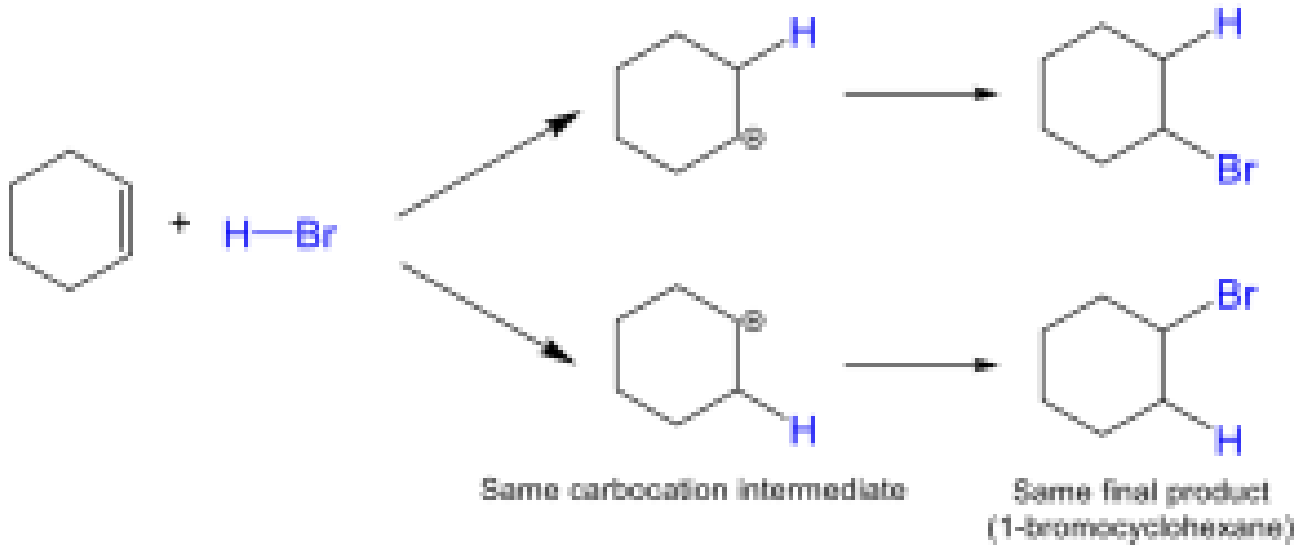

Figure 3.2.1.d. *Hydrohalogenation of symmetrical alkenes yields the same carbocation intermediate and the same product.*

For an asymmetrical alkene, where the double bonded carbons atoms have different substituents, the placement of the H and X atoms across the π bond is critical. For example, in the following reaction (Figure 3.2.1.e.), two possible products could be produced: 1-bromo-1-methylcyclohexane and 1-bromo-2-methylcyclohexane. Experimental observations demonstrate that 1-bromo-1-methylcyclohexane is the main product for the reaction. To explain and understand the outcome of the reaction, we need to consider the mechanism of the reaction and the stability of the intermediates formed.

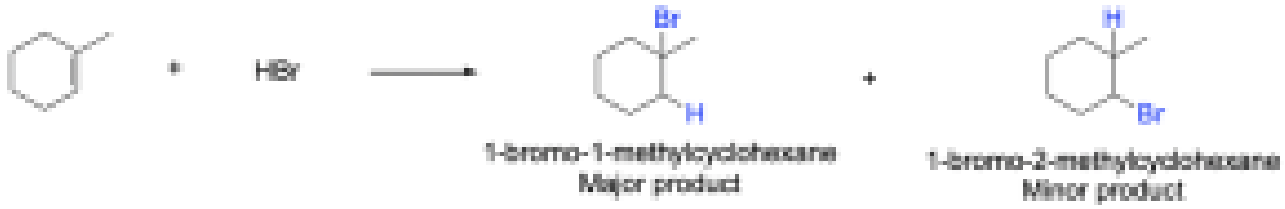

Figure 3.2.1.e. *Hydrohalogenation of 1-methylcyclohexene yields two possible products. The major product is 1-bromo-1-methylcyclohexane; the minor product is 1-bromo-2-methylcyclohexane.*

Are You Wondering? The Difference Between a Major and a Minor Product

In reactions where multiple products can form, the product that is formed in over 50% of the theoretical yield is referred to as the **major product**. This distribution in products is due to the energy required to form it. The major product requires less energy to form, so more will form per unit time.

In reactions where multiple products can form, the product that is formed in less than 50% of the theoretical yield is referred to as the **minor product**. This distribution in products is due to the energy required to form it. The minor product requires more energy to form, so less will form per unit time.

When the nucleophilic π bond attacks the electrophilic proton from H–X, a carbocation intermediate is formed. Recall carbocation stability (see Chapter 3.1.3): higher substituted carbocations are the most stable due to greater neighbouring electron density stabilization, while lowly substituted carbocations are less stable due to a lack of neighbouring electron density available to provide charge dissipation.

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The energy profile diagram for the hydrohalogenation of symmetric alkenes is shown below:

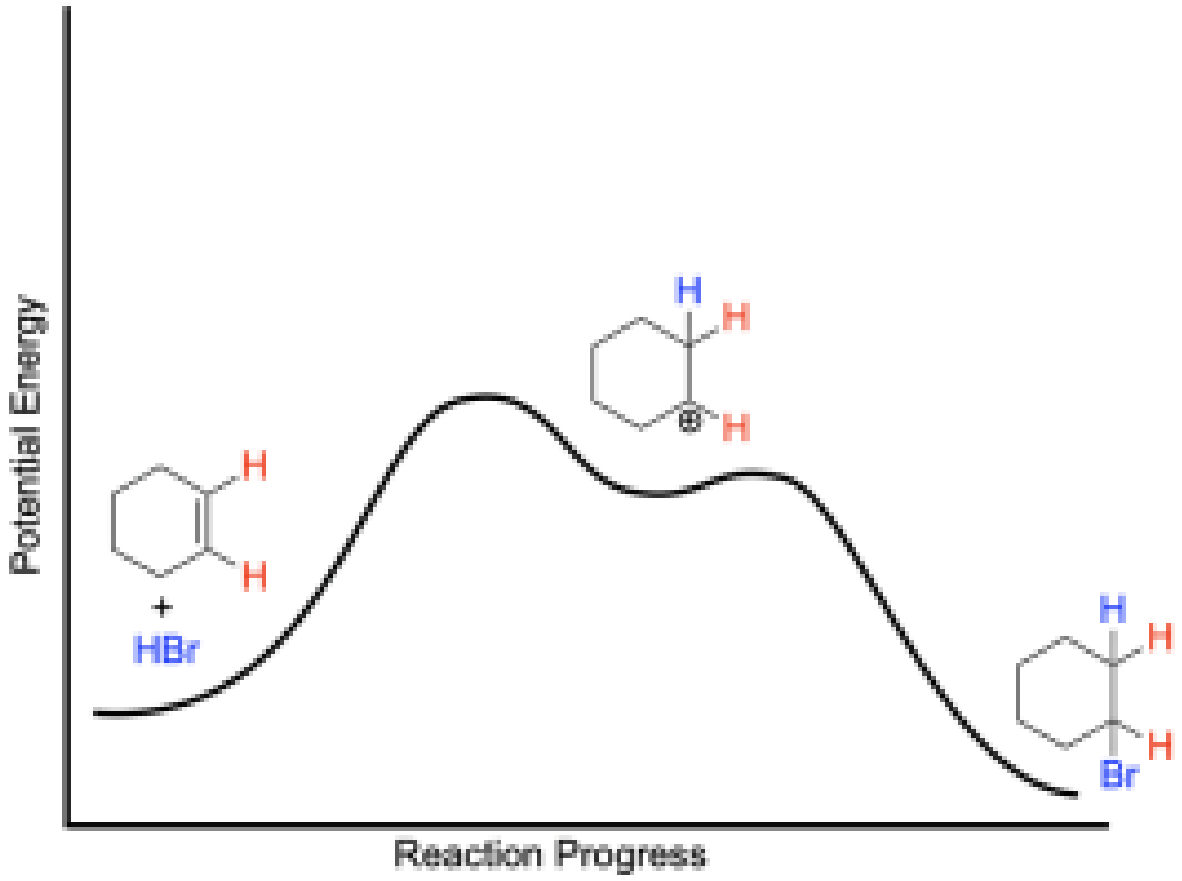

Figure 3.2.1.f. *Energy profile diagram for the hydrohalogenation reaction of the symmetric alkene, cyclohexene. The 2 maxima represent the two steps of the reaction. The first step (protonation of the alkene) is the slow step, hence the greater activation energy. The second step (nucleophilic attack of the carbocation by bromide) requires less energy and is therefore faster.*

The first step of the reaction, protonation of the alkene, yields the carbocation intermediate. Since the carbocation intermediate is unstable and high in potential energy, there is a large activation barrier associated with this step resulting in it being the rate limiting step. The second step, nucleophilic attack of the carbocation by bromide, results in the final alkyl halide product.

Since the first step of the addition mechanism is rate limiting, we will focus on it to justify the differences in product formation. Just as carbocation stability is important when discussing the unimolecular nucleophilic substitution (S_N1) mechanism, so too does it play a role in the hydrohalogenation mechanism (Figure 3.2.1.g). The first step of the hydrohalogenation mechanism adds a new C–H bond to one carbon atom and a formal positive charge to the other carbon atom (the carbocation). When looking at the possible carbocation intermediates formed, if the C–H bond was created on the more substituted carbon (tertiary position), then a secondary carbocation would form on the other carbon atom, leading to the 1–bromo–2–methylcyclohexane product (Figure 3.2.1.g, bottom). On the other hand, if the C–H bond was created on the less substituted

carbon (secondary position), then a tertiary carbocation is formed on the other carbon atom, leading to the 1–bromo–1–methylcyclohexane product (Figure 3.2.1.g, top). Since a tertiary carbocation intermediate is more stable than a secondary carbocation intermediate, the tertiary carbocation intermediate will have a smaller activation energy barrier associated to its formation, and will form faster. As a result, more tertiary carbocation intermediate produced per unit time result in more alkyl halide product produced per unit time, leading to a higher abundance of 1-bromocyclohexane (major product).

Therefore, when performing hydrohalogenation reactions to alkenes, the electrophilic hydrogen atom is added to the **least** substituted carbon because it results a more substituted and more stable carbocation The halide will then attack the more substituted position in the second step of the reaction. This reaction is said to be regioselective – there is a preference to which carbon atoms the hydrogen and halide form sigma bonds too. In this case, we call this Markovnikov regioselectivity , named after Vladimir Markovnikov who studied alkene addition reactions extensively in the mid 1800s. As a result, we apply something known as Markovnikov's rule to hydrohalogenation reactions, which states that the carbon that is already bonded to more hydrogen atoms (less highly substituted position) gets the hydrogen. This rule is also cleverly coined as the "rich get richer" rule, where a carbon atom with more hydrogen atoms bonded to it is considered "rich".

Are You Wondering? The Meaning of the Term *Regioselectivity*

Regioselectivity is when a reaction mechanism favours bond formation at a particular atom over other possible atoms. For alkene additions, we observe two types of regioselectivity – Markovnikov and Anti-Markovnikov. A Markovnikov regioselective product results from a mechanism that would result from the more stable of two possible carbocation intermediates. An Anti-Markovnikov regioselective product results from a mechanism that would result from the less stable of two possible carbocation intermediates.

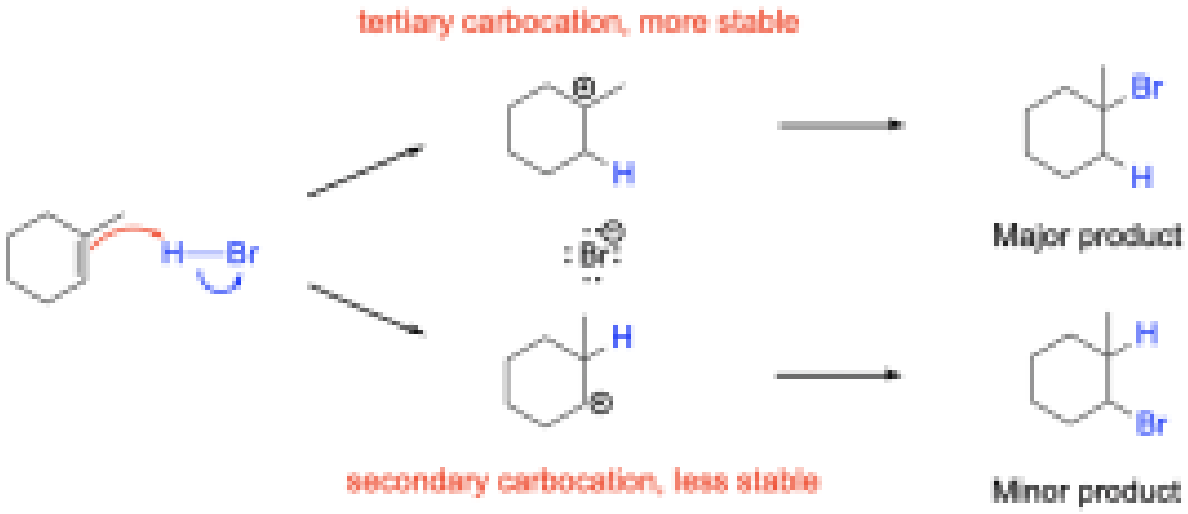

Figure 3.2.1.g. *Hydrobromination of 1–methylcyclohexene. The π electrons in the alkene attack the electrophilic hydrogen, breaking the H-Br bond. This causes a new C–H bond to be formed. On the top pathway, the new C–H bond is formed on the less substituted carbon, generating a tertiary carbocation on the more substituted carbon. On the bottom pathway, the new C–H bond is formed on the more substituted carbon, generating a secondary carbocation on the less substituted carbon. In the second step, the nucleophilic bromide anion attacks the carbocation. This yields two products: a major (Markovnikov) product (top pathway) and a minor product (bottom pathway).*

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Another way of naming the major and minor product of a reaction when there is Markovnikov regioselectivity is the Markovnikov and Anti-Markovnikov products.

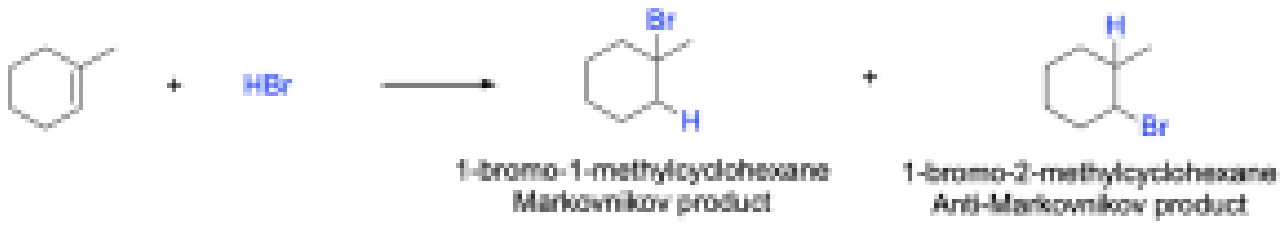

Figure 3.2.1.h. *Hydrobromination of 1–methylcyclohexene yields two products: 1–bromo–1–methylcyclohexene, the Markovnikov product, and 1–bromo–2-methylcyclohexene, the Anti-Markovnikov product.*

The Markovnikov product is formed through a lower energy pathway, where a more stable tertiary carbocation intermediate is formed, and the hydrogen atom is added to the carbon bonded to more hydrogens. The Anti-Markovnikov product is formed through a higher energy pathway, where a less stable secondary carbocation intermediate is formed, and the hydrogen atom is added to the carbon bonded to less hydrogens.

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The energy profile diagram for the hydrohalogenation of alkenes is shown below (Figure 3.1.2.i).

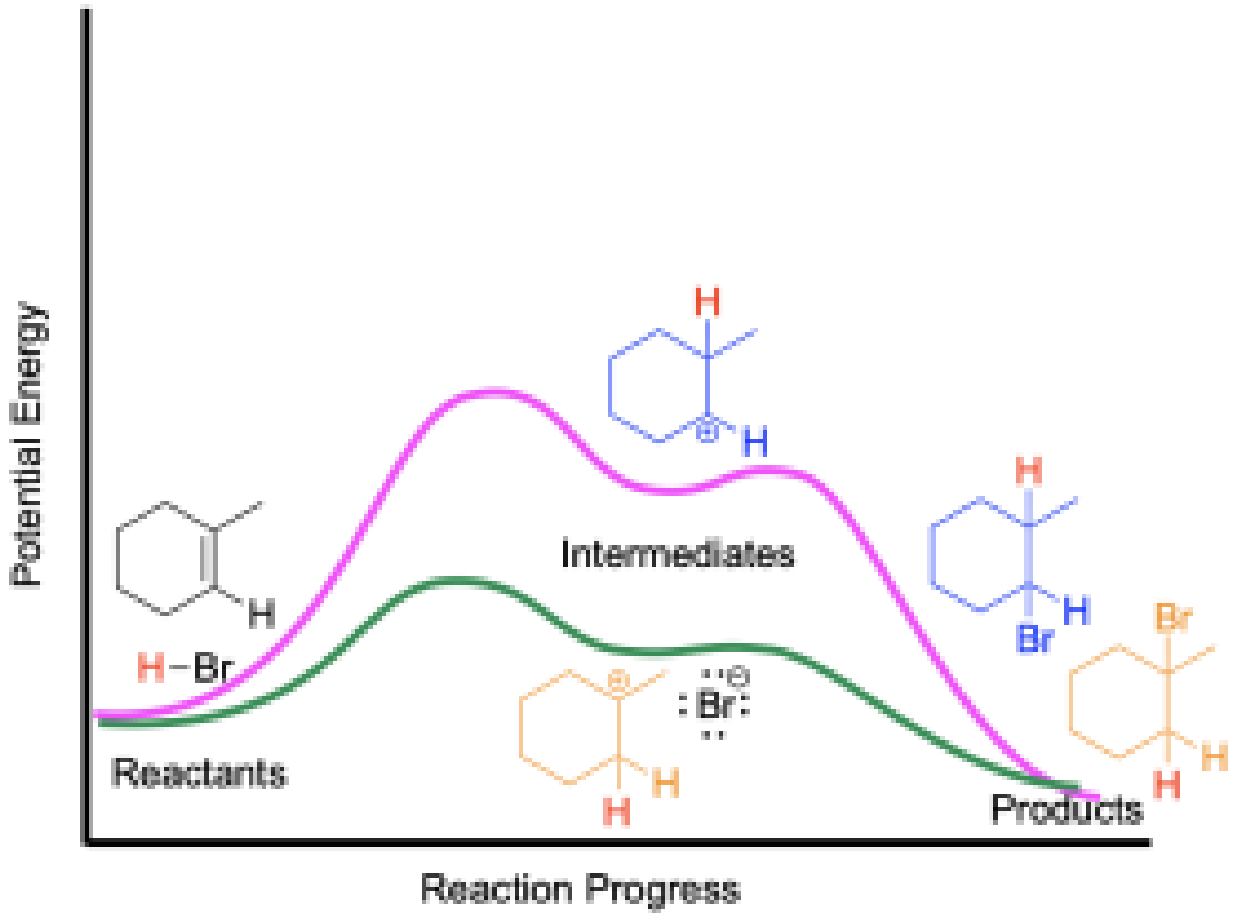

Figure 3.2.1.i. *Energy profile diagram for the electrophilic addition of HBr to 1–methylcyclohexene. The 2 maxima represent the two steps of the reaction. The first step (protonation of the alkene) is the slow step, hence the greater activation energy. The second step (nucleophilic attack of the carbocation by bromide) requires less energy and is therefore faster. The blue pathway is higher in energy because the secondary carbocation intermediate is less stable; the green pathway is lower in energy because the tertiary carbocation intermediate is more stable.*

The two maxima represent the two steps of the reaction, where the first step (protonation of the alkene) is the rate-limiting step. Carbocation stability dictates which product is formed: the more highly substituted the carbocation, the more stable it will be, and the reaction pathway that involves the more stable carbocation will require less energy to overcome the activation energy barrier and proceed faster.

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Key Takeaways

- Hydrohalogenation is a reaction using an alkene and a hydrogen halide (HX) as reactants, where the hydrogen and halogen are added to each alkene carbon
- The mechanism involves two steps, the first being rate limiting:
    - **Step 1:** The π electrons of the double bond nucleophilically attack the proton and form a σ bond to it, creating a carbocation and a halide as intermediates
    - **Step 2:** The halide nucleophilically attacks the carbocation, creating the product: an alkyl halide
- If the alkene is asymmetrical, then there's two possible products: major and minor
- Because of the carbocation stability, the more substituted carbocation intermediate will be the intermediate that leads to the major product
- The major product is also called the Markovnikov product, while the anti–Markovnikov product is also the minor product

Key terms in this chapter:

Key term	Definition
Hydrohalogenation reaction	The addition reaction of a hydrogen halide to an alkene. This produces an alkyl halide as a product.

Any feedback or comments on this chapter? You may either email chemoer@mcmaster.ca, access this MS Form, or provide a comment in the feedback box below.

3.2.2 - HYDRATION OF ALKENES

Addition of Water to Alkenes (Acid-Catalyzed Hydration of Alkenes)

In the presence of dilute, aqueous acid, water can be added across the double bond of an alkene, producing an alcohol. This is the acid-catalyzed addition reaction of water to an alkene (also called acid-catalyzed hydration). The most common acid catalyst is a dilute aqueous solution of sulfuric acid, H_2SO_4. This reaction does not occur without an acid catalyst, because water is a weak acid and is incapable of protonating the double bond to push the reaction mechanism forward.

Recall that in addition reactions, one π bond and one σ bond are broken, and two σ bonds are formed. In hydration of an alkene, the C=C π bond and an O–H bond are broken, while a new C–H σ-bond and a new C–O σ bond are formed. In addition, the hybridization at carbon changes: the C=C double bond of reactants have sp^2 hybridized carbon atoms, which become sp^3 hybridized in the products.

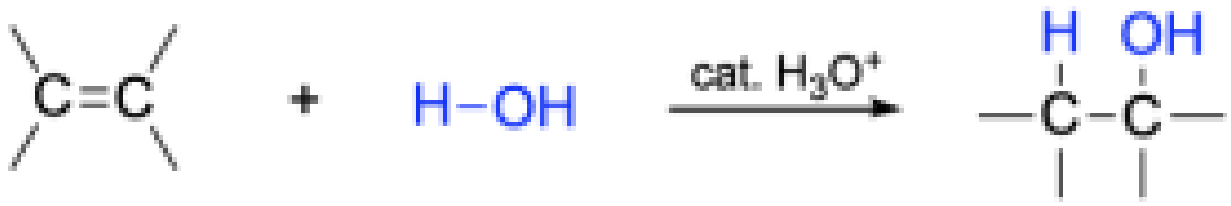

Figure 3.2.2.a. *Addition reaction of water to an alkene using dilute acid as a catalyst.*

Are You Wondering? The Role of Dilute Sulfuric Acid

Sulfuric acid is a strong acid, so it's conjugate base (HSO_4^-) is very weak and won't act as a nucleophile and add to the carbocation. This will eliminate any competition between water and the acid-workup, allowing for only one product to be obtained (the addition of water). If a strong acid

like HCl was used, we would see a mixture of hydration and addition products, since HCl also participates in hydrohalogenation reactions.

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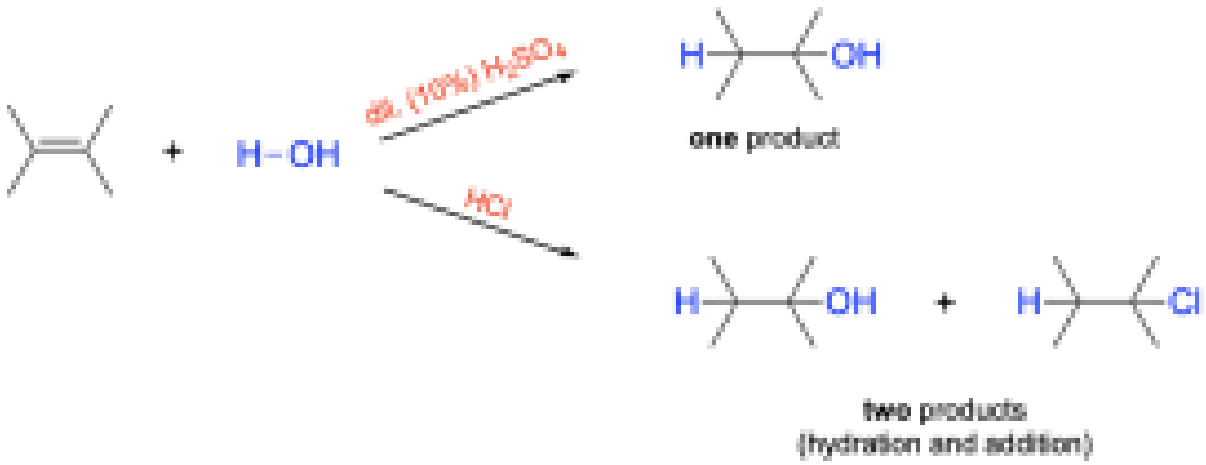

Figure 3.2.2.b. *Hydration reactions using dilute acid (H2SO4) vs. HCl. Using dilute acid will only produce one hydration product, while using a strong acid like HCl will yield both the hydration, and hydrohalogenation addition products.*

<<insert X here>>

The mechanism for the acid-catalyzed hydration of alkenes is very similar to the mechanism for the addition of a hydrogen halide, HX, to alkenes, and goes through a similar carbocation intermediate. As a result, the reaction therefore also follows Markovnikov's rule. The hydration mechanism of 1–methylcyclohexene is shown below (Figure 3.2.2.c).

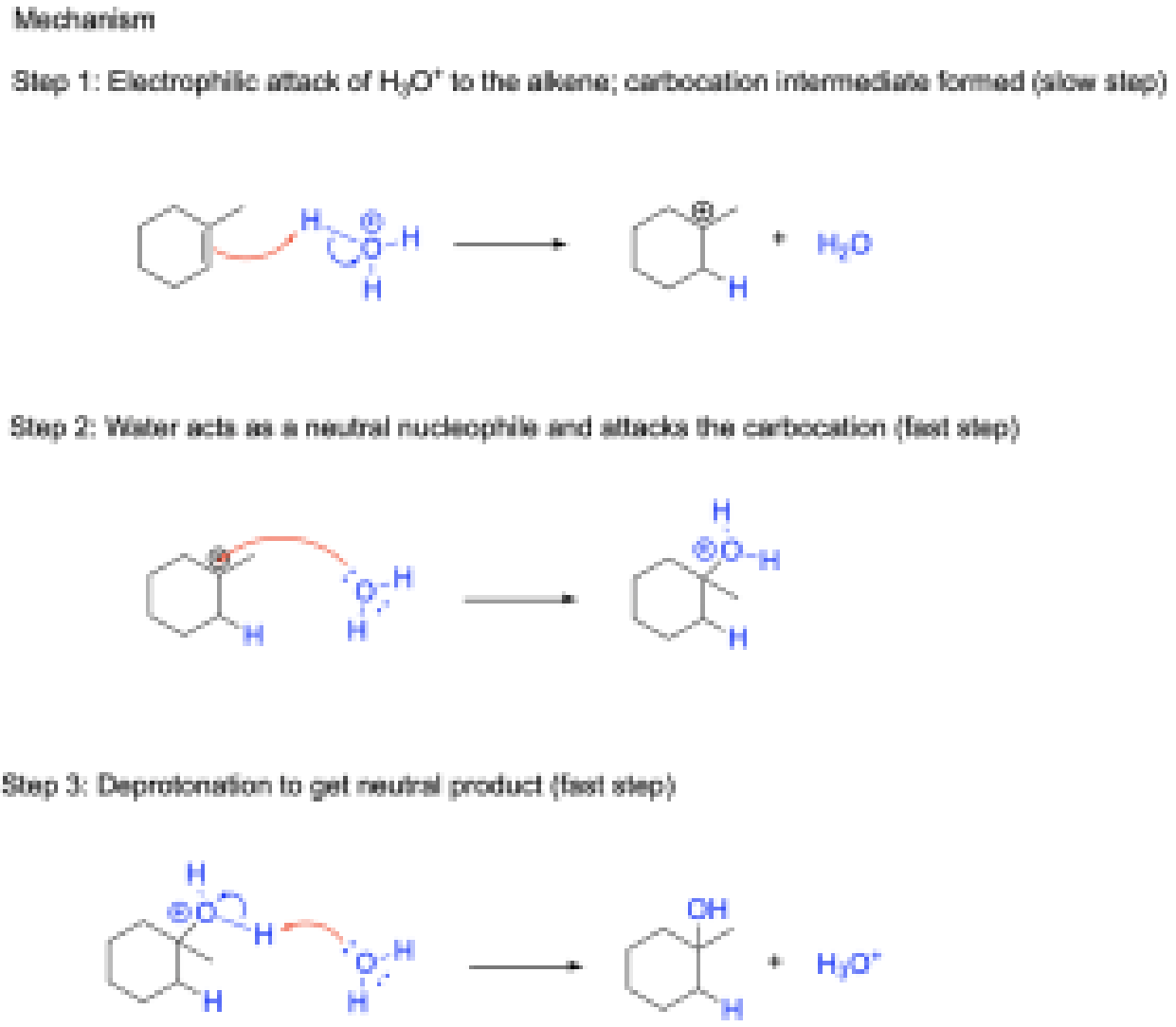

Figure 3.2.2.c. *Mechanism for acid-catalyzed hydration of an alkene.*

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For an unsymmetric alkene as shown in Figure 3.2.2.c, the π bond gets protonated by hydronium, resulting in the formation of a C–H bond at the least substituted position (i.e. the position that has more hydrogens initially). This will create a more stable, more highly substituted carbocation at the other carbon atom from the alkene. Subsequently, water acts as a nucleophile in the second step and attacks the electrophilic carbocation

intermediate, which generates an oxonium cation intermediate. Finally, water deprotonates the oxonium cation in the final step to form a neutral alcohol and regenerate the acidic hydronium ion catalyst ($H3O^+$). Since hydronium is consumed in the first step and regenerated in the final step, it can be classified as a catalyst in the reaction mechanism. Overall, this is a three-step mechanism, with the first two steps being the addition mechanism, and the third step being a deprotonation step to yield the neutral alcohol. When compared to acid halide addition, the third step is required in this case because we are using a neutral nucleophile in step 2 (H_2O) which yields a positively charged oxonium intermediate that requires deprotonation. The use of an anionic nucleophile (like a halide in acid halide addition) will result in a neutral product.

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If the alkene is symmetrical (Figure 3.2.2.d), then the hydrogen could add to either carbon atom, as both would produce the same carbocation intermediate and the same final product. This is similar to hydrohalogenation of symmetrical alkenes (see Chapter 3.2.1).

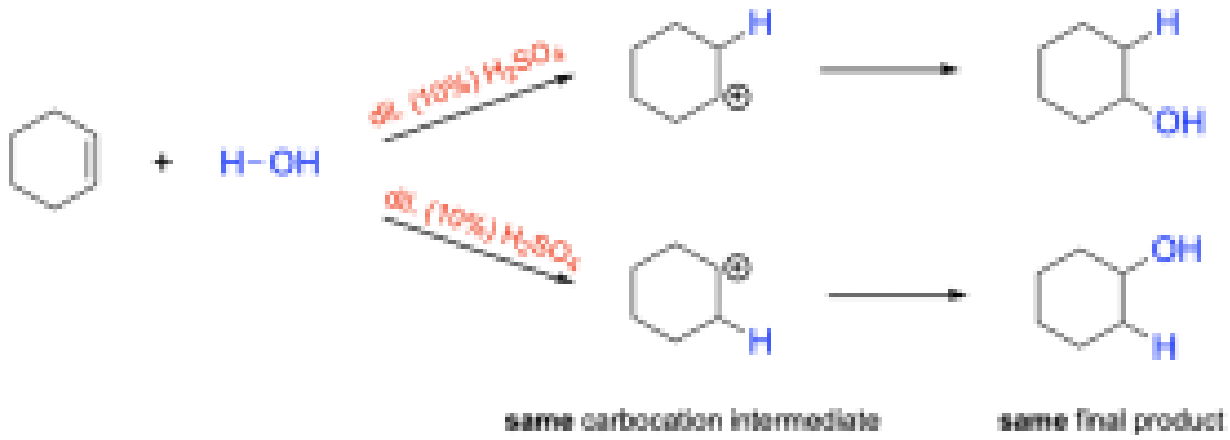

Figure 3.2.2.d. *Symmetric alkenes yield the same product. This is because the same carbocation intermediate is produced, so the stability of the carbocation is the same.*

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(The full solution to this problem can be found in Chapter 5.2)

The energy profile diagram for the hydration of an alkene is shown in Figure 3.2.2.e. The first step of the reaction (nucleophilic attack from the π electrons) is the rate limiting step and requires the greatest amount of energy, corresponding to the absolute maximum on the curve. This will generate a carbocation intermediate that water will nucleophilically attack to form the corresponding oxonium cation intermediate. The second step has a lower activation energy than the first step because forming a full octet at carbon is favourable and will lead to stabilization. The third step involves deprotonation of the oxonium cation intermediate which will yield the neutral alcohol.

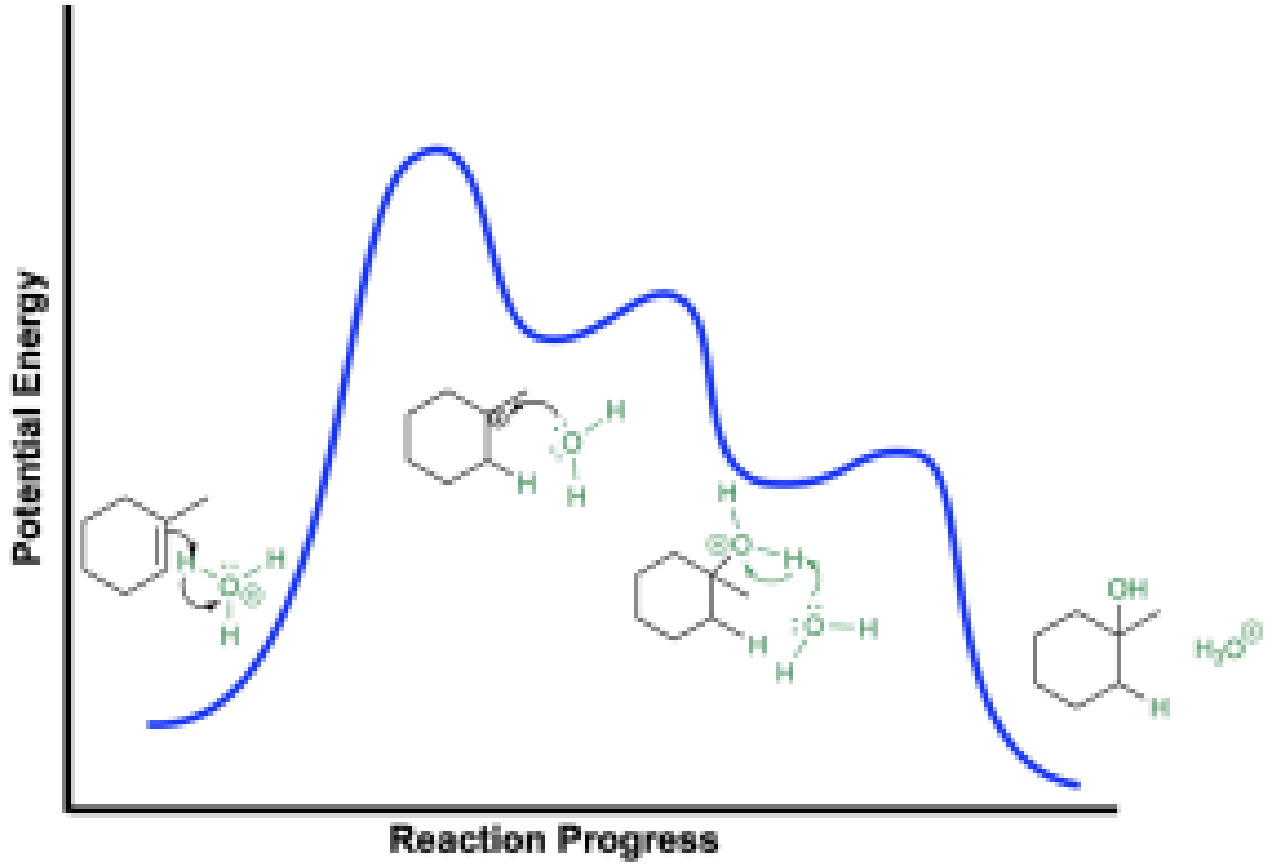

Figure 3.2.2.e. Energy profile diagram for the hydration reaction $C_7H_{12} + H_2O \rightarrow C_7H_{13}OH + H_3O^+$ using a dilute acid catalyst.

Note the similarities between hydration of an alkene (Figure 3.2.2.e) and the S_N1 mechanism that uses a neutral nucleophile (such as water), discussed in Chapter 3.1.3, and shown again here (Figure 3.2.2.f). For example, both mechanisms occur in three steps, with a slow first step, and a carbocation and oxonium cation intermediate. The last two steps of both mechanisms are identical: the electrophilic carbocation is attacked by the neutral water nucleophile, generating an oxonium cation intermediate, that will be deprotonated in the final step to form a new C–OH bond. However, the two mechanisms differ in the first step of the reaction: an S_N1 mechanism involves loss of a leaving group, whereas an alkene has no leaving group and is instead protonated in the first step.

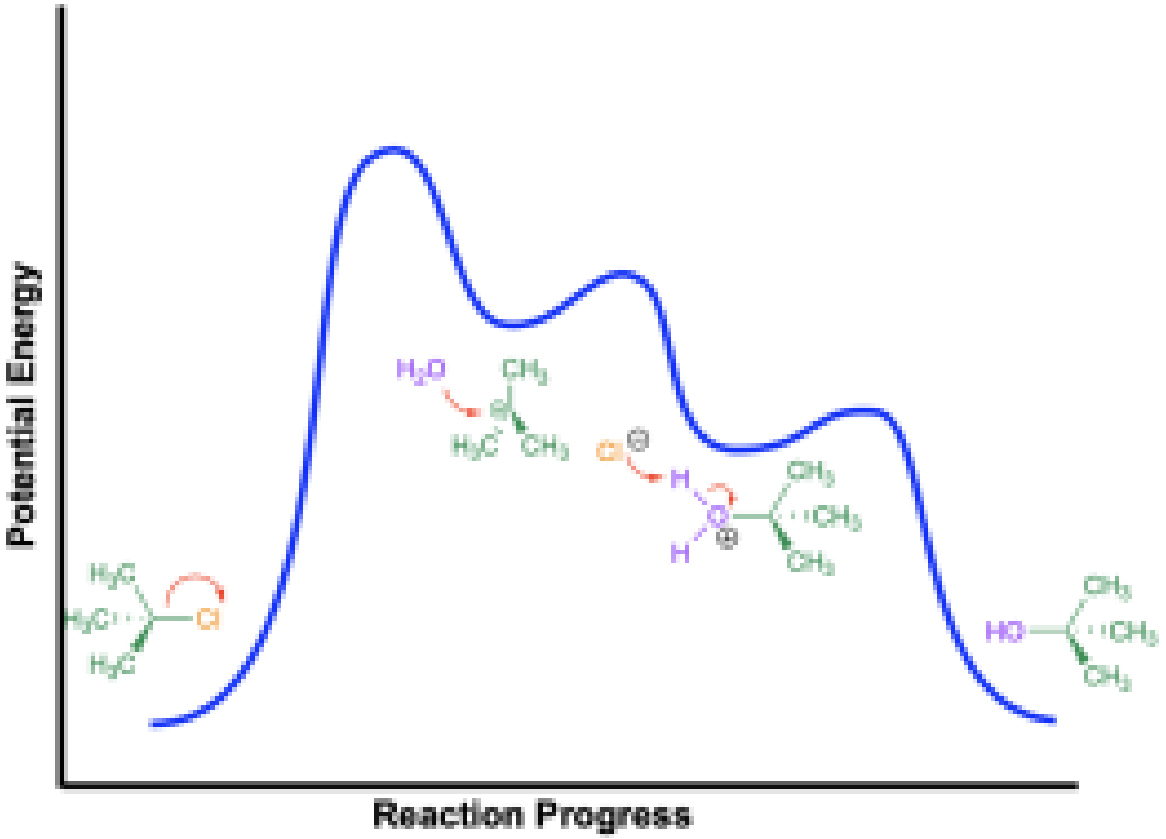

Figure 3.2.2.f. *S_N1 mechanism using a neutral nucleophile (water), discussed in Chapter 3.1.3.*

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Key Takeaways

- Acid–catalyzed hydrogenation of alkenes is a three-step reaction, using an alkene and water as reactants, and a catalytic acid catalyst, usually H_2SO_4. This creates an alcohol as a product
- The three steps are as follows, where the first step is rate limiting:
    - **Step 1**: The alkene's π electrons nucleophilically attack the hydrogen of a hydronium, H_3O^+, resulting in a carbocation intermediate and water
    - **Step 2**: The carbocation is nucleophilically attacked by water, resulting in an oxonium intermediate
    - **Step 3**: Another water molecule deprotonates the oxonium proton, giving an alcohol and and regenerating the hydronium catalyst as products.
- For acid-catalyzed hydrogenation, it resembles hydrohalogenation such that there is a major and minor product depending on the stability of the carbocation intermediate

Diversity in Chemistry: Tehshik Yoon

Catalysts can come in many forms to enable organic reactions. These can include dilute acid, which was discussed in this chapter, or metal solids, but one of the most interesting catalysts being explored nowadays is light. **TehshikYoon** is a professor at the University of Wisconsin-Madison and is currently researching how light can be harvested in order to drive chemical reactions to reduce waste and improve efficiency. In particular, he is interested in how metal complexes can be used to absorb visible light to selectively produce desired configurations of a molecule. Yoon is also a vocal advocate for diversity, equality, and inclusion in the STEM field. As a Korean American and an openly gay man, Yoon has commented on the difficulties he had faced when first entering the STEM field and focuses on mentoring and advising efforts to spread awareness and help students himself to improve queer representation in science. More information on Yoon and his journey can be found in his interview with the C&CE journal.

3.2.3 - HYDROGENATION OF ALKENES

Hydrogenation (Reduction) of Alkenes

When alkenes react with hydrogen gas in the presence of a variety of metal catalysts, a hydrogen molecule will be added to the double bond in a way that each carbon atom bonds with one hydrogen atom. Such an addition reaction is called **hydrogenation** (Figure 3.2.3.a).

Recall that in addition reactions, one π bond and one σ bond are broken, and two σ bonds are formed. In hydrogenation of an alkene, the C=C π bond and the H–H bond are broken, while two new C–H σ-bonds are formed. In addition, the hybridization at carbon changes: the C=C double bond of reactants have sp^2 hybridized carbon atoms, which become sp^3 hybridized in the products.

Catalysts are required for hydrogenation of alkenes, so the reaction can also be called catalytic hydrogenation. Commonly applied metal catalysts include "noble transition metals" like nickel, palladium, and platinum (group 10 metals).

Are You Wondering? The Meaning of Pd/C

You may see various catalysts written above the arrow in hydrogenation of alkenes. Pd/C is a common catalyst used in hydrogenation, where palladium metal (Pd) is embedded in charcoal (source of carbon atoms). Since the catalyst is heterogenous, its catalytic activity depends on his surface area. Charcoal is a highly porous solid, giving it a high surface area : volume ratio and making it an ideal candidate for heterogenous catalysis. It is also very inexpensive compared to the group 10 metals used in catalytic hydrogenation. The charcoal is embedded with small amounts of Pd (or Pt or Ni) to allow for heterogenous catalytic hydrogenation to occur.

Figure 3.2.3.a. Addition reaction of an alkene using hydrogen gas (H_2) and a group 10 metal catalyst (palladium, nickel, or platinum).

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Hydrogenation of an alkene has a high activation energy and will not take place at room temperature without a catalyst present. The catalyst lowers the activation energy by weakening the H-H bond, which makes the reaction feasible at room temperature. The explicit details of the mechanism of catalytic hydrogenation are not completely understood. What is known is that the reaction occurs on the surface of the metal catalyst, and involves both the adsorption of hydrogen gas and the alkene to the metal surface. The metal catalyst also facilitates the breaking of the H_2 σ bond and delivery of the hydrogen atoms across the π bond of the alkene. Since this reaction happens on the metal surface, it is observed that both hydrogen atoms are added to the same planar face of the alkene, which we describe as ***syn*** **addition** (Figure 3.2.3.c).

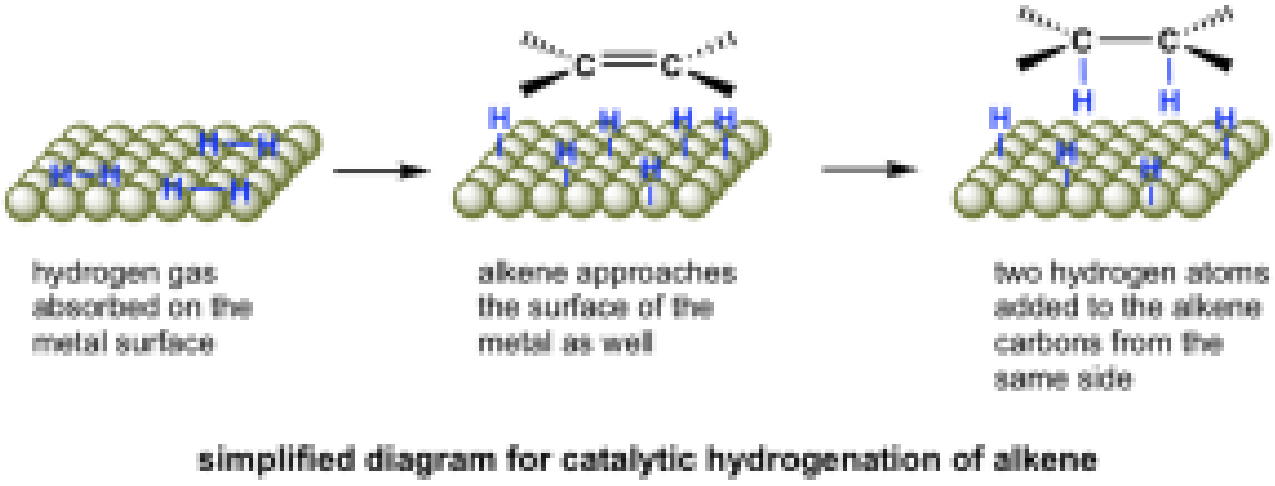

Figure 3.2.3.b. The mechanism for hydrogenation of an alkene is thought to involve several steps, including adsorption of hydrogen gas on the metal surface, H-H bond breaking, approach of the alkene to the surface, and then addition of two hydrogen atoms to the alkene carbons from the same side of the molecule, called "*syn* addition."

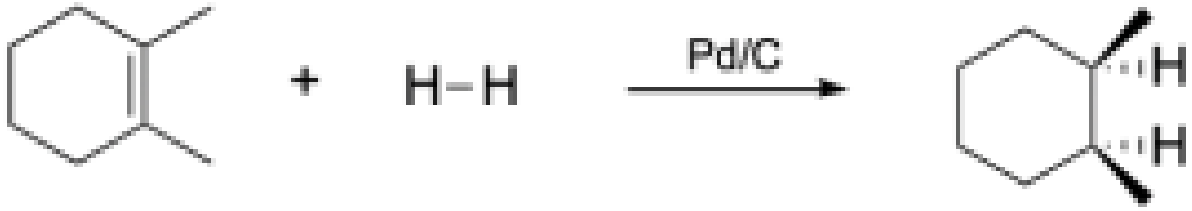

Figure 3.2.3.c. Halogenation reactions cause the hydrogens to be added *syn* (on the same face of the molecule), producing a *cis*-alkene.

Hydrogenation can also be performed on alkynes. An alkyne contains one σ-bond and two π-bonds. Either one or both π-bonds can undergo hydrogenation via a similar mechanism, to produce an alkene or an alkane, respectively. When adding an excess of hydrogen gas in the presence of a catalyst, the alkyne is **fully** reduced to an alkane (sp to sp^3 hybridization): two π-bonds are broken and four σ bonds (C–H) bonds are formed, with each π bond having hydrogen added across it in a sequential manner (Figure 3.2.3.d, top).

To halt the sequence after just a single addition of hydrogen and obtain an alkene from an alkyne, an alternative catalyst can be used. Lindlar's catalyst is a poisoned catalyst that will only allow partial reduction to produce an alkene, rather than an alkane. Lindlar's catalyst still utilizes Pd to facilitate *syn* addition of hydrogen to one face of the alkyne, but additives are introduced to 'poison' its function and prevent further addition of

hydrogen across the alkene π bond. Because *syn* addition adds the hydrogens on the same face of the alkyne, **only** the Z-isomer (*cis*-alkene) is produced (Figure 3.2.3.d, bottom).

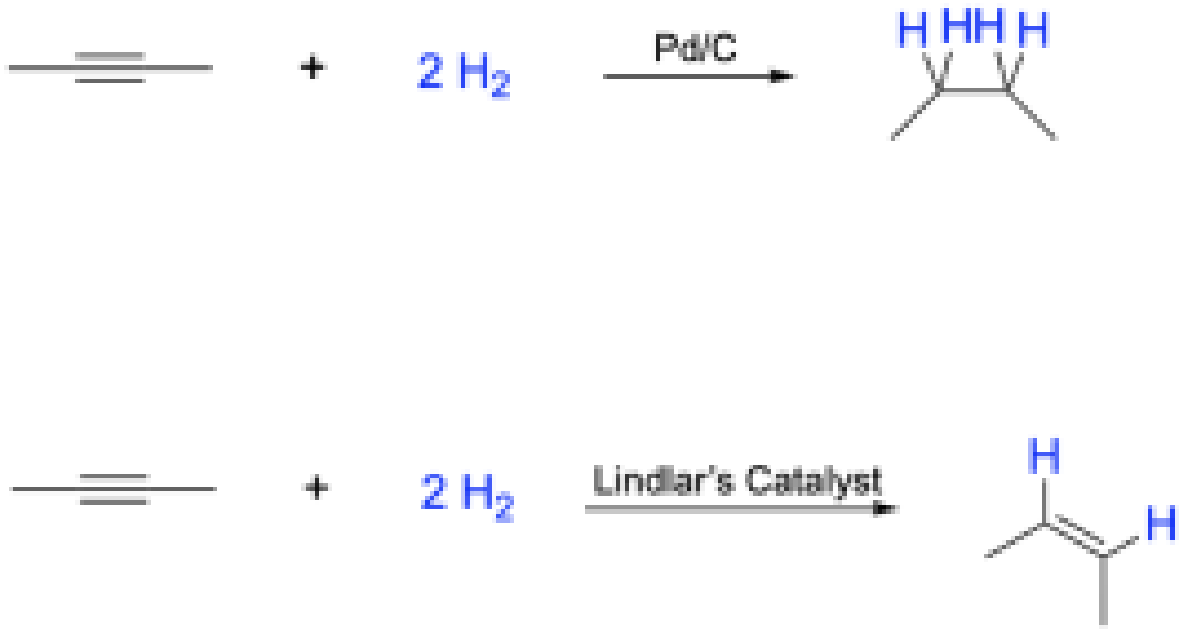

Figure 3.2.3.d. Alkynes can undergo two hydrogenation reactions. Top: When treated with 2 equivalents (excess) H_2 in the presence of a group 10 metal catalyst (such as Pd/C), the alkyne is fully reduced to an alkane. This removes two π-bonds and creates four new C-H bonds. Bottom: An alkyne can also yield an alkene when treated with H_2 in the presence of the poisoned Lindlar's catalyst. Note that *syn* addition results in only the Z isomer of the alkene being produced.

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(The full solution to this problem can be found in Chapter 5.2)

Key Takeaways

- Hydrogenation reactions involve the addition of hydrogen across a double or triple bond, resulting in either an alkane or alkene as products
- The reactants are either an alkene or alkyne, hydrogen gas, and a metal catalyst
- The metal catalyst is Pd/C (palladium and carbon)
- The mechanism involves the absorption of hydrogen on a metal surface, then the hydrogens are added onto the alkene on the same side
    - This kind of "same side" addition is known as *syn* addition
- An alternative catalyst can be used in the reaction of an alkyne to an alkene, known as Lindlar's catalyst, which is a poisoned (or weaker) catalyst
    - In this reaction, because of *syn* addition, a *cis*–alkene is the only possible product

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3.2.4 - HALOGENATION OF ALKENES

Halogenation of Alkenes

A halogenation addition reaction occurs between halogens (Br_2 and Cl_2) and alkenes, creating two adjacent CX bonds, where X is a halogen (Br or Cl). For example, bromination adds one bromine atom to each alkene carbon, resulting in a dibromoalkane.

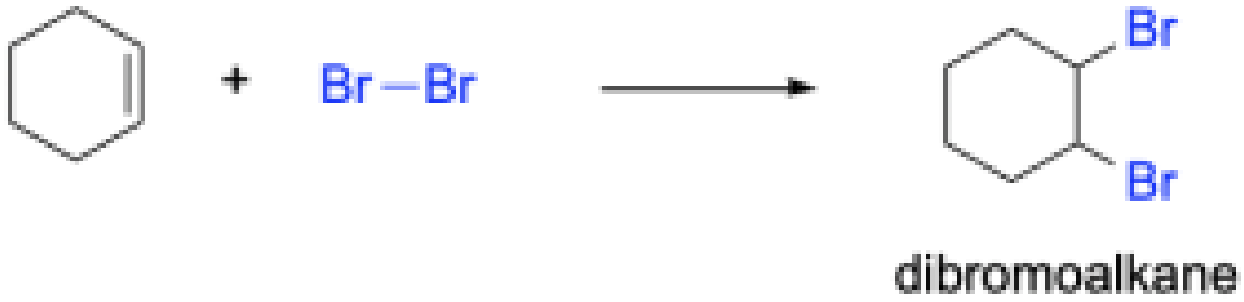

Figure 3.2.4.a. Addition reaction of an alkene using halogenation.

While you do not need to know the mechanism for this reaction (you will see it in year 2 organic chemistry) it's important to recognize that when two of the same atoms are added across the double bond, Markvonikov's rule does not apply.

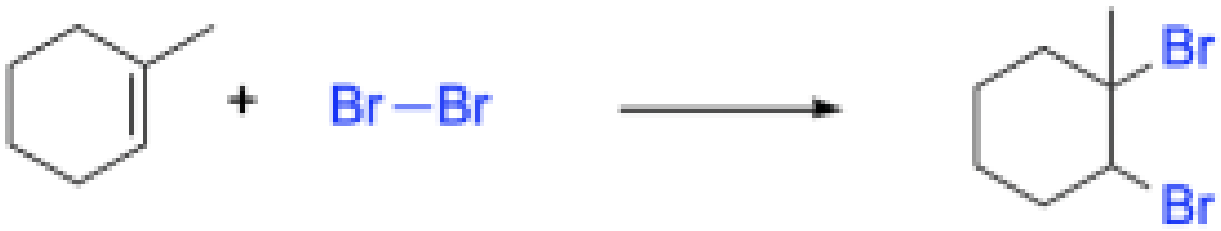

Figure 3.2.4.b. Halogenation of an unsymmetrical alkene to produce a dibromoalkane. Since the same atoms (Br) are added across the double bond and no carbocations are produced, Markovnikov addition does not apply.

Recall that in addition reactions, one π bond and one σ bond are broken, and two σ bonds are formed. In halogenation of an alkene, the C=C π bond and the X–X bond (where X is a halogen) are broken, while two new C–X σ bonds are formed. In addition, the hybridization at carbon changes: the C=C double bond of reactants have sp^2 hybridized carbon atoms, which become sp^3 hybridized in the products.

The following video includes a worked example from a previous CHEM 1AA3 test or exam that students struggled with involving alkene reactions. Try solving it on your own before looking at the solution.

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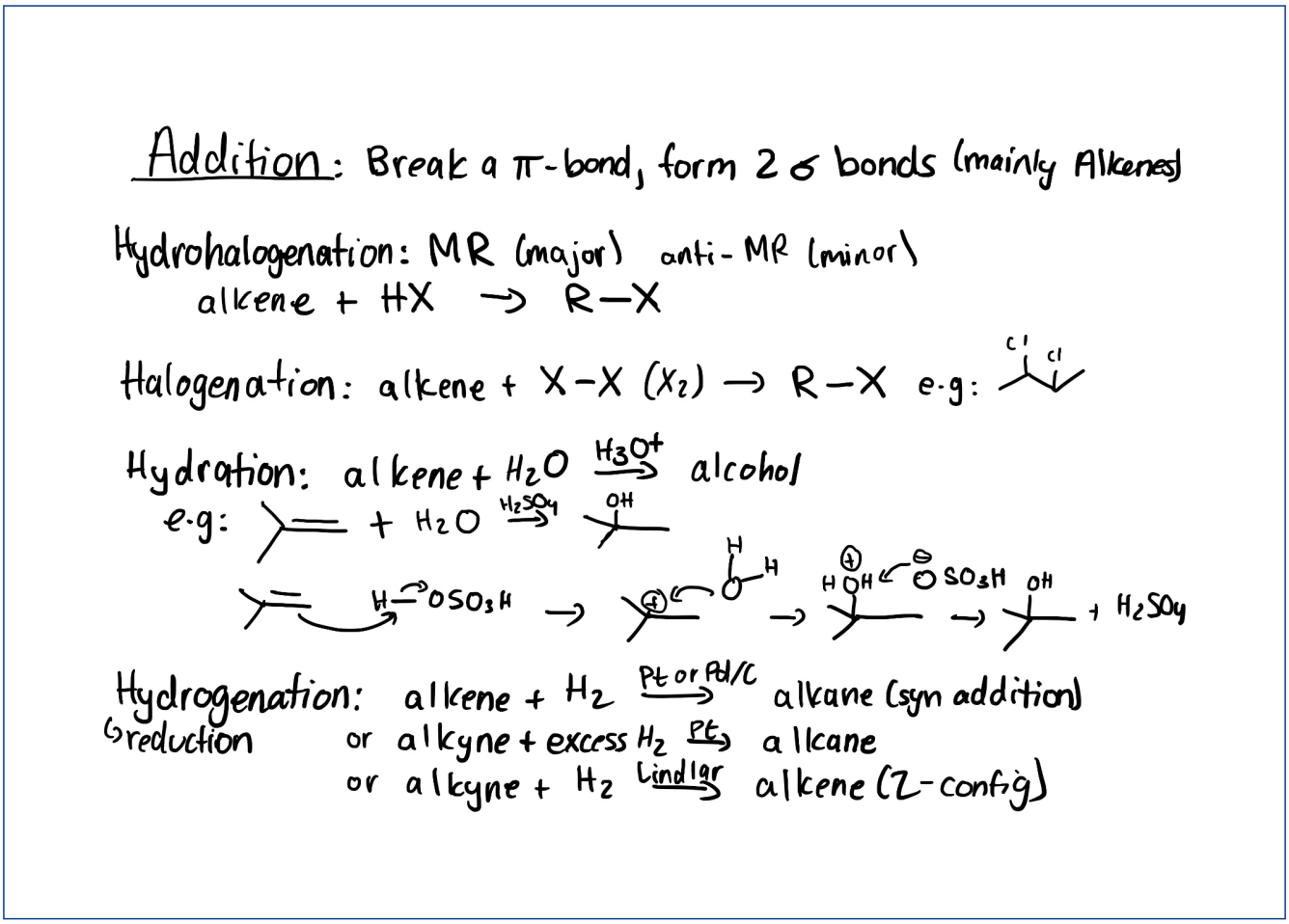
(The full solution to this problem can be found in Chapter 5.2)

Study Notes – Chapter 3.2



Diversity in Chemistry: Mario Molina

Although we go into detail about the halogenation of alkenes to form multi-halogenated molecules, in reality, halogenated compounds pose a huge environmental threat and must be carefully handled and disposed of. Before their effects were known, compounds such as chloroflurocarbon gases were commonly used in refrigerants, aerosol sprays, and in the process of making plastic foam. **Mario Molina** was the first to discover their toxic effects on the ozone layer, which is crucial for shielding the earth from the sun's ultraviolet radiation. These gases, when hit with ultraviolet radiation, would release Cl free radicals, which have an unpaired electron and makes them extremelyreactive. These would then interact with molecules of ozone (O_3) continuously, starting a chain reaction, resulting in the depletion of the layer ozone molecules. Due to his discovery, Molina became the first scientist of Mexican descent to be awarded a Nobel Prize in Chemistry in 1995 and also obtained the Presidential Medal of Freedom award from President Barack Obama himself in 2013.More information of Mario Molina can be found at the Science History Institute website.

3.3 - OXIDATION OF ALCOHOLS

Learning Objectives

1. Distinguish between oxidation and reduction in organic chemistry
2. Predict products (if any) and write reaction schemes for the following reactions (no curved arrow mechanisms or energy profile diagrams required)
    1. Reaction of primary, secondary, tertiary alcohols, or reaction of an aldehyde or ketone using $KMnO_4$, $K_2Cr_2O_7$, or PCC

Introduction to Oxidations and Reductions

In organic chemistry, oxidation and reduction reactions can change the oxidation state of a carbon atom. An easy way to remember what oxidation and reduction reactions entail is that **oxidation** reactions result in either the gain of an electronegative atom (like oxygen, nitrogen or a halide) or loss of hydrogens atoms. In contrast, the term **reduction** is the opposite, and can be defined as the loss of an oxygen atom or gain of two hydrogen atoms.

Figure 3.3.a below shows how oxidation and reduction reactions can be used to convert a functional group between an alcohol, aldehyde, and carboxylic acid.

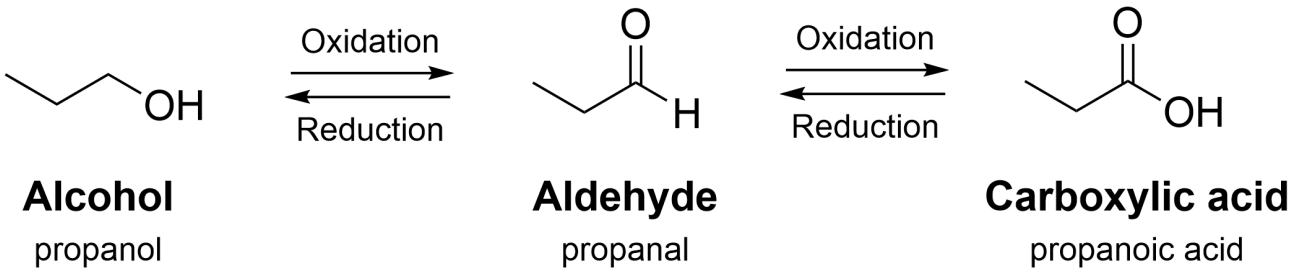


Figure 3.3.a. *The oxidation and reduction scheme of an alcohol to an aldehyde and carboxylic acid.*

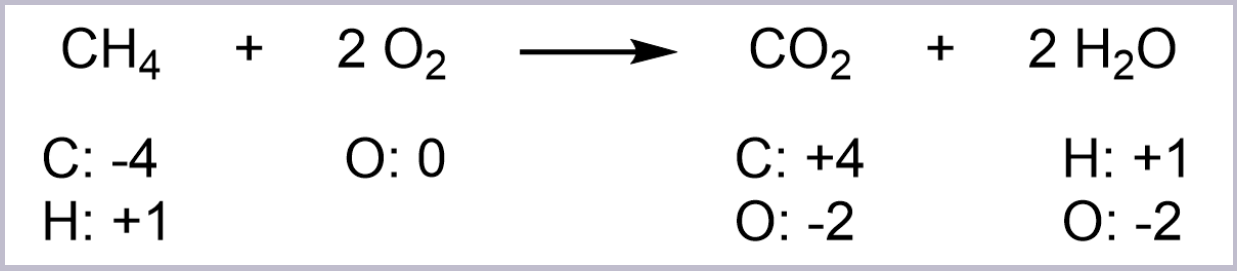
Oxidation of an alcohol or aldehyde increases the number of C–O bonds. while reduction of a carboxylic

acid, an aldehyde, or ketone will decrease the number of C–O bonds. For example, in Figure 3.3.a, the alcohol (propanol) contains one C–O σ bond. The aldehyde (propanal) contains two C–O bonds, counting the σ bond and the π bond. The carboxylic acid (propanoic acid) contains three C–O bonds, including two σ bonds and one π bond.

Are You Wondering? The Differing Definitions of Oxidation and Reduction in Organic Chemistry & Electrochemistry

Oxidation states are a way of keeping track of electrons. When we calculate the oxidation state of an atom, we consider all bonds to be ionic, and distribute the electrons to the more electronegative atom. The oxidation numbers can then be calculated by subtracting the distributed number of electrons from the number of valence electrons on the atom.

For example, consider the combustion reaction below, with oxidation numbers assigned to each atom.



A combustion reaction of methane showing the oxidation states of all atoms.

First, consider the oxidation numbers in methane, CH_4. The electronegativities of C and H are 2.5 and 2.1, respectively, on the Pauling electronegativity scale. The oxidation numbers of C and H are calculated by assigning the electrons in each C–H bond to the more electronegative atom (carbon). This process renders each hydrogen atom with an oxidation number of +1, and the central carbon with an oxidation number of -4.

Next, consider the oxidation numbers in carbon dioxide, CO_2. The electronegativities of C and O are 2.5 and 3.5, respectively, on the Pauling electronegativity scale. The oxidation numbers of C and O are calculated by assigning the electrons in each C–O bond to the more electronegative atom (oxygen). This process renders each oxygen atom with an oxidation number of -2, and the central carbon with an oxidation number of +4.

Thus, in this reaction, the oxidation number of carbon increases from -4 to +4, so carbon is being oxidized. At the same time, the oxidation number of oxygen decreases from 0 to -2, so oxygen is being reduced. Oxidation and reduction always occur together, whereby one element is oxidized, and another is reduced. However, an organic chemist would call this reaction an oxidation because they are focused on what is happening to the carbon-containing compound.

Oxygen is one of the most electronegative elements in the periodic table, and hydrogen is less electronegative than carbon. Therefore, a reaction that causes the number of C–O bonds to increase (or the number of C–H bonds to decrease) is considered an oxidation. Conversely, a reaction that causes the number of C–H bonds to increase (or the number of C–O bonds to decrease) is considered a reduction.

In conclusion, there are a few ways you can consider oxidation and reduction reactions:

1. **Electrochemistry method**: Calculate the oxidation numbers of each element and determine which species is being oxidized and which is being reduced. This method may be tedious and complicated, especially for large molecules.
2. **Counting C–O bonds**: The greater the number of C–O bonds (including both σ and π bonds), the more highly oxidized the compound. This method is faster and also works for large molecules.

Before discussing the oxidation of alcohols to carbonyls, recall how alcohols can be classified into one of three different categories: **primary**(1°), **secondary**(2°), and **tertiary**(3°) alcohols. To determine the classification of alcohol, focus on the carbon bonded to the hydroxyl group (Figure 3.3.b). If that carbon is bonded to one other carbon atom, then it is a primary alcohol – likewise, if bonded to two or three carbon atoms, it is a secondary or tertiary alcohol, respectively. This is important to understand as the degree of the alcohol will determine the reactivity and final products of the oxidation reaction.

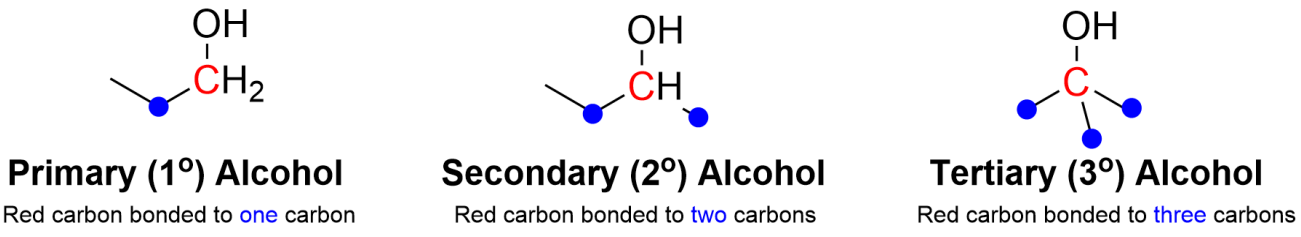


Figure 3.3.b. *Classifying alcohols as primary, secondary, and tertiary alcohols. The carbon bonded to the hydroxyl is highlighted in red. The blue dots represent the carbon atoms that it is bonded to, which dictate the alcohol classification.*

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Oxidizing Alcohols to Carbonyls

Figure 3.3.cdisplays the oxidation of a **primary alcohol**. The primary alcohol has one C–O σ bond and two C–H bonds that can be broken to oxidize the carbon. In the first oxidation reaction, the carbon atom of the alcohol becomes an aldehyde, which increases the number of C–O bonds to two, counting the σ bond and the π bond. As there is still another C–H bond that can be broken, a second oxidation reaction can occur. This results in the formation of a carboxylic acid,increasing the total number of C–O bonds to three, including two σ bonds and one π bond.

Comparing the number of C–O bonds, it can be said that alcohols are the **least oxidized**, as they only contain one C–O bond, whereas carboxylic acids are the **most oxidized**, containing three C–O bonds.

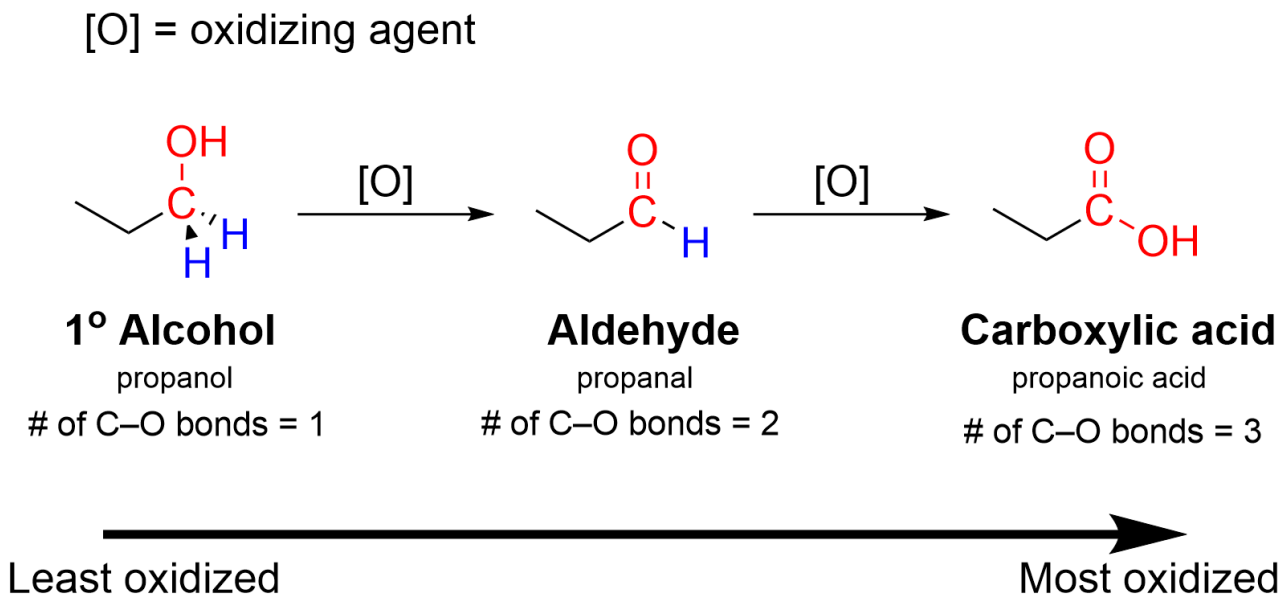

Figure 3.3.c. *The oxidation of 1-propanol (a primary alcohol) to propanal (an aldehyde), followed by oxidation of the aldehyde propanoic acid (a carboxylic acid). As the substrate becomes more oxidized, the number of C–O bonds increases.*

The same logic can be applied to the oxidation of secondary alcohols (Figure 3.3.d). The secondary alcohol has one C–O σ bond and one C–H bond that can be broken to oxidize the carbon. In the oxidation reaction, the carbon atom of the alcohol becomes a ketone, which increases the number of C–O bonds to two, counting the

σ bond and the π bond. However, unlike aldehydes, ketones cannot undergo another oxidation reaction. The central carbon already contains two bonds to oxygen and two bonds to carbon. For a third C–O bond to form, a C–C bond must break. The mechanism of this reaction requires C–H σbondson the carbon bound to the oxygen atom for oxidations to occur. If no such C–H bonds exist, then the oxidation process cannot proceed

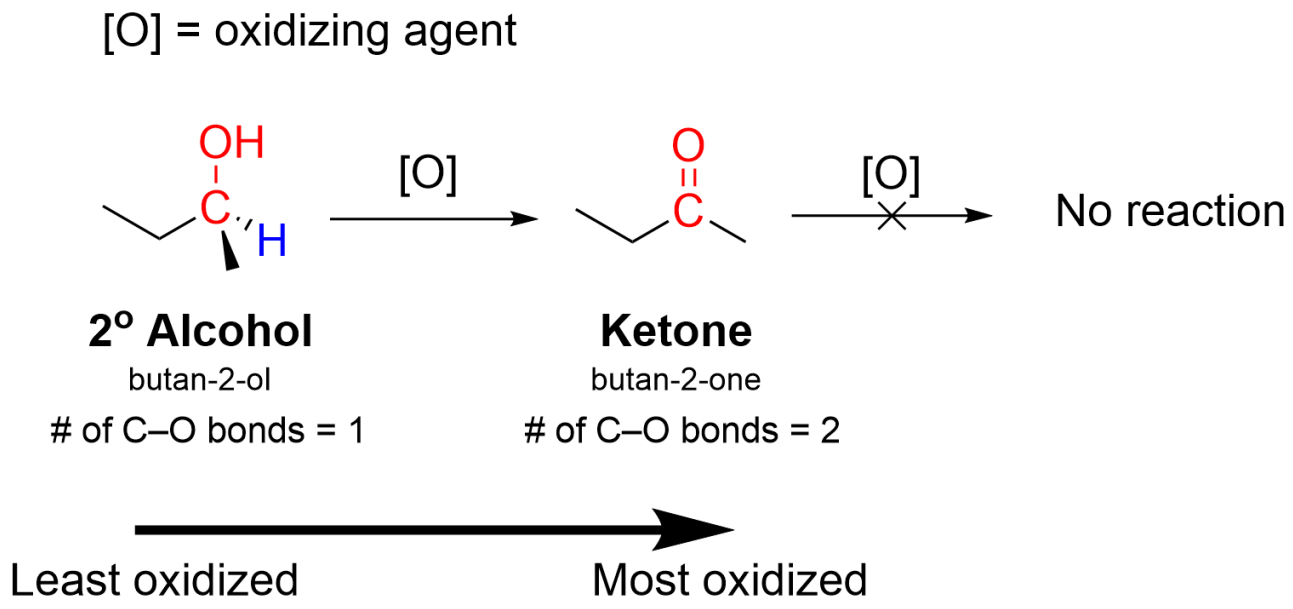

Figure 3.3.d. *The oxidation of butan-2-ol (a secondary alcohol) to butan-2-one (a ketone). A second oxidation event cannot occur as it would require the breakage of a C–C bond, which is unfavorable.*

Tertiary alcohols are unable to undergo any form of oxidation (Figure 3.3.e). Tertiary alcohols contain three C–C bonds and no C–H bonds, meaning the oxidation would require breaking a C–C bond, which cannot occur.

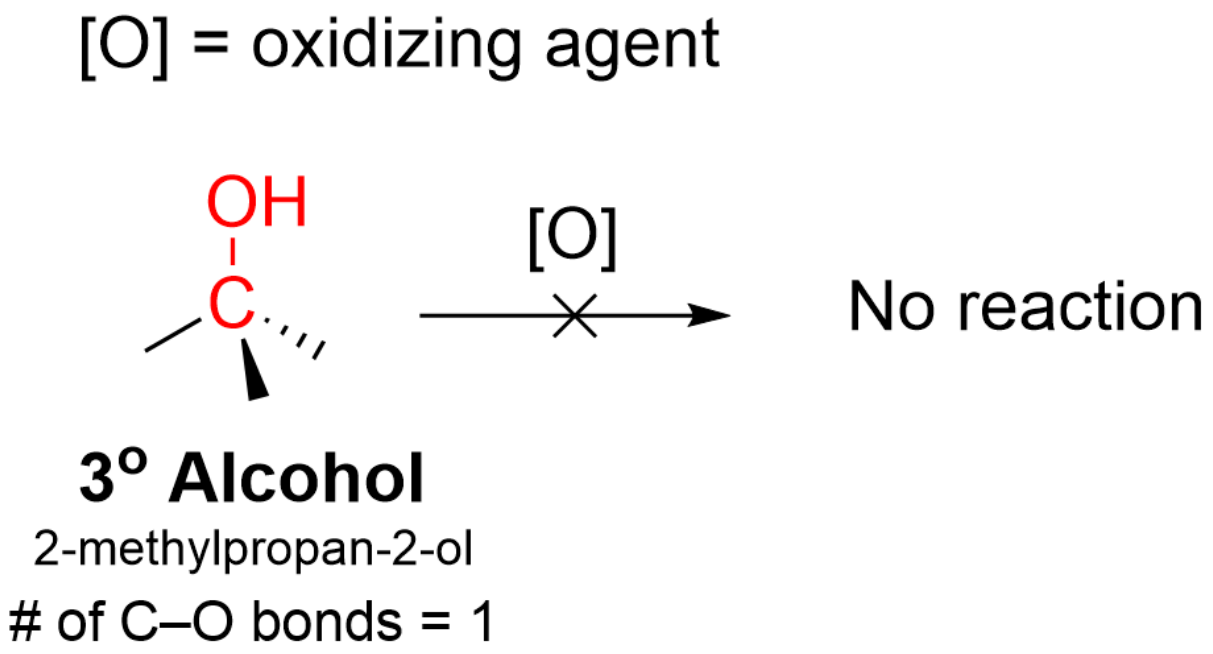

Figure 3.3.e. *The oxidation of a tertiary alcohol such as 2-methylpropan-2-ol cannot occur.*

In summary, primary alcohols can undergo two oxidation events while secondary alcohols can undergo one oxidation event. Tertiary alcohols cannot be oxidized at all.

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(The full solution to this problem can be found in Chapter 5.2)

Oxidizing Agents

Oxidizing agents are commonly metals with a high oxidation state. Examples of oxidizing agents include:

- **potassium permanganate**, $KMnO_4$, which contains Mn(VII)
- **potassium dichromate**, K_2Cr2O_7 , which contains Cr(VI)
- **pyridinium chlorochromate**, denoted PCC, which contains Cr(VI)

Due to their high oxidation state, the metals (manganese or chromium) are easily reduced (gain electrons), but they must oxidize another species. In this case, the organic compound is oxidized as a result.

Oxidation reactions using $KMnO_4$ or K_2Cr2O_7 are performed in water, in either acidic or basic conditions, to facilitate electron transfer. Using $KMnO_4$ or K_2Cr2O_7 results in oxidizing a molecule to its highest possible oxidation state. For example, reacting $KMnO_4$ with a primary alcohol produces a carboxylic acid. The aldehyde product cannot be isolated under most conditions. Similarly, reacting $KMnO_4$ with a secondary alcohol yields a ketone.

Oxidation reactions using PCC are performed in an organic solvent (CH_2Cl_2) rather than water, so the reagent is often written as PCC in CH_2Cl_2. PCC is a more selective oxidizing agent in that it reacts with alcohols, but not with aldehydes. Thus, reacting PCC in CH_2Cl_2 with a primary alcohol will only perform the first oxidation to produce an aldehyde and will not oxidize further to a carboxylic acid. PCC can similarly oxidize secondary alcohols to produce ketones.

If a reaction calls for the conversion of an alcohol to an aldehyde, only PCC can be used. Reagents like $KMnO_4$ or K_2Cr2O_7 cannot be used as they will oxidize the primary alcohol twice to yield a carboxylic acid. For a secondary alcohol, any of PCC, $KMnO_4$, or K_2Cr2O_7 could be used to produce a ketone.

These oxidation reactions can be summarized below in Figure 3.3.f. You do not need to know the reaction mechanism of these oxidation reactions.

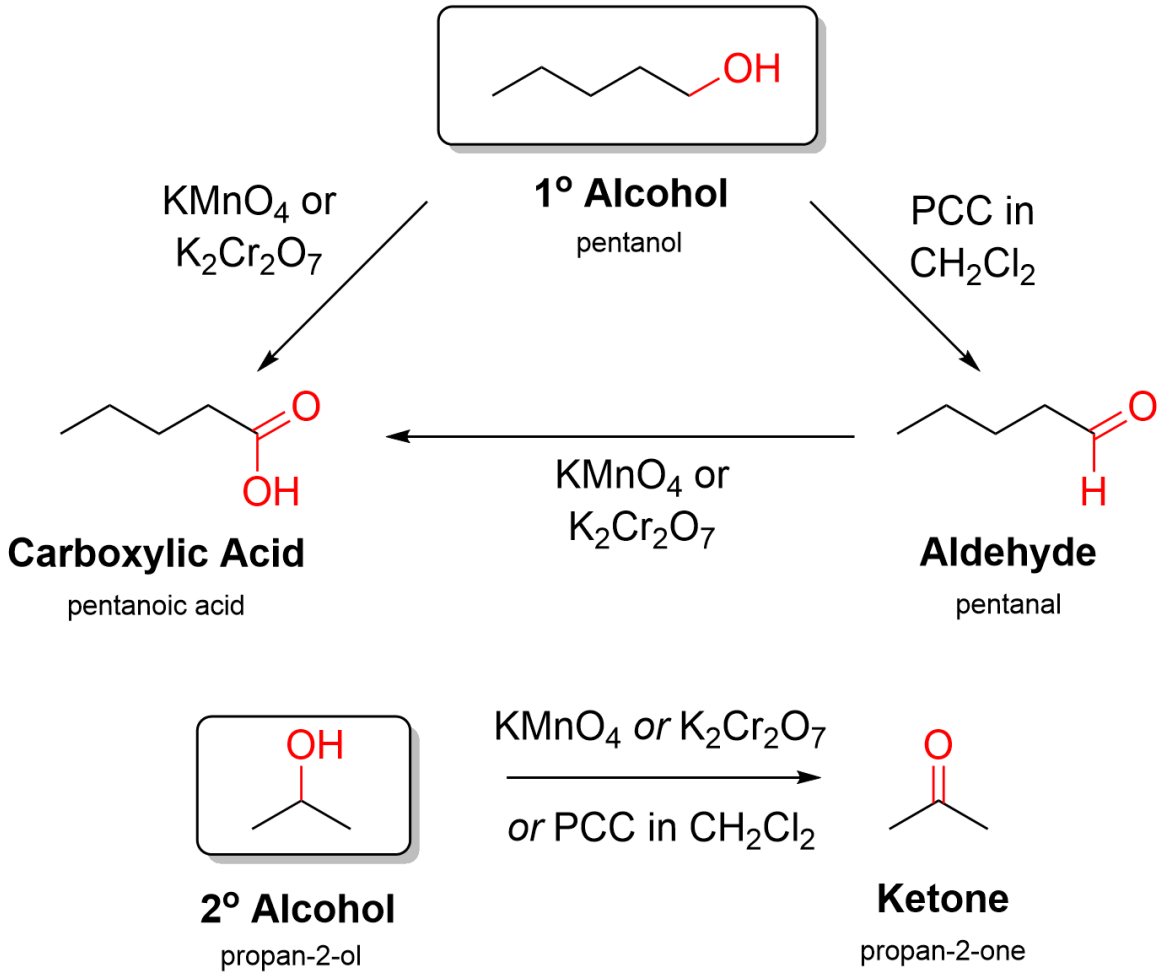

Figure 3.3.f. *The reaction scheme of primary and secondary alcohols with different oxidizing agents. Oxidizing with $KMnO_4$ or $K2Cr_2O_7$ will result in a full oxidation of a primary alcohol to its most oxidized form, a carboxylic acid. In contrast, reacting PCC in CH_2Cl_2 with a primary alcohol will obtain an aldehyde. Any reactant ($KMnO_4$, $K2Cr_2O_7$, or PCC in CH_2Cl_2) can be used to oxidize a secondary alcohol to give a ketone.*

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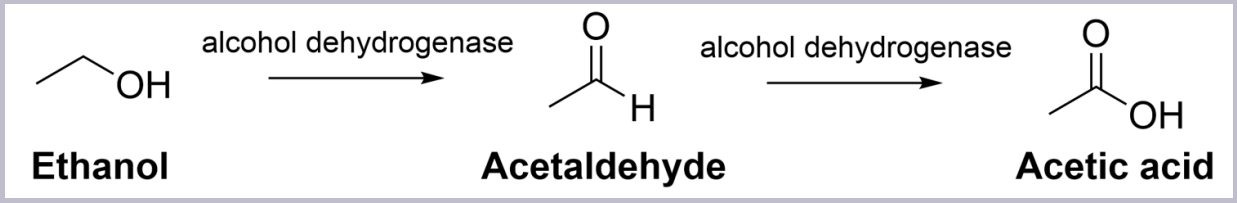
(The full solution to this problem can be found in Chapter 5.2)

Are You Wondering? More Sustainable Options for Oxidizing Compounds

Although we learn about oxidizing reagents through oxidizing agents such as PCC, chromium, and manganese, these methods are not very sustainable. **Sustainable chemistry** is a branch of chemistry that focuses on designing products and processes to minimize hazardous substances and byproducts, including the environmental impact of chemistry. Oxidation conditions including highly acidic environments and high heat levels tend to be unsafe, and reagents such as chromium are toxic carcinogens that can affect the user. Thus, it is imperative to develop more sustainable methods of oxidation that are safer and use less resources.

We can turn to biology to look for alternative methods of oxidation. **Alcohol dehydrogenase** is an enzyme found within our bodies that is oxidizes the alcohol we consume into acetic acid, a carboxylic acid. If the compound of interest is recognizable by the enzyme, alcohol dehydrogenase can be used for oxidation. This reaction takes place in water at near neutral pH as opposed to acidic conditions, making it a much safer and sustainable alternative as an enzyme catalyst is used rather than carcinogenic heavy metals.



The oxidation of ethanol to acetaldehyde and acetic acid by enzyme alcohol dehydrogenase in the body.

However, this method is not perfect. Not all molecules can be recognized by the enzyme, as it must fit within the binding pocket for this to occur. Furthermore, not all molecules can be dissolved in water, which is the solvent for this reaction. Not all reactions are perfect, however, this is an

alternative that can be used and is a step in the right direction to more sustainable chemistry practice.

