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INTRODUCTION

Celebrating Helmut Sigel

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This JBIC special issue celebrates the 80th birthday of Helmut Sigel and his 60 years of dedication to biological inorganic chemistry. The fundamental contributions of his research group in all aspects of nucleotide metal–ion interactions influenced deeply the Life Sciences field in general and medicinal chemistry, biophysics, and coordination chemistry in particular. Being one of the founders of the topic of biological inorganic chemistry, Helmut Sigel has constantly advanced the field over the past six decades and was always at its center.

Helmut Sigel was born on December 9, 1937, in Kirchheim/Teck, Germany. After his studies of chemistry at the University of Basel, Switzerland, graduating in 1961, he pursued a Ph.D. under the supervision of Hans Erlenmeyer at the same institution and defended in 1964 his thesis on "The Coordination Chemistry of Synthetic Nucleotide Derivatives and Model Compounds" (*Über das komplexchemische Verhalten von synthetischen Nukleotid-Derivaten und -Modellverbindungen*). Obviously, this already clearly marked his interest in bioinorganic chemistry (or biological inorganic chemistry), before the field even existed. He stayed as a Research Associate with Erlenmeyer and habilitated in 1967 on the "Metal ion-catalyzed decomposition of H_2O_2". An important paper of his early days "On the Discriminating Behavior of Metal Ions and Ligands with Regard to Their Biological Significance" resulted from his stay as a Visiting Staff Member at Cornell University in Ithaca, NY, USA, where he worked together with Don McCormick for one and a half years in 1968/69 [1]. He returned to Basel in 1971, where he stayed ever since, becoming *Dozent* in 1971 and Professor in 1978.

The research in his lab focused on all aspects of metal ion binding to ligands of biological interest. While probably best known for his work on nucleotides, his most cited paper (and still cited today) discusses the coordinating properties of the peptide bond [2] and was published together with Bruce Martin, a very good friend for many years. Most of Helmut Sigel's research deals with the stability and coordination chemistry of simple and mixed ligand metal ion complexes of nucleotides and nucleotide analogs, including those of relevance for antiviral and anticancer therapy [3]. He strongly believes that the fundamental coordinating properties of metal ions can be directly correlated to the activities of metalloenzymes, investigating for example the catalase- and peroxidase-like activity of transition metal ion complexes as well as the metal ion-promoted hydrolysis of nucleoside di- and triphosphates. Such, he predicted the two correct metal ion coordination modes at nucleoside triphosphate groups, which determine the kinase or the polymerase activity of the respective enzyme (Fig. 1) [4, 5]. While always being interested to understand the binding equilibrium down to the atomic coordination pattern [6], he also characterized weak interactions between metal ions and nucleotides in the past two decades, and transferred his findings to the situation in larger nucleic acid structures, where metal ions play a crucial role for structure and catalysis [7].

Until his retirement in 2003, he supervised about 50 PhD students and numerous postdocs, and at the same time also enjoyed teaching on all levels. His students very much appreciated his constant care and he collaborated with colleagues from many different countries. He gave lectures all around the world and published over 350 articles on metal ion complexes of nucleotides, coenzymes, and other ligands of biological relevance. Fifty of these articles were published after his retirement, which documents his never-ending inspiration and continued dedication to science. He received many honors, i.e., a *Doctor of Science honoris causa* degree from Kalyani University (India), the *Werner Award* of the

60 years dedicated to biological inorganic chemistry—a tribute to Helmut Sigel on the occasion of his 80th birthday.

