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Quantum Bio-Inorganic Chemistry (QBIC) Society Special Collection

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Metals and their ions are ‘elements of life’. They are intimately involved in most fundamental biological processes. Almost all redox reactions occurring in Nature as well as ‘difficult’ chemical transformations (O₂ bond cleavage, N₂ and C-H bond activations), including formally spin-forbidden processes, are catalyzed by metalloproteins. Of equal importance is the structure and function of RNA and DNA that critically depends on the presence of metals and it comes as no surprise that metal-containing complexes are to be found among anticancer drugs.

The enormous progress made in the field of *bioinorganic chemistry* over seven decades - since the first reports on the presence of metal ions in biological systems appeared - has been always supported by physico-chemical and spectroscopic methods. Since the 1990’s, computational and theoretical chemistry has played an indispensable and integral role in bioinorganic research. At the same time, the need for accurate treatments of open-shell, strongly-correlated, spin-coupled, entangled, or ‘relativistic’ systems – just to mention few of the common characteristics of bioinorganic systems – has led to the development of advanced quantum chemical methods and also stimulated formulations of new DFT functionals.

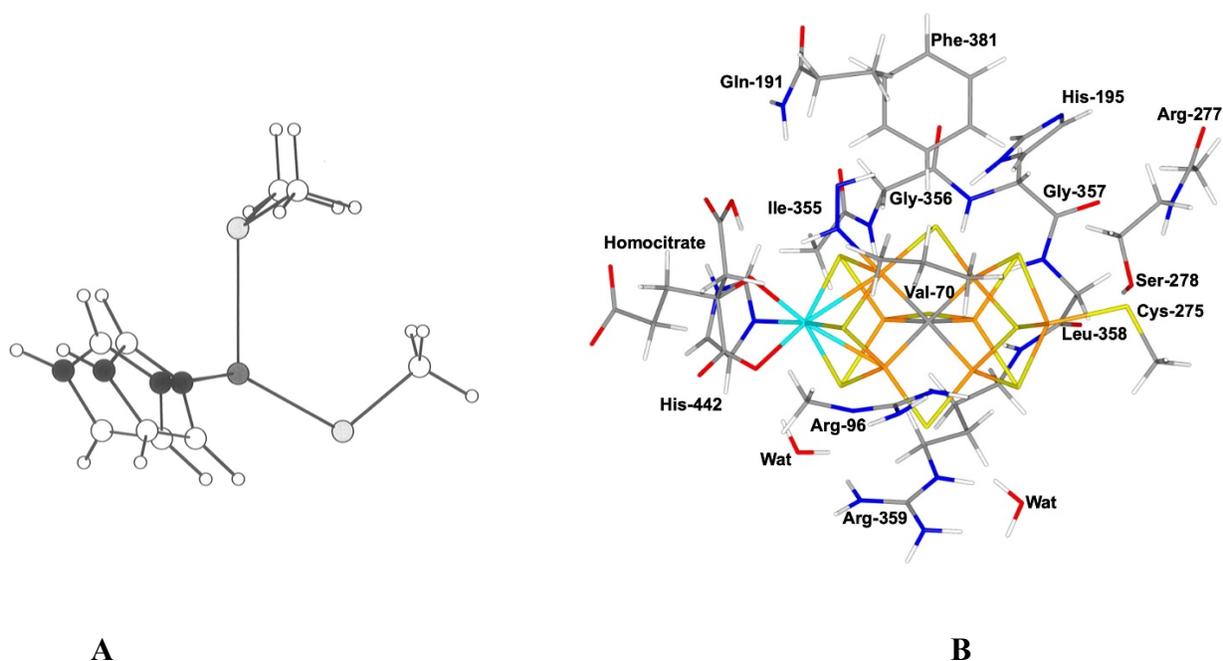


Figure 1: The typical size of the bioinorganic systems studied (A) in late 1990’s; (B) in early 2020’s. Both are taken from the work of Ulf Ryde. A is the optimized structure of $\text{Cu}(\text{imidazole})_2(\text{SCH}_3)(\text{S}(\text{CH}_3)_2)^+$ in C_s symmetry as the model of the active site of plastocyanine (<https://doi.org/10.1021/ja962381f>); B is the active site model of nitrogenase from this collection (<https://doi.org/10.1002/chem.202103933>).

