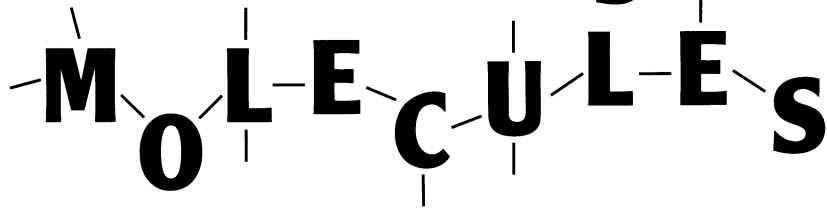


Mirror-Image



New techniques promise more potent drugs and pesticides

By KAREN F. SCHMIDT

The first inklings that chemicals could come in mirror-image pairs—as different from each other as right and left hands—emerged in the mid-1800s from two disparate minds.

The imaginative Lewis Carroll cooked up the possibility in *Through the Looking Glass*. Alice, talking to her cat, pondered whether looking-glass milk would be good to drink.

The classically trained scientist Louis Pasteur got the idea when he saw “right-handed” and “left-handed” crystal forms of a tartaric acid salt under his microscope. He sorted the two types of crystals with hand tweezers, dissolved them in separate flasks, and found that when he shone rays of plane-polarized light through each solution, one solution rotated the light plane toward the right and the other rotated it an equal angle to the left.

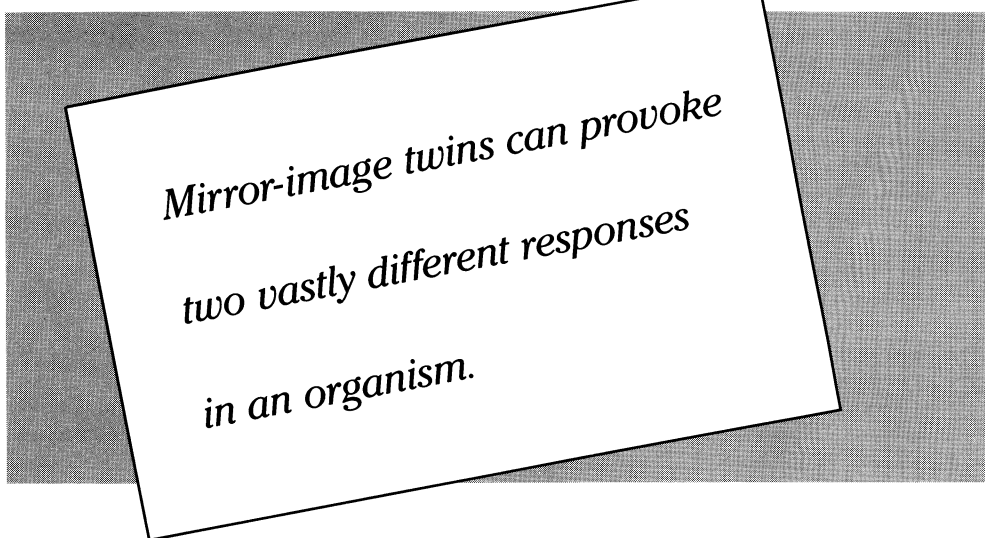
“Pasteur was doubly lucky,” notes Gerald L. Geison, a science historian at Princeton University. Few substances other than tartaric acid form crystal pairs that differ from each other so clearly in their visual appearance and in how they rotate light, Geison explains. And the air temperature in Pasteur’s lab that spring day happened to be just right for the final step of precipitating the crystals, which revealed a microscopic “handedness” that matched the optical properties Pasteur observed.

Pasteur’s discovery in 1848 led to the birth of stereochemistry, a subdiscipline of organic chemistry devoted to the study of the three-dimensional configurations of molecules. Today, stereochemistry is experiencing a renaissance, spurred less by luck and imagination than by technological advances. New methods are enabling chemists for the first time to deliberately synthesize one or the other twin of a pair of mirror-image molecules, or enantiomers. Like other chemical isomers, enantiomers are molecules that contain the same numbers and kinds of atoms but differ from each other in structural geometry.

“There’s been tremendous progress in making pure enantiomers,” says Eric N. Jacobsen, a chemist at the University of

Illinois at Urbana-Champaign. “It’s now one of the hottest areas of chemical research.”

