Chemical & Engineering News

Cover Story

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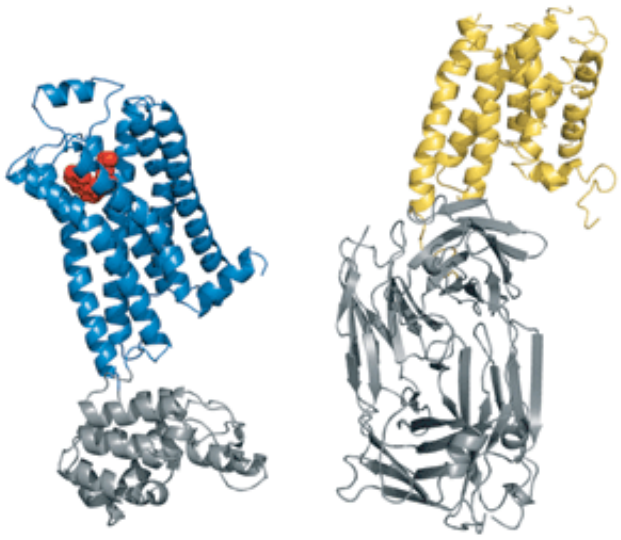
2007 Chemistry Highlights

This year's selections include numerous advances in structural analysis

Stu Borman

EACH YEAR the editors of C&EN select some of the most important research advances from among the stories we've reported throughout the year and highlight them in a year-end issue. This year we've selected about two dozen examples of chemistry-based research at its best.



Two Approaches Similar structures (one gold and one blue and red) of the membrane receptor β2AR were obtained by stabilizing the receptor with T4 lysozyme (gray, left) or an antibody fragment (gray, right). β2AR is only the second G-protein-coupled receptor ever analyzed structurally.

Of the various chemically related subdisciplines spanned by our selections, structural analysis stands out as the most prolific. Highlighted breakthroughs include structures of a G-protein-coupled receptor, a type of protein that's been nearly impossible to analyze; and a new technique that made it possible to obtain the first detailed structure of one of the largest biomolecular complexes in cells.

Other selections this year range from advances in neurochemistry and molecular biology to key discoveries in organic synthesis, nanotechnology, molecular imaging, and environmental chemistry. They

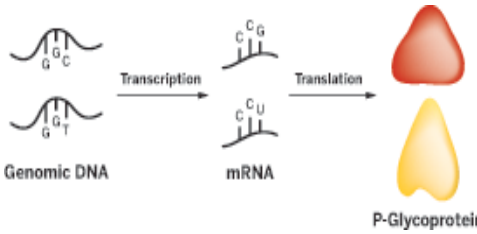
include a possible cure for a mental retardation disorder, a surprising finding about a common mechanism of different types of antibiotics, the design and synthesis of one of the lowest-density crystals ever known, a source of power for nanoelectronic devices, and the real-time imaging of gene regulation in living cells.

Our choices are necessarily subjective and do not pretend to be comprehensive. Indeed, these studies represent only a few examples of the many ways in which chemistry-related research advances our society and improves people's lives each and every year.


Rett Syndrome Research Foundation

Rett Reversed Rett syndrome patients often have trouble walking. A study showed that Rett syndrome could be reversed in mice.

A key **neurochemistry** advance this year offered hope that Rett syndrome and other autism-related disorders might become curable. Rett syndrome primarily strikes girls, who develop mental retardation and lose muscle tone, use of their hands, and the ability to speak. Adrian Bird of the University of Edinburgh and colleagues created a model of Rett syndrome in mice by blocking the animals' production of methyl-CpG-binding protein 2 ($MeCP_2$), which was already known to be implicated in Rett syndrome and related conditions. When the team unblocked $MeCP_2$ production, they were shocked to see that the mice recovered, even though some of them had been near death (*Science* **2007,** *315,* 1143). The results indicated unexpectedly that neurons affected by the disease do not degenerate but remain alive and may respond to therapy.

