ORGANIC CHEMISTRY

Chemists Clean Up Synthesis With One-Pot Reactions

LEEDS, U.K.—Filmgoers are familiar with Hollywood's vision of the organic chemist. In a dimly lit laboratory the mad scientist is bent over a flask attached to yards of elaborate twisting glasswork through which a bilious green liquid bubbles. Eyes rolling wildly, the scientist adds ingredients to the potion, which starts to fume, and with a cry of triumph he swallows the smoking elixir, certain that it will confer eternal life or regrow lost hair.

The real organic chemist usually lacks this cinematic poetry. What's more, actual organic chemistry just isn't that simple. The drugs and agrochemicals chemists create are rarely prepared in a single process. On the contrary, the target molecule is usually made via an elaborate chain of separate reaction steps that may take weeks to complete. And when that process is enlarged to industrial scale, it becomes an environmentally dirty business, using huge amounts of raw materials and energy and often creating equal quantities of toxic waste.

Part of the reason for the environmental burden is that each reaction step is carried out separately, with its own reaction conditions, temperature, solvent, and catalyst. After each reaction has finished, the mixture is "worked up": the catalyst and waste products are removed and discarded, and the desired compound is separated and purified.

That kind of synthesis has worked fine until recently. But now environmental pressures are forcing the chemical industry to look for "cleaner" methods, including biological techniques using enzymes or monoclonal antibodies. But Steven Ley of Cambridge University is optimistic that chemists can clean up their own act without so much help from biology. His secret? A "one-pot" method that, ironically, calls to mind the boiling beaker of the movie chemist. Says Ley: "I think we can move traditional organic chemistry forward by taking small, simple components and bringing them together so as to generate maximum complexity in an environmentally friendly way."

By carefully designing the reaction sequence so that the first step creates the conditions to trigger the next stage, and that in turn sets up the third reaction, and so on, chemists can put all the ingredients in together at the beginning. All that is then needed is to heat the mixture gently for a few hours, and, presto, you have your target material. This type of multistage reaction has always been a part of organic synthesis, but now chemists have latched onto it as a promising way of creating new environmentally acceptable reaction schemes for industry. They have also given it a name: cascade chemistry, a name given because each reaction step flows into the next like a series of waterfalls. This topic is rapidly gaining currency in the world of chemistry, as shown by the fact that last month, chemists gathered for the first international meeting on cascade chemistry at the University of Leeds in the United Kingdom.

Green chemistry is what cascade synthesis is all about, says one of its leading proponents, Lutz F. Tietze of the Georg-August University in Göttingen, Germany. "We are trying to copy nature by performing a reaction sequence without ever isolating the intermediate products and by retaining the same gentle reaction conditions throughout. This approach is not only selective but also highly efficient, saving time, energy, and raw materials," he says.

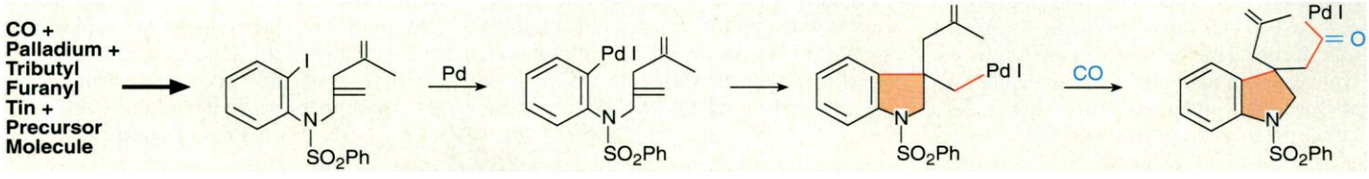
Tietze adds that cascade chemists aim to use the mildest possible conditions: ideally a temperature of 25°C, atmospheric pressure, and an environmentally safe solvent such as water, methanol, or acetone. Finding a suitable catalyst poses a bigger problem. "Ideally it should be a true catalyst, which is nontoxic," says Tietze. Not all sophisticated organic reactions can be carried out that way, however. Many require a heavy metal catalyst, but cascade chemists try to use it in an easily recoverable form.

