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Bioinorganic Studies on the Structure and Reactivity of Metal-Ion Complexes of Nucleotides and Related Compounds

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Abstract. The interactions of metal ions with nucleotides and related compounds is a fertile field in bioinorganic chemistry. An understanding of the quantitative origins of the stability of such complexes and of their structure in solution can lead to a better understanding of important biological processes and may lead to new drugs.

Helmut Sigel studied chemistry at the University of Basel, where he received his Ph.D in 1964 under the guidance of *H. Erlenmeyer*. He completed his habilitation in 1967, and from 1968 to 1969 he was a visiting staff member at Cornell University. He returned to Basel after this period and received the *Alfred Werner* Prize of the Swiss Chemical Society in 1977. He was promoted to Professor (Extraordinarius) in 1978. Professor *Sigel* is well-known in the bioinorganic community and beyond, not least for the series of books 'Metal Ions in Biological Systems' which he coedits with his wife, *Astrid*. Further details of his research interests are to be found at http://www.chemie.unibas.ch/AC/Sigel/Sigel.html.

Nucleotides belong to the most important derivatives of orthophosphoric acid which occur in nature [1]; they are at the crossroad of many metabolic processes and are substrates for numerous metal-ion-dependent enzymic reations [1][2]. The research of my laboratory focuses on the interrelations between stability, structure, and reactivity of nucleotide/metal-ion complexes in solution, using mainly potentiometric pH titrations, spectrophotometry, and ^{1}H-NMR spectroscopy as tools.

Binary nucleotide complexes can give rise to intramolecular macrochelate formation due to the ambivalent properties of nucleotides (*Scheme 1*) [3], while in ternary or mixed ligand complexes, intramolecular ligand-ligand interactions, mainly of a hydrophobic or aromatic-ring stacking kind, are possible (*Scheme 2*) [4].

The equilibria in *Schemes 1* and *2* provide information about '*recognition*' phenomena which are responsible for the *selectivity* observed in nature and which are reflected already in the simplest transphosphorylation, *i.e.*, in the transfer of a phosphoryl group to water [5][6]. For nucleoside 5'-triphosphates (NTP^{4-}) and diphosphates (NDP^{3-}) this is expressed in a simplified form in *Scheme 3* in which charges have been omitted for simplicity.

Some further examples of recent pertinent results are summarized below:

- The nucleobase residues of pyrimidine-nucleotides are not involved in binding metal ions such as Mg^{2+} or Zn^{2+} as is evident from straight-line relations between complex stability ($\log K^{M}_{ML}$) and phosphate-group basicity (pK^{H}_{HL})[7], whereas purine-nucleotides form macrochelates with ions such as Mn^{2+}, Cu^{2+}, and Zn^{2+} involving N(7) of the nucleobase (*Scheme 1*) [3].
- Similarly, intramolecular stacking interactions (*Scheme 2*) are also much more pronounced with purines than with pyrimidines [4]. For example, in the ternary Cu(1,10-phenanthroline)-(2'-deoxyguanosine 5'-monophosphate) complex, the stacked isomer (*Scheme 2*) reaches a formation degree of about 90% in aqueous solution, leaving for the 'open' and macrochelated isomers only *ca.* 5% each (*Schemes 1* and *2*) [8].
- Attempts to employ nucleotide analogs as therapeutic agents are longstanding. A promising approach focuses on 9-[2-(phosphonomethoxy)-ethyl]adenine (PMEA) and related derivatives [9], which may be considered as acyclic analogs of adenosine 5'-monophosphate (AMP^{2-}) and which have pronounced antiviral properties. We quantified the isomeric equilibria occurring in PMEA complexes [10] and showed, for example, that 17 (±3)% of Cu(PMEA) exist with a single Cu^{2+}-phosphonate interaction, 34 (±10)% involve in addition coordination of the ether O-atom, and a further 49 (±10)% of copper are bound to the phosphonate group, the ether O, and N(3) of the purine residue. In contrast, with AMP^{2-}, 54 (±8)% occur with a Cu^{2+}-phosphate interaction only and 46 (±8)% as a macrochelate involving also N(7) (*Scheme 1*) [11].
- Such structural differences are reflected in the reactivity. For example, PMEA is an excellent promotor of the Cu^{2+}-facilitated hydrolysis (*Scheme 3a*) of adenosine 5'-triphosphate (ATP^{4-}) [6] [12]. These and similar results also provide an explanation [13] for the observation that $PMEA_{PP}^{4-}$ (diphosphorylated PMEA) is initially a better

