breaks down into a drug—in this case a relative of aspirin.

The new polymer painkiller has yet to be tested in animals or humans. But the researchers think it may offer a welcome treatment for inflammatory bowel disease, which requires long-term administration of anti-inflammatory drugs delivered only to the intestine. The polymer should bypass the acidic environment of the mouth and stomach, then break down to form the drug under the alkaline conditions found in the intestine. "It's a very innovative approach," says chemical engineer Nicholas Peppas of Purdue University in West Lafayette, Indiana, who himself works in the field of biodegradable polymers and drug delivery. "It would be a very important development if it works."

The Rutgers team did not set out to make a polymeric painkiller at all, says its leader, chemist Kathryn Uhrich. Rather, they were working to alter a class of polymers to make it easier for the body to degrade them. The polymers they were using, known as polyanhydrides, already have a variety of medical uses, such as in biodegradable sutures. But certain bonds in the chemical "linking groups" between the polymer's individual units—or monomers—don't break down readily. To make the polymer suitable for use as a temporary scaffold for tissue regeneration and wound healing, Uhrich and her colleagues decided to replace one kind of linking group, known as ethers, with esters, which have bonds that break more readily.

Uhrich then recognized, she says, that the modified polymer itself "breaks down into something that is useful": salicylic acid, the same anti-inflammatory compound that results from the metabolism of aspirin. The breakdown also releases sebacic acid, an inert byproduct of other biodegradable polymers that have been approved by the Food and Drug Administration, says Uhrich.

When the polymer is swallowed, the breakdown should be delayed because the bonds that link the monomers are very stable under acidic conditions. When Uhrich and her colleagues tested their polymers in an acidic bath with a pH of 5—about the acidity of the mouth and stomach—they found little change. But when they raised the pH to 9, equivalent to what is found in the intestine, the polymers began to degrade, releasing first a burst of salicylic acid monomers, and then a steady stream of them.

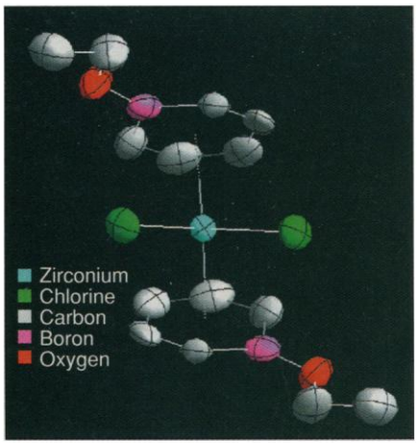
That behavior could give the polymer drug an edge over current treatments for inflammatory bowel disease. The most popular drug, sulfasalazine, breaks down in the intestine to release salicylic acid. But sulfasalazine also releases unwanted byproducts that can trigger skin rashes, headaches, and other problems. New formulations that have recently come on the market encase salicylic acid in polymers that degrade in the intestine. But the degradation does not always occur in the right place, says Kiron Das, chief of gastroenterology at the University of Medicine and Dentistry of New Jersey in New Brunswick. Uhrich and her colleagues should get an inkling of whether their polymer painkiller can do any better later this year, when they plan to begin testing it in animals.

–Robert F. Service

INDUSTRIAL CHEMISTRY

Olefin Catalyst Keeps Things Short

A new catalyst can be as big a boon for a chemical company as a blockbuster drug is for a pharmaceutical manufacturer. That is because catalysts are the key to many industrial processes, such as creating plastics and other materials. These matchmaker molecules, for example, can coax tens of thousands of identical chemical groups to link together into the polymer chains that are the basis of plastics. Now, a team of chemists from the University of Rochester in New York has created a catalyst with a new talent: keeping those chains short.



G. BAZAN/UNIV. OF ROCHESTER

Short and sweet. With the help of boron and zirconium atoms, a new catalyst creates ultrashort polymers known as α-olefins under industrially friendly conditions.

Reported in this week's issue of the *Journal of the American Chemical Society*, the new molecule belongs to a class of catalysts known as metallocenes, which have swept through the polymer industry in recent years because of their unmatched ability to form long chains without unwanted byproducts. The new catalyst creates ultrashort polymers called α-olefins, just a few units long, which serve as a feedstock for making everything from soaps and detergents to garbage bags. But like its fellow metallocenes, the boron- and zirconium-containing molecule does its job without creating unwanted byproducts, promising a jump in efficiency over conventional α-olefin catalysts based on either nickel or aluminum.

