11 Molecular Modeling

11.1 Introduction

Molecular Modeling is a general term that can refer to a wide range of activities from constructing simple physical models of compounds (e.g. “ball and stick” models) to sophisticated computational modeling carried out on computers. Computational modeling has been developed into a set of extremely powerful tools that can accurately predict detailed molecular structures and calculate relative energies of compounds. Computational modeling falls into two categories, molecular mechanics models that are based on simplified bonding descriptions (like Lewis structures) and force field calculations, and quantum chemical models that are based on approximating solutions to the Schrodinger equation. The latter calculations, known as molecular orbital (MO) calculations, vary widely in their degree of sophistication and computer memory/time required, but they are generally far superior to molecular mechanics calculations in accurately predicting structures and energies of compounds.

The enormous advancement in speed and memory capacity of desktop computers, combined with innovations in molecular modeling software, has made MO calculations a practical everyday modeling tool for use in predicting detailed structures of compounds (including lowest energy conformations), predicting the most likely products of reactions, and rationalizing reactions and mechanisms. The calculations are not limited to “stable” molecules; they can also be used to calculate the structures and energies of reactive intermediates and even transition states.

Another type of valuable information that comes out of a molecular orbital calculation is an electron density map that provides a picture of the distribution of the outermost electrons in the molecule. Superimposing a map of electrostatic potential onto a map of electron density can provide a very informative picture of the charge distribution in a molecule (or intermediate, or transition state) which relates to its reactivity.

In this molecular modeling experiment, an electrophilic aromatic substitution (EAS) reaction, nitration of anisole, as shown below, will be investigated using molecular orbital calculations.

\[ \text{O} \quad \text{C}_6\text{H}_5\text{O} \quad + \quad \text{HNO}_3 \quad \rightarrow \quad \text{O} \quad \text{C}_6\text{H}_5\text{NO}_2 \quad + \quad \text{H}_2\text{O} \]
After investigating nitration of anisole as an instructional exercise, a similar modeling approach will be used to investigate two electrophilic substitution reactions that are being carried out in the lab. The investigation will be carried out in the computer lab using Spartan Student Edition, a popular molecular modeling program from Wavefunction Inc.

11.2 Calculating the Structure and Energy of the Anisole Starting Material

Building a Starting Point Structure
Open Spartan ST. Under the File menu, select New. From the molecular model kit shown at right, select the Organic tab. Click the rings button and select benzene. Move the cursor to the turquoise field and click there to place a benzene building block in the field. Return to the model kit and select the oxygen atom with two single bonds. Bond the oxygen to the benzene ring by clicking on one of the bonds coming off of the ring. Return to the model kit and select the sp³ carbon with four single bonds. Bond the sp³ carbon to the oxygen atom on the benzene ring by clicking on the available bond on the oxygen. This completes the framework structure for anisole. It is not necessary to add all of the hydrogen atoms as these will be added automatically to any open bonds in the structure when you perform your MO calculation.

Optimizing the Structure by MO Calculation
Under the Setup Menu, select Calculations. In the calculations window, select Equilibrium Geometry with Hartree-Fock/3-21G. The Total Charge should be Neutral and the Multiplicity Singlet. Make sure the Global Calculations box is checked, and click OK to accept the parameters for the MO calculation. This is the second highest level of molecular orbital calculation that can be performed with the program. It provides very reliable molecular structures in lowest energy conformation. It also provides total energy calculations that are fairly reliable for comparing the relative energies of isomers that are closely related in structure.

Before submitting the calculation, go back to the Setup Menu and select Surfaces. Click on the Add box and select density under Surface and potential under Property. Use the default Isovalue of 0.002 and click OK. Close the Surfaces text box and select Submit under the Setup Menu. When prompted for a file name, enter an appropriate identifier and click Save to initiate the calculation. A notification box will appear when the calculation is complete. Click OK to proceed to analyze the results.

Examining the Optimized Structure
The optimized ball and spoke model of anisole should appear on the screen. Click on the model and hold the left mouse button down to rotate the model. Practice rotating the model to view it from all different angles. Go to the Model menu and select other model types to view the model (e.g. wire, ball and wire, tube, space filling). Return to the ball and spoke model before proceeding.

