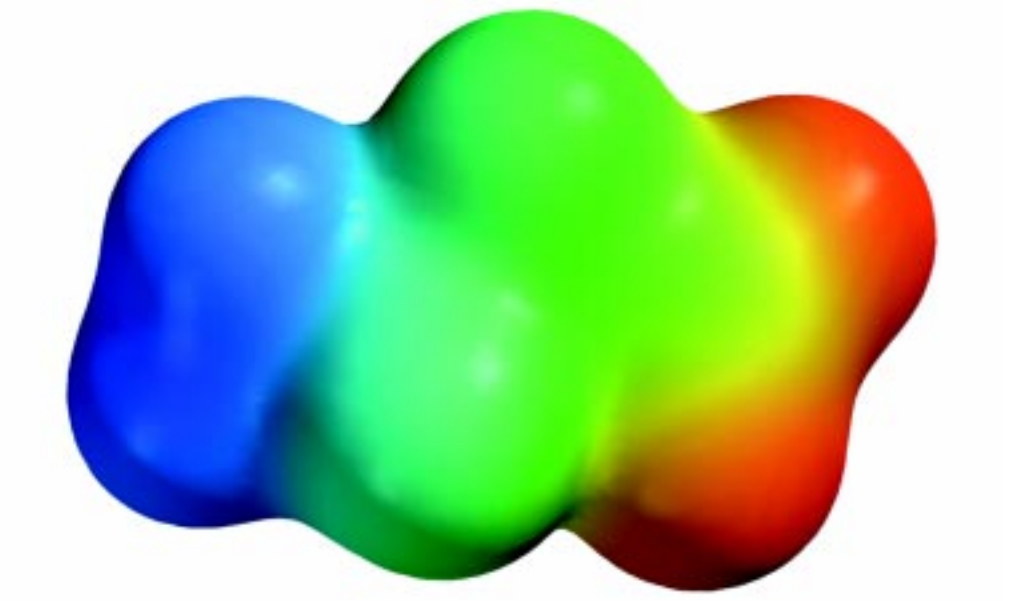
Molecular Modeling in Undergraduate Chemistry Education



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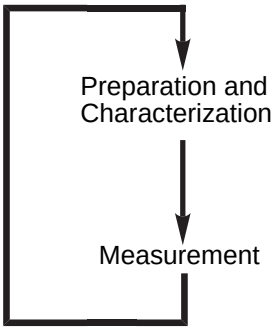
Introduction

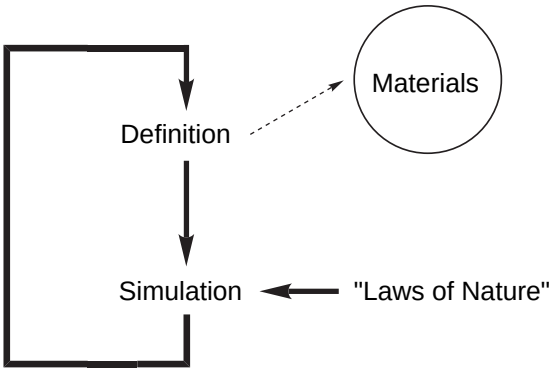
Chemistry . . .
by Experiment

Chemists make useful materials (pharmaceuticals, polymers, etc.). Typically, they do this by seeking to establish connections with molecular structure.



by Molecular Modeling

The goal is exactly the same as is the procedure. The difficult step (materials preparation) has been removed.



Why is molecular modeling important to the teaching of chemistry?

- Models are what we teach. Students need to learn to “think like a molecule”. To do this they need to “see” what a molecule sees and “feel” what a molecule feels. Models give us the best and most direct view of the molecular world.
- Modeling is the best tool for learning about chemical theory. VSEPR, Lewis structures, Hückel MO are all crude attempts to convert good theories into chemical predictions. Modern computational methods give a much more accurate assessment of theoretical predictions.
- Models are easy to use, inexpensive, safe. Modeling is a student-friendly educational too. It is not just for “experts”.

Should molecular modeling replace experimental chemistry?

Of course not!

The goals of chemistry are not changed by molecular modeling. On a practical level we want to learn how to make things (synthesis) and how to figure out what things are made of (analysis). On an intellectual level we want to understand the "rules" that describe chemical behavior.

Molecular modeling is, like NMR, a tool for achieving these goals. Since two of the goals - synthesis and analysis - are experimental, they cannot (and should not) be done away with. However, modeling does change the way we do syntheses and analysis. And, it speaks directly to the intellectual goals of chemistry.

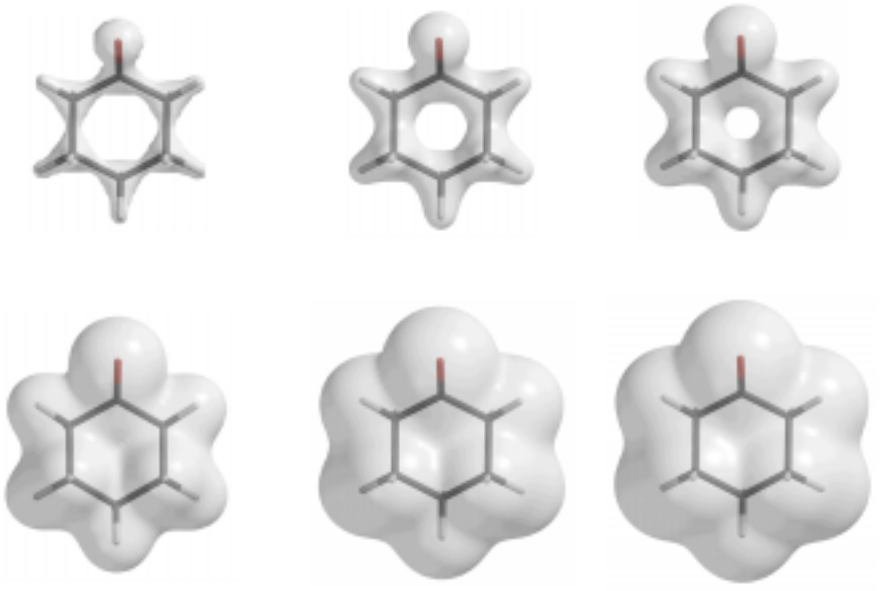
A modern chemical education still requires practical training in experimentation, but it requires training in modeling too.

Molecular Models

Electron Densities

Electron densities show the locations of electrons. Large values of the density will first reveal atomic positions (the X-ray diffraction experiment) and then chemical bonds, while smaller values will indicate overall molecular size.

