

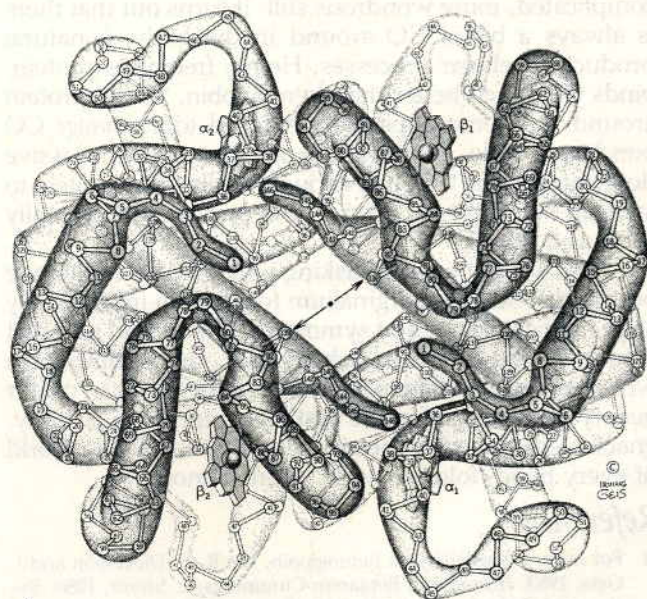
Marginalia

Molecular Beauty III: As Rich as Need Be

Roald Hoffmann

Look at molecule 1. It seems there's nothing beautiful in its involuted curves, no apparent order in its tight complexity. It looks like a clump of pasta congealed from primordial soup or a tapeworm quadrille. The molecule's shape and function are enigmatic (until we know what it is!). It is not beautifully simple.

Complexity poses problems in any aesthetic, that of the visual arts and music as well as chemistry. There are times when the Zeitgeist seems to crave fussy detail—



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Victorian times, the rococo. Such periods alternate with ones in which the plain is valued. Deep down, the complex and the simple coexist and reinforce each other. Thus the classic purity of a Greek temple was set off by sculptural friezes, pediments, and the statues inside. The clean lines and functional simplicity of Bauhaus or Scandinavian furniture owe much to the clever complexity of the materials and the way they are joined. Elliott Carter's musical compositions may seem difficult to listen to, but their separate instrumental parts follow a clear line.

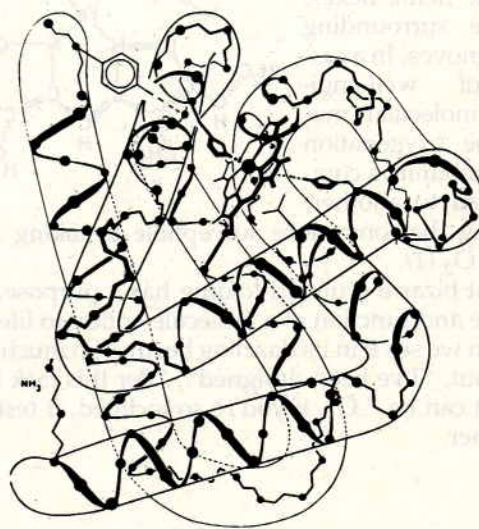
In science, simplicity and complexity always coexist. The world of real phenomena is intricate, the underlying principles simpler—if not as simple as our naive minds imagine them to be. But perhaps chemistry, the central science, is different, for in it complexity is cardinal. I call it simply richness, the realm of the possible.

Chemistry is the science of molecules and their transformations. It is the science not so much of the hundred elements, but of the infinite variety of molecules that may be built from them. You want it simple—a molecule shaped like a tetrahedron or the cubic lattice of rock salt? We've got it for you. You want it complex—intricate enough to run efficiently a body with its ten thousand concurrent chemical reactions? We've got that too. Do you want it done differently—a male hormone

here, a female hormone there; the blue of cornflowers or the red of a poppy? No problem, a mere change of a CH_3 group or a proton, respectively, will tune it. A few million generations of evolutionary tinkering, a few months in a glass-glittery lab, and it's done! Chemists (and nature) make molecules in all their splendiferous functional complexity.

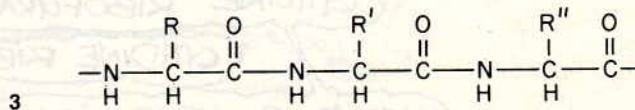
Beautiful molecule 1 is hemoglobin, the oxygen transport protein. Like many proteins, it is assembled from several fitted chunks, or subunits. The subunits come in two pairs, called α and β . Incredibly, these actually change chemically twice in the course of fetal development, so as to optimize oxygen uptake. The way the four subunits of hemoglobin mesh is requisite for the protein's task, which is to take oxygen from the lungs to the cells (1).