Although the field of cascade chemistry is too young to have yet come up with an industrially useful synthesis, many elegant prototypes of this new art were on display at the Leeds conference. Not surprisingly, all of these reaction schemes involved the formation of ring molecules, a procedure that is among the most important transformations in organic synthesis. Chemists at Leeds showed off ways of making rings with anything from three to eight carbon atoms, with single or double bonds, with bridges across them, and most important, fused ring systems often containing atoms other than carbon, such as sulfur, oxygen, or nitrogen, known as heteroatoms. Such heterocyclic structures are the basis of many important drugs.

A graceful example, which aspires to the environmental ideals of cascade chemists, is Tietze's own work on a cascade incorporating the best known ring-forming method, the Diels-Alder reaction, a common industrial procedure in the manufacture of drugs and agrochemicals. In the Diels-Alder reaction, a diene, which contains two double bonds separated by a single bond, reacts with a double bond (called a dienophile) in another molecule or in another part of the same molecule to create a new six-membered ring.

Tietze's reaction sequence is simple and economical (see diagram, middle of p. 33): First he creates a molecule with a diene and dienophile in close proximity by combining a benzaldehyde derivative, containing a dienophile, with a cyclic 1,3 dicarbonyl compound called Meldrum's acid, in a procedure known as the Knoevenagel reaction. Then the Diels-Alder reaction kicks in: Three neighboring double bonds form a ring, and the result is a compound with four fused rings obtained with an 84% yield, a good result by the standards of organic synthesis. The whole cascade is carried out at room temperature using an ammonium salt as a catalyst. "Thousands of different heterocyclic compounds of interest to the pharmaceutical industry can be made by this procedure, just by changing the starting material," says Tietze.

This kind of synthesis not only promises diversity, it also copes well with one of the major concerns of the pharmaceutical industry: getting the shape right. The effectiveness of many compounds, particularly biological ones, is critically dependent on the geometrical arrangement of the compound's parts. For instance, a simple compound with a central carbon atom attached to four different atoms or groups can exist in two different forms, called enantiomers, which are mirror images. Many compounds contain several such stereogenic centers, and the correct arrangement of groups at each center must be built in during synthesis. Because cascade chemistry involves careful planning of reaction sequences, it seems to take this problem



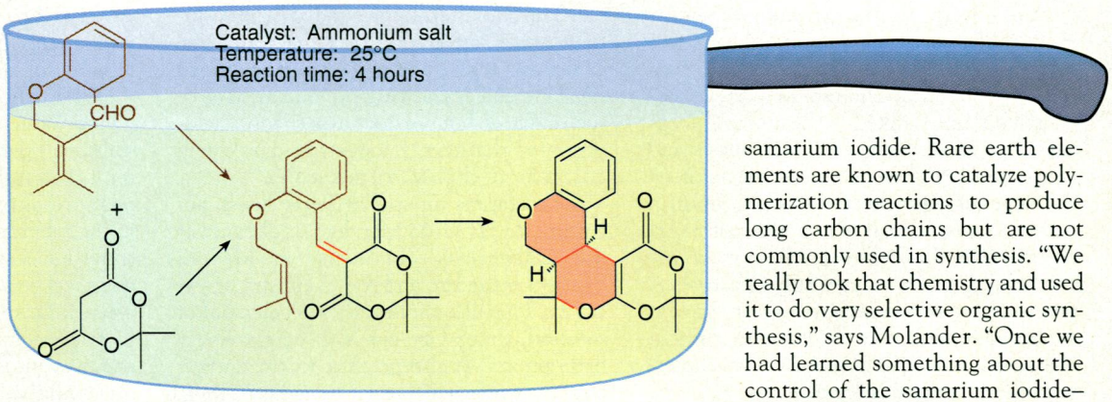
in its stride. For example, Tietze reports that the product of his cascade Diels-Alder reaction is 99% single enantiomer.