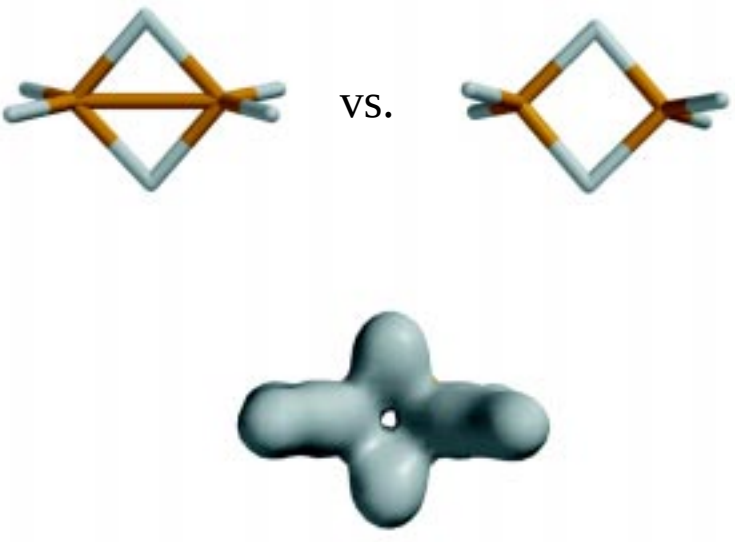
← increasing electron density



→ decreasing electron density

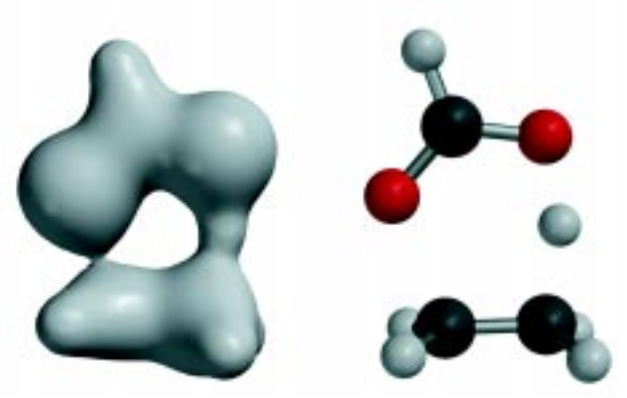
Electron Densities

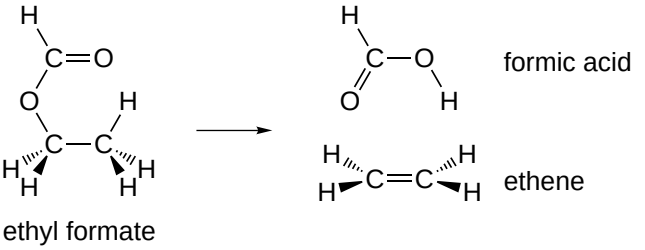
Unlike conventional structure models, electron densities assume no prior knowledge about bonding and, therefore, can be used to elucidate bonding. For example, the electron density for diborane shows no evidence for boron-boron bonding.



Electron Densities

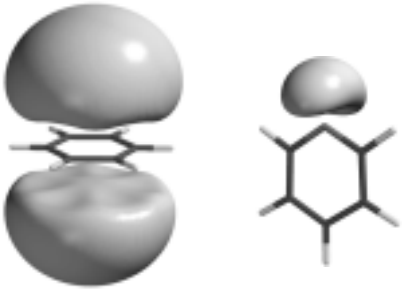
Electron densities allow description of the bonding in transition states where there can be no (direct) information from experiment. For example, the electron density for the transition state for pyrolysis of ethyl formate, leading to formic acid and ethene, shows that the CO bond has nearly fully cleaved and that the hydrogen is midway between carbon and oxygen.





Electrostatic Potentials

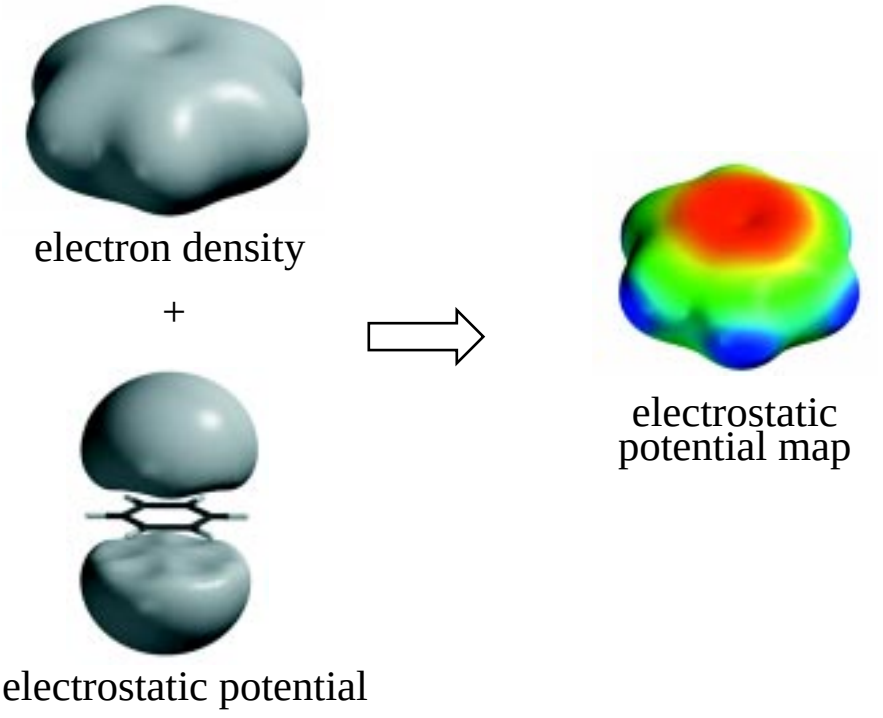
The electrostatic potential is the energy of interaction of a point positive charge (an electrophile) with the nuclei and electrons of a molecule. Negative electrostatic potentials indicate areas that are prone to electrophilic attack. For example, a negative electrostatic potential of benzene (left) shows that electrophilic attack should occur onto the π system, above and below the plane of the ring, while the corresponding electrostatic potential for pyridine (right) shows that an electrophile should attack the nitrogen in the σ plane, and not the π system of the ring.



The “electrophilic chemistry” of these two seemingly similar molecules is very different.

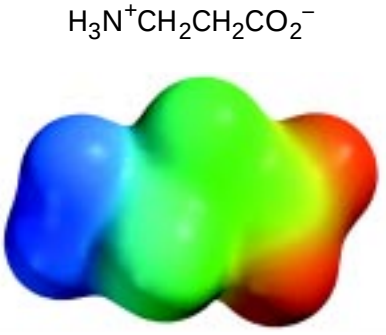
Electrostatic Potential Maps

A sufficiently small value of the electron density provides overall molecular size and shape (as given by a conventional space-filling or CPK model). The electrostatic potential can then be mapped onto the electron density by using color to represent the value of the potential. The resulting model simultaneously displays molecular size and shape and electrostatic potential value. For example, the electrostatic potential of benzene can be mapped onto the electron density. Colors toward “red” indicate negative values of the electrostatic potential, while colors toward “blue” indicate positive values of the potential.



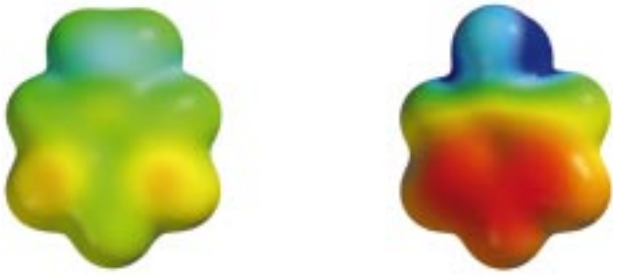
Electrostatic Potential Maps

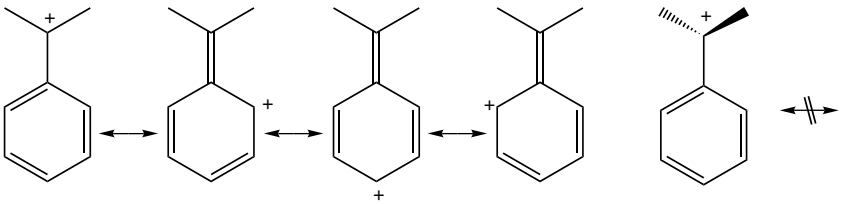
An electrostatic potential map conveys information about the distribution of charge in a molecule. For example, the electrostatic potential map of the zwitterionic form of β-alanine shows the negative carboxylate (red) and the positive ammonium (blue) termini separated by the neutral (green) carbon chain. This is consistent with the usual resonance structure.



