UNDERSTANDING ORGANIC CHEMISTRY THROUGH COMPUTATION

Nicholas Boaz and Orion Pearce
North Central College

LibreTexts™

Understanding Organic Chemistry Through Computation

Nicholas Boaz and Orion Pearce

North Central College

This text is disseminated via the Open Education Resource (OER) LibreTexts Project (https://LibreTexts.org) and like the thousands of other texts available within this powerful platform, it is freely available for reading, printing, and "consuming."

The LibreTexts mission is to bring together students, faculty, and scholars in a collaborative effort to provide an accessible, and comprehensive platform that empowers our community to develop, curate, adapt, and adopt openly licensed resources and technologies; through these efforts we can reduce the financial burden born from traditional educational resource costs, ensuring education is more accessible for students and communities worldwide.

Most, but not all, pages in the library have licenses that may allow individuals to make changes, save, and print this book. Carefully consult the applicable license(s) before pursuing such effects. Instructors can adopt existing LibreTexts texts or Remix them to quickly build course-specific resources to meet the needs of their students. Unlike traditional textbooks, LibreTexts' web based origins allow powerful integration of advanced features and new technologies to support learning.

LibreTexts is the adaptable, user-friendly non-profit open education resource platform that educators trust for creating, customizing, and sharing accessible, interactive textbooks, adaptive homework, and ancillary materials. We collaborate with individuals and organizations to champion open education initiatives, support institutional publishing programs, drive curriculum development projects, and more.

The LibreTexts libraries are Powered by NICE CXone Expert and was supported by the Department of Education Open Textbook Pilot Project, the California Education Learning Lab, the UC Davis Office of the Provost, the UC Davis Library, the California State University Affordable Learning Solutions Program, and Merlot. This material is based upon work supported by the National Science Foundation under Grant No. 1246120, 1525057, and 1413739.

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation nor the US Department of Education.

Have questions or comments? For information about adoptions or adaptions contact info@LibreTexts.org or visit our main website at https://LibreTexts.org.

This text was compiled on 05/10/2026

TABLE OF CONTENTS

Licensing

1: Introduction to Avogadro

- 1.1: Overview
- 1.2: Background
- 1.3: Computational Instructions
- 1.4: Exercise Questions

2: Bond Lengths and Resonance

- 2.1: Overview
- 2.2: Background
- 2.3: Computational Instructions
- 2.4: Exercise Questions

3: Visualizing Molecular Orbitals with Avogadro and Orca

- 3.1: Overview
- 3.2: Background
- 3.3: Computational Instructions
- 3.4: Exercise Questions

4: Measuring Equilibrium on Cyclohexane Chair Structures

- 4.1: Overview
- 4.2: Background
- 4.3: Computational Instructions
- 4.4: Exercise Questions

5: Computing and Visualizing Infrared Spectra of Organic Molecules

- 5.1: Overview
- 5.2: Background
- 5.3: Computational Instructions
- 5.4: Exercise Questions

6: Manipulating of Molecules in Three Dimensions

- 6.1: Overview
- 6.2: Background
- 6.3: Computational Instructions
- 6.4: Exercise Questions

7: Thermodynamics, Kinetics, and the Reaction Coordinate Diagram

- 7.1: Overview
- 7.2: Background
- 7.3: Computational Instructions
- 7.4: Exercise Questions

8: Understanding the Effect of Solvation on E2 Reactions

- 8.1: Overview
- 8.2: Background
- 8.3: Computational Instructions
- 8.4: Exercise Questions

9: Calculating Bond Dissociation Enthalpy and Analyzing the Radical Chlorination of Norbornane

- 9.1: Overview
- 9.2: Background
- 9.3: Computational Instructions
- 9.4: Exercise Questions

10: Examining the Synthesis of Naturally Occurring Cyclobutane Compounds

- 10.1: Overview
- 10.2: Background
- 10.3: Computational Instructions
- 10.4: Exercise Questions

11: Examining the Energetics of Selectivity in Electrophilic Aromatic Substitution

- 11.1: Overview
- 11.2: Background
- 11.3: Computation Assignment and Exercise Questions

12: Measuring the influence of ring strain in ether substitution

- 12.1: Overview
- 12.2: Background
- 12.3: Computational Instructions
- 12.4: Exercise Questions

Index

Glossary

Detailed Licensing

Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

CHAPTER OVERVIEW

1: Introduction to Avogadro

1.1: Overview
1.2: Background
1.3: Computational Instructions
1.4: Exercise Questions

This page titled 1: Introduction to Avogadro is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

1.1: Overview

Learning Objectives

- After completing this exercise students will be able to draw simple molecules and optimize their geometry in the Avogadro molecule editor.
- Students will be able to predict the geometry of a carbon atom (or heteroatom) using VSEPR theory and compare the bond angles to a molecule simulated in the Avogadro molecule editor.

This exercise seeks to help you reinforce the concept of molecular and electronic geometry and visualize molecules in 3-dimensions. To do this we will be introducing the use of Avogadro, an open-source program designed to edit and draw molecules in 3-dimensions.[1,2] This program will allow us to estimate geometries and measure bond lengths and bond angles. We will then compare these bond angles and molecular geometries to those predicted using valance shell electron pair repulsion theory (VSEPR).

Faculty Notes: This exercise is designed to help students visualize molecules in three dimensions and cement the concepts of VSEPR theory. This exercise is designed to be completed when students are learning about the molecular and electronic geometry of simple organic molecules. Because this work is primarily concerned with VSEPR in in the context of introductory organic chemistry, 5 coordinate and greater geometries will not be covered. This exercise takes students about 30 minutes to complete.

This page titled 1.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

1.2: Background

Atoms within an organic molecule can adopt a variety of differing geometries based upon the number and type of bonds that they contain as well as the number of non-bonding electrons that they have. One of the methods that organic chemists use to determine the geometry of atoms in a molecule is Valence Shell Electron Pair Repulsion (VSEPR). This method puts the bonding and non-bonding electrons in a molecule into groups.

Because the negative charges in each electron group repel each other, the atom is most stable when the electron groups are positioned as far apart from each other as possible. As shown in Figure 1, atoms with 2 VSEPR groups will put these groups in a linear arrangement. Atoms with 3 VSEPR groups will place these groups in a trigonal plane, while atoms with 4 VSEPR groups will place these groups at the corners of a regular tetrahedron. These three electronic geometries, linear, trigonal planar, and tetrahedral, compose most electronic geometries in organic chemistry.

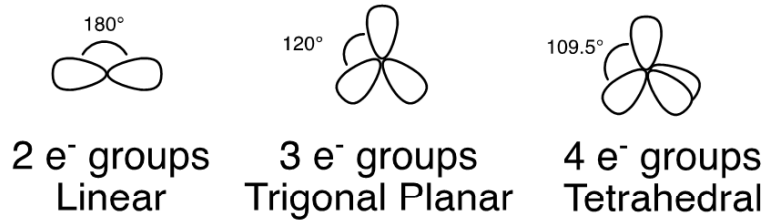


Figure 1. Electronic geometries for 2, 3, and 4 VSEPR electron groups.

In VSEPR theory a group of electrons is composed of either a σ (sigma or single) bond or a pair of non-bonding electrons. For example, as shown in Figure 2A, the nitrogen atom in trimethylamine has 4 groups, 3 σ bonds and one non-bonding pair of electrons.

This means that the nitrogen in this compound has a tetrahedral electronic geometry. The carbon atom in tetrachloroethene, however, only has 3 electron groups because it has 3 σ bonds and it doesn't have any lone pairs (Figure 2B). Remember that a double bond is made up of 1 σ bond and 1 π or pi bond; π bonds exist in the same area as the σ bond and so the electrons together only form one group. Therefore, the carbon in tetrachloroethene has a trigonal planar electronic geometry. Finally, the indicated carbon in 2-butyne (Figure 1C.) has a linear electronic geometry because it has two σ bonds and no pairs of non-bonding electrons. Similar to the double bond, a triple bond is made up of 1 σ bond and 2 π bonds and therefore only counts as one group.

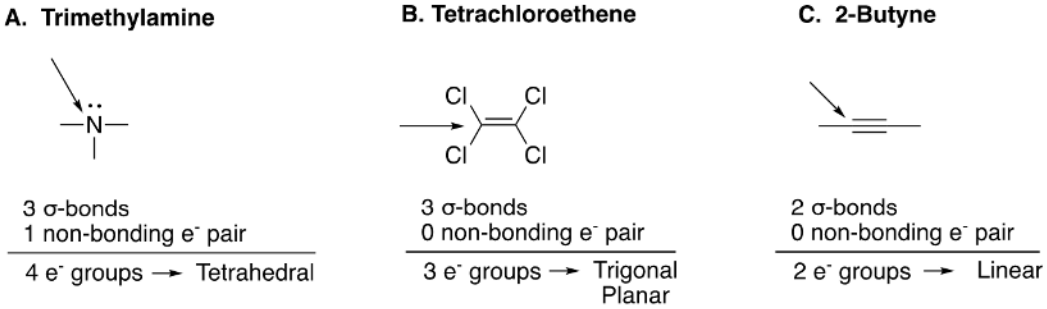


Figure 2. Determining the number of VSEPR groups for indicated atoms.

Electronic geometry reflects the position of electrons around each atom, but many molecular properties are only dependent on the position of the atoms, not those of the electrons. We define the molecular geometry based solely upon the position of atoms around a central nucleus, and not upon electron groups. The molecular geometry is however directly influenced by electronic geometry. For example, the electronic geometry of the oxygen in water (H_2O) is tetrahedral because it has four groups (2 σ bonds and 2 non-bonding electron pairs). However, when only the atoms in the water molecule are considered, water will appear bent rather than tetrahedral. The relationship between electronic geometry and molecular geometry is described in Figure 3.

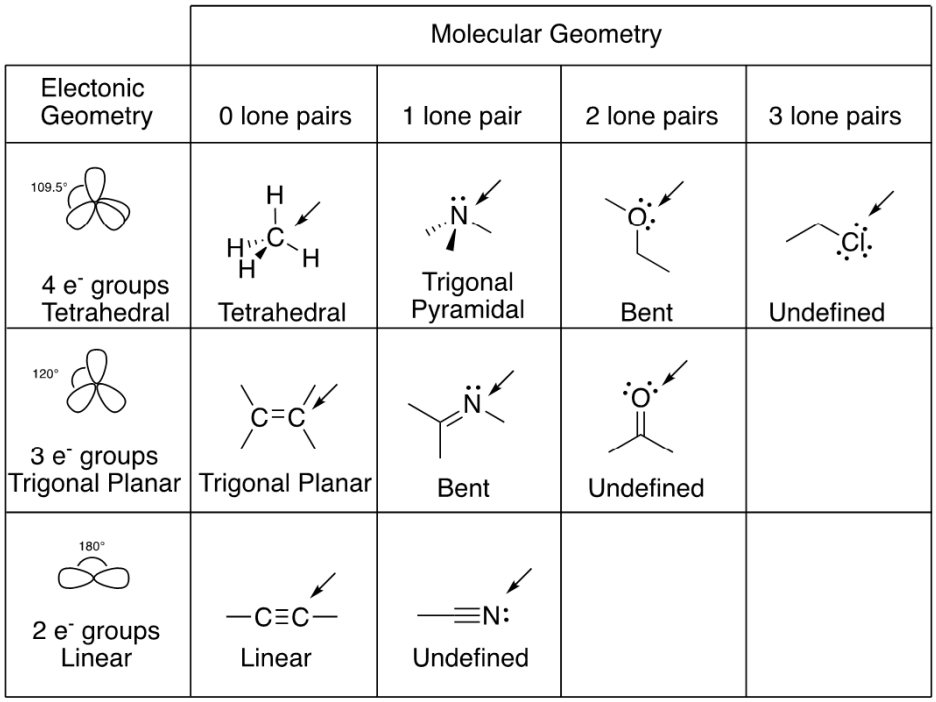


Figure 3. The relationship between the number of electron lone pairs and the molecular geometry of an atom.

An important point to note about VSEPR theory is that it provides idealized bond angles and geometries for atoms in molecules. The experimental or computed bond angles may be slightly different. For instance, the $\mathrm{H-O-H}$ bond angle in water would be predicted to be 109.5° because of its tetrahedral electronic geometry. The experimental value of this angle is slightly smaller at 104.45°. One reason for this is that the non-bonding electron pairs are better at repelling other groups than sigma bonds because they don't have any positively charged atomic nuclei to draw in the electrons. This has the effect of "squishing" the two $\mathrm{O-H}$ sigma bonds closer together than the ideal bond angle predicted by VSEPR (Figure 4).

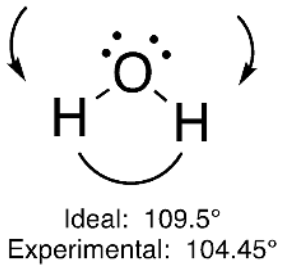


Figure 4. Efficient repulsion by the non-bonding electron pairs of water "squishes" the $\mathrm{O-H}$ bonds closer together than the idealized bond angle.

This page titled 1.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

1.3: Computational Instructions

In this exercise we will learn to draw simple molecules in Avogadro, an open-access molecular visualization software package. Start by opening Avogadro on your computer by double clicking on the Avogadro icon and click on the draw button (looks like a pencil) to open the drawing menu (Figure 5).

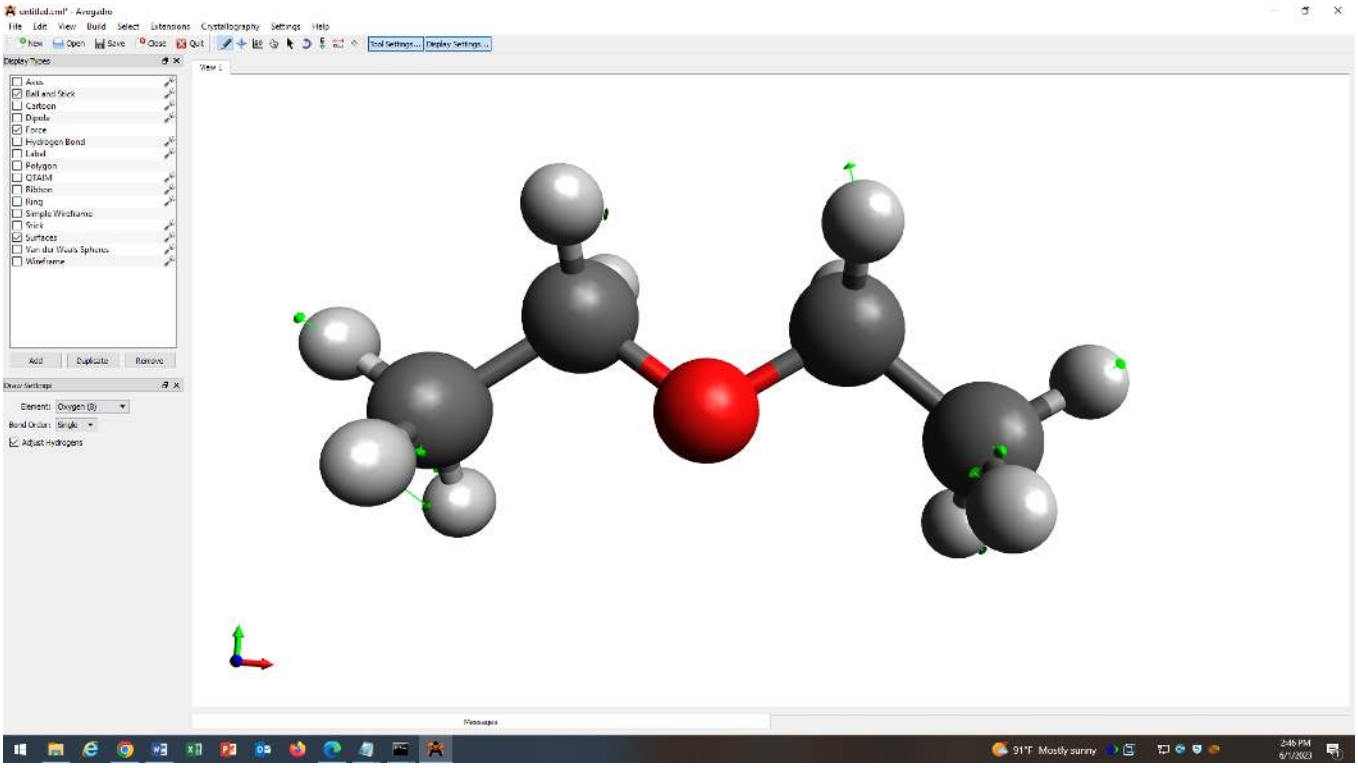


Figure 5. Avogadro with drawing menu button indicated with a red arrow and diethyl ether drawn.

From this menu you can select the atom that you would like to draw and the number of bonds that you would like it to make. Draw the structure of diethyl ether to learn how the molecular editor works. Note that with the adjust hydrogen button selected, Avogadro will automatically adjust the number of hydrogens to ensure that your molecule obeys the octet rule.

When drawing molecules your bond angles and lengths will often look different than ideal (drawing on a computer is not always easy). We can provide a more accurate geometry of your diethyl ether molecule by performing a quick optimization. You can perform this operation by clicking extensionsoptimize geometry.

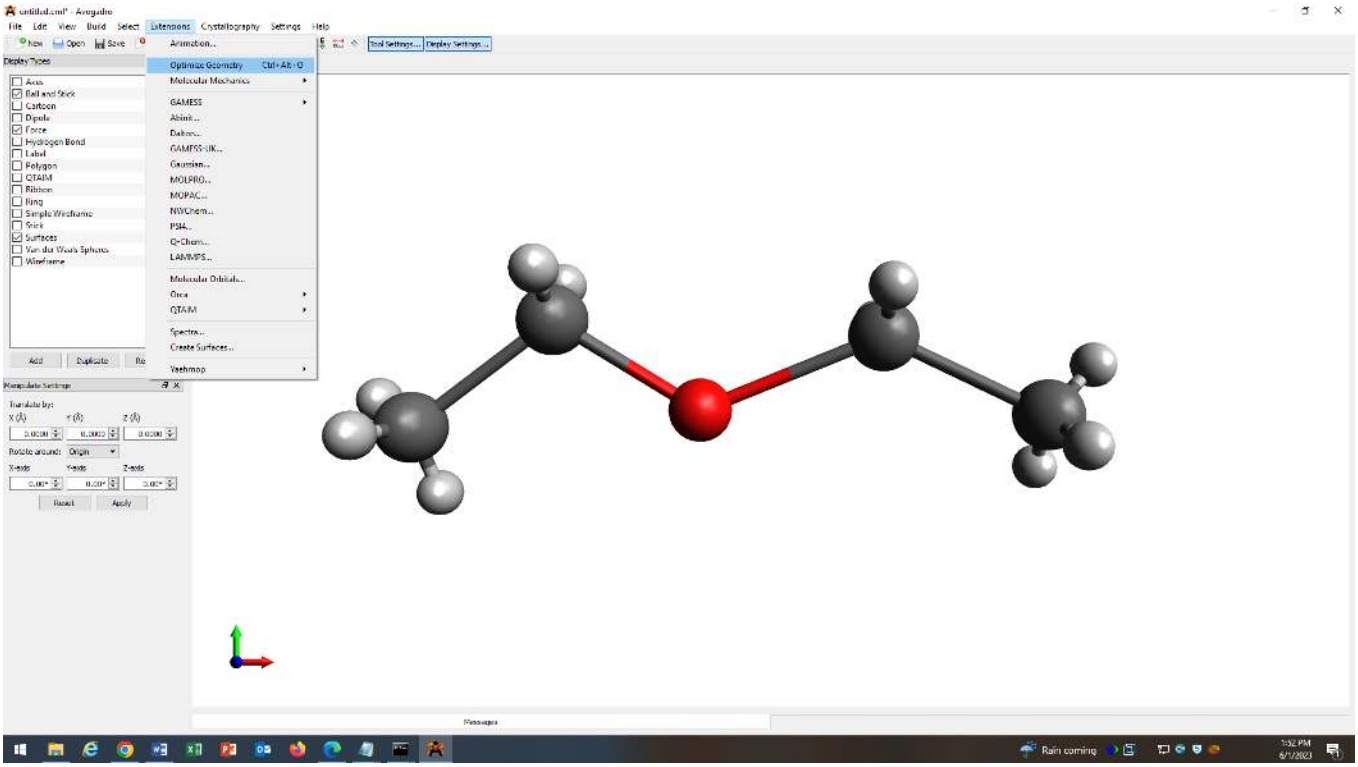


Figure 6. Avogadro with the optimize geometry option indicated.

After optimizing the geometry of your molecule, you can manipulate the molecule in three dimensions as well as measure properties such as bond lengths and angles. To rotate the molecule in three dimensions, press the navigation tool button which looks like a compass rose, as shown in Figure 7. You can then click and drag anywhere in the main display panel to rotate the molecule.

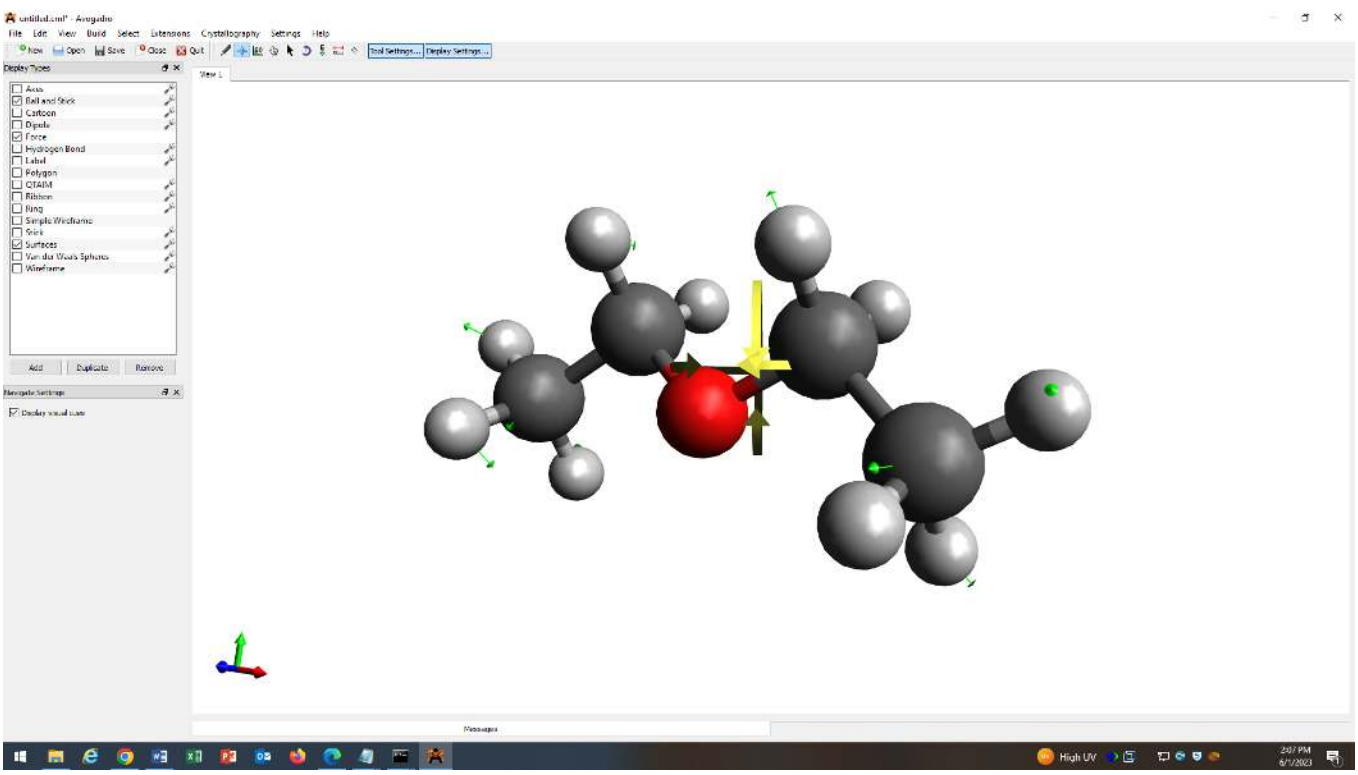


Figure 7. Avogadro with the navigation tool indicated. When rotating the molecule, the program will indicate the direction of rotation with bold yellow arrows.

To measure bond lengths, click the measurement tool, which looks like a ruler, in the main tool panel. Then left click on the two atoms (one after the other) that you would like to measure. When you have measured the length of interest you can reset the measurement tool by right clicking anywhere in the main display panel. To measure a bond angle, click the three atoms (one right after another) composing the angle that you would like to measure. The angle will appear on the bottom left of the main display panel as well as the individual bond lengths for atom 1 to atom 2 and atom 2 to atom 3. For example, we can measure the $C-O-C$ bond angle of diethyl ether using this method to find a bond angle of 111.7°.

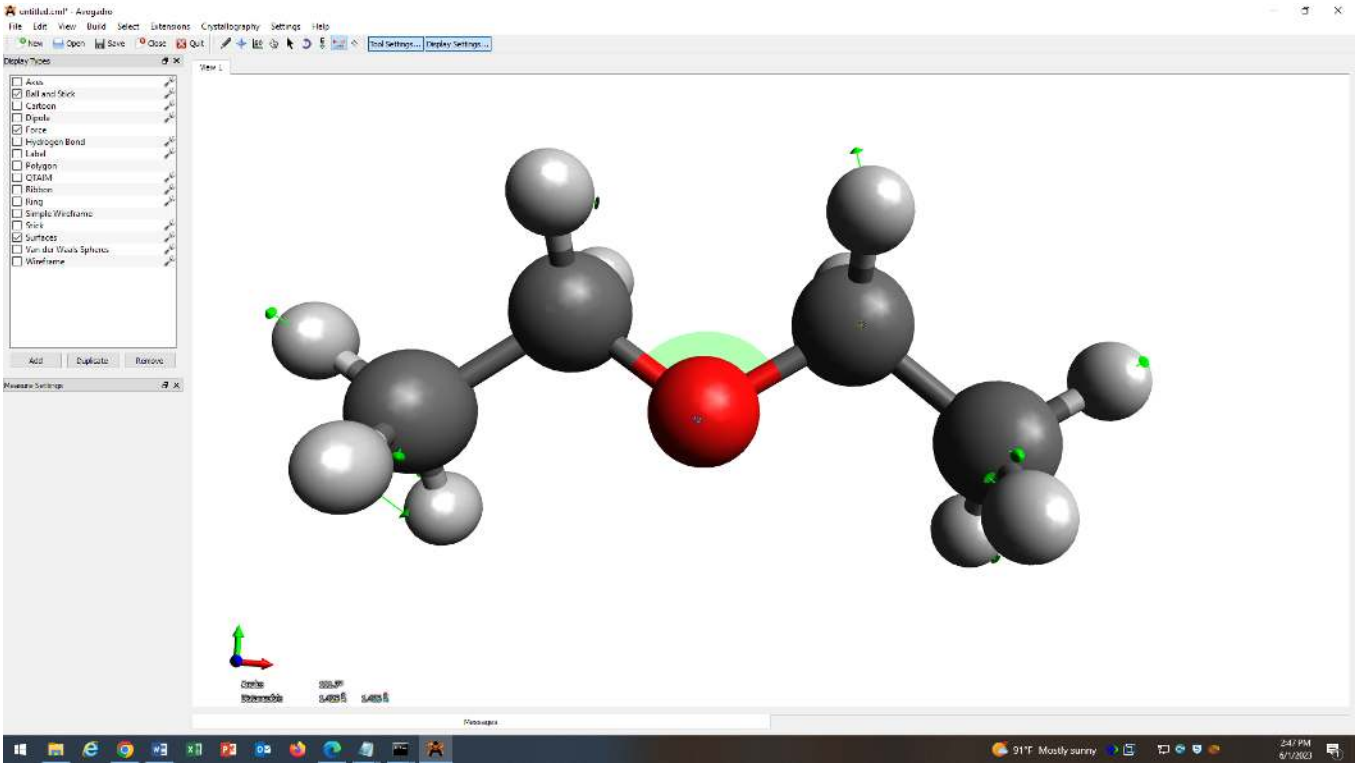


Figure 8. Avogadro with the measurement tool (Blue Arrow) open displaying the oxygen-carbon-oxygen bond angle of diethyl ether. The bond lengths for the carbon-oxygen bonds and the $C-O-C$ bond angle are shown at the bottom left of the screen (Red Arrow).

References

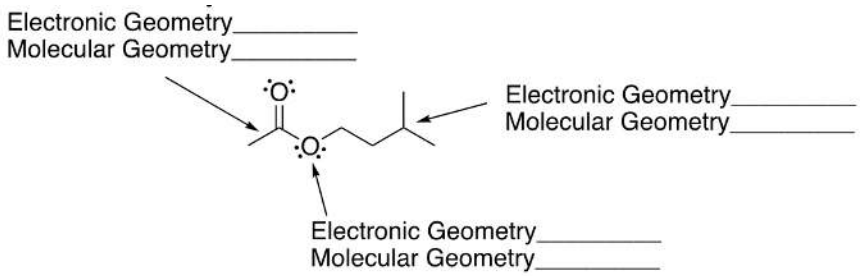
1. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminformatics* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
2. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/

This page titled 1.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

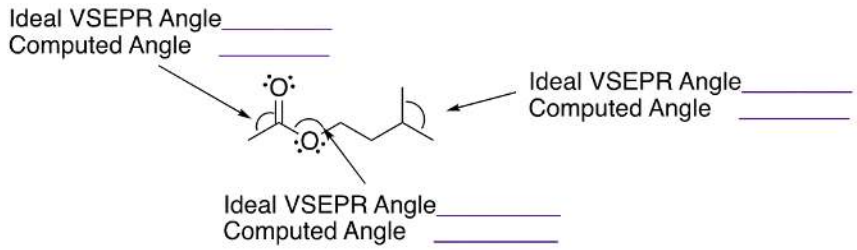
1.4: Exercise Questions

1. Consider the structure of the following isoamyl acetate molecule. This molecule is partially responsible for the taste and smell of a banana.

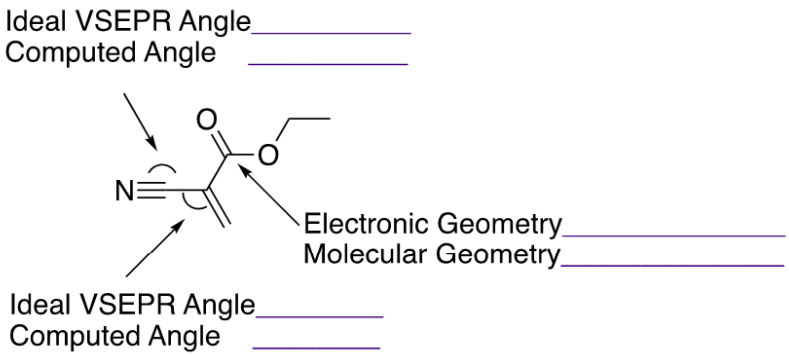
   A. Using VSEPR theory please show the indicated electronic and molecular geometries of isoamyl acetate.



   B. Draw isoamyl acetate in Avogadro and optimize its geometry. Measure the indicated bond angles and compare them to their predicted ideal bond angles.

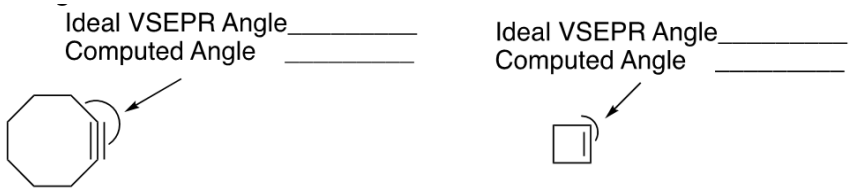


2. Please draw and optimize ethyl cyanoacrylate, as shown below, using Avogadro. Please use the bond angles in this structure and your knowledge of VSEPR to provide the missing information. Ethyl cyanoacrylate is often used as a component of fast drying glues often referred to as superglue.



3. Not all molecules have bond angles or molecular geometries that match what is predicted via VSEPR. There are instances when VSEPR theory breaks down and you have deviations in bond angles and molecular geometry.

   A. One instance of VSEPR theory failing to accurately predict the geometry of an atom occurs when a ring constrains the preferred bond angle. Please draw both cyclooctyne and cyclobutene and optimize their structure in Avogadro to provide the missing information.

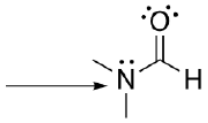


   B. Another instance when VSEPR theory fails to accurately predict the geometry of an atom is when an atom containing a non-bonding pair of electrons is adjacent to a double bond, which results in partial double bond character. For example, N,N-

dimethylformamide (DMF) has a nitrogen with a non-bonding pair of electrons next to a carbonyl functional group. In this case the nitrogen-carbonyl carbon bond will have the bond strength and length in between a single and double bond. This behavior is known as electron delocalization, and we will learn more about it in subsequent exercises. Please draw and optimize the geometry of a molecule of DMF in Avogadro and provide the missing information.

Predicted Molecular Geometry by VSEPR_____

Computed Molecular Geometry using Avogadro_____



This page titled 1.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

2: Bond Lengths and Resonance

This exercise seeks to reinforce the idea of resonance in describing the electronic structure of simple organic molecules. To do this, we will model simple molecules which do and do not have significant resonance using the Orca and Avogadro software packages. This exercise shows that molecules with significant resonance structures often have what is referred to as partial double bond character.

2.1: Overview

2.2: Background

2.3: Computational Instructions

2.4: Exercise Questions

This page titled 2: Bond Lengths and Resonance is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

2.1: Overview

Learning Objectives

- Students will be able to predict which bonds on a line bond structure will have partial double bond character.
- Students will be able to use Avogadro and Orca to calculate and visualize the geometry of molecules using density functional theory.

Overview: This exercise seeks to reinforce the idea of resonance in describing the electronic structure of simple organic molecules. To do this, we will model simple molecules which do and do not have significant resonance using the Orca and Avogadro software packages.[1–5] This exercise shows that molecules with significant resonance structures often have what is referred to as partial double bond character.

Faculty Notes: This exercise is designed to help students grasp the concept of resonance structures and resonance hybrids in the description of molecules with delocalized electrons. It is recommended that the concept of resonance structures and the arrow pushing required to interconvert them be covered in lecture prior to assigning this activity. A standard desktop computer takes about 6 minutes to run the computation in this exercise. Overall, the exercise should take students about an hour to complete.

This page titled 2.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

2.2: Background

Organic molecules are often represented using Lewis structures or the line bond formalism. In both molecular representations, a single line between atoms represents a single bond sharing a pair of electrons. Similarly, a double or triple bond, sharing 2 or 3 pairs of electrons, are represented by 2 or 3 lines between atoms respectively. Representing atomic bonding in this manner, however, doesn't always provide an accurate picture of electronic structure. Specifically, some molecular species have electron pairs that are spread over a larger area than just one bond in a concept known as delocalization. For example, the allyl anion, shown in Figure 1, has one carbon-carbon single bond and one carbon-carbon double bond. The actual structure of this allyl anion has two carbon-carbon bonds with a bond order of about 1.5.

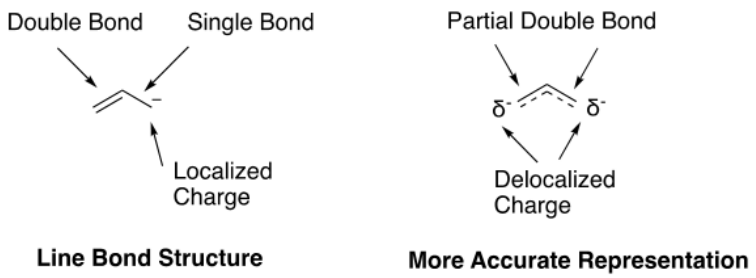


Figure 1. A comparison between the line bond structure and actual structure of the allyl anion.

Rather than throwing the proverbial baby out with the bathwater, chemists decided to adapt the method of drawing molecules using line bond structures to better represent the electronic geometry of species with delocalized electrons. In this method, multiple line bond drawings, known as resonance structures, represent different aspects of a molecule's electronic structure. An observer is then expected to mentally merge the resonance structures together to get a more realistic picture of the molecule. More often, chemists will average the resonance structures to produce a realistic picture known as a resonance hybrid. As shown in Figure 2, two resonance structures of the allyl anion are averaged to make a more accurate resonance hybrid.

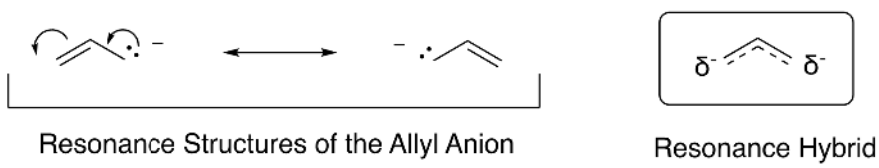


Figure 2. (Left) Two resonance structures of the allyl anion with their interconverting curved arrow shown. (Right) The resonance hybrid produced by the averaging of the two resonance structures.

In lecture, you will have learned how chemists create resonance structures of molecules using a series of curved arrows to push electrons from one part of the molecule to another. In the computational exercise that follows, you will examine resonance by optimizing the geometry of N, N-dimethylacetamide, whose structure is shown in Figure 3.

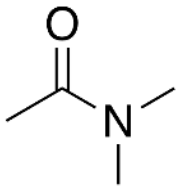


Figure 3. Line bond structure of N, N-dimethylacetamide.

In a previous exercise, we have done basic geometry optimization within Avogadro. This exercise utilizes a more powerful set of techniques based on Density Functional Theory (DFT). On a basic level, DFT assumes that the electrons reside in predefined regions of space around each atom, with a mathematical function describing how likely it is to find each electron in at a given location (its density functional). Starting from a predetermined set of these functions (called a basis set), our software ORCA will try to "wiggle" each atom, looking to see if by moving the atoms it can relax the molecule to a lower energy than its starting position. By successively moving atoms and recalculating the electron energies from the density functionals, ORCA is able to more

accurately find the structure of a molecule than Avogadro. This accuracy comes at a price however, as the calculations involved in density functional theory are quantum mechanical and take much more computing power than Avogadro's optimization.I

This page titled 2.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

2.3: Computational Instructions

Start by creating a folder on your desktop and naming it Resonance. Next, you should download the supplementary files associated with this exercise and move them to a folder that you just created. Contained within the supplementary files you will find a subfolder labeled DMA, which stands for dimethyl acetamide. Open DMA_coord.xyz in Avogadro to examine the structure of dimethyl acetamide. The starting structure of DMA should look like Figure 4 and show a functional group known as an amide, where a nitrogen is adjacent to a carbon-oxygen double bond. This file contains the input structure that we are going to tell our computational chemistry software package to optimize at the DFT level of theory.

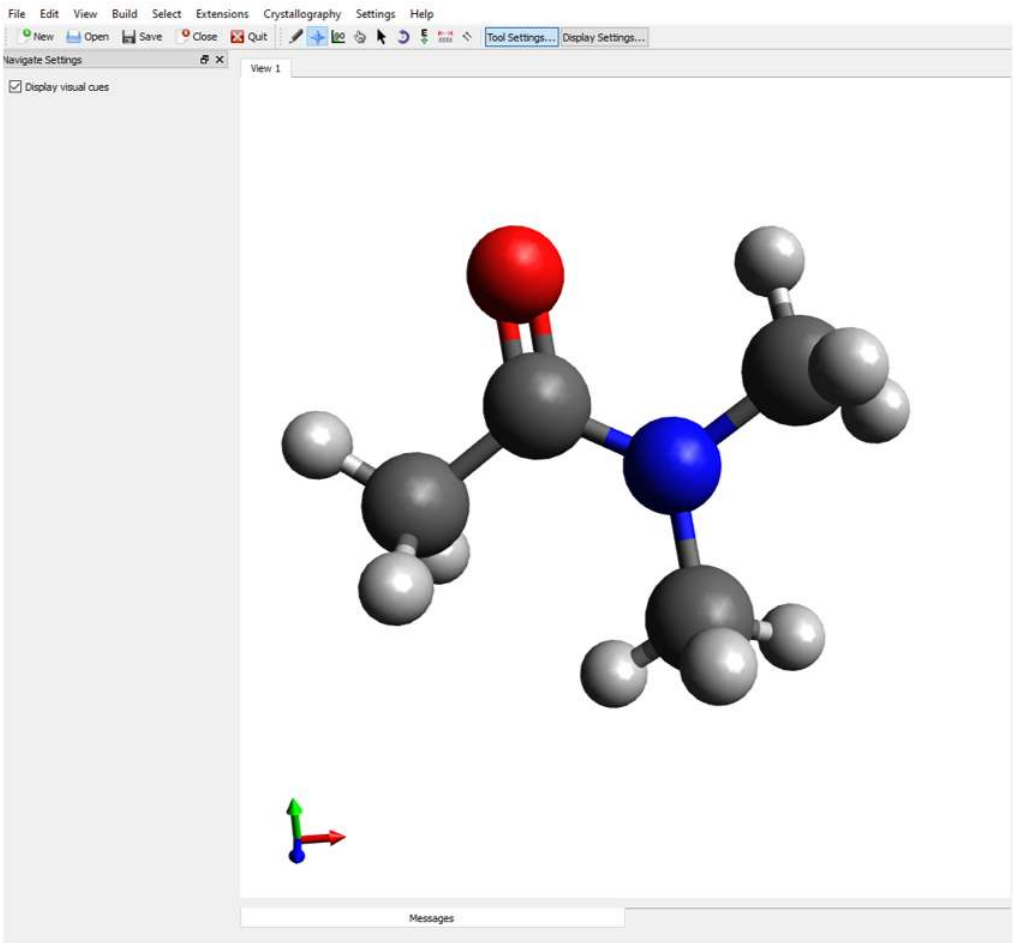


Figure 4. N, N-diemthylacetamide shown in Avogadro.

To optimize the structure of DMA we need to have an input file that tells Orca, the computational chemistry program that we are using, what we want to calculate and on what structure Orca should run the calculation. You can view this input file by clicking on DMA.inp within the DMA subfolder that you downloaded as part of the supplementary files. As shown in Figure 5, the input file is a brief text file with instructions for your computer. The first line of the input file, which starts with a number sign (#), is a comment indicating what the script is trying to accomplish. In this case, we are optimizing the geometry of DMA. The second line which begins with an exclamation point (!) tells Orca the functional of the calculation (B3LYP), the basis set (DEF2-SVP), and what we are asking the program to calculate (OPT-geometry optimization). Line 3, which beings with an asterisk (*), tells Orca what file contains the coordinate files for our molecule. The phrase xyzfile tells the computer that the file you are using has the molecule described using XYZ cartesian coordinates. There are then a series of two numbers which provide information about charge and spin of the chemical structure. The first number is the net charge of molecule(s) in the XYZ file. In this case it is zero because DMA is a neutral molecule. The second number is the net spin multiplicity (S) of the molecule that you are calculating, which in this case is 1 (singlet). We will talk more about the spin multiplicity of molecules in a later exercise, but for now you can

think about this meaning that all electrons are paired so that they have a partner of the opposite spin. Finally, this line has the name of the coordinates file for DMA that we examined earlier.

```
# DMA Geometry Optimization
!B3LYP def2-SVP OPT
* xyzfile 0 1 DMA_coord.xyz
```

Figure 5. The Orca input script for the geometry optimization of N, N-dimethylacetamide. The blue arrow indicates the calculations that Orca will run, and the method used to perform the calculation. The red arrow tells the computer what file to run the calculations on.