Key Takeaways

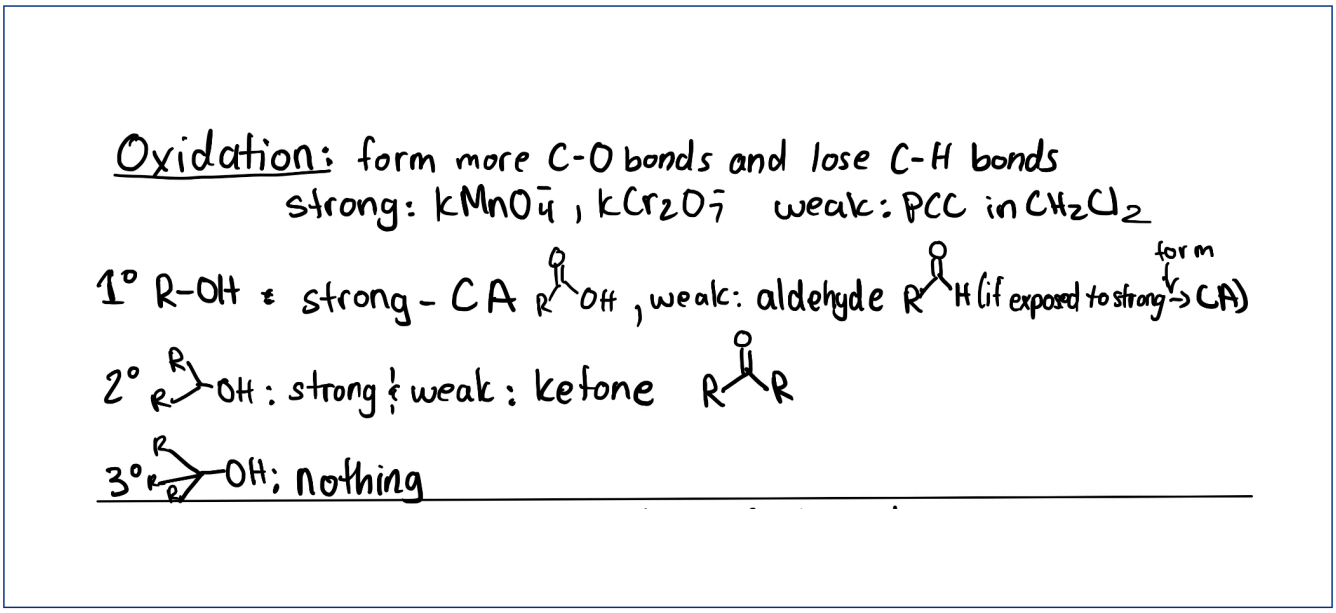
- Primary and secondary alcohols can undergo **oxidation reactions**. Oxidation of an alcohol occurs when the carbon bound to the hydroxyl group gains a π bond to oxygen, and loses a σ bond to hydrogen.
    - The reverse of an oxidation reaction is called a **reduction** reaction.
- Oxidation reactions of alcohols can yield an aldehyde, ketone or carboxylic acid, depending on the starting materials and oxidizing agent used.
- An **oxidizing agent** is required in oxidation reactions; it is a molecule which itself is highly oxidized.
- Three oxidizing agents are of interest: potassium permanganate ($KMnO_4$), potassium dichromate (K_2Cr2O_7) and pyridinium chlorochromate (PCC) in CH_2Cl_2.
    - $KMnO_4$ and K_2Cr2O_7 are strong oxidizing agents. These will always produce the most oxidized product, i.e. they will *fully* oxidize a 1° alcohol to a carboxylic acid.
    - PCC in CH_2Cl_2 is a selective oxidizing agent that will only oxidize a 1° alcohol to an aldehyde, or a 2° alcohol into a ketone.

Diversity in Chemistry: Mary Elliot Hill

A portrait of Mary Elliot Hill.

Although we only covered a handful of oxygen-containing functional groups, there are still numerous ones commonly employed in chemistry. For example, the ketone group is very similar to another functional group called a ketene, which consists of two subsequent C=C double bonds before the C=O bond (containing a structure of R-C=C=O). **Mary Elliot Hill** was a famous organic and analytical chemist who, alongside her husband, worked on the development of ketene synthesis which plays a significant role in plastic production. She also developed spectroscopic methods involving ultraviolet (UV) light to study ketene reaction progress. Hill graduated from Virginia State University with her bachelor's degree in 1925, before becoming a teacher. She then went on to continue her education at the University of Pennsylvania and is believed to be one of the first African American women to be awarded a master's degree in chemistry. Aside from her research, Hill was invested in education, instituting student chapters of the American Chemical Society at historically black colleges and universities where she taught. More information on Mary Elliot Hill can be found in this article celebrating her accomplishments.

Study Notes – Chapter 3.3



Any feedback or comments on this chapter? You may either email chemoer@mcmaster.ca, access this MS Form, or provide a comment in the feedback box below.

3.4.1 - SODIUM BOROHYDRIDE REDUCTION OF CARBONYLS

Learning Objectives: Chapter 3.4.1 – 3.4.3 (Reduction Reactions)

1. Predict products, write reaction schemes, draw curved arrow mechanisms, and draw energy profile diagrams, including all intermediates and transition states, for the following reactions:
    1. Reduction of a carbonyl compound
    2. Reaction of a carbonyl with a Grignard reagent
2. Understand the relationship between the curved arrow mechanism, energy profile diagram, and rate law for the addition reactions to carbonyl compounds
3. Write a reaction scheme to show the formation of a Grignard reagent, and explain the change in polarity at carbon
4. Understand the relationship between the curved arrow mechanism, energy profile diagram, and rate law for the addition reactions to carbonyl compounds.

Sodium Borohydride as a Reducing Agent

In previous chapters, we learned that the term **reduction** can be defined as the gain of two hydrogens. We also discussed how alkenes can be **reduced** to alkanes through the addition of hydrogen gas, H_2. Carbonyl groups, such as ketones and aldehydes, can also undergo a reduction reaction using the reagent sodium borohydride to yield alcohols. In both reduction of an alkene and reduction of an aldehyde or ketone, the overall reaction involves breaking a π bond, and addition of two new σ bonds to hydrogen atoms.

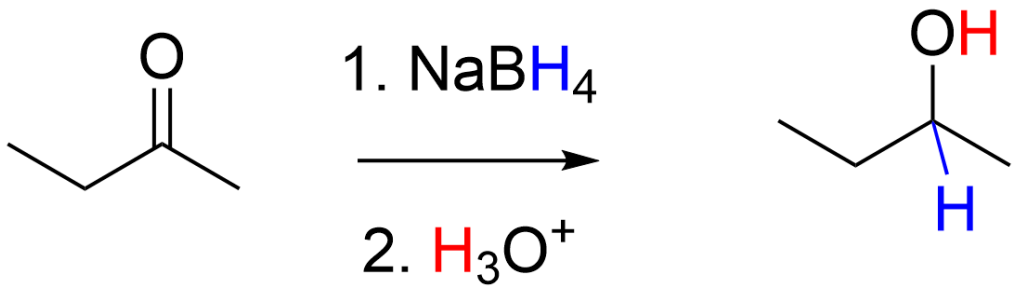
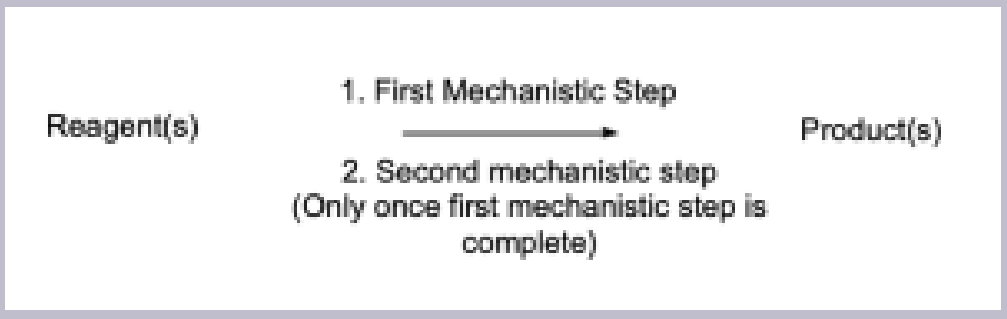


Figure 3.4.1.a. *An example of the reduction of a carbonyl group using sodium borohydride.*

Are You Wondering? Multi-Step Processes in Synthesis

Sodium Borohydride reduction of carbonyl's is the first example of a reaction where the reagents are numbered in sequence, indicated above and below the reaction arrow. The numbers represent individual sequential steps in a multi-step process. In this particular case, Sodium Borohydride ($NaBH_4$) is first added to a solution of the organic molecule containing a carbonyl group. After the first mechanistic step is allowed to come to completion, an aqueous acidic solution is then introduced which allows the second mechanistic step to occur. The inclusion of the sequence of steps is important – $NaBH_4$ decomposes in aqueous solutions. As a result, the water must be added after the $NaBH_4$ has completed its role in this reaction. You will see a similar setup next chapter with Grignard reductions.



A multi-step mechanism process exhibited through the two steps about the reaction arrow.

Sodium borohydride ($NaBH_4$) is a unique reagent that acts as a source of nucleophilic hydrogen, also known as a **hydride**, H^-. Sodium borohydride is a salt that consists of a sodium cation and a $[BH_4]^-$ anion. The central boron is bonded to four hydrogens and contains no lone pairs, giving it a formal charge of 1-. However, formal charge is merely a way of keeping track of electrons, and it does not show where the electron density resides. In BH_4^-, the electrons are localized not on the boron center, but rather the electron density is found closer to the hydrogen atoms.

In the B–H bond, hydrogen is *more* electronegative than boron (electronegativities for H and B are 2.20 vs. 2.04, respectively, according to the Pauling scale). This results in the polarization of electrons towards the hydrogen, represented by the partial negative charge on hydrogen and partial positive charge on boron (Figure 3.4.1.c). This can also be rationalized by Boron's role as a metalloid; hydrogen tends to behave as an anion when bound to metal or metalloid atoms. Due to this high electron density, the hydrogen behaves as though it has a lone pair of electrons and a formal negative charge, depicted as $H:^-$, called **hydride**. Hydride acts as a nucleophile and can attack an electrophile to deliver a hydrogen atom.

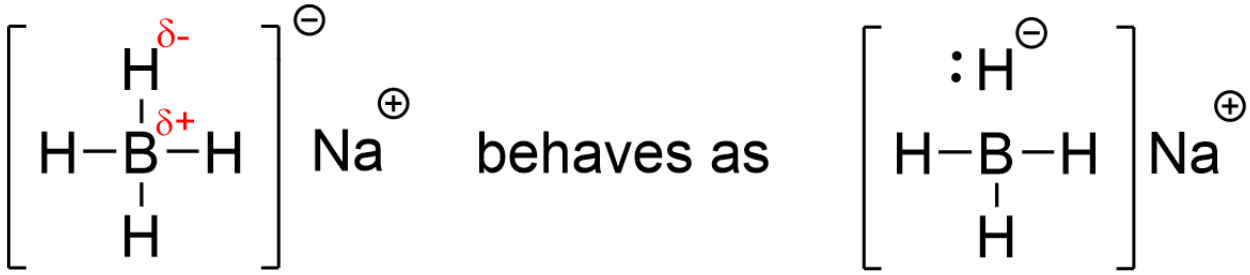


Figure 3.4.1.b. *The structure of sodium borohydride ($NaBH_4$). A partial positive charge is found on the boron and a partial negative charge is seen on the bonded hydrogen. This compound behaves as $H:^-$ (in close association with BH_3 and a Na^+ cation).*

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Reduction of Aldehydes and Ketones using Sodium Borohydride

Carbonyl groups, such as **aldehydes** and **ketones**, act as an electrophile due to the polar C=O bond, resulting in an electron-poor central carbon (Figure 3.4.1.d). Reaction with sodium borohydride delivers a hydride (H^-) to the electron-deficient carbon, forming a new C–H bond. Subsequent treatment with an acid delivers a

proton (H^+) to the oxygen, forming a new O–H bond. The net result is breaking the C=O π bond, and forming two new σ bonds to hydrogen, to produce an alcohol. Because a carbon-oxygen π bond is broken and two hydrogen atoms were added in the reaction, it is called a reduction reaction, and sodium borohydride is called a **reducing agent** for carbonyl groups**.**

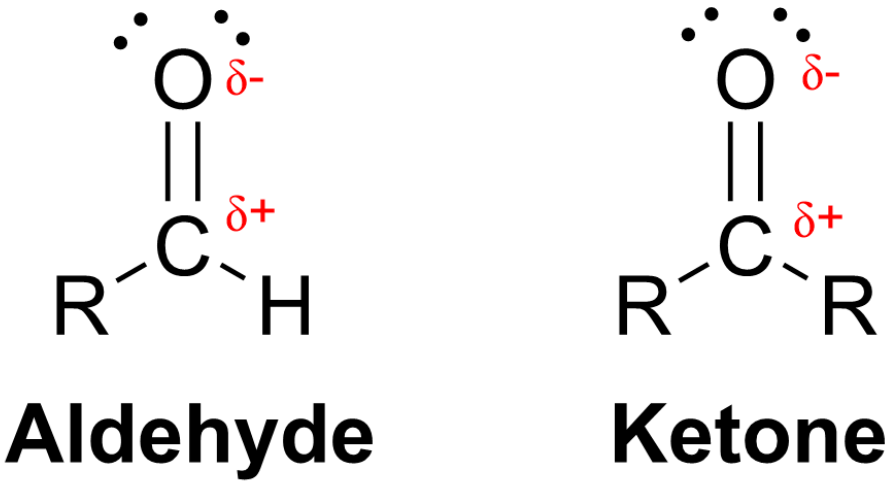

Figure 3.4.1.c. *The reactivity of aldehyde and ketone functional groups, showcasing a electron-deficient carbon center that acts as a electrophile.*

Reducing aldehydes with $NaBH_4$ results in **primary** alcohols, whereas reducing ketones with $NaBH_4$ generates **secondary** alcohols (Figure 3.4.1.e).

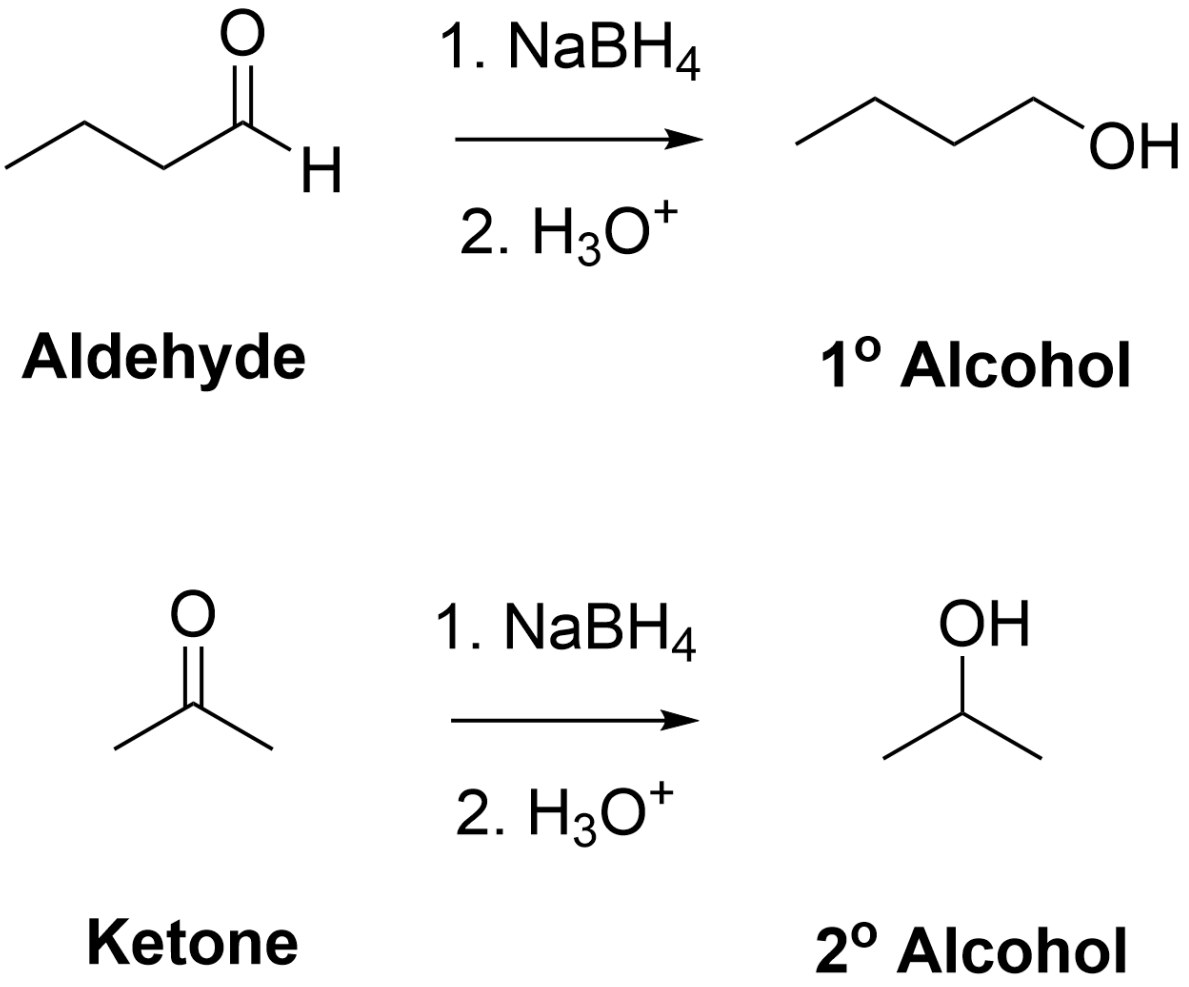

Figure 3.4.1.d. *Sodium borohydride reduction of an aldehyde yields a primary alcohol (top) while a ketone yields a secondary alcohol (bottom). The reaction involves two steps: treatment of $NaBH_4$ followed by acidification.*

Mechanism of Carbonyl reduction using Sodium Borohydride

This reduction of carbonyl groups is a **two-step process,** consisting of the nucleophilic attack of hydride to the carbonyl carbon and the protonation of the alkoxide intermediate.

Step 1: Nucleophilic attack of H^-

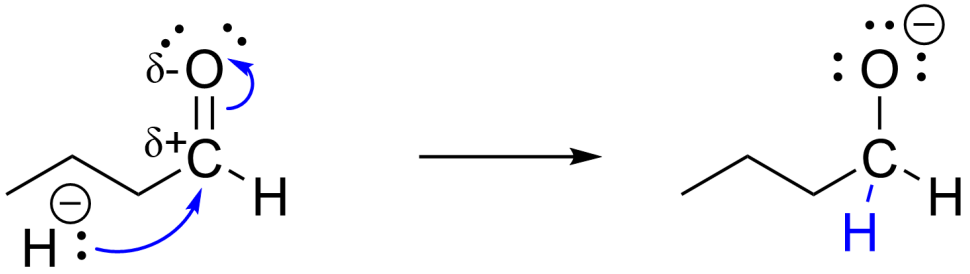

Figure 3.4.1.e. *The first step in the reduction of an aldehyde using sodium borohydride. Sodium borohydride, drawn as H^-, is shown attacking the electrophilic carbon of the aldehyde. A new C–H bond is formed, and the electrons in the π bond end up as a lone pair on oxygen, which then has a formal negative charge.*

The first mechanistic step is the **nucleophilic attack of the hydride** from sodium borohydride at the electrophilic carbon centre of the carbonyl group. The lone pair of electrons on hydrogen attacks the carbon centre of the aldehyde to form a new covalent bond. As a new bond is forming, another bond must break to ensure that the octet rule is not violated at the carbon. The π bond preferentially breaks, with the electron pair from the π orbital of the C=O bond moving towards the electronegative oxygen. This step results in the formation of a new C–H bond, the breaking of the carbonyl π bond, and formation of an alkoxide intermediate with a formal negative charge at the oxygen.

Step 2: Protonation of alkoxide

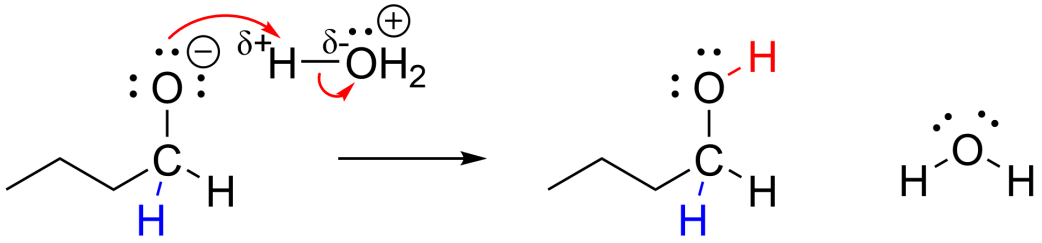

Figure 3.4.1.f. *The second step in the reduction of an aldehyde using sodium borohydride. The alkoxide is protonated by an acid, H_3O^+, resulting in the final products: a primary alcohol and water.*

The second mechanistic step of this reaction is the **protonation** of the negatively charged oxygen in the alkoxide intermediate. As the previous step ended with an anionic alkoxide as the intermediate, it must be protonated to stabilize the molecule and produce a neutral alcohol. This will occur by using **acid**, written as H_3O^+. The negatively charged oxygen on the alkoxide intermediate is similar in behavior to hydroxide and is found to be highly basic, like hydroxide. It uses a lone pair of electrons to abstract the proton from the acid.

This is an acid-base reaction between H_3O^+ (the acid) and the anionic alkoxide (the base). This second step results in our final product, a primary alcohol.

The reaction of an aldehyde with sodium borohydride produces a **primary alcohol,** because aldehydes have one carbon attached to the aldehyde group.

The same reaction process can be seen in the reaction between a ketone and sodium borohydride.

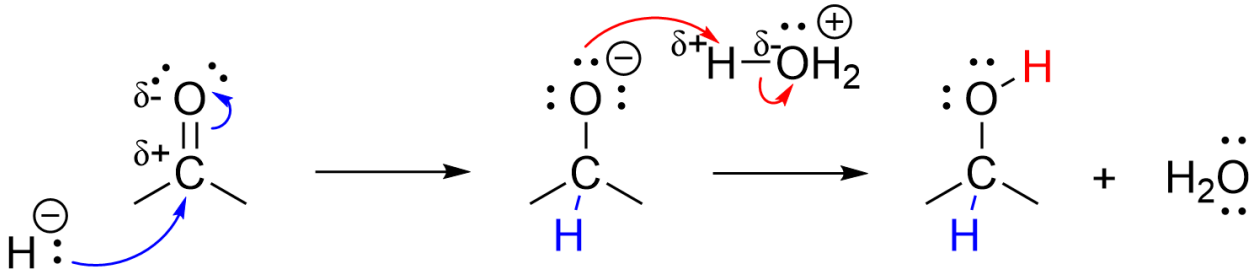

Figure 3.4.1.g. *The two-step process of the reduction of ketone, following the same steps as the reduction of aldehyde using sodium borohydride.*

The mechanistic steps for reduction of ketones is functionally identical to the mechanistic steps involved in the reduction of aldehydes. It follows the same pattern of an initial nucleophilic attack from the hydride, followed by the protonation of the anionic oxygen. Reducing a ketone with $NaBH_4$ produces a **secondary alcohol,** as ketones have two carbon-containing group attached to the central ketone group.

The two-step reaction can be summarized in the following manner, showing the intermediate as well as the starting reactant and product.

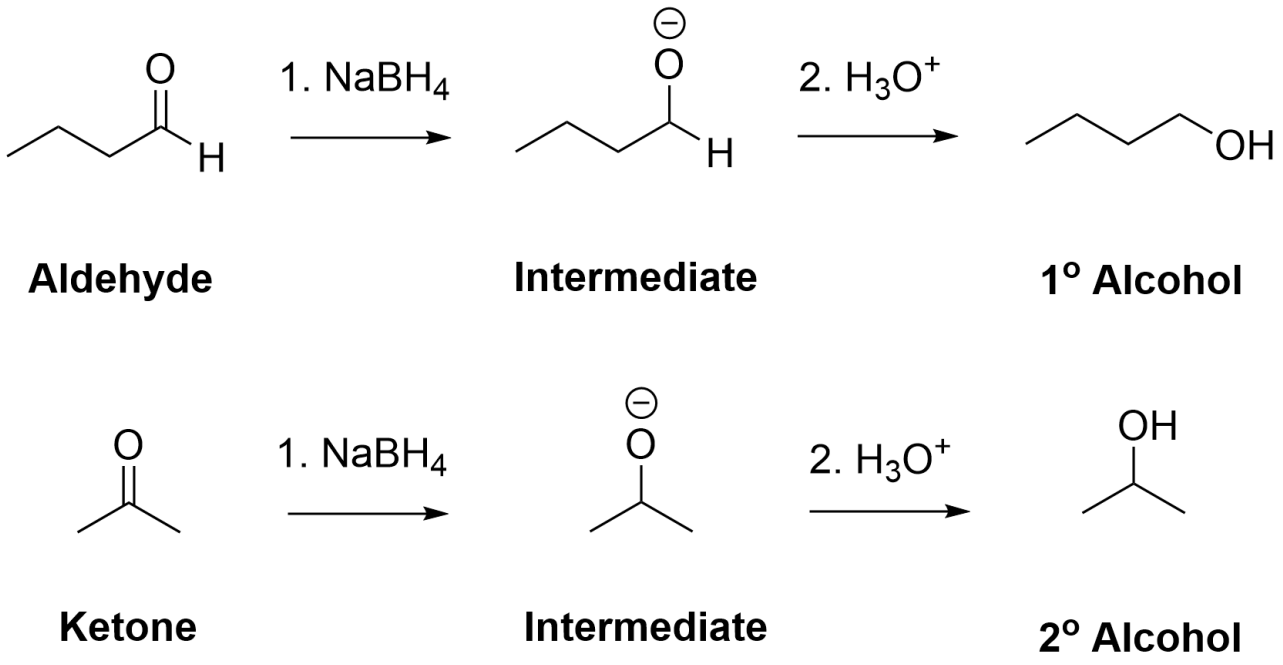

Figure 3.4.1.h. The reactants, intermediates and products in sodium borohydride reduction of carbonyls.

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(The full solution to this problem can be found in Chapter 5.2)

Energy Profile of Sodium Borohydride reductions

As this reaction follows a two-step process, we can draw an energy profile to show the changes in energy and the intermediate formed in the reaction. The potential energy **minimum** in the centre of the energy profile represents the alkoxide intermediate that is synthesized in the first mechanistic step. The two **maxima** correspond to the two transition states where bond breaking and forming are occurring.

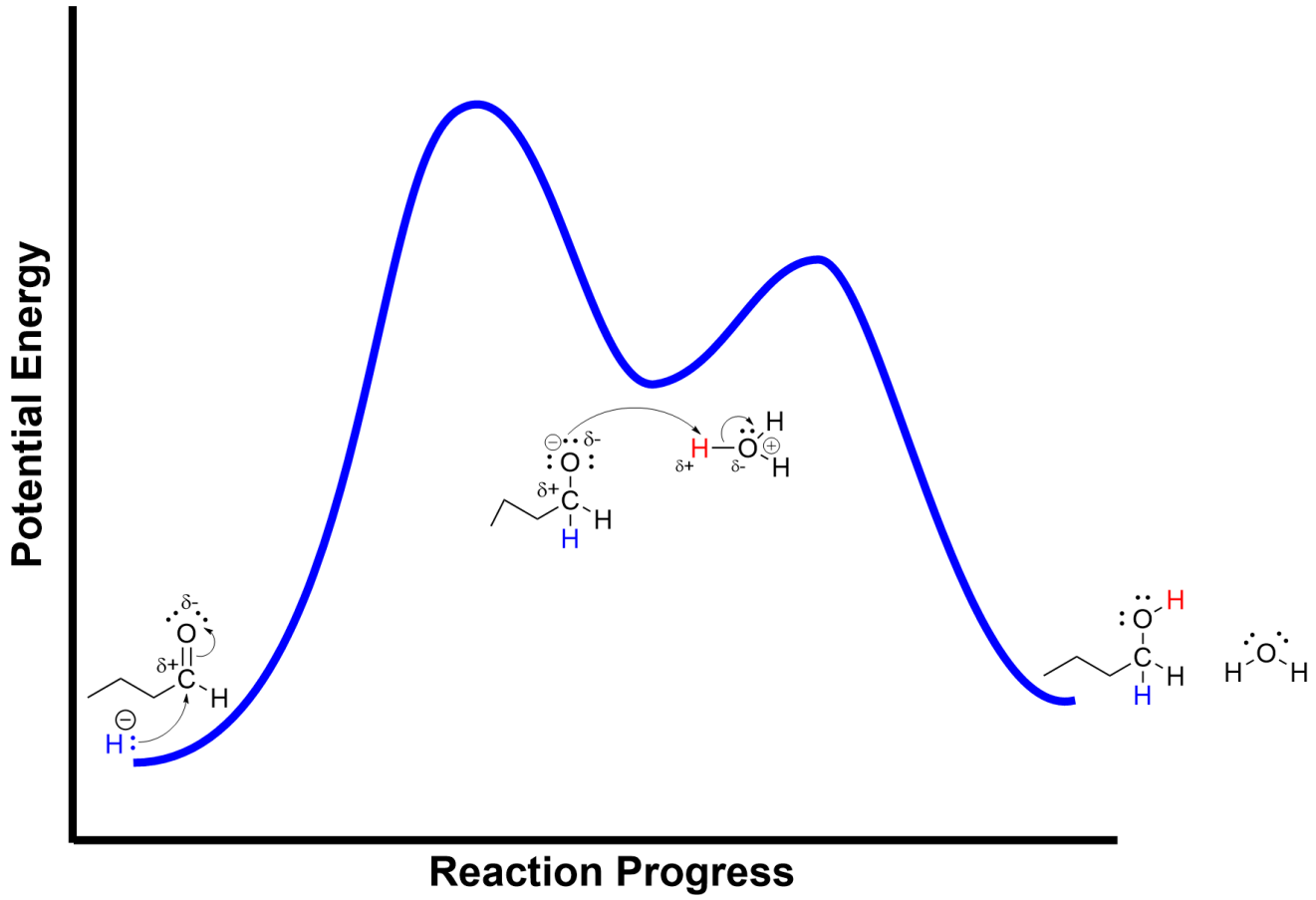

Figure 3.4.1.i. *An energy profile diagram of a sodium borohydride reduction of an aldehyde. The two energy maxima correspond to the transition states for each step, while the energy minimum corresponds to the alkoxide intermediate.*

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Key Takeaways

- Reduction reactions of carbonyl groups, including aldehydes and ketones, can be characterized as the addition of two hydrogens and the removal of one bond to oxygen to create an alcohol product.
- This type of reduction reaction occurs in **two steps** when starting with an aldehyde/ketone reagent:
    1. **Introduction of sodium borohydride ($NaBH_4$)**, which is a hydride (H^-) source. The hydride can attack the electrophilic carbonyl carbon to produce a negatively charged alkoxide intermediate. This step has the highest activation energy because of the charged intermediate.
    2. **Introduction of an acid**, which will protonate the alkoxide intermediate, will produce either a primary or secondary alcohol, depending on the starting materials.
- Overall, the first step makes a σ bond to hydrogen, and breaks a π bond to oxygen, and the second step makes a σ bond to hydrogen.

Diversity in Chemistry: Ryōji Noyori

A portrait of Ryōji Noyori.

Aside from sodium borohydride reductions, there are various other methods to reduce ketone groups to alcohols. One that is commonly used in present day in the pharmaceutical industry is the Noyori Reaction, pioneered by Japanese organic chemist **Ryōji Noyori**. This reaction uses a ruthenium (metal)-based catalyst to reduce a ketone to an alcohol. However, the key difference between the Noyori Reaction and a simple sodium borohyride reduction is that the Noyori Reaction is much more selective. It produces a specific configuration of the final product (you will learn more about this in second year organic chemistry), which is not possible with the sodium borohydride reaction, which results in a mixture of the two configurations. For his work, Noyori was awarded one third of the 2001 Nobel Prize in Chemistry. This method is still widely used today in commercial synthesis, such as in the production of levofloxacin, a commonly used antibiotic. More information on Ryoji Noyori can be found on his Nobel Prize page.

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3.4.2 - GRIGNARD REACTIONS WITH CARBONYLS

The **Grignard reaction** is an organic reaction used to form new carbon—carbon bonds by adding an alkyl or aryl group to an aldehyde or ketone carbon center. This results in an alcohol product.

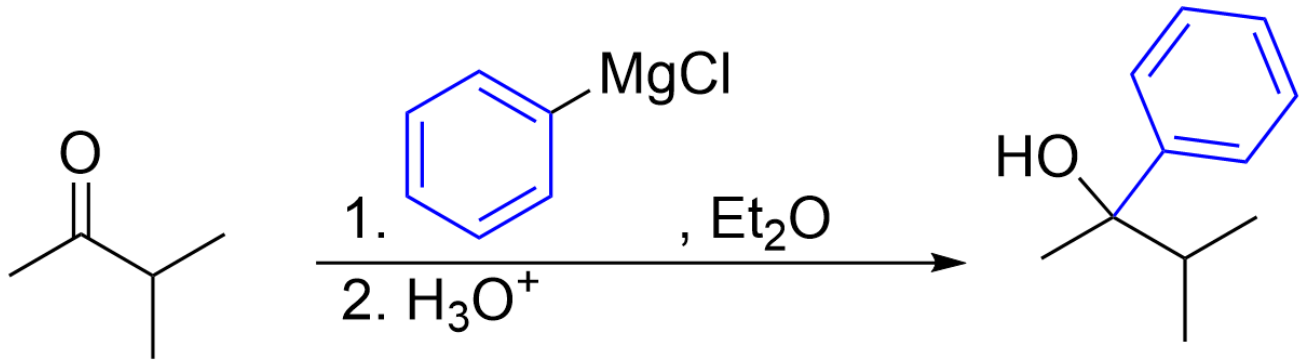

Figure 3.4.2.a. *Reaction of a ketone and a Grignard reagent to produce a tertiary alcohol.*

The Grignard Reagent

Before a Grignard reaction can be done, the **Grignard reagent** must first be synthesized. A Grignard reagent is made by treating an alkyl halide with elemental magnesium, Mg, using diethyl ether (Et_2O) as a solvent. The halogen in the alkyl halide is often Cl or Br. You do not need to know the exact mechanism of how this reaction occurs. However, it is important to understand that the Mg inserts itself *between* the carbon and halide, while donating its 3s electrons to carbon, reducing it to a carbanion. This reagent is often written as **R–MgX.**

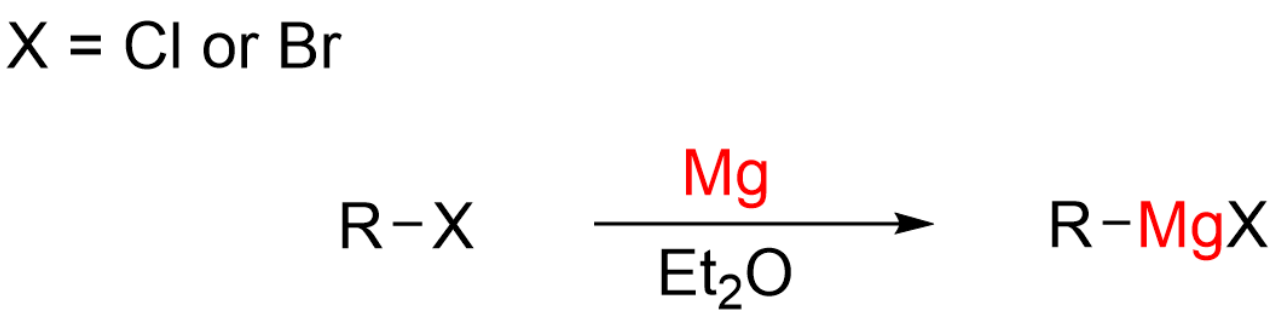

Figure 3.4.2.b. *The reaction of an alkyl halide with magnesium to synthesize the Grignard reagent, R–MgX.*

Magnesium is electropositive, with an electronegativity value of 1.31 on the Pauling scale. In comparison, carbon has an electronegativity of 2.02. As carbon is the more electronegative atom in the C–Mg bond, it exhibits a partial negative charge, whereas the Mg has a partial positive charge. Thus, this is one of the rare cases where the carbon acts as a **nucleophile,** rather than an electrophile. Another way to visualize this is with the carbon atom containing a lone pair of electrons and a formal negative charge, and write the Grignard reagent as an ionic salt, as shown below.

Figure 3.4.2.c. *The R-MgX Grignard reagent contains a carbon atom with a partial negative charge, which can also be depicted as a lone pair of electrons and a formal negative charge on carbon. The carbon atom acts as a nucleophile.*

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Reacting Carbonyls With a Grignard reagent

Grignard reagents react with aldehydes and ketones to form alcohols. The carbonyl group in the aldehyde or ketone contains an electrophilic carbon center due to the electronegative oxygen. Meanwhile, the Grignard reagent contains a nucleophilic carbon center. The nucleophilic Grignard reagent attacks the electrophilic carbonyl carbon atom, forming a new C–C bond while breaking a π bond to oxygen. Subsequent treatment with an acid delivers a proton (H^+) to the oxygen, forming a new O–H bond, to produce an alcohol. The net result is breaking the C=O π bond, and forming two new σ bonds (C–C and O–H).

Reacting aldehydes and ketones with a Grignard reagent will form **secondary** and **tertiary alcohols** respectively.

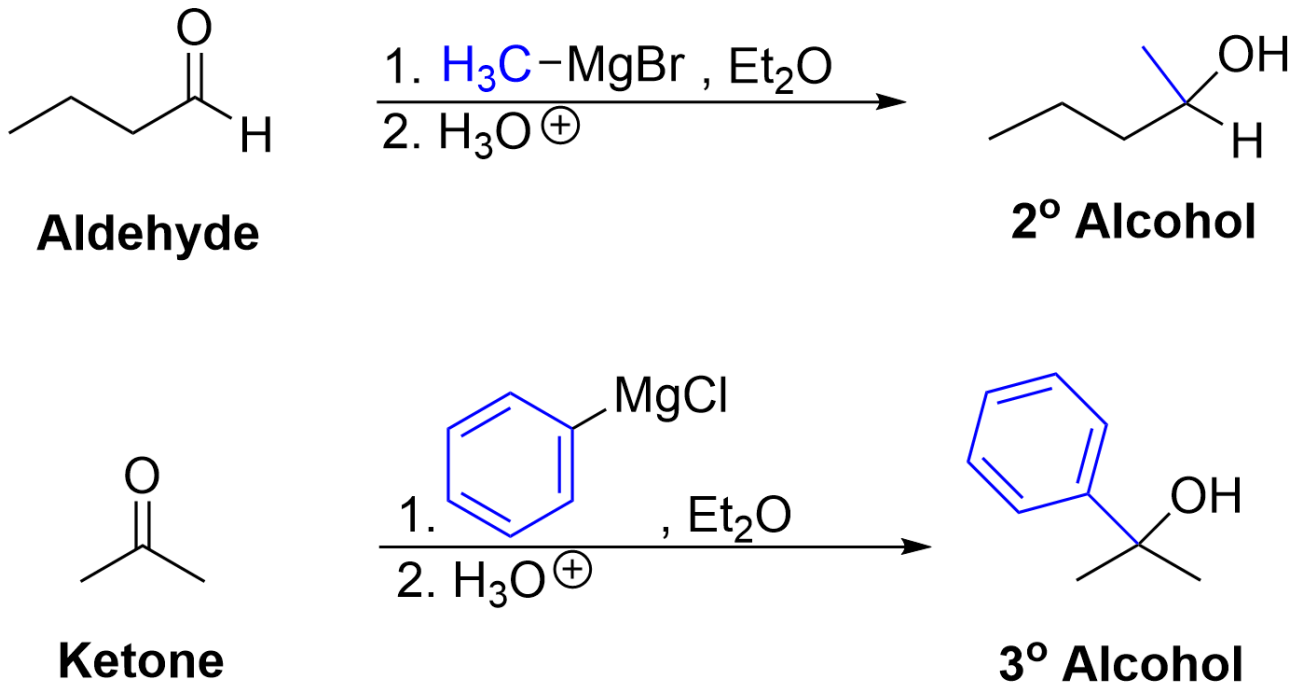

Figure 3.4.2.d. *Grignard reactions using both an aldehyde and a ketone and their respective products.*

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(The full solution to this problem can be found in Chapter 5.2)

Mechanism of Grignard Reaction for Aldehydes and Ketones

The reaction consists of two individual mechanistic steps, which include the **creation of the carbon—carbon σ bond** and then the **protonation** of the alkoxide intermediate across the carbonyl π bond.

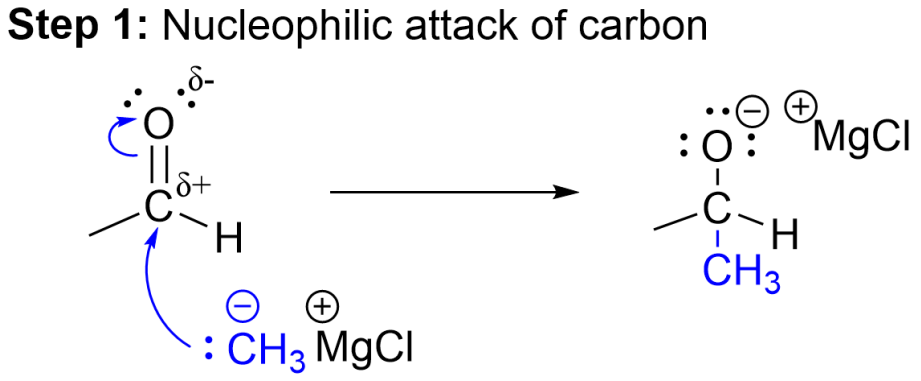

Figure 3.4.2.e. *The first step in the Grignard reaction with an aldehyde. In this step, the Grignard reagent, which contains a nucleophilic carbon, attacks the electrophilic carbon carbonyl center, breaking the C=O π bond.*

The first step of this reaction is the **nucleophilic attack of the Grignard reagent** at the electrophilic carbon centre of the carbonyl group. The lone pair of electrons on the Grignard reagent attack the carbon center of the aldehyde to form a new covalent bond. As a new bond is forming, another bond must break to ensure that the octet rule is not violated at carbon. The π bond preferentially breaks, with the electron pair from the π orbital of the C=O bond moving towards the electronegative oxygen. This step results in the formation of a new C–C bond and formation of an alkoxide intermediate with a formal negative charge at oxygen.

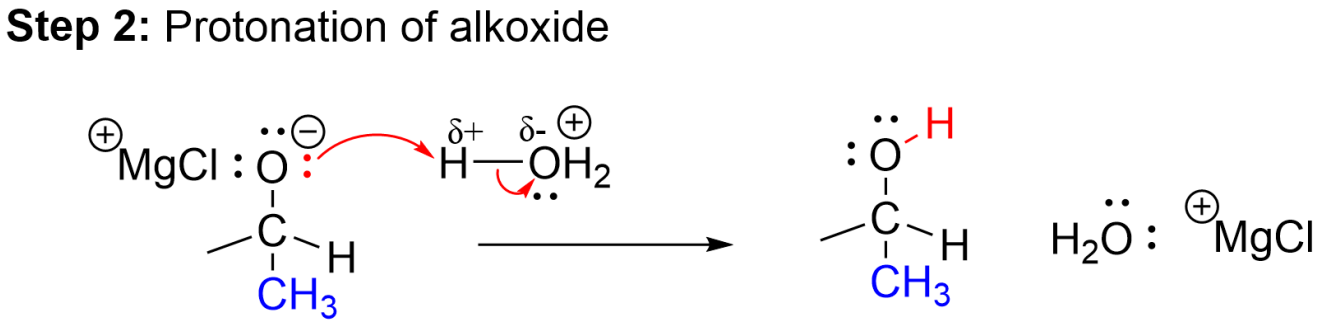

Figure 3.4.2.f. *The second step in the Grignard reaction with an aldehyde. In this step, the alkoxide is protonated by an acid, H_3O^+, resulting in the final products: a secondary alcohol and water, as well as $MgCl^+$ remaining after the first step.*

The second step of this reaction is the **protonation** of the negatively charged oxygen in the alkoxide intermediate. As the previous step ended with an anionic alkoxide as the intermediate, it must be protonated to stabilize the molecule and produce a neutral alcohol. This will occur by using **acid**, written as H_3O^+. The

negatively charged oxygen uses a lone pair of electrons to abstract the proton on the acid. This is essentially an acid-base reaction between H_3O^+ (the acid) and the anionic alkoxide (the base). This second step results in our final product, a secondary alcohol.

The addition of a Grignard reaction to an aldehyde produces a **secondary alcohol**. Aldehydes only contain one carbon attached to the central carbonyl carbon, but reaction with the carbon-containing Grignard reagent will increase the number of carbons attached to the central carbon to two.

The mechanism for Grignard reaction with ketones is functionally identical to that of aldehydes. It follows the same pattern of an initial nucleophilic attack from the Grignard reagent, followed by protonation of the anionic oxygen. Reacting a ketone with a Grignard reagent produces a **tertiary alcohol**. Ketones contain two carbons attached to the central carbonyl carbon, so reacting with the carbon-containing Grignard reagent will increase the number of carbons attached to the central carbon to three.

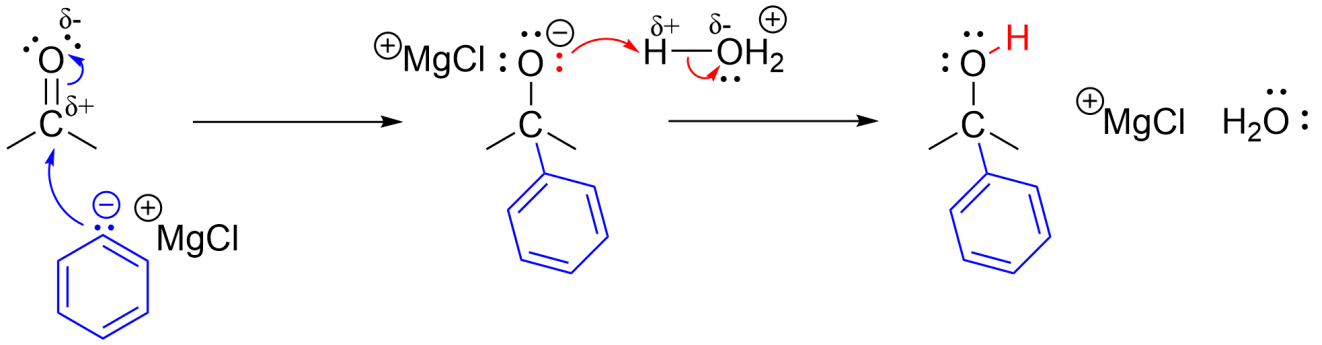

Figure 3.4.2.g. *The mechanism steps of the Grignard reaction with a ketone. It follows a similar two—step process that involves the nucleophilic attack of the alkyl chain, following by the protonation of the alkoxide.*

The two-step reaction can be summarized in the following manner, showing the intermediate as well as the starting reactant and product.

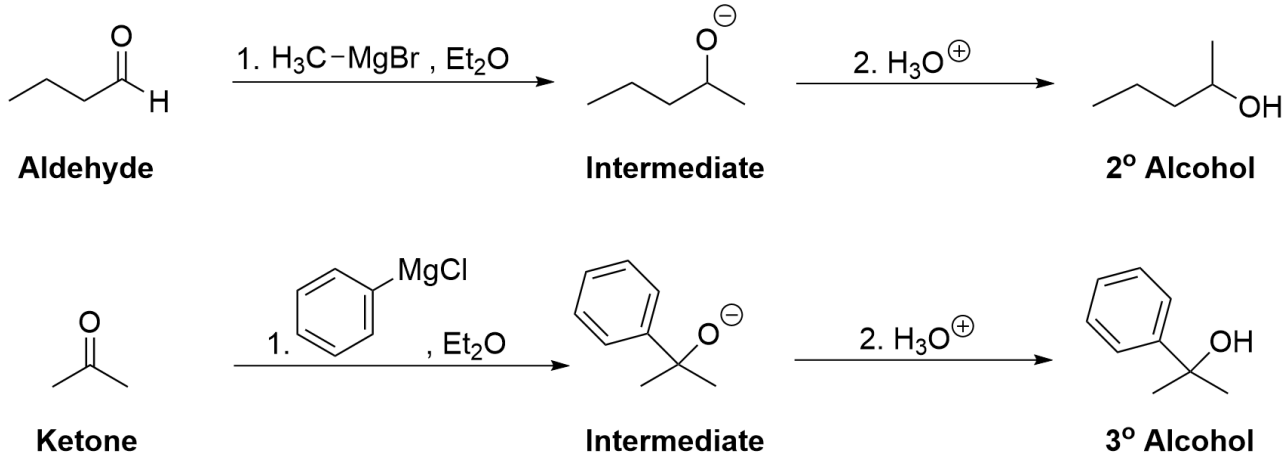

Figure 3.4.2.g. *The reactants, intermediates and products in a Grignard reaction of carbonyls.*

Energy Profile Diagram of Grignard Reactions

As this reaction follows a two-step process, we can draw an energy diagram to show the changes in energy and the intermediate formed in the reaction. The **minimum** of the energy profile represents the alkoxide intermediate that is synthesized in the first step after the addition of the C–C bond. The two **maxima** correspond to the two transition states where bond breaking and forming are occurring.

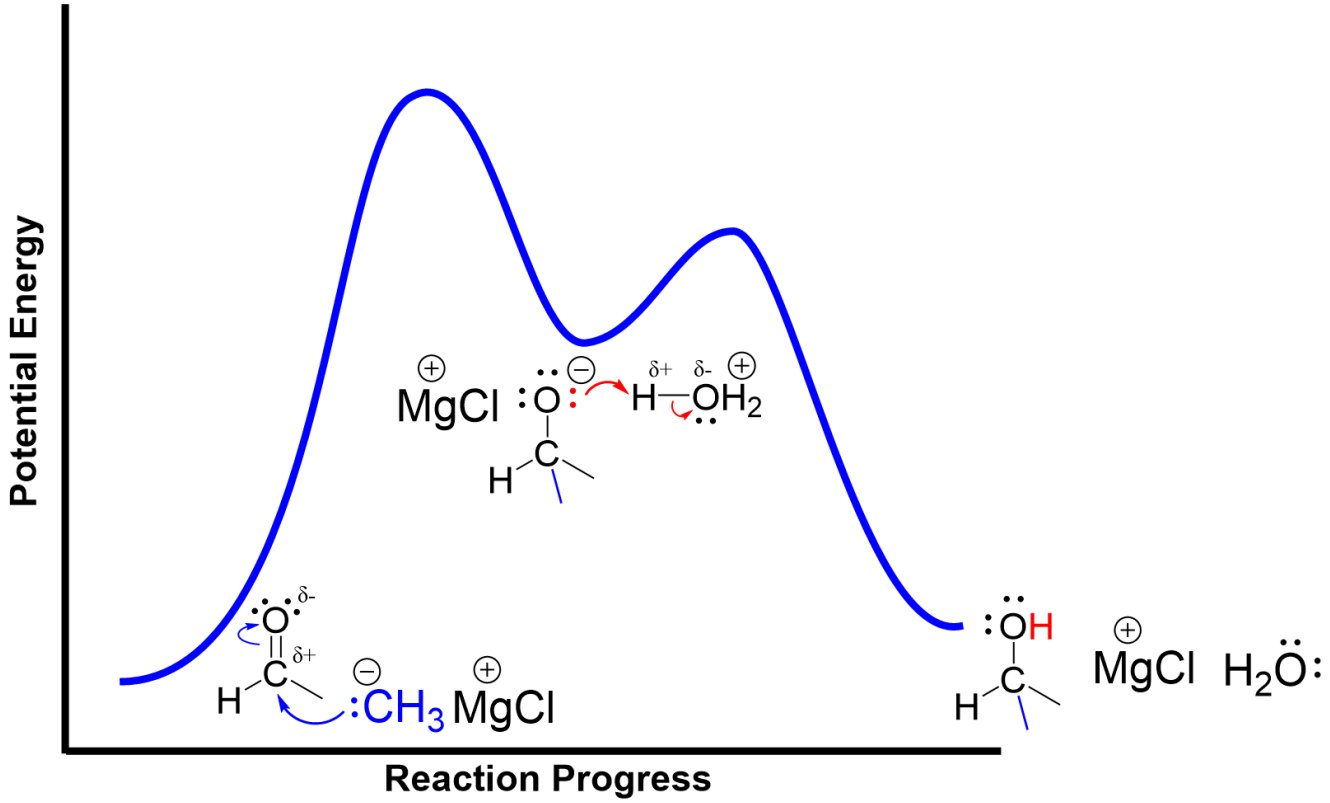

Figure 3.4.2.h. *An energy profile diagram of a Grignard reaction with an aldehyde. The two energy maxima correspond to the transition states for each step, while the energy minimum corresponds to the alkoxide intermediate.*

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(The full solution to this problem can be found in Chapter 5.2)

Key Takeaways

- A Grignard reagent is a specific molecule which has a nucleophilic carbon. It has the general form R–MgX, where X is usually Br or Cl.
- Grignard reagents are formed when alkyl halides react with elemental magnesium in Et_2O solvent.
- Grignard reagents can be used to form new carbon-carbon bonds when they are reacted with a carbonyl group containing reagent, as in an aldehyde or a ketone. This results in an alcohol product.
- There are **two steps** involved in the Grignard reaction with carbonyls:
    1. The nucleophilic Grignard carbon attacks the electrophilic carbon centre of the carbonyl group, breaking a π bond to oxygen in the process. This results in an alkoxide intermediate.
    2. The alkoxide intermediate is protonated in the presence of an acid to produce an alcohol.
- The degree of the alcohol product relies on how many carbons the carbonyl group was bound to initially.

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3.4.3 - COMPARING SODIUM BOROHYDRIDE REDUCTIONS AND GRIGNARD REACTIONS

The last two chapters discussed the reduction of carbonyl groups using sodium borohydride and the addition of a carbon-containing group using a Grignard reagent. Although these reactions may seem different at first glance, they have several similarities.

First, both reactions result in **the formation of alcohol**.

Second, both reactions result in the **reduction of the carbonyl group**. The C=O π bond is broken, and two new σ bonds are formed: an O-H σ bond and either a C–H σ bond (for sodium borohydride reduction) or a C–C σ bond (for the Grignard reaction).

Third, both reactions follow a **two-step process**. The first step involves attack of **electrophilic carbon** in the carbonyl group by the **nucleophilic hydride** (for the sodium borohydride reduction) or the **nucleophilic Grignard reagent** (for the Grignard reaction). The intermediate in both reactions is an **anionic alkoxide** (Figure 3.4.3.a). The second step (Figure 3.4.3.b) is the same for both reactions, involving an acid-base reaction between the anionic alkoxide (base) and hydronium (acid).

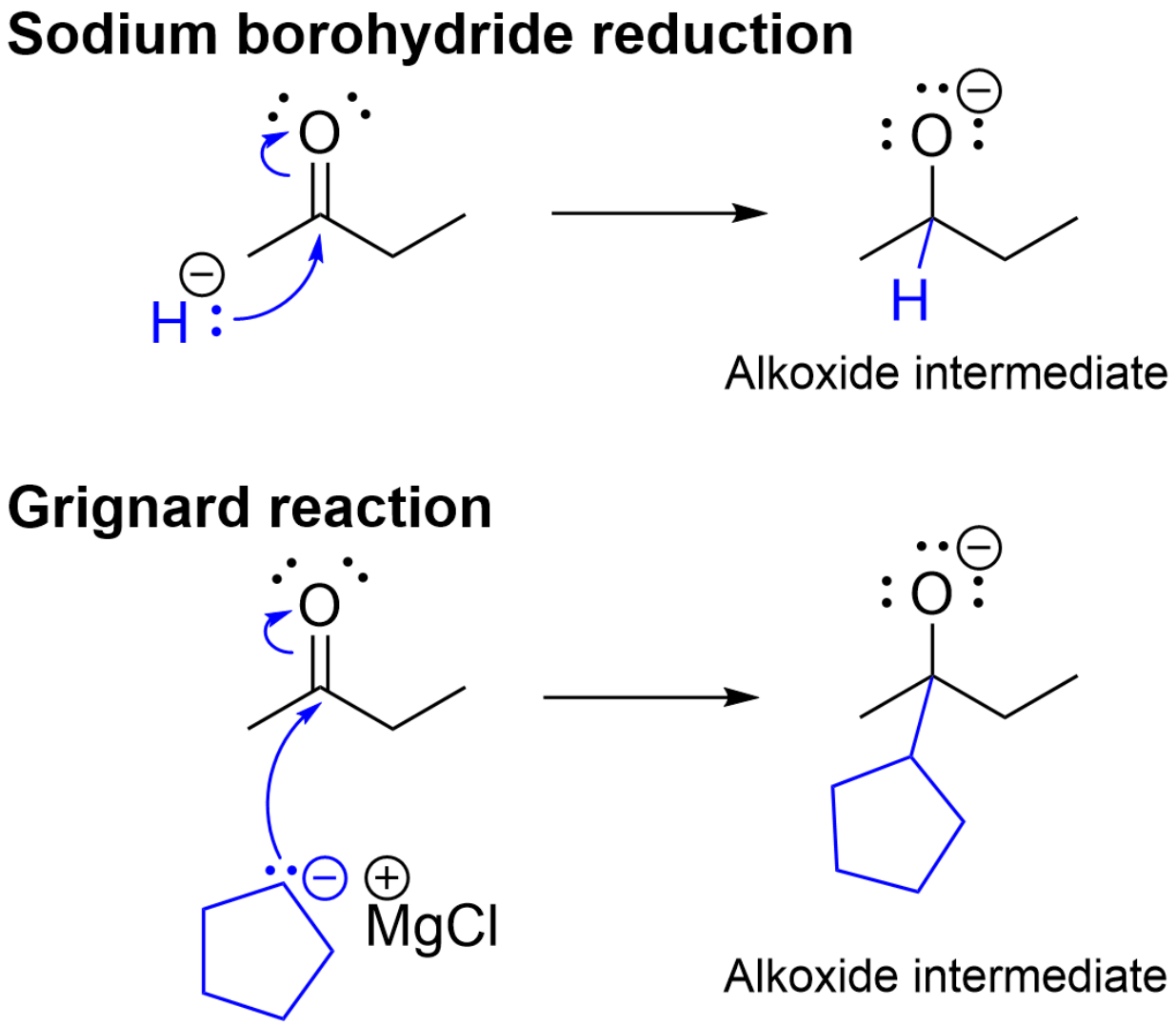

Figure 3.4.3.a. *The first step in the reduction of a ketone with sodium borohydride and the Grignard reaction with a ketone. Both reactions proceed with the attack of a nucleophile (hydride or carbon) to the electrophilic carbonyl carbon center.*

The difference between these reactions is that the Grignard reaction adds a new carbon-containing group whereas sodium borohydride a hydrogen to the carbon centre of the carbonyl group.

Table 3.4.3. A comparison between the sodium borohydride reduction of carbonyls and the Grignard reaction with a carbonyl group.

	$NaBH_4$ Reduction of Carbonyls	**Grignard Reaction with Carbonyls**
Product	Formaldehyde → Methanol Aldehyde → Primary alcohol Ketone → Secondary alcohol	Formaldehyde → Primary alcohol Aldehyde → Secondary alcohol Ketone → Tertiary alcohol
Bonds Broken and Formed	C=O π bond is broken C–H σ bond is formed O–H σ bond is formed	C=O π bond is broken C–C σ bond is formed O–H σ bond is formed
# of Mechanistic Steps	2 steps; first step is slow	2 steps; first step is slow
Intermediate	Anionic alkoxide	Anionic alkoxide
First Step	Attack of electrophilic carbon in the carbonyl group by the nucleophilic hydride	Attack of electrophilic carbon in the carbonyl group by the nucleophilic Grignard reagent
Second Step	Proton transfer from hydronium (acid) to alkoxide (base)	Proton transfer from hydronium (acid) to alkoxide (base)

The second step in both reactions are the exact same, in that the alkoxide must be protonated using mild acid. In both, the lone pair on the alkoxide abstracts a hydrogen from the H_3O^+ acid, leading to our final alcohol product. Note that the reduction results in a secondary alcohol, whereas the Grignard reaction results in a tertiary alcohol.

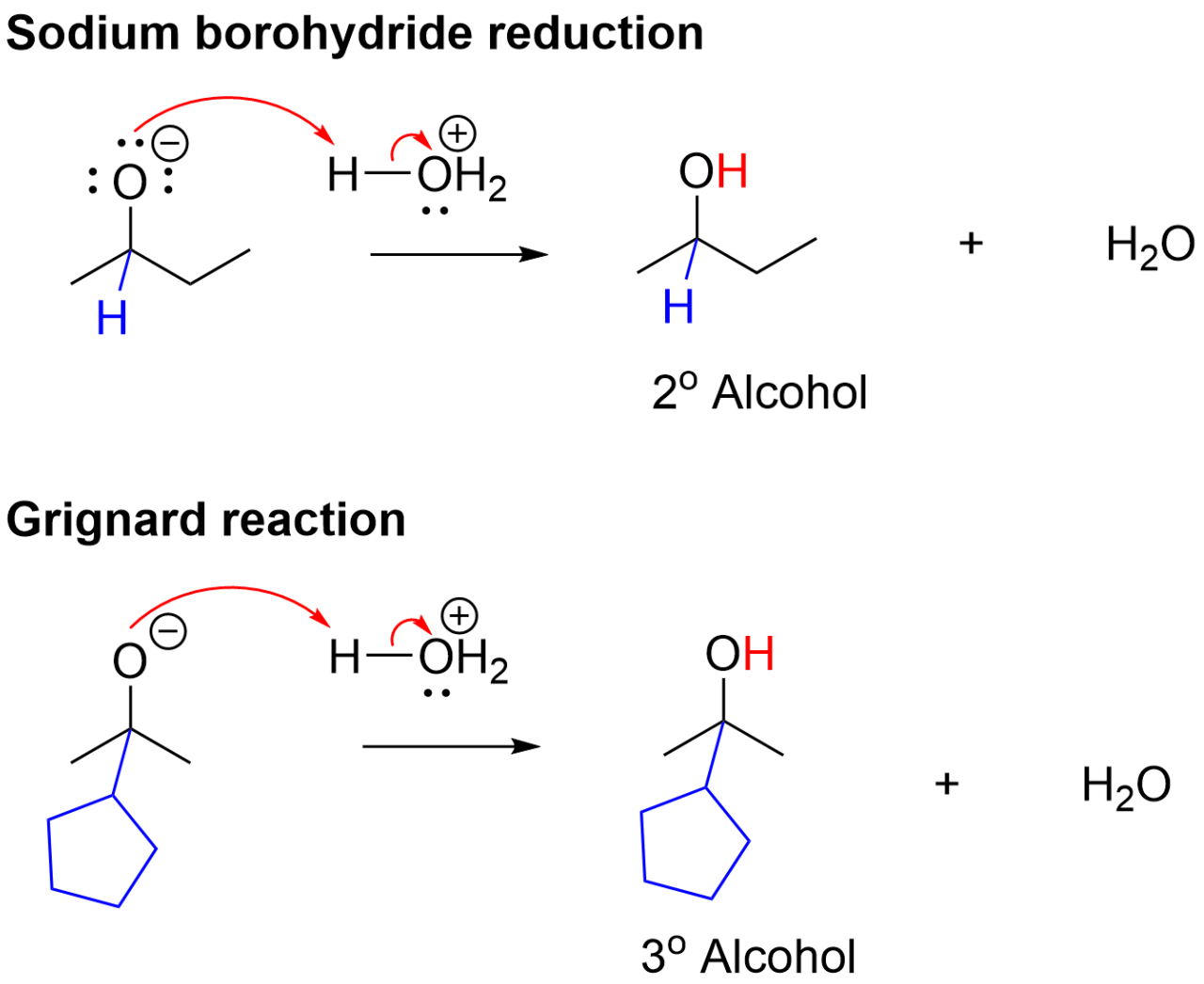

Figure 3.4.3.b. *The second protonation step in the reduction of a ketone with sodium borohydride and the Grignard reaction with a ketone. In both reactions, the alkoxide donates a lone pair to abstract a hydrogen from the acid.*

Discerning Between Sodium Borohydride Reduction and Grignard Reaction

To determine whether to use $NaBH_4$ reduction or a Grignard reaction to produce an alcohol from an aldehyde or ketone, you can take two different approaches (Figure 3.4.3.c).

The first method is to determine whether the number of carbon atoms has increased in the products relative to the reactants. If the number of carbon atoms is the same, then this is $NaBH_4$ reduction; if the number of carbons has increased, then this is a Grignard reaction.

The second method is to identify the functional groups, including whether the starting material is an aldehyde or a ketone, and whether the product is a primary, secondary, or tertiary alcohol. If an aldehyde reacts to form a primary alcohol, then this is $NaBH_4$ reduction. If an aldehyde reacts to form a secondary alcohol,

then this is a Grignard reaction. If a ketone reacts to form a secondary alcohol, then this is $NaBH_4$ reduction. If a ketone reacts to form a tertiary alcohol, then this is a Grignard reaction.

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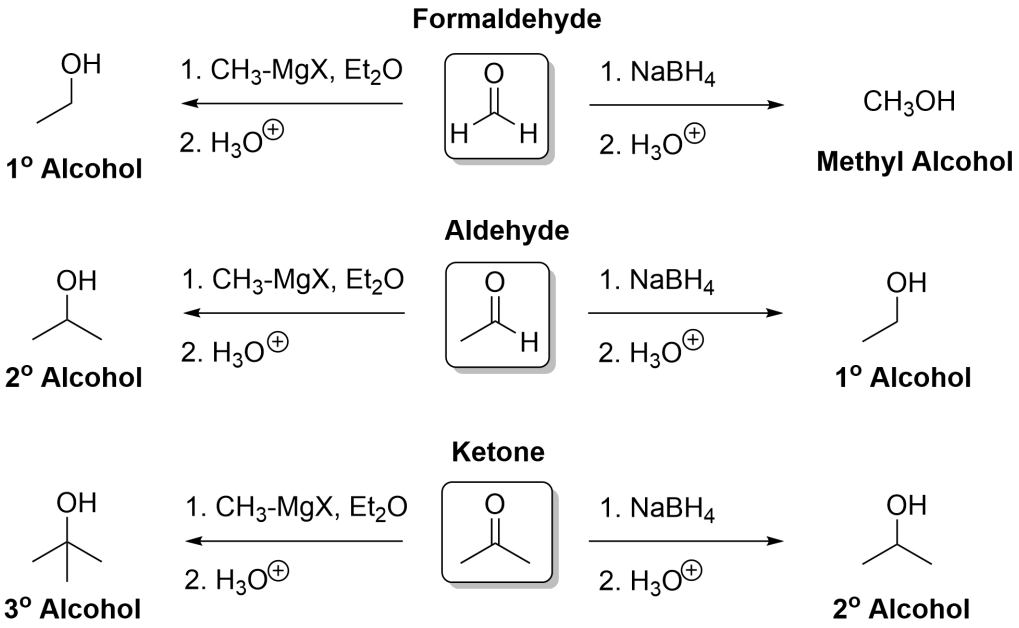


Figure 3.4.3.c. *The final products of an aldehyde and ketone when reacted with either sodium borohydride or a Grignard reagent.*

Study Notes – Chapter 3.4

Reduction: lose C-O bonds, form C-H bonds

Red w/ hydride: need a H^+ and H^- to reduce CA of carbonyls

e.g: aldehyde $\xrightarrow[2.\ H_3O^+]{1.\ NaBH_4}$ 1° alcohol

ketone $\xrightarrow[2.\ H_3O^+]{1.\ NaBH_4}$ 2° alcohol

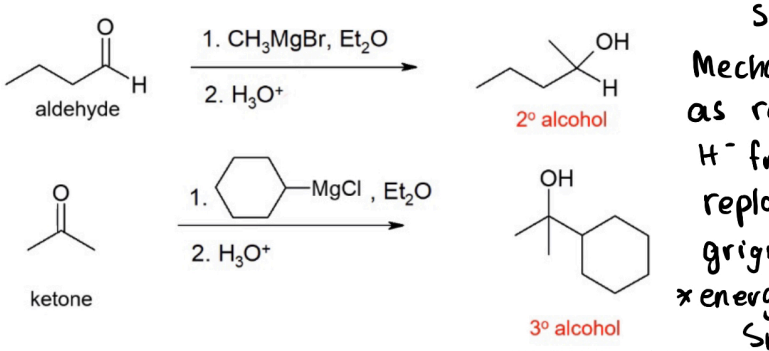
* carbon takes H^- and oxygen takes H^+

* energy diagram looks like S_N1

Red w/ grignard: takes place in non-polar sol. so Et_2O and involves insertion of metal (Mg) btwn PC and X of R-X so PC is negative

e.g: R-X $\xrightarrow[Et_2O]{Mg}$ R-MgX

Rxn. w/ grignard: R-MgX + carbonyls *note: no water in first step



Mechanism is the same as red. w/ hydride, just H^- from $NaBH_4$ is replaced with C^- from grignard.

* energy diagram looks like S_N1

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3.5 - REACTIONS OF CARBOXYLIC ACIDS AND DERIVATIVES

Learning Objectives

1. Predict products and write reaction schemes for the following reactions (no curved arrow mechanisms or energy profile diagrams required):
    1. Preparation and hydrolysis of an ester from a carboxylic acid and an alcohol, and the implications of the equilibrium reaction in terms of Le Châtelier's Principle
2. Predict products, write reaction schemes, draw curved arrow mechanisms, and draw energy profile diagrams, including all intermediates and transition states for the following reactions:
    1. Reaction of carbon dioxide with a Grignard reagent
    2. Preparation of an ester via a nucleophilic substitution reaction

Carboxylic Acids and its Derivatives

A**carboxylic acid** is a functional group containing a central carbon atom bound to both a carbonyl group and a hydroxyl group. Various examples of carboxylic acids are displayed below in Figure 3.5.a. The carbonyl carbon is electron-deficient due to the surrounding electronegative oxygen atoms, rendering this carbon electrophilic.

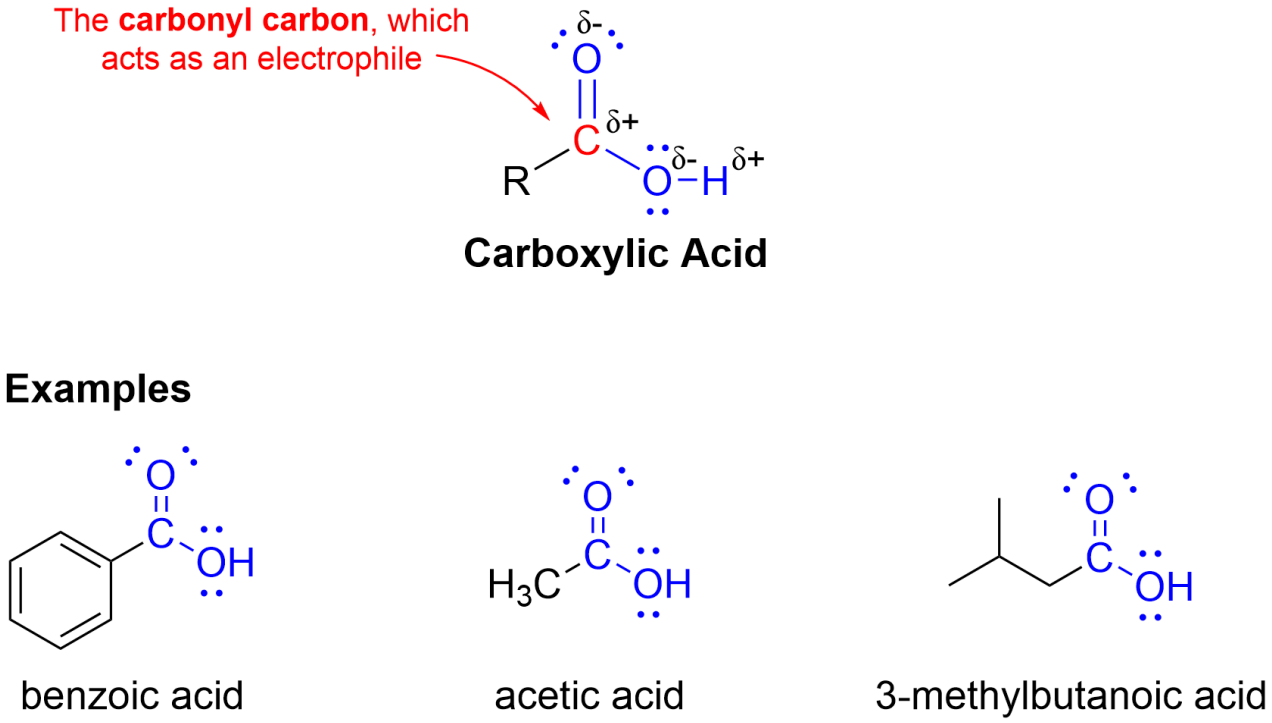

Figure 3.5.a. *Examples of carboxylic acids.*

There are also several **carboxylic acid derivatives** (Figure 3.5.b), as described in Chapter 2.3. These derivatives all contain a central carbon that contains a carbonyl group along with a single bond to an electronegative atom or group. In these derivatives, the carbon center contains *three* total bonds to heteroatoms that are more electronegative than carbon. As a result, carboxylic acid derivatives share a similar oxidation state around the central carbon. Many carboxylic acid derivatives have similar reactivity patterns, with the carbonyl carbon acting as an electrophile, similar to the reactivity to aldehydes and ketones.

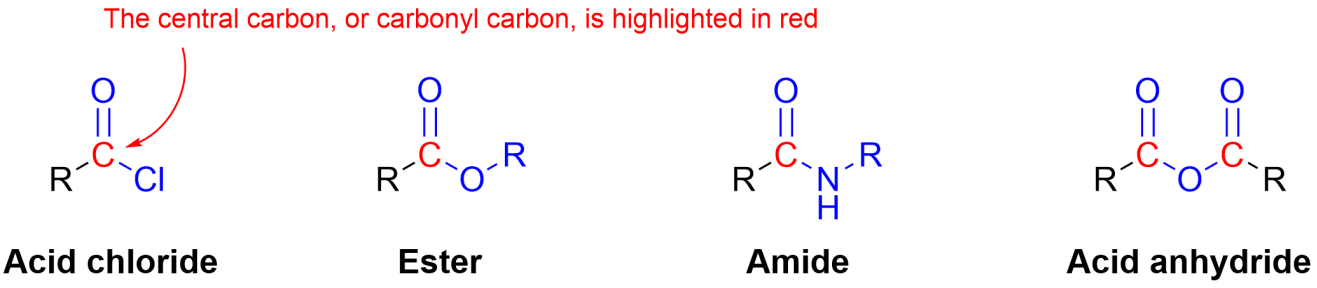

Figure 3.5.b. *The chemical structure of several carboxylic acid derivatives, including acid chlorides, esters, anhydrides, and esters. Note that all derivatives still contain the C=O carbonyl group, alongside an electronegative atom or group bonded to the central carbon.*

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Carboxylic acids are weakly acidic functional groups, with Ka values in the 10^{-5} range. Thus, carboxylic acids react with water in an equilibrium reaction to generate a small proportion of the conjugate base, known as a **carboxylate**, along with hydronium ions, H_3O^+ (Figure 3.5.c, top). Carboxylic acids also react with strong bases, such as sodium hydroxide, and the reaction goes to completion to generate the conjugate base carboxylate and water (Figure 3.5.c, bottom).

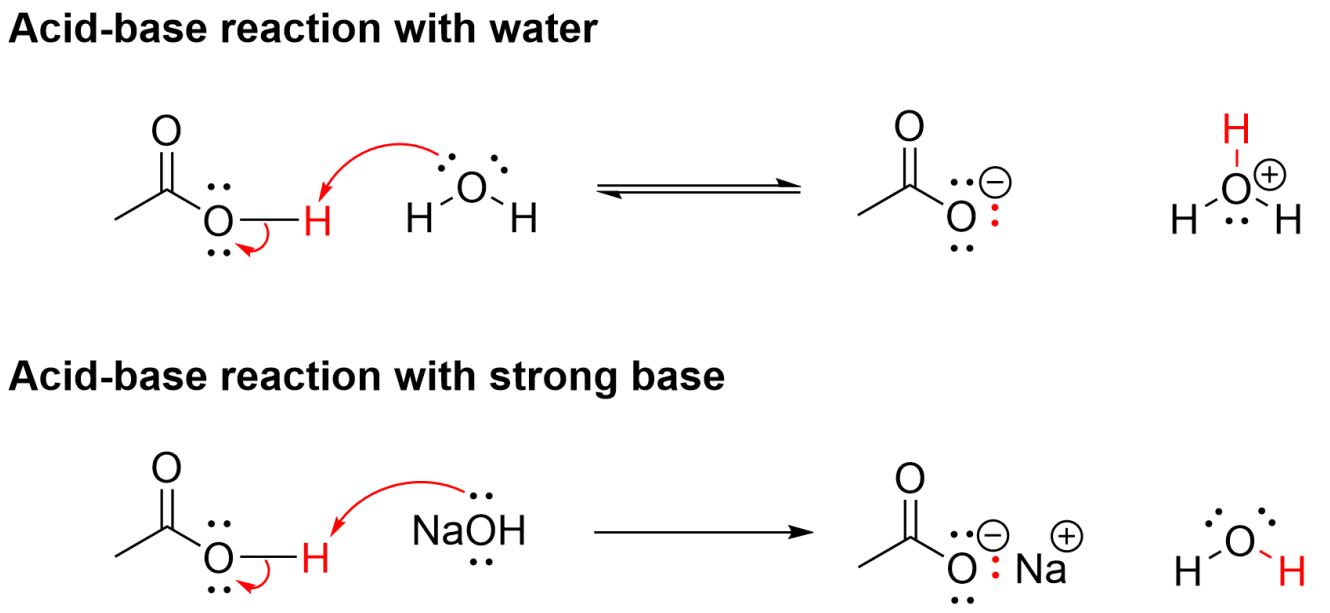

Figure 3.5.c. *Acid-base reactions involving a carboxylic acid and water or a strong base (sodium hydroxide). Both reactions form a carboxylate, however, only with use of a strong base will the reaction be irreversible.*

The Synthesis of Carboxylic Acids

Based on what has been covered in previous chapters, there are two major methods to synthesize carboxylic acids.

The first method involves the **oxidation of a primary alcohol or an aldehyde** to a carboxylic acid (Figure 3.5.d), which was discussed in Chapter 3.3. When reacting a primary alcohol with an oxidizing agent such as

$KMnO_4$ or $K_2Cr_2O_7$, two successive oxidations will occur. The primary alcohol will first be oxidized to an aldehyde, and then immediately oxidized further to a carboxylic acid. An aldehyde can also be reacted with these oxidizing agents to form a carboxylic acid in a single step.

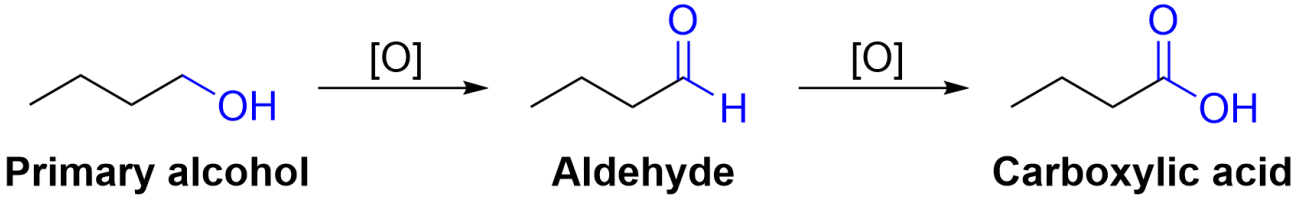

Figure 3.5.d. *The oxidation of a primary alcohol to a carboxylic acid. The starting reagent can either be a primary alcohol, which requires a two-step oxidation, or an aldehyde, which only requires one. Recall that [O] represents an oxidizing agent such as $KMnO_4$ or $K_2Cr_2O_7$.*

Another method to synthesize carboxylic acids involves reacting a **Grignard reagent with carbon dioxide**, CO_2 (Figure 3.5.e). The Grignard reagent acts as a nucleophilic carbon center as discussed in Chapter 3.4.2, while the CO_2 acts as an electrophile due to its electron-deficient carbon center. In the first step of the reaction, the nucleophilic Grignard reagent attacks the electrophilic carbon of the carbon dioxide, resulting in the formation of a new C–C bond. At the same time, one of the C=O π bonds breaks, with both electrons moving to oxygen. The result is a **carboxylate** anion. In the second step, the addition of acid protonates the carboxylate, producing a neutral carboxylic acid.

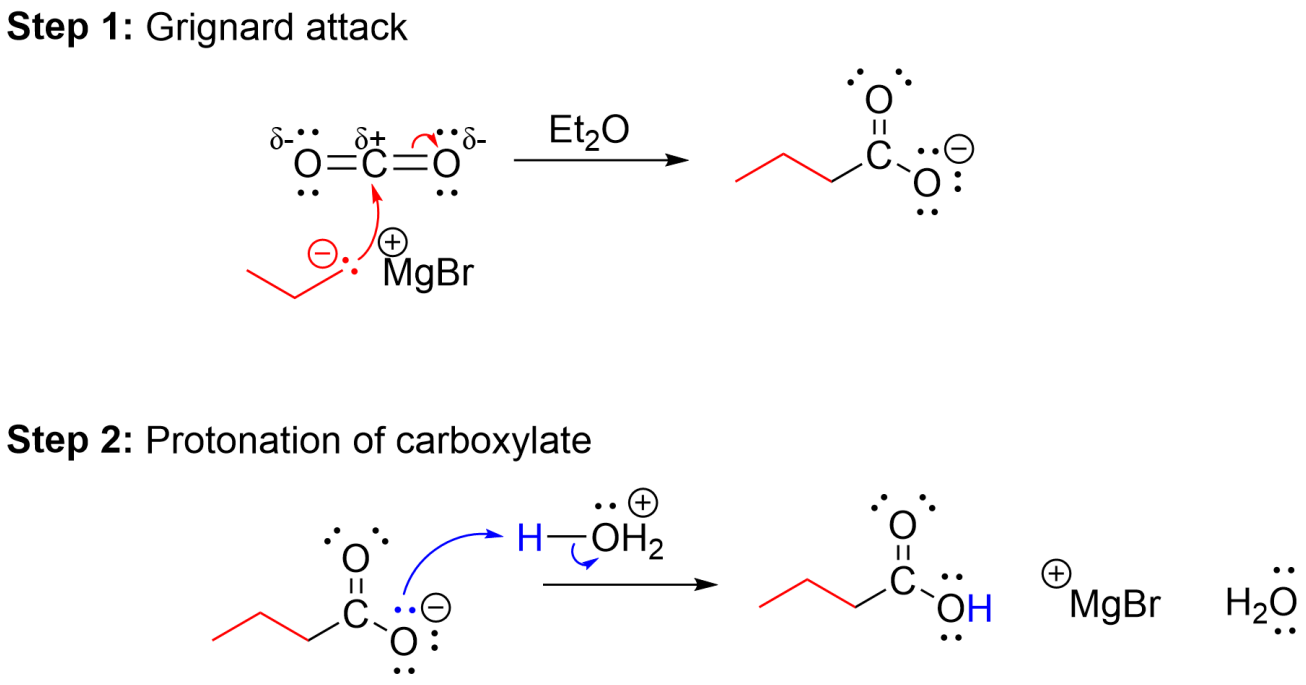

Figure 3.5.e. *The reaction of a Grignard reagent with carbon dioxide, CO_2, to form a carboxylic acid.*

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(The full solution to this problem can be found in Chapter 5.2)

The Synthesis of Esters

An **ester** can be synthesized through an **S_N2 reaction** (Figure 3.5.f), as discussed in Chapter 3.1.2. A carboxylate acts as a nucleophile due to the lone pairs on the negatively charged oxygen, while an alkyl halide acts as an electrophile.

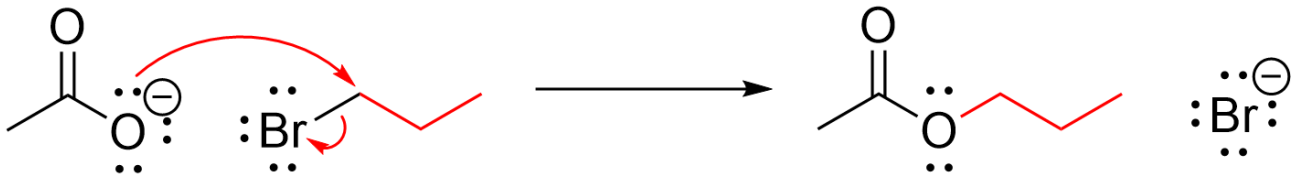

Figure 3.5.f. *An S_N2 reaction between a carboxylate and a primary alkyl halide, resulting in an ester.*

The carboxylate uses a lone pair of electrons on oxygen to attack the electrophilic carbon. With the introduction of a new bond, the bromine atom leaves simultaneously, taking the pair of electrons from the covalent bond with it to form a bromide anion. Recall that as an S_N2 reaction, these events happen via a concerted mechanism in one step, and primary and methyl alkyl halides work best due to the reduced steric bulk. This reaction introduces a new carbon chain to the oxygen, forming an ester.

Esters can also be formed through an acid catalyzed **reversible** reaction of carboxylic acids and alcohols. This reaction is an equilibrium, and appreciable amounts of all reactants and products are found at

equilibrium. The forward reaction to form an ester is called **esterification**, while the reverse reaction to break apart the ester is called **ester hydrolysis**.

In the **acid catalyzed esterification reaction**, a carboxylic acid and alcohol react to produce an ester and water under heated conditions with an acid catalyst. The reverse reaction is known as ester hydrolysis. **Hydrolysis** involves using water (*hydro*) to break a molecule apart (*lysis*), in this case an ester. The products of ester hydrolysis are a carboxylic acid and an alcohol.

