MEETING BRIEFS

Chemists React to New Compounds in Chicago

The 210th annual meeting of the American Chemical Society (ACS) convened on the big shoulders of Chicago from 20 to 24 August. Among the nearly 5000 papers presented in areas such as analytical chemistry and agrochemicals, researchers showcased new environmentally friendly catalysts, methods of building branched polymers, and a way to redeem the notorious drug thalidomide.

Catalysts Break a Vexing Bind

Drug manufacturers are plagued by evil twins. The compounds they synthesize often come in "chiral" molecular architectures—structures that are mirror opposites of each other, like a right and left hand. In many cases, one form is biologically active, while its twin is inactive or even harmful. To create only the active twin, drugmakers and agrochemical companies are increasingly relying on "asymmetric catalysts." But such catalysts require dangerous organic solvents, an evil in themselves.

At the Chicago meeting, a team of researchers from Duke University and Los Alamos National Laboratory reported a way out of this bind. The team has created asymmetric catalysts that work in a benign solvent of pressurized carbon dioxide known as supercritical CO_2. "This is groundbreaking work," says Paul Anastas, who heads the U.S. Environmental Protection Agency's (EPA's) industrial chemistry branch. He adds that the technique may ultimately help industry reduce the release of a wide variety of solvents such as benzene, chloroform, and methylene chloride, all undesirable substances under the Clean Air Act and the Superfund cleanup program.

Asymmetric catalysts are discriminating operators. The metal atoms in their core are adorned with chemical "arms"—complex molecules typically containing a phosphorous backbone to which is attached carbon-based phenyl rings. These structures are themselves chiral; thus they are compatible with only one face of a reactant, in the same way that a left-hand glove fits only a left hand. This limitation results in the creation of only one twin of a compound.

Unfortunately, these catalysts are also just as picky about their solvents. Compounds containing phenyl rings tend to be soluble only in organic solvents that are polar, which means that opposite electrical charges in the solvent molecules are segregated. Organic polar solvents include methanol and other toxins on the EPA hit list.

Supercritical CO_2—so-called because it is held between a liquid and gaseous state—is safe (*Science*, 25 August, p. 1065). But it isn't polar. To get around this impasse, Mark Burk and his colleagues at Duke redesigned the chemical arms. They replaced the phenyl rings on phosphorus with hydrocarbons known as alkyl groups. These hydrocarbons are themselves chiral but dissolve fairly easily in nonpolar solvents. They are hydrophobic, which means that they shun water, a highly polar substance, and are attracted to—and soluble in—nonpolar solutions. The researchers further enhanced solubility by adding hydrophobic fluorine-containing trifluoromethyl groups.

The redesign worked. When William Tumas and his colleagues at Los Alamos tested the new catalysts in supercritical CO_2, they found one that makes amino acid compounds of the desired handedness 99% of the time. This performance equals that of current asymmetric catalysts operating in more dangerous solvents. Another new catalyst, one that creates β-branched amino acids, achieved even higher selectivity than the conventional asymmetric catalysts.

Burk and his colleagues have also developed new catalysts for making other drug ingredients, such as alcohols and amines (see table). Although they are as yet untested in supercritical CO_2, Burk has high hopes for their effectiveness—and for ridding drug synthesis of its twin plagues.

SINGLE-HANDED CATALYSIS

Catalyst	Catalyzed Compound Class	Effectiveness at creating desired chiral "twin"
Ethyl-DuPHOS*-Rhodium	Amino Acids	99%
Methyl-DuPHOS-Rhodium	β-branched amino acids	96%
Ethyl-DuPHOS-Rhodium	Alcohols	90–99%
Iso-propyl-BPE†-Ruthenium	β-hydroxy-esters	95–99%
Ethyl-DuPHOS-Rhodium	Hydrazines	70–97%
Methyl-DuPHOS-Rhodium	Amines	93–98%

* DuPHOS=1,2-*bis*(*trans*-2,5-diethylphospholano)benzene
† BPE=1,2-*bis*(*trans*-2,5-diethylphospholano)ethene
Tested in supercritical CO_2

Green catalysis. New catalysts that produce one of two possible mirror-image molecules are designed to work with nontoxic solvents.

