

How Should Chemists Think?

Chemists can create natural molecules by unnatural means. Or they can make beautiful structures never seen before. Which should be their grail?

by Roald Hoffmann

The Vatican holds a fresco by Raphael entitled *The School of Athens*. Plato and Aristotle stride toward us. Plato's hand points to the heavens, Aristotle's outward, along the plane of the earth. The message is consistent with their philosophies—whereas Plato had a geometric prototheory of the chemistry of matter, Aristotle described in reliable detail how Tyrian purple (now known to be a precursor of indigo) was extracted from rock murex snails. Plato searched for the ideal; Aristotle looked to nature.

Remarkably, modern chemistry faces the quandary that Raphael's fresco epitomized. Should it follow the hand sign of Aristotle or that of Plato? Is nature as fertile a source for new materials as some assert it to be? Can we, for example, hope to make better composites by mimicking the microstructure of a feather or of a strand of spider's silk? Are chemists better advised to seek their inspiration in ideal mathematical forms, in icosahedra and in soccer balls? Or should we hazard chance?

To some, the division between natural and unnatural is arbitrary; they would argue that man and woman are patently natural, and so are all their transformations. Such a view is understandable and has a venerable history,

but it does away with a distinction that troubles ordinary and thoughtful people. So I will not adopt it and instead will distinguish between the actions, mostly intended, of human beings and those of animals, plants and the inanimate world around us. A sunset is natural; a sulfuric acid factory is not. The 1.3 billion head of cattle in this world pose an interesting problem for any definition. Most of them are both natural and unnatural—the product of breeding controlled by humans.

The molecules that exist naturally on the earth emerged over billions of years as rocks cooled, oceans formed, gases escaped and life evolved. The number of natural molecules is immense; perhaps a few hundred thousand have been separated, purified and identified. The vast majority of the compounds that fit into the unnatural category were created during the past three centuries. Chemists have added some 15 million well-characterized molecules to nature's bounty.

To every thing of this world, be it living or not, there is structure. Deep down are molecules, persistent groupings of atoms associated with other atoms. There is water in the distilled form in the laboratory, in slightly dirty and acid snow, in the waters associated with our protein molecules. All are H₂O. When chemistry was groping for understanding, there was a reasonable reluctance to merge the animate and inanimate worlds. Friedrich Wöhler convinced many people that the worlds were not separate by synthesizing, in 1828, organic urea from inorganic silver cyanate and ammonium chloride.

How are molecules made in nature—penicillin in a mold or a precursor of indigo in a rock murex snail? How are they made in glass-glittery laboratories—those acres of food wrap, those billion pills of aspirin? By a common process—synthesis.

Chemistry is the science of molecules and their transformations. Be it natural or human-steered, the outcome of transformation, A → B, is a new sub-

stance. Chemical synthesis, the making of the new, is patently a creative act. It is as much an affirmation of humanity as a new poem by A. R. Ammons or the construction of democracy in Russia. Yet creation is always risky. A new sedative may be effective, but it also may induce fetal malformation. A Heberto Padilla poem may be “counterrevolutionary” to a Cuban apparatchik. Some people in Russia still don't like democracy.

Wöhler mixed together two substances, heated them and obtained an unexpected result. Much has happened since 1828. To convey what the making of molecules is like today and to relate how the natural intermingles with the unnatural in this creative activity, let me tell you about the synthesis of two substances: Primaxin and the ferric wheel.

Primaxin is one of the most effective antibiotics on the market, a prime money-maker for Merck & Co. The pharmaceutical is not a single molecule but a designed mixture of two compounds, imipenem and cilastatin [see box on page 68]. These are their “trivial” names. The “systematic” names are a bit longer; for instance, imipenem is

[5R-[5 α , 6 α (R*)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Primaxin was created by a bit of unnatural tinkering, emulating the natural tinkering of evolution. Imipenem by itself is a fine antibiotic. But it is degraded rapidly in the kidney by an enzyme. This would give the drug limited use for urinary tract infections. The Merck chemists found in their sample collection a promising compound, synthesized in the 1940s, that inhibited that ornery enzyme. Modified for greater activity, this became cilastatin. It was obvious to try the combination of the antibiotic and the enzyme inhibitor, and the mix worked.

Imipenem derives from a natural

ROALD HOFFMANN shared the 1981 Nobel Prize in Chemistry with Kenichi Fukui. He was born in 1937 in Zloczow, Poland. Having survived the war, he came to the U.S. in 1949. He studied chemistry at Columbia University and received his Ph.D. from Harvard University. In 1965 he joined the faculty at Cornell University and is now the John A. Newman Professor of Physical Science. Hoffmann describes his contribution to science as “applied theoretical chemistry”—a particular blend of computations stimulated by experiment and the construction of generalized models. He writes essays and has published two poetry collections, *The Metamict State* and *Gaps and Verges*.



