Introduction to Molecular Modeling

ESSAY

Molecular Modeling and Molecular Mechanics

Since the beginnings of organic chemistry, somewhere in the middle of the nineteenth century, chemists have sought to visualize the three-dimensional characteristics of the all-but-invisible molecules that participate in chemical reactions. Concrete models that could be held in the hand were developed. Many kinds of model sets, such as framework, ball-and-stick, and space-filling models, were devised to allow people to visualize the spatial and directional relationships within molecules. These hand-held models were interactive, and they could be readily manipulated in space.

Today we can also use the computer to help us visualize these molecules. The computer images are also completely interactive, allowing us to rotate, scale, and change the type of model viewed at the press of a button or the click of a mouse. In addition, the computer can rapidly calculate many properties of the molecules that we view. This combination of visualization and calculation is often called **computational chemistry** or, more colloquially, **molecular modeling**.

Two distinct methods of molecular modeling are commonly used by organic chemists today. The first of these is **quantum mechanics**, which involves the calculation of orbitals and their energies using solutions of the Schrödinger equation. The second method is not based on orbitals at all, but is founded on our knowledge of the way in which the bonds and angles in a molecule behave. Classical equations that describe the stretching of bonds and the bending of angles are used. This second approach is called **molecular mechanics**. The two types of calculation are used for different purposes and do not calculate the same types of molecular properties. In this essay, molecular mechanics will be discussed.

MOLECULAR MECHANICS

Molecular mechanics (MM) was first developed in the early 1970s by two groups of chemical researchers: the Engler, Andose, and Schleyer group, and the Allinger group. In molecular mechanics, a mechanical **force field** is defined that is used to calculate an energy for the molecule under study. The energy calculated is often called the **strain energy** or **steric energy** of the molecule. The force field is comprised of several components, such as bond-stretching energy, angle-bending energy, and bond-torsion energy. A typical force field expression might be represented by the following composite expression:[1]

$$E_{strain} = E_{stretch} + E_{angle} + E_{torsion} + E_{oop} + E_{vdW} + E_{dipole}$$

To calculate the final strain energy for a molecule, the computer systematically changes every bond length, bond angle, and torsional angle in the molecule, recalculating the strain energy each time, keeping each change that minimizes the total

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[1]Other force fields may be found that include more terms than this one and that contain more sophisticated calculational methods than those shown here.

energy, and rejecting those that increase the energy. In other words, all the bond lengths and angles are changed until the energy of the molecule is *minimized.*

Each term contained in the composite expression (E_{strain}) is defined in Table 1. All of these terms come from classical physics, not quantum mechanics. We will not discuss every term, but will take $E_{stretch}$ as an illustrative example. Classical mechanics says that a bond behaves like a spring. Each type of bond in a molecule can be assigned a normal bond length, x_0. If the bond is stretched or compressed, its potential energy will increase, and there will be a restoring force that attempts to restore the bond to its normal length. According to Hooke's Law, the restoring force is proportional to the size of the displacement

$$F = -\text{k}_i (x_1 - x_0) \text{ or } F = -\text{k}_i(\Delta x)$$

where k_i is the **force constant** of the bond being studied (that is, the "stiffness" of the spring) and Δx is the change in bond length from the bond's normal length (x_0). The actual energy term that is minimized is given in Table 1. This equation indicates that all the bonds in the molecule contribute to the strain; it is a sum (Σ) starting with the first bond's contribution ($n = 1$) and proceeding through the contributions of all the other bonds (n_bonds).

These calculations are based on empirical data. To perform these calculations, the system must be **parameterized** with experimental data. To parameterize, a table of the normal bond lengths (x_0) and force constants (k_i) for every type of bond in the molecule must be created. The program uses these experimental parameters to perform its calculations. The quality of the results from any molecular mechanics approach directly depends on how well the parameterization has been performed for each type of atom and bond that has to be considered. The MM procedure requires each of the factors in Table 1 to have its own parameter table.

Each of the first four terms in Table 1 is treated as a spring in the same manner as discussed for bond stretching. For instance, an angle also has a force constant k that resists a change in the size of the angle θ. In effect, in the first four terms the molecule is treated as a collection of interacting springs, and the energy of this collection of springs must be minimized. In contrast, the last two terms are based on electrostatic or "coulomb" repulsions. Without describing these terms in detail, it should be understood that they must also be minimized.

MINIMIZATION AND CONFORMATION

The object of minimizing the strain energy is to find the lowest energy *conformation* of a molecule. Molecular mechanics does a very good job of finding conformations, because it varies bond distances, bond angles, torsional angles, and the positions of atoms in space. However, most minimizers have some limitations that users must be aware of which. Many of the programs use a minimization procedure that will locate a local minimum in the energy, but will not necessarily find a global minimum. The figure "Global and local energy minima" that is shown below illustrates the problem.

In the figure, the molecule under consideration has two conformations that represent energy minima for the molecule. Many minimizers will not automatically find the lowest energy conformation, the **global minimum**. The global minimum will be found only when the structure of the starting molecule is already close to the global minimum's conformation. For instance, if the starting structure corresponds to point B on the curve in the figure, then the global minimum will be found.

TABLE 1 Some of the Factors Contributing to a Molecular Force Field

Type of Contribution	Illustration	Typical Equation
$E_{stretch}$ (bond stretching)		$E_{stretch} = \sum_{i=1}^{n\_bonds} (k_i/2)(x_i - x_0)^2$
E_{angle} (angle bending)		$E_{angle} = \sum_{j=1}^{n\_angles} (k_j/2)(\theta_j - \theta_0)^2$
$E_{torsion}$ (bond torsion)		$E_{torsion} = \sum_{k=1}^{n\_torsions} (k_k/2)[1 + sp_k(\cos p_k \theta)]$
E_{oop} (out of plane bending)		$E_{oop} = \sum_{m=1}^{n\_oops} (k_m/2)d_m^2$
E_{vdW} (van der Waals repulsion)		$E_{vdW} = \sum_{i=1}^{n\_atoms} \sum_{j=1}^{n\_atoms} (E_i E_j)^{1/2} \left[\dfrac{1}{a_{ij}^{12}} - \dfrac{2}{a_{ij}^{6}} \right]$ $a_{ij} = r_{ij}/(R_i + R_j)$
E_{dipole} (electric dipole repulsion or attraction)		$E_{vdW} = K \sum_{i=1}^{n\_atoms} \sum_{j=i+1}^{n\_atoms} Q_i Q_j / r_{ij}^2$

Note: The factors selected here are similar to those in the "Tripos force field" used in the Alchemy III molecular modeling program.

