

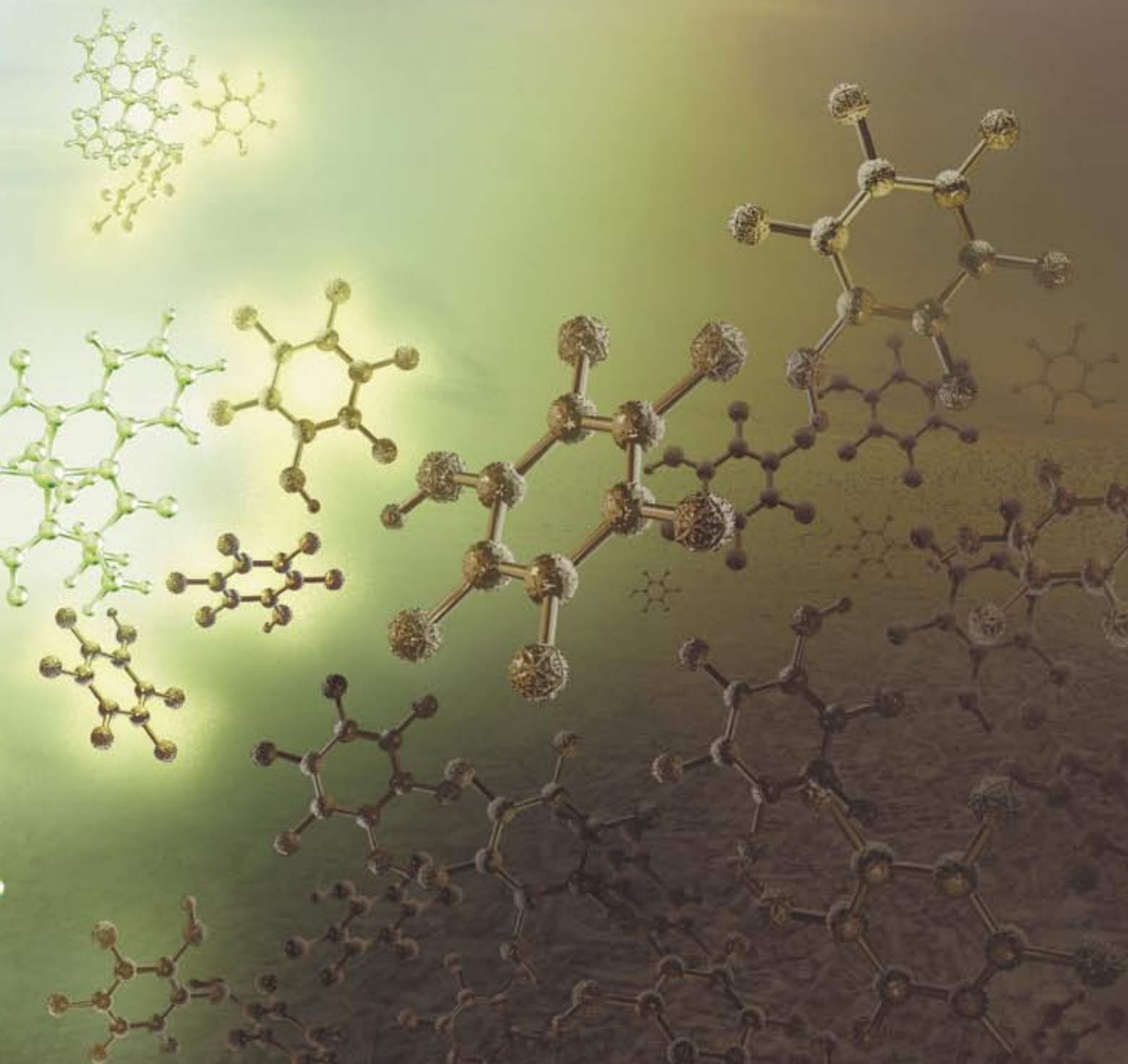


# LITTLE GREEN MOLECULES

By Terrence J. Collins and Chip Walter

**POLLUTION CONTROL:** Catalysts called TAMs (*green*) work with hydrogen peroxide (*blue*) to break down chlorophenols (*brown*), which contaminate the wastewater from many industrial sources.