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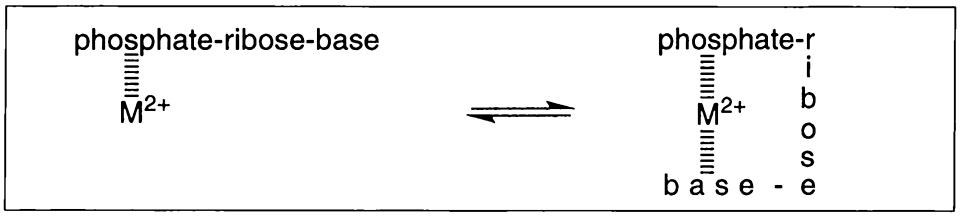
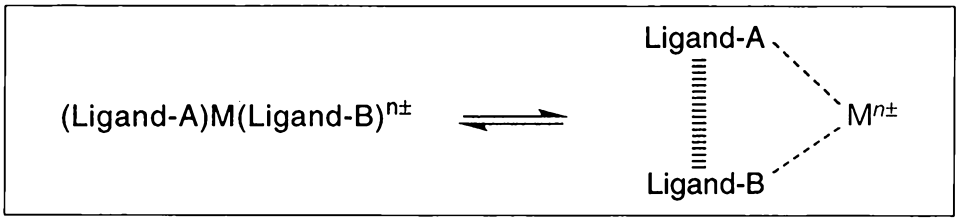
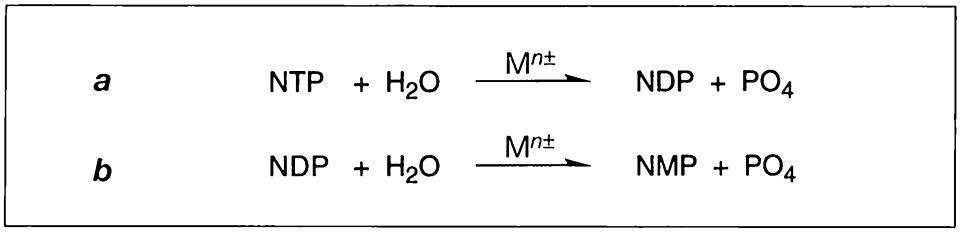
Scheme 1



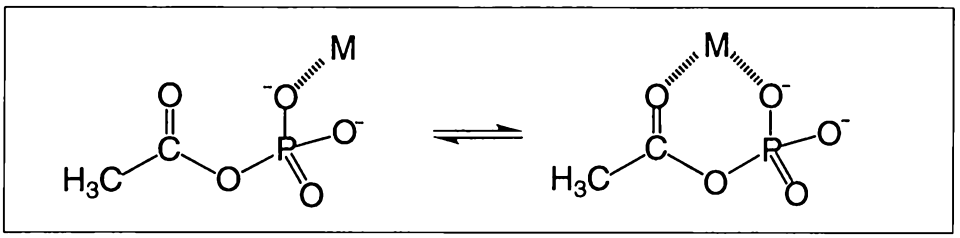
Scheme 2



Scheme 3



Scheme 4



substrate than 2'-deoxy-ATP^{4-}, *e.g.*, for reverse transcriptases [9].

- Acetyl phosphate (AcP^{2-}), the mixed anhydride of acetic acid and phosphoric acid, is one of the so-called 'energy-rich' anhydrides. It plays a significant role in many regulatory processes in biology and is also important for the regeneration of ATP. Despite the fact that many of these reactions involve also metal ions, no (reliable) stability constants for AcP complexes were available; the reason for this is that AcP is very unstable with respect to hydrolysis. By taking into account the recently measured stabilities of $M(HPO_4)$ species, the stability constants of AcP complexes could be determined [14], and it was shown that the 'closed' isomer indicated in *Scheme 4* occurs to an extent of 41 (±5)% for Mg(AcP) and 59 (±6)% for Zn(AcP).
- Little information exists on the metal-ion binding properties of phosphorothioate derivatives of nucleotides, which are employed in the antisense strategy or as tools for sequencing and mutagenizing DNA. The stabilities of metal-ion complexes of adenosine 5'-*O*-thiomonophosphate (AMPS^{2-}) have now been determined, and the ratios of *O/S* coordination were calculated for several divalent metal ions [15]. Work with uridine 5'-*O*-thiomonophosphate and methyl *O*-thiophosphate is in progress.
- Since the discovery of *Cisplatin*, *cis*-diamminedichloroplatinum(II), a powerful antitumor agent, the interest in interactions between kinetically inert metal ions and nucleobases, nucleotides, and nucleic acids has increased tremendously [2]. We have recently studied the effect of nucleobase-coordinated *cis*-$\{(NH_3)_2Pt\}^{2+}$ on the acid-base properties of guanine derivates [16] and on the metal-ion binding properties (towards Mg^{2+}, Cu^{2+}, Zn^{2+}) of the phosphate group in such derivatives [17][18], and quantified the extent of outer-sphere macrochelate formation, which occurs *via* $Pt(NH_3)\cdots O_3P$ hydrogen bonds, in the ternary *cis*-$[(NH_3)_2Pt(2'\text{-deoxyguanine } 5'\text{-monophosphate})_2]^{2-}$ complex [18].

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