However, if the starting molecule is not close to the global minimum in structure, a **local minimum** (one nearby) may be found. In the figure, if the starting structure corresponds to point A, then a local minimum will be found, instead of the global minimum. Some of the more expensive programs always find the global minimum because they use more sophisticated minimization procedures that depend on

Global and local energy minima.
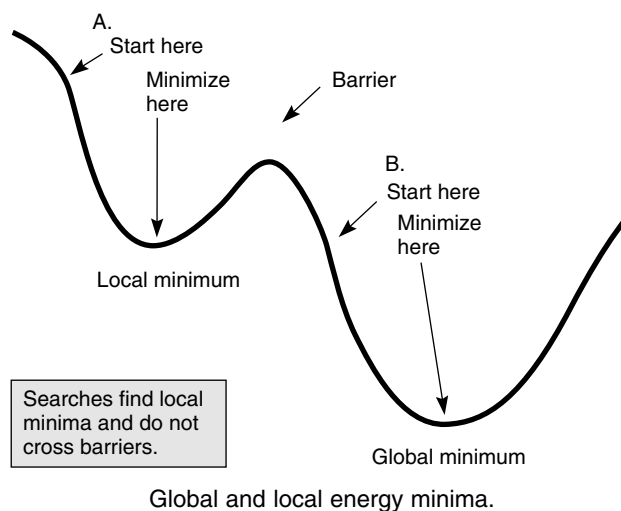
random (Monte Carlo) changes instead of sequential ones. However, unless the program has specifically dealt with this problem, the user must be careful to avoid finding a false local minimum when the global minimum is expected. It may be necessary to use several different starting structures to discover the global minimum for a given molecule.

LIMITATIONS OF MOLECULAR MECHANICS

From our discussion thus far, it should be obvious that molecular mechanics was developed to find the lowest energy conformation of a given molecule or to compare the energies of several conformations of the same molecule. Molecular mechanics calculates a "strain energy," not a thermodynamic energy such as a heat of formation. Procedures based on quantum mechanics and statistical mechanics are required to calculate thermodynamic energies. Therefore, it is very dangerous to compare the strain energies of two *different* molecules. For instance, molecular mechanics can make a good evaluation of the relative energies of *anti-* and *gauche-* butane conformations, but it cannot fruitfully compare butane and cyclobutane. Isomers can be compared only if they are very closely related. The *cis-* and *trans-*isomers of 1,2-dimethylcyclohexane, or those of 2-butene, can be compared. However, the isomers 1-butene and 2-butene cannot be compared; one is a monosubstituted alkene, whereas the other is disubstituted.

Molecular mechanics will perform the following tasks quite well:

1. It will give good estimates for the actual bond lengths and angles in a molecule.

2. It will find the best conformation for a molecule, but you must watch out for local minima!

Molecular mechanics will not calculate the following properties:

1. It will not calculate thermodynamic properties such as the heat of formation of a molecule.[2]

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[2]Some of the latest versions are now parameterized to give heats of formation.

2. It will not calculate electron distributions, charges, or dipole moments.

3. It will not calculate molecular orbitals or their energies.

4. It will not calculate infrared, NMR, or ultraviolet spectra.

CURRENT IMPLEMENTATIONS

With time, the most popular version of molecular mechanics has become that developed by Norman Allinger and his research group. The original program from this group was called MM1. The program has undergone constant revisions and improvements, and the current Allinger versions are now designated MM2 and MM3. However, many other versions of molecular mechanics are now available from both private and commercial sources. Some popular commercial programs that now incorporate their own force fields and parameters include Alchemy III, Alchemy 2000, CAChe, Personal CAChe, HyperChem, Insight II, PC Model, MacroModel, Spartan, PC Spartan, MacSpartan, and Sybyl. You should also realize, however, that many modeling programs do not have molecular mechanics or minimization. These programs will "clean up" a structure that you create by attempting to make every bond length and angle "perfect." With these programs, every sp^3 carbon will have 109° angles, and every sp^2 carbon will have perfect 120° angles. Using one of these programs is equivalent to using a standard model set that has connectors and bonds with perfect angles and lengths. If you intend to find a molecule's preferred conformation, be sure you use a program that has a force field and performs a true minimization procedure. Also remember that you may have to control the starting structure's geometry in order to find the correct result.

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17 **EXPEREIMENT 17**

An Introduction to Molecular Modeling

Molecular modeling
Molecular mechanics

REQUIRED READING

Review: The sections of your lecture textbook dealing with

1. Conformation of cyclic and acyclic compounds

2. The energies of alkenes with respect to degree of substitution

3. The relative energies of *cis-* and *trans-*alkenes

New: Essay: Molecular Modeling and Molecular Mechanics

SPECIAL INSTRUCTIONS

To perform this experiment, you must use computer software that has the ability to perform molecular mechanics (MM2 or MM3) calculations with minimization of the strain energy. Either your instructor will provide directions for using the software or you will be given a handout with instructions.

NOTES TO THE INSTRUCTOR

This molecular mechanics experiment was devised using the modeling program PC Sparta; however, it should be possible to use many other implementations of molecular mechanics. Some of the other capable programs available are Alchemy 2000, Spartan, Spartan '08, MacSpartan, HyperChem, CAChe and Personal CAChe, PCModel, Insight II, Nemesis, and Sybyl. You will have to provide your students with an introduction to your specific implementation. The introduction should show students how to build a molecule, how to minimize its energy, and how to load and save files. Students will also need to be able to measure bond lengths and bond angles.

17A   EXPERIMENT 17A

The Conformations of n-Butane: Local Minima

The acyclic butane molecule has several conformations derived by rotation about the C2−C3 bond. The relative energies of these conformations have been well established experimentally and are listed in the following table.

Conformation	Torsional Angle	Relative Energy (kcal/mol)	Relative Energy (kJ/mol)	Types of Strain
Syn	0°	6.0	25.0	Steric/torsional
Gauche	60°	1.0	4.2	Steric
Eclipsed-120	120°	3.4	14.2	Torsional
Anti	180°	0	0	No strain

In this section, we will show that although molecular mechanics does not calculate the precise thermodynamic energies for the conformations of butane, it will give

strain energies that predict the *order* of stability correctly. We will also investigate the difference between a local minimum and a global minimum.

When you construct a butane skeleton, you might expect the minimizer to always arrive at the *anti* conformation (lowest energy). In fact, for most molecular mechanics programs, this will happen only if you bias the minimizer by starting with a butane skeleton that closely resembles the *anti* conformation. If this is done, the minimizer will find the *anti* conformation (the *global* minimum). However, if a skeleton is constructed that does not closely resemble the *anti* conformation, the butane will usually minimize to the *gauche* conformation (the nearest *local* minimum) and not proceed to the global minimum. For the two staggered conformations, you will begin by constructing your starting butane molecules with torsional angles slightly removed from the two minima. The eclipsed conformations, however, will be set on the exact angles to see if they will minimize. Your data should be recorded in a table with the following headings: *Starting Angle, Minimized Angle, Final Conformation,* and *Minimized Energy.*

Your program should have a feature that allows you to set bond lengths, bond angles, and torsional angles.[1] If it does, you can merely select the torsion angle C1−C2−C3−C4 and specify 160° to set the first starting shape. Select the minimizer and allow it to run until it stops. Did it find the *anti* conformation (180°)? Record the energy. Repeat the process, starting with torsion angles of 0°, 45°, and 120° for the butane skeleton. Record the strain energies and report the final conformations that are formed in each case. What are your conclusions? Do your final results agree with those in the table?

If your minimizer rotated the two-eclipsed conformations (0° and 120°) to their closest staggered minima, you may have to restrict the minimizer to a single iteration in order to calculate their energies. This restriction calculates a **single-point energy**, and the energy of the structure is not minimized. If necessary, calculate the single-point energies of the eclipsed conformations and record your results.

The lesson here is that you may have to try several starting points to find the correct structure for the lowest energy conformation of a molecule! Do not blindly accept your first result, but look at it with the skeptical eye of a practiced chemist and test it further.

