The Ascent of Odorless Chemistry

A number-crunching brand of chemistry bypasses the traditional laboratory. Its practitioners create and study new molecules without ever leaving their computer terminals

The traditional picture of chemistry—white-coated scientists at black benches surrounded by chemical-filled cabinets, Rube Goldberg assemblies of glassware, beakers of sharp-smelling solutions, and a battery of analytical instruments—needs a serious overhaul. True, chemists are in the business of synthesizing and studying molecules, and for that there's no getting away from the lab bench. But lately the field's territory has expanded from conventional laboratories to less odoriferous environments, cluttered with software documentation, humming with computers, and glowing with colorful monitors.

Here, the computers do the chemistry, calculating in a few hours details of molecular structure and behavior that might have eluded top-notch bench chemists laboring for months or years, with money no object. The denizens of these electronic laboratories, so-called computational chemists—now roughly 2000 strong—are as at home with quantum mechanics and mathematically intense physical-chemical theories as their bench counterparts are with chemical laws and molecular synthesis. Computational chemists might seem to have abandoned the essence of chemistry, but actually they have gone back to basics: the spatial distribution and energy levels of a molecule's electrons, from which chemical properties arise.

Until recently, chemists who claimed they could calculate this electronic symphony risked their colleagues' scorn. "We used to laugh at theoreticians in chemistry," Harry Gray, director of Caltech's Beckman Institute of Chemistry, recalled during a public lecture in January at the Carnegie Institution of Washington, D.C. "Now we are not laughing." In the past few years, computational chemistry has been getting respect, first as a tool for double-checking and interpreting experiments and more recently as an independent route to chemical advances. When Henry F. Schaefer III, director of the Center for Computational Quantum Chemistry at the University of Georgia, reviewed the status of computational chemistry in *Science* 6 years ago, he could point to "a couple of dozen examples" of calculations that had predicted new compounds and reactions or showed where experiments had gone astray. "Now there are a couple of hundred" examples in such fields as rocket fuel development, polymer science, and pharmaceuticals. In some cases, it's now up to bench chemists to double check the theories, rather than the other way around.

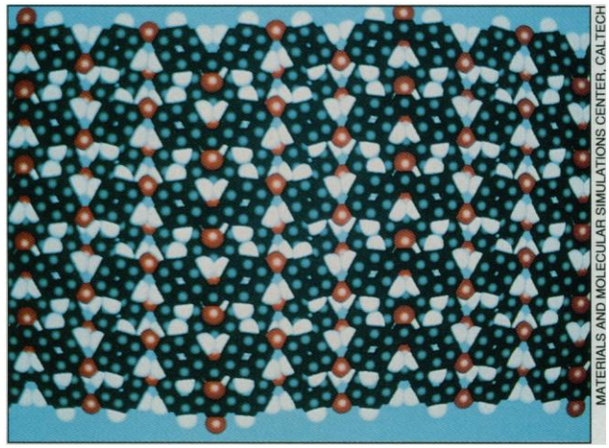
That's a remarkable transformation, say researchers—though some warn that such power can be seductive. By toying with molecules on a computer screen, some say, their colleagues risk losing the insights that come from handling real substances. But physicist Marvin L. Cohen of the University of California, Berkeley, who has been using computers to design carbon and nitrogen lattices that may be harder than diamond (see box), revels in the turnaround. "We can become the world's experts on a particular [molecule] or material, though we may have never seen it," he says.

First principles. Many of the foundations of computational chemistry were laid in the 1920s, with the formulation of quantum mechanics. By 1928, pioneering theorists were pointing out that Erwin Schroedinger's quantum-mechanical equation describing the energy and distribution of electrons around nuclei opens the way to calculating and predicting a molecule's complete chemical personality: its shape, stability, and how and when it reacts. Schroedinger's equation "provides, in principle, a complete description of almost any problem in chemistry," says Donald G. Truhlar, a computational chemist at the University of Minnesota.

"In principle" is right. Schroedinger's equation can be a wild mathematical behemoth for chemists. For exact solutions of the electron density around, say ethanol, which includes just nine atoms, the amount of number-crunching can choke even today's supercomputers. The simplest mathematical picture requires 26 functions, one for each electron. Worse, the behavior of each electron and atomic nucleus affects all the others, in an exponential web of interactions. All told, the calculation could end up involving more than half a million terms, each one containing a six-dimensional integral. Moreover, solving these huge equations is not a single gargantuan one-pass computation, but rather an iterative process in which the results of one pass feed into the next pass, and so on for tens or thousands of cycles.