Under the display menu, select Output and scroll down through the output from the MO calculation. After a series of number cycles of iterative energy calculations, you can see the minimum total energy shown as \( E(\text{HF}) = \) ______ a.u. The is the calculated total energy of formation of the molecule in atomic units. It is the energy of the molecule relative to the energy of all
of the nuclei and electrons as separated particles. This is a large negative number in all cases. The magnitude of the number is even greater than appears at first because the atomic unit is a very large unit of energy. Chemists are more accustomed to dealing with much smaller energy units, such as KJ/mole. The conversion between a.u. and KJ/mole is as follows:

\[
1 \text{ a.u.} = 2625 \text{ KJ/mole}
\]

Although the total energy for a single molecule such as anisole is not particularly meaningful or useful by itself, you will see later in this lab that total energies, calculated in this way for closely related molecules can be very useful to compare their relative energies and stabilities.

Returning to the ball and spoke model of the structure, look carefully at the conformation of the methoxy group. Click on the angle button on the menu bar above the structure and click the carbon-oxygen-carbon of the methoxy group. The bond angle will appear in the box in the lower right-hand corner of the frame. Sketch the structure in your lab notebook and record the carbon-oxygen-carbon bond angle on the sketch.

(Note: Clicking on the [V], View, icon will return to the previous view of the structures after performing any specific function such as the bond angle function just performed.)

Under the Display menu, select Surfaces and check the density box. The model should now appear as an electron density map with a color coded map of electrostatic potential on the surface. Red signifies areas of negative charge, blue signifies areas of positive charge. Yellow and green are neutral to slightly negative and neutral to slightly positive, respectively. Click on the structure and a style box will appear in the lower right of the screen. Try the alternate styles for viewing the electron cloud and charge distribution (i.e. transparent, dots, mesh). The solid view is best for seeing the charge distribution (by color code), while the other views allow the positions of the nuclei within the electron cloud to be seen.

Questions for Section 11.2
1. What is the hybridization of the oxygen of the methoxy group? Why does the methoxy group adopt the indicated conformation which places the methyl group in the plane of the benzene ring? This conformation is more sterically hindered than if the methyl group rotated out of the plane of the ring.

2. Viewing the map of electron density with electrostatic potential, what areas of the molecule have the most positive and negative charge? What atom or atoms carry the most positive charge? What atom or atoms carry the most negative charge? Which areas of the molecule are closer to neutral charge?

3. Do you see any indication from the electron density map that certain positions of the aromatic ring should be more susceptible to electrophilic attack than others?

4. Is the electron density map consistent with your predictions based on resonance structures? In other words, do resonance structures give a good indication of the actual electron density and charge distribution in the molecule?
11.3 Calculating the Structures and Energies of Reactive Intermediates (Arenium Ions) Resulting from Electrophilic Attack at the ortho, meta, and para Positions.

Importance of Arenium Ion Intermediates
It is well established that EAS reactions proceed through arenium ion intermediates as shown at the top of page 102 for ortho attack of an electrophile on anisole.

The arenium ion is a high energy intermediate on the path to the substitution product. Formation of this intermediate is the rate-limiting step in the EAS reaction, so the relative amounts of ortho, meta, and para substitution products formed depend on the relative rates of formation of the corresponding arenium ions. These rates depend directly on the activation energies to reach the transition states leading to them. Since calculating energies of transition states (energy maxima) is more difficult and error-prone than calculating energies of molecules that have some degree of stability (energy minima), we will employ the Hammond-Leffler postulate which tells us that transition states resemble the stable species closest in energy. (See pages 253-254 in Solomons 7th ed.) In this case, the structures and energies of the arenium ion intermediates will be used to gain insight into the relative energies of the transition states leading to them.

