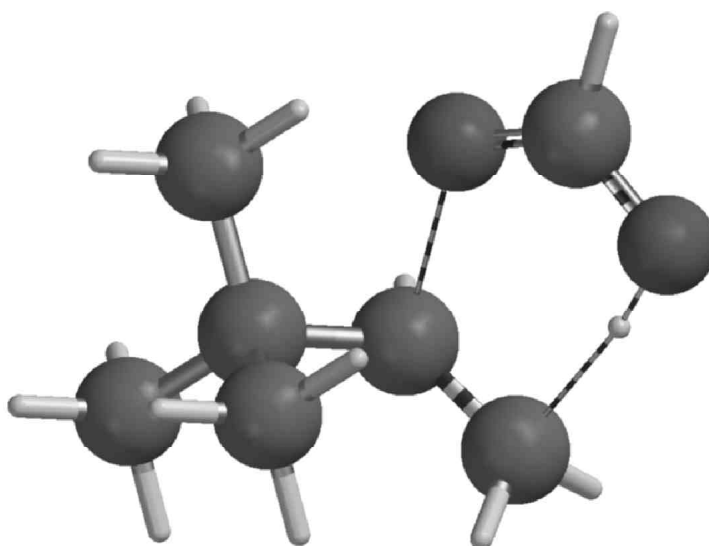


Molecular Modeling in Teaching Undergraduate Chemistry



Warren J. Hehre
Jurgen Schnitker

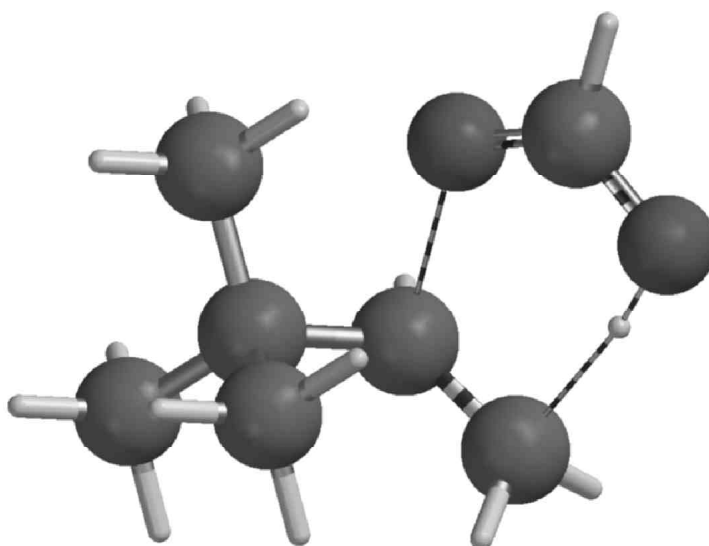
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Preface

Over a little more than a decade, molecular modeling has evolved from a specialized research tool of limited availability and (presumed) limited utility, to an important, if not essential, means with which to explore chemistry. The obvious catalyst has been an explosion in computer technology. Today's desktop and laptop computers are as powerful as yesterday's supercomputers. Computers have become common fixtures in our lives, and are well on their way to becoming ubiquitous appliances. Also paramount has been the continued development of more and more accurate models with which to describe molecular structure and properties and chemical reactivity. Qualitative models are rapidly giving way to quantitative treatments. Finally, computer graphics has made modeling easy to learn and easy to do.

It is inevitable that molecular modeling takes its rightful place in the teaching of chemistry. It offers a natural companion to both traditional lecture/textbook and laboratory approaches. Modeling not only facilitates communication of both concepts and content (as do lectures and textbooks), but also allows discovery of "new chemistry" (as does a laboratory).

Because molecular models offer an incredibly rich source of visual and quantitative information, they can be used to great effect to enhance traditional lectures and classroom discussions. More important, students can use models in a number of different ways on their own computers to learn and explore chemistry.

These notes are abstracted from a one-day introductory course intended to build a case for molecular modeling as an integral and active part of the undergraduate chemistry curriculum. They illustrate how both faculty and students can make use of molecular modeling to understand and to explore chemistry.

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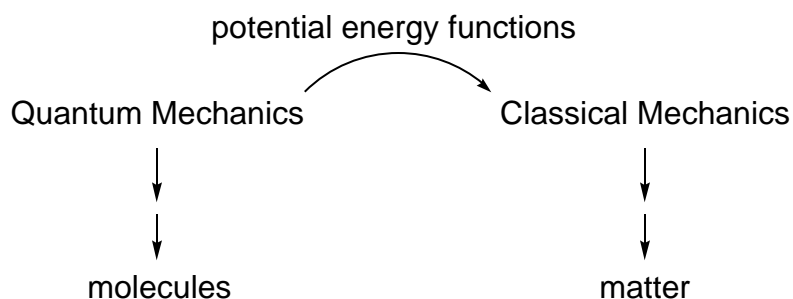
Introduction	1
Origins of Molecular Modeling	
Rationale for Molecular Modeling in Teaching Chemistry	
Quantum Mechanics	6
What Can Be Calculated	8
Equilibrium Geometry	
Molecular Mechanics	9
What Can Be Calculated (con't)	10
Conformation	
Transition-State Geometry and Reaction Pathway	
Reaction Energy	
Activation Energy	
Quantum Mechanics in Pictures	16
Electron Density	
Electrostatic Potential and Electrostatic Potential Map	
Intermolecular Interactions	
Molecular Dynamics	23
Role of Modeling	25
In Lecture	
Student Materials	
Problem Solving	
In Laboratory	
Take Home Messages	41
Spartan'02	42
Odyssey (Preliminary Description)	45

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Origins of Molecular Modeling



The quantum mechanical equations governing the interactions of nuclei and electrons may now be solved sufficiently accurately to permit quantitative descriptions of the properties of isolated molecules. Among the more important quantities are molecular geometries and conformations, and reaction and activation energies.

Calculated energies for pairs of molecules at different separations and relative orientations may be used to construct potential energy functions describing intermolecular interactions. These in turn may be used to solve the classical mechanical equations of motion for large collections of molecules as a function of time, a procedure which is commonly referred to as “molecular dynamics”. Time averages of structural and thermodynamic properties give rise to information about condensed-phase systems.

Structure of Xenon Compounds

Quantum mechanics is completely general. Any system . . . real or imaginary . . . may be explored with no reliance whatsoever on preconcieved ideas. For example, molecular orbital calculations on XeF_4 and XeF_6 show that the former adopts a square planar geometry and the latter a distorted octahedron, in line with what is known experimentally. Energy differences to alternative geometries are readily available.

(○)

Input to this calculation are the identities of the nuclei, the total number of electrons and a starting geometry.

Hydrogen Bonding in Liquid Water

Molecular dynamics is really the only way to explore and understand the way in which molecules interact and how those interactions may contribute to observed ("bulk") properties. For example, a simulation on a small sample of liquid water clearly reveals the extensive network of hydrogen bonds, and shows that hydrogen-bonding is not static but rather fluctuates in time.



Input to this simulation are the initial conditions (number of molecules, density and temperature) and a potential function describing the interaction between pairs of water molecules.