Because Orca does not have a graphical user interface (GUI), we will need to tell the computer to run the calculation using the command prompt of the computer. To do this, right click the start button on your PC and search for the command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter in the command prompt. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter, the computer will paste a new line indicating that the current directory has changed, as shown in Figure 6A. To find the file path of your input script, right click on the input script within the DMA subfolder and select properties. The file path will appear under location, and you can highlight and copy this file path as shown in Figure 6B.

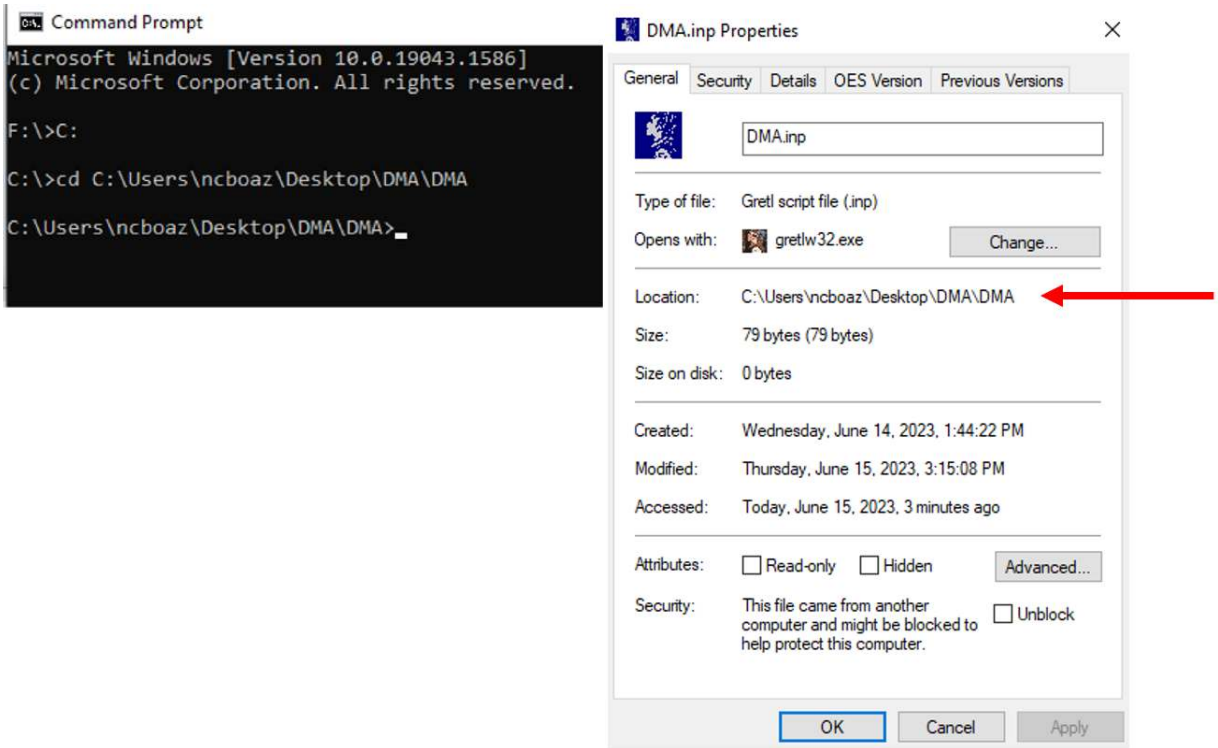


Figure 6A. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **6B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca DMA.inp > DMA.out and pressing enter in the command prompt. At first, it may not appear like anything is happening, but the folder on your desktop labeled DMA will quickly become populated with the output of your calculation. Depending upon the speed of your computer, the calculation will take from 1-5 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 7)

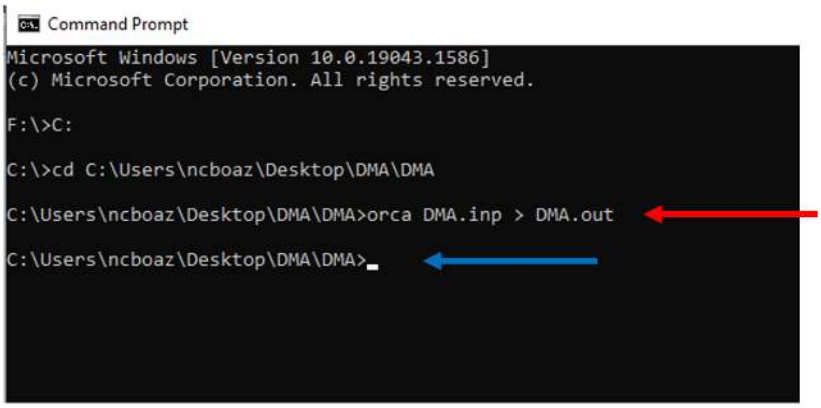


Figure 7. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in DMA.inp and that the results of this calculation should be placed in the output file DMA.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

You can examine your results by opening the final geometry file DMA.xyz in Avogadro. To measure the bond lengths and angles, click on the measure button (looks like a ruler) and click on the atoms whose bond lengths and angles you want to measure (Figure 8).

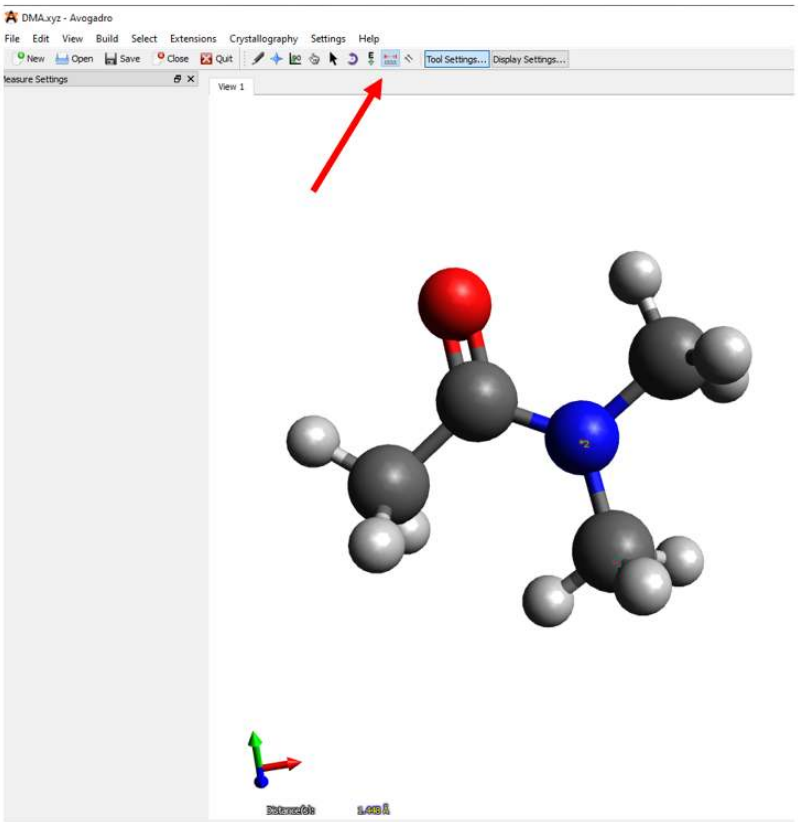


Figure 8. Opening the DMA.xyz file to examine the results of the calculation. To measure bond lengths and angles press the measure tool that is indicated by a red arrow.

References

1. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J Cheminform* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
2. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.

3. Neese, F. The ORCA Program System. *WIREs Computational Molecular Science* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
4. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Computational Molecular Science* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
5. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.

This page titled 2.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

2.4: Exercise Questions

1. Consider the structure of N,N-dimethylacetamide show below. Using your knowledge of resonance please draw the two additional resonance structures associated with this compound. For full credit, please show the curved arrows used to interconvert these structures.

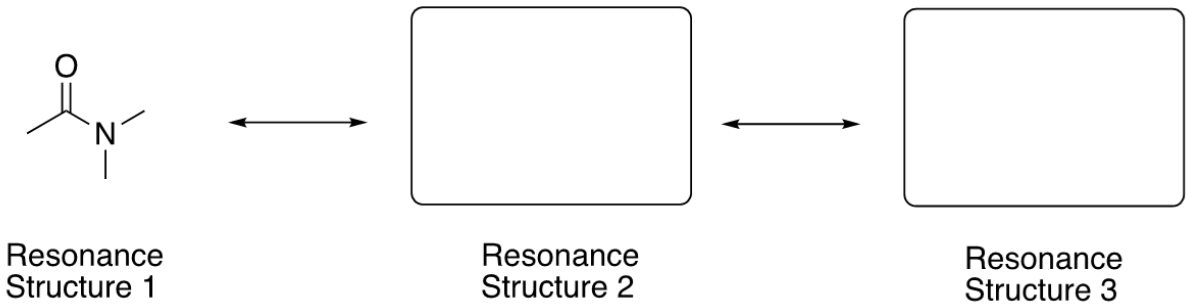


Figure 2.4.1: Copy and Paste Caption here. (Copyright; author via source)

2. Please average the structure of the three resonance structures and draw a resonance hybrid representing a more realistic picture of the electronic structure of the molecule (using dashed lines to indicate partial bonds).
3. In Avogadro, open the DMA.xyz file produced by ORCA and measure values indicated in the structure below.

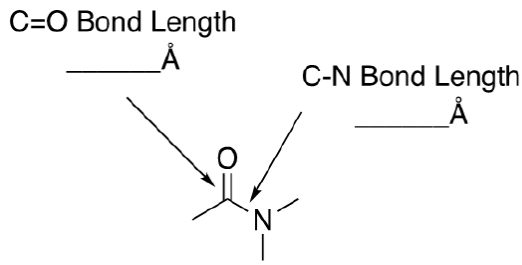


Figure 2.4.1: Copy and Paste Caption here. (Copyright; author via source)

4. To find computational evidence of electron delocalization we need to compare the bond length values of DMA to similar bonds that don't have the ability to form resonance structures with the lone pair on nitrogen. To do this we will examine bond lengths on acetone and trimethyl amine.
   A. Open the geometry coordinate files for acetone and dimethylamine in Avogadro and measure the values indicated in the structures below so that we can compare them to the bond lengths in DMA.

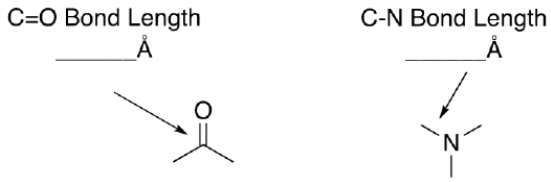


Figure 2.4.1: Copy and Paste Caption here. (Copyright; author via source)

   B. Calculate the % difference in bond lengths between the $\mathrm{C=O}$ bond in acetone and that in DMA.

$$\%\ \text{Difference} = \frac{(\text{ Bond Length DMA-Bond Length Acetone })}{\text{Bond Length Acetone}} \times 100\%$$

   C. Calculate the % difference in bond lengths between the C-N bond in trimethylamine and that in DMA.

$$\%\ \text{Difference} = \frac{(\text{ Bond Length DMA-Bond Length Trimethylamine})}{\text{Bond Length Trimethylamine}} \times 100\%$$

   D. Given the % difference calculations what do you think the bond order (single, double, 1.5 etc.) is for the $\mathrm{C=O}$ and $\mathrm{C-N}$ bonds in DMA? Please make a prediction for both the $\mathrm{C=O}$ and $\mathrm{C-N}$ bonds. Does this fit with the resonance hybrid that you constructed above? Please explain.

5. One of the ways in which resonance works is that electrons communicate between bonds and atoms via a network of unhybridized P orbitals. For example, in methyl vinyl ketone each of the atoms involved in the resonance associated with the molecule has an unhybridized p-orbital

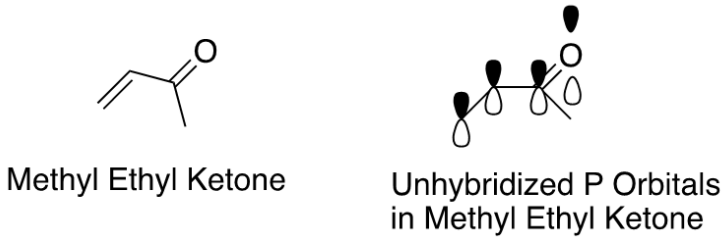


Figure 2.4.1: Copy and Paste Caption here. (Copyright; author via source)

A. Using your knowledge of VSEPR and hybrid orbital theory please indicate what the electronic geometry, molecular geometry, and hybridization would be expected to be of the nitrogen atom.

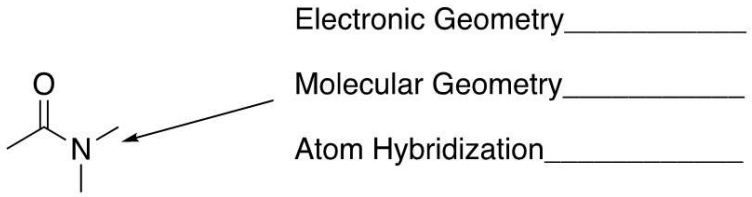


Figure 2.4.1: Copy and Paste Caption here. (Copyright; author via source)

B. Examine the dimethylacetamide output file and determine the molecular geometry of the nitrogen atom. What geometry best describes its bonding.

C. Using your answer from B. What hybridization best fits the geometry you described above? Does it have an unhybridized P orbital that the nitrogen could use to delocalize electrons via resonance?

This page titled 2.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

3: Visualizing Molecular Orbitals with Avogadro and Orca

This exercise will help you to better understand the concept of molecular orbital theory and visualize bonding and antibonding molecular orbitals. In the lecture portion of organic chemistry, you will have learned how to predict the geometry of molecular orbitals for specific functional groups (*e.g.* carbonyls, C-Br bonds etc.).

3.1: Overview

3.2: Background

3.3: Computational Instructions

3.4: Exercise Questions

This page titled 3: Visualizing Molecular Orbitals with Avogadro and Orca is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

3.1: Overview

Learning Objectives

- Students will be able to use Orca and Avogadro to generate molecular orbital diagrams of simple molecules containing common functional groups.
- Students will be able to identify HOMO's and LUMO's (Frontier Molecular Orbitals) of molecules and relate these to where reactions are likely to occur.
- Students will be able to relate their simplified molecular orbital diagrams of portions of molecules to those generated *in silico* (on a computer).

Overview: This exercise will help you to better understand the concept of molecular orbital theory and visualize bonding and antibonding molecular orbitals. In the lecture portion of organic chemistry, you will have learned how to predict the geometry of molecular orbitals for specific functional groups (*e.g*. carbonyls, C-Br bonds etc.). While this approach is extremely useful for determining the general shape of these orbitals, it isn't always convenient for molecules with large numbers of atoms. Moreover, this approach doesn't allow for the calculation of energy levels of molecular orbitals. The power of modern computers allows us to calculate the molecular orbitals of a small molecule in a few minutes. To do this, we will be using the quantum chemistry package called Orca to calculate the molecular orbital shapes and energy levels.[1–3] After this calculation, we will visualize the orbitals and read their energies using Avogadro. [4,5]

Faculty Notes: This exercise is designed to help students understand the shapes and energy levels of molecular orbitals. Specifically, this is designed to complement an introductory discussion of molecular orbital theory where students are taught to generate simplified molecular orbitals for diatomic molecules and/or two atom functionality of a more complex molecule. Before completing this exercise, students should have been exposed to the basics of molecular orbital theory including the HOMO and LUMO terminology. A standard desktop computer takes about 30 seconds to run the computation in this exercise. Overall, the exercise should take students about an hour to complete.

This page titled 3.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

3.2: Background

Molecular orbital theory uses orbitals that belong to the entire molecule to house electrons and represents a more complex theory of bonding than valence bond theory. Specifically, molecular orbitals are constructed by mathematically combining atomic orbitals (s, p, d etc.) using a process known as linear combination of atomic orbitals (LCAO). This process mathematically combines atomic orbitals of similar symmetry and energy both in phase to make bonding orbitals and out of phase to create antibonding orbitals. The mathematics used in LCAO is complex, but doesn't need to be understood to successfully use M.O. theory in a sophomore-level organic chemistry class. For example, we can create a simplified molecular orbital analysis of the H-F bond of hydrogen fluoride by visually combining the sp^3 orbitals of fluorine and the s orbital of hydrogen both in phase (to create the σ bonding orbital) and out of phase (to create the σ^* antibonding orbital) as shown in Figure 1. Recall that bonding orbitals have more electron density between the two nuclei, while antibonding orbitals have more electron density outside of the bond axis. The three additional sp^3 orbitals on fluorine act as non-bonding orbitals in the molecular orbital diagram and function as lone pairs on the fluorine.

These lone pairs represent the highest occupied molecular orbital(s) (HOMO) for HF. The lowest unoccupied molecular orbital (LUMO) represents the lowest energy orbital that doesn't have any electrons in it. In this example the LUMO is the σ* antibonding orbital. Please note that a more accurate molecular orbital picture would be generated by directly combining the s and p orbitals of fluorine with the s orbital of hydrogen, but this is more challenging to do.

The HOMO and LUMO are considered frontier molecular orbitals because they are at the frontier of where electrons are (or are not). When a molecule donates electrons, they will come from the HOMO and when a molecule accepts electrons, they will be placed in the LUMO. For example, if HF were to act as an electron pair donor (Lewis base) it would use one of the lone pairs that are acting as a HOMO. If HF were to act as an electron pair acceptor (Lewis acid) it would put a pair of electrons into the LUMO. (σ^* orbital). This would cause the corresponding H-F sigma bond to break as the LUMO is a σ antibonding orbital.

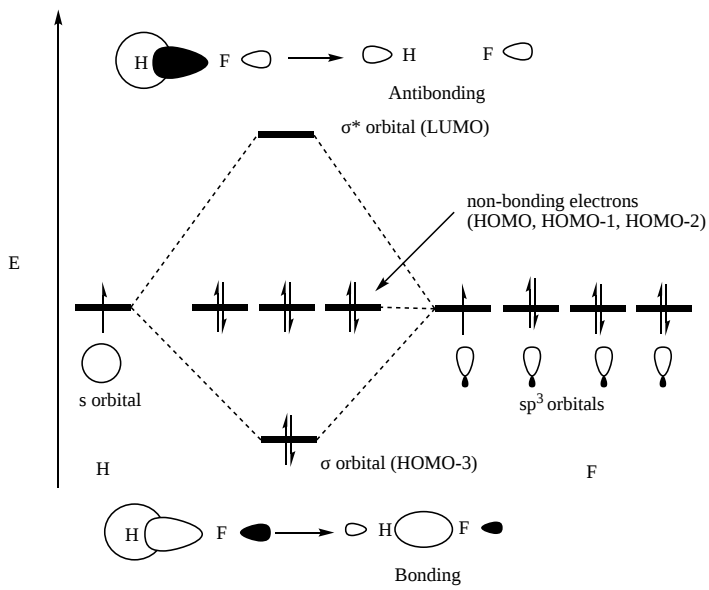


Figure 1. The simplified molecular orbital diagram of the H-F bond in hydrogen fluoride made by visually combining the sp^3 orbitals of fluorine and the s orbital of hydrogen in and out of phase.

While visually combining orbitals in and out of phase works in a qualitative sense for diatomic or selected portions of molecule (*e.g.*, π-systems), it becomes more difficult to do this for more complex systems. Moreover, it is not possible to compute the energy values of molecular orbitals with this visual simplification. With modern computers calculating the molecular orbitals of many different small molecules is convenient and easy. Specifically, in the computational exercise that follows we will be using the quantum chemistry program Orca and a method known as density functional theory to calculate the molecular orbitals of small molecules. By working through the following tutorial, you will learn how to calculate the molecular orbitals of simple molecules using Orca.

This page titled 3.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

3.3: Computational Instructions

Start by creating a file folder on your desktop and name it MO_Exercise. Next, you should open Avogadro on your computer and draw a molecule of hydrogen fluoride in drawing mode and minimize its energy by clicking extensions > optimize geometry. You should then save the file as HF_coord.xyz in the folder that you just created.

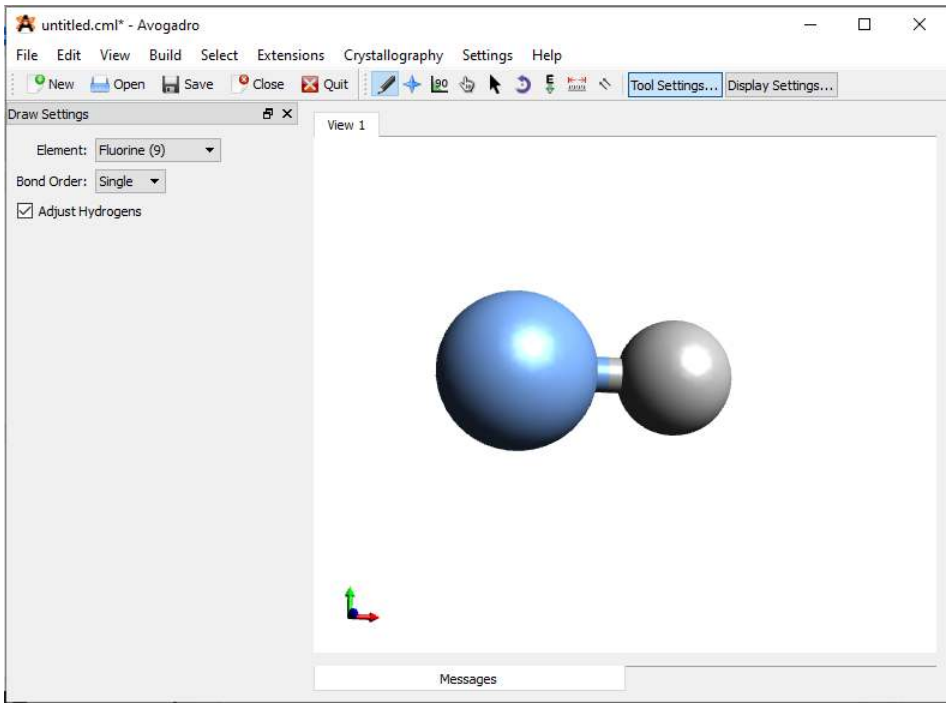


Figure 2. The structure of hydrogen fluoride shown in Avogadro.

After creating the hydrogen fluoride coordinate file, you should download the template Orca script that we will use to tell the computer what to calculate and what coordinates to run the calculation on. Save this Orca script template as HF.inp to the MO Exercise folder that you created above.

As was the case with the previous exercise, the Orca script template, shown in Figure 3, starts with a # symbol which indicates a comment line where we can describe the calculation that we are performing. The second line, which begins with a ! symbol, tells Orca the functional of the calculation (B3LYP), the basis set (6-31G*), and what we are asking the program to calculate (OPT-geometry optimization, FREQ-thermodynamic properties calculation). On line 4, which begins with a * symbol, you tell Orca what file contains the coordinate files for our molecule(s). The phrase xyzfile tells the computer that the file you are using has the molecule in XYZ cartesian coordinates. There are then a series of two numbers which provide information about charge and spin of the reaction. The first number is the total net charge of molecule(s) in the XYZ file, in this case it is zero because HF is a neutral molecule. The second number is the net spin multiplicity (S) of the molecule that you are calculating, which in this case is 1 (singlet) indicating that all electrons in the molecule are paired.

```
# HF Molecular Orbitals
!B3LYP 6-31G* OPT FREQ LARGEPRINT

* xyzfile 0 1 HF_coord.xyz
```

Figure 3. Orca input script for the calculation of molecular orbitals. The blue arrow indicates the calculations that will be performed by Orca. The red arrow tells the computer what file to run the calculations on.

We can now run our calculation using Orca via the command line as we did in the previous exercise. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: in the command prompt and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path into the command prompt. When you hit enter the computer will paste a new line indicating that the current directory has changed, as

shown in Figure 4A. To find the file path of your input script, right click on the input script (HF.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 4 B).

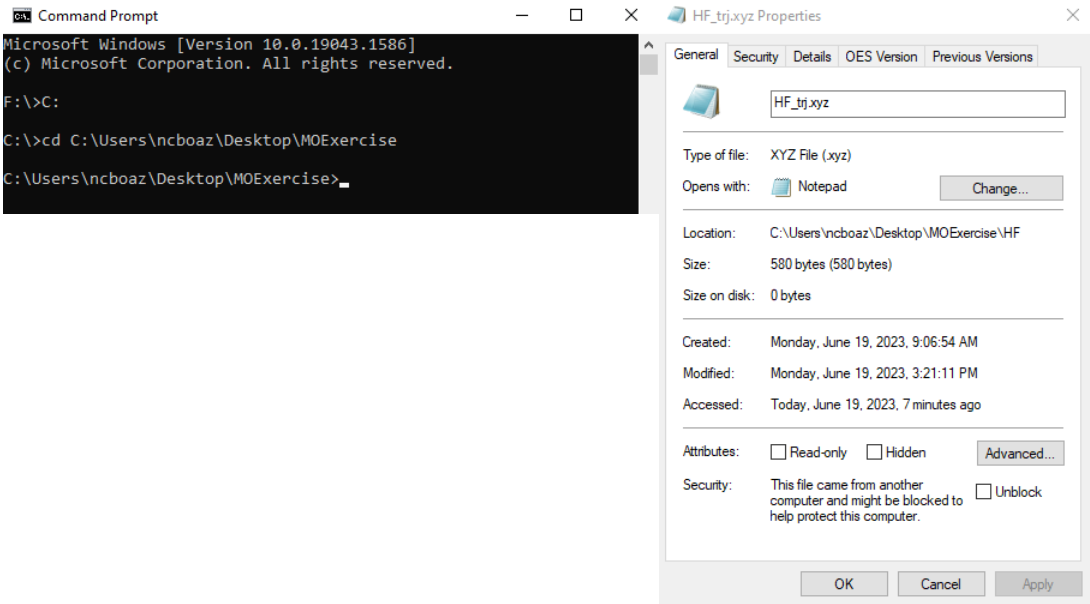


Figure 4A. (Left) Changing of the file path in the command prompt to match the location of our input script. 4B. **(Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca HF.inp > HF.out and pressing enter in the command prompt. At first, it may not appear like anything is happening but the folder on your desktop housing the input file will quickly become populated with the output of your calculation. Depending upon the speed of your computer the calculation will take from 1-5 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 5).

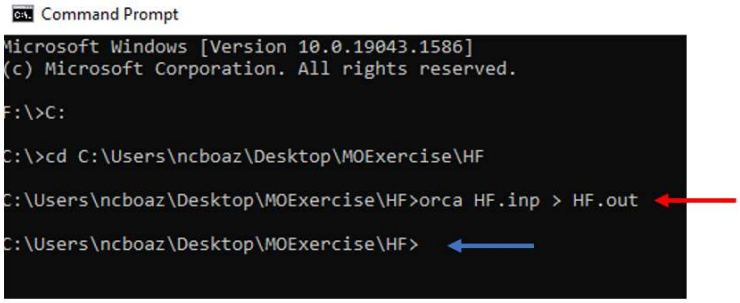


Figure 5. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in HF.inp and that the results of this calculation should be placed in the output file HF.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

Examining Calculated Molecular Orbitals

Upon completion of the calculation, Orca will deposit a series of files in your working folder as shown in Figure 6. The file containing the molecular orbitals that we calculated from HF is the HF.out file.

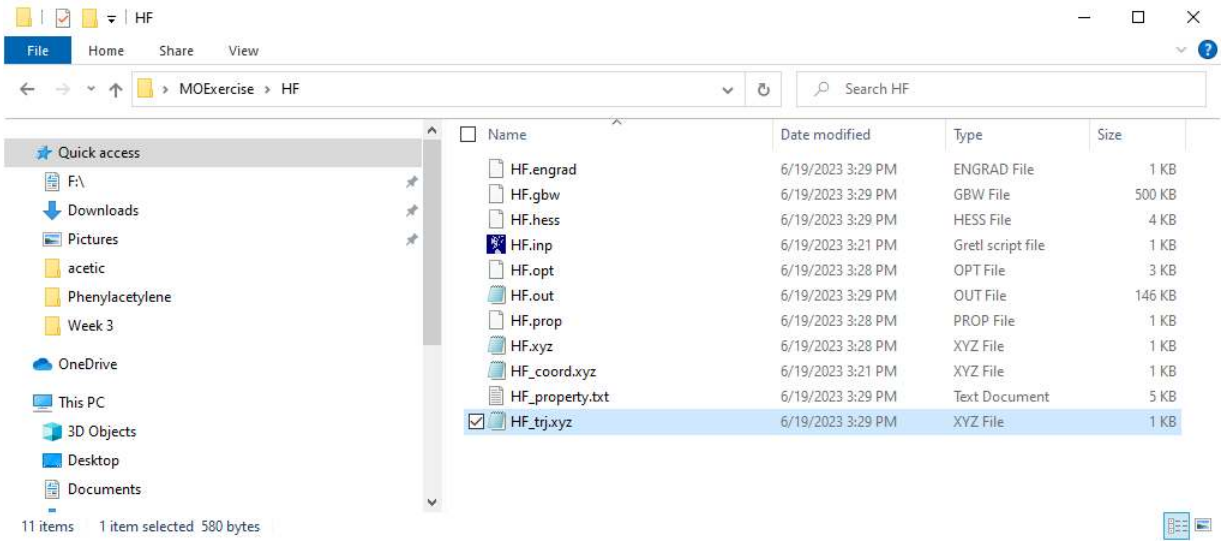


Figure 6. The folder containing the output files from the calculation of the molecular orbitals of HF.

To view the molecular orbitals of HF you will first need to open the output file HF.out from your calculation in Avogadro. As shown in Figure 7, the HF.out file will show the molecular orbitals in the upper right portion of the screen.

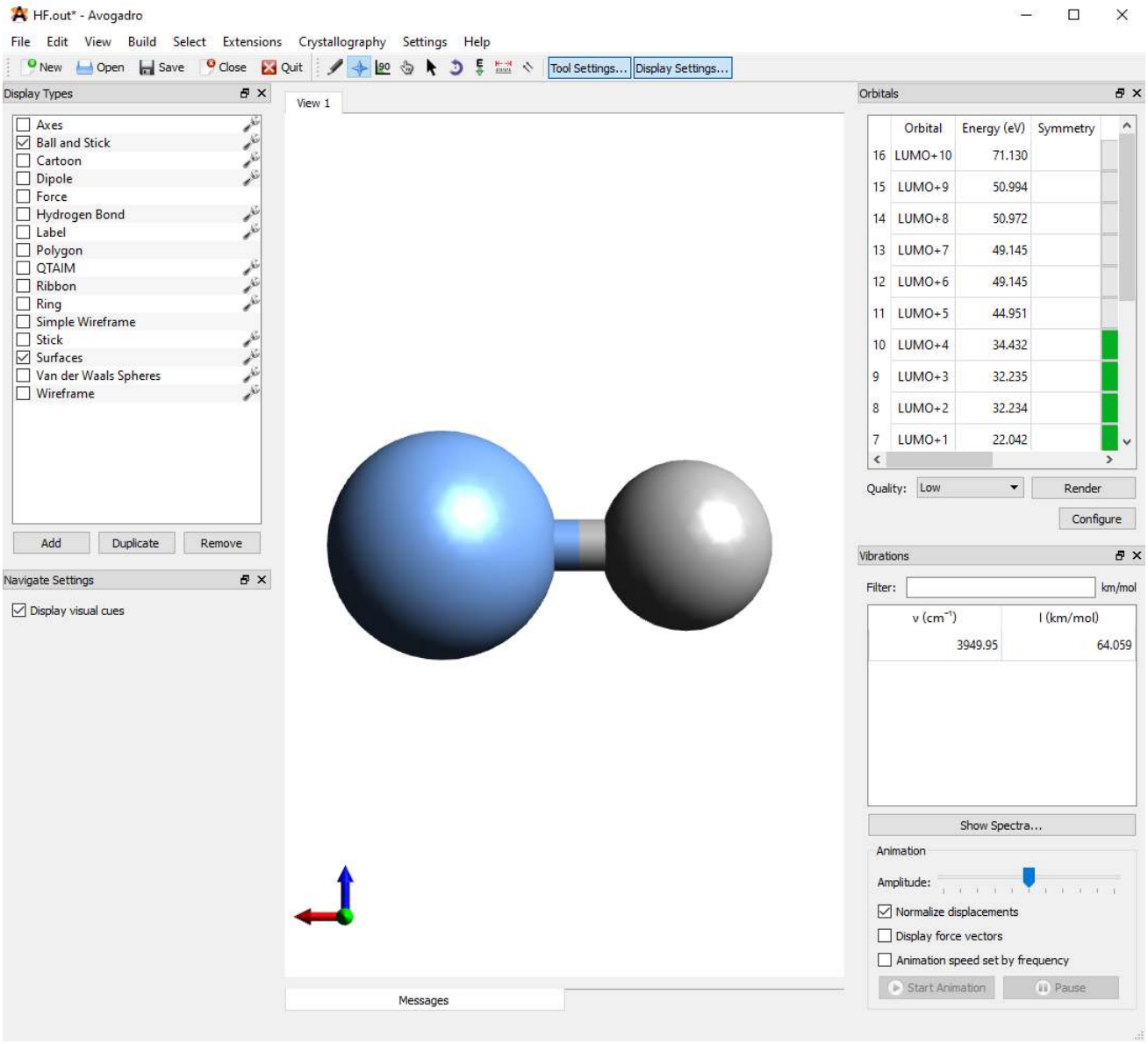


Figure 7. HF.out loaded into Avogadro. The molecular orbitals are in the upper right corner. The red arrow indicates the surfaces settings (little picture of a wrench) that you will use to change the color of the lobes of the molecular orbitals.

Before you view any of the molecular orbitals you will need to click on the wrench button adjacent to the surfaces option link (See Figure 7). This will bring up a panel where you can change the positive and negative surfaces to blue and red respectively as shown in Figure 8. Also, to make the orbitals easier to see you should change the background color by clicking View > Set Background Color > White.

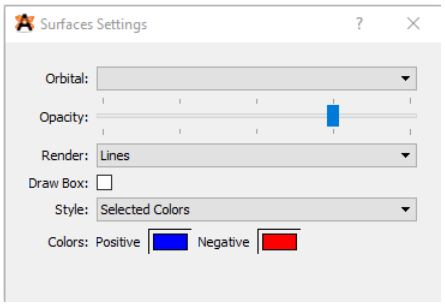


Figure 8. Setting the surface colors (colors of the lobes of the molecular orbitals) to blue and red respectively.

By clicking on any of the molecular orbitals in the upper right, you can visualize what these molecular orbitals will look like as well as see the energy levels of these orbitals (Figure 9). H.O.M.O-3 to LUMO represent the molecular orbitals shown in **Figure 1**. H.O.M.O-4 represents the $1S$ orbital of the fluorine atom. You will notice that the molecular orbitals don't look exactly like the versions of the molecular orbitals that we approximated by overlapping the hybrid orbitals of fluorine in and out of phase with the 1s orbital of hydrogen. The reason for this is that when molecular orbitals are constructed using a computer, non-hybridized atomic orbitals are directly used in the linear combination of orbitals to construct molecular orbitals. Moreover, Orca is going to compute these orbitals mathematically instead of just visually. Now that you've completed the computational exercise, please answer the questions at the end of this assignment.

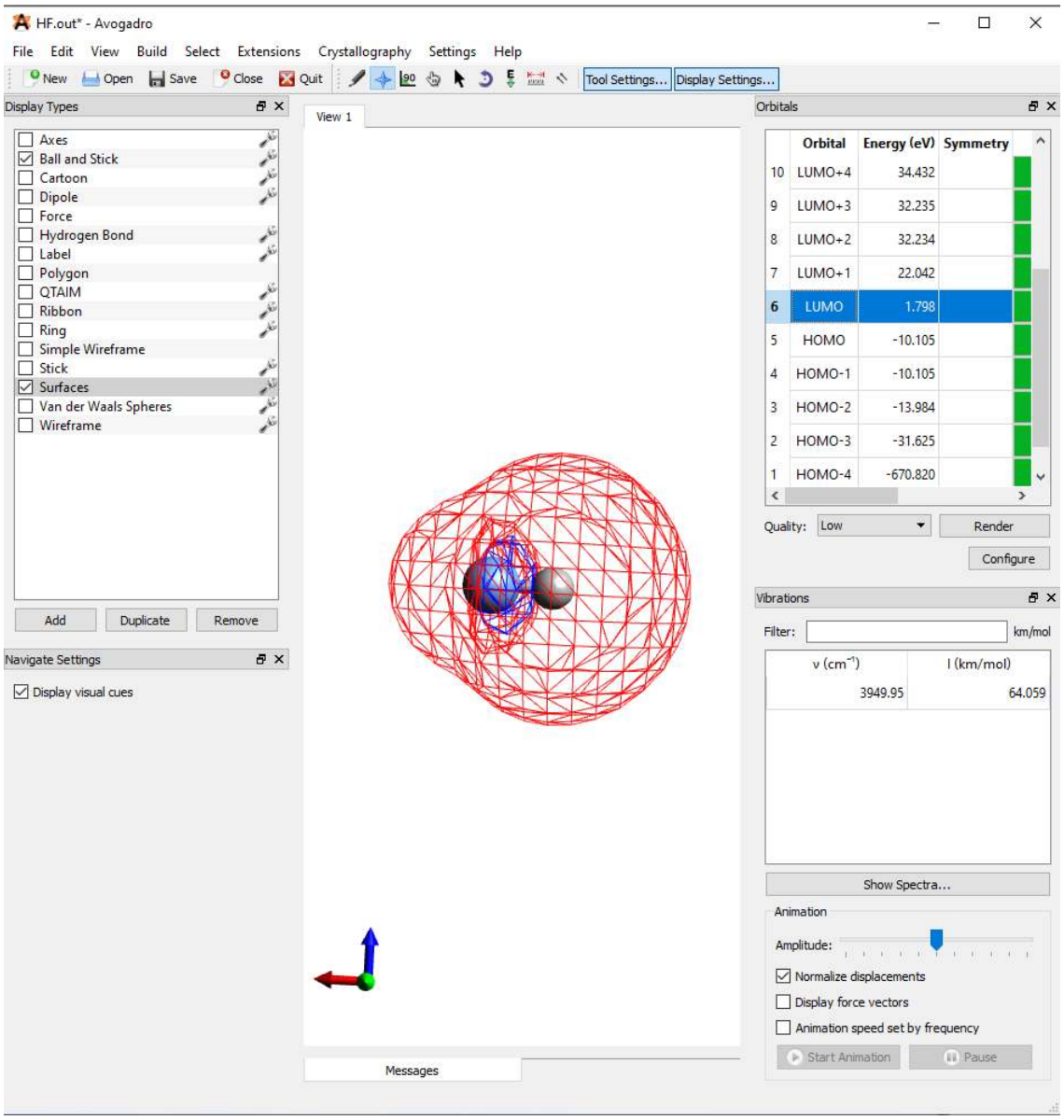


Figure 9. Visualizing the LUMO (the σ^* antibonding orbital) of HF.

References

1. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
2. Neese, F. The ORCA Program System. *WIREs Comput. Mol. Sci.* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.

4. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminformatics* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
5. *Avogadro: An Open-Source Molecular Builder and Visualization Tool*.

This page titled 3.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

3.4: Exercise Questions

1. The Molecular Orbitals of HF. For this part please use your knowledge of molecular orbital theory and the results from your calculations performed above to complete the questions.
   A. Please sketch pictures of the molecular orbitals of HF from HOMO-3 to LUMO.
   B. Please use the energy levels next to each of the molecular orbitals in Avogadro to draw the molecular orbital energy diagram for HF. While you should label each of the molecular orbitals, you do not need to sketch pictures of the orbitals.

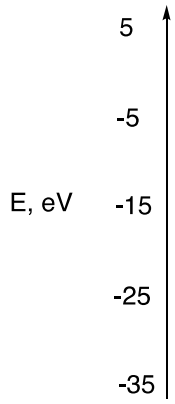
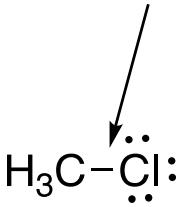
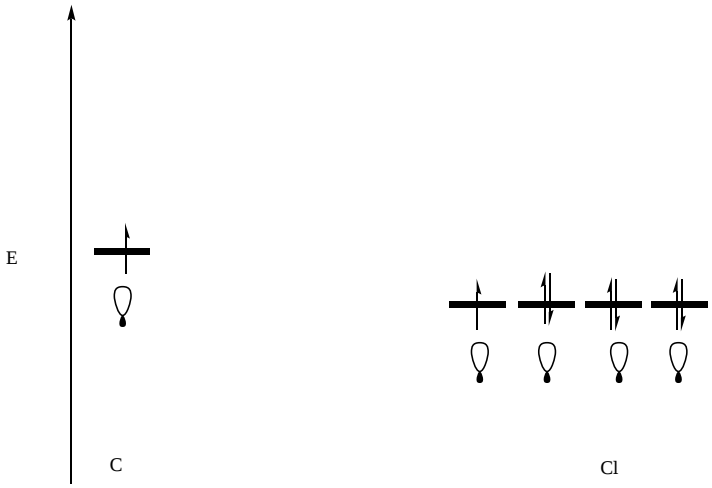


Figure $3.4.1$: Copy and Paste Caption here. (Copyright; author via source)

   C. Which orbital corresponds to the σ bonding orbital between hydrogen and fluorine in HF? Does this computer-generated orbital look like sigma bonding orbital generated by visually combining the orbitals of fluorine and hydrogen in and out of phase?
   D. If $\mathrm{H-F}$ were to act as an electron pair acceptor (Lewis acid) from a hydroxide anion ($\mathrm{OH-}$) $\mathrm{H-F}$ would accept these electrons into the LUMO. If this occurred, please predict what would happen to the $\mathrm{H-F}$ molecule.
2. The Molecular Orbitals of Chloromethane. For this part of the exercise please use your knowledge of molecular orbital theory and the provided calculations.
   A. Using your knowledge of M.O. theory, please construct a molecular orbital diagram for the $\mathrm{C-Cl}$ bond in chloromethane.



You should use an sp^3 orbital from carbon and all 4 sp^3 orbitals from chlorine to do this. Although ORCA models the electrons in the $\mathrm{C-H}$ σ bonding orbitals, we don't need to consider them here.



B. In your diagram above, please indicate the identity of the highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbital (LUMO).

C. Please open the provided output file for the chloromethane (MeCl.out) to view its molecular orbitals. Please sketch the HOMO and LUMO of chloromethane. How do these orbitals compare those that you sketched in part A?

This page titled 3.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

4: Measuring Equilibrium on Cyclohexane Chair Structures

4.1: Overview

4.2: Background

4.3: Computational Instructions

4.4: Exercise Questions

This page titled 4: Measuring Equilibrium on Cyclohexane Chair Structures is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

4.1: Overview

Learning Objectives

- Students will be able to use Avogadro to visualize 1,3-diaxial steric interactions by using space filling molecular models.[4,5]
- Students will use Orca to calculate the energy of substituted cyclohexane conformers.
- Students will learn to convert the ΔG° of an equilibrium into an equilibrium constant.