Chemists have invented a new class of catalysts that can destroy some of the worst pollutants before they get into the environment



The fish that live in the Anacostia River, which flows through the heart of Washington, D.C., are not enjoying its waters very much. The Anacostia is contaminated with the molecular remnants of dyes, plastics, asphalt and pesticides. Recent tests have shown that up to 68 percent of the river's brown bullhead catfish suffer from liver cancer. Wildlife officials recommend that anyone who catches the river's fish toss them back uneaten, and swimming has been banned.

The Anacostia is just one of dozens of severely polluted rivers in the U.S. The textile industry alone discharges 53 bil-

lion gallons of wastewater—loaded with reactive dyes and other hazardous chemicals—into America's rivers and streams every year. New classes of pollutants are turning up in the nation's drinking water: traces of drugs, pesticides, cosmetics and even birth-control hormones [see illustration on opposite page]. The amounts are often infinitesimal, measured in parts per billion or trillion (a part per billion is roughly equivalent to one grain of salt dissolved in a swimming pool), but scientists suspect that even tiny quantities of some pollutants can disrupt the developmental biochemistry that determines human behavior, intelligence, immunity and reproduction.

Fortunately, help is on the way. Over the past decade researchers in the emerging field of green chemistry have begun to design the hazards out of chemical

products and processes. These scientists have formulated safer substitutes for harmful paints and plastics and devised new manufacturing techniques that reduce the introduction of pollutants into the environment. As outlined by the Green Chemistry Institute of the American Chemical Society, the first principle of this community is: "It is better to prevent waste than to treat or clean up waste after it has been created." As part of this effort, however, researchers have also made discoveries that promise cost-effective methods for purging many persistent pollutants from wastewater.

In one example of this work, investi-

gators at Carnegie Mellon University's Institute for Green Oxidation Chemistry (one of us, Collins, is the institute's director) have developed a group of designer catalyst molecules called TAML—tetra-amido macrocyclic ligand—activators that work with hydrogen peroxide and other oxidants to break down a wide variety of stubborn pollutants. TAMLs accomplish this task by mimicking the enzymes in our bodies that have evolved over time to combat toxic compounds. In laboratory and real-world trials, TAMLs have proved they can destroy dangerous pesticides, dyes and other contaminants, greatly decrease the smells and color from the wastewater discharged by paper mills, and kill bacterial spores similar to those of the deadly anthrax strain. If broadly adopted, TAMLs could save millions of dollars in cleanup costs.

## The Need to Be Green

Moreover, this research demonstrates that green chemistry can lessen some of the environmental damage caused by traditional chemistry.

A FUNDAMENTAL CAUSE of our escalating environmental plight is that people perform chemistry in different ways than Mother Nature does. For eons, biochemical processes have evolved by drawing primarily on elements that are abundant and close at hand—such as carbon, hydrogen, oxygen, nitrogen, sulfur, calcium and iron—to create everything from paramecia to redwoods, clown fish to humans. Our industries, in contrast, gather elements from nearly every corner of the planet and distribute them in