Why are Molecular Models Good Teaching Tools?

- Molecular models allow students to "think like a molecule". Students "see" what a molecule sees and "feel" what a molecule feels. Molecular models provide a window on the molecular world.
- Molecular models provide simple yet truthful presentations of what may be difficult concepts. They are not only able to account for what is known experimentally but, because they are grounded in a fundamentally correct picture, are able to act as experiments in uncovering and exploring new chemistry.
- On the practical side, molecular models are easy and "fun" to use, they are inexpensive and they are safe. Molecular models are student-friendly educational tools.

Molecular Models Aren't New . . .

In fact, we already use a variety of "crude" molecular models to teach chemistry . . . Lewis structures, VSEPR theory and Hückel theory to name a few. What is new and what is important is that molecular models can now be based on a picture which is fundamentally correct and which can now accurately describe molecular structure and properties, and which in the future will be able to accurately portray the properties of bulk matter.

The obvious objection is that "modern" molecular models require a computer . . . and a powerful one at that . . . whereas "conventional" models can easily be constructed with a pencil.

The computer is the pencil of this generation.

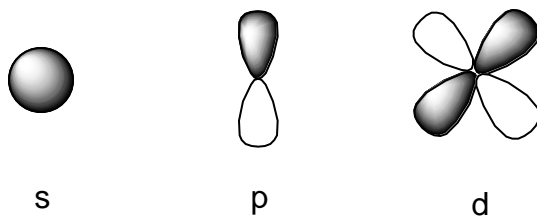
Quantum Mechanics . . .

Hydrogen Atom

Quantum mechanics took root in the 1920's with the formulation of the Schrödinger equation, which may be solved exactly for the hydrogen atom.

$$\left(\underbrace{\frac{-\hbar^2}{8m}}_{\text{kinetic}}^2 + \underbrace{V(x,y,z)}_{\text{potential}} \right) \underbrace{\psi(x,y,z)}_{\text{wavefunction}} = \underbrace{E}_{\text{energy}}(x,y,z)$$

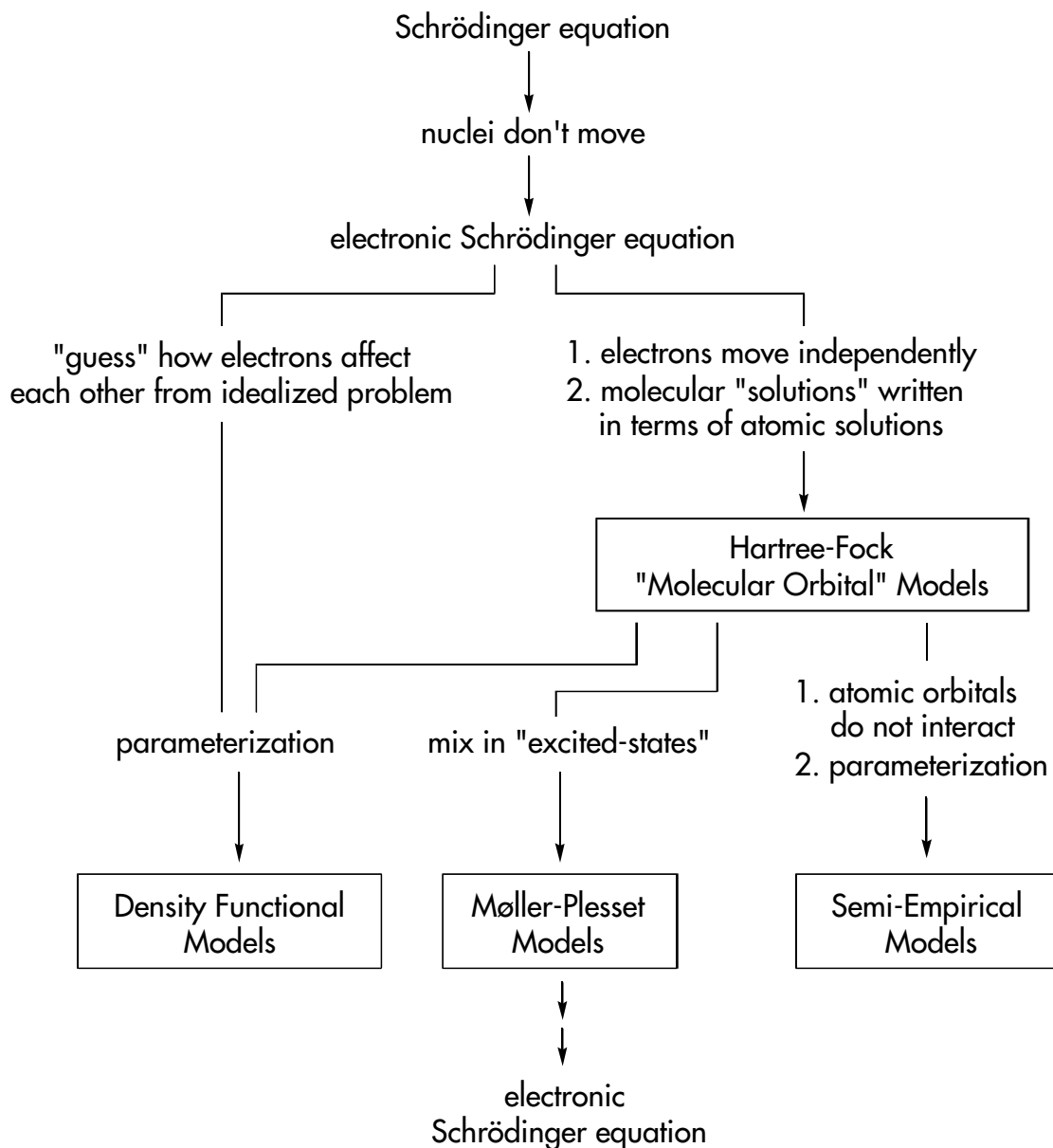
The solutions of the hydrogen atom are the familiar s, p, d . . . atomic orbitals.



Why do chemistry textbooks stop here (in the 1920's)?

The usual excuse is that, while the Schrödinger equation is easy to write down for any atom or molecule, it is impossible to solve. Approximations are needed, as are powerful digital computers. But the groundwork has been done and powerful computers are now widely available. It's time to stop making excuses!

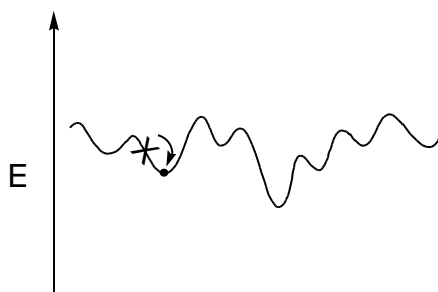
Quantum Mechanics . . . All of Chemistry



What Can Be Calculated . . .