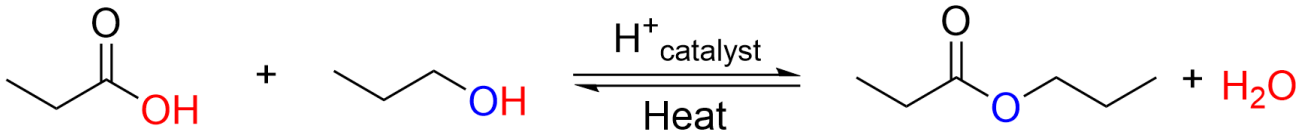

Figure 3.5.g. *The forward reaction shows esterification, in which a carboxylic acid reacts with an alcohol to generate an ester and water. The reverse reaction shows hydrolysis of an ester, in which an ester reacts with water to produce a carboxylic acid and an alcohol. Both the forward reaction and the reverse reaction require an acid catalyst and heat.*

These reactions are **equilibrium processes,** and thus, we can take advantage of Le Chatelier's principle to push the reaction one way or the other. For example, to drive the forward reaction, a high concentration of alcohol is used, and the amount of water used is minimized. Conversely, to drive the reverse reaction, a greater amount of water is used. An acid catalyst and heat are required for both the forward and reverse reactions.

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(The full solution to this problem can be found in Chapter 5.2)

Key Takeaways

- A carboxylic acid is a functional group containing a central carbon atom bound to both a carbonyl group and a hydroxyl group – where carbonyl carbon is electrophilic.
- There are several carboxylic acid derivatives containing a central carbonyl group with a single bond to an electronegative atom/group.
- Carboxylic acids are weakly acidic and form the conjugate base carboxylate in water.
- Carboxylic acids are synthesized by either oxidation of a primary alcohol or aldehyde, or through a Grignard reaction with carbon dioxide.
- An ester can be synthesized through an acid catalyzed **reversible** reaction of carboxylic acids and alcohols (esterification).
- Subsequently, the reverse reaction of esterification is ester hydrolysis, both reactions are in equilibrium and follow Le Chatelier's principle.

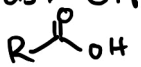
Diversity in Chemistry: Agnes Pockels

A portrait of Agnes Pockels.

A common use of carboxylic acids in our everyday life is for soaps, which are made from fatty acid carboxylate salts. Although most of us would probably not bat an eye at how these soaps interact with liquids, **Agnes Pockels** found an interest in surface tension after observing soapy water while doing the dishes at home. As a young child, Pockels developed an interest in science, but as women in Germany were not allowed to attend university, she self-studied at home using her brother's textbooks. At 18 years old though, inspired by her observations while washing dishes, Pockels started conducting experiments in her own home by constructing a slide trough to measure surface properties of soapy water. Her invention, later on, played a role in developing the widely used Langmuir-Blodgett Trough used in surface chemistry today. With her brother's connections, who was a developing scientist at the time, she was able to obtain a publication in 1891 in the well-renowned *Nature* journal with no formal scientific training. Although she never received a formal appointment for her research, she was acknowledged by commentators after Langmuir won the Nobel Prize in Chemistry in 1932, and is considered a pioneer of surface chemistry.

Study Notes – Chapter 3.5

Carboxylic acids: CA + H_2O or NaOH → carboxylate + H_3O^+ or H_2O

e.g:  + NaOH → Na^+ + H_2O

derivatives:

Acid chloride | Anhydride | Ester | Amide

2

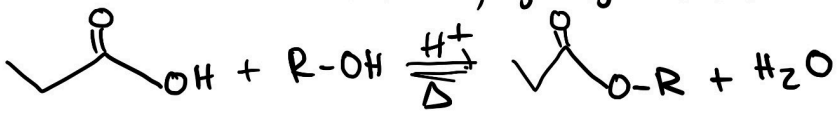
CA formed from R–MgX: R-MgX attacks CO_2 to break one C=O which then gets protonated (H^+) in H_3O^+ soln.

R-MgX $\xrightarrow[2.\ H_3O^+]{1.\ CO_2}$ 

Esterfication: forming esters

① Using Sn2: carboxylate + R-X → ester

② Fischer: esterfication (← condensation): CA + OH, hydrolysis: ester + H_2O



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3.6 - SYNTHESIS

Learning Objectives

1. Complete organic reaction schemes by providing reactants or products

Through stepwise reactions, organic chemists can take a simple molecule and add different functionalities to make a single, complex molecule. In this chapter, we will examine how to synthesize more complex molecules through one or more reactions, using the organic reactions we have covered so far in this course (Figure 3.6.a).

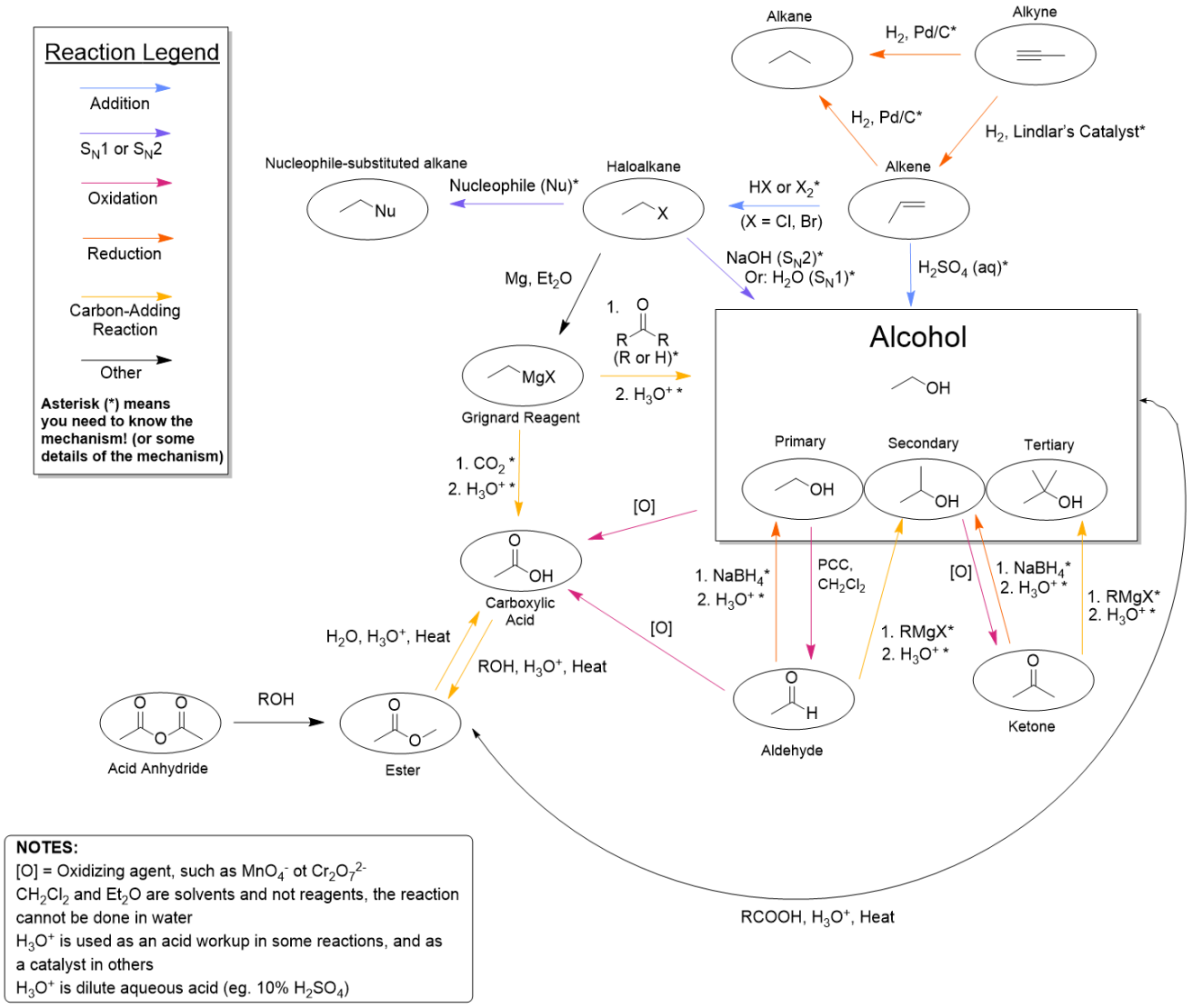

Figure 3.6.a. A synthesis chart showcasing all the reactions learned in CHEM 1AA3.

Reactions can be classified roughly into two different categories: (1) **functional group interconversion reactions** and (2) **skeletal structure expansion reactions**.

Most of what is covered in this course is categorized as **functional group interconversion reactions**. These reactions take one functional group, such as an alcohol, and convert it to something else, such as a carboxylic acid.

Reactions that **expand the skeletal structure** increase the number of carbon atoms in a molecule. The Grignard reaction is one example, which results in the formation of a new carbon-carbon bond. Esterification is another example as it introduces more carbon atoms. Note that reactions which expand the skeletal structure may also involve a change of functional group. For example, the Grignard reaction not only forms a new C–C bond, but also reduces a carbonyl group to an alcohol. In addition, esterification changes a functional group (carboxylic acid and alcohol, or carboxylate and alkyl halide) to an ester.

Some students find synthesis questions difficult due to the sheer number of reactions. Here are some tips to consider when approaching any synthesis question:

1. Count the carbons
2. Identify changes in functional groups
3. Work backwards
4. Consider a series of reactions

Count the Carbons

The first step when approaching any synthesis question is to count the number of carbons. Take note whether the number of carbons on the molecule has changed. If there are more carbon atoms in the product compared to the reactant, then (at this point) you can assume that it must have occurred through (1) a Grignard reaction or (2) an esterification reaction.

A sample question is shown in Figure 3.6.b.i.

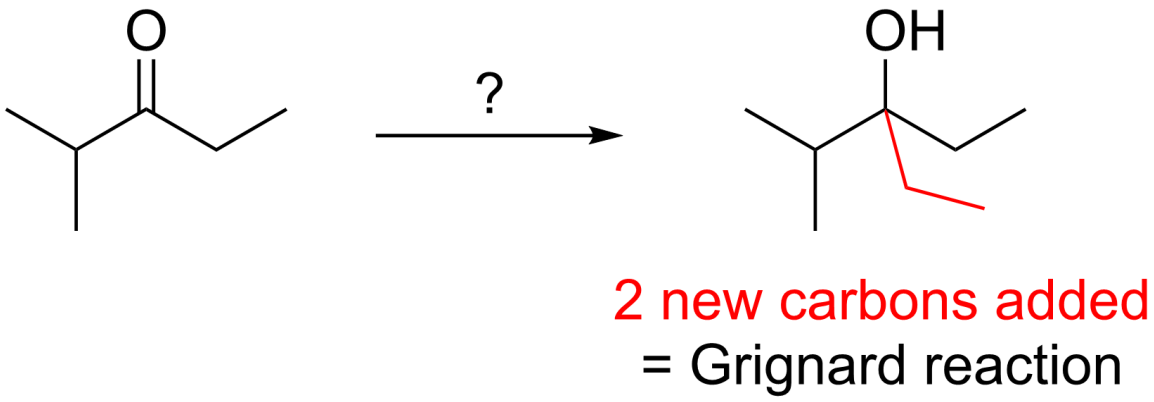

Figure 3.6.b.i. *An example synthesis question, starting with a ketone and resulting in an alcohol. As two new carbon atoms were added onto the skeletal chain, it can be concluded that an ethyl Grignard reagent (with two carbons) was used.*

In this example, we can see that there has been the addition of two carbons to the starting substrate. As we only know one C–C bond forming reaction, we can conclude that a Grignard reaction must have taken place. A Grignard reaction uses a Grignard reagent (R–MgX), which contains a nucleophilic carbon centre, to attack a carbonyl center of an aldehyde or ketone, forming a new C–C bond.

Since two new carbon atoms (plus five attached hydrogens) are seen on the product, the Grignard reagent

must have two carbon atoms. Thus, the reactant must be C_2H_5MgX (where X = Cl, Br). Recall that Grignard reactions involve a second step in which the alkoxide intermediate is protonated with a mild acid, as discussed in Chapter 3.4.2. The solution to this sample question is shown below in Figure 3.6.b.ii.

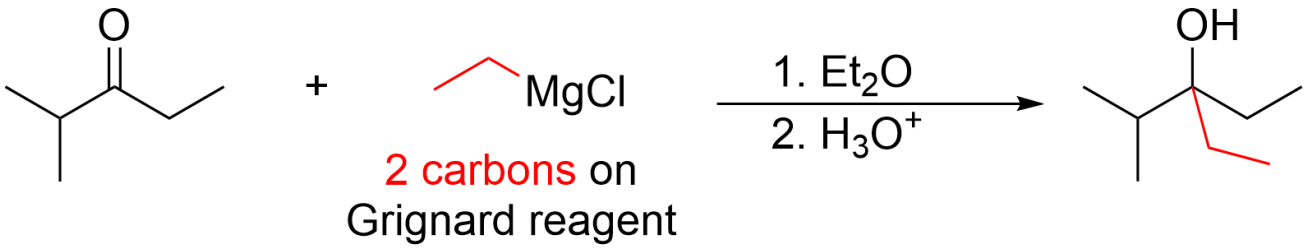

Figure 3.6.b.ii. *The full Grignard reaction between the starting alcohol and a Grignard reagent, resulting in the final alcohol product.*

Thus, counting carbon atoms, and identifying that a new C–C bond has formed, allows us to quickly determine that a Grignard reaction has occurred.

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

Identify Changes in Functional Groups

The next step is to identify the functional groups in the reactants and products, noting any changes. After you determine how the functional group is changing, you can think about what type of reaction can be used to make the change.

Let's think about the following synthesis question below in Figure 3.6.c.i.

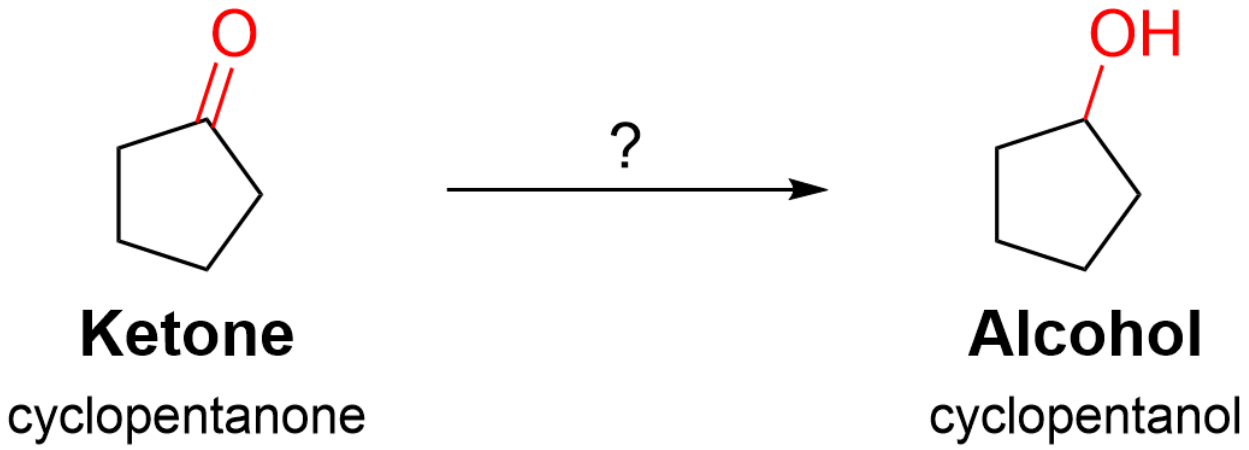

Figure 3.6.c.i. *An example that involves the reduction of a ketone, cyclopentanone, to an alcohol, cyclopentanol.*

In this example, the starting material contains a ketone functional group, which is converted to a secondary alcohol. No carbon atoms have been added to expand the skeletal structure, which means a Grignard reaction did not occur. The loss of a π bond here signifies a reduction is occurring. Recall in Chapter 3.4.1. that the reduction of carbonyls is performed with sodium borohydride ($NaBH_4$). Thus, it can be concluded that this reduction reaction occurred with $NaBH_4$, followed by protonation of the intermediate alkoxide.

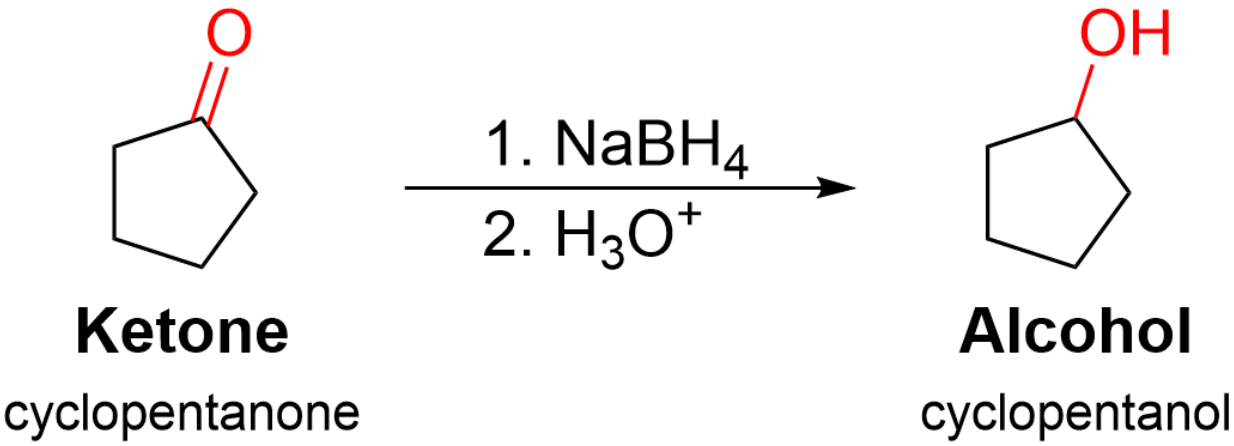

Figure 3.6.c.ii. *The full reduction reaction of cyclopentanone to cyclopentanol. This is accomplished using sodium borohydride, alongside an acid work-up step used to protonate the alkoxide.*

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

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Work Backwards

You may also be faced with a question where you must determine the starting molecule given the product and reagents. These questions require you to work backwards. If you can recognize what reaction is being performed, you can think about what the molecule looked like before the reaction took place. Figure 3.6.d.i. shows an example of this type of question.

Figure 3.6.d.i. *An example synthesis question where the product is 3-chloropentane and the reagent is HCl.*

The product is an alkyl halide, 3-chloropentane. The only reagent is HCl. You should be able to recognize that hydrohalogens (H–X) are used in the hydrohalogenation of alkenes. Next, we must then determine the

structure of the alkene starting material (pentene), including where the C=C double bond is located. There are two positions on a pentene where the double bond can reside: pent-1-ene and pent-2-ene. Which alkene would lead to 3-chloropentane as a product? Let's examine all possibilities.

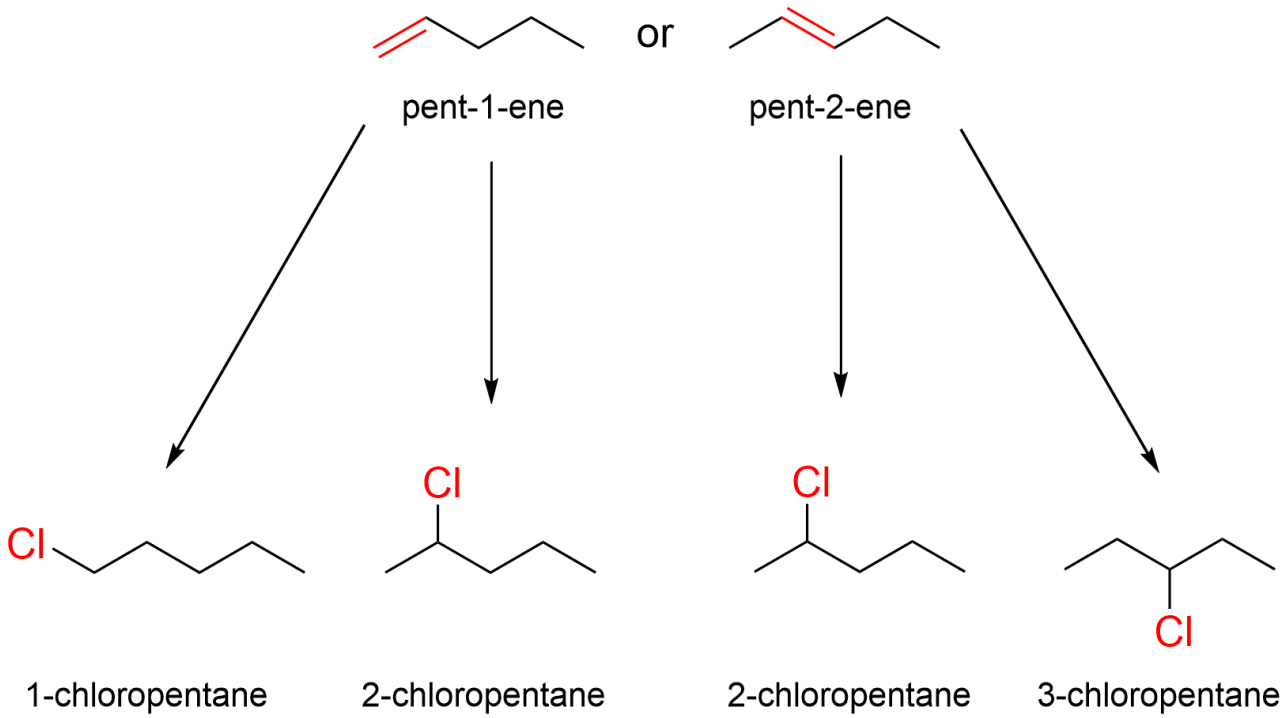

Figure 3.6.d.ii. *Hydrohalogenation of pent-1-ene (left) yields 1-chloropentane (minor product) and 2-chloropentane (major product). Hydrohalogenation of pent-2-ene (right) yields a combination of 2-chloropentane and 3-chloropentane (in roughly equal quantities). Only the reaction of pent-2-ene with HCl results in the formation of the target molecule, 3-chloropentane.*

If the starting reagent was pent-1-ene, then the major and minor products are 2-chloropentane and 1-chloropentane, respectively. Neither of these compounds are the target molecule. However, when pent-2-ene is the starting molecule, one of the products is 3-chloropentane, along with 2-chloropentane. Thus, the starting material must be pent-2-ene, as seen below in Figure 3.6.d.iii.

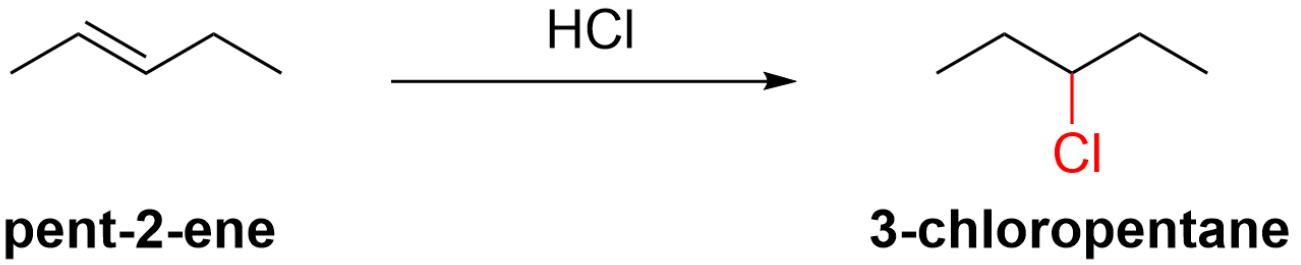

Figure 3.6.d.iii. *The final solution, with pent-2-ene reacting with HCl in an alkene addition to form the final product.*

Figure 3.6.e.i. gives a more difficult example of this kind of question.

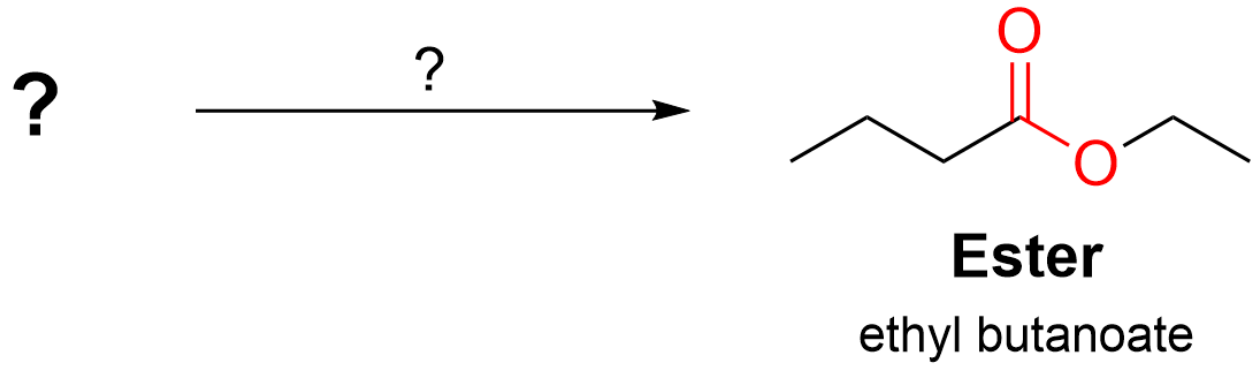

Figure 3.6.e.i. *An example synthesis question that only gives the product, an ethyl butanoate.*

In this example, the product is an ester, and the reagents are NOT given. Thus, we must think of what possible reactions can be used to synthesize this molecule. Recall that from Chapter 3.5, there are two ways to produce an ester: (1) an S_N2 reaction using a carboxylate nucleophile and an alkyl halide electrophile; or (2) an acid-catalyzed esterification reaction using a carboxylic acid and an alcohol.

First, we will examine the S_N2 reaction. To determine the reagents in this substitution reaction, the ester can be split into a carboxyl component, and the alkyl chain to the right of the carboxyl group (Figure 3.6.f.ii). The carboxylate portion (butanoate) on the left includes the ester functionality as well as the carbon chain on that side of the molecule. This portion of the molecule is derived from the nucleophile, which contains an oxygen atom with a lone pair of electrons and formal negative charge. Meanwhile, the ethyl chain (right) is derived from the electrophile, an alkyl halide. As discussed in Chapter 3.1.2., the carboxylate nucleophile attacks the alkyl halide electrophile, ejecting the halide as an anionic salt.

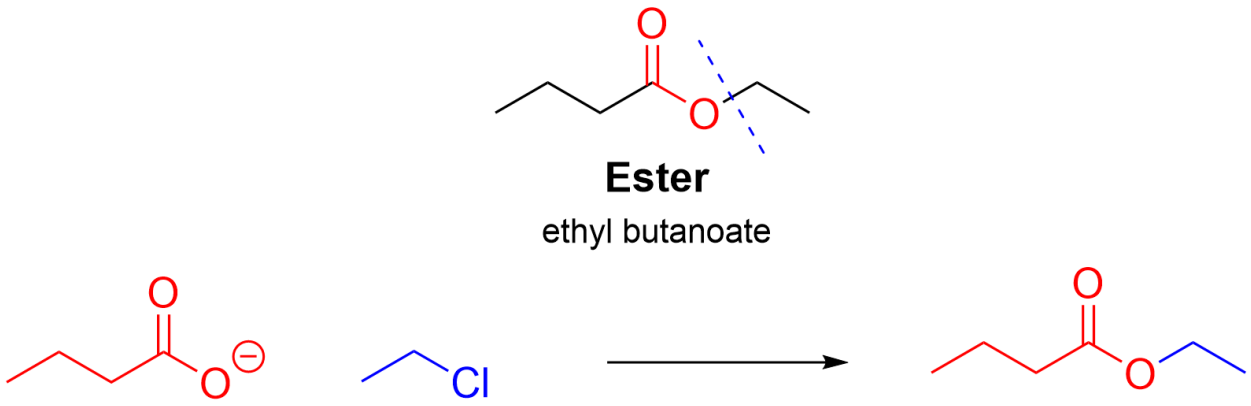

Figure 3.6.e.ii. *The reagents of an S_N2 reaction to produce ethyl butanoate. By cutting the molecule directly after the ester functional group, you can determine the structure of the carboxylate and alkyl halide reagents.*

Second, we will examine the acid-catalyzed esterification reaction. The same molecule can be synthesized using a carboxylic acid and an alcohol, this time splitting the ester product in the middle of the ester group (Figure 3.6.f.iii). The portion of the molecule that contains the carbonyl group (left) is derived from the carboxylic acid, while the other portion of the molecule (right) is derived from the alcohol.

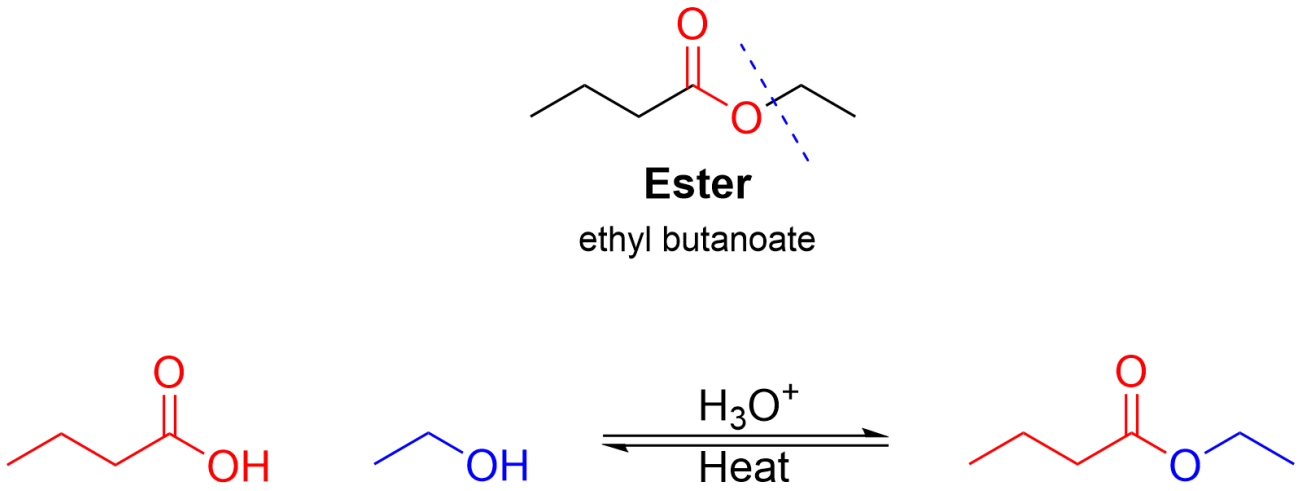

Figure 3.6.e.iii. *The reagents of an acid-catalyzed esterification reaction to produce ethyl butanoate. By cutting the molecule directly at the ester functional group, you can determine the structure of the carboxylic acid and alcohol reagents.*

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Consider a Series of Reactions

In other examples, however, the answer is not so straightforward. Sometimes there is no single reaction that can change one functional group to another, but rather a series of reactions. As an example, look at the following question below in Figure 3.6.f.i.

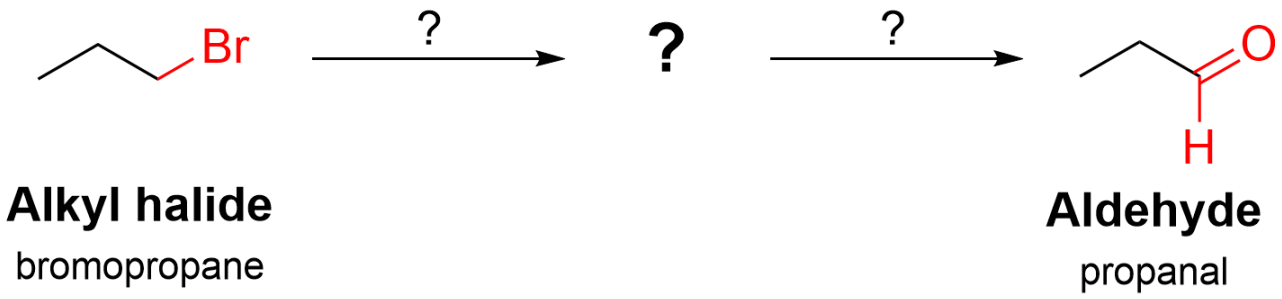

Figure 3.6.f.i. *An example where an alkyl halide, bromopropane, is converted into an aldehyde, propanal, after two reactions.*

The starting substrate in this synthesis is an alkyl halide, bromopropane, and the product is an aldehyde, propanal. As indicated by two arrows, the overall transformation occurs in a series of two reactions, where the product of the first reaction is the reactant in the second reaction.

The first step is to count the number of carbon atoms, noting that no carbon atoms have been added to the structure. This means that a Grignard reaction (or esterification) did not occur.

The next step is to notice the changes in the functional groups. There is no single reaction that converts an alkyl halide to an aldehyde. Instead, we must think about what functional groups an alkyl halide can be transformed into, and what functional groups can then be converted into an aldehyde.

An alkyl halide can be transformed into a Grignard reagent (as seen in Chapter 3.4.2), or into an alcohol via a nucleophilic substitution reaction (as seen in Chapter 3.1). Meanwhile, an aldehyde can be produced by oxidizing a primary alcohol (Chapter 3.3.). Thus, the most likely product after the first reaction, which serves as the reactant in the second reaction, is the *primary alcohol*.

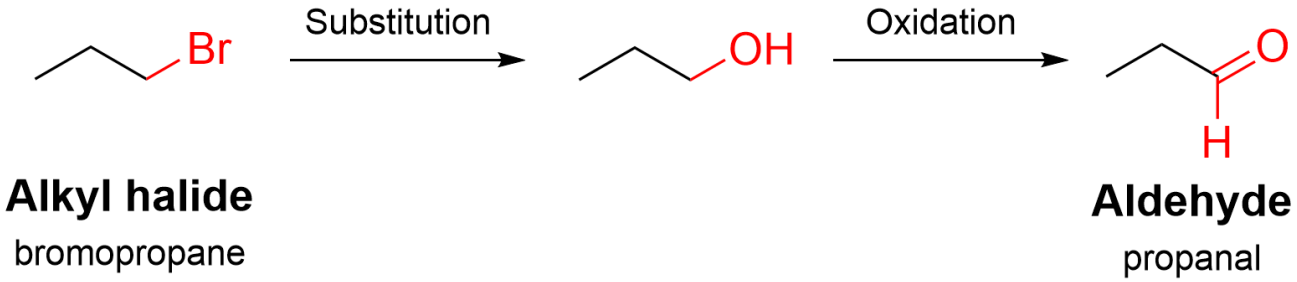

Figure 3.6.f.ii. *Bromopropane is converted into an alcohol (nucleophilic substitution), which is then converted into an aldehyde (oxidation).*

Now that we know which reactions occur and in what order, we can start working our way through to determine what reagents are used in each step. First, a substitution reaction occurs: an electron-rich nucleophile attacks the alkyl halide and replaces the Br. The nucleophile required in this case is hydroxide (OH^-).

Second, oxidation of the alcohol produces an aldehyde. Recall that there are several kinds of oxidizing agents: $K_2Cr_2O_7$ or K_2MnO_4 will oxidize a primary alcohol twice, leading to a carboxylic acid; PCC in CH_2Cl_2 is a more selective oxidizing agent, which allows the reaction to stop at the aldehyde. Thus, in this case, we should choose PCC in CH_2Cl_2.

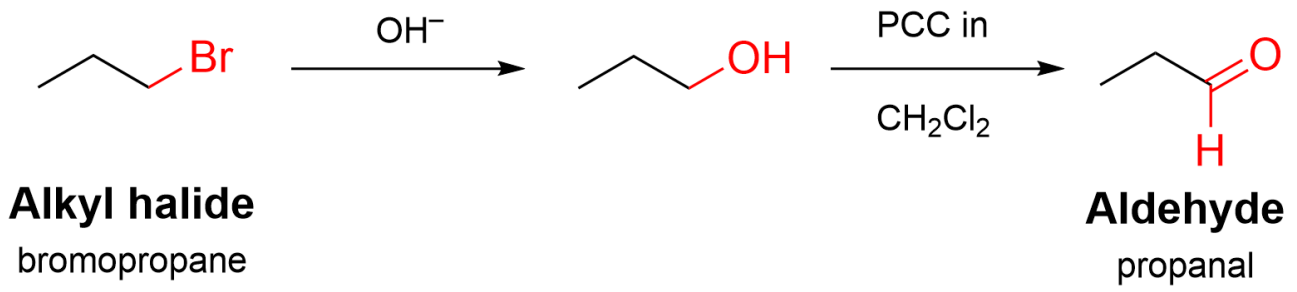

Figure 3.6.f.iii. *Substitution of the alkyl halide with hydroxide produces propanol, which is then reacted with PCC in CH_2Cl_2 to obtain the target molecule, propanal.*

The following video includes a worked example from a previous CHEM 1AA3 test or exam that students struggled with. Try solving it on your own before looking at the solution.

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Practice Questions

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

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(The full solution to this problem can be found in Chapter 5.2)

Key Takeaways

This may seem overwhelming, especially as you first start to work your way through a question. Rest assured that with more practice, synthesis questions will come more easily to you. To summarize, here is a list of questions to ask yourself when approaching a synthesis question.

1. **Count the carbons —** Has the skeletal structure changed? If so, a Grignard reaction or esterification likely occurred.
2. **Identify changes in the functional groups** — Which reaction(s) and which reagent(s) can be used to change one functional group to another?
3. **Work backwards** — Think about what bonds could be broken or formed to reach the desired product. Now that I know this reaction was used, are there different reagents I must choose between?
4. **Consider a series of reactions** — If the transformation cannot be accomplished using a single reaction, consider a series of reactions where the product of one reaction serves as the reactant for the next reaction.

Diversity in Chemistry: Donna Nelson

Synthesizing chemicals is not only done in science labs, but it is also done on screen as well. Recent media, such as TV shows *Bones* and *Breaking Bad*, have started to incorporate science as a running theme. Despite being viewed for entertainment, shows take their scientific fundamentals very seriously. **Donna Nelson**, a chemistry professor of Indigenous ancestry, acted as a scientific advisor for AMC's famous *Breaking Bad* series, which centers around an organic chemist. Nelson mainly assisted with organic nomenclature and stoichiometric calculations, such as helping write dialogue and providing chemical structures used as props on set. In addition to her work with *Breaking Bad*, she was also appointed as 2016 President of the American Chemical Society, the world's largest scientific society with over 155,000 members. Nelson is also very passionate about education and diversity, conducting research on underrepresented groups in science faculties across American universities

A portrait of Donna Nelson.

and aiding in improving chemistry textbooks. An interview with Donna Nelson can be found on the C&EN news site, exploring her role on set.

Donna Nelson on the set of *Breaking Bad* alongside actors Bryan Cranston and Aaron Paul in 2013.

CHAPTER 4 - CHEMICAL BIOLOGY

4.1 - OVERVIEW OF CHEMICAL BIOLOGY

Learning Objectives

1. Understand key points of the case study:
    1. Dopamine plays a role in learning and memory formation in bees and humans
    2. HVA (homovanillyl alcohol) acts to inhibit dopamine production in bee neural cells and suppresses negative memories, impacting on aversion learning.
    3. A chemical assay serves as a surrogate for a complex biological phenomenon such as the inhibition of dopamine production in bee neural cells

What is Chemical Biology?

A thorough understanding of chemistry is helpful to solve numerous problems in other science disciplines. One of the major applications of chemistry is to biological systems. This discipline is called **chemical biology.** Chemical biology is a rapidly growing field that does not have a precise definition. However, the main characteristic of chemical biology is using principles of chemistry to solve complex biological problems.

When the field of chemical biology first developed, the primary goal was to use small molecules to interact with biological systems such as proteins, nucleic acids, or other cellular components (Figure 4.1.a). The goal was to modulate the behavior of these biological systems to explore how the cellular system could be perturbed. This way, scientists could better understand the underlying biochemistry of cellular processes, or change biological outcomes to aid in drug discovery. The scope of the field has now greatly expanded, including novel research such as the synthesis of chemically modified proteins and DNA, alongside imaging and diagnostics.

We will highlight principles and techniques of chemical biology through the following case study. Specifically, we will examine how the field of chemical biology draws its inspiration from nature, and how we can use natural phenomena to develop new therapeutics to treat diseases.

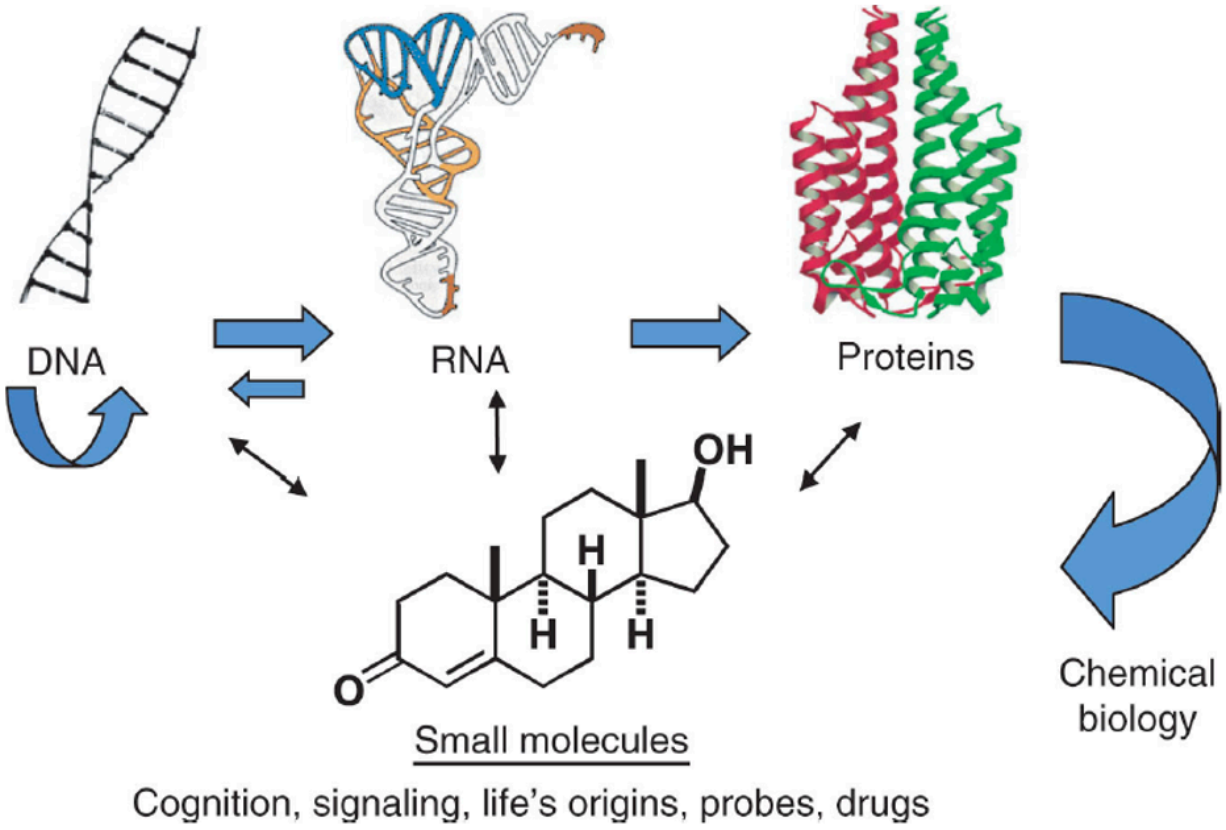

Figure 4.1.a. The field of chemical biology examines how small molecules like steroids (e.g. nandrolone, bottom) interact with biological systems such as DNA (top left), RNA (top middle), and proteins (top right).

Case Study: The Brainwashing of Bees

This case study explores the social structure of bee colonies. In a bee colony, there is a single queen bee, many drones (males) and many worker bees (female). The drones' main function is to fertilize the queen and then die instantly. The worker bees are responsible for building and maintaining the hive, gathering resources, and ensuring the survival of the queen.

The dominance of the queen bee and the hierarchy of the colony is established and maintained through a mixture of chemicals, called the **Queen Mandibular Pheromone (QMP)**. QMP is secreted from the jaw of the queen bee and exerts several effects on the bees in the colony. For example, QMP attracts young worker bees to the queen, so they can groom and feed her. In turn, they gather samples of QMP and spread it throughout the colony. QMP also inhibits rearing of new queen bees, influences comb-building, and controls worker bees' development.

Dopamine (Figure 4.1.b, right) is a neurotransmitter involved in the "reward center" of the brain, controlling mood, attention, and memory. In insects, dopamine signaling is necessary for learning how to avoid

unpleasant stimuli, called aversive learning. However, when young worker bees are exposed to QMP, their brain dopamine levels, as well as their expression of the dopamine receptor gene, are altered.

In Vergoz et al. (2007), researchers sought to understand: (1) whether exposure to QMP alters young worker bees' ability to establish aversive memories; (2) what aspect of QMP is responsible for these effects. If you would like to learn more about this study, click on the following link to access the journal article: https://doi.org/10.1126/science.1142448.

QMP contains several compounds, with the most vital compound to ensure the survival of the queen being **homovanillyl alcohol (HVA)** (Figure 4.1.b, left). The structure of HVA is quite similar to the structure of dopamine (Figure 4.1.b, right). HVA contributes to the effects of QMP on dopamine signaling in the brains of worker bees. Researchers found that HVA impairs the formation of aversive memories in young worker bees. In contrast, older worker bees, who are responsible for leaving the hive to forage, are unaffected by HVA, and can establish aversive learning.

The researchers postulated that because high exposure to QMP leads to unpleasant side effects, blocking aversive memories ensures that young workers will not associate QMP with these unpleasant side effects. As mentioned earlier, dopamine plays an important role in the formation of averse memories. As HVA is structurally very similar to dopamine, it can interfere with dopamine binding to its receptor by taking the place of dopamine in the dopamine-receptor binding interaction, resulting in a lack of aversive memory formation . In short, the researchers established that HVA is the component of QMP that allows young worker bees to be "brainwashed" by the queen. The young worker bees do not establish aversive learning and are less inclined to flee from the unpleasant experience of QMP. This results in the development of the social hierarchy necessary for hive function and survival of the colony.

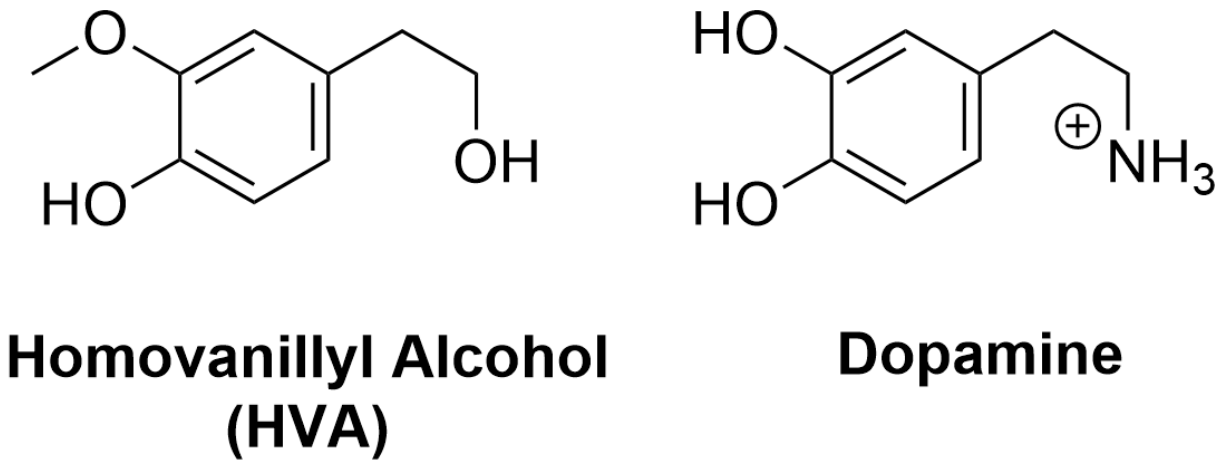

Figure 4.1.b. The chemical structure of homovanillyl alcohol (HVA, left), a compound contained in QMP, and dopamine (right), a neurotransmitter associated with learning and memory.

The Therapeutic Potential of HVA and HVA-like Compounds

Queen bees have a selective way to control young worker bees' memories, for a short part of their lifespan. Understanding this phenomenon presents opportunities for HVA or HVA-like molecules to be used as therapeutics for altering dopamine levels in animals, including humans.

However, altering dopamine levels in the brain is not an easy task. For example, several health conditions are characterized by abnormally *high* dopamine concentrations, such as schizophrenia and certain kinds of psychoses. At the same time, numerous diseases are characterized by abnormally *low* concentrations of dopamine, such as Parkinson's Disease and Attention Deficit Disorder. A therapeutic agent designed to suppress dopamine concentrations must be specific so that it only slightly suppresses dopamine concentrations, or so that it does so only in a certain area of the brain.

The Drug Discovery Process

The case study described here uses experiments on live animals, with replicate measurements, and waiting periods between experimentation. Instead, we wish to synthesize and screen thousands of drug candidates in a fast and efficient manner. This way, we can discover the most effective therapeutics for a target goal, like reducing dopamine levels.

For every successful drug that enters the market, there are thousands of unsuccessful drugs that were synthesized and screened for activity. The drug discovery pipeline is a lengthy process which requires a lot of time and resources to produce effective and safe medications for public use. The typical strategy for the initial discovery of new drugs tends to follow a three-step process, shown below in Figure 4.1.c.

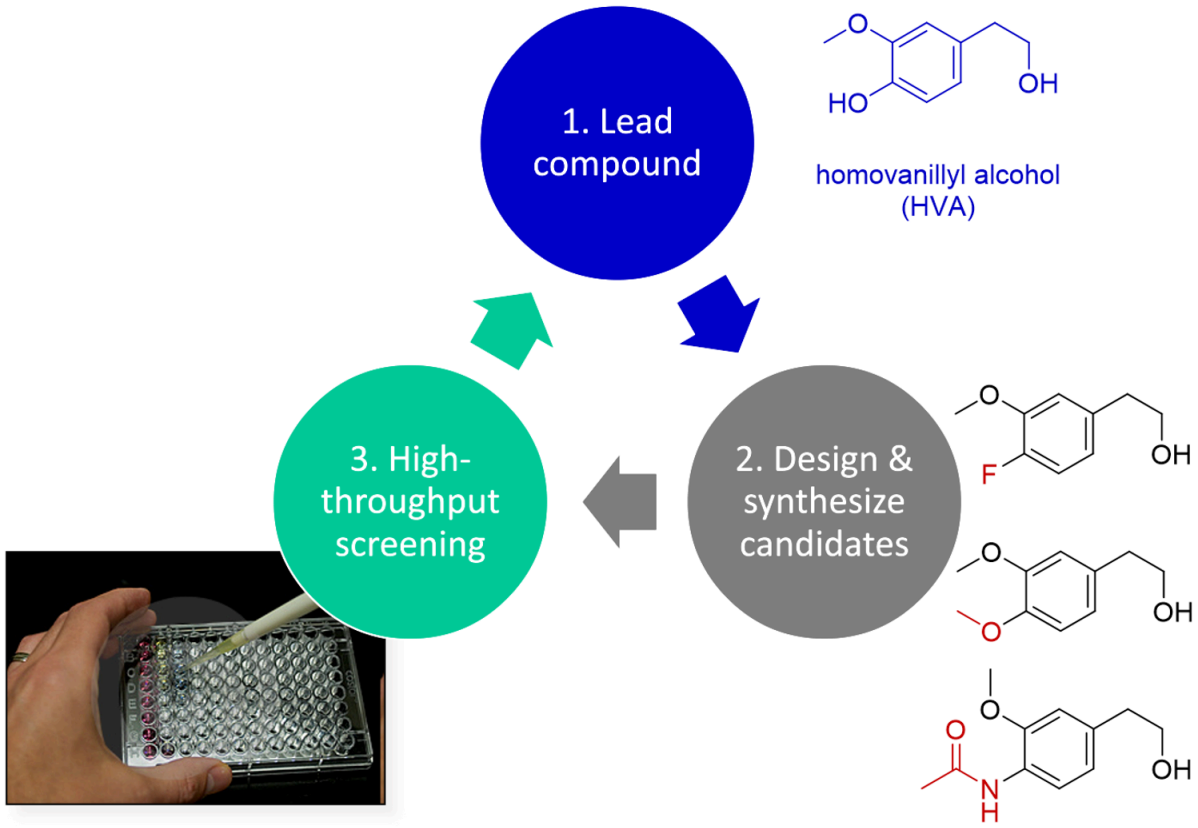

Figure 4.1.c. A graphical display of the three major steps in the drug discovery process.

The first step is to obtain a **lead compound**. A lead compound is some structure which has an effect on the biological target of interest. It can either be an existing drug that was synthesized for a different purpose, or a product that is found in nature such as **homovanillyl alcohol (HVA)**. HVA has been shown to decrease dopamine production in bee neural cells. Due to the potential therapeutic applications of lowering dopamine levels, HVA is used as a model compound in the drug discovery process.

The second step is to synthesize a library of compounds to act as candidates to test for drug-like activity. These are typically modelled after the lead compound and contain similar core structures in hopes of eliciting a similar or improved response. The library of candidates shares the same core structure, but they have variation in their outer functional groups. This allows scientists to determine which combination of functional groups produce the optimal response from the target. This is done through a process known as **combinatorial chemistry**.

The third step is to test the library of compounds to see if the desired effect can be obtained. This is typically done through a form of ***in-vitro* experiments** known as assays. An **assay** is an experiment that seeks to measure the activity or presence of a molecule. One approach for performing assays is through a **high-throughput screening** process that allows the rapid and efficient testing of a variety of compounds in parallel.

The following chapters will discuss the chemical biology principles involved in achieving this goal, including:

- Designing experimental protocols with a multitude of control experiments – Chapter 4.2
- Efficiently testing several drug candidates using high-throughput screening – Chapter 4.2
- Exploring common structural features of drug candidates such as aromaticity – Chapter 4.3
- Synthesizing a large library of compounds using combinatorial chemistry – Chapter 4.4

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Diversity in Chemistry: Carolyn Bertozzi

A picture of Carolyn Bertozzi.

In order to follow a target of interest within a cell or living system, a molecule known as a probe must react with it. This reaction must occur in a busy environment, with hundreds of other cell components present, and it must not interact or interfere with normal cell processes. This is a subfield of chemical biology known as bio–orthogonal chemistry. This field was developed by scientist **Carolyn Bertozzi** in 1999, with the name given in 2003. Bertozzi is a glycobiologist who studies oligosaccharides (polymeric sugars) found on the cell surface, and studies how they act when affected by disease. She was awarded one third of the 2022 Nobel Prize in Chemistry for her developments in bio-orthogonal chemistry, developing the widely used strain promoted alkyne azide cycloaddition. This is an extremely favorable and quick reaction that forms no byproducts using relatively rare functional groups not found in cells, thus, not perturbing the cell environment. Bertozzi is currently a chemistry professor at Stanford University and is an open member of the LGBT community, acting as a role model in academia and science. More information about Bertozzi can be found on her profile on the Proceedings of the National Academy of Sciences (PNAS) website.

Key Takeaways

Key terms in this chapter:

Key term	Definition
Chemical Biology	A scientific field between branching chemistry and biology. The discipline often involves the application of chemical techniques, analysis, and small molecule to the study and manipulation of biological systems
Pheromone	A chemical that is secreted and released outside the body to affect individuals of the same species. These tend to trigger a specific response in the receiving individual, often causing hormonal or behavioural changes.
Lead compound	A compound that already exists and its effects are well characterized. It is used to derive novel compounds to test for a desired therapeutic effect. This is done by changing the lead compound's functional groups.
In-vitro experiments	Experiments that are conducted in cells or microorganisms outside of their normal biological context. This includes cells grown in a well plate or flasks.
Assay	An experiment used to measure the activity or presence of a molecule.
High-throughput screening	A process used to screen many compounds of their therapeutic potential. Automated and robotic processes are utilized to run multiple assays in parallel, or all at once, to determine this. The two characteristics of this process is that it uses fast assays and that it uses massively parallel assays, where the large number of wells and automated processes enable this to occur.

Any feedback or comments on this chapter? You may either email chemoer@mcmaster.ca, access this MS Form, or provide a comment in the feedback box below.

4.2 - HIGH-THROUGHPUT SCREENING

Learning Objectives

1. Describe the process of high throughput screening in drug discovery:
    1. Describe the types of control wells used in an assay (positive control, negative control)
    2. Define the types of results that can be produced in an assay (true negative, false negative, true positive, false positive).
    3. Describe how robots and automation are used in high throughput screening.

High-Throughput Screening

With thousands of potential compounds to test each day, scientists require methods to quickly test multiple compounds simultaneously to expediate the process. This is a process known as **high-throughput screening (HTS)**. In HTS, robotics and automated processes are utilized to run multiple assays in parallel to determine whether a compound has the potential to be used as a therapeutic.

There are two characteristics of HTS which increase screening efficiency: the development of a **fast assay**, and the ability to perform parallel assays. To be useful in drug development, assays must be fast so that researchers can efficiently characterize various compounds. Using HVA as an example, viable drug candidates must replicate the effect of HVA on bees in a hive. While it is possible introduce a compound into a beehive to test its influence on worker bee dopamine levels, it would take weeks to properly observe the effects of these compounds, and you would need a separate hive for each test candidate. This is an ineffective way to screen thousands of compounds. Instead, bee neural cells can be grown in the lab and tested on directly. This approach isolates the biological component of bees that scientists are interested and allows for a streamlined testing process. The potential drug candidates can then be assayed with the neural cells to determine whether they inhibit dopamine production.

The second characteristic of HTS is the ability to perform **parallel assays,** where multiple compounds

can be tested simultaneously for their therapeutic potential. This is commonly done in multi-welled plates (Figure 4.2.a). These plates contain many wells which can all be analyzed simultaneously. Each well represents a single experiment and contains a combination of a different drug candidate and bee neural cells to determine the compounds effect on dopamine production. This way, many different compounds can be tested simultaneously. In addition, the experiments are performed at small volumes (< 0.5 mL per well), resulting in a minimum of resources required to perform each experiment. This is especially beneficial considering the costs associated with harvesting bee neural cells and producing large libraries of test compounds.

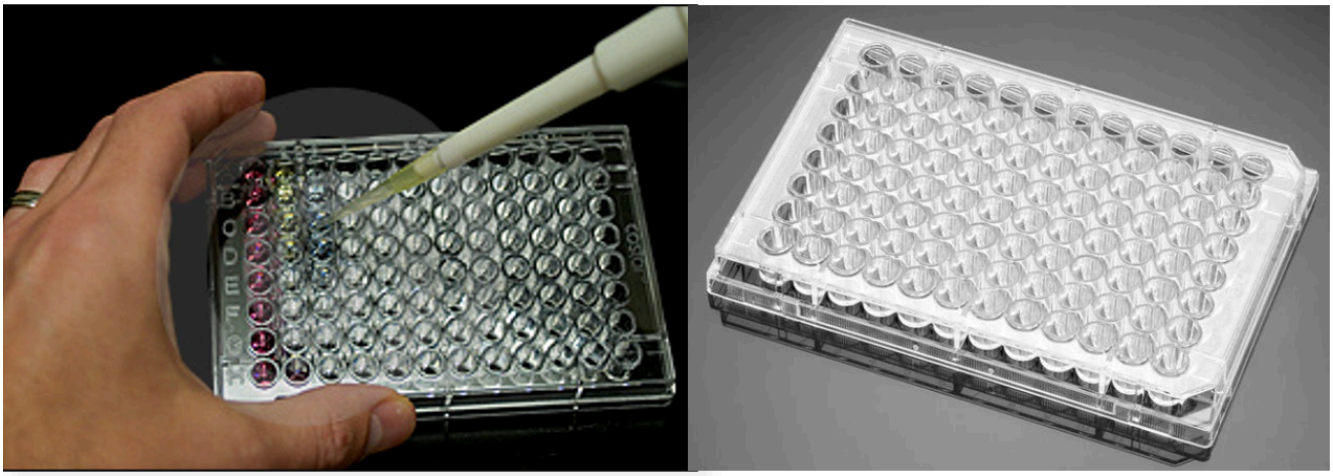

Figure 4.2.a. A 96-well plate used for high-throughput screening. By using 96-well plates and dopamine-producing neural cells that emulate a bee's brain, scientists can make a novel assay to test the effects of their drug candidates. This method is rapid, easy, and efficient. Microplates can contain 96, 384, 1536, and 3456 wells, all of which can be used for the HTS process.

Enzyme-linked Immunosorbent Assays

An **enzyme-linked immunosorbent assay**, commonly referred to as an **ELISA**, is a type of HTS assay that can identify the presence of a specific molecule. These assays utilize a series of protein interactions to **1)** bind to a molecule of interest, **2)** identify that the molecule was present and bound in step (1), and **3)** visualize the presence of the molecule through a colourimetric change.

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Returning to the example using HVA, ELISAs are used to visualize whether test compounds altered dopamine production levels in bee neural calls (Figure 4.2.b). For this purpose, bee neural cells are cultured in a lab, and then added to a 96 well plate. The drug candidates can be assayed with the cells, with a different candidate added into each well. In this assay, a primary antibody, is added to each well which selectively binds dopamine with high affinity. The well is then washed to ensure that only primary antibodies bound to dopamine remain present in the wells. A second antibody is subsequently added, which is covalently bound to the enzyme **horseradish peroxidase (HRPase).** This secondary antibody binds to the first antibody, which is bound only to dopamine. The wells are then washed again to remove any unbound secondary antibody. In the final step, a blue substrate is added into the wells. This substrate reacts with HRPase to form a green product that is detected using UV absorbance.

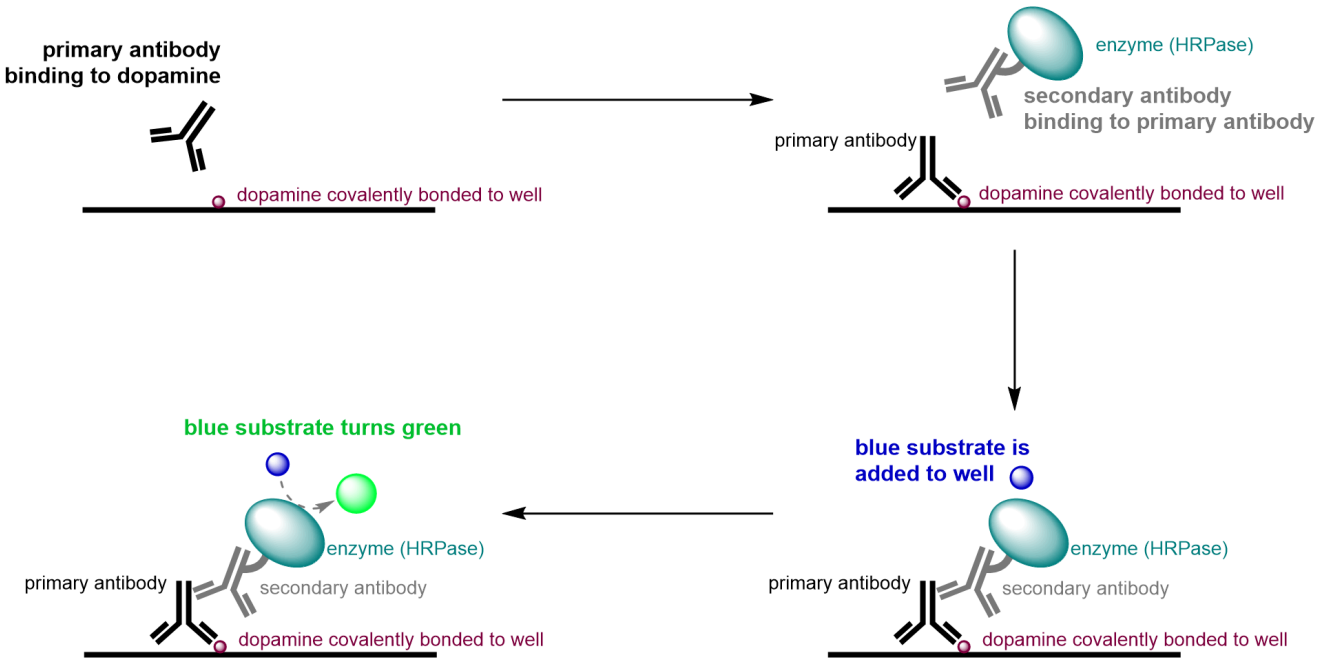


Figure 4.2.b. An overview for how an ELISA functions. A primary antibody first targets and binds to dopamine. In the second step, a secondary antibody, which contains the enzyme horseradish peroxidase, is added to bind to the primary antibody. In the third step, a blue solution is added to the well, which turns green due to the enzyme, indicating the presence of dopamine.

Given the experimental design, HRPase must be present to convert the blue substrate to a green product. Since the presence of the HRPase linked secondary body is dependent on the presence of the primary antibody, which in turn is dependent on the presence of dopamine, wells only appear green if **dopamine is present.** If **dopamine is not present,** there will be no binding cascade of antibodies, and the well will remain blue. This is because the primary antibody will have no dopamine to bind to in the first step and will therefore be removed when washing. Thus, the secondary antibody linked with HRPase will have no binding partner as there is no

primary antibody present and will also be washed away. Without the enzyme in the well, the substrate will remain blue as a result of the initial lack of dopamine in the well.

In this case, the therapeutic goal of this assay is to find a test candidate to inhibit dopamine production. Thus, the desired outcome is a *blue colour*. The well being blue tells us that the compound in the well is inhibiting dopamine production, since blue indicates there's no dopamine present for any antibodies to bind to. A well that appears blue after completion of the assay is referred to as a **hit.** After the HTS stage, the compounds that generate hits will be used to inform the design of the next generation of drug candidates and may undergo more rigorous testing to determine other characteristics, such as molecular stability, and human toxicity and dosage.

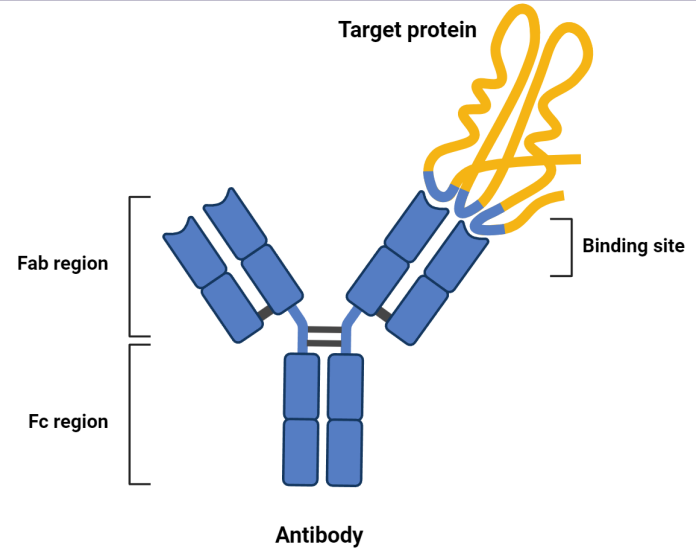
Are You Wondering? The Binding Capabilities of Antibodies

The underlying principle of an ELISA is the ability of antibodies to bind with high selectivity to a molecule of interest. Antibodies are proteins produced by your immune system to identify foreign molecules and cells.

The function of an antibody is derived from its structure. They are composed of two main regions: a fragment crystallizable (Fc) region and a fragment antigen binding (Fab) region.

The Fab is highly variable and gives antibodies the ability to bind to virtually any molecule. In an ELISA, the Fab of the primary antibody is what recognizes and binds to the molecule of interest, such as dopamine.

The Fc region, in comparison, is highly conserved between antibodies of the same class, even if they have different Fab regions. In an ELISA, the conserved Fc region of the primary antibody is recognized by the Fab region of the secondary antibody. Because Fc regions are functionally identical for antibodies within the same class, the secondary antibody of an ELISA can be used to identify many primary antibodies.



A diagram of an antibody bound to its targeting protein via the binding site. The Fab region is the top half of the antibody, whereas the Fc region makes up the lower half.

Setting Up Controls

When running any assay, it is of utmost importance to have controls. **Control experiments** ensure that the experimental design of an assay is sound and that the different components of the assay are working as intended. This ensures that the results of the assay are accurate, and not a result of interfering or unpredicted factors. Control experiments can contain different combinations of components used in the experiment and/or expected products from the assay. In most cases, many different control experiments are run for a given assay.

Controls can be categorized into two types: positive controls and negative controls. **Positive controls** are control wells that are expected to produce a positive signal, such as the colourimetric change from blue to green in the ELISA described previously. On the contrary, **negative controls** are expected not to produce any change in signal, such as no colour change from blue to green.

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Figure 4.2.c represents a set of 6 control experiments used in the ELISA mentioned throughout this chapter. Each well contains a different combination of experimental components and is intentionally designed to validate different aspects of the experiment and that the measurement made matches expectation.

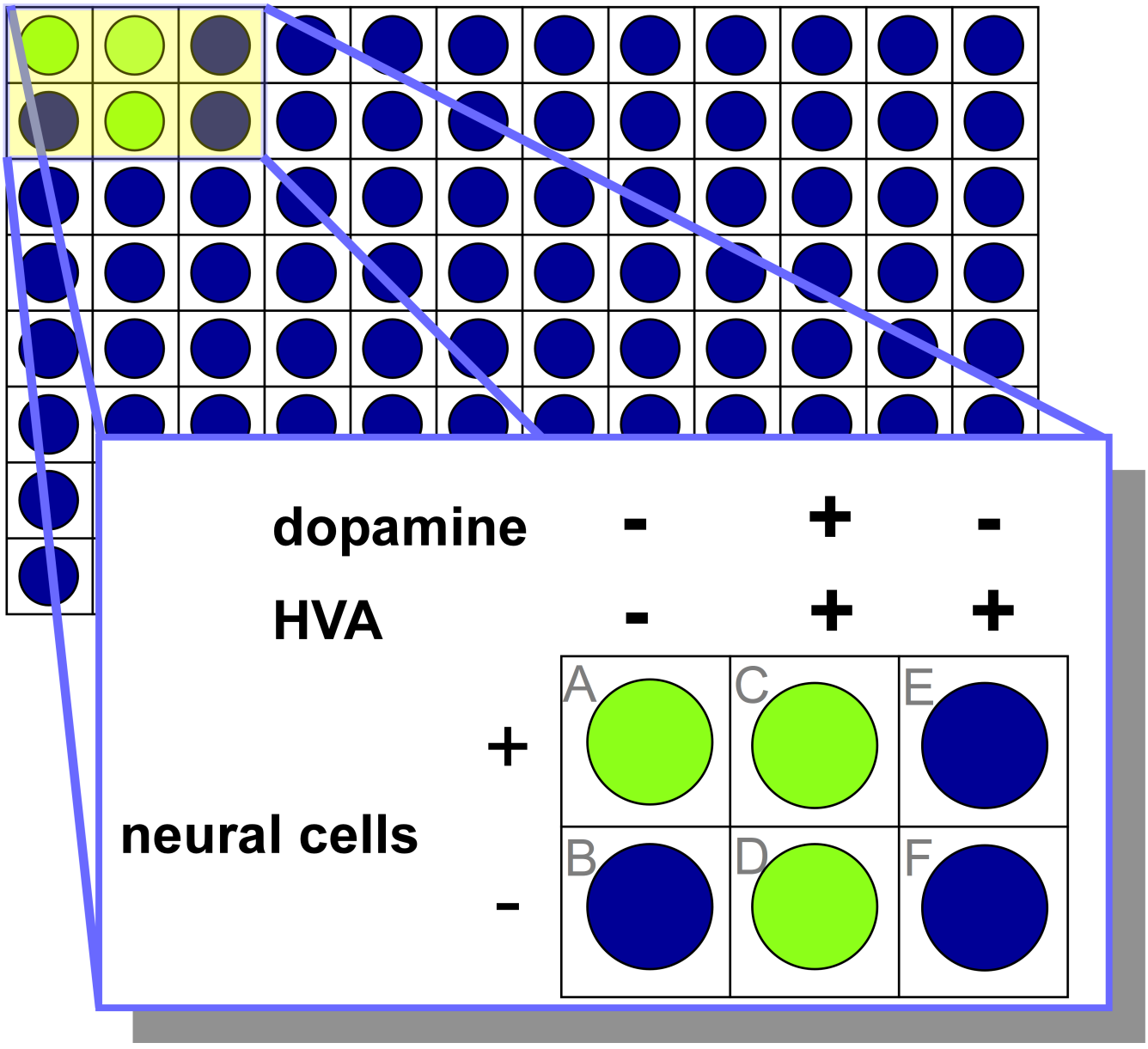

Figure 4.2.c. The 6 control wells are set up in the dopamine assay. The (+) and (-) symbols represents the presence or absence of each component in a given column and row. Green represents the presence of dopamine in a well, whereas blue represents the absence of dopamine.

The control well labeled 'A' contains only bee neural cells and lacks HVA or exogenous dopamine. This well is a **positive control** as it is designed to ensure that the neural cells are naturally producing dopamine under the assay conditions, and that it is identifiable by the ELISA (green signal).

The control well labeled 'B' contains no dopamine, HVA, or bee neural cells. This well is a **negative control**, as it verifies that dopamine is required to produce a green signal. No dopamine will be present or produced in this well, and as a result, no green signal is produced. The blue colour of this well validates that the ELISA will not proceed if no dopamine is present.

The control well labeled 'C' contains bee neural cells, HVA and dopamine. Although HVA inhibits dopamine production in bee neural cells, the addition of exogenous dopamine in this well results in positive signal in the ELISA. This well is a **positive control** since green signal is detected and ensures that dopamine can be detected in the presence of both HVA and bee neural cells.

The control well labeled 'D' contains HVA and dopamine, and no bee neural cells. Since dopamine is added to this well, the expectation is that it will be detected by the ELISA and a positive signal will result. This well is a **positive control** since the green signal is observed and demonstrates that HVA does not interfere with the detection of dopamine by the ELISA.

The control well labeled 'E' contains both bee neural cells and HVA and has no exogenous dopamine. Since HVA is an inhibitor of dopamine in bee neural cells, the expectation is that the well will remain blue because no dopamine will be produced by the bee neural cells. This well is a **negative control**, since no signal is measured, and verifies that the dopamine production can be inhibited by HVA.

The control well labeled 'F' contains only HVA, and no dopamine or bee neural cells. Since there is no dopamine added, and no bee neural cells present to produce dopamine, the expectation is that there will be no signal measured through the ELISA. This well is designed to test whether HVA, a structure that is structurally similar to dopamine, could potentially bind to the primary antibody and result in the detection of a green signal. This well is a type of **negative control** to test that HVA alone does not elicit a signal in the ELISA.

Since the experimental measurements in Figure 4.2.c match the expectations, it can be concluded that the ELISA is working as expected. None of the components interfere with the assay in an unexpected manner, and this provides confidence that any results obtained from this assay will be accurate.

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(The full solution to this problem can be found in Chapter 5.3)

Obtaining a Hit

Controls are experiments to ensure that the assay is working as intended, with positive denoting a positive signal (i.e. green color), and negative denoting a lack of signal (i.e. blue color). This has no correlation to what the desired results of the experiment are.

In contrast, **hits** are related to what the scientists want to see from the experiment. In this scenario, the assay is screening for molecules that can inhibit dopamine production – thus, the desired results are low dopamine concentration, denoted by a blue well. Because of this, a positive result means the desired outcome is seen, with low dopamine being represented by a blue well. In contrast, negative results mean the compound does not have any dopamine-reducing effects. This is the undesired outcome, with high dopamine represented by a green well. The terms 'true' and 'false' can also be applied to explain the validity of the results. True means that the results are caused by the drug candidate, whereas false means that factors other than the compound are leading to the observed results. Through the development of this highly efficient and automated process, thousands of compounds can be screened daily. With this technique, they can determine the most potent dopamine inhibitors from a large library of compounds for subsequent testing.

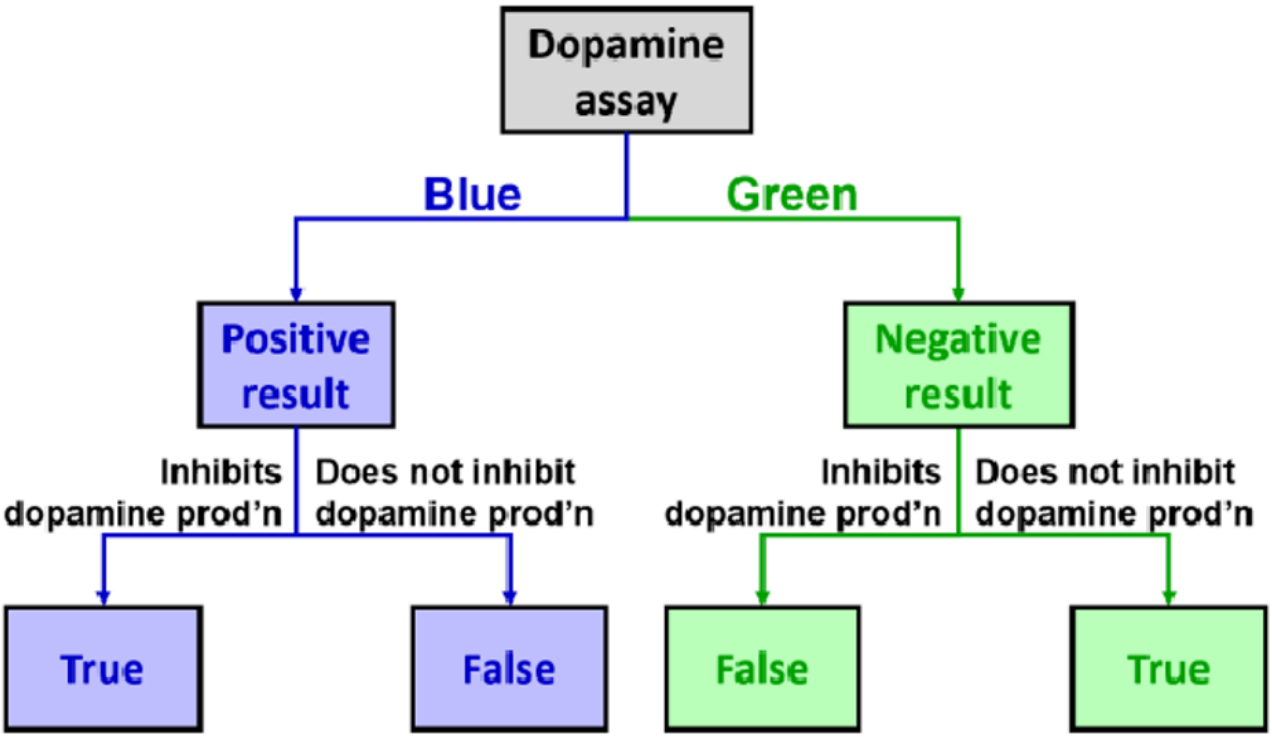

Figure 4.2.d. A flowchart to help determine whether a result in a true/false positive or negative well. This flowchart can only be applied to this dopamine assay, as the type of well will change depending on what the desired result is.

A **true positive** in the context of the ELISA is when a hit is obtained, and it is a result of the test compound

inhibiting dopamine production in the bee neural cells in a similar fashion to HVA. In a true positive hit, the well will remain blue, as there is no dopamine in the well to be detected.

A **false positive** is when a hit is obtained, but it is not a result of the test molecule inhibiting dopamine production in the bee neural cells Instead, it may be for other reasons, such as a mistake in the assay design where a component was not added to the well, or the test compound prevents dopamine production through an alternative mechanism, such as through cytotoxic killing of the bee neural cells As the word "false" suggests, this drug candidate is not actually inhibiting dopamine production in the desired manner but the results suggest that it is.

It is also possible to observe wells that are the opposite to the desired results, which means the neural cells are producing dopamine as normal which we call a **miss** . These can also be classified into either true or false negatives, as these are undesirable results.

A **true negative** is a well that produces negative results, meaning it does not result in the desired effect. The well would appear green as dopamine is produced normally. This is because of the compound itself, as it has no inhibitory properties.

A **false negative** is a well that appears to produce a negative result, but in reality contains a test compound that is capable of inhibiting dopamine production. This type of result could be due to a litany of reasons; a contamination of dopamine in the media, or the antibodies binding to something other than dopamine both represent scenarios where the ELISA results suggest dopamine is present even when the test compound inhibits dopamine production in bee neural cells. As the word "false" suggests, the results incorrectly suggest the drug candidate is responsible for the green colour.

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Are You Wondering? The True and False Results of COVID-19 Rapid Antigen Tests

By 2023, almost every student has likely contracted SARS-CoV-2, also known as COVID-19. These are typically discovered via take-home rapid antigen kits and are performed by the students

themselves. Although the mass production and distribution of these kits assisted in decreasing the pressures on the healthcare industry, the tests are not infallible. These terms for determining hits from an assay can similarly be applied to COVID tests.

For example, a **true positive** is when you test positive on the kit, and you are actually positive for COVID. Similarly, in a dopamine assay, positive results are seen, and it is actually positive due to the effects of the compound. On the contrary, a **false positive** is when you test positive for COVID, but you do not have the virus. You would assume that there is some mistake with the test – a similar thing can occur in the HVA assay. You can see positive results in the dopamine assay, but it is caused by another variable with the compound not having any dopamine-reducing effects.

A **true negative** on a COVID test occurs when you test negative for the virus and you are not sick. This term can also be used in the HVA assay, as it means there are negative (undesirable) results, which are truly because of the compound's characteristics. A **false negative** COVID test means that you test negative on the kit, but in actuality, you have the virus. There was some sort of other problem with the COVID test that gave you the wrong results – the same theory applies to scientific assays. A false negative could occur as the well could turn green to indicate high dopamine, which is not the desired results, but it is due to another variable and not because of the properties of the compound itself.

The following videos include two worked examples from a previous CHEM 1AA3 test or exam that students struggled with. Try solving them on your own before looking at the full video solutions.

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(The full solution to this problem can be found in Chapter 5.3)

Key Takeaways

- ELISA is a type of assay used in HTS to determine the absence or presence of a compound of interest colourmetrically. ELISA works with the following mechanism:
    - A primary antibody (Antibody 1) is added to specifically binds to the compound of interest.
    - A secondary antibody (Antibody 2) is introduced and binds to Antibody 1. Antibody 2 is itself bound to an enzyme, horseradish peroxidase, which changes the colour of an added substrate from blue to green.
    - This chain indicates the presence of the desired molecule from any colour changes that occur.
- The steps of ELISA process are as follows:
    - Introduce Antibody 1, which binds to the compound of interest.
    - Wash any unbound leftover antibody.
    - Introduce the Antibody 2-horseradish peroxidase compound.
    - Wash any unbound leftover antibody again.
- Control experiments are necessary to ensure the experiment is working as intended, and can be categorized as either positive or negative controls. Positive means positive outcome (colourimetric change) is expected, while the opposite is true with a negative control: a negative outcome (no colourimetric change) is expected.

- True vs False Negatives and Positives: True positives and true negatives are both “true” outcomes of an experiment, which accurately determine the effects of the drug candidate, and lead to the desired results and undesired results respectively. False positives and false negatives are results falsely being observed as a desired or undesired outcome due to other variables or experimental error.

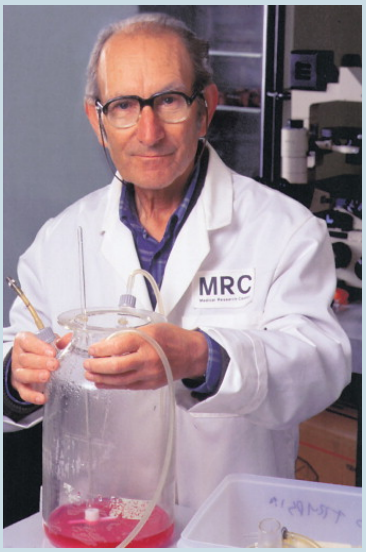
Key terms in this chapter:

Key term	Definition
Assay	An experiment used to measure the activity or presence of a molecule.
High-throughput screening	A process used to screen many compounds of their therapeutic potential. Automated and robotic processes are utilized to run multiple assays in parallel, or all at once, to determine this. The two characteristics of this process is that it uses fast assays and that it uses massively parallel assays, where the large number of wells and automated processes enable this to occur.
Enzyme-linked immunosorbent assay	Also known as an ELISA, it is a type of assay used to determine if a molecule of interest is present through colourimetric change. The assay works using horseradish peroxidase as a coloured indicator, which is bound to a secondary antibody. This secondary antibody will bind to a primary antibody that is specific for the molecule of interest. ELISAs are used in high throughput-screening as they can be performed in 96-well plates and give a coloured response to quickly determine the presence of a molecule
Control experiments	Control wells performed alongside the actual experiment to ensure that the experimental design is sound and that the different components of the assay are working as intended. The controls ensure experimental reliability, and that results are not due to other interfering or unpredictable factors. Control experiments may have combinations of components used in the experiment or expected products from the assay, and contain both a positive and negative control.
Positive controls	A control well expected to produce a positive signal. For example, in the ELISA assay, the colourimetric change from blue to green is a positive signal.
Negative controls	A control well expected to produce a negative signal. For example, in an ELISA assay, the lack of colour change is considered a negative signal for controls.
Hits	A compound in an assay which has been determined, through the assay, to have a desired effect.
Miss	A compound in an assay which has been determined, through the assay, to have a non-desired effect.

Diversity in Chemistry: From Yalow to Milstein

A picture of Rosalyn Yalow in the lab.

Assays are not only limited to being used for determining potency of potential drug candidates. There are numerous other assays developed for high through-put screening for other purposes, such as identifying analytes in a complex solution. **Rosalyn Yalow**, a Jewish-American scientist, was the second woman to win a Nobel Prize in Medicine in 1977 for her groundbreaking development of a new assay. Termed a radioimmunoassay, she developed a method of using radioactive isotopes to identify and measure minute concentrations of analytes in blood, such as proteins, vitamins, and drugs, measuring as low as the picogram range. This technique was first applied to determine the cause of type II diabetes, using radioactive iodine binded to insulin, as she had her own personal interest in this condition as her own husband had diabetes. Yalow succeeded in a period where women were undermined for their scientific abilities, with a young Yalow considering pursuing a career in teaching instead of science. More information on Rosalyn Yalow can be found on the Nobel Prize website.



An image of César Milstein in the lab.

Antibodies are commonly employed everywhere for many purposes, whether it be for radioimmunoassays, ELISAs or the commonly used COVID-19 rapid antigen tests. But how exactly are they produced for these purposes? Thank **César Milstein**, an Argentinian-born British biochemist. In 1975, Milstein, alongside a postdoctoral student in his lab, developed a novel method for the mass production of monoclonal antibodies called the hybridoma technique. This led to the expansion of antibody use in both diagnostics and therapeutics, winning him the 1984 Nobel Prize in Medicine. This technique involved the development of hybrid cells. By taking the antibody-producing immune cells (called B cells) out of a mammal and fusing it with immortal cells that reproduce indefinitely, they could harvest a theoretically infinite number of antibodies. Aside from his scientific achievements, Milstein devoted himself to help advance science in developing countries, and never patented his hybridoma technique as he believed it was mankind's intellectual property. More information on César Milstein can be found on his biography page on the American Association of Immunologists page.