Drug and pesticide developers are be-



coming increasingly interested in these paired compounds because mirror-image twins can provoke two vastly different responses in an organism. They hope the new synthesis techniques will give chemists control over the “handedness” of such products, leading to purer and potentially safer drugs and agrochemicals.

Fundamentally, chemists aim to mimic the selectivity of nature. Since the first chemicals assembled in the primordial ooze, life has been built with a preferential twist. Many of the most important biological molecules are chiral—that is, two mirror-image versions can exist because a carbon atom bonds to four different groups. Reversing the positions of two groups results in a molecular twin with identical bonding and the same physical properties—such as solubility—but with a three-dimensional image that can’t be superimposed on the original.

Ordinarily, only one of the twins occurs in nature. That’s because the enzymes produced by organisms have evolved to recognize, bind to, and spur the production of only one enantiomer. Thus, chiral

drugs extracted from plants and animals are enantiomerically pure.

But chemists now synthesize most drugs. Unfortunately, ordinary chemical reactions yield products that are 50:50 mixtures of enantiomers—called racemates—that are difficult to separate. Today, about 75 percent of the synthetic chiral drugs in the United States come in racemic form, estimates David Coffin of Hoffman-LaRoche, Inc., in Nutley, N.J.

In a review article in the Jan. 22 *SCIENCE*, a group of scientists from Du Pont Co. in Wilmington, Del., writes: “This approach [of making racemates] in effect meant that each dose of a drug was contaminated with an equal weight of an isomer, which usually had no therapeutic value but had the potential to cause unsuspected deleterious side effects.”

The thalidomide tragedy of the early 1960s poignantly demonstrates this point. Researchers now suspect that if pregnant

women had taken only the drug’s “right-handed” enantiomer, this sedative might have been safe. The “left-handed” enantiomer in the racemate, they say, was responsible for the resulting birth defects.

Several other drug molecules have well-known “evil twins.” One enantiomer of ethambutol fights tuberculosis, while the other causes blindness. One enantiomer of naproxen reduces arthritic inflammation, while the other poisons the liver.

The undesired enantiomer can also prove harmless in many cases. More rarely, it actually enhances the desired effect of a chemical. The pain reliever ibuprofen presents yet another scenario: The body converts the undesired enantiomer to the active twin.

Because it’s difficult to predict just how a racemate will affect people, pests, or the environment, most chemists would prefer to avoid such mixtures. But until recently, they’ve had few tools to aid them in this effort.

One of those tools is classical resolu-

tion, a technique developed by Pasteur and still used industrially to make naproxen. It requires converting the enantiomers in a racemate to a pair of diastereomers, or isomers that have different solubilities. Chemists can crystallize the two separately from solution and then convert them back to the original enantiomers. Unfortunately, this process works well for only a limited number of racemates.

Industrial chemists have also recruited legions of microorganisms and their enzymes to convert raw materials into enantiomerically pure products. For example, bacteria act as enzyme reactors to crank out huge quantities of one enantiomeric form of vitamin C, and enzymes isolated from other microbes help produce the desired enantiomer of aspartame, an artificial sweetener.

The chemical industry will never completely abandon these tried-and-true

Like many enzymes, chiral catalysts contain metal complexes, which dictate the geometry of how chemical groups interact and thus can shift a reaction to favor one product over another. But these catalysts hold several advantages over enzymes. They're sturdier, they can encourage reactions not known to occur in nature, and their products are easy to collect, says Du Pont's William A. Nugent. Furthermore, chemists can modify a given chiral catalyst to favor either enantiomer.

Many chiral catalysts work by guiding the addition of chemical groups to a specific side of a double bond. For instance, chemists can add two hydroxyl groups to the same side of a double bond by using a new osmium catalyst (SN: 1/2/93, p.6). The catalyst, developed by K. Barry Sharpless of Scripps Research Institute in La Jolla, Calif., enables pharmaceutical researchers to control the

cific ketone group in a molecule containing another similar ketone — a feat previously impossible, says Schultz.