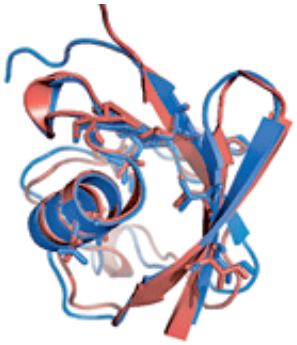


Same But Different Subtle genomic changes known as silent polymorphisms lead to coding-equivalent changes in messenger RNA (mRNA). During translation, these mRNAs yield proteins with identical amino acid sequences but different shapes. C = cytosine, G = guanine, T = thymine, U = uracil.

In **molecular biology,** a research team demonstrated conclusively in cells for the first time that a gene modified in a seemingly trivial way can produce a protein with a different fold. Researchers had speculated in the late 1980s that a "silent" polymorphism—a gene-codon sequence change that doesn't alter the amino acid sequence of the corresponding protein—could yield a protein with a modified folding pattern, but this had not been demonstrated conclusively. Chava Kimchi-Sarfaty, Jung Mi Oh, Michael M. Gottesman, and coworkers at the National Cancer Institute's Laboratory of Cell Biology, in Bethesda,

Md., showed that a multidrug resistance gene with a single-nucleotide, coding-equivalent sequence modification translates into a P-glycoprotein with a different conformation (*Science* **2007,** *315,* 525). They speculate that the difference may result from timing or other subtle changes in the translation process caused by the sequence modification. The work points to a previously unrecognized and potentially profound role of single-nucleotide polymorphisms in health and disease.

In a **nuclear magnetic resonance spectroscopy** (NMR) advance, Lucio Frydman of Weizmann Institute of Science, in Rehovot, Israel, and Damir Blazina of Oxford Instruments Molecular Biotools, in Oxford, England, devised a way to give unprecedented sensitivity and speed to two-dimensional NMR. The technique combines two previous methods—ultrafast multidimensional NMR and ex situ hyperpolarized dynamic nuclear polarization (*Nat. Phys.* **2007,** *3,* 415). It wasn't clear these methods could coexist, but Frydman and Blazina got them to work together. The combined technique, hyperpolarized ultrafast multidimensional NMR, makes it possible to collect 2-D NMR data within a fraction of a second (instead of the usual minutes to hours) and to analyze submicromolar samples (instead of the usual millimolar ones). Potential applications include studies of surface catalysis, dynamic phenomena, and intermediate species.

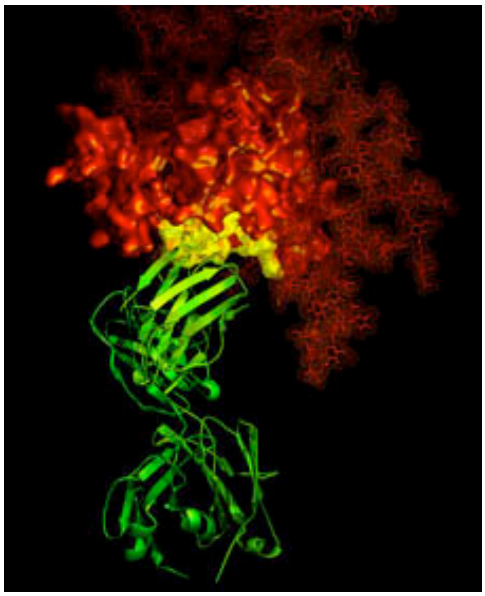


Shifty Technique Chemical-shift-based structure (blue) of the protein ubiquitin closely matches its X-ray crystal structure (red).

NMR is also one of the major techniques used to obtain structural information about biomolecules, and a significant enhancement in its ability to analyze proteins was one of several major **structural analysis** breakthroughs this year. Time-consuming measurements of NMR nuclear Overhauser effects (NOEs, which reflect the distances between specific atoms) have been the primary basis for determining most NMR protein structures. Since the early days of protein NMR, researchers have wanted to use simpler to obtain NMR chemical shifts, instead of NOEs, as a basis for such structures, and Michele Vendruscolo, Christopher M. Dobson, and coworkers at the University of Cambridge have made that possible (*Proc. Natl. Acad. Sci. USA* **2007,** *104,* 9615).

Their technique, CHESHIRE (for "chemical shift restraints"), divides a protein sequence into fragments, the likely structures of which are predicted on the basis of experimental chemical shift data. The fragments' structures are then assembled into a complete protein structure that is refined with chemical shift and molecular force field information and evaluated for reliability.

