Chemists Look to Follow Biology Lead

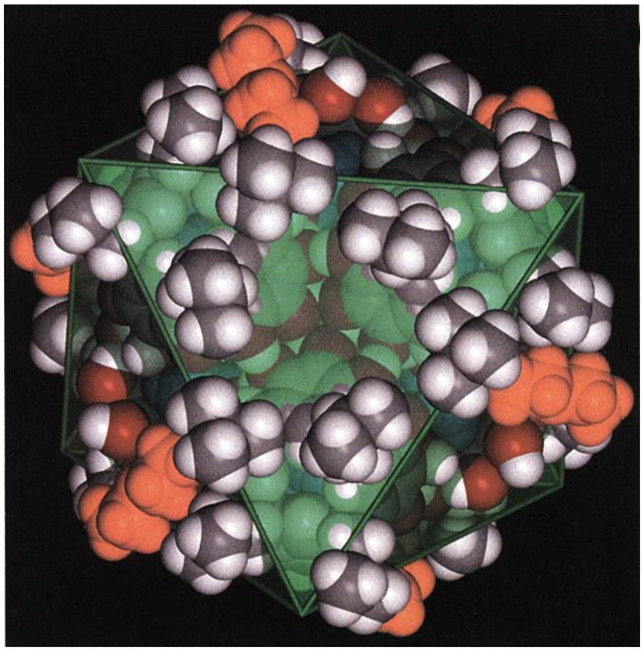
Covalent bonds provide the strongest connection between atoms in a molecule. But chemists are now using more tenuous links to assemble large molecular complexes

Over the past century, chemists have become lords of the covalent bond. They've invented hundreds of reactions that form and rearrange the ultrastrong coupling that results when two atoms share electrons, and they've used their knowledge to rival nature's ability to create everything from antibiotics to plastics. But it's only in recent years that chemists have begun to take advantage of another wonder of the natural world—the ability to form looser links between small molecules. That mechanism governs the assembly of molecules into living organisms, including sewing DNA strands into the familiar double helix and uniting the protective membrane that houses every cell. It's also the basis of one of the fastest-growing areas of research: supramolecular chemistry. "We're starting to bring supramolecular chemistry to the same level of predictability as traditional organic synthesis," says Jerry Atwood of the University of Missouri, Columbia.

This success, say chemists such as Atwood, in time may revolutionize fields ranging from polymer science to tissue engineering. "Supramolecular chemistry is going to allow us to bridge the gap between the macro world and the atomic world, and that will have a tremendous impact on a wide variety of fields, such as diagnostics and microelectronics," says Chad Mirkin, who heads the Institute for Nanotechnology at Northwestern University in Evanston, Illinois.

Despite biology's considerable lead in working with loose-knit bonds, scientists have learned plenty since chemists began dissecting the nature of the chemical bond. Starting in the mid-1800s, researchers characterized a variety of types of noncovalent bonds, such as hydrogen bonds, van der Waals forces, π-π interactions, and other energetic influences that attract atoms to one another without causing them to exchange electrons formally.

Even though these bonds are typically weak by themselves, clusters of them produce a powerful adhesive. Two of nature's favorites are links made with hydrogen bonds—formed when a hydrogen atom is shared by two electron-rich atoms, such as oxygen or nitrogen—and hydrophobic interactions, which occur when oily molecules pack together to limit their exposure to water. These two forces combine to stabilize the double helix of DNA: Hydrogen bonds pull the two strands together, while the hydrophobic rings of the nucleic acid bases stack upon one another to make the strands more rigid. This stacking is further stabilized by the interactions between π-electron clouds that circle above and below these rings.



Copycat. This organic compound mimics the simple structure of a virus by assembling itself along a series of symmetrical planes (green).

CREDIT: J. ATWOOD/UNIVERSITY OF MISSOURI, COLUMBIA

Chemists have long understood the basic workings of noncovalent bonds, but they're still getting a handle on manipulating large numbers of them. "Supramolecular chemistry is the science of the noncovalent bond, and this isn't an expertise that we synthetic chemists have really developed," says Sam Stupp, a materials scientist at Northwestern. "We still don't know many of the rules for how small molecules recognize one another and assemble to make stable, large structures." But, he adds, "we are getting to the point where we can think about how we would put together large molecular complexes and then actually develop a rational approach to accomplish that synthesis."