But Tietze's method isn't the only one that seems to share these advantages. At the Leeds conference, Andrew Holmes of Cambridge University presented a different approach to ring formation. Holmes starts with a linear chainlike molecule and loops it around into a pair of rings. Specifically, he aims to make nitrogen-containing rings; such rings are useful in drugs that inhibit biological processes by recognizing and latching onto particular proteins and peptides. The starting chain includes a triple bond and elsewhere a nitrogen-containing hydroxylamine group attached to the side. On heating, the chain closes on itself to form a five- or six-membered loop, leaving a dangling string that goes on to attach itself again, yielding a second ring. "The secret is to get the complexity of the rings from the simplicity of the chains by careful arrangement of the atoms in space and by the way the atoms are joined together," says Holmes.

In contrast to Holmes' simple scheme, one of the most elaborate cascades presented at the conference was one devised by Ronald Grigg, the conference organizer, who is based at the University of Leeds. "It's an excellent example of how highly complex compounds can be generated very quickly from simple starting materials," says Philip Parsons of Reading University, who also presented new cascade designs at the conference. Grigg's cascade is based on a ring-forming technique called the Heck reaction in which palladium acts as a catalyst for the bond making (see diagram below).

But one cascade didn't sate Grigg's taste for waterfalls. He extended the cascade by making the palladium catalyze more reactions and hop from place to place on the molecule in the process. In total, five new carbon-carbon bonds are formed, three molecules are added to the original precursor, and three new rings are created. "Although we haven't optimized the conditions yet, we have focused on a process that could be carried out easily in a standard pilot plant," says Grigg.

The key to this kind of cascade is tailoring the molecular environment at each stage in the synthesis so that the desired reaction is the fastest, and so takes place first at the active site created by the palladium. "You have to make a careful judgment on what is likely to be the rates of all the possible reactions," says Grigg. Five-membered rings are formed more quickly than six-membered ones, for example, while adding a carbonyl group from carbon monoxide, although slower than ring formation, is faster than other potentially competitive reactions.



Ring cycle. The gentlest of conditions will coax two single-ringed compounds into four fused rings.

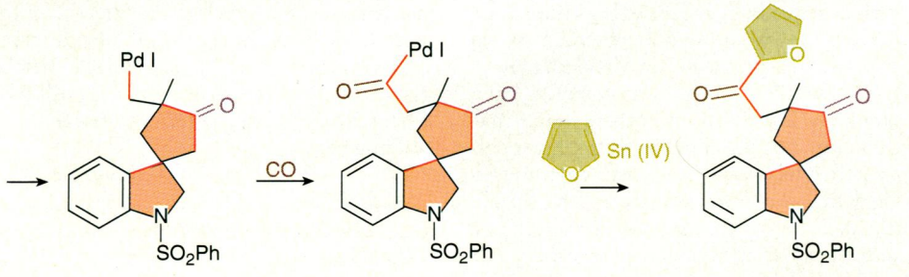
Such juggling of reaction rates is the key to another family of cascades based on radical reactions—multistage reactions in which intermediate compounds have unpaired electrons and therefore are highly reactive. Traditionally, radical chemistry has been considered too promiscuous for any practical use: The radical compounds will react with anything, or will react with several atoms or groups in a molecule, leaving the outcome of the reaction unpredictable. But with a better understanding of radical reaction mechanisms, that view has changed.

According to Willie Motherwell of University College London, radicals actually have many advantages. They tend, for instance, not to have molecules of the solvent clustered around them, and, as a result, they're small and penetrating enough to reach active sites tucked away in a crowded part of a molecule. With a thorough knowledge of radical reaction rates, Motherwell has designed cascades based on a strained, three-membered ring with chains containing triple bonds hanging off it. The ring is split open to form a radical compound, and all the bonds then rearrange themselves into a five-membered ring.