Electrostatic Potential Maps

An electrostatic potential map also gives information about delocalization of charge. For example, the electrostatic potential map for perpendicular benzyl cation (right) shows that the postive charge (blue) is localized on the benzylic carbon, while the charge in the planar cation (left) is fully delocalized. This agrees with conventional resonance arguments.

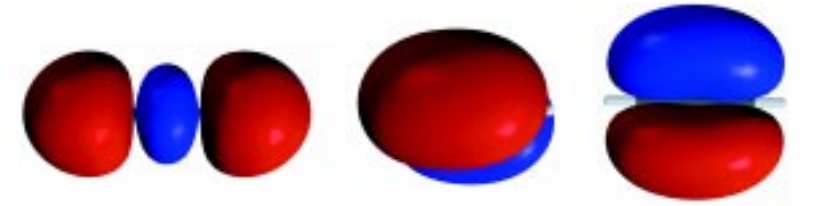




Molecular Orbitals

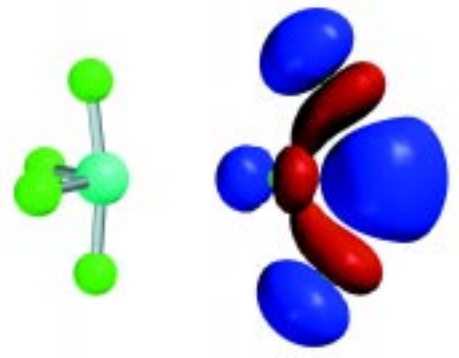
Molecular orbitals, solutions of the approximate quantum mechanical equations of electron motion, are made up of sums and differences of atomic solutions (atomic orbitals), just like molecules are made up of combinations of atoms.

Molecular orbitals for very simple molecules may often be interpreted in terms of familiar chemical bonds, for example, in acetylene,



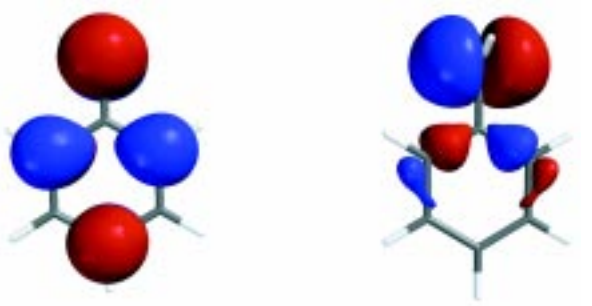
σ π π

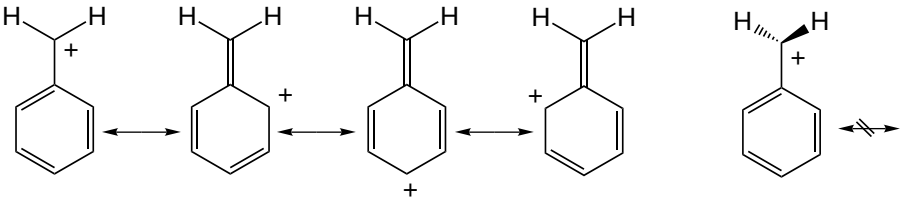
or of nonbonded lone pairs, for example, in sulfur tetrafluoride.



Molecular Orbitals

Unoccupied molecular orbitals may also provide useful information. For example, the lowest-unoccupied molecular orbital (LUMO) in planar benzyl cation (left) indicates that the positive charge is delocalized away from the benzylic carbon onto the *ortho* and *para* ring positions. The LUMO in perpendicular benzyl cation (right) resides almost entirely on the benzylic carbon. This agrees with conventional resonance arguments.





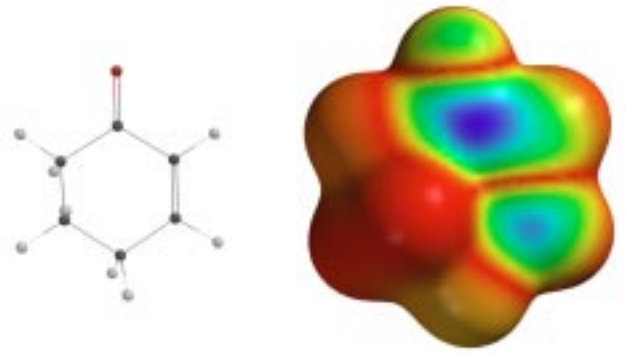
Molecular Orbitals

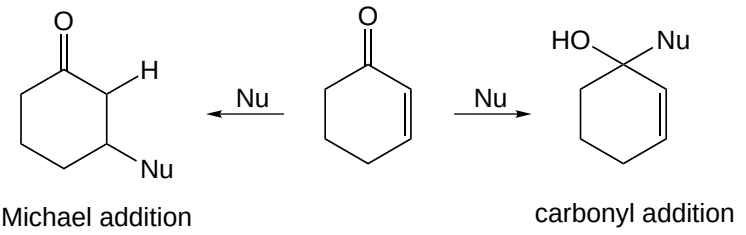
Why should molecular orbital descriptions be used instead of conventional Lewis structures?

1. Molecular orbitals descriptions are often more compact than Lewis structures.
2. Molecular orbital descriptions offer quantitative information about molecular charge distributions. Lewis descriptions are strictly qualitative.
3. Molecular orbital descriptions are more generally applicable than Lewis descriptions.

Molecular Orbital Maps

Molecular orbitals may also be mapped onto electron density surfaces. For example, a map of the lowest-unoccupied molecular orbital (LUMO) of cyclohexenone, where the “blue spots” indicate maximum values of the LUMO, reveals likely sites for nucleophilic attack, and anticipates both the “carbonyl chemistry” and “Michael chemistry” known for enones.



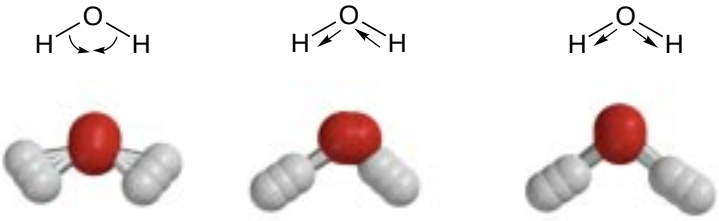


Michael addition

carbonyl addition

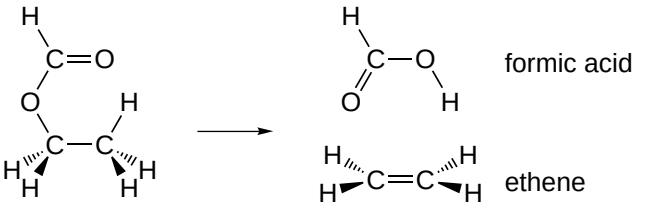
Models that Move

Models need not be limited to static pictures. “Movies” can be used to depict vibrations in stable molecules, for example, in water.