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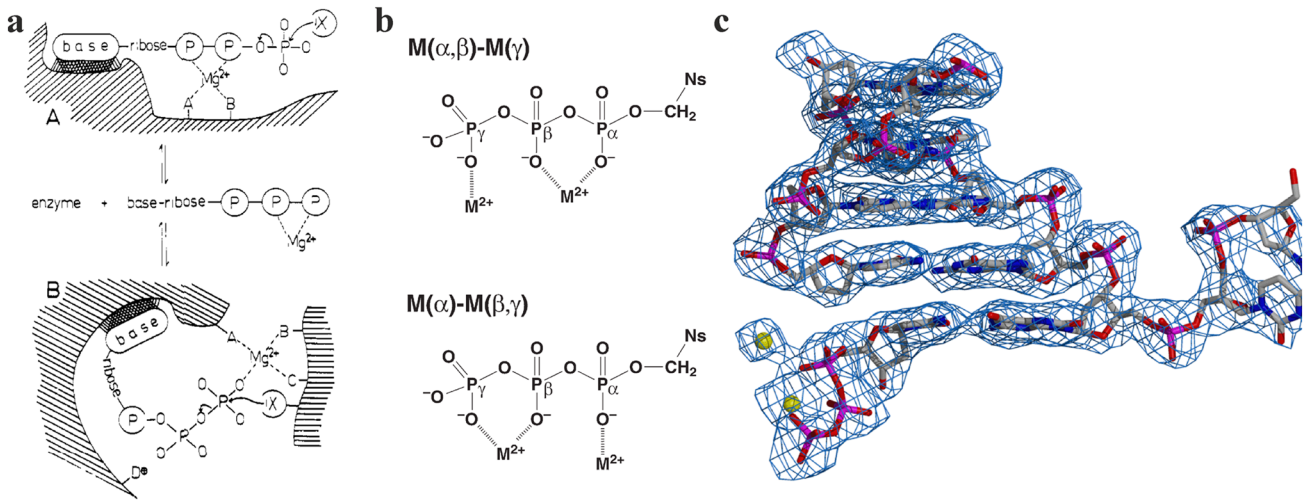

Fig. 1 Metal ion coordination specifies the cleavage site within a triphosphate group leading to either a kinase or a polymerase activity. **a** Proposal by Helmut Sigel from 1976 on the metal ion coordination of ATP within a kinase active site [4], long before the first X-ray structure of such an enzyme was solved. **b** Metal ion coordination in a kinase active site (top) and polymerase active center (bottom), as proposed based on extensive solution studies and reviewed in detail in 2005 [5]. **c** Such a *M* (*α*) – *M* (*β*, *γ*) coordination is indeed observed in polymerases, as in the crystal structure of a pol *α* family DNA polymerase (the protein scaffold is omitted for clarity) [8]. The panels are taken with permission from [4], [5], and [8]

Swiss Chemical Society, and the *P. Ray Award* of the Indian Chemical Society, of which he is also an honorary member.

Aside from his research, which had and still has a large impact on all aspects of metal ion coordination in living systems, his crucial contribution to biological inorganic chemistry is reflected in more ways: as early as in 1973 he began to edit the book series Metal Ions in Biological Systems, an interdisciplinary approach to open and to promote the field of bioinorganic chemistry and was soon supported by his wife, Astrid Sigel, as a co-editor. After 44 volumes, this series was continued as Metal Ions in Life Sciences, comprising today already 18 volumes [9]. There will be hardly any scientist in biological inorganic chemistry and related fields who has not studied one or more of these *green books*. In addition, three handbooks on the *Toxicity of Inorganic Compounds*, *Metals in the Clinics and Analytical Chemistry*, and on *Metalloproteins* are to be mentioned. The latter was edited together with Ivano Bertini, a good friend since the early days. Helmut, together with Ivano, Harry B. Gray, and Bo G. Malmström, initiated the International Conference on Biological Inorganic Chemistry series (ICBICs) and served as the co-organizer of the first conference in Florence, Italy, in 1983 (Fig. 2).

To promote the field in Europe, he served from 1991 to 1998 (partly as Chairman) in the Steering Committee of the European Science Foundation program "Chemistry of Metals in Biological Systems" as well as in several COST Actions. At the ICBIC-7 meeting in Lübeck, Germany, in 1995, he strongly promoted and supported the founding of the Society of Biological Inorganic Chemistry (SBIC) and

Fig. 2 The founders of the ICBIC conference series Harry B. Gray, Ivano Bertini, Helmut Sigel, and Bo G. Malmström (back row, from left to right), together with the organizers of ICBIC-2, Antonio Xavier, ICBIC-3, Jan Reedijk, and ICBIC-4, Ken Karlin (front row, from right to left). The picture was taken at ICBIC-3 in 1987 in Noordwijkerhout, NL

served as Founding Secretary until 2001. Without his fundamental contributions, his constant lively discussions, and his never-ebbing energy, the field of biological inorganic chemistry would today never be where it is–an outstanding achievement for which he was awarded Honorary Member of the SBIC.