Optional Exercise. Record the single-point energies for every 30° rotation, starting at 0° and ending at 360°. When these energies are plotted against their angle, the plot should resemble the rotational energy curve shown for butane in most organic textbooks.

17B   E X P E R I M E N T   1 7 B

Cyclohexane Chair and Boat Conformations

In this exercise, we will investigate the chair and boat conformations of cyclohexane. Many programs will have these stored on disk as templates or fragments. If they are available as templates or fragments, you will need only to add hydrogens to the template. The chair is not difficult to build if you construct your cyclohexane on the screen

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[1]If your program does not have this feature, you can approximate the angles specified by constructing your starting molecules on the screen in a Z-shape for one and in a U-shape for the other.

in such a way that it resembles a chair (that is, just as you might draw it on paper). This crude construct will usually minimize to a chair. The boat is more difficult to construct. When you draw a crude boat on the screen, it will minimize to a *twist* boat, instead of the desired symmetrical boat.

Before you construct any cyclohexanes, construct a propane molecule. Minimize it and measure the CH and CC bond lengths and the CCC bond angle. Record these values; you will use them for reference.

Now construct a cyclohexane chair and minimize it. Measure the CH and CC bond lengths and the CCC angle in the ring. Compare these values to those of propane. What do you conclude? Rotate the molecule so that you view it end-on, looking down two of the bonds simultaneously (as in a Newman projection). Are all the hydrogens staggered? Rotate the chair and look at it from a different end-on angle. Are all the hydrogens still staggered? The van der Waals radius of a hydrogen atom is 1.20 Ångstroms. Hydrogen atoms that are closer than 2.40 Ångstroms apart will "touch" each other and create steric strain. Are any of the hydrogens in the cyclohexane chair close enough to cause steric strain? What are your conclusions?

Now construct a cyclohexane boat (from a template) and do not minimize it.[1] Measure the CH and CC bond lengths and the CCC bond angles at both the peaks and the lower corner of the ring. Compare these values to those of propane. Rotate the molecule so that you view it end-on, looking down the two parallel bonds on the sides of the boat. Are the hydrogens eclipsed or staggered? Now measure the distances between the various hydrogens on the ring, including the bowsprit–flagpole hydrogens and the axial and equatorial hydrogens on the side of the ring. Are any of the hydrogens generating steric strain?

Now minimize the boat to a twist boat and repeat all of the measurements. Write all of your conclusions about chairs, boats, and twist boats in your report.

17C   E X P E R I M E N T   1 7 C

Substituted Cyclohexane Rings (Critical Thinking Exercises)

These exercises are designed to have you discover some not so obvious principles. Any conclusions and explanations that are requested should be recorded in your notebook.

Dimethylcyclohexanes. Using a cyclohexane template, construct *cis*(a,a)-1,3-dimethylcyclohexane, *cis*(e,e)-1,3-dimethylcyclohexane, and *trans*(a,e)-1,3-dimethyl-cyclohexane, and measure their energies. In the diaxial isomer, measure the distance between the two methyl groups. What do you conclude? Explain the result.

Similar comparisons can be made for the *cis*- and *trans*-1,2-dimethylcyclohexanes and the *cis*- and *trans*-1,4-dimethylcyclohexanes.

***cis*-1,4-Di-*tert*-butylcyclohexane.** Using hand drawings of chairs and boats, predict the expected conformation of this molecule. Then, construct *cis*(a,e)-1,4-di-*tert*-butylcyclohexane in a chair conformation, minimize it, and record its

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[1]A single-point energy may be obtained, if you desire.

energy. Next, construct *cis*(e,e)-1,4-di-*tert*-butylcyclohexane in a boat conformation, placing the *tert*-butyl groups in equatorial positions at the peaks (puckered carbon atoms). Minimize this conformation to a twist boat and record its energy. Should we always expect chair conformations to have lower energy than boat conformations? Explain. What conformation do you predict for the *trans* stereoisomer?

trans-1,2-Dichloro and dibromocyclohexanes. Build a model of *trans*(a,a)-1,2-dichlorocyclohexane, minimize it, and record its energy. Build a model of *trans*(e,e)-1,2-dichlorocyclohexane, minimize it, and record its energy. What is your conclusion? Now predict the result for the same two conformations of *trans*-1,2-dichlorocyclohexane. When you have made a prediction, go ahead and model the two dibromo isomers and record the energies. What did you find? Explain the result. Do you think the result would be the same in a highly polar solvent?

Now construct the *cis*-1,2-dichloro and dibromocyclohexanes and compare their energies. Once again, explain what you find.

17D   E X P E R I M E N T   1 7 D

cis- and *trans*-2-Butene

Heats of hydrogenation for the three isomers of butene are given in the following table. Construct both *cis*- and *trans*-2-butene, minimize them, and report their energies. Which of these isomers has the lowest energy? Can you determine why?

Compound	ΔH (kcal/mol)	ΔH (kJ/mol)
trans-2-butene	−27.6	−115
cis-2-butene	−28.6	−120
1-butene	−30.3	−126

Now construct and minimize 1-butene. Record its energy. Obviously, 1-butene does not fit with the hydrogenation data. Molecular mechanics works quite well for *cis*- and *trans*-2-butene because they are very similar isomers. Both are 1,2-disubstituted alkenes. However, 1-butene is a monosubstituted alkene, and direct comparison to the 2-butenes cannot be made. The differences in the stability of mono- and disubstituted alkenes require that factors other than those used in molecular mechanics be used. These factors are caused by electronic and resonance differences. The molecular orbitals of the methyl groups interact with the pi bonds of the disubstituted alkenes (hyperconjugation) and help to stabilize them. Two such groups (as in 2-butene) are better than one (as in 1-butene). Therefore, although the bond lengths and angles come out pretty well for 1-butene, the energy derived for 1-butene does not directly compare to the energies of the 2-butenes. Molecular mechanics does not include terms that allow these factors to be included; it is necessary to use either semiempirical or *ab initio* quantum mechanical methods, which are based on molecular orbitals.

Computational Chemistry—*ab Initio* and Semiempirical Methods

In an earlier essay ("Molecular Modeling and Molecular Mechanics" that precedes Experiment 17), the application of **molecular mechanics** to solving chemical problems was discussed. Molecular mechanics is very good at giving estimates of the bond lengths and angles in a molecule. It can find the best geometry or conformation of a molecule. However, it requires the application of **quantum mechanics** to find good estimates of the thermodynamic, spectroscopic, and electronic properties of a molecule. In this essay, we will discuss the application of quantum mechanics to organic molecules.

Quantum mechanics computer programs can calculate heats of formation and the energies of transition states. The shapes of orbitals can be displayed in three dimensions. Important properties can be mapped onto the surface of a molecule. With these programs, the chemist can visualize concepts and properties in a way that the mind cannot readily imagine. Often this visualization is the key to understanding or to solving a problem.

INTRODUCTION TO TERMS AND METHODS

For you to solve the electronic structure and energy of a molecule, quantum mechanics requires that you formulate a wavefunction Ψ (psi) that describes the distribution of all the electrons within the system. The nuclei are assumed to have relatively small motions and to be essentially fixed in their equilibrium positions (Born–Oppenheimer approximation). The average energy of the system is calculated by using the Schrödinger equations as

$$E = \int \Psi^* H \Psi \, d\tau / \int \Psi^* \Psi \, d\tau$$

where H, the Hamiltonian operator, is a multiterm function that evaluates all the potential energy contributions (electron–electron repulsions and nuclear–electron attractions) and the kinetic energy terms for each electron in the system.

