# Molecular Photography with an X-ray Flash

*X-ray diffraction patterns obtained at an exposure time of one ten-billionth of a second open a new window on molecular structure and function*

GOOD PICTURES OF MOLECULES have always been hard to shoot, but the job just got easier. Biochemists at Cornell University recently used an intense beam of x-rays to take flash pictures of an organic molecule with an exposure time of about one ten-billionth of a second. The ability to take such fast photos should prove important, researchers say, in a number of areas, from understanding enzyme reactions to custom designing pharmaceutical drugs.

Keith Moffat, Wilfried Schildkamp, Donald Bilderback, and Marian Szebenyi of Cornell report they have taken x-ray diffraction pictures of the enzyme lysozyme and of a second organic compound with exposures a million times faster than had been done before. Working at the Cornell High Energy Synchrotron Source, they used a beam-intensification device to create an x-ray beam so powerful it took usable snapshots in just 120 picoseconds. (A picosecond is one trillionth of a second.) The importance of the result lies not so much in obtaining pictures of the molecules, which have no special significance in themselves, but in demonstrating the success of the technique, which makes it possible to take molecular pictures much faster than before.

The key to the success was the performance of a special magnetic device called an undulator. Just as a bright flash on a 35-millimeter camera allows a shorter shutter speed, the intense beam of x-rays produced by the undulator allowed the experimenters to take their shots with very short exposure times. The undulator was designed by a team with members from Argonne National Laboratory, Cornell, and Spectra Technology Inc. of Bellevue, Washington, which built the device.

The undulator is a prototype for a number of such devices planned for the Advanced Photon Source (APS), a synchrotron to be built at Argonne National Laboratory in Argonne, Illinois. When completed in the mid-1990s, the APS will provide x-ray beams 10,000 times brighter than are now easily obtained. To test the undulator, the research team used x-rays emitted by the Cornell Electron Storage Ring, whose beam was altered to approximately mimic the synchrotron radiation of the APS.

"This is a major success," said Gopal Shenoy, Argonne's associate division director for the APS, adding that the undulator did everything it was designed to do. "It has given people a glimpse of what to expect from the APS in the future in the way of scientific possibilities."

Those possibilities include faster and more detailed pictures of large biological molecules, such as proteins or viruses. Researchers say that intense x-ray beams, such as those generated in the Cornell experiment, will allow them to overcome some of the limitations of current x-ray imaging techniques.

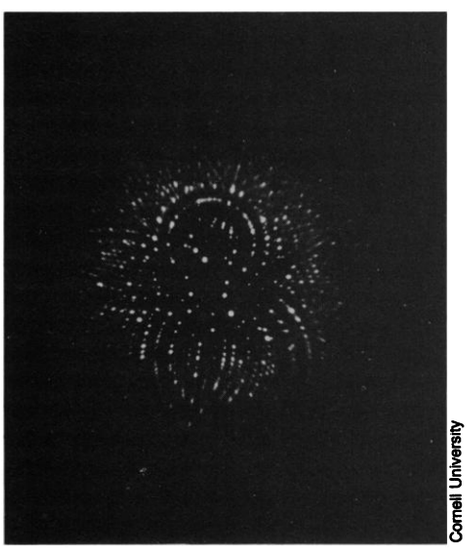
An x-ray picture of a molecule is not the same as a medical x-ray, but instead appears as a pattern of dots called a diffraction pattern. To photograph a molecule, a scientist first forms a large number of identical molecules into a crystalline structure—an ordered array where all the molecules are lined up in the same direction—and then aims a beam of x-rays at the crystal. The transmitted x-rays, when captured on film, show the pattern of dots called a diffraction pattern. By analyzing this pattern, a scientist can figure out the geometric structure of the molecule, thus forming a picture in an indirect way.

Diffraction patterns can reveal details as small as single atoms in a molecule. Electron microscopes, the only other viewing devices with similar resolution, demand special sample preparation and use in a vacuum, which makes them poorly suited for biological molecules.

A problem with diffraction patterns is that it is much more difficult to get good pictures of large molecules than of small ones. One reason is that the bigger the molecule, the farther apart are the repeated features in the crystal, and thus the weaker the diffraction pattern, since diffraction results from radiation passing through an ordered array. Another reason is that in crystals of biological molecules, much of the crystal may be water, which contributes nothing of use to the diffraction pattern.

To get a good diffraction picture of large molecules, then, a scientist must either make the crystals larger or increase the amount of x-rays in the exposure. Since it is difficult to grow crystals of macromolecules that are much larger than a millimeter across, the only practical option is to increase the exposure. This can be done by either lengthening the exposure time or increasing the brightness of the x-ray beam.

Until now, using a long exposure time was the only option, and researchers used exposures of anywhere from a few seconds to a few weeks. That limits the number of molecules that can be analyzed in a given period of time and it also prevents researchers from observing anything but the average structure of the molecule over time. Any movement that takes place in a fraction of a second, for instance, will be invisible in a 5-minute exposure.




**Diffraction pattern** *from a crystal of lysozyme molecules, taken with eight 120-picosecond flashes.*

With the several dozen intense x-ray beams that the APS will generate, researchers will be able to gather much more data on molecular structure in a much shorter period of time. They will be able to use smaller crystals, which will allow them to examine some molecules that have so far been out of reach, and they will be able to get greater detail on the molecular structures.

Perhaps the most exciting capability will be the much shorter viewing times the APS will make possible. Researchers are already making plans, for example, to watch how the shapes of enzymes change as they catalyze chemical reactions. In this way biochemists hope to understand exactly how enzymes work and perhaps then invent new compounds that can do the job of enzymes, only better. ■ ROBERT POOL