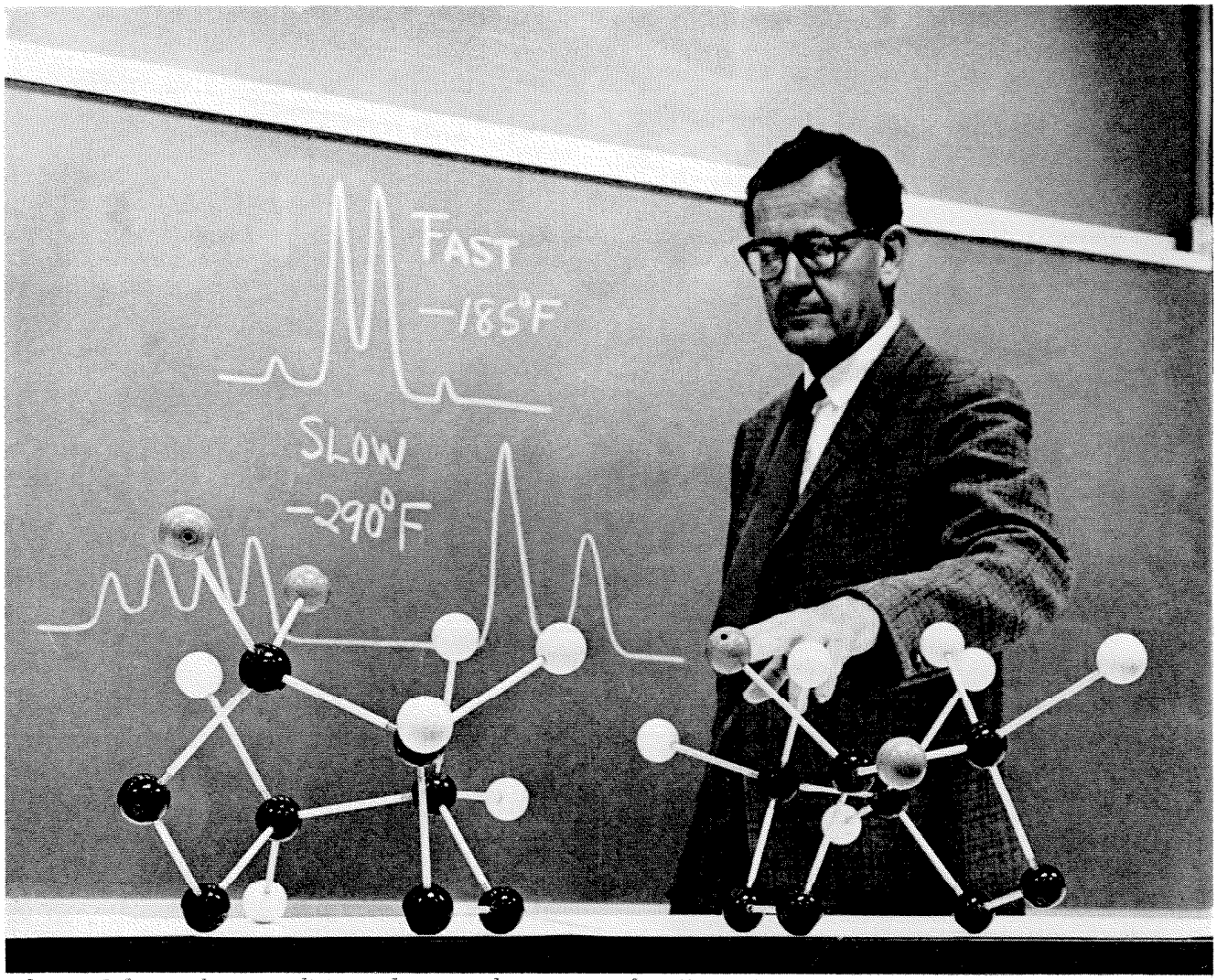


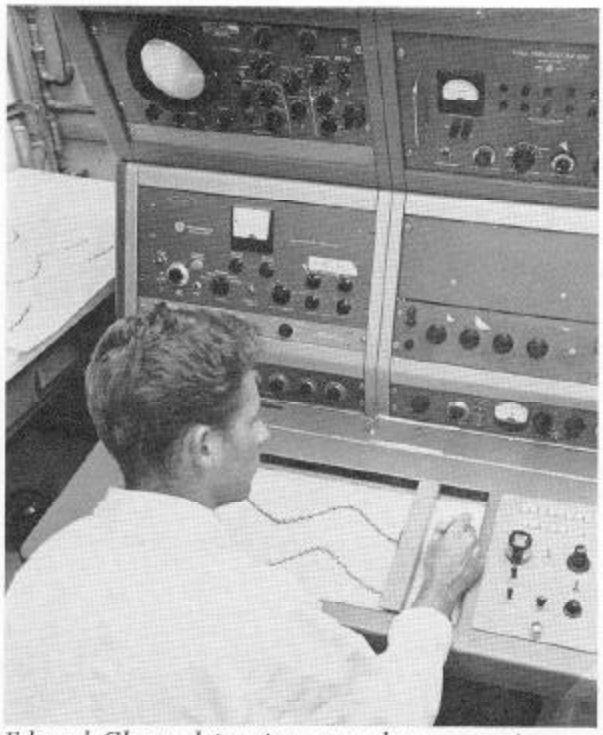
John D. Roberts, chemistry division chairman, demonstrates the effects of temperature on conformations of a molecule.

