



Connectivity patterns and rotamer states of nucleobases determine acid–base properties of metalated purine quartets



Marc Sven Lüth^{a,c}, Eva Freisinger^{b,*}, Gunnar Kampf^{a,c}, Marta Garijo Anorbe^a, Rolf Griesser^c, Bert P. Operschall^c, Helmut Sigel^{c,*}, Bernhard Lippert^{a,*}

^a Fakultät Chemie und Chemische Biologie (CCB), Technische Universität, Dortmund 44221 Dortmund, Germany

^b Department of Chemistry, University of Zürich, Winterthurerstrasse 190, 8057 Zürich, Switzerland

^c Department of Chemistry, Inorganic Chemistry, University of Basel, Spitalstrasse 51, 4056 Basel, Switzerland

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ABSTRACT

Potentiometric pH titrations and pD dependent ¹H NMR spectroscopy have been applied to study the acidification of the exocyclic amino group of adenine (A) model nucleobases (N9 position blocked by alkyl groups) when carrying *trans*-a₂Pt^{II} (with a = NH₃ or CH₃NH₂) entities both at N1 and N7 positions. As demonstrated, in trinuclear complexes containing central A–Pt–A units, it depends on the connectivity pattern of the adenine bases (N7/N7 or N1/N1) and their rotamer states (head–head or head–tail), how large the acidifying effect is. Specifically, a series of trinuclear complexes with (A–N7)–Pt–(N7–A) and (A–N1)–Pt–(N1–A) cross-linking patterns and terminal 9-alkylguanine ligands (9MeGH, 9EtGH) have been analyzed in this respect, and it is shown that, for example, the 9MeA ligands in *trans*-,*trans*-,*trans*-[Pt(NH₃)₂(N7-9MeA-N1)₂{Pt(NH₃)₂(9EtGH-N7)₂}(ClO₄)₆·6H₂O (**4a**) and *trans*-,*trans*-,*trans*-[Pt(NH₃)₂(N7-9EtA-N1)₂{Pt(CH₃NH₂)₂(9-MeGH-N7)₂}(ClO₄)₆·3H₂O (**4b**) are more acidic, by ca. 1.3 units (first pK_a), than the linkage isomer *trans*-,*trans*-,*trans*-[Pt(CH₃NH₂)₂(N1-9MeA-N7)₂{Pt(NH₃)₂(9MeGH-N7)₂}(NO₃)₆·6.25H₂O (**1b**). Overall, acidifications in these types of complexes amount to 7–9 units, bringing the pK_a values of such adenine ligands in the best case close to the physiological pH range. Comparison with pK_a values of related trinuclear Pt^{II} complexes having different co-ligands at the Pt ions, confirms this picture and supports our earlier proposal that the close proximity of the exocyclic amino groups in a head–head arrangement of (A–N7)–Pt–(N7–A), and the stabilization of the resulting N6H⁺⋯H₂N6 unit, is key to this difference.

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1. Introduction

The polarization of ligands as a consequence of coordination to a metal cation, and its effects on ligand acidity and/or reactivity has been known since the early days of coordination chemistry [1,2]. It took longer to recognize that additional factors and in particular the microenvironment around a potentially ionizable group and the medium (dielectric constant of solvent) markedly contribute to the overall effect. It was the undisputed achievement of model bioinorganic chemistry, among others, to provide a deeper understanding of this phenomenon [3–9]. When the field of metal–nucleic acid chemistry became popular during the second half of the last century, the topic of acidity/basicity alterations of nucleobases due to metal binding likewise started to receive attention, last but not least because of its potential impact on biorelevant features such as nucleobase tautomerism, base pairing and mispairing patterns, as well as acid–base catalysis involving nucleic acids [10–31].

