

# Trekking in the Molecular Forest

Entering a new league, scientists create enormous tree-like molecules

By IVAN AMATO

*"Organic chemistry nowadays almost drives me mad. To me it appears like a primeval tropical forest full of the most remarkable things, a dreadful endless jungle into which one does not dare enter, for there seems to be no way out."*

— Friedrich Wöhler, 1835

The mystery of life and the abilities of chemists simultaneously took on a decidedly modern hue in 1828. Friedrich Wöhler, a German chemist, had accidentally created the first laboratory duplicate of a simple biological molecule from entirely nonbiological ingredients. Like the cell-made originals, his synthetic urea molecules featured a specific geometric arrangement of eight atoms — one each of oxygen and carbon, two of nitrogen and four of hydrogen. Wöhler startled many of his contemporaries by showing that the molecules of life — organic chemicals, as he called them — apparently do not need a special "vital force" for their making.

Wöhler had no idea how apropos his comparison of organic chemistry to a forest would become for some of today's chemists. A growing community of molecular architects is now ushering in a new world of huge, branching, tree-shaped chemicals. Though many of their creations — which go by such names as starburst dendrimers, arborols and hyperbranched macromolecules — exhibit a brand of molecular beauty, these designers are driven by much more than aesthetics. Some describe their pursuits as nothing less than an attempt to mimic the skills of the world's best chemist: the living cell.

Wöhler's urea synthesis marked the birth of organic chemistry, a field then confined to biological molecules. "Organic" today refers more broadly to the chemistry of carbon-containing com-

pounds, no matter what their relevance to life. Since Wöhler's time, many chemists have dared to enter his "dreadful" organic jungle, where they continue to discover remarkable new molecular habitats.

Organic chemists now can synthesize compounds containing hundreds of specifically arranged atoms. Indeed, this year's chemistry Nobel went to an organic chemist who specializes in making laboratory duplicates of the complex chemical structures found in nature (SN: 10/27/90, p.252). But even these feats seem modest compared with the chemical accomplishments of enormous cell-made polymers such as proteins, which contain many thousands of atoms systematically assembled into unerringly specific arrangements.

This is the molecule-building big league that some human chemists now bid to enter. They chemically assemble many-thousand-atom sets into branching architectures almost as reliably as Wöhler constructed his countless eight-atom sets into point-like urea molecules. And their finesse in engineering the new synthetic polymers shows some resemblance to the precise architectural control exerted by biological cells as they assemble their own polymers.

Constructing huge tree-like molecules in the laboratory requires no new chemistry. The molecule builders use conventional synthesis techniques, but combine them in unique sequences to yield what some researchers call a new form of

matter (see sidebar, p.300). The largest structures rival a virus in size, with diameters of up to 200 angstroms — roomy enough to hold thousands of urea molecules.

"I see this as marvelously inventive science," remarks Norbert M. Bikales of the Washington, D.C., who directs the National Science Foundation's polymer program. "This is a new concept for making big molecules."

Classical organic chemistry is about making point-like molecules, under 10 or 15 angstroms," says chemist Donald A. Tomalia of the Michigan Molecular Institute in Midland. Tomalia, the developer of starburst dendrimers, has become the most vocal promoter of big-league chemistry. He now participates in a research effort with German and Japanese researchers sponsored by Japan's Ministry of International Trade and Industry.

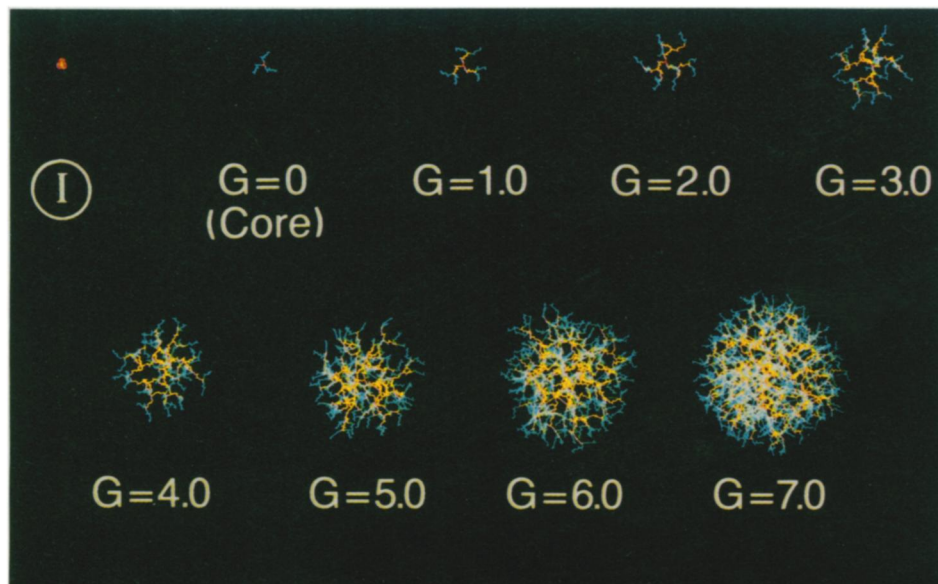
Microbes and cells — veteran molecule makers — long ago broke the "point-like" size barrier. They routinely manufacture proteins, polysaccharides and other molecules on the 100-angstrom and larger scale. Tomalia describes these structures as "mesoscopic," since their size hovers between the microscopic extremes of atoms and small molecules and the macromolecular dimensions of chromosomes.