Gary Molander from the University of Colorado has also adopted an unorthodox approach. He uses several different types of reactions, but what is unusual about his scheme is the use of a rare-earth catalyst, samarium iodide. Rare earth elements are known to catalyze polymerization reactions to produce long carbon chains but are not commonly used in synthesis. "We really took that chemistry and used it to do very selective organic synthesis," says Molander. "Once we had learned something about the control of the samarium iodide–promoted reactions, we found we could link them in different orders in a one-pot process to make polycyclic systems."

So far, cascade chemists have made structures containing just a few rings and a few new bonds in one pot. But the field is still in its infancy; in the future, with carefully tuned conditions, many more steps will surely be added. One possibility is combining traditional organic reactions with biotechnology. Says Grigg: "Biotechnology is clearly going to be a part of everyday chemical synthesis, and you may want to employ a step that uses biotechnology, but at the moment there are not sufficient biotechnological steps available to build up cascades."

An even more promising line of research, which several groups are now exploring, is taking a leaf from the notebook of chemists who do peptide synthesis and pinning the precursor molecule to a solid support, then sequentially adding molecular groups to it. "This will be an extremely useful approach



Cascade recipe. Put iodosulfonamide, palladium catalyst precursors, and tributyl furanyl tin in a flask. Attach a condenser to the top and place a child's balloon filled with carbon monoxide over the top end of the condenser. Use a magnetic stirrer to mix the ingredients at 110°C and leave overnight. If all goes well, the reagents should queue up to react as shown and create a new four-ringed compound.

for cascade reactions, because it will allow us to wash the product and remove it easily at the end. We are going to be working on it during the next year," says Grigg.

Judging from the number of industrial chemists at the Leeds conference, pharmaceutical companies are very interested in the possibilities opened up by the cascade of new synthetic methods. "The cascade approach potentially offers us a faster, simpler way to make [small molecules for drug development] that is also likely to be of benefit environmentally. This has to be an exciting prospect for any process chemist in the pharmaceutical industry," says David Marshall, head of process research at Britain's biggest drug company, Glaxo. But Grigg cautions that one-pot reactions will not transform the industry overnight: "It takes 10 years to get a new drug onto the market, so it will be some time before cascade chemistry is used in industrial plants."

That does not worry the new breed of cascade chemists, who have plenty to do in the meantime. Much of the basic research into understanding biology at the molecular level involves building complex natural products using more than 100 synthetic steps. Cascade chemistry could simplify the procedure considerably. Says Grigg: "Cascade chemistry is the future of organic chemistry. It will become a major guiding principle in the synthesis of any new biologically active compound." And if that is the case, then the benefits of cascade chemistry will follow as naturally as water flowing downhill.

–Nina Hall

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CHEMISTRY

Crafting a Cage for Cholesterol

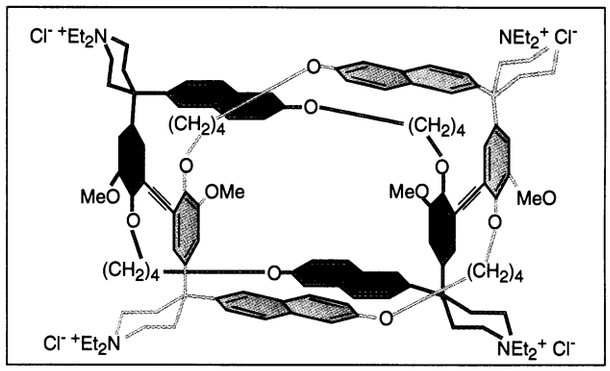
After a long, frustrating hunt, chemists have finally caged a rogue substance whose name evokes fear among the health conscious: cholesterol. Cholesterol in the bloodstream has been linked to the arterial blockages that cause cardiovascular disease, and consequently the steroid chemical has been the target of many diets and drugs. Unfortunately, current drugs, which attempt to interfere with the body's production of the chemical, have not been fully effective. A group of Swiss chemists, however, has recently built a cagelike molecule that might ultimately be used to filter out excess cholesterol from the bloodstream.