The field of quantum chemical modelling of bioinorganic systems has been given a name: *quantum bioinorganic chemistry* (QBIC). The QBIC community evolved around the series of QBIC conferences, the first one organized by Rob Deeth in Warwick, UK in 1999, the last ones taking place in 2018 (Bath, UK), 2019 (Marseille, France) and 2021 (on-line, hosted by University of Groningen, Netherlands). Proceedings of the QBIC conferences also provide historic evidence of how the field developed from its infancy to maturity (see Figure 1 for graphical visualization of the). From early attempts to model reaction mechanisms of metalloproteins by employing small model systems to evaluate interactions of metal ions with biomolecules in the gas-phase, or to reproduce rough trends in spectroscopic characterization of inorganic or bioinorganic systems, quantum bioinorganic chemistry has progressed enormously, as we hope this issue will show. Nowadays, it provides a robust and often quantitative framework that supports state-of-the-art experiments, and sometimes even directs experimental efforts. We believe that in near future, the theoretical expertise will be used for the rational design of new bioinorganic systems with desired properties and reactivities. This requires high cooperativity, transferring knowledge, and exchanging ideas which further motivated the foundation of the Quantum Bio-Inorganic Chemistry Society in 2018 to bring together scientists from academia and industry working in the broad fields of theoretical and computational inorganic, bioinorganic, and biological chemistry. Among the activities of the Society are the organization of regular international scientific meetings, the support of summer/winter schools oriented towards young scientists, and the coordination of networking actions.

The special virtual QBIC issue has collected diverse papers that have a common denominator: usage of state-of-the-art theoretical methods, often ‘synergistically’ coupled to first-class experiments, to study problems of enormous chemical and biochemical interest. The issue includes almost 30 contributions covering diverse bioinorganic topics, both original research articles and reviews.

The issue begins with three reviews. An ever-discussed dilemma of the applicability of density functional theory (DFT) *vs.* wave-function theory (WFT) methods for spin-state energetics is reviewed by Feldt and Phung (<https://doi.org/10.1002/ejic.202200014>). A highly relevant issue puzzling both theoreticians and experimentalists – reaction selectivity of metalloenzymes – has been reviewed by Wojdyla and Borowski, taking the Fe(II)/2-oxoglutarate dependent dioxygenases (<https://doi.org/10.1002/chem.202104106>) as an interesting and important example of the mechanistic dichotomy. Lastly, the review paper of Jensen (<https://doi.org/10.1002/cbic.202100554>) deals with one of the most abundant 3d-elements in nature: zinc(II). Zn(II) is not only utilized in many biological processes, but also plays a major role in the immune system, as is pointed out and thoroughly analyzed in the review.

Concerning original research articles, it can be highlighted that state-of-the-art studies of one of the most intriguing metalloenzymes in Nature – nitrogenase – are reported independently by three research groups, employing various theoretical approaches and methods. Nitrogenase is the only enzyme in nature that can fix N₂ from the air and contains a ‘formidable’ cofactor comprising seven irons and one molybdenum connected by sulfide bridges. Wei and Siegbahn

(<https://doi.org/10.1002/chem.202103745>) address computationally the loss of a sulfide, and argue that the barrier for the loss is much lower than the barrier for protonating the central carbide which is then protonated in the E₃ to E₄ step. They also present a complicated transition state for H₂ formation and correlate the computed data to experiments. Jiang and Ryde (<https://doi.org/10.1002/chem.202103933>) used quantum mechanical and molecular mechanical (QM/MM) calculations to present a contradicting hypothesis, assuming that none of the sulfide ligands dissociate. This leads to a formulation of an alternate reaction mechanism. Finally, Thorhallsson and Bjornsson (<https://doi.org/10.1002/chem.202102730>) present an exploration of the potential energy surface of the E₂ state. They utilize both cluster-continuum and QM/MM calculations and consider various classes of E₂ models: including terminal hydrides, bridging hydrides with a closed or open sulfide-bridge. A path back to the resting state, by H₂ evolution via a hydride-proton reaction is found.