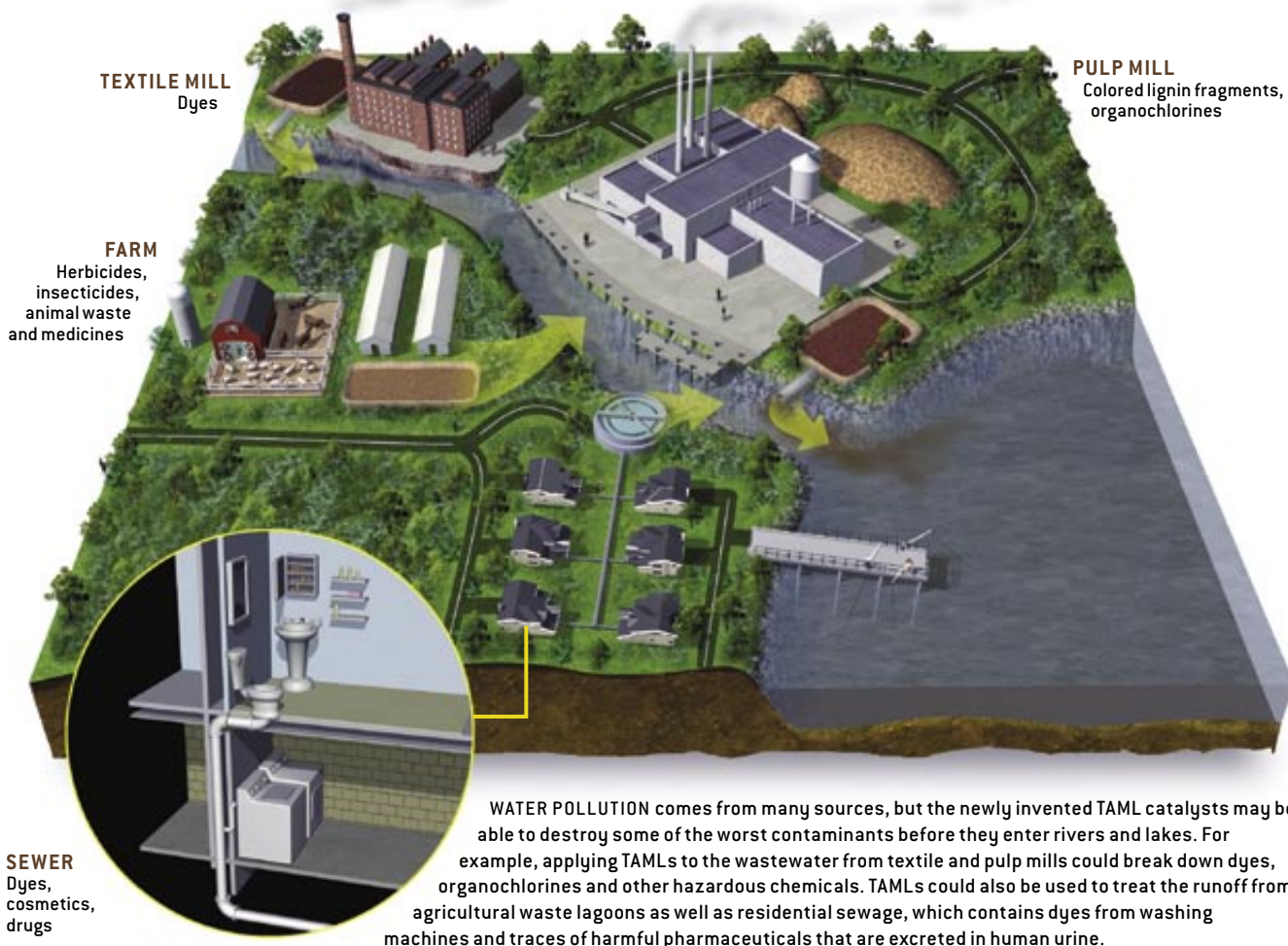
# Green chemistry can lessen some of the environmental damage caused by traditional chemistry.

ways natural processes never could. Lead, for example, used to be found mostly in deposits so isolated and remote that nature never folded it into living organisms. But now lead is everywhere, primarily because our paints, cars and computers have spread it around. When it finds its way into children, even at minuscule doses, it is severely toxic. The same can be said for arsenic, cadmium, mercury, uranium and plutonium. These elements are persistent pollutants—they do not degrade in animal bodies or in the surrounding environment—so there is a pressing need to find safer alternatives.

Some of the new synthetic molecules in medicines, plastics and pesticides are so different from the products of natural chemistry that it is as though they dropped in from an alien world. Many of these molecules do not degrade easily, and even some biodegradable compounds have become omnipresent because we use them so copiously. Recent research indicates that some of these substances can interfere with the normal expression of genes involved in the development of the male reproductive system. Scientists have known for several years that prenatal exposure to phthalates, compounds used in plastics and beauty products, can alter the reproductive tract of newborn male rodents; in

## Overview/Catalysts for Cleaning

- Many pollutants released into waterways, such as dyes and pesticides, have become so omnipresent that they pose a serious threat to human health.
- Chemists have recently created enzymelike catalysts called tetra-amido macrocyclic ligand activators (TAMLs, for short) that can destroy stubborn pollutants by accelerating cleansing reactions with hydrogen peroxide.
- When applied to the wastewater from pulp mills, TAMLs have reduced staining and hazardous chemicals. The catalysts may also someday be used to disinfect drinking water and clean up contamination from bioterror attacks.



**WATER POLLUTION** comes from many sources, but the newly invented TAML catalysts may be able to destroy some of the worst contaminants before they enter rivers and lakes. For example, applying TAMLs to the wastewater from textile and pulp mills could break down dyes, organochlorines and other hazardous chemicals. TAMLs could also be used to treat the runoff from agricultural waste lagoons as well as residential sewage, which contains dyes from washing machines and traces of harmful pharmaceuticals that are excreted in human urine.