"It's some very nice work," says Richard Kemp, a chemist at Union Carbide in Houston. "Nobody has come close to creating as pure a material as [the Rochester group]." Kemp notes that besides producing α-olefins more efficiently, the new metallocene works at ambient pressure, whereas current catalysts require high pressures. "That's a winner," says Kemp. "Anything you can do at atmospheric pressure is phenomenal," because it obviates the need for plants to install expensive high-strength reactors. Kemp and Guillermo Bazan—who led the Rochester team—are quick to point out, however, that the new catalysts are not ready for the factory floor just yet. Unlike the current variety, the new catalysts are difficult and expensive to produce, at least for now.

Metallocenes owe their finesse to their unique structure, in which a central metal atom is surrounded by a pair of five-membered carbon rings that can themselves be linked to other groups. The central metal atom is electron-hungry, which leads it to pull on the electron-rich parts of the olefin building blocks—simple hydrocarbons known as ethylenes—and draw them into the catalyst. Together, the rings and dangling groups force each ethylene to bind to the metal in a particular orientation. But the bond between the metal and the first carbon on the ethylene is highly reactive. This allows the next ethylene that is drawn in to insert itself between the first ethylene and the metal, forming the first link in the polymer chain.

In most metallocene catalysts, this chain growth continues on and on until the metal atom manages to yank an atom, usually a hydrogen, completely off the polymer, allowing the polymer to break free of the metal and stopping its growth. However, the chain is normally snipped only after the polymer has grown to great length. So Bazan and his Rochester colleagues Jonathan Rogers and Caroline Sperry looked for a way to speed up the process, so that chain growth would stop after two to 15 ethylenes—the length of an α-olefin.

That meant boosting the central metal's hydrogen-swiping ability. To do so, Bazan and his colleagues inserted a boron atom

into each of the catalyst's carbon rings. To each boron they then attached oxygen atoms linked to other small hydrocarbon groups. Borons are themselves electron-hungry, so they try to swipe electrons from neighboring atoms. Oxygen is reluctant to give up any electrons, so the borons end up snatching them from the zirconium, leaving it even more starved of electrons. "The zirconium atom needs to do something to compensate," says Bazan, and so it tries even harder to swipe a hydrogen from the growing polymer chain. It usually succeeds quickly, causing the polymer chain to break off almost as soon as it starts growing, thereby creating the short-chain α-olefin. "That's something no other metallocenes have done thus far," says Bazan.

The Rochester team believes that it may also be able to fine-tune the catalyst to produce α-olefins of a particular size. Changing the organic groups linked to the catalyst's oxygen atoms should change the electronic state of the zirconium atom and influence which α-olefins it produces. "It's a pretty unique system that you can tune the electronics," says Kemp. Bazan says he hopes to tune the catalyst to make just large α-olefins consisting of 10 or 12 ethylene units, which are currently expensive to produce.

The new catalyst still has a few hurdles to overcome before it gets to the market. For a start, although current-generation catalysts are less efficient at producing α-olefins, they are "dirt cheap," says Bazan. The new metallocenes, however, require several complicated and expensive synthesis steps just to insert boron atoms into the all-carbon rings. Also, Maurice Brookhart, a catalysis expert at the University of North Carolina, Chapel Hill, notes that the boron-based catalyst is slow compared to conventional catalysts. But Kemp believes that tinkering with the reactor conditions will likely improve its speed. "There's almost always room for optimizing a catalyst," he says. If that proves true in this case, metallocene catalysts may soon find themselves in command of a whole new market.