Overview: This exercise will help you to understand the underlying energetics behind the conformations of substituted cyclohexane chair conformations. In the lecture portion of this course, you learned that cyclohexane rings exist as an equilibrium between chair conformers that put substituents in axial or equatorial positions. Moreover, you learned that the cyclohexane chair equilibrium favors the conformer that places the bulky substituent in the equatorial position because it avoids a type of steric strain known as a 1,3-diaxial interaction. In this exercise, you will calculate the energy of both axial and equatorial cyclohexane chair molecules and convert that information into the "A" value for that substituent. You will then determine the equilibrium constant between axial and equatorial conformers of a substituted cyclohexane. To do this we will use the quantum chemistry package Orca to measure the energy of cyclohexane conformers using Density Functional Theory.[1–3]

Faculty Notes: This exercise is designed to help students understand how stability in organic chemistry relates to an equilibrium constant. Specifically, students will learn how differences in energy relate to equilibrium position. Moreover, students will use Avogadro to help visualize the steric interactions causing the 1,3-diaxial interactions. Before completing this exercise, students should have learned to draw both conformers of a substituted cyclohexane ring. A standard desktop computer takes about 50 minutes to calculate the geometry and energy of a cyclohexane chair conformer. Computational time can be decreased by encouraging students to run both calculations simultaneously. Moreover, if students are working in groups, they can distribute the calculations over more than one computer. Overall, this exercise should take students from 1.5 to 2 hours to complete.

This page titled 4.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

4.2: Background

As was discussed in the lecture portion of the course, substituted cyclohexane rings exist as chair structures that can place the substituent in either the axial or equatorial position. As shown in Figure 1, the equilibrium generally favors the conformer that places the substituent in the equatorial position over the one that places the substituent in the axial position. One measure of how much a substituent causes the equatorial conformer to be favored is known as an A value. An A value measures the difference in energy (ΔG°) in kcal/mol for a monosubstituted cyclohexane ring in the equilibrium as written in Figure 1. The bigger in magnitude an A value is, the greater the substituent will cause the equilibrium to favor the equatorial conformer.

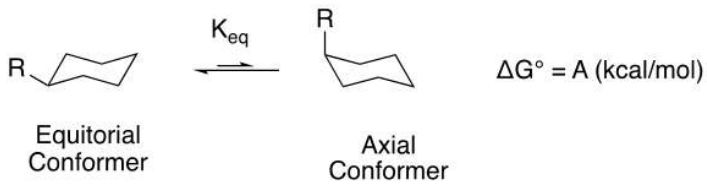


Figure 1. Equilibrium of monosubstituted cyclohexane chair conformers.

The difference in energy between conformers can also be related to the equilibrium constant (K_{eq}) by equation $4.2.1$. R represents the ideal gas constant [1.987 cal/(mol*K)] and T represents the temperature in Kelvin, and ln is the natural logarithm. This means if we can calculate the change in energy between two cyclohexane conformers, it will be possible to estimate the equilibrium constant of the process. By extension you can then estimate the proportion of each conformer (axial and equatorial) at equilibrium.

$$G_{ax} - G_{eq} = \Delta G^{\circ} = -R\,\mathrm{T}\ln\left(K_{eq}\right) \tag{4.2.1}$$

This page titled 4.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

4.3: Computational Instructions

Start by creating a folder for exercise 5 on the local hard drive of your computer and name it Chair Equilibrium. Within this folder, create a subfolder for the axial conformer and a subfolder for the equatorial conformer. In the next few steps, we will place the input files for computation into these nested folders. A description of this file structure is shown in figure 2.

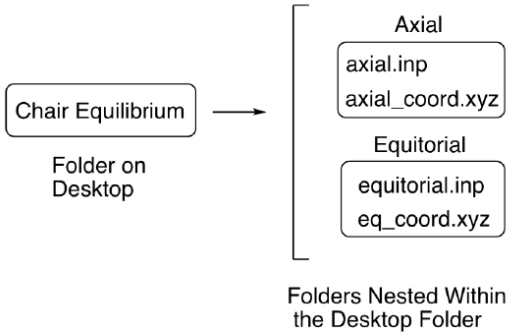


Figure 2: Example file structure for the cyclohexane chair computational exercise.

After you have created this set of nested folders, open Avogadro and draw the axial conformer of methylcyclohexane in the drawing window. The best way to accomplish this is to start by drawing cyclohexane (no specific orientation required) in Avogadro's drawing mode. After you have drawn a cyclohexane ring, optimize its geometry by clicking extensions → optimize geometry. This will form the cyclohexane ring into a chair. From here, go back into drawing mode by clicking the button shaped like a pencil and change one of the axial hydrogens into a methyl group **(Figure 3).** Save this file in the axial conformer folder that you created as axial_coord.xyz.

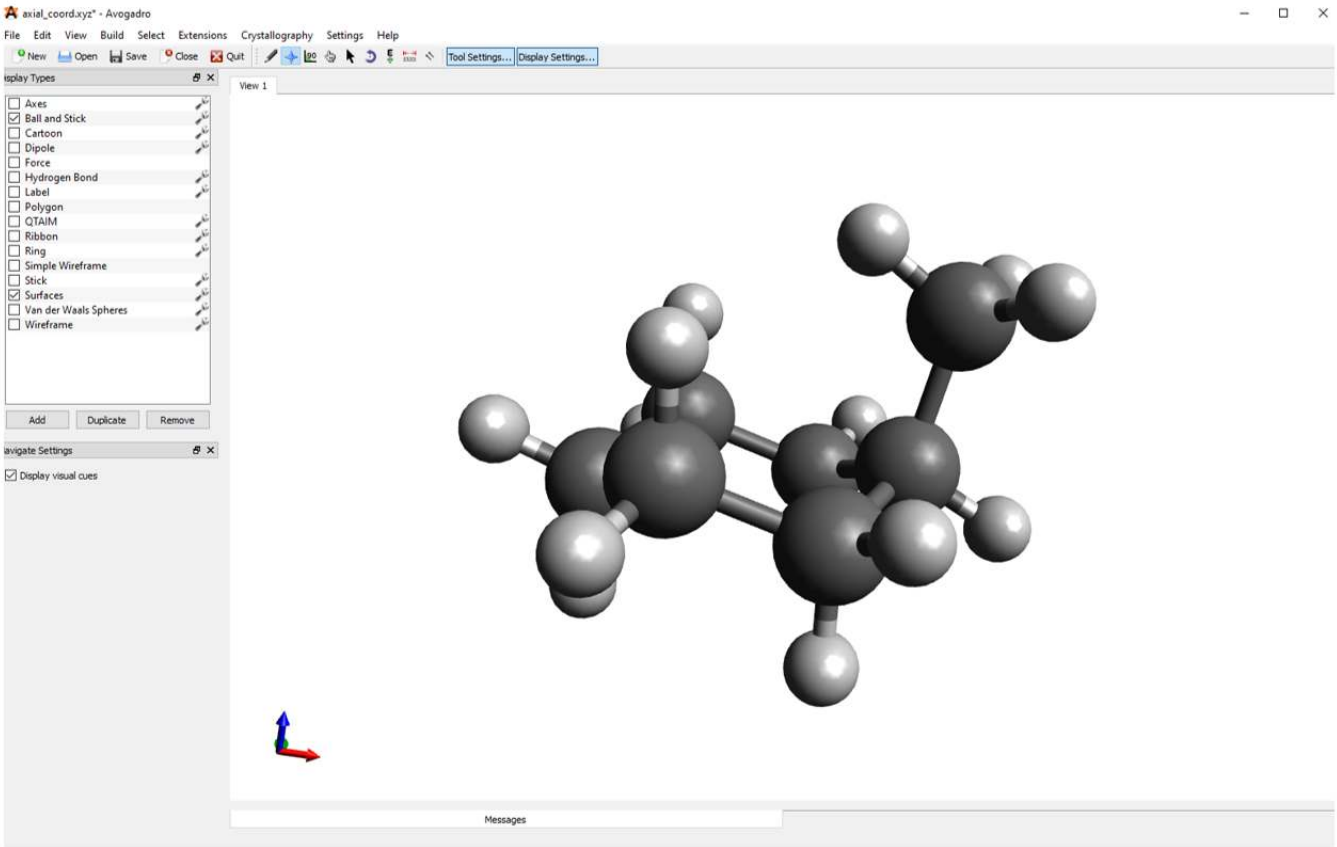


Figure 3. Drawing of the axial conformer of methyl cyclohexane

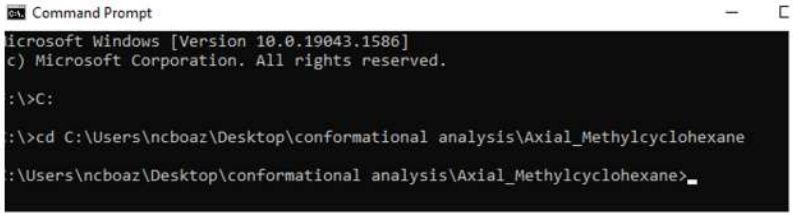
Next, you should download the template Orca input script and save it as axial.inp in the axial conformer folder that you have already saved the coordinate file. Open this file in notepad to modify it for use in determining the energy of the conformer. As shown in Figure 4**,** you need to change the last line of the input script to match the coordinate file that you have created. You should change filename.xyz to the exact name of the coordinate file. Be sure to include the .xyz file descriptor at the end of the name.

```
# Axial methylcyclohexane energy
!B3LYP def2-SVP OPT FREQ

* xyzfile 0 1 filename.xyz
```

Figure 4. Generic conformer input script. You should change filename.xyz to the exact name of the coordinate file for the compound that you are calculating (axial_coord.xyz).

We can now run our calculation using Orca via the command line as we did in the previous exercise. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter the computer will paste a new line indicating that the current directory has changed, as shown in Figure 5A. To find the file path of your input script, right click on the input script (axial.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 5B).



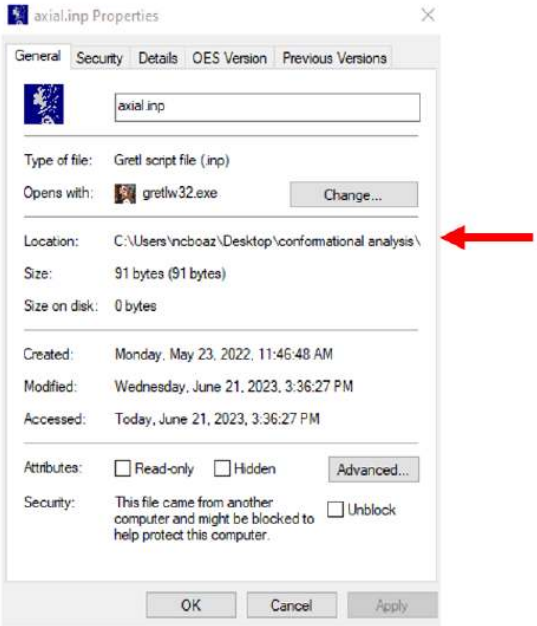


Figure 5A. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **5B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca axial.inp > axial.out and pressing enter. At first it may not appear like anything is happening, but the folder on your desktop labeled axial will quickly become populated with the output of your calculation. Depending upon the speed of your computer the calculation will take about 30-45 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 6).

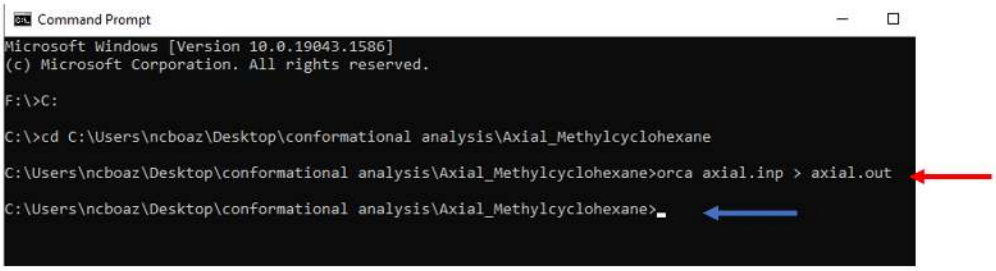
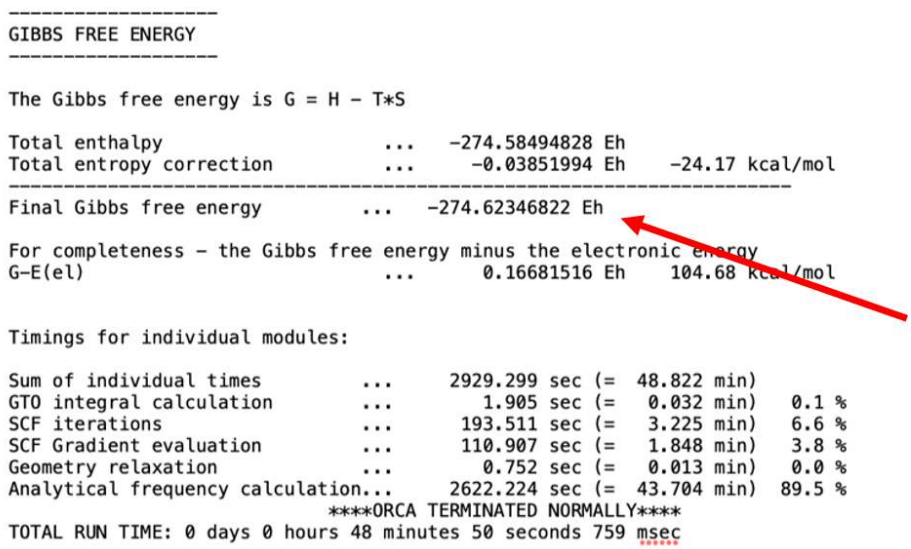


Figure 6. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in axial.inp and that the results of this calculation should be placed in the output file axial.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

After your Orca job has completed you can access the energy values by opening the output file (axial.out) in notepad. At the very end of the file (scroll to the bottom) will be the thermodynamic values that Orca calculated for the cyclohexane conformer as shown in Figure 7. The necessary value is adjacent to Final Gibbs free energy in the output file. Note that this value is given in Hartree (an energy unit). Your value of G may be very slightly different from the value below.



```
-------------------
GIBBS FREE ENERGY
-------------------

The Gibbs free energy is G = H - T*S

Total enthalpy                    ...   -274.58494828 Eh
Total entropy correction          ...     -0.03851994 Eh    -24.17 kcal/mol
-----------------------------------------------------------------------------
Final Gibbs free energy         ...   -274.62346822 Eh

For completeness - the Gibbs free energy minus the electronic energy
G-E(el)                           ...      0.16681516 Eh    104.68 kcal/mol


Timings for individual modules:

Sum of individual times         ...     2929.299 sec (=  48.822 min)
GTO integral calculation        ...        1.905 sec (=   0.032 min)   0.1 %
SCF iterations                  ...      193.511 sec (=   3.225 min)   6.6 %
SCF Gradient evaluation         ...      110.907 sec (=   1.848 min)   3.8 %
Geometry relaxation             ...        0.752 sec (=   0.013 min)   0.0 %
Analytical frequency calculation...     2622.224 sec (=  43.704 min)  89.5 %
                             ****ORCA TERMINATED NORMALLY****
TOTAL RUN TIME: 0 days 0 hours 48 minutes 50 seconds 759 msec
```

Figure 7. The output file for the axial conformer of methyl cyclohexane. The red arrow indicates where the Gibbs free energy value you should use.

At this point you have determined the energy of the axial conformer of methyl cyclohexane. To ascertain the difference in energy between the two conformers you will also need to determine the energy of the equatorial conformer of methyl cyclohexane. Using the method that you have determined the energy of the axial conformer as a guide, calculate the energy of the equatorial conformer of methyl cyclohexane. You can run both of the calculations at the same time by opening another command prompt window. After completing computational component of this exercise, please complete the questions at the end of this assignment.

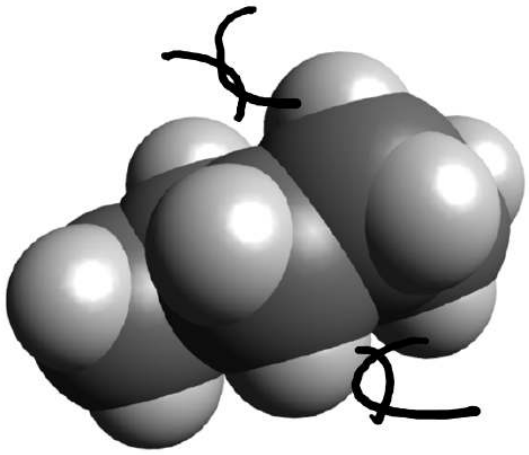
References

1. Neese, F. The ORCA Program System. *WIREs Comput. Mol. Sci.* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
2. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
4. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminformatics* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
5. *Avogadro: An Open-Source Molecular Builder and Visualization Tool.*

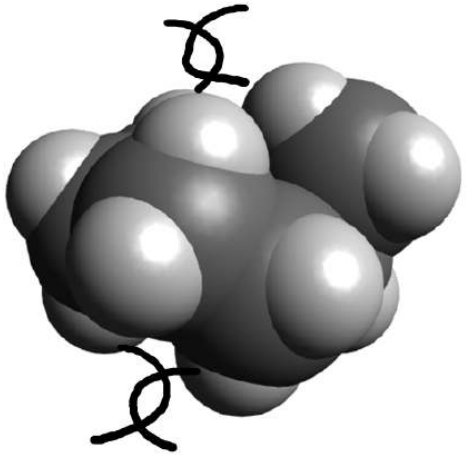
This page titled 4.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

4.4: Exercise Questions

1. Open output file for both axial and equatorial conformations of methyl cyclohexane in Avogadro and view the molecule in space filling mode by clicking on Van Der Waals Spheres in the Display Types Window. Print a screen shot of both conformers and paste it below. Using a pen, indicate where the 1,3-diaxial interactions exist on the axial conformer.



Equatorial Conformer

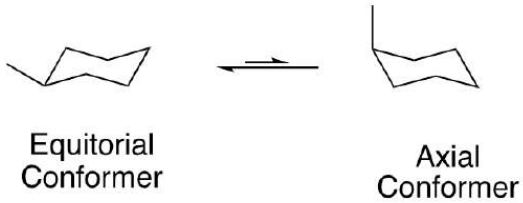


Axial Conformer

2. Please Complete the following table using the energy values you determined from your Orca output files. For the final conversion please note that 1 Hartree (E_H) = 627.5 kcal/mol.

Eq. Conformer Gibbs Free Energy (E_H)	Axial Conformer Gibbs Free Energy (E_H)	ΔG° (E_H) = Axial Energy – Equitorial Energy	A Value (Methyl Group), ΔG° converted to kcal/mol

3. Given the equilibrium from equatorial to axial conformers as written below, which side of the equilibrium is favored? Is the conformation change exergonic or endergonic?



4. Compare the A value that you obtained in question 3 to the literature A value. If there is a difference between the literature and calculated value, please propose a reason for the difference.
5. Using the equation that relates the change in free energy and the equilibrium (equation 1 shown above) constant, please calculate K_{eq} for the equilibrium as written in question 3.
6. What percentage of methyl cyclohexane is in the axial conformation and what percentage is in the equatorial conformation?

This page titled 4.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

5: Computing and Visualizing Infrared Spectra of Organic Molecules

This exercise seeks to help you visualize what is occurring with the IR spectra of organic compounds at the molecular level. IR spectra arise from molecular vibrations that are characteristic of each compound. This is particularly useful for organic chemists seeking to determine the structure of a molecule.

5.1: Overview

5.2: Background

5.3: Computational Instructions

5.4: Exercise Questions

This page titled 5: Computing and Visualizing Infrared Spectra of Organic Molecules is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

5.1: Overview

Learning Objectives

- Students will learn to use Orca and Avogadro to calculate and visualize the vibrational modes in the IR spectrum of simple organic molecules.
- Students will be able to describe the molecular motion involved in IR absorbances.

Overview: This exercise seeks to help you visualize what is occurring with the IR spectra of organic compounds at the molecular level. IR spectra arise from molecular vibrations that are characteristic of each compound. This is particularly useful for organic chemists seeking to determine the structure of a molecule. In this exercise you will model the vibrational spectrum of a molecule and visualize the vibrations giving rise to specific resonances. To accomplish this, we will use the quantum chemistry package called Orca to calculate the vibrational modes of hexane.[1–3] This predicted spectrum will be visualized in Avogadro and compared to the experimental IR spectrum of hexane to help assign its vibrational modes.[4,5]

Faculty Notes: This exercise is designed to help students better understand the molecular vibrations that underlie IR spectroscopy. Before completing this exercise, students should have been introduced to the concept of IR spectroscopy and basic interpretation using spectral tables. A standard desktop computer takes about 5 minutes to run the computation in this exercise. Overall, the exercise should take students about an hour to complete.

This page titled 5.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

5.2: Background

This absorption of infrared light energy causes functional groups in molecules to vibrate. This phenomenon serves as the basis of IR spectroscopy. At very small (molecular) scale the laws of physics work differently. In the macroscopic world, objects can have any value of energy on a spectrum. For example, imagine a ball placed on a hill (Figure 1). The higher on the hill the ball is placed the more potential energy that it can have. Because the ball can be placed anywhere on the hill, it can have any potential energy on a spectrum of potential energies. At the molecular scale, only certain energies are allowed. The energy levels are what scientists refer to as quantized in nature. Going back to our hill and ball analogy, the smooth side of the hill would be replaced with a set of steps. In such a case, not all values of potential energy are possible. Rather, the ball can only hold the values of potential energy corresponding to the height of each of the steps. The ability to only hold specific energy levels is referred to as quantization.

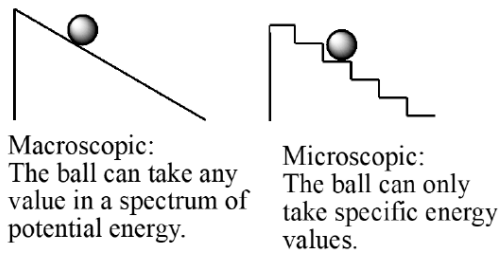


Figure 1. Potential energy in the macroscopic scale versus potential energy levels on the microscopic scale.

The same quantization of energy occurs within the vibrations of a molecule, meaning that only certain vibrational energies are allowed. The molecules can change the vibrational energy state that they are in by absorbing exactly the difference in energy between quantized energy levels. The energy required for this excitation depends strongly upon both the strength of the bond between atoms and the mass of atoms connected in the bond (Equation $5.2.1$).[6] In this equation, $\tilde{v}$ is the wavenumber of the absorption in cm^{-1} while c is the speed of light in a vacuum. The force constant of the bond (bond strength) is represented by f; stronger bonds have a larger force constant. The reduced mass, m_{red}, is a measure of the masses of the atoms involved in the vibration. If you have a bond between a heavy atom or functional group and a much lighter one (e.g. $\mathrm{H-Cl}$) the lighter object moves much more than the heavier one, so the reduced mass is close in value to the lighter mass. If you have a bond vibration between two things of equal mass (i.e. $\mathrm{H_3C-CH_3}$) both sides of the bond share the vibration, so the reduced mass is about half of the mass of one side.

$$\tilde{v} = \frac{1}{2\pi c} \times \sqrt{\frac{f}{m_{red}}} \tag{5.2.1}$$

In the simplest analysis of a vibrational spectrum, each bond can vibrate independently and should have its own force constant and reduced mass. In reality, some vibrations are spread out throughout the entire molecule while others are more localized on one bond. Think about the suspension of a car driving over a pothole. If one tire drives over the pothole the whole car shakes, not just the front half of the car. Similarly, if a molecule is excited by light, it's probable that the vibration won't just be concentrated in one bond.

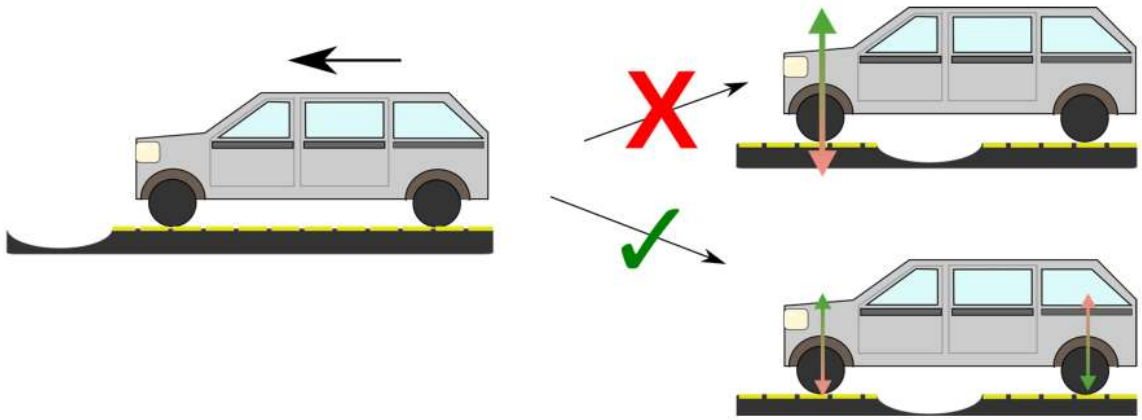


Figure 2. Normal modes in a car. Left: A car drives its front tires over a pothole. Right: Although only the front tires have passed over the bump, we see that the vibration does not stay in the front of the car. Rather, because the front and back tires are both attached to the body of the car, the vibration is delocalized to both front and rear tires. Similarly, many types of vibrations in molecules involve more than a single bond.

In this exercise, you will learn to use Orca to calculate the vibrational frequencies (in wavenumbers) and modes (how the atoms vibrate) of a small molecule, hexane. These data will then be used to help assign the resonances of an experimental IR spectrum of the same molecule. Moreover, you will use provided data to determine the effect of hybridization on bond strength and by extension vibrational frequency of a $C-H$ bond.

This page titled 5.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

5.3: Computational Instructions

As shown in Figure 3 the IR spectrum of hexane was acquired using an FT-IR spectrometer. Using the skills that you learned in lecture you should be able to pick out the main functional group stretches. This computational exercise will help you visualize what these vibrational modes look like on a molecular level.

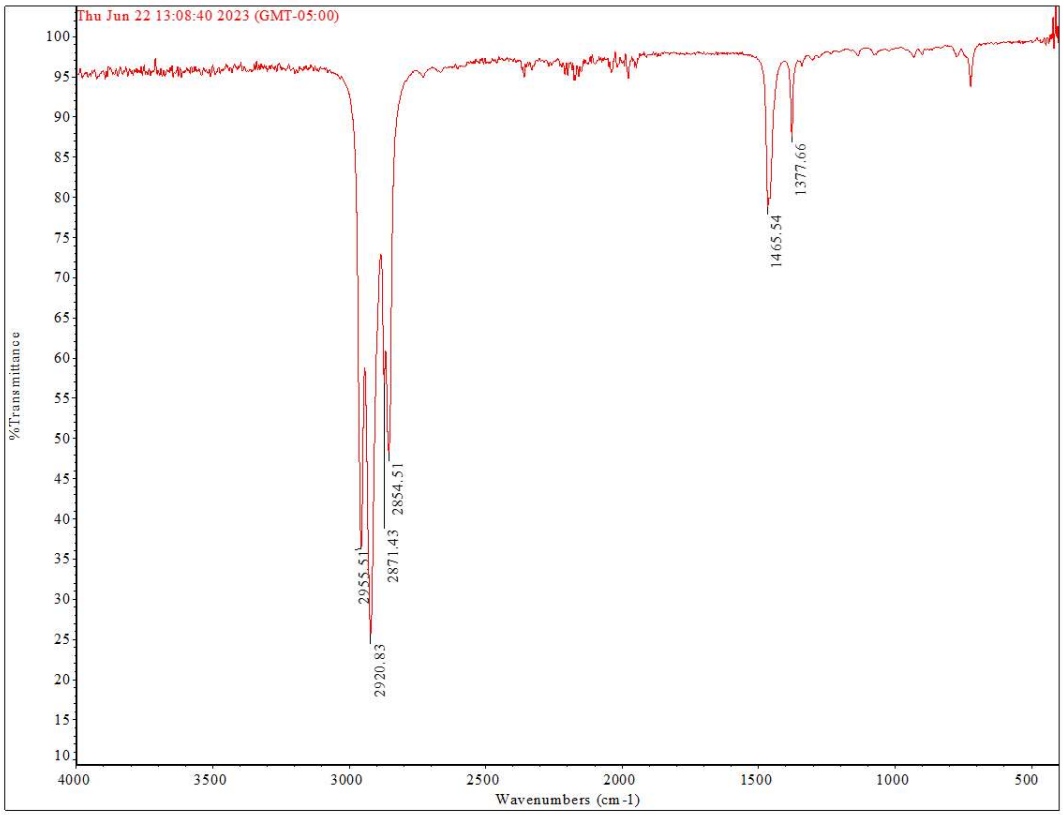


Figure 3. Experimental IR spectrum of n-hexane.

Start by creating a file folder on your local hard drive and name it IR. Next, open Avogadro and draw n-hexane using the drawing mode (Figure 4). After you have drawn this molecule, you should perform a quick preoptimization of the geometry by clicking extensionsà optimize geometry. Save this file in the folder that you created above as hexane_coord.xyz.

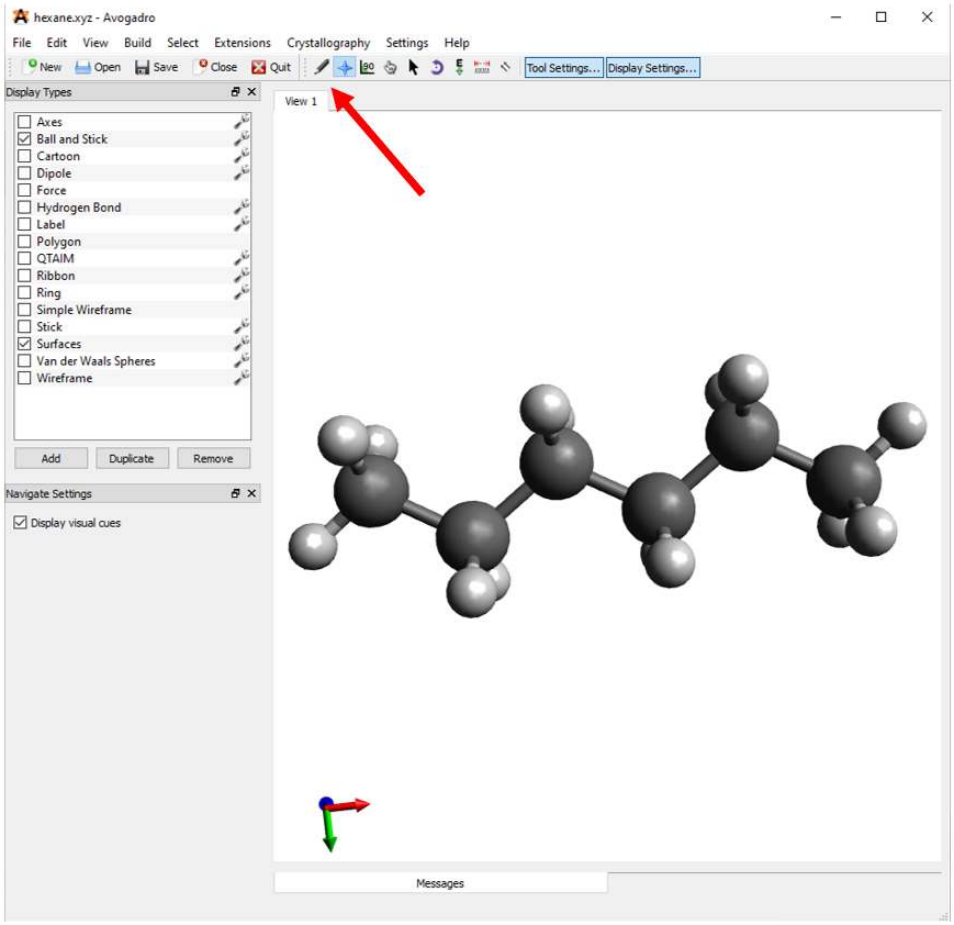


Figure 4. Drawing of n-hexane in Avogadro. The button to access the drawing mode of Avogadro is shown by the red arrow.

Next, you should download the Orca input script from supporting documents and save it in the IR folder as hexane.inp. After this, open this input script in notepad to view its contents. The text of the input file is shown in Figure 5. The first line of the input text (indicated by the blue arrow) tells Orca what calculations to run and how to run them. Specifically, the OPT command tells the computer to optimize the geometry of hexane and FREQ tells the computer to calculate hexane's vibrational frequencies. BP86 and DEF2-SVP tell the computer what functional and basis set, respectively to use in the calculation. The last line of the input script (indicated with a red arrow) tells the computer that we are using an XYZ file in our calculation. The two numbers, 0 and 1, indicate the charge of the molecule and the spin multiplicity of the complex. Finally, hexane_coord.xyz tells the computer what file to run the calculation on. Please check that the filename is exactly the same as the file name of the coordinates file that you created. If they are different, change them so that they are identical (or Orca will give you an error when you try to run the calculation).

```
# hexane IR
!BP86 DEF2-SVP OPT FREQ

* xyzfile 0 1 hexane_coord.xyz
```

Figure 5. Orca input script for the calculation of the IR spectrum of hexane. The line of the input script indicated by the blue arrow indicates the calculations that Orca will run. The line indicated by the red arrow tells orca what coordinates to run the calculation on.

We can now run our calculation using Orca via the command line as we did in previous exercises. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter, the

computer will paste a new line indicating that the current directory has changed, as shown in Figure 6A. To find the file path of your input script, right click on the input script (hexane.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 6B).

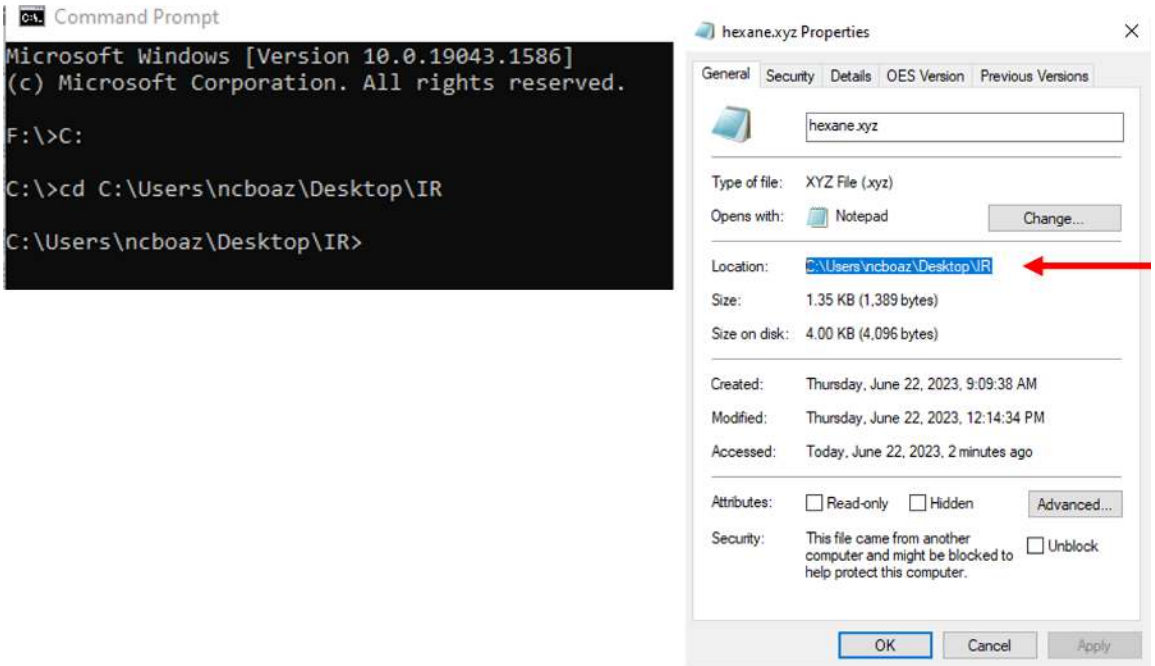


Figure 6A. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **6B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca hexane.inp > hexane.out and pressing enter. At first it may not appear like anything is happening but the folder on your desktop labeled IR will quickly become populated with the output of your calculation. Depending upon the speed of your computer, the calculation will take about 5-10 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 7).

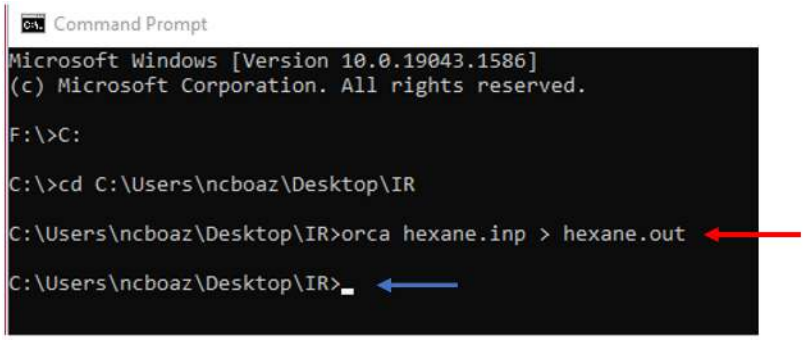


Figure 7. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in hexane.inp and that the results of this calculation should be placed in the output file hexane.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

To visualize the IR spectrum of hexane, you should open the hexane.out file in in Avogadro, which can be found in the folder you created labeled IR. This will open the file showing the vibrational modes in the right-hand corner. If you click on any of these vibrational modes, Avogadro will show you how the molecule vibrates in this mode in the main window. To show the entire IR spectrum please click on the Show Spectra button (Shown in Figure 8). This will open a window that displays the IR spectrum predicted by Orca (Figure 9). You will likely notice that this spectrum looks a little different than the experimental spectrum as shown in Figure 3 above. Specifically, the computational peaks are much skinnier than the peaks obtained experimentally. The reason for this is that the intermolecular interactions between the molecules slightly change the frequency of the peaks, broadening

the spectrum. Moreover, the experimental spectrum is limited by the resolution of the spectrometer while the computational spectrum is not.

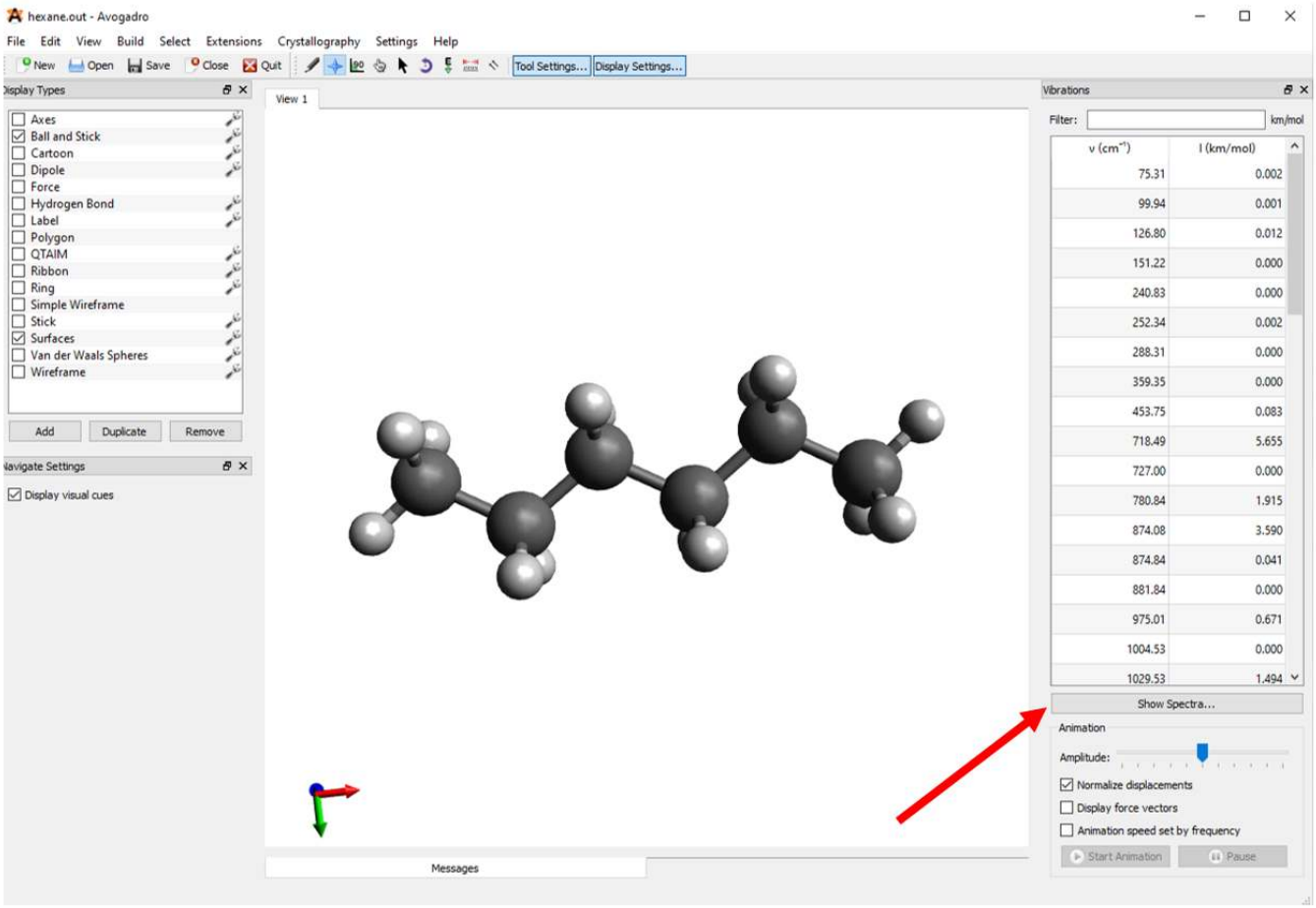


Figure 8. The hexane output file opened in Avogadro. The button to show the IR spectrum is indicated by a red arrow.

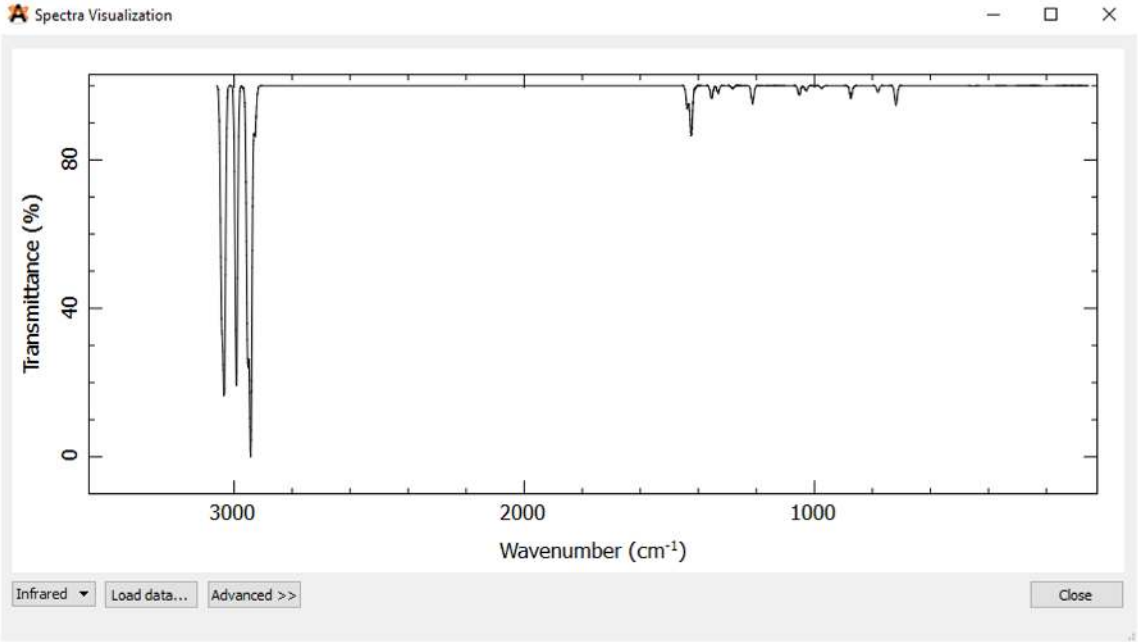


Figure 9. Computed IR spectrum of hexane.