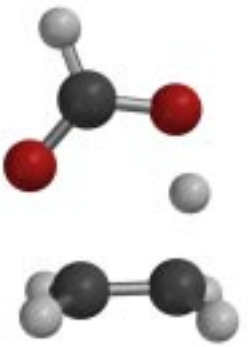


Models that Move

Motion along the reaction coordinate provides details about mechanism. For example, motion along the reaction coordinate for the pyrolysis of ethyl formate shows the simultaneous transfer of the hydrogen atom to the carbonyl oxygen along with carbon-oxygen bond cleavage.



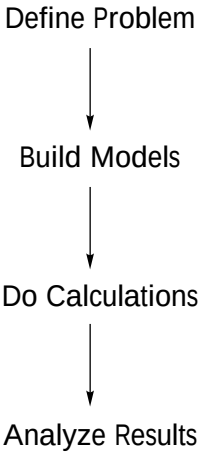
ethyl formate



Molecular Modeling Workbook

Molecular Modeling in the Curriculum

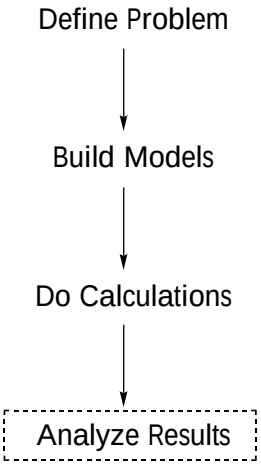
"Doing chemistry" with molecular modeling is a multi-step progress . . . not so different from doing experimental chemistry.



Given a "full" curriculum, the question that needs to be answered is how much of this process to turn over to students.

The Workbook Approach

This leaves only the analysis of modeling results (and learning the chemistry that follows from these results) to the student.



The advantage of this approach is that it requires the fewest resources (hardware and software support, student training), while guaranteeing high quality models and maximum student-model contact.

The Molecular Modeling Workbook for ORGANIC CHEMISTRY

A collection of over 200 problems arranged by chapters that parallel the contents of your organic chemistry textbook.

The Molecular Modeling Workbook for ORGANIC CHEMISTRY

Problems in each chapter address essential topics.

Chapter 11 Enolates as Nucleophiles

The Molecular Modeling Workbook for ORGANIC CHEMISTRY

Each problem uses one or more models, and students are required to look at and query these models to solve the problem. The models are contained on a CD-ROM that comes with the workbook, and can be viewed on a Mac or PC.

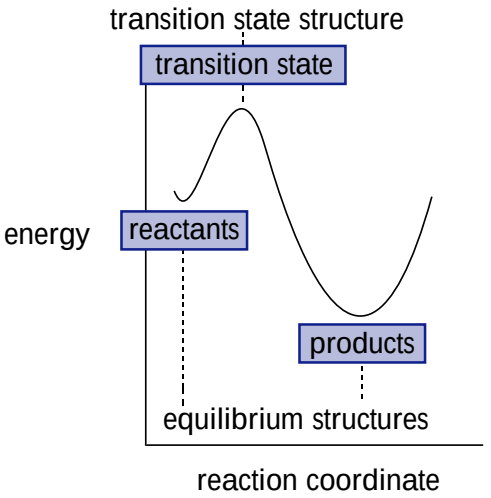
All models provide many types of information obtained from molecular orbital calculations, including structure, energy and atomic charges. Many models also provide molecular orbitals, electron density surfaces and electrostatic potential maps among other graphical displays.

Models include many types of molecular species, including conformers, reactive intermediates, transition states and weak complexes. A number of models involve sequences that can be animated.

Conceptual Background

Potential Energy Surfaces

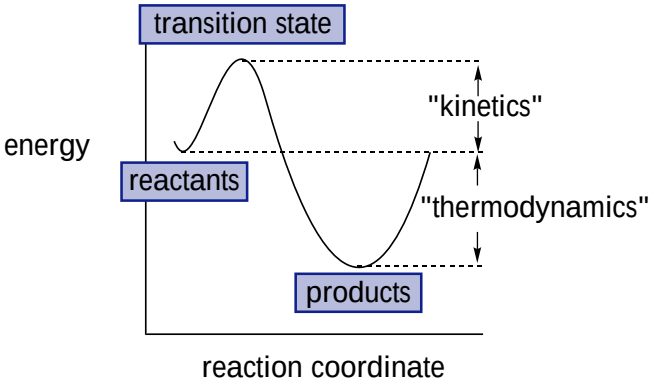
A potential energy surface is a plot of energy vs. reaction coordinate. It connects reactants to products via a transition state.



Energy minima correspond to **equilibrium structures**.

The energy maximum corresponds to a **transition state structure**.

Potential Energy Surfaces

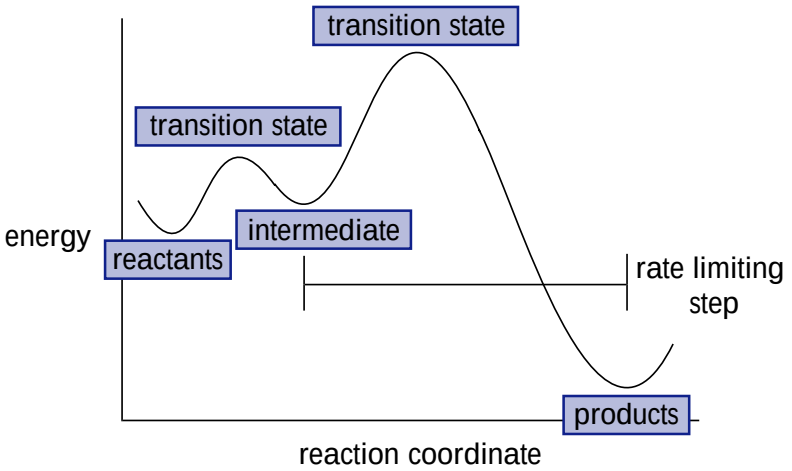


The relative energies of equilibrium structures give the relative stabilities of the reactant and product (the **thermodynamics** of reaction).

The energy of the transition state relative to the equilibrium structures provides information about the relative difficulties going on between them (the **kinetics** of reaction).

Potential Energy Surfaces

A complete reaction pathway may comprise several steps and involve several different transition states and high-energy **reactive intermediates**.



Such a diagram describes the **mechanism** of a reaction, the **rate-limiting step** for which proceeds via the highest-energy transition state.

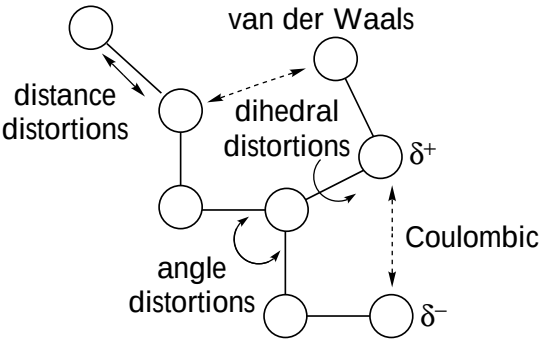
Potential Energy Surfaces

Molecular modeling is primarily a tool for calculating the energy of a given molecular structure. Thus, the first step in designing a molecular modeling investigation is to define the problem as one involving a structure-energy relationship.