A similar topic as reviewed by Wojdyla and Borowski (*vide supra*), reaction selectivity (regio- and chemoselectivity), is studied and discussed by de Visser and coworkers (<https://doi.org/10.1002/chem.202100791>) on an example of nonheme iron dioxygenase. They point out the role of charged residues and show that the selectivity is guided through electrostatic perturbations inside the protein from charged residues, external electric fields and electric dipole moments. They notice that the studied dioxygenase is a nice example of so-called negative (or non-Bell-Evans Polanyi) catalysis where the formation of a less thermodynamically stable product is promoted via the lower activation energy with respect to its more stable counterpart (product). Along similar lines, Bleher, Comba, and coworkers (<https://doi.org/10.1002/chem.202103452>) study the [(L¹)(Cl)Fe^{IV}=O]⁺ complex/intermediate (where L¹ is a tetradentate bispidine), presumably the most reactive small-molecule halogenase model. DFT calculations show that the intermediate has, as observed experimentally, a lower energy barrier to the halogenation than the hydroxylation product; and thus, calculations nicely explain the origin of the observed chemoselectivity. Heme chemistry is represented by the contribution of Rozza, Harvey, Olah and coworkers (<https://doi.org/10.1002/chem.202200930>). They present a computational study of the mechanism of biochemical NO-sensing. On an example of the NO-receptor in humans - soluble guanylyl cyclase (sGC) – a histidine-ligated heme protein, they show how the NO binding activates a downstream signaling cascade.

Two of the most advanced, but still reasonably practical, methods are the density matrix renormalization group-self consistent field (DMRG-SCF) and domain-based local pair natural orbital-coupled cluster DLPNO-CCSD(T) approaches. They are considered, by many application-oriented quantum chemists as the major developments in WFT in the last two decades. The application of DLPNO-CCSD(T) in the realm of bioinorganic chemistry is nicely demonstrated by Drousou and Pantazis (<https://doi.org/10.1002/chem.202101567>), in the case of the water-oxidizing complex of photosystem II. Their results enable the evaluation of conflicting models for the S₃ state of the oxygen-evolving complex (OEC) and thus provide deeper theoretical insight into its reaction mechanism. Csizi, Reiher, and coworkers (<https://doi.org/10.1002/chem.202103937>) apply DLPNO-CCSD(T) to evaluate the spin-state-dependent reaction energies and structural effects at the active site of naphthalene (Rieske) dioxygenase. Their results strongly indicate an allosteric control of the substrate on Rieske

dioxygenase reactivity to avoid unproductive O₂ activation. Freitag, González, and coworkers employed DMRG to calculate the low-lying excited states of CpMo(CO)₂NO (<https://doi.org/10.1002/cphc.202100549>) demonstrating a novel, relatively easy-to-use, procedure, employing the maximum single-orbital entropy scheme, applied to several states, to select an appropriate active space. This has often been the bottleneck of previous multi-reference methods that this new approach may overcome.

