Reflections

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Bioinorganic Chemistry: A New Field or Discipline?
Words, Meanings, and Reality

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To the uninitiated it may seem that bioinorganic chemistry is a new field although, on the other hand, reports on metals bound to proteins or enzymes date way back into the 19th century and may probably be found in earlier centuries if we replace the terms “proteins” and “enzymes” with “animal or plant tissues.” Potassium ferricyanide was prepared from blood, McMunn described what he called histohematin (now cytochromes) in tissues, Hoppe-Seyler made spectroscopic investigations on hemoglobin, G. Bertrand worked on what he called an oxidase from plant tissues, which he named laccase; he recognized that it was a metal protein and even proposed that the metal was a “coenzyme,” with which he may have been the first to propose the idea of a catalytic metal protein. Spitzer drew attention to the involvement of iron bound to protein or nucleic acid nitrogen in tissue respiration, Warburg and Keilin and their collaborators described polyphenol oxidase, a copper protein, and ferritin was described as an iron storage protein. In the 1930s Keilin and Hartree found copper in cytochrome c oxidase. By the middle of that century, zinc and molybdenum were discovered in enzymes, and non-heme iron was recognized as a necessary component in mitochondrial preparations that are active in substrate oxidation. Thus there is a long trail of discovery of metals in proteins or in other components of living creatures, metals that were required for their structure or function, although details of what the functions implied were initially missing and hard to come by.

At this point it seems worthwhile to define what is actually meant by the terms “inorganic” and “organic” in connection with our present theme or in the context of chemistry as a scientific discipline. Although the term “organic” will for many evoke the connotation that it has to do with life (the counterpart “inorganic” then referring to lifeless matter) in chemistry “organic” has come to mean merely pertaining to the chemistry of carbon compounds. Inorganic, on the other hand, is generally perceived as referring to the chemistry of metal compounds, whereas other non-carbon non-metal elements are not specifically excluded. Because metals of many kinds are found in living matter, e.g. sodium, potassium, and calcium in considerable quantities, and because all metals are subjects of inorganic chemistry, there must then, by definition, always have been an inorganic component of biochemistry. Thus, according to this reasoning, “inorganic biochemistry” and “bioinorganic chemistry” certainly are no new subjects; rather they may only be new words.

The Hassle About an Acceptable Name for the Field of Our Endeavors

Nevertheless, the terms obviously had to be justified. The editor of the first volume of Inorganic Biochemistry, Gunter L. Eichhorn, says in 1974 in the preface to the book: “Until recently, the title Inorganic Biochemistry would have appeared paradoxical to most, and it may even now appear so to many, because biochemistry sounds organic”; and this was about 30 years ago! As I have witnessed this period and also some decades before that, I will briefly describe my experiences. When I was a student in the 1930s, what Eichhorn calls paradoxical
would doubtless have been considered outright ridiculous, certainly in Germany. When I studied chemistry there it was the great period of the development of organic chemistry, synthetic and analytical, of natural products chemistry, the time of the discovery of “factors” (some of them later called vitamins), and I heard it said often in chemical circles that biochemistry was in essence nothing but organic chemistry. Actually even the word biochemistry was frowned upon, as it had acquired some taste of quackery through the use of the word by some eager promoters of what may today be called “alternative medicine.” The term “biochemistry,” as far as I know, was in some sense generally established when Sir Frederic Gowland Hopkins named his department in Cambridge by that title in 1914, although the actual building that had this name was only occupied in 1924. In Germany this subject, “biochemistry,” was not taught within a faculty of the Naturwissenschaften but had the designation “physiological chemistry” and was only accessible to medical students, and not to chemistry students, as I was. When I inquired whether I might get an exceptional permission, I was advised by friends in the faculty that physiological chemistry was actually largely a “Gemurkse,” which means a messy business, going under the slogan, “Tierchemie ist Schmierchemie,” and I would do better to concentrate on chemistry. It was only Felix Hoppe-Seyler who was influential enough to be allowed to establish an Institute of Applied Chemistry within the Faculty of Medicine at Tübingen, which then was soon renamed physiological chemistry and was assigned to a separate Faculty of Science. As such it has survived Hoppe-Seyler for many years as well as his journal, which now goes under the title “Biological Chemistry.” Feodor Lynen was the first to have a Max-Planck Institute for Biochemistry in Munich in 1954, after which biochemistry departments then started sprouting up elsewhere. However, even in the United States the departments of physiological chemistry only slowly disappeared.

