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Preface: Biomimetic Inorganic Chemistry

In 1996 we served as guest editors for the *Chemical Reviews* thematic issue on "Bioinorganic Enzymology" (Vol. 96, No. 11), which provided an introduction to metal sites in biology and critical reviews of over 20 types of metallobiomolecules by internationally recognized experts. The striking advances in the elucidation of structure and function in numerous native metallobiomolecular systems arise from the application of various methodologies, including inter alia protein crystallography, spectroscopic methods, site-directed mutagenesis, mechanistic enzymology, and state-of-the-art theoretical calculations. An additional significant factor has been biomimetic inorganic chemistry, which largely involves the synthesis and detailed structural and electronic characterization of model molecules—synthetic analogues—that approach or achieve one or more significant properties of a protein active site. Consequently, we envisaged a second thematic issue in bioinorganic chemistry, "Biomimetic Inorganic Chemistry", intended as a companion, albeit of more recent origin, to "Bioinorganic Enzymology". In proceeding with this issue, we were cognizant of the many review and other summary articles on various aspects of the subject that, however, had never been treated in a single-volume source devoted entirely to this domain of bioinorganic chemistry. "Biomimetic Inorganic Chemistry" is intended to redress, at least in part, this situation by disclosing in summary form many of the impressive advances brought about by perspicacious applications of principles and information databases of inorganic chemistry to problems of metal site elucidation. Coverage is extensive but not exhaustive. Proteins and enzymes per se are not considered at length; the emphasis is on synthetic systems.

Early in biomimetic inorganic chemistry, the operational principle of the synthetic analogue approach was set out as follows: "When reduced to practice, this approach necessitates the synthesis of relatively low molecular weight complexes which, ideally, are obtainable in crystalline form and approach or duplicate the biological unit in terms of composition, ligand types, structure, and oxidation level(s). Such models, or synthetic analogues, of course, cannot simulate the environmental effects of and whatever structural constraints are imposed by the normal protein conformation. Indeed, this may be considered an advantage of synthetic analogues, for, being unencumbered by the protein, they should reflect the intrinsic properties of the coordination unit unmodified by the protein milieu." (Holm, R. H.; Ibers, J. A. In *Iron−Sulfur Proteins*; Lovenberg, W., Ed.; Academic Press: New York, 1977; Vol. III, Chapter 7. Ibers, J. A.; Holm, R. H. *Science* **1980**, *209*, 223−235.) The approach is summarized in Figure 1. One of four types of metal sites is subjected to investigation by the indicated methods, leading to the formulation or deduction of a site analogue, which becomes a goal of synthesis. An appropriate analogue simulates or achieves the coordination sphere composition and stereochemistry of the native site. A *structural* analogue allows deduction of site characteristics common to the site and itself by possessing sufficiently high adherence to the indicated features. A *functional* analogue sustains a stoichiometric, or better, a catalytic reaction which transforms substrate to product as does the enzyme, albeit at a different rate and not necessarily with the natural stereochemical outcome. A functional model is not ineluctably a structural model, but, ideally, a high-fidelity structural model is a functional model. As implied in the figure, construction of an analogue complex can be an iterative process, until the desired level of similarity with the site is achieved. A mechanism of enzyme action can only be won from the enzyme itself. Functional models can disclose what is possible, in this way delimiting reaction pathways. At about the same time, a distinction had been drawn between corroborative and speculative models (Hill, H. A. O. *Chem. Br.* **1976**, *12*, 119−123), under which structural analogues are corroborative and all other models are speculative in the current use of the terms. Given the development of spectroscopic and magnetic methods for incisive interrogation of metal site structures and the dazzling progress in protein crystallography, the pursuit of structural analogues is now of lower priority than heretofore. Functional analogues and their reaction systems pose a greater contemporary challenge, when it is recalled that the chemist is yet to accomplish such fundamental transformations as $N_2 \rightarrow NH_3$, $CH_4 \rightarrow CH_3OH$, and $H_2O \rightarrow O_2$ under ambient conditions with molecular apparatus that bears a credible resemblance to the native catalytic center.

