

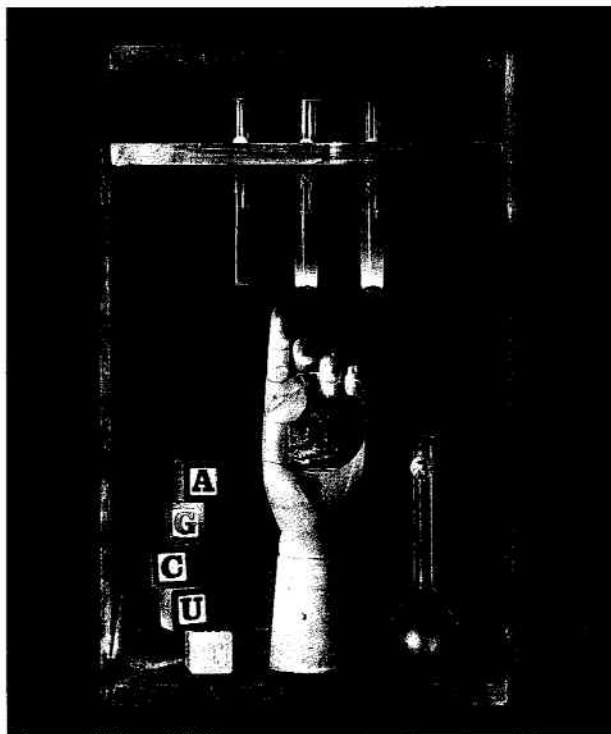
Unnatural Acts

BY ROALD HOFFMANN

HUMAN BEINGS HAVE BEEN PUT ON THIS EARTH to create. Some write poems. Others build additions to houses, draft new civil rights legislation, dig ditches. Some make molecules—these are the chemists. All—poets, builders, lawmakers, ditchdiggers, chemists—either create something new (call it man- or woman-made, synthetic, artifactual, or unnatural) or modify a product of nature. ■ Is the natural different from the unnatural? Yes, on the spiritual level, as the designers of food labels know too well. The words *natural*, *organic*, *unadulterated* have unmistakably positive connotations. No, on the material level. All stuff, whether natural or unnatural, is at the microscopic level molecular. And all observable macroscopic properties—color, toxicity, strength, conductivity—follow from that microstructure, from the arrangements of atoms in space. Synthetic molecules, carefully made, can replace natural ones. Your MSG headache is equally well induced by synthetic or natural MSG, your pneumonia cured by an antibiotic made either by a mold or in the laboratory.

The natural-unnatural distinction is made ambiguous by every aspect of human existence, not just by molecules in and around us. I look out my window and see a wonderful rolling landscape of green fields and forests—the foothills of the Appalachians. It is human agriculture that has shaped that view. My roses in bloom and my neighbor's sleek dachshund are curious and pleasing mixtures of nature and most deliberate intervention.

It's ambiguous not just to nonscientists but even to the molecule makers, the first ones to tell people that there is no



Chemists create molecules; so does nature. The difference remains tantalizingly elusive.

such distinction. People in the molecular trade talk of “natural product synthesis”—the laboratory crafting of the molecules of nature—to distinguish it from the synthesis of molecules never before present on Earth. Significantly, no chemist uses the term “unnatural prod-

ucts,” except as a joke. Even those who insist most vehemently that there is no difference between natural and unnatural, I suspect, go home to houses with windows, not photographs of landscapes on windowless walls; their furniture is made of wood, not an artful imitation.

Chemists, my gang, do have a special way of playing with the natural, however. First, they see it as a challenge to make any molecule nature can. And they do it, those master builders of tiny structures. They may manage their synthesis less efficiently than nature does, but then nature has had a few million more years to optimize almost any process.

Second, chemists want to make molecules that aren't present in nature. Why not a molecule that looks like an icosahedron ($B_{12}H_{12}^{2-}$)? Or one like a soccer ball (C_{60})? This is real fun. (And the fun wasn't spoiled by finding C_{60} in nature after it was made in the lab!)

Third, they want to make molecules that resemble natural ones but are better in some respect. There now exist polymers stronger than steel, and fats to fry your onion rings in that are calorie-free because they are not digested.

Fourth, chemists want to make molecules that are sort of like natural ones but a little different. Why? To fool bacteria and viruses, of course. To trick them into committing suicide or not reproducing. There is profit in this.

Fifth, chemists make synthetic molecules to understand nature—its highways and byways, how it got to be the beautiful way it is.