You can tell Avogadro to match the resolution of the IR spectrum measured experimentally by clicking on Advanced<< on the Spectra visualization window shown in Figure 9. From here click on Infrared Spectrum Settings and change the Gaussian width toggle to $10\ \mathrm{cm}^{-1}$ as shown in Figure 10.

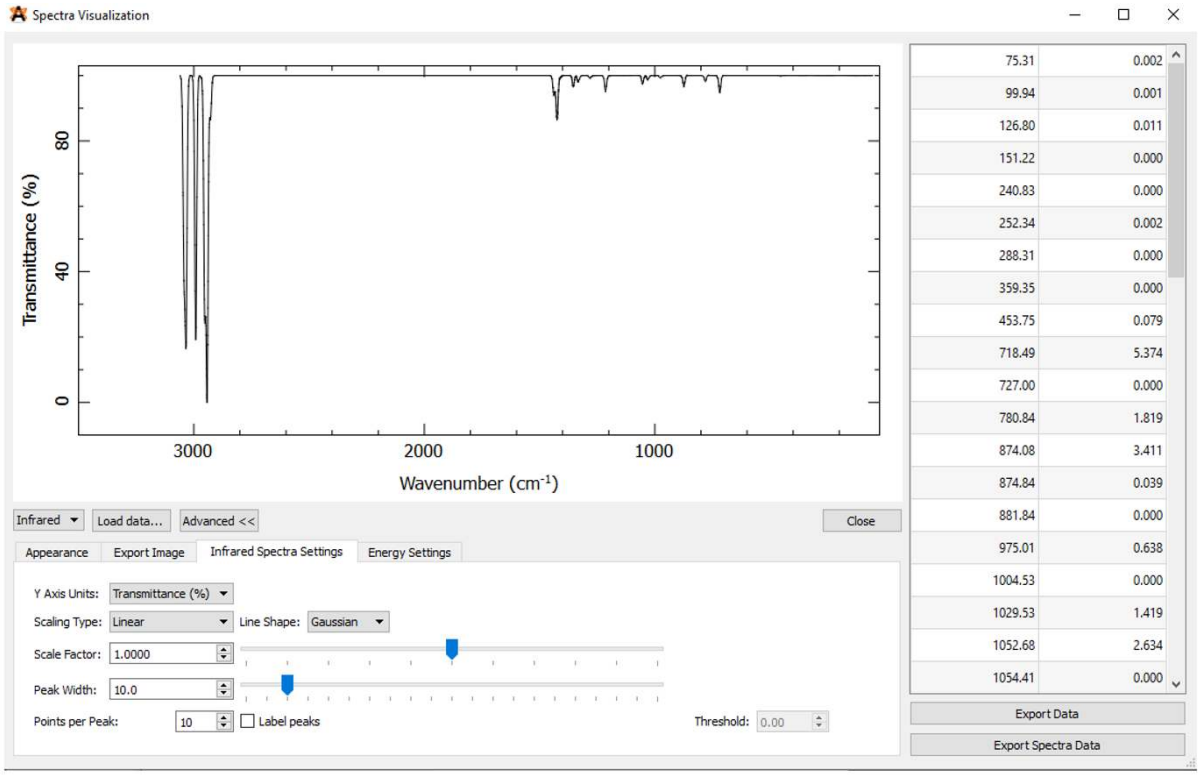


Figure 10. Changing the advanced settings to match the resolution on the experimental IR spectrum of n-hexane.

You now have all the information and computations necessary to complete the questions at the end of this exercise.

References

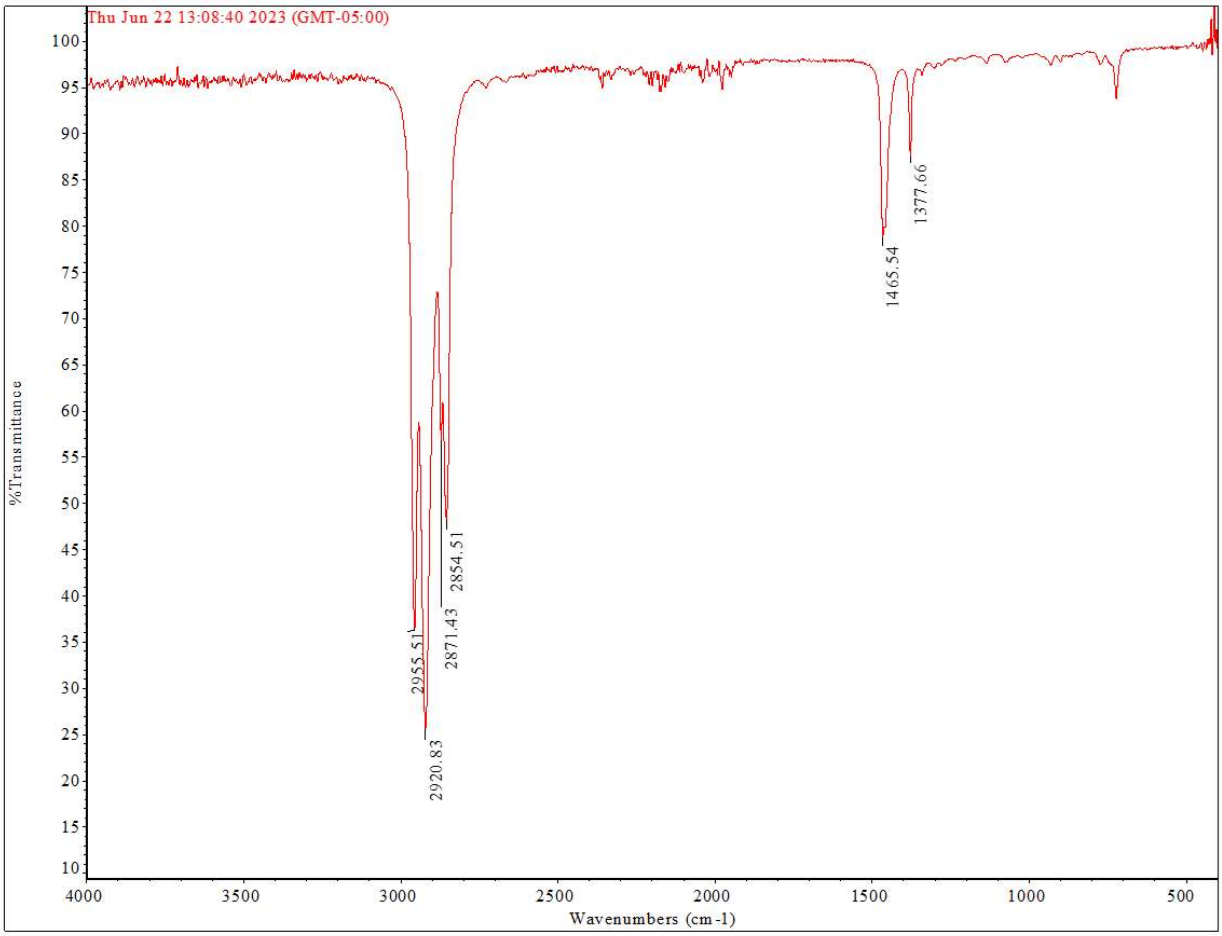
1. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Computational Molecular Science* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
2. Neese, F. The ORCA Program System. *WIREs Computational Molecular Science* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
4. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J Cheminform* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
5. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.
6. Klein, David. Infrared Spectroscopy and Mass Spectrometry. In *Organic Chemistry*; John Wiley and Sons: Hoboken, NJ, 2012; pp 683–730.

This page titled 5.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

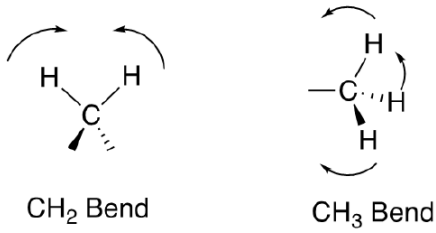
5.4: Exercise Questions

Part 1: Vibrational Modes of Hexane

1. Using your knowledge of IR spectra please assign the following stretches and bends to the experimental IR spectrum of hexane using an IR stretching chart: sp^3 $\mathrm{C-H}$ Stretch, $\mathrm{CH_2}$ bend/scissor, and $\mathrm{CH_3}$ bend.



2. By clicking on and viewing the vibrational frequencies, how many distinct vibrational modes does hexane have that involve the stretching of an sp^3 $\mathrm{C-H}$ bond? (Hint: where do these types of stretches occur on the IR spectrum)
3. Do the $\mathrm{C-H}$ stretching modes typically involve one $\mathrm{C-H}$ bond or multiple $\mathrm{C-H}$ bonds?
4. In addition to stretching, $\mathrm{C-H}$ bends can bend as well. As shown below, $-\mathrm{CH_2}-$ and $\mathrm{CH_3}$ groups will bend when excited by IR light. Please indicate the wavenumber of IR light that you have calculated that causes $\mathrm{CH_2}$ and $\mathrm{CH_3}$ bending as shown below. How do the calculated frequencies compare to the experimental frequencies in question 5.2.1?

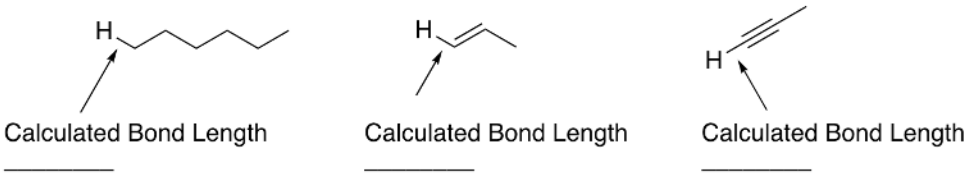


5. At around 720 $\mathrm{cm^{-1}}$ long chain alkanes tend to have a characteristic vibrational mode. In your computation, this absorption occurs at 718 $\mathrm{cm^{-1}}$. Please describe the molecular motion in this vibrational mode. Why do you think that this mode is used by scientists to determine the presence of a long chain alkane?

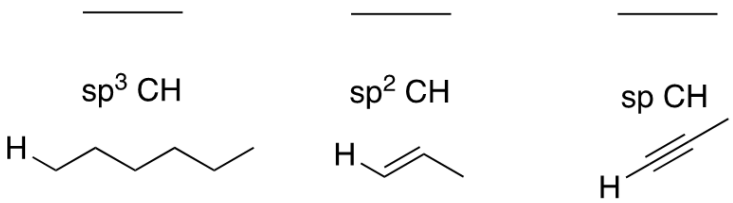
Part 2: Impact of Hybridization of the C-H Stretching Frequency

When examining the IR spectrum of hydrocarbons, you will see that the $\mathrm{C-H}$ stretching frequencies are strongly dependent upon the hybridization of the carbon. This is because the hybridization of the carbon influences the length and strength of the $\mathrm{C-H}$ bond. Let's examine this phenomenon using computation.

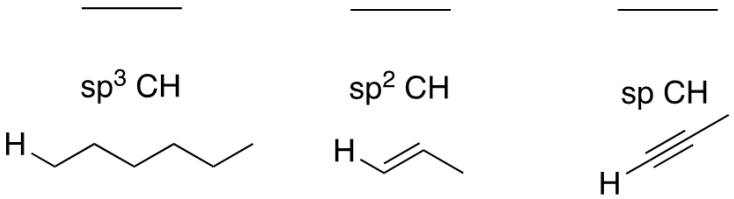
6. Open the output file of hexane (that you calculated), propene (provided), and propyne (provided) and measure indicated bond lengths.



7. Please briefly describe the relationship between carbon hybridization and bond length. Propose an explanation that describes why certain hybridizations have shorter bond lengths (Hint: remember that different hybridizations are made of differing proportions of s and p orbitals. S orbitals, on average, hold electrons closer to the nucleus than p orbitals.)
8. In the case of the three $\mathrm{C-H}$ bonds measured above, we can correlate homolytic bond strength with bond length. Specifically, the shorter the bond length, the stronger the corresponding bond. Please rank the three bonds in order of increasing strength (1 weakest, 3 strongest).



9. Given the relationship between bond strength (f) and vibrational frequency in wavenumber $\tilde{v}$ please rank the order of stretching frequencies involving the $\mathrm{C-H}$ bonds indicated above. Briefly explain the order that you chose. (1 lowest wavenumber, 3 highest wavenumber).



10. Examine the IR stretching modes of hexane, propene, and propyne. Were your predictions about the order of the stretching frequencies correct?

This page titled 5.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

6: Manipulating of Molecules in Three Dimensions

This exercise seeks to help you develop spatial skills that you will need to understand the three-dimensional structure of molecules. This is particularly important for visualizing and assigning chiral centers, where rotating the lowest priority back into the plane of the page is a vital, and often challenging, part of determining absolute configuration.

6.1: Overview

6.2: Background

6.3: Computational Instructions

6.4: Exercise Questions

This page titled 6: Manipulating of Molecules in Three Dimensions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

6.1: Overview

Learning Objectives

- Students will rotate molecules using Avogadro to aid in their understanding of how chiral centers exist in three-dimensional space.
- Students will examine the energy difference between enantiomers and diastereomers to cement the concept of differing properties of stereoisomers.

Overview: This exercise seeks to help you develop spatial skills that you will need to understand the three-dimensional structure of molecules. This is particularly important for visualizing and assigning chiral centers, where rotating the lowest priority back into the plane of the page is a vital, and often challenging, part of determining absolute configuration. Using Avogadro we can demonstrate how rotation effects chiral centers, making it easier to repeat this process in your mind's eye.[1,2] Moreover, we will use energy calculations, performed in Orca, to examine energy differences between sets of enantiomers and diastereomers.[3–6]

Faculty Notes: This exercise is designed to help students with the skills needed to rotate and view molecules from different perspective in three dimensions. Additionally, this exercise seeks to highlight the energetic differences between a set of enantiomers and a set of diastereomers. Before completing this exercise, students should have been introduced to the concept of chirality and chiral centers as well as the process of assigning the absolute configuration of chiral centers. Moreover, students should have learned to determine the relationship between two stereoisomers. This exercise should take students about an hour to complete.

This page titled 6.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

6.2: Background

During the lecture portion of your organic chemistry course, you learned about how when four different groups are bound to a tetrahedral carbon there are 2 different configurations. As shown in Figure 1, two absolute configurations are possible, labeled R or S. Determining the absolute configuration of a chiral center is vital when you are trying to elucidate the relationship between two different stereoisomers (enantiomers, diastereomers, or meso compounds).

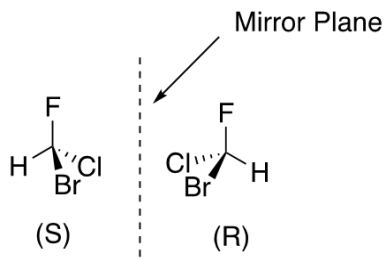


Figure 1. The S and R configurations of bromochlorofluoromethane.

As shown in Figure 2a, if two molecules with the same connectivity (molecular connections) have one or more stereocenters they will be enantiomers if all the stereocenters are of opposite configuration. If the stereocenters in two molecules are of the same configuration the molecules will be the same (Figure 2B). Two molecules with the same connectivity and two or more stereocenters will be diastereomers if some of the stereocenters are different. Enantiomers have the same chemical and physical properties such as their melting point, spectra, and reactivity. They differ, however, in their ability to rotate plane polarized light. Unlike a set of enantiomers, a set of diastereomers will have differing chemical and physical properties.

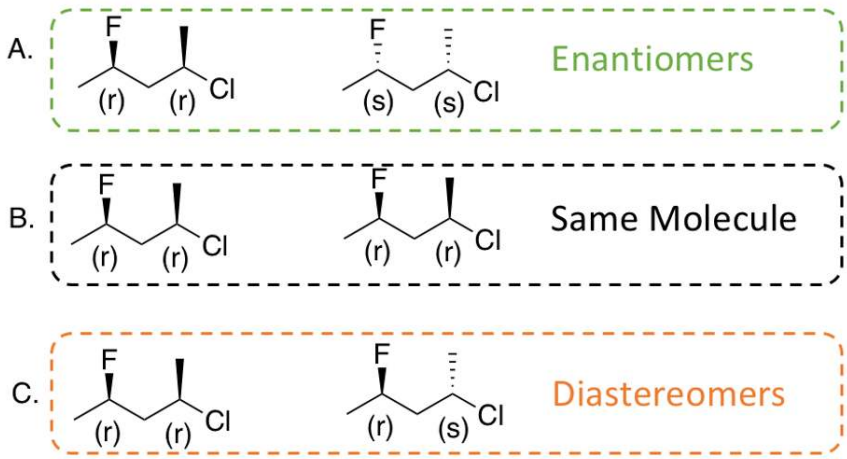


Figure 2. A. Two molecules with the same connectivity where all the chiral centers are inverted are enantiomers of each other. **B.** Two molecules with the same connectivity where all the chiral centers are the same are identical. **C.** Two molecules with the same connectivity but only some of the chiral centers are inverted.

This page titled 6.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

6.3: Computational Instructions

In this computational exercise, we will seek to accomplish two different objectives. First, we will use the molecular visualization capabilities of Avogadro to help us assign the absolute configuration of chiral centers of pharmaceuticals. Secondly, we will examine the energy values of a set of diastereomers and a set of enantiomers to illustrate their difference in properties.

Part 1: Using Avogadro to examine the chiral centers of pharmaceuticals.

Start by creating a folder on your PC's desktop and naming it Stereochemistry Exercise. Next you should download the supporting files for this exercise and save them to the Stereochemistry Exercise file that you just created. While you have likely learned to assign absolute configurations, let's work through the determination of the chiral center in the pharmaceutical pregabalin together. This will allow us to both review this important skill and learn how Avogadro can help us visualize molecules in three dimensions. Pregabalin, sold under the brand name Lyrica, is a pharmaceutical used in the treatment of pain caused by nerve damage.[7] As shown in Figure 3, pregabalin has a single chiral center in the middle of the molecule.

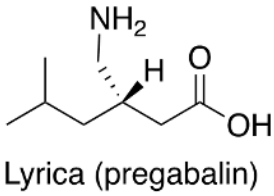


Figure 3. Structure of pregabalin, which is sold under the brand name of Lyrica.

As shown in Figure 4, we start by determining the location of the chiral center. A chiral center is an atom, often carbon, that is bound to four unique groups. This carbon is identified with a red circle.

Figure 4. Finding the chiral center of pregabalin

Next, we need to rank the priorities of the groups bound to the chiral center using the Cahn-Ingold-Prelog priorities. These priorities rank groups based upon atomic number. A group with highest priority will be 1 while the group with the lowest priority will be 4. As shown in Figure 5, hydrogen has the lowest priority as it has the lowest atomic number and is assigned priority 4. The other three groups begin with carbon, so we examine atoms bound to these carbons. The presence of a nitrogen (atomic number 7) breaks the tie allowing us to assign 1st priority to that group. The last two groups are still tied so we move outward and see that the group on the left is bound to two carbons and a hydrogen while the group on the right is making three bonds to oxygen. Because oxygen has a higher atomic number than carbon the tie is broken, and we assign the group on the right 2nd priority. The remaining group is assigned priority 3.

Step 2. Rank Groups According to CIP Priority.

- Atoms attached to a chiral center are ranked by atomic number.
- If two atoms have the same atomic number we examine what else is attached to the atom to look for a difference in atomic number.
- If there is still at tie we move outwards and repeat the process until a difference is found.

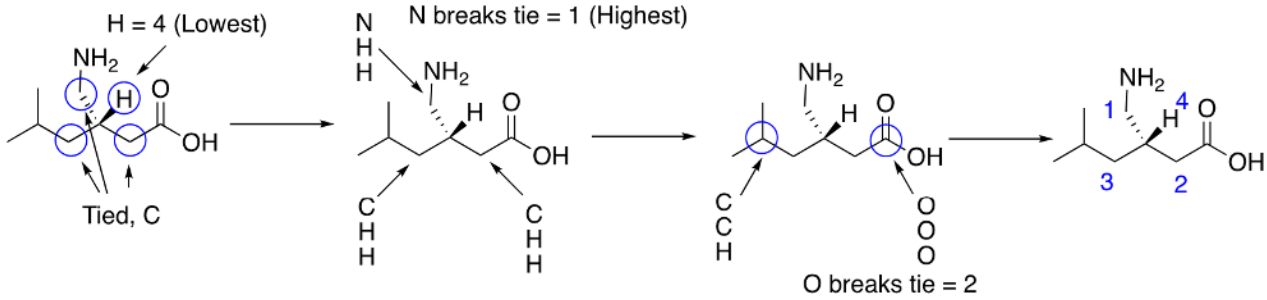


Figure 5. Assigning priorities using the Cahn-Ingold-Prelog system for pregabalin.

After assigning priorities, we need to rotate the molecule such that the lowest priority group is pointed to the back (dashed bond), into the plane of the paper. To do this, envision taking the $C-C$ bond between the chiral center and the group whose priority we assigned 2 and spinning it like you would an umbrella. This will place the hydrogen atom, which has the lowest priority, to the back.

Figure 6. Rotating the molecule so that the lowest priority group is pointing into the plane of the paper.

Finally, we draw an arrow connecting priorities 1-2-3 in order. If this arrow is rotating clockwise the configuration of the chiral center is R, while if the arrow is rotating counterclockwise the configuration is S.

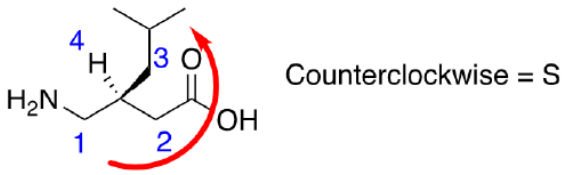


Figure 7. Determining whether the chiral center is R or S.

We will now use Avogadro to make this process of manipulating the molecule to determine its chirality much easier. In the Pharmaceutical Structures folder that you downloaded in the supporting files, open Pregabalin.xyz in Avogadro. As shown in Figure 8, the structure of pregabalin is shown in three dimensions. By clicking on the navigation button, which looks like a compass rose, you can rotate the molecule in three dimensions. Try to rotate the molecule such that the lowest priority of the chiral center is pointing into the screen. With this completed you can easily determine R or S.

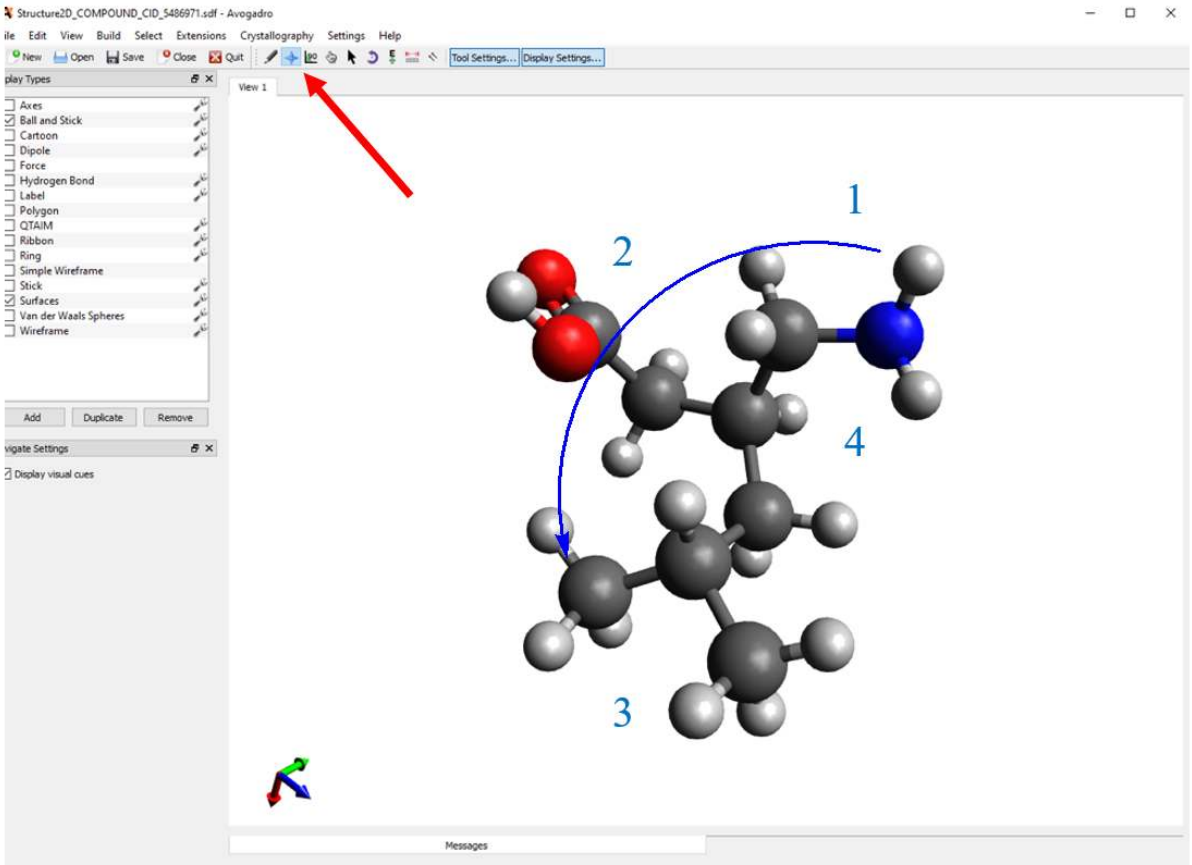


Figure 8.

The structure of pregabalin rotated such that the lowest priority group is pointed away from you into the screen. The navigation button is indicated by a red arrow.

One additional feature of Avogadro is that it makes creating an enantiomer of the structure that you have drawn easy and convenient. To create the enantiomer of the pregabalin molecule on your screen click on Build → Invert Chirality.

Please complete the questions for part 1 at the end of the assignment.

Part 2: Examining the energies of enantiomers versus diastereomers.

As described above, enantiomers of a compound have remarkably similar chemical properties. They will melt at the same temperature, have the same IR spectra, and react the same. One of the only places where enantiomers will differ is their interaction with plane polarized light. Specifically, enantiomers of a compound will rotate plane polarized light in opposite directions. This similarity does not extend to diastereomers. Unlike enantiomers, diastereomers will have different chemical properties and will often display unique melting points, different IR spectra, and they may react differently. In the second part of the computational exercise that follows we will examine the chemical properties of the amino acid threonine which has two chiral centers.

As shown in Figure 9, the amino acid threonine has two chiral centers. One set of enantiomers has historically been known as threonine while the other set of enantiomers is referred to as allothreonine, but these compounds have the same molecular connectivity. Given what we know about enantiomers and diastereomers, we would expect these L and D-threonine (enantiomers) to have identical energy values. L-Threonine and L-Allothreonine, however, would be expected to have different energy values because they are diastereomers.

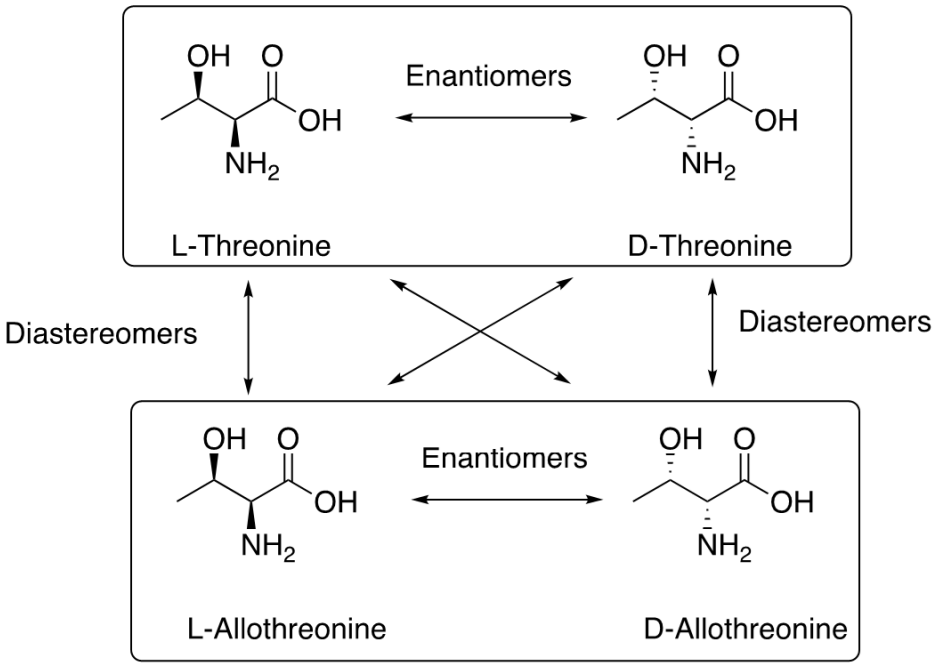


Figure 9. The diagrammed relationship between enantiomers of threonine and allothreonine.

The geometry of all four stereoisomers of threonine were optimized in the gas phase and an energy calculation performed on the optimized geometry using a B3LYP functional and DEF2-SVP basis set using Orca.[4–6] The Gibbs free energy values are summarized in the table below and the optimized structures are available in the supporting files. Please use these data and your knowledge of stereochemistry to complete the questions associated with part 2 of this exercise.

Table 1. Summary of ground state Gibbs free energy values for threonine and allothreonine.

Species	Gibbs Free Energy, Eh
L-Threonine	-437.599724
D-Threonine	-437.599618
L-Allothreonine	-437.609162
D-Allothreonine	-437.609163

References

1. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J Cheminform* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
2. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.
3. Neese, F. Software Update: The ORCA Program System—Version 5.0. *WIREs Comput Mol Sci* **2022**, *12* (5). https://doi.org/10.1002/wcms.1606.
4. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
5. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Computational Molecular Science* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
6. Neese, F. The ORCA Program System. *WIREs Computational Molecular Science* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
7. Silverman, R. B. From Basic Science to Blockbuster Drug: The Discovery of Lyrica. *Angew. Chem. Int. Ed.* **2008**, *47* (19), 3500–3504. https://doi.org/10.1002/anie.200704280.

This page titled 6.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

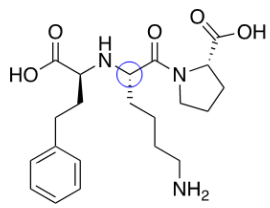
6.4: Exercise Questions

Part 1: Determining the absolute configuration of chiral centers in pharmaceuticals.

1. Please assign priorities for the groups on the indicated chiral centers and then rotate the molecule such that the lowest priority group is facing back into the plane of the paper. For help please view the chemical structures of these molecules using the supporting files.

Assign priorities to the indicated Chiral Center | **Redraw the molecule with the lowest priority to the back into the plane of the paper.**

A.

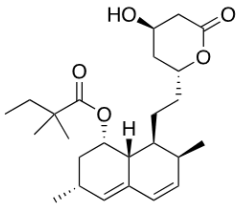


linospril (Dapril): Used in the treatment of high blood pressure

Rotate Lowest Priority to the Back →

The indicated chiral center is _____.

B.

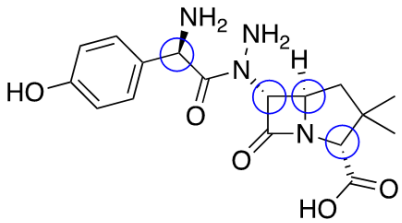


simvastatin (Zocor): used to treat high cholesterol

Rotate Lowest Priority to the Back →

The indicated chiral center is _____.

2. Using Avogadro to assist, please assign the absolute configuration all the chiral centers in the molecule amoxicillin.



Part 2: Examining the Energy Differences Between Enantiomers and Diastereomers.

3. Using the energy data provided in table 1, please determine the ΔG values for the D and L enantiomers of threonine in kcal/mol. 1 Hartree (Eh) = 627.5 kcal/mol.

$$\Delta G_{\text{Enantiomers}} = G_L - G_D$$

4. Using the energy data provided in table 1, please determine the ΔG between L-Threonine and L-Allothreonine in kcal/mol. 1 Hartree (Eh) = 627.5 kcal/mol. Is this number what you would have expected when compared to the ΔG value between the enantiomers of threonine? Explain.

$$\Delta G_{\text{Diastereomers}} = G_{\text{LThreonine}} - G_{\text{LAllothreonine}}$$

5. Examine the ground state structures L/D-Threonine and L/D-Allothreonine in Avogadro. Propose a reason why the energy values are different between enantiomers of threonine and enantiomers of allothreonine.

This page titled 6.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

7: Thermodynamics, Kinetics, and the Reaction Coordinate Diagram

The energy changes involved in reagents reacting to make products are extremely informative to chemists. Specifically, this information can give us insight into how much product can be formed and how fast the reactants can be converted into products. Organic chemists will often use simple methods to estimate the direction of a chemical reaction based on thermodynamic principles.

7.1: Overview

7.2: Background

7.3: Computational Instructions

7.4: Exercise Questions

This page titled 7: Thermodynamics, Kinetics, and the Reaction Coordinate Diagram is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

7.1: Overview

Learning Objectives

- Students will demonstrate the ability to estimate the sign of the ΔG° of a chemical reaction.
- Students will be able to calculate the ΔG°, ΔS°, and ΔH° of a reaction using density functional theory with Orca.
- Students will be able to search for a transition state of a simple one step reaction using Orca.
- Students will be able to relate the magnitude of $\Delta G^\ddagger$ to the rate of a reaction.

Overview: The energy changes involved in reagents reacting to make products are extremely informative to chemists. Specifically, this information can give us insight into how much product can be formed and how fast the reactants can be converted into products. Organic chemists will often use simple methods to estimate the direction of a chemical reaction based on thermodynamic principles. While such tools are useful as a first approximation, more accurate information can be very useful for chemists seeking to make a compound in the highest yield possible or to understand a chemical process. In the exercise that follows we will learn how to calculate both the thermodynamic equilibrium as well as the activation barrier of a simple chemical reaction using Orca.[1–3]

Faculty Notes: This exercise is designed to help students relate fast and simple thermodynamic approximations of a reaction to more accurate computations done using density functional theory. Before assigning this exercise, students should have been exposed to basic reaction thermodynamics. Specifically, students should have seen how Gibbs free energy can be related to entropy and enthalpy. Additionally, students should have a basic understanding of microscopic entropy, such as being able to predict whether a dissociation reaction will be entropically positive or negative. A standard desktop computer takes about 15 minutes to run the computation in this exercise. Overall, the exercise should take students about 1.5 hours to complete.

A note on reaction coordinate diagrams: in a typical reaction coordinate diagram as seen in organic chemistry textbooks, the x-axis is the reaction coordinate, and the y-axis is energy. This diagram describes the potential energy surface for a single molecule undergoing the reaction, and so energy is a reasonable choice of axis. This activity utilizes transition state theory which assumes an ensemble of molecules in quasi-equilibrium between the starting material and transition state. Entropic and energetic factors affect this ensemble, and the reaction coordinate diagrams address this by using Gibbs energy instead of energy. Based on this statistical treatment, showing structures, and using reaction coordinate is somewhat misleading, though it is still common practice. For pedagogical reasons, in the figures below we have chosen to include structures to indicate the reactants, products, and transition state on these diagrams.

This page titled 7.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

7.2: Background

A powerful piece of information for understanding what will happen during a chemical reaction is the standard Gibbs free energy change of reaction (ΔG°). This single quantity dictates the extent to which a reaction will proceed starting from pure reactants and no products. For example, a negative value of ΔG° indicates a spontaneous reaction will convert a majority of starting reactants into products (we say this reaction favors the products). Conversely, a positive value of ΔG° indicates that the reaction will favor the reactants and will result in a final mixture which contains more reactants than products. A change in Standard Gibbs free energy close to zero indicates that a reaction that doesn't favor reactants or products; starting this reaction with pure reactants will end up with a 50/50 mixture of products and reactants.

Table 1. The relationship between reaction spontaneity and ΔG°

ΔG°	Reaction Favors
Positive	Reactants, Nonspontaneous
Negative	Products, Spontaneous
Zero	Neither Reactants nor Products

The change in Gibbs free energy (ΔG°) is related to both the change in enthalpy (ΔH°), which measures heat given off in a reaction at constant pressure, and the change in entropy of the reaction (ΔS°) which measures a change in order (Equation $7.2.1$).

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{7.2.1}$$

To estimate the change in Gibbs free energy of a reaction we need information about both the ΔH° and ΔS° of the reaction. ΔH° is in large part determined by breaking or forming of bonds or intermolecular forces. Since intermolecular forces tend to be weaker than bonds, it's typical to ignore them (unless a phase change occurs!). The enthalpy from breaking or forming bonds can be estimated by subtracting the sum of the bond dissociation enthalpy (BDE) values of bonds formed from the sum of the bonds broken (Equation $7.2.2$). Generic BDE's are published tabular form in a variety of sources.[4]

$$\Delta H^\circ \approx (\text{ Sum of BDE of Bonds Broken }) - (\text{ Sum of BDE of Bonds Formed }) \tag{7.2.2}$$

The value for the change in entropy, ΔS°, of a reaction is more difficult to estimate. A useful approximation is that, for a gas phase reaction, the change in entropy is determined by the change in the number of gas particles. If a reactant has the same number of moles of gas on both sides of the reaction, $\Delta S^\circ \approx 0$. From this, you may directly estimate the ΔG° of a reaction, $\Delta G^\circ \approx \Delta H^\circ$. All of our computations today will be performed for gas phase reactions, so every separate particle must be counted to determine if the entropy change is zero.

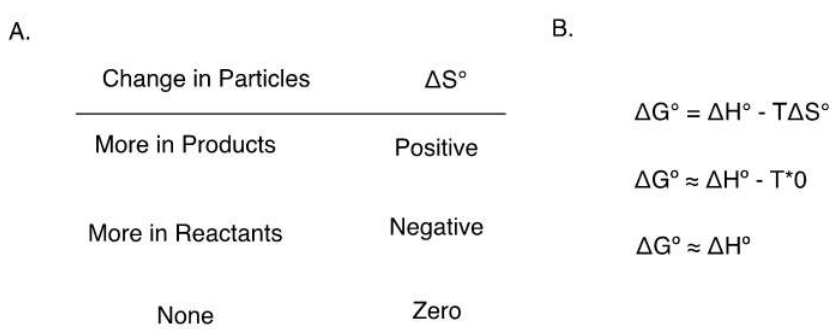


Figure 1. A. The relationship between the change in the number of particles and the ΔS° of the reaction. **B.** In the special case where the ΔS° of a reaction ≈ 0 the $\Delta G^\circ \approx \Delta H^\circ$

The proportion of products and reactants at equilibrium is determined by the ΔG° for a reaction, but this value has no bearing on how quickly a reaction progresses. Instead, the energy which influences the rate at which a reaction goes forward is called the energy barrier. The energy barrier associated with going from reactants to the transition state is referred to as $\Delta G^\ddagger$ (read as delta G double dagger). $\Delta G^\ddagger$ can be thought of as the free energy difference between the reactants and the transition state. The transition state of a reaction corresponds to a point during the reaction with the highest free energy. A transition state typically has a structure

where bonds being made or broken during the reaction step are partially formed. Note that the transition state is the same arrangement of atoms whether the reaction is going forward or backwards, but the energy is different because it is always measured with respect to the starting point for a given direction. Thus, if the products are downhill in energy from the reactants, there is a larger $\Delta G^{\ddagger}$ for the reverse reaction that there was for the forward reaction.

The energy of the transition state, when compared to the starting materials and products (or intermediates), can tell us valuable information about its structure. Specifically, Hammond's postulate states that the transition state of a reaction resembles the structure of the reactant, or product to which it is closer in energy. This means that if a reaction step is endergonic ($\Delta G^{\circ} > 0$) the transition state will look like the products more than the reactants. Conversely, if a reaction step is exergonic ($\Delta G^{\circ} < 0$), the transition state will more closely resemble the structure of the starting materials. When plotted versus reaction progress, the energies of starting materials, transition state(s), intermediate(s), and products are known as a reaction coordinate diagram.

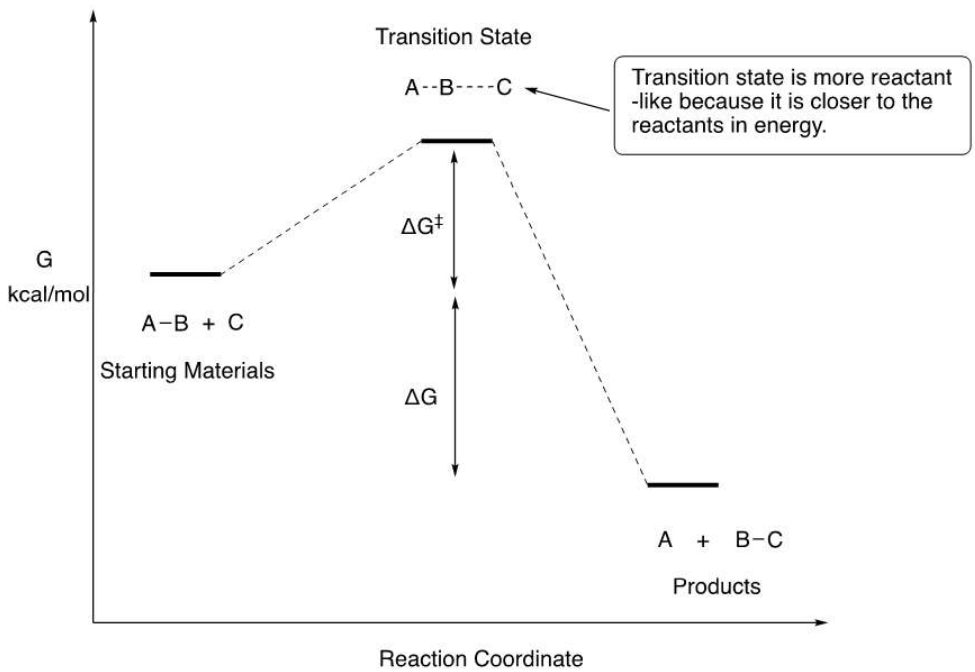


Figure 2. Example reaction coordinate diagram of a generic concerted substitution reaction. The value of ΔG° informs us as to the position of the equilibrium between the reactants and the products while the value of $\Delta G^{\ddagger}$ indicates how quickly the reaction will reach equilibrium.

In the computational exercise that follows you will learn to use Orca to calculate both the thermodynamic (ΔG°, ΔH°, ΔS°) and kinetic ($\Delta G^{\ddagger}$) values of a simple substitution reaction.

This page titled 7.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

7.3: Computational Instructions

The exercise that we will be completing today seeks to calculate the thermodynamic changes that occur in a substitution reaction between chloromethane and a bromide anion. As shown in Figure 3, the bromide ion will substitute for the chloride ion traveling through a transition state where the carbon bromide bond is forming while the carbon-chloride bond is breaking. This substitution is known as an SN2 reaction.

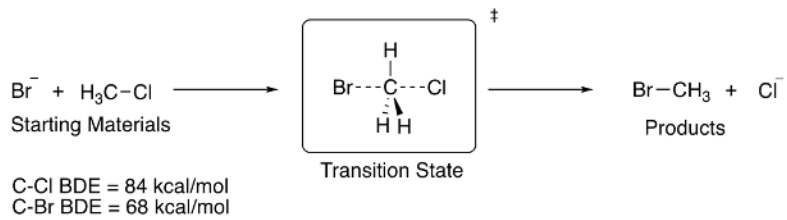


Figure 3: Substitution reaction between a bromide ion and chloromethane. The bond dissociation enthalpy for both the $\mathrm{C-Br}$ and $\mathrm{C-Cl}$ bond are shown below.

