A EUROPEAN JOURNAL
CHEMBIOCHEM
OF CHEMICAL BIOLOGY

14/2013

CHEMICAL BIOLOGY & CHEMISTRY
http://www.chembiochem.org

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CHEMBIOCHEM
EDITORIAL

ChemPubSoc Europe

DOI: 10.1002/cbic.201300451

Magnetic Resonance Spectroscopy in Bio(in)organic Chemistry and in Mechanistic Systems Biology: A Tribute to Ivano Bertini

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Thematic Introduction

The term "towering figure" is, as with most clichés, overused. In the case of the late Ivano Bertini (6 December 1940–7 July 2012; Figure 1), Italian—Florentine, to be precise—chemist it is, however, fully appropriate. Ivano, as he was known to all, was a physically imposing man with a booming voice. To us, Ivano seemed as someone one could easily imagine represented by a massive marble statue, suitably clad in a toga or suit of armour, in the piazza of a Tuscan town. But to say that Ivano was a towering figure solely for superficial, physical reasons is far off the mark. In essence, Ivano was one of the creators of the field of bioinorganic chemistry. As was evident even to non-Italians, his role in Italian science was massive, and his role in European science overall was enormous, especially in the context of the current development of European, as opposed to nationally based, science within the framework of the

Figure 1. Photo of Ivano Bertini in 2005.

Figure 2. SBIC logo with Venus by Botticelli.

European Community/Union. It is thus appropriate that *ChemBioChem* be a vehicle for a tribute to Ivano as this journal is one that represents this new era of unified European science. Although it might be less appropriate to promote here another publisher's journal, it must be noted that Ivano was one of, if not the, founder of the Society of Biological Inorganic Chemistry (SBIC) in 1995, its celebrated biannual conference—the International Conference on Bioinorganic Chemistry (ICBIC, which actually began in 1981, not surprisingly, in Florence), and its journal—the *Journal of Biological Inorganic Chemistry*—in 1996, for which he served as the first Editor in Chief. One of us (J.T.) can distinctly remember Ivano at a contemporary meeting promoting this journal, to which he referred as *JBIC*, heavily stressed on the second syllable, a pronunciation thus still used by some English speakers, who would otherwise stress the first syllable. Ivano also received some criticism at that time from the expected quarters for using the *The Birth of Venus* by Sandro Botticelli as the logo for SBIC (Figure 2).[1] Such criticism fortunately appears to have since subsided.

Ivano Bertini's scientific biography has been given elsewhere, notably in articles by his long-time collaborators (and one-time students) Lucia Banci and Claudio Luchinat[2] and by coauthors, such as Harry Gray.[3] His full CV is available on the website of his institution CERM (Centro di Ricerca di Risonanze Magnetiche), along with a brief, but interesting history of CERM.[4] There is therefore no need to reproduce such information here. However, we would like to make a few points in the context of the development of bioinorganic chemistry. Ivano was trained in classical coordination chemistry at the University of Florence by Prof. Luigi Sacconi.[5] Sacconi was in large part responsible for the development of inorganic chemistry in Italy in the post-war period concurrent with the explosive advances in inorganic chemistry world-wide. One person responsible for this development was the late Russell S. Drago at the University of Illinois (Urbana–Champaign; later at the University of Florida). "Doc", as his graduate students called him, was a proud Italian-American and great friend of Sacconi's, and by the early 1980s, Drago was a friend and supporter of Ivano and his coworkers. Claudio Luchinat visited the Drago group at that time and gave a talk on the applications of NMR (to Co-substituted Zn enzymes) that were amazing. The late Fred Basolo, another proud Italian-American, was largely responsible for building the foundation for the preeminent place in inorganic chemistry currently occupied by the chemistry department at Northwestern University in Evanston.[6] Basolo was also a contemporary and great friend of Sacconi and later of Bertini. In 1991, Northwestern established the Fred Basolo Medal for Outstanding Research in Inorganic Chemistry.[7] In autumn 2006, Ivano won the Basolo medal and travelled to Evanston to receive it. The award dinner was especially poignant because it was the last such event in Basolo's lifetime, as his health was evidently poor and he died several months later. Ivano realised this and in his acceptance speech (a formal lecture had been given earlier that day) made some touching comments directed at Basolo and his family. The last time that J.T. saw Ivano was at ICBIC-13 in Vienna in 2007, at which Ivano gave a plenary lecture on "Metal Ions in the 'omics' World" in memory of the great Portuguese bioinorganic chemist, Antonio Xavier. These anecdotes give evidence of Ivano's recognition of other scientists. Even near the end of Ivano's life there were such occasions.