Men and women seem to find ever more ingenious ways to confound the natural-unnatural dichotomy. A recent sample of minor and not-so-minor changes made to molecules critical to life gives a taste of what these molecular engineers are up to.

There was no greater chemical achievement (even if it was accomplished by two non-chemists) in midcentury than the recognition of the structure of DNA. And it has taken much ingenious work to explore fully the consequences and workings of what James Watson and Francis Crick divined. But now chemists are curious. Why this structure and not all others? Albert Eschenmoser of the Federal Institute of Technology in Zurich, one of the deepest-thinking chemists of our time, has focused on the sugars.

Nucleic acids, including DNA and RNA, are the information carriers of life. The two strands of DNA, a marvelous biopolymer, are each a chain of phosphates (PO₄)

mechanism for replication. The bases encode the information; the sugar rings are part of the backbone of the spiral ladder.

Because the sugars of RNA and DNA are made of five carbons (four in the ring and one more outside), chemists, prone just occasionally to fits of rationality in nomenclature, have called them pentoses. Much more common than the pentoses, however, are the six-carbon sugars called hexoses (containing a ring of five carbons and an oxygen, with an extra carbon outside the ring). An example is common glucose, maybe one of the few healthy delights left us.

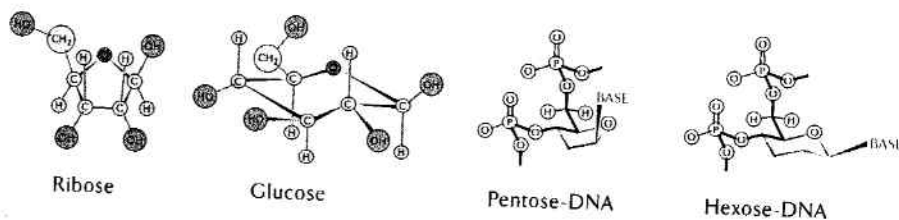
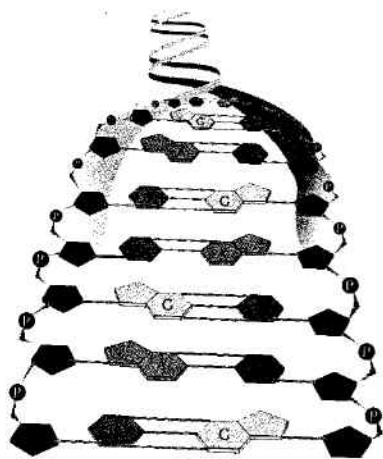
Eschenmoser argues convincingly that hexoses are not just popular today but were more than likely to have formed under prebiological conditions. Why, then, he asks, did nature choose pentoses and not hexoses as the sugar building blocks of nucleic acids?

The Swiss chemist follows up the question with . . . synthesis. He and his

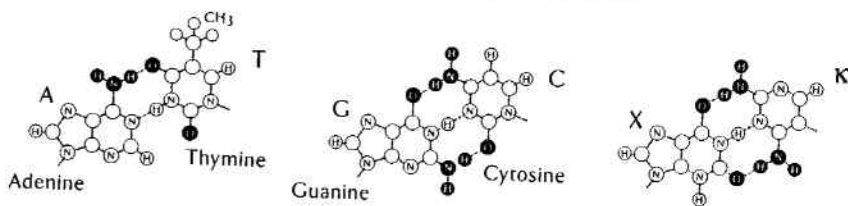
being cradled within a helix and perpendicular to it. And that cradling in turn can be traced to the angle at which the bases come off the sugar, relative to the chain axis formed by the phosphates and part of the pentose ring. Notice how in the hexose universe (unnatural, and even more so ours) the bases are attached at a very different angle. Computer modeling and experiment show that the hexose-DNA does not form helical structures. Hexose-DNA strands pair differently, pair more strongly, and thus are much less prone to the ready pairing-unpairing that is characteristic of normal pentose-DNA. The alternative universe is just not good enough, so it seems, to do what has been done.

NOT TOO FAR FROM ESCHENMOSER, in the same laboratories in Zurich, Steven Benner is playing with nature in another way. Recall the four bases, G, C, A, and T (U). These bases come together, through hydrogen bonds, in spe-

Variations on Natural Themes



EXPANDING THE RING: Substituting a six-carbon sugar ring (glucose) for the natural five-carbon ring (ribose) has a big effect on the way DNA's spiral ladder coils: the base comes off the new sugar at a much different angle (far right), and the "artificial" strand (hexose-DNA) does not form a helix like natural (pentose) DNA.