There are two conceptually different ways of thinking about energy.

Molecular Mechanics
A "Chemist's" Model

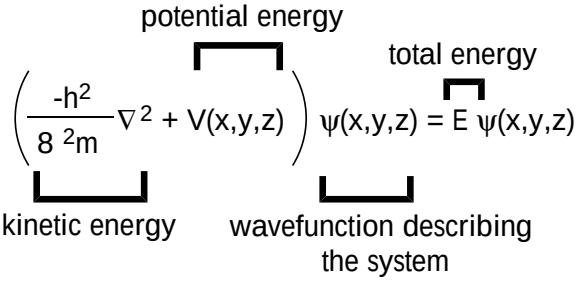
Molecular mechanics describes the energy of a molecule in terms of a simple function which accounts for distortion from "ideal" bond distances and angles, as well as and for nonbonded van der Waals and Coulombic interactions.



$$E = \underbrace{\sum_{\text{bonds}} \text{bond stretching} + \sum_{\text{angles}} \text{angle bending} + \sum_{\text{dihedral angles}} \text{dihedral twisting}}_{\text{energy of distortion from idealized values}} + \underbrace{\sum_{\substack{\text{pairs of} \\ \text{atoms}}} \text{van der Waals} + \sum_{\substack{\text{pairs of} \\ \text{atoms}}} \text{Coulombic}}_{\text{energy of nonbonded interactions}}$$

Quantum Mechanics
A "Physicist's" Model

Quantum mechanics describes the energy of a molecule in terms of interactions among nuclei and electrons as given by the Schrödinger equation. The solutions ("wavefunctions") for the hydrogen atom are the familiar s, p, d . . . atomic orbitals.



The square of the wavefunction gives the probability of finding an electron. This is the electron density, as obtained from an X-ray diffraction experiment.

Quantum Mechanics

While the Schrödinger equation is easy to write down for many-electron atoms and molecules, it is impossible to solve. Approximations are needed.

Schrödinger Equation $H\Psi = E\Psi$

assume that nuclei don't move → "Born-Oppenheimer Approximation"

separate electron motions → "Hartree-Fock Approximation"

get electron motion in molecules by combining electron motion in atoms → "LCAO Approximation"

Practical Molecular Orbital Methods

Molecular Modeling in Lecture

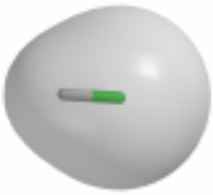
Molecular Modeling in Lecture

Molecular models can be introduced into almost any chemistry lecture. They not only liven the discussion with “pretty pictures”, but more importantly encourage students to see and think for themselves. They free teachers from the “limits of the chalkboard” and allow examination and discussion of “real” molecules.

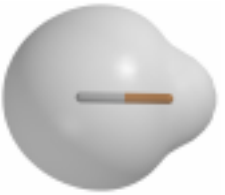
Visualizing Chemical Bonds

Are the different kinds of chemical bonds to which chemists refer (nonpolar covalent, polar covalent and ionic) fundamentally different? Look at electron densities.

H-H



H-F

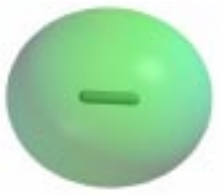


H-Li

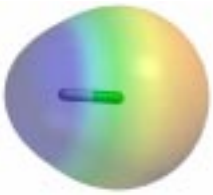
The size of the electron density surface indicates the size of the electron cloud. The H electron cloud is largest in HLi and smallest in HF. This is persuasive evidence that the atoms in these molecules do not “share” electrons equally.

Visualizing Chemical Bonds

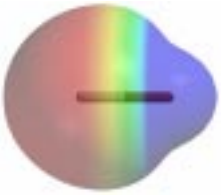
A clearer picture comes from electrostatic potential maps, where the color red demarks regions with excess negative charge and the color blue demarks regions with excess positive charge.



H-H



H-F

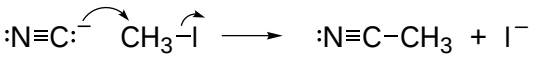


H-Li

Hydrogen fluoride and lithium hydride look very similar, except that the hydrogen in the former is positively charged while the hydrogen in the latter is negatively charged.

The S_N2 Reaction

Molecular modeling provides insight into the familiar S_N2 reaction.

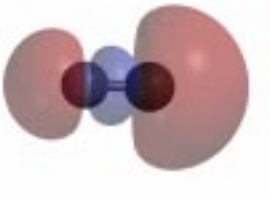


An animation of the reaction clearly shows the inversion at carbon, but there are other important questions.

The S_N2 Reaction

Why does cyanide attack from carbon and not nitrogen? Doesn't this contradict the fact that nitrogen is more electronegative than carbon?

Look at the highest-occupied molecular orbital of cyanide. This is where the "most available" electrons reside.

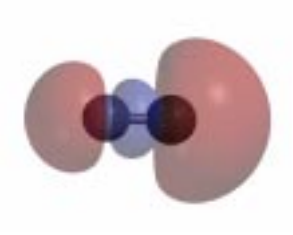
N≡C 

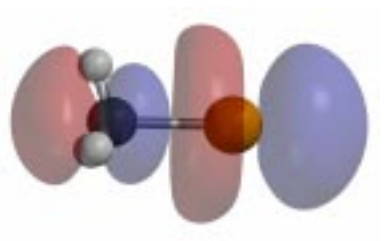
It is more heavily concentrated on carbon, meaning that cyanide is a carbon nucleophile.

The S_N2 Reaction

Why does iodide leave following attack by cyanide?

Look at the lowest-unoccupied molecular orbital of methyl iodide. This is where the electrons will go.



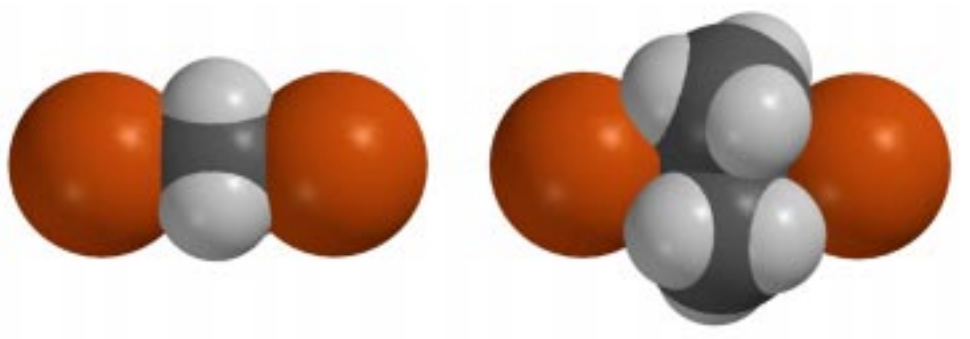


It is antibonding between carbon and iodine meaning that the CI bond will cleave during attack.