Equilibrium Geometry

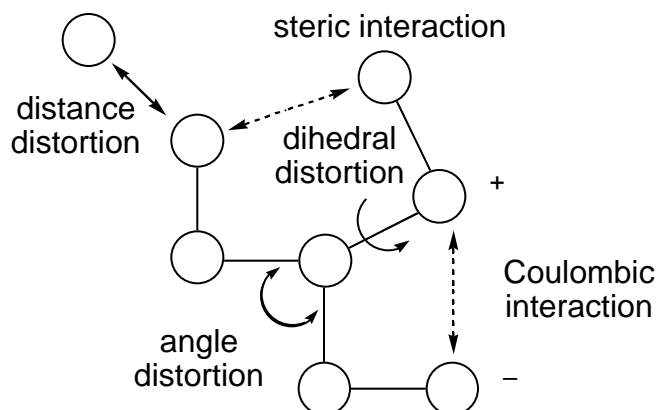
The task here is to locate the "closest" minimum on a multidimensional energy surface. (The remaining energy minima correspond to different isomers and/or different conformers.)



In principle, the geometry of any energy minimum . . . an equilibrium geometry . . . may be obtained from experiment. This allows the "quality" of the calculated geometry to be judged.

Molecular Mechanics

Molecular mechanics describes the energy of a molecule in terms of its geometry and the location and types of bonds. Minimum energy structures are found by reducing distortions from an "ideal geometry" while simultaneously reducing unfavorable non-bonded "steric" interactions, and optimizing non-bonded Coulombic interactions.



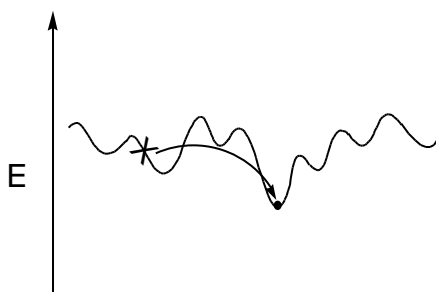
Aside from explicit bonding, molecular mechanics needs to be parameterized to fit results from either experiment or from reliable quantum chemical calculations.

Because of its simplicity . . . relative to quantum chemical models . . . molecular mechanics has found its greatest utility in establishing conformation. While present-generation molecular mechanics models are not in all cases likely to identify the "lowest-energy" conformer, and are certainly not able to quantify energy differences between conformers, they are able to select out particularly favorable arrangements from what might be an enormous number of possibilities.

What Can Be Calculated . . .

Equilibrium Conformation (Shape)

The task here is either to locate the deepest minimum on a multidimensional energy surface, or a set of “representative” low-energy minima.



In principle, equilibrium geometries of individual conformers may be obtained from experiment. In practice, different conformers are rapidly equilibrating and it is difficult to detect and characterize any but the lowest-energy form.

Conformation Equilibrium

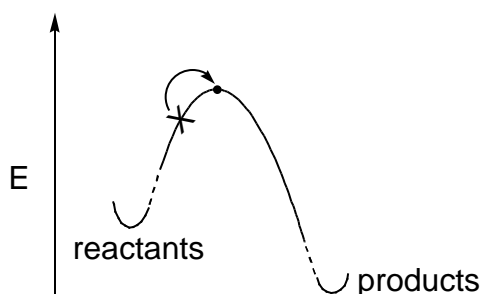
Where there are two or more low-energy conformers, molecular models can be employed to describe how they interconvert. A particularly simple and particularly important case is interconversion via single-bond rotation, for example in n-butane.

Very closely related . . . although not obviously so to students . . . is interconversion of equivalent "chair conformers" of cyclohexane.

What Can Be Calculated . . .

Transition State Geometry

The task here is to locate the highest point on a multidimensional energy surface along a "pathway" which smoothly connects reactants and products.

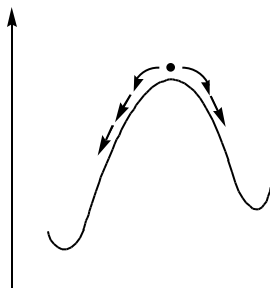


Transition states do not exist in terms of a discernable population of molecules. This means that transition-state geometry cannot be obtained from experiment. The calculation is on its own.

What Can Be Calculated . . .

Reaction Pathway

Having found a transition state, evaluating the second derivative of the energy leads to a vibration which corresponds to the motion of atoms leading up to and away from the transition state (the reaction coordinate).

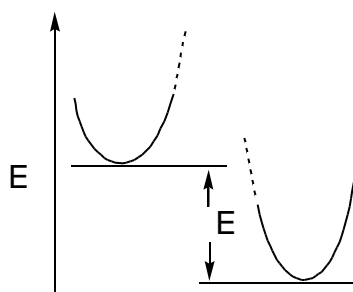


There is no way to experimentally verify this motion (except that it needs to smoothly connect reactants and products), just as there is no way to verify the geometry of the transition state.

What Can Be Calculated . . .

Reaction Energy

The task here is to obtain the difference in energy between two different minima on a multidimensional energy surface.

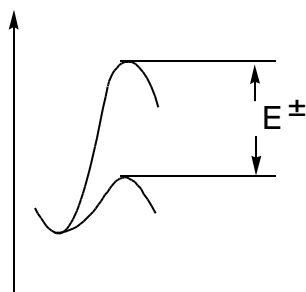


Reaction energies can be obtained from experimental enthalpies of formation which in turn are based on measured heats for "standard" reactions (typically combustion reactions). This allows the quality of calculated reaction energies to be judged.

What Can Be Calculated . . .

Relative Activation Energy

The task here is to obtain the energy difference between two (or more) different maxima on a multidimensional energy surface.

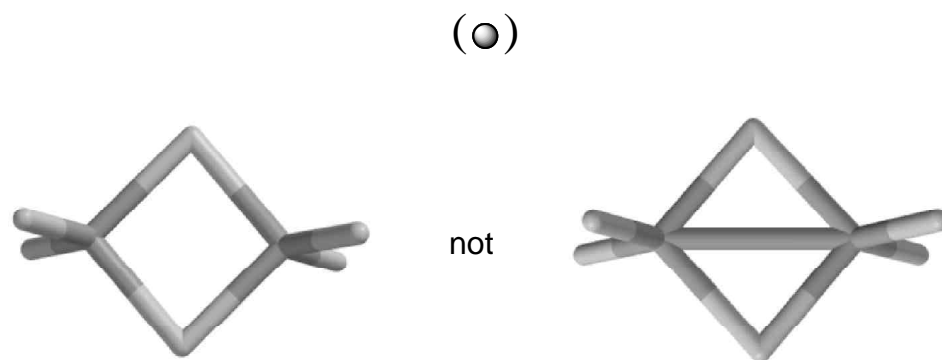


In principle, observed product distributions relate directly to relative activation energies. This allows the "quality" of calculated activation energy differences to be judged.

Electron Density

Quantum chemical models also provide the concentration of electrons at any location in a molecule. This is termed the electron density. A surface of constant electron density serves several functions depending on the value of the density at the surface.

Surfaces of very high electron density identify atomic positions (the basis of the X-ray diffraction experiment). Surfaces corresponding to somewhat lower electron density can be used to "assign" bonds in molecules where there may be more than one reasonable alternative. For example, the electron density for diborane shows no evidence for a bond between the borons.