Helmut Sigel is truly dedicated to science and biological inorganic chemistry. But besides, he also loves his family and friends, travelling, the mountains, and nature.

Skiing in Innsbruck, Austria, in spring and hiking in the Bernese Oberland, Switzerland, in summer have always been fixed points in his yearly planning. Together with Astrid as his patient wife, manager, and full-time companion for more than 50 years and kept safe by his favorite mountain guide, he has climbed more than 50 of the highest mountains in Europe (Fig. 3a), as well as mountains all around the world, like Fujiyama in Japan. He was also often accompanied by other members of his family. The long climbs prompted him to think about his research, and not infrequently would it happen that he outlined a publication on a piece of paper which he found in a remote alpine hut, or on one of the paper bags he always keeps ready to collect mushrooms. Nowadays, he prefers to take his leisure time more easily and pass on his knowledge of trout fishing to his grandchildren (Fig. 3b). Traveling is still one of his pastimes, as his latest trip with Astrid to Rome just 2 months ago proves (Fig. 4).

He continues to attend conferences all over the world to meet and discuss with colleagues and to learn about the newest developments in chemistry. His constant care for students, friends, and family is an outstanding feature of his life. We wish him good health, that his interest in science continues, and that he can carry on his activities to his satisfaction.

To honor Helmut Sigel and show the deep appreciation for his achievements and contributions to biological inorganic chemistry, we have collected for this special issue contributions from his long-standing collaborators, friends, and former students as well as colleagues at the University of Basel.

Fig. 4 Helmut Sigel together with his wife Astrid on a recent trip to Rome, Italy

The special issue starts with a minireview on binuclear copper A-type metal centers using nitrous oxide reductase and cytochrome c oxidase as examples. The friendship of Peter Kroneck and Helmut Sigel goes back to the early days

Fig. 3 **a** Helmut Sigel on his climb to the Strahlegghorn (Swiss Alps) in summer 1991. **b** Trout fishing 2016 together with his grandchildren in the small village in Germany, where he grew up

of their studies at the University of Basel, and this review traces the parallel history of the critical steps in understanding the nature of the Cu A centers in these two proteins [10].

A contribution follows from his son, Roland Sigel, on the characterization of metal ion binding to the branch domain of a catalytic self-splicing group II intron ribozyme that contains thiophosphate nucleotides, including the NMR solution structure of this domain [11]. The sulfur substitutions have surprisingly little effect on local structure. Chemical shift change titrations with Cd(II) show that the sulfur of thiophosphate groups is indeed a high affinity binding site for this metal ion, but still the coordination is determined to a large part by local structures as not all sulfur atoms are actually coordinated by Cd(II).

Staying with nucleic acids, Bernhard Lippert from the University of Dortmund and his collaborators investigate the effect of GA mismatches in mixed guanine–adenine quartet structures by Density Functional Theory methods. Possible structures of such mixed quartets in the presence of either protons or alkali metal ions are discussed hinting at a putative two-metal motif [12].

Transcription factors are extremely rich in histidine rich regions. Two such His tracts within the human genome, from the forkhead box and MAFA proteins, are investigated by Henryk Kozlowski to elucidate its Cu(II) and Zn(II) binding properties. They observe that the available imidazole nitrogen donors enhance the stability of the Zn(II) complex but exhibit the opposite tendency above physiological pH in the case of Cu(II), where the amide nitrogen atoms participate in binding [13].

More oriented towards medicinal inorganic chemistry is the contribution of Wolfgang Meier, Catherine Housecroft, and Ed Constable, three of his Basel colleagues for many years. They present a new water-soluble photocatalyst for singlet oxygen generation upon irradiation at 660 nm. *Escherichia coli* cultures exposed to this porphyrin-based conjugate are heavily damaged by oxidative stress when simultaneously exposed to red light [14].