One of the major uses of DFT calculations is to find and compute the energies of transition states between steps of a reaction. Because the heights of energy barriers to transition states from reactants directly correlate with rates of reaction, transition state modeling can be very informative with respect to the feasibility of proposed reaction steps. Orca has a convenient method for finding transition states between two chemical systems (reactants and products/intermediates).

We will now walk through the calculation you need to perform to produce a reaction coordinate diagram of a simple SN2 reaction. Start by creating a folder on your desktop and name it Transition_State. After this, you should download the associated files for this computation exercise and move them to the folder that you just created. As shown in Figure 4 (top) the Transition_State Folder should contain a Starting Output, Product Output, and TS subfolder that contains the files necessary to complete the experiment. To save computational time, the energy calculations for the starting materials and products have been provided for you and can be found in the Starting Output, and Product Output file. We will be calculating the energy and structure of the transition state using Orca. As indicated above, Orca has a convenient method for finding transition states between two chemical systems. This method is referred to as nudged elastic band with transition state optimization. This method works by creating a series of “images” as intermediates between the reactants and the products of a reaction step. Each image then undergoes a constrained geometry optimization and energy calculation creating a minimal energy path between the reactants and the products. The image that is the highest in energy is then utilized to help determine the structure of the transition state.

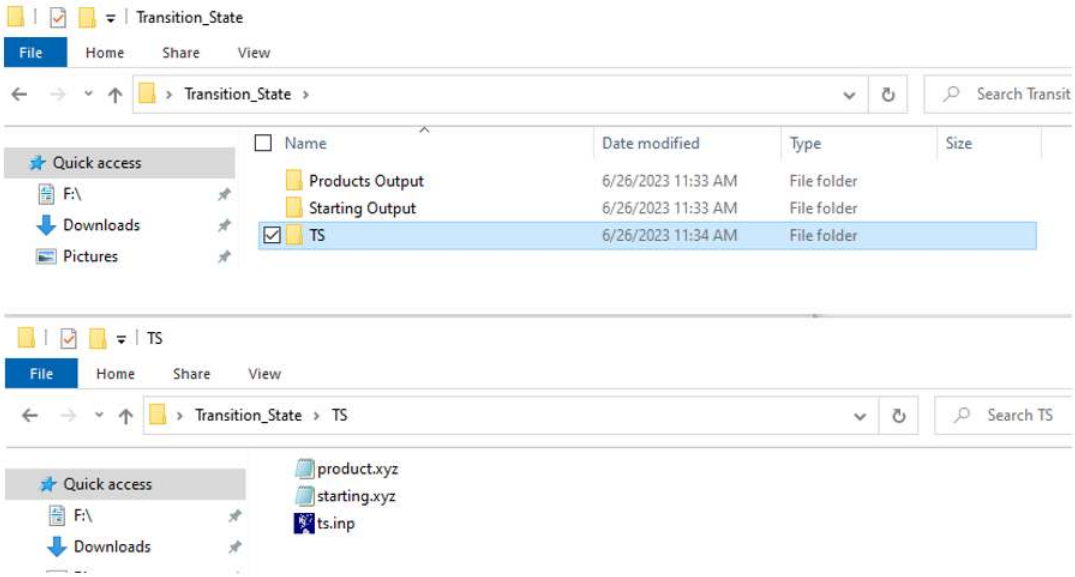


Figure 4. The supporting files for this experiment. (Top) The complete supporting files for this exercise. (Bottom) The contents of the TS folder nested in Transition_State.

Let's look through our input script to see what each command is doing (Figure 5). Like in previous exercises, the input script starts with a comment describing what we are trying to calculate. The second line, starting with a ! symbol, tells the computer the level of theory and basis set (B3LYP def2-SVP) as well as the calculations we want to perform (NEB-TS=Nudged Elastic Band Transition State Search, and FREQ=Frequency calculation necessary for thermochemistry data). The fourth line of the script, shown by a red arrow, indicates the ending structure to be used for the transition state search, product.xyz. The final line of the input script indicates that the starting coordinates of the structure can be found in starting.xyz. Moreover, the two numbers preceding the file name indicate the starting structure has an overall negative charge and a spin multiplicity of 1, meaning that all electrons in the structure are paired. You do not need to change any commands on this input file. The preceding description is included such that you can use this file to calculate other transition states should you desire.

```
# transition state search
!B3LYP def2-SVP NEB-TS FREQ

%NEB NEB_END_XYZFILE "product.xyz" END

* xyzfile -1 1 starting.xyz
```

Figure 5. The generic input script for determining a transition state. You do not need to change any commands within this input script. The line indicated by the red arrow shows the product of the reaction step, while the blue arrow indicates the starting materials.

We can now run our calculation using Orca via the command line as we did in the previous exercises. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter the computer will paste a new line indicating that the current directory has changed, as shown in Figure 6A. To find the file path of your input script, right click on the input script (ts.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 6B).

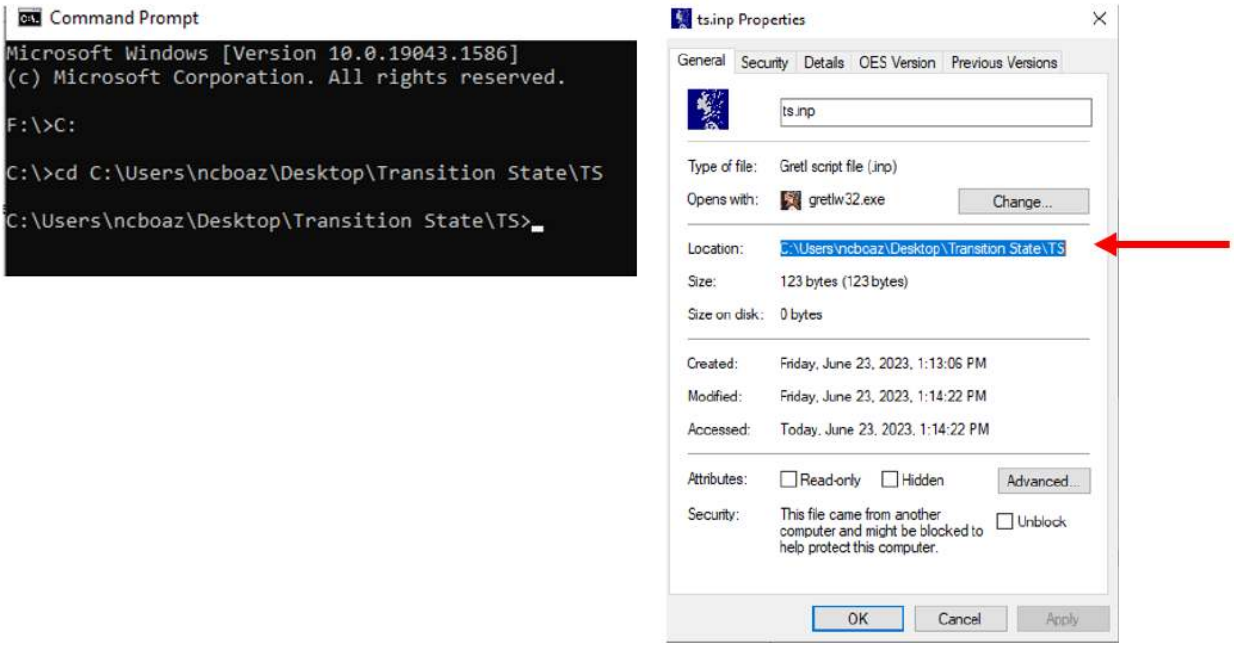


Figure 6. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **6B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca ts.inp > ts.out and pressing enter. At first it may not appear like anything is happening, but the folder on your desktop labeled TS will quickly become populated with the output of your calculation. Depending upon the speed of your computer, the calculation will take about 10-15 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 7).

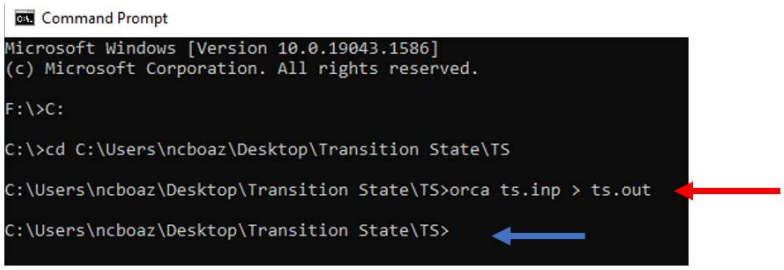


Figure 7. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in ts.inp and that the results of this calculation should be placed in the output file ts.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

Visualizing the Reaction and Transition State

You can visualize the reaction that you are modeling using some of the output files from the transition state calculation. Open the file ts_MEP _trj.xyz in Avogadro and click Extensions → Animation to bring up the window shown in Figure 8.[5,6] From here click dynamic bonds and use the slide button to move the reaction from reactants to products and back. About halfway from reactants to products will be a position where the $C-Cl$ bond is partially broken and the $C-Br$ bond is partially formed.

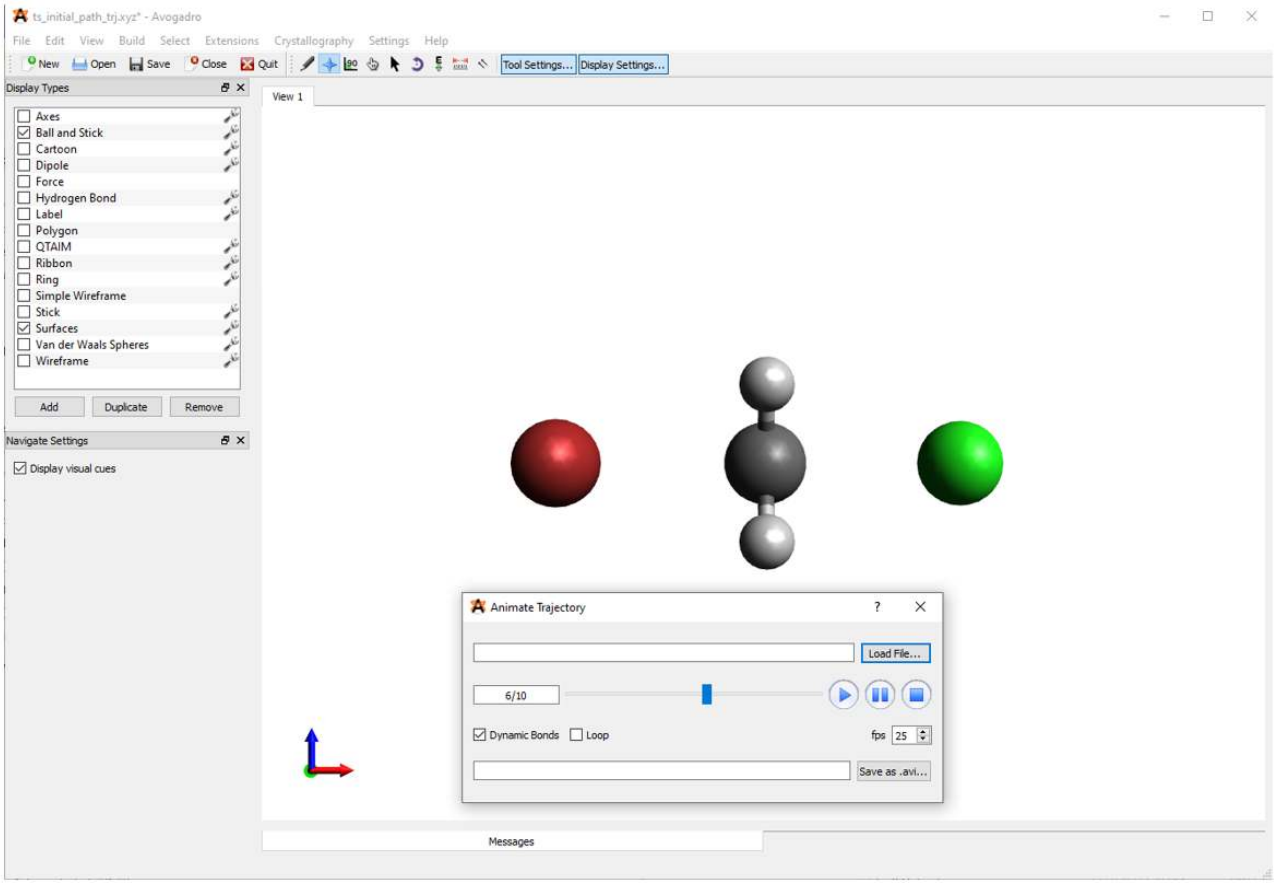


Figure 8. Examining the reaction trajectory file.

To visualize the optimized transition state please open the output file of our calculation, ts.out, in Avogadro. As shown in Figure 9 the optimized transition state shows the $Br-C$ bond being formed while the $C-Cl$ bond is being broken. Additionally, you will see a set of vibrational modes just like when you calculated the IR spectrum of hexane in a previous exercise. Unlike in the previous exercises, you will notice that one of the vibrational modes for this transition state will be imaginary in nature, as represented by a negative sign. Because a transition state represents the highest point on a reaction coordinate diagram there exists a vibrational mode (the imaginary mode) that if it vibrates will push the molecules either closer to products or closer to reactants.

This mode will show the bonds forming and breaking at the transition states. To see this motion, click on the negative vibrational mode in the list of vibrational modes and press start animation.

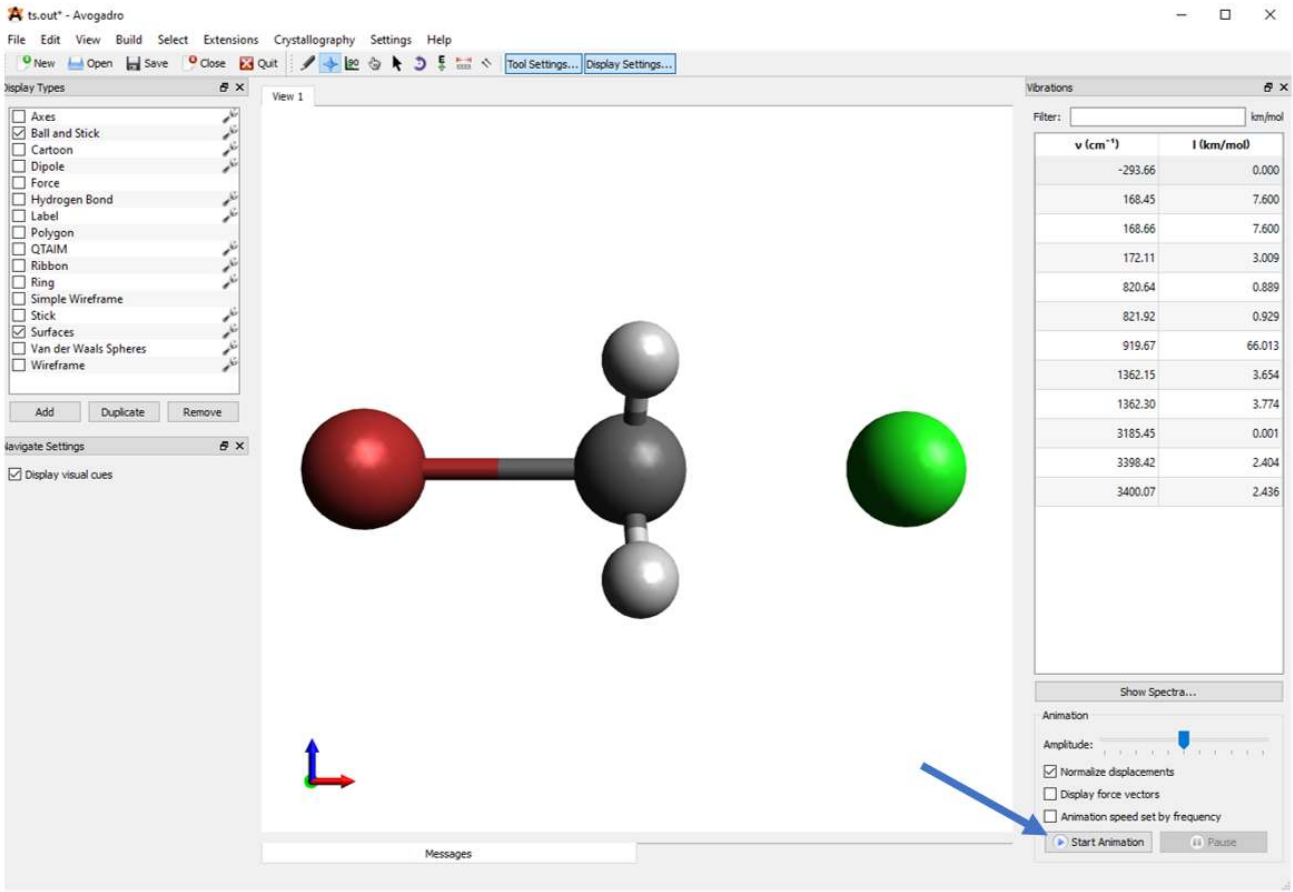


Figure 9. Examining the vibrational modes of the calculated transition states. The start animation button is shown with a blue arrow.

To view the energy values associated with the transition state (calculated), or the provided reactants/products please open the respective output files in notepad. By scrolling to the end of the file you can find the total Gibbs free energy (G), as well as the enthalpy (H) and entropy (S) of the starting materials. The position of these values is shown in Figure 10 for the starting materials of our substitution reaction. Please note that entropy values are shown as $S \times T$, $\text{entropy} \times \text{temperature}$ in Kelvin.

```
ENTHALPY
--------

The enthalpy is H = U + kB*T
                kB is Boltzmann's constant
Total free energy                ...  -3073.60932321 Eh
Thermal Enthalpy correction      ...      0.00094421 Eh       0.59 kcal/mol
-----------------------------------------------------------------------------
Total Enthalpy                   ...  -3073.60837900 Eh

Note: Only C1 symmetry has been detected, increase convergence thresholds
      if your molecule has a higher symmetry. Symmetry factor of 1.0 is
      used for the rotational entropy correction.


Note: Rotational entropy computed according to Herzberg
Infrared and Raman Spectra, Chapter V,1, Van Nostrand Reinhold, 1945
Point Group:  C1, Symmetry Number:   1
Rotational constants in cm-1:     5.222521     0.024622     0.024622

Vibrational entropy computed according to the QRRHO of S. Grimme
Chem.Eur.J. 2012 18 9955


-------
ENTROPY
-------

The entropy contributions are T*S = T*(S(el)+S(vib)+S(rot)+S(trans))
     S(el)   - electronic entropy
     S(vib)  - vibrational entropy
     S(rot)  - rotational entropy
     S(trans)- translational entropy
The entropies will be listed as mutliplied by the temperature to get
units of energy

Electronic entropy               ...      0.00000000 Eh      0.00 kcal/mol
Vibrational entropy              ...      0.00510554 Eh      3.20 kcal/mol
Rotational entropy               ...      0.01222782 Eh      7.67 kcal/mol
Translational entropy            ...      0.01924704 Eh     12.08 kcal/mol
-----------------------------------------------------------------------------
Final entropy term               ...      0.03658041 Eh     22.95 kcal/mol

In case the symmetry of your molecule has not been determined correctly
or in case you have a reason to use a different symmetry number we print
out the resulting rotational entropy values for sn=1,12 :
 -----------------------------------------------------
|  sn= 1 | S(rot)=       0.01222782 Eh      7.67 kcal/mol|
|  sn= 2 | S(rot)=       0.01157336 Eh      7.26 kcal/mol|
|  sn= 3 | S(rot)=       0.01119053 Eh      7.02 kcal/mol|
|  sn= 4 | S(rot)=       0.01091891 Eh      6.85 kcal/mol|
|  sn= 5 | S(rot)=       0.01070822 Eh      6.72 kcal/mol|
|  sn= 6 | S(rot)=       0.01053608 Eh      6.61 kcal/mol|
|  sn= 7 | S(rot)=       0.01039053 Eh      6.52 kcal/mol|
|  sn= 8 | S(rot)=       0.01026445 Eh      6.44 kcal/mol|
|  sn= 9 | S(rot)=       0.01015324 Eh      6.37 kcal/mol|
|  sn=10 | S(rot)=       0.01005376 Eh      6.31 kcal/mol|
|  sn=11 | S(rot)=       0.00996377 Eh      6.25 kcal/mol|
|  sn=12 | S(rot)=       0.00988162 Eh      6.20 kcal/mol|


-------------------
GIBBS FREE ENERGY
-------------------

The Gibbs free energy is G = H - T*S

Total enthalpy                   ...  -3073.60837900 Eh
Total entropy correction         ...     -0.03658041 Eh    -22.95 kcal/mol
-----------------------------------------------------------------------------
Final Gibbs free energy         ...  -3073.64495941 Eh
```

Figure 10. Example output file for the starting materials of the reaction. The values for G, H, and S are indicated by arrows. Please note that the entropy term has already been multiplied by the temperature (298.15 K). This means that the final entropy term is really $T \times S$.

References

1. Neese, F. The ORCA Program System. *WIREs Comput. Mol. Sci.* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
2. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
4. Luo, Y.R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, FL, 2007.

5. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminformatics* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
6. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.

This page titled 7.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

7.4: Exercise Questions

1. Please estimate the change in Enthalpy (ΔH°), Entropy (ΔS°), and Gibbs free energy (ΔG°) for the substitution reaction shown below using the BDE values provided in Figure 2. For full credit please show your work.

$$\begin{aligned}&\mathrm{Br}^- + \mathrm{H_3C-Cl} \longrightarrow \mathrm{Br-CH_3} + \mathrm{Cl}^-\\&\mathrm{C-Cl\ \ BDE} = 84\ \mathrm{kcal/mol}\\&\mathrm{C-Br\ \ BDE} = 68\ \mathrm{kcal/mol}\end{aligned}$$

2. Given your answer above, what side of the reaction (reactants or products) will be favored?
3. Please use the thermodynamic values found at the end of the output files for the starting materials and products to complete the following table. Please provide all energy in Hartree (E_H). The temperature that the thermochemical calculations were performed at was 298.15 K.

	Gibbs Free Energy, $G(E_H)$	Enthalpy, $H(E_H)$	Product of Entropy and Temperature, $T \times S, (E_H)$	Entropy, $S(E_H/K)$
Products				
Starting Materials				

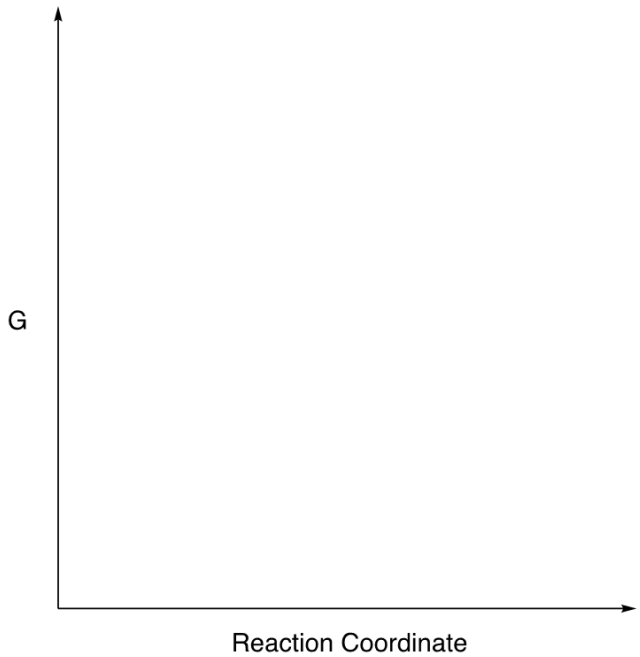
4. Using the values from the table in question 3, please complete the following table calculating the change in Enthalpy (ΔH°), Entropy (ΔS°), and Gibbs free energy (ΔG°) in Hartree and in kcal/mol. For conversion there are 627.5 kcal/mol in 1 Hartree.

ΔG°	ΔH°	ΔS°
Eh	Eh	Eh/K
kcal/mol	kcal/mol	cal/mol*K

5. Please discuss the difference between the estimated thermochemical values from question 1 and the calculated thermochemical values from question 4. Are the calculated values of ΔG°, ΔH°, and ΔS° close to what you expected? Please explain.
6. To help determine the activation free energy of the reaction ($\Delta G^\ddagger$) please complete the following table. We will normalize all the energies so that the energy of the starting materials will be zero. Do this by adding the energy value of the starting materials (in kcal/mol) to the energy values of the transition state and that of the products. (Note: a correct answer will have a TS that is higher in energy than the starting materials which should have a normalized value of 0)

	$G(E_H)$	G (kcal/mol)	Normalized G (kcal/mol)
Starting Materials			
Transition State			
Products			

7. Please draw a reaction coordinate diagram of the substitution reaction between bromide and chloromethane using the data from question 6. For full credit your reaction coordinate diagram should label the starting material, transition state, ΔG°, and $\Delta G^\ddagger$.



8. A. According to the Hammond postulate the transition state should resemble the species it is closest to in energy. Using your data from question 6, should the transition state look more like the reactants or the products?
   B. Using the measuring tool in Avogadro (looks like a ruler) determine the distances between the carbon and bromine atoms and the carbon and chlorine atoms in the transition state to complete the table below.

	$\mathrm{C-Br}$ Bond Distance	$\mathrm{C-Cl}$ Bond Distance
Distance, Angstroms		

   C. For this question you know that $\mathrm{C-Br}$ distance is 2.075 Angstroms in the products and the $\mathrm{C-Cl}$ bond distance in the starting materials is 1.846 Angstroms. Does the computer structure of the transition state fit your expectation of what it should look like given the Hammond postulate? In other words, does it look like either the product or starting material as expected? Please explain.

$\mathrm{C-Br}$

$$\%\ \text{Difference} = \frac{\mathrm{C-Br_{Ts}} - \mathrm{C-Br_{Product}}}{\mathrm{C-Br_{Product}}} \times 100\% =$$

$\mathrm{C-Cl}$

$$\%\ \text{Difference} = \frac{\mathrm{C-Cl_{Ts}} - \mathrm{C-Cl_{Product}}}{\mathrm{C-Cl_{Product}}} \times 100\% =$$

This page titled 7.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

8: Understanding the Effect of Solvation on E2 Reactions

8.1: Overview
8.2: Background
8.3: Computational Instructions
8.4: Exercise Questions

This page titled 8: Understanding the Effect of Solvation on E2 Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

8.1: Overview

Learning Objectives

- Students will be able to use implicit solvation in Orca to add energy of solvation to their energy calculations.[1–3]
- Students will be able to describe energetically why E2 and SN2 reactions proceed more quickly in polar aprotic solvents than in polar protic solvents.

Overview: This exercise seeks to help you understand the role that solvent can play in the energetics of a reaction. SN2 and E2 reactions are favored by conditions such as high concentrations of reactants and polar aprotic solvents. On the other hand, SN2 and E2 reactions are disfavored by polar aprotic solvents. This disparity is the result of nucleophiles (or bases) being stabilized through strong intermolecular forces with polar protic solvents. In this exercise we will calculate the energies involved in the E2 reaction of 2-chloro-2-methylpropane with a hydroxide ion. We will contrast these energies as measured in water, a polar protic solvent, and dimethylsulfoxide (DMSO), a polar aprotic solvent. This data will illustrate why polar aprotic solvents accelerate SN2 or E2 reactions.

Faculty Notes: This exercise is designed to help students understand the effects of solvation on substitution and elimination reactions. Before assigning this exercise, students should have learned about the mechanism of both bimolecular and unimolecular substitution and elimination reactions. Specifically, students should be able to predict the predominant reaction mechanism given a set of conditions. A standard desktop computer takes about 30 seconds to calculate the solvation energy for each set of conditions. Overall, the exercise should take students about 1.5 hours to complete.

This page titled 8.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

8.2: Background

When determining whether a substitution/elimination reaction will proceed via an SN1/E1 or SN2 E2 reaction, one of the first questions that we ask concerns reaction conditions. Reactions run under high concentrations and with polar aprotic solvents tend to favor E2 and SN2 reactions. The underlying reason why high concentrations of reagents favor concerted substitutions and eliminations is due to kinetics. Specifically, SN2 and E2 reactions are bimolecular in nature and have a rate law (see equation 8.2.1) with terms including both the concentration of electrophile and nucleophile/base. This means that if we double the concentration of everything in the reaction, we would see a 4-fold increase in the rate of the reaction. Such a rate increase would not occur in a SN1/E1 reactions, which have a rate law that only includes a term for the concentration of the electrophile.

$$\text{Rate}_{\text{SN2/E2}} = \text{k [electrophile][nucleophile/base]} \tag{8.2.1}$$

$$\text{Rate}_{\text{SN1/E1}} = \text{k [electrophile]} \tag{8.2.2}$$

The use of polar aprotic solvents encourages SN2/E2 reactions by ensuring that the nucleophile/base is reactive, something that polar protic solvents will not be able to do. As shown in Figure 1, when a strong base and nucleophile such as sodium methoxide is dissolved in a polar aprotic solvent such as dimethylsulfoxide (DMSO) the lone pairs on the oxygen of DMSO can form stabilizing ion-dipole interactions with the sodium cation. The anion on oxygen, however, is unable to be stabilized effectively by lone pairs on DMSO. This means that the oxygen anion in sodium methoxide is reactive. If sodium methoxide were dissolved in a polar protic solvent, such as water, both the cation and the anion can be stabilized via intermolecular forces. Specifically, the sodium cation can be stabilized by ion-dipole interactions via lone pairs on the oxygen of water. The oxygen anion of sodium methoxide can also be stabilized by hydrogen bonding with the hydrogens on water molecules. This means that in water the nucleophile/base is stabilized, making it less reactive. Because an E2/SN2 reaction relies on a strong nucleophile/base, polar protic solvents slow down this bimolecular reaction.

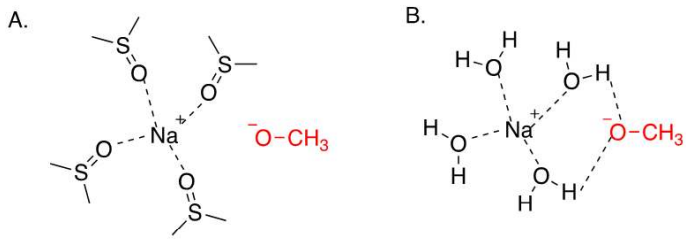


Figure 1A. Sodium methoxide solvated by (DMSO). Here the oxygen of the sulfoxide solvent can stabilize the sodium cation but unable to effectively stabilize the oxygen anion of the methoxide. **1B.** Sodium methoxide solvated by water. In this case both the sodium cation and oxygen anion of the compound are stabilized by intermolecular forces.

When talking reactivity in organic chemistry we often use a very qualitative description of stability. For example, a highly reactive species will be unstable and high in energy, while a stable species will be low in energy and less reactive. To determine how much more or less reactive one species is compared to another, energies can be calculated using quantum chemistry programs such as Orca. In the exercise that follows we calculate the thermodynamic values for an E2 reaction in a polar protic versus a polar aprotic solvent to help illustrate the role of solvation in SN2/E2 reactions.

This page titled 8.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

8.3: Computational Instructions

In this exercise we will be examining the energetics of the starting materials, transition state, and products of an E2 reaction in a solvent of water or DMSO. Specifically, we will be examining the energies associated with the E2 reaction between the methoxide anion and 2-chloro-2-methylpropane (Figure 2).

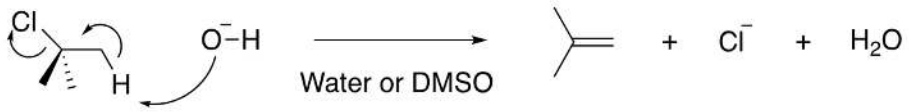


Figure 2. E2 elimination between the hydroxide anion and 2-chloro-2-methylpropane.

Up until this point, all of the calculations that we have performed have been in the gas phase. While this allows us to calculate energy levels and transitions states, these calculations don't accurately reflect many organic reactions which occur in a solvent. Intermolecular attractions between a solvent and reactants, referred to as solvation, can have a dramatic effect on the energies of chemical species. When calculating the interaction of solvent with reactants, known as solvation, many programs will use what is referred to as implicit solvation. In this case, individual molecules of solvent are not modeled but rather the program considers the bulk properties of the solvent, such as the dielectric constant, when surrounding molecules of interest. The advantage to this type of modeling as opposed to the modeling of explicit solvent molecules is that it takes less computational power and time while providing reasonable results.

The dielectric constant of a solvent is a property which you may have been exposed to in a physics but isn't always discussed explicitly in chemistry. Materials with a high dielectric constant are effective at shielding charges from each other. The force pushing apart two negative charges is much weaker if they are separated by a material with a high dielectric constant. Likewise, a positive and negative charge attract each other much more weakly in a high dielectric medium. Most polar solvents tend to have larger dielectric constants, and non-polar solvents tend to have smaller dielectric constants. By asking ORCA to use a specific solvent for a calculation, the program assumes that charged moieties have weaker or stronger effects depending on if it is a high or low dielectric solvent.

Computing the Energy of Reactants and Products

Despite using the computationally more efficient implicit solvation methods, calculating the energy values of starting materials, transition states, and products is time intensive for systems involving more than a few atoms. Because of this, you will be provided with energy values and geometry coordinate files for each step of the E2 reaction, shown below in Figure 3.

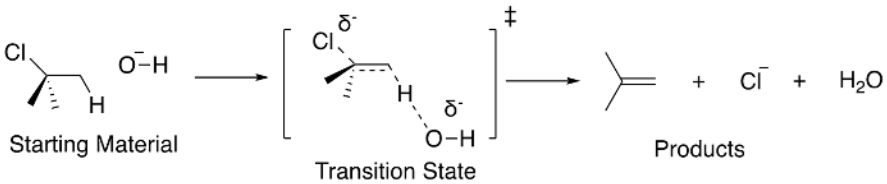


Figure 3A. Reaction scheme for the E2 reaction being modeled in this exercise.

Please note that the geometries that you will be provided with have been optimized in the indicated solvent while the energies you are provided are gas phase energies.Your goal in performing this exercise will be to compute the energy of solvation for each step of the reaction and use this information to create a reaction coordinate diagram comparing the E2 reaction in water and DMSO as a solvent.

Figure 3B. (Bottom) Summary of the gas phase energy values for the reaction. Please note that the values are slightly different for each condition because the geometries were determined in the indicated solvent.

	Starting Material	Transition State	Products
Energy in DMSO (Eh)	-693.3164355	-693.31569972	-693.38054907
Energy in H_2O (Eh)	-693.3416374	-693.32910367	-693.38044269

Start by creating a folder on the desktop of your computer and label it as solvation. Within this folder, please create the following subfolders: SM_DMSO, TS_DMSO, PR_DMSO, SM_H2O, TS_H2O, and PR_H2O. Next, you should download the supporting files for this exercise. These files will include a generic input script (denoted by a .inp file extension), and molecular coordinates for the geometry optimized starting materials, transition state and products (denoted by a .xyz file extension). Place a copy of the generic input file that you downloaded into each of the nested subfolders. Next you should place the molecular coordinates file for each step into its corresponding subfolder. A description of the file structure is shown in Figure 4.

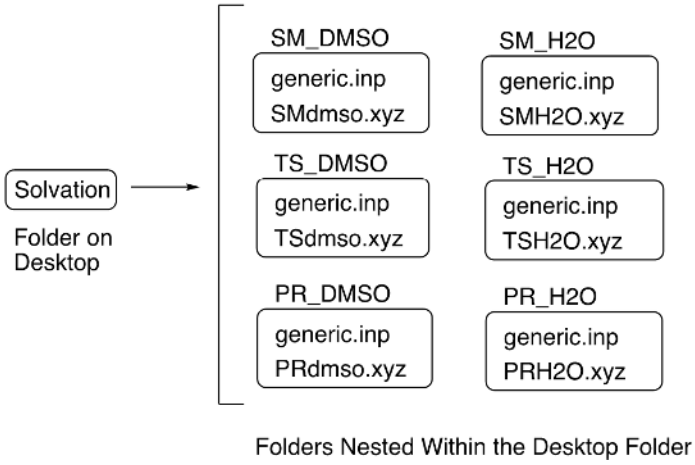


Figure 4. Description of the nested files used in this exercise.

The process for computing the solvation energies of each of these steps is the same so we will walk you through the first calculation step-by-step and then allow you to perform the rest of the calculations using the same procedure. Specifically, we will work on calculating the solvation energy of the starting material in DMSO. Start by opening the starting coordinate files in Avogadro and check that the structure looks correct for the combination of the hydroxide anion and 2-chloro-2-methylpropane as shown in Figure 5.

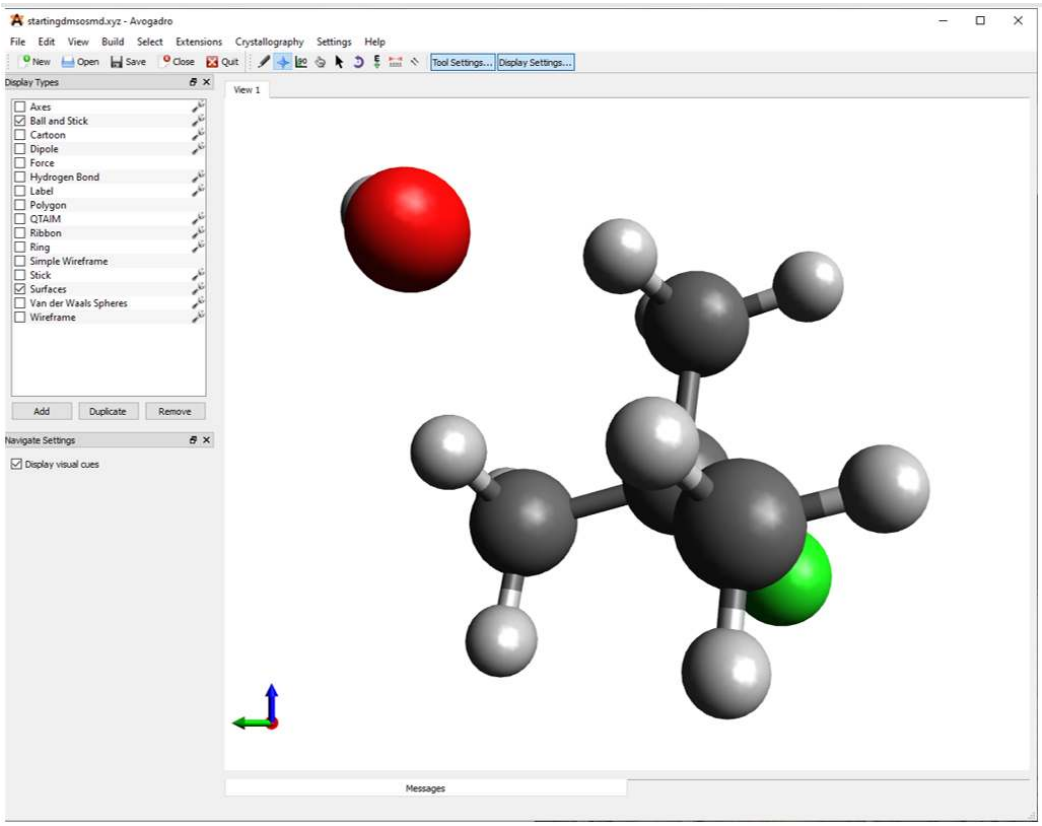


Figure 5. Starting coordinates visualized in Avogadro.

Next, you should rename the generic input file within the SM_DMSO subfolder. Save the generic input file as SM_DMSO.inp. You will then need to modify the generic input file so that it refers to the coordinate file within the starting_DMSO subfolder. Specifically, you should replace file.xyz in the input file with SMdmso.xyz. Additionally, you will need to change the SOLVENT keyword to the solvent that you want to model. In this case, you will change SOLVENT to DMSO, as shown in Figure 6. After you have made these changes, please be sure to save the file. When you compute structures later in water you can use the WATER keyword.

```
# Solvation energy E2
!B3LYP def2-SVP
% CPCM SMD TRUE
     SMDSOLVENT "SOLVENT"
END

* xyzfile -1 1 file.xyz
```

Figure 6. The generic input script for Orca. The SOLVENT keyword shown by a red arrow should be replaced with the solvent you are using. The generic coordinate file shown by a blue arrow, file.xyz, should be replaced with the coordinates that you are looking to calculate.

We can now run our calculation using Orca via the command line as we did in the previous exercise. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter, the computer will paste a new line indicating that the current directory has changed, as shown in Figure 7A. To find the file path of your input script, right click on the input script (SM_DMSO.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 7B).

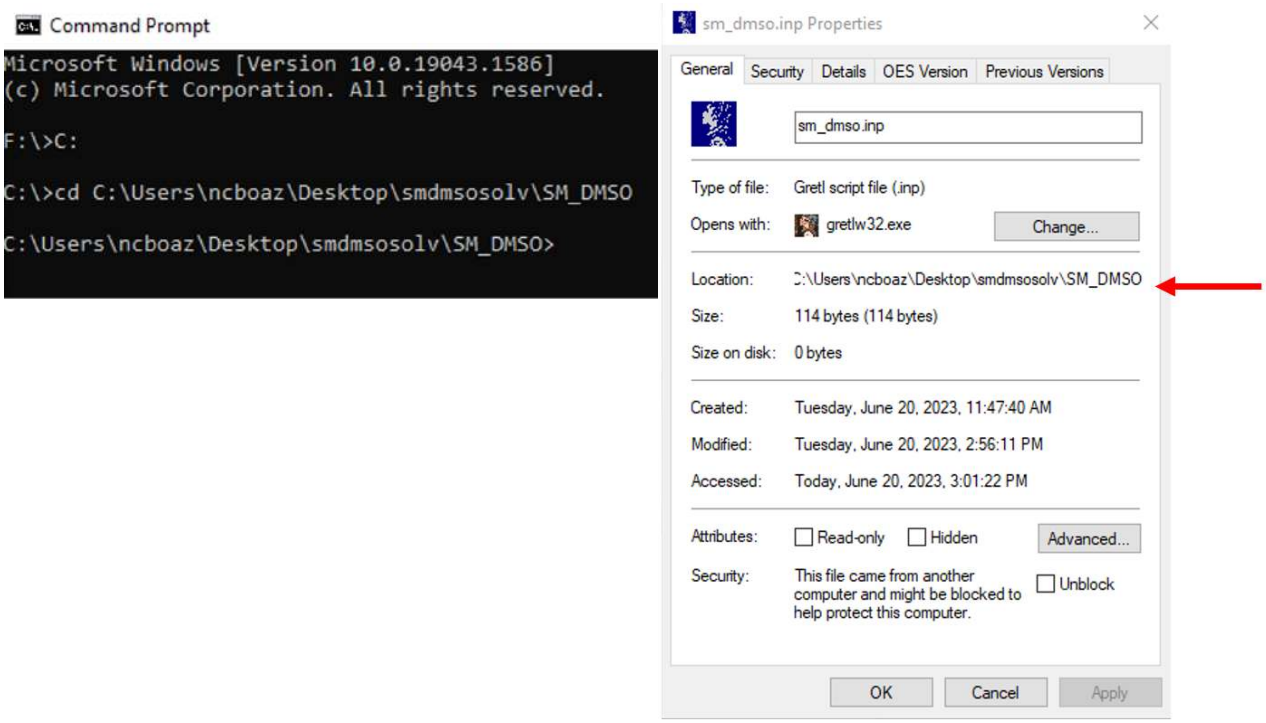


Figure 7A. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **7B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca SM_DMSO.inp > SM_DMSO.out and pressing enter. At first it may not appear like anything is happening but the folder on your desktop labeled SM_DMSO will quickly become populated with the output of your calculation. Depending upon the speed of your computer the calculation will take from 1-5 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 8).