Molecular weights provide a means of comparison. Urea weighs in at about 60; hemoglobin, the protein carrier of oxygen in the blood, tips the scale at about 64,000; a chromosome's molecular weight can loom into the billions. Tomalia says his largest dendrimers approach the 1 million mark.

Polymer chemists also have gone beyond making small, point-like molecules. They have transformed the materials landscape with their family of huge molecules, usually composed of identical building blocks linked together like pearls in a long necklace. *En masse*, these conventional synthetic-polymer molecules resemble and behave like a bowl of tangled spaghetti strands, says Jean M.J. Fréchet of Cornell University. The new dendritic polymers bear more resem-

*Growth of a PAMAM dendrimer: Three amidoamine molecules first bond to a three-pronged ammonia molecule; successive additions of hundreds of amidoamines build a huge dendrimer molecule.*

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blance to marbles. "And marbles in a dish don't behave like spaghetti," he notes. Some of the behavioral differences may come in handy — at least that's what Fréchet and others hope.

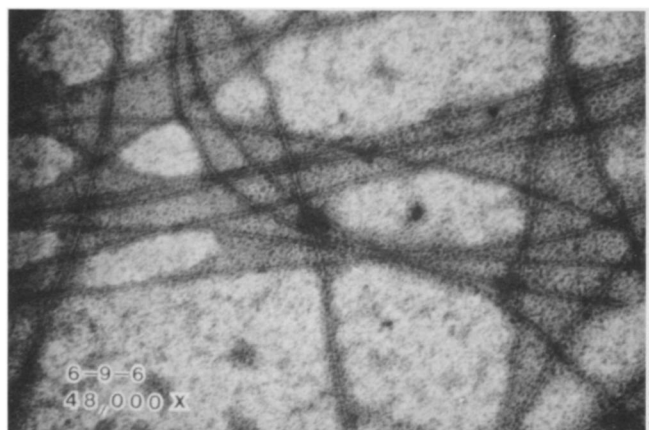
In living organisms, the more complex biologically derived polymers such as proteins and DNA take on complicated and functionally crucial three-dimensional shapes. But their underlying structure is linear, and that makes them susceptible to unfurling, or denaturing. Because dendritic molecules fan out from a central core, they can't denature. "It's like a pom-pom," Tomalia suggests. "You can only expand them to the extent that the tethering allows."

In the mid-1980s, Tomalia and others, including arborol maker George R. Newkome at the University of South Florida in Tampa, began synthesizing small amounts of large, branched molecules with unprecedented architectural uniformity. They, and now others, have been developing schemes for precisely controlling the shape, size and chemical properties of these monster molecules as they expand from small cores the size of urea molecules, through intermediate structures containing tens or hundreds of atoms, to virus-sized molecules containing many hundreds or thousands of atoms. Fréchet points out that as far back as 1974, chemist Fritz Vögtle at the University of Bonn in Germany made modest molecular progenitors to these, which Vögtle dubbed "octopus molecules."

For some, the structure of the molecular giants brings onions to mind. Consider one of Tomalia's favorite constructions, which he calls PAMAM (short for polyamidoamine) dendrimers. Each begins as a small core — a molecule of ammonia with three bonding branches. Tomalia and his co-workers assemble the innermost onion layer by linking a multi-limbed molecule called amidoamine (structurally related to the amino acid alanine) to each of the core's three branches. In the case of PAMAM dendrimers, this step yields six new branches available for building the next onion layer.

By repeating this sequence, each time taking steps to ensure that all component molecules of a new layer, or generation, form bonds only with the adjacent underlying layer, the chemists construct ever growing, branching molecules with concentric layers. In Tomalia's case, these dendrimers grow like starbursts — first three new amidoamine components join in, then six, then 12, then 24, and so on until the final, ninth generation yields a shell made from 1,533 amidoamine units. At some point — which depends on the particular core, layering constituents and branching pattern — a starburst dendrimer becomes too congested at the surface to allow further growth. The

*The threads shown in this electron micrograph most likely form when dumbbell-shaped arborol molecules stack in criss-cross fashion into a rod-shaped aggregate.*



chemists use that natural limit on construction as a way to ensure that they get dendrimer molecules of uniform size.

