Intimate Relationships between Metal Ions and Nucleic Acids**

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The recent High-Level Research Conference in Inorganic Chemistry of the European Science Foundation (ESF), which takes place biannually, focused this time entirely on the interactions of metal ions with nucleic acids and the multiple research areas and applications resulting thereof. The conference chair, Jan Reedijk (Leiden University, The Netherlands), together with Rachid Adghoughi (ESF) and his team, brought together 68 participants from 18 countries, all devoted to nucleic acids in some way or another. The "Pallas Athene" of the John S. Latsis Benefit Foundation at the outskirts of Athens provided a splendid setting for intense scientific discussions. The scientific program encompassed 24 lectures, covering all major areas of bioinorganic nucleic acid chemistry. An additional six short oral presentations, 25 3-minute poster presentations, and about 35 posters yielded further highly interesting aspects within the different subfields. In particular, the 3-minute "flash" poster presentations proved to be a great success, as they stimulated intense discussions between younger and more senior scientists throughout the week.

On Monday morning, after an adventurous bus ride through Athens' heavy traffic and a few introductory words by Jan Reedijk on the "rules" of this conference, Bernhard Lippert (University of Dortmund, Germany) opened the meeting with an exciting overview of what metal ions can do to nucleobases in terms of altering their acid–base and hydrogen-bonding properties: In some cases, a drop in pK_a value of up to 7 log units may be achieved![1] With this lecture, the basis was set for the week. Einar Sletten (University of Bergen, Norway) continued with the unexpected outcome of his NMR studies regarding the interaction of a helical cylinder with a palindromic DNA double helix. The cylinder, built of two M^{n+} centers connected by three bipodal bisazopyridine ligands (Figure 1 A, upper), breaks up the double-stranded (ds) DNA and reassembles the pieces into a three-way junction with the cylinder in its center (Figure 1 A, lower). Anne Hotze and Michael Hannon (both University of Birmingham, UK), in whose laboratory the cylinder was developed,[2] elaborated then on various derivatives and further modes of interaction with DNA: With longer non-palindromic dsDNA, binding to the major groove was observed and atomic force microscopy revealed a histone-like wrapping of the DNA around the cylinder. In addition to these fascinating modes of interaction, derivatives of the cylinder show an unexpected high antitumor activity and represent a new class of antitumor agents, thus opening up completely new directions in this field.[3]

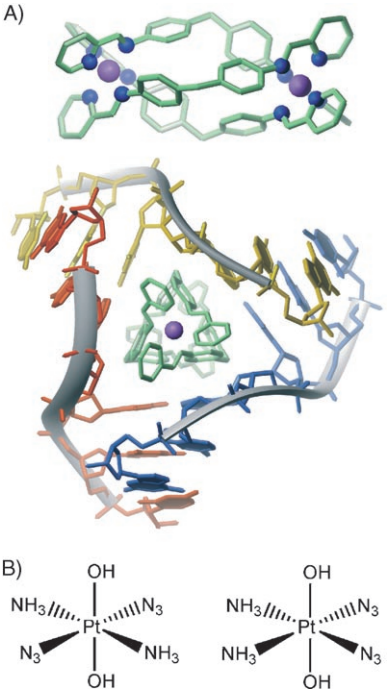

Figure 1. Metal-ion complexes that interact with DNA: A) A molecular cylinder (top) wraps a DNA three-way junction around its hydrophobic center (below, PDB no. 2ET0).[2] B) New photoactivatable drugs based on $Pt^{2+/4+}$. Interestingly, the *trans* complex (left) is as cytotoxic as the *cis* form (right).[4]

Following these presentations, a series of talks covered the still highly active field of cisplatin chemistry: Jiri Kozelka (Université René Descartes, Paris, France) began by discussing the latest insights into the kinetics and structure of the platinum(II)–DNA cross-link. Paolo Carloni (International School for Advanced Studies, Trieste, Italy) presented highly sophisticated QM/MM calculations on the cisplatin–DNA adduct, and Giovanni Natile (Universita degli Studi di Bari, Italy) talked about the noncovalent interactions between this drug and DNA. Overall, it becomes increasingly clear that weak interactions within the proximity of the platinum(II)–DNA adduct sum up to a considerable force that must not be neglected when investigating this complex. Finally, Victor Brabec (Academy of Sciences of the Czech Republic, Brno) wrapped up the classical platinum(II) field by looking at the biological aspects of Pt^{2+}-induced DNA lesions, that is, how coordinated nucleotides are repaired and thus how cellular resistance is built up.