Because we can never know the true wavefunction Ψ for the molecule, we must guess at the nature of this function. According to the **Variation Principle**, a cornerstone idea in quantum mechanics, we can continue to guess at this function forever and never reach the true energy of the system, which will always be lower than our best guess. Because of the Variation Principle, we can formulate an approximate wavefunction and then consistently vary it until we minimize the energy of the system (as calculated using the Schrödinger equation). When we reach the variational minimum, the resulting wavefunction is often a good approximation of the system we are studying. Of course, you can't just make any guess and get good results. It has taken theoretical chemists quite a few years to learn how to formulate both wavefunctions and Hamiltonian operators that yield results that agree quite closely with experimental data. Today, however, most methods for performing these calculations have been well established, and computational chemists have devised easy-to-use computer programs, which can be used by any chemist to calculate molecular wavefunctions.

Molecular quantum-mechanical calculations can be divided into two classes: *ab initio* (Latin: "from the beginning" or "from first principles") and *semiempirical*.

1. ***Ab initio* calculations** use the fully correct Hamiltonian operator for the system and attempt a complete solution without using any experimental parameters.

2. **Semiempirical calculations** generally use a simplified Hamiltonian operator and incorporate experimental data or a set of parameters that can be adjusted to fit experimental data.

Ab initio calculations require a great deal of computer time and memory, because every term in the calculations is evaluated explicitly. Semiempirical calculations have more modest computer requirements, allowing the calculations to be completed in a shorter time and making it possible to treat larger molecules. Chemists generally use semiempirical methods whenever possible, but it is useful to understand both methods when solving a problem.

SOLVING THE SCHRÖDINGER EQUATION

The Hamiltonian. The exact form of the Hamiltonian operator, which is a collection of potential energy (electrostatic attraction and repulsion terms) and kinetic energy terms, is now standardized and need not concern us here. However, all the programs require the **Cartesian coordinates** (locations in three-dimensional space) of all the atoms and a **connectivity matrix** that specifies which atoms are bonded and how (single, double, triple, H-bond, and so on). In modern programs, the user draws or constructs the molecule on the computer screen, and the program automatically constructs the atomic-coordinate and connectivity matrices.

The Wavefunction. It is not necessary for the user to construct or guess at a trial wavefunction—the program will do this. However, it is important to understand how the wavefunctions are formulated, because the user frequently has a choice of methods. The complete molecular wavefunction is made up of a determinant of molecular orbitals:

$$\Psi = \begin{vmatrix} \phi_1(1) & \phi_2(1) & \phi_3(1) & ....\, \phi_n(1) \\ \phi_1(2) & \phi_2(2) & \phi_3(2) & ....\, \phi_n(2) \\ \phi_1(n) & \phi_2(n) & \phi_3(n) & ....\, \phi_n(n) \end{vmatrix}$$

The molecular orbitals $\phi_i(n)$ must be formulated from some type of mathematical function. They are usually made up of a **linear combination of atomic orbitals** χ_j (LCAO) from each of the atoms that make up the molecule.

$$\phi_i(n) = \Sigma_j\, c_{ji}\, \chi_j = c_1\, \chi_1 + c_2\, \chi_2 + c_3\, \chi_3 \cdots$$

This combination includes all the orbitals in the *core* and the *valence shell* of each atom in the molecule. The complete set of orbitals χ_j is called the **basis set** for the calculation. When an *ab initio* calculation is performed, most programs require the user to choose the basis set.

BASIS-SET ORBITALS

It should be apparent that the most obvious basis set to use for an *ab initio* calculation is the set of hydrogen-like atomic orbitals $1s$, $2s$, $2p$, and so on that we are all familiar with from atomic structure and bonding theory. Unfortunately, these "actual"

orbitals present computational difficulties because they have radial nodes when they are associated with the higher shells of an atom. As a result, a more convenient set of functions was devised by Slater. These **Slater-type orbitals** (**STO**s) differ from the hydrogen-like orbitals in that they have no radial nodes, but they have the same angular terms and overall shape. More importantly, they give good results (those that agree with experimental data) when used in semiempirical and *ab initio* calculations.

Slater-Type Orbitals. The radial term of an STO is an exponential function with the form $R_n = r^{(n-1)} e^{[-(-Z-s)r/n]}$, where Z is the nuclear charge of the atom, and s is a "screening constant" that reduces the nuclear charge Z that is "seen" by an electron. Slater formulated a set of rules to determine the values of s that are required to produce orbitals that agree in shape with the customary hydrogen-like orbitals.

Radial Expansion and Contraction. A problem with simple STOs is that they do not have the ability to vary their radial size. Today it is common to use two or more simpler STOs so that expansion and contraction of the orbitals can occur during the calculation. For instance, if we take two functions such as $R(r) = r e^{(-\zeta r)}$ with different values of ζ, the larger value of ζ gives an orbital more contracted around the nucleus (an inner STO), and the smaller value of ζ gives an orbital extended further out from the nucleus (an outer STO). By using these two functions in different combinations, any size STO can be generated.
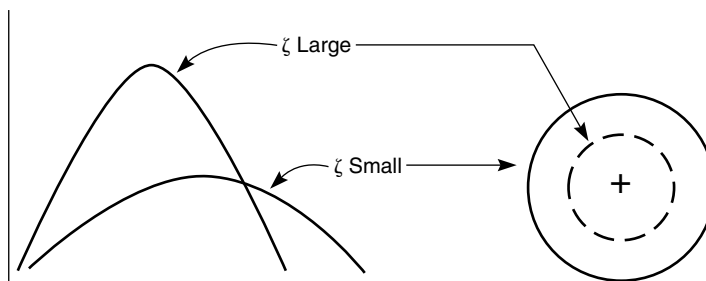

Variation of the radial size of an STO with the value of the exponent ζ (zeta).

Gaussian-Type Orbitals. The original Slater-type orbitals were eventually abandoned, and *simulated* STOs built from Gaussian functions were used. The most common basis set of this kind is the **STO-3G basis set**, which uses three Gaussian functions (3G) to simulate each one-electron orbital. A Gaussian function is of the type $R(r) = re^{(-\alpha r^2)}$.

In the STO-3G basis set, the coefficients of the Gaussian functions are selected to give the best fit to the corresponding Slater-type orbitals. In this formulation, for instance, a hydrogen electron is represented by a single STO (a 1s type orbital) that is simulated by a combination of three Gaussian functions. An electron on any period 2 element (Li to Ne) will be represented by five STOs (1s, 2s, 2p_x, 2p_y, 2p_z), each simulated by three Gaussian functions. Each electron in a given molecule will have its own STO. (The molecule is literally built up by a series of one-electron orbitals. A spin function is also included so that no two of the one-electron orbitals are exactly the same.)