By cyclic and differential pulse voltammetry and supported by DFT calculations, Osamu Yamauchi and coworkers characterize the one-electron oxidation of Cu(II)-salen type complexes modeling redox-active metal ion cores within metalloproteins like galactose oxidase [15]. They find that indole substitution best stabilizes the Cu(II)-phenoxyl radical species, most probably by stacking interactions with the phenoxyl moiety.

Two contributions are from the Magnetic Resonance Center at the University of Florence, with which Helmut Sigel has had a very close connection over the past 50 years, originating from his friendship with Ivano Bertini. Lucia Banci and coworkers report on the intracellular metal ion binding and redox behavior of the conserved and ubiquitous protein DJ-1 by NMR studies within human cells [16]. Although DJ-1 has been shown to bind Zn(II) and Cu(II) in vitro, no indication for complexation of these two metal ions was detected in vivo, despite the fact that the reported role of DJ-1 as a redox sensor was supported. And Claudio Luchinat and his coworkers describe how magnetic susceptibility anisotropy tensors of Co(II) and Ni(II) can be used to probe the molecular structure in the vicinity of the metal ion, as exemplified by a study of human carbonic anhydrase [17]. Hence, this information can be used to probe the coordination sphere of the metal center upon inhibitor binding in pharmaceutically relevant proteins, contributing to the design of selective drugs in a structure-based approach.

Larry Que and coworkers characterize a series of Fe(III)–O–Cr(III) and Fe(III)–O–Mn(III) complexes, the latter serving as direct models of the Fe(III)–X–Mn(III) active site in Fe/Mn enzymes such as Class 1c ribonucleotide reductase and R2-like ligand-binding oxidase. They report the first directed synthesis of a Fe–O–Mn complex capable of binding exogenous ligands and show that the asymmetric Fe–O–M vibration correlates with the Fe–O bond length [18].

Aside from metal ion coordination, also non-covalent weak interactions, like hydrophobic and hydrogen bond interactions, play crucial roles in controlling the functions of biomolecules.

Shun Hirota and his colleague review the recent progress in protein design, including redesign and reuse of the heme pocket and other protein scaffolds, design of the heme protein interface, as well as the de novo design of metalloproteins [19].

De novo design of thiolate-rich proteins is used by Vince Pecoraro and coworkers to incorporate second coordination sphere D-amino acids to alter the coordination geometry of the incorporated Cd(II) center [20]. The D-amino acid changes the chirality within the central hydrophobic packing region of a three-stranded coiled coil. When incorporated above and below the Cd(II), a substantially higher percentage of four-coordinate species is formed. Hence, a powerful tool is presented to open up new directions in metalloprotein design.

Continuing with metalloproteins, Claudia Blindauer, a former Ph.D. student and now at the University of Warwick, investigates in detail the dynamics of Zn(II) binding to two seed-specific metallothionein homologues from *Arabidopsis thaliana* by MS and NMR [21]. Interestingly, in the homologue Zn_6MT4a, Zn(II) dynamics are much faster than in Zn_6MT4b.

This special issue closes with the contribution of Helmut Sigel's daughter-in-law Eva Freisinger, who together with coworkers characterizes the metal ion binding abilities and metalation pathway of a plant metallothionein from the banana *Musa acuminata* [22]. With a combination of multiple spectroscopic and biochemical techniques, the protein

fold as well as the role of a single histidine residue in metal ion coordination of Zn(II), Cd(II), and Co(II) is characterized. It is shown that the metalation pathway follows an unprecedented route via a $M(II)_3$-species with the metal ions coordinated separately to the N- and C-terminal cysteine-rich regions, and only the fourth M(II) brings the two terminal ends together leading to a globular protein arrangement.

With the help of many of Helmut Sigel's long-term friends and colleagues and also with contributions from family members we were able to assemble this special issue that shows the wide variety of topics nowadays defining the field of biological inorganic chemistry. Together with many more friends and colleagues from all over the world we join and congratulate Helmut on this special occasion!

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