Three insightful and conceptual papers deal with classical concepts in bioinorganic chemistry that are shown to be still very useful, despite the availability of more and more accurate and (at the same time) computationally demanding methods. Deeth (<https://doi.org/10.1002/ejic.202100936>) discusses the failure of crystal-field theory (CFT) for simple linear complexes, such as CuCl₂. He proposes a new cellular ligand field (CLF) analysis, including the equatorial toroidal void and presents the ‘distributed donation’ model that correctly describes the bonding in simple terms. Buchkorn, Deeth, and Krewald (<https://doi.org/10.1002/chem.202103775>) present a model case of tetrahedral halido metalates ([M^{II}X₄]²⁻, M=Mn–Cu) an inspirational usage of *ab initio* ligand-field theory (LFT), coupled with a generalised, symmetry-independent and automated fitting procedure for angular overlap model (AOM) parameters that is even applicable to formally underdetermined or experimentally inaccessible systems. Li, Nam and coworkers (<https://doi.org/10.1002/chem.202103295>) revive the multi-state reactivity concept and utilize it for high-valent iron-imido complexes. These can perform C–H activations and sulfimidations, but are far less studied than the more ubiquitous iron-oxo species. It is concluded that their electronic structures may change to perform efficient oxidations, thus emulating the multi-spin state reactivity in Fe^{IV}O systems.

With respect to current societal needs, a very important reaction to be understood and ultimately utilized in industry is H₂ production. It is addressed in four papers in this Special Virtual Issue. Barozo and Orio (<https://doi.org/10.1002/cphc.202200056>) present a study aiming to develop and optimize catalysts for H₂ production. Trying to fully understand the reaction mechanism of the Co- and Ni- thiosemicarbazone-based complexes, they notice the differences in catalysis when considering ligand- and metal-centered reactivity. This might be important to find the most optimal mechanisms for hydrogen evolution reaction. Natarajan, Stein, Kaur-Ghumaan and coworkers (<https://doi.org/10.1002/open.202100238>) report a synthesis, crystallization, spectroscopic and computational characterization of a series of new diiron hydrogenase mimic complexes with one or two terminal tris(4-methoxyphenyl)phosphine and different μ -bridging dithiolate ligands that have catalytic activity towards electrochemical proton reduction in the presence of weak and strong acids. They show that the nature of the μ -bridging dithiolate is critical for controlling the reaction and the catalyst performance in the H₂ evolving reaction. Arrigoni and Zampella (<https://doi.org/10.1002/ejic.202200153>) report the design of dinuclear iron systems, originating from the electron rich [Fe₂(pdt)(RNC)₆] (pdt=CH₂(CH₂S⁻)₂) complex. The purpose of computationally-aided design was to find a stable inverted (or rotated) disposition of the two FeL₃ pyramidal moieties in the dimetallic core which is a key feature of the [FeFe]-hydrogenase cofactor. Finally, a reverse reaction, the H₂-oxidation by enzymes, employed for example in the reaction cycle of the molybdenum and cobalt-containing carbon monoxide dehydrogenase (MoCu–CODH), is studied by Rovaletti, Ryde, Greco and coworkers

(<https://doi.org/10.1002/cphc.202200053>) employing QM/MM methods. They test the hypothesis whether a water molecule present in the active site might act as a nucleophile upon formation of the new C–O bond.

Another bioinorganic ‘classic’ is presented by Han Du and Noodleman (<https://doi.org/10.1002/cphc.202100831>). Very meticulous and state-of-the-art computations of Mössbauer isomer shift and quadrupole splitting properties for the resting oxidized “as-isolated” $\text{O}[\text{Fe}_{\text{a}3}^{3+}-\text{H}_2\text{O}-\text{Cu}_{\text{B}}^{2+}]$ state of the Fe/Cu dinuclear center clusters of cytochrome *c* oxidase (CcO) are presented, employing the OLYP-D3(BJ) density functional method. It is nicely demonstrated how tiny structural changes are imprinted in the Mössbauer parameters; the computations thus provide an important link in structure/spectroscopy correlations. The same adjective (classic) can be used for the study of Stanczak, Straka and coworkers (<https://doi.org/10.1002/cphc.202200076>) that examines the “enigmatic” $[\text{Cu}_2\text{O}_2]$ peroro- vs. bis- μ -oxo equilibrium including various physical contributions, such as relativity and solvent effects, plus a calibration of various wave-function and DFT methods. The presented results provide insight into understanding of the reactivity of the coupled binuclear copper proteins and their biomimetic models.