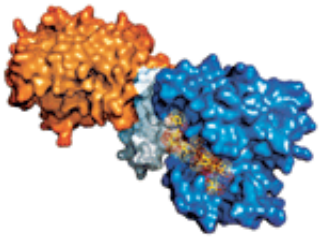
The researchers demonstrated the approach by using it to accurately define the high-resolution structures of 11 proteins of known structure. In addition to easing the determination of native structures of globular proteins, they believe the technique will also make it easier to obtain structures of transient or excited states of proteins, for which chemical shifts are often the only type of NMR data available.


Jonathan Stuckey, Vaccine Research Center, NIAID/NIH

View Enlarged Image

TIGHT FIT This structure, which shows how a potent antibody (green) binds to an HIV envelope protein (red), could ease vaccine development.

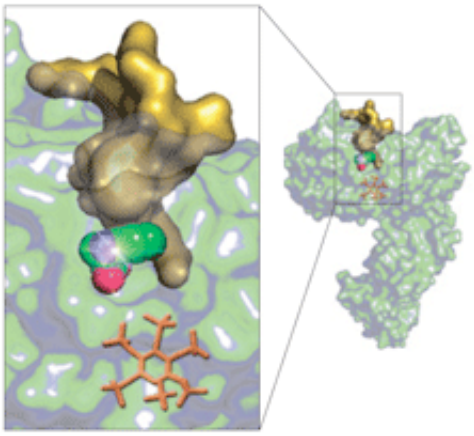
Another structural analysis advance was an X-ray structure that revealed the binding interaction between a powerful blocking antibody and a vulnerable spot on HIV's envelope protein. The work provides a possible blueprint for designing an AIDS vaccine directed at the same site on HIV. The structure revealed two exposed loops that make 10 hydrogen bonds between the antibody and the HIV protein—a molecular motif that vaccine designers will now want to emulate. A collaborative team from the National Institutes of Health; Scripps Research Institute in La Jolla, Calif.; and Harvard Medical School, led by Peter D. Kwong of NIH, solved the structure (*Nature* **2007,** *445,* 732).


Natalie Strynadka

Target Revealed This penicillin-binding protein structure shows the protein's TP (orange) and GT (blue) regions, its central linker domain (gray), and the way the antibiotic moenomycin (stick structure) binds.

The first structural snapshots of a penicillin-binding protein (PBP), a type of enzyme involved in forming bacterial cell walls, were also obtained this year in a study that should facilitate the rational design of molecules that can hit this promising target. One of the enzyme's domains, a transpeptidase (TP), is the target of β-lactam antibiotics like penicillin. That interaction is understood from structural studies of other TP enzymes, but many bacteria, including those that cause hospital infections, have developed resistance to such antibiotics. Researchers would like to target antibiotics to the other component of PBPs, the glycosyltransferase (GT) domain, but structures of GTs of this type have not been available. Natalie C. J. Strynadka and coworkers at the University of British Columbia obtained the first structures of a complete PBP, with and without a bound inhibitor, the antibiotic moenomycin (*Science* **2007,** *315,* 1402). And Suzanne Walker of Harvard Medical School and coworkers obtained a higher resolution structure, but only of PBP's GT domain and without an inhibitor (*Proc. Natl. Acad. Sci. USA* **2007,** *104,* 5348). The work could lead to new types of antibiotics and better versions of existing ones.

A groundbreaking crystal structure of the plant hormone auxin bound to its receptor, obtained by Ning Zheng of the University of Washington, Seattle, and coworkers, revealed auxin's molecular mechanism of action for the first time (*Nature* **2007,** *446,* 640). Auxin can trigger fruit ripening, root branching, the reorientation of leaves toward light, and the flowering of some plants. Its receptor, TIR1, shuttles proteins to degradation centers in cells. The structure showed that binding of auxin to TIR1 promotes the degradation of gene-transcription repressors. Destruction of the repressors unblocks the expression of a range of key genes, thus activating diverse plant processes. Judy Callis of the University of California, Davis, commented that the new mechanism, in which a small molecule essentially directs proteins to be degraded, could prove to be operative not only in plants but "in all eukaryotic cells, from plants to humans."