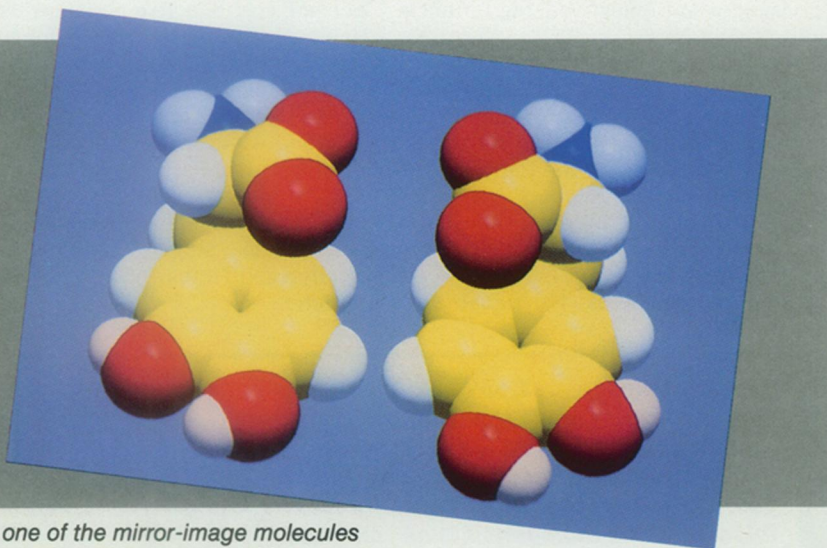
The ability to dictate the "handedness" of chiral molecules opens up new vistas for chemists interested in synthesizing compounds. For one, it enables them to make useful biological materials that they couldn't create before. Donald S. Matteson of Washington State University in Pullman can now make a beetle pheromone, or sex attractant, in the enantiomerically pure form needed to draw the insects to a trap. "To make some pheromones, you need precise chiral control," he says. "Although it's only important in a minority of cases, when you've gotta have it, you've gotta have it."

In addition, scientists can now entertain the possibility of synthesizing complex molecules that have more than two enantiomers. For instance, many drug manufacturers are trying to make compounds that inhibit HIV protease, an enzyme essential to the replication of the virus that causes AIDS. Inhibitor molecules that bind tightly to the enzyme, blocking its activity, can have as many as six chiral carbons — each with two possible conformations — totaling 64 possible versions. The new asymmetric synthesis techniques may allow chemists to make the single most potent of these isomers.

The ability to make chiral chemicals as single enantiomers also gives researchers many more building blocks to use in creating new drugs. Chemists hope to use this approach to expand the number of amino acids well beyond the current cast of 20, says John Talley of Monsanto Co. in St. Louis. He and his colleagues incorporate amino acid enantiomers into protein mimics. For instance, by replacing a single glycine amino acid with an alanine enantiomer, he says, chemists have converted the protein LHRH (luteinizing-hormone-releasing hormone) into a new drug called nafarelin, which shows promise as a treatment for endometriosis, a reproductive disorder affecting women.

Talley and his colleagues believe enantiomers will also help drug developers extend the short half-life of protein drugs in the body. They're aiming to replace the amino acids at a drug molecule's weak points with sturdier enantiomers. Enzymes in the body that normally degrade the drug will not bind to the mirror-image amino acid and thus will fail to snip apart the protein at that location, Talley explains.

Many researchers expect asymmetric synthesis techniques to play a big role in the future competitiveness of the U.S. chemical and biotechnology industries. Synthetic enantiomers could provide inexpensive, high-quality replacements for natural flavors and fragrances, suggests Du Pont's Nugent. Since developing a method for synthesizing the l-menthol



Clark Still, Columbia Univ.

Only one of the mirror-image molecules of dopa is biologically active. Monsanto scientists use a rhodium catalyst to make the L-dopa enantiomer, a drug used to treat Parkinson's disease.

techniques, says Charles Zepp of Sepracor, Inc., a company in Marlborough, Mass., that specializes in the synthesis and production of single-isomer drugs. "It's hard to beat a cheap enzyme if you can find one that works and is commercially available."

But for most stereochemical reactions, researchers have no enzymes or microbes to use as industrial catalysts. Says Zepp, "You have to screen dozens or hundreds of enzymes, or thousands of microorganisms, and hopefully one will work well. Generally, that doesn't happen."