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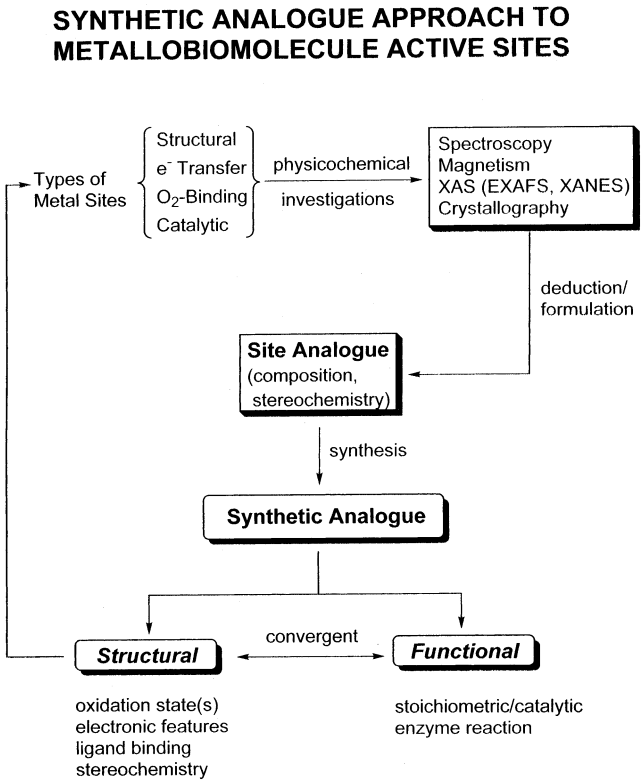

Figure 1.

Site analogues have contributed significantly to physicochemical methodology by facilitating correlation of composition and structure to spectroscopic and magnetic observables. Among frequently applied methods, paramagnetic resonance, X-ray absorption, magnetic circular dichroism, and Mössbauer spectroscopies in particular have profited, such that empirical correlations with structure can now often be drawn and experimental insight into electronic structure obtained. Because of their relative simplicity, synthetic analogues provide suitable molecular vehicles for theoretical calculations of geometry and electronic structure. Indeed, the detailed correlation of electronic with geometric structure can provide fundamental insight into reactivity. It can be safely anticipated that these activities will expand in scope, being an integral part of protein site elucidation at increasingly higher resolution.

This issue contains contributions which encompass most of the current activities in biomimetic inorganic chemistry. The first section is comprised of conceptual subjects useful for a general knowledge of the field and introductory to certain articles that follow. The topics covered include ligand design, small-molecule binding and activation, protein ligand and electronic structure contributions to function, and the biosynthesis of metalloenzyme sites. The second section describes iron−sulfur and heme systems, two of the earliest types of active sites addressed by the synthetic analogue approach. Heme and copper electron-transfer species are described in the third section which, together with the account of iron−sulfur analogues, affords a broad prospectus of synthetic redox models. Non-redox sites are the subjects of the following section, which among other information makes evident the diverse functions of zinc in native sites and their analogues. The final section delineates a variety of analogue systems, containing manganese, iron, copper, molybdenum, and tungsten, in which oxidation state changes are requisite to function.

It is perhaps axiomatic that the general problem of site elucidation in biomolecules has injected renewed vigor and new science into the otherwise mature subject of coordination chemistry. Certainly, the synthetic analogue approach and all research associated therewith has had the profoundly positive function of bringing together the seemingly disparate subjects of inorganic chemistry and biochemistry into an enterprise of incontestable success. Indeed, this approach has produced contributions to inorganic chemistry—both synthetic and physicochemical—that would not have been achieved without the imperative of protein site elucidation. Beyond site analogue synthesis lies the vastly more difficult goal of defining the biosynthetic pathways to metal sites. At present, there is no general agreement on the pathway leading to any metal site—mononuclear or polynuclear—in biology. This is clearly a research area for both the present and the future. Toward that end, we have included two articles on the formation of metal sites in proteins.

Our intent in formulating this issue is the same as with “Bioinorganic Enzymology”, viz., “to produce a unique resource in the literature of bioinorganic chemistry that should find wide application in both teaching and research.” We trust that the outstanding contributions of our authors will achieve that goal.

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