That sort of calculation was simply out of the question for decades. But when computers became sparsely available to scientists in the 1960s, computational chemistry experienced something of a false start, according to Charles Bauschlicher Jr., head of a computational chemistry group at the National Aeronautics and Space Administration's (NASA) Ames Research Center in Mountain View, California. In those days chemists still couldn't hope to get exact solutions for Schroedinger's equations. So they greatly simplified these so-called ab initio (from the beginning) calculations by ignoring or approximating big hunks of the quantum mechanical equations. But the simplifications were so extreme that the computed results often didn't agree with experimental measurements of the real things. Experimentalists like Gray had little incentive to begin trusting newfangled, hit-or-miss, computational results over time-tested experimental ones.

Since then, though, computers have multiplied in power and accessibility, and they've been joined by an array of molecular graphics software that can turn the mathematical description of a molecule into a dazzling animated drama on a monitor. As a result, says Jan Almlöf, Truhlar's colleague at Minnesota, "we now can treat molecules made of a couple hundred of atoms with accurate calculations from first principles." Another advocate, Lt. Col. Larry W. Burggraf of the Air Force Office of Scientific Research (AFOSR) in Washington, D.C., claims that parallel processing supercomputers open the way to ab initio calculations of 1000-atom molecules. That sounds impressive, but where does that leave chemists, biologists, drug-



MATERIALS AND MOLECULAR SIMULATIONS CENTER, CALTECH

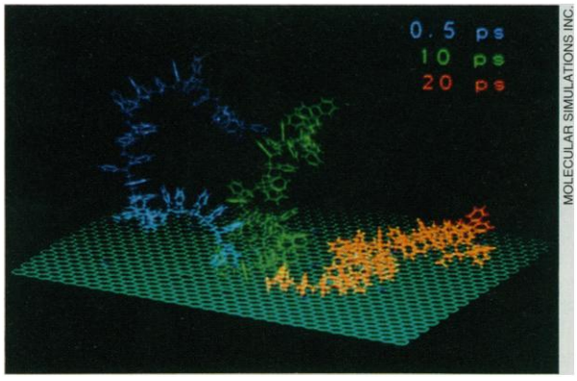
A digital PEEK. A simulation shows how molecules of polyetheretherketone (PEEK), a common polymer, pack together.

makers, and materials scientists whose labors of love and profit involve thousands or millions of atoms?

To cope with these larger molecules, an entire sub-specialty has grown up devoted to developing "new computational strategies and algorithms," says Almlöf. These strategies link the equations of quantum mechanics and other physical theories that describe chemical phenomena to the number-crunching ways of computers. "Half of what we do is to develop methods [of computation]," concurs Schaefer.

In many cases, Schaefer and his colleagues strike a compromise with experiment, reducing the computational burden by using some laboratory data in the calculations. Workstation programs based on that strategy are already available commercially, and they can calculate stable structures (including such features as bond distances and angles) for 50-atom molecules in as little as 2 minutes, according to an in-depth market analysis of computational chemistry published this year by Charles T. Casale of the Aberdeen Group Inc., a private industry and technology assessment firm in Boston. Meanwhile, by pushing such methods, solid state scientists like Berkeley's Cohen have been extending computational chemistry to the architectures of periodic materials such as crystals, with atomic constituencies numbering in the millions. To do so, Cohen and his colleagues resort to "molecular mechanics" and "empirical force field" calculations. These techniques sidestep computer-choking quantum mechanical computations by portraying molecules as, say, sets of balls linked by springs, which represent the balance of electron-electron repulsions and electron-nucleus attractions.

Such computational advances have given experimentalists a way to keep a critical eye on their laboratory measurements: On finding a mysterious peak in an infrared absorption measurement, for example, researchers can calculate whether it is a plausible one for that molecule. But chemistry by computer is also taking the place of experiment. At NASA Ames, for example, Bauschlicher and his colleagues are using computational methods to investigate the rate of reactions that might occur as fuel burns in rocket engines and other advanced propulsion systems, places too hostile and chemically complicated even for the most bold and capable of chemists. Bauschlicher suspects that his team's ab initio studies of hydrogen atoms recombining into hydrogen molecules, for example, will help designers of engines for the hypersonic National Aerospace Plane (NASP) or the High Speed Civil Transport project (a proposed new generation of supersonic airliners) set optimum lengths for nozzles or combustion chambers.



Molecular tango. A computer calculates a time-lapse view of a polystyrene molecule adhering to a graphite surface.