When Tomalia first published his work on dendrimers in 1984, Newkome and his colleagues were busily building giant molecules that they call arborols. Both chemists say their inspiration came largely from branching systems in nature, such as trees, ferns and circulatory systems. These natural branching patterns often correspond to mathematical progressions such as 1, 3, 9, 27...

Ever since Newkome read a paper on the branching patterns of trees growing in South American forests, he says, he has pursued two questions: "Can I make molecular trees?" and "How big can I make them?"

His first efforts yielded compounds that budded out in one direction, like a rootless tree. But now his team also routinely builds dumbbell-shaped arborols, called sylvanols. "It's like adding a root system to the tree," Newkome remarks. In solvents, these sylvanols self-assemble into crisscrossing dumbbells that stack into insoluble fibrous structures. Newkome admits that no practical uses for these structures seem imminent, but he envisions them eventually serving in applications such as molecular-scale electronic devices and batteries.

Some of the molecules his group assembles begin as a glimmer in a three-branched core. The chemists expand each of these with a three-branched molecule, yielding nine new branch points. To each of these, they append yet another three-branched unit in a progression that builds from three branches to nine, then to 27 and 81, and so on. The researchers also are investigating more highly branched cores. To Newkome, arborols resemble the ultimate bonsai trees and collectively create marvelous molecular forests, not nearly as dreadful as Wöhler envisioned.

Others are seeding this molecular forest with species that they grow using quite different synthesis

techniques. A case in point is the effort of polymer chemist Thomas X. Neenan of AT&T Bell Laboratories in Murray Hill, N.J. "For the past 150 years, chemists have concentrated on small molecules such as aspirin," he says. Also known as salicylic acid acetate, aspirin molecules consist of 21 atoms, but chemists now have bigger molecules on their minds, Neenan says.

He and organic chemist Timothy M. Miller, also at Bell Labs, recently reported making "large organic spheres" out of benzene-based building blocks. Though the final structure of their molecules closely resembles Tomalia's dendrimers, the construction techniques differ markedly. Rather than building their molecules as successive onion shells, the AT&T researchers prefer a more "convergent" approach. They link prefabricated chemical chunks — each more like an orange wedge than an onion layer — into a final, spherical structure.

"The big advantage we have is that, in the last step, all we have to do is attach three arms to the core," Neenan says. With this technique, compared to Tomalia and Newkome's more "divergent" approach, fewer things must go right and fewer things can go wrong, he says. Moreover, Neenan and Miller note, should any of the three final bonds fail to form, the unwanted reaction products would differ considerably in size from the target molecule, making separation and purification a cinch. In Tomalia's case, a failed bond or two during the last stages of a dendrimer's synthesis could result in such small differences in the size of resulting molecules that the separation of imperfect dendrimers could prove difficult and expensive.

The behavior of Neenan and Miller's molecules hints at the advantages of playing big-league chemistry with marble-like polymers. The precise and uniform three-dimensional shapes of these structures render them up to 100 million times more soluble than the more amorphous, stringy molecules of similar size made by conventional polymer-chemistry techniques. That suggests chemical engineers might eventually process some dendritic polymers in water, rather than in environmentally troublesome solvents.

Fréchet and Craig Hawker are developing a related convergent synthesis at Cornell University. They recently reported making dendritic molecules with a branched structure consisting of 2,687 carbon atoms, 2,304 hydrogen atoms and 381 oxygen atoms — always bound into the same arrangement. These molecules have a molecular weight in the 40,000 range. Fréchet says the researchers have even succeeded in studding the surface of their dendritic molecules with chemical units that could do specific jobs, including analytic and medical tasks.

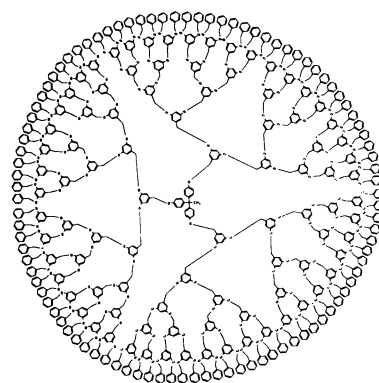
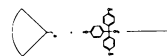
The work of Young H. Kim and Owen Webster of E.I. du Pont de Nemours & Co. in Wilmington, Del., provides a remarkable illustration of how linking small molecular parts into dendrimer structures leads to significant changes in the molecules' properties. Their molecules resemble spherical vesicles, called micelles, which spontaneously form in water when long oily molecules huddle into spheres to minimize their contact with water. The new "unimolecular micelles," which dissolve in water, are composed of benzene-based building blocks that normally display a powerful aversion to water.