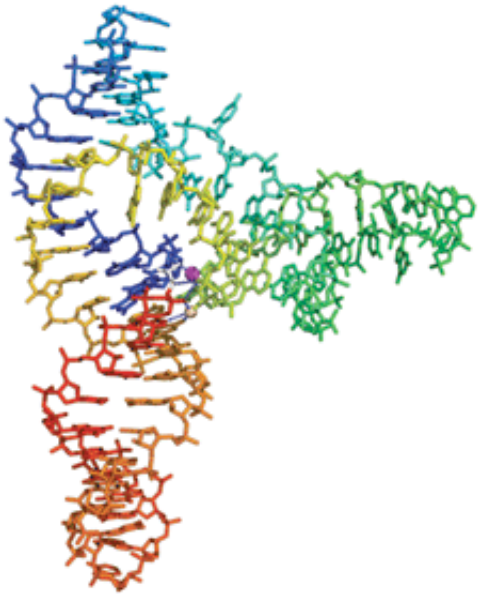


Ning Zheng

Auxin's Action A complex of auxin (green and red space-filling molecule), TIR1 (light green), and an inositol hexakisphosphate cofactor (orange) unblocks gene expression in plants, thereby turning on a range of plant processes, such as flowering and fruit ripening.

This year also saw major progress in the race to structurally characterize G-protein-coupled receptors (GPCRs). Although they are one of the most important families of proteins in the human body and a common target of drugs, GPCRs have been almost impossible to analyze structurally. Only one crystal GPCR structure, that of the light-sensitive protein rhodopsin, had been obtained. This year, two groups obtained the second GPCR structure, that of the human β2 adrenergic receptor (β2AR), by two different approaches.

Brian K. Kobilka of Stanford University School of Medicine and coworkers stabilized the protein for structural analysis by binding an antibody fragment to GPCR (*Nature* **2007**, *450,* 383; *Nat. Methods* **2007**, *4,* 927). And Kobilka, Raymond C. Stevens of Scripps, and coworkers enhanced β2AR's stability by linking the enzyme T4 lysozyme to it (*Science* **2007**, *318,* 1258 and 1266). Researchers will now try to adapt these approaches to solve the structures of other GPCRs more easily than has been possible before. Such a capability would have major implications for drug discovery and could lead to a better understanding of receptor biology.

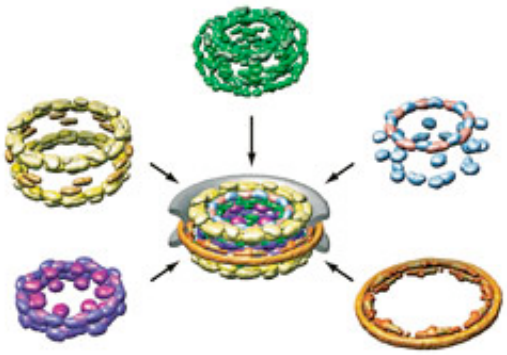


RNA Catalyst The X-ray crystal structure of this RNA ligase reveals a magnesium ion (purple) in the catalytic core at the center of three stems.

The first atomic-level structure of a ribozyme (an RNA-based enzyme) that can join two RNAs was solved this year by Michael P. Robertson and William G. Scott of UC Santa Cruz (*Science* **2007,** *315,* 1549). The reaction catalyzed by the RNA ligase, the linking of two pieces of RNA, is essential for replicating RNA sequences. The enzyme's structural analysis has implications for a better understanding of the RNA world hypothesis, the idea that RNA was evolution's first self-replicating biological molecule. The structure shows that the ribozyme's catalytic core is located centrally, at the conjunction of three RNA stems, and that an octahedrally coordinated magnesium atom and five precisely positioned nucleoside bases play key roles in the ligase's catalytic mechanism of action.

In addition, a collaborative team developed a new structural analysis technique this year and used it to obtain the first detailed structure of the 456-protein nuclear pore complex (NPC), one of the largest biological assemblies found in cells. The technique uses structurally related data from different types of experiments as restraints for a computational method that explores possible configurations of assembly components. It was developed by Michael P. Rout and Brian T. Chait of Rockefeller University; Andrej Sali of UC San Francisco; and coworkers (*Nature* **2007,** *450,* 683 and 695).