2005 Shanna H. Swan of the University of Rochester School of Medicine and Dentistry reported similar effects in male infants. Another study headed by Swan found that men with low sperm counts living in a rural farming area of Missouri had elevated levels of herbicides (such as alachlor and atrazine) in their urine. Starting from our factories, farms and sewers, persistent pollutants can journey intact by air, water and up the food chain, often right back to us.

To confront this challenge, green chemists at universities and companies are investigating the feasibility of replacing some of the most toxic products and manufacturing processes with more environment-friendly alternatives [see box on page 88]. The work of Collins's team at Carnegie Mellon traces its origins back to the 1980s, when public health concerns about chlorine were intensifying. Chlorine was then, and still is, often used for large-scale cleaning and disin-

fection in manufacturing, as well as for the treatment of drinking water. Although chlorine treatment is inexpensive and effective, it can create some ugly pollutants. The bleaching of wood pulp with elemental chlorine in paper mills had been a major source of cancer-causing dioxins until the Environmental Protection Agency banned the process in 2001. (Most mills now bleach wood pulp with chlorine dioxide, which reduces the production of dioxins but does not eliminate it.) By-products created by the chlorination of drinking water have also been linked to certain cancers. Chlorine in its common natural form—chloride ions or salts dissolved in water—is not toxic, but when elemental chlorine reacts with other molecules it can generate compounds that can warp the biochemistry of living animals. Dioxins, for instance, disrupt cellular development by interfering with a receptor system that regulates the production of critical proteins.

Rather than relying on chlorine, we wondered if we could put nature's own cleansing agents—hydrogen peroxide and oxygen—to the work of purifying water and reducing industrial waste. These cleansers can safely and powerfully obliterate many pollutants, but in nature the process usually requires an enzyme—a biochemical catalyst that vastly increases the rate of the reaction. Whether natural or man-made, catalysts act as old-fashioned matchmakers, except that rather than bringing two people together they unite specific molecules, enabling and accelerating the chemistry among them. Some natural catalysts can boost chemical reaction rates a billionfold. If not for an enzyme called ptyalin, found in our saliva, it would take several weeks for our bodies to break down pasta into its constituent sugars. Without enzymes, biochemistry would move at a numbingly slow pace, and life as we know it would not exist.

In nature, enzymes called peroxidases catalyze reactions involving hydrogen peroxide, the familiar household chemical used to bleach hair and remove carpet stains. In forests, fungi on rotting trees use peroxidases to marshal hydrogen peroxide to break down the lignin polymers in the wood, splitting the large molecules into smaller ones that the fungi can eat. Another family of enzymes, the cytochrome p450s, catalyzes reactions involving oxygen (also called ox-

structive because the bonds it makes with other elements (especially hydrogen) are so strong. And because each molecule of hydrogen peroxide ( $H_2O_2$ ) is halfway between water ( $H_2O$ ) and molecular oxygen ( $O_2$ ), this compound is also strongly oxidizing. In water, hydrogen peroxide often produces a kind of liquid fire that demolishes the organic (carbon-containing) molecules around it. A lesson from the enzymes was that a working catalyst would probably need to have

and perhaps produce a pollution problem of its own. All our existing Fe-TAML catalysts (TAMLs with iron as the central metal atom) decompose on time-scales ranging from minutes to hours.

Building the ligand firewalls was not easy. It required developing a painstaking four-step design process in which we first imagined and then synthesized ligand constructions that we hoped would keep the firewall in place. Second, we subjected the catalyst to oxidative stress until the firewall disintegrated. Third, we looked for the precise location where the breakdown began.

## Whether natural or man-made, catalysts act as old-fashioned matchmakers.

dation reactions). Cytochrome p450s in our livers, for example, use oxygen to efficiently destroy many toxic molecules we inhale or ingest.

For decades, chemists have been struggling to build small synthetic molecules that could emulate these enormous enzymes. If scientists could create designer molecules with such strong catalytic abilities, they could replace the chlorine- and metal-based oxidation technologies that produce so many pollutants. In the early 1980s, however, no one was having much luck developing test-tube versions of the enzymes. Over billions of years of evolution, nature had choreographed some wonderfully elegant and extremely complex catalytic dances, making our efforts in the laboratory look clunky. Yet we knew that we could not achieve our goal of reducing pollution unless we found a way to mimic this molecular dance.