**Development of the Field**

It is true that the major polymers in living matter are carbon compounds, whereas the transition metals are only present in traces (except *e.g.* for iron in the globins or in ferritin); however, there is no life without transition metals, which are required as catalysts. From what was said above, there was a gap of about 30 years between the 1940s and the 1970s when there must have been a great step forward in appreciating the significance of transition metals in biology. I experienced the transition during that period most vividly in two typical examples. I had the fortune to meet Edward Hartree during a visit to Oxford and I asked him, of course, about his work with Keilin in the 1930s on copper in cytochrome c oxidase, which had also been the object of my studies (1). He said that they were absolutely sure copper was there and was bound tightly to the protein; they determined how much was there in comparison to heme, but after that what else could they do? As spectroscopy was not applicable to copper,¹ they had no method to tell them about its function. Thus Keilin decided not to pursue this aspect further. I may call this the “Keilin-Hartree dilemma”; almost all of metal biochemistry suffered from this shortcoming. The second example came with my good fortune to be invited to all seven sessions in the series on copper proteins, usually referred to as the “Manziana Conferences,” initiated and perpetuated by Bruno Mondovi of Rome, Jack Peisach of New York, and Bo Malmström of Göteborg and their colleagues until 1995 (3). The 1972 to 1976 meetings still were under the spell of the Keilin-Hartree dilemma. The aspect of function largely eluded us. In the copper field the advent of EPR clearly broke the ice. With this technique (and thereafter with other spectroscopies) much more sense could be made of the metal-to-protein stoichiometry and the electronic absorption spectra that had been available so far. Now, all of a sudden, those designations, such as CuA and CuB in cytochrome oxidase or Type I, II, or III copper in ceruloplasmin assumed distinct character. Things were not as simple with iron, because there a new type of iron protein had to be discovered, the iron-sulfur (Fe-S) proteins. The discovery predates somewhat the developments just presented, but the more detailed exploration of this new field approximately also falls into the same period. The coordination chemistry of copper is relatively simple as compared with that of iron, and it eventually took several different types of spectroscopies such as Mössbauer (MB), electron nuclear double resonance (ENDOR), x-ray absorption spectroscopy (XAS), extended x-ray absorption fine structure (EXAFS), magnetic circular dichroism (MCD), and NMR, which were just developed in those years to a state such

¹The broad 830 nm absorption of cytochrome c oxidase was only discovered in 1961 (2) and was probably not observable with Keilin’s microspectroscope.
that it became feasible to apply them to biological material with relatively low concentrations of the target structures and with limited stability.

**Approach between Disciplines**

In those copper protein meetings it was a most stimulating get together of groups that had barely talked to each other before: the chemical physicists that were trained in ligand field theory and were on speaking terms with pioneers such as Carl Ballhausen (4) and on the other side us, the enzyme chemists, used to getting our hands dirty with awkward messes of animal, plant, or bacterial origin, from which our objects had to be purified. We could not understand our data without the wisdom of the spectroscopists, and they were anxious to get their minds on the challenging and fascinating problems in metal coordination that nature had to offer. This fortunate mutual approach between these disciplines (the coordination chemists, the spectroscopists or chemical physicists, and the biochemists) took place in that 10–20-year span starting around the 1970s. There followed a period of intensive research on the functions of these proteins, and, no wonder, enzymes played a dominant role in this as compared with other metal proteins that serve other roles with the result that biological inorganic chemistry was often identified with the biochemistry of metal enzymes. This, of course, led to some resentment (5) in the ranks of those interested in metal proteins with other functions such as transport, as e.g. hemocyanins, or metals involved in geological processes or stabilization of biological structure (6). In this period as more structural and spectroscopic data became known, chemists started taking considerable interest in complex biological structures such as hemocyanin for instance or polyphenol oxidases, exploring their copper-oxygen chemistry. This then led to similar investigations on iron-oxo-systems, which eventually opened up the whole new field of Fe-oxo-proteins (7). A strong relationship of the chemistry of the metal-oxygen reactions to those involving free radical mechanisms soon became apparent (8). A similar relationship was found in the Fe-S protein field (9).