Building Starting Point Structures for the Arenium Ions
Under the File menu, select New to open the model kit and field. The arenium ion cannot be easily made from a benzene template, so you will need to assemble it from individual carbon atoms. In the model kit at right, click on the Inorganic tab and a periodic table will appear. Select carbon on the periodic table and select the box below the table that shows three bonds coming off of a center atom. This provides a trivalent sp² carbon atom. Click in the turquoise structure field to place the first sp² carbon of the ring. Add four more of these carbons to place them at 5 out of 6 positions of a benzene ring. Now return to the model kit, click the organic tab and select a tetravalent sp³ carbon to place in the 6th position of the benzene ring. The final bond of the ring can be closed by selecting the Make bond icon from the tool menu above the field and clicking on open valences of each carbon to form the final bond and close the ring. (This can be a little tricky and you might have to try it a couple of times to get the last bond of the ring to form.) Return to the model kit, select the electrophile (NO₂) from the under the Groups button and bond it to the one of the open valences of the sp³ carbon of the ring. Finally, add a methoxy group onto the position ortho to the sp³ carbon. This completes the starting point structure for the arenium ion resulting from ortho attack of nitronium ion on anisole. The structures for meta and para attack are constructed similarly.
**Optimizing the Structures by MO Calculations**

The steps for running the MO calculations are the same as those used for the anisole starting material, except in this case you will use semi-empirical calculations to get a quick rough estimate of the energies. Under the Setup Menu, select **Calculations**. In the calculations window, select **Equilibrium Geometry** with **Semi-Empirical**. In this case the Total Charge should be **Cation**. The Multiplicity is **Singlet**. Make sure the Global Calculations box is checked, and click **Submit** to accept the parameters and run the MO calculation. When prompted for a file name, enter an appropriate identifier and click **Save** to initiate the calculation. A notification box will appear when the calculation is complete. Click **OK** to proceed to analyze the results.

After running semi-empirical calculations on all three arenium ions, bring all three of the optimized structures up on the screen by opening each of the three files. The structures can be selected, moved, and rotated one at a time by clicking on each one. Select each structure one at a time, go to the Display menu, and select **Output** to view the energy calculation for that structure. Record the total energy calculated for each arenium ion in your lab notebook. These energies are heats of formation in KJ/mole. These are the calculated total energies of the arenium ions relative to the elements in their standard states. Note the differences in energies of the three ions.

**Examining the Optimized Structures Resulting from Hartree-Fock MO Calculations**

Because the Hartree-Fock MO calculations for the arenium ion intermediates take a long time to run, these have been run for you and the results are available on your computer in the Spartan file folder in a folder named **Nitration of Anisol**. Open the files for each of the three possible arenium ion intermediates so that the optimized structures are displayed side-by-side on the screen. Select each structure one at a time, go to the Display menu, and select **Output** to view the energy calculation for that structure. Record the total energy calculated for each arenium ion in your lab notebook. Convert the energies from atomic units to KJ/mole and express the differences in energies of the arenium ions in the latter units. Compare these energy differences from Hartree-Fock MO calculations with those you determined using semi-empirical calculations. The Hartree-Fock energies should be the more reliable numbers.

Return to the structures displayed in the ball and spoke format. Check and record the bond angles and bond distances within the methoxy and nitro groups and between these groups and the ring carbons they are bonded to. (Note: Bond distances are obtained by clicking on the [? ] icon above the structure field, then clicking on the two atoms at either end of the bond. Clicking on the [V], **View**, icon will return to the previous view of the structures after performing any specific function.) Record the bond angle and bond distance data in your lab notebook. Note any important differences among the three structures.

Select **Surfaces** under the Display menu and click the **density** box to see the electron density/electrostatic potential map for each structure. With the surface potential style selection on **Solid**, carefully examine the areas of positive (blue) and negative (red) charge in each of the structures. Note any important differences that you observe.
Questions for Section 11.3

1. Which of the arenium ions has the lowest, second lowest and highest energy?

2. From the electrostatic potential maps, do you see any evidence for differences in the degree of charge delocalization in the three arenium ions? Describe any differences you observe. What atom or atoms in each structure carry the greatest positive and negative charge? Is this consistent with what you would predict from resonance structures?

3. With respect to EAS reactions, the methoxy group is classified as an electron donating, (i.e. activating) ortho/para directing substituent. Carefully examine the methoxy group in the structure of each arenium ion. Is there any evidence from charge, bond distances, or bond angles that the methoxy group is acting as a better donor in one structure than another?

4. Provide a rational for the energy differences calculated for the three ions. Support your rational with specific observations you made on the three structures.