The High Energy Density Materials Program—a joint effort of the AFOSR and a team at the Edwards Air Force Base in California—takes computation in a different direction. While Bauschlinger and his colleagues are studying familiar reactions under unfamiliar conditions, the Air Force project aims to come up with entirely new substances that will serve as better liquid and solid rocket propellants. "Our aim is to store as much chemical energy as we can in light chemical compounds," notes Burggraf of AFOSR, the program's manager. And computational chemistry, by suggesting new molecules that might be stable yet release exceptional amounts of energy when they burn, is proving invaluable. "The computational chemists have predicted new systems," Burggraff says. Schaefer of the University of Georgia, for example, proposed rings of oxygen atoms—a form that chemists had never synthesized—as an energy-packing form. Rings of four oxygen atoms turned out to be unstable, says Burggraf. "But there is hope for eight-member rings."

Streamlined discovery. Even the kind of molecular tinkering to improve an existing compound's properties that used to be done at the lab bench is now moving into computers. In one ongoing project, computational chemists at the General Electric Co. in Schenectady, New York, model polycarbonate molecules, the chemical basis of their company's Lexan line of plastics, seeking molecular variants that might hold colors better or be easier to mold. Having chemists synthesize and test hundreds of slightly altered molecules is one route to the desired properties, says Mike O'Mara, GE's manager of chemical research at the company's Research and Development Center, "but it's not a very efficient way to work." Using computers to first edit down the possibilities saves time and money. "The computational approach will lead us to answers faster," O'Mara says.

That prospect is bringing many other industries into the computational fold. "In the last few years, companies specializing in polymers, ceramics, and materials in general have come to believe that theory can now provide good enough information that they can do

A Gem of a Diamond-Beater?

Computational chemists are becoming ever more adept at conjuring up new compounds and structures (see main text). But all this digital artistry still has to face the test of the laboratory. Just last week came evidence that one of computational chemistry's more dramatic predictions—of a material that might be harder than diamond—has been realized.

The quest began 3 years ago, when Northwestern University materials scientist Yip-Wah Chung came across the work of Amy Liu and Marvin Cohen. Liu and Cohen, a materials scientist and a physicist, respectively, at the University of California, Berkeley, had used a supercomputer to predict that a superhard material might be made from carbon and nitrogen atoms (*Science*, 25 August 1989, p. 841). Their calculations indicated that if the atoms were arranged in structures similar to certain forms of silicon nitride (Si_3N_4), the carbon-nitrogen bonds might be stronger than the carbon-carbon bonds of diamond.

At last week's International Conference on Metallurgical Coatings and Thin Films in San Diego, Chung reported that his lab has synthesized a material that may fit the bill. Using a process known as magnetron sputtering, in which an argon-nitrogen plasma interacts with high-purity graphite, Chung and his colleagues were able to coat a number of surfaces with thin carbon nitride films.

The group hasn't yet confirmed that their material has the predicted structure, but they do know that, like diamond, it is an excellent lubricant and extremely wear-resistant. And preliminary tests suggest it may indeed be harder than diamond. For example, nanoindentation, a test using a small diamond point, produced no holes in the films—which could mean either that the coating is harder than diamond or that it is highly elastic. Further tests scheduled at Sandia National Laboratory should settle that question.

If Chung really has made a diamond-beater, Liu and Cohen will breathe easier. Their prediction had faced a certain skepticism, says Cohen, since materials scientists tend to see the hardness of diamond as a natural superlative, "like the speed of light." Says Cohen: "We were hoping for some experimental confirmation. I hope he has it."

–John Travis

fewer experiments," says William A. Goddard III, director of the Materials and Molecular Simulation Center at Caltech's Beckman Institute. Reducing overhead is just one benefit, adds Herman Finkbeiner, manager of GE's chemical/biological research laboratory. "We want more wild ideas tried out on computers," he says.

Finkbeiner and other industrial chemists are following a computational trail blazed by the pharmaceutical industry, the first to run with the computational ball starting about 10 years ago. Drug developers routinely compute hundreds of variants on a molecular theme, rotate them any which way in space, and probe their interactions with a specific receptor, biochemical, or pathogen, remarks Donald Boyd, a research scientist at Eli Lilly. The computerless alternative, which characterized the field for all but its most recent history, was to synthesize and test real molecules, an extremely costly and inefficient process. Even now, there's no getting around synthesizing and testing actual compounds; no drug yet on the market was invented solely by a computer, says Mark A. Murcko, a molecular modeler at Vertex Pharmaceuticals Inc. in Cambridge, Massachusetts. But any streamlining of the time and expense of developing a marketable drug—one estimate puts the average at 12 years and $125 million—can yield big payoffs.

Hot numbers. The potential gains are turning computational chemistry itself into a hot item commercially. In 1990, according to the 1992 Aberdeen Group report, the "overall market for computational-chemistry hardware, software, service, database, and other sales was $530 million," up from $330 million in 1988. "We conservatively project the market to increase to $2 billion by 1996," continues the report. To supply the expanding job market, the field has even spawned its own recruiting agency: Molecular Solutions in St. Louis.