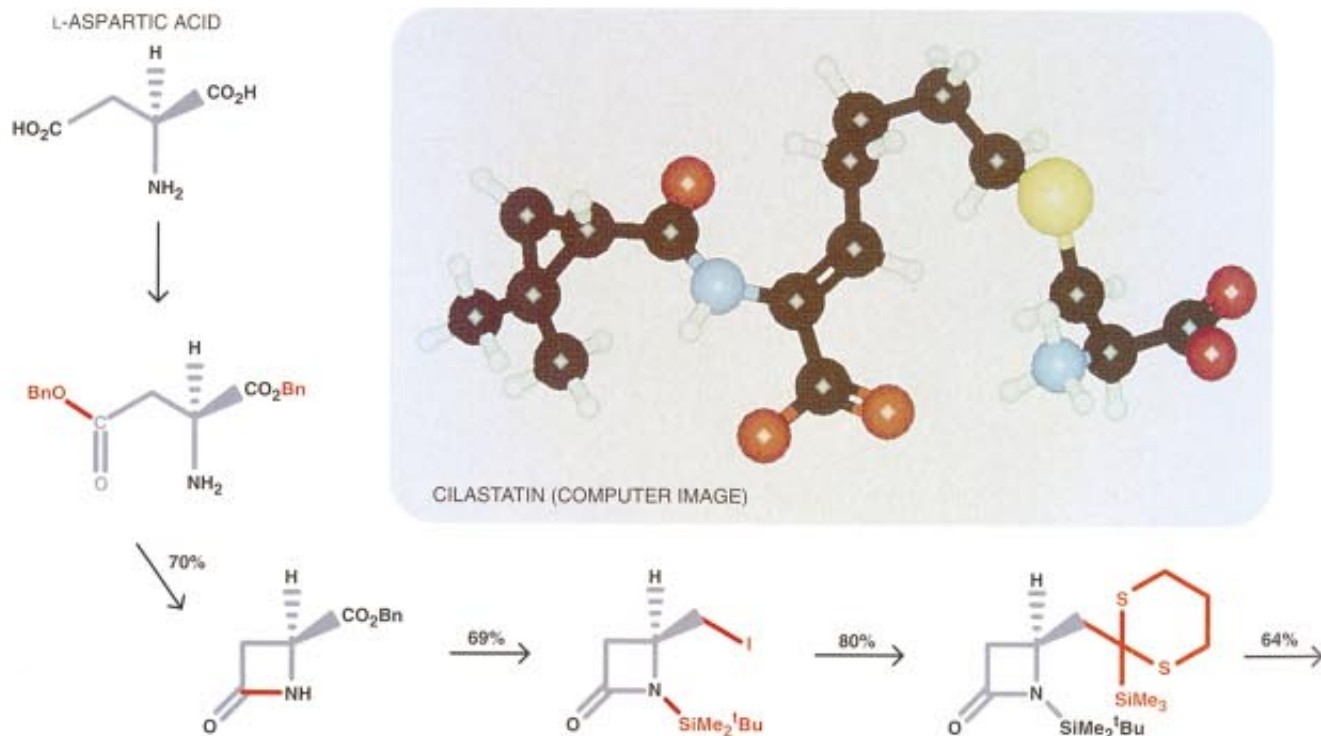
PLATO AND ARISTOTLE in a detail of Raphael's fresco *The School of Athens* are depicted in a way that symbolizes their approach to knowledge. Aristotle gestures toward the earth;

Plato points his finger to the heavens. Aristotle looked to nature for answers; Plato searched for the ideal. Should chemists follow the hand sign of Aristotle or that of Plato?

The Making of an Antibiotic

The antibiotic Primaxin is a mixture of two compounds known as imipenem (*ball-and-stick model at right*) and cilastatin (*model at left*). Imipenem is a slightly modified form of thienamycin, which is produced naturally by a mold. Chemists developed a procedure (summarized below) that

produces thienamycin more efficiently than any known natural process. The stick figures shown are the chemist's typical notation; not all atoms are identified. Those vertices that do not have atomic labels represent carbon atoms. Most of the hydrogen atoms have been left out. It is possible to de-



product; cilastatin does not. Both are made synthetically in the commercial process. I will return to this after tracing further the history of one of the components.

Imipenem was developed in the 1970s by a team of Merck chemists led by Burton G. Christensen. It is a slightly modified form of another antibiotic, thienamycin. That, in turn, was discovered while screening soil samples from New Jersey. It is produced by a mold, *Streptomyces cattleya*, so named because its lavender color resembles that of the cattleya orchid. The mold is a veritable drug factory, producing thienamycin and several other varieties of antibiotics.

Unfortunately, thienamycin was not chemically stable at high concentrations. And, to quote one of the Merck crew, "The lovely orchid-colored organism was too stinky." The usual fermentation processes, perfected by the pharmaceutical industry over the past 50 years, did not produce enough of the molecule. So the workers decided to produce greater quantities of thienamycin in the laboratory.

The production of thienamycin required 21 major steps, each involving several physical operations: dissolution, heating, filtration, crystallization. Between the starting material—a common amino acid, L-aspartic acid—and the desired product—thienamycin—20 other molecules were isolated and purified. Of these, only eight are shown in the condensed "reaction scheme" above.

The first impression that one gets is of complexity. That intricacy is essential, a laboratory counterpoint to the biochemical complexity of bacteria and us. We would like there to be "magic bullets" of abiding simplicity. The real world is complicated and beautiful. We had better come to terms with that richness.