Perhaps the most important use of electron density surfaces is to depict overall molecular size and shape, the same information that is provided by a space-filling model.

Electrostatic Potential

The electrostatic potential is the energy which a positive charge (an "electrophile") feels at any location in a molecule. A surface of constant negative electrostatic potential indicates areas that are prone to electrophilic attack. For example, a negative electrostatic potential surface for benzene shows that electrophilic attack should occur onto the π system, above and below the plane of the ring, while the corresponding electrostatic potential surface for pyridine shows that an electrophile should attack the nitrogen in the ring plane, and not the π system of the ring. Electrostatic potential surfaces clearly show that the "chemistry" of these two seemingly similar molecules is very different.

Electrostatic Potential Map

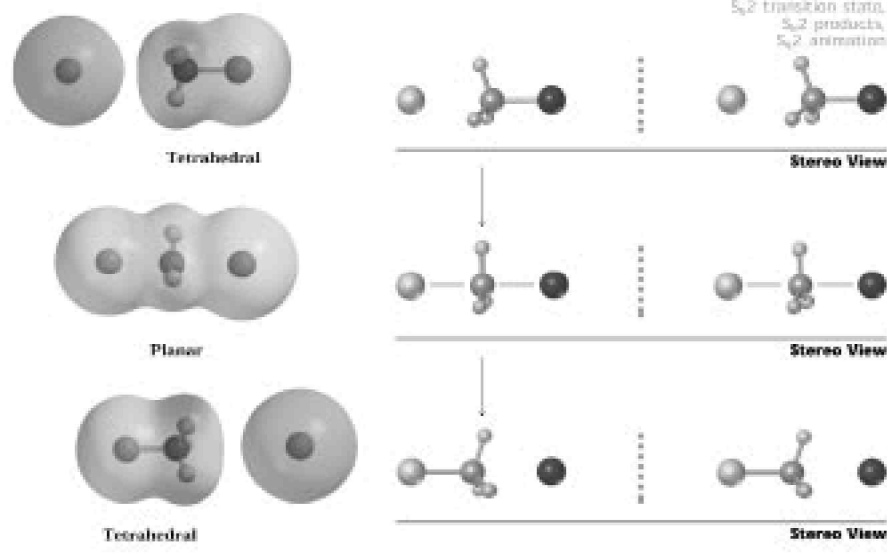
A more useful model follows from "color mapping" the value of the electrostatic potential onto an electron density surface which corresponds to a conventional space-filling model. The resulting model simultaneously displays molecular size and shape and electrostatic potential value. Colors toward "red" indicate negative values of the electrostatic potential, while colors toward "blue" indicate positive values of the potential. For example, the "red" (negative potential) area in benzene subject to electrophilic attack is the π face while the corresponding area in pyridine is in the π system at nitrogen.

Electrostatic Potential Maps . . . in Organic Textbooks


Mainstream organic textbooks now incorporate electrostatic potential maps both as illustrations and (in some cases) as manipulatable and queryable models.

FIGURE 11.4 *

The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups. Electrostatic potential maps show that negative charge (red) is delocalized in the transition state.



J. McMurry, Organic Chemistry, fifth edition, Brooks/Cole, Pacific Grove, CA 2000.

The icon  indicates that the model is available on a supplementary CD.

Electrostatic Potential Maps . . . in Organic Textbooks

The more ambitious textbooks (McMurry and Carey among them) provide problems which make use of electrostatic potentials and other molecular modeling tools.

Molecular Modeling *



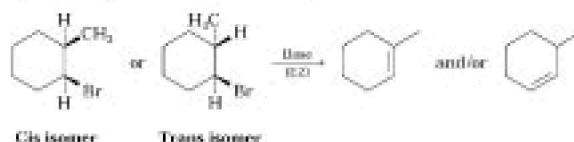
11.70 The idealized S_N2 transition state has a linear arrangement of NuZ , CZ , X . Use SpartanView to examine S_N2 transition states for the reaction of Cl^- with CH_3Br , CH_3CH_2Br , $(CH_3)_2CHBr$, $(CH_3)_3CBr$, and $(CH_3)_3CCH_2Br$. Which transition state is most ideal? Identify significantly distorted bond angles in the other transition states, and account for the distortions.



11.71 Suppose a chemist wants to use KF as a nucleophilic reagent in an S_N2 reaction. Use SpartanView to compare electrostatic potential maps of water, acetonitrile, and $DMSCl$, and tell which solvent(s) you expect to bind strongly to F^- and to K^+ . Which solvent(s) should promote a rapid S_N2 reaction?



11.72 The *cis* and *trans* isomers of 2-bromo-1-methylcyclohexane react at different rates and give different $E2$ elimination products. Use Spartanbuild to build the two chair conformations for both isomers, and minimize the structures of each. Identify the reactive conformation of each molecule and the expected reaction product from each. Is the reactive conformation the one with lower strain energy? Which isomer, *cis* or *trans*, will undergo elimination more readily?



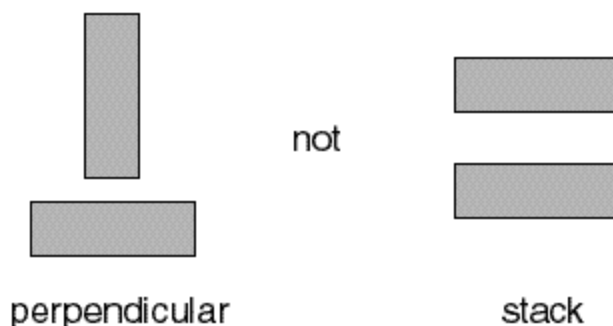
J. McMurry, Organic Chemistry, fifth edition, Brooks/Cole, Pacific Grove, CA 2000.

Electrostatic Potential Maps . . . and Intermolecular Interactions

Because electrostatic potential maps provide quantitative information about charge distributions in molecules, they allow inferences to be drawn regarding how molecules interact. For example, the electrostatic potential map for benzene shows a marked difference in charge distribution between the face and the edge.

(●)

Electrostatics (Coulombs law) clearly favors a perpendicular structure for benzene dimer rather than a parallel structure.



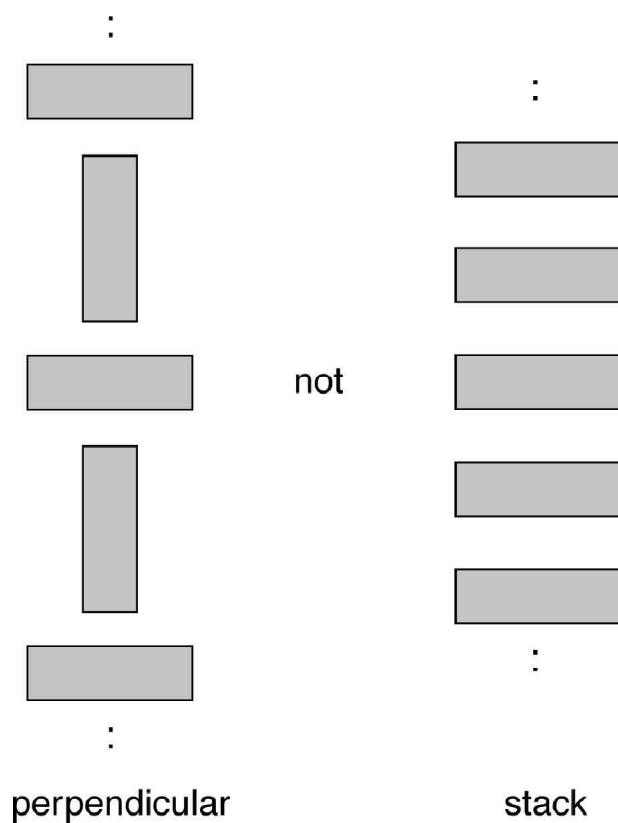
(●)

This is in accord with the experimental (microwave) structure.

