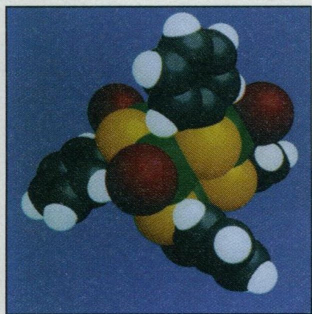
CHEMISTRY

Analyzing Molecular Structure With Astronomical Speed

Like proud parents, chemists Louis Pignolet and Leon Rubinstein wanted to take a portrait of their newborn molecule. Unlike most parents, though, the University of Minnesota scientists were after more than a snapshot to decorate a birth announcement. Their phosphine-studded gold-platinum cluster—named $[(H)Pt(AuPPh_3)_9](NO_3)_2$—had some unusual catalytic abilities, and to help them figure out why, the researchers wanted a picture of its internal structure. They turned to x-ray crystallography, a technique that scatters radiation off a crystallized version of the molecule in thousands of directions, revealing the identities of atoms and their relationships. But the molecules, although small, were large enough that a conventional x-ray diffractometer, which images one direction at a time, would take weeks to produce a finished picture. "In the old days," says Pignolet, "we would have thrown the crystals away and given up."



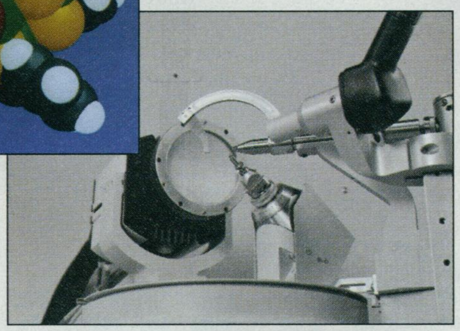
SIEMENS

But in Pignolet and Rubinstein's laboratory, the old days are history. That's because they have a diffractometer with a difference: a chip called a charge-coupled device (CCD), whose two-dimensional array of pixels—each acting as an independent detector—allows hundreds of x-ray reflections to be gathered at once. In a mere 6 hours, Pignolet and Rubinstein recently caught their molecule locked in two different forms in the same crystal, each with a unique arrangement of gold-phosphine groups: Flipping back and forth between such forms, they surmise, may explain its catalytic talents. Says Pignolet, "It's like taking instantaneous photos of what's going on."

Indeed, the machine—the Siemens Molecular Analysis Research Tool (SMART)—and similar devices recently announced by four other firms may fast become the 1-hour photo shops of analytic chemistry. CCDs' swiftness at gathering diffraction data means researchers can solve the structures of several molecules in a single day. The chips' great sensitivity, moreover, means structural information can be obtained even from crystals so small or low in quality that they would have stymied conventional detectors. Using SMART is "like going from a Model T to the Japanese shinkansen bullet train," says Jack M. Williams, a chemist at Argonne National Laboratory in Illinois.

Siemens began shipping SMART 15 months ago and will demonstrate the machine's software at the Pittcon chemistry conference in Pittsburgh next month. The device has disadvantages: Its $300,000 price tag is twice that of a conventional diffractometer, and it's not suitable for truly large molecules such as proteins. Still, Larry Dahl, a chemist at the University of Wisconsin, predicts that within a few years "half of the small-molecule diffractometers in use at major universities will have CCD detectors."

CCDs' first scientific applications were in astronomy, where they revolutionized the field with their ability to generate a measurable electric charge after being struck by a single photon. And that makes them a natural for crystallography. The patterns and intensities of x-rays bouncing off a crystal's ordered atomic lattice carry a wealth of information about the crystal's structure and makeup. But these reflections must be intercepted over an entire hemisphere before the information can be mathematically recombined into a model of the molecules' specific components; to gather this data, researchers must create a mosaic of shots from many different angles. The commonly used automated "serial" diffractometer, employing a point detector called a scintillation counter to measure x-ray intensities, can take days to rotate through all of the reflections generated by complex inorganic molecules. So-called "area detection" techniques such as photographic film and devices called multiwire counters capture more data simultaneously, but these are too insensitive for the study of small compounds, explains Charles Campana, an inorganic chemist and senior applications scientist at Siemens Analytical Instruments in Madison, Wisconsin.



Structure while-U-wait. This SMART diffractometer lets x-ray crystallographers analyze a new molecule ($C_{44}H_{54}N_2Br_2Zn_4Se_6$) in 2 hours, a chore that used to take days.

In the SMART system, which Siemens began developing in 1990, radiation beamed at a crystal sample by a molybdenum x-ray tube first bounces off the sample and then strikes a phosphor in the detector's 9-centimeter-diameter outer window, generating visible light. This light is picked up by the million-pixel CCD, which converts it into electronic data on position and intensity. The detector gathers whole swaths of reflections at once, so researchers take far fewer shots of a crystal. The results: No more long queues of chemists need to wait for diffractometer time, and researchers learn more quickly whether their experiments are on the right track.

Researchers analyzing lightweight, hard-to-crystallize superconductor materials in Williams's lab at Argonne are among the converts to the new technology. One substance formed such tiny, needlelike crystals that the lab's conventional diffractometer ran all night without collecting a speck of data, Williams recounts. When they mounted the same crystal on a SMART setup, he says "we saw hundreds of spots with 3 minutes of exposure. ... It has basically made our regular diffraction equipment obsolete."

SMART can't do everything, though. The x-ray wavelengths are too short, and the phosphor screen too small, for routine use on large molecules such as proteins. But a modular detector built by San Diego–based Area Detector Systems Corp., priced at $325,000, attempts to solve the second problem by linking a two-by-two array of phosphor x-ray converters to a single CCD. Molecular Structure Corp. of Houston will deliver a similar detector to its first customer next month. Two other firms have devices in the works, and Argonne National Laboratory's Structural Biology Center is building a dif5fractometer with a CCD 7.5 centimeters square for the detection of high-energy x-rays beamed at macromolecules by the lab's Advanced Photon Source.

Even with the current limits, those who don't have one already are eager to get their hands on a CCD-based machine. "It would be a real asset for our department and all departments to have something like this," says Joseph O'Connor, an organometallic chemist at the University of California, San Diego. "The big question is the expense. But that won't be so big a problem if the demand is there, since the throughput is so high." And the real payoff, says chemist Michael Scott of the Massachusetts Institute of Technology, is that "instead of worrying about crystallography, it enables you to spend a lot more time doing science."

–Wade Roush