Biological inorganic chemists pay tribute to Ivano Bertini

Lucia Banci · Claudio Luchinat

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It is a real pleasure for us to introduce this special issue of JBIC dedicated to Ivano Bertini, which has been realized thanks to the initiative of the Editor-in-chief Larry Que. The two of us helped in the organization of the issue which, as it can be seen, gathers a number of stimulating contributions, either as research articles or reviews, covering many aspects and topics relevant to the field of Biological Inorganic Chemistry.

Ivano was known to many and had many friends, especially in the field of Biological Inorganic Chemistry, and therefore it was difficult to draft a list of only 20 colleagues to contribute to this issue. We take this opportunity to apologise immediately to the many others who might have been equally qualified, both as Ivano's friends and as eminent scientists, to feature in this volume.

Since Ivano left us, almost 2 years ago, there have been many initiatives to honor his memory, from dedicated talks at conferences, to obituaries in several international journals, and to special issues such as the one in *ChemBioChem* edited by H. Schwalbe and J. Telser. However, a special JBIC issue is special in more than one way. Ivano was the founder and first Chief Editor of JBIC, which was born in 1996, 18 years ago. The journal was established with the help of many colleagues, but Ivano was rightly considered its "father". It is thus very appropriate that his child, who has been then nurtured and raised by several of us over the years, now pays tribute to him as it enters its adulthood.

It is also gratifying for us to remember that Ivano was appointed honorary member of the Society of Biological Inorganic Chemistry (SBIC) in Spring 2012, while he was still alive and could appreciate this recognition by the Society. Ivano contributed greatly to building the Society and energizing the International Conferences of Biological Inorganic Chemistry (ICBICs) and to some extent their European and Asian counterparts EuroBIC and AsBIC. Broadly speaking, the whole Bioinorganic Chemistry community benefited tremendously for his efforts. Ivano also built many other things, including CERM, an NMR facility that is one of the best equipped in the world, and the European NMR Consortia. He also helped to build a European Infrastructure of Structural Biology, and so on and so forth. Above all, he managed to build, in all of those who were fortunate to work with him, the awareness that science is something that one must love without reservations.

On a sunny day early in March 2014 we were watching, from a window of CERM, the construction-in-progress of two additional buildings designed to host the new 1.2 GHz NMR instrument and the new laboratory for our Biobank. We were of course pleased to see the work progressing well, but were struck by the thought of how much more Ivano would have enjoyed the view. Seeing something being built was always for him a source of childlike excitement!

As this introduction is not meant to be an obituary, we would like to move to the best way to honor Ivano, and that is to concentrate on Science. We do think this JBIC issue is a collection of good Science, and in a field, Bioinorganic Chemistry, that was very dear to him. A number of papers report on the detailed characterization of enzymatic reactions, catalytic pathways and on the factors affecting the catalytic activity. Specifically, the paper by L. Que et al.

L. Banci (✉) · C. Luchinat (✉)
CERM and Department of Chemistry, University of Florence,
Florence, Italy
e-mail: banci@cerm.unifi.it

C. Luchinat
e-mail: luchinat@cerm.unifi.it

(doi:10.1007/s00775-014-1122-9) addresses the issue through the analysis of various intermediates in the mechanism of extradiol catechol ring-cleavage by catechol dioxygenases, with the objective of showing how Nature can utilize the enzyme structure and the properties of both metal and substrate to select among many possible chemical paths, and achieve both specificity and efficiency. The reaction mechanism and the factors affecting it have been addressed also for the glycosyl hydrolase arabinanase from *B. subtilis* by M.A. Carrondo et al. (doi:10.1007/s00775-014-1105-x). In particular, from the crystal structure of an inactive mutant, together with functional and modeling studies, the key role of calcium in the overall reaction has been shown. Model compounds have been used by K. Karlin et al. (doi:10.1007/s00775-013-1081-6) to investigate the nitrite reductase processes performed by the binuclear heme a₃/CuB active site of cytochrome c oxidase. It has been found that different nitrite coordination modes to copper(II) affect differently the kinetic aspects of the reaction, while the latter do not depend on the nature of the substituents on the porphyrin ring of the heme. The review by Y. Watanabe et al. (doi:10.1007/s00775-014-1106-9) covers various aspects and contributions addressing enzymatic monooxygenation reactions catalyzed by P450s and occurring through the H₂O₂-shunt pathway. This pathway is attractive from an industrial point of view for monooxygenation processes because of the low cost of H₂O₂. The review by I. Pecht et al. (doi:10.1007/s00775-013-1080-7) summarizes the structural and functional properties of multicopper oxidases and how these properties determine the catalytic reduction of O₂ to water by the oxidases. Particular focus was put on the kinetics of the internal electron transfer between the copper sites of the protein.