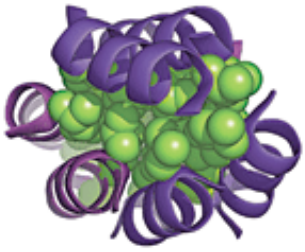
Unlike crystallography and NMR, which are generally used to analyze smaller structures, and electron microscopy, which often cannot distinguish protein locations in large assemblies, the new technique makes it possible to determine the architecture of very large complexes and to localize their molecular parts, albeit at modest resolution. The new structure doesn't reveal exactly how NPC works on a molecular level, but it provides a springboard for further studies on its mechanism and helps show how it and similar structures likely evolved.



Nature © 2007

Assembly Required Protein-based substructures-outer rings (yellow), inner rings (purple), membrane rings (brown), linker nucleoporins (green), and FG (phenylalanine-glycine) nucleoporins-make up the nuclear pore complex (center), analyzed structurally in better than ever detail this year. Pore membrane is gray.

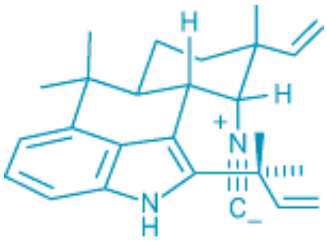
In **pharmacology,** a research team made an unexpected and surprising finding about antibiotics this year—that the major classes of bacteria-killing antibiotics may all have a related mechanism of action. Antibiotics are usually classified by the biological function they disrupt, such as DNA replication, protein synthesis, and cell-wall synthesis. James J. Collins of Boston University and coworkers reported that different antibiotics, whatever their initial target, trigger a common cell death mechanism downstream of their first targets: generating hydroxyl radicals that damage DNA, proteins, and lipids (*Cell* **2007,** *130,* 797). The hydroxyl radicals are the product of an oxidative damage pathway. How the interaction between each of the antibiotics and its initial target triggers the pathway is not yet known, but the findings could lead to novel ways to improve antibiotics.



J. Am. Chem. Soc.

β-Bundle This model of β-peptide synthetic protein shows how its interior β-homoleucine residues (green) form a well-packed hydrophobic core.

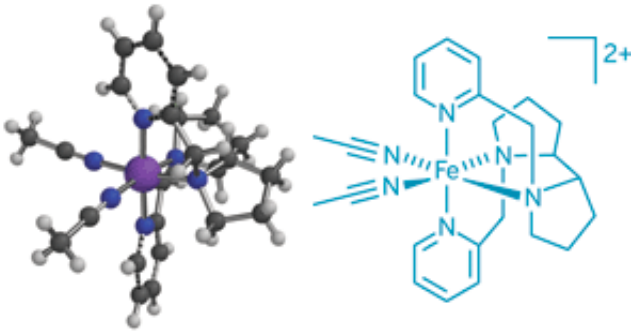
In **molecular design,** Alanna Schepartz and coworkers at Yale University created the first nonprotein oligomer found experimentally to look and act like a true protein (*J. Am. Chem. Soc.* **2007,** *129,* 1532). The structure, a β-peptide bundle, exhibits several hallmarks of real proteins, including exceptional stability, an interior core of hydrophobic amino acid side chains, and the ability to fold and unfold reversibly. The group made the structure by synthesizing an oligomer from 12 β-amino acids. The oligomer forms a helix with three faces, and the helices self-assemble into an octameric bundle. Complementary interactions between hydrophilic side chains on the bundle's surface appear to help it adopt its higher-order structure. The β-peptide bundle "is an important step toward a long-term goal of creating nonnatural molecules with the structure, function, and complexity of proteins," one observer noted.



Ambiguine H

Unprotected Synthesis of (+)-ambiguine H without using protecting groups required only 10 steps, half that required with a conventional protection approach.