Intermolecular Interactions . . .

Benzene Crystal

More interesting, this suggests that the crystal structure of benzene is not, as might be expected, a "stack", but much closer to a perpendicular arrangement, albeit in three dimensions.

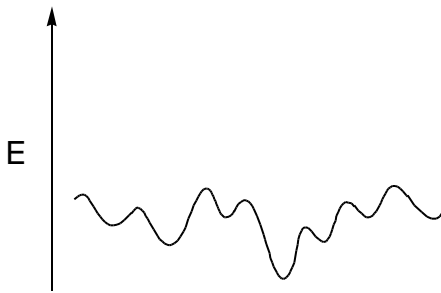


This is in fact what is observed.

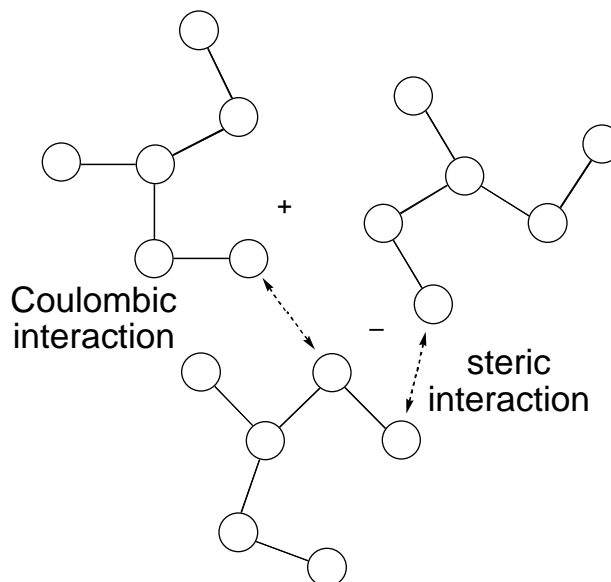
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Molecular Dynamics

A liquid or solution is a “molecule” with a huge number of degrees of “conformational” freedom.



In order to calculate properties for such a system, it is necessary to average over a large sample of possible arrangements. Molecular dynamics, as it is commonly referred to, follows a single arrangement in time, using the classical mechanical equations of motion (Newton's second law), together with an empirical energy function describing intermolecular interactions.



Liquids and Solutions

Molecular dynamics simulations not only yield quantitative information, but are also able to furnish qualitative insight into the nature of liquids and solutions. For example, molecular dynamics simulations of sodium in water and chloride in water clearly and beautifully show how the solvent "responds" to its guest.

(●)

In the case of the former, the “negative” oxygen on the solvent associates with sodium cation. In the case of the latter, the “positive” hydrogens on the solvent associate with the chloride anion.

Role of Modeling

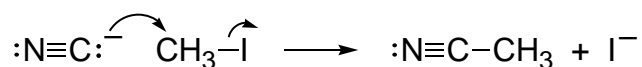
Assist Lecture Presentations?

Certainly . . . 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 more importantly from the limits of all too primitive models, and allow examination and discussion of "real" molecules, and ultimately of real matter.

In Lecture . . .

S_N2 Reaction

The first reaction encountered by a student in an elementary organic chemistry course is inevitably S_N2, and what is stressed is the inversion at carbon.



While a conventional "blackboard" presentation could certainly be enhanced with a computer animation, and while molecular models can be employed not only to show the change in geometry throughout the reaction, but also the transfer of negative charge, there are other important questions about the S_N2 reaction which molecular models can help to pose and answer.

Why is Cyanide a Carbon Nucleophile?

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 (the HOMO) of cyanide. This is where the "most available" pair of electrons resides, that is, the "nucleophilic site".



The HOMO is concentrated on both carbon and nitrogen, meaning that two different S_N2 products are possible. However, it is more heavily concentrated on carbon, meaning that acetonitrile will be the dominant product. This result is entirely consistent with the relative electronegativities of carbon and nitrogen. The fact that nitrogen is more electronegative than carbon means that it will hold its electrons more tightly.

Why is Iodide Leaving the Group?

Why does iodide leave following attack by cyanide? Can we do better than simply stating that this is what happens . . . so accept it?

Look at the lowest-occupied molecular orbital (the LUMO) of methyl iodide. This is where the pair of electrons from cyanide will go, that is, the site of nucleophilic attack.



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

We've Got it Wrong!

We tell students that bromide reacts faster with methyl bromide than with *tert*-butyl bromide because of increased crowding in the transition state of the *tert*-butyl system. **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 longer than that in the methyl system, about 2.9Å compared to 2.5Å. The atoms have moved apart to avoid crowding. This leads to an increase in charge separation as clearly shown by electrostatic potential maps for the two transition states.

Electrostatics and not steric crowding is the cause of the decrease in reaction rate.

Gases, Liquids and Solids

Molecular dynamics simulations on gaseous, liquid and solid bromine . . . simple but "real" . . . clearly point out the differences in the three states of matter.



