

## CH 241 EXPERIMENT #4

### WEEK OF OCTOBER 15, 2001 MOLECULAR MODELING PART II

Introduction: In this lab you will continue to hone your modeling skills using the Spartan program. Several key concepts that were recently covered in class will be examined computationally and compared with known experimental data. As with the other experiments, the goal here is not to simply get the "right" or "expected" answer but to gain an appreciation of the techniques that organic chemists employ to solve problems. If necessary, please look up your notes from Part I to reacquaint yourself with Spartan, and review some of its basic commands.

#### Part I. Substituted cyclohexanes

In this part, you can explore the relative stabilities of several substituted cyclohexanes and also investigate their chirality. In all cases, you will need to optimize the geometry using the semi-empirical AM1 method. Feel free to turn the structures around as much as you wish and make sure that you see the interactions that might stabilize or destabilize the individual conformer. The cyclohexane template provided under the "Rings" menu is a useful tool for building your structures.

- Build and minimize both chair conformers of methylcyclohexane and record their heats of formation. Using the difference in the heats of formation, calculate the amount of each species present at equilibrium. Repeat this calculation for *tert*-butylcyclohexane.
- Build and minimize both chair conformations of *cis*-1,3- and *trans*-1,3-dimethylcyclohexane. As before, compute the equilibrium ratios of the conformers for each compound. Note how these structures are related to each other and determine whether or not each structure is chiral.

#### Part II. Investigating relative acidities with electrostatic potential maps

As you might expect, the hydrogen in a stronger acid has a greater partial positive charge than that in a weaker acid. In other words, a stronger acid has a more "electron poor" hydrogen than a weaker one. In this exercise, you will assess the acidity of various compounds by examining their electrostatic potential maps. The electrostatic potential maps will let you identify electron poor (blue) and electron rich (red) regions of the molecule.

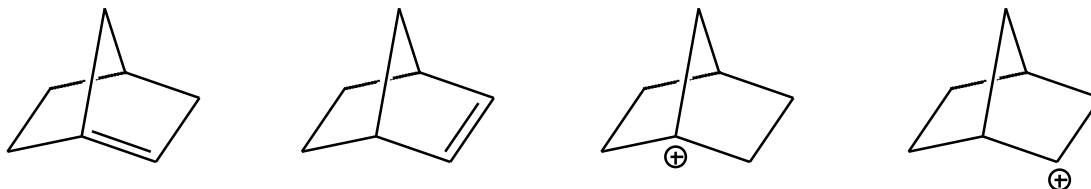
- Comparing the acidities of ethane, ethylene, and acetylene: Build these three compounds and minimize using semi-empirical AM1 method. Be sure to request to request the electron density (for surface) and electrostatic potential (for property) before submitting the calculation. Display the electrostatic potential map of all three molecules on the same screen and record the most positive value of the potential at the hydrogen for each compound.
- Effect of substituents on acidity: Build acetic acid, trifluoroacetic acid, and trichloroacetic acid. Submit the calculations as before and record the most positive value of the potential at the carboxyl hydrogen for each compound.
- Acidity of alcohols versus phenols: Repeat the above calculations for ethanol and phenol and record the appropriate potential values each.

### Part III. Relative stabilities of cations

Build models of 1°, 2°, and 3° butyl cations. Submit a calculation using the AM1 method. Be sure to specify that the molecule has a positive charge before submitting the job. Record the heats of formation for each cation.

### Part IV. Bridgehead alkenes and cations

Build and minimize the following four species using the AM1 method. Record the heats of formation in each case. Also note the angles around the positively charged carbon in the bridgehead cation. For the bridgehead alkene, note the H-C=C-C dihedral angles.



### Part V. Models of molecules in the news

Using your prelab, build a model of crixivan and/or mifepristone. Minimize your model using the AM1 method and cast it in different views. Request a 3D structure and use the red and blue glasses to examine the molecule. Finally, have the Spartan program identify the stereogenic centers in the molecule. Print out the model of one of the two compounds

### Pre-Lab Exercises for Experiment #5

- (1) Write both chair conformations for cis-1,3- and trans-1,3-dimethylcyclohexane. How are these structures related to one another? Label each conformer as chiral or achiral.
- (2) Look up the pKa values of ethane, ethylene, acetylene, acetic acid, trifluoroacetic acid, trichloroacetic acid, ethanol, and phenol. Record these values in your notebook.
- (3) Look up and draw the structures of the following compounds that have important medical applications. Identify the stereogenic centers in each compound.

Crixivan (a drug used in the treatment of AIDS)

Mifepristone (the controversial abortion pill, also known as RU 486, that was recently approved by the FDA for use in the US)

## Laboratory Report for Experiment #3

Name\_\_\_\_\_

Section\_\_\_\_\_

Date\_\_\_\_\_

### Data Section

#### Part I.

Tabulate the energies and equilibrium ratios of the substituted cyclohexanes.

#### Part II.

Tabulate the electrostatic potential and the pKa values for all the compounds in this part.

#### Part III.

Arrange the cations according to stability using their AM1 heats of formation.

#### Part IV.

Tabulate the heats of formation for all four species, the angles around the bridgehead cation, and the dihedral angles of the bridgehead alkene.

#### Part V.

Record the number of stereogenic centers in each compound. Submit the printout of one of the compounds.

### Discussion Section

- (1) How do the calculated equilibrium ratios for methylcyclohexane and *tert*-butylcyclohexane compare with the experimental values reported in your text.
- (2) Rationalize the observed trend in the pKa values of ethane, ethylene, and acetylene. Compare this trend with the electrostatic potentials that you calculated.
- (3) Explain the effect of substituents on acidity in going from acetic acid to trichloroacetic acid to trifluoroacetic acid?
- (4) Account for the observed trend in the relative acidities of phenol, ethanol, and acetic acid.
- (5) What conclusions can you draw from your data in Part III and Part IV of this lab.
- (6) Only particular stereoisomers of crivivan and mifepristone are responsible for biological activity? Compute the maximum number of stereoisomers possible for each compound?