Any feedback or comments on this chapter? You may either email chemoer@mcmaster.ca, access this MS Form, or provide a comment in the feedback box below.

4.3 - AROMATICITY

Learning Objectives

1. Use the criteria for aromaticity to determine whether a compound is aromatic or non-aromatic, including neutral, cationic, and anionic compounds, as well as heterocyclic compounds.
2. Use valence bond theory to explain the hybridization of atoms and where the electrons are located in an aromatic compound.
3. Draw resonance structures of aromatic compounds, using the appropriate chemical arrows.
4. Explain how electron delocalization stabilizes aromatic rings, and how this impacts their reactivity.
5. Describe applications of aromaticity in DNA bases and other systems.

Introduction to Aromaticity

One notable feature about homovanillyl alcohol (HVA) is that it is an **aromatic compound**. HVA contains a benzene ring: a six-membered ring structure consisting of three alternating single and double bonds (Figure 4.3.a).

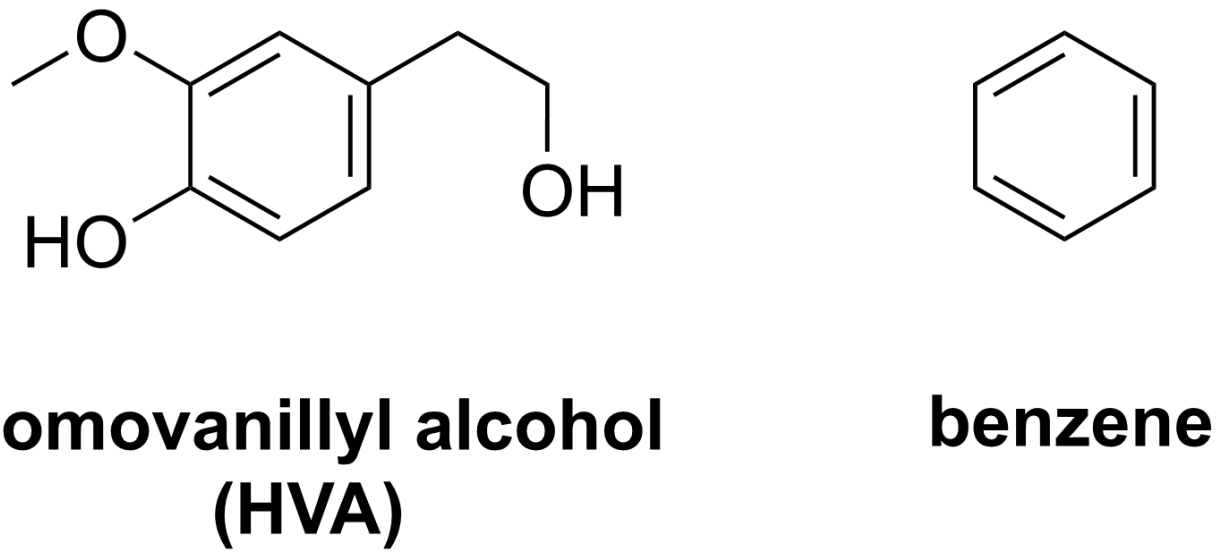


Figure 4.3.a. The chemical structures of HVA (left) and benzene (right).

Aromatic structures exhibit different reactivity than alkenes, despite having a similar electronic arrangement. Figure 4.3.b showcases the reaction of bromine (Br_2) with cyclohexane, cyclohexa-1,3-diene and benzene. While cyclohexane and cyclohexa-1,3-diene react readily with bromine in a halogenation reaction at room temperature, benzene does not react with bromine under these same conditions. Aromatic structures are found to be **significantly more stable** than regular alkene structures as they are resistant to addition, halogenation, oxidation and reduction reactions to which alkenes are typically susceptible.

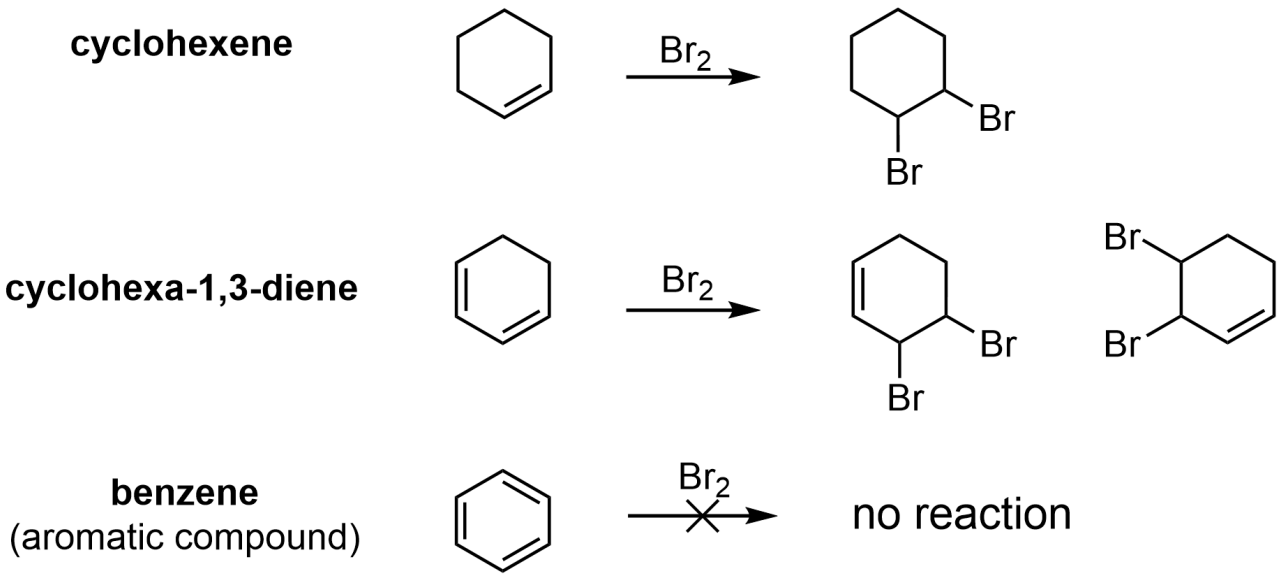


Figure 4.3.b. The reactivity of an alkene such as cyclohexene (top), a conjugated alkene such as cyclohexa-1,3-diene (middle), and a benzene (bottom). Benzene does not undergo the same halogenation reaction as the other alkenes.

An experimental observation of benzene is that all six of the carbon-carbon bonds are all the same length, 1.39 **Angstrom** (Å). This length is intermediate between the typical C–C single bond (1.53 Å) and the typical C=C double bond (1.32 Å), suggesting that the bonds have equal bond order and equal energy. In benzene, each carbon-carbon bond has a bond order of 1.5.

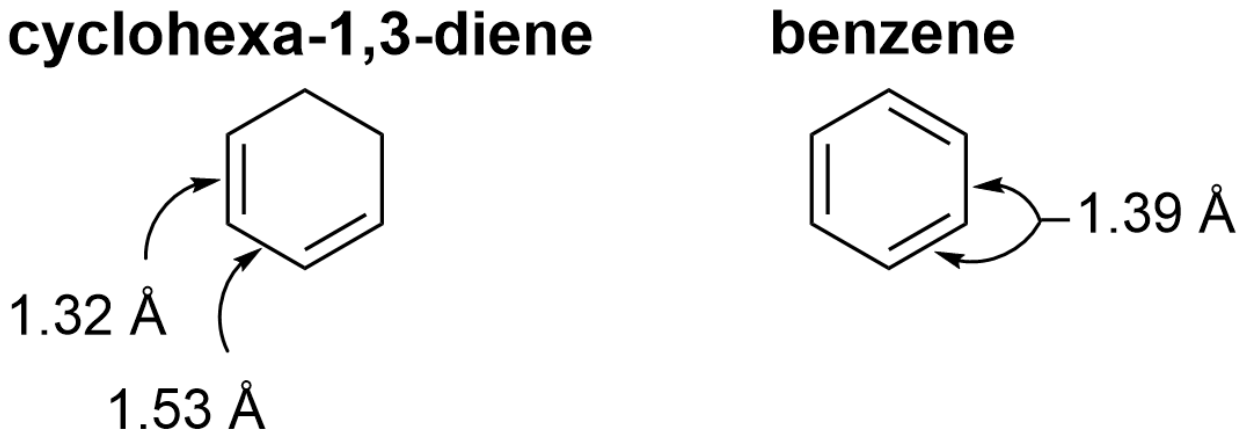


Figure 4.3.c. Bond lengths of carbon-carbon bonds in a cyclic di-alkene (cyclohexa-1,3-diene, left) differ from aromatic benzene (right).

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https://ecampusontario.pressbooks.pub/mcmasterchem1aa3/?p=462#h5p-141

Electron Delocalization in Aromatic Compounds

The defining characteristic of aromatic compounds, and the source of their stability, is the **delocalization of electrons within the cyclic structure.** In a benzene ring, each carbon is trigonal planar and sp^2 hybridized, with one *p* orbital on each carbon available to overlap and form π bonds. All carbon atoms in benzene occupy the same plane, and all p orbitals occupy the space above and below that plane. Each carbon atom contributes one p orbital and one electron, to form a single aromatic π orbital system with 6 electrons. This aromatic π orbital system occupies the space directly above and below the plane of the ring. The six electrons are considered **delocalized** as they form **one large electron cloud** and are free to move anywhere throughout the system (Figure 4.3.c and 4.3.d).

The delocalization of electrons is supported by the observation of a carbon-carbon bond order of 1.5 in benzene. This is also observed with many other ring systems with π electron density, suggesting that aromaticity is a property that is not restricted to benzene alone. Thus, benzene behaves as though all six *p* orbitals overlap together, rather than as three isolated π bonds.

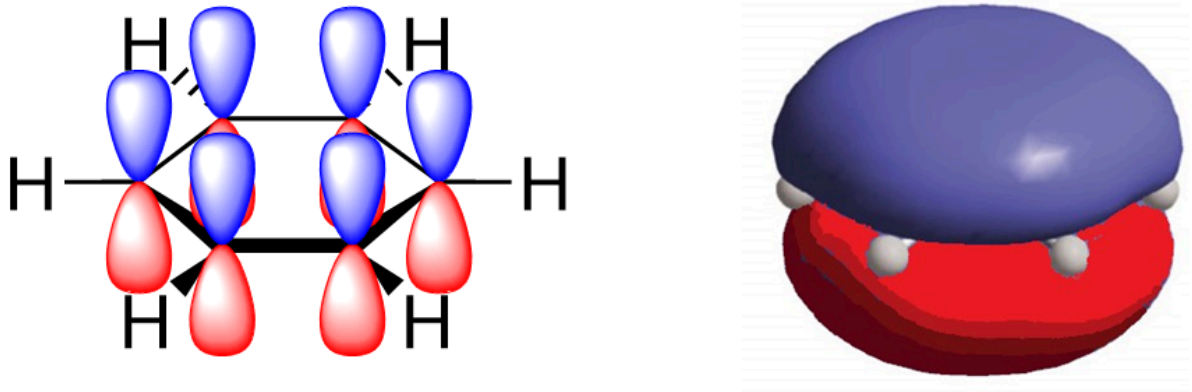


Figure 4.3.d. Each carbon in benzene has one p orbital that lies directly above and below the plane of the molecule. As each p orbital contains one electron, there are a total of six electrons in the p orbitals, which are considered delocalized in an aromatic π orbital above and below the plane of the ring.

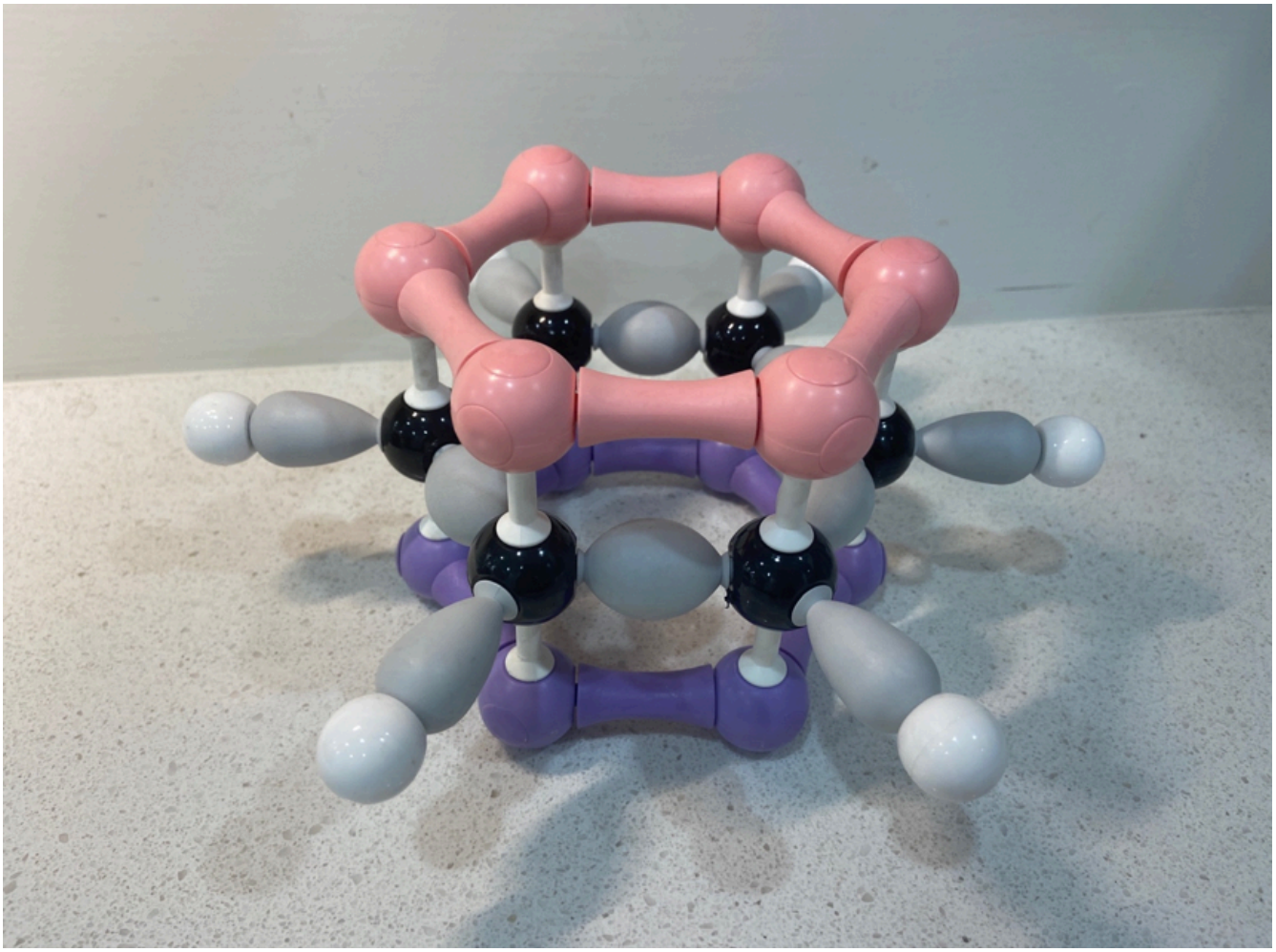


Figure 4.3.e. Molecular orbital model for benzene. The pink and purple orbitals refer to the aromatic π-orbitals where electrons are delocalized. The grey orbitals refer to the C–C (black) sigma bonds and the C–H (white) sigma bonds. Since the electrons are delocalized and can reside throughout the molecule, an aromatic π-orbital system is created.

Curved arrows show the movement of electrons through the aromatic compound, demonstrating the electron delocalization (Figure 4.3.d). This results in 2 equivalent line bond representations of benzene, which are referred to as **resonance contributors**. A double-sided arrow is used to distinguish one resonance contributor from another, as both structures represent the same molecule**.**

Because the electrons are delocalized throughout the aromatic π orbital system, neither of the individual resonance contributors showing alternating single and double bonds are an accurate representation of the molecule. In reality, the molecule exists as a **resonance hybrid**, which is a weighted average of all resonance contributors.

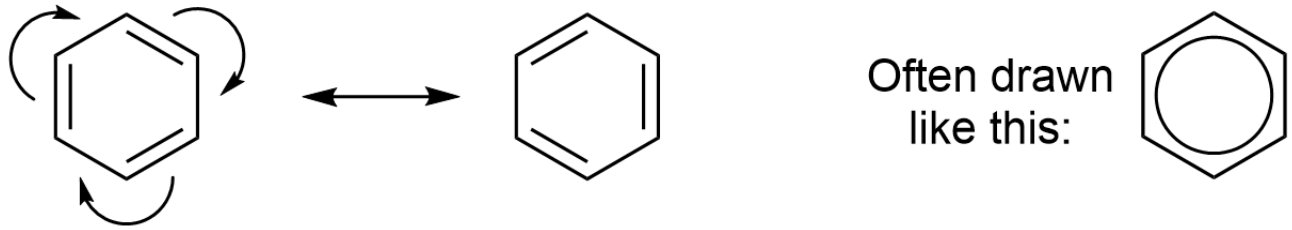
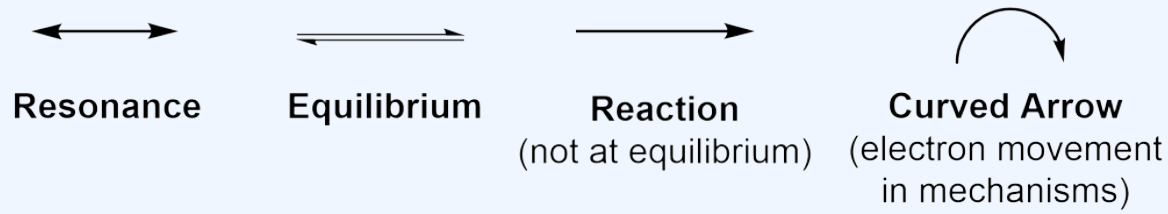


Figure 4.3.f. (Left) Two resonance structures of benzene, depicted with a double-sided arrow. (Right) Benzene is often shown as a six-membered ring with a circle in the middle due to the delocalized electron cloud. This is another way to represent the resonance hybrid.

There are numerous kinds of arrows used in organic chemistry. Here is a quick summary of the different arrows you will see. Ensure that you are always using the correct arrow!



Drawings of different types of arrows in organic chemistry. Resonance, equilibrium, reaction, and curved arrows all look slightly different and represent something entirely different.

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Criteria for Recognizing Aromaticity

Aromaticity is a characteristic that extends beyond benzene rings. Many ring systems that contain π bonds are observed to be resilient to reactions that alkenes are generally susceptible to. Aromatic systems can contain any

number of atoms in their rings, and they can contain heteroatoms and/or formal charges within their cyclic system.

The following three criteria are used to predict whether a structure is aromatic:

1. The structure is cyclic

Aromaticity requires a ring structure in the molecule. The cyclic structure can either be the entire molecular skeleton or one (or more) cyclic region(s) within a larger molecule. If there is no ring present, then the compound is not aromatic.

2. All atoms are sp^2– or sp-hybridized

Aromaticity requires continuously overlapping *p* orbitals. As a result, all atoms must be sp^2– or sp-hybridized, in order to contribute a *p* orbital to the π orbital system. If any atoms in the ring are sp^3-hybridized, then the compound is not aromatic.

3. The number of π electrons obeys Hückel's rule

Hückel's rule states that aromatic compounds must have a specific number of electrons in the aromatic π orbital system. We call this the 'number of π electrons'. An aromatic compound must have $4n+2$ number of π electrons, where *n* is any whole number (0, 1, 2, 3, ...). Note that the value of *n* is not important: *n* does not correspond with any property of the molecule. What is important is that the number of π electrons is 2, 6, 10, 14, and so forth. If there are an odd number of π electrons, or $4n$ π electrons (e.g., 4, 8, 12, etc.), then the compound is not aromatic.

$$\pi\text{-electrons} = 4n + 2$$

For example, benzene contains six π electrons, one in each p orbital at each carbon atom (Figure 4.3.g). Thus, benzene follows Hückel's rule and is aromatic. When counting electrons, ensure that only π electrons in the cyclic system are being counted in Hückel's rule. For example, benzaldehyde (Figure 4.3g) is an aromatic molecule with six π electrons in the ring. Although benzaldehyde also contains a π bond in the carbonyl group, those electrons are not counted towards Hückel's rule. Naphthalene (Figure 4.3g) is another example of an aromatic compound containing 10 π electrons (Figure 4.3.g). As a bicyclic structure, it is made of 10 sp^2-hybridized carbons, with 10 π electrons, one in each p orbital, which follows Hückel's rule.

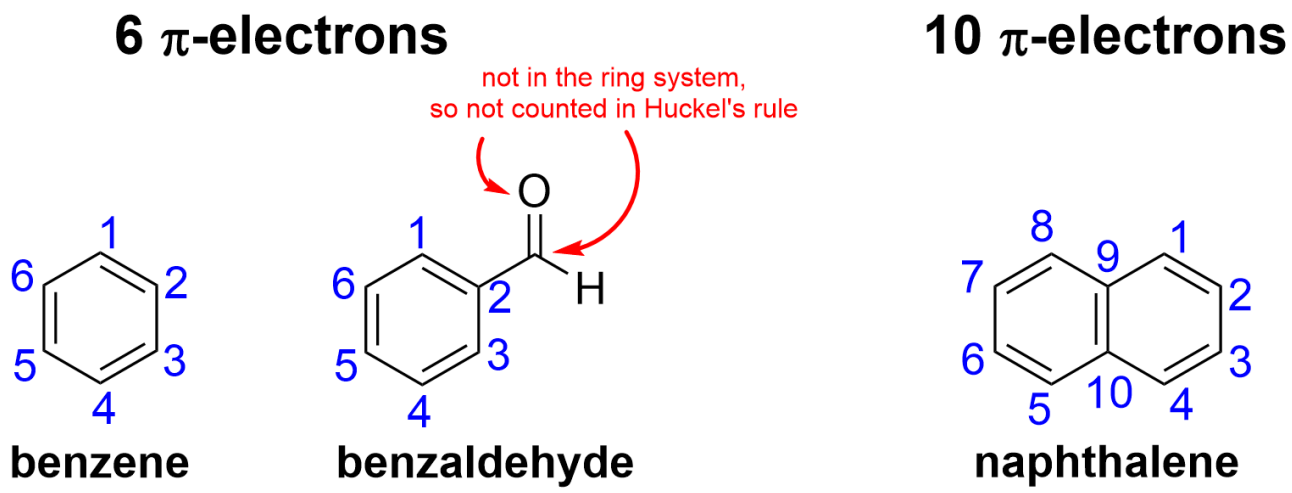

Figure 4.3.g. Examples of aromatic compounds that follow Hückel's rule either with six π electrons (benzene, benzaldehyde) or ten π electrons (naphthalene).

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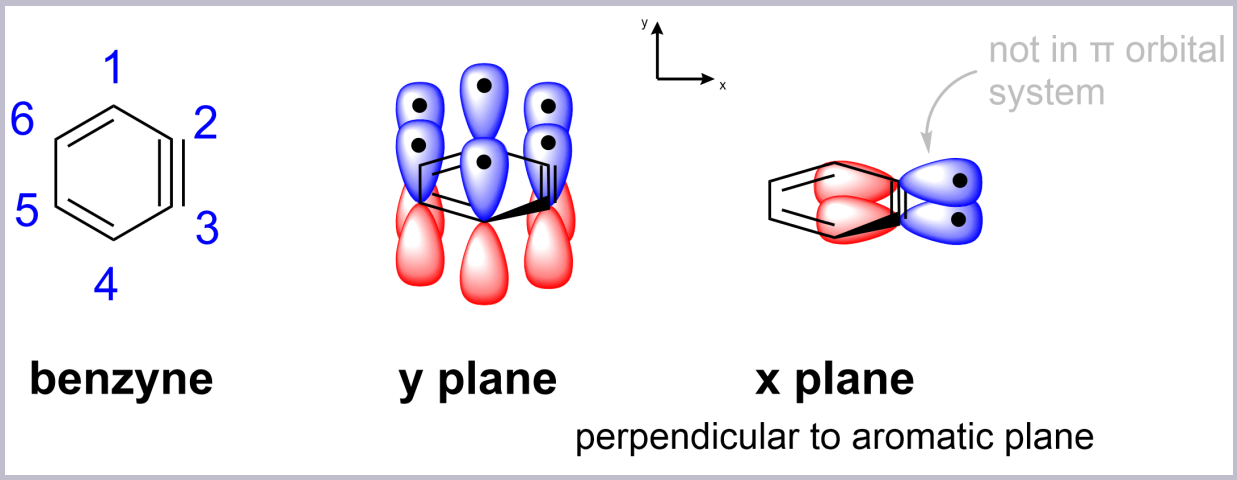
Are You Wondering? Sp-Hybridized Atoms in Aromatic Structures

Earlier, it was mentioned that the atoms in an aromatic structure must be either sp^2– or sp-hybridized to contribute at least one p orbital to the pi orbital system. Despite so, most aromatic structures are observed to only have sp^2-hybrdized atoms. In fact, sp-hybridized atoms are rarely seen in aromatic structures as they require the presence of **an alkyne in a cyclic structure**, which are highly unstable. Alkynes prefer to be in a linear geometry of 180^o to maximize repulsion of the orbitals, and thus, are highly strained in a ring system and are prone to degrading or reacting.

They may exist as brief intermediates, however, such as **benzyne**. As the name suggests, a benzyne is similar in structure to a benzene, with the replacement of one double bond for a triple

bond (as seen below). It has never been isolated and is only inferred to exist based on the products of certain reactions. Using Hückel's rules, we can classify a benzyne as an aromatic structure. It is cyclic and comprised entirely of sp^2– or sp-hybridized atoms. Lastly, it contains 6 π electrons.

You may ask yourself if the molecule actually contains 8 π electrons due to the presence of the second set of p orbitals on the alkyne. However, as these p orbitals are in a different plane perpendicular to the aromatic system, it is not counted when counting π electrons for Hückel's rules.



The molecular structure of benzyne is displayed on the left-hand side. In the y plane, it can be seen that all carbon atoms contribute one p electron to the π system. However, the carbons engaged in the triple bond have their other p electron in a different plane, and thus, it is not apart of the π orbital system.

Identifying Aromatic Ions

Aromatic structures can also be cationic or anionic and satisfy all the criteria for aromaticity explained above.

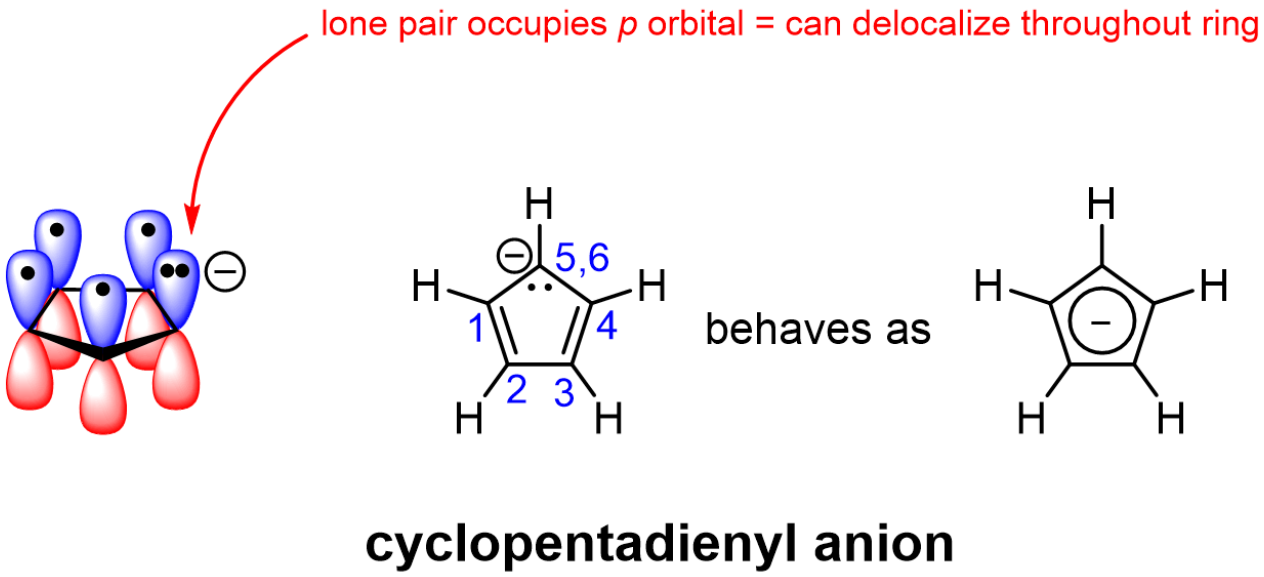


Figure 4.3.h. Cyclopentadienyl anion contains five carbon atoms arranged in a ring, as well as a lone pair of electrons. Each double-bonded carbon atom contains one electron in its p orbital, while one carbon atom contains two electrons in its p orbital, for a total of six π electrons.

For example, consider the five-carbon **anionic aromatic ring, cyclopentadienyl anion**. This molecule contains an anionic carbon atom with a lone pair (Figure 4.3.h). This anionic carbon atom, although it is not part of a π bond, is experimentally observed to have trigonal planar geometry, making it sp^2-hybridized. The lone pair of electrons must therefore occupy the unhybridized *p* orbital. This *p* orbital overlaps with all the other *p* orbitals in the ring to form the aromatic π orbital system. This allows all π electrons, including the lone pair, to delocalize throughout the ring. Therefore, all five carbon atoms in cyclopentadienyl anion are sp^2-hybridized, with overlapping *p* orbitals, and a total of six π electrons to satisfy Hückel's rule. Moreover, each carbon in the cyclopentadienyl anion has been experimentally observed to bear some of the negative charge due to the electron delocalization.

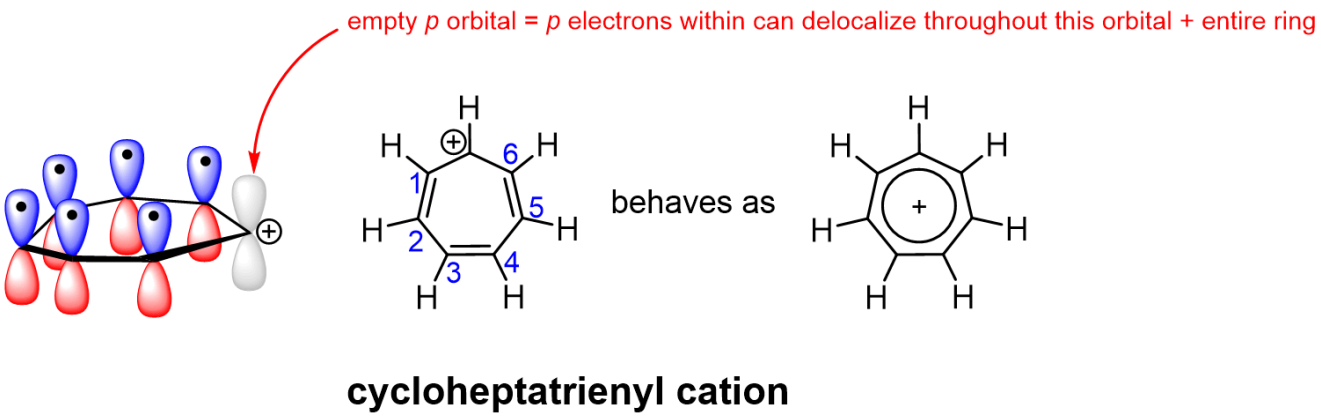


Figure 4.3.i. Cycloheptatrienyl cation contains seven carbon atoms arranged in a ring, as well as a formal positive charge. Each double-bonded carbon atom contains one electron in its p orbital, while one carbon atom has an empty p orbital, for a total of six π electrons.

In contrast, the seven-membered **cationic aromatic ring, cycloheptatrienyl cation**, has a cationic carbon atom (Figure 4.3.i). The cationic carbon is sp^2-hybridized, with an empty *p* orbital. The empty *p* orbital overlaps with all the other *p* orbitals in the ring to form the aromatic π orbital system. This allows all π electrons to delocalize throughout the ring. Although the cationic carbon does not have an electron in its *p* orbital to contribute to the electron cloud, its empty *p* orbital still allows it to participate in aromaticity. Therefore, all seven carbon atoms in cycloheptatrienyl cation are sp^2-hybridized, with overlapping *p* orbitals, and a total of six π electrons to satisfy Hückel's rule. Moreover, each carbon in the cycloheptatrienyl cation has been experimentally observed to bear some of the positive charge due to the electron delocalization.

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Identifying Heteroaromatics

Heteroaromatics, also called heterocyclic aromatic compounds, are aromatic compounds that contain **heteroatoms** in the aromatic ring. A heteroatom is an atom other than carbon, such as boron, nitrogen, oxygen, sulfur, etc. Heteroatoms also contribute a *p* orbital and a certain number of electrons to the π orbital system. For example, a heteroatom can contribute one electron (from a π bond), zero electrons (from an empty *p* orbital), or two electrons (from a filled *p* orbital with a lone pair). Below are examples of a heteroatom contributing one electron or two electrons to the π orbital system.

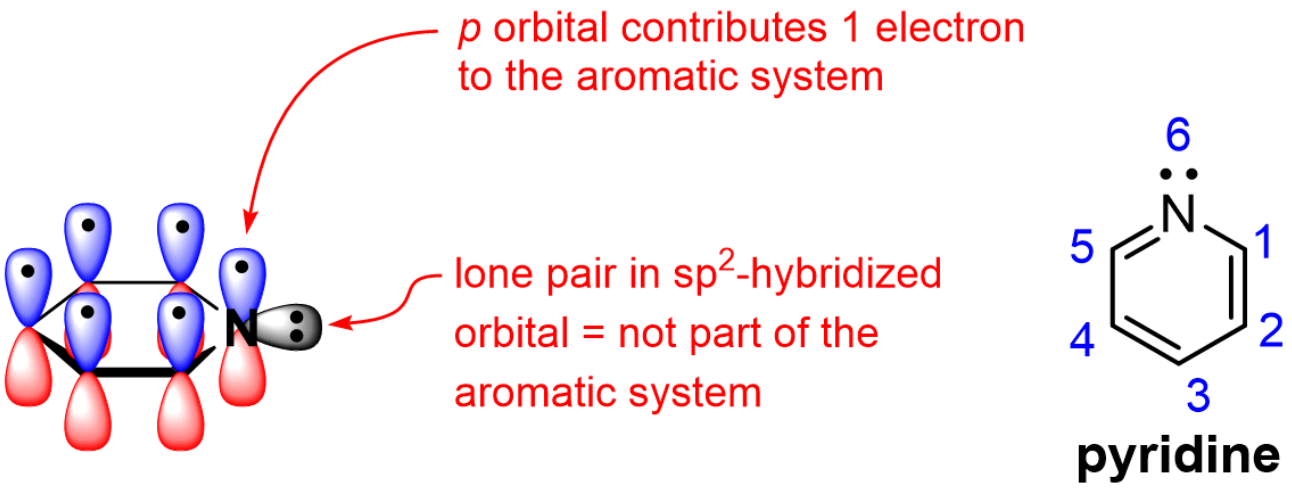

Figure 4.3.j. Pyridine is a six-membered ring with five carbon atoms and one nitrogen atom. The nitrogen atom is sp^2 hybridized, with one electron in its unhybridized p orbital and a lone pair in an sp^2-hybrid orbital. The p orbital is part of the π orbital system, while the sp^2-hybrid orbital is perpendicular to, and not part of, the π orbital system. In total, there are six electrons in the π orbital system.

A common heteroaromatic molecule is **pyridine** (Figure 4.3.j), a six-membered ring containing one nitrogen atom. Experimental observations show that the nitrogen atom has a trigonal planar geometry, making it sp^2 hybridized, with an unhybridized *p* orbital. Since the nitrogen atom is already using its *p* orbital to contribute to the aromatic π orbital system, the lone pair must occupy the sp^2 hybridized orbital. The sp^2 hybrid orbital is perpendicular to the π orbital system, and is therefore not part of the π orbital system. The electrons in the sp^2 hybrid orbital are not included when counting electrons for Hückel's rule. Therefore, there are six π electrons in the π orbital system.

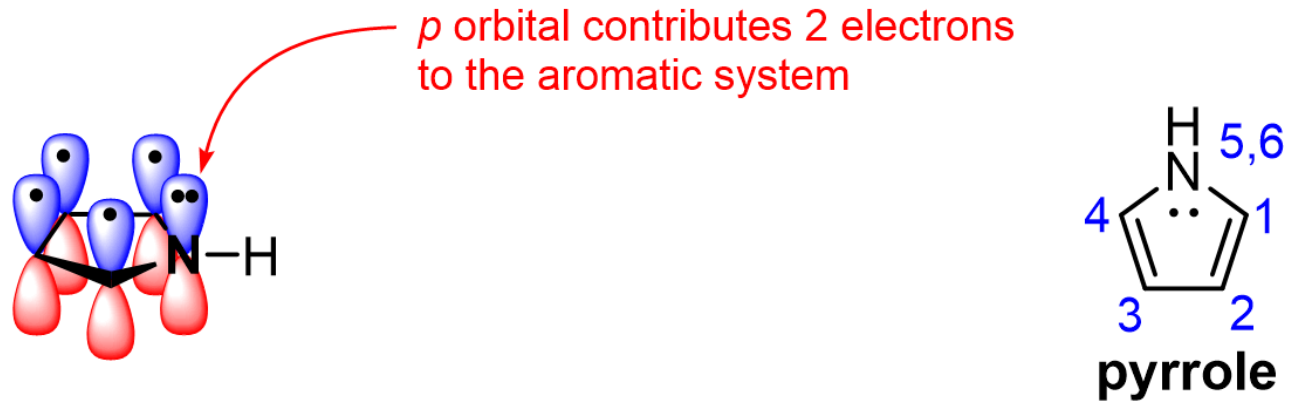

Figure 4.3.k. Pyrrole is a six-membered ring with four carbon atoms and one nitrogen atom. The nitrogen is sp^2 hybridized, with a lone pair in its unhybridized p orbital. The lone pair contributes two electrons to the π orbital system. In total, there are six electrons in the π orbital system.

Another common heteroaromatic is **pyrrole** (Figure 4.3.k), a five-membered ring containing one nitrogen

atom. Like pyridine, experimental observations show that the nitrogen atom has trigonal planar geometry, making it sp^2 hybridized, with an unhybridized *p* orbital. Unlike pyridine, the nitrogen is not part of any double bond, and contains only single bonds to all its neighbouring atoms. Thus, the lone pair of electrons must occupy the unhybridized *p* orbital.

As mentioned above for cyclopentadienyl anion (Figure 4.3.h), the electrons that form the π system of an aromatic ring do *not* have to come from a π bond. Instead, nitrogen can use its lone pair to contribute two π electrons to the aromatic system to satisfy Hückel's rule with six π electrons. In fact, pyrrole is isoelectronic with cyclopentadienyl anion.

In this example, you might have expected nitrogen to be tetrahedral and sp^3 hybridized to maximize the distance from other neighbouring electron pairs. However, the sp^2 hybridized nature of the nitrogen atom allows the electron pair to delocalize across the ring, which is a stabilizing force, making it thermodynamically favorable.

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(The full solution to this problem can be found in Chapter 5.3)

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(The full solution to this problem can be found in Chapter 5.3)

Aromatic Molecules in Biology: DNA

Aromatic structures are heavily abundant in biological systems due to their stabilizing characteristics. For example, the nitrogenous bases in **deoxyribonucleic acid (DNA)**, which form the building blocks of our genetic material, are made up of heteroaromatics.

For example, thymine and cytosine (Figure 4.3.l, top) have six-membered heterocyclic rings in which all atoms are sp^2 hybridized, with an unhybridized *p* orbital that can overlap to form the aromatic π system. Like the resonance contributors shown for benzene (Figure 4.3.d, above), thymine and cytosine also have various resonance contributors, which can be drawn to better indicate the sp^2 hybridization of the ring atoms.

Adenine and guanine (Figure 4.3.l, bottom) have two fused rings with 9 atoms. All atoms in the rings are sp^2 hybridized. Nine unhybridized *p* orbitals overlap to form the aromatic π system, containing ten π electrons, which obeys Hückel's rule. For adenine and guanine, note that the singly bonded nitrogen atom in the five-membered ring is sp^2 hybridized, like pyrrole (Figure 4.3.k). For guanine, a resonance contributor can be drawn to better indicate the sp^2 hybridization of the ring atoms.

Because of the sp^2 hybridization and the aromatic π system, these molecules are planar and highly stable. Planarity allows the nitrogenous bases to easily stack and align in the DNA double helix, while stability limits DNA degradation.

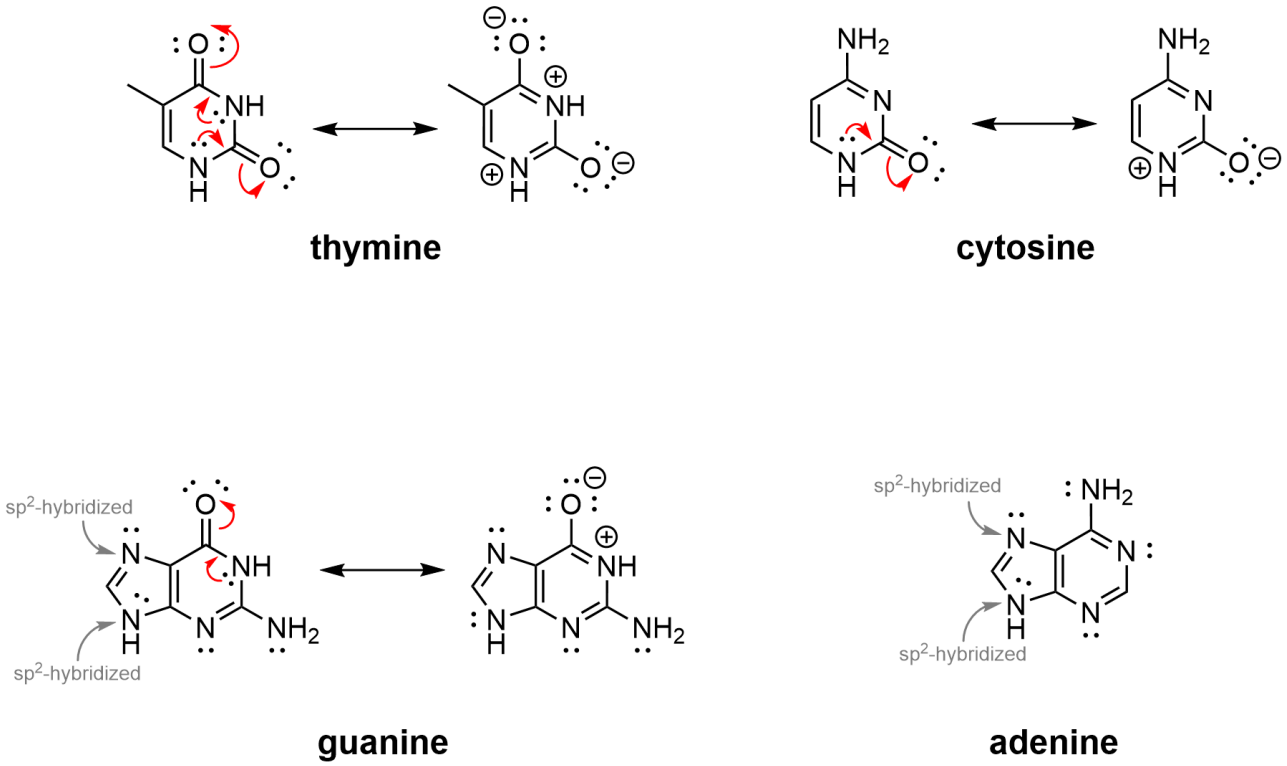

Figure 4.3.l. Resonance contributors for the nitrogenous bases thymine and cytosine (top) and guanine and adenine (bottom). Each atom in the ring is sp^2 hybridized, providing p-orbitals on each ring atom that overlap to form the aromatic π system. Thymine and cytosine contain six π electrons aromatic π system, while guanine and adenine contain ten π electrons.

Are You Wondering: Resonance of Aromatic Molecules

As you may recall, in CHEM 1A03 there was content concerning how resonance structures contribute to the stability of molecules. The movement of electrons in resonance structures is a bit beyond the scope of CHEM 1AA3, but below is an explanation of how it works for those who are curious.

Recall that resonance structures occur as movements of electron pairs which form new bonds, then breaking a neighbouring bond in the process. Carbonate is a great example of this, where a lone pair of oxygen can form a double bond to carbon (Figure A). The carbon has to break its existing double bond to another oxygen to ensure it follows the octet rule. If carbon could not do this, then the resonance cannot occur.

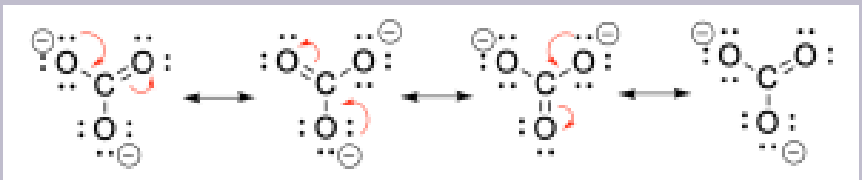

Figure A. Carbonate resonance structures.

Misconceptions may occur with molecules that may appear non-aromatic, which need resonance for further evaluation of aromaticity. One such molecule is caffeine (Figure B).

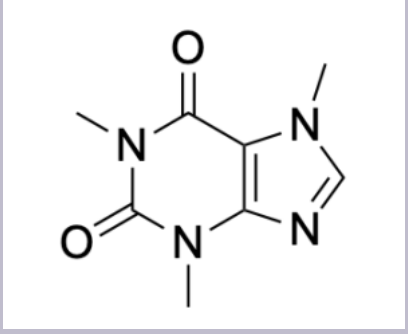

Figure B. The molecular structure of Caffeine.

Caffeine appears non-aromatic in the six-membered ring structure, until its nitrogen lone pairs are considered. They can form double bonds, since the neighbouring carbon can lose a bond to the double-bonded oxygen (Figure C).

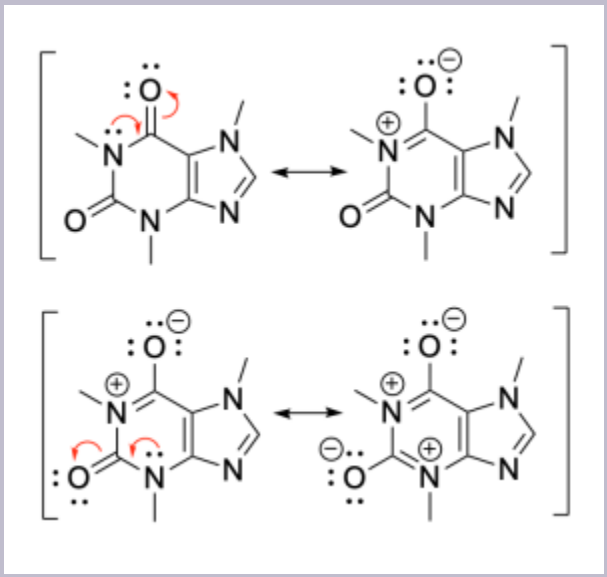

Figure C. Resonance structures of Caffeine exhibiting its aromatic nature.

The resonance structure at the very end is aromatic, as evidenced in Figure D, with a simplified version of the ring structure indicating 10 π electrons. This follows Hückel's rule. Despite the final structure having 4 formal charges, the structure's aromaticity stabilization favours this conformation's formation.

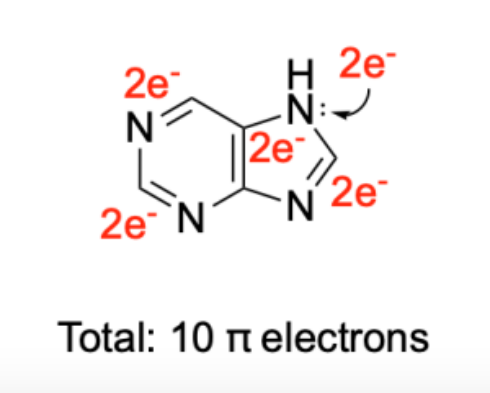

Figure D. The skeleton of caffeine exhibiting the aromatic structure.

The following videos include two worked examples from a previous CHEM 1AA3 test or exam that students struggled with. Try solving them on your own before looking at the full solution.

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Key Takeaways

- **Aromatic structures** exhibit different reactivity than alkenes, as they are more stable and resistant to addition, halogenation, oxidation and reduction reactions, which alkenes typically undergo.
- In benzene or aromatic compounds, each carbon atom contributes one p orbital and one electron, to form a single aromatic π orbital system which occupies the space directly above and below the plane of the ring.
- The electrons are considered **delocalized** as they form **one large electron cloud** and are free to move anywhere throughout the system. The movement is represented through curved arrows, and are referred to as resonance contributors.
- The three characteristics of an aromatic compound are: it is cyclic, it is sp or sp^2 hybridized, and it follows Hückel's rule.
- There are also anionic and cationic aromatic compounds where the extra electron (anionic) can contribute to an even number of pi electrons following Hückel's rule, or the lack of an electron helps in maintaining Hückel's rule and allowing for an empty p-orbital to interact with the system allowing for electrons to be delocalized in the ring/move around.
- Heteroaromatics are aromatics containing heteroatoms, where the heteroatom contributes 0,

1, or 2 electrons to the pi orbital system, which can help in maintaining Hückel's rule.

- Aromatic compounds are found in biological systems sue to their stability, especially DNA, as the nitrogenous bases (adenine, thymine, cytosine, guanine) are made of heteroaromatics.

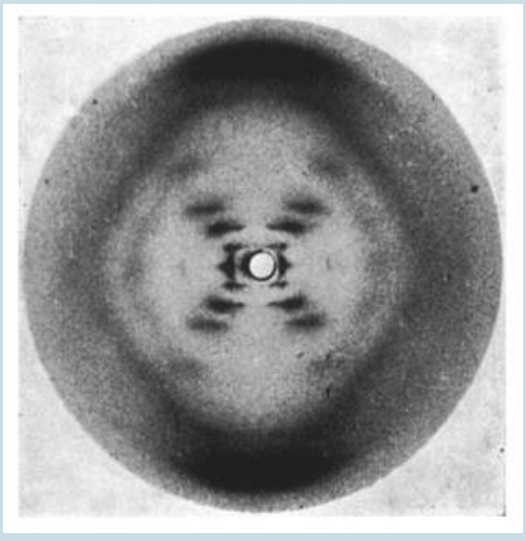
Key terms in this chapter:

Key term	Definition
Aromatic compound	A property of certain molecules that make it extremely stable due to the delocalization of the electrons located in the p orbitals, forming an aromatic π orbital system. There are three criteria for a molecule to be aromatic. It must (1) contain a ring structure, (2) be comprised of either sp2-hybrdized or sp-hybridized atoms, and (3) follow Hückel's rule.
Angstrom	A unit of length, equal to 0.1 nanometer.
Hückel's rule	1 of the 3 requirements of aromaticity which represents the amount of π electrons needed to maintain aromaticity calculated by the formula 4n+2 where n represents a non-negative whole number (0, 1, 2...).
Heteroatoms	An atom other than carbon, such as oxygen, nitrogen, and sulfur.

Diversity in Chemistry: Rosalind Franklin

A portrait of Rosalind Franklin.

The aromaticity of the nitrogenous bases in DNA gives it a highly planar structure, which allows it to form the double helix structure. This structure was elucidated in 1953 by the pair of scientists James Watson and Francis Crick, winning them the Nobel Prize in Medicine in 1962. However, unbeknownst to many, **Rosalind Franklin**, a British-Jewish chemist, contributed heavily to this discovery with her role in this research going unrecognized for most of her life. Franklin was a scientist at King's College in London, using X-ray diffraction to study and deduce the structure of DNA. Alongside her Ph.D student, Franklin took the famous Photo 51, an X-ray image capturing the helical structure of DNA in its B-form. This, alongside an unpublished report with her conclusions, was shown to Watson and Crick. These helped facilitate the discovery of the DNA double helix model, with the pair going as far as saying that this discovery would not be possible without Franklin's data. Many have agree that she should have been awarded a part of Nobel Prize (which did not give out posthumous awards), with her contributions being a hot topic of discussion (there is even a musical about her titled "Double Helix" performed at Bay Street Theatre in New York!). More information on Rosalind Franklin can be found on her biography page on the Rosalind Franklin University of Medicine and Science website.



The famous Photo 51, taken in 1952 by one of Franklin's postdoctoral students.

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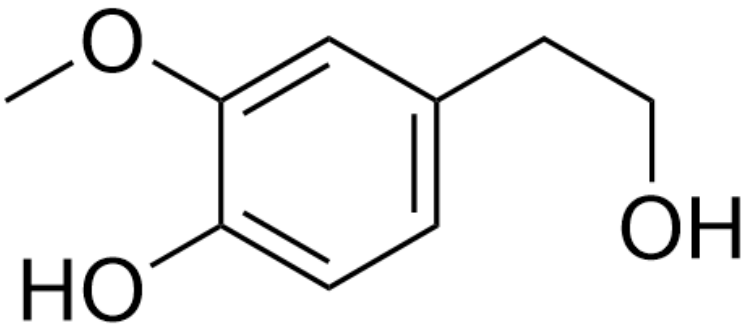
4.4 - COMBINATORIAL CHEMISTRY

Learning Objectives

1. Define and identify "sites of diversity"
2. Determine the number of compounds in a combinatorial library.

Introduction to Combinatorial Chemistry

Once an assay has been developed for testing HVA-like compounds for dopamine inhibition, the next step is to synthesize a library of test compounds to screen. As HVA is the lead compound (Figure 4.4.a), the goal is to synthesize thousands of new compounds that share the core aromatic structure but differ in other aspects. This is done through an approach known as combinatorial chemistry. **Combinatorial chemistry** is the mixing and matching of substituents at different sites on the molecule to create libraries of unique compounds.



Homovanillyl Alcohol (HVA)

Figure 4.4.a. The chemical structure of homovanillyl alcohol, HVA, the lead compound for this drug discovery process.

This can be applied to HVA through the manipulation of the diversity sites on the compound. **Diversity sites** are parts of a molecule which can be substituted with different atoms or functional groups. The molecule HVA below has several diversity sites, three of which are labelled as R1, R2 and R3 (Figure 4.4.b).

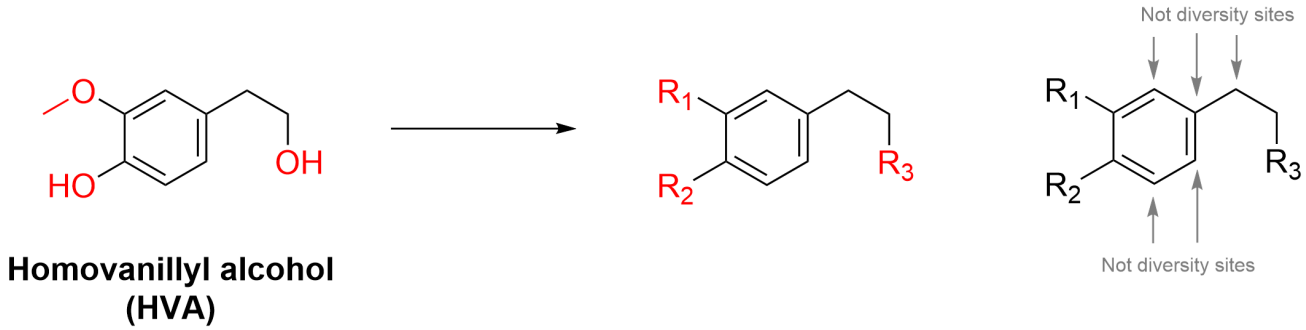


Figure 4.4.b. Three diversity sites in HVA are shown in red. The main aromatic structure and ethylene chain on the compound remain the same, seen in the black outline. Grey arrows point to sites that are not diversity sites for this molecule.

With these three diversity sites, various functional groups or substituents can be added to one or more of them

to make different compounds. For example, one substituent, fluorine (F), can be substituted at one or more of the sites to make 8 unique compounds, including HVA.

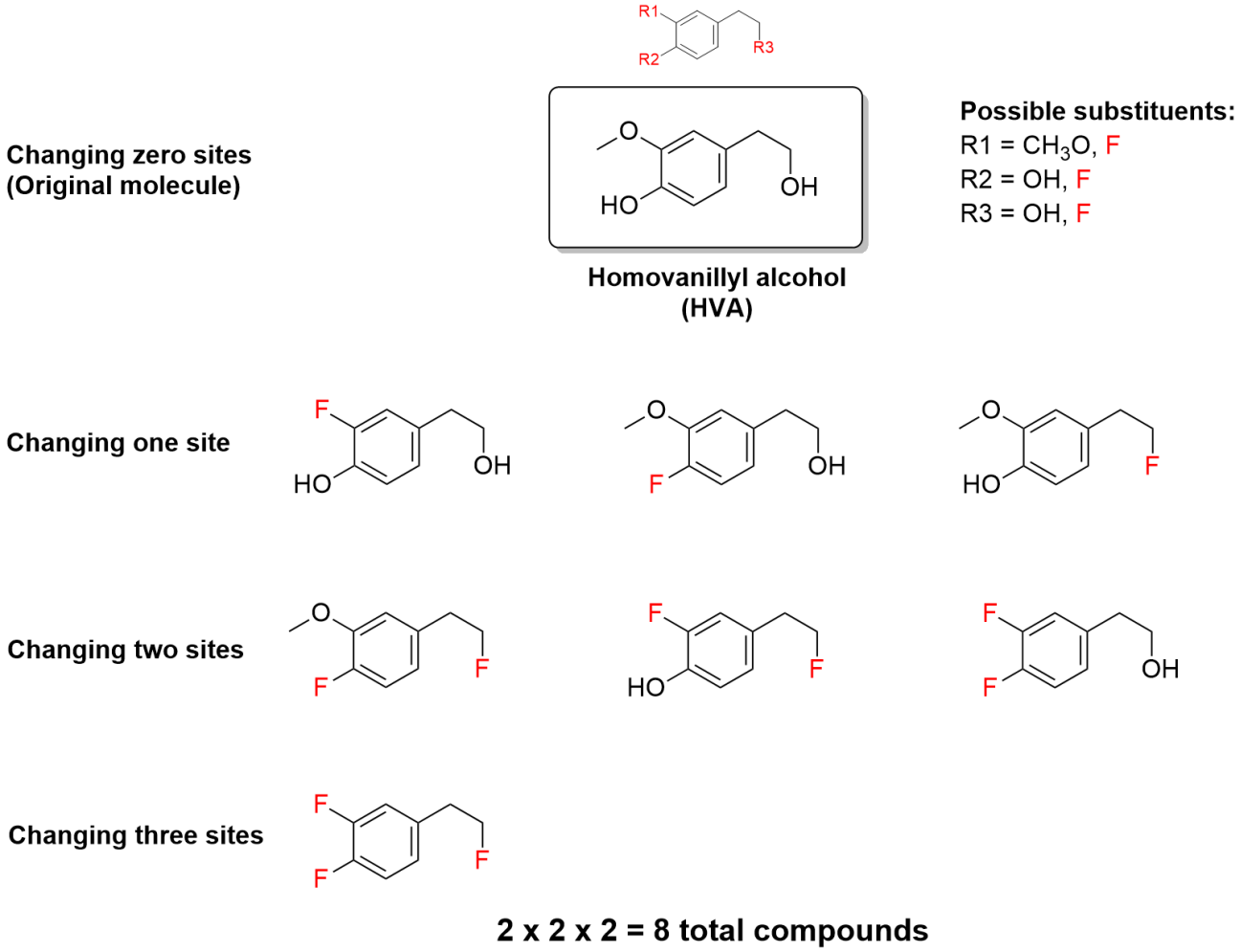


Figure 4.4.c. By introducing a different substituent (a fluorine atom) at one or more diversity sites on HVA, eight unique compounds can be synthesized.

To further expand this idea, we can introduce a second functional group to substitute at each site of diversity, such as chlorine (Cl). Now there are even more possibilities for mixing-and-matching (Figure 4.4.d).

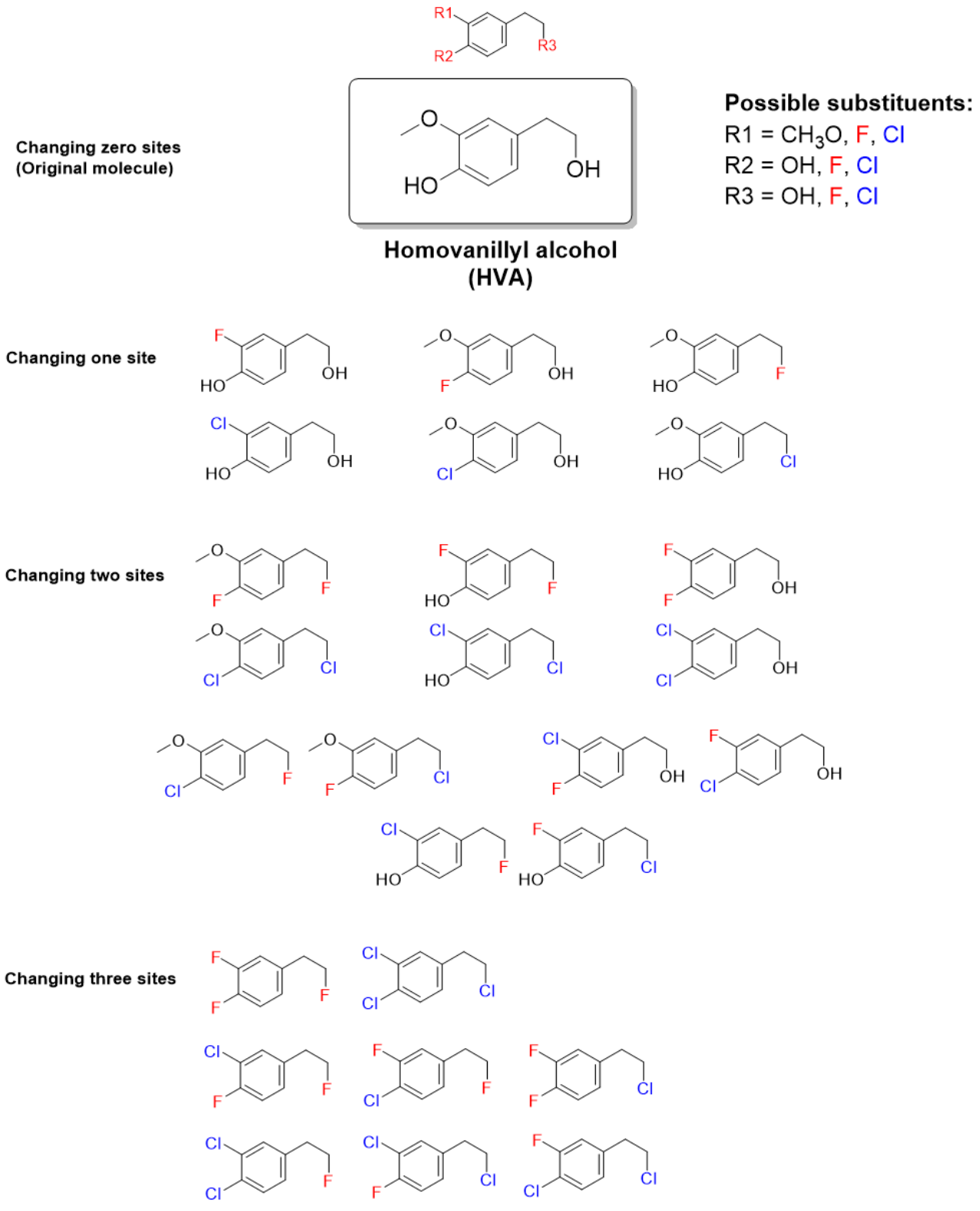


Figure 4.4.d. By introducing two different substituents (a fluorine atom or a chlorine atom) at one or more diversity sites on HVA, 27 unique compounds can be synthesized.

The complete set of compounds that can be produced is called a **combinatorial library**. The library size refers to the total number of compounds in the library. It is a function of both the number of substituents and the number of diversity sites, expressed in the equation:

$$\text{library size} = (\#\ \text{substituents})^{\#\ \text{diversity sites}}$$

The equation for the size of the combinatorial library derives from combinatorics. For example, in Figure 4.4.c, there are two different substituents at three diversity sites. To create any molecule in the library, you have two choices for the first diversity site, two choices for the second diversity site, and two choices for the third diversity site. Therefore, there are 2x2x2 = 8 different possibilities.

For a molecule to become an approved drug, the typical success rate is approximately one in 5 000 to 10 000. Therefore, chemists must create libraries of at least 5000 compounds to screen. This is where combinatorial chemistry plays an important role. By increasing the number of substituents at each diversity site, thousands of novel drug candidates can be produced. All these compounds are synthesized by automated robotic processes, which simplifies and speeds up the synthetic process.

For example, with 18 different substituents at each site, a total of 5832 unique compounds can be synthesized ($18^3 = 5832$), all of which can be screened for dopamine inhibition in the hopes of developing a potential therapeutic. Figure 4.4.e below shows a sample of 18 substituents that could potentially be used for this process.

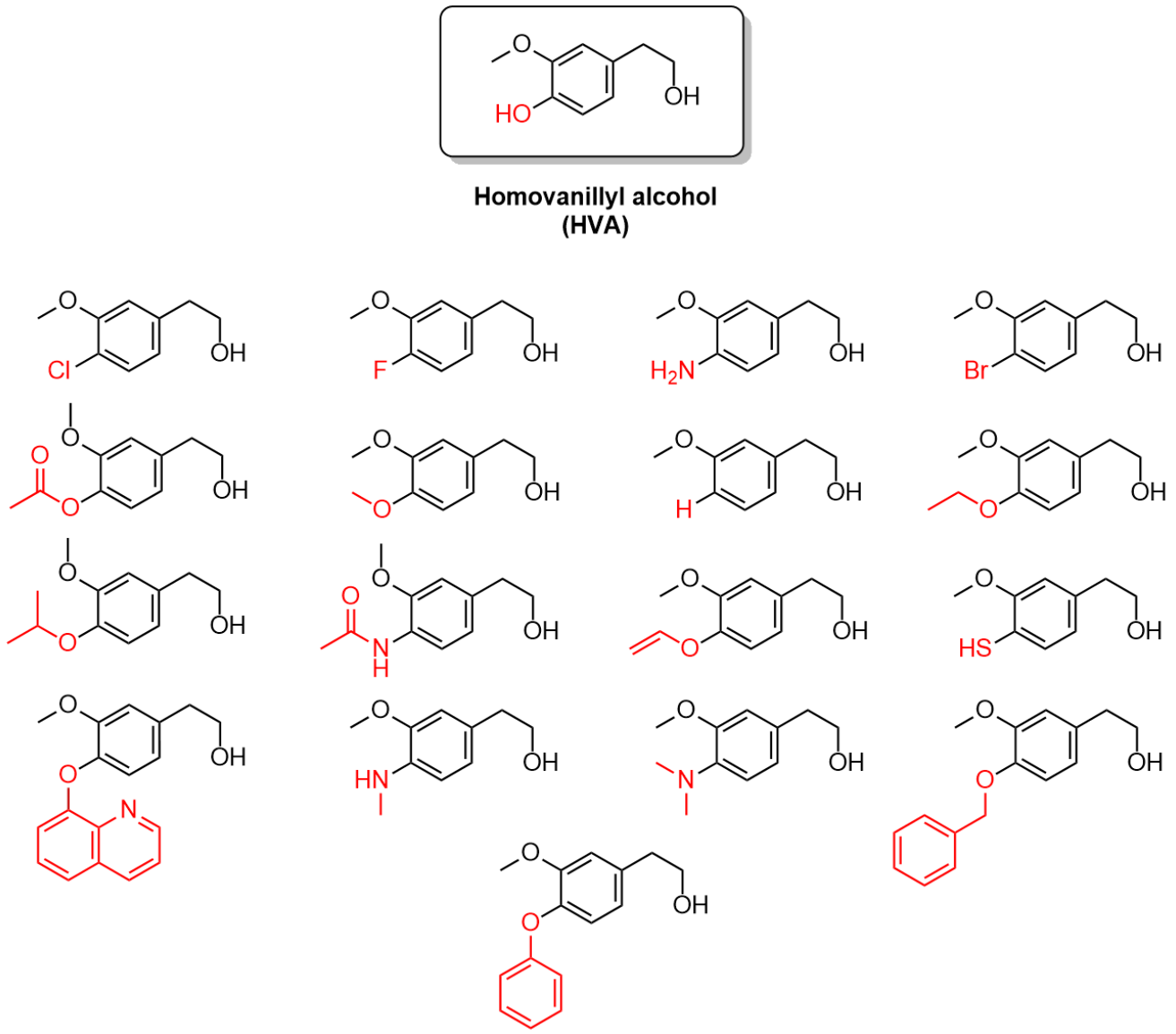


Figure 4.4.e. A sample of 18 possible substituents at R2, including the original -OH group in HVA, shown in red, with the remaining backbone of the molecule shown in black.

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(The full solution this solution can be found in Chapter 5.3)

Identifying Diversity Sites on a Library of Molecules

Given several molecules in the combinatorial library, it is possible to infer the number of substituents and diversity sites present, and calculate the maximum size of the combinatorial library. For example, three molecules in a library of drug candidates are shown in Figure 4.4.f.

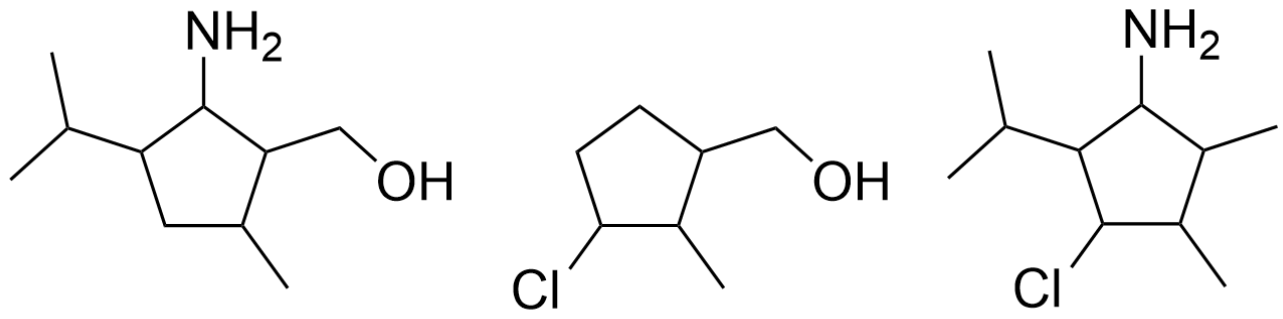

Figure 4.4.f. Three different molecules that are part of a combinatorial library.

To determine the number of diversity sites, the first step is to determine the core structure that stays constant throughout all the molecules. In this example, the core structure includes carbon atoms within the ring and outside of the ring, shown in blue in Figure 4.4.g.

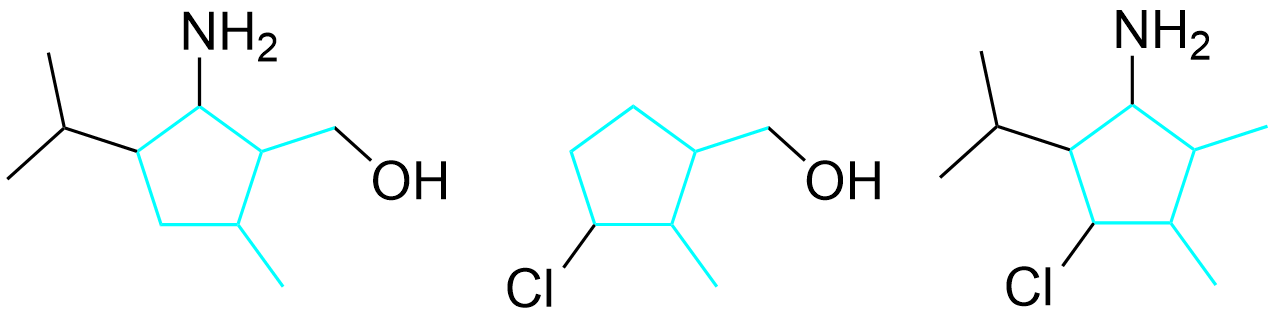

Figure 4.4.g. Three different molecules that are part of a combinatorial library. The portion shown in blue is the core structure conserved in all compounds within the combinatorial library.

After determining the core structure, the diversity sites can be identified (Figure 4.4.h). These are the locations that have different substituents in the three molecules. For example, diversity site 1 could have the substituent NH_2 (in the molecules on the left and right) or the substituent H (in the molecule in the center). Similarly, diversity site 2 could have the substituents OH or H, diversity site 3 could have the substituents Cl or H, and diversity site 4 could have the substituents H or isopropyl. The carbon group on the bottom right highlighted

by the gray arrow is commonly mistaken to be a diversity site as it is a substituent outside of the ring; however, as this carbon group shows up in all three molecules, it is *not* changing and thus, is *not* a diversity site.

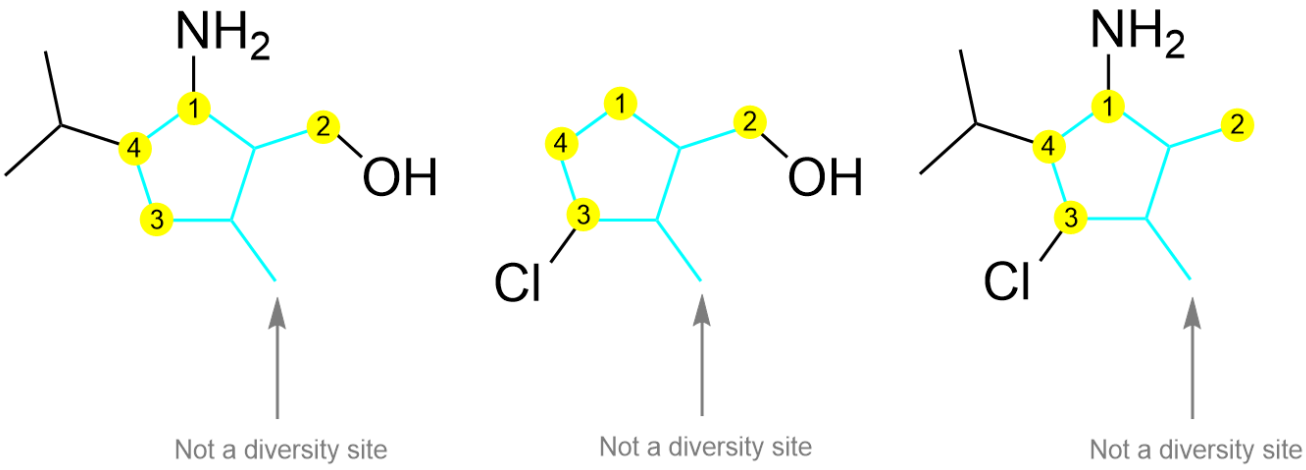

Figure 4.4.h. Three different molecules that are part of a combinatorial library. The portion shown in blue is the core structure while the red dots represent the four diversity sites which have variable substituents.

The next step is to identify the different substituents that are used to create this library. In these three compounds, there are a total of five different substituents present on the various diversity sites: NH_2, OH, H, Cl, isopropyl. Thus, when constructing a full library of drug candidates, all five of these substituents can be used on each diversity site. Thus, a total of $5^4 = 625$ unique compounds can be synthesized.

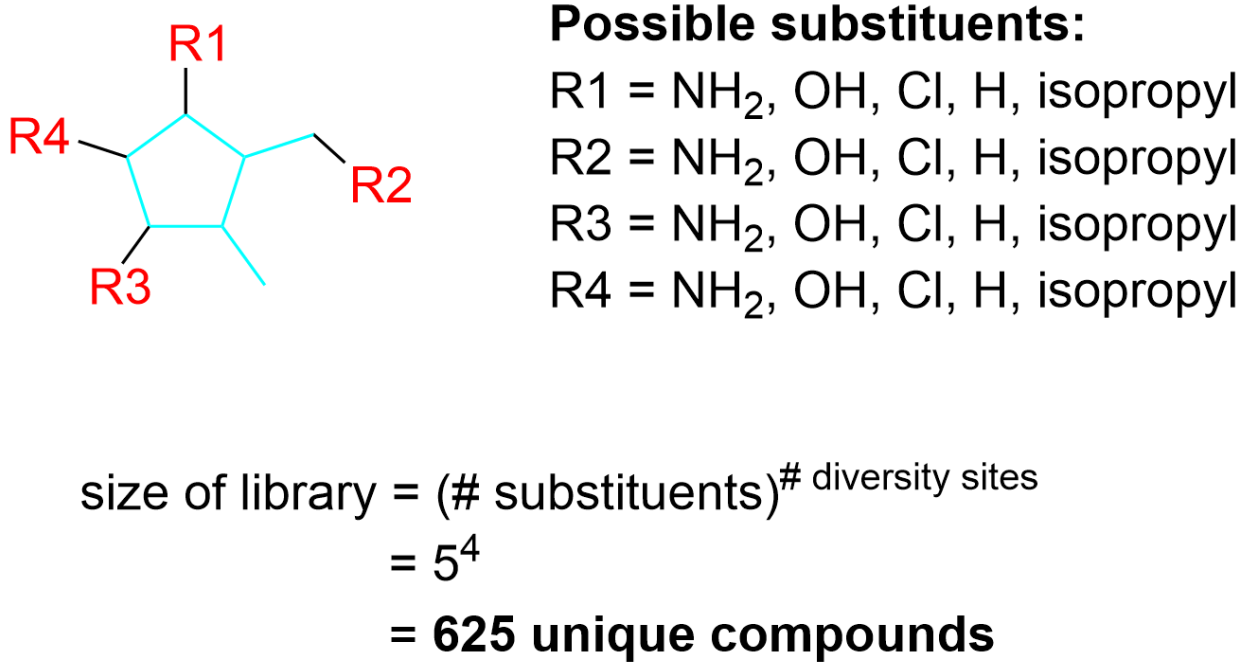

Figure 4.4.i. The core structure of compounds in the combinatorial library is shown in blue and the four diversity sites are shown in red, indicated as R1, R2, R3, and R4. There are five substituents that can be present at each diversity site. Thus, the library size is 5^4, or 625.

The following video includes a worked example from a previous CHEM 1AA3 test or exam that students struggled with. Try solving it on your own before looking at the solution.

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(The full solution to this problem can be found in Chapter 5.3)

Key Takeaways

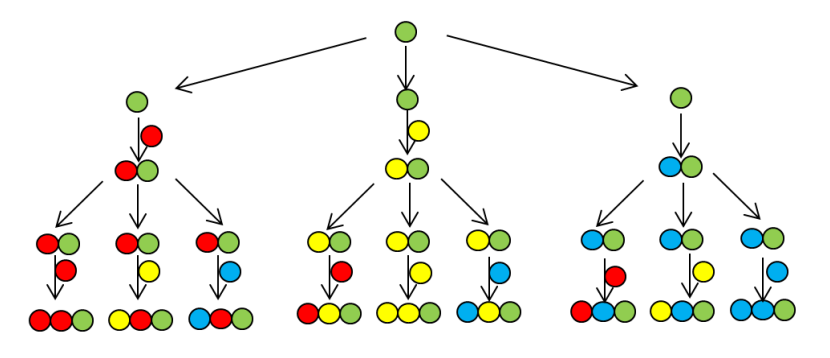
- In the drug delivery process, combinatorial chemistry can be utilized on a lead compound of choice, such as HVA, to create a library of compounds to test.
- Combinatorial chemistry involves "mixing and matching" various substituents onto specific atoms of the lead compound called diversity sites. These sites can have the functional groups modified or substituted to other substituents of choice.
    - The resulting library of different but similar compounds is called a combinatorial library.
- The amount of compounds in a library is given by the equation below:
    - $(\#\ \text{substituents})^{(\#\ \text{diversity sites})}$

Key terms in this chapter:

Key term	Definition
Combinatorial chemistry	The process of modifying a lead compound with various functional groups at multiple sites to create a large library of compounds.
Diversity sites	An atom on a lead compound which can have its functional groups modified to other functional groups of choice.
Combinatorial library	A library, or large collection, of unique compounds, all with the same core structure derived from a lead compound.

Diversity in Chemistry: Árpád Furka

The field of combinatorial chemistry is a lot broader than discussed in this chapter, with not only diverse small molecules being synthesized, but also larger polymers made of amino acids and nucleotides. **Árpád Furka** is considered one of the pioneers of combinatorial chemistry, developing a method known as the split-and-mix synthesis. This technique uses solid-phase synthesis, where a growing peptide is bonded to a solid bead, and reactants are added to the resin to react with the reactive growing chain. As the name suggests, different combinations of amino acids can be made, and then these small chains can be divided and react with each other to form larger ones. The cycle can repeat infinitesimally to synthesize millions of different combinations of peptides or DNA for testing. This technique was first developed in 1982 at the Eötvös Loránd University in Budapest, Hungary. As a young boy born into poverty, Furka faced many challenges as he mainly worked in his adolescence to support his family, and was behind his peers in academics as he did not have the opportunity to study. Despite so, after attending school in his early twenties, Furka managed to become a trailblazer in combinatorial chemistry, developing one of the most powerful techniques in the field.



The split-and-mix synthesis technique pioneered by Furka.

Any feedback or comments on this chapter? You may either email chemoer@mcmaster.ca, access this MS Form, or provide a comment in the feedback box below.

CHAPTER 5 - SOLUTIONS TO CHAPTER PROBLEMS

5.1 - SOLUTIONS FOR CHAPTER 2 - ORGANIC STRUCTURE AND BONDING

Chapter 2.2 – Valence Bond Theory

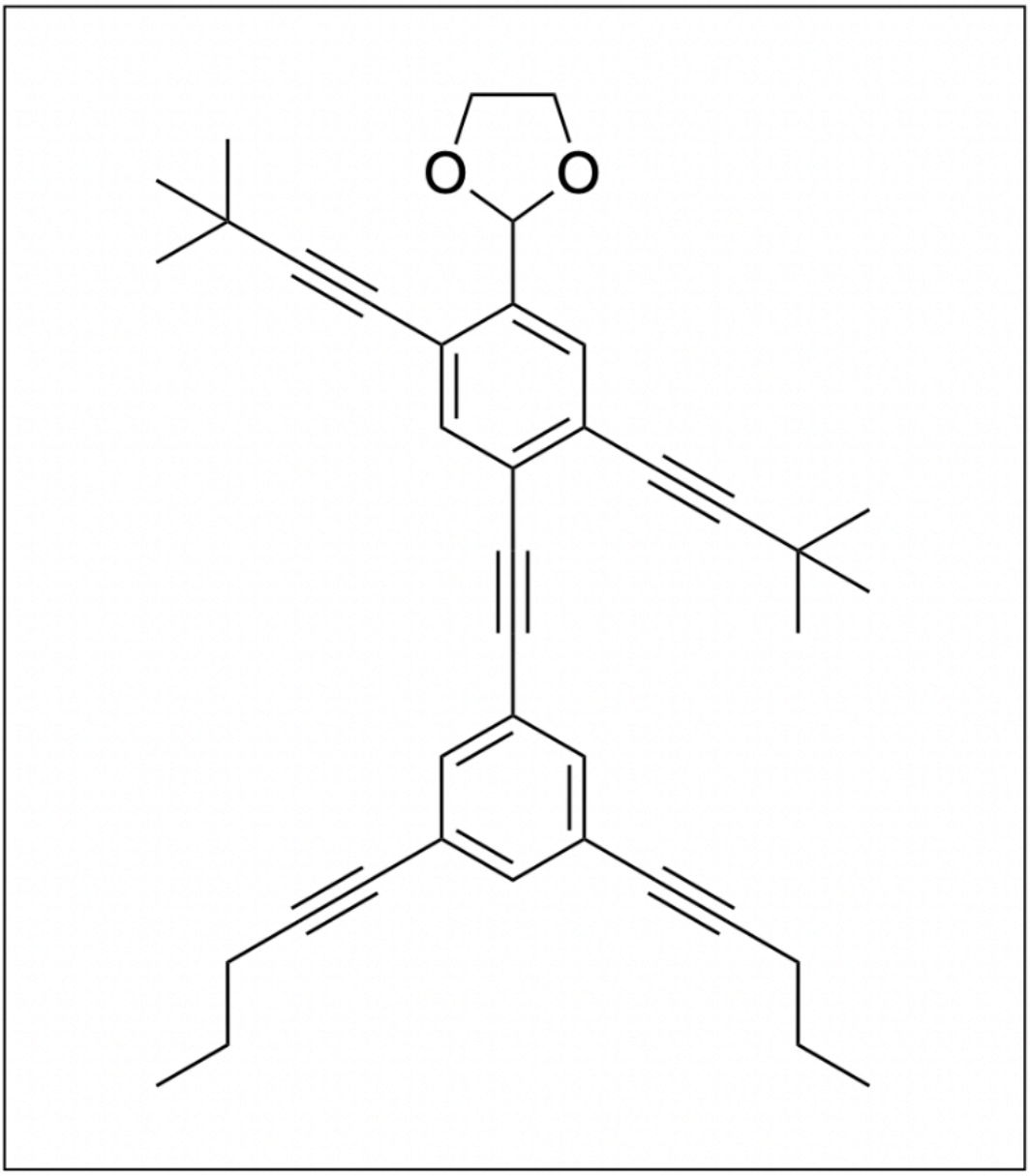
1. The following molecule is called "NanoPutian", which was synthesized by Professor James Tour in 2003. How many sp^3, sp^2 and sp hybridized carbons are there in the molecule respectively?