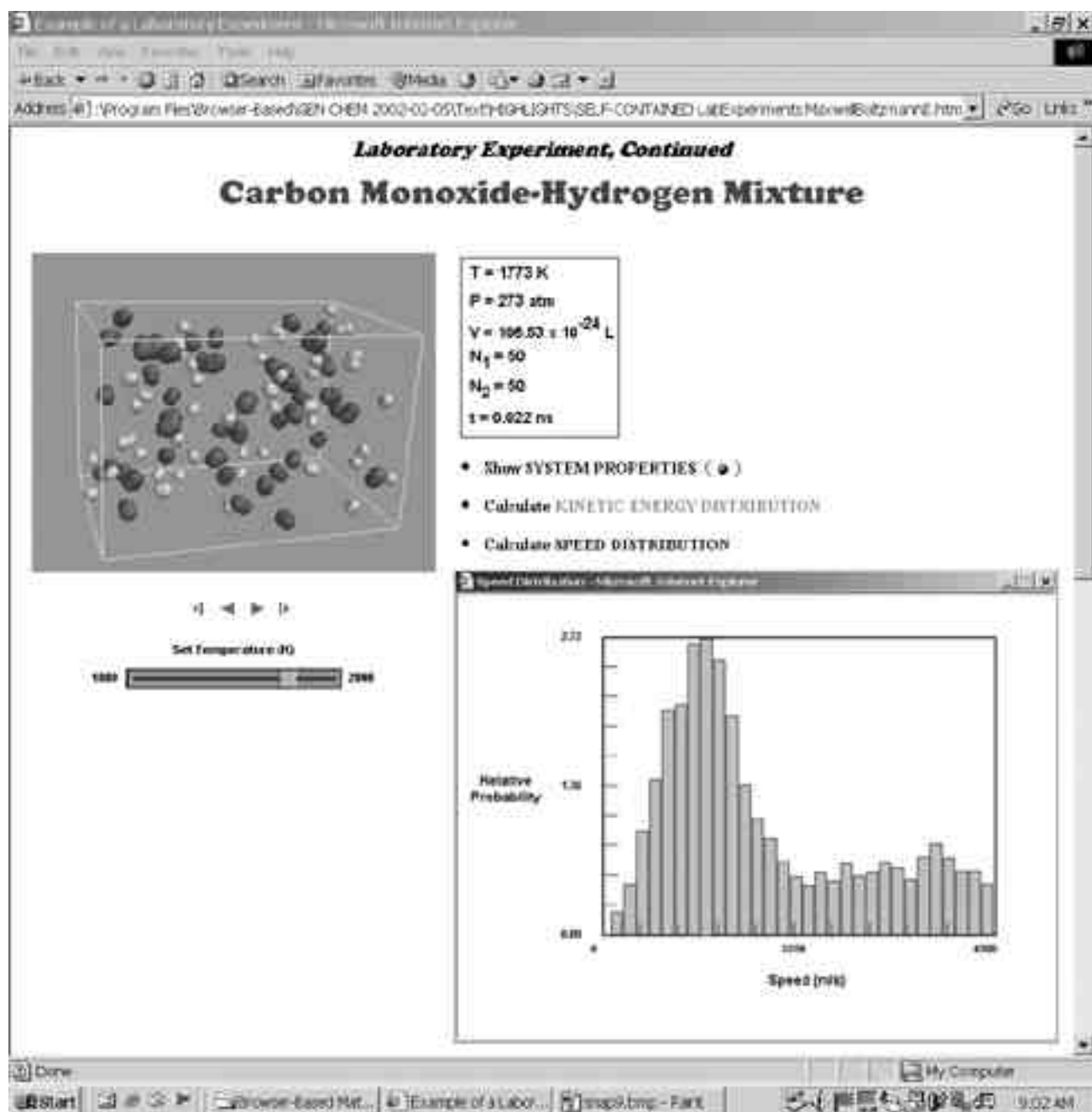
Intermolecular forces in gases are much weaker than those in liquids and solutions, and individual molecules would be expected to move much more freely. On the other hand, the forces in solids would be expected to be stronger and motions much more confined.

Role of Modeling

Amplify Student Reading Materials?

In the future. . . Student materials may become much more like computer programs and much less like present-day textbooks. Passive one-way transfer of information will be exchanged for active open-ended dialogs accessing real modeling tools.

This is not to be confused with current efforts to produce CDROM versions of textbooks or even textbooks, "on line". These use the computer only for its video display . . . which some might argue is inferior to a printed book.



Role of Modeling

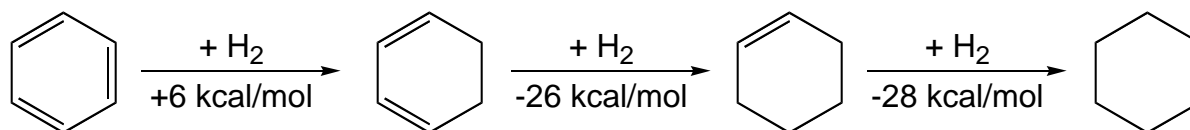
Assist Development of Problem Solving Skills?

Certainly . . . "Textbook problems" are "passive" and require little more of the student than extracting materials from lecture notes and the textbook. They do not . . . and cannot . . . develop the essential skills of "asking the next question" and "constructing a scenario to answer it". Molecular modeling . . . like experiment . . . is "active" and encourages the student to move beyond the initial question.

A Typical Modeling Problem . . .

Aromaticity

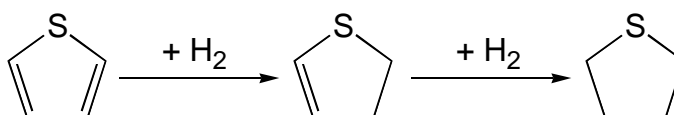
We teach students that benzene is more stable than expected . . . that it is "aromatic". The extent to which benzene is in fact "more stable" can be quantified by comparing energies for successive hydrogenation reactions.



Addition of H_2 to benzene "trades" an H-H bond and a C-C bond for two C-H bonds, but in so doing destroys the aromaticity, whereas H_2 addition to either cyclohexadiene or cyclohexene "trades" the same bonds but does not result in any loss of aromaticity. Therefore, the difference in the heats of hydrogenation (32 kcal/mol referenced to cyclohexadiene and 34 kcal/mol referenced to cyclohexene) is a measure of the aromaticity of benzene.

Is Thiophene Aromatic?

To answer, calculate energies for the successive hydrogenation reactions.



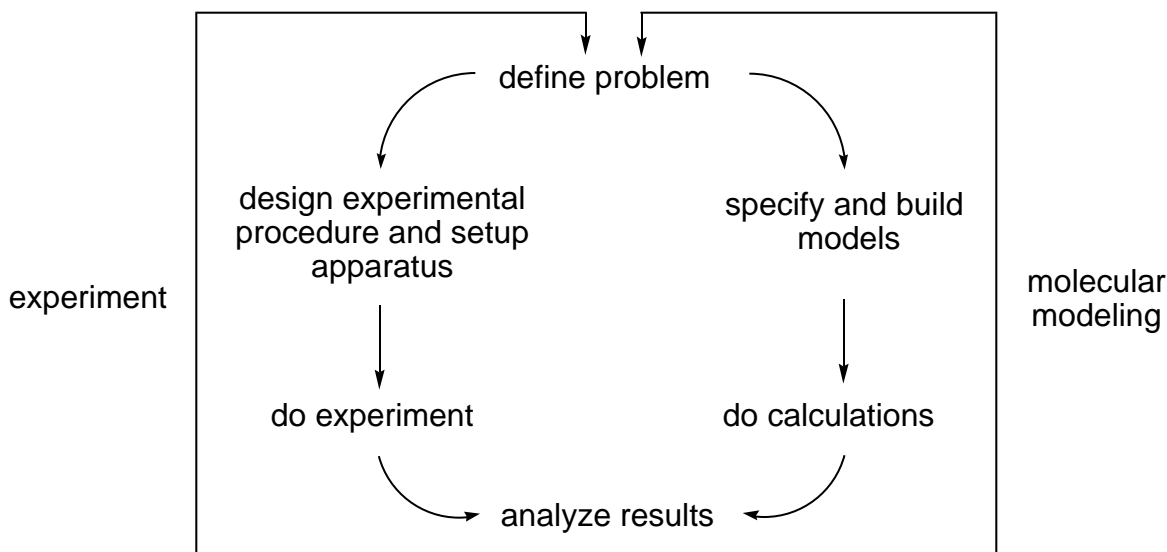
The difference of 17 kcal/mol suggests that thiophene is stabilized by aromaticity, but only to about half the extent as benzene. (For reference, hydrogenation energies calculated for cyclohexadiene and for cyclohexene are both 37 kcal/mol higher than that calculated for benzene.)

