MEETING AMERICAN CHEMICAL SOCIETY

Chemists Mix It Up In California

ANAHEIM, CALIFORNIA—Nearly 15,000 scientists gathered here from 21 to 25 March for the American Chemical Society's (ACS's) semiannual research powwow. The week's highlights included an effort to combine tissue engineering with gene therapy, new ways to synthesize polymers, and the welcome news that caffeine doesn't affect the brain like more potent stimulants.

New Routes to Polymer Synthesis

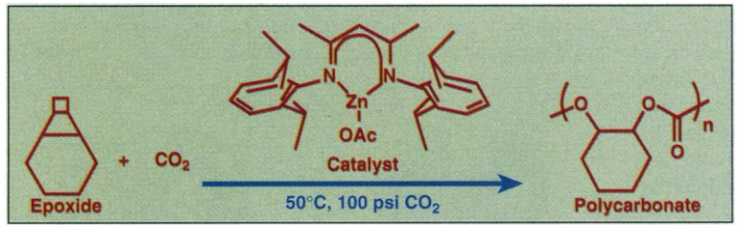
In the chemical industry, fine-tuning a reaction can make a giant difference in the bottom line. Because the quantities of product are so large, a more efficient synthesis can mean millions of dollars in cost savings. And a better product can open up whole new markets. At the meeting, chemists described schemes to improve the synthesis of two polymers—one a type of polycarbonate used in making ceramics and the other a plastic used in semiconductor manufacture.

In an effort to use cheap and abundant CO_2 as a feedstock for polymer synthesis, Geoffrey Coates and his colleagues at Cornell University developed a novel zinc-based catalyst that makes a specialized family of polycarbonates. Used as binders in making ceramics, these polycarbonates are chainlike molecules formed by condensing two chemicals, carbon dioxide and an oxygen-containing hydrocarbon known as an epoxide. This is not the first time a zinc catalyst has been devised for coupling CO_2 and epoxides. But previous versions have been notoriously slow on the job, taking an hour for a gram of catalyst to synthesize a gram of plastic, and thus find only limited use.

Still, Coates says, the earlier catalysts provided lessons that helped in the current work. Those catalysts consisted of zinc atoms, each attached via oxygen atoms to bulky hydrocarbon groups, and analysis suggested that they failed because the oxygen links broke and the hydrocarbons fell off during the reaction. That allowed the zincs to clump together, which halts the catalyst. To combat this problem, the Cornell researchers came up with a new bulky hydrocarbon arm that is securely bound to the zinc with a pair of nitrogen atoms.

The new catalyst also carries another group—either an acetate or methoxide—bound to the zinc. By controlling the chemistry at the reactive end of the polymer, that component helps the CO_2 and epoxide molecules link up in an alternating sequence. It also helps the polymers all grow to roughly the same length. In contrast, those produced by typical catalysts can vary in sequence and length.

But more important, the new catalyst works over 50 times faster than its predecessors, and at a temperature of 20 to 50 degrees Celsius and a CO_2 pressure of 100 pounds per square inch (psi)—mild conditions compared to those required by conventional catalysts. As a result, the new catalyst may help keep down the costs of polycarbonate synthesis and be environmentally friendly to boot. And because the catalyst can polymerize a wide variety of epoxides, it should help polymer chemists create a range of new polycarbonates. Indeed, Robert Weymouth, a polymer catalyst expert at Stanford University in California, describes the achievement as "great science."



Swift action. A novel zinc-based catalyst speeds production of polycarbonates.

SOURCE: G. COATES/CORNELL UNIVERSITY

The other polymer-making scheme, by researchers at the IBM Almaden Research Center in San Jose, California, and the University of California, Santa Cruz (UCSC), could open a new application for the polyacrylate polymers now found in everything from paints to rubber. In particular, they could come in handy in crafting computer chip circuitry.

Chipmakers currently use patterned films of a different polymer, polystyrene, as "photoresists" to control which regions of a silicon wafer are eaten away by chemicals. Patterning these polymers requires that they be semitransparent, so that a polymer layer can absorb light throughout its full depth. Yet in an effort to create ever finer features on the chips, chipmakers want to reduce the wavelength of the ultraviolet light used to create the patterns. Polystyrene absorbs such short wavelengths too strongly, preventing it from penetrating throughout the polymer. So the IBM team, led by Craig Hawker, was looking for an alternative.