To get a feeling for the sweat, if not the blood and tears, of the process, we need to turn to the experimental section of the paper reporting the synthesis. Here is an excerpt of that experimental protocol, describing a critical, inventive step in the synthesis—the transformation from compound 8 to 9:

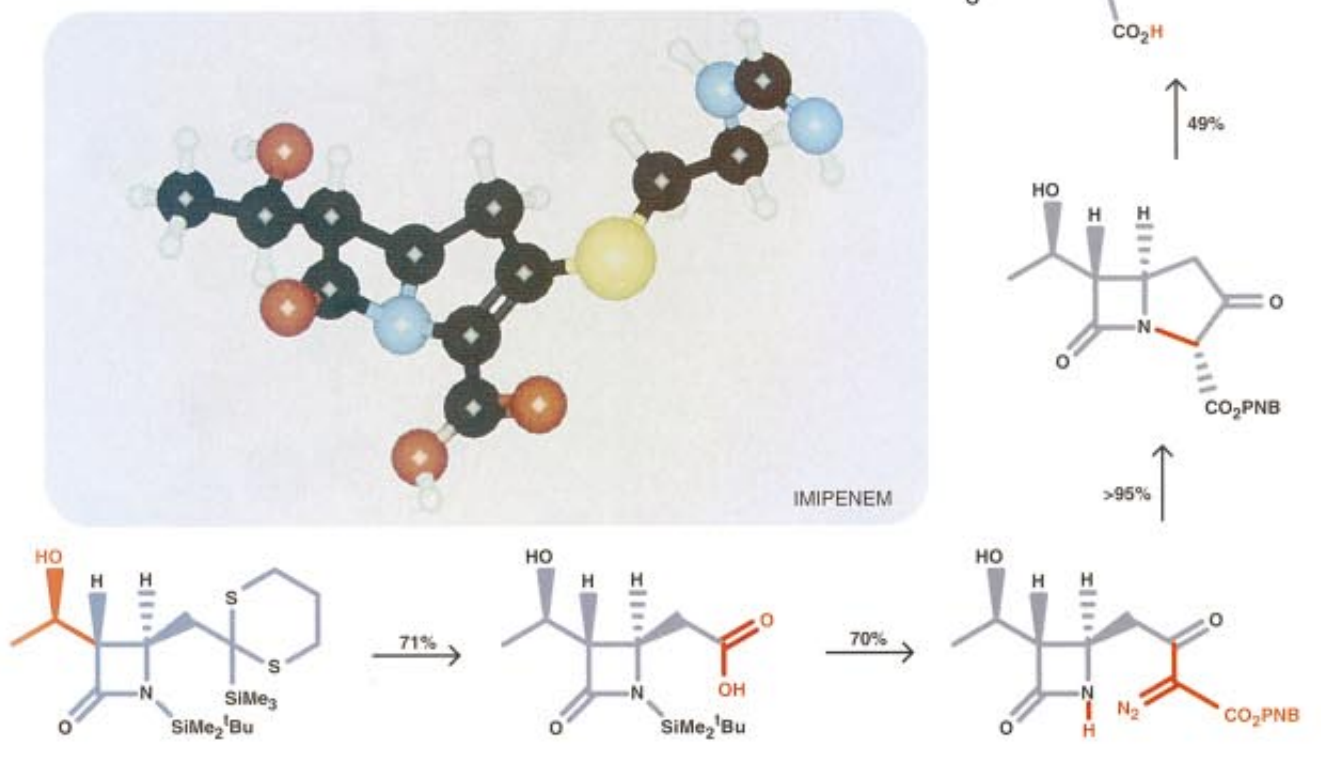
A suspension of diazo keto ester 8

(3.98g, 10.58 mmol) and rhodium(II) acetate dimer (0.04 g, 0.09 mmol) in anhydrous toluene (250 mL) was thoroughly purged with nitrogen, and then heated with stirring in an oil bath maintained at 80°C. After heating for two hours, the reaction mixture was removed from the bath and filtered while warm through a pad of anhydrous magnesium sulfate. The filtrate was evaporated under vacuum to afford the bicyclic keto ester 9 (3.27 g, 89%) as an off-white solid....

You can be sure that this jargon-laden account of an experimental procedure is a sanitized, too linear narrative; it is the way things were at the end: neat, optimized. Not the way it first happened. Putting that aside, you feel work, a sequence of operations that take time and effort. Sometimes, just as in our romantic notions of words springing from the brow of inspired poets, we forget the sheer labor of creation. Even the Creator rested on the seventh day.

You might be interested to see the way these experimental procedures change when the very same process is

duce the location of the missing hydrogen atoms because every carbon atom should form four bonds. An arrow represents each chemical transformation in the process. The percent figure near each arrow is the experimental yield. The symbols highlighted in red indicate changes in the structure. In the models of cilastatin and imipenem, black is carbon, blue is nitrogen, yellow is sulfur, red is oxygen and white is hydrogen. Wedges indicate details of geometry, atoms above or below the plane.



scaled up. You can't make hundreds of millions of dollars' worth of thienamycin the same way you make a few grams in the laboratory. Here is the description of the industrial synthesis, for the very same step:

The solids containing 200 kg of 8 are dropped into 476 gallons of MeCl_2 in tank TA-1432. Meanwhile, the reactor ST-1510 is cleaned out by a 200-gallon MeCl_2 boilout. The slurry is transferred to ST-1510, followed by a 50-gallon MeCl_2 line flush. An additional 400 gallons of dry MeCl_2 are added to ST-1510, and hot water (65°C) is applied to the jackets to concentrate the batch to 545 gallons where the slurry KF (Karl Fischer) is approximately 0.5 g/l H_2O . Distillates are condensed and collected in another tank.