During that period, starting with the 1970s, the flood of volumes on inorganic biochemistry, bioinorganic chemistry, metals in biological systems or whatever they were called started pouring out and there soon was also a *Journal of Inorganic Biochemistry*, starting in 1972, joined more recently, in 1996, by the *Journal of Biological Inorganic Chemistry*. A particularly good example of the rapid progress in that period is the role that x-ray crystallography played in the meeting series on copper proteins that we have followed above. At the 1979 meeting we all listened with awe to the only crystallographer present, Hans Freeman of Sydney, who showed the structure of poplar plastocyanin, one of the smallest blue copper proteins containing a single copper ion. The data on the immediate environment of the copper confirmed the conclusions drawn by the spectroscopists. At the 1985 meeting, Freeman presented further detail such as structures of reduced plastocyanin and of plastocyanins from different plant sources. Then, at the 1990 meeting, there were five crystallographers in the audience who presented three new structures, namely those of the considerably more complicated multicopper enzyme ascorbate oxidase, bacterial nitrite reductase, and galactose oxidase. Finally, at the 1995 meeting there were presented such impressive accomplishments as the structure of beef heart cytochrome *c* oxidase, of human ceruloplasmin, and amine oxidase of *Escherichia coli*. Of course, it must also be mentioned that it was not only the development of crystallographic methods and of more efficient light sources, it was also the progress in the preparation of proteins in high purity and quantity and the possibility of introducing new groups or exchanging amino acids (all this via molecular genetic procedures) that contributed to the remarkable advances. An example here is the preparation and structure determination of the CuA module of cytochrome *c* oxidase through such approaches (10).

**Development and Applications of Spectroscopies**

Similar advances were made in other areas using spectroscopy with radiation all over the range of energies from γ rays to radio frequencies. As my personal experience was mainly with spectroscopy, I may be forgiven if, among examples, I will mainly draw on those that I was directly involved in or that are in my field of interest.

Before we leave the realm of high energy radiation, we must mention the relatively recent development of x-ray absorption spectroscopy, which became feasible when sufficiently powerful beam lines became more generally available at the reactor sites. Various features of these spectra have attracted attention: XANES, x-ray absorption near edge structure and more recently also pre-edge structure, and EXAFS, from which distances to neighboring nuclei can
be determined or estimated, or certain types of nuclei can be excluded, depending on the quality of the spectra. EXAFS, for instance, has played a decisive role in the discovery and structure determination of the 3Fe cluster of Fe-S proteins (11), and particular attention has been paid recently to the pre-edge features in XANES (12), as it can furnish quantitative information on the degree of covalency of metal-ligand bonds (13). This has been successfully accomplished for Fe-S proteins and has given new insights into the electronic structure of Fe-S proteins.

