

# CHEMISTRY BY COMPUTER

As organic chemists need more detailed descriptions of reactions, some are relying on theoretical calculations rather than on experiments

BY JULIE ANN MILLER

Stoked with legends of heroic feats once performed with desk calculators, theoretical physical organic chemists are getting up steam. Shapes, energy levels and electron distributions of the molecules that make up living creatures chug through university and industry computer systems. And the numbers, patterns and graphs that result can guide the experiments of those other chemists who still wear lab coats and put compounds into test tubes and far more delicate apparatus.

Theoretical organic chemists will reach their ultimate destination, according to Frank Westheimer of Harvard University, when they can use their models to design an enzyme to catalyze a chosen reaction and, when synthetic chemists construct the molecule, it will fold itself and work. "The millenium has not yet arrived," Westheimer points out.

At the annual Peter A. Leermakers Symposium at Wesleyan University in Middletown, Conn., theoretical organic chemists described their advances and argued the details of their computational techniques. Among the general disagreements were how complex an analysis must be made to give reliable results, what approximations may be made and how much experimental data may be included.

To determine the exact shape of a com-

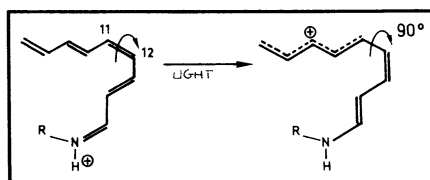
plex molecule, for example, Norman L. Allinger of the University of Georgia takes the constant parameters for his equations from experimental data on simpler molecules. Then he computes the energies of all the possible geometries and settles for the most stable shape. At the other extreme, some theoretical chemists use no experimental data, but do "ab initio" calculations. They employ the complicated Schroedinger equation to describe the probability of finding each electron at all points around the nuclei, and thus determine the most likely configuration.

Understanding the electronic structure of static molecules, both among theoretical and experimental chemists, is far more advanced than knowledge of those fleeting structures that appear and disappear during a chemical reaction. Yet it is the many reactions that provide the compelling mysteries of chemistry. Klaus Ruedenberg of Iowa State University has developed computer programs to describe in detail the electronic rearrangements during chemical reactions. The program generates diagrams showing which molecular orbitals dominate the changes and how each atom participates in electron bond rearrangements. Several reactions have now been investigated by this technique.

Although far from their visions of designing enzymes and simulating detailed reactions on the computer, theoretical organic chemists have directed experimenters to interesting problems. Sudden charge separation in the visual pigment is one exciting finding that will soon be tested by experiment. Lionel Salem of the University of Paris-South reports his investigations of the uncoupling of electron pairs. Light can cause violations of what

Salem calls the eleventh commandment: "Thou shalt not break an electron couple." Photons, however, can punch one electron right out of its orbital.

Pairs of electrons are the cement that holds the atoms of a molecule together, Salem explains. After one electron is ejected from the pair, the molecule adjusts its geometry to find the most stable new structure. "The subtle manner in which