Of course, this is only a starting point for the inquisitive student. Apply a similar analysis to other molecules or to transition states. Explore other measures of aromaticity.

Role of Modeling

Supplement or Replace Laboratory Chemistry?

With Care . . . Molecular modeling, like a laboratory, offers "hands-on" experience. Both can either "turn-on" or frustrate students. Both require careful planning "experimental design".

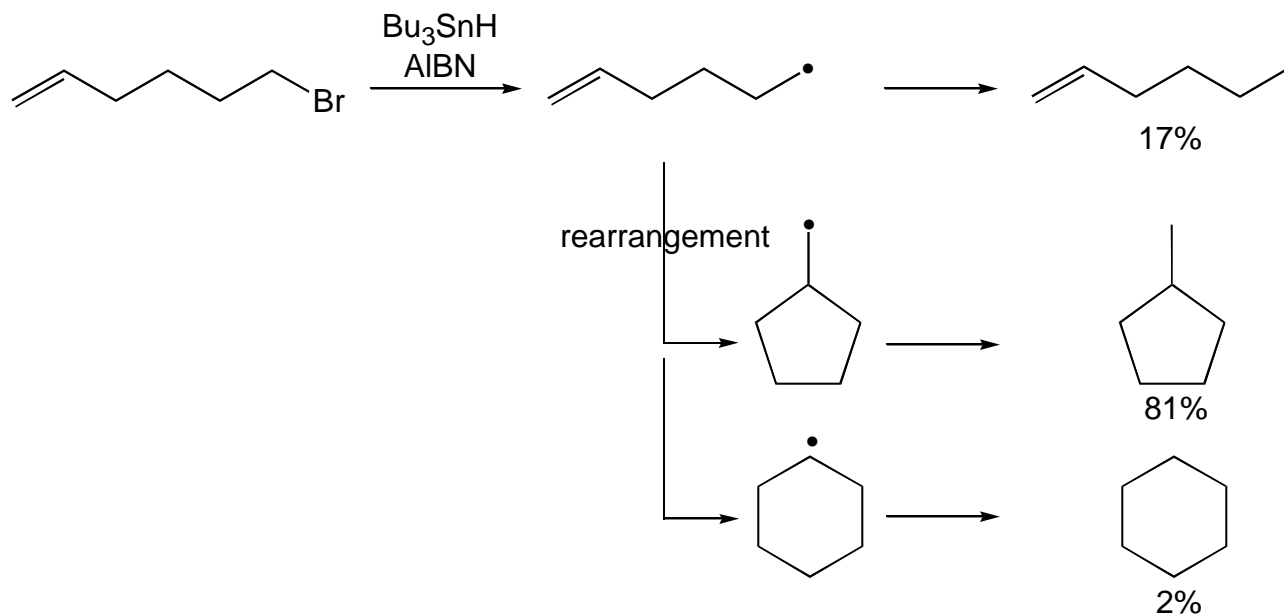


There are important differences. Modeling doesn't make "stuff" . . . although it certainly can help choose what to make and tell how to make it . . . nor does it tell what the "stuff" is . . . although along with experiment, it can help to limit the possibilities. Synthesis and analysis will remain cornerstones of chemistry.

A modern chemical education requires training in both experimentation and modeling.

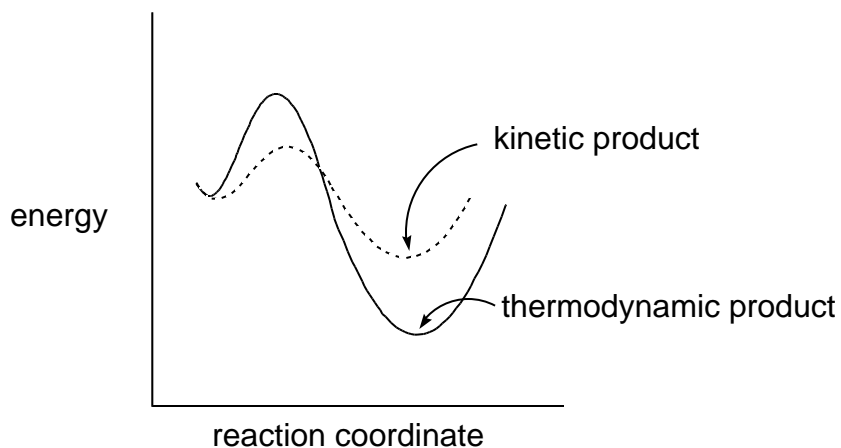
A Typical "Laboratory Experiment" . . . Thermodynamic vs. Kinetic Control

We spend a great deal of time teaching students how to pick out the "stable molecule" from among the alternatives. For example, we teach them to pick cyclohexyl radical over cyclopentylmethyl radical, because "6-membered rings are better than 5-membered rings", and because "2° radicals are better than 1° radicals". However, chemistry is often not controlled by what is "best" (thermodynamics) but rather by what forms most readily (kinetics). Consider for example, that loss of bromine from 6-bromohexene (leading initially to hex-5-enyl radical), results primarily in product from cyclopentylmethyl radical.



Thermodynamic vs. Kinetic Product

The thermodynamic product is that with the lowest energy irrespective of reaction pathway, while the kinetic product is that which follows from the lowest-energy transition state, irrespective of final product energies.



Thermodynamic or Kinetic Control?

This example allows students to go beyond the "theory" and to learn first hand what is meant by thermodynamic and kinetic control. In addition, it provides practical experience in dealing with transition states for real reactions. The latter opens the door to the investigation of reaction mechanisms.

The first objective is to establish whether or not cyclohexyl radical is in fact "better" than cyclopentylmethyl radical, and that cyclohexane and not methylcyclopentane is the thermodynamic product. This requires calculating energies for the two radicals at their respective equilibrium geometries. The calculated difference is almost 7 kcal/mol in favor of cyclohexyl radical. Were the reaction under thermodynamic control, only cyclohexane would be observed.

The next objective is to establish which ring closure, to cyclohexyl radical or to cyclopentylmethyl radical, is easier, that is, which product, cyclohexane or methylcyclopentane is the kinetic product. This requires calculating energies for the two transition states. The calculated difference is almost 3 kcal/mol in favor of ring closure to cyclopentylmethyl radical. Methylcyclopentane is the kinetic product and only about 1 - 2% of the total product mixture should be cyclohexane. This is what is observed, suggesting that the reaction is under kinetic control.

Blurring the Boundaries

Molecular modeling helps to "blur" the artificial boundaries between lecture and homework, between homework and the "laboratory" and, most importantly, between the laboratory and chemical research.

In short, modeling allows the educational environment to more closely approach the "real world".