The IBM team turned to polymer building blocks known as acrylates, which are transparent to the shorter wavelength light. But there was a problem: To get the uniform etching needed for chip patterning, all the chains in a polymer have to be roughly the same length. For polystyrenes, a capping group called TEMPO (for tetramethylpiperidine-*N*-oxide) ensures this consistency. During synthesis, TEMPO essentially jumps on and off the growing polymer chain, ensuring that neighboring chains don't react with each other and suddenly double their length. The capping group thus helps all the polymer chains grow to be the same length. But TEMPO doesn't work for polyacrylates.

For completely unrelated studies, however, Rebecca Braslau and Vladimir Chaplinski at UCSC had synthesized a library of TEMPO-like compounds called nitroxides. And when Hawker's team tested the nitroxides, they found one that controls the polymerization, producing uniform chain lengths.

The new work is an "important development," says Xerox polymer researcher Peter Odell—only in part because of the polyacrylates' potential as new photoresists, he adds. Hawker also found that depending on the sequence in which different monomers are added to the reaction, the nitroxide can control whether the polymer develops as a linear chain or branches like a tree. It also works with other polymer building blocks, such as acrylamides. That could open new uses for these materials as well.

Merging Tissue and Gene Engineering

Engineering new tissues to grow in the human body is a hot area of research. So is developing ways to introduce healthy genes into cells with missing or defective copies. Now these two hot areas may be merging. At the meeting, University of Michigan, Ann Arbor, chemical engineer David Mooney reported creating polymer scaffolds that both seed the growth of cells and provide them with new genes. Preliminary results show that the scaffolds are already as successful at delivering new genes to cells as viruses, the most successful gene transfer vehicles to date.

"I think it's a pioneering contribution" that other groups will definitely pick up on, says Anthony Mikos, a tissue engineering specialist at Rice University in Houston, Texas. The

approach, say Mikos and others, could prove useful for treating wounds, heart disease, cancer, and other conditions that might benefit from genes added locally to, say, increase blood flow or block cell growth.

Groups including the Michigan team had already shown that, as Mooney puts it, "these scaffolds can be used for a lot more than just their mechanical properties." Although tissue-engineering scaffolds are primarily designed as just a friendly surface onto which cells can bind, grow, and spread, implantable capsules made from the same polymers can release therapeutic proteins, such as growth factors that induce the growth of new blood vessels. But the capsules can exhaust their protein supplies quickly. So Mooney and his colleagues wanted to see if they could use the polymers to deliver the genes for making the proteins instead.

First, Mooney and fellow Michigan researchers Lonnie Shea and Jeff Bonadio had to find a way to trap a lot of DNA inside a polymer scaffold and then have it be released to cells over time. They started with a rigid biodegradable tissue engineering polymer, known as polylactide coglycolide, or PLG, to which they added a mixture of salt and DNA. To encourage the polymer to take up the mix, the researchers also exposed it to pressurized carbon dioxide, which dissolves in the polymer, softening it and creating a network of gas bubbles. The DNA and salt could then diffuse into the polymer, where it became trapped in the bubbles. Finally, the Michigan researchers immersed the polymer in water, which washed out the salt, leaving the DNA behind.

The researchers next shaped the DNA-laden polymer into 1.5-centimeter-wide disks, which they implanted under the skin of rats. Mooney and his colleagues hoped that as the DNA diffused out of the polymer, the cells growing on the scaffold would take it up.

In their first trial, the DNA stored in the polymer coded for a test protein called β-galactosidase. After waiting 4 weeks, Mooney and his colleagues retrieved tissue from around the disks and stained the cells to see which were making the protein. They found that up to 1000 times more cells expressed the introduced gene compared with cells from controls that just had the naked DNA injected into similar wounds.

The researchers then repeated the study with a gene for a protein called platelet-derived growth factor, which stimulates the growth of new blood vessels. After 4 weeks, they tested the tissue next to the implant and found increased vascularization compared to control animals that had received the tissue scaffold with the β-galactosidase gene.