Split-Valence Basis Sets. A further step of evolution has made it now common to abandon attempts to simulate the hydrogen-like orbitals with STOs. Instead, an optimized combination of the Gaussian functions themselves are used for the basis set. The 3-21G basis set has largely replaced the STO-3G basis set for all but the
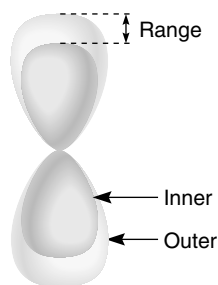
Split-valence orbitals.

largest molecules. The 3-21G symbolism means that three Gaussian functions are used for the wavefunction of each core electron, but the wavefunctions of the valence electrons are "split" two-to-one (21) between inner and outer Gaussian functions, allowing the valence shell to expand or contract in size.

A larger basis set (and one that requires more calculation time) is 6-31G, which uses six Gaussian "primitives" and a three-to-one split in the valence shell orbitals.

Polarization Basis Sets. Both the 3-21G and 6-31G basis sets can be extended to 3-21G* and 6-31G*. The star (*) indicates that these are **polarization sets**, in which the next higher type of orbital is included (for instance, a p orbital can be polarized by adding a d orbital function). Polarization allows deformation of the orbital toward the bond on one side of the atom.
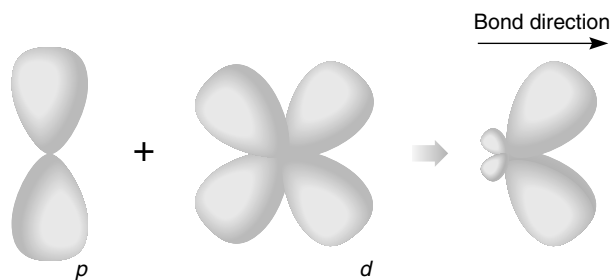
Polarization orbitals.

The largest basis set in current use is 6-311G*. Because it is computationally intensive, it is used only for **single-point calculations** (a calculation on a fixed geometry—no minimization performed). Other basis sets include the 6-31G** (which includes six d orbitals per atom instead of the usual five) and the 6-31+G* or 6-31++G* sets, which include diffuse s functions (electrons at a larger distance from the nucleus) to better deal with anions.

SEMIEMPIRICAL METHODS

It would be quite impossible to give a short and complete overview of the various semiempirical methods that have evolved over time. One must really get into the mathematical details of the method to understand what approximations have been made in each case and what kinds of empirical data have been included. In many of these methods, it is common to omit integrals that are expected (either from experience or for theoretical reasons) to have negligible values. Certain integrals are stored in a table and are not calculated each time the program is applied. For

instance, the **frozen core approximation** is often used. This approximation assumes that the *completed shells* of the atom do not differ from one atom to another in the same period. All the core calculations are stored in a table, and they are simply looked up when needed. This makes the computation much easier to perform.

One of the more popular semiempirical methods in use today is AM-1. The parameters in this method work especially well for organic molecules. In fact, whenever possible, you should try to solve your problem using a semiempirical method such as AM-1 before you resort to an *ab initio* calculation. Also popular are MINDO/3 and MNDO, which are often found together in a computational package called MOPAC. If you are performing semiempircal calculations on inorganic molecules, you must make sure the method you use is optimized for transition metals. Two popular methods used by inorganic chemists wishing to involve metals in their calculations are PM-3 and ZINDO.

PICKING A BASIS SET FOR *AB INITIO* CALCULATIONS

When you perform an *ab initio* calculation, it is not always easy to know which basis set to use. Normally you should not use more complexity than is needed to answer your question or solve the problem. In fact, it may be desirable to determine the approximate geometry of the molecule using *molecular mechanics.* Many programs will allow you to use the result of a molecular mechanics **geometry optimization** as a starting point for an *ab initio* calculation. If possible, you should do so to save computational time.

Usually, 3-21G is a good starting point for an *ab initio* calculation, but if you have a very large molecule, you may wish to use STO-3G, a simpler basis set. Avoid doing geometry optimizations with the larger basis sets. Often you can do the geometry optimization first with 3-21G (or a semiempirical method) and then polish up the result with a **single-point energy** calculation with a larger basis set, such as 6-31G. You should "move up the ladder": AM1 to STO-3G to 3-21G to 6-31G, and so on. If you don't see any change in the results as you move up to successively more complex basis sets, it is generally fruitless to continue. If you include elements beyond period 2, use polarization sets (PM3 for semiempirical). Some programs have special sets for cations and anions or for radicals. If your result doesn't match experimental results, you may not have used the correct basis set.

HEATS OF FORMATION

In classical thermodynamics, the **heat of formation**, ΔH_f, is defined as the energy consumed (endothermic reaction) or released (exothermic reaction) when a molecule is formed from its elements at standard conditions of pressure and temperature. The elements are assumed to be in their standard states.

$$2\text{ C (graphite)} + 3\text{ H}_2\text{ (g)} \rightarrow \text{C}_2\text{H}_6\text{ (g)} + \Delta H_f \qquad (25°C)$$
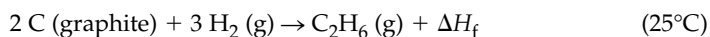
Both *ab initio* and semiempirical programs calculate the energy of a molecule as its "heat of formation." This heat of formation, however, is not identical to the thermodynamic function, and it is not always possible to make direct comparisons.

Heats of formation in semiempirical calculations are generally calculated in kcal/mole (1 kcal = 4.18 kJ) and are similar but not identical to the thermodynamic function. The AM1, PM3, and MNDO methods are parameterized by fitting them

to a set of experimentally determined enthalpies. They are calculated from the binding energy of the system. The **binding energy** is the energy released when molecules are formed from their separated electrons and nuclei. The semiempirical heat of formation is calculated by subtracting atomic heats of formation from the binding energy. For most organic molecules, AM1 will calculate the heat of formation correctly to within a few kilocalories per mole.

In *ab initio* calculations, the heat of formation is given in **hartrees** (1 hartree = 627.5 kcal/mole = 2625 kJ/mole). In the *ab initio* calculation, the heat of formation is best defined as total energy. Like the binding energy, the **total energy** is the energy released when molecules are formed from their separated electrons and nuclei. This "heat of formation" always has a large negative value and does not relate well to the thermodynamic function.

Although these values do not relate directly to the thermodynamic values, they can be used to compare the energies of isomers (molecules of the same formula), such as *cis*- and *trans*-2-butene, or of tautomers, such as acetone in its enol and keto forms.

$$\Delta E = \Delta H_f(\text{isomer 2}) - \Delta H_f(\text{isomer 1})$$

It is also possible to compare the energies of balanced chemical equations by subtracting the energies of the products from the reactants.

$$\Delta E = [\Delta H_f(\text{product 1}) + \Delta H_f(\text{product 2})] - [\Delta H_f(\text{reactant 1}) + \Delta H_f(\text{reactant 2})]$$
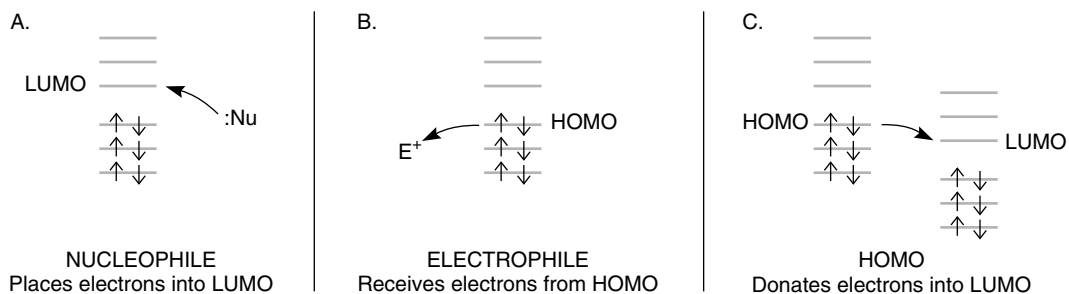
GRAPHIC MODELS AND VISUALIZATION