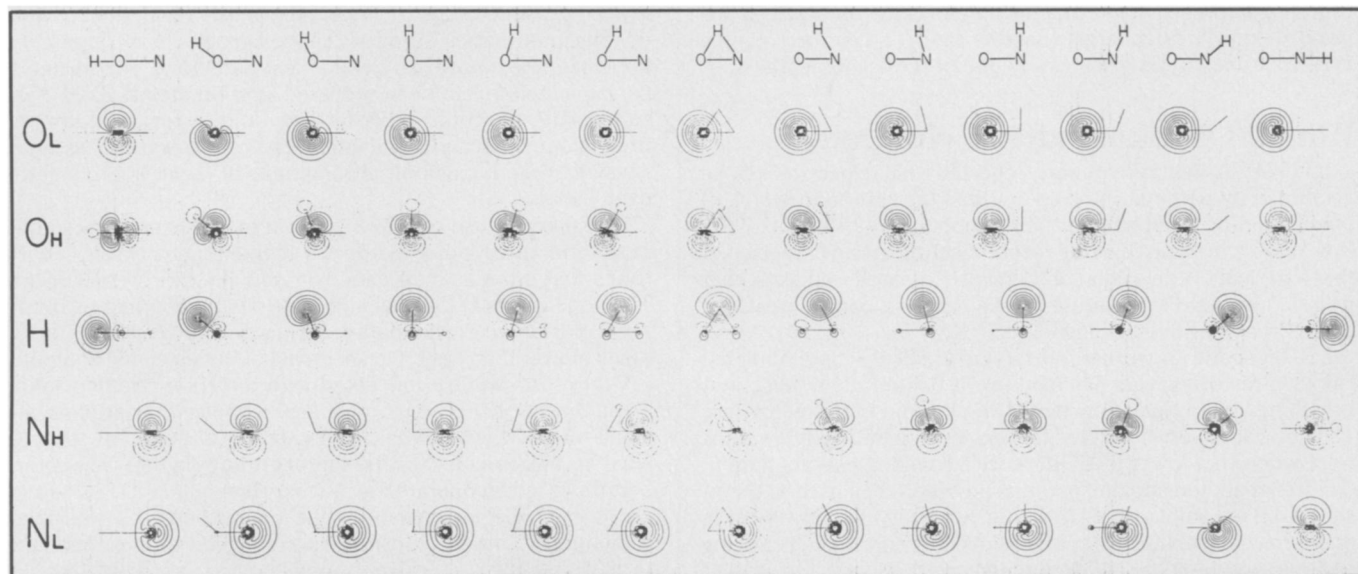


Theory predicts that, on excitation by light, this portion of the visual pigment twists and the charge migrates.

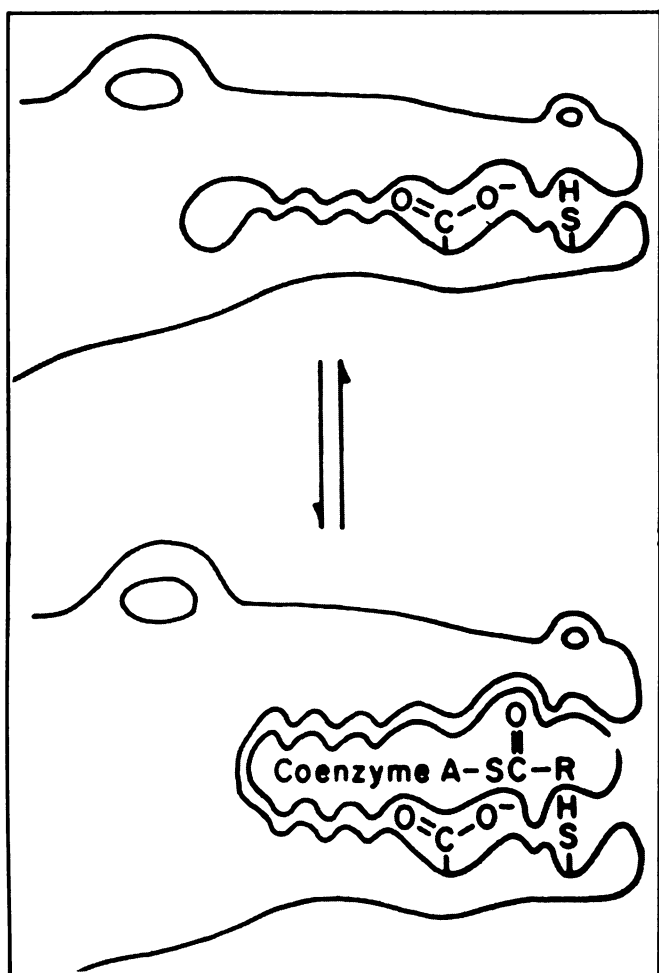
the electrons thus rearrange is one of the problems which make theoretical chemistry so attractive," Salem says.

A subtle rearrangement can result in a drastic change. One type of reaction Salem has studied is a model of the fate of retinal, the light-absorbing portion of the human visual pigment. After a photon hits, electric excitation produces a twisted molecule with a new electron pair. When the molecule twists 90°, an electron migrates from one end of the molecule to the other, over the length of seven bonds. This surprising theoretical result, which has now been observed in five laboratories, may be a crucial event in vision. In the fall, Harvard chemist Kevin Peters will perform laboratory experiments to test that theoretical prediction.