A. 17 ,11, 10

B. 17, 12, 10

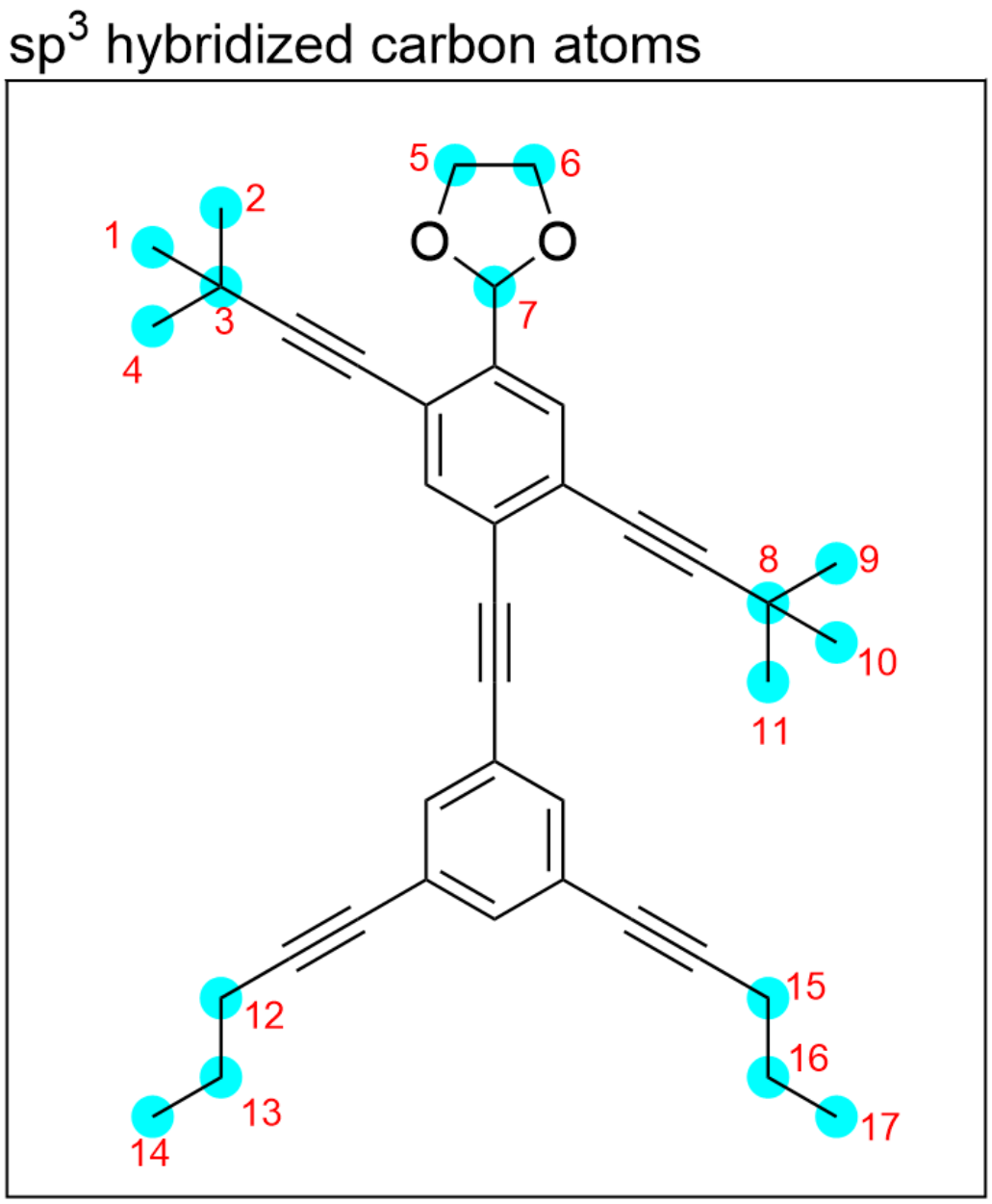
C. 16, 12, 9

D. 16, 11, 9



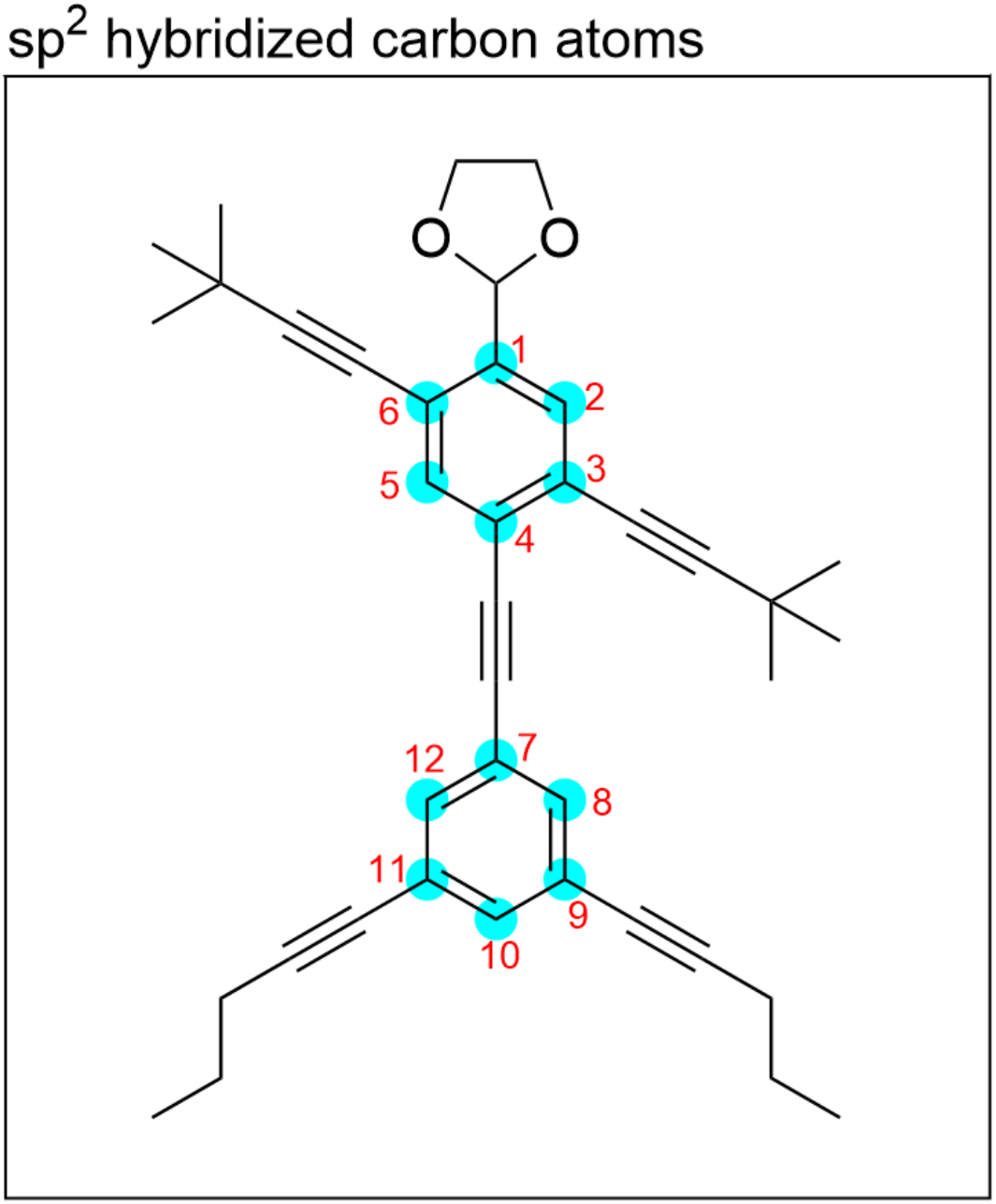
The correct answer to this question is **Option B.** To determine the hybridization of the various carbon atoms, we can look at how many other atoms the carbon atom is bound to, and we can also use VSEPR theory to help us.

sp^3 hybridization involves the mixing of **four** atomic orbitals, so carbon atoms that are bonded to **four other atoms** will be sp^3 hybridized. Additionally, atoms that have a tetrahedral geometry will also be sp^3 hybridized due to the 90.5° bond angles that minimize repulsion.



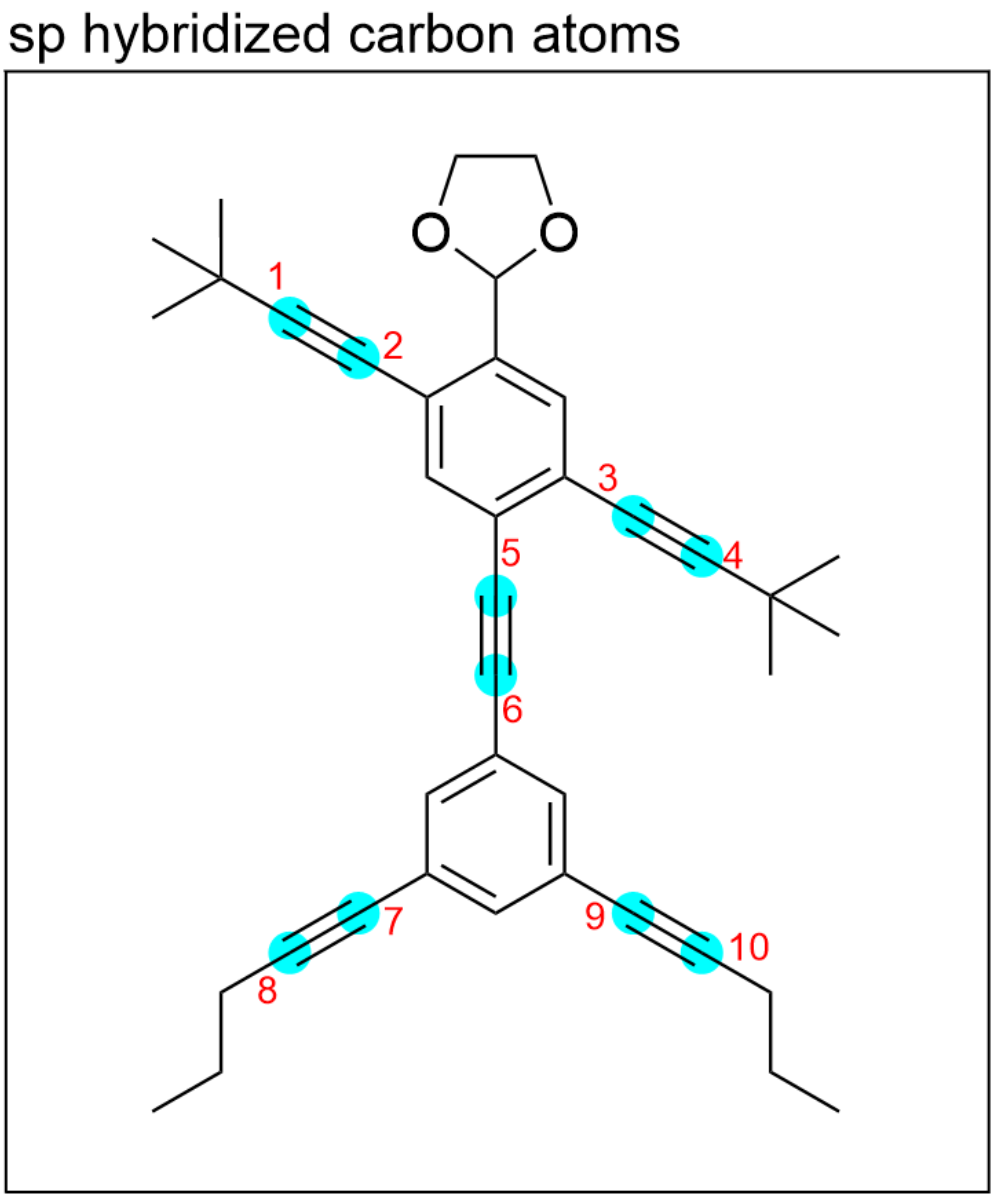
There are 17 carbon atoms (highlighted in blue), that are bonded to 4 **other** atoms and have tetrahedral geometry, therefore there are 17 sp^3 hybridized carbon atoms.

sp^2 hybridization involves the mixing of **three** atomic orbitals, so carbon atoms that are bonded to **three other atoms** will be sp^2 hybridized. Additionally, atoms that have a trigonal planar geometry will also be sp^2 hybridized due to the 120° bond angles that minimize repulsion.



There are 12 carbon atoms (highlighted in blue), that are bonded to 3 **other** atoms and have trigonal planar geometry, therefore there are 12 sp^2 hybridized carbon atoms.

sp hybridization involves the mixing of **two** atomic orbitals, so carbon atoms that are bonded to **two other atoms** will be sp hybridized. Additionally, atoms that have a linear geometry will also be sp hybridized due to the 180° bond angles that minimize repulsion.



There are 10 carbon atoms (highlighted in blue), that are bonded to 2 **other** atoms and have linear geometry, therefore there are 10 sp hybridized carbon atoms.

Therefore, **the correct answer is Option B**.

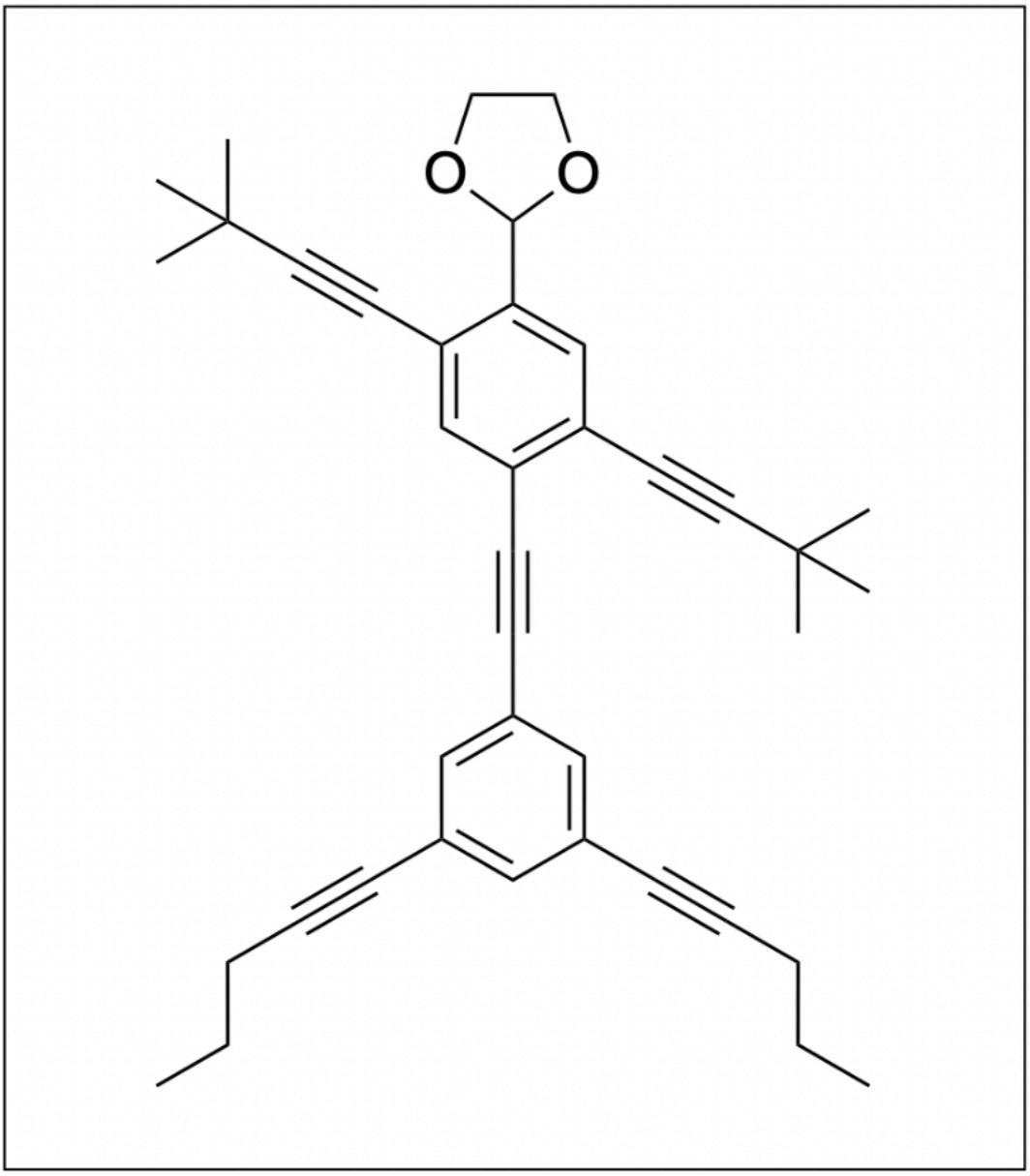
2. The following molecule is called "NanoPutian", which was synthesized by Professor James Tour in 2003. How many carbons have a bond angle of 120º?

A. 22

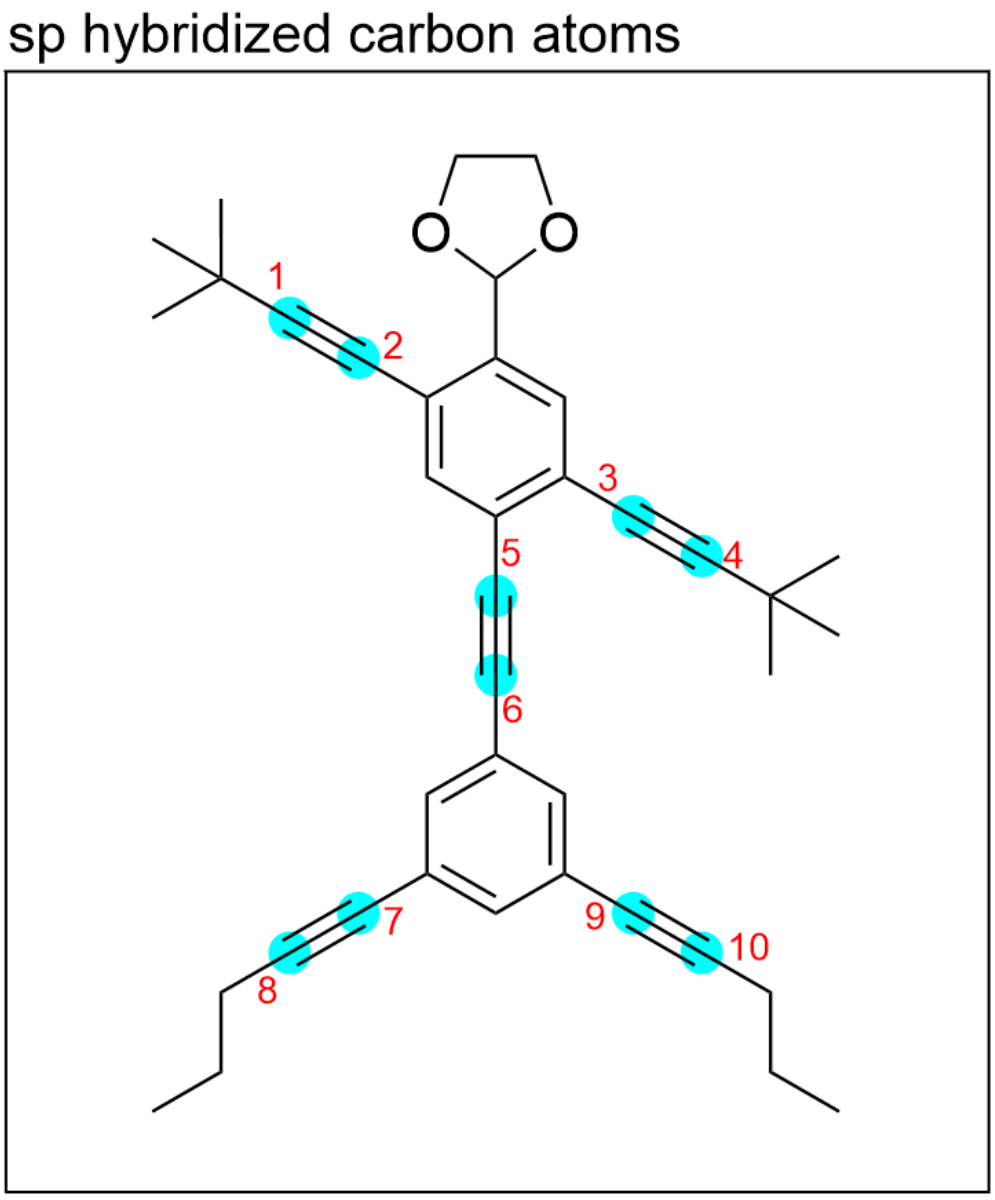
B. 10

C. 17

D. 12



The correct answer to this question is **Option D**. Recall that only are sp^2-hybridized carbons have a bond angle of 120º. In order to minimize repulsion between the three bonds to carbon, the bonds are separated by 120° to maximize the distance between each bond. Sp^3 and sp-hybridized atoms also rearrange to minimize repulsion; however, with 4 and 2 bonds on the atom respectively, their bonds angles are at 109.5° and 180°. Thus, to answer this question, we must identify all sp^2-hybridized carbons. There are 12 carbon atoms (highlighted in blue), that are bonded to **3 other atoms** and have trigonal planar geometry. Therefore there are 12 sp^2 hybridized carbon atoms.



Chapter 2.3 – Functional Groups

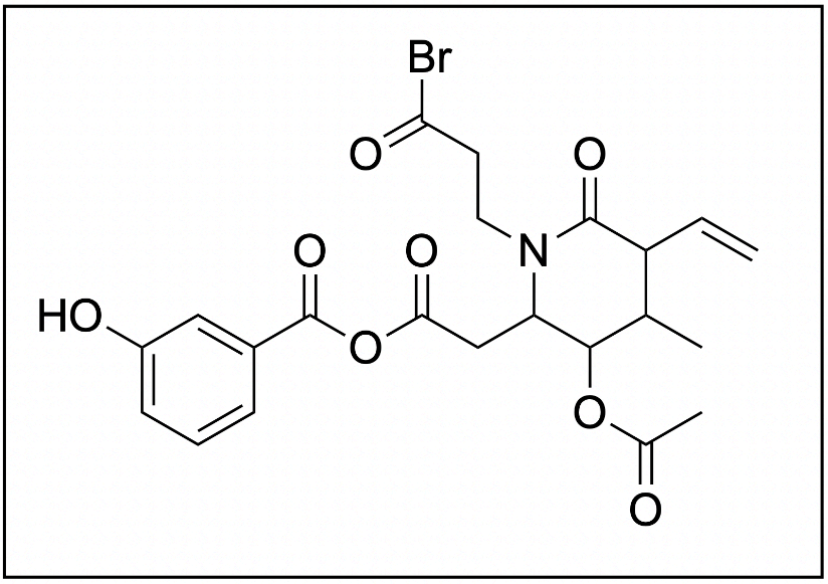
1. Which two functional groups are not present in the following molecule?

A. carboxylic acid anhydride, alkene

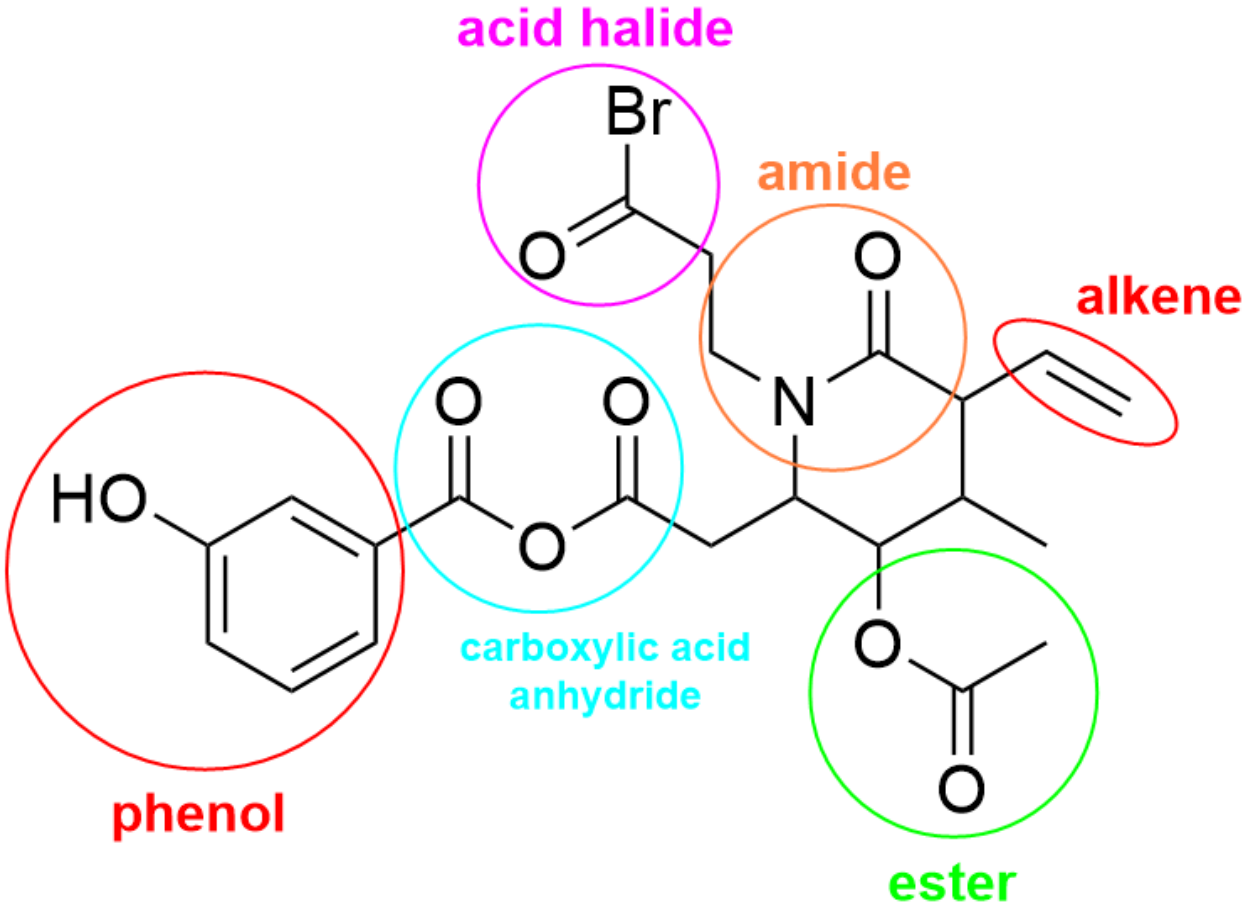
B. amide, phenol

C. amine, ether

D. acid halide, ester



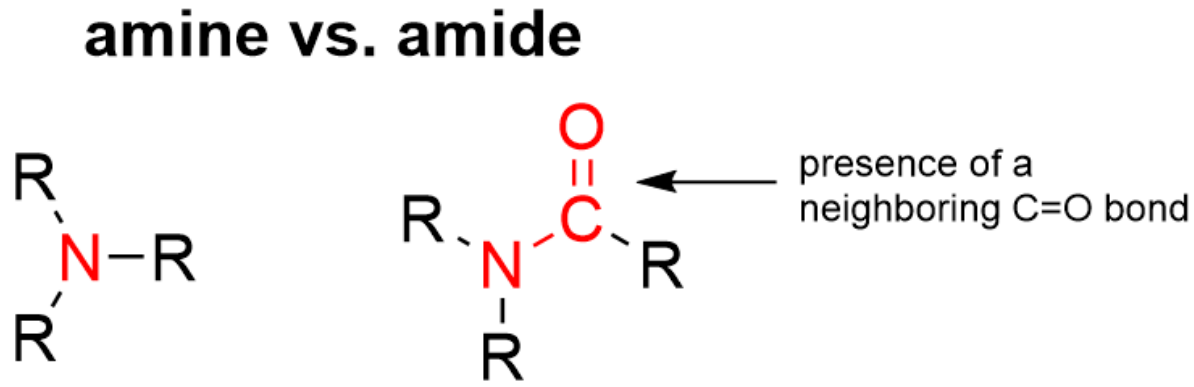
The correct answer to this question is **Option C**. The first step to this question is to identify the functional groups on the molecule. Below shows an image with each functional group circled and named.



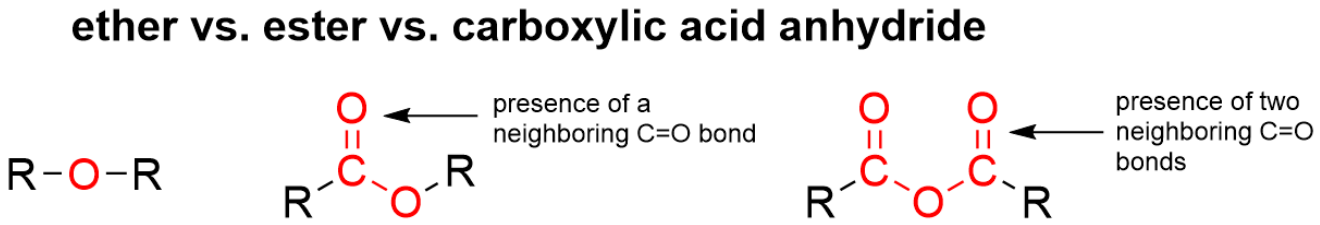
Now that we know what functional groups are present on the compound, we can start going through and

eliminating certain options. For example, option A mentions the presence of a carboxylic acid anhydride and an alkene. As both these groups can be found on the molecule (in cyan and red respectively), this option is incorrect. Similarly, option B mentions the presence of an amide and phenol, which are both identified to be on the molecule in orange and red. Option C is also incorrect, as an acid halide and ester are both present on the molecule circled in magenta and green respectively.

Option C mentions the presence of an amine and an ether. Differentiating amines and amides can be difficult, as they both contain a nitrogen group. Remember that amides have a neighboring C=O bond, whereas amines will have nitrogen bonded only to carbon groups (see below). As the nitrogen in this molecule is beside a C=O group, this is considered an amide. Thus, an amine is **not** present on this molecule.



For the ether, recall that it is a functional group that contains an oxygen bonded to two carbon (R) groups on each side, as seen below (R–O–R). This R–O–R arrangement is also observed in an ester functional group and a carboxylic acid anhydride group, which are both found in the compound. However, these are **not** considered ethers as the oxygen contains either one C=O bond (ester) or two neighboring C=O bonds (carboxylic acid anhydride). This classifies the functional group as something entirely different from an ether. The difference is illustrated below.



Therefore, as both an amide and ether are not on this molecule, **Option C is the correct answer.**

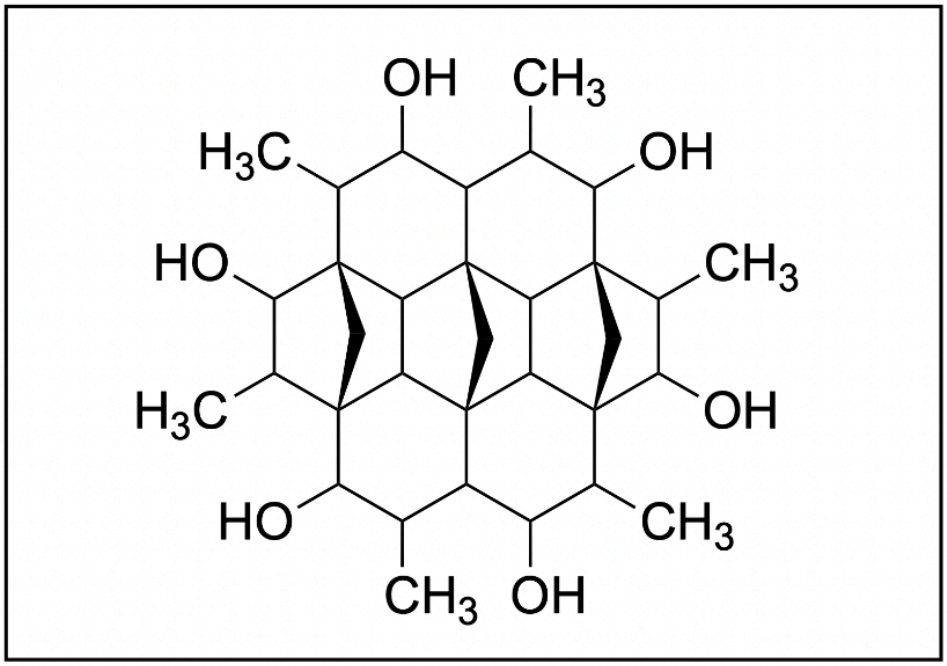
2. How many primary, secondary, tertiary, and quaternary carbons are there in the following molecule respectively?

A. 12, 9, 6, 6

B. 6, 9, 12, 6

C. 6, 6, 12, 6

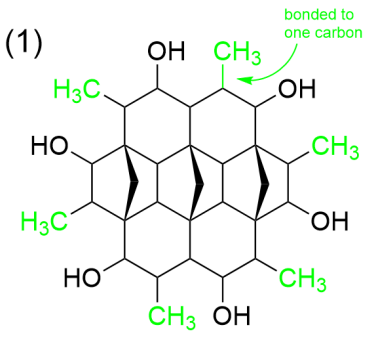
D. 12, 6, 6, 6



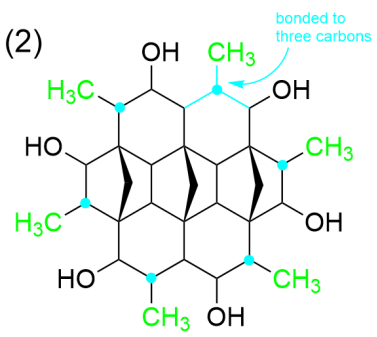
The correct answer to this question is **Option B**. The best way to solve this question is to count the number of primary, secondary, tertiary and quaternary carbons while keeping track to ensure you don't mess up and recount carbons. Below details a method of counting carbons to determine the correct option.

You can realistically start counting anywhere on the molecule, but we will start with the outer carbons. Specifically, we will start with the carbons highlighted in green, which are sticking out from the ring shape. The carbon group ($-CH_3$) is only bonded to **one** other carbon (as shown in the green bond), thus, it is a primary carbon. Going around the entire ring, there are 6 CH_3 groups identical to this one, thus we determine that there are 6 primary carbons so far.

Moving one atom inward, highlighted in a cyan circle, there is another carbon. It is bonded to three carbons, as seen by the cyan bonds, and thus, it is a tertiary carbon. Looking at the full molecule, we can see a repeating pattern in the arrangement of carbon atoms. There are 6 carbons in total with this structure, which gives us a total of 6 tertiary carbons.



6 primary carbons

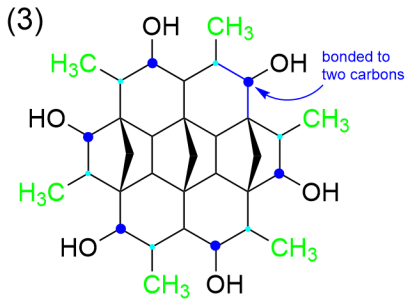


6 primary carbons

6 tertiary carbons

We can then move one atom to the side, highlighted in a dark blue dot, which is bonded to an -OH group. Remember that the classification is based on the number of **carbon groups** the carbon is bonded to and no other substituents. This carbon group is only bonded to two carbons, as seen by the dark blue bonds, making it a secondary carbon. When we count around the ring, we can see that there are 6 identical carbons with this arrangement, giving us 6 secondary carbons.

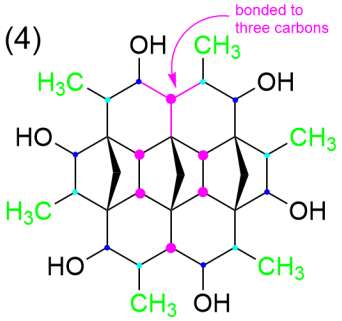
Moving to another carbon, as seen by the magenta circle, we can determine that it is a tertiary carbon, as it is bonded to three carbon groups. Looking around, we can find a total of 6 more carbons that are tertiary carbons, bringing up the total number of 12.



6 primary carbons

6 secondary carbons

6 tertiary carbons



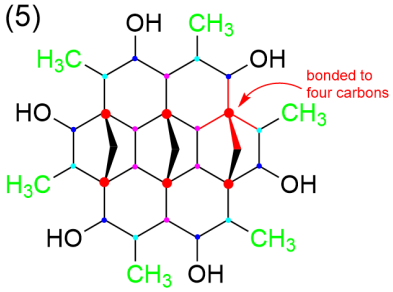
6 primary carbons

6 secondary carbons

6 tertiary carbons
+ 6 tertiary carbons

There are also a number of carbons that are bonded to four different carbon groups, which is found in the middle of molecule (red) These give us a total of 6 quaternary carbons.

The only carbons remaining then are in the very middle of the molecule, highlighted in orange. With only two bonds to carbon, these add another 3 secondary carbons to the list, giving us 9 in total.

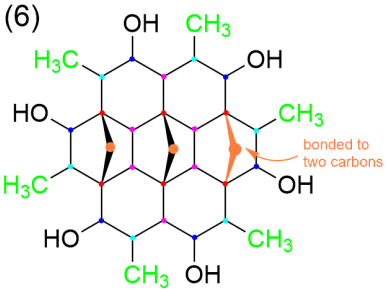


6 primary carbons

6 secondary carbons

6 tertiary carbons
+ 6 tertiary carbons

6 quaternary carbons



6 primary carbons

6 secondary carbons
+ 3 secondary carbons

6 tertiary carbons
+ 6 tertiary carbons

6 quaternary carbons

In conclusion, there are 6 primary carbons, 9 secondary carbons, 12 tertiary carbons, and 6 quaternary carbons. This matches up with **Option B, the correct answer to this question.**

Chapter 2.4 – IUPAC Nomenclature

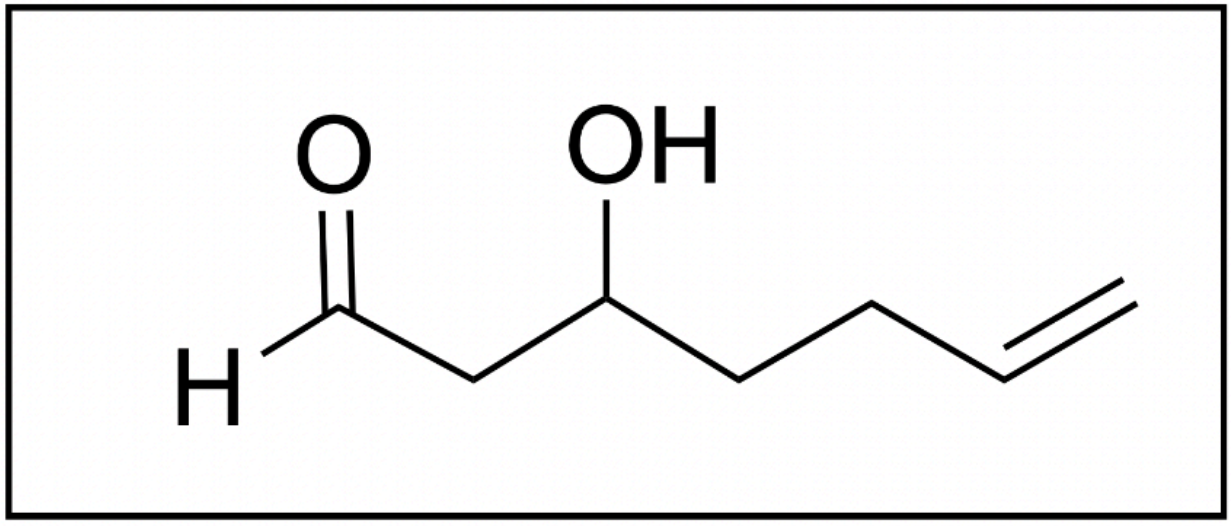
1. Which is the correct name for the following molecule?

A. 3-hydroxyhept-6-enal

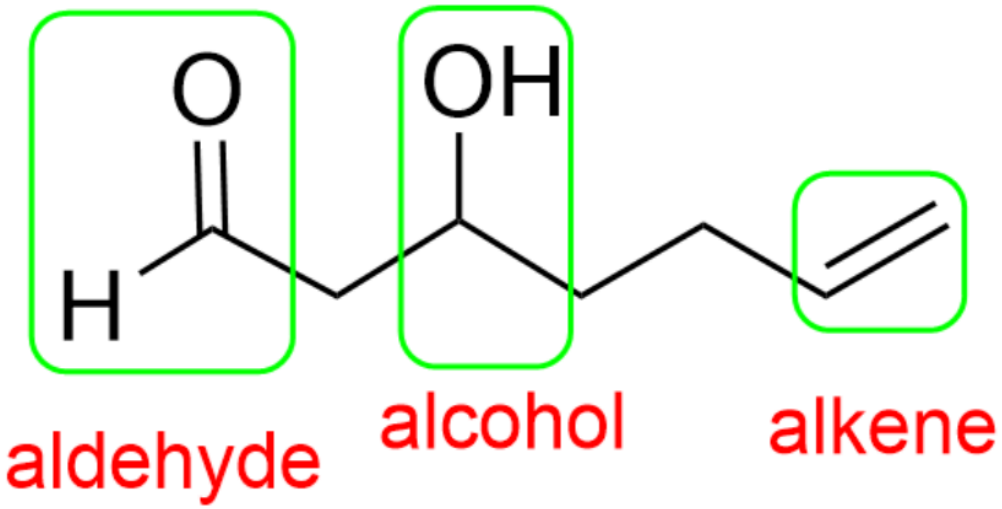
B. 5-hydroxyhepten-7-al

C. 3-hydroxyhept-7-enal

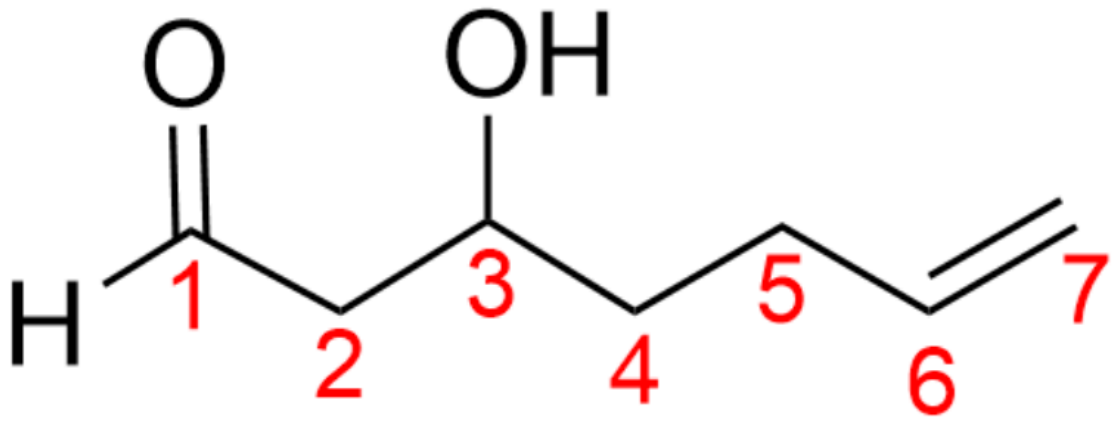
D. 5-hydroxyhepten-6-al



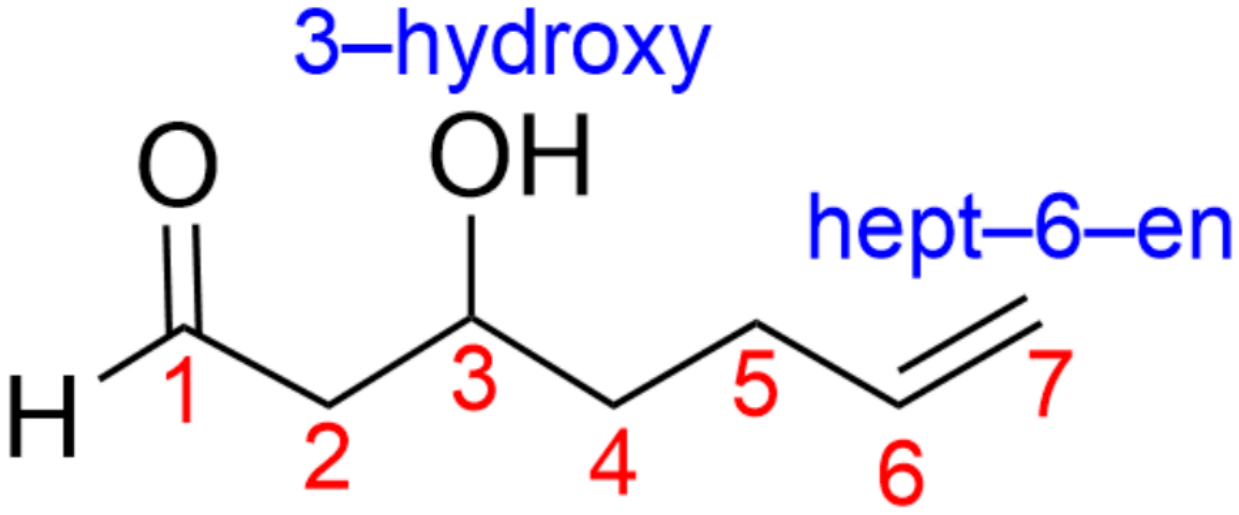
The correct answer is **Option A**. When naming organic molecules, the first thing you should do is identify the functional groups present to determine priority.



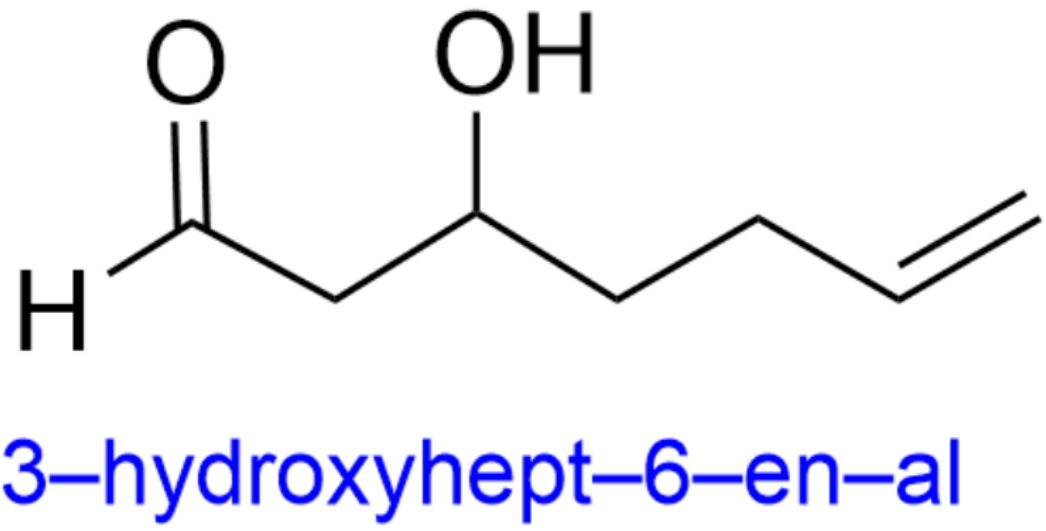
In this molecule, there is an aldehyde, alcohol and alkene present. The aldehyde is the highest priority group, so the final suffix is "-al", while the alcohol will be treated as a substituent with the "hydroxy-" prefix.



The next thing you should do is count the number of carbon atoms in the chain and decide which carbon atom is carbon 1. There are 7 carbon atoms present, so the prefix will be “hept”, and the number should begin by the highest priority group (the carbonyl is carbon 1).



The hydroxy group is therefore at position 3 (3-hydroxy), while the alkene is at position 6 (hept-6-en).



By putting all of this information together, we get the final name, **3-hydroxyhept-6-en-al**. Therefore, **the correct answer is Option A.**

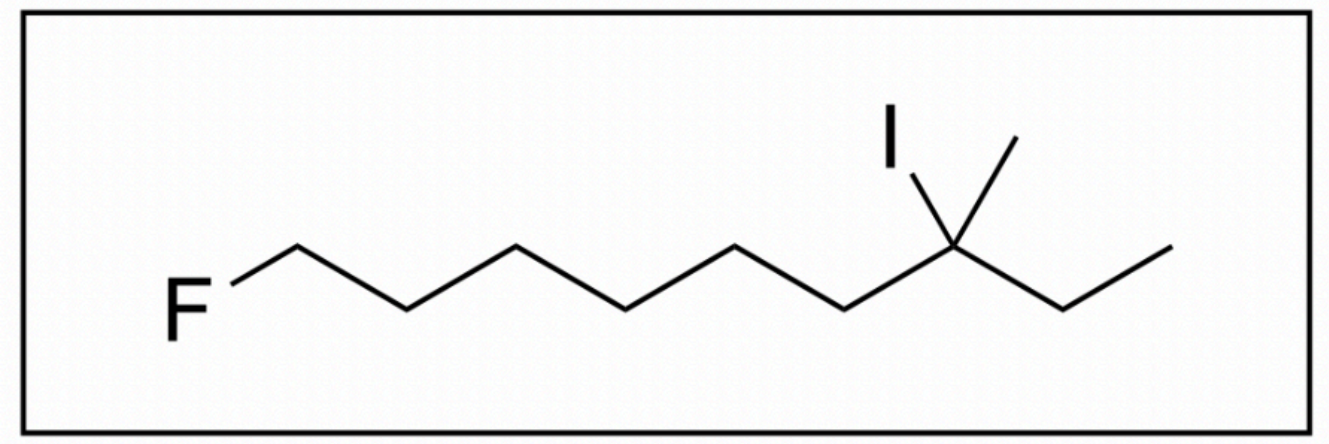
2. Which is the correct name for the following molecule?

A. 9-fluoro-3-iodo-3-methylnonane

B. 9-fluoro-3-methyl-3-iodononane

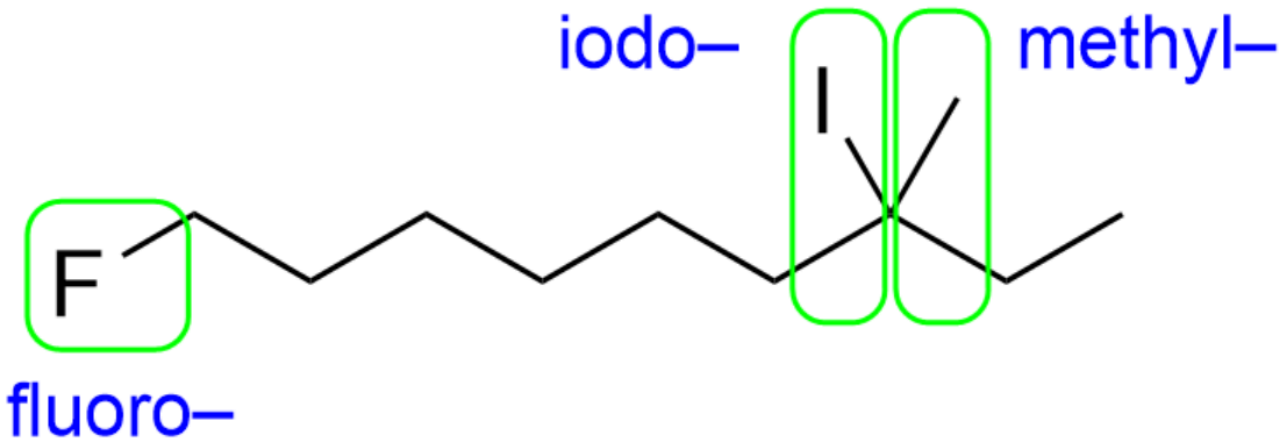
C. 1-fluoro-7-iodo-7-methylnonane

D. 7-iodo-1-fluoro-7-methylnonane



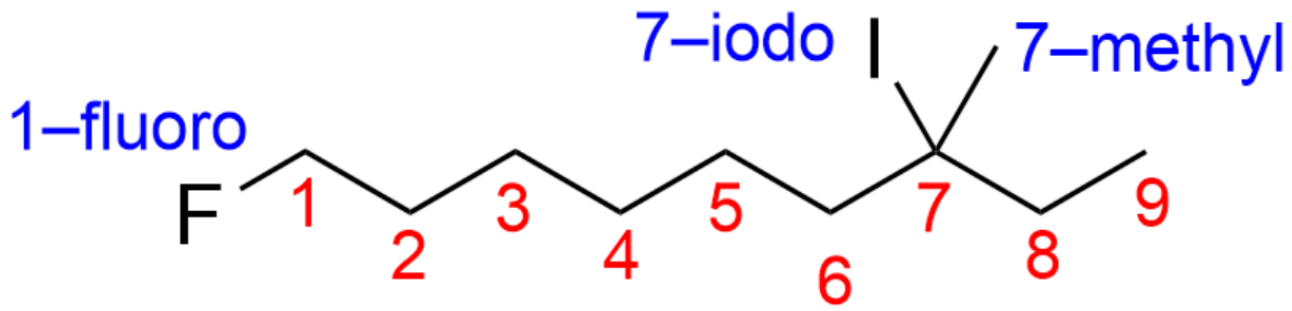
The correct answer is **Option C.** When naming organic molecules, the first thing you should do is identify the functional groups present to determine priority.

This organic molecule only contains an alkane functional group, so the final suffix will be "-ane".

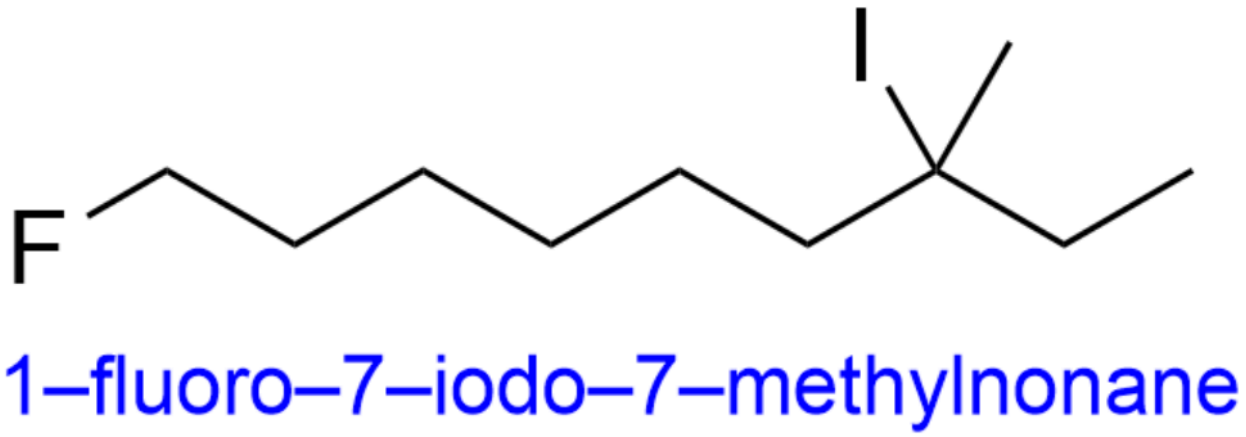


The next step you should take is to identify any branches/substituents. This organic molecule contains a "fluoro-", "iodo-", and "methyl-" substituent.

You should also count how many carbon atoms are in the longest chain, and decide which carbon atom is carbon 1. In this case, the longest carbon chain contains nine carbon atoms yielding the prefix "non-", while carbon 1 is adjacent to the fluoro substituent. This is because all substituents contain the same priority, and it is the pathway where you encounter a substituent the earliest.

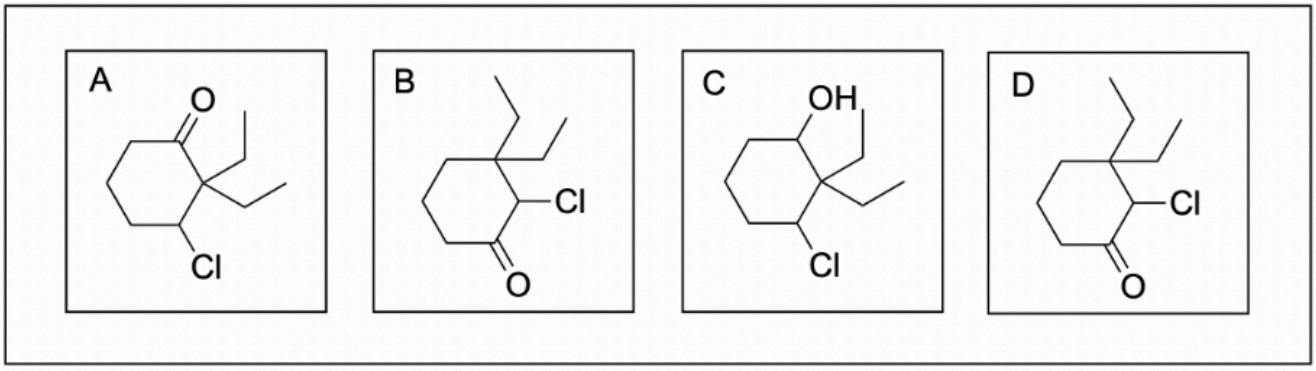


We therefore have "1-fluoro", "7-iodo" and "7-methyl" as substituent names **in that order** (alphabetical).

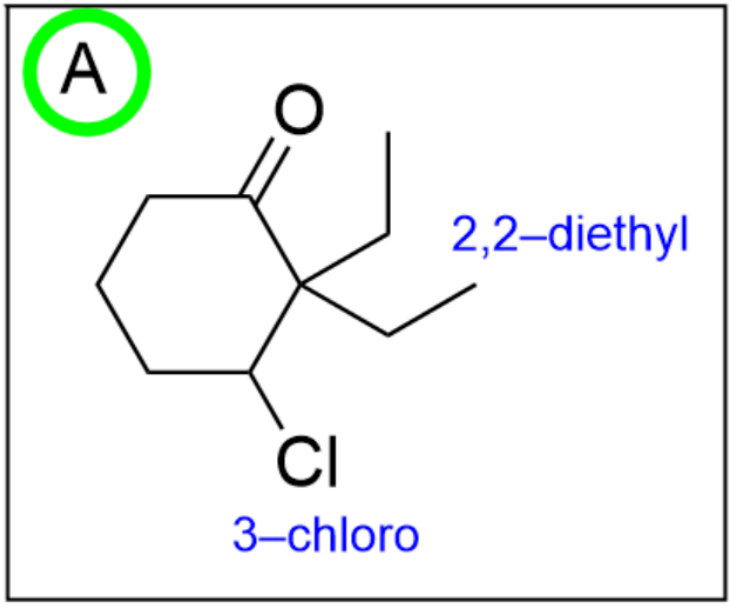


By putting all of this information together, we get the final name, **1-fluoro-7-iodo-7-methylnonane**. Therefore, **the correct answer is Option C**.

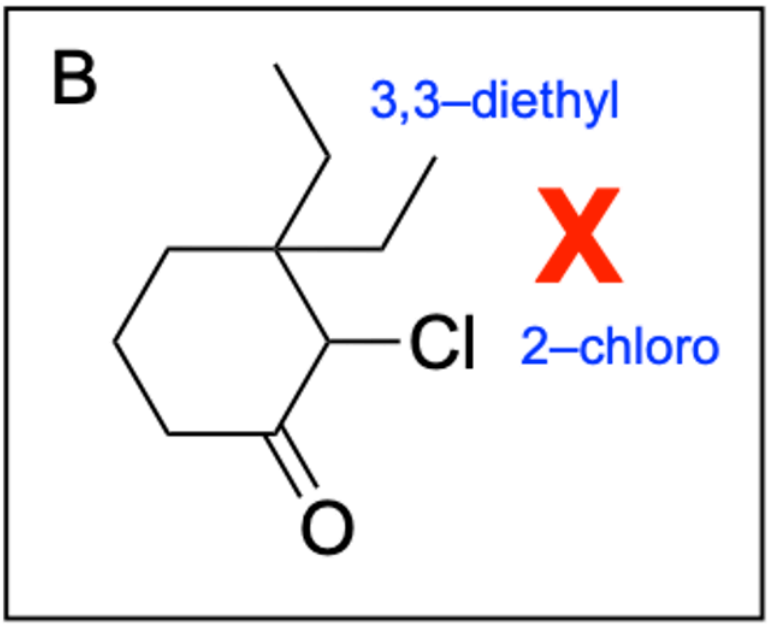
3. Which of the following molecule is 2,2-diethyl-3-chlorocyclohexanone?



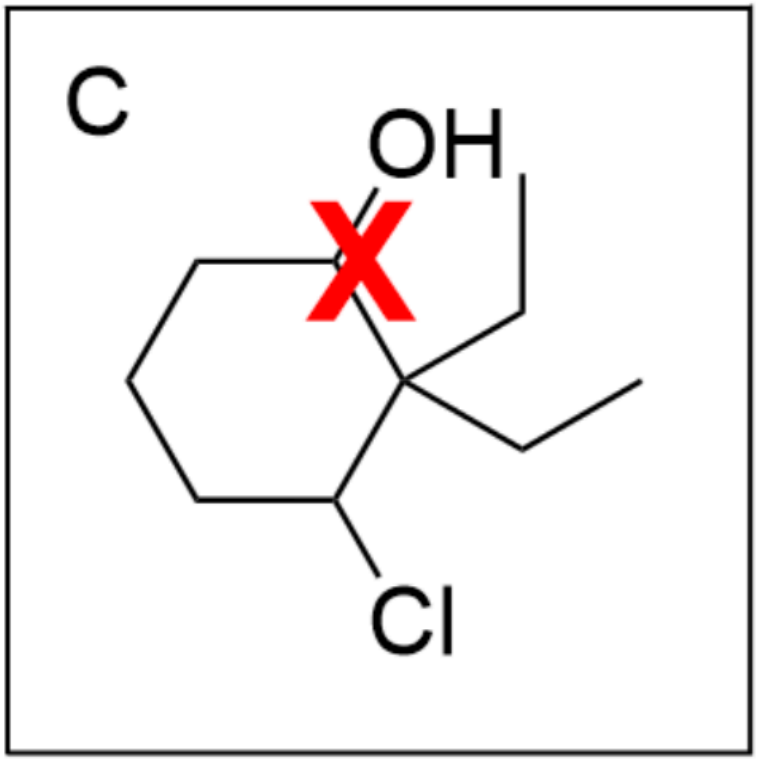
Option A is correct. The first thing you should do is ensure all of the functional groups are present. Based on the final suffix, there should be a ketone present in the molecule, attached to a 6-membered ring (cyclohex-), which we see in this option. Next, you should check if the positions of the substituents are correct. Since the ketone is not numbered, you can assume that the ketone is at position 1. Therefore, the 2 ethyl groups should be 2 carbon atoms away from the ketone while the chlorine atom should be 3 carbon atoms away from the ketone. We see all of these conventions on Option A.



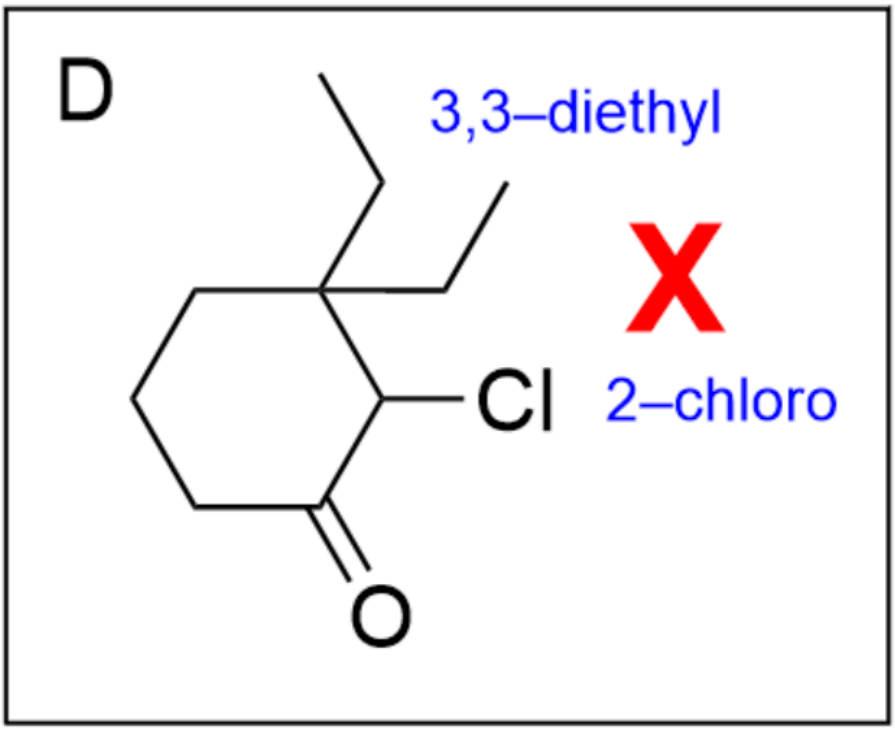
Option B is incorrect. While there is a 6-membered ring with a ketone at position 1 present, the positions of the chloro and diethyl groups are switched (the chloro group should be in position 3 while the diethyl groups should be at position 2).



Option C is incorrect. While there is a 6-membered ring present, there is an alcohol instead of a ketone. For this option to be correct, the final suffix should be "-ol".



Option D is incorrect. While there is a 6-membered ring with a ketone at position 1 present, the positions of the chloro and diethyl groups are switched (the chloro group should be in position 3 while the diethyl groups should be at position 2).



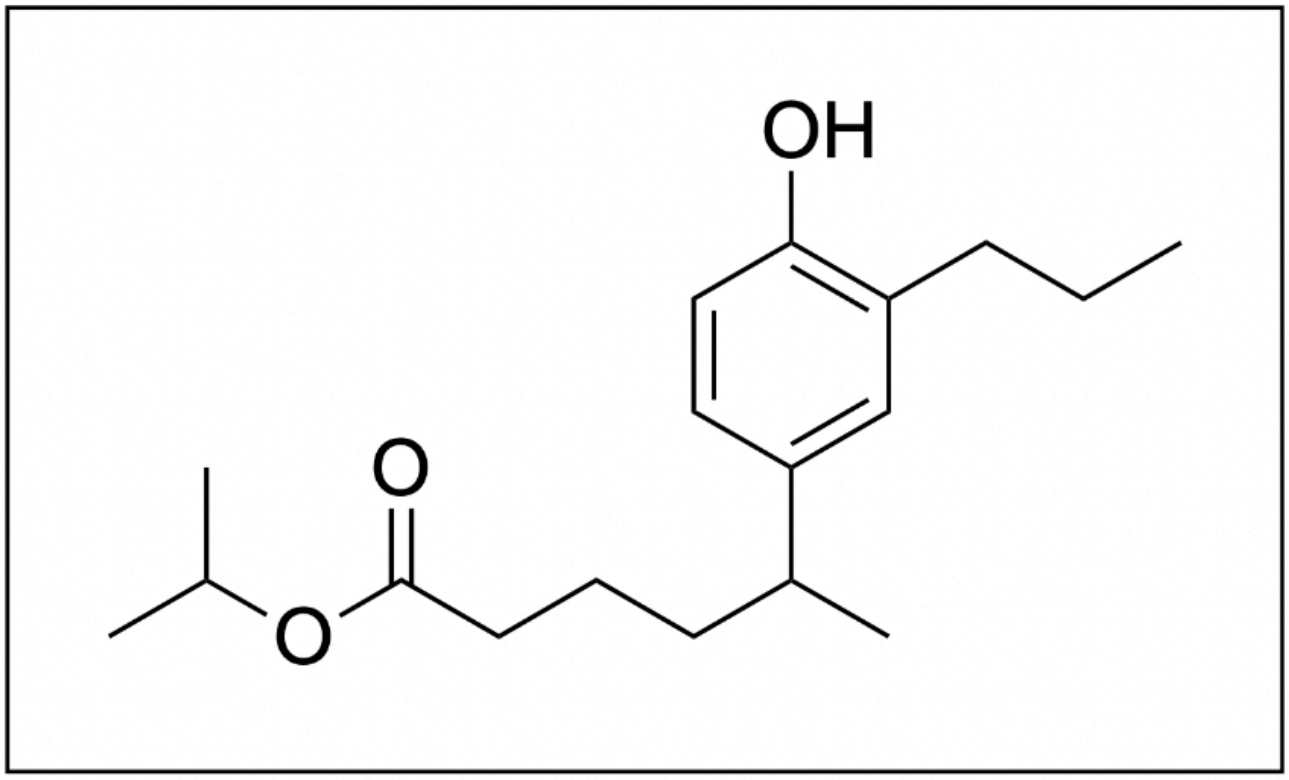
4. What is the name of the following molecule?

A. isopropyl 5-(1-hydroxy-2-propylphenyl)hexanoate

B. propyl 5-(1-hydroxy-2-propylphenyl)hexanoate

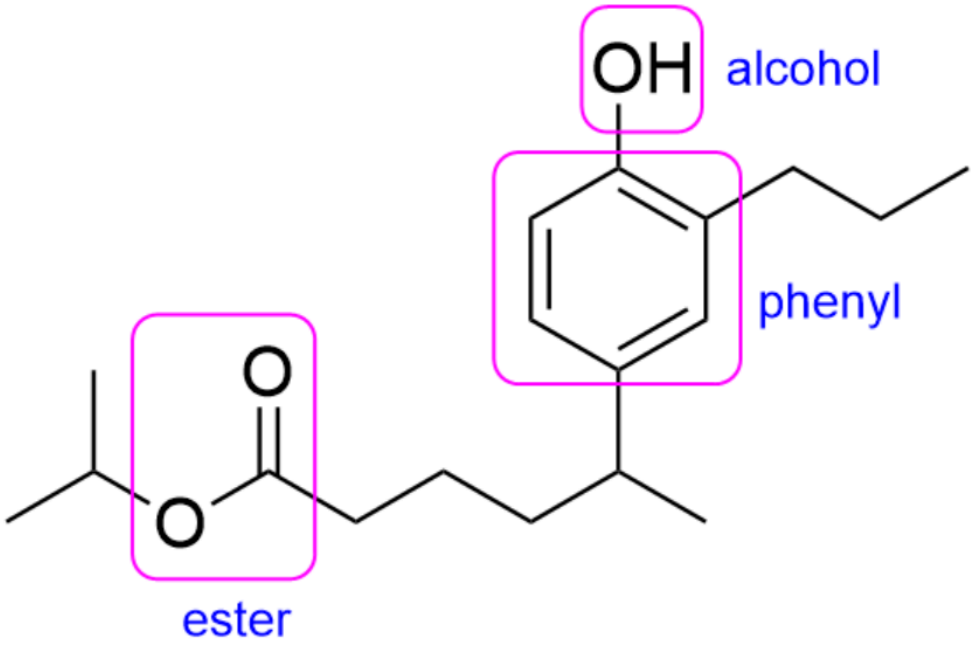
C. propyl 5-(4-hydroxy-3-propylphenyl)hexanoate

D. isopropyl 5-(4-hydroxy-3-propylphenyl)hexanoate

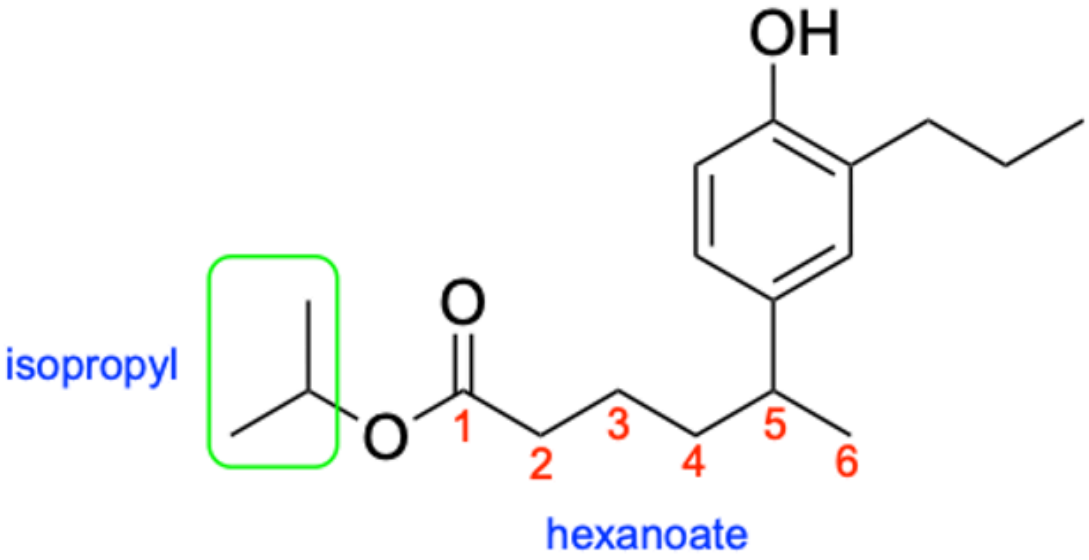


The correct answer to this question is **Option D.** When naming organic molecules, the first thing you should do is identify the functional groups present to determine priority.

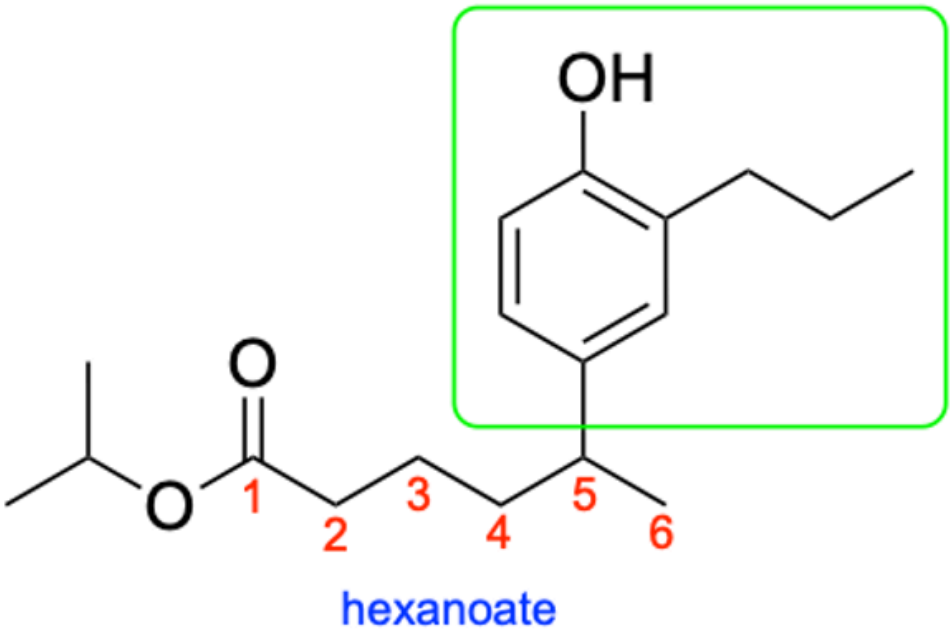
In this molecule, there is an ester, phenyl and alcohol group present. The ester takes priority, so the final suffix should be "-oate".



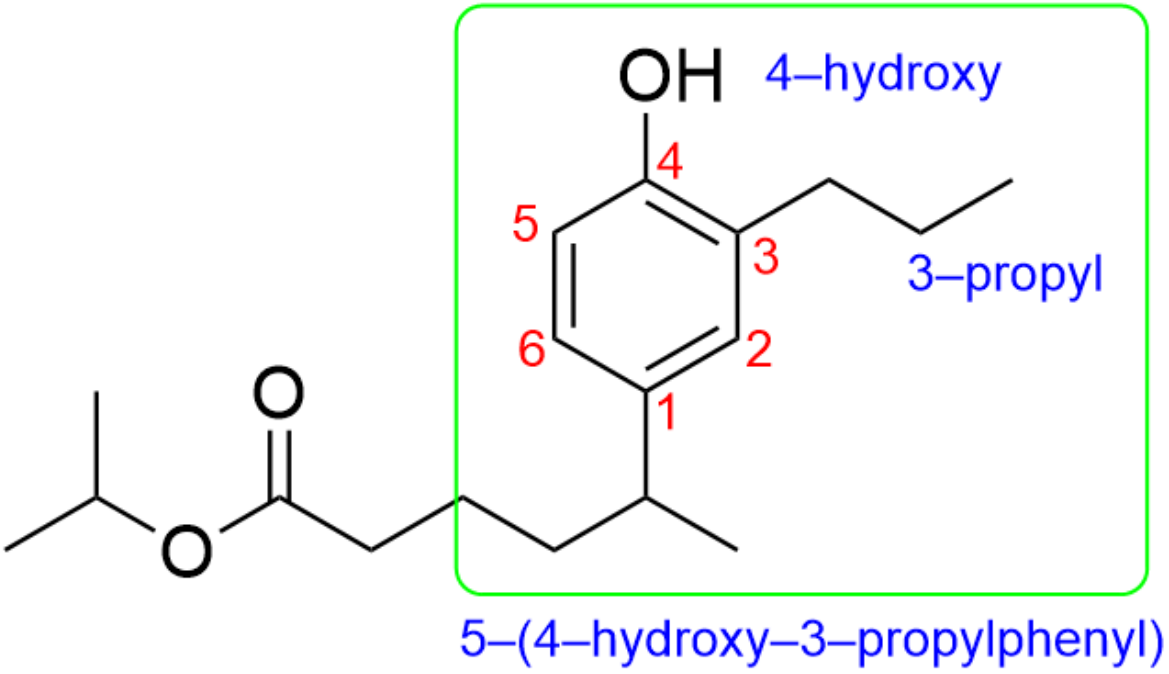
Additionally, when naming esters, the group branching off of the oxygen will be treated as substituents while the chain closest to the carbonyl will be part of the parent chain. Therefore, the substituent name is "isopropyl", while the 6-carbon long parent chain would be "hexanoate".



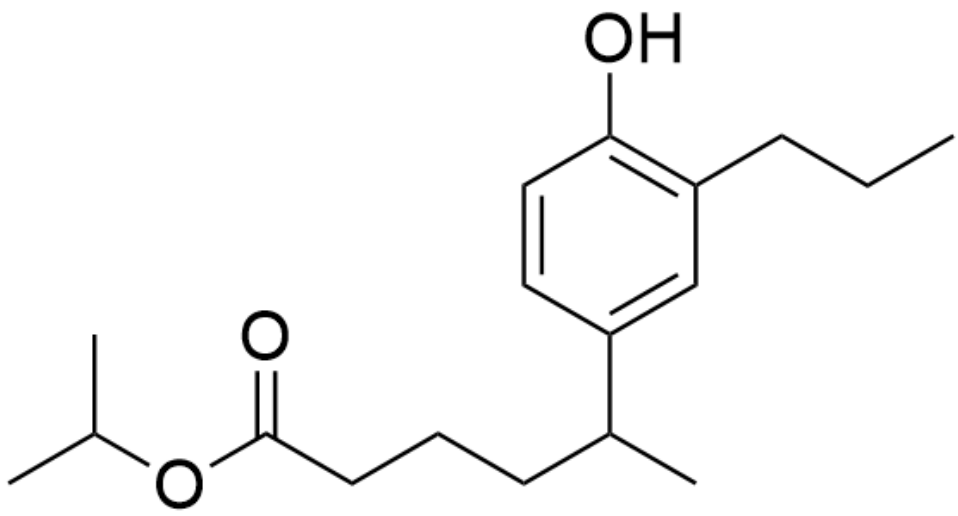
Unfortunately, this molecule also contains branches in the parent chain portion at position 5. We will therefore have to include the name of these substituents in brackets to show that these substituents belong to the carbonyl portion and not the oxygen portion of the ester, and the position in the parent chain where this branch is located.



The branch contains a phenyl, alcohol and propyl (3-carbon) group. The phenyl group will take priority and will be named last, while the hydroxy and propyl groups will be alphabetically ordered. The hydroxy group is 4 carbon atoms away from the parent chain while the propyl group is 3 carbon atoms away from the parent chain, yielding the name (4-hydroxy-3-propylphenyl). Additionally, since the parent chain contains branches at position 5, the name of the branch would be 5-(4-hydroxy-3-propylphenyl).



Putting all of this information together, we get the name, **isopropyl 5-(4-hydroxy-3-propylphenyl)hexanoate**. Therefore, **Option D is the correct answer.**



isopropyl–5–(4–hydroxy–3–propylphenyl)hexanoate

Chapter 2.5.1 – Alkene Structure

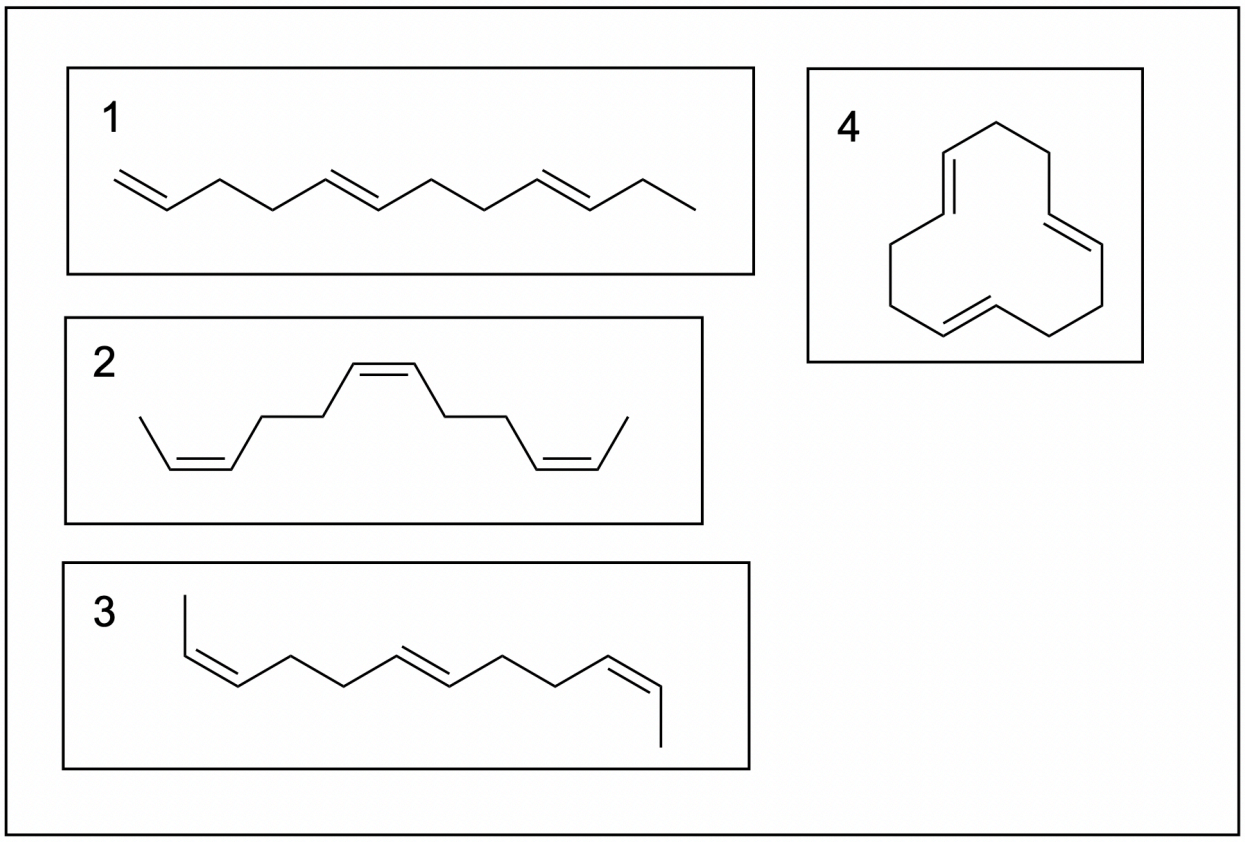
1. Which is the correct ranking of the melting point of the molecules from lowest to highest?

A. 4, 3, 2, 1

B. 4, 2, 3, 1

C. 2, 3, 1, 4

D. 3, 2, 1, 4

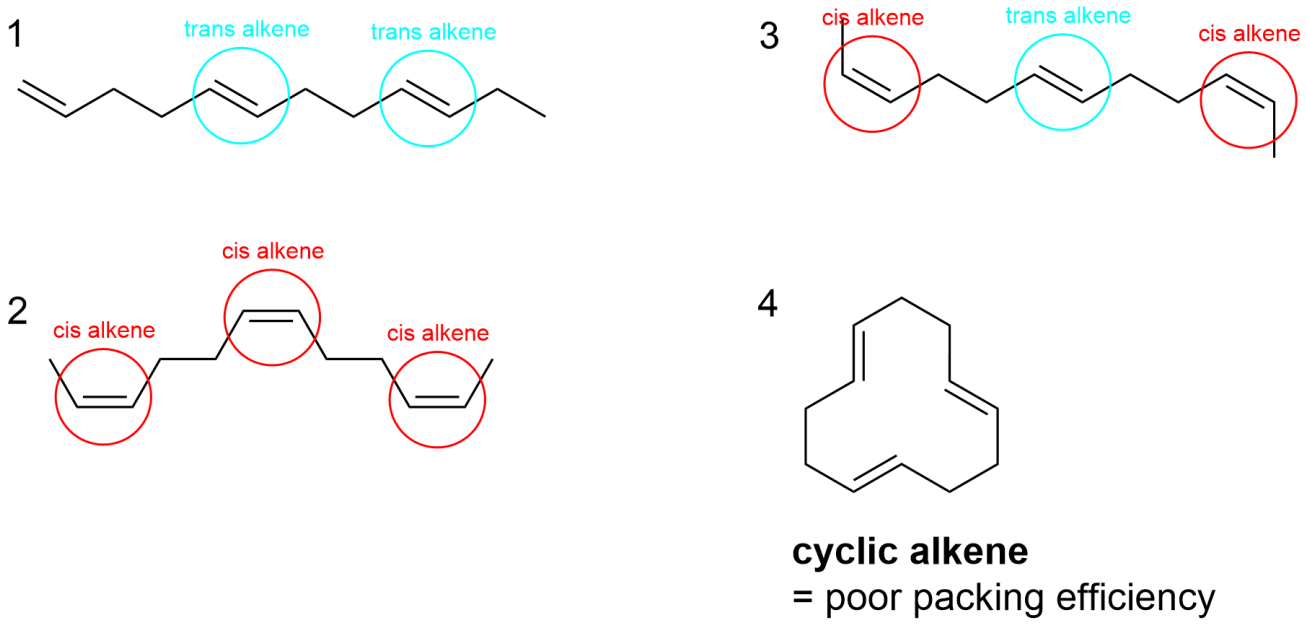


The correct answer to this question is **Option B**. Recall that melting point is correlated with the number of intermolecular forces, such as hydrogen bonding, Van der Waals and hydrophobic interaction. The more stacking that can occur between different molecules, the higher the melting point. Thus, *trans* alkenes have a significantly higher melting point as they can stack more efficiently, whereas *cis* alkenes introduce kinks that disrupt stacking.

As a ring, molecule 4 has the most trouble stacking on top of one another, giving it the lowest melting point. It does not matter whether the double bonds are *trans* or *cis* – all that matters is that it is cyclic. This eliminates two options, only leaving Option A and B as potential answers.

Molecule 1, as the only *cis* alkene on the list, automatically has the highest melting point due to its stacking efficiency.

Between molecule 2 and 3, it can be difficult to determine which would result in a greater number of intermolecular interactions. However, molecule 2 has three *cis* double bonds, whereas molecule 3 has only two. As it is the *cis* bonds that impede bonding, molecule 2 would have a lower melting point as it has more *cis* bonds.



Therefore, the overall order from lowest to highest melting point would be: **4, 2, 3, 1 (Option B)**.