Several **organic chemistry** advances are notable this year. One was the development of novel synthetic approaches that avoid the conventional use of protecting groups, by Phil S. Baran and coworkers at Scripps. Protecting groups can play an important role in complex syntheses by preventing sensitive functional groups from being modified in undesirable ways during reactions. But they can make syntheses much longer and reduce their yields, among other problems. Baran and coworkers found that some synthetic procedures are better off without protecting groups (*Nature* **2007,** *446,* 404). They carried out the total synthesis of (+)-ambiguine H without using protecting groups in only 10 steps—at least 10 steps shorter than with a conventional protection strategy. The protection-free approach enabled them to exploit the innate reactivity of a key indole group in an innovative way. And they synthesized welwitindolinone A by an eight-step protection-free sequence that is 17 steps shorter than another approach reported last year.



M. Christina White

Oxidizing Catalyst This catalyst (shown in molecular model and line structure representations) enables oxidation of the unreactive aliphatic C–H bonds at tertiary carbons in complex molecules without the need for directing or activating groups.

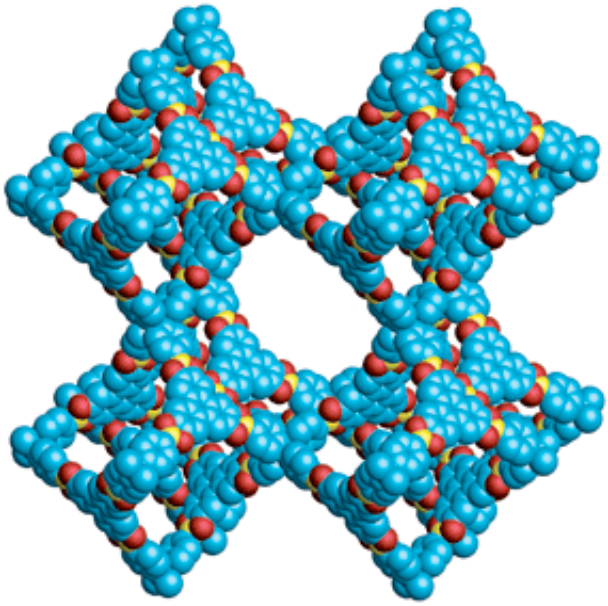
A new catalyst developed by M. Christina White and Mark S. Chen at the University of Illinois, Urbana-Champaign, simplifies the synthesis of highly complex organic molecules in an environmentally friendly way. The iron-based catalyst makes it possible to oxidize the unreactive aliphatic C–H bonds at tertiary carbons in complex molecules without the need for directing or activating groups (*Science* **2007,** *318,* 783). It uses hydrogen peroxide to oxidize C–H to C–OH bonds. Given a choice of C–H bonds in a complex molecule, it preferentially targets sterically accessible, electron-rich bonds at tertiary carbons. The researchers used the catalyst to oxidize the antimalarial natural product (+)-artemisinin primarily at only one of its five tertiary C–H bonds. The reaction not only eliminates the need for wasteful protecting groups but also produces water as the only catalytic by-product.

Also this year, White and Kenneth J. Fraunhoffer developed the first method to carry out aminations by catalytically converting allylic C–H bonds directly to C–N bonds. Chemists had long sought a direct catalytic form of the reaction, skipping a preceding oxygenation that was formerly necessary. The direct reaction has become possible with White and Fraunhoffer's Pd(II)/sulfoxide catalyst (*J.Am. Chem. Soc.*

2007, 129, 7274).

Amide Route Coupling reaction generates amide catalytically from alcohol and amine.

In another organic synthesis advance, chemists in Israel developed a new ruthenium catalyst that can make amides simply by coupling alcohols and amines (*Science* **2007,** *317,* 790). Routes to amides usually require toxic reagents like thionyl chloride and corrosive acidic or basic conditions, and they often generate unwanted by-products. The catalytic reaction developed by David Milstein and coworkers Chidambaram Gunanathan and Yehoshoa Ben-David of Weizmann Institute couples alcohols and amines under neutral conditions. It is both clean and selective, sidestepping the need for harsh reagents and conditions and creating H_2 gas as the only by-product. The rationally designed ruthenium catalyst works by a unique mechanism involving metal-ligand cooperation. Potential applications include the synthesis of industrially important amides and polyamides.