One of the innovations Ivano was proud of were the Chianti meetings,[8] with their thematic cartoon describing "relaxation" better than any textbook could (Figure 3). In June 2012, the

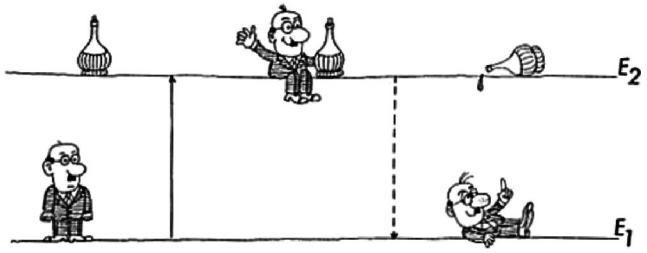

Figure 3. Chianti meeting "relaxation" cartoon.

12th edition was held in Montecatini (Figure 4) and Ivano, already suffering from the effects of chemotherapy, was amidst his friends and colleagues, accompanied his wife, "mamma" to our scientific community. Having to take cisplatinum, Ivano invited Steve Lippard to express his gratitude to an inorganic chemist so much involved in the development of the drug.

It is perhaps for the application of (paramagnetic) NMR spectroscopy to bioinorganic chemistry and later to mechanistic systems biology, a term he coined, that Ivano is best known. No extensive bibliography is needed here, but a few key review works on that topic can be cited.[9–11] Ivano's work in this century moved with the times, both responding to external developments (the "-omics" era) and creating new areas for others to follow.[12] It is thus appropriate that the bulk of this special issue of *ChemBioChem* focuses on current applications of NMR spectroscopy to problems in bioorganic and bioinorganic chemistry. The specific contributions will be summarised below.

Concurrent with, and to some extent preceding his use of NMR, Ivano was also heavily involved in the use of EPR spectroscopy. This application had its origin directly in his classical coordination chemistry training by Sacconi. The EPR properties of paramagnetic ions such as Cu^{II}[13] and Co^{II}[14] were studied early on. It should be noted that some of this early work was in collaboration with the other great student of Sacconi, Dante Gatteschi, whose contributions in the area of molecular mag-

Figure 4. Group photo of 12th Chianti workshop on BioNMR, Montecatini, Italy, 17–22 June, 2012. Ivano Bertini is seated in the centre, above the shrub.

netism are well known. In addition to zinc enzymes, another area of bioinorganic chemistry in which Ivano and co-workers made major advances is that of iron–sulfur proteins, whose roles in biochemistry continue to expand.[15] In studying FeS proteins, paramagnetic NMR and EPR spectroscopy could be beautifully combined. Many works by Ivano and colleagues on FeS proteins could be cited here, but we name (for what we hope are understandable reasons) the one for which J.T. had a direct editorial interaction with Ivano.[16] Therefore, a second portion of this special issue describes the application of EPR spectroscopy and related techniques to contemporary areas of primarily bioinorganic chemistry.

