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# Molecular Mechanics and Modeling: Overview

Molecular mechanics is an approach to modeling the behavior of matter. It begins with a fundamental assumption that matter consists of "atoms" and the potential energy of a collection of atoms can be defined for every set of positions. The collection of atoms is treated as a mechanical system moving with this potential energy and subject either to Newton's or Schrödinger's equations. Details about the system, such as the equilibrium structure, the vibrational spectrum, thermodynamic properties, equations of state, and reaction rates, can then be computed.

The introduction of the Schrödinger equation in 1927 provided the theoretical link between the potential energy surface (PES) and the observed rotational and vibrational spectrum. This allowed a reconstruction of the PES from the spectra near the equilibrium structure of a molecule. This approach was summarized in the books by Herzberg *Spectra of Diatomic Molecules* and *Infrared and Raman Spectra* and by Wilson, Decius, and Cross in their book *Molecular Vibrations.* A major discovery from this approach was that the force constant for stretching each "type" of bond was nearly transferable between molecules.

Within the adiabatic approximation, the electronic structure and the motion of the nuclei are nearly separable. The energy eigenvalue of the electronic structure problem provides the PES for the nuclear motion. This view of the origin of the PES surface allowed functional forms to be derived that were appropriate for describing interactions between atoms or molecules far from the equilibrium structure.

From the viewpoint of the PES, a chemical reaction is just a rearrangement of the atoms to a different local minimum. The relative depths of local minima are not predicted by the vibrational spectra or intermolecular interactions. It was found, however, that the enthalpies of molecules could be predicted fairly well by adding bond enthalpies. Schemes to correct the errors in this model led to the ability to predict enthalpy changes for most organic molecules.

From these beginnings, molecular modeling has developed into a major tool for the understanding of molecules. Organic chemists developed simple empirical potential energy surfaces, incorporating the functional forms needed for internal distortion, intermolecular interaction, and reaction enthalpy changes. These potential energy surfaces are also called "force fields" because the derivative of the potential energy determines the force acting on the atom when dynamics are considered. As computers became inexpensive, programs were developed that allowed convenient graphical description of molecules in input and colorful, easily visualized output. These programs are able to predict the equilibrium structure of organic molecules and their relative enthalpies. More elaborate programs are also able to sample the dynamics of atomic motion and predict the free energies. At present, molecular modeling has become a major industry with many programs available.

In this thematic issue of *Chemical Reviews*, a few aspects of this broad field are reviewed. Dykstra describes the electrostatic part of the intermolecular interaction and the types of terms needed in the force field to accurately model this part of the energy. Steele treats experiments and results for the interaction of molecules with solid surfaces. Ohmine and Tanaka describe in detail the fluctuating structure of liquid water. Berry reviews the problems in visualizing global potential energy surfaces for many atoms and the difficult problem of locating all the low-energy minima and transition states. Most of the systems he describes are small clusters of atoms or ions. Kollman covers the methods for calculating free-energy changes in solution. Missing from this thematic issue are any articles on modeling reactive scattering and the details of fitting data to obtain the PES.

Cohen and Benson review one approach to estimating the enthalpies of molecules by additivity methods. Sadowski and Gasteiger consider the methods for constructing reasonable three-dimensional structures from atoms and bonds using rules and empirical data. For many purposes, these structures are sufficient without further refinement by force field calculations. Eksterowicz and Houk treat recent developments in modeling transition states. This is more difficult than modeling equilibrium structures and is an area of current research. Åqvist and Warshel describe an approach to modeling reactions in polar solvents using valence bond force fields. Both of these reviews deal with a situation in which more than one resonance structure must be considered in the model.

Lipkowitz and Peterson describe the important area of applications of molecular mechanics in computer-aided molecular design and synthesis planning. Several reviews deal with important biochemical applications. Brooks and Case review simulations of peptides in solutions including the problem of secondary structure formation. Marlow et al. consider the effect of dissolved salts on peptides in solution. Åqvist and Warshel consider enzyme reactions in solution.

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