### Catalytic Converters

CREATING SYNTHETIC enzymes also meant assembling molecules that would be robust enough to resist the destructive reactions they were catalyzing. Any chemistry involving oxygen can be de-

an iron atom placed inside a molecular matrix of organic groups. So we had to toughen the molecular architecture of such groups to ensure they could survive the liquid fire that would result from the activation of hydrogen peroxide.

Borrowing further from nature's design, we eventually solved this problem by creating a catalyst in which four nitrogen atoms are placed in a square with a single iron atom anchored in the middle [see box on opposite page]. The nitrogen atoms are connected to the much larger iron atom by covalent bonds, meaning that they share pairs of electrons; in this kind of structure, the smaller atoms and attached groups surrounding the central metal atom are called ligands. Next we linked the ligands to form a big outer ring called a macrocycle. Over time we learned how to make the ligands and linking systems tough enough to endure the violent reactions that the TAMLs trigger. In effect, the ligands we invented became a kind of firewall that resisted the liquid fire. The longer it resisted, the more useful the catalyst. Of course, we did not want to create an indestructible catalyst, which could end up in effluent streams

(We found that ligand degradations always start at the most vulnerable site.) And in the final step, once we had pinpointed the weakest link, we replaced it with groups of atoms we believed would hold up longer. Then we started the whole design cycle again.

After 15 years, we finally created our first working TAML. We knew we had succeeded one morning when Colin Horwitz, a research professor at our institute, showed off the results of a bleaching experiment that featured our most advanced design at the time. We looked at the results, and there it was: every time Horwitz squirted dark dye into a solution containing the TAML catalyst and hydrogen peroxide, the solution quickly turned colorless. We now knew that our firewalls were finally holding up long enough to allow the TAMLs to do their job. The molecules were acting like enzymes, and yet they were much, much smaller: the molecular weight of a TAML is about 500 daltons (a dalton is equal to one twelfth the mass of carbon 12, the most abundant isotope of carbon), whereas the weight of horseradish peroxidase, a relatively small enzyme, is about 40,000 daltons. The diminutive TAML activators are easier and cheaper to make, and much more versatile in their reactivity, than their natural counterparts.

Since then, we have evolved more than 20 different TAML activators by reapplying the same four-step design process that enabled us to create the first

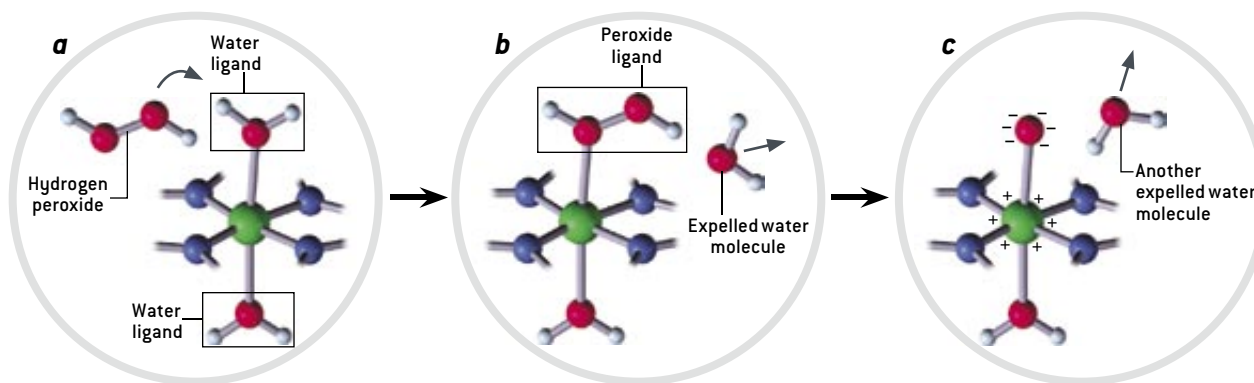
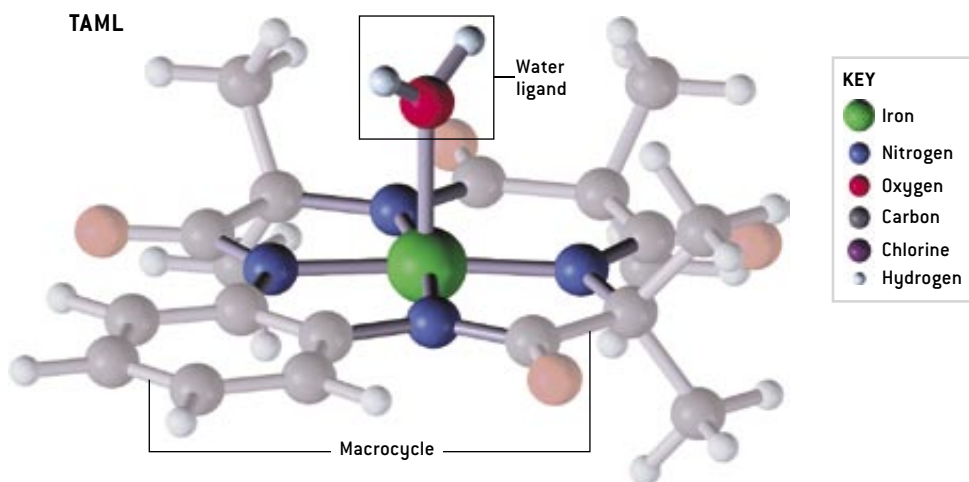
THE AUTHORS