Fine-Tuning Polymers

Just as virtuoso musicians tune their instruments to perfect their tone, chemists often try to tune their reactions, striving for a product with just the right composition. At the Chicago meeting a group of chemists at the University of North Carolina, Chapel Hill (UNC), reported on new catalysts that fine-tune reactions that build the ubiquitous molecules known as polymers.

The catalysts—compounds based on nickel and palladium—actually elicited a variety of notes from a reaction notorious for delivering one monotonous tone: the long, stiff polymer chains of polyethylene used to make plastic milk bottles and other containers. Used in place of the standard metal catalysts that stitch together polymer building blocks, or monomers, they made not just straight chains but branched polyethylene structures of many varieties, which can yield plastics with many degrees of flexibility. And the new catalysts allowed all of this to occur just by changing the temperature and pressure at which the reaction took place.

The catalysts turn similar tricks on other industrially important polymers as well. "I expect that all companies involved in polymers will start programs in this area," says Tom Baker, a chemist at DuPont Central Research & Development in Wilmington, Delaware. "This is a very interesting result."

Like many such results, it was a byproduct of research with a different goal: in this case, finding catalysts that work on complex monomers. The current generation of titanium- and zirconium-based catalysts is good at assembling simple hydrocarbon monomers such as ethylene into polymer chains. But more complex monomers, such as methyl acrylate, include functional chemical groups dangling off the hydrocarbon, which tend to gum up the works. They bind tightly to the metal atoms and prevent them from interacting with the additional monomers needed to form a polymer.

Nickel and palladium don't bind to these functional groups so tightly, a property that has drawn the interest of many polymer chemists. But catalysts based on these metals have a problem of their own: They tend to break off growing chains prematurely, before the chains reach a useful length.

The reason: weak links between the metal

atom and the chain. The metals typically have two binding sites that help build the polymer. Chain construction usually starts when one is filled by a methyl group, which ends up becoming one end of the polymer chain. The other site is taken up by a monomer. This arrangement is energetically rather costly—it requires less energy if the methyl group jumps to the end of the other monomer, and that's exactly what happens. Thus a chain begins to grow: Another monomer fills the newly opened site, the larger group jumps over to it, and the process is repeated.

But sometimes, before the open site snares a free monomer, it pulls a hydrogen atom away from a carbon near the base of the chain instead. This creates the weak link. A free monomer can force its way in, breaking the chain off the catalyst and ending its growth.

The solution was a chemical shield for the vulnerable area. The UNC researchers—Maurice Brookhart, Lynda Johnson, and Christopher Killian—had been experimenting with attaching complex organic molecules to metal atoms to orchestrate other polymerization reactions. These molecules, it turned out, also functioned nicely as shielding chemical "arms" for simple monomers such as ethylene. They protected the chain near the metal, preventing an intrusive monomer from butting in. That gave the errant hydrogen atom time to jump back up to the chain, restoring its integrity and allowing continued growth.

These shields also produced another bonus. At the ACS meeting and in the 14 June issue of the *Journal of the American Chemical Society*, Brookhart and his colleagues reported that the shields not only allowed the assembly of long polymers; they also helped the catalysts create branches.

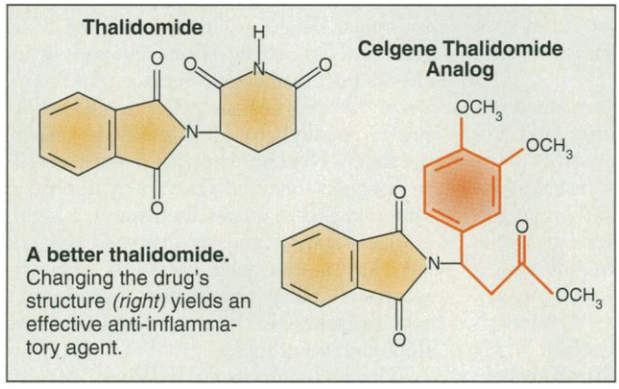
"This was somewhat of a surprise," says Brookhart, but in retrospect he and his colleagues theorize that when a hydrogen atom jumps from the chain to an open binding site on the metal, the rearrangement of the bonds near the start of the polymer chains allows the metal to "skip" up the chain from the first to the second carbon. Once there, it begins stitching a new chain of monomers together, creating a branch off the main line.