Although the solution of the Schrödinger equation minimizes the *energy* of the system and gives a heat of formation, it also calculates the shapes and energies of all the molecular orbitals in the system. A big advantage of semiempirical and *ab initio* calculations, therefore, is the ability to determine the energies of the individual molecular orbitals and to plot their shapes in three dimensions. For chemists investigating chemical reactions, two molecular orbitals are of paramount interest: the HOMO and the LUMO.
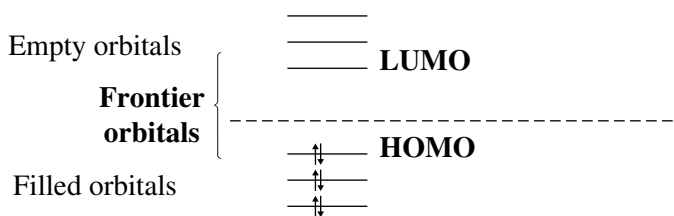
The **HOMO**, the highest occupied molecular orbital, is the last orbital in a molecule to be filled with electrons. The **LUMO**, the lowest unoccupied molecular orbital, is the first empty orbital in a molecule. These two orbitals are often called **frontier orbitals**.

The frontier orbitals are similar to the valence shell of the molecule. They are where most of the chemical reactions occur. For instance, if a reagent is going to react with a Lewis base, the electron pair of the base must be placed into an empty orbital of the acceptor molecule. The most available orbital is the LUMO. By examining the structure of the LUMO, one can determine the most likely spot where the addition will take place—usually at the atom where the LUMO has its biggest lobe.

A.

LUMO ——————

⬆⬇
⬆⬇
⬆⬇

← :Nu

NUCLEOPHILE
Places electrons into LUMO

B.

⬆⬇   HOMO
⬆⬇
⬆⬇

E⁺ ←

ELECTROPHILE
Receives electrons from HOMO

C.

HOMO ⬆⬇
⬆⬇
⬆⬇

→ LUMO ——————

⬆⬇
⬆⬇
⬆⬇

HOMO
Donates electrons into LUMO

Conversely, if a Lewis acid attacks a molecule, it will bond to electrons that already exist in the molecule under attack. The most likely spot for this attack would be the atom where the HOMO has its biggest lobe (the electron density should be greatest at that site). Where it is not obvious which molecule is the electron pair donor, the HOMO that has the highest orbital energy will usually be the electron pair donor, placing electrons into the LUMO of the other molecule. The frontier orbitals, HOMO and LUMO, are where most chemical reactions occur.
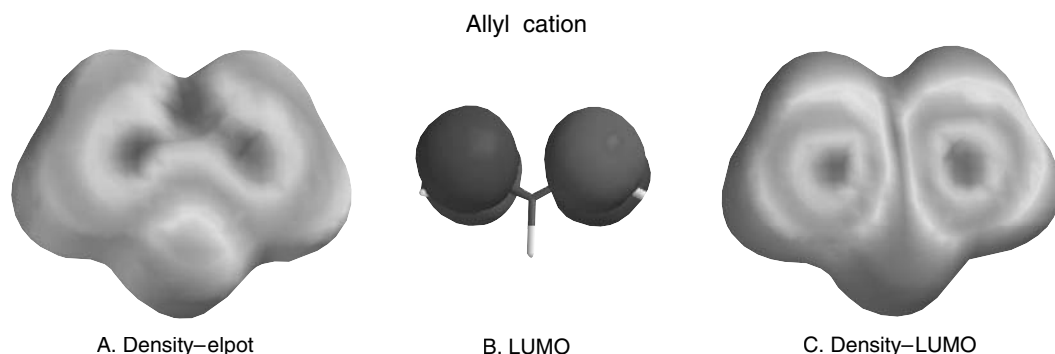
SURFACES

Chemists use many kinds of hand-held models to visualize molecules. A framework model best represents the angles, lengths, and directions of bonds. A molecule's size and shape are probably best represented by a space-filling model. In quantum mechanics, a model similar to the space-filling model can be generated by plotting a surface that represents all the points where the electron density of the molecule's wavefunction has a constant value. If this value is chosen correctly, the resulting surface will resemble the surface of a space-filling model. This type of surface is called an **electron-density surface**. The electron-density surface is useful for visualizing the size and shape of the molecule, but it does not reveal the position of the nuclei, bond lengths, or angles because you cannot see inside the surface. The electron-density value used to define this surface will be quite low because electron density falls off with increasing distance from the nucleus. If you choose a higher value of electron density when you plot this surface, a **bond-density surface** will be obtained. This surface will not give you an idea of the size or shape of the molecule, but it will reveal where the bonds are located, because the electron density will be higher where bonding is taking place.

Cyclopentane

A. Electron-density surface   B. Bond-density surface
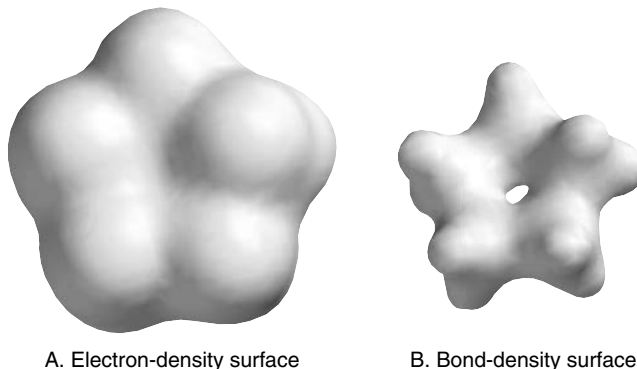
MAPPING PROPERTIES ONTO A DENSITY SURFACE

It is also possible to map a calculated property onto an electron-density surface. Because all three Cartesian coordinates are used to define the points on the surface, the property must be mapped in color, with the colors of the spectrum red–orange–yellow–green–blue representing a range of values. In effect, this is a four-dimensional plot (x, y, z, + property mapped). One of the most common plots of this type is the **density–electrostatic potential,** or **density–elpot,** plot. The electrostatic potential is determined by placing a unit positive charge at each point on the surface and measuring the interaction energy of this charge with the nuclei and electrons in the molecule. Depending on the magnitude of the interaction, that point on the surface is painted one of the colors of the spectrum. In the Spartan program, areas of high electron density are painted red or orange, and areas of lower electron density are plotted blue or green. When you view such a plot, the polarity of the molecule is immediately apparent.

Allyl cation

A. Density–elpot   B. LUMO   C. Density–LUMO

The second common type of mapping plots values of one of the frontier orbitals (either the HOMO or the LUMO) in color on the density surface. The color values plotted correspond to the value of the orbital where it intersects the surface. For a density–LUMO plot, for instance, the "hot spot" would be where the LUMO has its largest lobe. Because the LUMO is empty, this would be a bright blue area. In a density–HOMO plot, a bright red area would be the "hot spot."