This more rational approach has been particularly useful in designing molecules capable of assembling themselves. Several groups have begun doing just that by mimicking the way viral coat proteins self-assemble into beautifully symmetric, hollow capsules. These capsules are rugged enough to survive both inside and outside of the body, yet fragile enough to dissolve and release their contents once they burrow their way inside a target cell.

Atwood, for example, teamed with graduate student Leonard MacGillivray, who has since moved to the Steacie Institute for Molecular Sciences in Ottawa, Canada, to design capsules that can put themselves together and even repair tears. After examining the crystal structure of viruses, the two chemists created small molecules with the correct symmetry and placement of atoms to allow multiple hydrogen bonds to form.

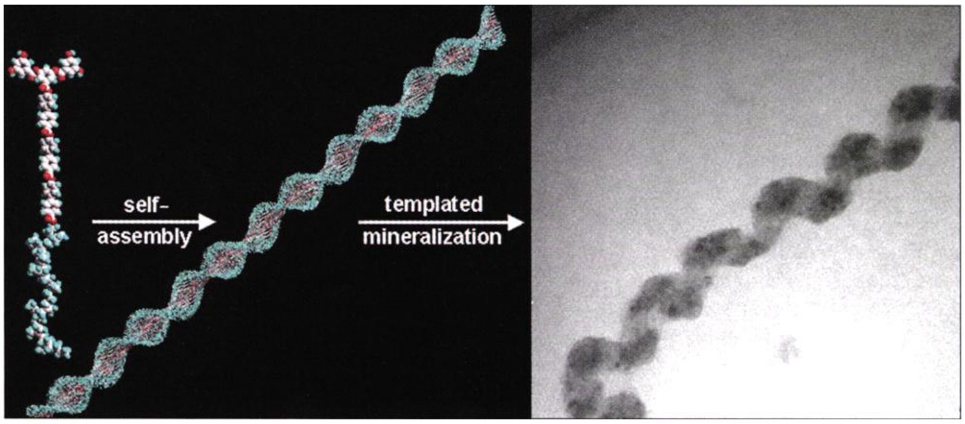
Using this scheme, last year, Atwood's group created hollow spheres from six identical subunits in which each is held to its neighbor by eight hydrogen bonds. Crystallographic analysis showed that each sphere contained 1510 cubic angstroms of empty space. Such hollow molecules are typically very difficult to create by traditional organic synthesis. More importantly, says Atwood, these large cavity-containing structures self-assemble even when closely related building blocks are present in solution. "So there's not only self-assembly occurring, but also a recognition process that we don't yet understand," he adds. Atwood believes that someday such capsules could be used to release drugs in the vicinity of their selected targets and help separate large molecules on the basis of size or shape.

Other groups are looking to DNA for a little guidance in making new polymers. At the European Institute of Chemistry and Biology in Talence, France, for example, Ivan Huc and his colleagues last year created the first synthetic polymer that in solution assembles itself into a double helix. The team started with two closely related subunits—2,6-pyridine dicarboxylic acid and 2,6-diaminopyridine—that they could link together covalently into single strands. In dilute solution, the resulting polymer twists into a helix, which the researchers determined by using nuclear magnetic resonance (NMR) spectroscopy.

Many polymers, both natural and synthetic, form similar single-stranded helices. Huc's polymer, however, matches up with a second strand, creating a DNA-like double helix, a structure his team confirmed with NMR and crystallographic studies. Still, the two had one big difference: The bonding that creates the polymer double helix was the reverse of what happens in DNA.

In DNA, hydrogen bonds between the base pairs hold the separate strands together while the interaction between electron clouds that hover above and below the ring-shaped bases helps stabilize the helical structure. Meanwhile, in the French team's polymer, interaction between electron clouds around the pyridine rings holds the two strands together, while hydrogen bonds within each strand provide rigidity to the resulting structure.

Huc's group has since created other double helices using a variety of different pyridine groups as building blocks. Its next goal is to increase the distance between the two strands enough to make supramolecular structures that mimic ion channels. Those structures, in theory, could be used to deliver drugs across the cell membrane.



Assembly two-step. Organic molecules (left) self-assemble into long, helical supramolecules, which then serve as the templates upon which dissolved minerals crystallize (micrograph at right).

