New catalyst yields one-handed compounds

Like a pair of hands, molecules often come in mirror-image, or chiral, forms. Though this facet of nature has many virtues, it can be troublesome to chemists seeking to synthesize a particular drug, toxin, or insecticide.

Often during synthesis, the fabrication process yields both versions of a molecule, even though only one is desired. The two types appear nearly identical, yet display remarkably different properties. The chemist's craft lies in devising simple methods of separating such enantiomers — the left-handed or right-handed versions of a molecule — from one another.

In the Aug. 11 NATURE, Kam T. Wan and Mark E. Davis, both chemists at the California Institute of Technology in Pasadena, tell of a new way to achieve chiral separation. They describe the design and synthesis of a catalyst that favors enantiomers of only one type.

Their new catalyst, which they can tailor to speed up a wide range of reactions, has three critical features that distinguish it from similar catalysts, says Wan. It is heterogeneous, remaining a solid even when mixed into a liquid undergoing a reaction. This enables researchers to filter the catalyst out and reuse it easily once the chemical transformation is complete.

The catalyst is also asymmetric, says Wan: It facilitates the making of either a left-handed or a right-handed version of a specific molecule. "The catalyst itself is an enantiomer," says Wan, "so you can make it either way." Depending on the details of the reaction to be enhanced, a chemist can design the catalyst to speed up many kinds of chemical processes, creating the desired enantiomeric form.

A third noteworthy feature of this catalyst is its high selectivity, says Wan. The compound yields the correct form of a desired molecule at least 95 percent of the time, making it both practical and commercially viable. In one test, Wan and Davis designed the catalyst to reduce the compound 2-(6'methoxy-2'-naphthyl)-acrylic acid, yielding the anti-inflammatory agent naproxen. The catalyst achieved a selectivity above 96 percent, they report.

Only homogeneous catalysts have proved so highly selective. Yet these catalysts are difficult to separate from the final product once the reaction is finished.

"For this type of catalyst, this is unique," says Wan. "No one has reached that level of selectivity before with a heterogeneous asymmetric catalyst."

Indeed, high selectivity in a catalyst makes a great difference during drug synthesis. In the case of naproxen, for example, "the right-handed version relieves pain, while the left-handed form is a toxin," Wan observes.

One problem that has plagued previous attempts to make this type of catalyst is leaching, says Wan. During reactions, the catalytic agent will sometimes seep into the final product and contaminate it. Yet with this catalyst, leaching does not occur, he points out.

To prevent leaching, maximize the surface available for a reaction, and make it easy to recycle the catalyst, the chemists first dissolve the compound in ethylene glycol. They then soak tiny, porous glass beads in this solution. When added in this form to a chemical reaction, the catalyst promotes the making of one enantiomer, yet remains a solid, Wan says.

"This is a general type of catalyst," Wan adds. "It could be used to make many kinds of drugs or compounds — and almost any molecule that involves an asymmetric reaction. I don't really see any limitations." — *R. Lipkin*

Lake Apopka pollution hurts bass population

Lake Apopka near Orlando covers 38,000 acres and is one of Florida's largest freshwater lakes. It's also one of the state's most polluted. The reasons, says Tim Gross of the University of Florida in Gainesville, include a large chemical spill in 1980, pesticide pollution from the citrus industry, and chemical drainage from "muck farms," the marsh-rich farmland that is drained, farmed, and flooded two to four times a year.

The desire to understand this pollution's effects on lake animals steered Gross toward the largemouth bass. Earlier work by Gross and colleagues Franklin Percival and Louis Guillette suggested that pollution, particularly estrogenic pesticides, had caused Lake Apopka's alligator population to suffer reduced fertility and a surprising feminization of males (SN: 1/8/94, p.145).

The bass research, carried out by Gross, Percival, and William Johnson of the Florida Game and Freshwater Commission, began this April and ended in August. They collected 60 fish from each of three comparably sized lakes — Lake Woodruff, pristine; Lake Griffin, mildly polluted; and Lake Apopka, heavily polluted. "The numbers of bass [in Apopka] are a tenth of what they'd be on most lakes," says Gross. In 2 to 4 hours, the team collected 30 bass from Lakes Woodruff and Griffin; it took 8 to 16 hours to collect the same number of fish from Lake Apopka.