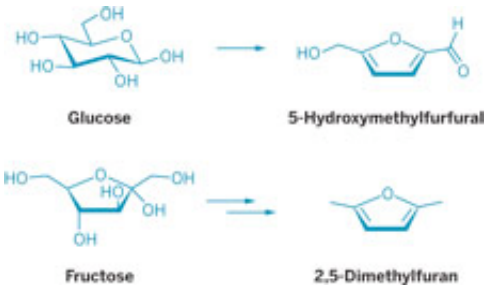
Courtesy of Adrien P. CÔté

Pores Galore This highly porous and low-density crystalline organic framework belongs to the same family of structures as the one on the cover. Carbon is blue; oxygen, red; and boron, yellow.

Also this year 3-D covalent organic frameworks (COFs) with remarkable properties were designed and synthesized for the first time by Omar M. Yaghi of UCLA and coworkers (*Science* **2007,** *316,* 268). The materials are constructed of light elements such as carbon, boron, and oxygen. They are stable at temperatures above 450 °C, their surface areas are among the highest known for any materials, and they have extremely low densities. In fact, one member of the new family, called COF-108, has a density of 0.17 g/cm^3, making it one of the lowest-density crystals known. Yaghi says he believes the materials will have a major impact "on the synthesis of extended structures by design and, in the short term, on the storage and separation of gases."

In **carbohydrate chemistry,** Todd L. Lowary and coworkers at the University of Alberta, Edmonton, synthesized key oligosaccharides from cell walls of tuberculosis bacteria (*J. Am. Chem. Soc.* **2007,** *129,* 9885). The structures are a 22-unit arabinan domain, which is among the largest oligosaccharides ever made chemically, and an 18-unit putative precursor. The arabinan domain was especially challenging to synthesize because it contained four β-D-arabinofuranosides, which are hard to introduce in a

stereocontrolled manner. Other groups had earlier synthesized large fragments of similar lipoarabinomannan domains, but those did not contain β-D-arabinofuranosides. The new synthesis could lead to a better understanding of microbial cell wall construction and could aid design of tuberculosis drugs.



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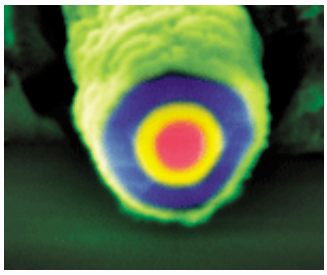
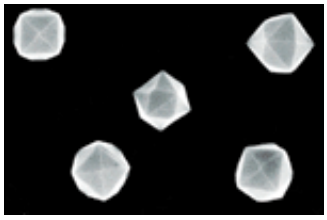
Sweeteners To Fuels New techniques convert simple sugars like glucose and fructose, respectively, into biofuel precursors like 5-hydroxymethylfurfural and biofuels like 2,5-dimethylfuran.

In another sugar chemistry advance, two research groups independently reported catalytic methods to convert biomass-derived sugars into renewable fuel and feedstock (*Science* **2007,** *316,* 1597; *Nature* **2007,** *447,* 982). Either method could be used to supplement fermentation, the current way to manufacture bioethanol. At Pacific Northwest National Laboratory, Z. Conrad Zhang and coworkers used a chromium chloride catalyst in an ionic liquid solvent to catalytically convert glucose to 5-hydroxymethylfurfural (HMF). HMF and its derivatives can serve as fuel precursors and can replace petroleum-based building blocks used to make some plastics, pharmaceuticals, and fine chemicals. And James A. Dumesic of the University of Wisconsin, Madison, and coworkers devised a technique to catalytically dehydrate fructose (made from glucose or directly from biomass) to HMF, which is then converted by hydrogenolysis to 2,5-dimethylfuran (DMF). DMF could be a better transportation fuel than ethanol because it has a 40% higher energy density and is less volatile.


Bozhi Tian/Harvard University

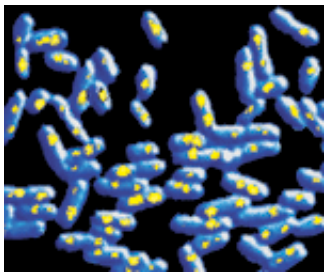
Layered Look This coaxial nanowire is a three-layer device (pink, yellow, and blue) topped with SiO_2 (green), as shown in this artificial-color scanning electron micrograph.