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18   E X P E R I M E N T   1 8

Computational Chemistry

Semiempirical methods

Heats of formation

Mapped surfaces

REQUIRED READING

Review: The sections of your lecture textbook dealing with

     18A: Alkene Isomers, Tautomerism, and Regioselectivity—the Zaitsev and Markovnikoff Rules

     18B: Nucleophilic Substitution—Relative Rates of Substrates in S_N1 Reactions

     18C: Acids and Bases—Inductive Effects

     18D: Carbocation Stability

     18E: Carbonyl Additions—Frontier Molecular Orbitals

New: Essay: Computational Chemistry—*ab Initio* and Semiempirical Methods

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SPECIAL INSTRUCTIONS

To perform this experiment, you must use computer software that can perform semi-empirical molecular orbital calculations at the AM1 or MNDO level. In addition, the later experiments require a program that can display orbital shapes and map various properties onto an electron-density surface. Either your instructor will provide direction, for using the software, or you will be given a handout with instructions.

NOTES TO THE INSTRUCTOR

This series of computational experiments was devised using the programs PC Spartan and MacSpartan; however, it should be possible to use many other implementations of semiempirical molecular orbital theory. Some of the other capable

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programs for the PC and the Macintosh include HyperChem Release 5 and CACHe Workstation. You will need to provide your students with an introduction to your specific implementation. The introduction should show students how to build a molecule, how to select and submit calculations and surface models, and how to load and save files.

It is not intended that all these experiments be performed in a single session. They are intended to illustrate what you can do with computational chemistry, but are not comprehensive. You may wish either to assign them with specific lecture topics or to complement a particular experiment. Alternatively, you may wish to use them as patterns that students can use to devise their own computational procedures to solve a new problem.

For Experiments 18A and 18B, if your software will perform both AM1 (or a similar MNDO procedure) and calculations that include the effect of aqueous solvation (such as AM1-SM2), it may be instructive to have the students work in pairs. One student can perform gas-phase calculations, and the other can perform the same calculations, including the solvent effect. They can then compare results in their reports.

## 18A E X P E R I M E N T   1 8 A

Heats of Formation: Isomerism, Tautomerism, and Regioselectivity

Part A. Isomerism

The stability of isomers may be directly compared by examining their heats of formation. In separate calculations, build models of *cis*-2-butene, *trans*-2-butene, and 1-butene. Submit each of these to AM1 calculation of the energy (heat of formation). Use the geometry optimization option in each case to find the best possible energy for each isomer. What do your results suggest? Do they agree with the experimental data given in Experiment 17D?

Part B. Acetone and its Enol

In this exercise, we will compare the energies of a pair of tautomers using the heats of formation calculated by the semiempirical AM1 method. These two tautomers can be directly compared because they have the same molecular formula: C_3H_6O. Most organic textbooks discuss the relative stability of ketones and their tautomeric enol forms. For acetone, there are two tautomers in equilibrium:
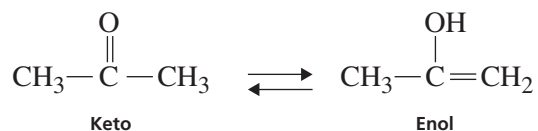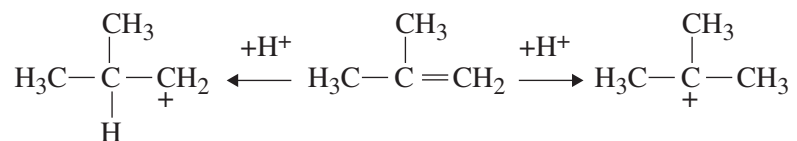
In separate calculations, build models of both acetone and its enol. Submit each model to AM1 calculation of the energy (heat of formation). Use the geometry optimization option in each case to find the best possible energy for each tautomer.

Experimental results indicate that there is very little enol (<0.0002%) in equilibrium with acetone. Do your calculations suggest a reason?
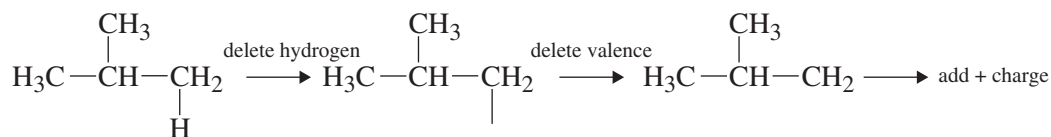
Part C. Regioselectivity

Ionic addition reactions of alkenes are quite regioselective. For instance, adding concentrated HCl to 2-methylpropene produces largely 2-chloro-2-methylpropane and a much smaller amount of 1-chloro-2-methylpropane. This can be explained by examining the energies of the two carbocation intermediates that can be formed by adding a proton in the first step of the reaction:

$$\underset{\underset{H}{|}}{\overset{\overset{CH_3}{|}}{H_3C-\underset{+}{C}-CH_2}} \xleftarrow{+H^+} \overset{\overset{CH_3}{|}}{H_3C-C=CH_2} \xrightarrow{+H^+} \overset{\overset{CH_3}{|}}{H_3C-\underset{+}{C}-CH_3}$$

This first step (adding a proton) is the rate-determining step of the reaction, and it is expected that the activation energies for forming these two intermediates will reflect their relative energies. That is, the activation energy leading to the lower-energy intermediate will be lower than the activation energy leading to the intermediate that has higher energy. Because of this energy difference, the reaction will predominantly follow the pathway that passes through the lower-energy intermediate. Because the two carbocations are isomers and because both are formed from the same starting material, a direct comparison of their energies (heats of formation) will determine the main course of the reaction.

In separate calculations, build models of the two carbocations and submit them to AM1 calculations of their energies. Use a geometry optimization. When you build the models, most programs will require you to build the skeleton of the hydrocarbon that is closest in structure to the carbocation and then to delete the required hydrogen *and its free valence.*
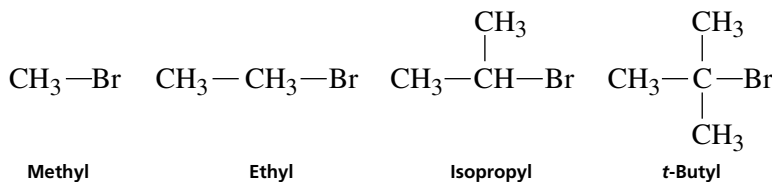
$$\underset{\underset{H}{|}}{\overset{\overset{CH_3}{|}}{H_3C-CH-CH_2}} \xrightarrow{\text{delete hydrogen}} \underset{|}{\overset{\overset{CH_3}{|}}{H_3C-CH-CH_2}} \xrightarrow{\text{delete valence}} \overset{\overset{CH_3}{|}}{H_3C-CH-CH_2} \longrightarrow \text{add + charge}$$

Remember also to assign a positive charge to the molecule before submitting it to calculation. This is usually done in the menus where you select the type of calculation. Compare your results for the two calculations. Which carbocation will lead to the major product? Do your results agree with the prediction made by Markovnikoff's Rule?