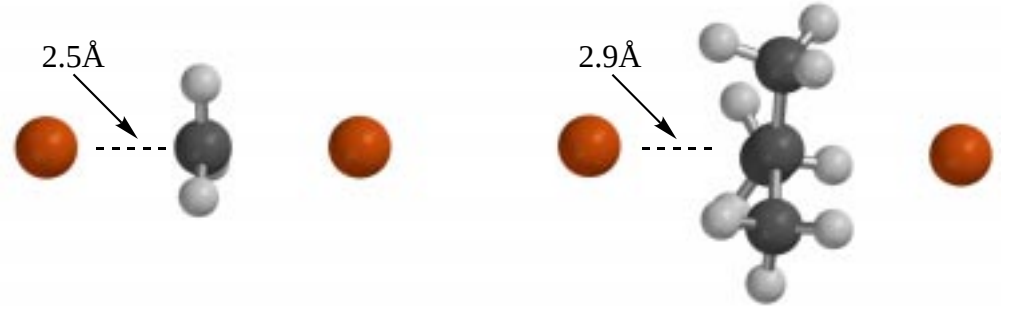
The S_N2 Reaction

We tell students that bromide reacts faster with methyl bromide than with *tert*-butyl bromide because of steric effects, that is, increased crowding of the transition state.

This is not true. Space-filling models of the two transition states show both to be uncrowded.

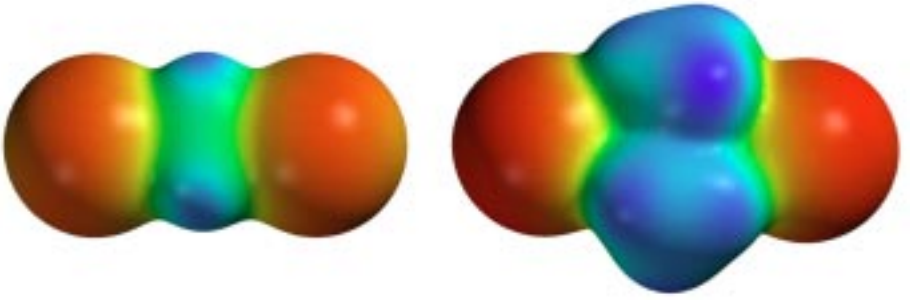


What is true is that the carbon-bromine distance in the transition state in the *tert*-butyl system is larger than that in the methyl system.



The S_N2 Reaction

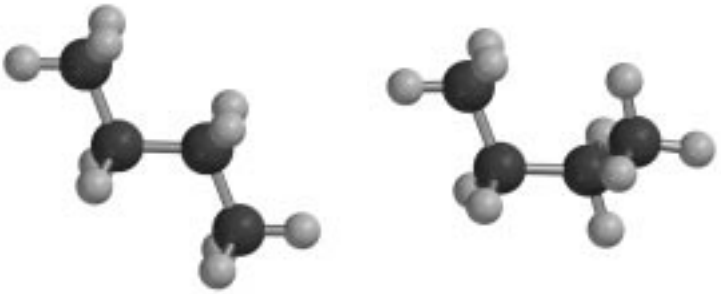
This leads to an increase in charge separation as clearly shown by electrostatic potential maps for the two transition states.



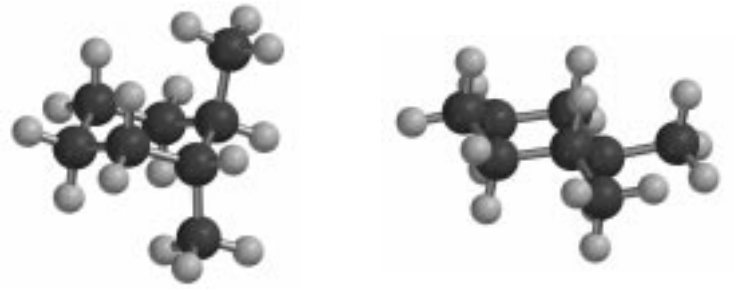
This is the cause of the decrease in reaction rate.

Flexible Molecules

Interconversion of *anti* and *gauche* forms of *n*-butane is readily visualized “on a blackboard” using conventional structure models.

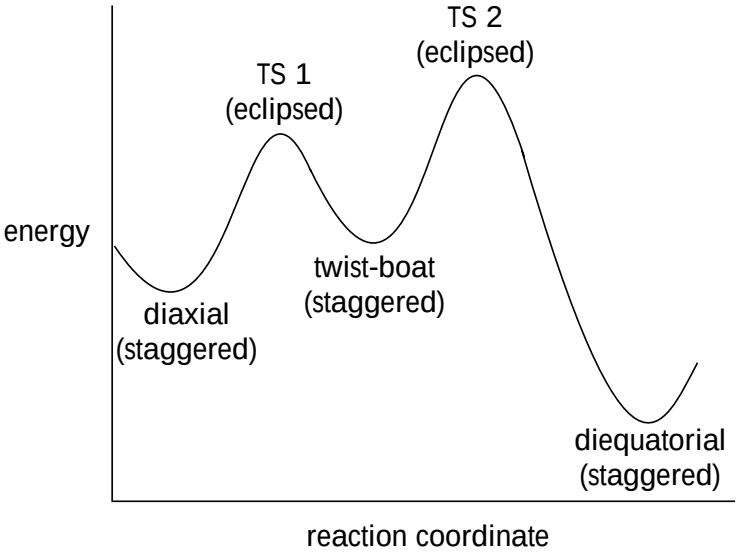


Trans-1,2-dimethylcyclohexane undergoes the same type of conformational change as *n*-butane. The difficulty for the lecturer is that this change is not easily portrayed “on a blackboard”. This obstacle is readily overcome with molecular models.



diaxial diequatorial

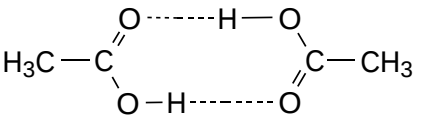
Flexible Molecules



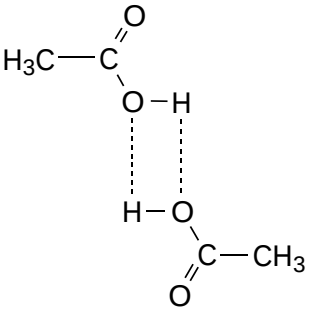
An animation shows that the conformational change in *trans*-dimethylcyclohexane is not so different from that in *n*-butane. There are two distinct steps in the ring flip mechanism, but each involves rotation about carbon-carbon bonds. The three minima all correspond to structures in which bonds are staggered. The two transition states involve eclipsing interactions.

Intermolecular Interactions

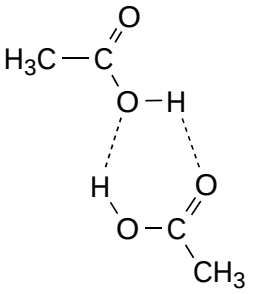
Acetic acid is known to form a stable hydrogen-bonded dimer. What is it's structure?



A



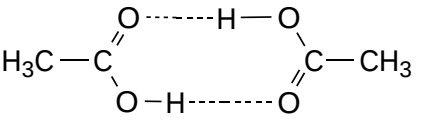
B



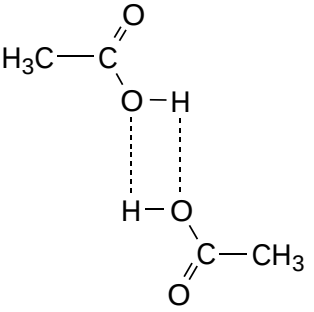
C

Instead of giving students the right structure, give them the tools to find it for themselves.