One of the hemoglobin subunits is shown in structure 2. It's a curled-up polypeptide chain carrying a



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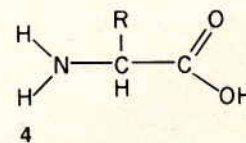
"heme" molecule nestled within the curves of the chain. All proteins, not just hemoglobin, contain such polypeptide chains (see structure 3 for a schematic formula),



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which are assembled in turn by condensation of the building block amino acids, shown in structure 4. These come in about 20 varieties, distinguished by their "side chains" (R, in structures 3 and 4).

A typical protein, the hemoglobin β -chain is made up of 146 amino acid links. Here is richness, reaching out to us! Think how many 146-link chain molecules there *could* be, given the freedom to choose the side chains in 20 possible ways. The incredible range of



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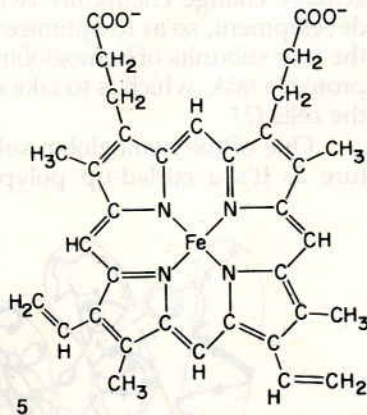
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chemical structure and function that we see in those tiny molecular factories, enzymes, or in other proteins, derives from that variety. The side chains are not adornment, they make for function.

The protein folds on itself, the diversity of the side chains provides opportunity, the particular amino acid sequence enforces a specific geometry and function. Extended pieces of hemoglobin curl in helical sections, clearly visible in 2. At other places the chain kinks, not at random, but preferentially at one amino acid, called proline. The globular tumble of helical sections, nothing simple, but functionally significant, emerges.

Significant in what way? To hold the molecular piece that binds the oxygen, and to change, in a certain way, once the oxygen is bound. The O_2 winds its way into a just-right pocket in the protein and binds to the flat, disk-shaped heme molecule. The structure of heme is shown in 5. The oxygen binds, end-on, to the iron at the center of the heme. As it does, the iron changes its position a little, the heme flexes, and the surrounding protein moves. In a cascade of well-engineered molecular motions the oxygenation of one subunit is communicated to another, rendering that one more susceptible to taking up still another O_2 (1).

That bizarre sculpted folding has a purpose, in the structure and function of a molecule critical to life. All of a sudden we see it in its dazzling beauty. So much so that it cries out, "I've been designed"; "For this task I'm the best that can be." Or, if you're so inclined, it testifies to a Designer.



Beautiful? Certainly. The best, fashioned to a plan? Hardly. It only takes a moment to get us back to earth, a few bubbles of CO, the lethal, odorless product of incomplete combustion of fires and car exhaust. Carbon monoxide fits into the same wondrously designed protein pocket, and it binds to hemoglobin several hundred times better than oxygen.

So much for the best of all possible worlds and the evolutionary Plan. As F. Monod has written, Nature is a tinkerer (2). It has a wonderful mechanism for exploring chance variation, and, until we came along, much time on its hands. While it was banging hemoglobin into shape there wasn't much CO around. So it didn't "worry" about it.

Actually the story of molecular evolution is more complicated, more wondrous still. It turns out that there is always a bit of CO around in the body, a natural product of cellular processes. Heme, free of its protein, binds CO much better than hemoglobin. So the protein around the heme apparently evolved to *discourage* CO bonding a little. Not enough to take care of massive doses of external CO, just enough to allow the protein to take up sufficient O_2 even in the presence of naturally produced CO (1).

This series began by asking what makes a molecule beautiful. The first marginalium focused on immediately appealing simplicity and symmetry. The second said that it may be the drama of a high pass, the coming from where one was to where one wants to be, that can confer beauty. In hemoglobin the aesthetic imperative is crafty, enabling complexity, the richness of the possible world of every bend, fold, or twist. There is more.

References

1. For more information on hemoglobin, see R. E. Dickerson and I. Geis, 1983, *Hemoglobin*, Benjamin-Cummings; L. Stryer, 1988, *Biochemistry*, 3rd ed., W. H. Freeman. I owe much to these books and to the original work of Max Perutz.
2. F. Monod. 1977. *Science* 196:1161.
3. Structure 1 is reproduced with permission of Irving Geis; structure 2, courtesy of Max Perutz. All other figures are by the author.