Chapter 2.5.2 – Alkene Stereochemistry & Nomenclature

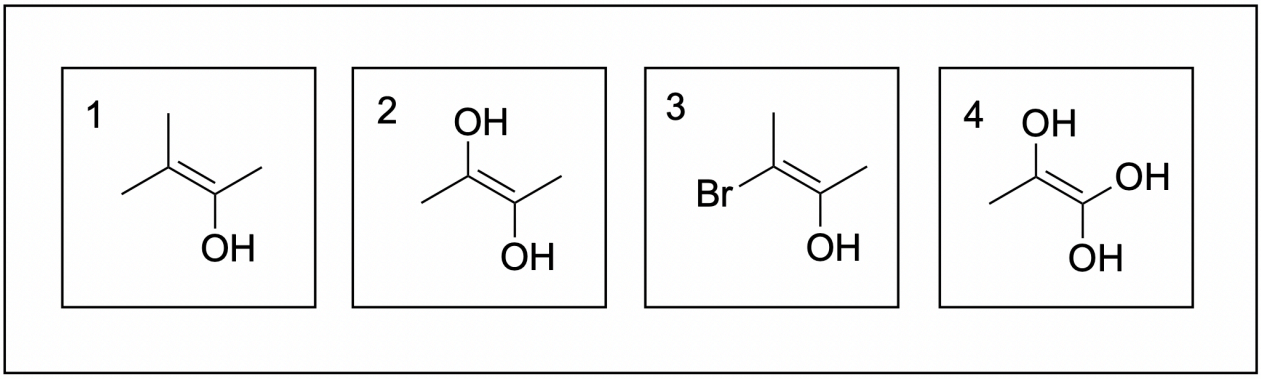
1. Which of following molecules can use *E/Z* designation for nomenclature?

A. 1, 2

B. 2, 3

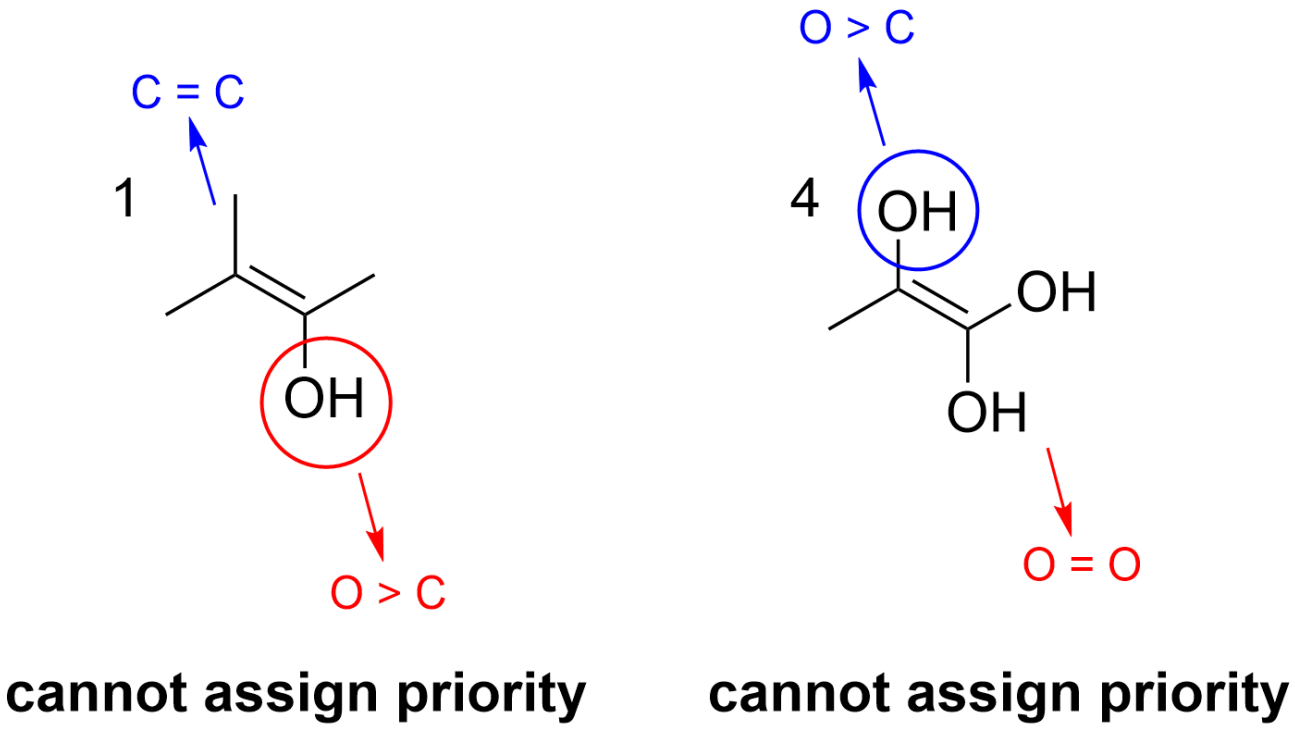
C. 3, 4

D. 2, 4

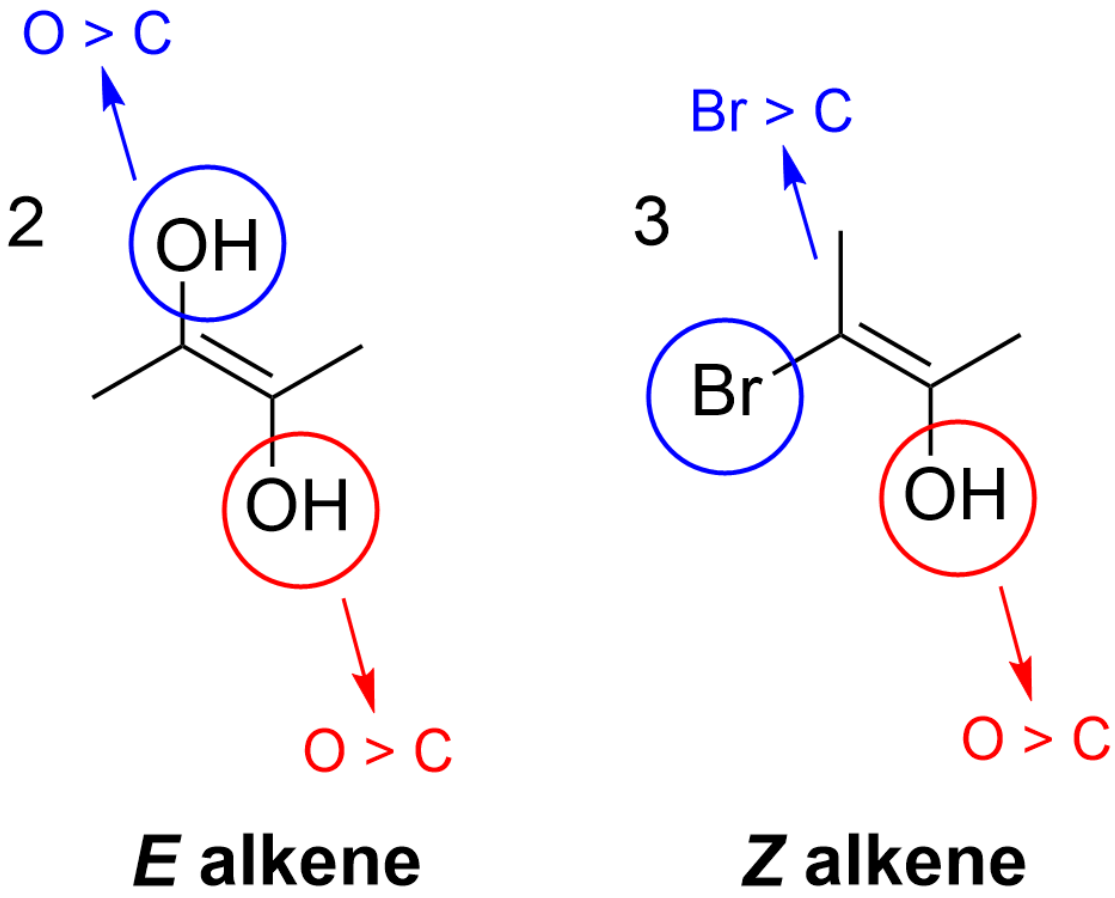


The correct answer to this question is **Option B**. The easiest way to determine this is to identify the substituents on each side of the C=C double bond and determine if it is possible to assign priority to the substituents. If it is not possible, then an *E/Z* designation cannot be used.

For example, in molecule 1, it is not possible to give an *E/Z* designation. The left side of the alkene contains two methyl groups, making it impossible to give one priority over the other. As assigning priority is crucial for naming, this means this compound cannot be named via *E/Z* designation. Molecule 4 faces the same problem as both substituents on the right side of the alkene are hydroxyl. Once again, it is not possible to assign priority.



This issue is not faced in molecule 2 or 3, where it is possible to assign priority between the substituents on each side of the alkene. For example, in molecule 2, –OH takes priority over the methyl group, giving it an *E* arrangement. In molecule 3, the Br and OH take priority respectively, giving it a *Z* notation.



Thus, the **correct answer is Option B** (molecules 2 and 3).

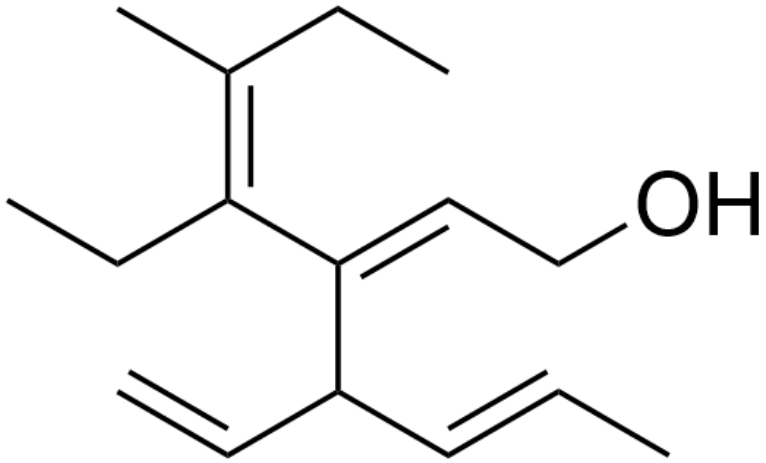
2. Which of the following is the correct name for the molecule?

A. (2Z,5E)-4-ethenyl-3-((E)-3-methylhex-3-en-4-yl)hepta-2,5-dien-1-ol

B. (2Z,5E)-4-ethenyl-3-((Z)-3-methylhex-3-en-4-yl)hepta-2,5-dien-1-ol

C. (2Z,4E)-4-ethyl-3-((E)-hexa-1,4-dien-3-yl)-5-methylhepta-2,4-dien-1-ol

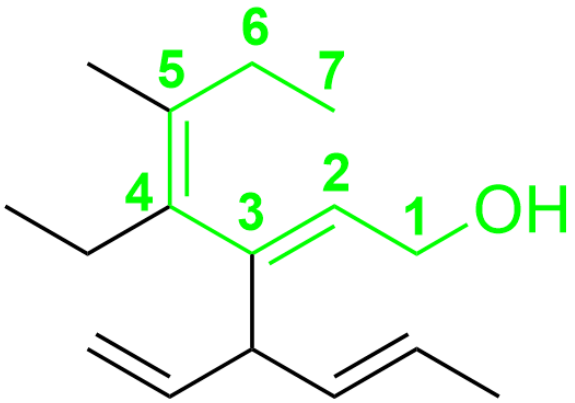
D. (2E,4Z)-4-ethyl-3-((E)-hexa-1,4-dien-3-yl)-5-methylhepta-2,4-dien-1-ol

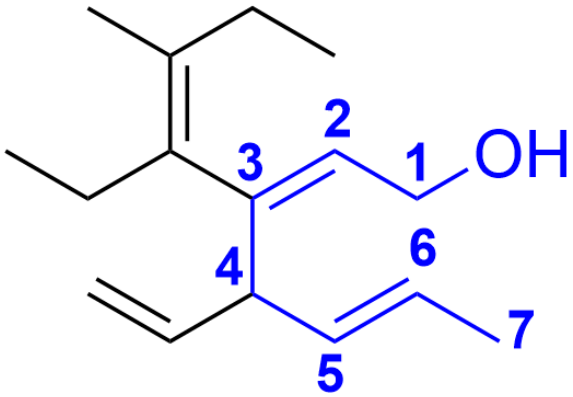


The correct answer is **Option D**.

Although this may look like a challenging question, this can be easily solved by only looking at specific parts of the full IUPAC name, specifically the *E/Z* notation. This can be done by (1) determining the parent chain and (2) looking at the E/Z designation for each double bond.

Determining the parent chain will help us know what positions the double bonds are in. As this compound only contains one functional group (the hydroxyl), we know the parent chain must contain this group. Furthermore, it should be the longest carbon chain encompassing the greatest number of double bonds. There are currently two options for the longest carbon chain – either the first one (in green) which goes upwards, or the second one (in blue) which goes downwards (pictured below)



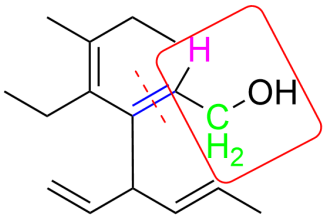


As both chains contain 7 carbons and 2 alkenes, it is equivalent in this sense. The next rule we must follow then, is to choose the chain where the positions of the functional groups are lower. As the carbon bonded to the hydroxyl group is designated as position 1, the green chain has the alkenes located at positions 2 and 4. In

contrast, the blue chain has the alkenes at positions 2 and 5. As the double bonds appear on the green chain at lower position numbers, this is considered the parent chain of the molecule.

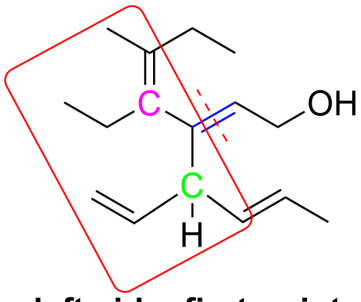
We can then identify the positions of each double bond and designate them as *E* or *Z*. There is a double bond found at position 2 and 4 on the parent chain. Just from determining the *E/Z* notations of these double bonds will give us the answer through process of elimination.

Let's determine the *E/Z* notation at position 2 first. On the right side, it is easy to determine that priority is given to the carbon chain, as C has an atomic number of 6, whereas the other substituent is H, which has an atomic number of 1. The other side is slightly more difficult because both substituents attached to the double bond are carbon groups (green dots). However, the top carbon is counted to be bonded to three carbons (magenta dots) as it contains one C=C double bond and one C–C single bond. In contrast, the bottom carbon is bonded to only two carbons (magenta dots) and also contains one C–H bond. As C has a higher priority over H, the top carbon substituent takes priority on the left side. Thus, as this double bond has the higher priority groups pointing in opposite directions, this is an *E* alkene, and would be written as 2*E* in the IUPAC name.



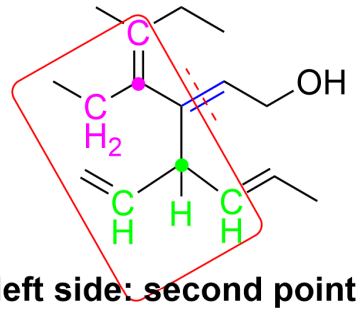
right side

C > H



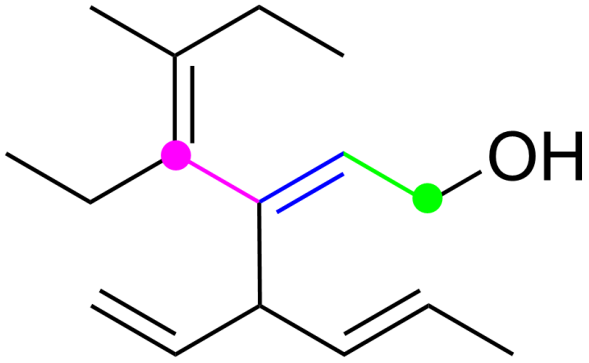
left side: first point

C = C



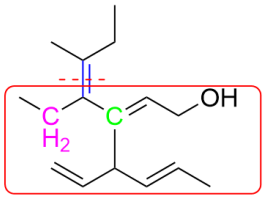
left side: second point

C = C
C = C
C > H



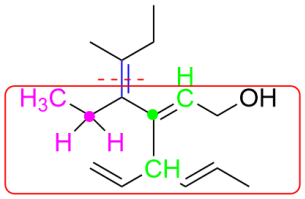
opposite = 2E

As only Option D contains 2*E* in the name, these two steps will quickly give us the correct answer already. For your own reference, the diagram below also explains the steps to determine the *Z* designation for the alkene at position 4.



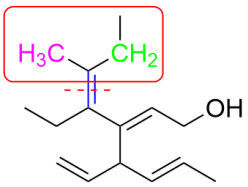
bottom side: first point

C = C



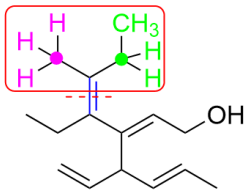
bottom side: second point

C = C
H < C
H < C



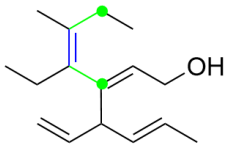
upper side: first point

C = C



upper side: first point

H < C
H = C
H = C

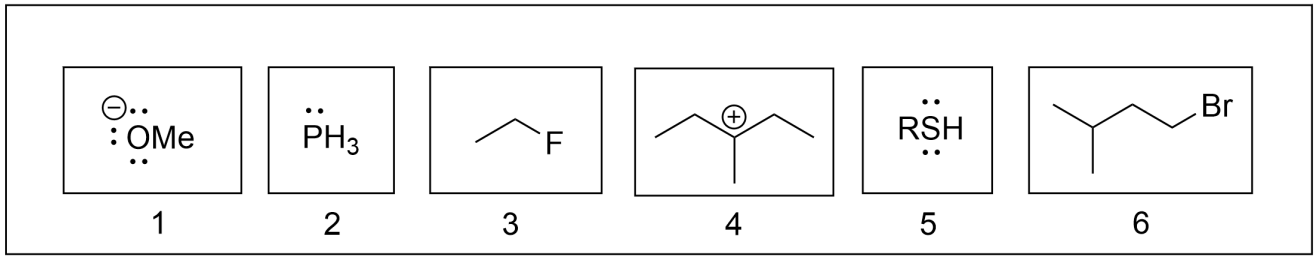


same = 4Z

5.2 - SOLUTIONS FOR CHAPTER 3 - REACTIVITY

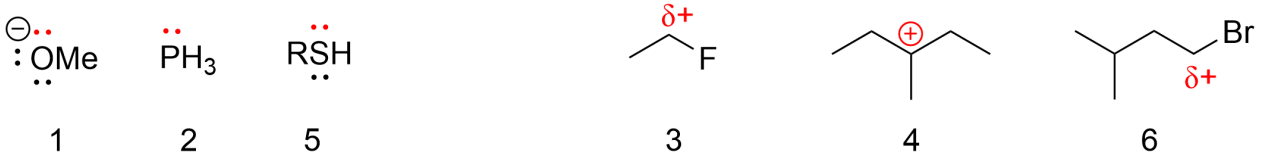
Chapter 3.1.1 – Introduction to Nucleophiles, Electrophiles and Curved Arrows

1. Which of the following are electrophiles?



The correct answers to this question are **compounds 3, 4, and 6**. The easiest way to identify electrophiles is to look for either a positive charge or a partial positive charge on a molecule. Positive charges will be clear (as seen with a + symbol), whereas partially positive carbons will be bonded to a highly electronegative atom, such as halides (Cl, Br, F, I) or oxygen. Molecules 3 and 6 both contain a halide, a highly electronegative group. Therefore, the carbon it is bonded to is partially positive, making it an electrophile. Molecule 4 contains a carbon with an incomplete octet, as seen by the positive charge, making it an electrophile.

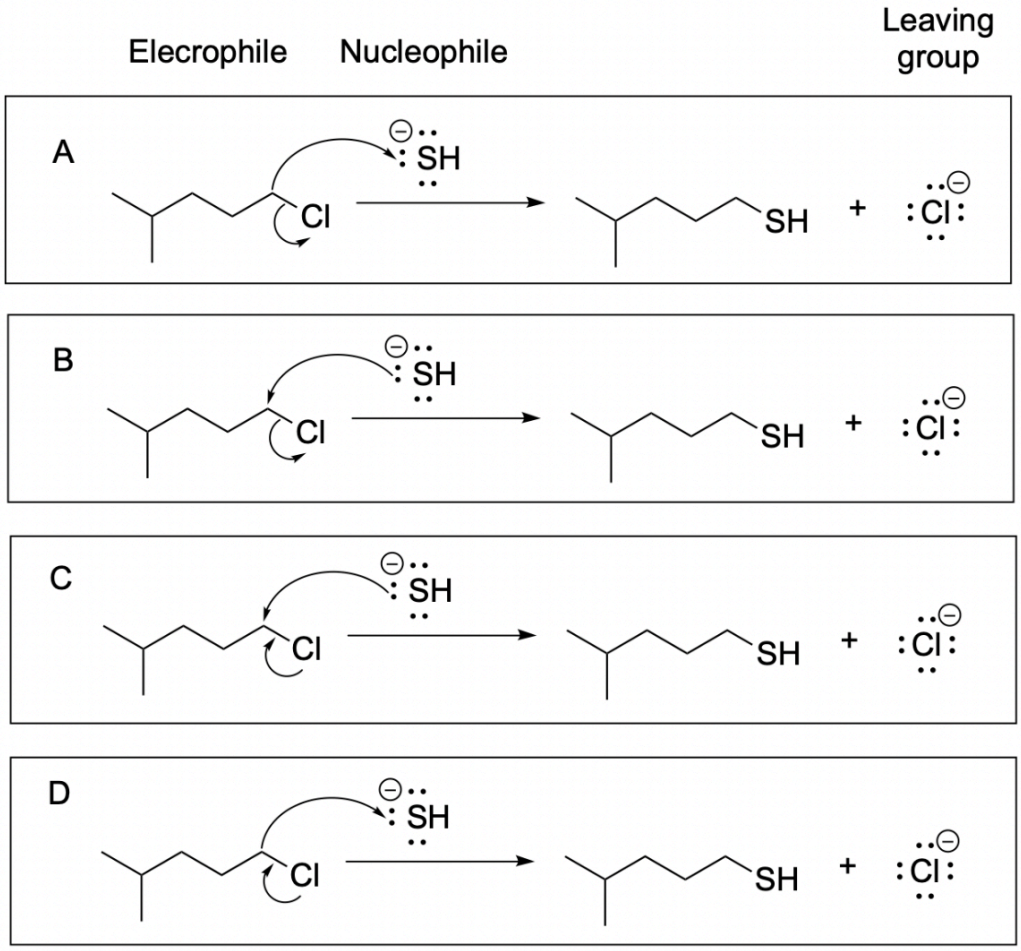
Nucleophiles, in contrast, can be identified by having at least one lone pair, typically found on a heteroatom such as oxygen, phosphorus, or sulfur. This is seen on molecules 1, 2 and 5. There are no partially or fully positive charges on these molecules, as they mainly consist of lone pairs. These lone pairs can be used to form a new bond with another molecule, making them nucleophiles.



Nucleophiles
All contain at least one lone pair

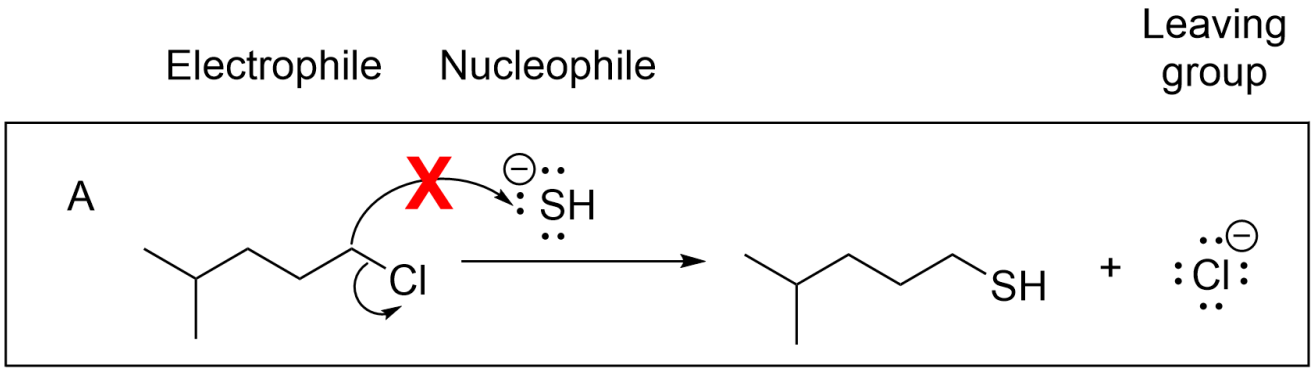
Electrophiles
All contain a positive or partial positive charge

2. Which of the following arrow-pushing reaction diagrams is correct?



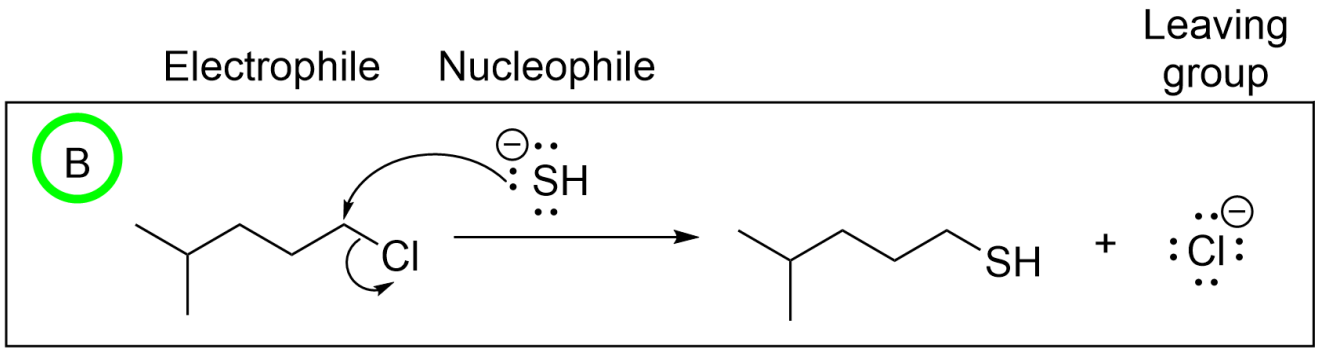
The correct answer to this question is **Option B.**

Option A is incorrect due to the direction of the first arrow. Recall that arrows must **start at the source of electron** (the nucleophile) and **point towards the electron-deficient area** (the electrophile). This arrow is pointing in the opposite direction; there are no lone pairs on the carbon to move, and there is also no need for sulfur, which has a full octet, to gain more electrons. Thus, this answer is wrong.

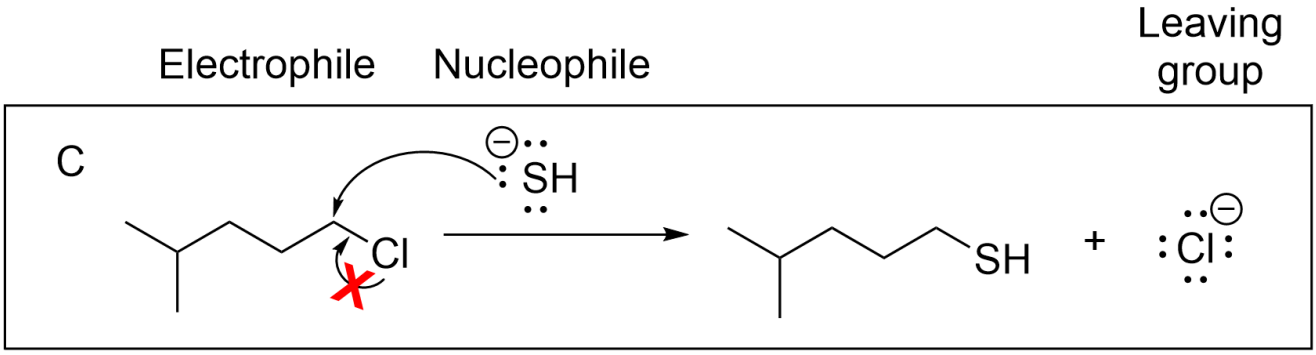


Option B shows the correctarrow pushing mechanism. The arrow starts at the nucleophile (source of

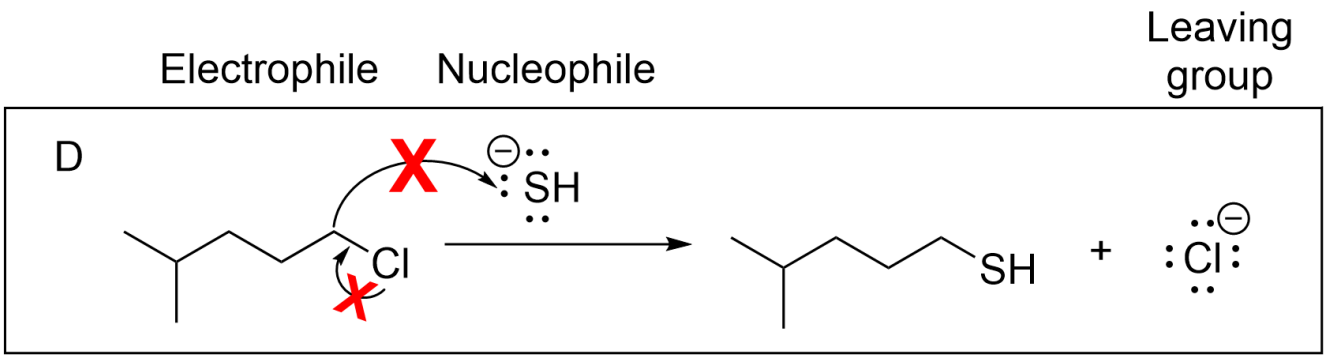
electrons) and points towards the electron-deficient carbon. As this carbon has a full octet, it must lose a bond to make room for the new bond to sulfur. This is seen in the second arrow, pointing from the bond (source of electrons) to the electronegative chlorine, which takes the lone pair with it.



Option C is incorrect due to the second arrow. The nucleophile attacks an electrophilic carbon which already contains a full octet, with two explicit bonds and two more implicit bonds to hydrogen. Thus, the second arrow must **break** a bond. The arrow must start at the bond and move towards the leaving group, which is Cl in this case. This incorrect arrow makes it seem like a new bond is forming from a lone pair on Cl, which is not possible.



Option D is incorrect as both arrows are pointing in the wrong direction. Recall that arrows must start at the source of electrons (nucleophile) and point towards the electron-deficiency (electrophile). The top arrow is pointing in the opposite direction; there are no lone electrons on the carbon to move, and there is no need for sulfur, which has a full octet, to gain more electrons. The second arrow is also pointing in the opposite direction. As Cl is the leaving group, the C–Cl bond must break. The arrow must start at the bond and move towards the leaving group,which is Cl in this reaction.



3. Which of the following statements regarding organic reactions is FALSE?

A. The nucleophile is the electron donor, and is a Lewis base.

B. Forming a bond in a nucleophilic substitution reaction involves electrons moving from the nucleophile to the electrophile.

C. Nucleophiles and electrophiles must be properly aligned with each other for the reaction to occur.

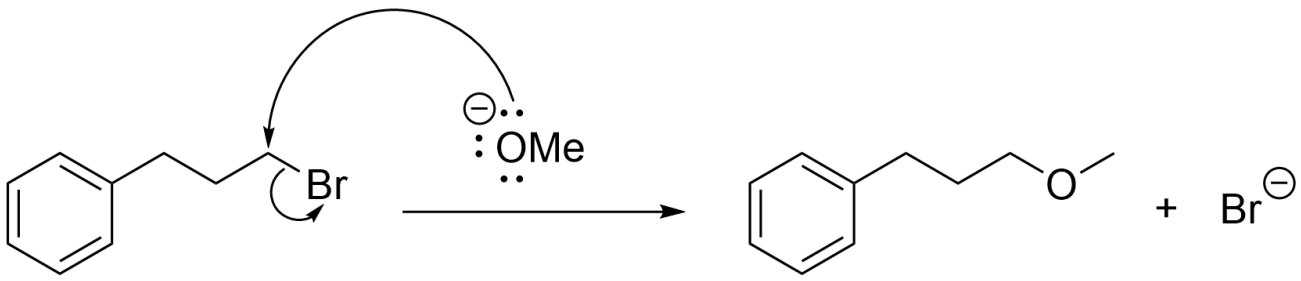
D. When writing a mechanism, the tail of the double-barbed curly arrow is at the electrophile while the arrowhead is at the nucleophile.

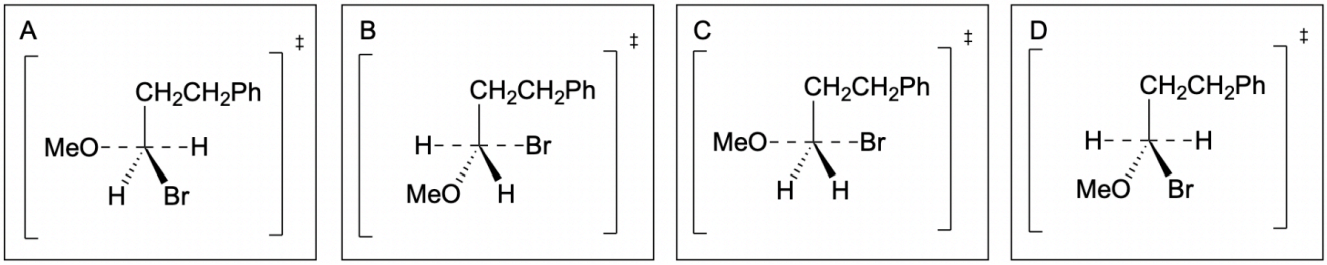
The correct answer is **Option D**. When drawing mechanisms, the tail always starts at the source of electrons, which would be the nucleophile. The head always points towards the area of electron-deficiency, which would be the electrophile. This is to showcase the movement of electrons. This answer is the opposite of that, and thus, is FALSE and therefore the correct answer to the question.

Options A, B, and C are all true statements, which is not what the question asks for.

Chapter 3.1.2 – S_N2 Reaction Mechanism

1. Which of the following is the transitional state of the following reaction? (Ph is the abbreviation of a benzene ring.)

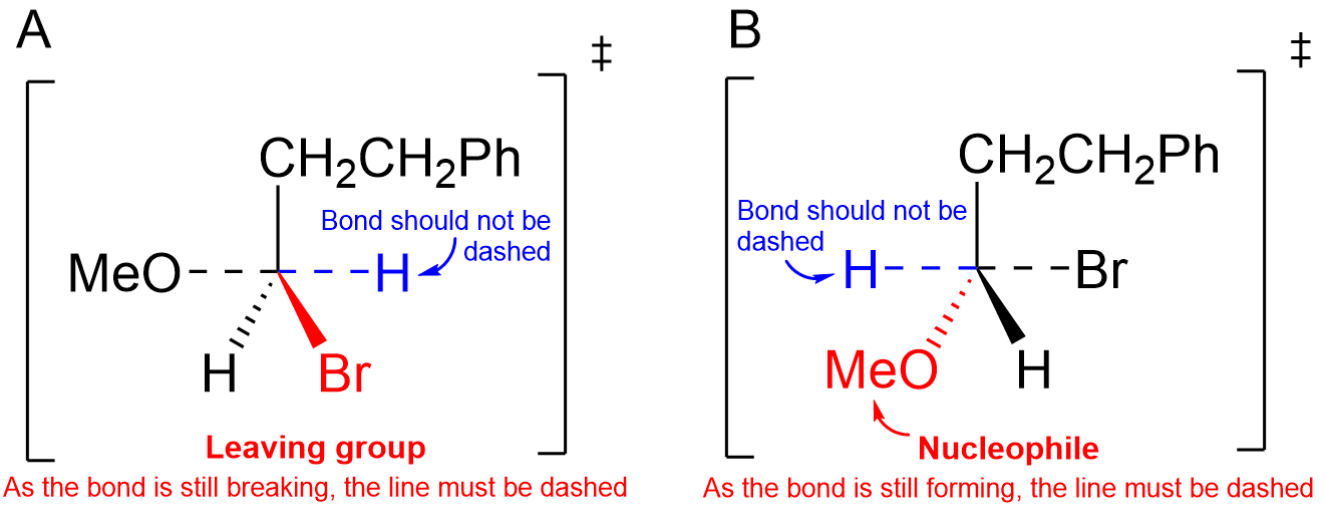




The correct answer to this question is **Option C.** Recall that in the transition state, the electrophilic carbon consists of 5 total bonds. In the trigonal bipyramidal geometry, the incoming nucleophile and the leaving group are on the same plane as the carbon, appearing on its left and right respectively, and are drawn with partial (dashed) bonds as they are forming and breaking.

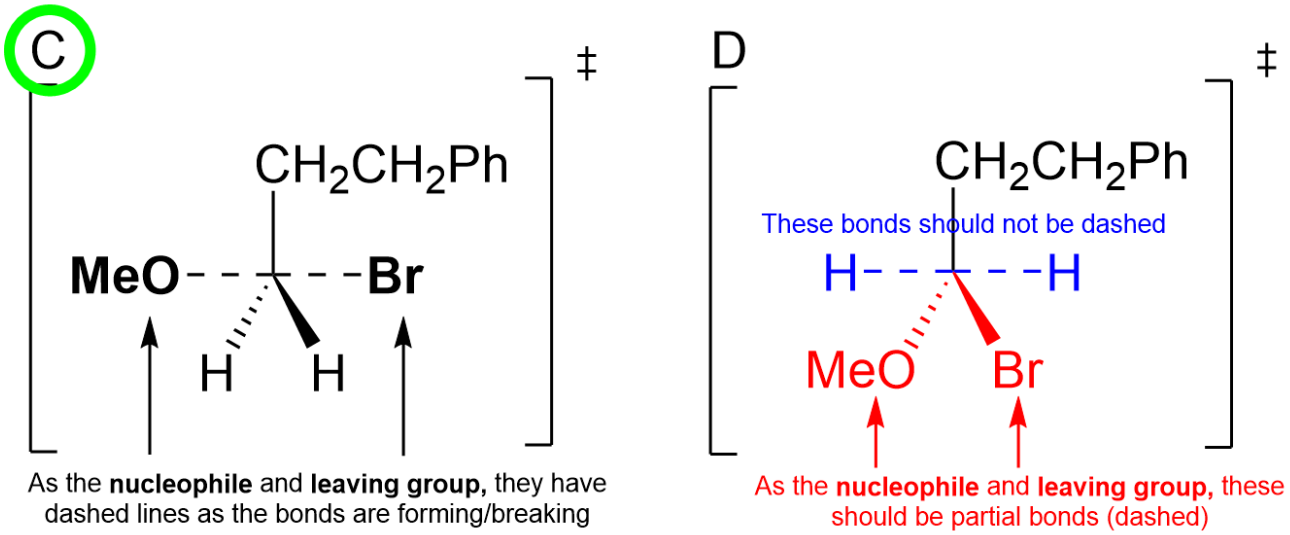
Option A is incorrect as Br, the leaving group in the molecule, is not drawn with a partial bond. As seen in the reaction mechanism, the arrow indicates that the Br is going to leave with a lone pair of electrons. Thus, in the transition state, it should have a partial bond to carbon, depicted with dashed lines, as it is still in the process of leaving. Furthermore, the H bonded to carbon is not leaving or forming a new bond, and thus, should be bonded with a solid line.

Option B is also incorrect as MeO, the nucleophile, is not drawn with a partial bond. As seen in the reaction mechanism, the curved arrow indicates that MeO is attacking the carbon with its lone pair. Thus, in the transition state, it should have a partial bond to carbon, depicted with dashed lines, as it is still in the process of forming the new bond. Furthermore, the H bonded to carbon is not leaving or forming a new bond, and thus, should be bonded with a solid line.



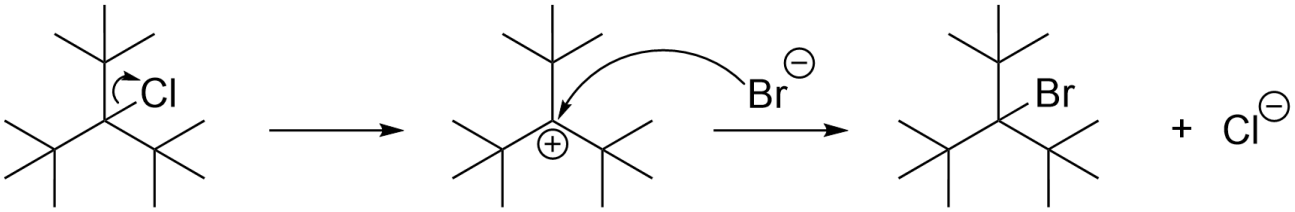
Option C is the correct answer. The nucleophile and leaving group are both drawn with dashed lines to the central carbon, as both bonds are either forming or breaking.

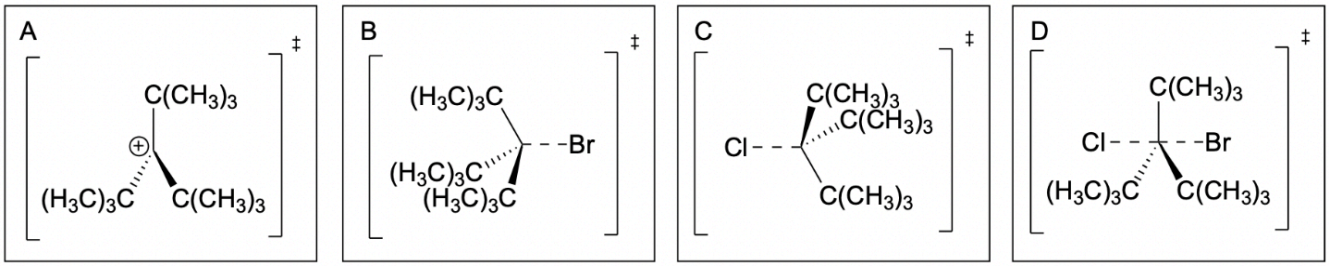
Option D is incorrect, as both the nucleophile (MeO) and the leaving group (Br) are not drawn with partial bonds. The hydrogen atoms should not be drawn with dashed lines, as they are not partial bonds.



Chapter 3.1.3 – S_N1 Reaction Mechanisms

1. Which of following is the transition state of the non-rate determining step of the following S_N1 reaction?



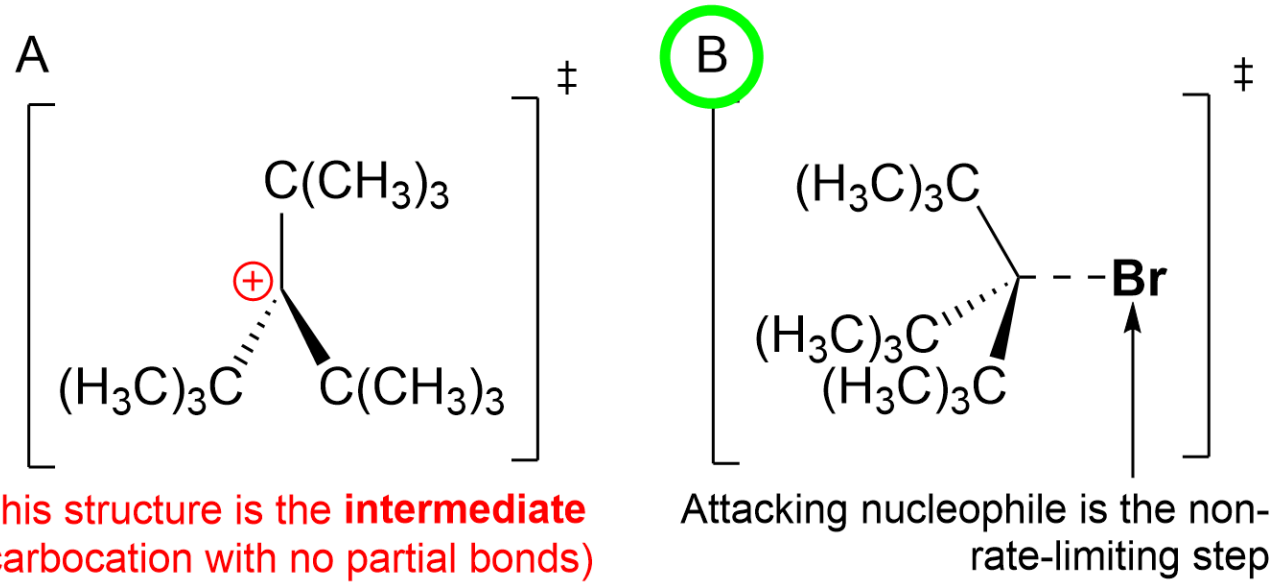


The correct answer to this question is **Option B.** The first step to answering this question is to understand which step is rate-limiting and which is non-rate-limiting. Recall that the first step of an S_N1 reaction is the

spontaneous dissociation of the leaving group. This is the rate-limiting step as it occurs slower. Thus, it can be determined that the question is asking for the transition state of the second step, the nucleophilic attack of Br.

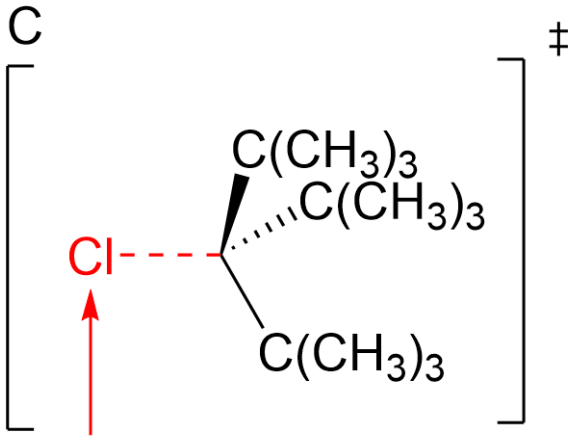
Option A is incorrect, as it shows the intermediate of the S_N1 reaction, not a transition state. This can be seen as there are no partial bonds and the carbon is positively charged due to the lost leaving group. This is the structure that is obtained after the first step where Cl leaves from the molecule, taking the lone pair of electrons with it.

Option B is correct, as it shows the correct transition state. Since the non-rate-determinant step is the nucleophilic attack of Br, the transition state should show the partially formed bond between the carbon and the Br. Thus, this is the correct answer as it shows the proper dashed line to Br.

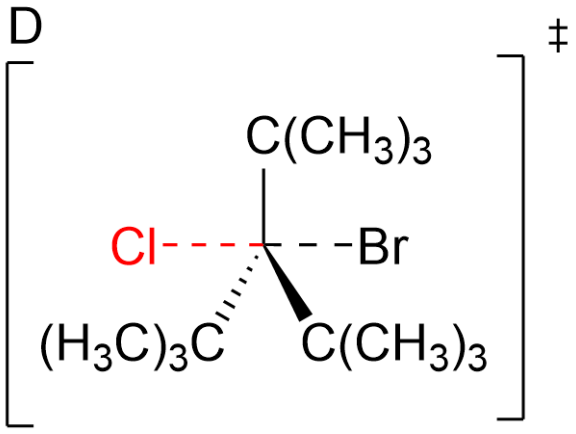


Option C is incorrect, as it shows the transition state of the first step, with the Cl leaving the molecule. This is seen by the dashed line to Cl. This first step is considered the slowest step of the reaction, and thus, it is rate-limiting.

Option D is incorrect, as it shows two partially formed bonds to both Cl and Br. Recall that S_N1 reactions occur via a two-step mechanism where the leaving group departs before the carbocation is attacked by a nucleophile. Due to this mechanism, it is not possible for the transition state to contain two partially formed bonds, as one happens before the other. Thus, the chlorine should be fully dissociated from the molecule and not have a partial bond to the central carbon.



As the leaving Cl is the slowest step, this is the rate-limiting transition state



In S_N1, Cl fully leaves before Br starts to form the new bond

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Chapter 3.1.4 – S_N1 VS S_N2

1. Indicate the false statement concerning organic reactions:

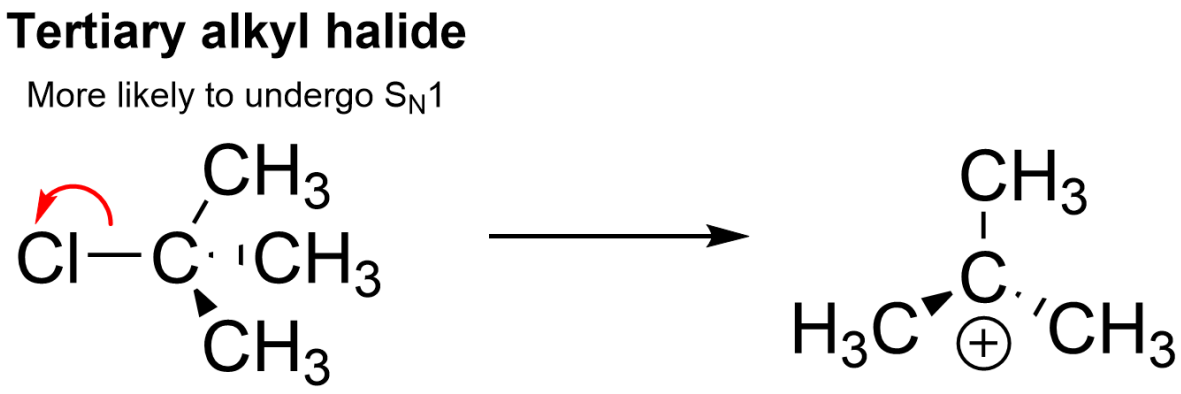
A. In the reaction of H_2O with $ClC(CH_3)_3$, doubling [$ClC(CH_3)_3$] will not double the rate of reaction.

B. S_N1 reactions of tertiary alkyl halides are faster than S_N1 reactions of secondary alkyl halides.

C. The reaction of HO^- with $ClCH_2CH_3$ does not involve a carbocation intermediate.

D. S_N2 reactions become nine times faster when [nucleophile] and [electrophile] both increase by a factor of three

The correct option in this question is **Option A.** Before thinking about the rate law, you must first consider whether $ClC(CH_3)_3$ would undergo an S_N1 or S_N2 reaction. $ClC(CH_3)_3$ is a tertiary alkyl halide, as the carbon bonded to Cl has three alkyl groups around it. It is easier to see if drawn out, as seen below. As an S_N1 reaction mechanism, the rate law is only influenced by the alkyl halide, as it is the rate-limiting step. Because of this, doubling the concentration of ClC(CH3)3, the alkyl halide, **would** double the rate of reaction. Therefore, this statement is false and is the correct answer.

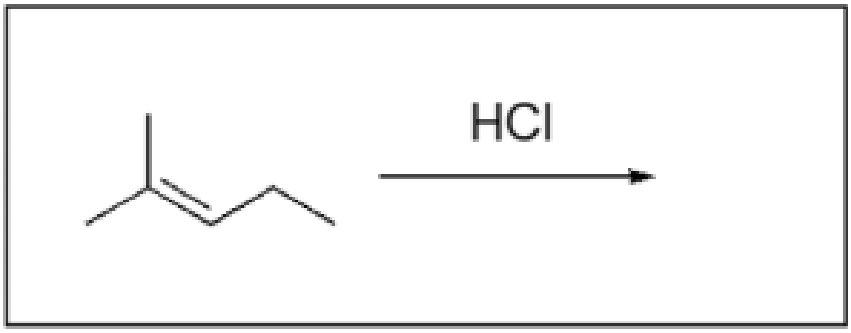


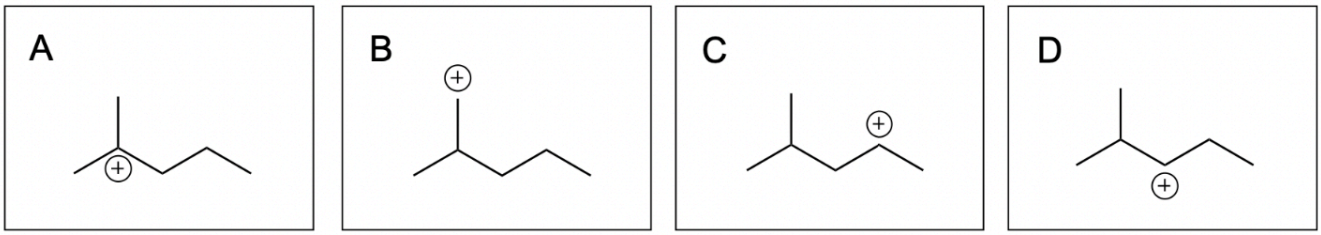
$$\text{Rate} = k_{obs}[ClC(CH_3)_3]$$

Options B, C and D are incorrect as they are all true statements. S_N1 reactions always occur faster with tertiary alkyl halides compared to secondary alkyl halides due to the stabilization of the carbocation from the surrounding alkyl groups. In option C, the molecule $ClCH_2CH_3$ is a primary alkyl halide, and thus, will go through the S_N2 process. Recall that S_N2 reactions do not go through a carbocation intermediate as the steps happen simultaneously, with the nucleophile attacking to kick out the leaving group. For option D, we know that the rate law of an S_N2 reaction is rate = k_{obs}[Alkyl halide][Nucleophile]. Thus, increasing both by a factor of three would make the reaction nine times faster.

Chapter 3.2.1 – Hydrohalogenation of Alkenes

1. Which of the following are two possible intermediate states during this hydrohalogenation reaction?

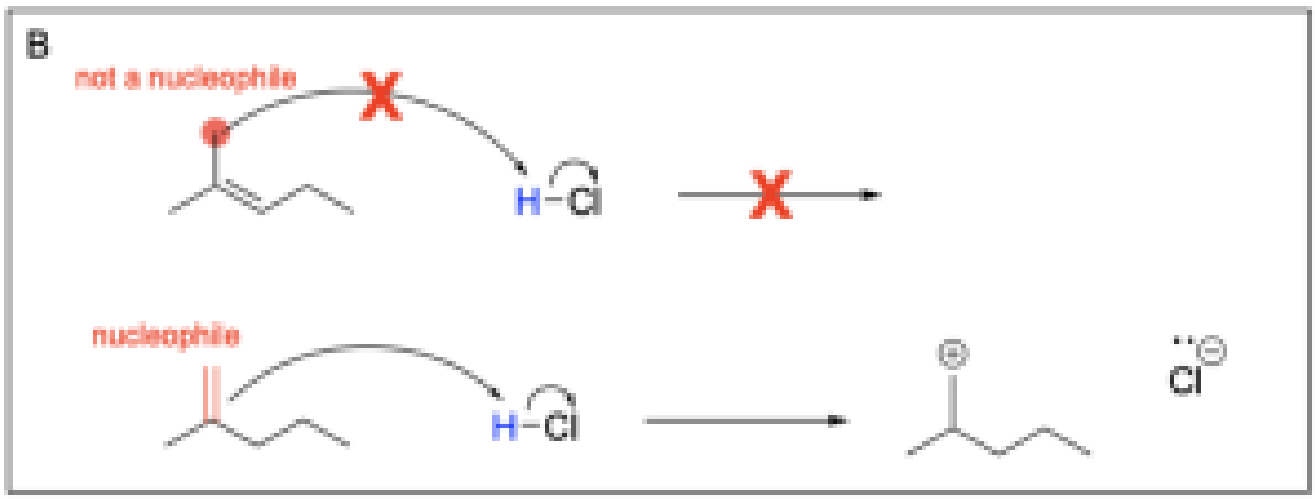




The correct answers to this question are **Option A and Option D.** Organic reactions involve an electron-rich source (the nucleophile) attacking an electron-deficient source (the electrophile). In hydrohalogenation, the alkene is nucleophilic and attacks the electrophilic hydrogen in the hydrogen halide in a mechanism similar to S_N1, where there is a carbocation intermediate.

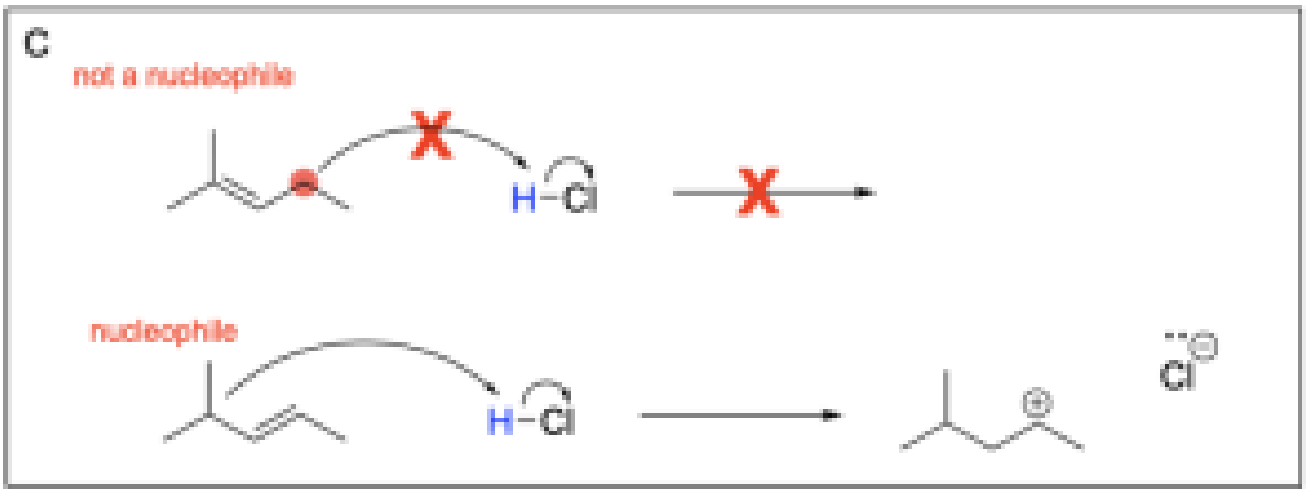
Option A is correct. This option illustrates the major product, or Markovnikov product, where the hydrogen atom is added to the less substituted carbon. This leaves a more stable carbocation intermediate that will then undergo nucleophilic attack by the chloride ion.

Option B is incorrect. There is not a nucleophilic source (such as an alkene) on the carbon atom indicated. There must be a nucleophilic source (second reaction scheme in the photo below) to attack the electrophilic hydrogen atom in order to undergo a hydrohalogenation reaction.



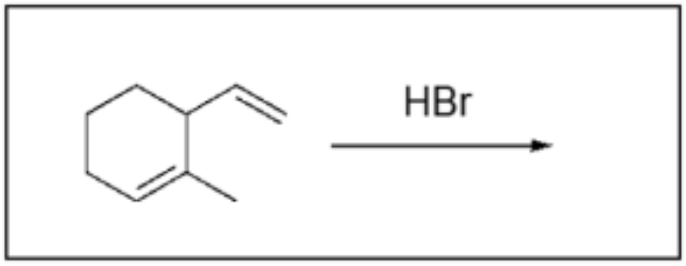
Option C is incorrect. There is not a nucleophilic source (such as an alkene) on the carbon atom indicated.

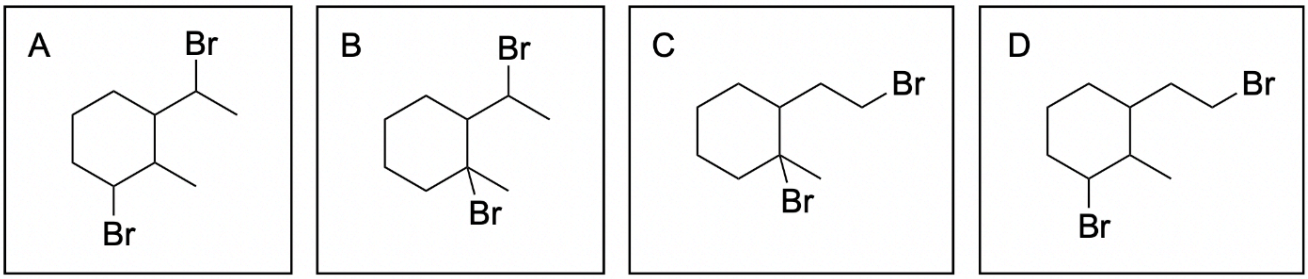
There must be a nucleophilic source (second reaction scheme in the photo below) to attack the electrophilic hydrogen atom in order to undergo a hydrohalogenation reaction.



Option D is also correct. This option illustrates the minor product, or Anti–Markovnikov product, where the hydrogen atom is added to the more substituted carbon, leaving a less stable carbocation intermediate that will then undergo nucleophilic attack by the chloride ion.

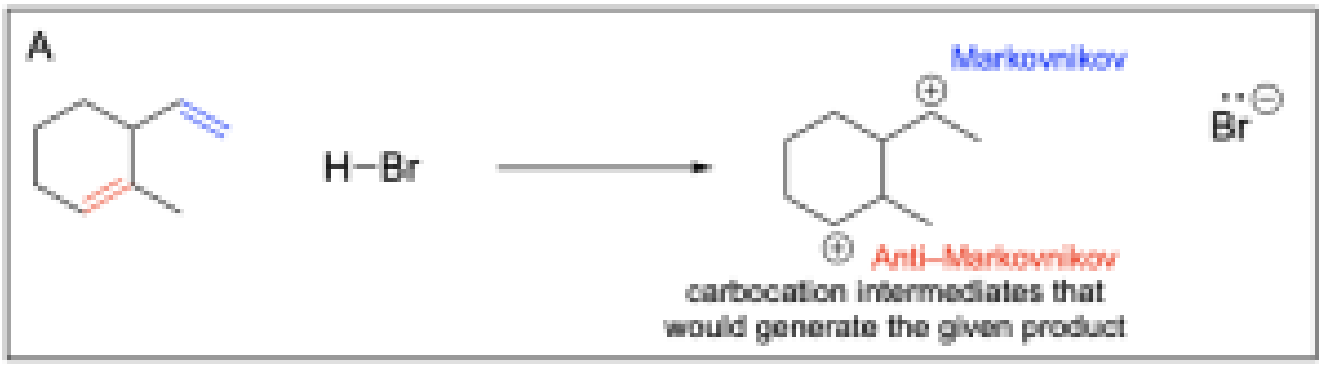
2. Which of following is the most likely product of hydrohalogenation?



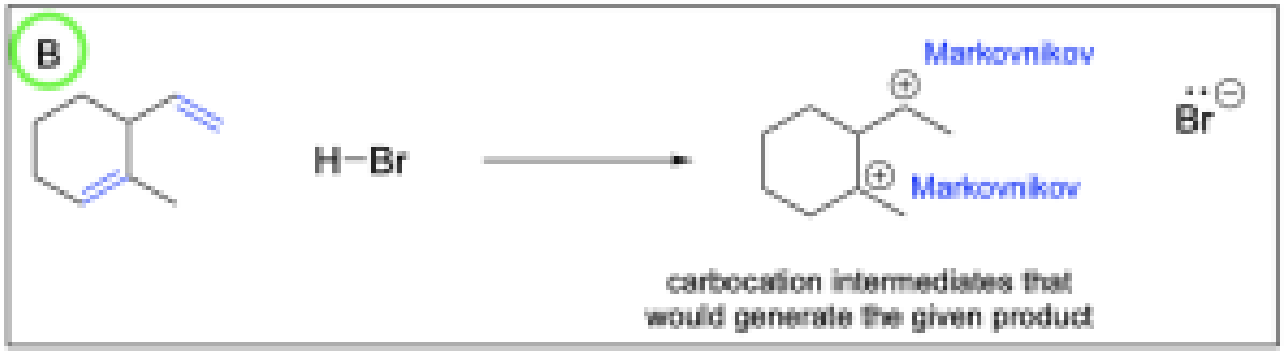


The correct answer to this question is **Option B.** Hydrohalogenation reactions involve a nucleophilic alkene attacking an electrophilic hydrogen halide where the hydrogen and halogen are added to a carbon atom in the alkene in a mechanism similar to S_N1, where there is a carbocation intermediate. In unsymmetrical alkenes, there are 2 atoms the hydrogen and halide can be added to: the more substituted and less substituted carbon atom. The more stable carbocation intermediate is at the more substituted carbon where the nucleophilic halogen can attack. This will generate the more favourable Markovnikov product, which will form more readily than the Anti–Markovnikov product.

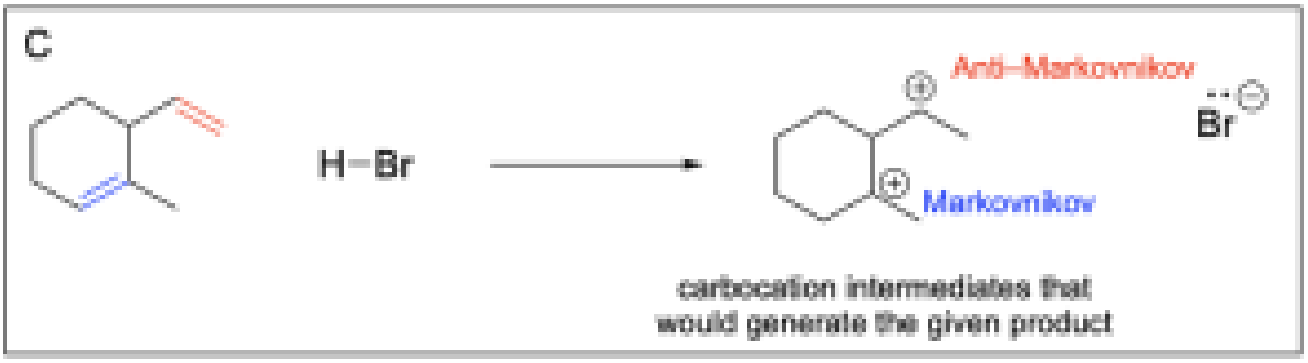
Option A is incorrect. This can be a product of hydrohalogenation, but it is not the most favourable out of the options listed. While the alkene on the right forms the more substituted and favourable Markovnikov product, the alkene on the left forms the less substituted Anti–Markovnikov product. This is less favourable and will not form as readily.



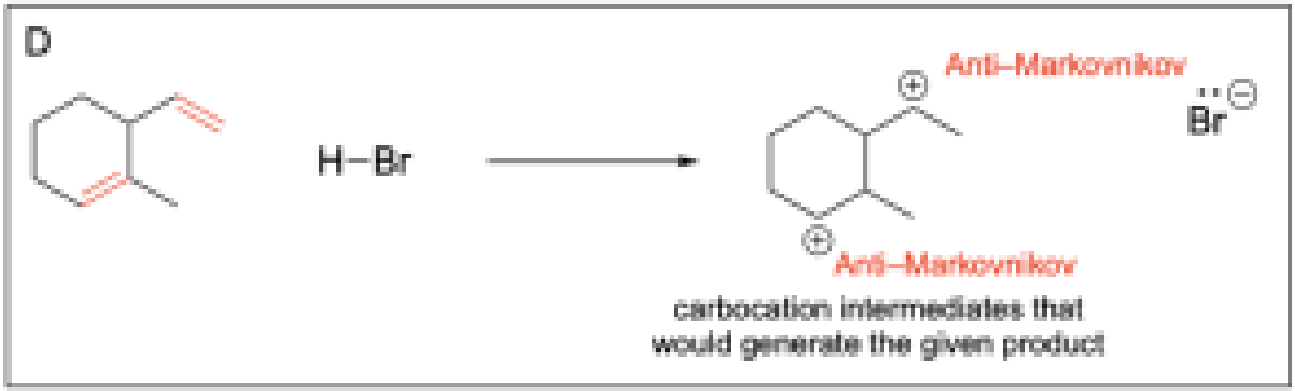
Option B is correct. This is the most favourable product of hydrohalogenation out of the options listed. Both alkenes form the more substituted and favourable Markovnikov product. Both are favourable and will readily form.



Option C is incorrect. This can be a product of hydrohalogenation, but it is not the most favourable out of the options listed. While the alkene on the left forms the more substituted and favourable Markovnikov product, the alkene on the right forms the less substituted Anti–Markovnikov product. This is less favourable and will not form as readily.

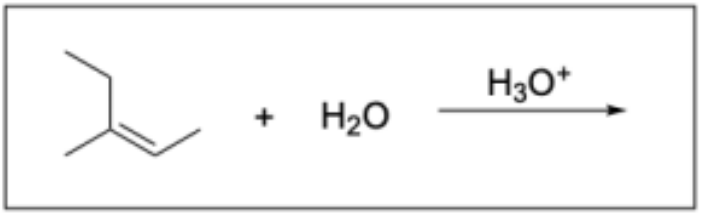


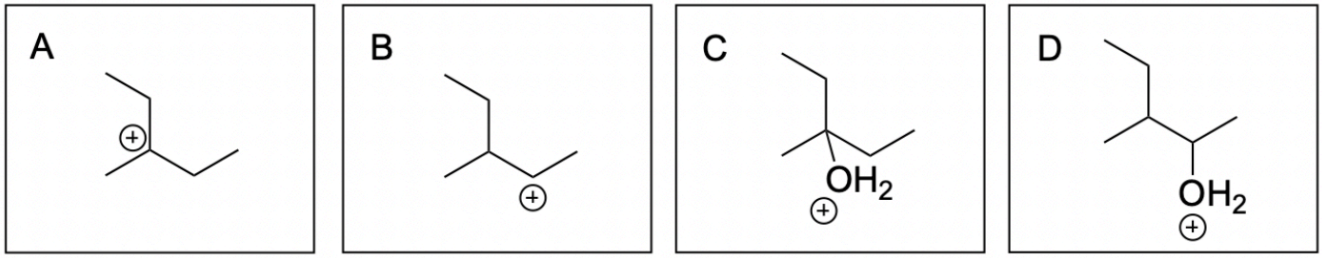
Option D is incorrect. This can be a product of hydrohalogenation, but it is the least favourable out of the options listed. Both alkenes form the less substituted and less favourable Anti–Markovnikov product. Both are not favourable and will not readily form.



Chapter 3.2.2 – Hydration of Alkenes

1. Which of the following are intermediates of alkene hydration?



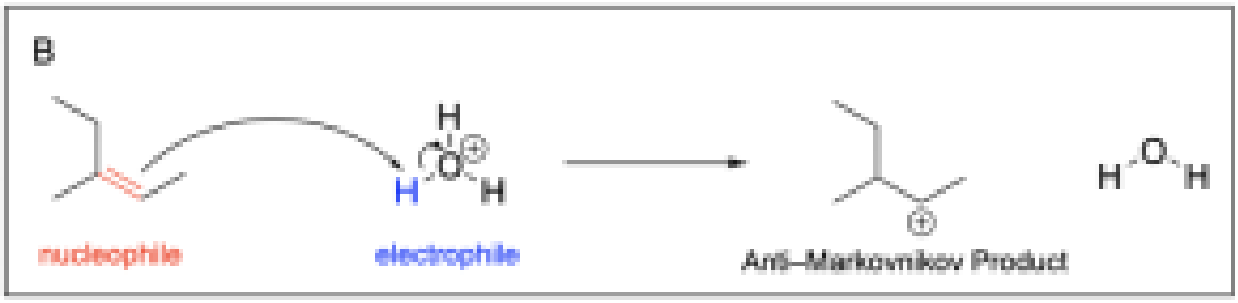


The correct answer to this question is **Option A.** Hydration reactions involve the nucleophilic alkene attacking hydronium, where the hydrogen and hydroxide are added to a carbon atom in the alkene in a mechanism similar to S_N1, where there is a carbocation intermediate. A key difference between the mechanism in a hydration reaction vs. an S_N1 reaction is that hydration reactions contain an extra deprotonation step since water is neutral. In unsymmetrical alkenes, there are 2 atoms the hydrogen and hydroxide can be added to: the more substituted and less substituted carbon atom. The more stable carbocation intermediate is at the more substituted carbon where the nucleophilic water can attack. This will generate the more favourable Markovnikov product, which will form more readily than the Anti–Markovnikov product.

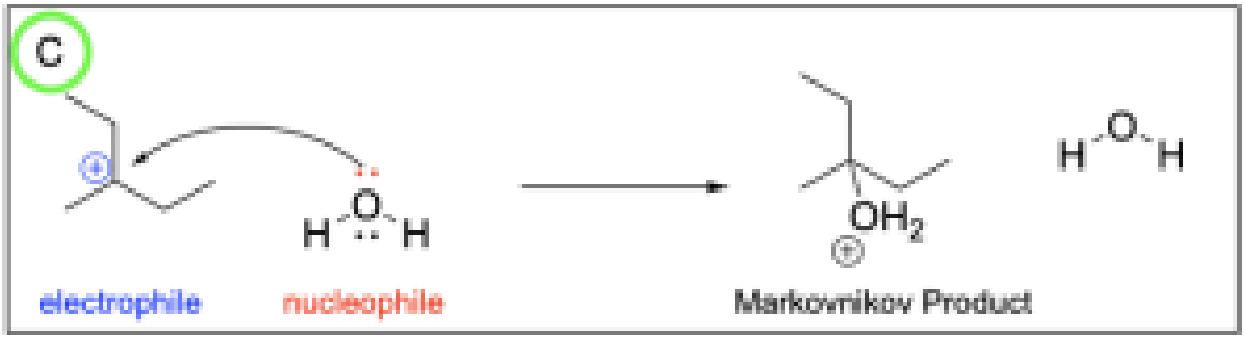
Option A is correct. This is one of the most favourable hydration intermediates out of the options listed. The nucleophilic alkene attacks the electrophilic hydronium generating a carbocation intermediate on the most substituted carbon atom. This is more favourable and will occur more readily.

Option B is incorrect. This is not the most favourable hydration intermediate out of the options listed.

The nucleophilic alkene attacks the electrophilic hydronium generating a carbocation intermediate on the least substituted carbon atom. This is less favourable and will not readily occur.

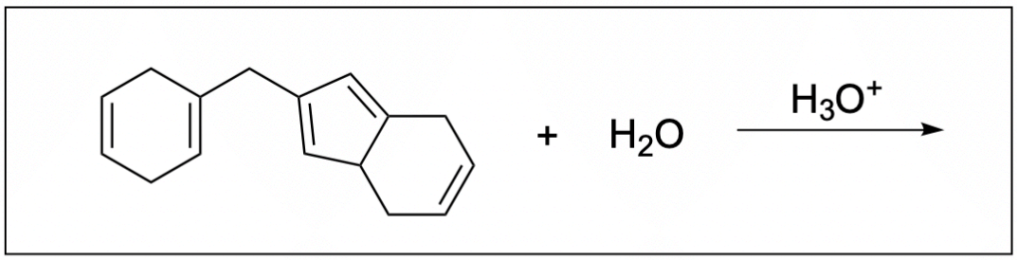


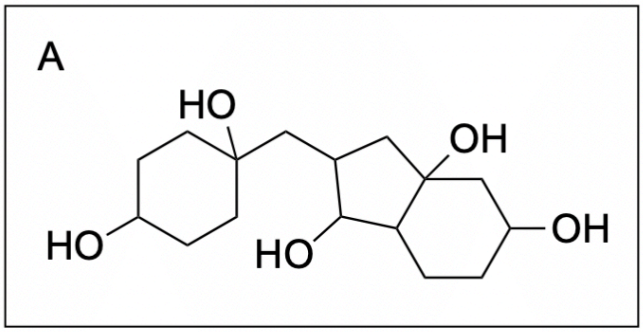
Option C is correct. This is one of the most favourable hydration intermediates out of the options listed. The neutral water will attack the carbocation intermediate generating an oxonium cation intermediate. Due to the favourable more substituted carbocation intermediate, this intermediate will form more readily.

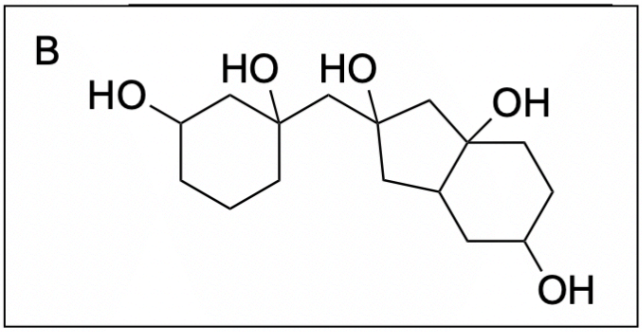


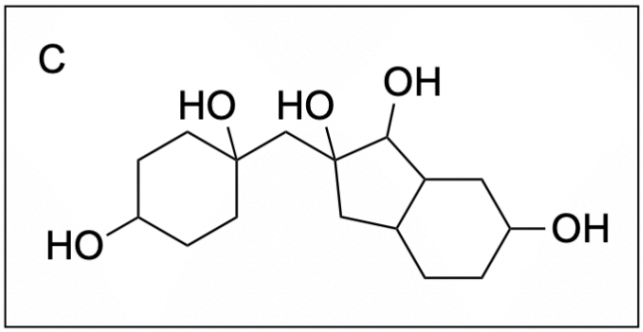
Option D is incorrect. This is not the most favourable hydration intermediate out of the options listed. The neutral water will attack the carbocation intermediate generating an oxonium cation intermediate. Due to the unfavourable less substituted carbocation intermediate, this intermediate will not readily form.

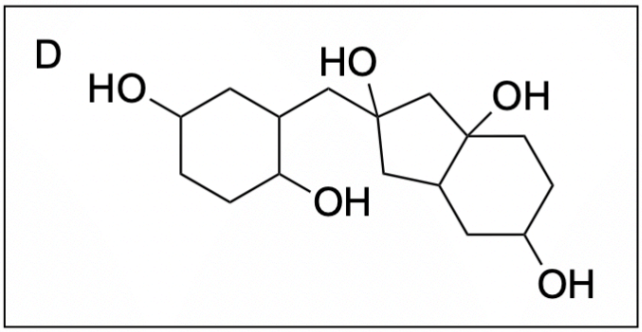
2. Which of following is a possible product of the alkene hydration reaction?





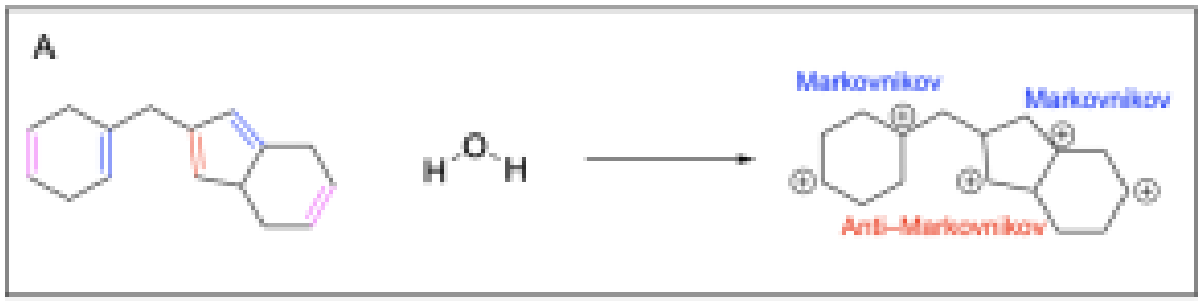




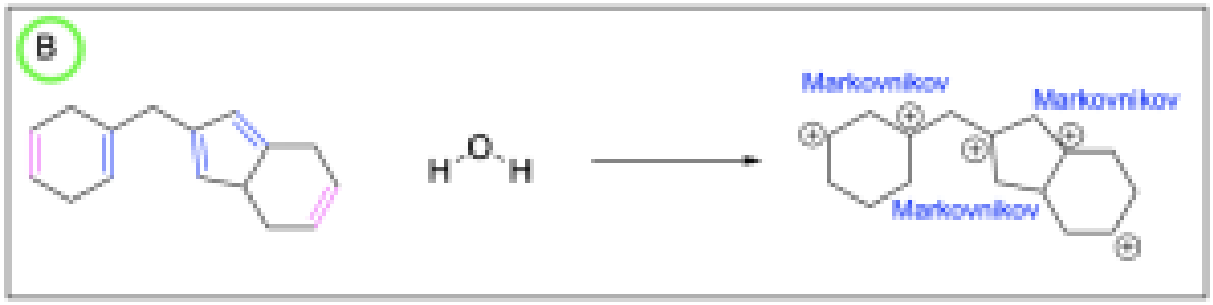


The correct answer to this question is **Option B.** Hydration reactions involve the nucleophilic alkene attacking hydronium, where the hydrogen and hydroxide are added to a carbon atom in the alkene in a mechanism similar to S_N1, where there is a carbocation intermediate. In symmetric alkenes, there is no preference in which carbon the water is added to since the same carbocation intermediate is generated. In unsymmetrical alkenes, there are 2 atoms the hydrogen and hydroxide can be added to: the more substituted and less substituted carbon atom. The more stable carbocation intermediate is at the more substituted carbon where the nucleophilic halogen can attack. This will generate the more favourable Markovnikov product, which will form more readily than the Anti–Markovnikov product.

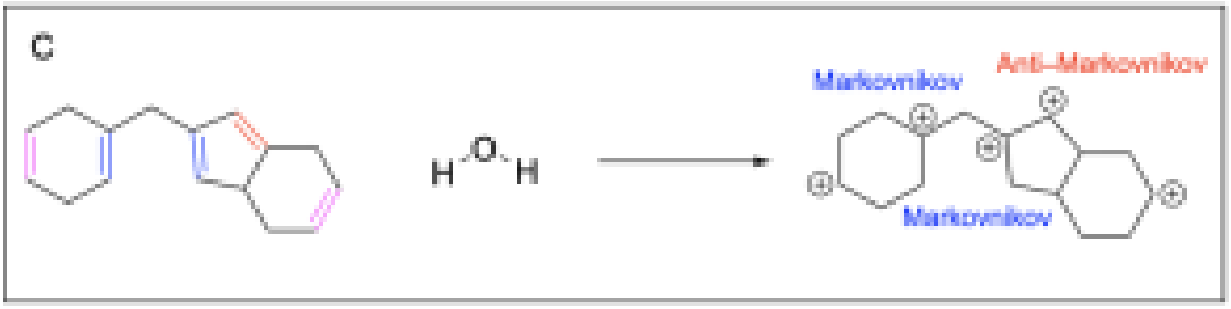
Option A is incorrect. This can be a product of hydration, but it is not the most favourable out of the options listed. The alkenes highlighted in pink are symmetric, so water is equally likely to attack either carbon atom. The alkenes highlighted in blue generated a favourable and more substituted carbocation intermediate (Markovnikov product), which will form more readily. The alkene highlighted in red generated an unfavourable carbocation intermediate (Anti–Markovnikov product), which will not readily form.



Option B is correct. This is the most favourable out of the options listed. The alkenes highlighted in pink are symmetric, so water is equally likely to attack either carbon atom. The alkenes highlighted in blue generated a favourable and more substituted carbocation intermediate (Markovnikov product), which will form more readily.

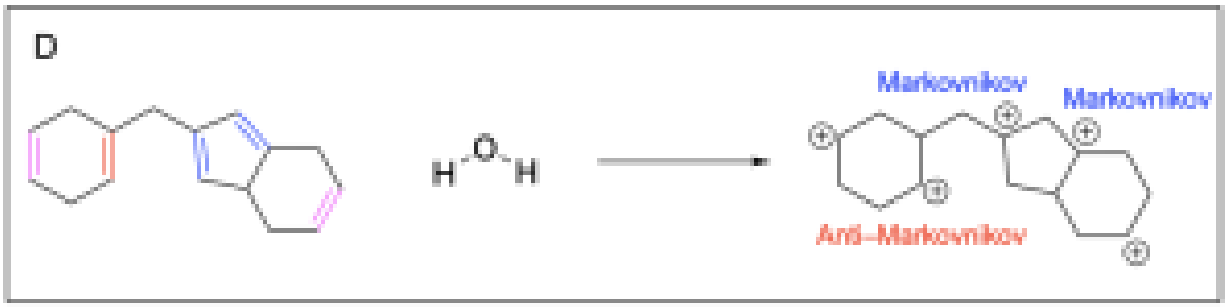


Option C is incorrect. This can be a product of hydration, but it is not the most favourable out of the options listed. The alkenes highlighted in pink are symmetric, so water is equally likely to attack either carbon atom. The alkenes highlighted in blue generated a favourable and more substituted carbocation intermediate (Markovnikov product), which will form more readily. The alkene highlighted in red generated an unfavourable carbocation intermediate (Anti–Markovnikov product), which will not readily form.



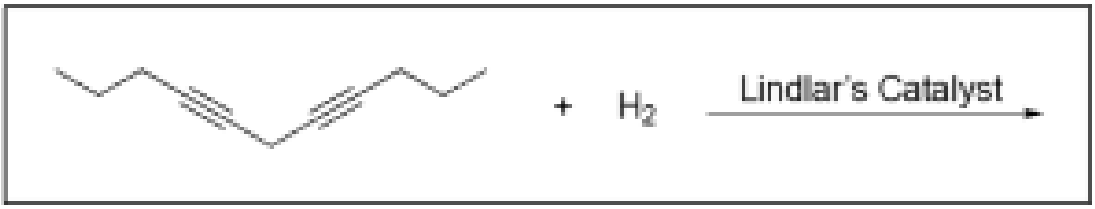
Option D is incorrect. This can be a product of hydration, but it is not the most favourable out of the options listed. The alkenes highlighted in pink are symmetric, so water is equally likely to attack either carbon atom. The alkenes highlighted in blue generated a favourable and more substituted carbocation intermediate

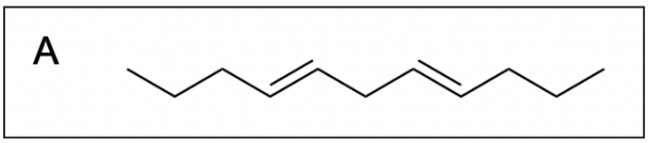
(Markovnikov product), which will form more readily. The alkene highlighted in red generated an unfavourable carbocation intermediate (Anti–Markovnikov product), which will not readily form.

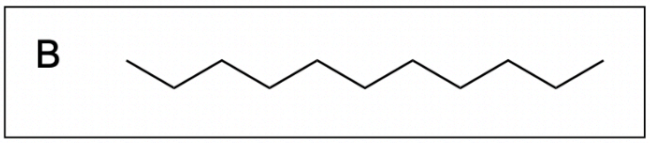


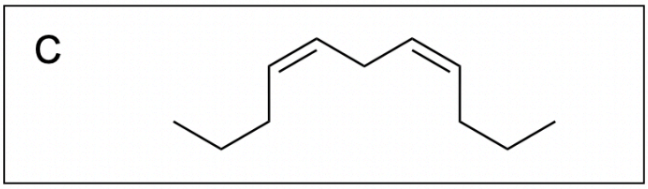
Chapter 3.2.3 – Hydrogenation of Alkenes

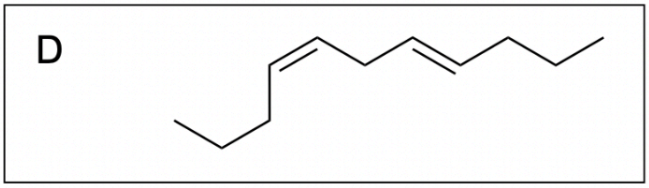
1. Which of the following is the product of the alkyne hydrogenation?