Making veal stroganoff for a thousand people is not the same as cooking at home for four.

The synthesis of thienamycin is a building process, proceeding from simple pieces to the complex goal. It shares many features with architecture. For in-

stance, a necessary intermediate structure may be more complicated than either the beginning or end; think of scaffolding. Chemical synthesis is a local defeat of entropy, just as our buildings and cities are. The analogy to architecture is so strong that one forgets how different, how marvelous, this kind of construction is. In a flask there may be 10^{23} molecules, moving rapidly, colliding often. Hands off, following only the strong dictates of thermodynamics, they proceed to shuffle their electrons, break and make bonds, do our bidding. If we're lucky, 99 percent of them do.

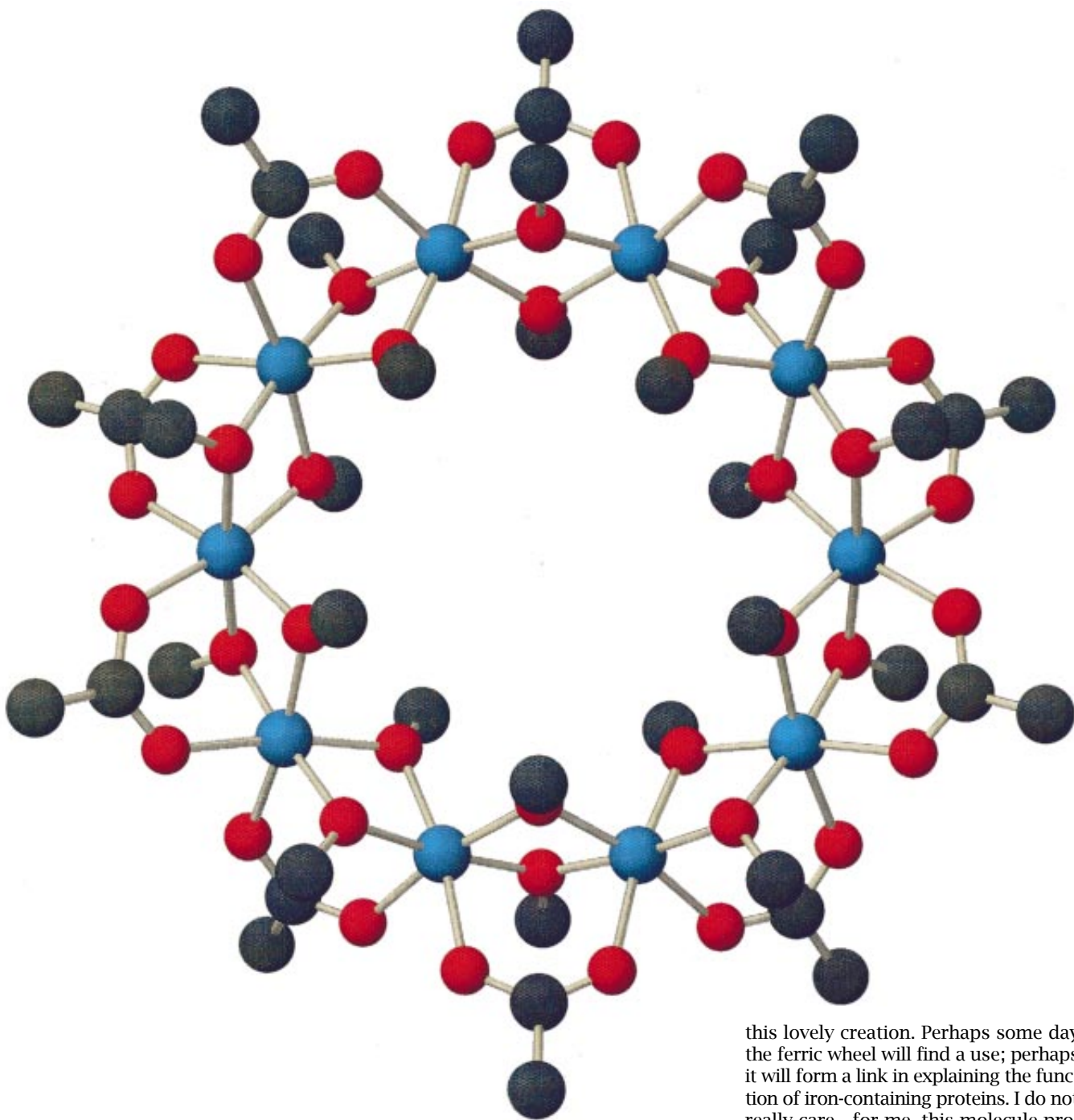
Chemists can easily calculate, given a certain number of grams of starting material, how much product one should get. That is the theoretical yield. The actual amount obtained is the experimental yield. There is no way to get something out of nothing but many ways to get less than you theoretically could. One way to achieve a 50-percent yield is to spill half the solution on the floor. This will impress no one. But even if you perform each transfer as neatly as possible, nature may not give you what you

desire but instead transform 70 percent into black gunk. This is also not impressive, for it does not demonstrate control of mind over matter. Experimental yields are criteria not only of efficiency, essential to the industrial enterprise, but also of elegance and control.

There is more, much more, to say about the planned organic synthesis. But let me go on to my second case study: the ferric wheel.