All this ferment is a bit unsettling to some chemists, who fear the ascendancy of chemistry-by-computer could spawn generations of chemists who lack hands-on experience with chemicals and reaction. When theoretical chemist Roald Hoffman of Cornell University wants to get a real feel for a molecule, for example, he builds a three-dimensional model so he can hold it in his hands and run his fingers around its contours. "There's no better way" to understand chemical structure, he says. And he worries that the visual appeal of molecular modeling programs could end up wooing researchers away from this tactile route to chemical intuition.

The boom in computational methods makes it inevitable that, well-grounded or not, those fears will get a thorough testing. By Murcko's reckoning, the computational chemistry wave is just coming in. "Maybe 1% of computational chemistry's potential has been tapped."

–Ivan Amato

MEETING BRIEFS

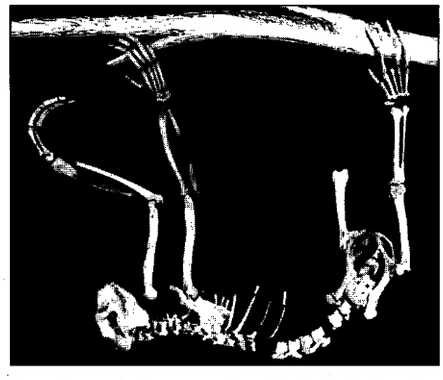
Anthropologists Bet on Their Latest Data in Las Vegas

Anthropologists need luck on their side when they search for key fossils or study monkeys in the wild, but their work can still hit the jackpot. That was clear at the 61st annual meeting of the American Association of Physical Anthropology, which brought more than 800 anthropologists to Las Vegas in early April. Among the reports was one on new fossils of early hominids in Ethiopia and another on extinct giant sloth lemurs in Madagascar.

Extinct Lemurs in Madagascar

Last July, anthropologists Elwyn Simons of Duke University and Laurie Godfrey of the University of Massachusetts were deep inside the dank Cave of the Lone Barefoot Stranger in northern Madagascar, busily wrapping up bone fragments after a hard day's work, when a student in another part of the cave yelled out: "You better come over here." They found Ted Roese, now a graduate student at the University of Iowa, standing beside a muddy pool of water with a grin on his face and a large skull, still dripping, in his hand. "What do you think it is?" he asked.

Even in the dark, Godfrey and Simons knew the answer immediately: It was an extinct species of giant sloth lemur they had recently named *Babakotia radofilai*. "We said,



Hanging out. A composite of *Babakotia* fossils.

'That's it,'" Godfrey told the audience in Las Vegas. And their excitement built as they drained the pool and found a nearly complete skeleton of the creature. Their excitement was well founded: The discovery is causing anthropologists to revise their notions of how lemurs evolved. And that's important because the work could shed light on primate evolution since lemurs preserve some features that were found in the earliest primates—creatures that were ancestral to both lemurs and the primate branch that includes humans, apes, and monkeys.

What's more, the lemurs give anthropologists a glimpse of an alternate world that might have evolved if apes and monkeys had never come onto the scene. Since monkeys never made it to Madagascar, they weren't able to crowd out lemurs, which flourished there as a result. "Probably in Madagascar there was an amazing radiation in lemurs that took place millions of years ago to develop and produce all kinds of strange end products," says Simons.

Indeed, Madagascar has proved to be an extremely rich source of lemur fossils. The first fossils of giant sloth lemurs were discovered at the turn of the century, although anthropologists did not search for more until the mid-1980s. That's when Simons joined forces with researchers from the University of Antananarivo in Madagascar to explore the so-called Crocodile Caves, a warren of underground caverns that extends 100 kilometers through a limestone range called Ankarana Mountain. Right from the start, Simons' team found thousands of bones of extinct lemurs, culminating in 1988 in the discovery of the fragments of a jaw from what proved to be the first example of a new genus and species. The researchers called the species *Babakotia radofilai* in honor of French mathematician and spelunker Jean Radofilao, who mapped the caves.

But it wasn't until after Roese's discovery last summer that they began to appreciate just how different this primate species is. It's "one of the most strangely adapted creatures that ever lived," says Simons. Unlike living lemurs, which are agile leapers and sometimes as small as mice, *Babakotia* was as big as a baboon and probably slow moving. Indeed, its fossils suggest that it acted more like a sloth, spending much of its time hanging upside down in trees.

The team proposes that the *Babakotia*'s skull and upper limbs suggest that is related to a family of living lemurs known as the Indri—and that is challenging the notion that the Indri's dramatic ability to leap was a primitive condition for all primates. Now the team thinks that the Indri's agility and the *Babakotia*'s slothfulness were more recent adaptations.