"Take Home" Messages

Molecular modeling is a tool which allows you and your students to explore and interpret chemistry from a molecule's point of view. Empirical "molecular mechanics" models provide semi-quantitative descriptions of complex phenomena, while models based on quantum mechanics offer a fundamentally correct picture of the molecular world and, like experiments, can be used to discover new chemistry.

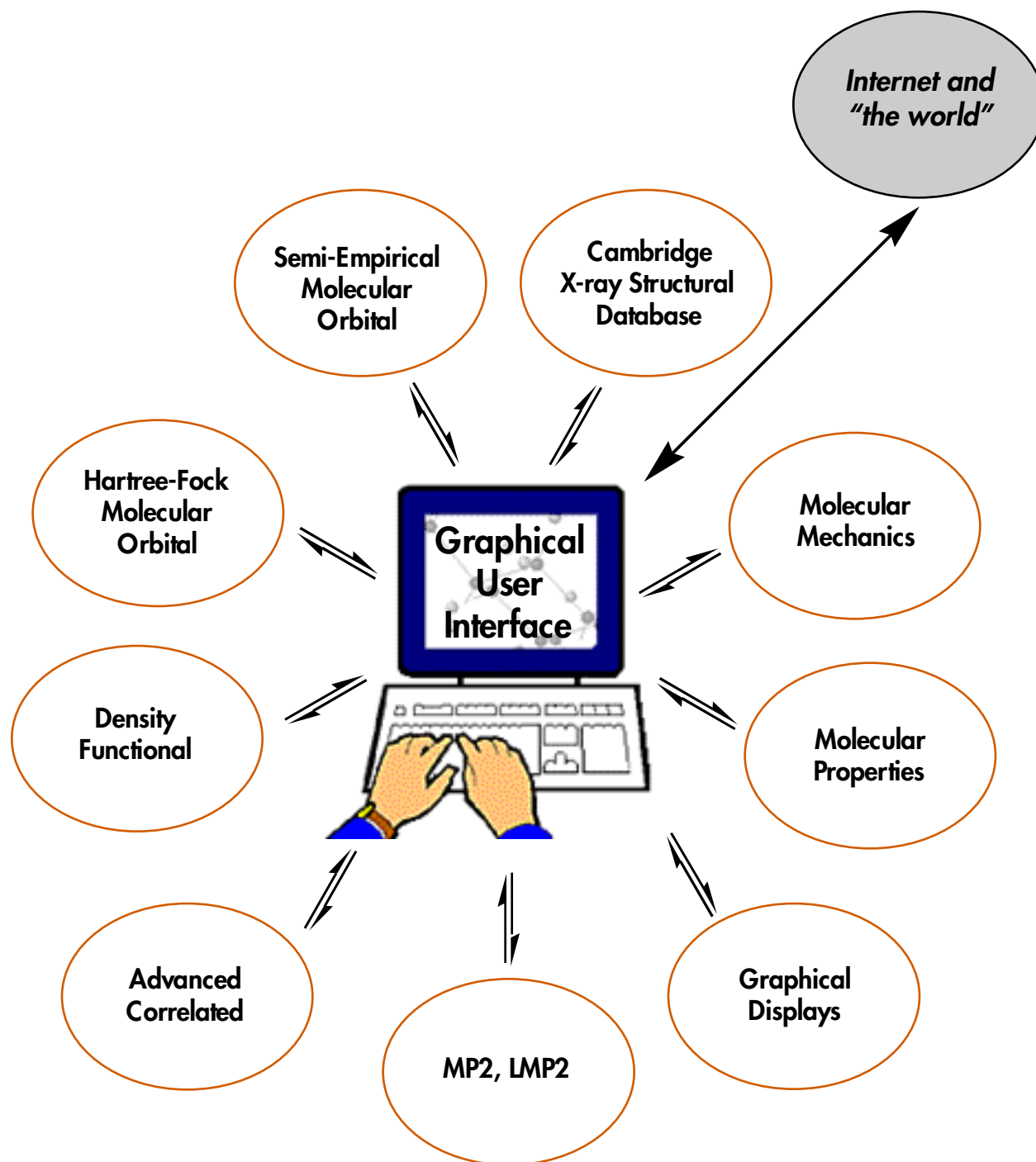
Molecular modeling is accessible. Anyone can build a useful model and, given today's software, using models is no more difficult than taking an NMR spectrum. The difficulty lies in asking the right questions of the models and properly interpreting what comes out of them.

Molecular modeling need not 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.

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

Spartan'02

Architecture



Spartan'02

Graphical User Interface

- fragment-based molecule builders for organic, organometallic and inorganic molecules, polypeptides and polynucleotides
- molecular mechanics for preliminary structure refinements
- extensive library of reactions and substructure search engine for guessing transition states
- display, manipulation and querying of molecular structures as wire, ball-and-wire, spoke, ball-and-spoke and space-filling models
- display and manipulation of polypeptides and polynucleotides as ribbons
- menu-driven dialogs to oversee all aspects of job setup
- display and manipulation of molecular orbitals, electron and spin densities and electrostatic potentials, as contour plots, isosurfaces and property maps
- animation of structure models and/or graphical displays along normal (vibrational) coordinates or user-defined coordinates
- automated searching of low-energy conformers
- automated searching of tautomers
- molecule alignment
- “export” and “import” of structures to and from other programs
- printing and clipboard manipulations
- spreadsheet for data tabulation, statistical analyses and plotting
- substructure searching of Cambridge X-ray structural database (presently >250K organic and organometallic molecules), and automatic transfer of molecular structure, along with literature reference to the file system for further processing

Spartan'02

Computation

Molecular Mechanics

- calculation of equilibrium geometry, and vibrational frequencies
- searching conformation space
- SYBYL and MMFF94 (Merck Molecular Force Field)

Semi-Empirical

- calculation of energy and wavefunction, equilibrium and transition-state geometry and vibrational frequencies
- searching conformation space
- MNDO, MNDO/d, AM1 and PM3 (including parameters for metals)

Hartree-Fock, Density Functional, Møller-Plesset and Advanced Correlated

- calculation of energy and wavefunction, equilibrium and transition-state geometry and vibrational frequencies
- searching conformation space
- Hartree-Fock molecular orbital
- local density and BP, BLYP, EDF1 and B3LYP density functional
- MP2, MP3, MP4 and LMP2 Møller-Plesset
- CCSD, CCSD(T), OD, OD(T), QCISD, QCISD(T), QCCD and QCCD(T) correlated
- CIS, CISD, local density and BP, BLYP, EDF1 and B3LYP density functional for excited states
- built in STO-3G, 3-21G, 6-31G, 6-311G, cc-pVDZ, cc-pVTZ and cc-pVQZ, basis sets with diffuse and polarization extensions
- built in LANL pseudopotentials

Odyssey (early 2003)

A program for interactive molecular dynamics simulations and visualization of chemical matter: gases, liquids and solutions, solids and materials and biomolecules.

- solvent effects
- supermolecular structure
- thermodynamics
- diffusive behavior
- packing problems
- spontaneous processes
- condensed phase chemistry
- biomolecular structure and dynamics