The researchers report that though the female bass appeared fertile, there were far fewer juvenile and adult bass in Lake Apopka than in the other two lakes. Gross notes that they found no fingerlings. "This suggests," he says, "that [the Apopka bass] are not producing as well." In addition, the team observed that 90 percent of the Lake Apopka bass contained high numbers of parasites, cysts, and liver tumors, whereas only 5 percent of the fish from the other lakes did. Next year, the team will further investigate these abnormalities, says Gross. "This [work] may indicate that the immune system is affected." — *G. Marino*

AIDS research: From vaccines to safer sex

This week, researchers from around the world met at the Tenth International AIDS Conference in Yokohama, Japan, to report scientific findings on topics ranging from vaccine development to long-term survivors of HIV infection. At the same time, several major journals published updates on this devastating disease.

• At the AIDS meeting, National Institute of Allergy and Infectious Diseases (NIAID) Director Anthony S. Fauci and his colleagues reported preliminary results from a study of people who had remained healthy despite being infected with HIV for about a decade. Their study suggests that such people may show a more aggressive immune response to HIV, the virus that causes AIDS. Compared to HIV-infected people who progressed to AIDS, those who did not had very high concentrations of HIV-destroying antibodies.

• In the Aug. 10 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, Robert B. Belshe of the St. Louis University School of Medicine and his colleagues demonstrated that a genetically engineered vaccine triggers the production of antibodies that attack several strains of HIV.

The study involved 57 volunteers who were not infected with the AIDS virus. Forty-eight of them received varying amounts of vaccine, a product genetically engineered to look like the gp 120 protein that sits on the surface of the AIDS virus. The remaining nine recruits got an inactive placebo.

"We were delighted to learn that two shots of the vaccine stimulated antibodies that could attack and kill a strain of HIV in the laboratory," Belshe says. After giving three or four doses of vaccine, the researchers documented antibodies that neutralize additional strains of HIV. An effective vaccine must recognize and kill many different types of HIV, Belshe points out.

The vaccine, made by Genentech of South San Francisco, seemed to spur the production of an antibody that attacks

virus-infected cells. The body may rely on such antibodies to clear the blood of HIV-tainted cells, an important step in fighting off infection.

• At the AIDS meeting, M. Juliana McElrath of the University of Washington in Seattle presented results from a larger study of the same Genentech gp 120 vaccine and another gp 120 vaccine, this one made by Biocine Co. of Emeryville, Calif. The study involved 296 people, including some volunteers at high risk of HIV infection. Thirty-nine people received a placebo; the remainder got either the Genentech or the Biocine vaccine.

This study revealed no safety problems with either product. The side effects appeared mild, says one coauthor, Patricia Fast of NIAID. Some people experienced a mild malaise after getting the injections, she noted.

Both vaccines spurred the production of antibodies that killed several laboratory strains of HIV, Fast says.

While the antibodies triggered by both of these experimental vaccines can neutralize HIV growing in laboratory culture, they do not appear to destroy HIV taken directly from the bloodstream of AIDS patients, Belshe cautions. Such uncertainties helped fuel the decision to hold off on expanded testing of these vaccines (SN: 6/25/94, p.404).

• In the Aug. 11 NEW ENGLAND JOURNAL OF MEDICINE, Isabelle de Vincenzi of the Saint Maurice National Hospital in France and her colleagues address the question of safe sex. The team studied 256 uninfected men and women. All were in a heterosexual relationship with an HIV-infected partner.

The researchers discovered that only 124 of the couples used condoms consistently. More important, however, none of the healthy partners in this group became infected with HIV, despite an estimated 15,000 episodes of intercourse. In contrast, 121 couples used condoms on occasion; the study found that 12 of the healthy partners in this group became infected. Eleven couples refused to answer questions about condom use.

Such findings help scientists quantify more precisely the protection offered by condoms, according to an editorial written by Anne M. Johnson of the University College Medical School in London. "We should now have greater confidence that condoms really can save lives."

— K.A. Fackelmann

Four awarded Fields Medals for mathematics

From Paris to Princeton, for research subjects ranging from harmonic analysis to complex dynamics, four mathematicians have won the Fields Medal, the most prestigious award in mathematics.

First presented in 1936 at the International Congress of Mathematics (ICM), the Fields Medal, which carries no remuneration, is awarded every 4 years to mathematicians age 40 and younger whose work is "of a seminal nature, pointing the way to current and future progress in mathematics research."