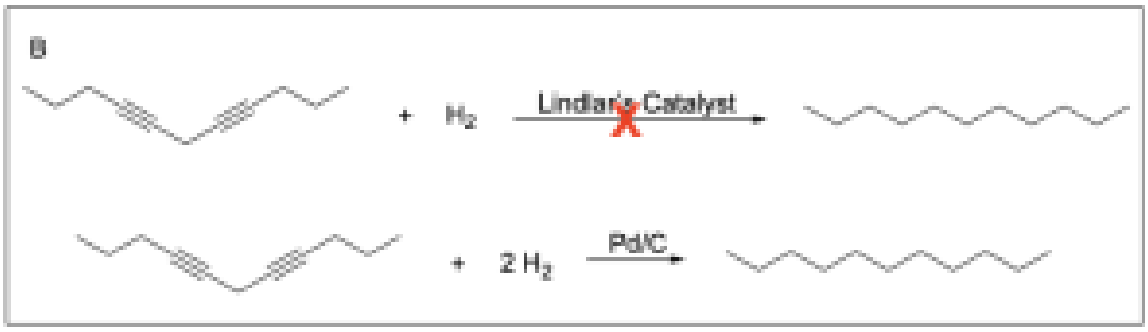




The correct answer to this question is **Option C.** Hydrogenation reactions involve the addition of hydrogen to an alkene or alkyne due to the presence of a metal catalyst. Lindlar's catalyst is a poisoned catalyst, so it **does not fully reduce the alkyne to an alkane**. It will instead reduce an alkyne to a *cis*-alkene.

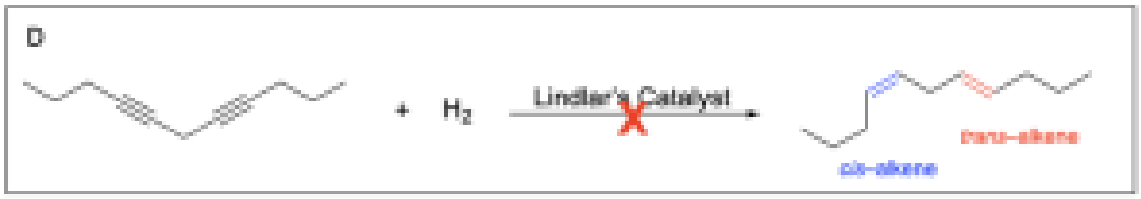
Option A is incorrect. While Option A does correctly show partial reduction to an alkene, it does not correctly show a *cis*-alkene as a product, and instead shows a *trans*-alkene. Note that it is possible to reduce an alkyne to a *trans*-alkene, but it is **not** under these conditions, and you will learn more about this is your second year organic chemistry class.

Option B is incorrect. Lindlar's catalyst does **not** fully reduce an alkyne to an alkane. To do this, you would need excess hydrogen gas in the presence of Pd/C catalyst (shown in the second reaction scheme below).



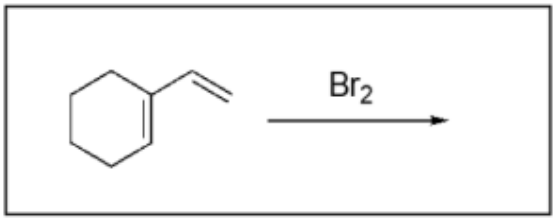
Option C is correct. Lindlar's catalyst will reduce an alkyne to a *cis*–alkene.

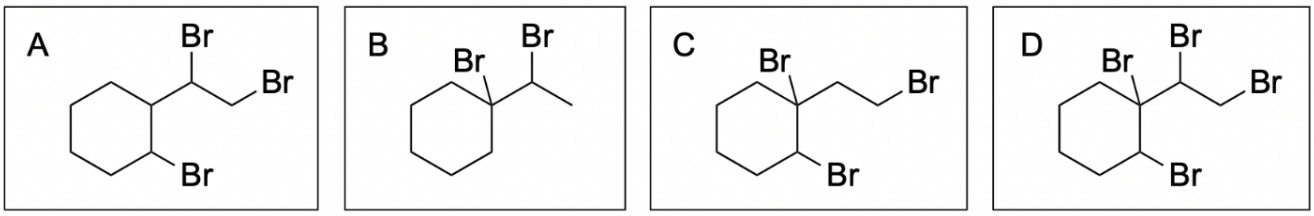
Option D is incorrect. While the alkene highlighted in blue has been correctly reduced to a *cis*–alkene, the alkene highlighted in red has not been correctly reduced. It should have been reduced to a *cis*, not a *trans*–alkene.



Chapter 3.2.4. – Halogenation of Alkenes

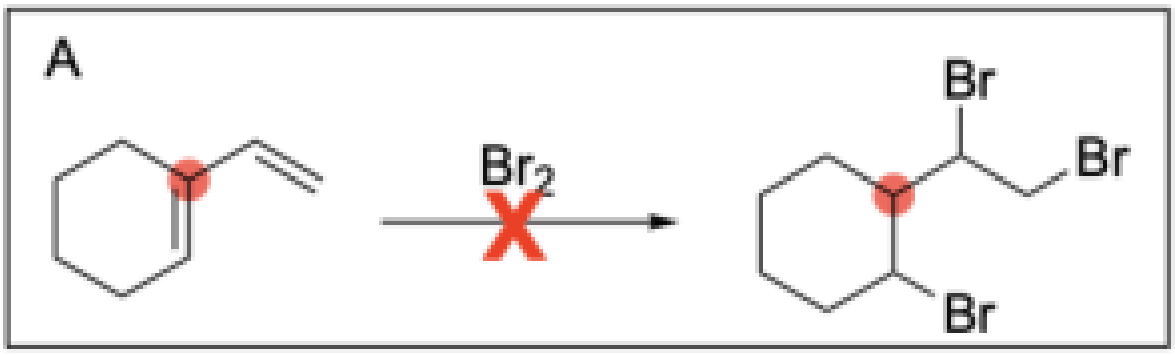
1. Which of the following is the product of halogenation?



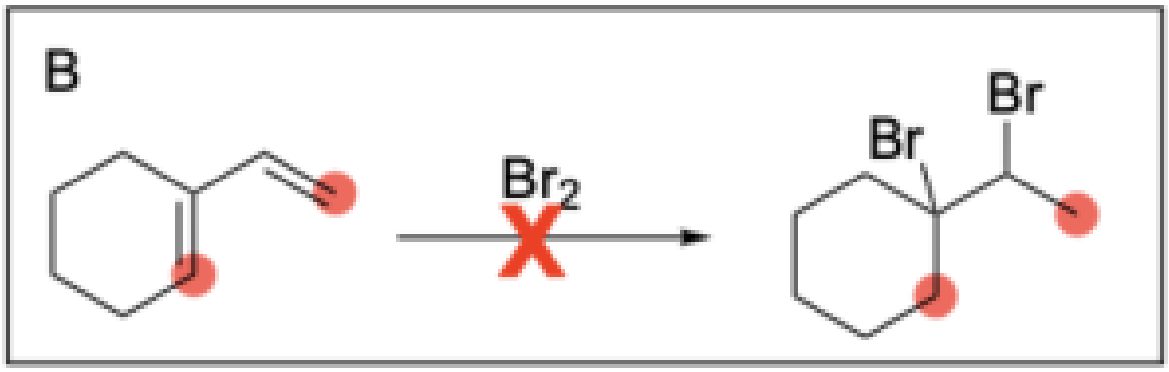


The correct answer to this question is **Option D.** Halogenation reactions involve the addition of a halogen across an alkene. A key difference between halogenation and hydrohalogenation is that there is no Markovnikov addition in halogenation reactions since the same atom is being added across the double bond.

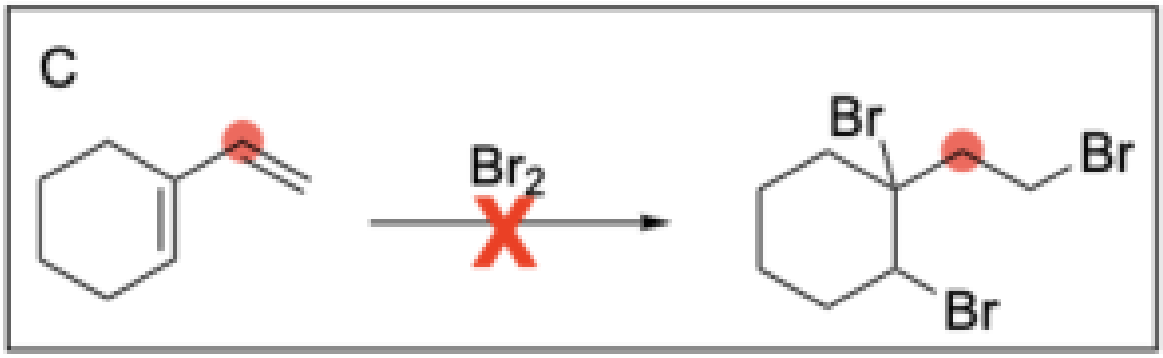
Option A is incorrect. In halogenation, the halogen will be added to **both** alkene carbons. The option illustrates this for the alkene on the right, but does not show this for the alkene on the left.



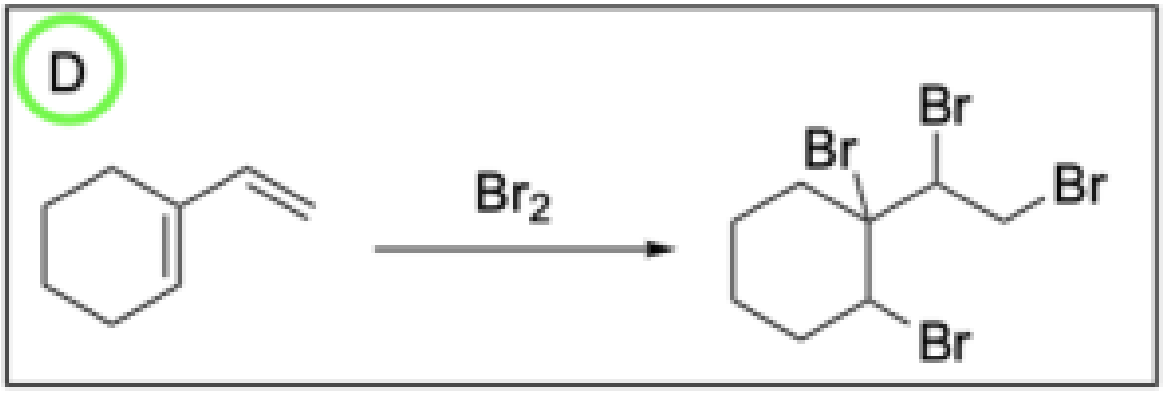
Option B is incorrect. In halogenation, the halogen will be added to **both** alkene carbons. The option does not illustrate this for either alkene.



Option C is incorrect. In halogenation, the halogen will be added to **both** alkene carbons. The option illustrates this for the alkene on the left, but does not show this for the alkene on the right.

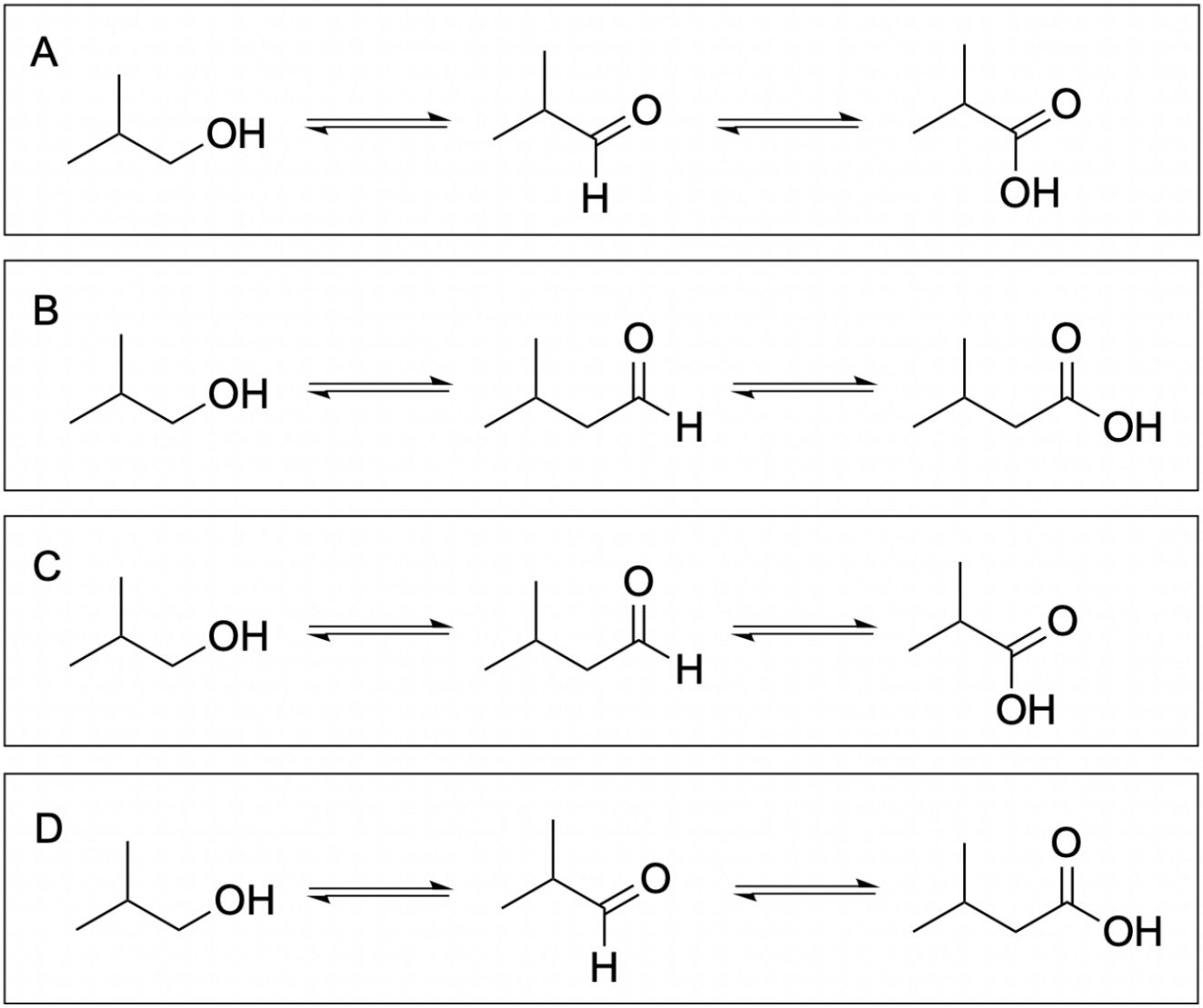


Option D is correct. In halogenation, the halogen will be added to **both** alkene carbons. This option illustrates this for both alkenes.

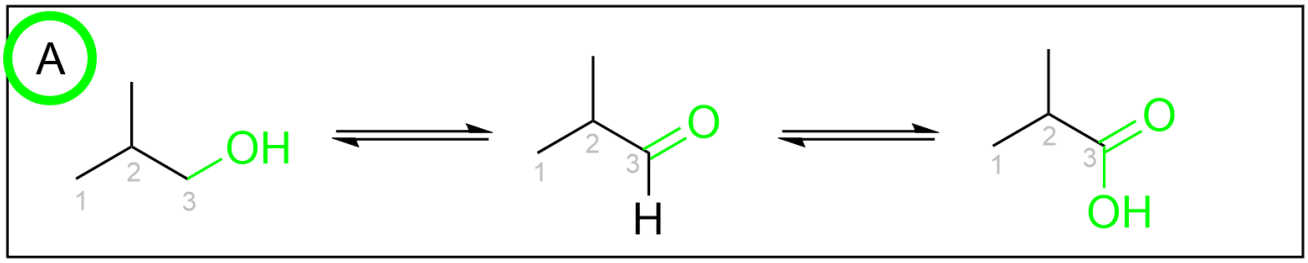


Chapter 3.3 – Oxidation of Alcohols

1. Which of the following is the correct alcohol oxidation-reduction reaction chain?

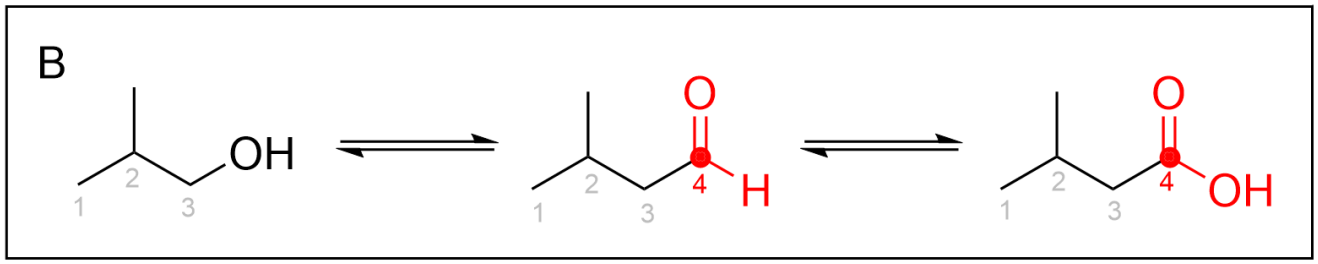


Option A is correct. In each oxidation event, the same carbon is becoming more oxidized, as it gains more bonds to oxygen. It starts as an alcohol with one C–O bond, becomes an aldehyde with two C–O bonds, and ends up as a carboxylic acid with three C–O bonds.

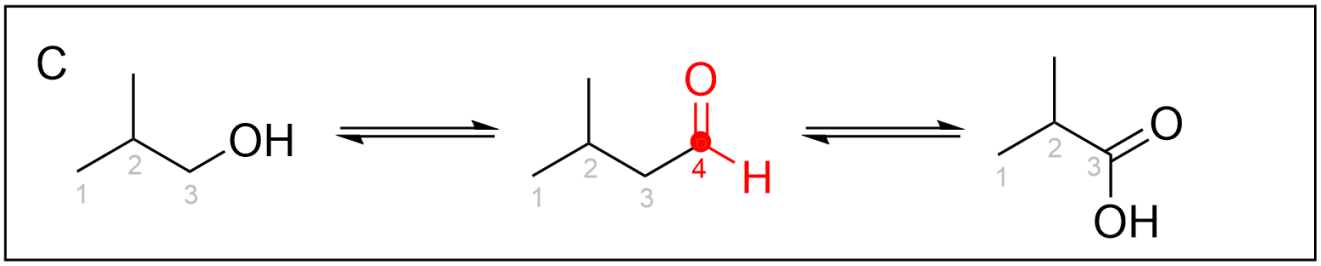


Option B is incorrect due to the number of carbon atoms in the aldehyde and carboxylic acid. Although at first glance the answer may also seem correct, what is important to notice is the **number of carbons** on each

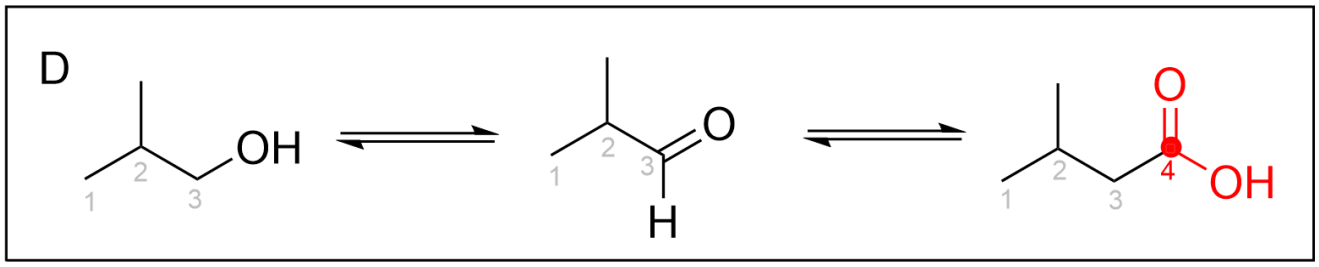
molecule. Oxidation reactions do not add any carbon atoms to a molecule. Taking a closer look at this reaction scheme, the starting molecule, propanol, has three carbons. However, the following aldehyde and carboxylic acids both contain four carbon atoms. Thus, this answer is incorrect as every molecule should only contain three carbon atoms.



Option C is incorrect due to the number of carbon atoms in the aldehyde. As the starting molecule, propanol, contains three carbons, each successive product should also contain only three carbons. Although the final product also contains three carbons, the middle aldehyde contains four carbons. Oxidation reactions do not add any carbon atoms to a molecule, and thus, this reaction scheme is impossible.



Option D is incorrect due to the number of carbon atoms in the carboxylic acid. As the starting molecule, propanol, contains three carbons, each successive product should also contain only three carbons. Although the aldehyde also contains three carbons, the final carboxylic acid contains four carbons. Oxidation reactions do not add any carbon atoms to a molecule, and thus, this reaction scheme is impossible.



2. Which statement about the oxidation of alcohols is false?

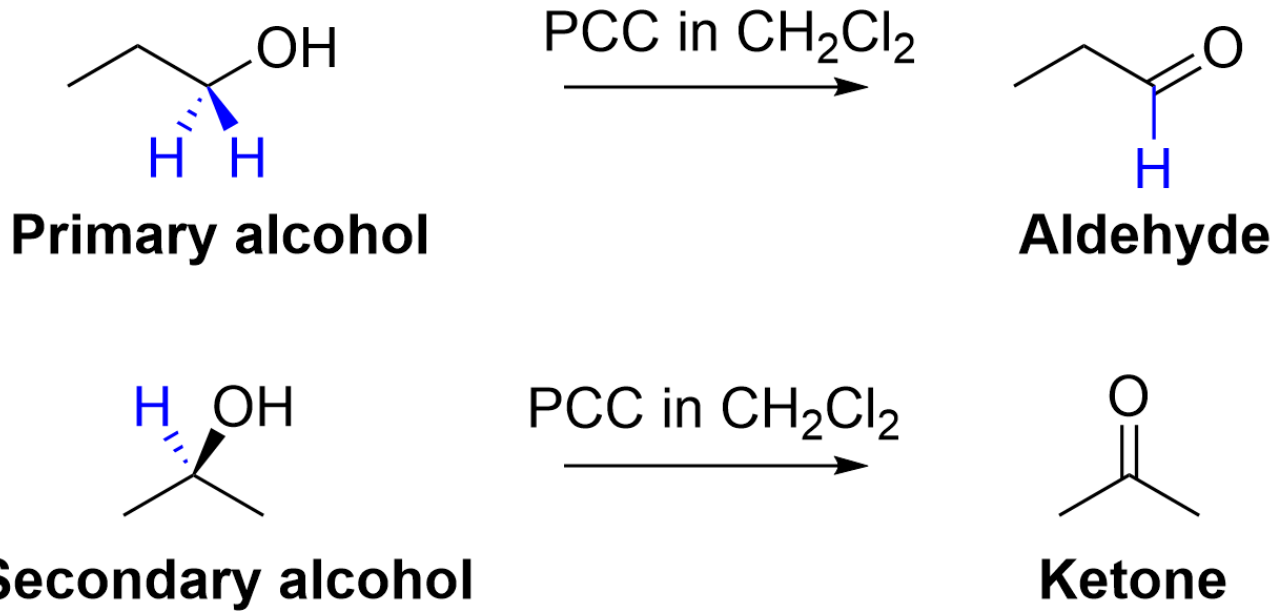
A. Primary alcohols can be oxidized to form either an aldehyde or a carboxylic acid.

B. Ketones and tertiary alcohols cannot be oxidized using $KMnO_4$ or $K_2Cr_2O_7$.

C. Primary alcohols can be oxidized using permanganate, dichromate, or PCC/ CH_2Cl_2.

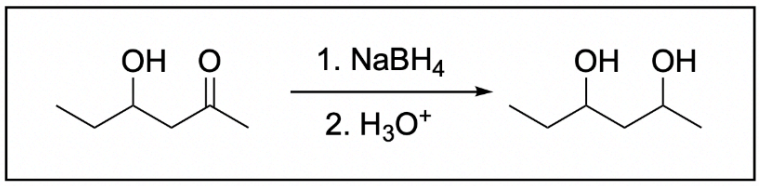
D. PCC/CH_2Cl_2 can be used to selectively oxidize secondary alcohols to aldehydes.

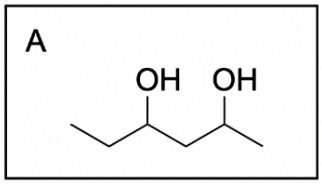
The correct answer is **Option D**. Although it is true that PCC in CH_2Cl_2 is a selective oxidizing agent, the wording of the statement makes it incorrect. Secondary alcohols **cannot** be oxidized into aldehydes and can only be oxidized into ketones. This is because of the number of carbons that the carbon on the C–O bond contains. The carbon in the C–O bond is only bonded to one hydrogen atom, as it is also bonded to two more carbon atoms. Thus, when oxidized with PCC in CH_2Cl_2, it loses that one hydrogen and will have no more C–H bonds. With no hydrogen, this classifies the functional group as a ketone rather than an aldehyde. It is only primary alcohols that can be oxidized into aldehydes. Refer to the diagram below for a more visual explanation of the oxidation of primary vs. secondary alcohols.

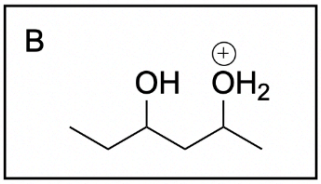


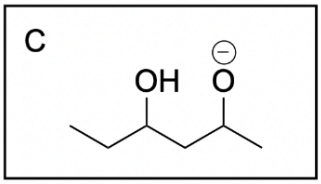
Chapter 3.4.1 – Sodium Borohydride Reduction of Carbonyls

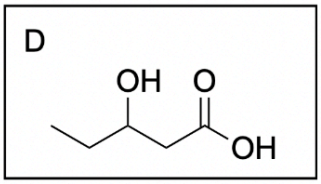
1. **Which of following is the intermediate state of the reaction?**



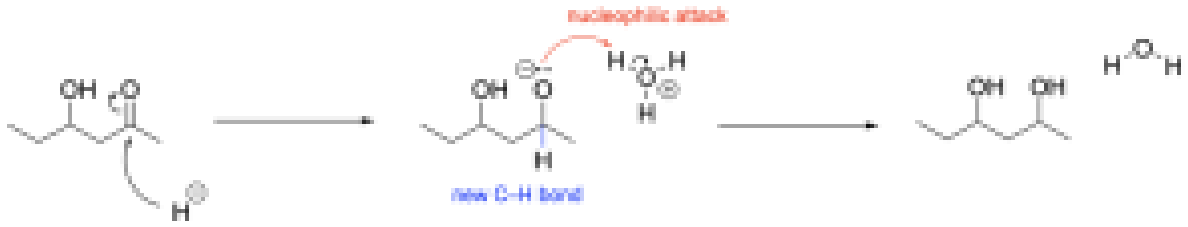






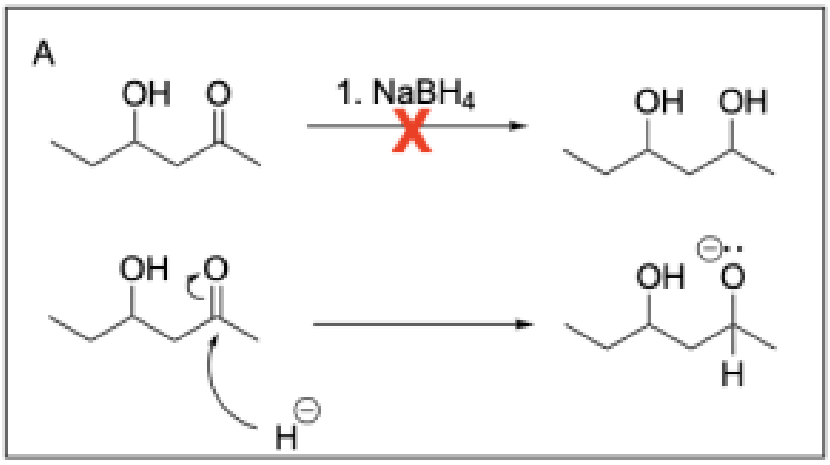


The correct answer to this question is **Option C.** Sodium borohydride is a reducing agent and will reduce a carbonyl to an alcohol by acting similar to the nucleophilic hydride ion. It will attack the electrophilic carbonyl carbon atom, which forms a C–H bond, while pushing electron density onto the oxygen, making it negatively charged. Adding hydronium provides a source of hydrogen atoms to protonate the negatively charged oxygen, yielding an alcohol.

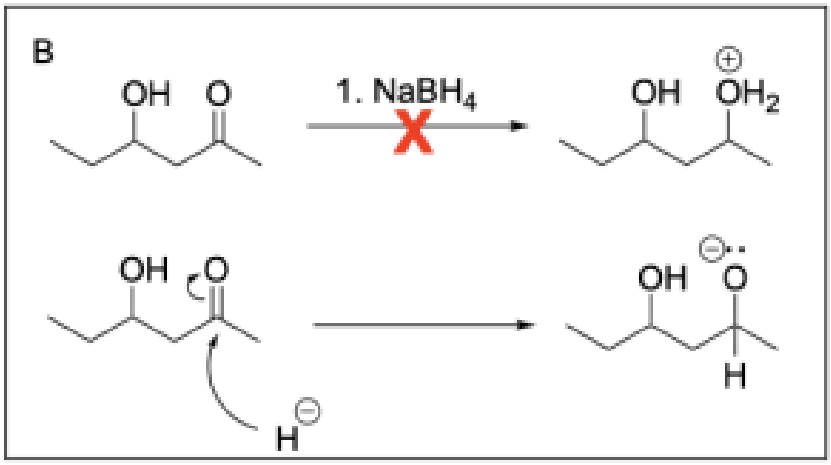


The intermediate in this reaction is present **after** sodium borohydride is introduced and **before** hydronium is introduced. These two steps are kept separate because the nucleophilic sodium borohydride would attack hydronium to protonate itself, leaving water as a by-product, and no reaction.

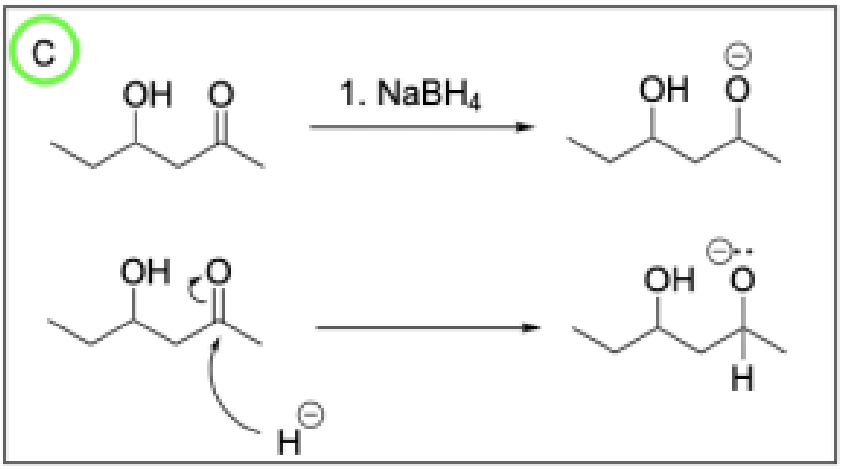
Option A is incorrect. This option illustrates the final product, **not** the intermediate product. The intermediate is an alkoxide, and sodium borohydride will not protonate the alkoxide. Instead, a proton source such as hydronium would need to be introduced **after** to obtain the final product.



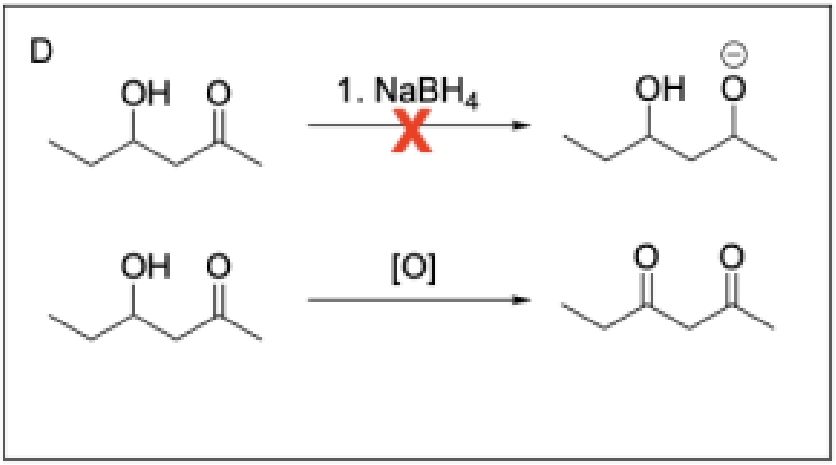
Option B is incorrect. Sodium borohydride is a reducing agent and will attack the electrophilic carbonyl carbon atom which pushes electron density onto the oxygen atom, generating a negatively charged alkoxide. There are no proton sources to protonate the oxygen atom, so the oxonium cation would not be generated, nor would it be an intermediate in this reaction.



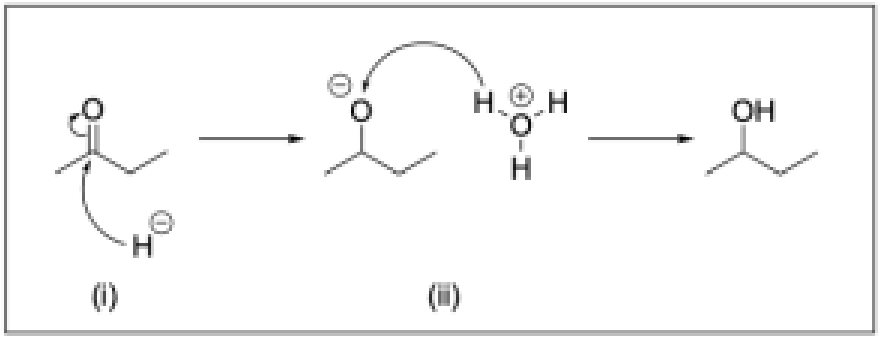
Option C is correct. Sodium borohydride is a reducing agent that will attack the electrophilic carbonyl carbon atom which pushes electron density onto the oxygen atom generating a negatively charged alkoxide as an intermediate.



Option D is incorrect. Sodium borohydride is a reducing agent, **not** an oxidizing agent. In addition, a ketone **cannot** be further oxidized to a carboxylic acid, as it would require the unfavourable breakage of a C–C bond. The secondary alcohol could be oxidized to a ketone, but the ketone could **not** be oxidized to a carboxylic acid.



2. Which of following statements about the mechanism is true?



A. Both (i) and (ii) are drawn correctly.

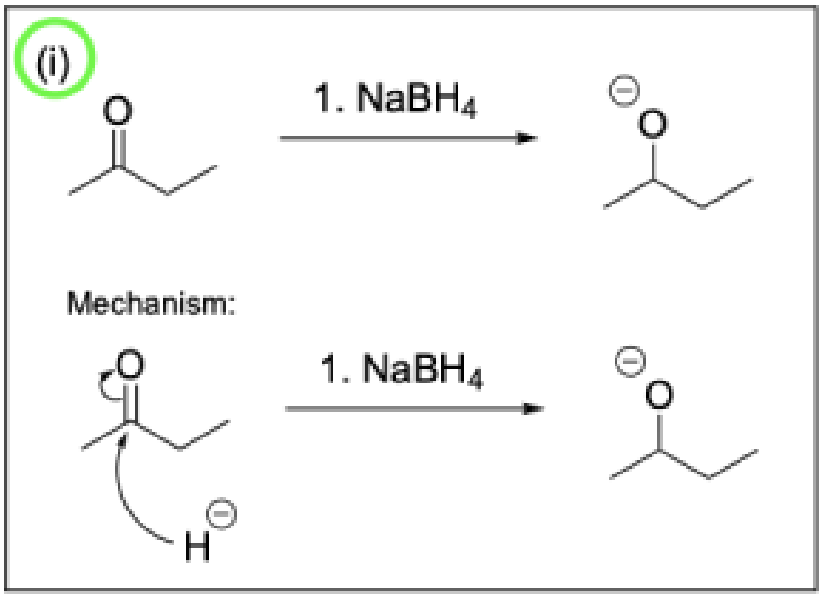
B. The step (ii) is drawn incorrectly.

C. The step (i) is drawn incorrectly.

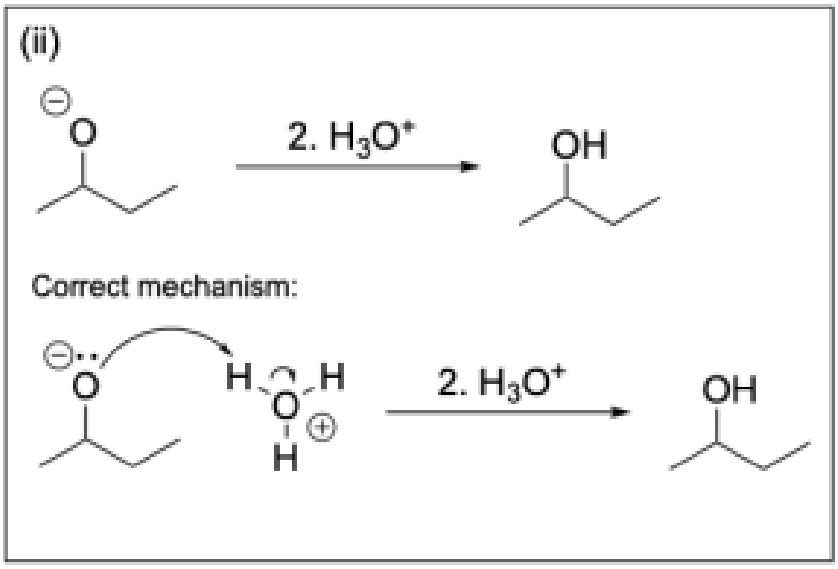
D. Both (i) and (ii) are drawn incorrectly.

The correct answer to this question is **Option B.** This mechanism shows sodium borohydride reduction of carbonyls. Sodium borohydride is a reducing agent that will reduce a carbonyl group to an alcohol by acting similar to the nucleophilic hydride ion. It will attack the electrophilic carbonyl carbon atom, which forms a C–H bond while pushing electron density to the oxygen making it negatively charged. Adding hydronium provides a source of hydrogen atoms to protonate the negatively charged oxygen, yielding an alcohol.

Step (i) is drawn **correctly.** The nucleophilic hydride will attack the electrophilic carbonyl, pushing electron density onto the oxygen forming an alkoxide and a new C–H bond.

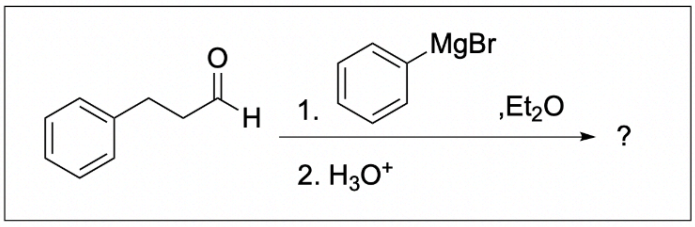


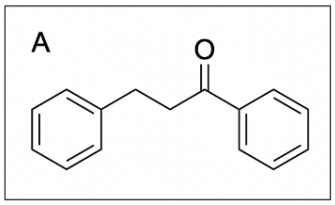
Step (ii) is drawn **incorrectly**. Hydronium is **not** nucleophilic and will **not** attack the alkoxide. Instead, the nucleophilic alkoxide will attack hydronium, which will protonate the alkoxide and form an alcohol and water. Chapter 3.1.1. discusses the direction of the arrows in organic reactions. The tail of the arrow should point to the electrophile while the head of the arrow should originate from the nucleophile. Therefore, Option B is the correct answer.

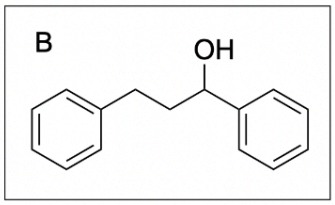


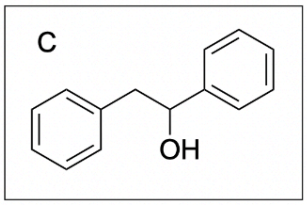
Chapter 3.4.2 – Grignard Reactions with Carbonyls

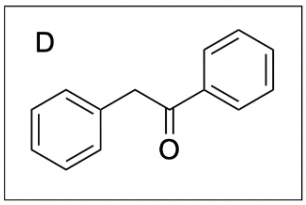
1. **Which of the following is the product of the reaction?**



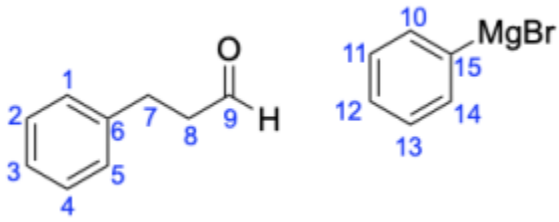




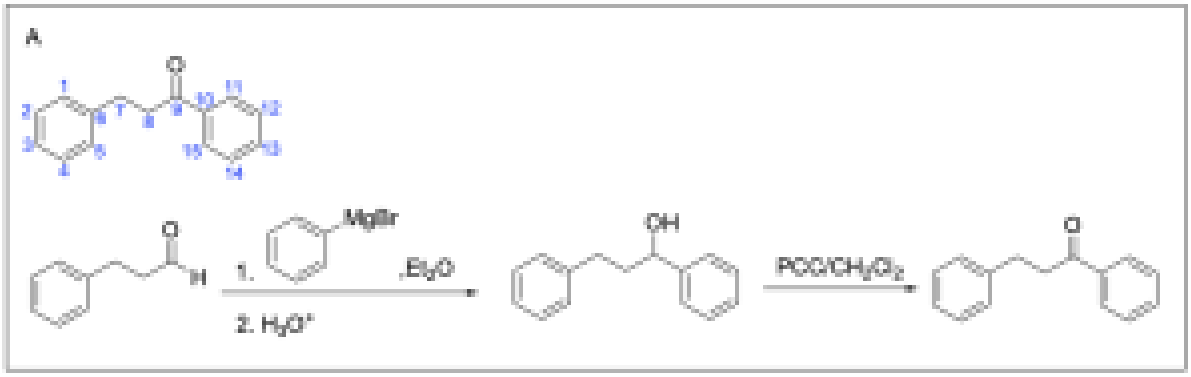




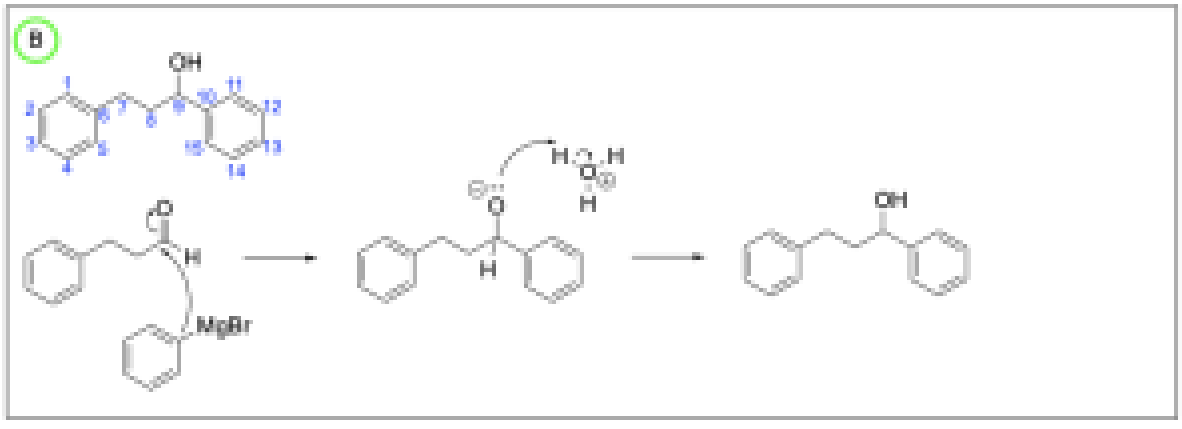
The correct answer to this question is **Option B.** This is a Grignard reaction, where the Grignard reagent (containing either magnesium chloride or magnesium bromide) is nucleophilic and attacks the electrophilic carbonyl forming new C–C bonds. The carbon atom adjacent to the magnesium bromide is nucleophilic and will perform the nucleophilic attack. Since Grignard reactions form new C–C bonds, the **first thing you should do is count the number of carbon atoms in the carbonyl–containing compound and in the Grignard reagent**, as this amount **must** add up to the number of carbon atoms in the product. There are 15 carbons in total from the reagents, so the product must contain 15 carbon atoms.



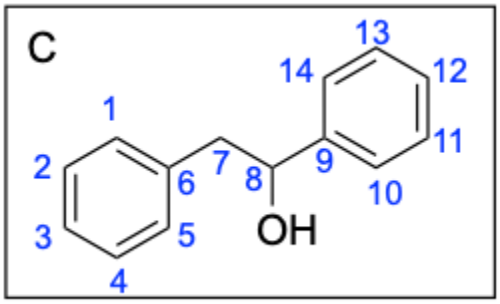
Option A is incorrect. While this compound contains the correct number of carbon atoms, a Grignard reaction reduces a carbonyl to an alcohol by forming a new C–C bond. This compound is fully oxidized and is **not** reduced. To obtain this compound after a Grignard reaction, you would need to add an oxidizing agent (such as PCC/CH_2Cl_2).



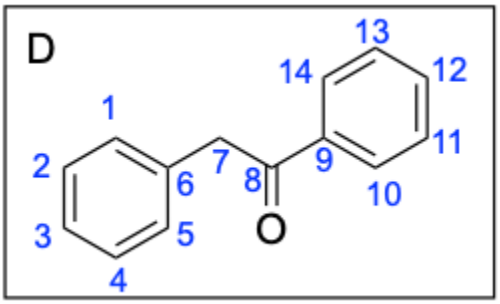
Option B is correct. A Grignard reaction reduces a carbonyl to an alcohol by forming a new C–C bond. This compound also contains the correct number of carbon atoms.



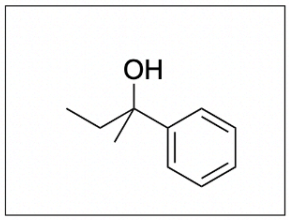
Option C is incorrect. While this option does show a reduced compound with a new C–C bond, it is **not** the correct amount of carbon atoms.

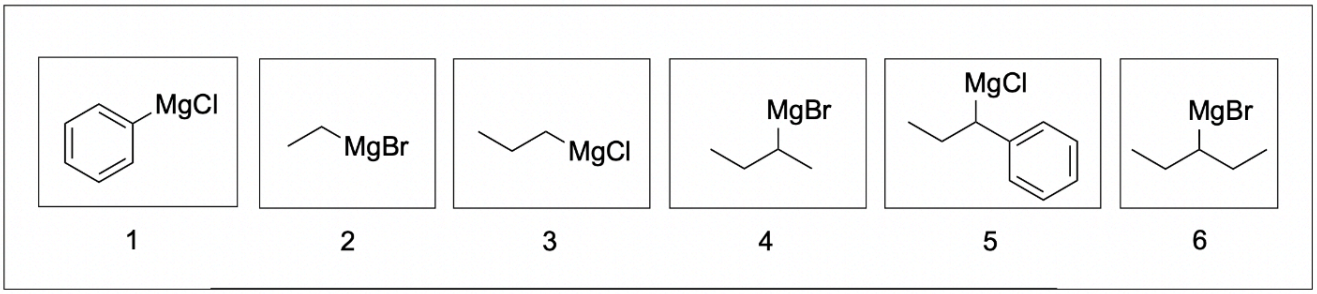


Option D is incorrect. A Grignard reaction reduces a carbonyl to an alcohol by forming a new C–C bond. This compound is fully oxidized and is **not** reduced. Additionally, this compound does **not** contain the correct amount of carbon atoms.



2. Given the following product, which of following are possible Grignard reagents in this reaction? (Select all that apply.)

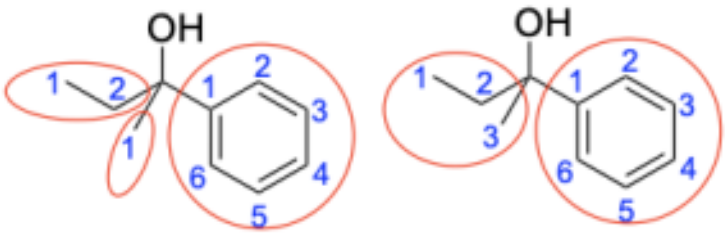




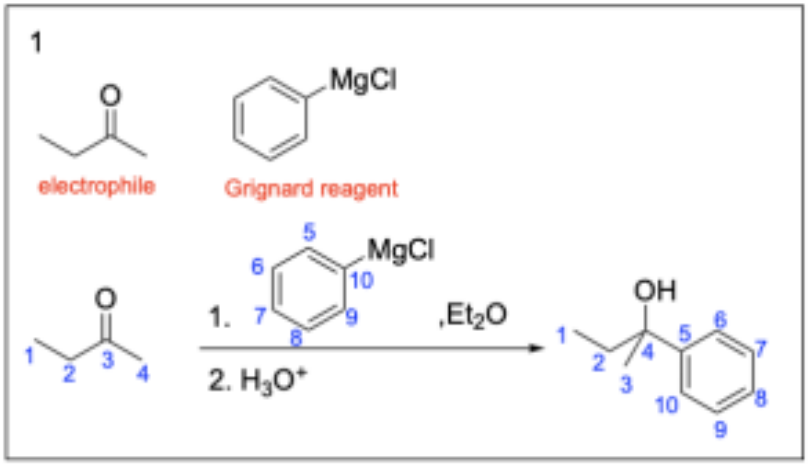
The correct answers to this question are **Compound 1, 2 and 5.** Grignard reactions form new C–C bonds,

so **it's important to count all of the carbon atoms in the starting materials to ensure they add up to the products**. Grignard reagents acts as nucleophiles and attack the electrophilic carbon center to form new C–C bonds. The addition of hydronium protonates the alkoxide to form an alcohol.

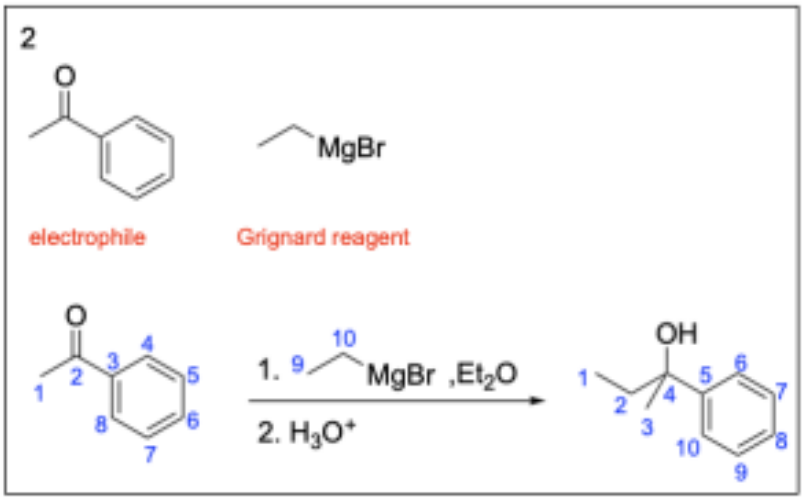
To identify potential Grignard reagents, start from the carbon atom bonded to the hydroxide (since this carbon atom was initially the electrophilic carbonyl), and treat each carbon group as a "branch". For example, the compound can contain 3 carbon branches with 2, 1 and 6 carbon atoms respectively. The compound can also contain 2 branches with 3 and 6 carbon atoms respectively. Note that there are various combinations of "branches" that can be made, but the number of carbon atoms in the Grignard reagent **must** add up the number of carbon atoms in one of those branches since the Grignard reagent contains the exact number of carbon atoms being added to the compound. An example of 2 combinations of "branches" is shown in the photo below.



Option 1 is correct, as it is a possible Grignard reagent. It contains 6 carbon atoms in an aromatic structure like the product contains.

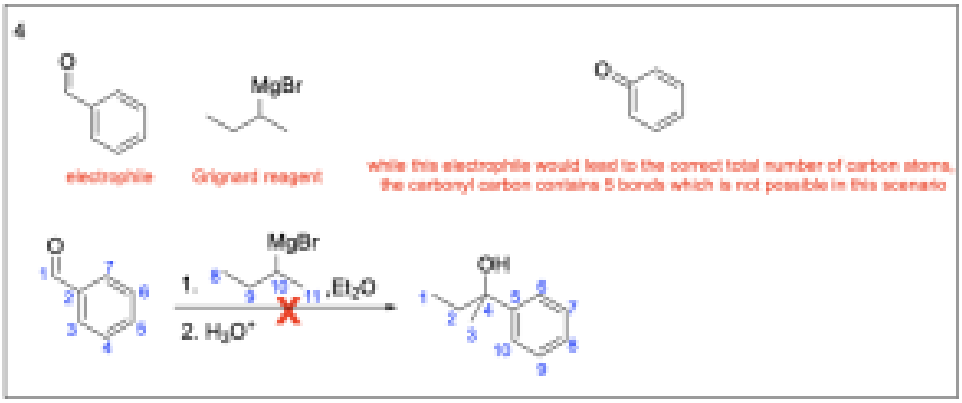


Option 2 is correct, as it is a possible Grignard reagent. It contains 2 carbon atoms in a linear structure like the product contains.

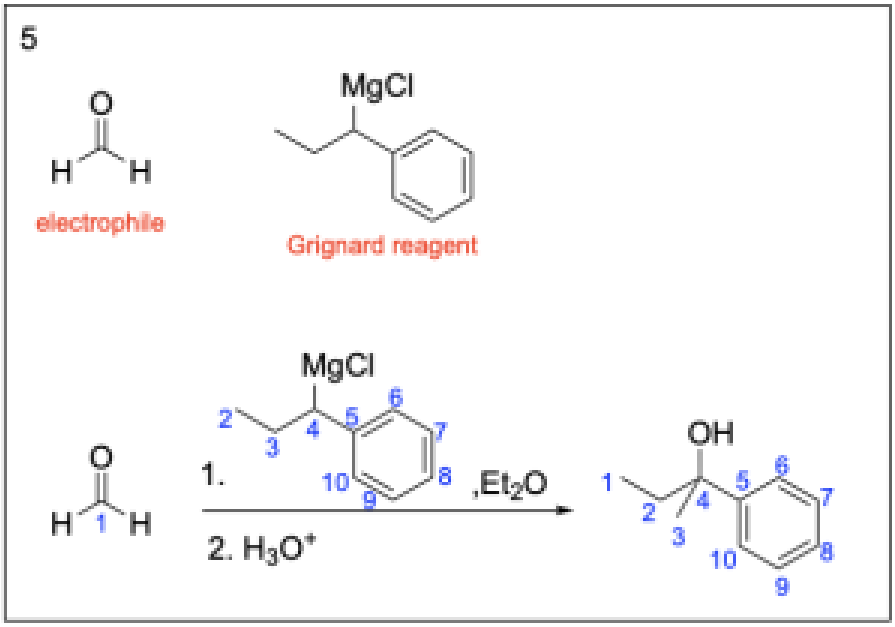


Option 3 is **not** a possible Grignard structure. It contains 3 carbon atoms in a linear structure, while the product does not contain any "branches" with 3 carbon atoms in a linear structure.

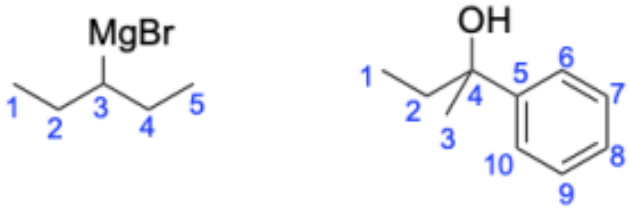
Option 4 is **not** a possible Grignard structure. The electrophile needed to obtain the end product with the given Grignard reagent is shown on the top–left corner, and it would lead to a product that contains an extra carbon atom. You would not be able to reduce the size of the electrophile because that would lead to a compound that contains 5 bonds to carbon (shown on the top–right corner), which is not possible.



Option 5 is correct, as it is a possible Grignard reagent. It contains 9 carbon atoms (6 are in an aromatic structure while 3 are in a linear structure) like the product contains.

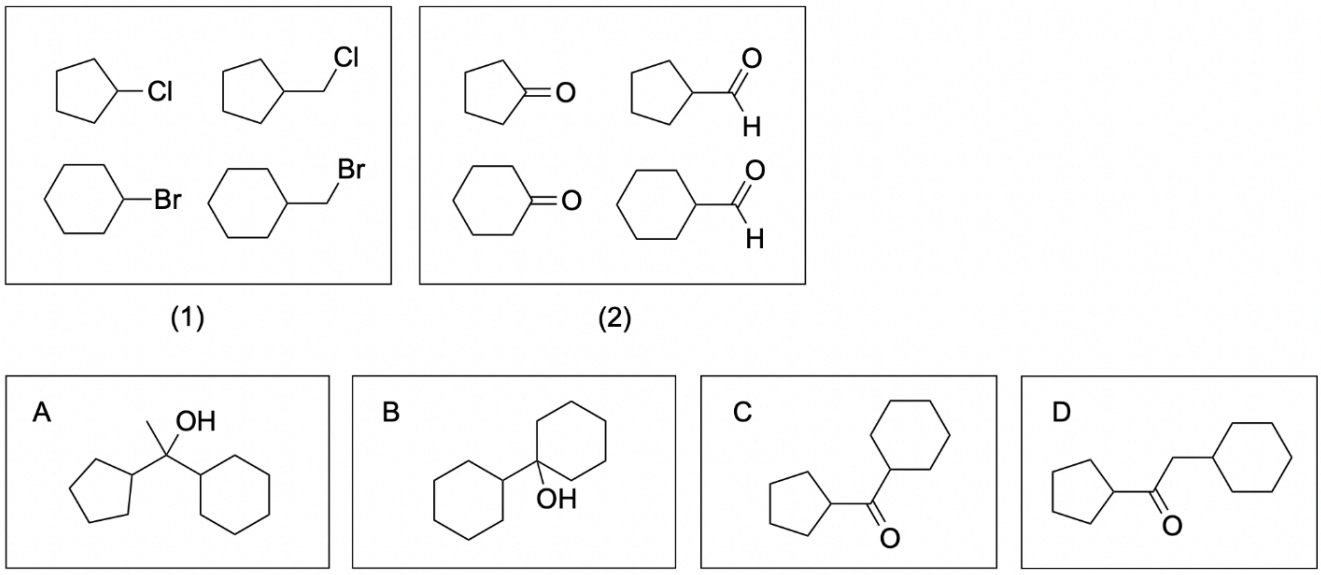


Option 6 is **not** a possible Grignard reagent. It contains 5 carbon atoms, and we know the final product must contain a 6–carbon benzene ring. That means that there would be at least 11 carbon atoms in the final product. But, the final product only has 10 carbon atoms, so this is not possible.

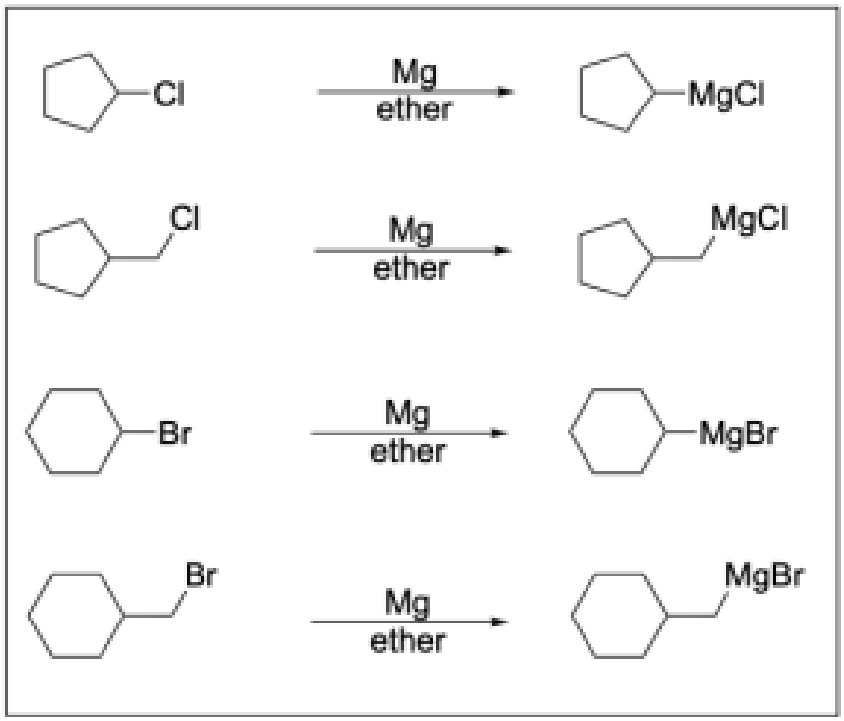


Chapter 3.4.3 – Comparing Sodium Borohydride Reductions and Grignard Reactions

1. **Use group (1) to make Grignard reagent by reacting with Mg in diethyl ether, and then perform Grignard reaction with group (2). The product is then further reacted with KMnO4. Which of following molecules is not a possible final product?**



The correct answers to this question are **Option B, C and D.** Reacting an alkyl halide with magnesium in diethyl ether produces a Grignard reagent. By reacting all alkyl halides in group (1) with magnesium in diethyl ether, you will get the following Grignard reagents:



The question then tells us that the group 1 Grignard reagents are reacted with the carbonyl–containing compounds in group 2. The Grignard reagent is nucleophilic and attacks the electrophilic carbonyl forming

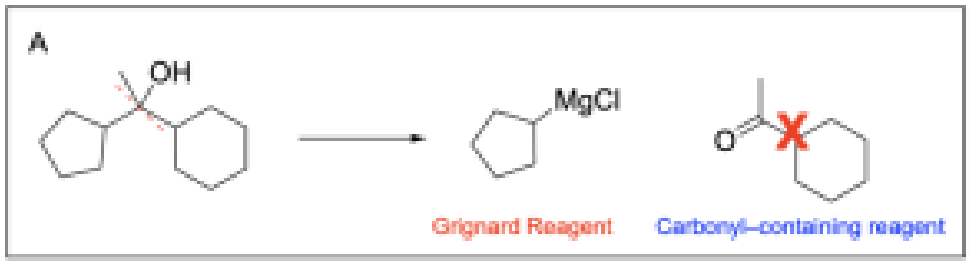
new C–C bonds. The addition of hydronium will provide a proton source to form a reduced alcohol. Therefore, the products from step 2 would include an alcohol with a larger carbon chain.

The last piece of information the question tells us is that the product of the Grignard reaction is reacted with $KMnO_4$. This is a strong oxidizing agent, and it can oxidize primary and secondary alcohols formed from the Grignard reaction in the previous step. Note that tertiary alcohols **cannot** be oxidized, so tertiary alcohols formed from the Grignard reactions will remain as is after being reacted with $KMnO_4$.

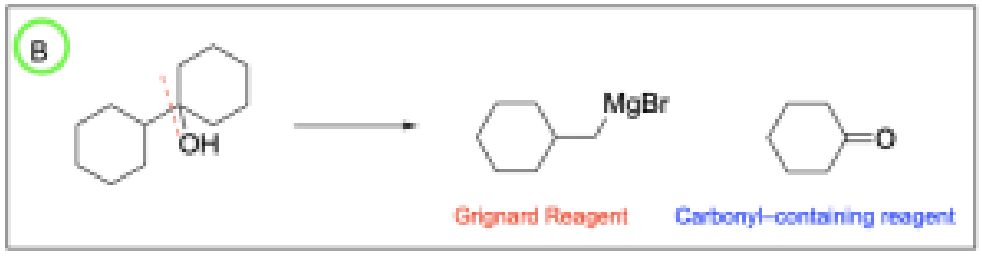
The first thing you should always do with Grignard reactions is count the number of carbon atoms. Since there are 16 possible products formed when reacting groups 1 and 2, it's best to first check if the number of carbon atoms in the starting materials add up to the number of carbon atoms in the product, as this can allow you to quickly eliminate some options. The **maximum** number of carbon atoms possible with the various reagents is 14, and all options have less than 14 carbon atoms, so the carbon count looks good.

The next thing you should do is "break up" the end product to try and decipher the reagents. You can do this by splitting the molecule in half where the alcohol/carbonyl is, because the Grignard reagents will react with the carbonyl–containing compound to form the alcohol.

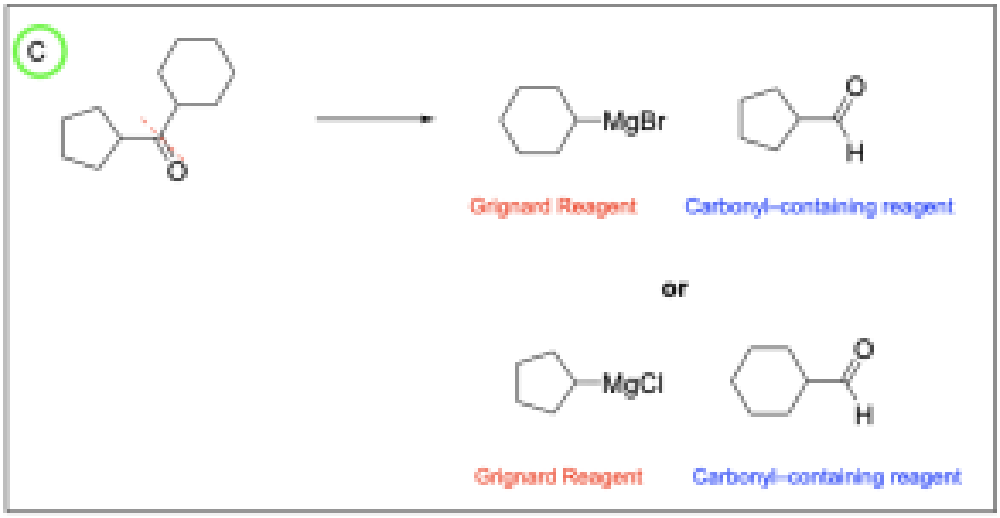
Option A is incorrect. When "breaking up" the end product to decipher the reagents, the only possible Grignard reagent is the first, but the number of carbon atoms in the carbonyl–containing compound does not match any of the options listed.



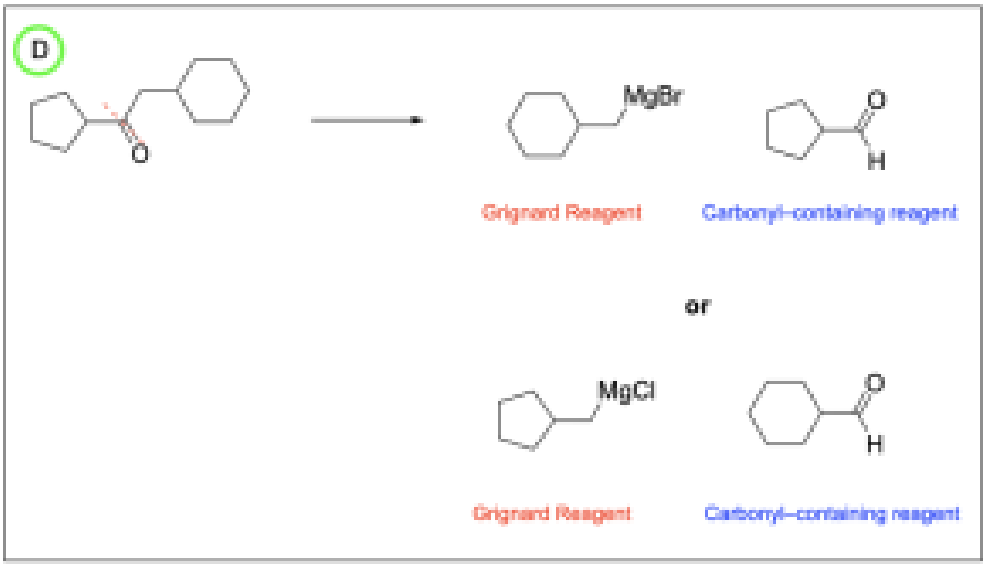
Option B is correct. When "breaking up" the end product to decipher the reagents, both the Grignard reagent and the carbonyl–containing compound needed are listed as options in groups 1 and 2.



Option C is correct. When "breaking up" the end product to decipher the reagents, both the Grignard reagent and the carbonyl–containing compound needed are listed as options in groups 1 and 2, and there are 2 possible combinations that can lead to the end product.



Option D is correct. When "breaking up" the end product to decipher the reagents, both the Grignard reagent and the carbonyl–containing compound needed are listed as options in groups 1 and 2.



Chapter 3.5 – Reactions of Carboxylic Acids and Derivatives

1. Which of the following statements is false about the synthesis of carboxylic acid?

A. The carboxylic acid can be synthesized by either alcohol oxidation under $K_2Cr_2O_7$ or reacting Grignard reagent with CO_2.

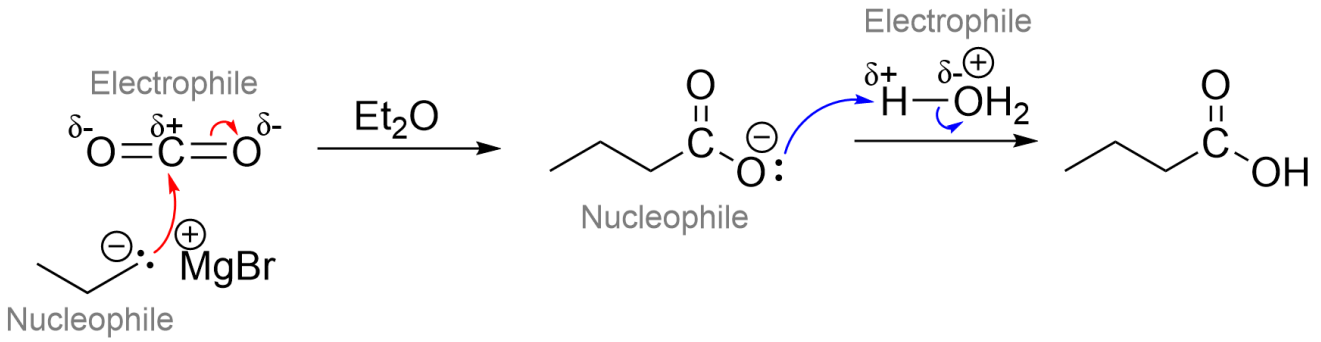
B. When making carboxylic acid by reacting CO_2 and Grignard reagent, the CO_2 and H_3O^+ act as electrophiles.

C. When making carboxylic acid by reacting CO_2 and Grignard reagent, the Grignard reagent and

carboxylate anion act as nucleophiles.

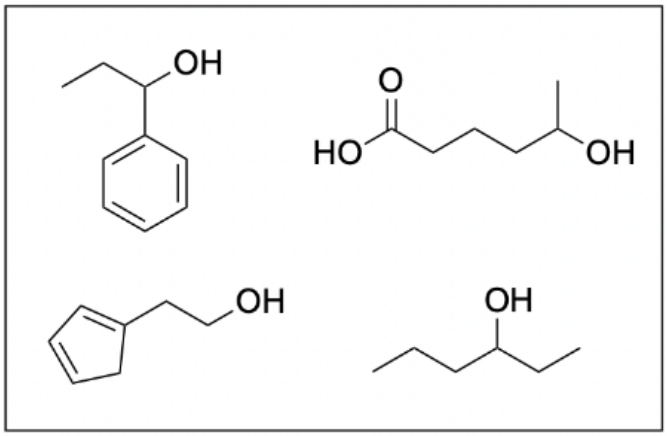
D. When making carboxylic acid by reacting CO_2 and Grignard reagent, the CO_2 and carboxylate anion act as nucleophiles.

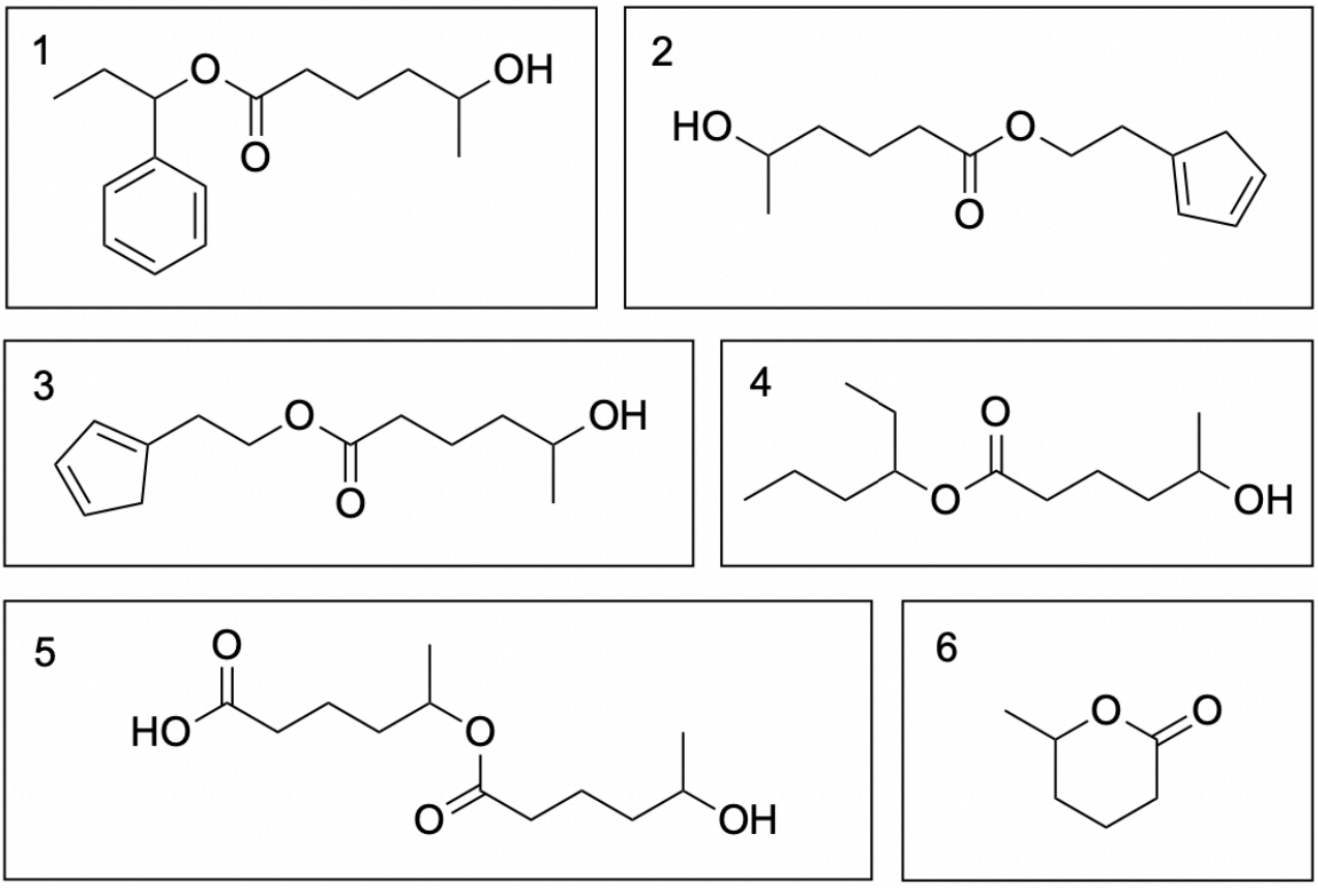
Option D is the correct answer to this question, as the statement is false. The easiest way to determine the validity of these statements is to draw out mechanism of carboxylic acid formation with CO_2 and a Grignard reagent. In this reaction, the Grignard reagent acts as a nucleophile and attacks CO_2, hence, this statement is false. Recall that the central carbon in CO_2 is partially positive due to the electronegative oxygens. This makes it an electrophile in this step, as it is attacked by the nucleophilic Grignard reagent.



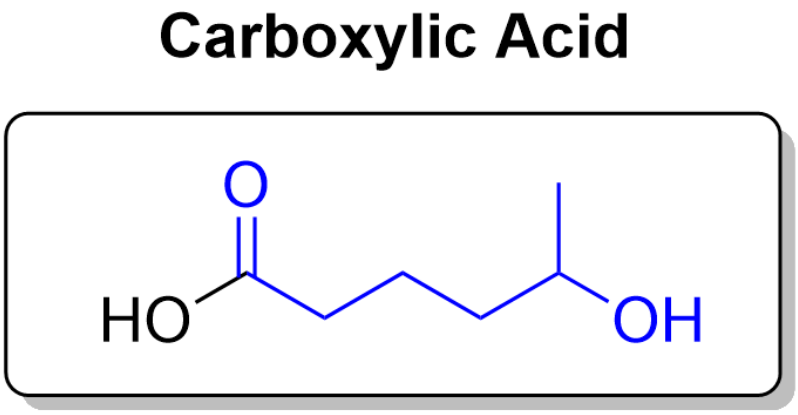
Answers A, B, and C are also true statements, meaning they are not the correct answer. CO_2 can be oxidized by $K_2Cr_2O_7$, a non-selective oxidizing agent, to a carboxylic acid. It can also react with a Grignard reagent (seen above) to form a carboxylic acid. In this reaction, the CO_2 and H_3O^+ act as the electrophiles, as both have areas of electron-deficiency, as seen by the partial positive charges. On the contrary, the Grignard reagent and carboxylate anion act as nucleophiles due to the presence of lone pairs and negative charges.

2. Given the following molecules in the system, which of following are possible products under heat and acidic conditions?



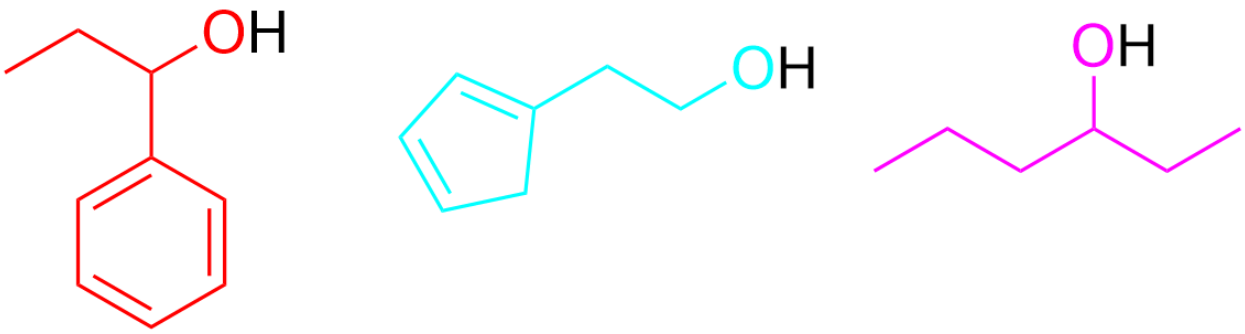


All six molecules are correct and can form under heat and acidic conditions. When determining the products of an acid-catalyzed esterification reaction, the first thing you should do is determine the structure of the carboxylic acid that will retain after esterification. This can allow you to quickly eliminate options that do not have the correct structure. As seen below, the structure in blue will be conserved in every ester product.

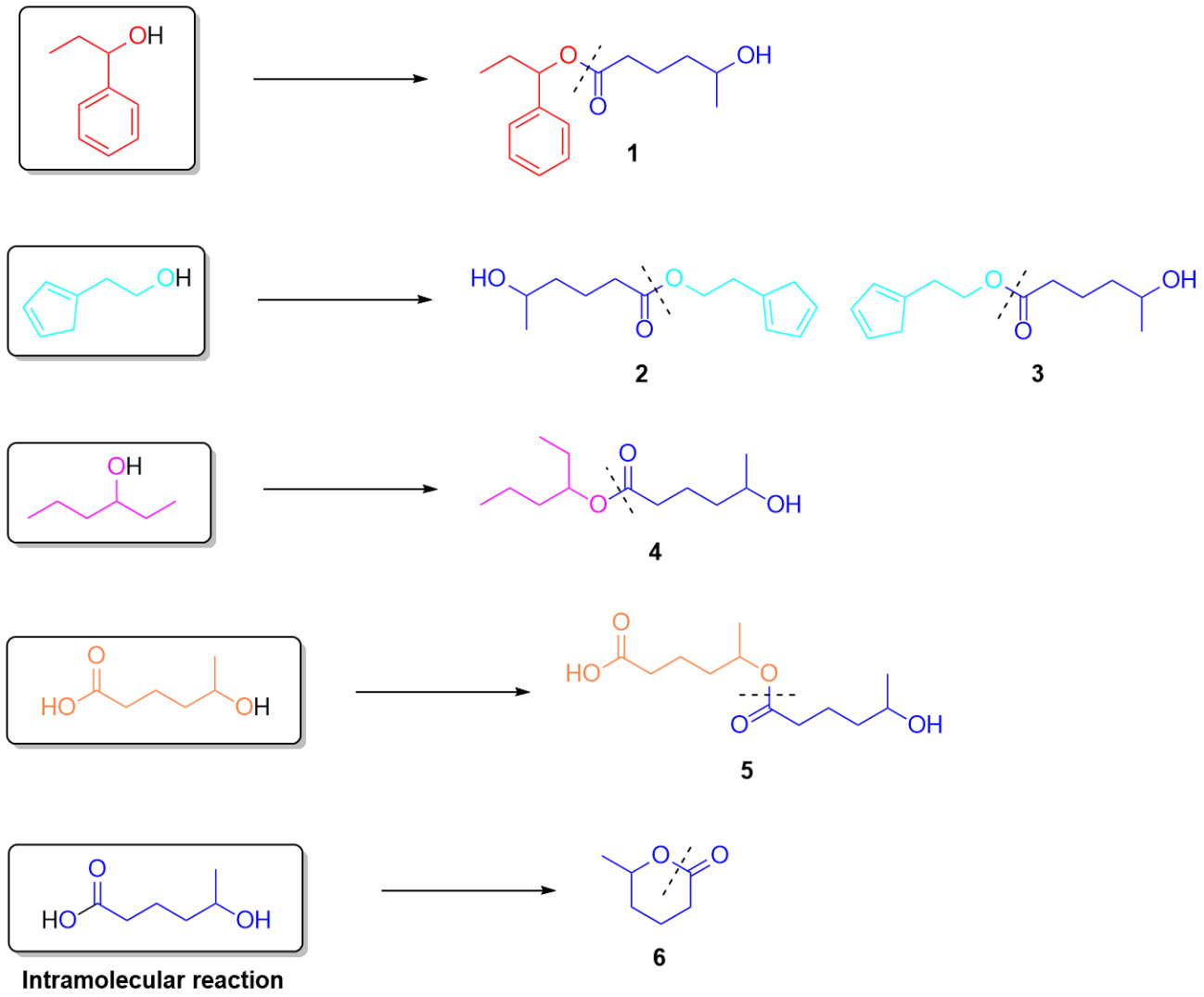


Products of esterification will always contain the structure in blue from the carboxylic acid

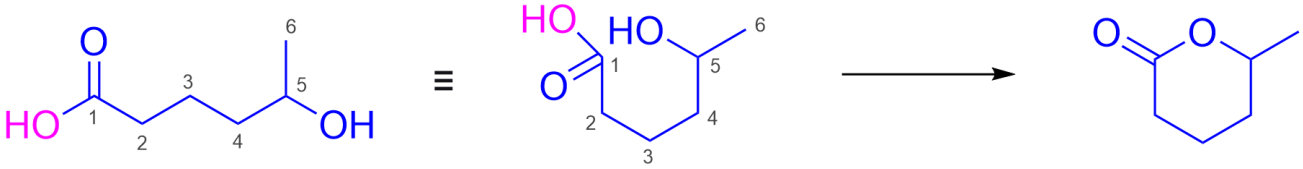
The other three molecules are alcohols, meaning they can react with the carboxylic acid to form an ester. Each compound can donate their alkyl chain to react and attach itself onto the end of the carboxylic acid. The coloured parts of the structure below indicate what will be added to the final product.



An easy way to determine whether the given options are real products is to cut through the COO (carboxylate) group and look at the carbon structure on each side. If one side matches with the carboxylic acid, and the other side matches with the carbon structure of the alcohol, then the product can be formed. For example, the first ester conserves its red carbon structure from the alcohol and the blue structure from the carboxylic acid. Thus, this is a possible product in this reaction. The same can be done for every other ester product, as shown below. Molecules 2 and 3 are the same molecule, except mirrored horizontally.

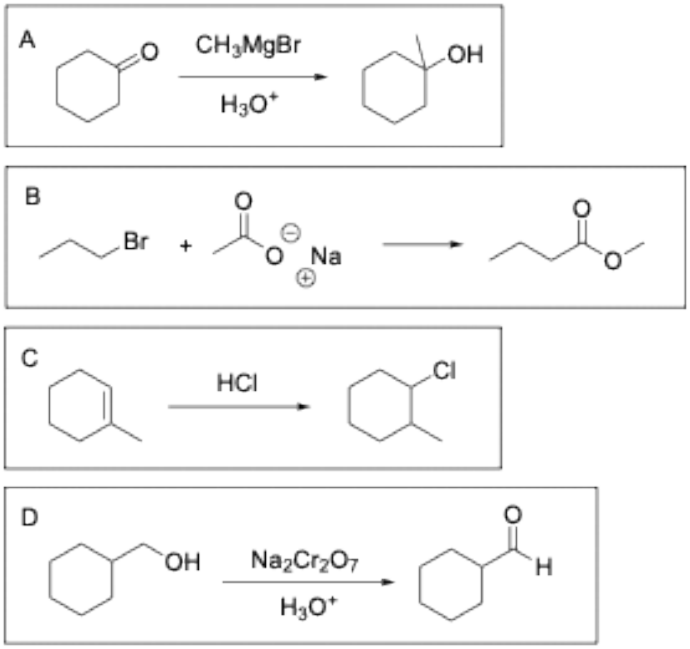


Molecules 5 and 6 may be difficult to identify as correct as these show the carboxylic acid reacting with itself. As the carboxylic acid contains an alcohol on the other side of the compound, it is possible for it to react with another molecule of itself to form Molecule 5. It can also react intramolecularly with itself to form a ring, as seen in Molecule 6. The ring may be difficult to visualize at first– one way to understand how it forms is to imagine the two -OH groups on each side of the carboxylic acid overlapping with each other to form the singular oxygen (found in between the two carbons). Refer to the image below for a visual explanation of the ring forming process.

