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Metal-ion nucleic-acid interactions: A personal account

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ABSTRACT

A brief personal account is given on how I observed and enjoyed studying metal-ion nucleic-acid binding over the last 40 years, based on contributions from my own group and from our collaborators and competitors.

Metal ions do bind to ligands, and the nucleic acids not only can act as metal-binding ligands, but also as hydrogen-bonding species, as typically known for Watson–Crick base pairs. In the study of metal-nucleic acid binding, coordination and hydrogen bonding do often occur together and may act synergistically. In this account I will highlight a selection of our most important findings within the context of this special issue.

1. Introduction

The interaction between metal ions and nucleic acids has been of interest for many disciplines and for several decades. The interests of inorganic chemists in this field was no doubt boosted by the early indications that the anticancer drug cisplatin and analogs would bind to DNA, as Rosenberg hypothesized in the early 1970s [1] and it were in fact papers of Bau, Jordanov and Dehand in the mid-nineteen seventies [2–4] on studies with DNA fragments, that hinted towards Guanine-N7 as a likely primary target.

Of course all DNA (and RNA) bases have donor sites that could bind to metal ions, platinum not excluded. In Fig. 1 I have schematically depicted the structures of the 4 DNA bases connected in an oligonucleotide and indicated their heavy metal-ion binding sites at ambient pH; of course metal ions (being acidic) can also bind while removing a hydrogen ion from an N—H – even at neutral pH. Binding to oxygen atoms of DNA bases is also known, but this is rare for transition-metal ions and heavy metal ions.

2. The start

My own interest in the fundamentals of metal-ion nucleic-acid binding, for sure was inspired by the interest in the mechanism of action of cisplatin during the mid 1970s, mentioned above, and it was stimulated by my work on the coordination chemistry of heterocycles, the azoles, started after my PhD [5]. In an early review in this journal, almost 25 years ago, i.e. in the jubilee 200th volume [6], I addressed for the first time the issue of synergy between hydrogen bonding and coordination. And later this synergy has returned several times in our work; most recently I discussed this issue in more general terms in an Alfred Werner centennial and memorial paper [7].

Below I shall highlight a selection of our most important findings in the context of this special issue. It should be clear that this is not a review, neither comprehensive, nor selective. In fact I will primarily deal with some personal experiences and feedback, by using this short account on the occasion of a special thematic issue of Inorganica Chimica Acta.

With the transfer of my group from Delft to Leiden – in 1979 – a flourishing collaboration started with (the late) Jacques H. Van Boom. He and his group were able to synthesize small DNA fragments at the 10–50 mg scale, allowing the synthesis of its metal coordination compounds on the 10 mg scale. Subsequent collaborations in Leiden with (the late) Cees Altona, an expert in conformational analysis of sugars using high-resolution NMR, allowed us to study the 3D structure of Pt-DNA adducts on the double-stranded (ds) oligonucleotide level, well before any XRD structures were available, see below.

The collaboration was extended to the team of Jean-Claude Chottard (Paris) during the 1980s, after having met at the Toulouse ICCC. In a project sponsored by the Dutch–French Cultural Agreements we had a very stimulating cooperation for about a decade, resulting in joint papers [8,9]. Since 1992 our international collaborative work was further stimulated and expanded by several COST collaborations (see acknowledgements below for details).

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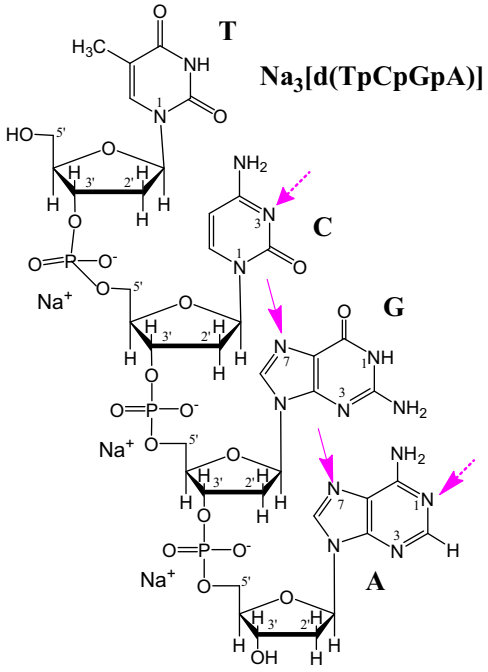