CONFORMATIONAL CHANGES

Caltech scientists study molecules that twist and flip-flop, often at very high speeds

Caltech chemists, under the direction of Professor John D. Roberts, are investigating conformational changes in certain types of hydrocarbon-ring molecules, some of which occur in pharmaceutical and industrial products. Conformational changes are changes in the spatial arrangements of the atoms within a molecule and may play a major role in influencing chemical and physical properties. (The coiling and uncoiling of DNA molecules is an example of a conformational change.) Knowledge of conformations of molecules and how they change is important in understanding drug action and the ways in which molecules are broken apart by enzymes, as in digestive processes.

For many molecules, conformational changes are amazingly rapid, often occurring as fast as billions of times per second. However, for other molecules, even of closely related structures, conformational changes may be extremely slow, so that some take place only once in 10,000 years.

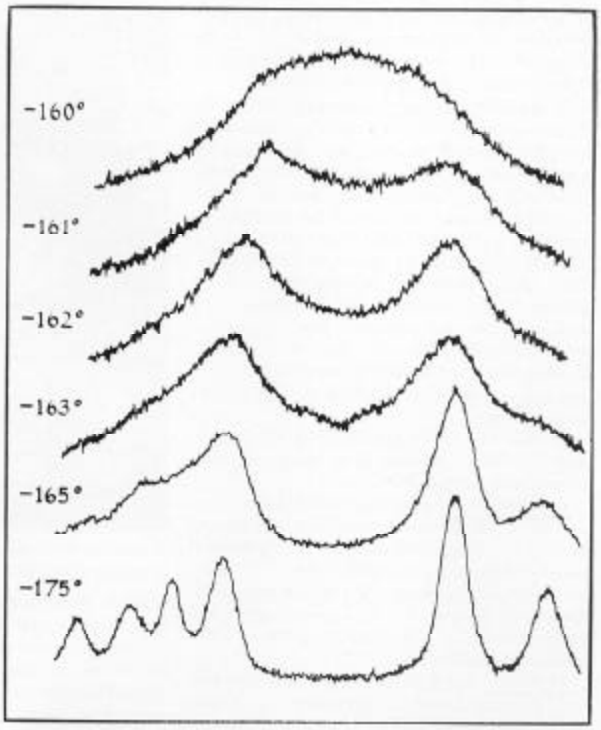


Edward Glazer determines a nuclear magnetic spectrum. The sample is in an adjoining 12-inch electromagnet. The spectrum recorded at the console will later be compared with other spectra of the same material taken at different temperatures.

The stable conformation of a molecule is one in which the atoms interfere with each other as little as possible within the constraints put on them by the chemical bonds between atoms. However, intermolecular collisions can deform them, "knocking" them into other conformations. Professor Roberts, Edward S. Glazer, and Drs. Gerhard Binsch, J. Thomas C. Gerig, and Dean L. Griffith have been studying conformations of rings of hydrocarbon molecules (cycloalkanes) to determine the favored conformations (if any) of those with six to ten carbons in the rings. Changes in the shapes of the rings as the carbon atoms flip from one position to another are basically mechanical processes that can be demonstrated and, to a degree, predicted with ball-and-stick models of molecules. These models show graphically that, in general, the larger the ring, the easier it is for the ring to twist and flip-flop without the carbon atoms having to break the chemical bonds with neighbor atoms.

Experimental technique

The technique used to analyze the conformations of these molecules is nuclear magnetic resonance (NMR), an extremely precise and comparatively rapid method that is also widely used in industry for chemical analysis of liquids and, sometimes, gases. In the apparatus used at Caltech, NMR measurements are made on samples in a strong magnetic field (14,000 gauss), which partially aligns the nuclei of the hydrogen or fluorine atoms in the field direction. The aligned nuclei can absorb energy in the radio frequency region, the specific frequencies being determined by the kind and chemical environment of the nuclei. The record of absorbed frequencies, which results in a series of peaks on a graph, permits determination of the type and number of atoms in the molecule. Rate processes such as conformational changes may show up as a blurring or averaging of the NMR spectrum. The changes, because they are caused by intermolecular collisions, are temperature-dependent. For that reason, molecules having a high rate of change are studied at low temperatures. Cyclooctane, an eight-membered ring for which a hitherto unsuspected form (the "twist boat") was found to be most stable, had to be cooled to −300° F for determination of its structure, because at room temperatures the ring changes between conformations more than a billion times per second. This research in conformational changes has been supported by the National Science Foundation and the Office of Naval Research.



Between -160° and -175°C the spectrum of 1,1-difluorocyclooctane changes drastically. At -160°C the rate of conformational change becomes slow enough that the fluorine atoms can begin to be detected in the extreme positions; at -175°C the molecule is essentially frozen, and the different locations of the fluorines are clearly distinguished.