5. Based on the energy calculations and observations you made on the arenium ions, predict the major product that should form from nitration of anisol. Predict the second most likely and least likely product that should form.

Before coming to the computer lab on day two, decide what structures need to be evaluated for analysis of the EAS reactions carried out in lab. Sketch the structures in your lab notebook. Your TA will check this prelab exercise before you start.

11.4 Analysis of EAS Reactions Carried Out in Lab

For this part of the lab, you will conduct a molecular modeling analysis of the two EAS reactions that you will carry out (or have carried out) in lab. These reactions are shown below. Because the MO calculations for all of the possible arenium ion intermediates in these reactions take a long time to run, these have been run for you and the results are available on your computer in the Spartan file folder in a folder identified by the reaction name.

Chlorination of Acetanilide

\[
\text{HN} \quad \text{O} \quad \text{Cl}_2 \quad \text{HN} \quad \text{O} \quad \text{Cl} \quad \text{HCl}
\]

Open the files for each of the three possible arenium ion intermediates so that the optimized structures are displayed side-by-side on the screen. Perform a detailed analysis of each struc-
ture as done in Section 11.3. Record the total energy calculated for each arenium ion in your lab notebook. Convert the energies from atomic units to KJ/mole and express the differences in energies of the arenium ions in the latter units. Check and record the bond angles and bond distances within the acetamido group and between the nitrogen and the ring. Record the bond angle and bond distance data in your lab notebook. Note any important differences among the three structures.

Questions for Chlorination of Acetanilide
1. Which of the arenium ions has the lowest, second lowest and highest energy?

2. From the electrostatic potential maps, do you see any evidence for differences in the charge distribution in the three arenium ions? Describe any differences you observe. What atom or atoms in each structure carry the greatest positive and negative charge? Is there any apparent difference in the amount of charge carried by these atoms from one structure to another?

3. With respect to EAS reactions, the acetamido group is classified as a moderately electron donating, (i.e. activating) ortho/para directing substituent. Carefully examine the acetamido group in the structure of each arenium ion. Is there any evidence from charge, bond distances, or bond angles that the acetamido group is acting as a better donor in one structure than another?

4. Provide a rational for the energy differences calculated for the three ions. Support your rational with specific observations you made on the three structures.

5. Based on the energy calculations and observations you made on the arenium ions, predict the major product that should form from chlorination of acetanilide. Predict the second most likely and least likely product that should form. Is this prediction consistent with the results of this reaction when you carried it out in lab?

Nitration of 4-methylacetanilide

![Chemical reaction diagram]

Open the files for each of the two possible arenium ion intermediates so that the optimized structures are displayed side-by-side on the screen. Perform a detailed analysis of each struc-
ture as done above for chlorination of acetanilide. Record the total energy calculated for each arenium ion in your lab notebook. Convert the energies from atomic units to KJ/mole and express the differences in energies of the arenium ions in the latter units. Check and record the bond angles and bond distances within the acetamido group, the methyl group and the nitro group and between these groups and the ring carbon they are bonded to. Record the bond angle and bond distance data in your lab notebook. Note any important differences among the three structures.

**Questions for Nitration of 4-Methylacetanilide**

1. Which of the arenium ions has the lowest and highest energy?

2. From the electrostatic potential maps, do you see any evidence for differences in the charge distribution in the two arenium ions? Describe any differences you observe. What atom or atoms in each structure carry the greatest positive and negative charge? Is there any apparent difference in the amount of charge carried by these atoms from one structure to the other?

3. With respect to EAS reactions, the acetamido group is classified as a moderate electron donating substituent whereas the methyl is classified as weak electron donating group. Both are ortho/para directing substituents. Carefully examine the acetamido group and the methyl group in the structure of each arenium ion. Is there any evidence from charge, bond distances, or bond angles that either of these groups is acting as a better donor in one structure than another?

4. Provide a rational for the energy differences calculated for the two ions. Support your rational with specific observations you made on the structures.

5. Based on the energy calculations and observations you made on the arenium ions, predict the major product that should form from nitration of $p$-methylacetanilide. Is this prediction consistent with the results of this reaction when you carried it out in lab?