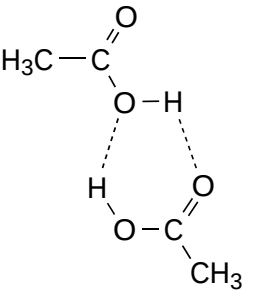
Intermolecular Interactions



A



B



C

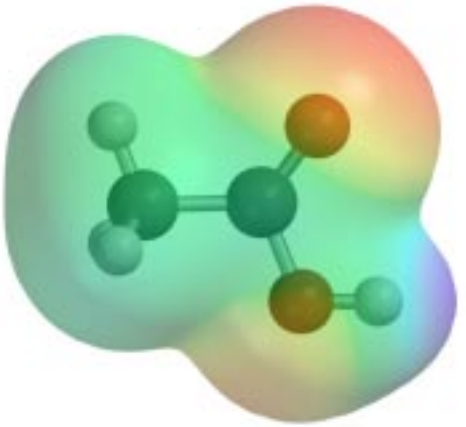
Energy Tool

Energies follow the order A<C<B (A is best). The alert student will be surprised. This is because six-membered rings (as in C) are common while eight-membered rings (as in A) are not.

Intermolecular Interactions

Electrostatic Potential Tool

Look at an electrostatic potential map for acetic acid.



Which atom is positively charged and most likely to act as a hydrogen-bond donor?

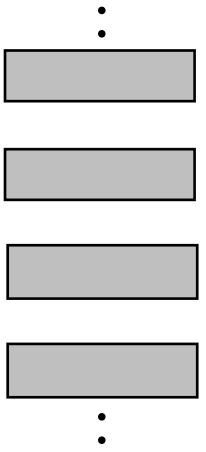
Which atom is most negatively charged and most likely to act as a hydrogen-bond acceptor?

The model gives the answers and allows assignment of the proper dimer structure.

Intermolecular Interactions

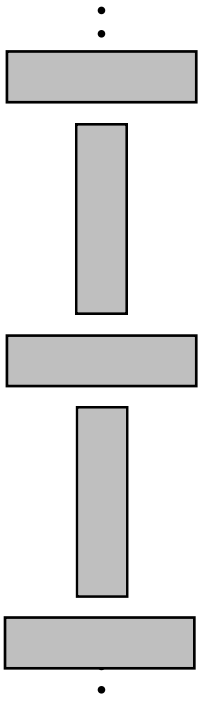
Apply these same “tools” to a related question where you don’t know the answer (or where you “know” the wrong answer).

What is the crystal structure of benzene?



stacked

or

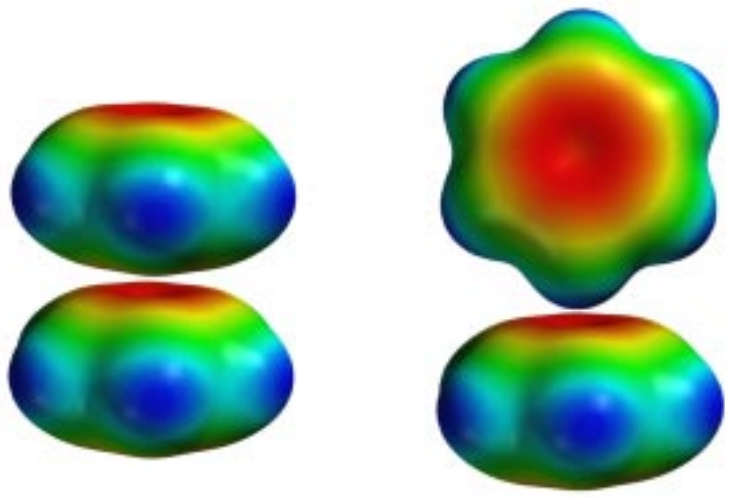


perpendicular

Intermolecular Interactions

The **energy tool** shows that the “stacked” benzene dimer dissociates into the two benzenes, while the perpendicular dimer sticks together. It does not show why.

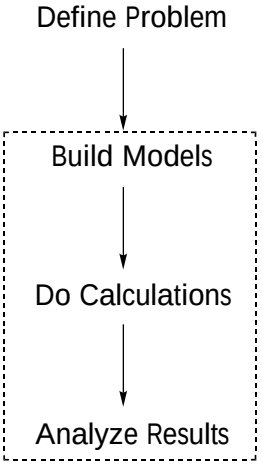
The **electrostatic potential tool** clearly shows that stacking the rings results in unfavorable electrostatic interactions, while a perpendicular arrangement of benzene rings results in favorable electrostatic interactions between π and σ systems.



Molecular Modeling in the Laboratory

The Laboratory Approach

Teachers who want their students to "get their hands dirty" will find that students can learn much from "hands-on" modeling. Here, most of the steps involved in actually "doing chemistry" are left up to the student.



The "laboratory approach" offers students and teachers much greater flexibility than the "workbook approach". Because it puts students directly in contact with actual molecular modeling software, it teaches them that calculations, like experiments, are not instantaneous, and that good "experimental design" is important.

The Laboratory Book of Computational Organic Chemistry

A collection of over 80 experiments covering topics relevant to both elementary and advanced organic chemistry courses. The experiments require access to a modeling program, such as MacSPARTAN or PC SPARTAN.

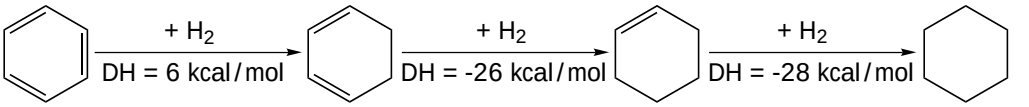
Is Thiophene Aromatic?

Objective:

To quantify the “extra stability” of thiophene due to aromaticity.

Background:

Hydrogenation of benzene to 1,3-cyclohexadiene is slightly endothermic, whereas the corresponding reactions taking 1,3-cyclohexadiene to cyclohexene and then to cyclohexane, are both significantly exothermic.

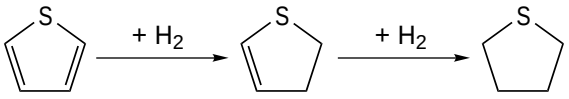


The first hydrogen addition “trades” an H-H bond and a C-C π bond for two C-H bonds, but in so doing destroys the aromaticity of benzene, whereas the second hydrogen addition “trades” the same bonds but does not result in any loss of aromaticity. Therefore, the difference in the heats of hydrogenation of benzene and 1,3-cyclohexadiene (or cyclohexene) corresponds to the aromatic stabilization of benzene. This difference is approximately 33 kcal/mol.

Is Thiophene Aromatic?

Procedure:

Calculate the energetics of hydrogen addition to thiophene and to the intermediate dihydrothiophene.



The difference provides a measure of the aromaticity of thiophene.

Questions:

Is thiophene as aromatic as benzene? Half as aromatic?

Gas and Aqueous-Phase Basicities of Methylamines

Objective:

To quantify changes in nitrogen base strength from the gas phase into water and to provide rationalization for these changes.