After this consideration of x-ray spectroscopy in connection with the discussion of the development of x-ray diffraction and crystallography, I will now briefly mention examples of the successful use of spectroscopy at other frequencies, starting from the low energy end. After a slow start, as far as application to proteins goes, NMR has undergone a very impressive development after the introduction of two- and higher-dimensional techniques, in combination with elaborate pulsing techniques and Fourier transform analysis, particularly also by the use of isotopes of a nuclear spin different from that of the naturally occurring atoms, such as $^2$H, $^{15}$N, $^{13}$C, $^{17}$O, and $^{57}$Fe. For use with metal proteins the exploration of “paramagnetic NMR,” that is NMR on paramagnetic substances, has had great success (14) and has now become a routine procedure and the method of choice for answering specific questions. When the sequence of a protein is known and preferably also the three-dimensional structure around the metal site, the unpaired spin density on specific atoms can be determined. It has even been possible to observe the migration of spin density between sites (15). Moving on to the millimeter and centimeter range, EPR has been mentioned above as one of the first decisive tools in approaching the aspects of the function of copper proteins. It has played the decisive role in the discovery of Fe-S proteins and the exploration of the electronic structure and other properties of these proteins (16). The hybrid methods such as ENDOR and ESEEM or optical detection of magnetic resonance are making use of the relatively slow relaxation of electron spins, so that saturation with incident radiation (microwaves in EPR) may occur, which can then be relieved through energy transfer by exciting neighboring atoms with other frequencies (radiowaves in ENDOR or ESEEM). Again, by the use of isotopes of different nuclear spin, very specific information can be obtained on the kind of neighboring atoms, on interatomic distances, and even on the mutual orientation of interacting species. Thus, for instance, we have been able to determine that in the 4Fe cluster of aconitase the specific iron atom (Fe$_a$) that has no cysteine ligand has a hydroxyl bound in the absence of substrate, which becomes protonated on addition of substrate to the enzyme (17). We could also show with this enzyme and with substrate labeled with $^{17}$O or $^{13}$C in different positions that the $\alpha$-hydroxyl of isocitrate and the $\beta$-carboxyl of citrate bind to Fe$_a$ (18).

The ESEEM method is applicable for the detection of more distant neighboring atoms. Again pulse and Fourier transform techniques are required in this instance. An example of the combined use of both ENDOR and electron spin echo envelope modulation (ESEEM) is the identification of the sequence of radicals formed in the conversion of $\alpha$-lysine to $\beta$-lysine by 2,3-lysine aminomutase (19). A condition necessary for all the work mentioned here is that a measurable EPR signal can be observed. In the cases cited it was the EPR signal of a reduced [4Fe-4S] cluster or of a free radical.

Resonance Raman (RR) spectroscopy is based on the enhancement of ordinarily observed Raman lines by a transition metal ion present in a molecule. This technique is therefore able to provide specific information concerning the ligands of the metal center and their position with respect to the metal. Again the use of specific isotopes of different molecular mass, such as $^2$H, $^{12}$C, $^{15}$N, $^{18}$O, $^{34}$S, and $^{54}$Fe is very helpful and decisive. For instance it has been argued early on the basis of RR (20) that the newly discovered 3Fe cluster could not have the [3Fe-3S] benzene-like ring structure first assumed but must have a structure closely related to the 4Fe cluster, as was shown by EXAFS and chemical analysis (11).

An impressive example of the analytical power of infrared spectroscopy when applied to proteins was furnished when it was discovered that hydrogenases have CO and CN ligands bound to their 2Fe cluster (21). It has also been possible to detect subtle changes in substrates by infrared (22).

Among the methods relying on magnetism the simplest may seem to be direct measurement of magnetic susceptibility. However, it is technically quite difficult to achieve the desired sensitivity. MCD and more so yet VTMCD, namely variable temperature MCD, has taken a prominent position for discriminating different components in e.g. a protein containing a
number of different heme groups. This technique furnished the clue in the determination of the different Fe-S clusters in succinate dehydrogenase (23). It has also been useful in the determination of the spin state of a substance when EPR is ambiguous. An example here is the determination of the spin state of the reduced [3Fe–4S]$^0$ cluster (24).