The extent of this branching, adds Brookhart, can be controlled by the temperature and pressure of the reaction. "At high temperatures, you get more branches because the catalyst moves up and down the chain faster," he says. High pressures, in contrast, slow the process by accelerating the rate at which monomers bind to the catalyst, which can only change its position when it has an empty binding site. "The [monomer] intercepts the catalyst before it can run down the chain," he says. So "by changing the pressure, temperature, or structure of the catalyst, we can make a range of polyethylenes with a wide range of different properties" from stiff to flexible, says Brookhart. And in polymer reactions, a wide range of products from just one starting material makes for a sweet sound indeed.

Can Thalidomide Be Rehabilitated?

Thalidomide has lived in infamy since a 1961 study linked its use to birth defects. But although sales of the sedative were banned in most countries, research interest in the compound and its chemical relatives never fully subsided. Now that work may end up restoring some luster to thalidomide's reputation—through the ability of some of its close kin to inhibit a key factor in inflammation.

In 1991, Gilla Kaplan and her colleagues at Rockefeller University found that thalidomide itself inhibits tumor necrosis factor–α (TNF-α), an immune system modulator that—when overexpressed—can lead to rheumatoid arthritis and other inflammatory diseases. But the drug's action against TNF-α is only modest, and that, along with its potential developmental side effects, is a serious drawback. At the ACS meeting, however, researchers from Celgene Corp., a New Jersey–based pharmaceutical company, reported that they've designed thalidomide variants that inhibit TNF-α 100 times more effectively than does native thalidomide. And although their effects on development are still not known, the compounds showed no obvious toxic effects in preliminary in vitro and animal tests.



A better thalidomide. Changing the drug's structure *(right)* yields an effective anti-inflammatory agent.

"I think it's promising," says Georgia Vogelsang, an oncologist at Johns Hopkins University Medical School, who has tested the effectiveness of native thalidomide against an immune ailment known as graft versus host disease that afflicts bone marrow transplant patients. She explains that in diseases such as rheumatoid arthritis, experimental drugs active specifically against TNF-α have proven better than existing treatments—immune suppressants such as steroids, which tend to affect a broad range of immune factors. "We have been very interested in making the drug more active against TNF-α," she says.

Immunologists have suspected that thalidomide—or derivatives created when the drug begins to break down—blocks production of TNF-α by entering the macrophages and other immune cells that make the immune modulator and binding to some yet-unidentified receptor essential for its synthesis. So the Celgene researchers, led by George Muller and David Stirling, tried to alter the compounds to stabilize them and improve their transport into the cell, rendering them more potent.

In making one of their most potent compounds, the scientists started with the native thalidomide and knocked off a carbon-based ring on the molecule's right-hand side, which is easily degraded by water. When they replaced this with a more stable ring structure called a phenyl group, the researchers found that the molecule was still nearly as good at inhibiting the production of TNF-α. One reason, says Muller, may be that the phenyl group is more fat-soluble than the original ring, which may help the compound cross lipid-based cell membranes.

To further increase the activity of the compounds, the researchers added additional chemical recognition groups known as methyl ether groups and a methyl ester. The result: a stable compound that is nearly 100 times more potent than native thalidomide at inhibiting TNF-α synthesis in human white blood cells exposed to inflammatory agents. When given orally to mice, the compounds had no obvious toxic effects. But Muller admits that only further testing can determine whether they are free of developmental effects. Scientists don't know the mechanism by which thalidomide causes birth defects, so the Celgene researchers were unable to modify the compounds to avoid the problem.

If the thalidomide relatives do turn out to be free of developmental effects, they could pose competition for another specific TNF-α inhibitor—an antibody developed by Centocor, a small Pennsylvania pharmaceutical company. The antibody can't be administered orally, as proteases in the digestive system will break it down. The thalidomide analogs are not proteins and thus should not be vulnerable to these enzymes. So Celgene researchers are pushing ahead with more extensive studies on a number of their compounds which—if all goes well—may help redeem thalidomide's reputation after all.

–Robert F. Service