Studies in particular with complexes of Pt^{II} and model nucleobases, nucleosides, and nucleotides [17–25] as well as DNA fragments [32–39] have revealed moderate pK_a shifts of N–H groups of nucleobases [32–34,37] following metal binding to an endocyclic ring N atom, unless a change in the tautomeric structure of the nucleobase (“metalated rare tautomer”) had occurred [29,30,40–44]. While in the first case pK_a values typically dropped by 1–2 units, e.g., for N1H in guanine complexes with Pt^{II} at the N7 position [24,45], larger shifts of several units were seen in complexes in which the metalated nucleobase had adopted a rare tautomer structure [29,40–44,46]. However, even in the absence of any tautomerization process, the pK_a shift can be dramatic (9–10 units), provided that two metal ions coordinate simultaneously and the anion formed is favorably stabilized by an intramolecular interaction with a second nucleobase [47]. We had first observed this phenomenon with a trinuclear Pt^{II} complex consisting of two 9-methyladenine (9MeA) ligands cross-linked by a *trans*-(NH₃)₂Pt^{II} unit via the two N7 positions of the nucleobase, with two additional Pt^{II} units coordinated at the N1 positions [47–50]. Here the pK_a value of the exocyclic amino group had shifted from ca. 17 in the free base [51,52] to 7.9 (pK_{a1}) in the metal complex. It had been proposed by us, as later supported by X-ray data on a related model system with

* Corresponding authors.

E-mail addresses: freisinger@chem.uzh.ch (E. Freisinger), helmut.sigel@unibas.ch (H. Sigel), bernhard.lippert@tu-dortmund.de (B. Lippert).

1,9-dimethyladenine ligands [53] as well as a series of mixed nucleobase complexes containing adenine ligands [48,49], that the stabilization of the N6H^- group by the N6H_2 donor across the N7-Pt-N7 linkage was primarily responsible for the large drop in $\text{p}K_a$, possibly reinforced by hydrogen bond formation involving the ammonia co-ligands of the Pt^{II} and/or water molecules [48,54]. In any case, the relatively short distance between the two N6 positions of the cross-linked adenine bases (if in a head-head rotamer state) seemed to be important to facilitate this interaction.

Two follow-up questions emerged from this initial finding, namely (1) to what extent do the two other feasible adenine cross-linking patterns, N1-Pt-N1 and N1-Pt-N7 influence the acidity of N6H_2 , and (2) what is the effect of the co-ligands of the two Pt ions at the two available N7 and N1 sites? It is obvious, that all three cross-linking patterns (Chart 1) require a head-head orientation of the two adenine bases in order to allow for relatively short separations of the exocyclic N6 atoms. In the following we shall discuss the situation with the N1-Pt-N1 cross-link and compare it with that in N7-Pt-N7 . Unfortunately we do not have a structurally characterized example of a trinuclear Pt complex with a central N1-Pt-N7 cross-link presently available.

2. Results and discussion

2.1. Acidity of metal-coordinated ligands

Before discussing the acid-base properties of adenine complexes, a brief summary of factors influencing these shall be made:

- (i) Charge of metal ion: In the simplest case, with all ligands being identical, the higher oxidation state of a metal causes a more pronounced ligand acidification [55]. π -donating properties of the metal ion (example Ru^{II}) may reverse this trend, however [56].
- (ii) Distance between metal ion and acidic proton: A two-bond distance between the metal and the proton, such as in aqua complexes, can cause dramatic $\text{p}K_a$ shifts, from 15.7 (water) to 2.2 in $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$ ($\text{p}K_{a1}$) [57], for example. In metal nucleobase complexes distances between the metal ion and an acidic proton are usually considerably larger, and consequently the acidification caused solely by the charge effect of the metal ion is smaller.
- (iii) Co-ligands: In square-planar and octahedral metal complexes the co-ligands in general and the ligand *trans* to the acidic ligand in particular has an effect on the latter (“*trans* influence”), subject to variations in charge and electronegativity (with simple ligands such as Cl^- or H_2O) as well as donor strength and π -bonding properties (donors or acceptors). Ligands such as 2,2'-bipyridine or 2,2',2''-terpyridine have marked acidifying effects on water ligands [58–60], for example, whereas strongly electron-donating ligands have the opposite effect.
- (iv) Linkage isomerism: With larger ligands having more than a single metal binding site, such as with nucleobases, the site of metal attachment can have a distinct effect on the acidity of a proton remote from the metal ion (or the basicity of the site without a proton bonded), even if no change in tautomeric structure is involved. Binding of a metal to either N1 or N7 of an adenine nucleobase is a prime example: The acidifying effect of a (dien) Pt^{II} entity (dien = diethylenetriamine, 1,4,7-triazaheptane) on N6H_2 of 9MeA is higher if the metal sits at N1 rather than at N7 [61], and ring-N protonation to give the 9-methyladeninium cation ligand occurs at lower pH at N7 if a Pt^{II} is bonded to N1 , than the other way around [62].
- (v) Microenvironment: As briefly mentioned above, and substantiated in more detail below, the microenvironment around the