At about the middle of the 1960s I was invited to give a lecture at the Max-Planck Institute for Medical Research in Heidelberg. It was there in the Physics Division where Rudolf Mössbauer as a graduate student had discovered the effect now bearing his name. Richard Kuhn, the director of the Institute, introduced me in his unmistakable Viennese accent and his at such occasions usually somewhat pompous way: “Warburg has given us, who are interested in biological oxidations, the heme iron; you have now given us the non-heme iron” (referring to my work on Fe-S proteins). There happened to be in the audience Ekkehard Fluck, a young “Dozent” at the university, who was one of the early explorers of the MB effect in chemistry; he jumped up and commented that I should use MB to find out what these non-heme iron compounds were. When I asked how much iron (and that was to be $^{57}$Fe) and in what volume was needed for this, his answer made it clear that this was definitely not the method to use. Nevertheless, it was not even 10 years before my friend Richard H. Sands and others (25) indeed successfully used MB on purified ferredoxins of relatively low molecular weight (though not on mitochondria yet), but it was then 20–30 years later that MB could be applied with success to identify iron in whole bacterial cells (26) and that specific compounds could be recognized and quantitatively determined (27). There was an effect of mutual stimulation, similar to what I described above, when the first EPR data appeared but, of course, at a much more advanced level. Although we biochemists learned something about our proteins and enzymes, so did our challenge stimulate the spectroscopists to optimize the conditions and particularly also to dig out from the literature applicable theoretical concepts that could explain the observations, extend them, or even develop new ones of their own. This led to a closer approach between theoreticians and us at the bench, which turned out to be very

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**Fig. 1.** Tentative view of adjacent and overlapping fields seen from the horizon of a biochemist.
productive. Thus, for instance, the concept of “spin-dependent delocalization (SDD)” (also called “double exchange” or “resonance”) was so clearly demonstrated, first by the reduced 3Fe cluster [3Fe-4S]\(^{2-}\) (28) and then also for the 4Fe cluster that it is now one of the main features considered important for understanding the electronic structure and reactivity of these clusters. The concept was, of course, not new but was hidden in mathematical equations and under designations that are not easily understood. It is the merit of the colleagues whose names appear in the given references that has brought these concepts to our attention in terms understandable to us (29). The electronic structure of the clusters with more than two iron atoms can now be understood in terms of these interacting forces: 1) SDD, which favors a parallel spin orientation and thus formation of mixed valence (MV) pairs with one shared electron; 2) J, which favors antiparallel coupling as in the 2Fe cluster; and 3) what is called vibronic coupling, which has to do with the symmetry of the surrounding protein environment (e.g. a non-Cys ligand) and may favor one or the other spin arrangement. Cases for this are documented, with one of the simplest and most impressive examples being the 2Fe ferredoxin from a mutant of *Clostridium pasteurianum* in which one serine replaces one of the cysteine ligands of the native structure (30).

All the in some way related areas of endeavor mentioned above have, in their own way, become specialty fields, encompassing already a voluminous literature. Thus, definitions of fields are becoming blurred, and we must recognize the fallacy of trying to categorize with any rigidity while still preserving real meaning. Fig. 1 may represent a possible way to depict the situation, as seen from the horizon of a biochemist. The fact that biochemistry occupies a space productive. Thus, for instance, the concept of “spin-dependent delocalization (SDD)” (also called “double exchange” or “resonance”) was so clearly demonstrated, first by the reduced 3Fe cluster [3Fe-4S]\(^{2-}\) (28) and then also for the 4Fe cluster that it is now one of the main features considered important for understanding the electronic structure and reactivity of these clusters. The concept was, of course, not new but was hidden in mathematical equations and under designations that are not easily understood. It is the merit of the colleagues whose names appear in the given references that has brought these concepts to our attention in terms understandable to us (29). The electronic structure of the clusters with more than two iron atoms can now be understood in terms of these interacting forces: 1) SDD, which favors a parallel spin orientation and thus formation of mixed valence (MV) pairs with one shared electron; 2) J, which favors antiparallel coupling as in the 2Fe cluster; and 3) what is called vibronic coupling, which has to do with the symmetry of the surrounding protein environment (e.g. a non-Cys ligand) and may favor one or the other spin arrangement. Cases for this are documented, with one of the simplest and most impressive examples being the 2Fe ferredoxin from a mutant of *Clostridium pasteurianum* in which one serine replaces one of the cysteine ligands of the native structure (30).

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