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Bioinorganic Chemistry

Biological *inorganic* chemistry is decidedly not an oxymoron. Metal ions are acknowledged to be essential to the function and structure of a large variety of proteins, and to be important participants in biological processes that involve nucleic acids.

In the past three decades bioinorganic chemistry (the study of metals in biological systems) has been focused primarily on metalloenzymes, electron transfer proteins, and proteins that transport small molecules. Two main branches of bioinorganic chemistry were followed: the study of the proteins themselves, and the design and synthesis of model metal complexes that were inspired by the natural systems. The metal site in the protein was the obvious locus of interest, because it was recognized that this was the site of biological activity. Oxygen binds to the iron in hemoglobin; copper changes oxidation state in the blue copper proteins that transfer electrons; and molybdenum is at the center of the chemistry of xanthine oxidase. Bioinorganic chemists became adept at applying sophisticated spectroscopic methods to metalloproteins to determine structural and electronic details of these metal sites. Often an x-ray crystal structure of the metalloprotein served as a final confirmation of the deductions first made from spectroscopy.

In recent years new tools and preoccupations have come to the bioinorganic chemist. In this short essay it is my purpose to highlight a few of these new frontiers in the study of metals in biology, and perhaps attract the attention of the reader to the *Prospects* in this and other recent issues of the Journal that delve more deeply into examples of future directions in bioinorganic chemistry.

The spectacular advances in molecular biology and genetic engineering have not escaped the attention of the inorganic chemist. The ability to make directed changes in the amino acid sequence of a protein has provided an alternative to organic synthesis for making new ligands for metals. The role of a particular ligand in the chemistry of a metal in a protein can now be addressed by changing the identity of that amino acid. Subtle questions about the path an electron takes in going from one metal in a protein to another are now open to investigation by changing selected amino acids.

Perhaps less generally appreciated is how bioinorganic chemistry is making substantial contributions to molecular biology. One way involves the harnessing of the chemistry of metal complexes to provide tools for cleaving, footprinting, and otherwise manipulating nucleic acids and their complexes with proteins. Metal complexes can be designed to incorporate ligands that confer affinity for particular nucleic acid sequences, producing synthetic restriction enzymes with arbitrarily high degrees of specificity. Another strategy is to employ a metal complex that cleaves nucleic acids with extraordinary *lack* of specificity, for use in making images of the structure of the DNA or RNA molecule. Such metal complexes are now standard equipment for the study of gene regulation systems, and will likely find use in the Human Genome Project as precise scalpels for dissecting the genome into manageable pieces.

A second area of overlap between molecular biology and inorganic chemistry is the involvement of metals in gene regulation. A well known example is the protein structural motif called the zinc finger that is the key element in nucleic acid sequence recognition of an ever expanding class of transcription factors. Another type of zinc finger, the retroviral finger, is the subject of the *Prospect* by Summers. The ubiquity of the zinc finger and its variants makes the connection between inorganic chemistry and genetics a surprisingly direct one.

An obvious corollary to the occurrence of metalloproteins is the fact that organisms must have ways of acquiring and using certain metals, while discriminating against other metals that are harmful. Study of such systems is experiencing rapid expansion. The metallothioneins were the first class of proteins recognized to function in the sequestration of metal ions. Mehra and Winge, in their *Prospect,* discuss the variety of

systems that exist in fungi to protect the cell from toxic metals, and to maintain the concentrations of required metals. One system that was recently uncovered is remarkable: the use of small peptides to coat the surface of cadmium sulfide which is to be excreted from the cell. The metal particles produced in this way are of sharply defined size, which was detected as a result of their unusual optical properties. The particles show the characteristic electronic spectrum of a quantum crystallite, which had heretofore been observed in inorganic semiconductors. The amount of sulfide in the particle, and the size of the peptide, govern the size of the particle formed. One can speculate that someday we will be using yeast to produce precisely tailored nonlinear optical devices.

A third connection between inorganic chemistry and molecular biology is the ability of cells to sense the presence, identity, and concentration of metal ions in the environment, and to adjust the synthesis of proteins in response to these signals. Some of these metals, like mercury, are noxious. To eliminate mercury from the surroundings, bacteria first transport mercury compounds *into* the cell, and then subject these compounds to a series of enzyme-catalyzed reactions to ultimately produce mercury(0), which is volatile and much less toxic. In the presence of mercury, the metalloregulatory protein MerR activates transcription of the genes which code for the detoxification enzymes. One could imagine adapting the principle of coupling a metal sensor to gene expression in designing new biologically based devices that sense and respond to metals in the environment.

Another system in which the link between the regulator of gene expression and the metal-sequestering protein is becoming clear is yeast metallothionein. This protein binds eight copper(I) ions in a cluster in which the coppers are bridged by thiolate sulfurs from cysteines. The regulator of yeast metallothionein synthesis, the protein CUP2, is activated for DNA binding by copper(I). Recent work has shown that the CUP2 protein also binds several copper(I) ions in a cysteine thiolate-bridged cluster. The DNA-binding domain of CUP2 occurs in the same part of the protein as the copper cluster. How this regulatory system developed is an intriguing question.

I have tried here to point out a few of the newer areas of bioinorganic chemistry which connect most directly with molecular biology. These experimental systems and approaches are giving us new insight into how nature takes advantage of the diverse chemistry of metals, and are influencing the development of both inorganic chemistry and molecular biology.

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