"Chemzymes" Mimic Biology in Miniature

These smallish molecular catalysts have all the selectivity of natural enzymes—and could transform synthetic chemistry

LAST FEBRUARY, when first-year graduate student Gregory Reichard was ready to begin his research, Harvard University chemistry professor Elias J. Corey came up with a little problem to get him started: synthesize fluoxetine, an antidepressant and antiobesity agent that Eli Lilly & Company introduced just 2 years ago under the trade name Prozac and that is already ringing up sales of more than $100 million per year.

As a student project it was a bit ambitious, perhaps, especially considering that fluoxetine synthesis is still a tricky business for Lilly's army of professionals. And yet, despite the inevitable false starts, plus the distractions of course work and teaching, Reichard finished his synthesis in only 6 weeks—having demonstrated a method that is simpler, faster, and more effective than anything Lilly had known about.

"I like to give beginning students something to build up their confidence," says Corey.

That sort of confidence is fast becoming the norm in Corey's laboratory. The key to Reichard's coup was his use of a "chemzyme," one of a unique series of molecular catalysts that Corey and his group have been developing for about 2 years now. Still so new that few outside researchers have had a chance to work with them, chemzymes offer synthetic chemists unprecedented control over their reactions. And with their potential applications ranging from basic research on reaction mechanisms to multimillion-dollar pharmaceutical manufacture—Eli Lilly, for one, is now deep in negotiation with Harvard, which owns the basic patent on chemzymes—chemzymes are fast gaining a reputation among chemists generally as being among the most intriguing innovations of the decade.

"It's one of the most exciting things in academic research," says Burton Christensen, senior vice president for chemical research at the giant drug firm Merck & Company, which is watching Corey's work very closely.

"The kinds of things Corey is doing are going to be enormously helpful to synthetic chemists, the people who *make* things," agrees Cornell University's Bruce Ganem, who organized a recent organic chemistry symposium at which Corey reviewed his work.*

Harvard University

"This is a brand new thing in chemistry—a rational design of molecules that work in a known way." —Elias J. Corey

Chemzymes, explains Corey, are small, soluble organic molecules that can catalyze certain reactions in much the same way that natural enzymes catalyze biochemical reactions. Indeed, he coined the word as a contraction of "chemical enzymes." Think of a submicroscopic production-line worker: over and over again, the chemzyme grabs a pair of reactant molecules out of the surrounding solution, twists them into position, welds them together into a precise three-dimensional structure, and then tosses the product molecule away to free itself for the next pair of reactants.

But the most striking thing about chemzymes, says Corey, is that they share natural enzymes' ability to tell left from right. Like a demented glover who only makes gloves for the left hand, a given chemzyme will churn out all its product molecules alike—and ignore the possibility of making a mirror image of the product.

Getting this kind of handedness, or "chirality," in a product is absolutely essential when you are dealing with biological systems, says Corey. In much the same way that a left-handed glove will fit only the left hand, enzymes, cell receptors, and all the other molecular components of life are structured so that they will respond only to molecules of precisely the correct chirality. Eat a steady diet of mirror-image glucose and you will starve. Take a drug of the wrong chirality and your body will ignore it.

Producing biologically active chemicals with the correct handedness has been a chronic problem for the drug companies. Conventional methods of chemical synthesis tend to produce right-handed and left-handed molecules in equal amounts, which means that a large fraction of expensive raw materials may be wasted from the beginning. And even when techniques *are* available for chiral synthesis, they tend to be complicated, slow, and relatively unselective. Either way, there is usually a lot of trash left in the mixture to be separated from the useful compounds—if this can be done at all. Often, in fact, the companies simply sell their drugs as equal mixtures of right-handed and left-handed forms.

Small wonder, then, that pharmaceutical houses and university chemists alike have put improved methods of chiral synthesis at the top of their research agenda. And small wonder that Christensen, Ganem, and others have gotten so excited over Corey's chemzymes. Instead of struggling with natural enzymes that are hard to work with, hard to come by, and poorly understood, here is a set of molecules that achieve equal selectivity with molecular weights of less than 500 and can be readily tailored to generate the desired product.

Corey traces the origin of the chemzyme concept back to 1968, when his group was engaged in a pioneering synthesis of the prostaglandins, a family of hormone-like compounds that serve as regulators for reproductive functions and a wide variety of other processes. "At the time we had trouble controlling the stereoselectivity at the 15th carbon atom of a side chain," he says, "and it was clear even then that a chiral catalyst would have been valuable."

Indeed, he says, over the next decade or so that little problem of the 15th carbon atom was to inspire a lot of innovative chemistry from a lot of different laboratories. Ways were found to solve it—but not with a chiral catalyst. It was only in the early 1980s that anyone even got a glimmer of how such a catalyst might work.

"We started working on our current mechanistic model about 1982," says Corey. "What we wanted was a catalyst that would combine with the first reactant, A, and form a new species that would combine more avidly with the second reactant, B, than either one alone. This would lead to an

*National Organic Chemistry Symposium, American Chemical Society, Cornell University, 19 to 21 June 1989.

accelerated reaction." At the same time, he says, this mechanism could also provide spatial control: with both A and B hooked firmly onto different points of an appropriate catalyst molecule, there would be only one way they could reach across, touch each other, and merge to form a product.

The trick was to find a catalyst molecule with the right properties. A search through what Corey calls "a very confusing literature" on chiral synthesis, together with a few years of laboratory study, eventually led his group to a certain organic compound containing the element boron. It had been investigated several years earlier in the laboratory of Japanese chemist Shinichi Itsuno. But what they found was that a slight modification caused it to have a dramatic catalytic effect, with one chiral form of the product molecule being enhanced over the other by factors averaging 20 to 1.