Recently Salem has been working on yet another way to violate the eleventh com-



Computer programs describe how probability distributions of electrons change during chemical reaction converting HON to HNO.



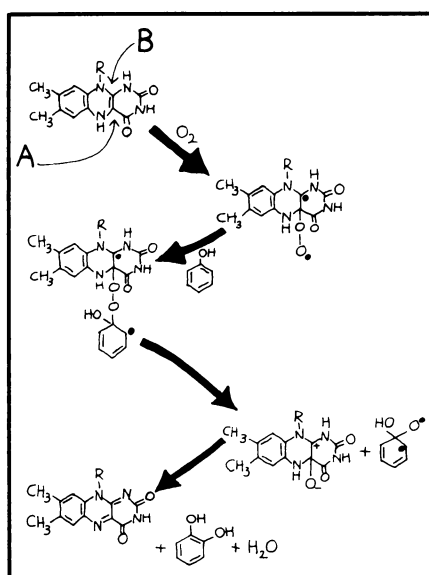
*Jencks jokingly predicts the three-dimensional structure of an enzyme will be a crocodile. The interactions between enzyme and substrate force the active site (mouth) to open wider.*

mandment. Using electrodes as sinks and sources, he takes an electron out of a pair or puts an extra electron in. But three is a crowd in a chemical bond; competition seems to weaken the cement. For example, Salem adds electrons to methylchloride ( $\text{CH}_3\text{Cl}$ ) to produce a radical, a molecule with an unpaired electron ( $\text{CH}_3\text{Cl}^\cdot$ ). That molecule immediately dissociates into methyl radical ( $\text{CH}_3^\cdot$ ) and chloride ion. Salem says the added electron pumps the chemical up to an energy level ("surface" in theoretical chemistry lingo) where it can dissociate without trouble. Similarly, Salem finds that removing an electron from an acetate molecule produces an acetoxy radical, which dissociates.

Electron pairs cement together some amazing molecules. William N. Lipscomb of Harvard University described molecules built of boron and hydrogen atoms and of boron, carbon and hydrogen. In these structures the charges of some electrons are not confined to bonds between atoms but seem more widely distributed. For instance, decaborane ( $\text{B}_{10}\text{H}_{14}$ ) must be represented as a composite of 24 different structures in which the electrons are assigned to different bonds.

"Funny delocalizations appear throughout chemistry," Lipscomb says. In his recent work he has identified "nontraditional" bond patterns in many amino acids, the building blocks of protein. The

bonds resemble the "three-center" bonds that Lipscomb previously described in boron compounds (SN: 10/23/76, p.261). At those junctions, a pair of electrons seems to hold together three, instead of two, nuclei. In his most recent work on boron compounds, Lipscomb reports, a molecule with such nonclassical bonds is



*The design of the co-enzyme flavin helps drive oxidation reactions, according to a model proposed by Goddard.*

not barred from traditional bonding. He finds that nonclassical molecules temporarily remodel into classically structured ions during their chemical rearrangements.

The most impressive, and the most useful, organic molecules are the enzymes. They can accelerate a chemical reaction of a specific compound by a factor of  $10^{15}$ , says William Jencks of Brandeis University. When compared with chemical catalysis, an enzyme is far more active and displays a much higher specificity for its substrate.

Jencks believes that most of an enzyme's rate-boosting action is due, not to the obvious electron-pair bonds that form between the enzyme and its substrate, but to more subtle attractive interactions between the two molecules. He compared the effect of one enzyme on a reaction of its normal substrate and of a smaller molecule that had all the essential bonding sites, but not the more peripheral chemical groups. The normal substrate easily won the race, reacting  $10^{12}$  times faster than its stripped down opponent. Jencks concludes that the overall binding thus causes most of the rate increase.

To be effective an enzyme must bind its substrate in a configuration with sufficient energy to hurdle the reaction energy barriers. Those configurations, called the transition states or transition structures, are stabilized by tight overall binding of enzyme and substrate. Jencks looks at the energy economics of enzyme systems. "You have to pay for what you get," he says.