18B   EXPERIMENT 18B

Heats of Reaction: S_N1 *Reaction Rates*

In this experiment, we will attempt to determine the relative rates of selected substrates in the S_N1 reaction. The effect of the degree of substitution will be examined for the following compounds:

$$CH_3{-}Br \qquad CH_3{-}CH_3{-}Br \qquad CH_3{-}\overset{\overset{\textstyle CH_3}{\textstyle |}}{\underset{}{C}H}{-}Br \qquad CH_3{-}\overset{\overset{\textstyle CH_3}{\textstyle |}}{\underset{\underset{\textstyle CH_3}{\textstyle |}}{C}}{-}Br$$

| **Methyl** | **Ethyl** | **Isopropyl** | ***t*-Butyl** |

Because the four carbocations are not isomers, we cannot compare their heats of formation directly. To determine the relative rates at which these compounds react, we must determine the *activation energy* required to form the carbocation intermediate in each case. Ionization is the rate-determining step, and we will assume that the activation energy for each ionization should be *similar in magnitude* (Hammond Postulate) to the calculated energy difference between the alkyl halide and the two ions that it forms.

$$R\text{-}Br \rightarrow R^+ + Br^- \qquad [1]$$

$$\Delta E_{activation} \cong \Delta H_f(\text{products}) - \Delta H_f(\text{reactants}) \qquad [2]$$

$$\Delta E_{activation} \cong \Delta H_f(R^+) + \Delta H_f(Br^-) - \Delta H_f(RBr) \qquad [3]$$

Because the energy of the bromide ion is a constant, it could be omitted from the calculation, but we will include it because it must be computed only once.

Part A. Ionization Energies

Using the AM1 semiempirical level of calculation, compute the energies (heats of formation) of each of the starting materials and record them. Next, compute the energies of each of the carbocations that would result from the ionization of each substrate—follow the instructions given in Part C of Experiment 18A—and record the results. Be sure to add the positive charge. Finally, compute the energy of the bromide ion, remembering to delete the free valence and add a negative charge. Once all the calculations have been performed, use equation 3 to calculate the energy required to form the carbocation in each case. What do you conclude about the relative rates of the four compounds?

Part B. Solvation Effects (Optional)

The calculations you performed in Part A did not take the effect of solvation of the ions into account. At your instructor's option (and if you have the correct software), you may be required to repeat your calculations using a computational method that includes stabilization of the ions by solvation. Will solvation increase or decrease the ionization energies? Which will be solvated more, the reactants or the products of the ionization step? What do you conclude from your results?

EXPERIMENT 18C

Density–Electrostatic Potential Maps: Acidities of Carboxylic Acids

In this experiment, we will compare the acidities of acetic, chloroacetic, and trichloroacetic acid. This experiment could be approached in the same fashion as the relative rates in Experiment 18B, using the ionization energies to determine the relative acidities.

$$RCOOH + H_2O \rightarrow RCOO^- + H_3O^+$$
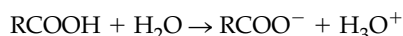
$$\Delta E = [\Delta H_f(RCOO^-) + \Delta H_f(H_3O^+)] - [\Delta H_f(RCOOH) + \Delta H_f(H_2O)]$$

In fact, the water and hydronium ion terms could be omitted, because they would be constant in each case.

Instead of calculating the ionization energies, we will use a more visual approach involving a property map. Set up an AM1 geometry optimization calculation for each of the acids. In addition, request that an electron-density surface be calculated with the electrostatic potential mapped onto this surface in color. In this procedure, the program plots the density surface and determines the electron density at each point by placing a test positive charge there and determining the coulomb interaction. The surface is colored using the colors of the spectrum—blue is used for positive areas (low electron density), and red is used for more negative areas (high electron density). This plot will show the polarization of the molecule.

When you have finished the calculations, display all three maps on the screen at the same time. To compare them, you must adjust them all to the same set of color values. This can be done by observing the maximum and minimum values for each map in the surface display menus. Once you have all six values (save them), determine which two numbers give you the maximum and minimum values. Return to the surface plot menu for each of the molecules and readjust the limits of the color values to the same maximum and minimum values. Now the plots will all be adjusted to identical color scales. What do you observe for the carboxyl protons of acetic acid, chloroacetic acid, and trichloroacetic acid? The three minimum values that you saved can be compared to determine the relative electron density at each proton.

EXPERIMENT 18D

Density–Electrostatic Potential Maps: Carbocations

Part A. Increasing Substitution

In this experiment, we will use a density map to determine how well a series of carbocations disperses the positive charge. According to theory, increasing the number of alkyl groups attached to the carbocation center helps to spread out the charge

(through hyperconjugation) and lowers the energy of the carbocation. We approached this problem from a computational (numerical) angle in Experiment 18B. Now we will prepare a visual solution to the problem.

Begin by performing an AM1 geometry optimization on methyl, ethyl, isopropyl, and *tert*-butyl carbocations. These carbocations are built as described in Part C of Experiment 18A. Don't forget to specify that each one has a positive charge. Also select a density surface for each one with the electrostatic potential mapped onto the surface.

When the calculations are completed, display all four density–electrostatic potential maps on the same screen and adjust the color values to the same range as described in Experiment 18C. What do you observe? Is the positive charge as localized in the *tert*-butyl carbocation as in its methyl counterpart?

Part B. Resonance

Repeat the computational experiment described in Part A, using density–electrostatic potential maps for the allyl and benzyl carbocations. These two experiments can be performed without displaying them both on the same screen. What do you observe about the charge distribution in these two carbocations?

| 18E | **E X P E R I M E N T   1 8 E** |

Density–LUMO Maps: Reactivities of Carbonyl Groups

In this experiment, we will investigate how frontier molecular orbital theory applies to the reactivity of a carbonyl compound. Consider the reaction of a nucleophile such as hydride or cyanide with a carbonyl compound.

According to frontier molecular orbital theory (see the section "Graphic Models and Visualization in the essay that precedes this experiment), the nucleophile, which is donating electrons, must place them in an empty orbital of the carbonyl. Logically, this empty orbital would be the LUMO—the **L**owest (energy) **U**noccupied **M**olecular **O**rbital.
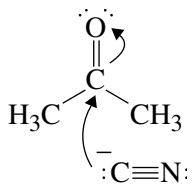

Make a model of acetone and submit it to an AM1 calculation with geometry optimization. Also select two surfaces to display, the LUMO and a mapping of the LUMO on a density surface.

When the calculations are finished, display both surfaces on the screen at the same time. Where is the biggest lobe of the LUMO, on carbon or on oxygen? Where does the nucleophile attack? The density–LUMO surface displays the same thing,

but with color coding. This plot shows a blue spot on the surface where the LUMO has its greatest density (largest lobe).

Next, continue this experiment by calculating the LUMO and the density–LUMO plots for the ketones 2-cyclohexenone and norbornanone.
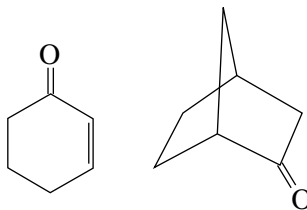
Where are the reactive sites in cyclohexenone? According to the literature, strong bases, such as Grignard reagents, attack the carbonyl, and weaker bases or better nucleophiles, such as amines, attack the beta carbon of the double bond, performing a conjugate addition. Can you explain this? Will a nucleophile attack norbornanone from the exo (top) or the endo (bottom) face of the molecule? See Experiment 31 for the answer.

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