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## A MOLECULAR CLEANING MACHINE

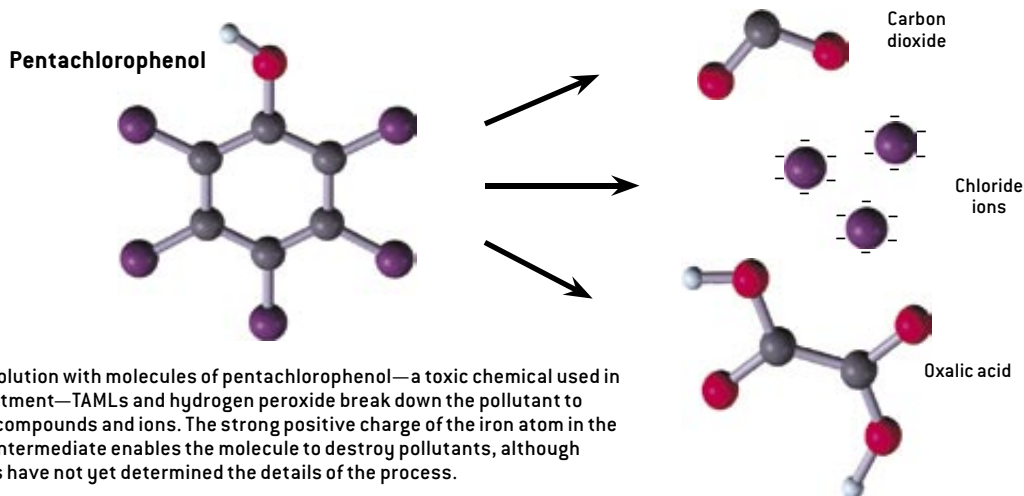
Chemists designed TAMLs to emulate the natural enzymes that catalyze reactions involving hydrogen peroxide. TAMLs, though, are hundreds of times smaller than enzymes, so they are easier and cheaper to manufacture.

At the center of each TAML is an iron atom bonded to four nitrogen atoms; at the edge are carbon rings linked to form a big outer ring called a macrocycle. This linking system acts as a firewall, enabling the molecule to endure the violent reactions it triggers. In its solid state the TAML also has one water molecule ( $H_2O$ ) attached to the iron atom. (The attached groups are called ligands.)



When a TAML dissolves in water, another molecule of  $H_2O$  connects to the catalyst (a). If hydrogen peroxide ( $H_2O_2$ ) is also in the solution, it can replace one of the water ligands, which are loosely attached and easily expelled (b). The peroxide ligand then discards both its



hydrogen atoms and one oxygen atom in the form of a water molecule, leaving one oxygen atom attached to the iron (c). The oxygen pulls electrons farther away from the iron atom, turning the TAML into a reactive intermediate.



When in solution with molecules of pentachlorophenol—a toxic chemical used in wood treatment—TAMLs and hydrogen peroxide break down the pollutant to nontoxic compounds and ions. The strong positive charge of the iron atom in the reactive intermediate enables the molecule to destroy pollutants, although scientists have not yet determined the details of the process.

## CHEMISTRY GOES GREEN

The invention of TAML catalysts is just one of the many achievements of green chemistry, which strives to develop products and processes that reduce or eliminate the use and generation of hazardous substances. Some other accomplishments are listed below.