Last month, François Diederich and Blake Peterson of the Organic Chemistry Laboratory at Eidgenossische Technische Hochschule, Zurich, reported in the journal *Angewandte Chemie* (vol. 33, p. 1625) that they had formulated a compound from two ring-shaped molecules called cyclophanes that trapped cholesterol molecules in its central cavity while ignoring a similar compound. "What Diederich has done is very clever. There's no doubt this is a major advance [in recognition chemistry]," says David Leigh, an organic chemist at the University of Manchester Institute of Science and Technology.

The cyclophane cage might be used to reduce cholesterol levels in patients with extremely high blood cholesterol, or hypercholesterolemia, when drug treatment is ineffective. Leigh cautions, however, that much more needs to learned about the selectivity of the trap before it is ready for clinical use. There's still a chance the molecule might trap small amounts of similar steroids, such as hormones, which are vital for bodily functions.

Scientists have been trying for years to find a highly selective cholesterol trap. The key to making such a trap is to take advantage of cholesterol's chemistry: It is intensely hydrophobic—like oil, it is repelled by water molecules. Any trap that would lure cholesterol out of a water-based solution, like blood, needs a cavity that is also hydrophobic. The cholesterol, surrounded by inhospitable water molecules, sees the water-free cavity as a refuge and dives in. Ring-shaped sugar molecules known as cyclodextrins have such cavities, but previous experiments demonstrated that the cyclodextrins didn't grab onto a lot of cholesterol molecules.

The reasons for this ineffectiveness, according to Javier de Mendoza, a chemist at the Universidad Autonoma in Madrid, Spain, are the size and the chemistry of the cavity. To pull a cholesterol molecule out of solution, the cavity needs to be extremely hydrophobic. It also needs to fit the cholesterol molecule, which is 1.1 nanometers long. Cyclodextrin cavities failed on both counts.



Stuck in the middle. The cavity in the center of two cyclophane molecules can grab cholesterol and hold it.

So about 4 years ago, Diederich's team turned to synthetic ring-shaped molecules called cyclophanes, which they could tailor to larger sizes using organic synthesis. "The encapsulation of large [hydrophobic] guests, such as steroids, by means of big cyclophane cavities is perhaps the only practical way to approach the problem," de Mendoza says.

But simple cyclophanes proved to have problems. Diederich and others found that they were not big enough or strong enough to pull cholesterol into their cavities. So Diederich and Peterson decided to double the molecules, increasing the cage size. They coupled two cyclophanes, linking them with chemical bridging groups called acetylenes, and in this way created a molecule with a cavity 0.9 by 1.3 nanometers wide and 1.1 nanometers deep—just the right size for a cholesterol molecule.

When cholesterol was added to a cyclophane-water solution, they reported, that solution accepted 190 times more cholesterol than normal. This indicates the cyclophanes took up the cholesterol, leaving room in the solution for more to be dissolved. Testosterone, a steroid hormone with a similar chemical structure, was trapped much less often, indicating the trap was fairly selective.

Diederich believes these cyclophanes could eventually be incorporated into the membrane of a dialysis machine that would vacuum cholesterol from the bloodstream of patients with severe hypercholesterolemia in a "blood washing" procedure. He now plans to test such a membrane on a hypercholesterolemic animal model. De Mendoza notes that "a dialysis membrane to filter out the cholesterol from blood is clever, since it drastically avoids any toxicity problems."

Leigh, however, injects a note of caution. "Don't expect a cholesterol dialysis machine in the next 10 years," he says. Although the Swiss group demonstrated that cyclophanes can discriminate between cholesterol and testosterone, there might still be another vital hormone that gets inadvertently caught. The Swiss team "is still a long way from proving that the receptor won't bind to other steroids or biomolecules in the bloodstream and cause problems," he says. Diederich agrees, but notes that time and tests will tell whether he's built a specific cage or a general holding pen.

–David Bradley

David Bradley is a science writer based in Cambridge, England.