Stephen J. Lippard and Kingsley L. Taft of the Massachusetts Institute of Technology synthesized the ferric wheel, also known as $[\text{Fe}(\text{OCH}_3)_2(\text{O}_2\text{CCH}_2\text{Cl})]_{10}$. They discovered this exquisite molecule while studying model molecules for inorganic reactions that occur in biological systems. For instance, a cluster of iron and oxygen atoms is at the core of several important proteins, such as hemerythrin, ribonucleotide reductase, methane monooxygenase and ferritin (not household words these, but essential to life).

In the course of their broad attack on



such compounds, Lippard and Taft performed a deceptively simple reaction. Just how simple it seems may be seen from their experimental section, reproduced in its entirety:

Compound 1 was prepared by allowing the monochloroacetate analogue of basic iron acetate, $[\text{Fe}_3\text{O}(\text{O}_2\text{CCH}_2\text{Cl})_6(\text{H}_2\text{O})_3](\text{NO}_3)_3$ (0.315 g, 0.366 mmol), to react with 3 equiv of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (0.444 g, 1.10 mmol) in 65 mL of methanol. Diffusion of ether into the green-brown solution gave a yellow solution, from which both gold-brown crystals of 1 and a yellow precipitate deposited after several days.

Using x-ray diffraction on the gold-

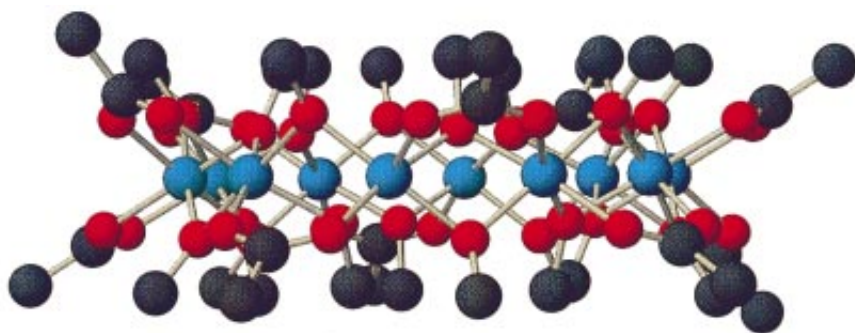
brown crystals, Lippard and Taft determined the arrangement of atoms in the molecule. The structure consists of 10 ferric ions (iron in oxidation state three) in a near circular array. Each iron atom is joined to its neighbors by methoxide and carboxylate bridges, "forming a molecular ferric wheel," to quote its makers.

No one will deny the visual beauty of this molecule. It does not have the annual sales of Primaxin, estimated to be \$500 million. On the contrary, it probably cost the U.S. taxpayer several thousand dollars to make it. But I do not know a single curmudgeonly chemist who would not respond positively to

this lovely creation. Perhaps some day the ferric wheel will find a use; perhaps it will form a link in explaining the function of iron-containing proteins. I do not really care—for me, this molecule provides a spiritual high akin to hearing a Haydn piano trio I like.

Why is this molecule beautiful? Because its symmetry reaches directly into the soul. It plays a note on a Platonic ideal. Perhaps I should have compared it to Judy Collins singing "Amazing Grace" rather than the Haydn trio. The melodic lines of the trio indeed sing, but the piece works its effect through counterpoint, the tools of complexity. The ferric wheel is pure melody.

Were we to write out the synthesis of the ferric wheel, there would be but a single arrow, from the iron chloroacetate and ferric nitrate to the product. This is a very different type of synthesis—the product essentially self-assembles to its final glory. When I see such a process, much more typical of inorgan-



he antibiotic Primaxin is a mixture of two compounds known as imipenem (*ball-and-stick model at right*) and cilastatin (*model at left*). Imipenem is a slightly

ic systems than organic ones, I immediately wonder what I'm missing. The Swedish chemist Sture Forsén has aptly expressed the frustration in not being able to observe the intermediate stages of a reaction:

The problem facing the scientist has been compared with that of a spectator of a drastically shortened version of a classical drama—"Hamlet," say—where he or she is only shown the opening scenes of the first act and the last scene of the finale. The main characters are introduced, then the curtain falls for change of scenery, and as it rises again we see on the scene floor a considerable number of "dead" bodies and a few survivors. Not an easy task for the inexperienced to unravel what actually took place in between.

Wheels, ferric or ferris, don't really self-assemble in one fell swoop. It remains for us to learn in the future how those bridges and irons come together.

Some chemists, especially those who practice the mentally demanding, intellectually exhilarating many-step, planned synthesis of the thienamycin type look askance at one-step self-assembly. Such one-fell-swoop syntheses are especially common in solid-state chemistry, in the formation of materials extended infinitely in one, two or three dimensions. The high-temperature superconductors are a good example of molecules made just this way. Their synthesis does not appear to show control of mind over matter. It looks like magic.

I exaggerate, but this is one strand of thought in the community. If I could corner my straw-man scoffer at self-assembly, typically an organic chemist, and engage him or her in a Socratic dialogue, I would begin with the question "When have you made any diamond for me lately?" Diamond is a beautifully simple three-dimensional structure (natural!). It contains in it six-membered rings, the bread-and-butter of organic chemistry. Such rings of carbon atoms are easy to make in a discrete molecule.

But diamond can be made only by techniques organic chemists find unsporting, by discharges forming a plasma in methane or by pressing graphite.