PROJECT	PARTICIPANTS	STATUS
Using plant sugars to create polylactic acids (PLAs), a family of biodegradable polymers that could replace many traditional petroleum-derived plastics	Patrick Gruber, Randy L. Howard, Jeffrey J. Kolstad, Chris M. Ryan and Richard C. Bopp, NatureWorks LLC (a subsidiary of Cargill)	NatureWorks has built a factory in Nebraska to manufacture PLA pellets, which are used to make water bottles, packaging materials and other products 
Discovering synthesis reactions that allow manufacturers to substitute water for many common organic solvents, some of which can cause cancer	Chao-Jun Li, McGill University	Pharmaceutical and commodity chemical companies are investigating the process
Developing metathesis chemistry, a method of organic synthesis that can produce drugs, plastics and other chemicals more efficiently and with less waste	Robert H. Grubbs, California Institute of Technology; Richard R. Schrock, Massachusetts Institute of Technology; Yves Chauvin, French Petroleum Institute	Widely applied in the chemical, biotechnology and food industries, this research was awarded the 2005 Nobel Prize in Chemistry 
Replacing toxic petroleum-based solvents with supercritical carbon dioxide, a high-temperature, high-pressure fluid that has the properties of both a liquid and a gas	Martyn Poliakoff, Michael George and Steve Howdle, University of Nottingham, England	Thomas Swan & Co., a British manufacturer of specialty chemicals, has built a plant that uses supercritical fluids
Inventing a new method for producing sertraline, the key ingredient in the antidepressant Zoloft	James Spavins, Geraldine Taber, Juan Colberg and David Pfisterer, Pfizer	The process has reduced pollution, energy and water use while improving worker safety and product yield

working model. Each TAML has its own reaction rate and lifetime, allowing us to tailor the catalysts to match the tasks we want them to perform. Most of the catalysts incorporate elements such as carbon, hydrogen, oxygen, nitrogen and iron, all chosen for their low toxicity. We call some of the molecules “hunter TAMLs” because they are designed to seek out and lock onto specific pollutants or pathogens, in much the same way that a magnetized mine seeks out the metal hull of a ship. Other TAMLs act as blowtorches that aggressively burn most of the oxidizable chemicals with which they come into contact. Still others are less aggressive and more selective, so that they will, for example, attack only certain parts of molecules or attack only the more easily oxidized molecules in a group. We expect to adapt TAMLs to advance green chemistry for decades to come. Although more toxicology testing must be done, the results so

far indicate that TAMLs break down pollutants to their nontoxic constituents, leaving no detectable contamination behind. We now have more than 90 international patents on TAML activators, with more in the pipeline, and we also have several commercial licenses.

Interestingly, we still do not know all the details of how the TAMLs work, but recent studies have provided deep insights into the key reactions. In their solid state, Fe-TAMLs generally have one water molecule attached as a ligand to the iron atom, oriented perpendicularly from the four nitrogen ligands; when put in solution, another water molecule connects to the opposite side of the iron atom. These water ligands are very loosely attached—if hydrogen peroxide is also in the solution, a molecule of it easily replaces one of the water molecules. The peroxide ligand swiftly reconstitutes itself, expelling both its hydrogen atoms and one oxygen atom (which escape as

H<sub>2</sub>O, a water molecule) and leaving one oxygen atom attached to the iron at the center of the Fe-TAML, which is now called the reactive intermediate (RI).

Oxygen is much more electronegative than iron, which means that its nucleus pulls most of the electrons in the complex bond toward itself and away from the iron nucleus. This effect increases the positive charge of the iron at the center of the TAML, making the RI reactive enough to extract electrons from oxidizable molecules in the solution. We have not yet determined how the RI breaks the chemical bonds of its targets, but current investigations may soon reveal the answer. We do know, however, that we can adjust the strength of the TAMLs by changing the atoms at the head and tail of the molecule; putting highly electronegative elements at those locations draws even more negative charge away from the iron and makes the RI more aggressive.

## Industrial Strength

**BUILDING TAMLs** in the laboratory is one thing; scaling them up for commercial use is another. So far the lab tests and field trials have been promising. Tests funded by the National Science Foundation, for example, demonstrated that Fe-TAMLs plus peroxides could clean up the contamination from a bioterror attack. We found that when we combined one TAML with tertiary butyl hydroperoxide—a variation of hydrogen peroxide that replaces one of the hydrogen atoms with a carbon atom and three methyl (CH<sub>3</sub>) groups—the resulting solution could deactivate 99.99999 percent of the spores of *Bacillus anthracis*, a bacterial species very similar to anthrax, in 15 minutes. In another important potential application, we hope to use Fe-TAMLs and hydrogen

peroxide to someday create an inexpensive disinfectant to tackle the infectious waterborne microbes that account for so much death and disease worldwide.