In **nanotechnology,** researchers synthesized coaxial silicon nanowires that can directly absorb light and turn it into electricity. The nanowires could serve as a source of power for nanoelectronic devices and as scalable building blocks for commercial solar panels. Charles M. Lieber of Harvard University and coworkers shrank conventional diodes to the nanoscale by creating coaxial layered nanowires and then demonstrated that they could be used to power a nanoelectronic device, such as a nanowire pH sensor (*Nature* **2007,** *449,* 885). Although the coaxial nanowire solar cells do not show a huge improvement in efficiency over earlier nanoenabled devices, they are more stable, especially under intense light. Due to their small size, "they have the unique potential to be seamlessly integrated into more complex, self-powered electronic circuits," Lieber says.


Courtesy of S. G. Sun & Z. L. Wang
Multifaceted These tetrahexahedral platinum nanocrystals are members of a new family of highly efficient catalysts.

And an international team of scientists used electrochemical synthesis to create a highly efficient new class of multifaceted catalysts-platinum nanocrystal catalysts with 24 facets (*Science* **2007,** *316,* 732). The rough facets on these "tetrahexahedral" structures provide unsaturated surface areas that help make the catalysts up to 4.3 times more efficient than spherical platinum nanoparticles (per unit platinum surface area) at oxidizing organic fuels such as formic acid and ethanol. The increased efficiencies could give a boost to hydrogen fuel cells, according to Shi-Gang Sun of Xiamen University, China, and Zhong Lin Wang of Georgia Institute of Technology, who led the study. In addition, the nanoparticles are remarkably robust—they remain stable at temperatures up to 800 °C, making them recyclable in some applications.

In a key molecular imaging advance, X. Sunney Xie of Harvard and coworkers achieved the first real-time single-molecule images of gene regulation in live cells. The images showed the binding and unbinding of fluorescently labeled single molecules of a protein transcription factor to a specific sequence on DNA in response to metabolic signals (*Science* **2007,** *316,* 1191). The study demonstrated that the transcription factor initially binds to the wrong spot and then slides along DNA until it finds the right one. The behavior is similar to what Xie, his Harvard colleague Gregory L. Verdine, and coworkers observed last year for the in vitro binding of single molecules of a DNA repair enzyme to DNA. Xie and coworkers noted that the new method should be applicable to studies of a range of other nucleic acid-binding proteins.


Courtesy of Gene-Wei Li, Johan Elf & Peter Sims/Harvard University
Flash Single transcription-factor molecules (yellow) are shown binding to DNA in single bacterial cells (blue) in real time.

Gerhard Ertl of the Fritz Haber Institute of the Max Planck Society, in Berlin, was awarded the 2007 Nobel Prize in Chemistry for pioneering studies of chemical processes on solid surfaces. He is the first surface science researcher to receive the chemistry Nobel since Irving Langmuir won the award in 1932 (C&EN, Dec. 3, page 60). The Nobel Committee singled out Ertl for his studies of fundamental processes at the gas-solid interface. He developed a quantitative description of how hydrogen organizes itself on the surfaces of catalytic metals such as platinum, palladium, and nickel, and he produced key insights on the mechanism of the Haber-Bosch process, in which nitrogen and hydrogen combine to form ammonia.

In an important **environmental chemistry** finding, researchers discovered this year that some persistent organic pollutants (POPs) can reach high concentrations in humans and other air-breathing animals even if the compounds are only moderately hydrophobic and don't bioconcentrate in fish (*Science* **2007,** *317,* 236). Screening of commercial chemicals to identify compounds that might bioaccumulate in people and other air-breathing species is usually based on whether the compounds are highly hydrophobic and fat-soluble or are highly absorbed and bioconcentrated in fish. But Frank A. P. C. Gobas, Barry C. Kelly, and

coworkers at Simon Fraser University, in Burnaby, British Columbia, showed that step-by-step concentration increases of POPs can occur in food webs that include humans and other air-breathing animals even when they don't show a tendency to bioaccumulate in aquatic food webs. The work suggests that regulatory criteria used to flag potential POPs may need to change and that a greater number of chemicals may need to be classified as POPs than in the past. It's but one more example of the way chemistry-related research can be used to improve our understanding of the world so we can address the many challenges we face.

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