CREDIT: ELI D. SOHN *ET AL.*, IN PRESS, *ANGEWANDTE CHEMIE*, INT. ED. ENGL. NO. 10 (2002)

Steven Zimmerman, an organic chemist at the University of Illinois, Urbana-Champaign, says he believes that polymers such as Huc's also may make excellent candidates for novel self-healing materials such as plastics. "Because you have multiple noncovalent interactions holding such a polymer together, you can actually break a few of these bonds without having the material fall apart," he says. "It would be like having molecular Velcro, where the strength comes from the fact that you have hundreds of attachment points between pieces." The arrangement, he adds, "gives broken contact points a good chance of reforming before the bulk connection is destroyed."

While Huc has been studying the noncovalent attachments between polymer strands, several groups have been examining the connections within strands. Zimmerman, for example, has developed pairs of molecules with various electron-swapping groups that will recognize each other in solution and form multiple hydrogen bonds between them, analogous to the base pairs of DNA but with far greater sticking power.

In their latest success, to appear in an upcoming issue of the *Proceedings of the National Academy of Sciences*, Zimmerman's group synthesized four-part building blocks capable of linking to form 12-membered chains that loop into rings. "We were somewhat surprised to get such large, stable structures, but now that we have, we think we will be able to rationally create monomers that will self-assemble to form interesting materials," says Zimmerman. If successful, he adds, one result could be a new breed of polymers that could be molded in place when still malleable and unbonded and then coaxed to link up and form a rigid structure.

Beyond polymers and molecular capsules, some chemists see a role for supramolecular chemistry in engineering replacement tissues and creating replacement parts more readily accepted by the body. In particular, chemists imagine a new way to forge links between organic and inorganic materials, a tough nut for materials scientists to crack. "If you don't have to rely on covalent bonds, then there are many avenues to bring organic and inorganic molecules together in a structurally durable manner," says bioengineer Buddy Ratner, director of the Center for Engineered Biomaterials at the University of Washington, Seattle.

Last year, for example, Northwestern's Stupp and postdocs Jeffrey Hartgerink and Elia Beniash created two-part organic molecules that automatically assemble themselves into fibers. When placed in the solution of calcium, phosphate, and hydroxide ions, these fibers coax tiny crystallites to form on top that are made of hydroxyapatite, the same material that gives bone its toughness. Such self-assembled materials, Stupp believes, open the door to making synthetic bone replacements (Science, 23 November 2001, p. 1635). Stupp's group has extended the work to topping self-assembled organics with other minerals such as cadmium sulfate, which could prove useful as low-resistance wires for molecular-scale electronics.

Ratner's group is starting with the inorganics and topping them with organics. For example, together with chemist Thomas Boland, who is now at Clemson University in South Carolina, Ratner showed in 1995 just how easy this melding could occur. "We made the accidental discovery that if you dipped a piece of gold into a dilute solution of nucleic acid in ethanol, boom, they self-assembled into ordered two-dimensional films that were anchored to the gold. It was that simple," says Ratner.

Ratner's group has gone on to develop several systems that self-assemble into large supramolecules capable of coating the metallic surfaces of implantable medical devices. In its most recent work, the Seattle team has developed a method for depositing polyethylene glycol studded with wound-healing proteins onto metallic surfaces. "Repairing a wound is actually a fine example of supramolecular chemistry, and we're trying to encourage that to happen in such a way that the collagen and extracellular matrix components of tissue will form a supramolecular complex with an organic coating on an implant," explains Ratner. "In essence, we want to build a supramolecular complex on a supramolecular complex, to reconstruct a more natural anatomy around a device."

One hundred years ago, Hermann Emil Fischer of Germany won the second Nobel Prize awarded in chemistry for synthesizing complex organic molecules using new covalent-bond–forming reactions. That feat ushered in a golden century for synthetic chemistry. In 1987, the Nobel committee recognized the emergence of supramolecular chemistry by awarding the chemistry prize to Donald Cram, Jean-Marie Lehn, and Charles Pederson for work on creating small molecular complexes held together by noncovalent forces. In the 15 years since then, researchers have labored to extend the power of organic synthesis from forming single complex molecules to forming entire molecular assemblies. "There's tremendous science to do here," says Northwestern's Mirkin. "And if we're successful, the impact on materials science and on everyday life will be enormous."

–JOE ALPER

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