In three field trials, we explored how well TAMLs can alleviate the pollution created when paper is manufactured. Every year the paper and wood pulp industry produces more than 100 million metric tons of bleached pulp, which is turned into white paper. Besides generating dioxins, chlorophenols and other hazardous organochlorines, many pulp mills discharge a coffee-colored effluent that stains streams and rivers and blocks light from penetrating the water. The reduction of light interferes with photosynthesis, which in turn affects organisms that depend on plants for food. The sources of the staining are large colored fragments of lignin, the polymer that binds the cellulose fibers in wood. Bleaching with chlorine dioxide removes the lignin from the cellulose; the smaller lignin fragments are digested by bacteria and other organisms in treatment pools, but the larger pieces are too big to be eaten, so they end up in rivers and lakes.

We have tested the effectiveness of Fe-TAMLs at decolorizing these fragments at two pulp mills in the U.S. and one in New Zealand. In New Zealand we com-

bined Fe-TAMLs and peroxide with 50,000 liters of effluent water. In the U.S. we directly injected Fe-TAMLs into a pulp-treatment tower or an exit pipe over the course of several days to bleach the wastewater. Overall, the Fe-TAMLs reduced the staining of the water by up to 78 percent and eliminated 29 percent of the organochlorines.

The development of other TAML applications also looks exciting. Eric Geiger of Urethane Soy Systems, a company based in Volga, S.D., has found that Fe-TAMLs do an excellent job processing soybean oil into useful polymers that display physical properties equal to, if not better than, those of current poly-

Building TAMLs in the laboratory is one thing;  
**scaling them up** for commercial use is another.

urethane products. TAMLs may even find their way into washing machines: in another series of tests, we found that a tiny quantity of catalyst in certain household laundry products eliminated the need to separate white and colored clothing. TAMLs can prevent staining by attacking dyes after they detach from one fabric but before they attach to another. We are also working on a new family of TAMLs that can break the very stable molecular bonds that allow drugs and agricultural chemicals to pass intact into drinking water.

Despite the success of these trials, we have not resolved all the questions about TAML activators. More testing on industrial scales remains to be done, and it is important to ensure that TAMLs do not create some form of pollution we have not yet observed. Too often chemical technologies have seemed completely benign when first commercialized, and

the devastating negative consequences did not become clear until decades later. We want to do everything in our power to avoid such surprises with TAMLs.

Cost is also an issue. Although TAMLs promise to be competitive in most applications, large corporations are deeply invested in the chemical processes they currently use. Shifting to new systems and techniques, even if they work, usually requires significant investments. One great advantage of TAML technology, though, is that it does not require major retooling. What is more, TAMLs may ultimately save companies money by offering a cost-effective way to meet increasingly stringent environmental

laws in the U.S., Europe and elsewhere.

The advances of green chemistry to date represent only a few interim steps on the road to dealing with the many environmental challenges of the 21st century. The deeper question is, Are we going to practice acute care or preventive medicine? Right now most chemists are still trained to create elegantly structured compounds that solve the specific problem for which they have been engineered, without regard to their broader impact. We are in effect performing global-scale experiments on our ecosystems and ourselves, and when these experiments fail the cost can be catastrophic. New green chemical techniques offer an alternative. The Industrial Revolution has unfolded, for the most part, without design or forethought. Perhaps now we can take some creative steps to reverse that trend and help make a world, and a future, that we can live with. SA

### MORE TO EXPLORE

**Toward Sustainable Chemistry.** Terrence J. Collins in *Science*, Vol. 291, No. 5501, pages 48–49; January 5, 2001.

**Rapid Total Destruction of Chlorophenols by Activated Hydrogen Peroxide.** Sayam Sen Gupta, Matthew Stadler, Christopher A. Noser, Anindya Ghosh, Bradley Steinhoff, Dieter Lenoir, Colin P. Horwitz, Karl-Werner Schramm and Terrence J. Collins in *Science*, Vol. 296, pages 326–328; April 12, 2002.

More information can be found online at [www.cmu.edu/greenchemistry](http://www.cmu.edu/greenchemistry) and [www.chemistry.org/portal/a/c/s/1/acdisplay.html?DOC=greenchemistryinstitute/index.html](http://www.chemistry.org/portal/a/c/s/1/acdisplay.html?DOC=greenchemistryinstitute/index.html)