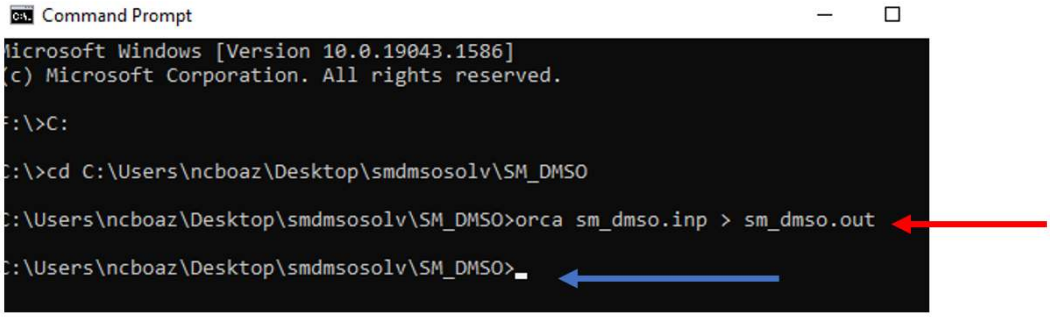


Figure 8. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in SM_DMSO.inp and that the results of this calculation should be placed in the output file SM_DMSO.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

Correcting Energies for Solvation

As mentioned above, a correction needs to be applied to the gas phase energy of a molecule or system if you want to find its energy in solution. The change in energy of a system when solvated is referred to as solvation, or $\Delta G^{\circ}_{\text{solv}}$. The solvation model that we are using, Solvent Model Density or SMD, treats solvent at a continuum that surrounds your molecule.[4] There are three components to the solvation of your system of interest, indicated graphically in figure 9. The electrostatic term of solvation, ΔG_{ENP}, describes the electrostatic interaction of your system with the solvent. The cavity-dispersion term ΔG_{CDS} describes the London Dispersion interaction between the solvent and the cavity in the solvent continuum occupied by your system. The final term in the solvation energy of your system is the energy associated with changing from gas phase at 1 atm. to a solution phase at a concentration of 1M. Luckily, this last correction is easily calculated and remains the same for all your calculations at 0.003012 Eh or 1.89 kcal/mol.[5]

$$\Delta G^{\circ}_{\text{solv}} = \Delta G_{\text{ENP}} + \Delta G_{\text{cos}} + \Delta G^{\circ}_{\text{conc}} \tag{8.3.1}$$

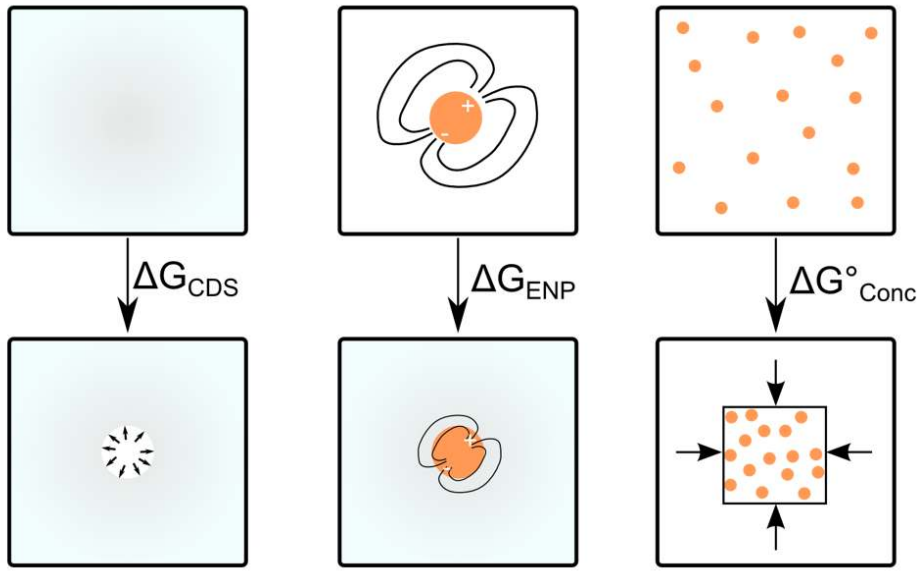


Figure 9. Three corrections applied to molecular free energy when going from the gas phase to solution phase. Solute particles are indicated in orange, and solvent is indicated by a blue background. **Left**: ΔG_{CDS} corresponds to the energy required to form the cavity which contains the solvated molecule. **Center**: ΔG_{ENP} accounts for attenuation of electric fields by the solvent. Solvent molecules in more polar solvents localize charge, leading to changes in energy. **Right**: $\Delta G^{\circ}_{\text{conc}}$ corrects for the energy requirements to compress them from a low-density gas to the higher densities found in a 1 M solution.

The electrostatic and cavity-dispersion contributions to solvation can be found in your output file under the Total SCF Energy header. The easiest way to find this is to search (Ctrl F) Total SCF Energy. Under this heading the ΔG_{ENP} can be found next to CPCM Dielectric: and the ΔG_{CDS} can be found next to SMD CDS (Gcds) as shown in Figure 10.

```
----------------
TOTAL SCF ENERGY
----------------

Total Energy       :        -693.41516076 Eh          -18868.78579 eV

Components:
Nuclear Repulsion  :         307.69055579 Eh           8372.68568 eV
Electronic Energy  :       -1001.10571656 Eh         -27241.47148 eV
One Electron Energy:       -1573.75063189 Eh         -42823.93182 eV
Two Electron Energy:         572.64491534 Eh          15582.46034 eV
CPCM Dielectric    :          -0.08322694 Eh             -2.26472 eV
SMD CDS (Gcds)     :          -0.00121145 Eh             -0.03297 eV

Virial components:
Potential Energy   :       -1383.47074976 Eh         -37646.15299 eV
Kinetic Energy     :         690.05558900 Eh          18777.36720 eV
Virial Ratio       :           2.00486855
```

Figure 10. Ascertaining solvation energy terms from orca. The ΔG_{ENP} is shown by the blue arrow and the ΔG_{CDS} is shown by the red arrow.

We can now use these calculated solvation energy values to determine the energy of our starting materials in a solvent of DMSO. To determine the energy of solvation we start by adding together the ΔG_{ENP} and ΔG_{CDS} that we determined from the output file with the correction for taking the species from the gas phase to a solution at 1M concentration. For the starting materials in DMSO this yields a Gibbs free energy of solvation of -0.08142612 Hartree.

$$\begin{aligned} \Delta G^{\circ}_{\text{solv}} &= \Delta G_{\text{ENP}} + \Delta G_{\text{CDS}} + \Delta G^{\circ}_{\text{conc}} \\ &\downarrow \\ \Delta G^{\circ}_{\text{solv}} &= -0.083227 \text{ Eh} + -0.001211 \text{ Eh} + 0.003012 \text{ Eh} \\ \Delta G^{\circ}_{\text{solv}} &= -0.08142612 \text{ Eh} \end{aligned} \tag{8.3.2}$$

We can then use this value to correct the gas phase Gibb free energy that was provided earlier in Figure 3B. As shown below adding the $\Delta G^{\circ}{}_{\text{solv}}$ to the gas phase Gibbs free energy yields the solvated Gibbs free energy of the starting materials in DMSO.

$$
\begin{aligned}
\mathrm{G_{SM_Solv}} &= \mathrm{G_{SM}} + \Delta \mathrm{G^{\circ}{}_{solv}} \\
&\downarrow \\
\mathrm{G_{SM_Solv}} &= -693.3164355\ \mathrm{Eh} + -0.08142612\ \mathrm{Eh} \\
\mathrm{G_{SM\ Solv}} &= -693.3978616\ \mathrm{Eh}
\end{aligned}
\tag{8.3.3}
$$

You should now repeat this process to determine the energies of solvation for the remaining species that we are studying: TS in DMSO, Products in DMSO, Starting Materials in Water, TS in Water, and Products in DMSO.

References

1. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
2. Neese, F. The ORCA Program System. *WIREs Comput. Mol. Sci.* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
4. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113* (18), 6378–6396. https://doi.org/10.1021/jp810292n.
5. *Implicit Solvation Models — ORCA tutorials 5.0 documentation*. https://www.orcasoftware.de/tutorial...prop/CPCM.html (accessed 2023-08-11).

This page titled 8.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

8.4: Exercise Questions

1. Using your knowledge of elimination chemistry, please indicate which solvent, water or DMSO, would you expect to better favor the E2 elimination from this exercise and why? For full credit be sure to explain your answer.
2. Using information from your calculations or your starting materials and products please complete the following tables. Please note that the solvated value of Gibbs Free Energy is the sum of G in the gas phase, ΔG_{ENP}, ΔG_{CDS}, and $\Delta G^{\circ}{}_{\text{Conc}}$.

Starting Materials

Solvent	G (Eh) Gas Phase	ΔG_{ENP} (Eh)	ΔG_{CDS} (Eh)	$\Delta G^{\circ}{}_{\text{Conc}}$ (Eh)	Solvated G (Eh)
DMSO	-693.3164	-0.083226	-0.001211	0.003012	-693.3978
Water	-693.3416			0.003012	

Transition States

Solvent	G (Eh) Gas Phase	ΔG_{ENP} (Eh)	ΔG_{CDS} (Eh)	$\Delta G^{\circ}{}_{\text{Conc}}$ (Eh)	Solvated G (Eh)
DMSO	-693.3157			0.003012	
Water	-693.3291			0.003012	

Products

Solvent	G (Eh) Gas Phase	ΔG_{ENP} (Eh)	ΔG_{CDS} (Eh)	$\Delta G^{\circ}{}_{\text{Conc}}$ (Eh)	Solvated G (Eh)
DMSO	-693.3805			0.00301	
Water	-693.3804			0.00301	

3. To make our reaction coordinate diagram easier to interpret we will be normalizing all of our energy values to the energy of the starting materials in water. To do this, all you need to do is add the value of the Solvated Gibbs free energy (G) you are interested into the Solvated Gibbs free energy (G) of the starting materials in water. Using the values that you have documented in question 2 please complete the following tables. Please note that he conversion between energy in Hartree (Eh) and kcal/mol is 1 Eh = 627.5 kcal/mol. **Hint**: you will have completed this calculation correctly if the Normalized Solvated G for the starting materials in water is 0 Eh.

Water Solvent

Water Solvent	Solvated G (Eh) (See Question 2)	Normalized Solvated G (Eh)	Normalized Solvated G (kcal/mol)
Starting Materials			
Transition State			
Products			

DMSO Solvent

DMSO Solvent	Solvated G (Eh) (See Question 2)	Normalized Solvated G (Eh)	Normalized Solvated G (kcal/mol)
Starting Materials	-693.39786		
Transition State			
Products			

4. Using the thermodynamic data (in kcal/mol) please create a reaction coordinate diagram that includes a pathway for both the reaction in DMSO and in Water.

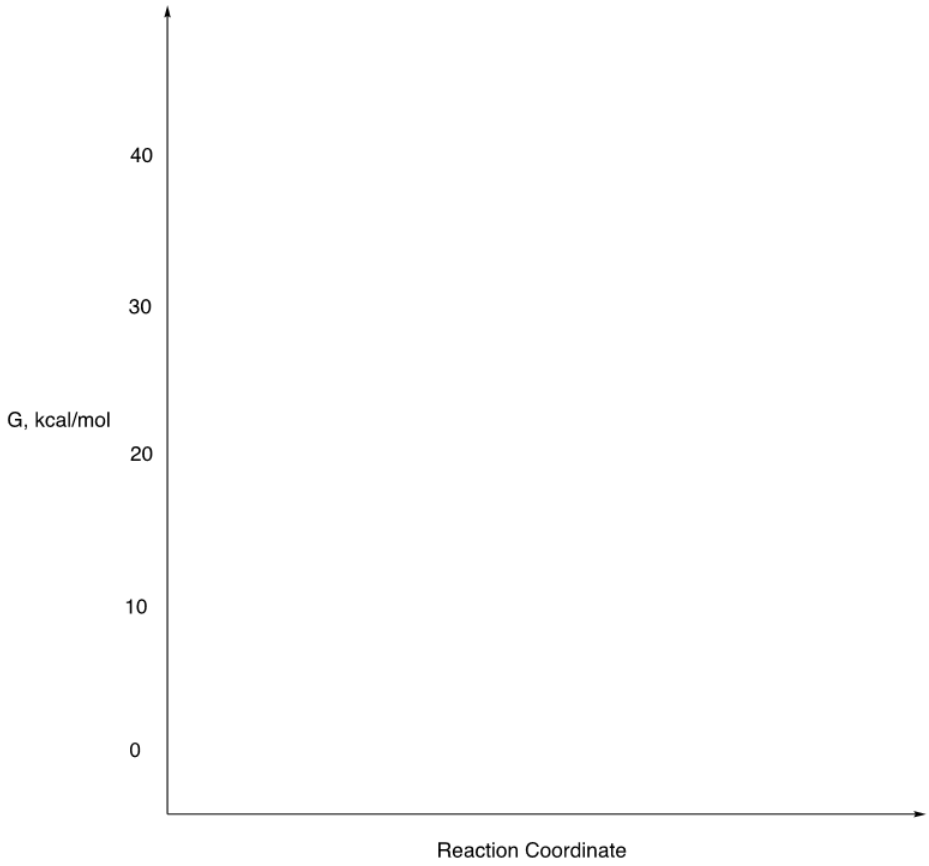


Figure 8.4.1: Copy and Paste Caption here. (Copyright; author via source)

5. Using your data and the reaction coordinate diagram in question 4 for support, please indicate which reaction you would expect to proceed more quickly and explain why you believe this is the case.

This page titled 8.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

9: Calculating Bond Dissociation Enthalpy and Analyzing the Radical Chlorination of Norbornane

9.1: Overview

9.2: Background

9.3: Computational Instructions

9.4: Exercise Questions

This page titled 9: Calculating Bond Dissociation Enthalpy and Analyzing the Radical Chlorination of Norbornane is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

9.1: Overview

Learning Objectives

- Students will build understanding of radical reactions.
- Students will build knowledge of what drives selectivity in radical halogenation reactions.
- Students will be able to use Orca to calculate the bond dissociation enthalpy of $C-H$ bonds and the stability of carbon-based radicals.
- Students will be able to use calculated BDE values, and radical stability calculations to interpret the experimental halogenation of norbornane.

Overview: This exercise seeks to help you understand how the concept of bond dissociation enthalpy (BDE) can serve help predict reactivity of $C-H$ bonds in a radical reaction. Halogenation of aliphatic $C-H$ bonds proceeds via a hydrogen atom abstraction from the hydrocarbon by a radical halogen atom. The identity/reactivity of the radical halogen species and the stability of the carbon-based radical formed upon hydrogen atom abstraction play a large role in what $C-H$ bond of a molecule is halogenated. In this exercise we will calculate the bond dissociation enthalpy of $C-H$ bonds of norbornane using Orca and Avogadro.[1–5] By comparing these values to the experimental results of a radical chlorination of norbornane, we can gain insight into the surprising selectivity of this reaction.

Faculty Notes: This exercise is designed to help students understand what bond dissociation enthalpies are and how they relate to the regioselectivity of radical $C-H$ halogenation. Before assigning this exercise, students should have learned the mechanism of radical $C-H$ halogenation and how to use the relative reactivity of halogen radicals to predict the distribution of halogenated products.

There are a total of 4 calculations that students will need to perform with Orca in this exercise. Each of these calculations can take 30-40 minutes if run on a single processor. To minimize the amount of time that this exercise takes, students should be advised that they can run more than one calculation at the same time. Moreover, if working in groups, students can distribute these calculations over several computers. Alternatively, the output files for all calculations are provided in the faculty resources for this exercise. These files can be given to students to analyze and answer the questions at the end of the exercise. Overall, this exercise should take students about 2 hours to complete.

This page titled 9.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

9.2: Background

Introduction

While often unreactive, aliphatic $C-H$ bonds can be functionalized via a radical halogenation reaction. Radical halogenation reactions are sensitive to the type of $C-H$ bond being halogenated and the identity of the halogen being used in the reaction. Weaker 3° $C-H$ bonds are typically more reactive than stronger 1° $C-H$ bonds. This reactivity is relatively predictable, leading to reactivity charts that allow you to estimate the relative ratio of products in a radical halogenation reaction. For example, as shown in Figure 1, a secondary $C-H$ bond is, on average, 3.9 x more likely to be chlorinated than a primary $C-H$ bond.

Decreasing C-H Bond Strength →

Increasing Reactivity ↑

Radical	1 C-H	2 C-H	3 C-H
F•	1	1.2	1.4
Cl•	1	3.9	5.2
Br•	1	82	1600

Figure 1. The relative reactivity of halogen radicals towards differing $C-H$ bonds. These values represent average reactivity and will change due to the specific electronic and steric nature of a molecule. Darker colors in this scheme represent greater selectivity for the indicated $C-H$ bond type by the indicated radical.

These values, however, are for average $C-H$ bonds and can be influenced by the local environment of the bonds undergoing halogenation. For example, a primary $C-H$ bond adjacent to the oxygen atom in an ether is often more reactive than would be predicted in Figure 2. Moreover, $C-H$ bonds on a carbon adjacent to a π bond are more reactive than predicted because the radical formed upon hydrogen atom abstraction is resonance stabilized. For this exercise, we will be examining the radical chlorination of norbornane, a bicyclic hydrocarbon molecule. When chlorinated, the hydrocarbon norbornane does not yield the expected distribution of products. As shown in Figure 3, radical chlorination of norbornane yields exo-2-chloronorbornane **(1)** and endo 2-chloronorbornane **(2)** as the majority products, while 1-chloronorbornane **(3)** is only found in a trace amount. No 7-chloronorbornane **(4)** was detected.[6] In this case, some secondary $C-H$ bonds would appear to be more reactive than a tertiary $C-H$ bond; this is the opposite selectivity that we would expect.

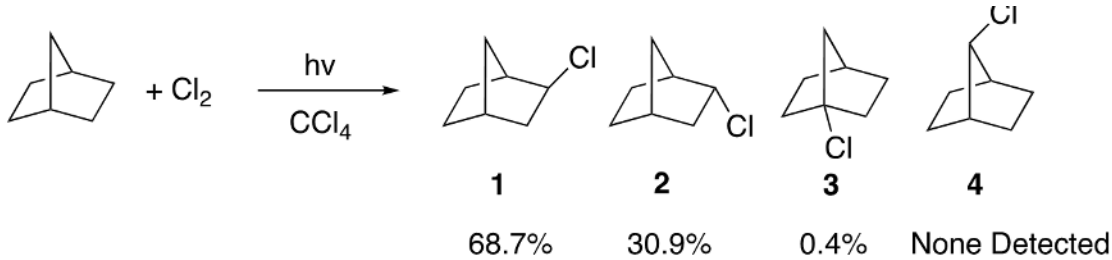


Figure 2. The radical chlorination of norbornane. The yields reported represent the relative percent of the monochlorinated product.

The goal of our exercise today is to use computation to gain understanding as to why the halogenation of norbornane yields results different than those that would be predicted by the relative reactivity table in Figure 1.

Background

A $C-H$ halogenation reaction occurs via a radical, or single electron, process. This reaction first involves a radical initiation where high-energy, unpaired-electron species known as radicals are produced from even electron precursors. As shown in Figure 4, the reaction begins when light promotes the homolytic cleavage of an $X-X$ bond, yielding halogen radicals ($X\cdot$). The halogen radical ($X\cdot$) will then abstract a hydrogen atom from the hydrocarbon substrate, yielding a carbon-based radical ($R\cdot$) and an equivalent of $H-X$. This hydrogen atom abstraction is typically the slow or rate-determining step of this reaction. The carbon-based radical will then abstract a halogen atom from an equivalent of molecular halogen ($X-X$), yielding halogenated product and another equivalent of halogen radical. The process whereby a halogen radical is both consumed and regenerated yielding product and $H-X$

is known as the propagation phase of the reaction. This is where most alkyl halide product is produced in a radical halogenation reaction. Finally, in the termination phase of the reaction, radical species dimerize to yield even electron compounds.

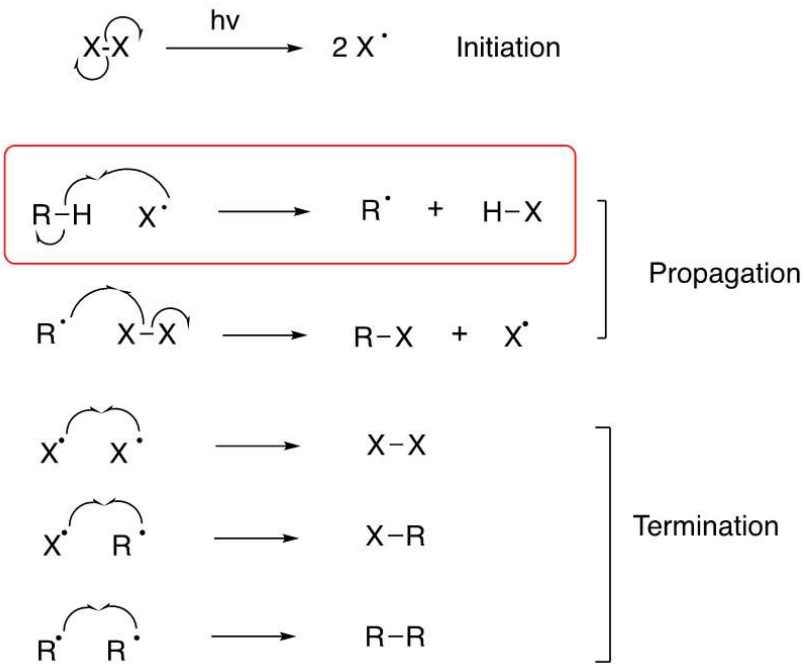


Figure 3. Mechanism of radical halogenation. The rate determining, or slow step, of this reaction is the hydrogen abstraction step. This is indicated in the figure above by a red box.

The substitution of a carbon-based radical, such as those formed in a radical halogenation reaction, dramatically influences its stability. Radicals can be stabilized via hyperconjugation if an adjacent bond is oriented parallel to the orbital where the radical resides. If the orientation is right, electrons from the filled bonding orbital can be shared with the half-filled p-orbital of the carbon-based radical. Primary radicals are less stable than secondary radicals or tertiary radicals because they have fewer $\mathrm{C-C}$ and $\mathrm{C-H}$ bonds available with the correct orientation to engage in **hyperconjugation** (Figure 4).

The greater the opportunity for hyperconjugation, the more stable the radical is because the other parts of the molecule help stabilize the unpaired electron.

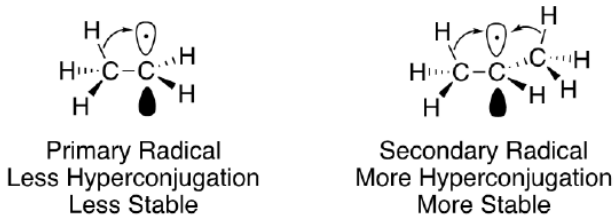


Figure 4. Increased opportunity for hyperconjugation leads to greater stability in a carbon-based radical.

The dominant product of a radical halogenation is determined by the reactivity of the halogen radical, and the carbon-centered radicals formed upon removal of a hydrogen atom (H·). The selectivity of the overall halogenation reaction is determined by the rate of the most difficult step, the so-called rate determining step. Because it is difficult to make a carbon-centered radical, removal of a hydrogen atom from a $\mathrm{C-H}$ bond is the rate determining step of this reaction. The stability of the formed radical influences the energy of the transition state and by extension $\Delta G^{\pm}$. According to Hammond's postulate, the transition state of a reaction resembles the structure of the reactant, or product to which it is closer in energy. Because chlorine radicals are more reactive than most carbon-centered radicals, the transition states of the reactions studied today are more reactant-like. Thus, the $\Delta G^{\pm}$ for this process varies based upon the stability of the carbon based radical. A similar reaction with less reactive bromine radicals (Br) more strongly depends upon the stability of the carbon-based radical because the abstraction step is endergonic (Figure 5).

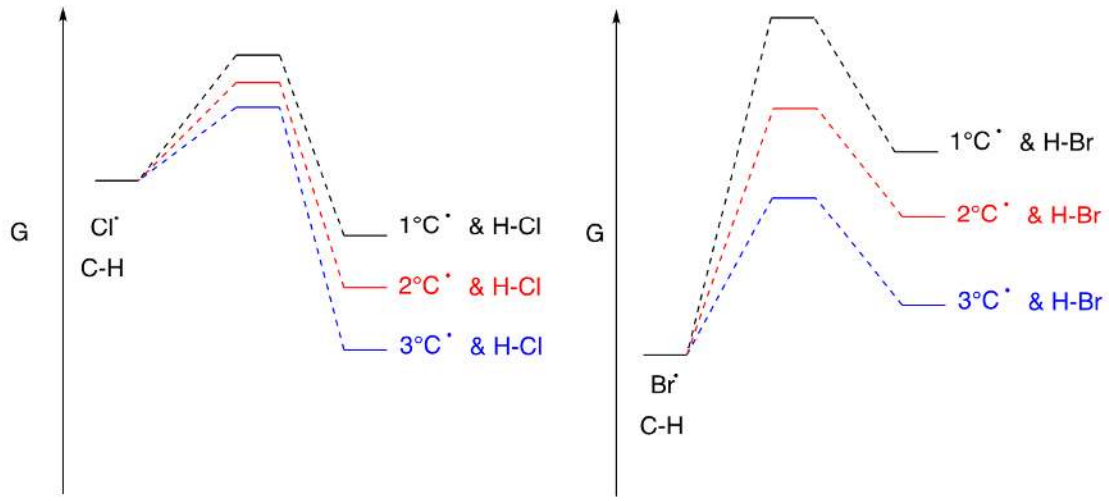


Figure 5. Reaction coordinate diagrams of the hydrogen atom abstraction step of radical halogenation. Please note that the ΔG± energy value decreases as the formed radical becomes more stable (lower in energy).

The concept of bond dissociation enthalpy, known as BDE, is a measure of the stability of radicals. As shown in Figure 6, the bond dissociation enthalpy is simply the difference in enthalpy between products and reactants of a reaction where a bond is broken homolytically (each atom keeps one electron from the bond). Because the enthalpy of forming a hydrogen radical will be the same for each reaction, differences in the value of BDE reflect the stability of the carbon-centered radical. The higher the BDE of a $C-H$ bond, the less stable a radical formed at that position will be.

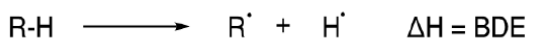


Figure 6. The definition of bond dissociation enthalpy (BDE) for a $C-H$ bond.

In this way, we can use DFT to estimate the bond dissociation enthalpy of $C-H$ bonds in an organic molecule to determine the relative reactivity of each bond toward a radical halogenation reaction. To understand the math involved, let's work through the simple example of methane. As shown in Figure 7, the methane $C-H$ BDE represents the enthalpy change in the homolytic cleavage of a $C-H$ bond yielding a methyl radical and a hydrogen atom (H·). The absolute enthalpy (H) of methane and the methyl radical were calculated in Orca (B3LYP, DEF2-SVP) and the enthalpy of the hydrogen atom was reported in the chemical literature.[7] The BDE of methane's $C-H$ bond can then be calculated by finding the difference between the enthalpies of the products (H· and methyl radical) and the reactant (methane). As shown below, we calculate a value of 101.8 kcal/mol. This value is consistent with experimental values of the methane $C-H$ bond strength of 104.9 kcal/mol, indicating that this method is yielding a reasonable answer for our purposes.[8]

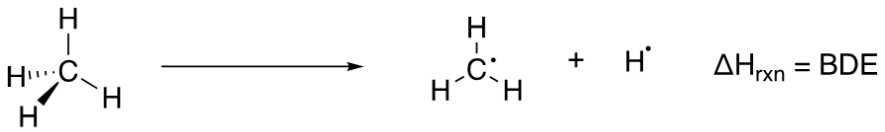


Figure 9.2.1: Copy and Paste Caption here. (Copyright; author via source)

Species	Enthalpy (EH)	Enthalpy (kcal/mol)
Hydrogen Atom	-0.49764	-312.119808
Methane	-40.40362394	-25341.15294
Methyl Radical	-39.74373799	-24927.27247

The calculation of the BDE of the $C-H$ bond of methane:

$$
\begin{aligned}
BDE &= \sum(H_{\text{Products}}) - \sum(H_{\text{Reactants}}) \\
&= (-312.119808 \text{ kcal/mol} + -24927.27247 \text{ kcal/mol}) - (-25341.15294 \text{ kcal/mol}) \\
&= 101.8 \text{ kcal/mol}
\end{aligned}
$$

This page titled 9.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

9.3: Computational Instructions

The goal of this computational exercise is to compute the C-H BDE values of each unique type of C-H bond in norbornane and use this information to shed insight on the “unexpected” selectivity of shown in its radical chlorination. To compute these BDE values, we will need the enthalpies of the parent norbornane, the norbornyl radicals produced in hydrogen atom abstraction, and the hydrogen radical (H·). With this information, we can compute the BDE values for each unique type of hydrogen atom on norbornane. You will be provided with the enthalpy values for the parent norbornane and the hydrogen atom (H). You will need to calculate the enthalpy values associated with radicals formed by the abstraction of each unique type of hydrogen on norbornane. As shown in Figure 8, there are 4 unique types of hydrogen on norborane and the removal of any one of these hydrogens will produce a unique radical. The radicals are numbered so that they represent the chlorinated product they would make with a “rad” subscript. For example, $\mathbf{3_{rad}}$ is the radical that would make product **3**.

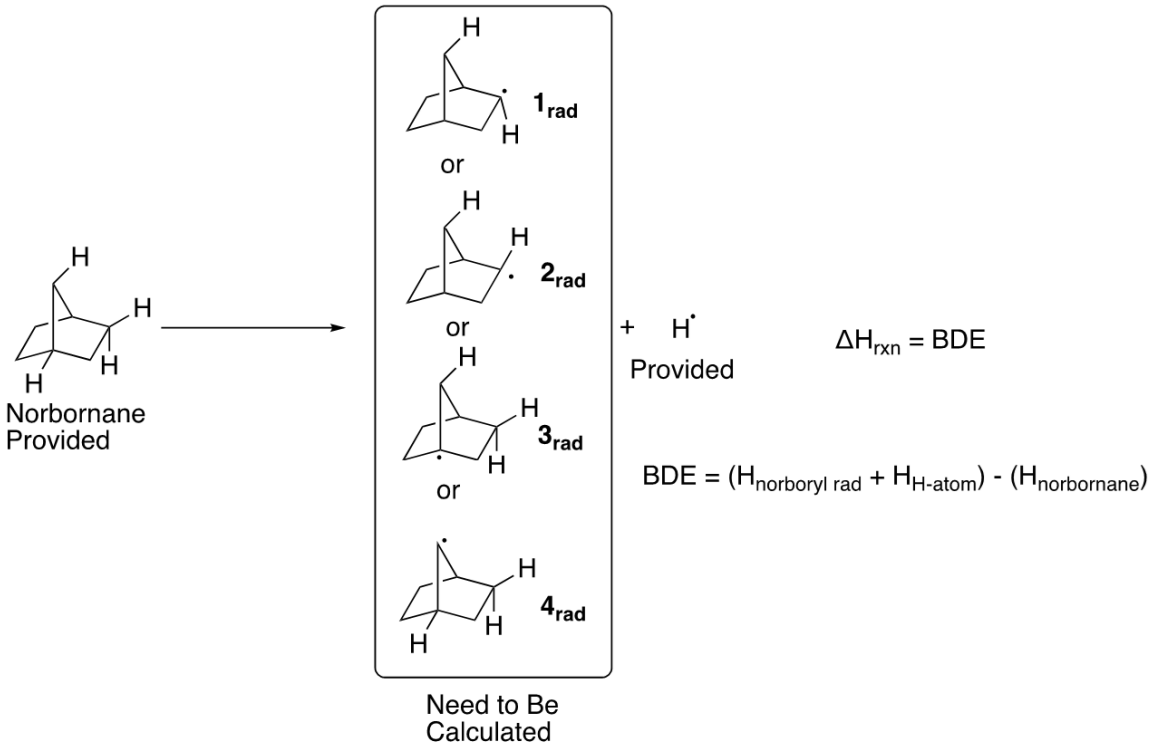


Figure 8. Species whose enthalpy values are provided and those that need to be calculated.

The process for calculating the enthalpy for the radical species is identical for each calculation. To illustrate this process, we will walk through the calculation of the enthalpy for $\mathbf{1_{rad}}$ as shown in Figure 8. The three other calculations can then be performed using the same process.

Start by creating a folder on your desktop and naming it BDE exercise. Within this folder create 4 subfolders named 1_{rad}, 2_{rad}, 3_{rad}, and 4_{rad}. Next you should download generic.inp and norbornane.xyz, which are the supporting files for this exercise. Save a copy of the generic input file within each of the subfolders that you have created. You can save the norbornane.xyz within the BDE exercise folder. The file structure described is illustrated in Figure 9.

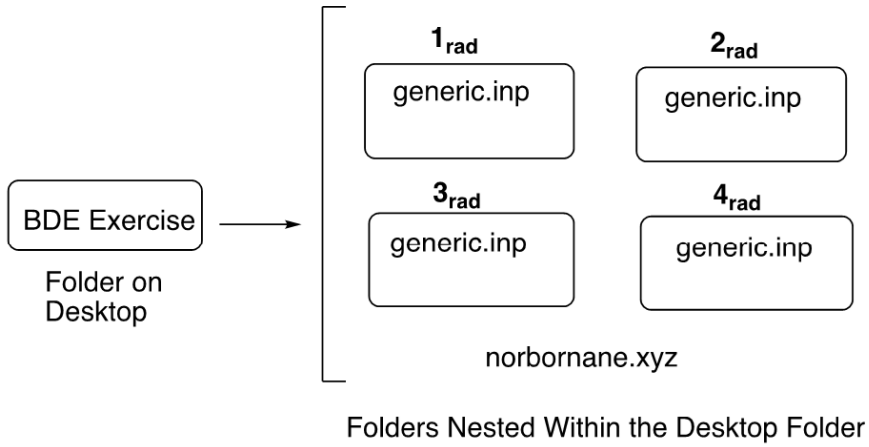


Figure 9. Representation of the file structure used in this exercise.

Next, you should open norbornane.xyz in Avogadro. Click on the selection button (looks like an arrow) and select the exo hydrogen on carbon 2, as shown in Figure 10. The hydrogen will turn blue. Delete this atom by pressing backspace to create the coordinates for 1_{rad}. Save the new structure as 1rad_coord.xyz within the 1rad subfolder.

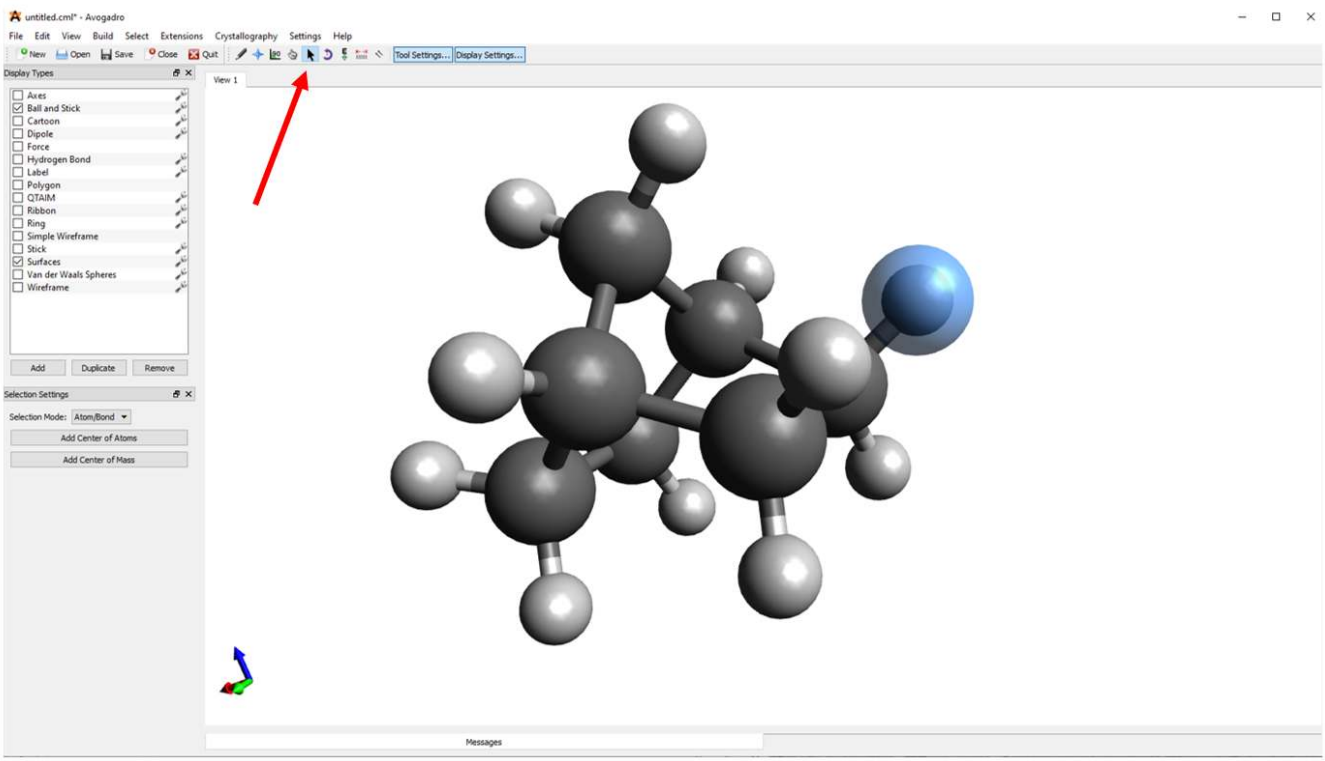


Figure 10. Norbornane shown in Avogadro with the 2-exo hydrogen selected. The selection button is indicated by a red arrow.

Next, you should open the generic input file within **1rad** folder. As shown in Figure 11, the text of the file is very similar to energy calculations that we have done in previous exercises. Briefly, the first line of the input file begun with a # is a comment where you can indicate the type of calculation being performed. The second line that starts with an ! symbol indicates the functional (B3LYP) and basis set (DEF2-SVP) for the calculation. Moreover, it tells the computer we want to perform a geometry optimization (OPT) and a frequency calculation (FREQ). The final line of text tells the computer that we want to use a .xyz file for coordinates and that the compound has a charge of 0 with a spin multiplicity of 2. The spin multiplicity of the system, S, is equal to the sum of the absolute value of spin quantum numbers, s (remember that each unpaired spin has a value of ½) times 2 plus 1. For example, a molecule without any unpaired spin would have an $S = 1$ (singlet) because the sum of the spin quantum numbers (+1/2 and -1/2) is

zero. An organic radical (7 electrons, which results in one unpaired electron or net ½ spin) would have an $S = 2$ (doublet), and a diradical such as dioxygen would have an $S = 3$ (triplet).

$$S = 2s + 1 \tag{9.3.1}$$

Finally, the generic script has the name of the .xyz coordinates file upon which the computer will run the calculation. To allow our calculation to run successfully you need to change generic_coord.xyz to the name of the coordinates file of the species you are investigating. In this case you should change generic_coord.xyz to 1rad_coord.xyz.

```
# comment (what we are trying to calculate)
!B3LYP def2-SVP FREQ OPT

* xyzfile 0 2 generic_coord.xyz
```

Figure 11. Generic input script for the calculation of the energy of a norbornyl radical. You should change generic_coord.xyz to the name of the coordinates file you are looking to use. In the case we are working on together it should be 1rad_coord.xyz.

We can now run our calculation using Orca via the command line. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter the computer will paste a new line indicating that the current directory has changed, as shown in Figure 12A. To find the file path of your input script, right click on the input script (1rad.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 12B).

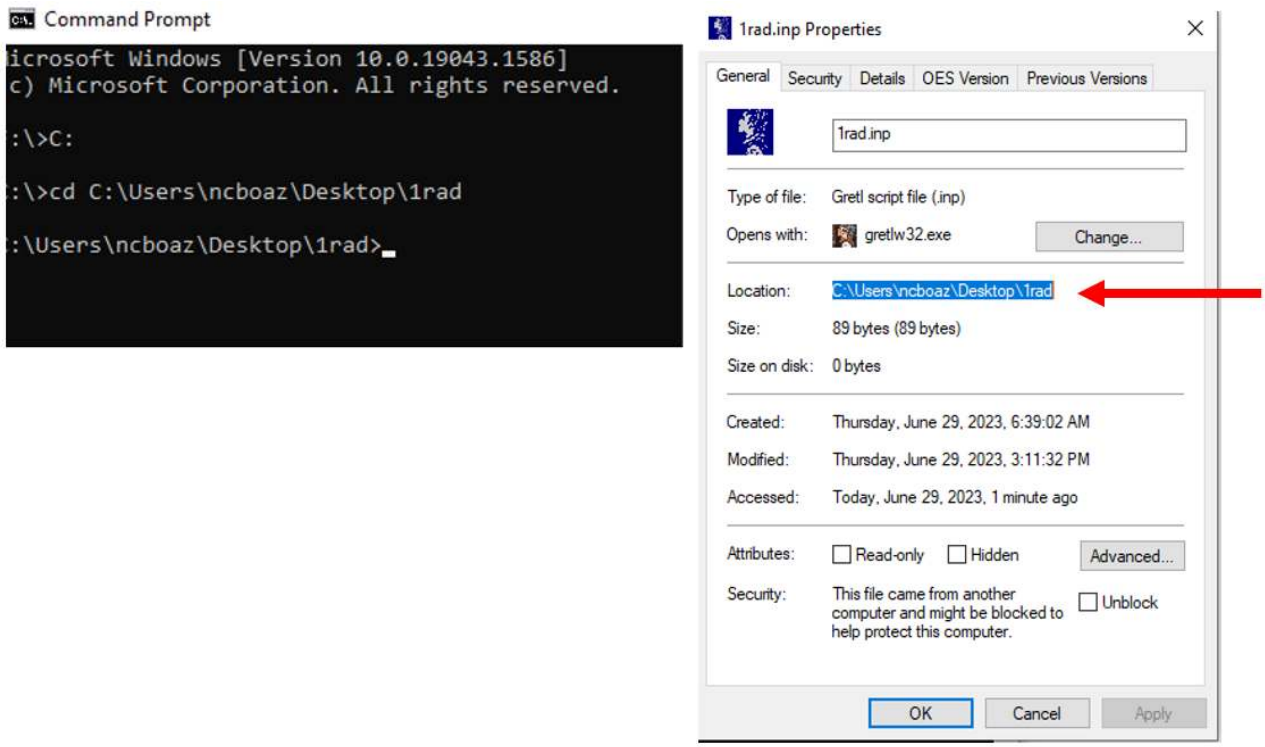


Figure 12. (Left) Changing of the file path in the command prompt to match the location of our input script. 12B. (Right) Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca 1rad.inp > 1rad.out and pressing enter. After pressing enter it may not appear that much is happing, but your computer is working on the calculation and the folder 1rad will quickly become populated with the output of your calculation. Depending upon the speed of your computer, the calculation will take about 30-45 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 13). Given the time it takes to complete this calculation it is a good idea to run more than one calculation at the same time by opening a new command

prompt window. Alternatively, if you are working in a group, assign different computations to different group members and compare your results at the end.