DOUBLE HELIX: The base pairs AT and GC spell out genetic information, while the sugar-phosphate (P) chain forms the backbone of the spiral ladder.

alternating with sugar rings made up of carbons and a single oxygen. Coming off the rings are flat platelet-like molecular units, the "bases" that are the letters of the genetic alphabet: adenine (A), guanine (G), cytosine (C), and thymine (T, in DNA) or uracil (U, in RNA). The sequence of the bases within one strand codes the message; the pairing of the bases in that strand with specific partners in the other strand is the

EXTENDING THE ALPHABET: Adding two new letters to the genetic alphabet (the X and K base pair at far right) increases the potential for a richer array of proteins, which are strings of amino acids built up from combinations of bases. Nature's alphabet (ATGC) stopped at four letters. The artificial alphabet might make more versatile molecules.

able co-workers build up an entire alternative universe, constructing not just the sugars but single-stranded phosphate-sugar chains as well. They add the bases. They do what nature chose not to do.

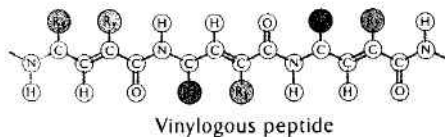
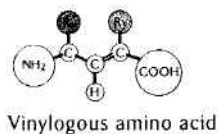
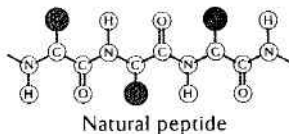
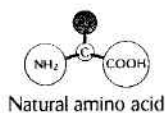
The alternative world in their grasp, the chemists look for differences. These are easy to find. The beauty and efficient replication properties of the pentose universe (natural, ours) derive from the bases

cific pairs. A fits with T (or U, in RNA) like the clasp on a necklace; it will not pair with G or C. G and C are, likewise, perfectly and monogamously matched. This pairing is the heart of the replication mechanism that is needed if information is to be passed along. A sequence of three bases translates into an amino acid of a protein. So GCU codes the eventual synthesis of an alanine, and

GGU gets us a glycine. In this way the very specific amino acid sequences of the protein chemical factories of our bodies are built up.

Benner's group thought that nature's alphabet might be extended. So they designed another base pair, κ (kappa) and X, to fit into the double helix. Neither κ nor X pairs with known bases, so the new letters do not sow confusion; they just extend the alphabet from four letters to six.

The new letters give the *potential* for—but don't guarantee—increased richness in the genetic vocabulary. Nature chooses four letters. Would six produce a richer universe of proteins? I don't know the answer. English is a richer language in number of words than either French or Anglo-Saxon, but that's no guarantee that you'll write great literature in English. Still, it's interesting to try to create a new language and see if you can make some new words with it. The analogue of making new words is mak-



PROTEIN GAMES: The R group makes one amino acid different from the next, providing the variety nature needs to build up various kinds of peptides. Stitching in an extra R group (bottom) adds even more variety.

ing new molecules. It's possible you could in this way make some new proteins that could be interesting drugs, that could be different in some slight way.

Put more letters, weird new ones, into English, and you can certainly make more words. But they'll be nonsense, or near nonsense. With time, if needed, those additional letters may shape new words, new meanings in a richer language of the fu-

ture. So the expanded genetic alphabet needs to pass through the selection process of evolution before it begins to create molecules more diverse, more versatile, than the ones we already have.

There is a kind of chutzpah in Benner's game, but it sure is pretty.

STILL MORE MOLECULAR GAMES ARE afoot, this time with proteins. Proteins are biopolymers built up from long chains of linked amino acids. A piece of a protein, assembled from two or more of these amino acids, is called a peptide. Imagine each amino acid as a tool with a bit and two sources of attachment (see preceding page). These two "handles" are always the same—an amino (NH_2) and an acid (COOH)—and they allow one peptide to link up, interchangeably, with others. But the bits come in 20 different varieties, called R groups. The differences create variety, like different tool bits on the same machine, allowing for different functions. If the R group is a single hydrogen, H, then the resulting amino acid is glycine (gelatin is full of it); when it's CH_3 —three hydrogens and a carbon—then the amino acid is alanine, which is especially common in silk fibers. When it's $\text{CH}_2\text{CH}_2\text{COOH}$, the amino acid is glutamate; replace the last H by a sodium and you've got the primary ingredient for the MSG—natural or unnatural—that produces your headache.