A second area of anticancer research that has developed over the past few years from the cisplatin field involves drugs with a different activation mechanism as well as drugs based on metal ions other than Pt^{2+}/Pt^{4+}. Peter Sadler (University of Edinburgh, UK) began with two highly interesting Pt^{IV}-diazide

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compounds (Figure 1B): Complexes of the type $[Pt(N_3)_2(NH_3)_2(OH)_2]$ are nontoxic in the dark, but they are activated upon irradiation with light through loss of dinitrogen and thereby become cytotoxic.[4] As a consequence, only the irradiated tumor tissue is affected by this platinum compound—a very elegant trick indeed. Further potential photoactivatable drugs, this time based on dirhodium complexes, were presented by Claudia Turro (Ohio State University, USA). Helen Chifotides (Texas A&M University, College Station, USA) and Patrick McGowan (University of Leeds, UK) nicely rounded up this topic with results from experiments on potential drugs based on rhodium, ruthenium, and titanium.

An ongoing challenge remains the development of highly sensitive and selective sensor molecules to detect metal ions or other molecules at low concentrations. Yi Lu (University of Illinois at Urbana-Champaign, USA) presented in a "firework" the latest results from his group on the highly selective sensing of metal ions, metabolites, or drugs such as cocaine by using a combination of DNAzymes and aptamer sequences with different fluorophores.[5] After a short presentation by Andriy Mokhir (University of Heidelberg, Germany) on DNA sensing, Chuan He (University of Chicago, USA) introduced the participants to the fascinating field of metal detoxification in bacteria. Proteins bind with high selectivity and affinity to metal ions and subsequently to promoter regions of genes, thereby initiating the cellular detoxification mechanism. Modification of these proteins with fluorophores gives highly efficient sensors.[6]

Besides these more "encompassing" themes, several talks were also devoted to smaller equally interesting subjects. Juan Subirana (ETSEIB, Barcelona, Spain) summarized a multitude of X-ray crystal structures of DNA oligonucleotides focusing on metal-ion coordination and hydrogen-bonding networks, and Valérie Pierre (California Institute of Technology, Pasadena, USA) described a fascinating structure of a DNA intercalation complex. Two lectures highlighted different aspects of oligonucleotide-modifying metal-ion complexes: Sunhee Choi (Middlebury College, USA) reported on the usage of a Pt^{4+} complex (normally used as an anticancer drug) to oxidize guanine at its 8-position, and Fabrizio Mancin (Università di Padova, Italy) described the optimization of various Zn^{2+} complexes used as artificial DNA nucleases. That such complexes can be used not only to cut DNA but also to change the helical shape was demonstrated by Bernhard Spingler (University of Zürich, Switzerland), who introduced us to a less common form of DNA, namely, left-handed Z-DNA.

Another highlight of the conference were the lectures on the rapidly evolving use of DNA in nanotechnology. Andrew Houlton (University of Newcastle-upon-Tyne, UK) started this series of talks by discussing several aspects of his work on the development of DNA-based electronics; for example, the shift in reduction potential of ferrocenyl-modified DNA, which is attached to semiconductor electrodes of silicon. Two further talks by Jens Müller (University of Dortmund, Germany) and Mitsuhiko Shionoya (University of Tokyo, Japan) concentrated on different strategies to incorporate metal ions within the double-helical structure of DNA. Shionoya presented data on a very fruitful cooperation with the group of Thomas Carell (LMU Munich, Germany) on the programmable self-assembly of metal ions within DNA (Figure 2A): A clever choice of modified nucleobases in a dsDNA enabled the researchers to incorporate both Cu^{2+} and Hg^{2+} ions in a controlled way at specific locations.[7] The last speaker in this series on the nucleic acid nanoworld, Catalina Achim (Carnegie Mellon University, Pittsburgh, USA), reported on a bipyridine-modified peptide nucleic acid (PNA) and its metal-ion-binding properties. Such molecules may also well find potential applications as nanomagnets or devices.