Overview of Contributions

When we asked for contributions to this special edition of *ChemBioChem*, everybody immediately accepted the invitation. The contributions would nicely reflect Ivano's broad interest in everything that is concerned with the molecular understanding of the basis of life. Ivano raised a badge in CERM (Figure 5), based on Linus Pauling's statement about a new structural chemistry, "We may, I believe, anticipate that the chemist of the future who is interested in the structure of proteins, nucleic acids, polysaccharides, and other complex substances with high molecular weight will come to rely upon a new structural chemistry, involving precise geometrical relationships among the atoms in the molecules and the rigorous application of the new structural principles, and that great progress will be made, through this technique, in the attack, by chemical methods, on the problems of biology and medicine."[17]

Ivano was deeply convinced that magnetic resonance spectroscopies (NMR and EPR) are among the most powerful methods to determine what Linus had envisioned, as shown in their juxtaposition in Figure 5. Ivano would see the investigation of intrinsically disordered proteins, proteins with no persistent structure, highlighted by I. Felli's, M. Pons' and V. Sklenar's contributions with great sympathy. Ivano understood that the application of NMR spectroscopy under more and more physiological conditions, as highlighted here by contributions from L. Banci and M. Pons, would enormously broaden our understanding. NMR under all circumstances, in the liquid and the solid (here with articles by M. Baldus and C. Luchinat), to study dynamics (in the articles of C. Redfield and L. Kay), the influence of pressure on proteins (A. Bax and H.S.), this was what Ivano was striving for. In the end, Ivano was certain that NMR spectroscopy needed to have an impact on human health. Consequently, he founded companies towards this goal, and applied and developed methods to understand the structural basis of drug discovery; contributions by Jiménez-Barbero and H. Molinari are wonderful gems showing what NMR spectroscopy can do.

Figure 5. NMR magnet at CERM with Linus Pauling plaque.

Every progress in his technique made Ivano glad and proud. And he could show his proudness—loudly. Ivano wanted to be the father of all of us, wanted to embrace all of us, and by doing so, he could appraise and congratulate all colleagues on their wonderful results, and stimulate his team, the CERMians (the senior ones: Lucia Banci, Claudio Luchinat, Isabella Felli, Roberta Pieratelli, Antonio Rosato, Giacomo Parigi, Paola Turano, Mario Piccioli, Vito Calderone, Claudia Andreini, Simone Ciofi Baffoni, Francesca Cantini, and many, many others) in Florence, to follow, improve upon and overcome all developments outside Florence. For Ivano, Florence was the birthplace of the Renaissance and therefore the birthplace of rational natural science, and, being from Tuscany, he felt it was his inheritance, his hard-felt duty and simultaneously his joy to represent natural science in as broad a manner as it could be. Being narrow in mind and emotion was an attitude Ivano could not support: you have to grow, in personality, in ambition, in wisdom, and in capabilities to stay where you are.

Concerning the contributions that focus primarily on EPR spectroscopy and/or bioinorganic chemistry, we note first that by Kurt Warncke (Emory University, Atlanta, USA) and co-workers. In a way, this paper is on Cu^{II} coordination chemistry and, as such, is related to Ivano's early work in this area. However, it is connected to Ivano's later interests in that it addresses a key problem in biochemistry, namely the β-amyloid protein (relevant to Alzheimer's disease (AD)) and employs a start-of-the-art paramagnetic resonance technique: electron spin echo modulation (ESEEM) spectroscopy. The contribution by Daniella Goldfarb (Weizmann Institute, Rehovot, Israel) and co-workers uses ESEEM, along with Double Electron Electron Resonance (DEER, also known as Electron Electron Double Resonance (ELDOR)), but uses spin labels as the paramagnetic probe and attacks an even more biological problem, the T-cell receptor-CD3 complex (TCR-CD3). The contribution by Peter Qin, Daniel Herschlag, and co-workers (USC and Stanford, CA, USA) also employs spin labels, but here these probes provide information on ribozyme structure. The contribution by Gunnar Jeschke (ETH, Zürich, Switzerland) and co-workers also uses DEER, but in this case with f-block ions (Dy^{III}) as the paramagnetic probe of, in this case, T4-lysozyme.