Two papers address the dynamical properties of proteins, either through MD calculations or via analysis of experimental data. The paper by H.B. Gray and coworkers (doi:10.1007/s00775-013-1077-2) presents a new approach for describing structural changes and protein segment displacements occurring upon protein unfolding. The behavior of azurin is analyzed also with respect to MD simulations, showing that a region remains stationary upon unfolding as a fine balance of competing motions. MD simulations were also applied to five cupredoxins by A. Vila et al. (doi:10.1007/s00775-014-1108-7) in their copper-free form, which was found in the X-ray structures in the closed conformation apparently unable to bind copper. From the MD simulations it appears that the copper-binding regions are characterized by extensive flexibility, being able to sample a broad range of conformations. The paper by F.A. Walker et al. (doi:10.1007/s00775-013-1063-8) shows that NMR is an exquisitely sensitive technique to address small changes in shape and size of the heme-binding cavity of nitrophorin

2, and a NO-storing and NO-releasing protein present in the saliva of blood-sucking insects.

The properties of the metal-binding site in metalloproteins, how they affect the functional behavior and the way the proteins reach their mature, fully metal-bound state, have been addressed by a number of contributions. V. Culotta et al. (doi:10.1007/s00775-013-1045-x) analyzed the maturation processes of SOD1 from the pathogenic yeast *C. albicans* and in particular, its mode of copper acquisition and its enzymatic activation. A number of reconstitution procedures of the mixed-metal sulfide cluster (of the S₂MoS₂CuS₂MoS₂ type) in a bacterial Orange Protein are designed and discussed in the contribution by J.J. Moura et al. (doi:10.1007/s00775-014-1107-8), and their effectiveness is tested. Ferritin has been analyzed with respect to its function of reversible synthesis of protein-caged iron biomineral by E. Theil et al. (doi:10.1007/s00775-014-1103-z). The functional importance of the structural properties and of the symmetry of several ferritin protein cages is discussed, also focusing on conserved amino acids that facilitate dissolution of ferritin-caged iron biominerals.

Health-related aspects involving metal ions are the subject of a number of contributions which developed mainly along two lines: one on metal-induced or related protein aggregation and neurological diseases, and the other on metal-based drugs. Along the former line, the minireview by A. Graslund et al. (doi:10.1007/s00775-014-1131-8) summarizes recent results on the structural properties of Aβ peptides at various stages of aggregation and the role of Cu(II) and Zn(II) binding in the aggregation process. The prion protein involved in Transmissible Spongiform Encephalopathies (TSEs) tends to form amyloid-type aggregates, while copper binding to it prevents this aggregation. In the work by H. Kozłowski et al. (doi:10.1007/s00775-014-1132-7) the structural features produced by Cu(II) binding, i.e. α-helix formation, was related to the decreased tendency of the protein to aggregate. The metal binding features through NMR studies of ALS-related SOD1 mutants were addressed in the contribution by J.S. Valentine et al. (doi:10.1007/s00775-014-1126-5), exploiting the native metal substitution with the more NMR-amenable nickel(II) ion. The effects of the ALS mutations on the stability and the metal binding properties of the protein were discussed and the implications for the causes of SOD1-linked ALS commented upon. In the contribution by L. Banci and C. Luchinat et al. (doi:10.1007/s00775-014-1130-9), it is shown that structural information on apo-SOD1 fibrils can be obtained at a site-specific level from solid state NMR: it is found that the residues that are in a more ordered state are indeed located at the previously proposed putative nucleation site.

A number of contributions describe some features of metal-based drugs. In their contribution, S.J. Lippard et al.

(doi:[10.1007/s00775-014-1109-6](https://doi.org/10.1007/s00775-014-1109-6)) determined the high-resolution crystal structure of a Pt(IV) complex, which is an intermediate in the synthesis of Pt(IV) anticancer prodrugs, and reinterpret, based on the structural properties, the vibrational spectroscopic properties of the complex. The preparation and characterization of some Ru(II) and Ru(III) complexes have been reported by J. Reedijk et al. (doi:[10.1007/s00775-013-1083-4](https://doi.org/10.1007/s00775-013-1083-4)), who also analyzed their cytotoxic properties and the role of the co-ligand in modulating the cytotoxic properties. It resulted that some of those ruthenium complexes have cytotoxicity even higher than that of cisplatin. These complexes often target nucleic acids. Aromatic ring stacking is a quite general non-covalent interaction occurring in nucleic acids, and is therefore important in analyzing binding of drugs. Ring stacking features are summarized in the paper by H. Sigel

et al. (doi:[10.1007/s00775-013-1082-5](https://doi.org/10.1007/s00775-013-1082-5)). The effects of metal coordination on ring stacking are also discussed, as well as the energies involved in those interactions also with respect to their biological relevance. The interactions and links between cisplatin and copper transporters are analyzed in the contribution by G. Natile et al. (doi:[10.1007/s00775-014-1138-1](https://doi.org/10.1007/s00775-014-1138-1)), which reports on the cisplatin binding to a copper chaperone and on its negligible transfer to another copper-binding protein.

As an example from the broad field of metal complexes in diagnosis, the synthesis and characterization of a new gadolinium(III) containing contrast agent for Magnetic Resonance Imaging are described in the contribution by S. Aime et al. (doi:[10.1007/s00775-014-1111-z](https://doi.org/10.1007/s00775-014-1111-z)) The new contrast agent features higher efficiency, enhancing more effectively the contrast in tumor regions in MR images.