**A** transformation [in chemistry] is occurring," Newkome says. Rather than feeling limited to making small molecules with specific

structures or huge polymer molecules with ill-defined structures, chemists now can make huge polymer molecules always with the same "size, shape and description," he says. By "description," he means the chemical features of the surface and internal layers. These include electrical charges that attract or repel other atoms and molecules, catalytic sites for hastening reactions, and chemical environments conducive either to water-loving molecules or to oily, water-avoiding molecules.

The technical difficulty of making large, specific molecular structures had long quenched chemists' ambitions, Newkome observes. "Now it's our imaginations that will be the limiting factor," he says.

At present, starburst dendrimers (commercially available from one company) seem suited only for arcane applications such as calibrating specialty filters. For instance, Tomalia suggests that electronics manufacturing facilities might use dendrimers for monitoring filters that keep dust particles from entering their "clean rooms."



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Nicholas Turro, a chemist at Columbia University in New York City, uses starburst dendrimers as tiny chemical reactors for his research. He focuses on how molecules transfer electrical charges. These transfers are key events in such processes as chemical catalysis and photosynthesis.

Like Newkome, he also imagines making solar-driven molecular batteries. One might accomplish this, he speculates, by studding different parts of the dendrimer onions with molecules that harvest solar energy and store it — as positive and negative electrical charges — segregated on different layers.

Tomalia notes that Army researchers at the Aberdeen (Md.) Proving Ground are investigating starburst dendrimers as tools for chemically disarming nerve gases and other chemical warfare agents. Drug delivery is another possible role for dendrimers, he says.

## Superatoms: A new form of matter?

"We believe these dendrimers we are creating are very precise molecular analogues of atoms," says Donald A. Tomalia of the Michigan Molecular Institute. Electron microscope pictures of dendrimers packed into a lattice look strikingly like a layer of gold atoms. Materials made by these atom-like molecules may be unlike anything people have known or imagined, he says.

By changing the core and controlling the branching patterns as dendrimers grow out to their largest spherical state, Tomalia envisions creating a "molecular-level periodic table" of superatoms. Like the periodic table of the elements, this table of dendrimers would have several families which differ greatly from one another in their chemical and physical properties, while members within one family might differ in size yet share many properties.

Tomalia argues that the analogy between atoms and dendrimers goes beyond mere appearances. Dendrimers begin with a small chemical core, sort of like a nucleus. These organize successive outer molecular layers, he says, the way an atom's positive nuclear charge dictates the geometry of its orbiting electrons. However, the bulk of mass

resides on the periphery rather than in the central nuclear region.

"Maybe we can make cells out these superatoms," muses physical chemist William A. Goddard of the California Institute of Technology. He and Adel M. Naylor are using computer modeling to examine Tomalia's dendrimer structures to better anticipate what architectures and properties the huge molecules are likely to assume.

"New forms of matter potentially can be created if one has new building blocks," Tomalia says, "and we have defined some new building blocks."

While agreeing that dendritic molecules represent a "new form of matter," Jean M.J. Fréchet of Cornell University is wary of making predictions about their practical utility. To make industrial quantities, chemists may have to sacrifice some of the uniformity that makes the small experimental preparations so scientifically notable. His group has come up with a simple, one-step synthesis that produces a spectrum of dendritic products. Though making the molecules in this way leads to imperfect, less uniform products, it may be the key to putting the new polymers to commercial use, he says. — I. Amato

**A**t the moment, Tomalia, Newkome, Fréchet and others have more chemistry to do. They have entered uncharted regions of Wöhler's molecular jungle, and they need to get better oriented.

In most cases, it takes days to make even tiny amounts of the molecular trees. Chemists also need to develop reliable and versatile tactics for studding the outside and inside of their products with functional components that will harvest light energy, or can splice or slice specific chemicals that will latch onto unhealthy cells or serve some other role. They need to understand more fully how marble-like dendritic polymers differ from the spaghetti-like conventional polymers. Finally, they need to assemble these superatoms into supermolecules and find out what new materials emerge.

William A. Goddard of the California Institute of Technology in Pasadena models Tomalia's starburst dendrimers on computers. Since most of the potential uses for dendritic molecules have yet to emerge even in chemists' dreams, Goddard reminds his colleagues traveling in the Wöhler's ever-growing molecular forest that "we can't let our imaginations go wild enough." □