Stuart Schreiber at Harvard and Jon Clardy at Cornell have designed a set of stretched, or "vinylogous," peptides. You see the same handles that confer the ability to form a chain at the ends. But in the middle there is something different, two extra carbons sewed in, with a second R on one of them, providing potentially more variety than the single R group of a normal amino acid. The two-carbon spacer in the chain also gives the polymer the ability to fold up in a way similar to, but different from, normal protein folding. What could these modified peptides do? They would be the same and not the same, and among them some might fool and subdue the pathogens that threaten our well-being.

For example, enzymes are protein powerhouses built up bit by bit by the peptide pieces. They bind some molecule and then do chemistry with it. The binding often depends on their recognizing just one piece of the molecule, not the whole thing. You could conceivably make a molecule with one piece that

would be recognized, but with another piece that would throw a wrench into the works and essentially shut down the molecular factory. So being slightly unnatural can be very dangerous—to harmful bacteria, we hope.

Incredibly, a molecule that strongly resembles one of these vinylogous peptides has turned up in nature, in a marine sponge; in humans the peptide inhibits blood clotting. This discovery offered strong psychological support to the chemists. They thought they were making things that were very far out, but it turned out that nature had played that same variation on a theme. All the more reason to believe that a library of such modified peptides might be of value in drug design.

The three examples I picked of chemists ringing changes on nature are not peripheral; they touch on central issues of biology. Eschenmoser's work deals

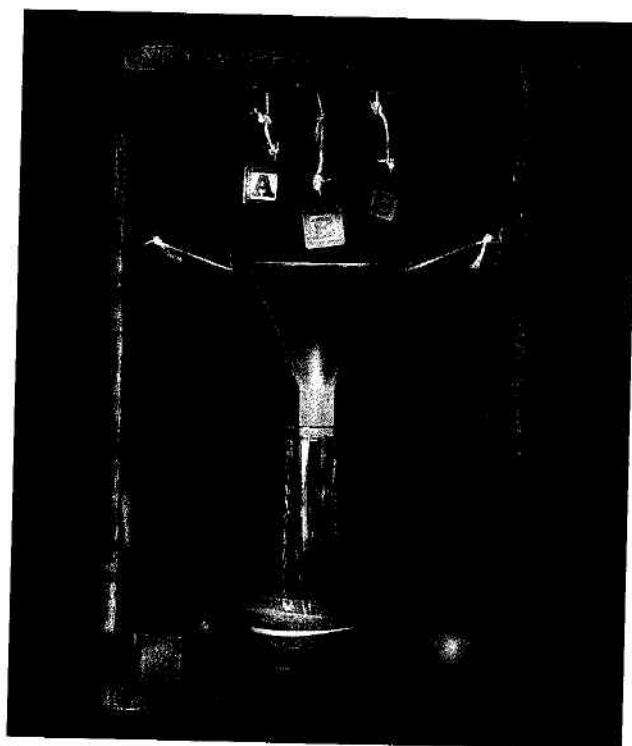
I change things just a little? The power to effect such change is in our hands. There is real adventure in creating an alternative world.

Then there is benefit and its sidekick, profit. Some of these molecules may be useful drugs just because they are small variations on a natural theme. When curiosity and benefit find themselves on the same trail, the hands and minds of human beings seem to quicken. You can see this in the current flurry of activity in the making of slightly unnatural molecules.

Yet some people are scared by these molecular games, as they are by genetic engineering. The range of concerns is wide: even if there are safeguards against letting loose possible new pathogens, even if these molecules save lives or improve our standard of living, what right do we have to tamper with a God-given universe?

I do not have a full answer to these

concerns, but I would begin a dialogue as follows: We have tampered irreversibly with nature from the time we became a species, from the moment prehistoric people (like the one recently thawed from Tirolean ice) used a copper ax, to modern times, to the 10 billion chickens that now share the world with us. Before us, cataclysmic natural events, as destructive of other species as we are, shaped this world. We did not invent species extinctions. The difference in our transformation of nature is its larger scale and faster pace. But there is another



with the structural prerequisites for the storage and replication of molecular information. Benner's touches on the transcription of this information from one biopolymer family to another. Clardy and Schreiber, meanwhile, study the type of structure created from this information.

The motivations of the chemists engaged in this work are clear. First, there is the sense of wonder. Why did nature do it this way and not another? What if

tial for repair. There is a human creation, ethics—fully as unnatural as all those new molecules—which makes every chemist think about the consequences, the possible harm, the potential ill use of the new molecules he or she makes. We have no choice but to make these molecules, for curiosity drives us relentlessly on. But we also have no choice but to worry about what we do. And act upon it. □