Organic chemists are masterful at exercising control in zero dimensions. To one piece of carbon, perhaps asymmetric, they add another piece. Slowly, painstakingly, a complex edifice emerges. (Thienamycin is pretty simple compared to what you can do today.) One subculture of organic chemists has learned to exercise control in one dimension. These are polymer chemists, the chain builders. Although they may not have as much honor in organic chemistry as they should, they do earn a good bit of money.

But in two or three dimensions, it's a synthetic wasteland. The methodology for exercising control so that one can make unstable but persistent extended structures on demand is nearly absent. Or to put it in a positive way—this is a certain growth point of the chemistry of the future.

Syntheses, like human beings, do not lend themselves to typology. Each one is different; each has virtues and shortcomings. From each we learn. I will stop, however reluctantly, with primaxin and the ferric wheel and turn to some general questions they pose, especially about the natural and the unnatural.

Two paradoxes are hidden in the art of synthesis. The first is that the act of synthesis is explicitly human and therefore unnatural, even if one is trying to make a product of nature. The second is that in the synthesis of ideal molecules, where doing what comes unnaturally might seem just the thing, one sometimes has to give in to nature. Let me explain in the context of the two syntheses I have just discussed.

Imipenem, one component of the successful Merck antibiotic, is made from thienamycin. The thienamycin is natural, to be sure, but an economic and chemical decision dictated that in its

commercial production thienamycin be made synthetically.

There is no doubt in this case that the natural molecule served as an inspiration for the synthetic chemists. But, of course, they did not make thienamycin in the laboratory the way it is made by the mold. The organism has its own intricate chemical factories, enzymes shaped by evolution. Only recently have we learned to use genetic engineering to harness those factories, even whole organisms, for our own purposes.

We have grown proficient at simpler, laboratory chemistries than those evolved by biological organisms. There is no way that Christensen and his team would set out to mimic a mold enzyme in detail. They did have confidence that they could carry out a very limited piece of what the lowly mold does, to make thienamycin, by doing it differently in the laboratory. Their goal was natural, but their process was not.

To make thienamycin, Christensen and his co-workers used a multitude of natural and synthetic reagents. For instance, one of their transformations—the synthesis of compound 3 [*see box on page 68*—uses a magnesium compound, $(\text{CH}_3)_3\text{CMgCl}$, known as a Grignard reagent. Magnesium compounds are abundant in nature (witness Epsom salt and chlorophyll). But the reagent in question, a ubiquitous tool of the synthetic chemist, was concocted by Victor Grignard some time around the turn of the century. The creation of compound 3 also requires treatment with hydrochloric acid and ammonium chloride, both natural products. (Your stomach has a marginally lower concentration of hydrochloric acid than that used in this reaction, and ammonium chloride is the alchemist's sal ammoniac.) But even though these molecules occur in nature, they are far easier to make in a chemical plant.

Because everything in the end does come from the earth, air or water, every unnatural reagent used in the synthesis ultimately derives from natural organic or inorganic precursors. The very starting material in the synthesis of imipenem is an amino acid, aspartic acid.

Now consider the most unnatural and beautiful ferric wheel. It was made simply by reacting two synthetic molecules, the iron monochloroacetate and ferric nitrate, in methanol, a natural solvent. The methanol was probably made synthetically; the two iron-containing reagents derive from reactions of iron metal, which in turn is extracted from iron ores. And the final wrinkle is the method of assembly: the pieces of the molecule seem to just fall into place (self-assembly). What could be more nat-

ural than letting things happen spontaneously, giving in to the strong dictates of entropy?

It is clear that in the unnatural making of a natural molecule (thienamycin) or of an unnatural one (the ferric wheel), natural and synthetic reagents and solvents are used in a complex, intertwined theater of letting things be and of helping them along. About the only constant is change, transformation.

We may still wonder about the psychology of chemical creation. Which molecules should we expend our energies in making? Isn't there something inherently better in trying to make the absolutely new?

Four beautiful polyhedra of carbon have piqued the interest of synthetic organic chemists during the past 40 years: tetrahedrane (C_4H_4), cubane (C_8H_8), dodecahedrane ($C_{20}H_{20}$) and buckminsterfullerene (C_{60}). Cubane is quite unstable because of the strain imposed at each carbon. (In cubane the angle between any three carbon atoms is 90 degrees, but each carbon would "prefer" to form angles of 109.5 degrees with its neighbors.) C_{60} is also somewhat strained because of both its nonplanarity and its five-membered rings. Tetrahedrane is particularly unstable. One has to create special conditions of temperature and solvent to see it; even then, the parent molecule has not yet been made, only a "substituted derivative," in which hydrogen is replaced by a bulky organic group.

As far as we know, tetrahedrane, cubane and dodecahedrane do not exist naturally on the earth. C_{60} has been found in old soot and a carbon-rich ancient rock, shungite. It may turn up elsewhere. Be that as it may, all four molecules were recognized as synthetic targets at least 20 years, in some cases 50 years, before they were made. Some of the best chemists in the world tried to make them and failed. The syntheses of cubane and especially dodecahedrane were monumental achievements in unnatural product chemistry.