ionizable entity and its deprotonated entity, respectively, has a major influence on the $\text{p}K_a$ of a metalated nucleobase. This includes also differences in rotamer states of metal ions attached to deprotonated exocyclic nucleobase groups, e.g., N4 of cytosine or N6 of adenine [63].

2.2. Types of Pt^{II} complexes studied

The three types of Pt^{II} complexes schematically depicted in Chart 1 belong to a larger class of molecular architectures consisting of three or four metal entities of linear coordination geometry and four nucleobases, giving rise to open or closed nucleobase quartets. We became interested in such complexes both by aspects of supramolecular chemistry (“metalated nucleobase quartets”) [64–66] and by possible uses as telomere-targeting units [67–72]. Their geometries are governed by right angles provided by N1,N7 bridging purine bases

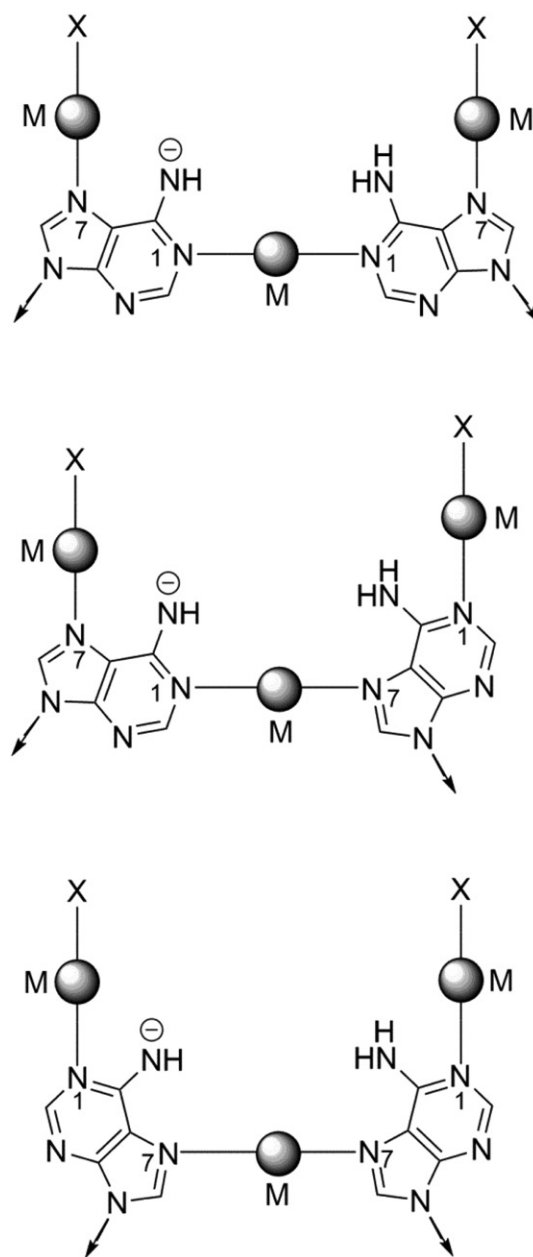


Chart 1. Three principal arrangements of two hemi-deprotonated adenine ligands in head-head orientation and cross-linked by linear metal ions ($\text{M} = \text{trans-}a_2\text{Pt}^{\text{II}}$): N1-Pt-N1 , N1-Pt-N7 , and N7-Pt-N7 (top to bottom).

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