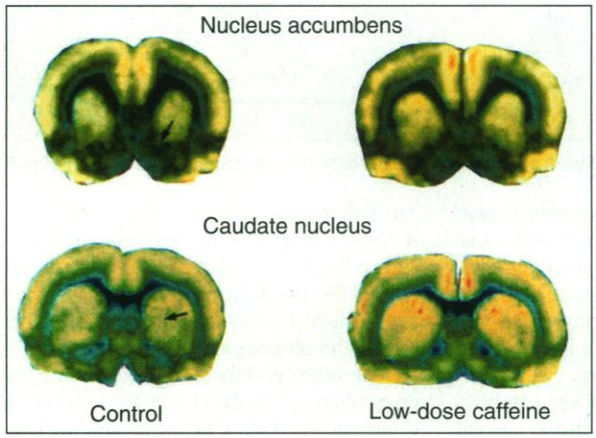
Mooney says that a key advantage of the gene-bearing polymers is that, unlike viral vectors, they are not likely to trigger an immune response that can limit the effectiveness of the gene transfer. He adds that by altering the composition of their scaffold polymer, "we can control the time release [of DNA] from a couple of days to over 1 month." That may help tissue engineers further control how much DNA finds its way into neighboring cells.

This localized approach to gene therapy isn't likely to be useful for treating illnesses such as muscular dystrophy, where genes must be delivered to muscle cells throughout the body, says Robert Langer, a tissue engineering specialist at the Massachusetts Institute of Technology in Cambridge. But for treating local conditions, gene-therapy scaffolds may soon find themselves to be a hot commodity.

Coffee Cravers Are Not Addicts

Sure, we may have a few jitters and facial tics. But fellow caffeine drinkers: Rest easy. Animal studies presented at the ACS meeting show that the juice in java is not an addictive drug.

Found in coffee, tea, and chocolate, not to mention many soft drinks, caffeine is the most widely used psychoactive drug in the world. Few researchers contend that the mild stimulant is as dangerous as potent and illegal stimulants such as cocaine, but some behavioral scientists have argued that because users seek out caffeine repeatedly, it should be considered a drug of dependence. Other experts counter that caffeine use doesn't bear other hallmarks of dependence, such as increased usage over time and the inability of users to give it up.



No problem. In rats, modest doses of caffeine had no effect on the nucleus accumbens, one of the brain's reward centers *(top)*, but as the orange color indicates, they did increase activity in the caudate nucleus, a locomotion center *(bottom)*.

To try to settle this dispute, neuroscientist Astrid Nehlig and her colleagues at the French National Institute for Health and Medical Research (INSERM) in Strasbourg decided to see if caffeine triggers the same kind of brain effects as cocaine and other addictive stimulants. Those drugs are thought to foster dependence partly by increasing activity in certain brain regions, such as the nucleus accumbens, that are involved in the brain's reward system.

For their experiments, the INSERM team injected rats with a radioactive form of glucose, followed by varying caffeine doses, equivalent to the amounts consumed by people drinking one to 10 cups of coffee. Next they killed the animals and determined how much radioactive glucose the nucleus accumbens and several other brain regions contained. Higher levels indicate higher metabolic rates and therefore higher activities.

By that measure, Nehlig's team found, the brain activity of animals given caffeine rose in brain regions involved in locomotion, mood, and awakeness. But the researchers found virtually no added activity in the nucleus accumbens except at an extremely high caffeine dose—the equivalent, for a person, of drinking seven cups of coffee in one sitting. Those findings were further buttressed by the results of a study of one human subject—an epilepsy patient who was undergoing brain scans before surgery.

With the human subject, Nehlig and her colleagues adopted a different strategy for mapping brain activity: a relative of the common PET brain-imaging technique called SPECT, which tracks blood flow in different parts of the brain. The images showed no change in nucleus accumbens activity after the person consumed caffeine equivalent to that found in three cups of coffee. "I do not think caffeine shows any evidence of dependence," concludes Nehlig.

Dan Steffen, a caffeine expert at Kraft Foods—which manufactures some caffeine-containing products—says that if the new work holds up in humans, it should end the debate over whether people become addicted to caffeine. "It's pretty powerful in that it indicates the reward system is not being activated at levels where caffeine is normally consumed," says Steffen. Instead, Nehlig proposes, people become regular caffeine users because of the positive reinforcement of feeling more alert and able to concentrate. With that said, would you please pass the cream?

–ROBERT F. SERVICE

CREDIT: A. NEHLIG/INSERM