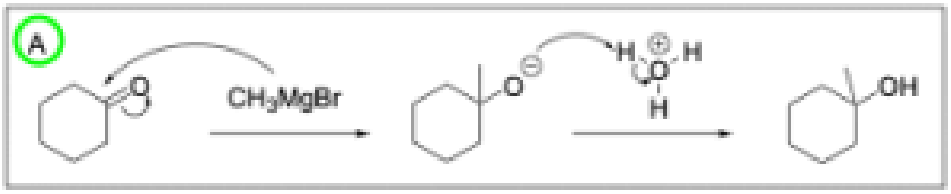


Chapter 3.6 – Synthesis

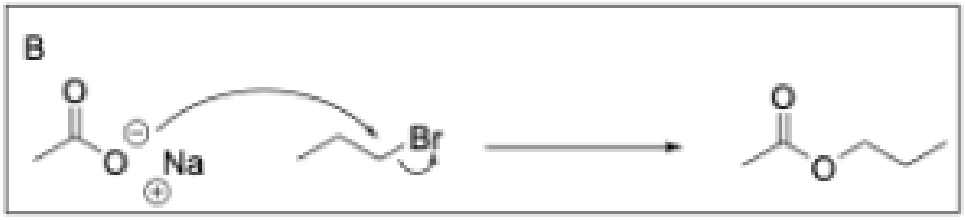
1. **Which of the following reactions are drawn correctly?**



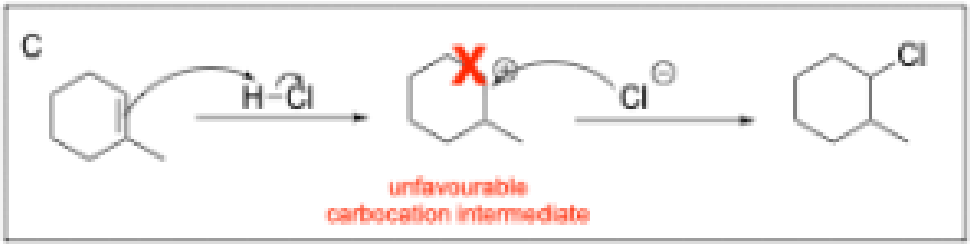
Option A is correct. When reacting a carbonyl–containing compound with a Grignard reagent in the presence of a proton source (such as hydronium), the carbon chain is elongated and the carbonyl is reduced to an alcohol.



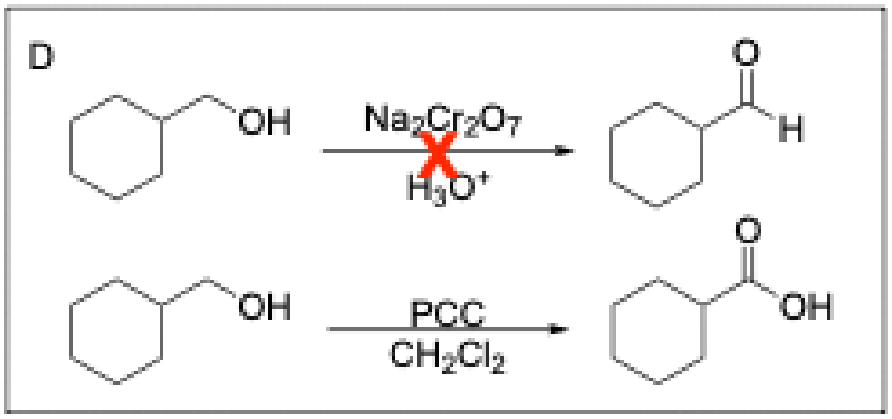
Option B is incorrect. When reacting an alkyl halide with a carboxylate, this is an S_N2 reaction where the negatively charged oxygen will attack the electrophilic alkyl halide, kicking out the halide and creating an ester. While the product is an ester, it is not the correct product. The carbonyl portion of the carboxylate **does not change**, so there should be **no chain elongation** from that side. This is because the negatively charged oxygen is the nucleophile and will attack the electrophilic alkyl halide to grow the chain/undergo a reaction.



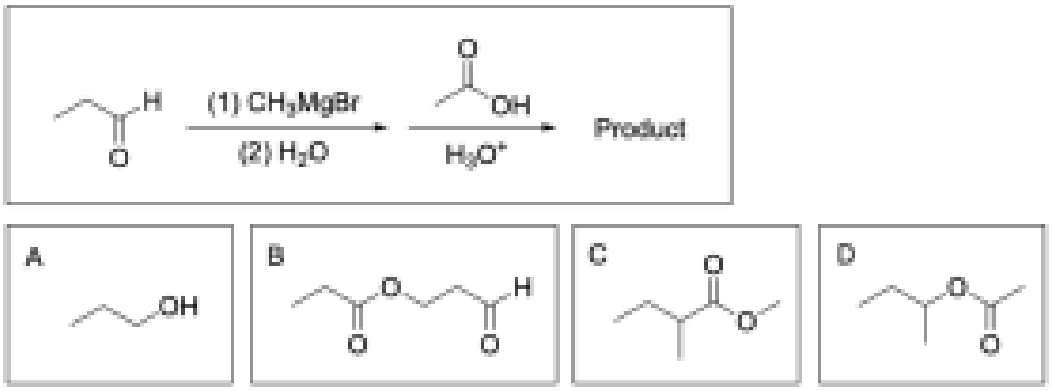
Option C is incorrect. This is a hydrohalogenation reaction where an alkene will attack an electrophilic hydrogen halide to form a new C–X bond. With unsymmetric alkenes, there are 2 products: the Markovnikov and Anti–Markovnikov product. The Markovnikov product is also known as the major product since it has a more favourable/stable carbocation intermediate. This product is the Anti–Markovnikov product, and while it is possible, it is not likely.



Option D is incorrect. This is an oxidation reaction involving a primary alcohol. Primary alcohols can be oxidized to aldehydes or carboxylic acids depending on the oxidizing agent used. PCC/CH_2Cl_2 is poisoned, so it will oxidize primary alcohols to aldehydes, while stronger oxidizing agents like $KMnO_4$ or $NaCr_2O_7$ will oxidize a primary alcohol to a carboxylic acid. This reaction scheme shows a primary alcohol being oxidized to an aldehyde with a strong oxidizing agent which will not occur. Instead, a carboxylic acid would be produced. A poisoned oxidizing agent would be needed to obtain an aldehyde.



2. What is the product of the following reaction scheme?

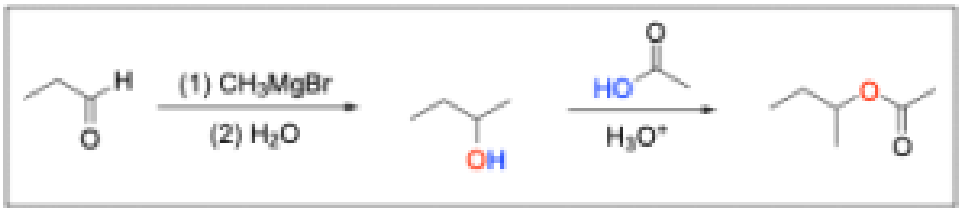


The correct answer is **Option D**. This multi–step synthesis question involves an aldehyde undergoing a Grignard reaction, and that product undergoing esterification. Whenever you see a synthesis question, it is best to draw out the mechanism to identify the product.

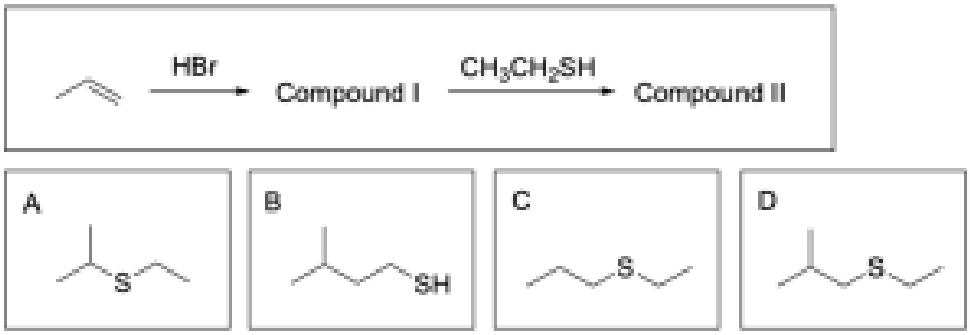
When the aldehyde undergoes a Grignard reaction, an alcohol with an elongated carbon chain will form.

The next step is acid–catalyzed esterification, where the alcohol and carboxylic acid join to form an ester under acidic conditions. The oxygen atom from the alcohol is the oxygen atom present in the ester (shown in red), while the other atoms form water as a by–product (shown in blue).

A breakdown of the products and intermediates is shown below.



3. Thiols (R–SH) can act as a nucleophile. What is the expected final product (compound II) in this reaction?

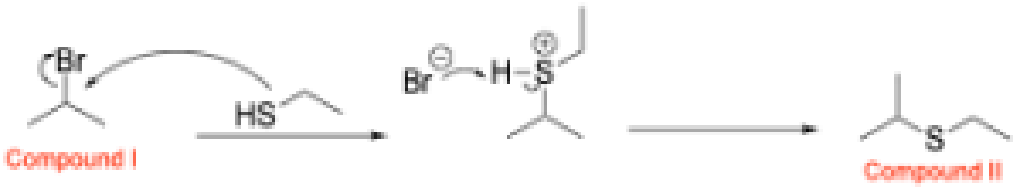


The correct answer is **Option A.** This multi–step synthesis question involves an alkene undergoing

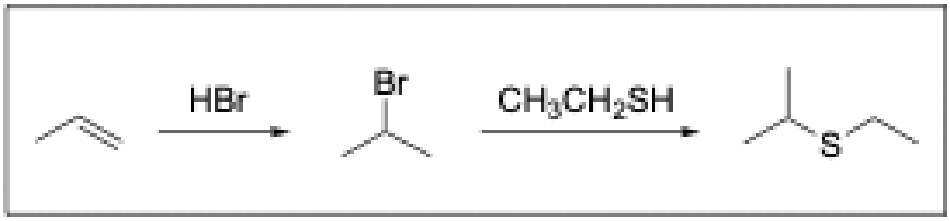
hydrohalogenation to yield a hydrogen halide (Compound I), while Compound I is then reacted with a thiol to yield a sulfide/thioether (Compound II). Whenever you see a synthesis question, it is best to draw out the mechanism to identify the product.

As previously stated, the first step is hydrohalogenation of the alkene to yield a hydrogen halide as shown below. Note that regioselectivity is a factor, and the Markovnikov product will be the major product (Compound I).

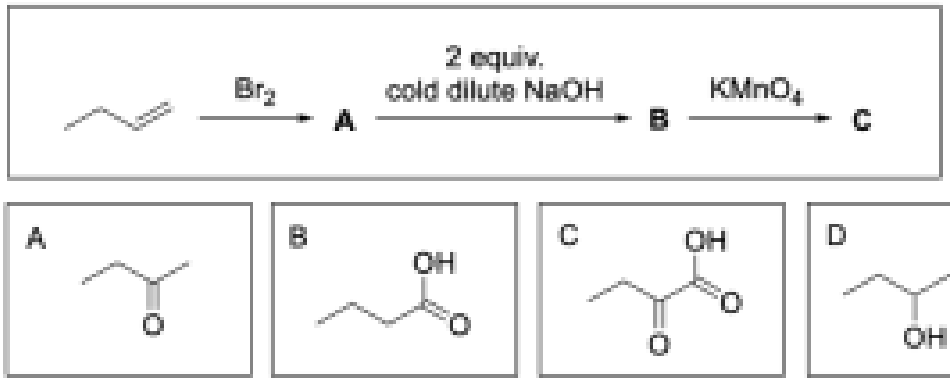
The next step is reacting the alkyl halide with a thiol. Note that thiols behave very similar to alcohols due to similarities in properties between oxygen and sulfur. Therefore, the thiol will act nucleophilic in an S_N2–like mechanism and will attack the electrophilic hydrogen halide to form a new C–S bond. Note that because the thiol used is neutral, an extra deprotonation step is required.



A breakdown of the products and intermediates is shown below.

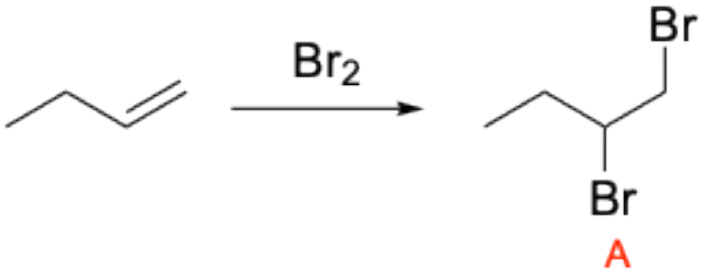


4. What is product C, given the reaction sequence below?



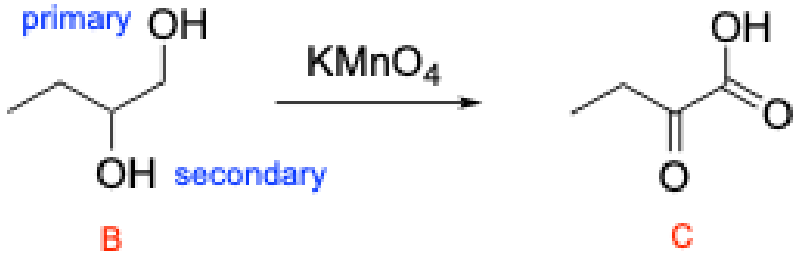
The correct answer is **Option C**. This multi–step synthesis question involves an alkene undergoing halogenation to yield a dibromoalkane (Compound A), while Compound A is then reacted with 2 equivalents of sodium hydroxide to yield a diol (Compound B). Compound B is then oxidized, which can yield a carboxylic acid or a ketone depending on if the alcohol is primary or secondary.

As previously stated, the first step is bromination of an alkene which will yield the dibromoalkane shown below.



The second step is to react Compound A with 2 equivalents of sodium hydroxide. This will react in an S_N2 mechanism to form a diol.

The third step is to oxidize Compound B to form Compound C. Potassium permanganate is a strong oxidizing agent, so it will oxidize primary alcohols to carboxylic acids and secondary alcohols to ketones. The alcohol on the left is a secondary alcohol so it would be oxidized to a ketone. The alcohol on the right is a primary alcohol so it would be fully oxidized to a carboxylic acid.



A breakdown of the products and intermediates is shown below.

5. Reacting 2-pentanol with pyridinium chlorochromate (PCC) in dichloromethane generates compound I. Compound I is then reacted with ethylmagnesium bromide in diethyl ether, followed by aqueous acidic workup (H_3O^+) to generate compound II. What is the name of compound II?

A. ethyl 2-pentanoate

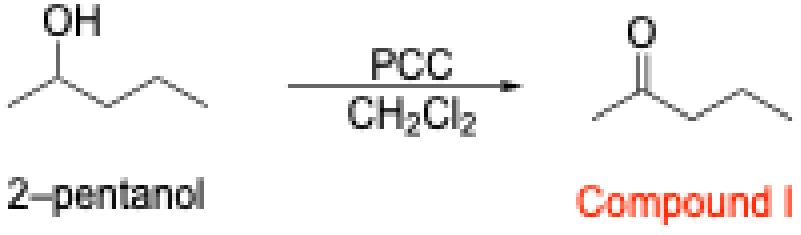
B. 3-methyl-3-hexanol

C. 3-heptanol

D. ethyl 2-pentyl ether

The correct answer to this question is **Option D.** The first thing you should do when you see multi-step synthesis questions without pictures is to draw out all of the information given to help you visualize the reagents. This is shown in the reaction scheme below.

The first step is oxidation of a secondary alcohol. The oxidizing agent used is poisoned, and the secondary alcohol will be oxidized to a ketone.



The second step is a Grignard reaction. The Grignard reagent will attack the ketone, which will grow the C–C skeleton and form a negatively charged oxygen. Hydronium is then introduced as a proton source to protonate the negatively charged oxygen and form an alcohol (Compound 2).

Using our knowledge of IUPAC nomenclature, we can name this compound. The highest priority functional group in this molecule is an alcohol at position 3, so the suffix will end in "–ol". The longest chain present is 6 carbon atoms long, so the prefix will be "hex–", yielding "3–hexanol". Lastly, there is a methyl substituent at position 3, yielding the branch name "3–methyl". Putting these 2 names together, the final name of Compound II is "3–methyl–3–hexanol". Therefore, **the correct answer is Option D.**

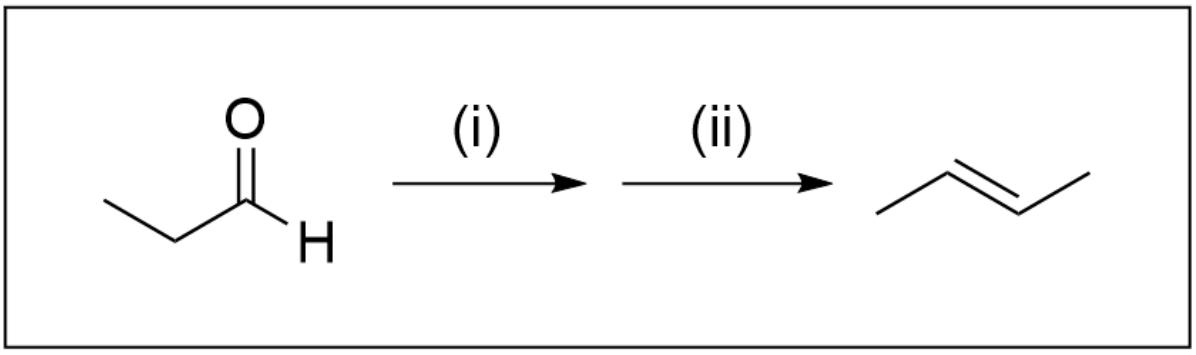
6. Which reagents are needed to carry out the following synthesis?

A. (i) CH_3MgBr/ether ; (ii) dilute HCl(aq)

B. (i) H_2,Pt ; (ii) conc. H_2SO_4(aq)

C. (i) (1) $NaBH_4$ (2) conc. H_3O^+(aq) ; (ii) conc. H_2SO_4(aq)

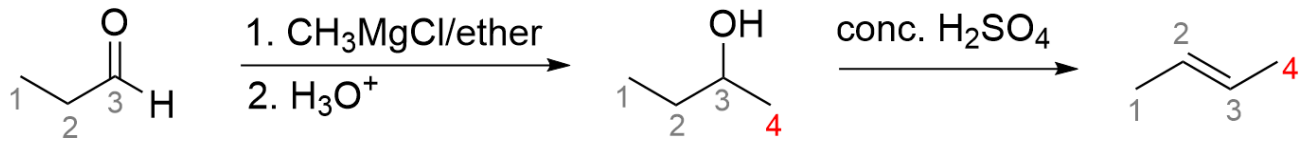
D. (i) (1) CH_3MgBr/ether, (2) H_3O^+(aq) ; (ii) conc. H_2SO_4(aq)



Option D is the correct answer. Our first step in a synthesis question, as always, is to count the carbons to see if a Grignard reaction occurred. It can be determined quickly that the starting molecule has 3 carbons,

whereas the product has four. Thus, we know the Grignard reaction must have occurred in either step one or two. As Grignard reactions must occur with a carbonyl group, it must occur in step one. The reagents in a Grignard reaction are the Grignard reagent, which contains the added carbon(s) bonded to MgX, performed in ether. Since only one carbon has been added, the Grignard reagent must be CH3–MgX. Do not forget the second step of the Grignard reaction, which involves using H_3O^+ to protonate the alkoxide.

Using the process of elimination, only **Option D** remains as a possible answer to this question.



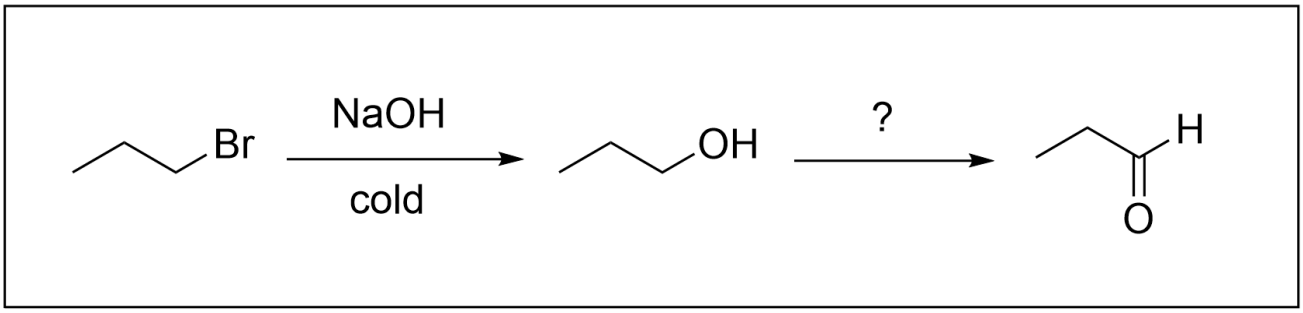
7. Which of the following statements about this 2-step reaction scheme is true?

A. The first step goes through an S_N1 mechanism, and the second step requires PCC in CH_2Cl_2.

B. The first step goes through an S_N2 mechanism, and the second step requires PCC in CH_2Cl_2.

C. The first step goes through an S_N1 mechanism, and the second step requires $KMnO_4$.

D. The first step goes through an S_N2 mechanism, and the second step requires $KMnO_4$.

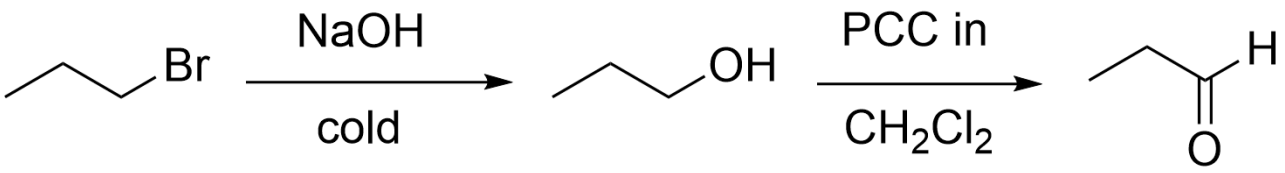


The correct answer to this question is **Option B.**

The first part of each statement specifically speaks to the mechanism of nucleophilic substitution that occurs in the first step. The starting reagent is a primary alkyl halide, as the carbon bonded to the bromine only has one other bond to carbon. Because of this, this reaction occurs through an S_N2 reaction mechanism. Recall that primary alkyl halides are more prone to undergoing through the S_N2 pathway due to the steric effect. As there are no bulky alkyl groups blocking the electrophilic carbon, it is very easy for OH^- to come around and attack it. This means options A and C are incorrect, as they state it reacts through an S_N1 reaction, which tends to mainly happen with tertiary alkyl halide.

The second step involves the reagents in the reaction. Looking at the functional groups of the second and third molecules, it is clear an oxidation event has happened. The choices that we have are either $KMnO_4$ or

PCC in CH_2Cl_2. As the starting alcohol is a primary alcohol, the alcohol can either be oxidized to an aldehyde, which contains 2 bonds to oxygen, or a carboxylic acid, which contains 3 bonds to oxygen. As the final product is an aldehyde, this is not the most oxidized form, and thus, it calls for a more selective oxidizing agent. Recall that $KMnO_4$ (as well as KCr_2O_7) always oxidizes to the most oxidized state (which would be either a carboxylic acid for primary alcohols or a ketone for secondary alcohols). On the contrary, PCC in CH_2Cl_2 is more selective and only oxidizes to an aldehyde or ketone. Thus, **the correct option for this question is Option B.**



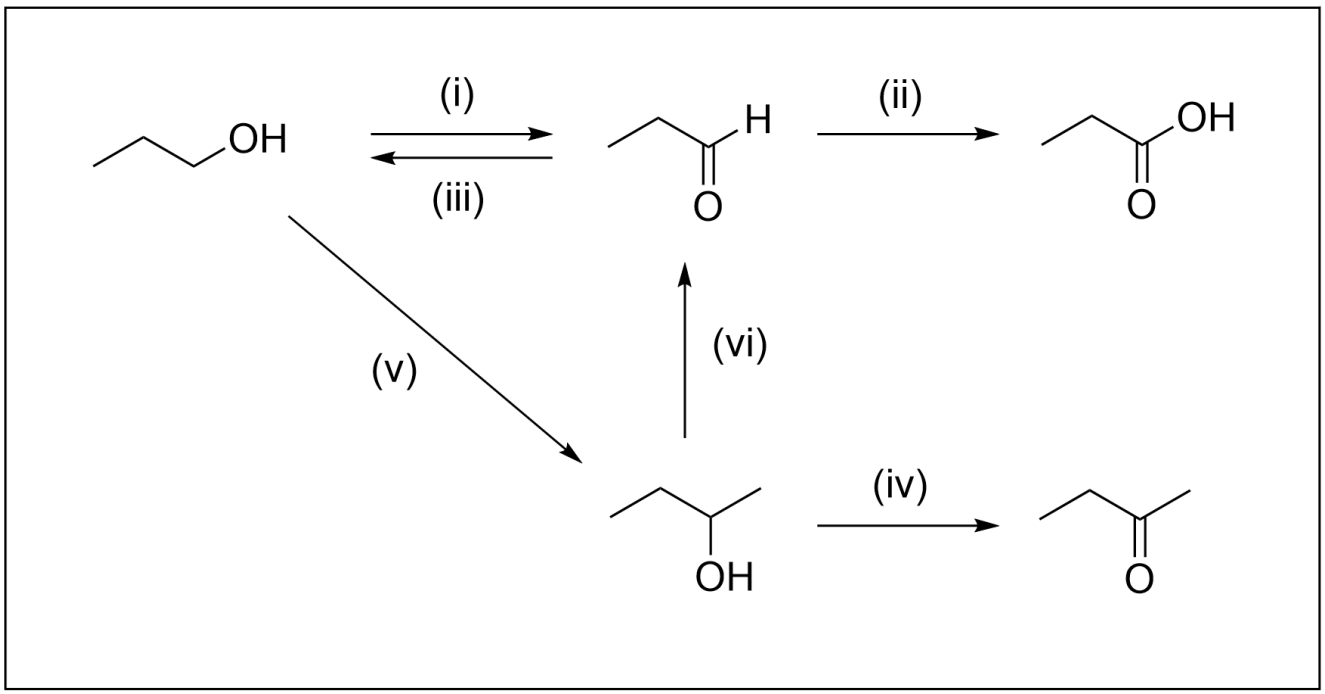
8. Which statement regarding the synthetic steps below is incorrect?

A. Step (iii) can be achieved by reaction with $NaBH_4$ followed by addition of H_3O^+(aq).

B. Step (vi) can be achieved by reaction with H_2O, and H_3O^+(aq)

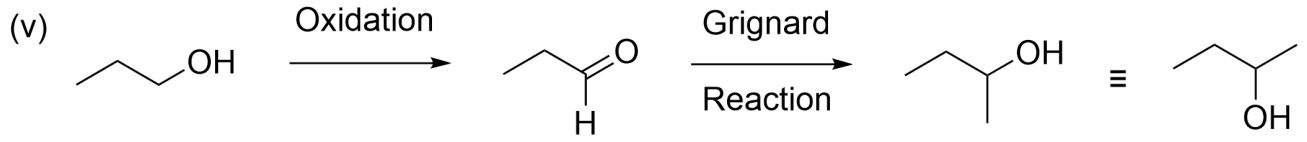
C. Step (v) can be achieved via an oxidation reaction, followed by a Grignard reaction and acid work-up.

D. Steps (ii) and (iv) can both be achieved by reaction with $KMnO_4$(aq).

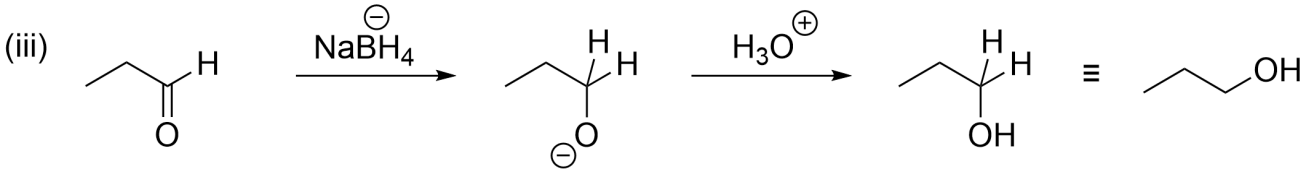


The correct answer to this question is **Option B.**

Option A is true, making this the incorrect answer. Step (iii) is a reduction reaction starting for an aldehyde and producing an alcohol. Reductions of carbonyl groups are performed using sodium borohydride ($NaBH_4$), as discussed in Chapter 3.4.1, which donates a hydride to the electrophilic carbon. As this question is looking for the incorrect statement, this is an incorrect choice.



Option B is false, making it**the correct answer** to this question. Step (vi) is impossible to perform, as this involves the loss of one carbon. The starting reagent in this reaction contains four carbons, whereas the product contains three. We have not yet learned any reactions to lose carbon atoms, making this statement false.



Option 3 is also true, making it incorrect. As this is a multi-step reaction, we suggest that you write down the products at each step to see if it leads to the correct product. Following what the statement tells us, the starting alcohol can easily be oxidized to an aldehyde. As a carbonyl, it can then react with a Grignard reagent which adds another carbon onto the alkyl chain. This statement is true, as the final product in this stepwise reaction matches the product seen in the question. Thus, this is not the correct answer.

Option 4 is also true, making it an incorrect choice. Both starting products can be oxidized using $KMnO_4$, which oxidizes to the most oxidized form. Thus, it is possible for an aldehyde to be oxidized to carboxylic acid, and a secondary alcohol to a ketone.

9. Which of the following statements about the reduction of an aldehyde by sodium borohydride is true?

A. The aldehyde acts as a nucleophile and the intermediate has a negative charge.

B. The aldehyde acts as an electrophile and the intermediate has a positive charge.

C. The aldehyde acts as an electrophile and the intermediate has a negative charge.

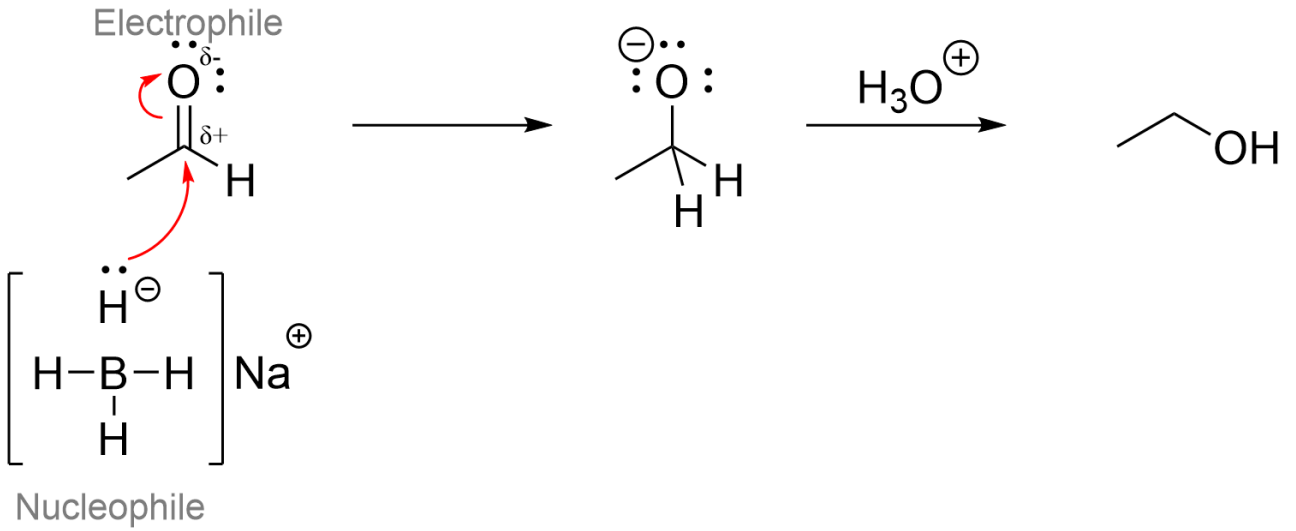
D. The aldehyde acts as a nucleophile and the intermediate has a positive charge.

The correct answer is **Option D.**

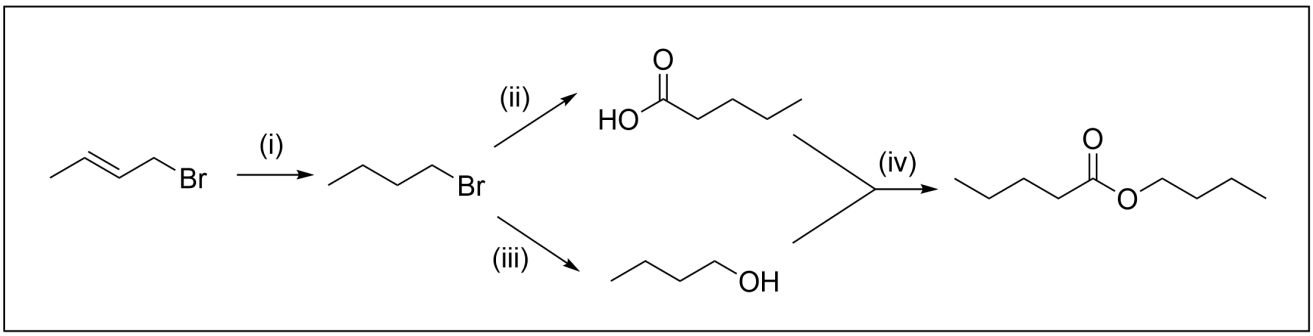
To visualize the process, we recommend drawing out the reduction mechanism of an aldehyde by sodium borohydride. Recall that carbonyls contain the polar bond between carbon and oxygen, giving carbon a partial positive charge due to the electronegativity of oxygen. As it contains a partial positive charge, the aldehyde acts as an electrophile.

As the hydride attacks the central carbon, it pushes the electrons from the double bond up towards the electronegative oxygen. This is to avoid the carbon exceeding 8 electrons in its valence shell. Thus, as the oxygen now contains an extra two electrons and loses one bond to carbon, it becomes negatively charge. This makes the correct answer to the question **Option D**.

For more information on sodium borohydride reductions, please consult Chapter 3.4.1,



10. What reagents and conditions are needed for this synthetic scheme?



A. H_2, Pd/C ; (ii) Mg, Et_2O, CO_2, H_3O^+ ; (iii) cold dilute NaOH ; (iv) H^+

B. H_2, Lindlar's catalyst ; (ii) $KMnO_4$; (iii) H_2O ; (iv) H^+

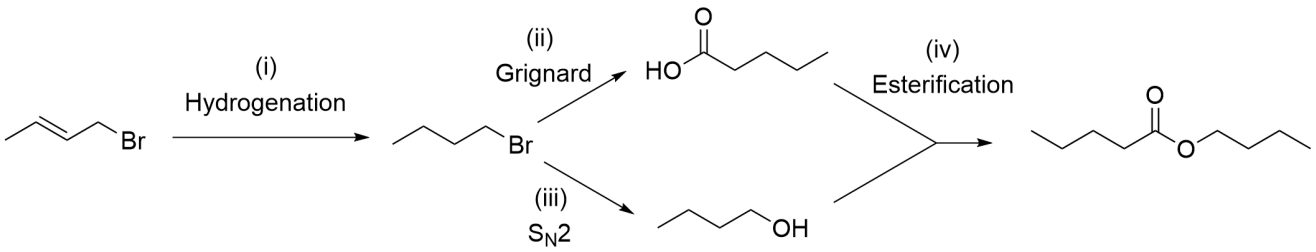
C. H_2, Pt(s) ; (ii) $KMnO_4$; (iii) H_2O ; (iv) H_3O^+

D. H_2, Pd/C ; (ii) PCC, CH_2Cl_2 ; (iii) H_2O ; (iv) CH_3OH, H^+

The correct answer is **Option A.**

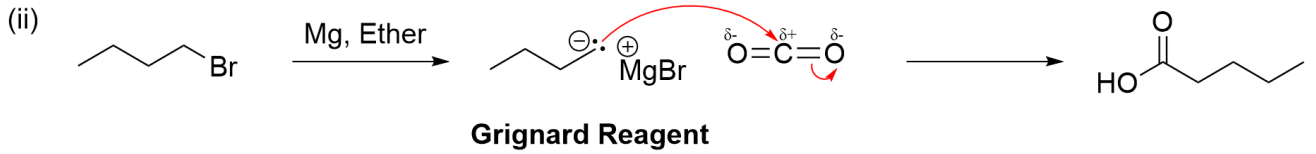
The first thing to do in questions with synthetic schemes is to identify the reactions that are occurring in each step. By knowing the reactions, it will make it much easier to determine what reagents are used at each step. You can do this by counting carbons and looking at the changes in functional groups. For example, step

(i) shows an alkene becoming an alkane, which is achieved through hydrogenation. In step (ii), it can be seen that there is a fifth carbon added onto the alkyl chain, which means a Grignard reaction must have taken place to make a carboxylic acid. Step (iii) showcases a change from an alkyl halide to an alcohol, which we known is achieved through nucleophilic substitutions. Lastly, step (iv) shows a carboxylic acid and an alcohol reacting together to make an ester.



With this information, we can then determine the reagents used at each step. Hydrogenation always involves the uses of hydrogen gas (H_2). Typically, a catalyst is used alongside H2, either a noble transition metal such as Pd or Lindlar's catalyst. In this case, since we are going from an alkene to an alkane, it does not matter what type of catalyst used. This is only important if the reduction is from an alkyne to a cis alkene, in which Lindlar's catalyst must be used. For more information, please refer to Chapter 3.2.3.

Step (ii), as we know, is Grignard reaction. This is because there are five carbons on the alkyl chain, whereas previously, there were only four. Although Grignard reactions require a carbonyl group (such as an aldehyde, ketone, or carbon dioxide CO_2), recall the Grignard reagent also participates in the reaction. It is an alkyl chain containing the group –MgX, which gives the carbon its nucleophilic properties. Since this molecule is an alkyl halide, this can actually react with magnesium (Mg) to create a Grignard reagent (as seen in Chapter 3.4.2). To add a single carbon and make a carboxylic acid, this can then react with CO_2 to make the desired product . Using the process of elimination, it is easy to determine the correct multiple choice answer from these two steps.



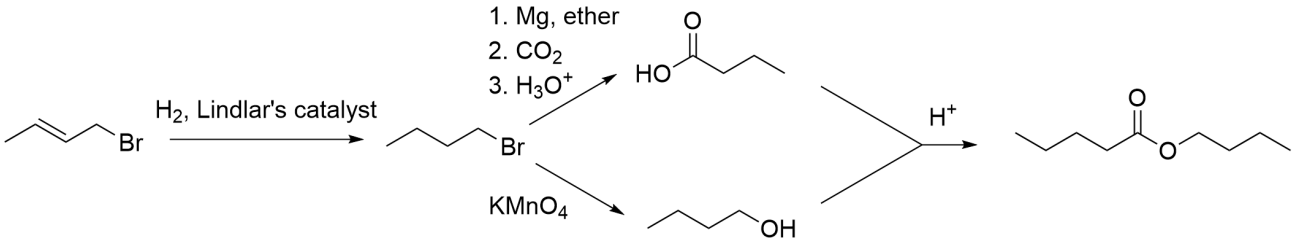
Grignard Reagent

To fully understand the reaction schematic, the remaining steps will be explained. Step (iii) showcases a nucleophilic substitution reaction. As the bromine group is substituted with an alcohol group, this means OH^- must be the nucleophile. Therefore, reagents that contain an OH group such as NaOH can react to form the desired product.

Step (iv) showcases an esterification reaction between a carboxylic acid and an alcohol. Recall that this is referred to as an acid-catalyzed esterification. This reaction requires the use of two catalysts: heat and

concentrated acid, such as H_2SO_4. Thus, these are the two required reagents to form the final ester product. For more information, please refer to Chapter 3.5.

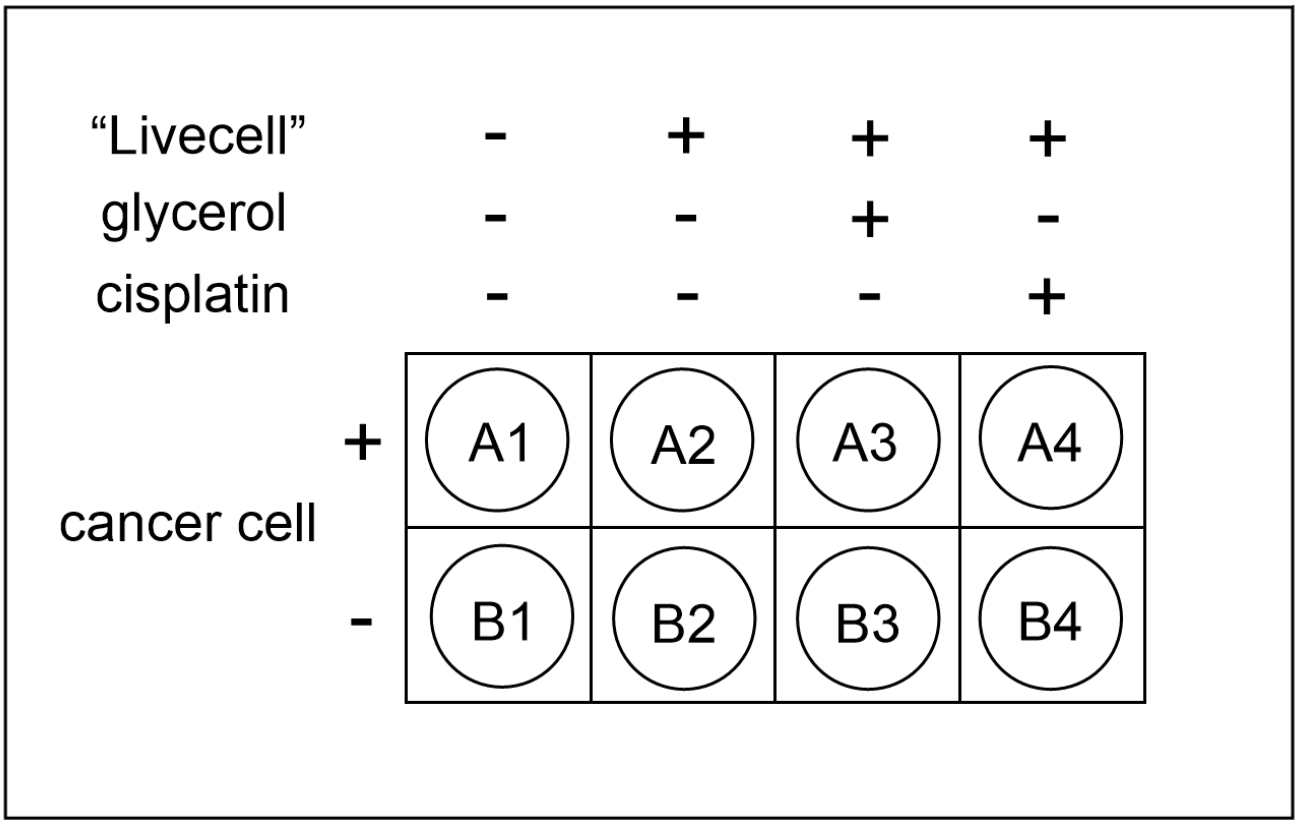
With each of the steps' reagents, below shows the completed reaction schematic. This corresponds to **Option A as the correct answer**.



5.3 - SOLUTIONS FOR CHAPTER 4 - CHEMICAL BIOLOGY

Chapter 4.2 – High-Throughput Screening

1. Potential anti-cancer compounds to kill cancer cells are being tested using a high-throughput assay in a 96 well plate. Live cancer cells are detected using "Livecell", a dye which is initially blue, but turns colourless in the presence of live cells. The control wells are shown below. Cisplatin kills cancer cells; glycerol does not affect them. Which of the control wells will appear blue at the end of the assay?



A. A4, B1, B2, B3, B4

B. A2, A4, B2, B3, B4

C. A4, B2, B3, B4

D. A1, A3, B1, B2, B3, B4

The correct answer is **Option C**. Going through each well, the resulting colour of the well can be

determined through a step-by-step process. This will involve understanding what's in the well, then applying that to what conditions need to be met for the blue colour to occur.

Well A1 has no Livecell dye, glycerol or cisplatin, and does have cancer cells. This is indicated on the negatives for the three conditions above, and a positive on the left for cancer cell. The question tells us that the blue colour occurs when the Livecell dye is NOT in the presence of living cells. However, since there is no dye added to A1 in the first place, we can conclude that there will be no colour in the well.

Well A2 has Livecell dye, but does not have cisplatin nor glycerol added, and the well also has cancer cells within. The dye, as the question states, will only change to colourless if there are live cells in the well. Because the cancer cells in the well have no other compounds present to kill them, they remain living and thus the dye will turn colourless.

Well A3 has Livecell dye and glycerol along with cancer cells, but no cisplatin present. The glycerol, as the question states, will not affect the cancer cells in any way, so they will continue living in the well. Because of this, the dye will be exposed to live cells, making it colourless.

Well A4 has Livecell dye and cisplatin, along with cancer cells present, with no glycerol. The question states that cisplatin will kill cancer cells, so we can conclude that the cells should be dead in the well.

The Livecell dye only turns colourless in the presence of live cells, and otherwise it remains blue. Because of the lack of live cells, therefore, the well will appear blue.

Well B1 has no Livecell dye, glycerol, cisplatin or cancer cells. Because of the lack of dye added to the well, the well cannot have any blue colour. Therefore, it remains colourless.

Well B2 has Livecell dye, but no glycerol, cisplatin or cancer cells. Livecell dye only turns colourless in the presence of live cells, and it otherwise will be blue. Because there are no cells in the well, it should appear blue.

Well B3 has Livecell dye and glycerol, but no cisplatin or cancer cells. The Livecell dye will only turn from blue to colourless if it's in the presence of live cells. There are no living cells in the well, therefore the dye will remain blue.

Well B4 has Livecell dye, glycerol and cisplatin, but has no cancer cells. The Livecell dye will only turn from blue to colourless if it's in the presence of live cells. There are no living cells in the well, therefore the dye will remain blue.

Out of the wells listed above, only A4, B2, B3 and B4 will appear blue, thus option C is correct.

2. A high-throughput screen is performed to test compounds for anti-cancer activity. A compound is considered a hit only if it kills the cancer cells, but not normal cells. One test compound kills both the cancer and normal cells, and this is correctly detected by the assay. What kind of result is this?

A. A false control result.

B. A true negative result.

C. A false positive result.

D. A false negative result.

The correct answer is **Option B**, a true negative result. The first thing is identifying what result we wanted to see which would be denoted as a positive result: after adding the compound, cancer cells die but normal cells are preserved/alive. Anything other than that positive result would be a negative result, which there are 3 outcomes. The negative results could be that no cells are affected (including both cancer and normal cells) which means there is no activity, or all cells die/are affected (including both cancer and normal cells), and lastly, cancer cells survive but normal cells die which is the reverse of what we are looking for. Knowing this, we can strike out option A and option C as control results are not a thing (controls are used for experimental reliability, not to classify results), and we did not see a positive result in this scenario.

Now that we only have 2 options left, we need to identify whether the negative result was a true or false result. True and false are used to define whether the compound that is being tested is responsible for the result (true) or if the result occurred due to any external factors other than the compound itself (it did not interact at all) which in this case making it appear negative when it is actually positive (false). Because the observed death of cells occurred after the addition of the compound, we can confirm the compound was responsible for the negative result, making this result Option B: a true negative result.

Chapter 4.3 – Aromaticity

1. Indicate the FALSE statement concerning aromatic compounds:

a) 1,3,5-Triacetylbenzene contains 12 π-electrons but is nevertheless aromatic.

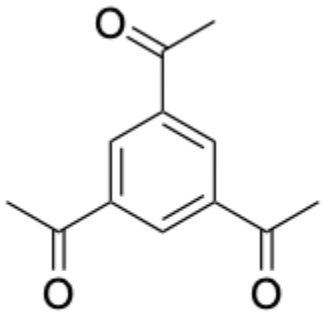
b) The Hückel rule predicts that planar cyclic systems having (4n + 2) conjugated π -electrons are aromatic

c) Aromatic systems are planar in order to allow maximum overlap between adjacent p-orbitals.

d) π -bonds in aromatic systems are more reactive towards bromine than those in linear alkenes.

The correct answer is **Option D.** We will go through each statement one by one to determine how we reach this conclusion.

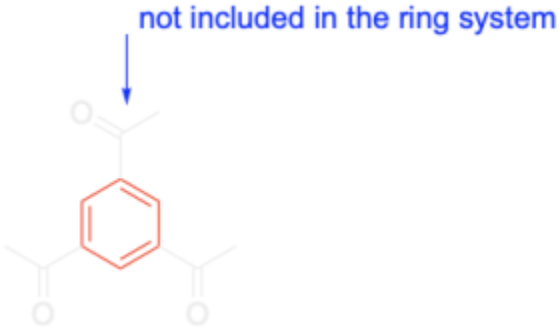
Option A is a true statement. The first thing you should do is draw out the compound. This compound contains a benzene ring with acetyl groups on positions 1, 3, and 5.



1,3,5– triacetylbenzene

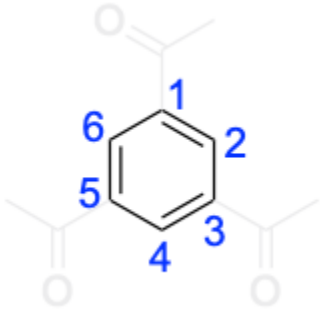
There are 3 rules to satisfy for a compound to be aromatic: cyclic, hybridization and Huckel's rule.

1. This compound **is** cyclic because benzene is cyclic, so we will only focus on the benzene portion. Note that the acetyl groups are **not** included in the ring system, so they will not be considered for the other 2 criteria.



2. This compound **does** contain sp^2 –hybridization for all atoms that are in the ring system (shown in the blue highlight).

3. This compound **does** satisfy Huckel's rule. For the atoms that are in the ring system, there are 6 π-electrons that satisfies the criteria for aromaticity as it is a number that can be generated from (4n+2).



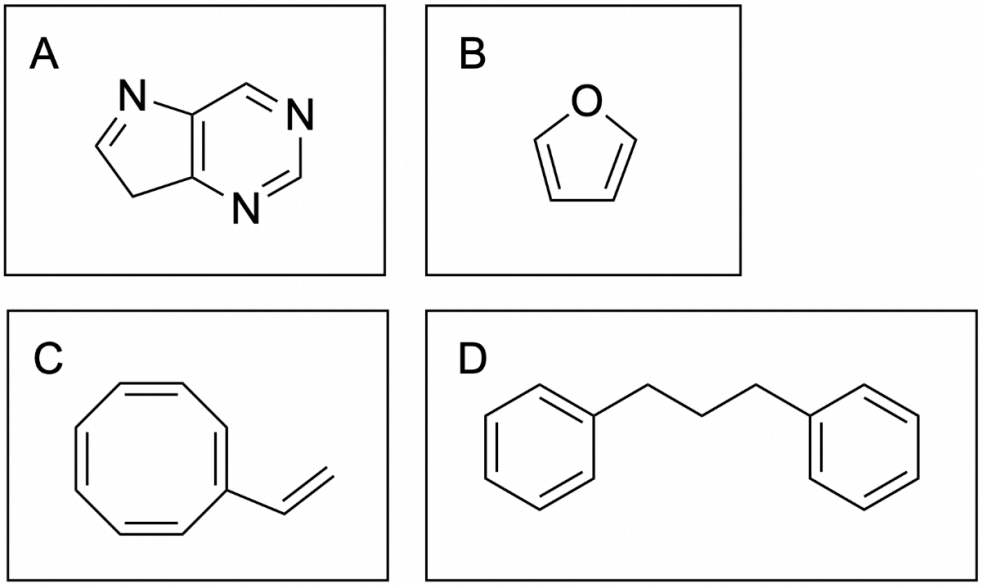
Therefore, 1,3,5–triacetylbenzene **is** aromatic.

Option B is a true statement. Huckel's rule is one of the criteria used to evaluate the aromaticity of a compound. It states that if a planar and cyclic compound contains a number of electrons that satisfies the (4n+2) rule (which contains electron numbers in the order 2, 6, 10, 14, 18, 22, etc.,) it is considered aromatic.

Option C is a true statement. Aromatic systems **must** be planar. This is because the p–orbitals **must** be able to overlap to allow for delocalization of the electrons.

Option D is an FALSE statement, making **Option D the correct answer**. π-bonds in aromatic systems are **not** more reactive towards bromine than those in linear alkenes. This is because the π-bonds in aromatic systems are significantly more stable than in linear alkenes, so it is **less** reactive and will not undergo addition, halogenation or oxidation and reduction reactions like alkenes.

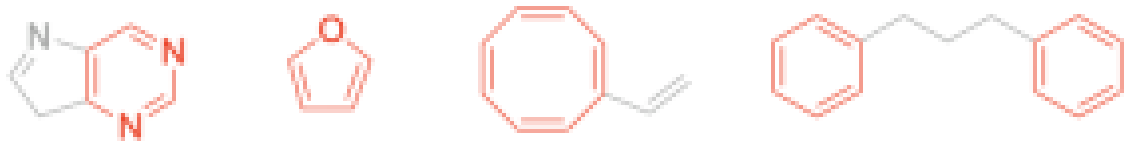
2. Which compound below is not aromatic? (You may assume that a compound is planar if it meets the other criteria for aromaticity.)



The correct answer is **Option C,** the third compound.

There are 3 rules to satisfy for a compound to be aromatic: cyclic, hybridization and Huckel's rule.

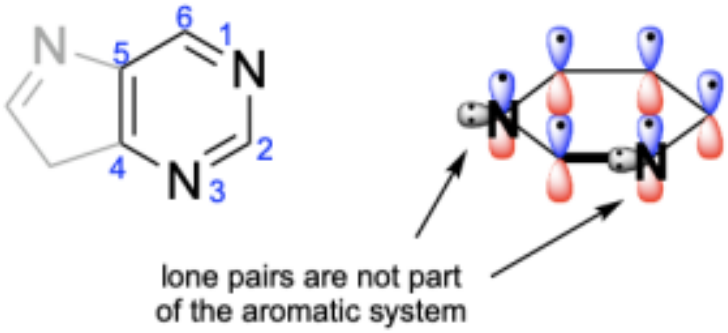
All of the compounds contain cyclic portions (shown in red), while the portions that do not contribute to the ring system are highlighted in grey. Note that in the first molecule, there are 2 cyclic portions. The left-most portion is **not** included in the ring system because one of the atoms is sp^3–hybridized, so it would not allow for the planar overlap of p–orbitals, and is **not** aromatic.



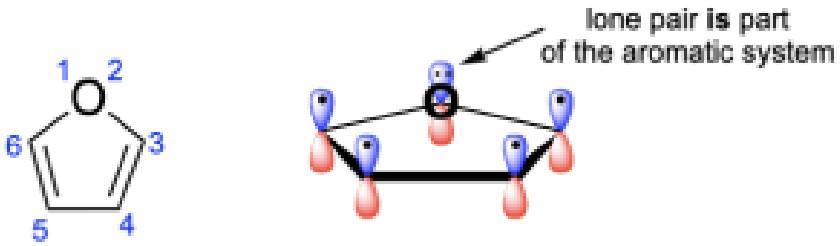
All atoms in the ring system in the 4 compounds can also be sp^2 or sp–hybridized.

The last criteria to check for is Huckel's rule.

For the first compound, there are **six** π-electrons. This is a number that will satisfy Huckel's (4n+2) rule. Note the **none** of the nitrogen atoms contribute a lone pair to the ring system since the p–orbital is already contributing 1 electron to the aromatic system. Therefore, this compound **is** aromatic.

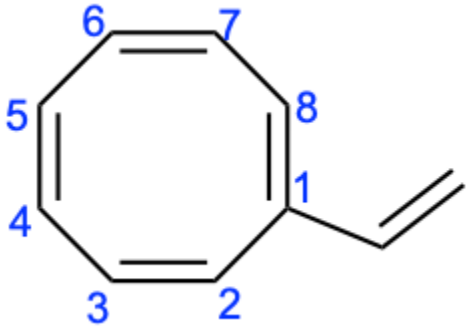


In the second compound, there are also **six** π-electrons. This is a number that will satisfy Huckel's (4n+2) rule. In this example, oxygen **does** contribute its lone pair to the π-system since there are **no** adjacent p–orbitals that can contribute 1 electron. Therefore, this compound **is** aromatic.

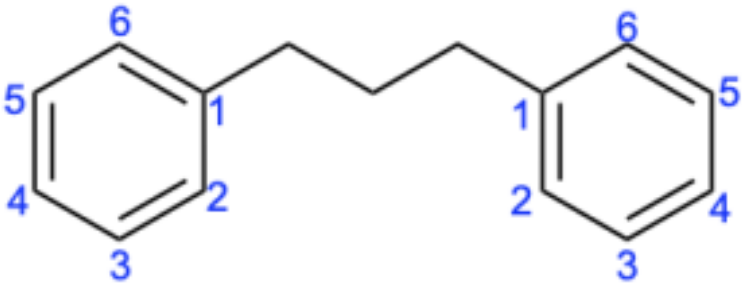


In the third compound, there are **eight** π–electrons. This is a number that will **not** satisfy Huckel's (4n+2)

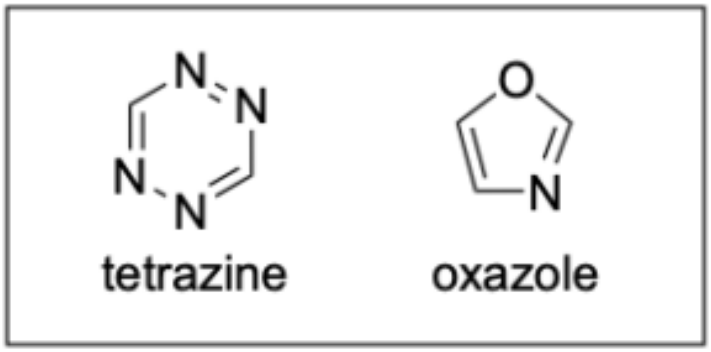
rule, as there are 4n (8) electrons. Note that there is another double bond in this compound, but because it is **not** part of the cyclic ring system, it cannot contribute its electrons. Therefore, this compound is **not** aromatic.



In the fourth compound, there are 2 cyclic systems, each with **six** π-electrons. This is a number that will satisfy Huckel's (4n+2) rule. Note that you do **not** add up the number of electrons in each aromatic system to get 12 π-electrons, as this would suggest the compound is not aromatic. Since they are **separate** cyclic systems, you need to ensure that **each** ring meets this criteria, rather than looking at the sum. Therefore, this compound **is** aromatic.



3. Which of the following statements about tetrazine and oxazole is FALSE?



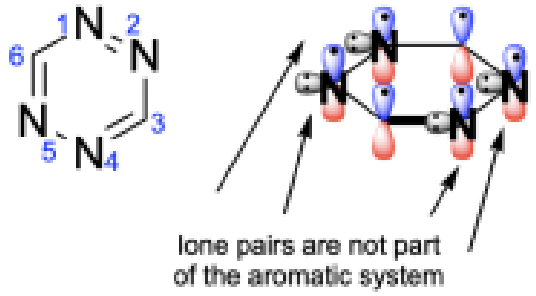
A. Both molecules are aromatic.

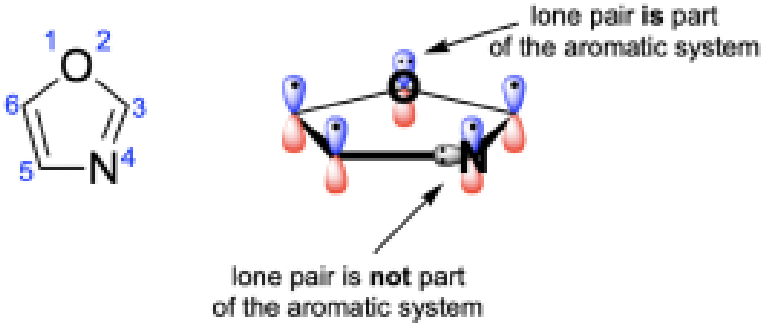
B. The oxygen atom of oxazole is sp^3 hybridized.

C. Every nitrogen atom contributes 1 electron to the π-system.

D. Each molecule contains 6 delocalized electrons.

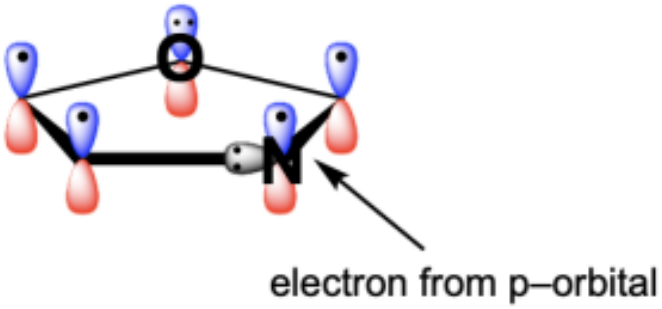
Option A is a true statement, making this an incorrect answer. To satisfy aromaticity, there are 3 criteria that must be met: cyclic, hybridization and Huckel's rule. Both compounds are cyclic and contain atoms that are all sp^2-hybridized. Additionally, the compounds satisfy Huckel's rule and have **six** π-electrons. Note that none of the nitrogen atoms contribute their lone pairs to the π–system (as the p–orbitals contribute 1 electron), but the oxygen atom in oxazole **does** contribute its lone pair to the aromatic system. They are therefore **both** aromatic.



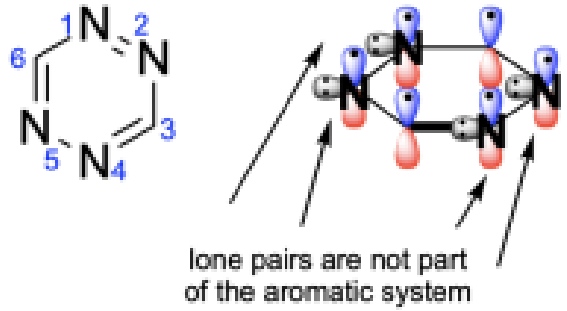


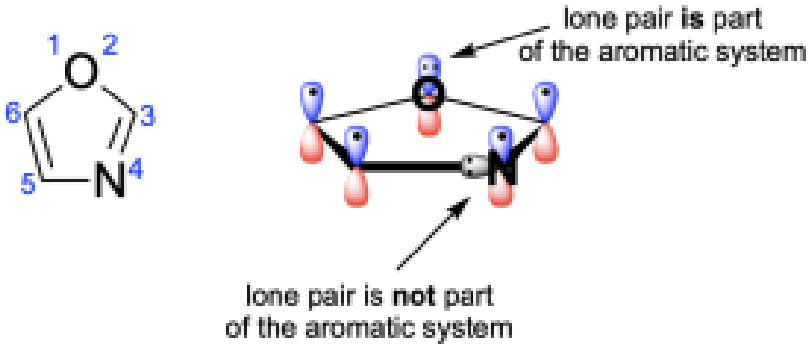
Option B is a false statement, making **Option B the correct answer.** The oxygen atom in oxazole is **not** sp^3 hybridized. This is because the oxygen atom donates one of its lone pairs to the aromatic π–system. The oxygen atom is therefore involved in 2 bonds (both are to carbon atoms), and it only has one lone pair (since the other one is involved in the aromatic π–system). This creates an sp^2 hybridized atom with trigonal planar geometry.

Option C is a true statement, making this an incorrect answer. As shown in Option A, nitrogen's lone pair is **not** involved in the aromatic system and is instead perpendicular to the delocalized electrons in the p–orbitals. But, an electron from nitrogen's p–orbital will be contributed to the aromatic system.



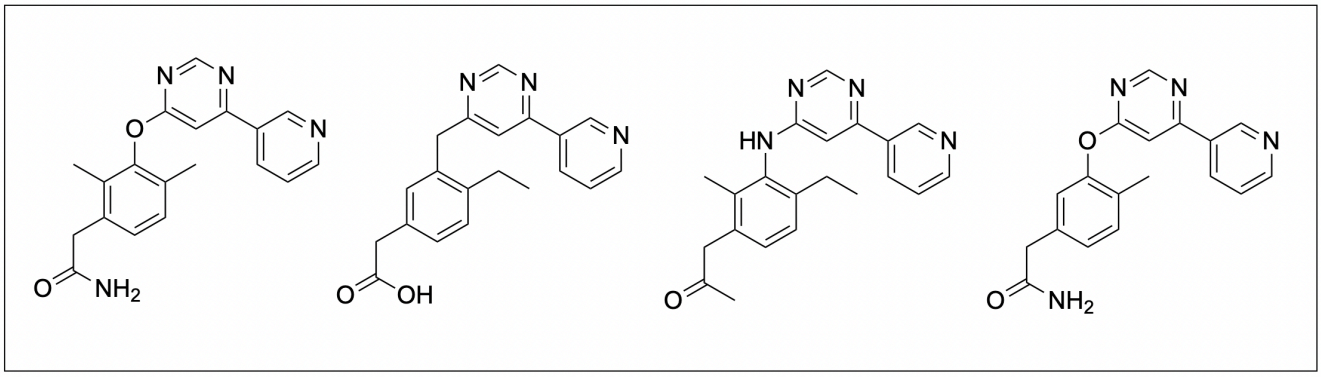
Option D is a true statement, making this an incorrect answer. As shown in Option A, the compounds have **six** π-electrons. Note that none of the nitrogen atoms contribute their lone pairs to the π–system (as the p–orbitals contribute 1 electron), but the oxygen atom in oxazole **does** contribute its lone pair to the aromatic system.





Chapter 4.4 – Combinatorial Chemistry

1. How many sites of diversity are there in this combinatorial library?



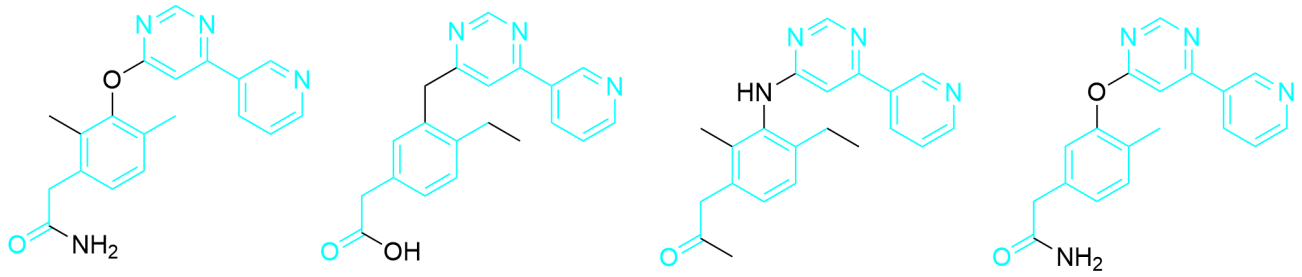
A. 6

B. 4

C. 8

D. 3

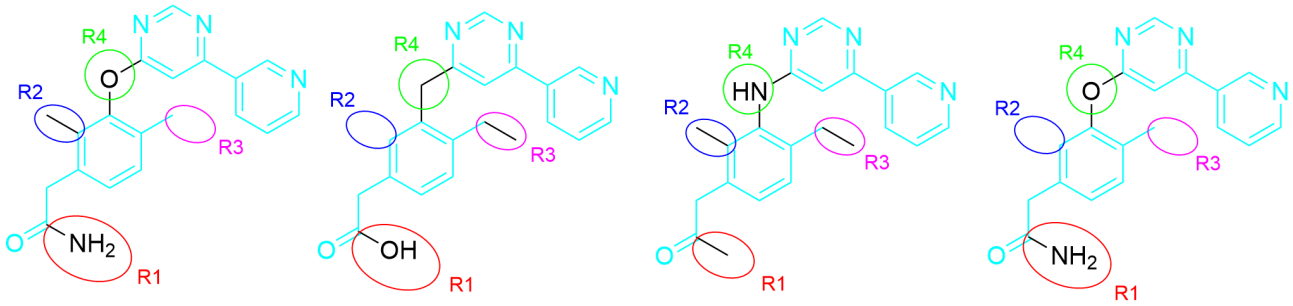
The correct answer to this question is **Option B.** The first step in determining the sites of diversity is to determine the core structure of the compounds. The core structure stays consistent and appears in every compound shown. If a substituent only appears in some of the molecules, then it is not considered part of the core structure. The figure below highlights it in cyan.



Now that the core structure has been determined, we can look at the points at each part of the molecule where there is a different substituent. For example, the bottom left can either be NH_2, OH or CH_3, making this one site of diversity. The same can be said for the site on the left of the central ring, where there is either a carbon group (CH_3) or no visible groups, meaning it only has the substituent H. This is the second site of diversity.

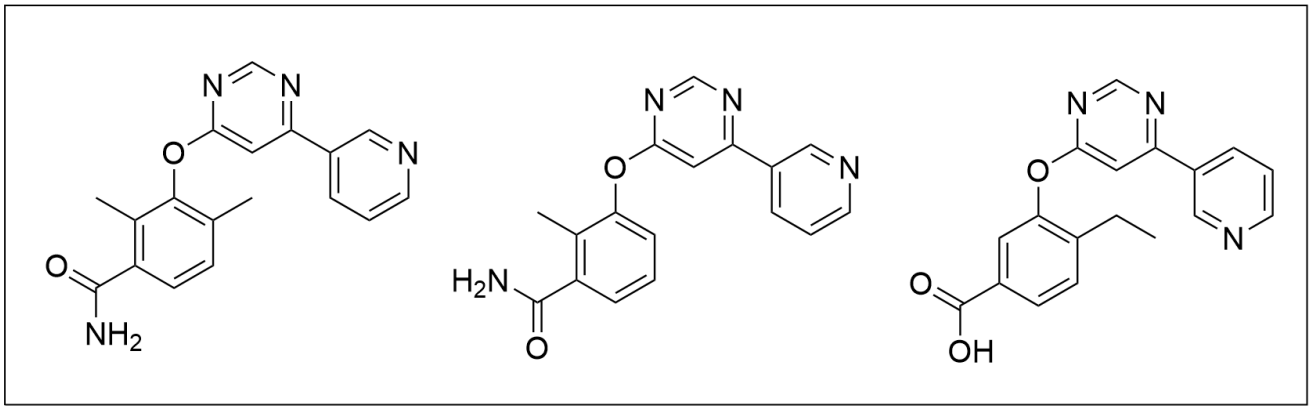
On the right of the central ring, once again, it is shown to either be CH_3 (a carbon group) or H. This is the third site of diversity.

The last site of diversity may be tricky because it occurs right in the middle of the molecule, rather than branching out somewhere. However, since it is different in each compound (containing either an oxygen, carbon, or nitrogen group), it can be considered a fourth site of diversity.



This makes the answer to this question **Option B**, with 4 sites of diversity seen in this library of compounds.

2. How many compounds would a combinatorial library contain based on the compounds below? (Every substituent can be found at every diversity site.)



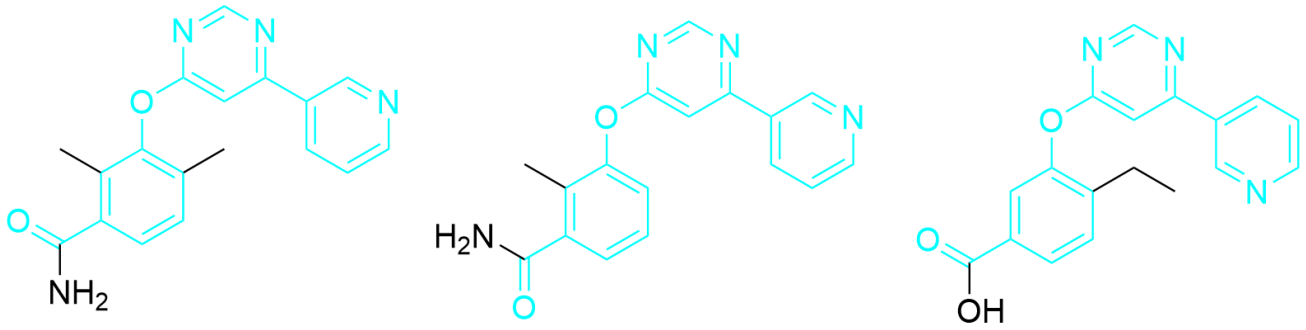
A. 125

B. 216

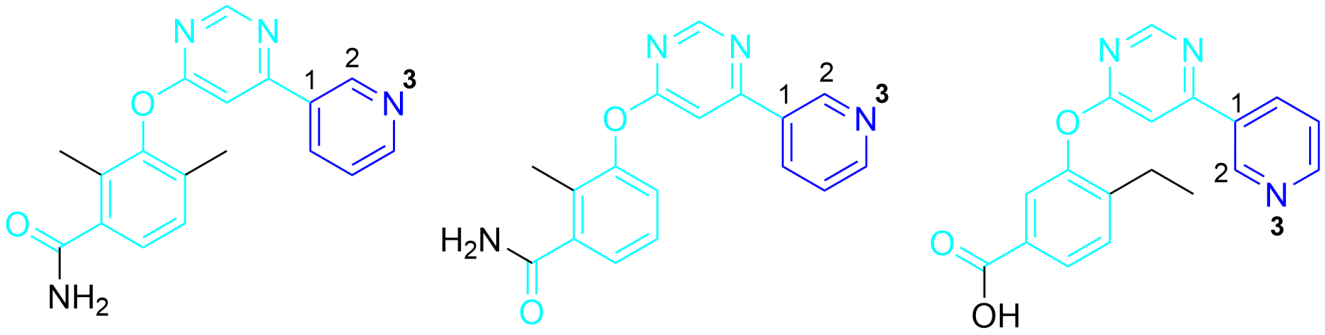
C. 512

D. 1296

The correct answer to this question is **Option A**. The first step in determining the sites of diversity is to determine the core structure of the compounds. The core structure stays consistent and appears in every compound shown. If a substituent only appears in some of the molecules, then it is not considered part of the core structure. The figure below highlights it in cyan.

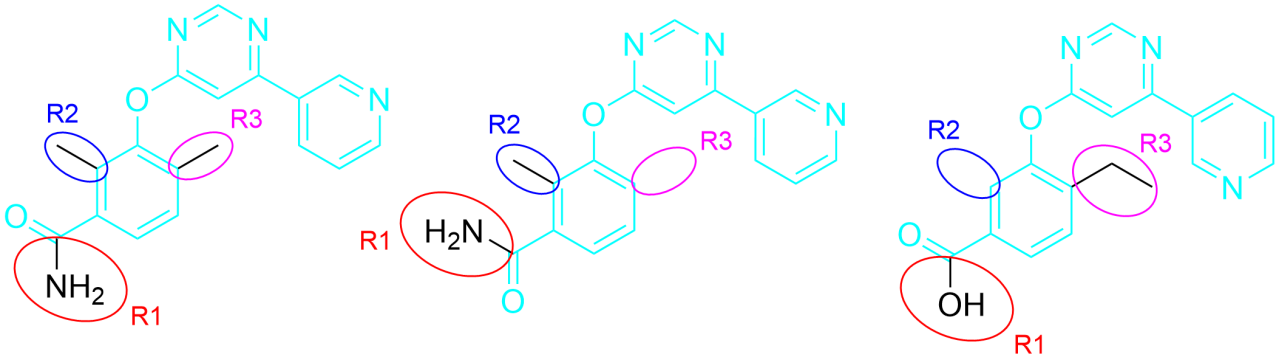


One difficult core structure to locate is the top-right ring, which is highlighted below in dark blue. Although the third molecule seemingly looks different than the first two, prompting you to think it is a diversity site, these sites are actually **exactly the same** – the rings are simply flipped. An easy way to decipher this is to count what position the nitrogen is relative to the carbon bonded to the rest of the structure. If we label carbon bonded to the rest of the structure as position 1, it can be seen that in all three molecules, the nitrogen is three positions away. As the rest of the ring looks the same with the double bonds in the same locations, this is NOT a site of diversity and is actually part of the core structure of the compounds.



Now that the core structure has been determined, we can look at the points at each part of the molecule where there is a different substituent. For example, the bottom left of the molecule next to the carbonyl group is shown to either contain a nitrogen group (NH_3) or hydroxide group (OH). Thus, this can be considered a site of diversity.

The same can be done for the sites on the left and right of the bottom central ring. On the left side, there can either be one carbon group (CH_3) or no groups (H). On the right side, there is seen to either be no groups (H), one carbon group (CH_3) or two carbons (CH_2CH_3). Thus, these are the second and third sites of diversity.



R1 = NH_2, OH
R2 = H, CH_3
R3 = H, CH_3, CH_2CH_3

Now that we know the sites of diversity, we can identify the different substituents at each site. This is best done in a list format to sort what substituents are found at each site. As the question states that every substituent can be found at every site, we can then extend the list of possible substituents to include ones that are found at other sites of diversity as well. An example of a list is found below. The left side lists what substituents are found on the three molecules at each site. We then extend the list by ensuring every substituent is listed at each site. A total of **five unique substituents** are found at each diversity site.

Substituents at Each Site:
R1 = NH_2, OH
R2 = H, CH_3
R3 = H, CH_3, CH_2CH_3

Applying every substituent to every site →

Possible Substituents:
R1 = H, CH_3, CH_2CH_3, NH_2, OH
R2 = H, CH_3, CH_2CH_3, NH_2, OH
R3 = H, CH_3, CH_2CH_3, NH_2, OH

Lastly, we can apply our formula, which is the number of substituents to the power of the number of diversity sites. This gives the final answer to be **Option A**, or 125 different compounds.

$$\text{library size} = (\#\text{ substituents})^{\#\text{ diversity sites}}$$
$$= (5)^3$$
$$= \mathbf{125\ different\ compounds}$$

GLOSSARY

Acid-catalyzed esterification

A reversible reaction where a carboxylic acid and alcohol react to produce an ester and water under heated conditions with an acid catalyst. The reverse reaction is known as **ester hydrolysis.** Le Chatelier's principle is used to drive this forward reaction by using a high concentration of alcohol and a minimal amount of water.

Addition reaction

A small molecule (such as water) is added to a multiple bond (a double or a triple bond). This results in one π–bond and one σ–bond being broken and two new σ–bonds being formed.

Angstrom

A unit of length, equal to 0.1 nanometer.

Aromaticity

A property of certain molecules that make it extremely stable due to the delocalization of the electrons located in the p orbitals, forming an aromatic π orbital system. There are three criteria for a molecule to be aromatic. It must (1) contain a ring structure, (2) be comprised of either sp2-hybrdized or sp-hybridized atoms, and (3) follow Hückel's rule.

Assay

An experiment used to measure the activity or presence of a molecule.

Bond

The result of the overlap of individual atomic orbitals, with the pair of electrons occupying the overlapping orbital space

Chemical Biology

A scientific field between branching chemistry and biology. The discipline often involves the application of chemical techniques, analysis, and small molecule to the study and manipulation of biological systems

Combinatorial chemistry

The process of modifying a lead compound with various functional groups at multiple sites to create a large library of compounds.

Combinatorial library

A library, or large collection, of unique compounds, all with the same core structure derived from a lead compound.

Concerted mechanism

A mechanism in which bonds are broken and formed simultaneously, occurring all in one step. This is typically seen when an anionic nucleophile attacks an electrophile that is not sterically hindered (such as in SN2 reactions).

Configuration

A permanent geometry of a molecule resulting from spatial arrangements of its bonds, usually seen in alkenes.

Conformation

Different 3-dimensional spatial arrangements which atoms in a molecule can freely change between

Control experiment

Control wells performed alongside the actual experiment to ensure that the experimental design is sound and that the different components of the assay are working as intended. The controls ensure experimental reliability, and that results are not due to other interfering or unpredictable factors. Control experiments may have combinations of components used in the experiment or expected products from the assay, and contain both a positive and negative control.

Covalent Bond

A bond where the two atoms share a pair of electrons between the two nuclei.

Dissociative mechanism

A mechanism where bonds are broken and formed in multiple steps. This is typically seen when a neutral nucleophile attacks a sterically hindered electrophile, with the first step being the loss of a leaving group followed by a nucleophilic attack (SN1 reaction).

Diversity sites

An atom on a lead compound which can have its functional groups modified to other functional groups of choice.

Electrophile

An electron-deficient species, such as an alkyl halide (C–X). It accepts electrons from nucleophiles (electron donors) in a chemical reaction. These often have a positive charge, partially positive charge, or an incomplete octet. The **electrophilic center** is the specific atom on the electrophile that is electron-deficient and will accept electrons.

Enzyme-linked immunosorbent assay

Also known as an ELISA, it is a type of assay used to determine if a molecule of interest is present through colourimetric change. The assay works using horseradish peroxidase as a coloured indicator, which is bound to a secondary antibody. This secondary antibody will bind to a primary antibody that is specific for the molecule of interest. ELISAs are used in high throughput-screening as they can be performed in 96-well plates and give a coloured response to quickly determine the presence of a molecule

Formal Charge

The charge assigned to atoms in molecules to keep track of electrons.

Functional Group

A group of atoms bonded together in a particular way that impact the molecule's chemical behaviour. Examples include alkanes, hydroxyls, and amines.

Halogenation reaction

The addition of halogens (Cl2 or Br2) across a double bond, creating two adjacent C–X bonds, where X is a halogen (Br or Cl).

Heteroatoms

An atom other than carbon, such as oxygen, nitrogen, and sulfur.

High-throughput screening

A process used to screen many compounds of their therapeutic potential. Automated and robotic processes are utilized to run multiple assays in parallel, or all at once, to determine this. The two

characteristics of this process is that it uses fast assays and that it uses massively parallel assays, where the large number of wells and automated processes enable this to occur.

Hit

A compound in an assay which has been determined, through the assay, to have a desired effect.

Hückel's rule

1 of the 3 requirements of aromaticity which represents the amount of π electrons needed to maintain aromaticity calculated by the formula $4n+2$ where n represents a non-negative whole number (0, 1, 2...).

Hybridization

The mixing of two or more standard atomic orbitals (such as s, p, d, f orbitals) to form new hybrid orbitals (such as sp3 orbitals) suitable for bonding.

Hydration reaction

Also known as an acid-catalyzed hydration, this reaction involves the addition of water (H2O) across a double bond, producing an alcohol. This is commonly performed in a dilute aqueous solution of sulfuric acid, H2SO4.

Hydrogenation reaction

Also known as a reduction of alkenes, this reaction adds a hydrogen molecule (H2) to a double bond in a way that each carbon atom bonds with one hydrogen atom. This requires the presence of a metal catalyst.

Hydrohalogenation reaction

The addition reaction of a hydrogen halide to an alkene. This produces an alkyl halide as a product.

Hydrolysis reaction

A reaction which involves using water (*hydro*) to break a molecule apart (*lysis*), such as an ester. The products of ester hydrolysis are a carboxylic acid and an alcohol. This is a reversible reaction, in which the reverse reaction is known as **acid-catalyzed esterification.** Le Chatelier's principle is used to drive this reaction by using a larger amount of water. Heat and an acid catalyst is required for this reaction.

In vitro experiments

Experiments that are conducted in cells or microorganisms outside of their normal biological context. This includes cells grown in a well plate or flasks.

Lead compound

A compound that already exists and its effects are well characterized. It is used to derive novel compounds to test for a desired therapeutic effect. This is done by changing the lead compound's functional groups.

Less substituted

Refers to a carbon atom that is bonded to more hydrogen atoms and less substituents. SN2 reactions favour less substituted carbons.

Miss

A compound in an assay which has been determined, through the assay, to have a non-desired effect.

More substituted

Refers to a carbon atom that is bonded to less hydrogen atoms and more substituents, such as other carbon atoms. SN1 reactions favour more substituted carbons.

Negative control

A control well expected to produce a negative signal. For example, in an ELISA assay, the lack of colour change is considered a negative signal for controls.

Non-polar Bond

A covalent bond where the electron density resides equally between the two atoms, as the electrons aren't largely attracted to one atom over the other.

Nucleophile

An electron-rich species, such as hydroxide (OH-). Nucleophiles seek positively charged or electron-deficient species to form bonds with. Generally, any species, either neutral or anionic, which contains a lone pair of electrons can behave as a nucleophile in an organic reaction.

Nucleophilic substitution reaction

A reaction type which involves the substitution of a leaving group with a nucleophile. The reactants are a nucleophile and an electrophile bonded to a leaving group. The products are the lone leaving group and an electrophile now bonded to the nucleophile. It can be also viewed as the nucleophile "taking place" of the leaving group.

Octet Rule

The tendency of atoms to prefer to have eight electrons in the valence shell to increase its stability. This rule generally holds true for second row elements such as C, N, and O.

Oxidation

In the field of organic chemistry, an oxidation reaction results in either the gain of an electronegative atom (like oxygen, nitrogen or a halide) or the loss of hydrogens atoms. Typically, oxidation of an alcohol or aldehyde increases the number of C–O bonds.

Oxidizing agent

Oxidizing agents are commonly metals with a high oxidation state. Examples of oxidizing agents include potassium permanganate (KMnO4), potassium dichromate, (K2Cr2O7), and pyridinium chlorochromate (PCC).

Oxonium

A cation intermediate that is typically formed when water performs a nucleophilic attack on an electrophilic substrate. The oxygen atom will have a formal charge of +1.

Pheromone

A chemical that is secreted and released outside the body to affect individuals of the same species. These tend to trigger a specific response in the receiving individual, often causing hormonal or behavioural changes.

Polar Bond

A covalent in which the electron density is more biased towards one atom over the other. This is because one atom is more electronegative than the other, pulling electrons towards itself.

Positive control

A control well expected to produce a positive signal. For example, in the ELISA assay, the colourimetric change from blue to green is a positive signal.

Reduction

In the field of organic chemistry, a reduction reaction is defined as the loss of an oxygen atom or gain of two hydrogen atoms. Reducing a carboxylic acid, an aldehyde, or ketone will decrease the number of C–O bonds

Second-order kinetics

A reaction in which the concentrations of two molecules influence the rate of reaction.

SN1 reaction

An SN1 reaction is a nucleophilic substitution reaction that occurs in multiple steps. The leaving group first dissociates, breaking a bond, and the nucleophile subsequently attacks, forming a new bond.

SN2 reaction

An SN2 reaction is a nucleophilic substitution reaction that occurs in a single step with both bond breaking and bond forming happening *simultaneously*.

Stereochemistry

The relative spatial arrangement of groups relative to a carbon-carbon double bond.

Steric effect

The effect that substituents have on a reaction due to the spatial arrangement of the groups. This plays a large part in determining the rate of SN2 reaction for primary, secondary, and tertiary alkyl halides. More sterically hindered compounds, such as the tertiary alkyl halides, have a larger steric effect resulting in a very slow rate for SN2 reactions.

Transition state

The highest energy structure found in a reaction, which shows the partially formed and partially broken bonds. This is found at the maximum of an energy profile diagram.

Trigonal bipyramidal geometry

A geometry where a central carbon is bonded to five substituents. Two groups in the same plane, with two groups pointing downwards, and one pointing upwards.