Background:

Experimentally, increasing methyl substitution greatly increases amine basicity in the gas phase, but leads to different results in water.

Energies of: $BH^+ + NH_3 \rightarrow B + NH_4^+$, kcal/mol

B	ΔH_{rxn}(gas)	$\Delta H_{rxn}(H_2O)$
CH_3NH_2	9	2
$(CH_3)_2NH$	16	2
$(CH_3)_3N$	19	1

Gas and Aqueous-Phase Basicities of Methylamines

Procedure:

Calculate gas-phase energetics of proton transfer reactions for B=methylamine, dimethylamine and trimethylamine. Calculate solvation energies for all neutral and ionic species, and estimate energies for aqueous phase proton transfer reactions.

Examine electrostatic potential maps. Specifically, examine changes in charge distributions and accessibility to solvent in both neutral and ionic species.

Questions:

Where are solvent effects greater - on the neutral molecules or on the ions? What is the cause for reversal in basicity?

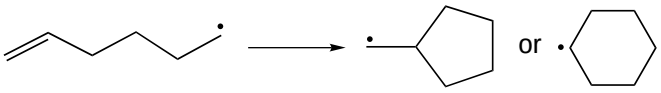
Thermodynamic vs. Kinetic Control of Intramolecular Radical Addition to Multiple Bonds

Objective:

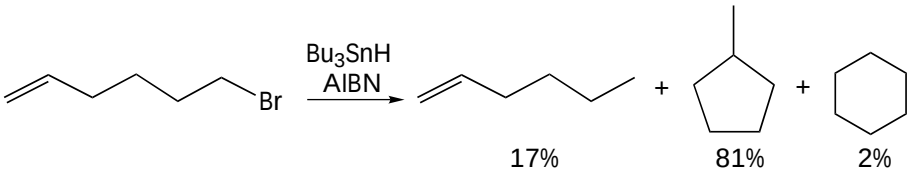
To assign thermodynamic or kinetic origin to the products in an intramolecular radical addition reaction.

Background:

Cyclization of hex-5-enyl radical can either yield cyclopentylmethyl radical or cyclohexyl radical.



While the latter might be expected (it should be less strained, and 2° radicals are generally more stable than 1° radicals), the opposite is normally observed, e.g.,



Thermodynamic vs. Kinetic Control of Intramolecular Radical Addition to Multiple Bonds

Procedure:

Calculate the energies of both cyclopentylmethyl and cyclohexyl radicals. Assume that the reaction is thermodynamically controlled, and use the Boltzmann equation (with T = 298K) to calculate the product distribution.

Locate transition states for cyclization reactions leading to cyclopentylmethyl and cyclohexyl radicals. Assume that the reaction is kinetically controlled, and use the transition state energies together with the Eyring equation to calculate the product distribution.

Questions:

Is the cyclization reaction under thermodynamic or kinetic control or is it not possible to tell?

Molecular Recognition. Hydrogen-Bonded Base Pairs

Objective:

To model hydrogen-bonding between DNA base pairs in terms of charge-charge interactions. To identify nucleotide mimics.

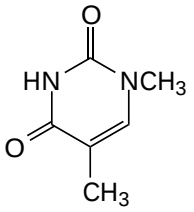
Background:

The genetic code is “read” through the selective formation of hydrogen-bonded complexes, or Watson-Crick base pairs, of adenine (A) and thymine (T) (forms A-T base pair), and guanine (G) and cytosine (C) (forms G-C base pair). The importance of this hydrogen bond-based code lies in the fact that virtually all aspects of cell function are regulated by proper base pair formation, and many diseases can be traced to “reading” errors, i.e., the formation of incorrect base pairs.

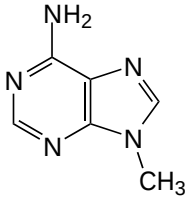
Molecular Recognition. Hydrogen-Bonded Base Pairs

Procedure:

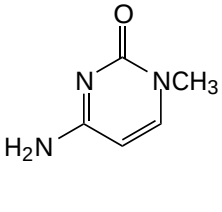
Calculate geometries, energies and electrostatic potential maps for **MeT**, **MeA**, **MeC** and **MeG**.



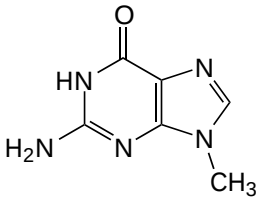
1-methylthymine
(**MeT**)



9-methyladenine
(**MeA**)



1-methylcytosine
(**MeC**)



9-methylguanine
(**MeG**)

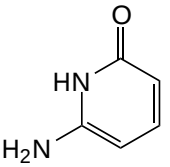
Identify electron-rich and electron-poor sites that would be suitable for hydrogen bonding (consider only sites in the plane of the molecules). Draw all possible base pairs that involve two or three hydrogen bonds (do not limit yourself to Watson-Crick pairs).

Choose one system (your best guess for the most favorable base pair involving two hydrogen bonds or most favorable base pair involving three hydrogen bonds). Obtain the geometry and energy of this base pair and calculate the total hydrogen bond energy.

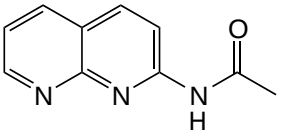
Molecular Recognition. Hydrogen-Bonded Base Pairs

Procedure:

Calculate the geometries, energies and electrostatic potential maps for **AP** and **NA**, heterocyclic molecules that mimic the hydrogen bonding properties of DNA nucleotides.



6-amino-2-pyridone
(**AP**)



N-naphtharidinyl acetamide
(**NA**)

Identify electron-rich and electron-poor sites for each to see if either would be a suitable partner for one of the bases in your chosen base pair. Obtain the geometry and energy of the resulting hydrogen-bonded adduct and calculate the total hydrogen bond energy.

Questions:

Does it mimic bind as tightly as the “natural” base?

Proper Role of Molecular Modeling

Focus on Chemistry

Modeling is a tool for doing chemistry. Molecular modeling is best treated in the same way as NMR - as a tool, not a goal. A good model has the same value as a good NMR spectrum. Molecular modeling allows you to “do” and teach chemistry better by providing better tools for investigating, interpreting, explaining, and discovering new phenomena.

Don’t be Afraid

Modeling is accessible. Anyone can build a useful model.

Modeling is “hands on”. Molecular modeling, like experimental chemistry is a “laboratory” science, and must be learned by “doing” and not just reading.

Modeling does not need to be intimidating. The underpinnings of molecular modeling (quantum mechanics) are certainly intimidating to many chemists, but so too are the underpinnings of NMR. Using molecular modeling should be no more intimidating than obtaining an NMR spectrum.

Modeling is not difficult to learn and do. Molecular modeling is easy to do given currently available software (probably easier than taking an NMR spectrum). The difficulty lies in asking the right questions of the models and properly interpreting what comes out of them.

Stick with Standard Models

Standard models are a must. While there is only one experimental “result”, different models will yield different results. It is necessary to define a small number of “standard models” and to fully document the performance of each. These should range from very simple, which may not be very accurate but are applicable to very large systems, to very sophisticated, which are accurate but may be applicable only to very simple systems.

While the models are not perfect, they can be of great value in learning and researching chemistry. They will continue to improve and in time it will be possible to model important chemical quantities as accurately as they can be measured.