The recipients — announced last week at ICM's quadrennial conference, held this year in Zurich — are Jean Bourgain of the Institute for Advanced Study (IAS) in Princeton, N.J.; Pierre-Louis Lions of the University of Paris-Dauphine; Jean-Christophe Yoccoz of the University of Paris-Sud; and Efim Isaakovich Zelmanov, now at the University of Chicago while on leave from the University of Wisconsin-Madison.

Bourgain, 40, a classical mathematician, conducts research in number theory, combinatorics, and probability. But his primary work in harmonic analysis, one of the oldest and most fundamental tools of modern mathematics — and wavelets in particular — suggests new and far-reaching applications in oil exploration, medicine, and computing.

According to Norman McNatt of IAS, Bourgain's "problem-solving capacity is extraordinary.... He's published 184 papers, not one of them trivial.... He's left a mark of some significance."

Lions, 37, specializes in nonlinear partial differential equations. Mike Crandall of the University of California, Santa Barbara, notes that these equations arise in "a startling array of fields: control theory, fluid dynamics, nuclear and statistical physics, image processing, and others." Lions, Crandall adds, "has made brilliant contributions to the understanding" of these diverse equations.

Yoccoz, 37, masters complex dynamical systems, among other things. He has worked to understand the intricate connections of the Mandelbrot set (SN: 11/23/91, p.331), in addition to supplying paradigms and models of one-dimensional systems for other mathematicians. Yakov Pesin of Pennsylvania State University in University Park says, "He created new ideas that can be used by mathematicians in completely different fields. His ideas and methods of study are so promising ... a most important achievement."

Zelmanov, 38, recently received a great deal of attention for solving the long-standing "restricted Burnside problem," which has baffled mathematicians since 1902. The problem questions whether the algebraic structures that arise naturally in the symmetry of geometric objects are finite. He has also worked extensively with questioning — and dismissing — the assumption of the finite nature of "Jordan algebras." Richard Brualdi of the University of Wisconsin-Madison, calls Zelmanov "one of the most brilliant mathematicians of this century."

— G. Marino

Meaty carcinogens: A risk to the cook?

Grilling meat fosters the formation of potentially cancer-causing heterocyclic amines (HCAs). To date, most investigations of the health risks posed by these compounds have focused on ingestion as the primary route of human exposure. But new research indicates that inhaling the aromatic vapors emitted by grilling steaks, burgers, chicken, and chops could serve as an alternative route of exposure for some people — even those who don't eat meat.

Hervé P. Thiébaud of the University of California, Davis, and his colleagues fried 20 3.5-ounce hamburgers for 6 minutes on each side in nonstick pans. Exhaust systems collected the greasy fumes. Afterward, the researchers analyzed separately samples of the burgers and their trapped vapors for the seven most common HCAs.

A compound known as PhIP accounted for 62 percent (by weight) of the burgers' HCAs, the scientists report in the just-released July JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY. Though PhIP is far from the most potent HCA, calculations by team members at Lawrence Livermore (Calif.) National Laboratory indicate that because the chemistry of cooking meat overwhelmingly favors the production of PhIP, this compound accounts for nearly half the cancer risk to humans posed by HCAs (SN: 4/23/94, p.264).

A less potent HCA predominated in a condensate of the cooking meat's fumes. Known as AαC, it represented 57 percent of the HCAs present. That very different ratios of the seven HCAs might develop in meat and its smoke extract came as quite a surprise, notes analytical chemist Mark G. Knize, one of Thiébaud's collaborators at Livermore. Because the temperature at which most HCAs form is too low to transform them into a gas, he explains, scientists have assumed that HCAs would "volatilize" by hitching a ride on passing water or fat molecules. But in that case, he says, "You'd expect the ratios to be [comparable] — and they weren't." His group is now focusing more of its attention on resolving why AαC preferentially escapes.

The data suggest that airborne HCAs, if they pose a risk at all, will be the greatest threat to those who fry a lot of meat, such as many short-order cooks, according to these California-based researchers.

Thiébaud's team found that the quantity of HCAs in a gram of fried meat was about three times as mutagenic (a rough gauge of its carcinogenicity) as the quantity of HCAs in fumes emitted by that gram of meat. As a result, Knize now suspects that for most people, eating meats — not cooking them — will pose the greatest risk from HCAs. *— J. Raloff*