A very interesting contribution comes from Auth, Stein, and coworkers (<https://doi.org/10.1002/chem.202103130>). In recent years, a lot of insight into the origin of bioinorganic reactivity has been obtained from gas-phase (fragmentation) experiments. Herein, the authors report a study of the high-valent tetraalkylcuprates(III) and -argentates(III) which are key intermediates of copper- and silver-mediated C–C coupling reactions. Correlating collision-induced dissociation experiments with advanced quantum-chemical calculations and kinetic computations, they obtained detailed mechanistic insights for these important and catalytically relevant gas-phase reactions. The heavier counterpart of the Cu(III) and Ag(III), namely gold(III), is investigated by Engbers, Klein, and coworkers (<https://doi.org/10.1002/chem.202200599>). Specifically, the $\text{C}(\text{sp}^3)\text{-H}$ and O-H bond breaking steps in the oxidation of 1,4-cyclohexadiene and phenol by a Au(III)-OH complex are studied computationally. For both types of bonds the initial X–H cleavage step proceeds via concerted proton coupled electron transfer (cPCET) which seems to be quite distinct from the chemistry of analogous Cu(III)-OH species complexes studied by the Tolman group. Hence, the authors issue a warning that care should be taken when transferring concepts between Cu–OH and Au–OH species. Similarly, in concerted experimental and theoretical efforts, Heinrich, Kulak, and coworkers (<https://doi.org/10.1002/chem.202102601>) demonstrate that an exchange of the α -amino acid Gly with the β -amino acid β -Ala in the $[\text{Cu}(\text{II})\text{ATCUN}]$ complex (ACTUN = GGH tripeptide) reinstates ROS production ($\cdot\text{OH}$ and H_2O_2), i.e., it ‘wakes up’ the originally redox silent species. This replacement is also accompanied by higher cytotoxic activity against several human cancer cell lines where β -Ala2 peptide complexes have lower IC_{50} values compared to Gly2. Of a similar importance is the study of Arrigoni, Bertini, and coworkers (<https://doi.org/10.1002/ejic.202200245>) dealing with the oxidative stress and copper dyshomeostasis which are well established factors in the course of Alzheimer's disease (AD). The computations yield detailed energy profiles for the final two steps of O_2 reduction to superoxide and hydroperoxide radicals by ascorbate, on different $\text{Cu}(\text{II}) \cdot \text{A}\beta$ coordination models. The results obtained are discussed from the perspective of the recent findings in the $\text{A}\beta$ redox

chemistry in AD pathology. Both of these copper-related studies may ultimately lead to important applications in medicine.

Last, but not least, two studies from the realm of nucleic acids are presented. As mentioned above, Zaccaria, Fonseca Guerra and coworkers present a study (<https://doi.org/10.1002/cphc.202100529>) of how the internal guanine quadruplex channel site interacts with alkaline earth metal (Mg^{2+} , Ca^{2+} , Sr^{2+} , and Ba^{2+}), and (post-)transition metal (Zn^{2+} , Cd^{2+} , Hg^{2+} , and Pb^{2+}) cations, using density functional theory computations. It is found that divalent cations generally bind to the GQ cavity with a higher affinity than conventional monovalent cations (*e. g.* K^+). Their findings may contribute to a deeper understanding of how pollution metals could induce genomic instability. Nieuwland, Bickelhaupt and coworkers (<https://doi.org/10.1002/open.202100231>) study quantum chemically the influence of nucleotide composition and sequence on the stability of double-stranded B-DNA triplets in aqueous solution. Their calculations reveal enhanced stabilities for duplexes possessing a higher GC base pair content.

In summary, we believe that the QBIC Special Virtual Issue is a timely showcase of the contemporary achievements in the field, covering diverse topics, demonstrating an insight obtained by correlating experiment and theory, suggesting new design principles, while not forgetting the older but still useful theories, such as crystal-field/ligand-field theories, or multi-state reactivity. We thank all the authors for contributing to the issue and wish them success in their future work.