Astrid Gräslund (Stockholms Universitet, Sweden) and co-workers provide the sole review article in this special issue, which is related to the above-mentioned articles in that it reviews biophysical studies of the amyloid β peptide, specifically, interactions with metal ions and small molecules. The literature on AD is immense, but this review is helpful in focussing on basic science. The highlight, by H.S., discusses a contribution by Banci and co-workers on in-cell NMR in eukaryotic cells to follow cysteine oxidation states.

Next are contributions that deal with endogenous paramagnetic centres in metalloproteins. The contribution by Pierre Dorlet (CEA Saclay, Gif-sur-Yvette, France) and co-workers covers another area of paramount importance in bioinorganic chemistry, namely haem proteins, specifically nitric oxide synthase (NOS). Here, EPR is used to study the binding of NO to a mammalian NOS and to a bacterial NOS-like protein. The contribution by Kara Bren (University of Rochester, USA) and Kristoffer Andersson (University of Oslo, Norway) is also on haem proteins, namely, cytochromes *c*. EPR spectroscopy and X-ray crystallography are used complementarily, which is gratifying given the unfortunate belief by some in structural biology that there is no need for spectroscopy when one has a crystal structure.

The contribution by Michael Bowman (University of Alabama, Tuscaloosa, USA) and co-workers is indirectly related to haem proteins as it describes pulsed-EPR studies on radical intermediates in the Rieske (a [2Fe–2S] protein)/cytochrome *c* redox pathway.

The contribution by José Moura (Universidade Nova de Lisboa, Portugal) and co-workers describes studies on a mononuclear Fe enzyme; although this description could apply to a haem, this work is on a non-haem Fe enzyme, superoxide reductase (SOR), the active site of which represents a unique type of biological Fe coordination and whose substrate has been the source of much investigation, as well as notoriety in popular culture.[18]

The contribution by Wolfgang Lubitz and Hannah Shafaat (Max-Planck-Institut für Chemische Energiekonversion, Mülheim/Ruhr, Germany) and co-workers is on an enzyme whose active site, at least conceptually, links the non-haem iron proteins with the iron–sulfur proteins. This is nickel hydrogenase (Ni-H_2ase), in which an unusual dinuclear active site (here NiFe, but those with FeFe are also known and studied by Lubitz and colleagues) is linked to an [4Fe–4S] cluster. An intriguing aspect of the Ni-H_2ase described here is Ni coordination by selenocysteine. The discovery in nature of amino acids in addition to the 20 proteinogenic ones should generate interest even among those chemical biologists not directly involved in bioinorganic chemistry. A parallel contribution is that by Maurice van Gastel and Frank Neese (from the same institution) on computational studies of the vibrational frequencies of the other unusual—perhaps even bizarre—aspect of the Fe and Ni H_2ases, namely their coordination by CO and cyanido ligands. Such ligation in nature provides a connection to the classical coordination chemistry not only of Bertini and Sacconi, but of Basolo and Bailar, and back one century to the work of Alfred Werner.

A related work, the contribution by Fraser Armstrong (University of Oxford, UK), Stephen Ragsdale (University of Michigan, Ann Arbor, USA) and co-workers, is veritable bioinorganic chemistry, albeit lacking magnetic resonance studies. However, their use of electrochemistry combined with exogenous ligand binding to study the active site [Ni–4Fe–4S] cluster of carbon monoxide dehydrogenase, fits in with Ivano's early coordination chemistry work in which the redox properties of the complexes studied were as important as their spectroscopic properties.

Lastly, the contribution by Charles Dismukes (Rutgers University, New Brunswick, USA) and co-workers covers an area of bioinorganic chemistry that is notable in that it was not directly touched on by Ivano Bertini, namely, photosynthesis.

In conclusion, this special issue of *ChemBioChem* provides a worthy tribute to the breadth and depth of Ivano Bertini's contributions to mechanistic systems biology, bioinorganic chemis-

try and magnetic resonance spectroscopy—in all of its multitudinous forms.


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Keywords: bioinorganic chemistry · bioorganic chemistry · EPR spectroscopy · Ivano Bertini · NMR spectroscopy · systems biology

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