C_{60} was different. The pleasing polyhedral shape was first noted by some theoreticians. Their calculations indicated some stability; such indications as the theoreticians had at their command were sometimes unreliable. These theoreticians' dreams were ignored by the experimentalists and by other theoreticians. It is sometimes difficult to see the shoulders of the giants we stand on when we are looking so intently ahead. I myself have suggested a still unsynthesized metallic modification of carbon, different from diamond or graphite, and even though I have substantial-

ly more visibility among chemists than the proposers of buckminsterfullerene, no one has paid much attention to my pipe dream either, probably for good reason. We see what we want to see.

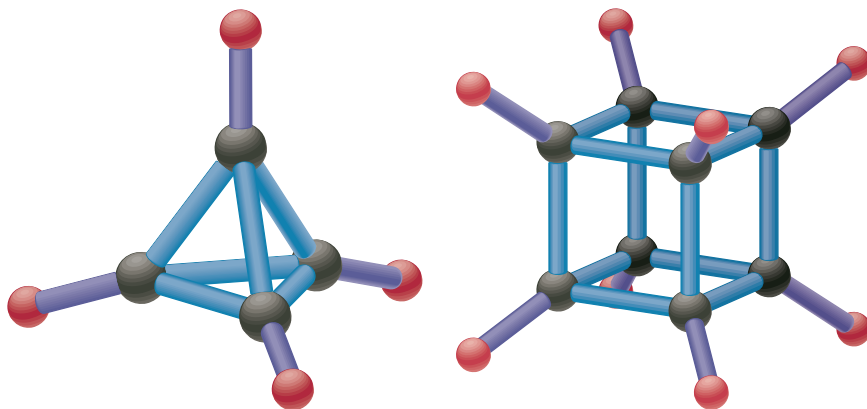
One organic chemist I know, a very good one, Orville L. Chapman of the University of California at Los Angeles, independently thought up the structure and devoted much time to the planned, systematic making of C_{60} . After all, this was a "simple" molecule, not an extended material like the repeating lattice of carbon atoms that make up a diamond. So it should be possible to make it. Despite persistent efforts over a 10-year period, Chapman and his students failed in their effort.

The first evidence, indirect but definitive, for C_{60} was obtained from a very different branch of our science, physi-

Heidelberg. Striking a carbon arc in a helium atmosphere (which is what they did) is about as unsporting as firing a laser at graphite (the Smalley-Kroto-Curl synthesis). But it certainly makes plenty of C_{60} , enough of the molecule to determine its structure by typical organic methods, enough to convince any chemist that it has the soccer-ball structure ["Fullerenes," by Robert F. Curl and Richard E. Smalley; *SCIENTIFIC AMERICAN*, October 1991].

I think many chemists wished C_{60} had been made in a planned, unnatural way. I am happy that—just to make the world slightly less rational than we would like it to be—it was made in a serendipitous way.

Serendipity—a word invented by Horace Walpole—has come to mean "a discovery by chance." Yet whether it is a



modified form of thienamycin, which is produced naturally by a mold. Chemists developed a procedure (summarized below) that produces thienamycin more effi-

cal chemistry. The credit for the discovery belongs properly to Richard E. Smalley and Robert F. Curl of Rice University and Harold W. Kroto of the University of Sussex. They obtained hard evidence for tiny amounts of C_{60} in the gas phase, assigned the molecule its name and, more important, deduced its structure. Did they make it? Absolutely. It did not matter to me or to other believers in their evidence that they had made "just" 10^{10} molecules instead of the 10^{20} we need to see in a tiny crystal. But there were doubters, many I suspect, in the organic community. One wanted to see the stuff.

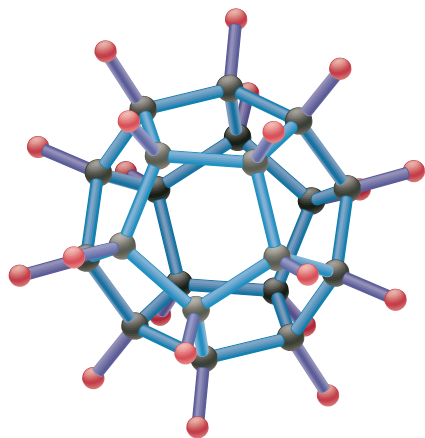
Grams of buckminsterfullerene were provided by a synthesis by Donald R. Huffman of the University of Arizona and Wolfgang Krätschmer and Konstantinos Fostiropoulos of the Max Planck Institute for Nuclear Physics in

chemical synthesis or a Japanese master potter piling organic matter around the ceramic objects in his Bizen kiln, chance favors the prepared mind. You need to have the knowledge (some call it intuition) to vary the conditions of striking the arc or the arrangement of the leaves in the kiln just so. You need to have the instruments and intuition to deduce structure from a few fuzzy lines in a spectrum and to reject false leads. And you need to have the courage to shatter a vase that didn't come out right and to learn from one firing what to do in the next.

Many chemical syntheses, even if part of a grand design, proceed by steps that are serendipitous. One wants to link up a bond here, but it doesn't work. So one follows a hunch, anything but the codified scientific method. One knows that if a reaction works, one can construct a

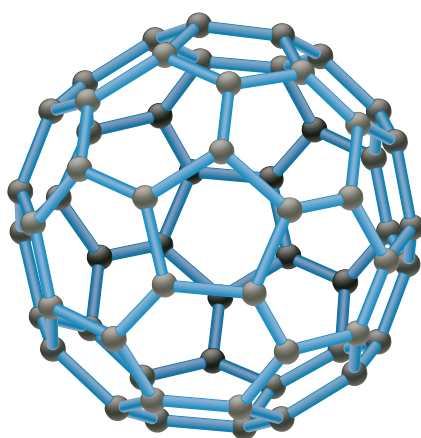
rationalization for it—an argument spiffy clean enough to make an impression on one's colleagues. Eventually one can make the damned reaction work if it is a necessary step in the design.