Molding the enzyme and restricting the freedom of the substrate are two expenses that are met by the energy gained in the tight binding of enzyme and substrate. Jencks has evidence, for example, that in one reaction binding forces the enzyme to open. He finds an enzyme sulfide group 100 times more accessible to external inactivation when substrate is attached than in the vacant enzyme. Jencks points out that the energy gained by binding is only available to promote the reaction if the compounds form transition structures. Other complexes of enzyme and substrate must be less stable.

The fine details of biologically important reactions are also being examined by other theoretical organic chemists. William A. Goddard and colleagues at California Institute of Technology have developed a model that predicts the operation of flavins, co-enzymes that activate oxygen molecules to bind to organic compounds. Experimentalists disagree about the nature of the flavin-oxygen intermediates. The reactive part of the flavin has a number of sites where the oxygen could attach. From theoretical computations Goddard offers the experimenters a short cut; some of the apparent possibilities are energetically unreasonable. "We are just at the point to use theory to make prediction," he says.

*Continued on page 367*

## Who Won What When

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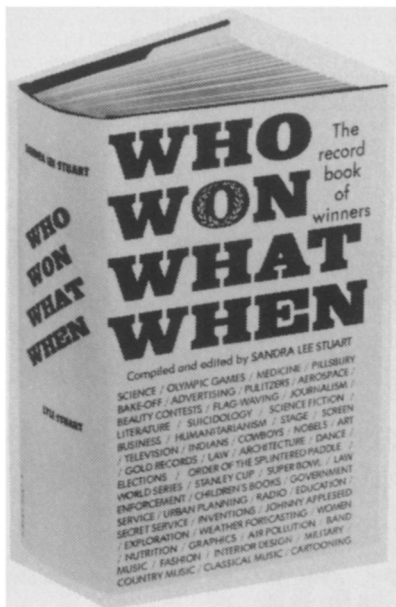
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## ... Chemistry

Goddard calculates that the most likely sites for oxygen attachment are the carbons shared by flavin's second and third rings (see diagram). The site (A) opposite the two nitrogens is the more probable, requiring 3 kilocalories per mole less energy. "Three more kilocalories can be the whole ball game," Goddard says.

The resultant structure with two unpaired electrons (designated with dots) is the activated oxygen-flavin complex. The oxygen arm next attacks phenol, a benzene ring having one hydroxyl group. Again Goddard's computation differentiates among various plans of attack. He calculates that it takes 10 kilocalories less energy for the oxygen to attach to the carbon atom with the hydroxyl group than to any other carbon on the ring. The oxygen later shifts position. The idea that attacking oxygen favors hydroxyl sites has been previously proposed, Goddard says, but no one suspected such a big effect.

While Goddard feels that theory is finally reliable enough to get answers to interesting problems and he urges experimenters to put trust in theoretical results, other chemists are more skeptical. The case of a simple molecule, methylene ( $\text{CH}_2$ ), served as a focus of argument at the Leermakers symposium. Experiments as well as theory have given a two-fold range of values for the difference in energy between two states of this molecule. Lawrence B. Harding, Goddard's colleague, pointed out that methylene is an important test case for theory. "And for experiment," Goddard interrupted. In addition, it is a key intermediate of many important organic reactions. Further experiments aimed at resolving this controversy are being done by W. Carl Lineberger at the University of Colorado in Boulder.

Even while dispute rages on some very basic questions, theoretical organic chemists are eyeing exciting problems for future application. Two of the most intriguing are the effects of solvents on chemical reactions and the catalytic role of metal surfaces. Because up to 50 solvent molecules can affect a single solute molecule, Goddard says, "solvent effects are crucial." Jencks describes an enzymatic reaction that occurs one hundred thousand times faster when the substrates are dissolved in ethanol than in water. The other intriguing puzzle, metal catalysis, fascinates chemists because of the possibility of designing alloy surfaces that will catalyze just the reactions industry requires.

Although it is clear that theoretical organic chemists have plenty of work to do, interest is on the rise. Things have changed since the time when Lipscomb first submitted a paper on the exact structure of a 2-sulphur, 4-carbon ringed compound. The referee then rejected the paper with the remark, "It's a 6-member ring. That's all an organic chemist needs to know." □