4.4: Dioxygen Carriers and Bioinorganic Chemistry

To the student the subject of biological and synthetic molecular-oxygen carriers offers unusual insights into how bioinorganic chemistry works and what its aims and uses are. First, consider another bioinorganic problem, that of the nature of the blue copper proteins. When bioinorganic chemists entered the scene, the nature, function, and structure of copper blues were largely unknown. To take a Cu(lI) solution, add a nitrogen base, and obtain a spectrum that "resembled" that of the proteins was not a contribution to the solution of the biological puzzle, although it was the activity of some bioinorganic chemists. The difficulty here was that too little was known about the protein system. But the challenge did not diminish once the structure of a blue copper protein was known, for that structure allowed definition of the active site, one that contained (in the oxidized form) a Cu(lI) center surrounded by two imidazole, one cysteine, and one methionine residue. Now the bioinorganic chemist was faced with the formidable (and still incompletely solved) synthetic problem of designing a tetradentate ligand that (i) would present two N atoms, one thiolate S atom, and one thioether SR_2 group to a Cu(lI) center and (ii) would remain intact if the Cu(lI) center were reduced to Cu(I). If we could prepare such complexes, we would be in a position to examine in some detail the effects on physical properties, such as redox potentials or spectra, of chemical substitution. In other words, we could learn about structure-function relationships in the copper blues. But the risks involved included the possibility that the specially designed ligand, even if it could be synthesized, might not bind Cu(Il) or Cu(l) in the desired manner.

Contrast such a situation with that of the oxygen carriers. Hemoglobin[208] and myoglobin[209] were the first crystallized proteins to have their structures determined. Their functions were well-known. They had been studied by a wide variety of physical techniques, in part because their structures were known, and even before that because of their role in human health. The central tetradentate ligand of the heme group, namely, the porphyrin, was well-defined and much porphyrin chemistry was known. The structural puzzles that intrigued chemists and biologists were not answered in the initial, early structural studies of the proteins; for example, how is O_2 bound and why is CO not bound more firmly? Model chemistry in this area looked as though it would be easy; after all, the metalloporphyrins were readily synthesized, and all one needed was an axial base, some spectroscopic equipment, perhaps some single crystals, and then the structure-function relationships in the biological oxygen carriers would be understood! Indeed, as often happens, the situation was more complicated than it appeared. The irreversible oxidation of iron porphyrins was a major stumbling block to simple modeling. This obstacle was overcome in solution studies through the use of low temperatures and aprotic solvents; some very useful measurements of O_2 and CO binding were made on model systems in such solutions. But in order to isolate oxygen complexes so that they could be studied by diffraction methods, another approach, that of synthesizing elaborated porphyrins, such as those in Figure 4.23, was necessary. This task entailed difficult organic chemistry that ultimately led to successful models that proved to be stable under ambient conditions. From such models we have learned much about local stereochemistry and, through spectroscopic congruence, about the biological systems. In short, bioinorganic chemistry has made a major contribution to the understanding of biological molecular-oxygen carriers, primarily because knowledge of the biological systems was advanced, the systems "self-assemble," and the goals of the studies were well-defined.

The complementarity of the two approaches continues. There are several unanswered questions, including:

1. What is the structural basis for cooperativity? Indeed, is there a structural basis at all, or is the ~6 kcallmol that represents the effect spread over many interactions, so that there is no obvious structural effect to be modeled?
2. Can one design a model where hydrogen bonding to the bound O_2 molecule can be demonstrated by diffraction experiments? How will the oxygen uptake properties depend on the strength of the hydrogen bond?
3. Can one design a "high-affinity" model system? What will this tell us about the largely ill-defined high-affinity systems that are found in Nature?

There remain many intriguing questions about biological molecular-oxygen carriers, questions that will be answered by complementary studies on the biological and model systems. To make and study such model systems is an example of the challenge and excitement of this aspect of bioinorganic chemistry.