For several decades now, organic chemists have been searching for ways to coax a broader range of reactions to yield single enantiomers. In the past few years, those efforts have begun to bear fruit. With the advent of a strategy called asymmetric synthesis, which uses new, lab-made chiral catalysts, chemists can now make any chiral chemical in an enantiomerically pure form.

"handedness" of products when oxidizing olefins to make drugs. A manganese catalyst developed several years ago by Jacobsen's team at the University of Illinois uses a similar tactic to add chiral control to epoxidation reactions.

Both the osmium and manganese catalysts are proving commercially useful, as are others containing rhodium and ruthenium, which promote hydrogenation reactions, and a catalyst with boron that reduces chemical groups known as ketones. Researchers are reporting new chiral catalysts all the time. "The field is moving into a mature phase now where every year something exciting comes out," says Sharpless.

Investigators are finding still other types of catalysts in their quest to control chirality. In the April 16 SCIENCE, researchers led by Peter G. Schultz of the University of California, Berkeley, describe how they engineered antibodies to convert ketones to alcohols in which one enantiomer makes up 95 percent of the product. Moreover, the catalytic antibodies facilitate the reaction at one spe-

enantiomer, he notes, a Japanese company has become the supplier for one-third of the world's mint flavoring.

"These guys are in direct competition with farmers in the American Midwest who grow mint plants, and they're turning a profit," Nugent says. "This could be a very economically viable technology."

Chemists see exciting new opportunities, but the prospects come at a price. Because of the expensive rare metals used to construct chiral catalysts, single enantiomers usually cost more than racemates to produce. Their high cost has fueled a controversy: Should federal agencies, for safety reasons, require that drug and agrochemical manufacturers make all of their chiral products as single enantiomers?

Some researchers liken the use of drug racemates to dumping toxic waste in the body. They believe these mixtures should be completely phased out. "I think we should always use a pure enantiomer unless it's proven that the mixture is better," argues Jacobsen. "It comes down to an issue of: Does it make sense to allow an impurity in your drug?"

Others shy away from a wholesale ban on racemates because not all such mixtures pose a threat. "It's the tail wagging the dog," contends one industry scientist. "The technology gets developed so we

can make these compounds, and then companies try to figure out what the heck to do with them."

In May 1992, the Food and Drug Administration took the middle road in a policy statement describing guidelines for the U.S. pharmaceutical industry. On the one hand, the agency asks pharmaceutical companies to disclose the enantiomeric composition of new chiral drugs and to test the biological activities of each enantiomer during the drug development process. On the other hand, FDA notes that racemates have resulted in few adverse consequences overall. "Although it is now technologically feasible to prepare purified enantiomers, development of racemates may continue to be appropriate," the agency asserts in its policy statement.

"We're not taking a position that either encourages or discourages enantiomeric purity," Wilson H. De Camp of FDA's Division of Anti-Infective Drug Products told SCIENCE NEWS.

The Environmental Protection Agency takes a slightly different approach. When EPA reviews pesticides, it informally gives the advantage to pure enantiomers, says Richard Schmitt of the agency's Office of Pesticide Programs. Pesticides made with pure enantiomers are more potent than racemates, allowing farmers to reduce the amount of bulk chemicals applied in the fields, he explains. A

farmer who uses the enantiomerically pure form of a synthetic pyrethroid insecticide, for instance, might spray only one-quarter as much as a farmer using the racemate.

"Frequently, the enantiomer that is removed is not active against the target pest but may be active against fish, mammals, or people," Schmitt adds. "It is definitely an advantage to have less of those chemicals out there in the environment."


For now, drug and agrochemical makers must determine case by case whether the expense of making a pure enantiomer can be justified. "Just to know if it's worthwhile, you've got to make both enantiomers and then test each and the racemate for their biological effects," says Matteson. "That takes a lot of research and a lot of money."

However, Sharpless believes asymmetric synthesis techniques will ultimately become cost-effective and gain recognition as a preferred method for making new drugs. He speculates that in 10 years drug companies may be making all chiral compounds as single enantiomers.


"It's obvious that we need to make chemicals more selectively, that we need to make purer substances for their specific purposes," Sharpless says. "Being able to make single enantiomers is basically a good thing and a step in the right direction." □

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