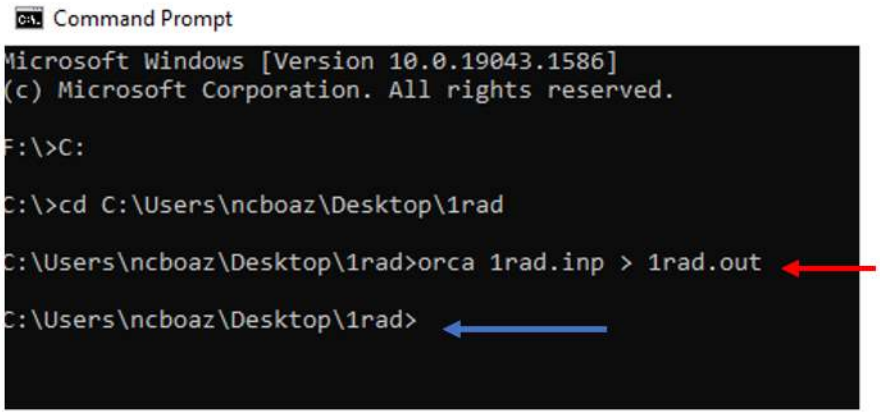


Figure 13. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in 1rad.inp and that the results of this calculation should be placed in the output file 1rad.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

You can now find the enthalpy value for the norbornyl radical **1rad** by opening 1rad.out in notepad. Scroll to the end to find the Thermochemistry section of the results and under the ENTHALPY header you can find the enthalpy value of **1rad** in Hartree, as shown in Figure 14.

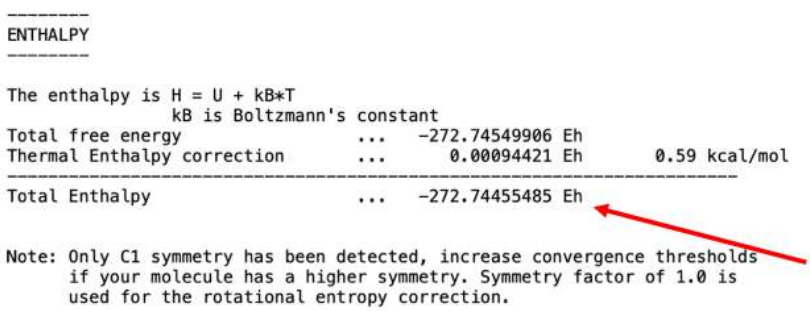


Figure 9.3.1: Copy and Paste Caption here. (Copyright; author via source)

Finally, you can view the optimized geometry of your calculated radical species by opening the output file (.out file extension) with Avogadro as shown in Figure 15. Note the geometry on the carbon containing the radical.

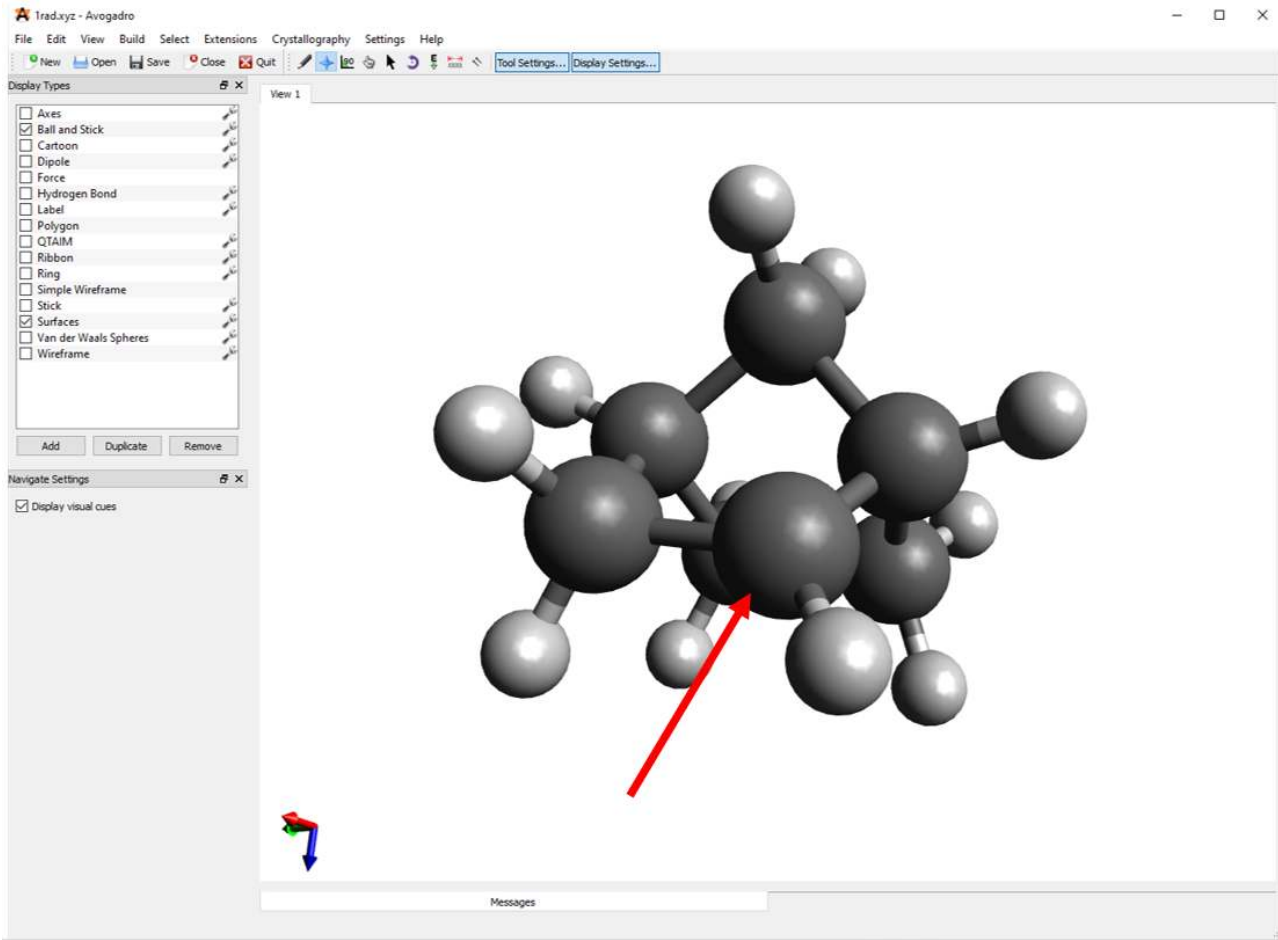


Figure 15. Output structure of the norbornyl radical with the unpaired electron centered on carbon 2. The radical is centered on the carbon indicated by a red arrow.

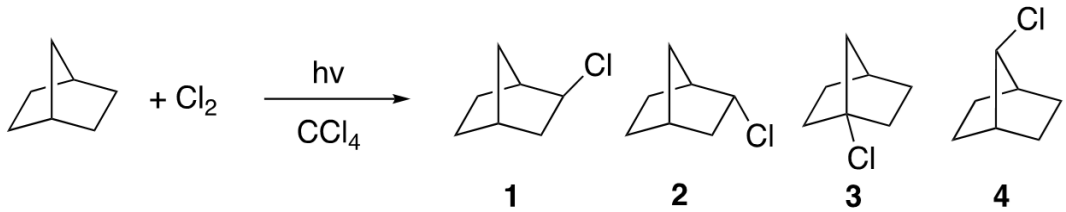
References

1. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
2. Neese, F. The ORCA Program System. *WIREs Comput. Mol. Sci.* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
4. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminformatics* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
5. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.
6. Smith, C. V.; Billups, W. E. Chlorination of Norbornane, Bicyclo[2.2.2]Octane, and Adamantane Using Nitrogen Cation Radicals. Bridgehead Chlorination. *J. Am. Chem. Soc.* **1974**, *96* (13), 4307–4311. https://doi.org/10.1021/ja00820a042.
7. Wright, J. S.; Johnson, E. R.; DiLabio, G. A. Predicting the Activity of Phenolic Antioxidants: Theoretical Method, Analysis of Substituent Effects, and Application to Major Families of Antioxidants. *J. Am. Chem. Soc.* **2001**, *123* (6), 1173–1183. https://doi.org/10.1021/ja002455u.
8. Ruscic, B. Active Thermochemical Tables: Sequential Bond Dissociation Enthalpies of Methane, Ethane, and Methanol and the Related Thermochemistry. *J. Phys. Chem. A* **2015**, *119* (28), 7810–7837. https://doi.org/10.1021/acs.jpca.5b01346.

This page titled 9.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

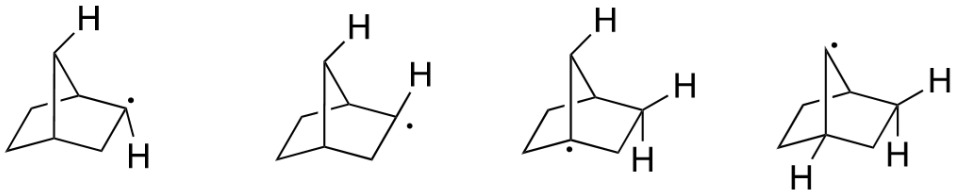
9.4: Exercise Questions

1. Using the relative reactivity table shown in figure 2, please calculate the expected ratio of products for the radical halogenation of norbornane. Does your estimated product ratio's match those found experimentally (see Figure 3)? For full credit please show your work. (Hint: Remember that each unique $\mathrm{C-H}$ bond is present in different numbers)



2. Use the computational data that you have generated to complete the table below for each of the norbornyl radicals that can be formed under reaction conditions. There are 627.5 kcal/mol for every 1 Hartree (Eh). Please rank the formed radicals in order of increasing stability (Low Ranking (e.g., 1) =least stable, High Ranking= most stable). Hint: 1_{rad} and 2_{rad} have extremely similar enthalpy values you should give them the same number.

Radical	Enthalpy, H (EH)	Enthalpy, H (kcal/mol)
1_{rad}		
2_{rad}		
3rad		
4_{rad}		

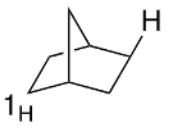
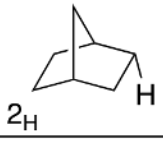
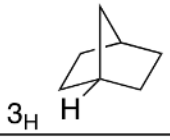
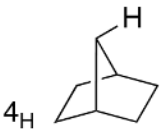


_____ _____ _____ _____

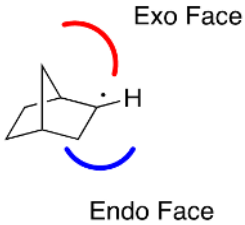
3. Using the equation provided below and the data that you calculated, please determine the bond dissociation enthalpy for each distinct type of $\mathrm{C-H}$ bond in norbornane. Please show you work.

$$BDE = \Sigma\left(H_{\text{Products}}\right) - \Sigma\left(H_{\text{Reactants}}\right)$$

Species	Enthalpy, H (EH)	Enthalpy, H (kcal/mol)
Hydrogen Atom	-0.49764	-312.119808
Norbornane	-273.3914137	-171553.11

C-H Bond				
BDE (kcal/mol)				

4. Because 1rad and 2rad have the same enthalpy values, the $C-H$ bonds broken to form these radicals will have the same BDE. Examine the structure of both optimized radicals and propose why they should have the same stability.
5. Examine the structure of 3rad. Why do you think that it is so much less stable than we would have expected?
6. Do the $C-H$ BDE values and radical structures explain the experimental selectivity of the chlorination of norbornane?
7. Examine the structure of 1rad or 2rad in Avogadro in space filling mode. To do this click the Van der Waals Spheres option in the left “display types” window. Pay special attention to the accessibility of the exo and endo face of the radical. Using this structure, propose a reason why the exo chlorinated product is produced in higher yield than the endo product.



8. Norbornane can also be halogenated using bromine. Using your data indicating $C-H$ BDE values, predict the product distribution yielded by reaction of norbornance with a less reactive bromine radical. How would this product distribution compare to the chlorination product distribution?

This page titled 9.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

10: Examining the Synthesis of Naturally Occurring Cyclobutane Compounds

10.1: Overview
10.2: Background
10.3: Computational Instructions
10.4: Exercise Questions

This page titled 10: Examining the Synthesis of Naturally Occurring Cyclobutane Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

10.1: Overview

Learning Objectives

- Students will be able to use Orca[1–4] and Avodagro[5,6] to calculate and visualize the molecular orbitals of cinnamic acid.
- Students will be able to relate the HOMO-LUMO gap of a compound to the wavelength of light necessary to cause the promotion of an electron,

Overview: This exercise seeks to help you understand how the frontier molecular orbitals interact to allow for a light-mediated [2+2] cycloaddition. Specifically, you will calculate and examine the molecular orbitals of cinnamic acid to determine which orbitals will overlap to form the [2+2] cyclized product, truxillic acid. From these data you will calculate the wavelength of light required to mediate the [2+2] cycloaddition between two molecules of cinnamic acid to yield truxillic acid.

Faculty Notes: This exercise is designed to help students better understand the molecular orbital overlap required for a successful 2+2 cycloaddition. Before assigning this exercise, students should have learned the basic concepts of Frontier Molecular Orbital Theory, and the mechanism of [2+2] and [4+2] cycloaddition reactions. Using a standard desktop computer, the computation in this exercise takes 45 minutes. Overall, this exercise should take students about an hour and 15 minutes.

This page titled 10.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

10.2: Background

In the lecture portion of your organic chemistry course, you likely learned that in a cycloaddition reaction two π bonds are converted into two σ bonds. As shown in Figure 1, the most well-known of the cycloaddition reactions is the [4+2] or Diels-Alder cycloaddition. In this reaction, a 4π electron diene reacts with a 2π electron dieneophile in a concerted reaction forming a cyclohexene molecule. As shown in Figure 1, this reaction is successful because the frontier molecular orbitals of the diene (HOMO) and the dienophile (LUMO) overlap with the correct symmetry and similar energies.

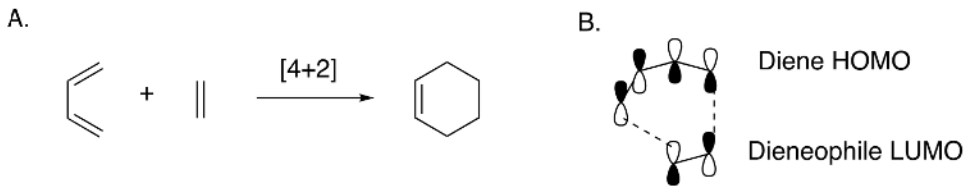


Figure 1A. Diels-Alder Cyclization. **B.** The overlap of Frontier Molecular Orbitals allowing for the formation of the cyclohexene ring.

While similar [2+2] cycloaddition reactions are possible, they are thermally forbidden and require light to proceed. This difference is related to the symmetry of the frontier molecular orbitals. Unlike in a Diels-Alder reaction where the frontier molecular orbitals of the diene and the dieneophile overlap in phase to form the ring, the HOMO and LUMO of the 2+2 cycloaddition don't have the correct symmetry to overlap in phase (Figure 2). For this reaction to occur, photoexcitation of electrons from the HOMO to the LUMO must occur.

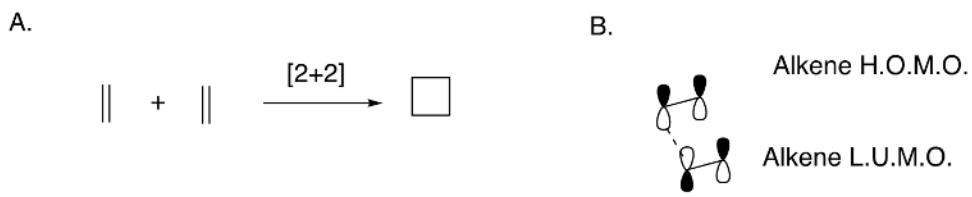


Figure 2A. The formation of a cyclobutene ring via a [2+2] cycloaddition. **B.** The HOMO of one alkene does not have the same symmetry of the LUMO of another alkene. The result is no net bonding without photoexcitation of one alkene.

The cyclobutanes created in a [2+2] cycloaddition are found natural products. One example of this is in the dimerization of cinnamic acid to yield different stereoisomers of truxillic acid, as shown in Figure 3. Truxillic acid is found in the leaves of the coca plant, and a derivative of truxillic acid, known as incarvillateine, has shown promise as a powerful analgesic.[7,8]

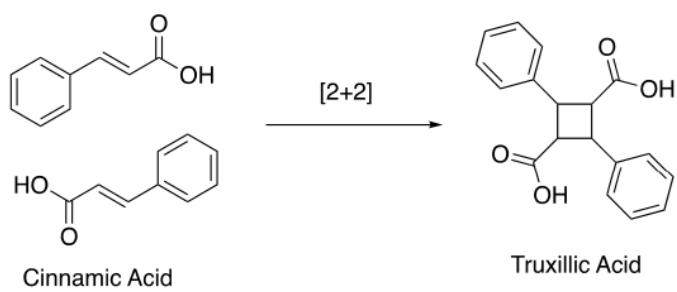


Figure 3. [2+2] cycloaddition of cinnamic acid yielding truxillic acid.

In the computational exercise that follows, you will calculate the molecular orbitals of cinnamic acid to determine which orbitals will overlap to yield the desired cyclobutane-containing truxillic acid. Moreover, you will use the energy values of the molecular orbitals generated to estimate the wavelength of light needed to cause the photoexcitation.

This page titled 10.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

10.3: Computational Instructions

Start by creating a new file on your desktop and naming it cinnamic_acid. You should download the supporting files for this experiment and save them to the file that you just created. Start by opening cinnamic_coord.xyz in Avogadro and examining its structure, as shown in Figure 4.

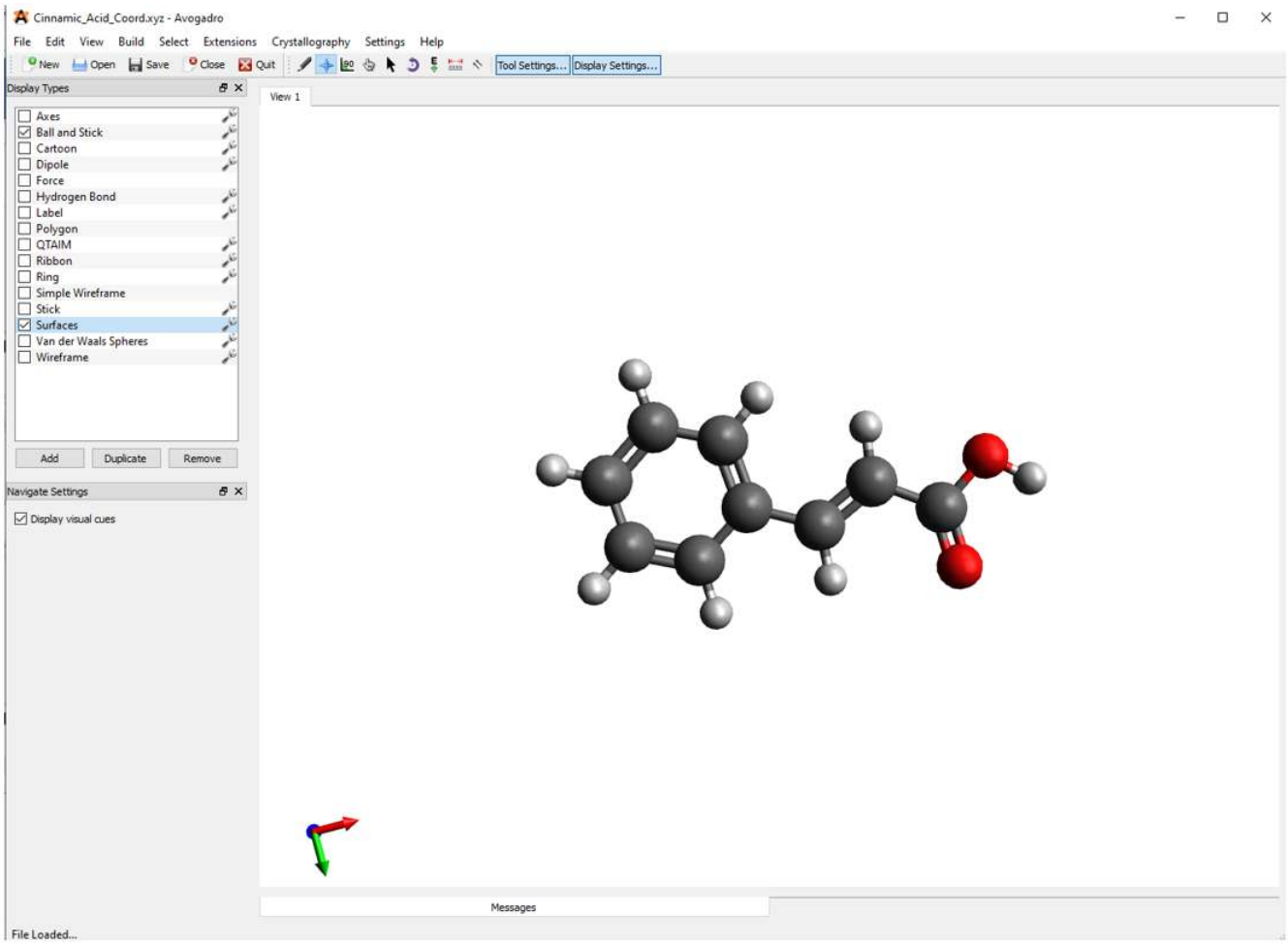


Figure 4. Cinnamic acid geometry shown in Avogadro.

Next, you should open the input script, which you can find in the supporting files for this exercise, in notepad. This script contains the instructions for the computer to calculate the molecular orbitals of cinnamic acid. The text of the input file is very similar to that of previous exercises. It starts off with a # symbol, indicating a comment which describes calculation. The next line, which begins with a ! symbol, indicates the calculations and level of theory at which we want to perform the calculations. One difference from previous calculations is the inclusion of the LARGEPRINT keyword. This command directs the computer to include more information in the output file about the calculation than it usually would. Contained within this extra information are the molecular orbitals calculated during the computation. The last line begins with a * and indicates the coordinates file that the calculation will use.

```
# Cinnamic_Acid Molecular Orbitals
!B3LYP def2-SVP OPT FREQ LARGEPRINT

* xyzfile 0 1 cinnamic_coord.xyz
```

Figure 5. Input script for the generation of molecular orbitals of cinnamic acid. Please note the name of the geometry input files, indicated by a red arrow, that you will need to change to ensure that it matches the name of your geometry file that you created.

We can now run our calculation using Orca via the command line as we did in previous exercises. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: in the command prompt and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path into the command prompt. When you hit enter, the computer will paste a new line indicating that the current directory has changed, as shown in Figure 6A. To find the file path of your input script, right click on the input script (cinnamic.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 6 B).

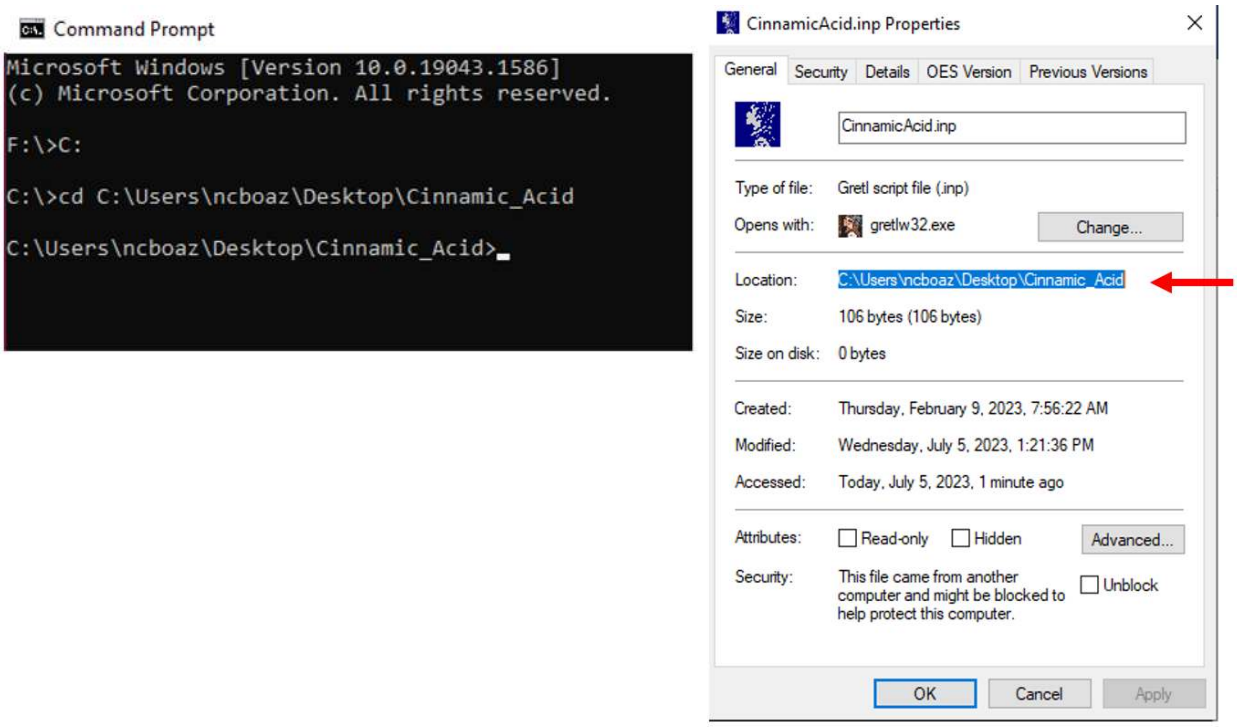


Figure 6A. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **6B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca cinnamic.inp > cinnamic.out and pressing enter in the command prompt. At first, it may not appear like anything is happening but the folder on your desktop housing the input file will quickly become populated with the output of your calculation. The calculations should take 30-45 minutes depending upon the speed of your computer and how many other processes your machine is running at the time.

After you have submitted your calculation, it is a good time for a cup of coffee or a nice walk! When the calculation is complete, your command prompt window will display a new line indicating it is ready for the next command.

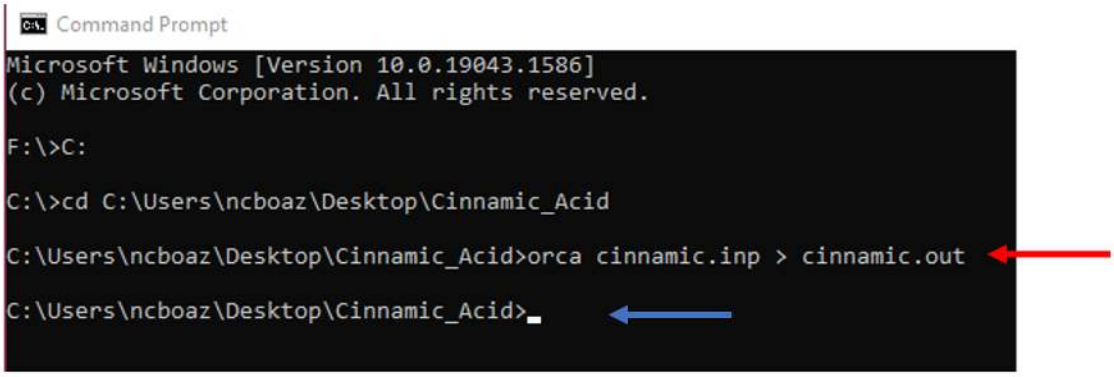


Figure 7. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in cinnamic.inp and that the results of this calculation should be placed in the output file cinnamic.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

As shown in Figure 8, the folder where you put your initial coordinates file, is now populated with your experimental output.

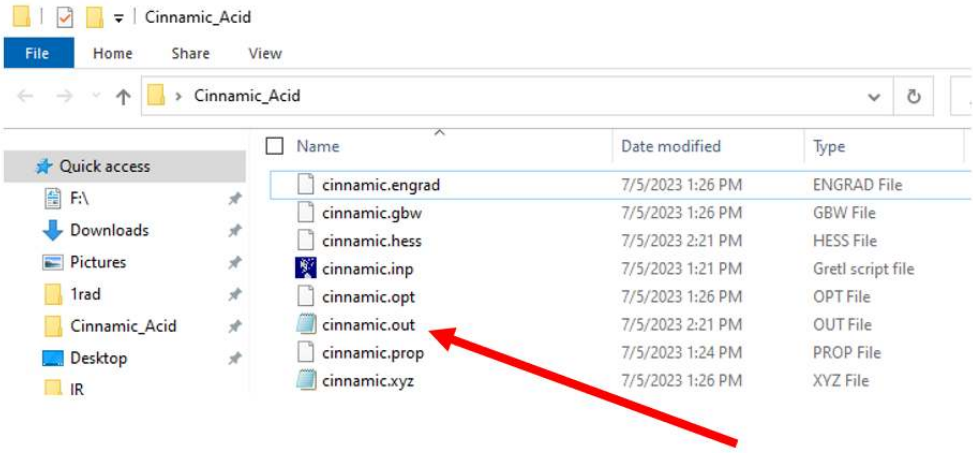


Figure 8. The output of the molecular orbital calculation for cinnamic acid contained within the cinnamic acid file that you created.

To view the molecular orbitals of cinnamic acid you will first need to open the output file (has the .out file extension) with Avogadro to view the molecular orbitals of the species. As shown in Figure 9, the output file will show the molecular orbitals in the upper right portion of the screen.

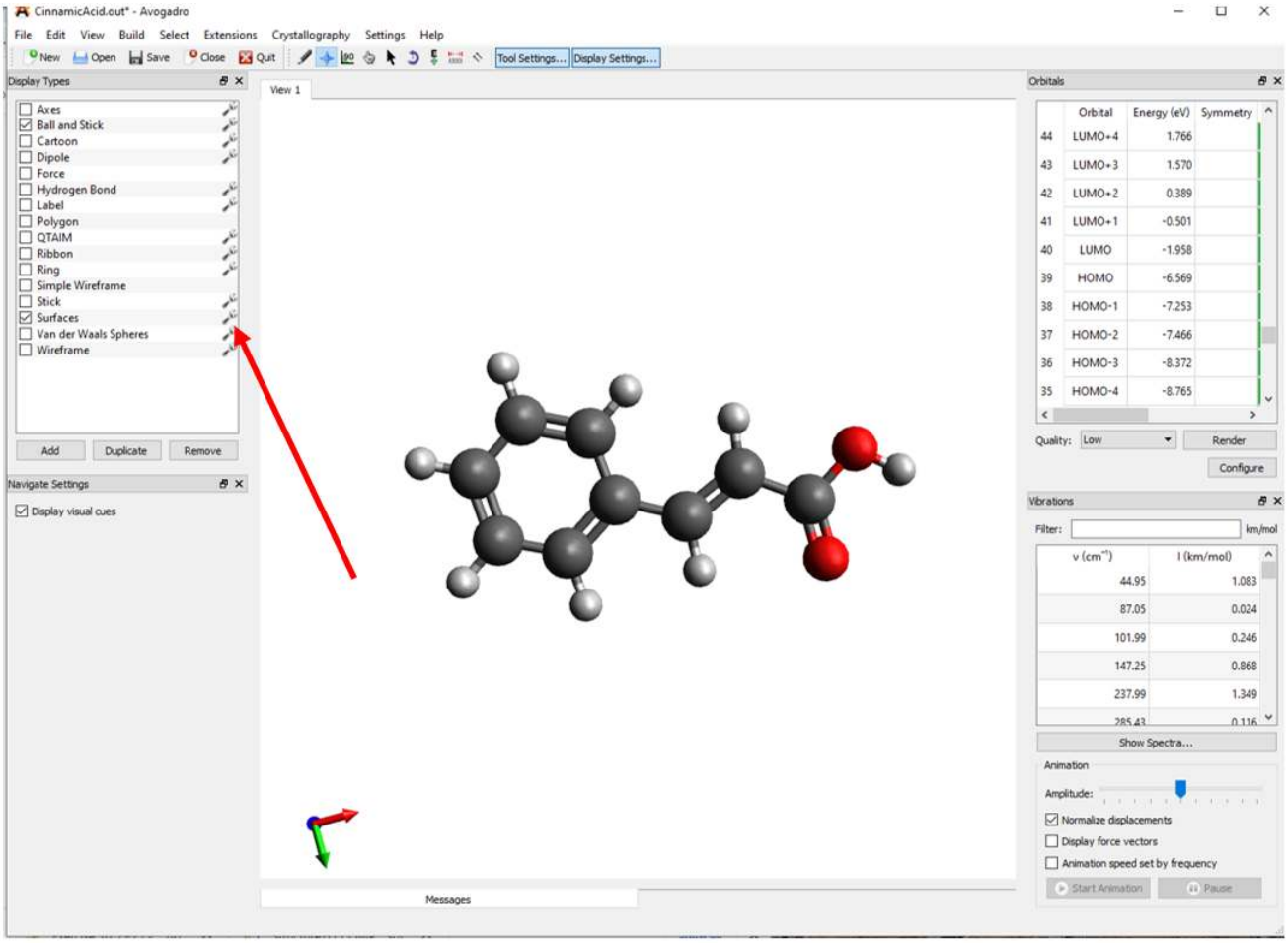


Figure 9. The output file of cinnamic acid loaded in Avogadro. The surface button is indicated by a red arrow.

Before you view any of the molecular orbitals you will need to click on the wrench button adjacent to the surfaces. From the surface settings window that appears you can change the positive and negative surfaces to blue and red respectively (**Figure 10**). Also, to make the orbitals easier to see you should change the background color by clicking View→Set Background Color→White.

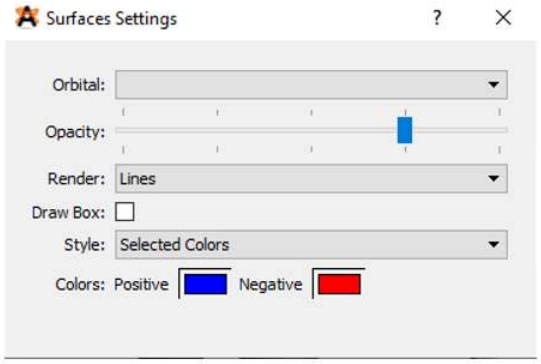


Figure 10. Setting the surface colors (colors of the lobes of the molecular orbitals) to blue and red respectively.

You should now be able to click on the each of the molecular orbitals to examine them individually. Please note that the energy levels of each molecular orbital can be found in the panel in the top right of the Avogadro screen. You should now be able answer the questions at the end of the exercise.

References

1. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Comput. Mol. Sci.* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.

2. Neese, F. The ORCA Program System. *WIREs Comput. Mol. Sci.* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
3. Neese, F. Software Update: The ORCA Program System—Version 5.0. *WIREs Comput. Mol. Sci.* **2022**, *12* (5). https://doi.org/10.1002/wcms.1606.
4. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
5. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J. Cheminformatics* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
6. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.
7. Liebermann, C. Ueber Cinnamylcocaïn. *Berichte Dtsch. Chem. Ges.* **1888**, *21* (2), 3372–3376. https://doi.org/10.1002/cber.188802102223.
8. Nakamura, M.; Chi, Y.-M.; Yan, W.-M.; Nakasugi, Y.; Yoshizawa, T.; Irino, N.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. Strong Antinociceptive Effect of Incarvillateine, a Novel Monoterpene Alkaloid from *Incarvillea s Inensis*. *J. Nat. Prod.* **1999**, *62* (9), 1293–1294. https://doi.org/10.1021/np990041c.

This page titled 10.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

10.4: Exercise Questions

1. Please draw a representation of the HOMO and LUMO of cinnamic acid.
2. Can the HOMO of one molecule of cinnamic acid interact with the LUMO of another molecule of cinnamic acid? If not, why?
3. If excited by light, what orbital would the electron be promoted into? Please describe which orbital this would be the in the ground state. (Please note that this orbital would now be referred to as the photo HOMO.
4. Please show the overlap of the LUMO of the ground state of cinnamic acid with the photo HOMO you drew in the previous question. Do these orbitals have appropriate symmetry and similar energy to be able to react?
5. This question will walk you through the process (step-by-step) of calculating the wavelength of light needed to mediate the promotion of an electron from the HOMO to the LUMO.

   A. Please fill out the following table with energy values for the L.U.M.O. and H.O.M.O. of cinnamic acid. The HOMO – LUMO gap is the absolute value of the difference in energy between the HOMO and LUMO.

	Energy, eV
HOMO	
LUMO	
HOMO-LUMO Gap	

   B. Next you should take the HOMO-LUMO gap in electron volts (eV) and convert the energy gap to joules (j) using the conversion of 1 eV = 1.6 x 10-19 j. For full credit you should show your work.

   C. Light has what we call wave particle duality. This means that light has properties that are wavelike and properties that are particle light. The energy of a particle of light, known as a photon, is related to the frequency of the light wave by the equation shown below. For full credit you must show your work.

$$\begin{gathered} \mathrm{E} = \mathrm{hv} \\ \text{where E is the energy of a photon in joules} \\ \text{h is Plank's constant} = 6.6 \times 10^{-34} \mathrm{J} \cdot \mathrm{s} \\ \text{v is the frequency of light in } \mathrm{s}^{-1} \text{(also known as Hz)} \end{gathered}$$

   D. Next you should convert the frequency of light from Hz to nm by using the equation that relates wavelength of light to frequency of light. For full credit you should show all of your work.

This page titled 10.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

11: Examining the Energetics of Selectivity in Electrophilic Aromatic Substitution

11.1: Overview

11.2: Background

11.3: Computation Assignment and Exercise Questions

This page titled 11: Examining the Energetics of Selectivity in Electrophilic Aromatic Substitution is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

11.1: Overview

Learning Objectives

- Students will be able to draw a direct comparison between the selectivity of a reaction and the free energy of activation ($\Delta G^{\ddagger}$) of the rate determining step of the reaction.
- Students will be able to indicate which directing groups have the greatest impact upon selectivity and how this selectivity correlates to reaction rate.

Overview: This exercise seeks to help you understand the root of selectivity in electrophilic aromatic substitution. Specifically, you will analyze data for the rate determining breaking of aromaticity in the electrophilic aromatic nitration of toluene and 1-methoxy-2-methyl-3-nitrobenzene. From these analyses you will compare the stability of the resonance stabilized σ (sigma) complexes and how they relate to the transition states separating them from the starting arene.

Faculty Notes: This exercise is designed to help students better understand the underlying cause of ortho/para or meta selectivity in an electrophilic aromatic substitution reaction. Before assigning the exercise, students should have covered the concept of electron-donating and electron-withdrawing arene substituents and their effect of rate of reaction and selectivity. This exercise should take students about an hour to complete.

This page titled 11.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

11.2: Background

In lecture we learned that substituent groups to benzene rings can influence the regiochemistry of an electrophilic aromatic substitution (EAS) reaction. These groups behave differently depending on whether they are withdrawing or donating electron density into the aromatic system. During an aromatic substitution reaction an initial nucleophilic attack by an arene results in a resonance-stabilized carbocation intermediate known as a σ (sigma) complex. If the substituent on an arene has the ability to donate electron density into the arene ring, it is able to stabilize the carbocation of a σ complex, but only if the incoming electrophile adds ortho or para to the existing substituent.

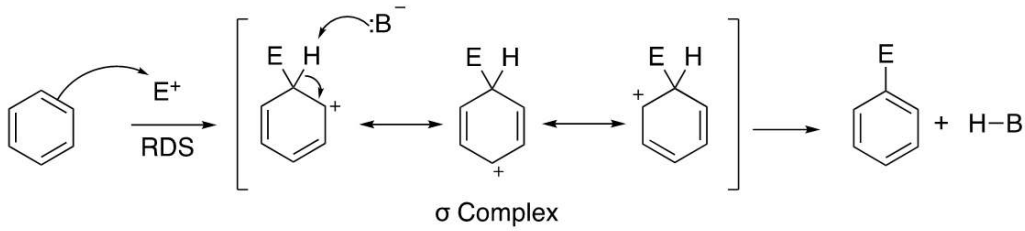


Figure 1. Electrophilic aromatic substation mechanism illustrating rate determining generation of the σ complex

The ability of a methoxy group to direct EAS regioselectivity is shown in Figure 2. When an incoming bromine electrophile is added ortho or para to a methoxy group, a σ complex is created where the lone pairs on oxygen can help to stabilize the carbocation via resonance. In fact, there is a resonance structure created where all atoms obey the octet rule. However, if an incoming bromine electrophile adds to the meta position, the carbocation of the σ complex is unable to be stabilized via resonance. When a base in solution removes a proton and restore aromaticity, the dominant products of this reaction are ortho and para substituted.

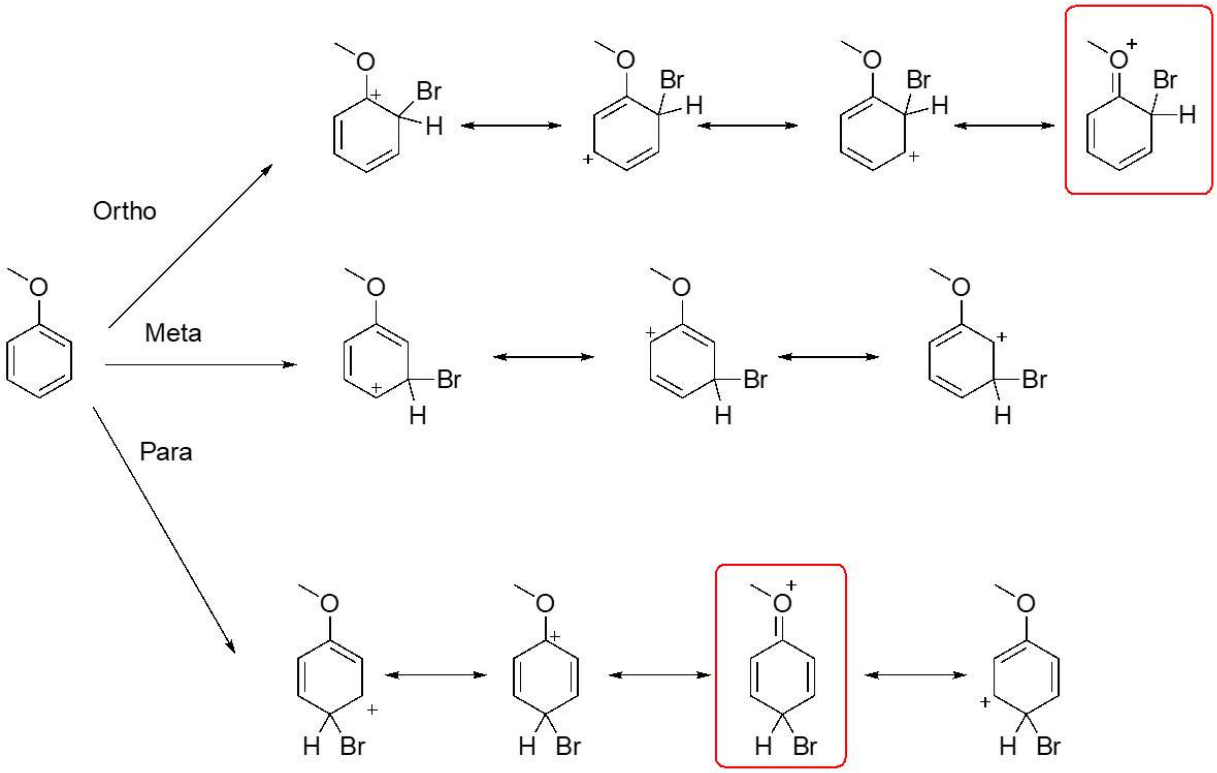


Figure 2. Addition of a bromine electrophile to anisole (methoxy benzene). Please note how resonance stabilization of the carbocation by the methoxy group only occurs with ortho or para substitution. Resonance structures utilizing this additional stabilization, and thus generating a resonance structure where all atoms are obeying the octet rule are indicated by red boxes.