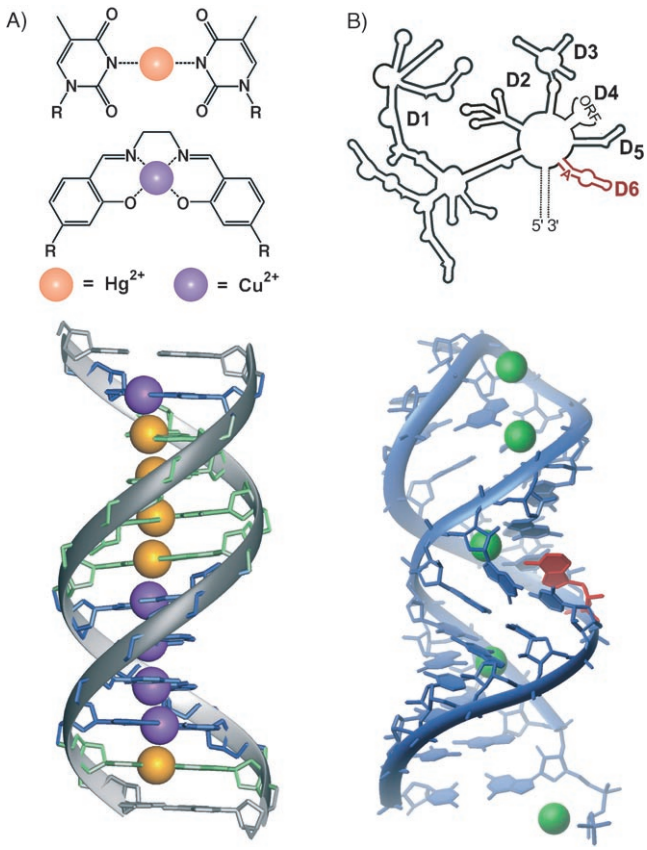

Figure 2. Different modes of metal-ion coordination to nucleic acids. (A) Specific coordination of Hg^{2+} and Cu^{2+} ions by modified nucleobases in the center of a dsDNA. The metal ions line up like a wire, promising a potential application in nanoelectronics.[7] (Coordinates of the model structure[7b] are provided courtesy of Jens Müller, University of Dortmund). B) Five Mg^{2+} ions bind in the major groove of the branch domain 6 (D6) of a self-splicing group II intron ribozyme.[10] Branch A is shown in red, and the Mg^{2+} ions are modeled into the coordinates of the NMR structure (PDB no. 2AHT).

The presentations on Thursday then focused almost entirely on the complicated and manifold world of metal-ion interactions with RNA. Following up on the lecture by Sofi Elmroth (Lund University, Sweden) two days earlier on RNA as a potential target of platinum(II) drugs, catalytic RNAs, that is, ribozymes, now became the focus. The first two lectures were devoted to small ribozymes. Victoria DeRose (University of Oregon, Eugene, USA) described EPR and kinetic studies on the hammerhead ribozyme, which shows some unexpected properties with regards to metal-ion binding: Mg^{2+} is usually considered the natural cofactor for catalysis of

ribozymes,[8] but in the light of recent results that Mn^{2+} accelerates the cleavage reaction tremendously,[9] one could ask if indeed this transition-metal ion also binds to the hammerhead ribozymes within living systems—after all, the employment of transition-metal ions is very common in metalloproteins. As a second small ribozyme, the hepatitis delta virus sequence and its interaction with antibiotic Cu^{2+} complexes were discussed by Wojciech Szczepanik (University of Wroclaw, Poland).

Monitoring the binding of Mg^{2+} to RNA in general is very challenging owing to its inherent spectroscopic silence. Lanthanide(III) ions have been shown before to be good mimics of Mg^{2+}, and hence one can make use of their intrinsic luminescent properties as was explained by Janet Morrow (SUNY Buffalo, USA). Although quite tricky, luminescence lifetime measurements allow determination of the coordination number as well as of the state of dehydration. The final lecture in this RNA series was devoted to the large group II intron ribozymes and their interactions with Mg^{2+} ions. Roland Sigel (University of Zürich, Switzerland) described the NMR solution structure of the branch domain 6 of these self-splicing introns[10] and the subsequent experiments to elucidate the coordinating sites and the thermodynamic properties of Mg^{2+} binding to this part of the catalytic core. Surprisingly, five Mg^{2+} ions bind to specific sites within this 27-nucleotide-long hairpin, one of them in close proximity to the reaction center (Figure 2B).

The honor to deliver the final talk in this conference belonged to Bengt Nordén (Chalmers University of Technology, Göteborg, Sweden): He presented a fascinating overview of the different possibilities that linear dichroism spectroscopy offers to investigate the molecular recognition of DNA by dyes and metal-ion complexes, but also other oligonucleotides including PNAs. Jan Reedijk together with Istvan Horvath (Eötvös University, Budapest, Hungary), the organizer of the 2008 conference, delivered the concluding remarks, before the generous Greek banquet.

To conclude, these four days provided the bioinorganic nucleic acid community with an excellent stage and setting to share the latest developments in their laboratories and to intensely discuss future directions. Among those, new approaches in the search for metal-ion-based anticancer drugs, detailed characterization of structure, function, and application of catalytic nucleic acids, as well as further development of DNA-based nanotechnology should be mentioned. It is beyond doubt that quite a number of new ideas and collaborations have been implemented at this meeting.

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