Dubbed the "CBS" catalyst after the initials of the three authors on the 1987 paper—Corey, Raman K. Bakshi, and Saizo Shibata—it was the first of the chemzymes. Since then it has grown into a family of about 20 different catalysts, each with a slight modification to the basic molecule designed to enhance its usefulness to a particular reaction. At the same time, moreover, Corey and his co-workers have developed several other chemzyme families, one of which works beautifully for that original prostaglandin synthesis.

Looking to the future, Corey is particularly excited by the possibility of designing chemzymes that incorporate atoms of a transition metal such as nickel, molybdenum, or rhodium. Not only are metals very good at making molecules more reactive, he says, but because they are so big and have so many electrons in their outer layers, they can also coordinate as many as seven or eight groups at once. "And that gives you tremendous potential for much more sophisticated, information-rich catalysts," he says.

Meanwhile, Corey likes to think that the chemzyme work is important for another reason as well: it exemplifies a movement in modern chemistry known as "rational" molecular design.

"CBS was unique in that it was not found by trial and error," he says. "We started out by understanding the reaction and the chemical mechanisms involved. And then we looked for a system with the right 3-D control and reactivity enhancement, sorting through what we knew about molecular structure and reaction pathways."

"This is a brand new thing in chemistry," he says, "a rational design of molecules that work in a known way. I like to think that CBS was a first step in that direction."

■ M. MITCHELL WALDROP

DNA Typing Is Called Flawed

One month after a group of scientists made legal history in a Bronx courtroom, the case which brought them together is about to come to a verdict.

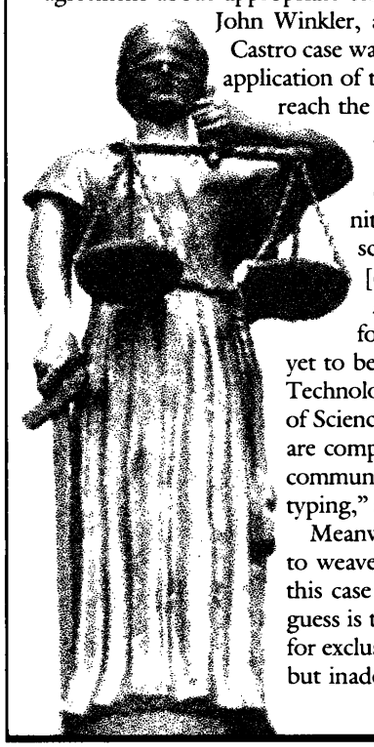
In June, four scientists called as expert witnesses for both the prosecution and the defense rewrote judicial practice when they banded together and declared that the scientific evidence—DNA typing—in the pre-trial hearing of this double murder case was no good and should be dumped (*Science*, 2 June, p. 1033). The unusually long hearing is now at an end, and just last week, in the final briefing to the judge, prosecution counsel made a dramatic concession: the DNA results that were supposed to link the accused murderer to his alleged victims are so flawed as to be inadmissible. And yet, proposed the prosecuting attorney, the judge should make a ruling on the admissibility of such evidence in general.

"Bizarre," says defense counsel Peter Neufeld. "How can the prosecution argue that the technique is acceptable, when the only example of it the court has seen has been described as grossly inadequate by scientists on both sides?"

The Castro case, as this trial has come to be called in the national press, was by no means the first in which the relatively novel technique of DNA typing has been used to try to tie an accused to his victim: since it was introduced a couple of years ago, the method has been on the witness stand more than 200 times. But Castro became a cause célèbre when defense counsel decided to launch the first serious challenge to the reliability of the technique. "The Castro hearing put DNA typing as a whole on trial," says Neufeld. "And from the evidence we've seen, you'd have to say it fails."

Done properly, DNA typing compares the genetic material from two sources and, if they match, gives an estimate of the probability of such a match occurring by pure chance: it is a combination of modern molecular biology and standard population genetics, and holds the promise of being extremely powerful. The evidence in *People v. Castro*, which was produced by Lifecodes Corporation, New York, a major player in forensic DNA typing, was said to demonstrate that a spot of blood on Joseph Castro's watch genetically matched the blood of one of the victims, the likelihood of a match by chance being one in 189,200,000.

"In the Castro case both parts of the technique—the molecular biology and the population genetics—were scientifically unacceptable," says the Whitehead Institute's Eric Lander, a witness for the defense. The joint statement from all expert witnesses was blunt on this point this, and added: "There is a need to reach general scientific agreement about appropriate standards for the practice of forensic DNA typing."



John Winkler, a spokesman for Lifecodes, told *Science* that "The Castro case wasn't our best work—it was early days in the forensic application of the technique." Nevertheless, he added: "Would we reach the same conclusion today? Yes, we would."

Although legal standards vary from state to state, acceptability of scientific evidence includes some element of consensus among the scientific community. "The record in this case makes it plain that the scientific community has not resolved these questions [of standard practice]," argues the defense counsel.

As further evidence to the current immaturity of forensic DNA typing, defense counsel also points to a yet to be completed study of the technique by the Office of Technology, and a soon to be announced National Academy of Sciences' panel on the subject. "Until these various studies are complete, it is surely premature to say that the scientific community has come to a consensus on forensic DNA typing," says Neufeld.

Meanwhile, the judge—Gerald Sheindlin—whose task it is to weave science and the law into some compatible mix in this case is expected to deliver his decision next week. One guess is that, as currently practiced, DNA typing is adequate for exclusions (saying that two DNA samples do not match), but inadequate for inclusions (saying two samples match).

■ ROGER LEWIN