A similar analysis of the addition of a bromine electrophile to an arene with an electron withdrawing substituent yields different results. As shown in Figure 3, when an incoming bromine electrophile is added ortho or para to the ammonium (positive nitrogen)

substituent, a σ complex with a resonance structure is created with two adjacent positive charges. This highly energetic arrangement makes addition para and ortho to an electron withdrawing group difficult. On the other hand, if an incoming bromine electrophile adds meta to the ammonium group the σ complex created does not allow for the carbocation to be formed adjacent to the electron withdrawing group. This difference in stability makes is easier for an incoming electrophile to add meta rather than ortho/para to a withdrawing substituent.

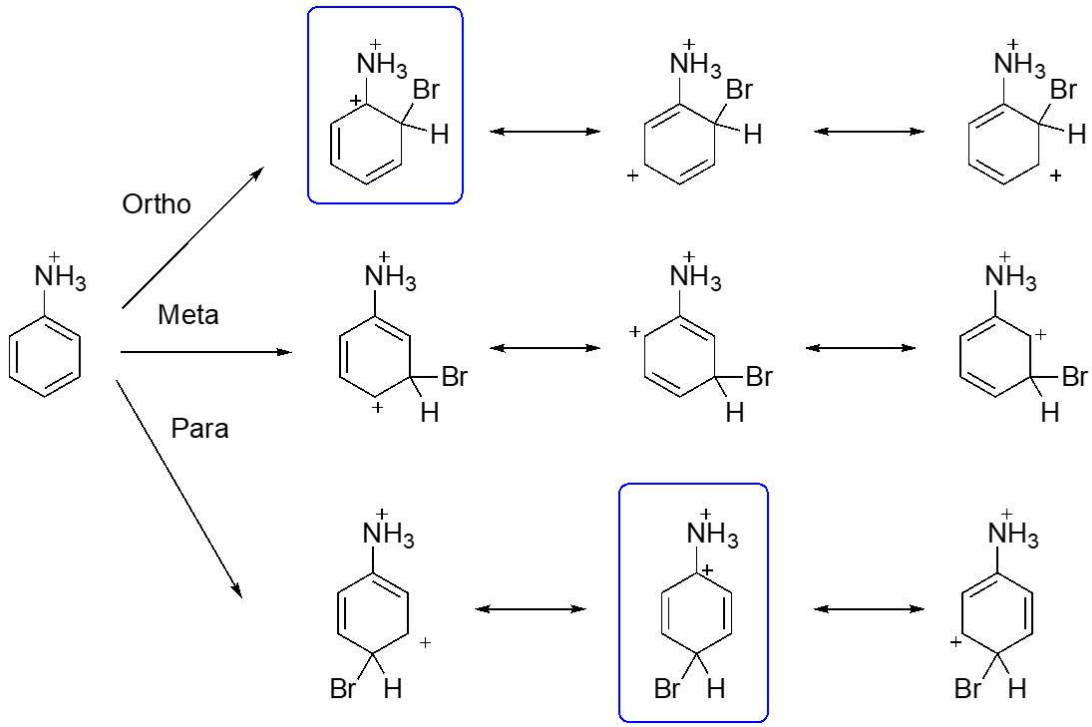


Figure 3. Addition of a bromine electrophile to the anilinium ion. Please note that addition of the electrophile to the ortho or para position creates a high energy σ complex with two adjacent positive charges (indicated by a blue box). When the electrophile adds to the meta position, the two positive charges cannot be placed adjacent to one another.

Generation of the σ complex is the rate-determining or most difficult step of the substitution reaction and the magnitude of the $\Delta G^{\ddagger}$ of this reaction directly correlates with the rate of the reaction. Via the Hammond postulate, the transition state of a reaction step resembles the species that is closest to it in energy. The more unstable the σ complex is, the higher in energy the transition state will be. A higher energy transition state will decrease the rate at which product is formed via that pathway. Put more simply, the higher energy σ complexes will be formed more slowly, resulting in less product formed via that pathway.

In the exercise that follows you will examine the energy levels of various σ complexes and transition states leading to the σ complexes to probe the origin of ortho, meta, and para selectivity.

This page titled 11.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

11.3: Computation Assignment and Exercise Questions

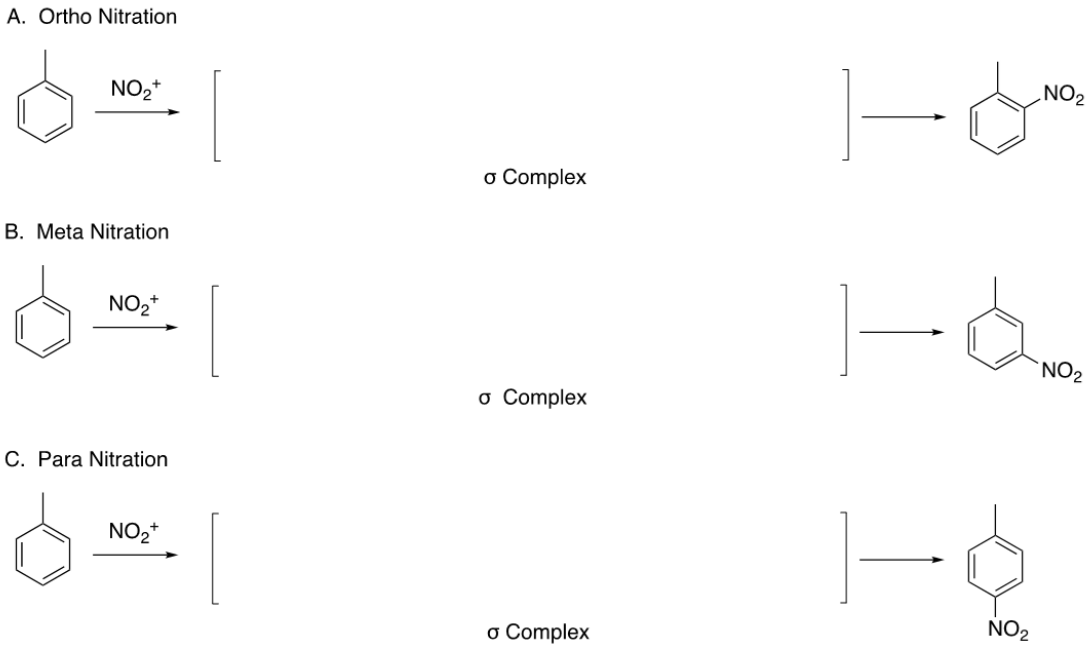
For this exercise you will be provided with data from calculations performed in Orca. All the computations have already been completed for these structures; you do not need to further optimize them. Use the provided results of the energy calculations to determine the influence of electron withdrawing or donating groups on the regiochemistry of electrophilic aromatic substitution.

Part 1: Nitration of Toluene

1. Please use the supplied energy values to complete the following table. You should normalize all these energy values to the starting materials energy values by subtracting the energy of each species by the energy of the starting material in kcal/mol. If you have done this correctly, the normalized energy of the starting materials should be 0 kcal/mol.

Species	Energy (Eh)	Energy (kcal/mol)	Normalized Energy (kcal/mol)
Starting Material (Benzene and Nitronium Ion)	-62.001583		
Ortho Transition State	-61.992944		
σ Complex, Ortho Addition	-62.008034		
Meta Transition State	-61.991557		
σ Complex, Meta Addition	-62.008034		
Para Transition State	-61.994192		
σ Complex, Para Addition	-62.008034		

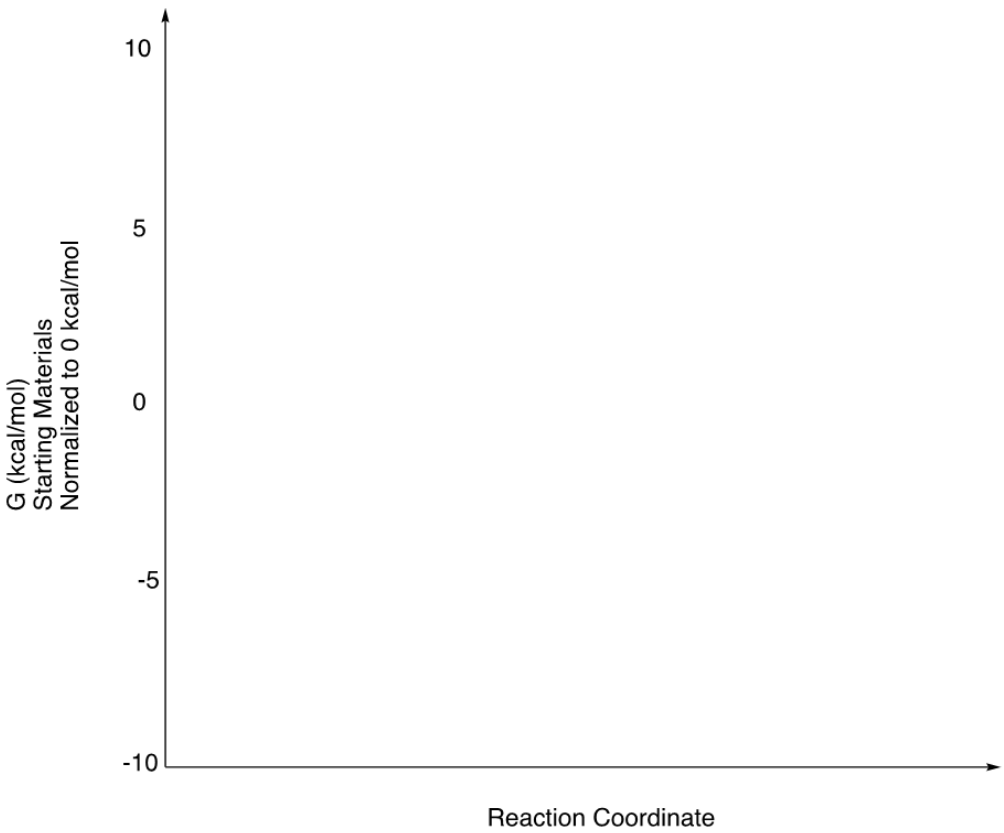
2. Please show the structure of the σ complexes in the nitration of toluene with ortho, meta, and para selectivity in the space provided below.



3. Using your energy numbers from question 1, which of the formed complexes is the most stable? Which is the least stable? Do these answers match the stability that you would expect from the structure of the σ complexes that you drew in question 2? Please explain.
4. Please determine the ΔG° and $\Delta G^\ddagger$ of the first step of the electrophilic aromatic nitration of toluene for ortho, meta, and para-addition of the electrophile.

Reaction Selectivity	ΔG° (kcal/mol)	$\Delta G^\ddagger$ (kcal/mol)
Ortho nitration		
Meta nitration		
Para nitration		

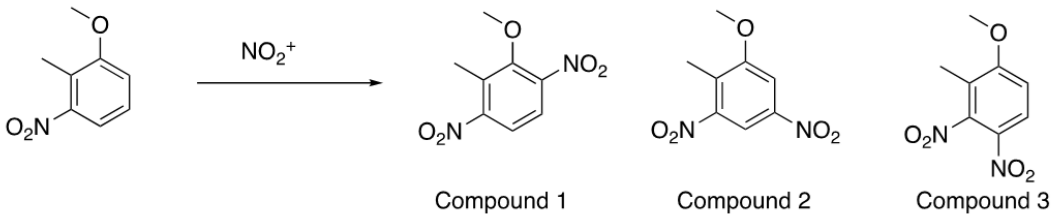
5. Please construct a reaction coordinate diagram showing the data for ortho, meta, and para-nitration that you determined in question 4. You should use different colors for ortho meta and para selectivity. For full credit please label the ΔG° and $\Delta G^\ddagger$ of each reaction.



6. Assuming that the nitration of toluene will yield all possible isomers, please indicate the relative (in broad terms) amounts of each product that you should obtain. Compare these to the experimental results for nitration of toluene which can be found in *J. Am. Chem. Soc.* 1941, 63, 11, 3230-3231. Do relative amounts of ortho, meta, and para product that you predicted match the experimental results? Please explain.

Part 2: Nitration of 1-methoxy-2-methyl-3-nitrobenzene

In this part of the computational exercise, we will be examining the nitration of 1-methoxy-2-methyl-3-nitrobenzene, a molecule whose directing groups do not reinforce each other.



7. Using your knowledge of directing groups in EAS reactions, predict the relative amounts of product 1, 2 and 3 would one expect from the reaction shown above, assuming that all three isomers are detected. Please explain.
8. Please use the supplied energy values to complete the following table. You should normalize all these energy values to the starting materials energy values by subtracting the energy of each species by the energy of the starting material in kcal/mol. If you have done this correctly, the normalized energy of the starting materials should be 0 kcal/mol.

Species	Energy (Eh)	Energy (kcal/mol)	Normalized Energy (kcal/mol)
Starting Materials	-105.15579		
Transition State, Compound 1	-105.09292		
σ Complex, Compound 1	-105.10636		
Transition State, Compound 2	-105.09415		
σ Complex, Compound 2	-105.10478		
Transition State Compound 3	-105.10492		
σ Complex, Compound 3	-105.11378		

9. Please determine the ΔG° and $\Delta G^{\ddagger}$ of the first step of the electrophilic aromatic nitration of 1-methoxy-2-methyl-3-nitrobenzene to produce compound 1, 2, and 3.

Reaction Selectivity	ΔG° (kcal/mol)	$\Delta G^{\ddagger}$ (kcal/mol)
Compound 1		
Compound 2		
Compound 3		

10. Using the data from Question 9, please indicate the relative amounts of compounds 1, 2, and 3 that you would expect from a nitration reaction assuming that all products are produced and the reaction is kinetically controlled.
11. Given the computational data, do you expect the nitration of toluene or 1-methoxy-2-methyl-3-nitrobenzene to be more selective? Please explain.
12. Comparing the nitration reaction of toluene with that of 1-methoxy-2-methyl-3-nitrobenzene, which do you think would be nitrated faster, assuming similar reaction conditions. Please explain.

This page titled 11.3: Computation Assignment and Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

CHAPTER OVERVIEW

12: Measuring the influence of ring strain in ether substitution

12.1: Overview
12.2: Background
12.3: Computational Instructions
12.4: Exercise Questions

This page titled 12: Measuring the influence of ring strain in ether substitution is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

12.1: Overview

Learning Objectives

- Students will be able to use Orca[1–3] to calculate the energy of starting materials and products of nucleophilic opening of cyclic ethers.
- Students will determine if the extent of angle strain in a cyclic ether influences the rate at which a nucleophile can open the ring.
- Students will build intuition relating the amount of ring strain in a molecule to its reactivity.

Overview: This exercise seeks to help you understand the role that the release of strain plays in the reactivity of epoxides. Specifically, HO- or RO- are typically poor leaving groups when engaged in substitution reactions. One exception is the epoxide also known as an oxirane whose ring strain allows RO- to act as an effective leaving group. In this exercise, you will calculate the activation energy of a nucleophile opening 3-membered and 4-membered cyclic ethers.

Faculty Notes: This exercise is designed to help students better understand how ring strain influences electrophilicity of ethers. Before assigning this exercise, students should have learned SN2 reactions as they apply to epoxide opening. Please note that in the interest of computation time, this exercise is run at a relatively low-level of theory (semi-empirical). While the reaction energies show the trend needed to illustrate the core concept of the exercise, the values of ΔG° and $\Delta G^\ddagger$ should be viewed with the level of theory in mind. On a standard desktop computer, the calculation in this exercise takes about 20 minutes. Overall, this assignment should take students about an hour to complete.

This page titled 12.1: Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

12.2: Background

SN2 reactions occur via the backside attack of a carbon leaving group bond. From a molecular orbital perspective, the highest occupied orbital (HOMO) of the nucleophile (typically a lone pair of electrons) overlaps with the carbon-leaving group antibonding orbital (The lowest unoccupied molecular orbital or LUMO).

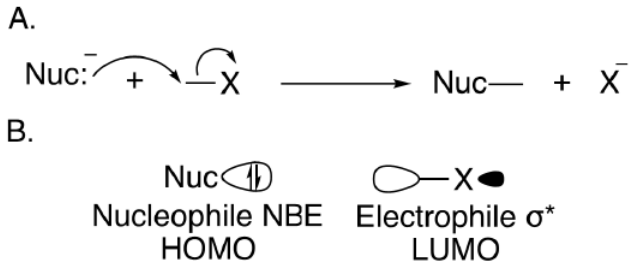


Figure 1A. Generic SN2 reaction. **B.** The frontier molecular orbitals overlapping to cause an SN2 reaction.

Typically, HO- or RO- are not effective enough leaving groups to allow an SN2 reaction to occur without some type of activation. Cyclic ethers containing a significant amount of angle strain, however, allow SN2 reactions to occur. The angle strain inherent in 3 and 4 membered cyclic ethers, known as epoxides and oxetanes respectively, increase the reactivity of the ether as an electrophile. In the exercise that follows, you will be examining the reaction of both a 3-membered epoxide, and a 4-membered oxetane of the same molecular formula to examine the effect of angle strain upon the substitution reaction.

This page titled 12.2: Background is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

12.3: Computational Instructions

To calculate the energetics of the reaction we will need to calculate the starting materials and products for both the opening of oxetane and propylene oxide, as shown in Figure 2. While we have learned to calculate the transition states of substitution reactions in a previous computational exercise, the transition states for these reactions will be provided to help save time.

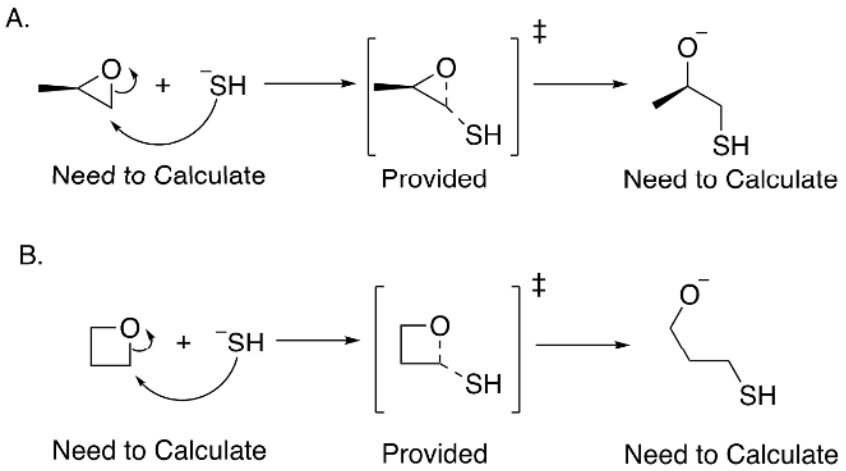


Figure 2A. Opening of propylene oxide with the hydrosulfide anion. **B.** Opening of oxetane with the hydrosulfide anion.

Start by creating a folder on the desktop of your computer and label it as Ether Substitution. Within this folder, please create the following subfolders: SM_Epox, PR_Epox, SM_Oxet, and PR_Oxet. Next you should download the supporting files for this exercise. These files will include a generic input file (denoted by a .inp file extension), and molecular coordinates for the products and starting materials that you will run your calculations upon. Place a copy of the generic input file into each of the nested subfolders and place the appropriate coordinates file into each subfolder. A description of this file structure is shown in Figure 3.

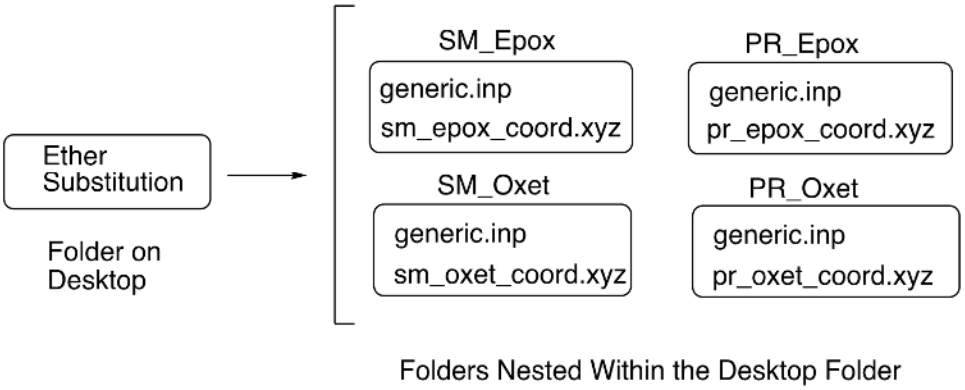


Figure 12.3.1: Copy and Paste Caption here. (Copyright; author via source)

The process for calculating the energy of the products or reactants of the oxetane or epoxide opening is the same for each calculation. To illustrate this process, we will walk through the calculation of the starting materials for the epoxide reaction. Begin by opening the starting coordinates file sm_epox_coord.xyz in Avogadro[4,5] and make sure that it has the starting propylene oxide and hydrosulfide anion as shown in Figure 4.

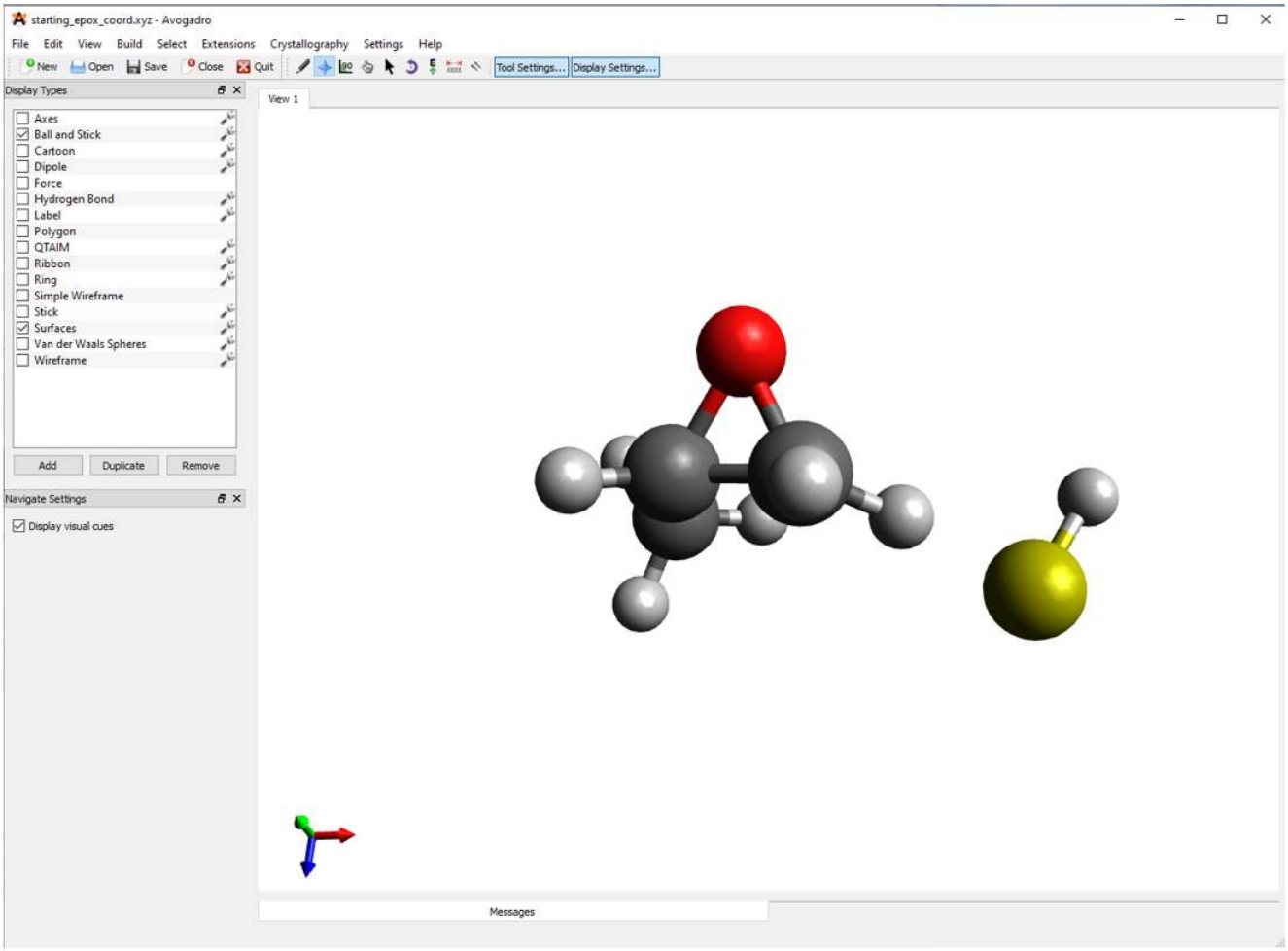


Figure 4. Expoxide opening reaction starting material viewed in Avogadro.

You should then open the generic input file in notepad and save it as sm_epoxide.inp. As shown in Figure 5, please change the name of the file from coord.xyz to sm_epox_coord.xyz so that the computer knows to look for the epoxide starting material coordinates in your folder. Be sure to save your changes.

```
# starting material energy
!PM3 Opt Freq

%geom maxiter 500
End

* xyzfile -1 1 sm_epox_coord.xyz
```

Figure 5. Generic input script for determining the energy values of starting materials or products.

We can now run our calculation using Orca via the command line as we did in previous exercises. Briefly, open the command prompt to your PC by right clicking on the start button and searching for command prompt. First, we need to tell the computer to look on the C drive and we do this by typing C: and hitting enter. Next, we need to tell the computer where the input script and the coordinates file are to run the calculation. We do this by typing cd (space) and pasting the file path. When you hit enter, the computer will paste a new line indicating that the current directory has changed, as shown in Figure 6A. To find the file path of your input script, right click on the input script (sm_epoxide.inp) and select properties. The file path will appear under location, and you can highlight and copy this file path (Figure 6B).

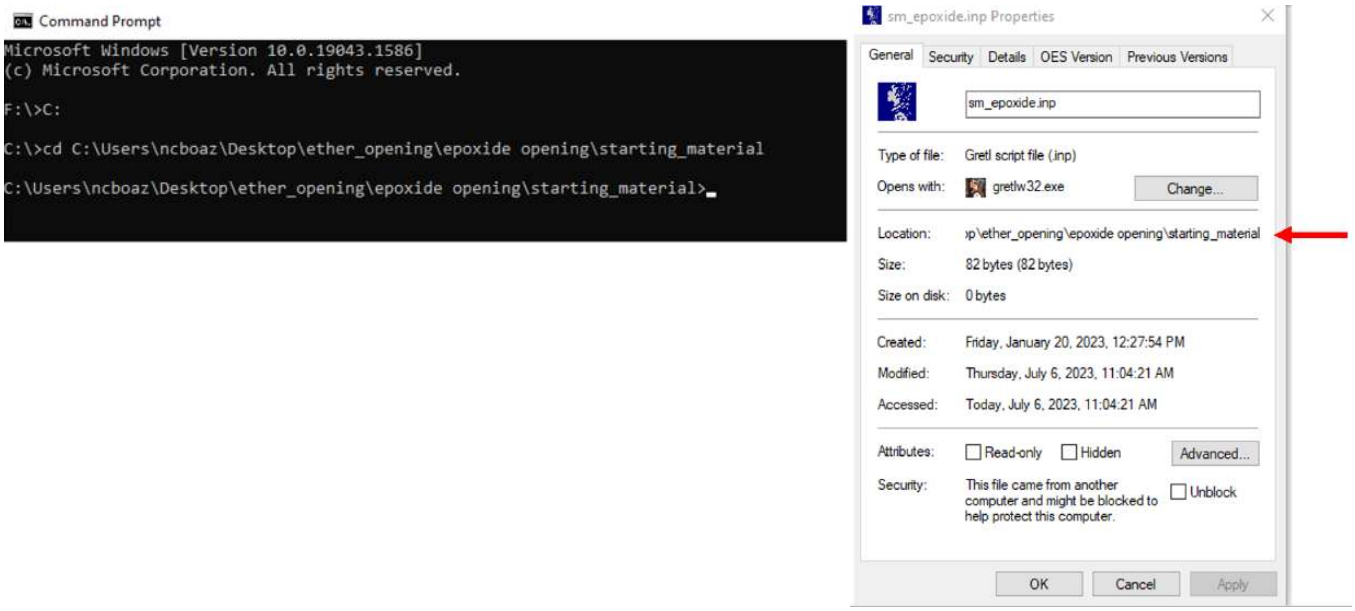


Figure 6A. (**Left**) Changing of the file path in the command prompt to match the location of our input script. **6B. (Right)** Locating the file path on the properties window of the input script (Red Arrow).

Next, we will run the calculation by typing orca sm_epoxide.inp > sm_epoxide.out and pressing enter. After pressing enter it may not appear like much is happening, but the computer is working on your computation and depositing the results in the SM_Epox folder that you created. Depending upon the speed of your computer, the calculation will take about 1-3 minutes, and upon completion the command prompt will print another line indicating that it is ready for the next command (Figure 7).

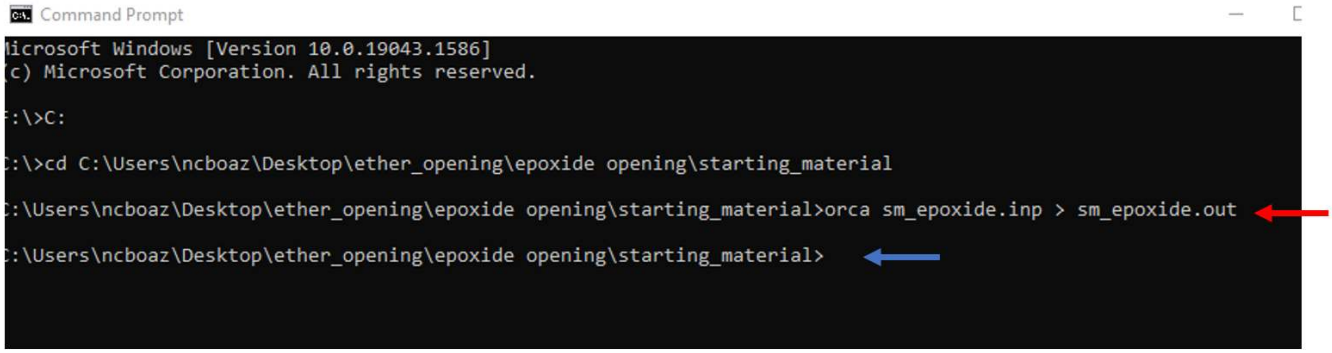


Figure 7. Running the calculation using the command line. The line indicated by the red arrow shows the computer that we want to use Orca to calculate the commands in sm_epoxide.inp and that the results of this calculation should be placed in the output file sm_epoxide.out. The line indicated by the blue arrow is the computer indicating that the calculation is complete, and the command prompt is ready for the next command.

After the Orca job has completed you can access the energy values by opening the output file (sm_expoxide.out) in notepad. At the very end of the file (scroll to the bottom) will be the thermodynamic values that Orca calculated for the starting materials of the epoxide opening reaction. As shown in Figure 8, the value of Gibbs free energy in Hartree (Eh) can be found under the heading of Final Gibbs free energy.

```
-------------------
GIBBS FREE ENERGY
-------------------

The Gibbs free energy is G = H - T*S

Total enthalpy                    ...    -34.57632764 Eh
Total entropy correction          ...     -0.04005359 Eh    -25.13 kcal/mol
-----------------------------------------------------------------------
Final Gibbs free energy         ...    -34.61638123 Eh

For completeness - the Gibbs free energy minus the electronic energy
G-E(el)                           ...      0.05618773 Eh     35.26 kcal/mol


Total Time for Numerical Frequencies  :       180.476 sec

Timings for individual modules:

Sum of individual times         ...       24.887 sec (=   0.415 min)
STO integral calculation        ...        1.554 sec (=   0.026 min)   6.2 %
SCF iterations                  ...       17.987 sec (=   0.300 min)  72.3 %
SCF Gradient evaluation         ...        1.083 sec (=   0.018 min)   4.4 %
Geometry relaxation             ...        4.262 sec (=   0.071 min)  17.1 %
                             ****ORCA TERMINATED NORMALLY****
TOTAL RUN TIME: 0 days 0 hours 3 minutes 29 seconds 733 msec
```

Figure 8. The Gibbs free energy of the starting material of the epoxide opening reaction (indicated by a red arrow).

Please repeat this process for the products of the epoxide opening, the starting materials of the oxetane opening, and the products of the oxetane opening. After completing these computations use these results to complete the questions at the end of this assignment.

References

1. Neese, F. The ORCA Program System. *WIREs Computational Molecular Science* **2012**, *2* (1), 73–78. https://doi.org/10.1002/wcms.81.
2. Neese, F. Software Update: The ORCA Program System, Version 4.0. *WIREs Computational Molecular Science* **2018**, *8* (1), e1327. https://doi.org/10.1002/wcms.1327.
3. Neese, F.; Wennmohs, F.; Becker, U.; Riplinger, C. The ORCA Quantum Chemistry Program Package. *J. Chem. Phys.* **2020**, *152* (22), 224108. https://doi.org/10.1063/5.0004608.
4. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform. *J Cheminform* **2012**, *4* (1), 17. https://doi.org/10.1186/1758-2946-4-17.
5. Avogadro: An Open-Source Molecular Builder and Visualization Tool. http://avogadro.cc/.

This page titled 12.3: Computational Instructions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

12.4: Exercise Questions

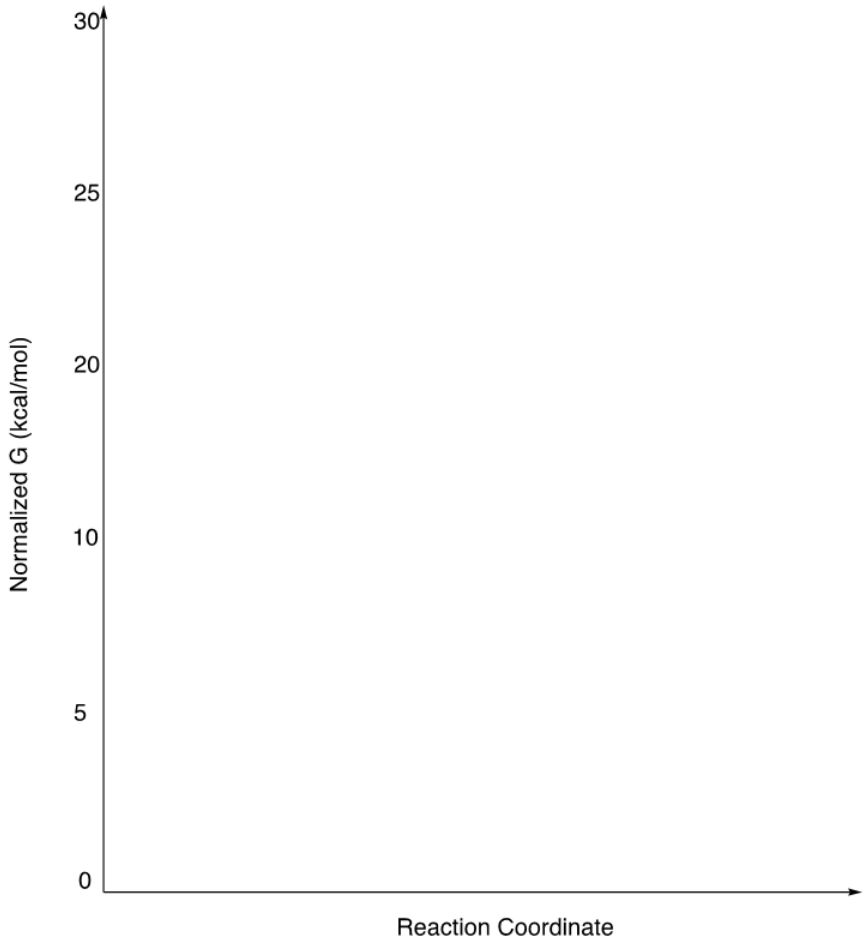
1. Please use the energy values that you calculated in addition to the transition state calculations (provided) to complete the following table. The values provided by Orca are in Hartree. You can then convert these values to kcal/mol by multiplying the values in Hartree by 627.5 kcal/mol. You should then normalize all the values to the oxetane opening starting material by subtracting all energy values by the Gibbs Free Energy that the Oxetane Opening starting material. If done correctly your normalized Oxetane Opening Starting Material should be 0 kcal/mol.

Species	Gibbs Free Energy (Eh)	Gibbs Free Energy (kcal/mol)	Gibbs Free Energy (kcal/mol), normalized to Oxetane Starting Material
Oxetane Opening Starting Material			
Oxetane Opening Transition State	-34.57930416		
Oxetane Opening Products			
Epoxide Opening Starting Material			
Epoxide Opening Transition State	-34.57906255		
Epoxide Opening Products			

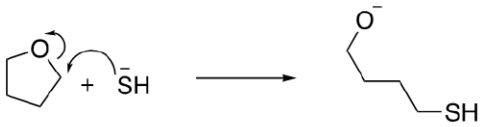
2. Using the values from the table in question one, please calculate the ΔG° and $\Delta G^{\ddagger}$ for the epoxide and oxetane opening reactions.

Reaction	ΔG° (kcal/mol)	$\Delta G^{\ddagger}$ (kcal/mol)
Epoxide Opening		
Oxetane Opening		

3. Using the data from question 1 and question 2, please compose a reaction coordinate diagram showing the energetics of both reactions (on the same diagram). For full credit you should draw depictions of the starting materials, transition state, and products of both reactions. Moreover, you should label the ΔG° and $\Delta G^{\ddagger}$ (with specific values) for both reactions.



4. Are the epoxide and oxetane opening reactions spontaneous? Which reaction do you think will be faster? Please explain.
5. Which cyclic ether is more reactive, the oxetane or epoxide? How does ring strain influence this reactivity? Please explain briefly (~1 paragraph).
6. Tetrahydrofuran (C_4H_8O) is a five-membered cyclic ether analogous to epoxide and oxetane. Predict whether tetrahydrofuran would be more or less reactive to substitution from hydrosulfide than oxetane. Please predict how the $\Delta G^{\ddagger}$ for the opening of THF with the hydrosulfide anion would compare to the $\Delta G^{\ddagger}$ for the opening of an epoxide or an oxetane. Please explain.



7. Which of the measured transition states, epoxide-opening or oxetane-opening, do you expect to be more product like? Please explain your answer using the Hammond Postulate.
8. By pulling up the output files in Avogadro please measure the distances of the carbon-oxygen bonds broken in the reaction and complete the table below. Which transition state has a C-O bond length closer to that of their corresponding starting material? Do these data fit with your answer in question 7?

Reaction	Starting Material C-O Bond Distance, Å	Transition State C-O Bond Distance, Å	Difference, Å
Epoxide Opening			
Oxetane Opening			

This page titled 12.4: Exercise Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Nicholas Boaz and Orion Pearce.

Detailed Licensing

Overview

Title: Understanding Organic Chemistry Through Computation (Boaz and Pearce)

Webpages: 69

Applicable Restrictions: Noncommercial

All licenses found:

- CC BY-NC-SA 4.0: 97.1% (67 pages)
- Undeclared: 2.9% (2 pages)

By Page

- Understanding Organic Chemistry Through Computation (Boaz and Pearce) - *CC BY-NC-SA 4.0*
  - Front Matter - *CC BY-NC-SA 4.0*
    - TitlePage - *CC BY-NC-SA 4.0*
    - InfoPage - *CC BY-NC-SA 4.0*
    - Table of Contents - *Undeclared*
    - Licensing - *CC BY-NC-SA 4.0*
  - 1: Introduction to Avogadro - *CC BY-NC-SA 4.0*
    - 1.1: Overview - *CC BY-NC-SA 4.0*
    - 1.2: Background - *CC BY-NC-SA 4.0*
    - 1.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 1.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 2: Bond Lengths and Resonance - *CC BY-NC-SA 4.0*
    - 2.1: Overview - *CC BY-NC-SA 4.0*
    - 2.2: Background - *CC BY-NC-SA 4.0*
    - 2.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 2.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 3: Visualizing Molecular Orbitals with Avogadro and Orca - *CC BY-NC-SA 4.0*
    - 3.1: Overview - *CC BY-NC-SA 4.0*
    - 3.2: Background - *CC BY-NC-SA 4.0*
    - 3.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 3.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 4: Measuring Equilibrium on Cyclohexane Chair Structures - *CC BY-NC-SA 4.0*
    - 4.1: Overview - *CC BY-NC-SA 4.0*
    - 4.2: Background - *CC BY-NC-SA 4.0*
    - 4.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 4.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 5: Computing and Visualizing Infrared Spectra of Organic Molecules - *CC BY-NC-SA 4.0*
    - 5.1: Overview - *CC BY-NC-SA 4.0*
    - 5.2: Background - *CC BY-NC-SA 4.0*
    - 5.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 5.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 6: Manipulating of Molecules in Three Dimensions - *CC BY-NC-SA 4.0*
    - 6.1: Overview - *CC BY-NC-SA 4.0*
    - 6.2: Background - *CC BY-NC-SA 4.0*
    - 6.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 6.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 7: Thermodynamics, Kinetics, and the Reaction Coordinate Diagram - *CC BY-NC-SA 4.0*
    - 7.1: Overview - *CC BY-NC-SA 4.0*
    - 7.2: Background - *CC BY-NC-SA 4.0*
    - 7.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 7.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 8: Understanding the Effect of Solvation on E2 Reactions - *CC BY-NC-SA 4.0*
    - 8.1: Overview - *CC BY-NC-SA 4.0*
    - 8.2: Background - *CC BY-NC-SA 4.0*
    - 8.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 8.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 9: Calculating Bond Dissociation Enthalpy and Analyzing the Radical Chlorination of Norbornane - *CC BY-NC-SA 4.0*
    - 9.1: Overview - *CC BY-NC-SA 4.0*
    - 9.2: Background - *CC BY-NC-SA 4.0*
    - 9.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 9.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 10: Examining the Synthesis of Naturally Occurring Cyclobutane Compounds - *CC BY-NC-SA 4.0*
    - 10.1: Overview - *CC BY-NC-SA 4.0*
    - 10.2: Background - *CC BY-NC-SA 4.0*
    - 10.3: Computational Instructions - *CC BY-NC-SA 4.0*
    - 10.4: Exercise Questions - *CC BY-NC-SA 4.0*
  - 11: Examining the Energetics of Selectivity in Electrophilic Aromatic Substitution - *CC BY-NC-SA 4.0*

- 11.1: Overview - *CC BY-NC-SA 4.0*
- 11.2: Background - *CC BY-NC-SA 4.0*
- 11.3: Computation Assignment and Exercise Questions - *CC BY-NC-SA 4.0*

12: Measuring the influence of ring strain in ether substitution - *CC BY-NC-SA 4.0*

- 12.1: Overview - *CC BY-NC-SA 4.0*
- 12.2: Background - *CC BY-NC-SA 4.0*
- 12.3: Computational Instructions - *CC BY-NC-SA 4.0*
- 12.4: Exercise Questions - *CC BY-NC-SA 4.0*

Back Matter - *CC BY-NC-SA 4.0*

- Index - *CC BY-NC-SA 4.0*
- Glossary - *CC BY-NC-SA 4.0*
- Detailed Licensing - *Undeclared*