–Robert F. Service

EVOLUTIONARY BIOLOGY

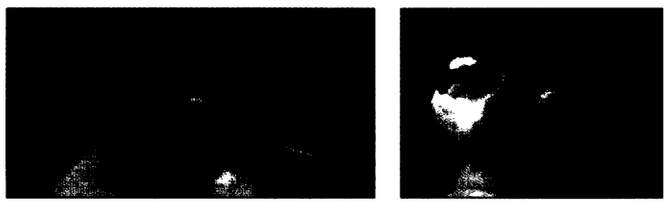
Males Mutate More, Bird Study Shows

You can't choose your parents. But if you could, you might want to pick a father who is young. For the last 90 years, geneticists, including the illustrious J.B.S. Haldane, have noted that children of older fathers tend to suffer more from genetic diseases. The standard explanation has been that fathers pass on more genetic mutations because their sperm-producing cells divide throughout their lifetimes—as many as 400 times in a 30-year-old man. This provides many more opportunities for mistakes to occur as the DNA copies itself than in egg cells, which only divide about 24 times. The notion has been hard to prove directly. But in this month's *Nature Genetics*, a pair of Swedish researchers present evidence that in a father, age can have a genetic cost.

By analyzing a gene found on both the male and female sex chromosomes of birds, evolutionary geneticist Hans Ellegren of the Swedish University of Agricultural Sciences in Uppsala and his graduate student Anna-Karin Fridolfsson showed that mutation rates really are higher in males. "These data show that male-driven mutation appears to be a general phenomenon" in both mammals and birds, says population geneticist Brian Charlesworth of the University of Edinburgh in the United Kingdom. Not only does the result support the idea that older males are a source of the mutations that lead to genetic disease, but it also suggests that males have more input into evolutionary change than females do.

The Uppsala team turned to birds in order to avoid a problem that has confounded efforts to resolve the issue of why males have higher mutation rates. The most obvious way to determine the relative mutation rates in the two sexes is to look at genes found on the sex-determining X and Y chromosomes. But there are fewer Y chromosomes in the population overall (only one Y for every three X's), and in population genetics, a decrease in population size renders natural selection less effective. Consequently, the likelihood that deleterious mutations on the Y will slip through to the next generation is greater than the corresponding chance for mutations in genes on the X.

But in birds, it's the females that have the mismatched sex chromosomes, designated "W" and "Z," while males have two "Z's." So in birds, the chromosome arrangement should drive down the apparent mutation rate in the male chromosome—the Z. If the male mutation rate is still higher, the elevated rate is likely to be a real effect. "Using birds is a really nice way of sorting this out," says evolutionary biologist Linda Partridge of University College, London.



H. ELLEGREN

Flighty genes. A new finding indicates that a male collared flycatcher *(right)* passes on more mutations to his offspring than a female does.

Before the Uppsala researchers could do the experiment, they needed a gene found on both bird sex chromosomes. Such a gene did not turn up until 1996, when it was shown that the CHD gene, which makes a protein involved in gene control, occurs on both the W and Z chromosomes. "Suddenly," Ellegren recalls, "we could test the hypothesis" that mutation rates are higher among males. And that's what they found.

The Ellegren team sequenced the CHD gene from males and females of birds, including warblers, flycatchers, and yellowhammers. Applying a statistical method for analyzing mutation rates, they then showed that the gene accumulated mutations in males as much as 6.5 times faster than in females.

Charlesworth cautions, however, that more work will be needed to verify the Ellegren team's conclusion. Indeed, other recent findings have "muddied the waters," Partridge says. In the 27 March issue of *Nature*, Gilean McVean of Cambridge University and Laurence Hurst of the University of Bath, both in the United Kingdom, reported that genes on the X chromosomes of mice and rats have significantly lower mutation rates than genes on the nonsex chromosomes. That finding suggests that the apparently lower female mutation rate the Swedish researchers found could be just a peculiarity of the female sex chromosome.

But Ellegren notes that that is not necessarily the case. He points out that if McVean and Hurst's finding about a lower mutation rate on the X chromosome applies to the Z chromosome of birds, it would tend to counteract the mutation-enhancing effect of more DNA replication in males, as males have two Zs. "In spite of [the expected reduction in male mutation rates], we found the male bias," says Ellegren. Charlesworth suggests that the Swedish researchers now need to compare the mutation rates of the CHD and other Z-linked genes to those on nonsex chromosomes in birds to verify that the excess mutations arise in other genes as well—a task on which Ellegren's laboratory is working. Already, though, the new results should tell baby boomers and birds alike to beware: There may be unintended consequences to siring a family when you are a senior citizen.

–Steven Dickman

Steven Dickman is a writer in Cambridge, Massachusetts.