Fig. 1. The 4 nucleic acid bases of DNA, depicted in a single-strand chain, with sodium counter cations. The heavy-metal binding sites at ambient pH are indicated with pink arrows. The dashed pink arrows show the metal-binding sites that are not directly accessible in double-stranded DNA. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Given the fact that we could also chromatographically separate and subsequently structurally characterize small platinated DNA fragments by NMR, Annemarie Fichtinger-Schepman, at that time (1983–1985) a postdoc in my group, could for the first time prove that "real" DNA (calf thymus), after platination, could be *in vitro* degraded by "cutting" enzymes to form smaller fragments and nucleosides. We found that the major metal adduct (in fact about 2/3 of all platinated species) appeared to be *cis*-Pt(NH$_3$)$_2$(dGdG), i.e. with the metal chelated to the N7 atoms of 2 neighboring guanines. The structures of such adducts with Pt compounds were first studied by high-field solution NMR, and a few years later proven in the solid XRD by Lippard et al. [10], followed by others and us [11,12]. At that stage these adducts consisted only of single stranded DNA and they comprised small fragments only.

The rationales for the preferred binding at the N7 of guanosine, over that of adenosine, were proposed to be related to both steric hindrance and hydrogen bonding, as schematically illustrated in Fig. 2.

3. Kinked ds-DNA after platination

Thanks to the availability of oligonucleotides in large enough amounts from direct synthesis in the Van Boom laboratory the next major stage, i.e. the step to determine structures of platinated double-stranded DNA became possible, well before the commercial DNA synthesizers could produce mg amounts of oligonucleotides. Based on a full conformational analysis of a such a synthetic platinated double-stranded DNA fragment, Jeroen den Hartog managed to be the first to conclude for a relatively small kink in the ds-DNA [13] after the platination, by using high-field high-resolution NMR. Initially this outcome was hard to believe, but meanwhile it has become a generally accepted fact. This kinked structure has been confirmed by several groups in subsequent NMR studies, using similar DNA sequences [14–17] and ultimately by X-ray structures from the Lippard team [18,19].

In the early days when it was realized that Pt would preferentially bind to guanine-N7, speculations had appeared that the O6 of guanosine could be involved, in binding and perhaps form a so-called Pt-N7O6 chelate [3]. However, so far this has never been proven by XRD structures for guanine derivatives (Cambridge database, release 2015; in fact only some structures with hypoxanthine and theophyllinato chelating to a metal ion are known [20]). It was subsequently believed that perhaps the guanine-O6 only plays a role in H bonding to the co-ligands at platinum, and this idea initially was supported by the observation that – at the time – all antitumor-active Pt compounds at least contained a H-bond donor group at the amine, able to donate a H bond to O6. (*NB: Later, a number of Pt compounds were reported to display anticancer activity and that do not contain the N—H group; this is not discussed further here, as such compound may not necessarily bind to nucleic acids*).

From a personal perspective the discovery of the kink in the double-stranded DNA by NMR of an oligonucleotide in the PhD work of Jeroen den Hartog in 1985 and the almost simultaneous discovery by postdoc Annemarie Fichtinger-Schepman that some 2/3 of all adducts are Pt(GpG-N7,N7), were perhaps the most exciting observations from our work in the 1980s. Independent of the sequence of the DNA, the same kink was found at GG in all cases and in most of them amounts to some 40 ± 15 degrees. Later, in 1995 this kinked structure was confirmed by the Lippard team in the solid state by using X-ray diffraction [18].

4. Latest developments

In the 1990s our lab also focused on the kinetics of Pt binding to guanine and trying to understand why N7 binding takes places, with many S-donor ligand in the cell. We found that certain S-donor ligands, especially methionines, could act as intermediates

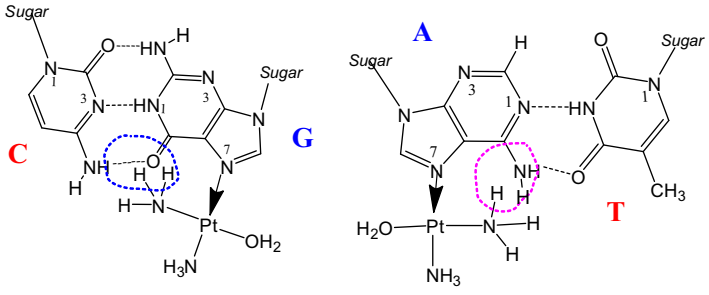

Fig. 2. Coordination of N7 atoms of base-paired Adenine and Guanine to a *cis*-bis(ammine)aquaplatinum(II) cation. Hydrogen bonding (G) stabilization versus hydrogen–hydrogen repulsion (A) is illustrated and highlighted with dashed curves.

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