Because chance also operates to foil every design, it is almost certain that in the course of any planned synthesis there will be a step that will not work by any known process. So a new one will be invented, adding to the store of the chemists, aiding others around the world facing the same problem. Some synthetic chemists—for instance, E. J. Corey of Harvard University, a grand master of the art—have a special talent for not only making interesting molecules but also using the opportunity of the synthesis to introduce a brilliant, unprecedented methodology, applicable to other syntheses.



fishing nets, nylon instead of silk in women's stockings. No one, least of all Third World fishermen, will go back to the old nets. Some people may go back to silk stockings, but they will only be the rich, out to impress. There are new chemical materials and new combinations of old materials for dental restorations. They make a world of difference to older people in this world, and their benefit cannot be dismissed.

Yet the thought that we can do better than nature is provocatively arrogant. As we have attempted to improve on nature (while failing to control the most natural thing about us, our drive to procreate), we have introduced so many transformations and in such measure that we have fouled our nest and intruded into the great cycles of this planet. We must face the reality that natural evolution



ciently than any known natural process. The stick figures shown are the chemist's typical notation; not all atoms are identified. Those vertices that do not have atomic

When the synthesis is planned, be its aim a natural or unnatural molecule, we suppress the aleatory nature of the enterprise. We want to project an image of mind over matter, of total control. When the molecule made is unanticipated, as the ferric wheel was, we find it very difficult to hide the workings of chance. But hazard—to use the meaning that is dominant in the French root of our word, and secondary in ours—plays an unrecognized and enlivening role in all synthesis.

Let us return to nature and our struggles to emulate it. Or surpass it. Can we make substances that have properties superior to those found in nature? I say “yes” while recognizing that the phrase “superior to nature” is patently value laden and anthropocentric and should immediately evoke ecological concerns.

There is nylon instead of cotton in

proceeds far too slowly to cope with our changes. This is a concern that, just as much as utility, should guide the industrial-scale syntheses of the future.

I want to touch on another kind of human arrogance implicit in the intellectual drama of synthesis. A French chemist, Alain Sevin, has put it well:

The incredible richness and fantasy of Nature is an act of defiance to Man, as if he had to do better in any domain. Flying faster than birds, diving deeper than whales.... We are Promethean characters in an endless play which now is in its molecular act.

We are driven to transform. We have learned to do it very well. But this play is not a comedy.

Were chemical synthesis in search of a single icon, the outstretched hand of

Prometheus bringing fire to humanity would serve well. Prometheus, a name meaning “forethought,” represents the element of design, the process of fruitfully taking advantage of chance creation. Fire is appropriate because it drives transformation. The hand of Prometheus is the symbol of creation—the hand of God reaching to Adam in Michelangelo's fresco, the hands in contentious debate in Dürer's *Christ among the Doctors*, the infinite variety of hands that Rodin sculpted. Hands bless, caress and hide, but most of all, they shape.

The sculptor's art itself mimics the complexity of motion of a chemist across the interface between natural and unnatural. Rodin, in his human act of creation, sketches, then shapes by hand (with tools) an out-of-scale yet “realistic” artifact, a sculpture of a hand, out of materials that are synthetic (bronze) but that have natural origins (copper and tin ores). He uses a building process (maquettes, a cast) that is complex in its intermediate stages. The sculptor creates something very real, whose virtue may reside in calling to our minds the ideal.

Margaret Drabble has written that Prometheus is “firmly rooted in the real world of effort, danger and pain.” Without chemical synthesis, there would be no aspirin, no cortisone, no birth-control pills, no anesthetics, no dynamite. The achievements of chemical synthesis are firmly bound to our attempt to break the shackles of disease and poverty. In search of an ideal, making real things, the mind and hands engage.

FURTHER READING

SYNTHESIS. R. B. Woodward in *Perspectives in Organic Chemistry*. Edited by A. R. Todd. Interscience, 1956.

A STEREOCONTROLLED, ENANTIOMERICALLY SPECIFIC TOTAL SYNTHESIS OF THIENAMYCIN. T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard and B. G. Christensen in *Philosophical Transactions of the Royal Society of London, Series B*, Vol. 289, No. 1036, pages 191-195; May 16, 1980.

MOLECULES. Peter W. Atkins. Scientific American Library, 1987.

THE LOGIC OF CHEMICAL SYNTHESIS. E. J. Corey and Xue-Min Cheng. John Wiley and Sons, 1989.

SYNTHESIS AND STRUCTURE OF $[\text{Fe}(\text{OMe})_2(\text{O}_2\text{CCH}_2\text{Cl})]_{10}$, A MOLECULAR FERRIC WHEEL. Kingsley L. Taft and Stephen J. Lippard in *Journal of the American Chemical Society*, Vol. 112, pages 9629-9630; December 19, 1990.

THE ORGANIC CHEMISTRY OF DRUG DESIGN AND DRUG ACTION. Richard B. Silverman. Academic Press, 1992.

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