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Book review

Handbook of metalloproteins

Edited by A. Messerschmidt, R. Huber, T. Poulos and K. Wieghardt, John Wiley & Sons, New York, 2001, 2 volumes. ISBN 0-471 62743 7; £645

This two volume Handbook, published in 2001, is a marvellous collection of articles on metalloproteins. Mostly superbly illustrated, the articles concentrate on metalloproteins whose structures have been determined, though the aim of the handbook is to be more than just a 'coffee-table' compilation of pictures of protein structures; each article has sections dealing with biological function, occurrence, amino acid sequence, metal content, and spectroscopic properties, and many consider important mechanistic aspects of the proteins. In 1472 A4-sized pages some of the leading experts in the metalloprotein field describe the proteins they work with: 105 articles ranging in size from 7 to 23 pages each, every article with at least one colour figure, describing metalloproteins that contain iron, nickel, manganese, cobalt, molybdenum, tungsten, copper and vanadium. Wait, you may say, as I did since I started skimming the book first without reading the Preface, where are calcium and zinc? They may not be redox-active or coloured but surely they are important, and certainly there are large numbers of proteins containing them whose structures have been determined, biological functions mapped, and mechanisms of action delineated? But of course, the Editors will reply, having already pre-empted the question in their Preface: the plan is to publish additional volumes dedicated to these and other metal ions.

The first articles I read were on the heme-containing electron-transfer cytochromes *c* and the iron-storage bacterioferritin and ferritin. All are proteins I have worked on and know quite a bit about. So, how did the articles stack against what I thought they should be? On the whole, pretty well. The article by Banci and Assfalg on mitochondrial cytochrome *c* provides a well-balanced account of the X-ray and NMR structure studies of this class of protein from authors who have a natural preference for NMR spectroscopy over X-ray crystallography. All the key X-ray papers I am aware of were mentioned, though the statement regarding comparison of structures of the ferric and ferrous forms of the proteins being 'more reliable in solution through NMR' (than X-ray crystallography) is not one I share. Both methods have their flaws, but there are no real competitors to these, and we have to make the most of what they give us. I may well have an unhealthy fixation on the burial of the heme propionate groups in these proteins—they are largely removed from bulk water, which is rare for acidic groups in proteins—and wanted to see what the latest ideas were concerning their ionisation properties, but the issue was not mentioned at all. The descriptions of functional aspects and physico-chemical properties were necessarily brief, given the size of the article, though many issues were covered. This review was followed by others on monoheme cytochromes: cytochrome c', cytochrome c_2, cytochrome c_{551}, cytochrome c_{553}, cytochrome c_6 and cytochrome c_4. All I found interesting and informative concerning the structural features, though I often thought that I would have emphasised different aspects of the structures; but a common fault, and a serious one in a Handbook that many might regard as a definitive compilation, is that there were frequent errors in referencing with key observations mis-referenced. This might well be a result of the authors wanting to reference recent publications without having a burdensome reference list but it does a disservice to those who will use the Handbook as their introduction to an area.

And so to ferritin—by Theil—and bacterioferritin—by Frolow and Kalb (Gilboa). Theil has been at the forefront of the ferritin field for many years, making major contributions ranging from details of the chemical mechanisms of Fe^{2+} oxidation and polynuclear Fe^{3+} cluster formation, to determination of protein structures (both amino acid sequences and atomic-resolution molecular structures) and biological function. I had great expectations of this article, and I was not disappointed. Though at 10 pages it was one of the smaller articles, Theil covered all the features I thought were significant and provided the kind of insights expected of someone who leads the field. The bacterioferritin article was also good, but only as far as the structure went. Doubtless this is a reflection of the authors approach: both are protein crystallographers whose papers focus on structure to the exclusion of most other matters. They were the first to describe the structure of bacterioferritin, though by the time they did so there were predicted structures available that turned out to be remarkably accurate. I was not surprised that the predicted structures were not mentioned—after all an experimental result is better than a guess, no matter how the guess is put together—but their authors (of whom I was one) went on to carry

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out mechanistic experiments based on the predicted models that complement the X-ray structure well and provide a chemical perspective on how these proteins can accommodate many thousands of Fe^{3+} ions per molecule in a mineral form. Unfortunately, this is one of the few articles I read that did not contain a mechanistic view of the protein. So focussed on structure is it that the authors have provided an in-depth account of their unpublished work alongside their published work. I found this extremely useful but surely this is not the purpose of an authoritative Handbook?

Moving away from my own direct interests, what else is there in these volumes? Too much for me to describe in a short review, though the following list of metalloproteins that catalyse chemical transformations of carbon-containing compounds, chosen because they might be of interest to readers of the *Journal of Organometallic Chemistry*, will give some idea of their scope: prostaglandin endoperoxide H2 synthases-1 and -2 (heme iron), naphthalene 1,2-dioxygenase (mononuclear non-heme iron), methane monooxygenase hydroxylase (dinuclear iron), urease (dinuclear nickel), arginase (dinuclear manganese), cobalamin-dependent methionine synthase (corrin cobalt), dimethylsulfoxide reductase (pterin molybdenum), galactose oxidase (copper) and vanadium haloperoxidases (vanadate)? You might ask, are all these articles focused on structure? The answer is no. All of the articles mentioned provide mechanistic descriptions, and in some cases with considerable detail. For example, Hausinger and Karplus provide a thorough review of urease that ends with a detailed description of the proposed mechanism by which urea is converted to ammonia and carbamate. Perhaps no reader of the *Journal of Organometallic Chemistry* will be convinced of the merits of a publication without knowing what is said about a metal–carbon bond, and so we should consider the articles on cobalamin-containing metalloproteins. There are three—glutamate mutase, methylmalonyl CoA mutase, and cobalamin-dependent methionine synthase—all with the same figure of coenzyme B_{12}, which I think should be reassuring. Each has a detailed figure illustrating the proposed reaction mechanism that shows the cobalt d_z^2 orbital! Perhaps you may feel, as I did, the Handbook is vindicated: a metal ion atomic orbital is described. It is rare that metal ion atomic orbitals and protein structures feature in the same article.

So do these volumes meet the ambitions of the Editors in providing an 'indispensable source of information'? The opinion of this reviewer is no. Wonderful though some of the articles are, and superbly illustrated as they all are, I do not believe that this is a definitive text. The aim was to include only metalloproteins that are structurally well-characterised, and then to build onto the structural descriptions a biological, chemical and mechanistic perspective. In some cases I doubt that the structures really are well defined, and even when they are, details of the chemistry of the proteins are lacking. Perhaps most telling is that the Protein Data Bank (PDB) allows metalloprotein structures to be viewed sitting at ones' desk. Downloading the coordinates allows us to look at the structures with whatever software tools we have, and even if we just use the default tools provided on the PDB web-site we can get as good, and often better, pictures than those provided in the Handbook. So I will continue to access the PDB for structural information that I require and look to the primary literature for chemical and mechanistic details of metalloprotein action. Perhaps this Handbook is a victim of the same kind of technical development that allowed it to be conceived. Advances in computational and physical methods contributed to a rapid increase in high-resolution protein structures, but similar advances allowed the structures to become widely accessible. By the time it went to press, the Handbook was probably out-of-date in some areas, and with the recent publication of completely new structures that merit extra chapters being added and refinement of some of the stories described in existing chapters, the second edition, were there to be one, would look different. However, my comments should not overly detract from a heroic effort that; like the protein structures themselves, mostly determined by X-ray crystallography, provides a snapshot of a rapidly moving field.

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