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Review

Steric guiding of metal ion binding to a purine residue by a non-coordinating amino group: Examplified by 9-[(2-phosphonomethoxy)ethyl]-2-aminopurine (PME2AP), an isomer of the antiviral nucleotide analogue 9-[(2-phosphonomethoxy)ethyl]adenine (PMEA), and by related compounds☆

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Contents

☆ Abbreviations and definitions (further abbreviations are defined in the legends to Figs. 6 and 9): Ade, adenine; Ado, adenosine; AMP^{2-}, adenosine 5′-monophosphate (Fig. 8); 2A9MP, 2-amino-9-methylpurine (Fig. 1); 6A9MP, 6-amino-9-methylpurine=9-methyladenine (=9MAde; Fig. 1); 6A9RP, 6-amino-9-(β-D-furanosyl)purine=adenosine (=Ado; Fig. 1); ATP^{4-}, adenosine 5′-triphosphate; BI, benzimidazole=1,3-dideazapurine (Fig. 2); ClBI, 5(6)-chlorobenzimidazole (Fig. 2); ClFBI, 6-chloro-5-fluorobenzimidazole (Fig. 2); DMBI, 1,4-dimethylbenzimidazole (=6,9-dimethyl-1,3-dideazapurine) (Fig. 4); dATP^{4-}, 2′-deoxyadenosine 5′-triphosphate; 2,9DMP, 2,9-dimethylpurine (Fig. 1); 6,9DMP, 6,9-dimethylpurine (Fig. 1); DNBI, 5,6-dinitrobenzimidazole (Fig. 2); dPMEA^{2-}, dianion of 9-(5-phosphonobutyl)adenine=3′-deoxa-PMEA^{2-} (see legend for Fig. 8); DRB, 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (Fig. 2); I, ionic strength, k_a, micro acidty constant = intrinsic acidity constant; K_a, acidity constant (=macro acidity constant or global acidity constant); L, general ligand; M^{2+}, general divalent metal ion; MABI, 1-methyl-4-aminobenzimidazole (=9-methyl-1,3-dideazapurine) (Fig. 4); 9MAde, 9-methyladenine (=6-amino-9-methylpurine=6A9MP) (Figs. 1 and 4); MBI, 1-methylbenzimidazole (Fig. 2); 9MP, 9-methylpurine (Fig. 1); NBI, 5(6)-nitrobenzimidazole (Fig. 2); PM^{2-}, =PMEA^{2-} and PME2AP^{2-}, sometimes also including PME-R^{2-} (Fig. 8), dPMEA^{2-}, and AMP^{2-} (Fig. 9); PMEA^{2-}, dianion of 9-[(2-phosphonomethoxy)ethyl]adenine (Fig. 8); PME2AP^{2-}, dianion of 9-[(2-phosphonomethoxy)ethyl]-2-aminopurine (Fig. 8); PMEApp^{4-}, diphosphorylated PMEA^{2-}; PME-R^{2-}, R is always a non-interacting residue (Fig. 8) [dianion of (phosphonomethoxy)ethane=ethoxymethanephosphonate if R = H]; Pu, purine derivative; 9RP, 9-(β-D-ribofuranosyl)purine (Fig. 1); R–PO_3^{2-}, simple phosphate monoester or phosphonate ligand with R representing a non-interacting residue (Fig. 9). In formulas like M(H;PM)$^+$ the H$^+$ and the PM^{2-} are separated by a semicolon to facilitate reading, yet they appear within the same parentheses to indicate that the proton is at the ligand without defining its location. Species written without a charge either do not carry one or represent the species in general, i.e., independent of their deprotonation or complexation degree, e.g., PMEA; which of the two possibilities applies is always clear from the context.

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ABSTRACT

The role that the amino group plays in the metal ion (M^{2+}) binding properties of the adenine residue is of great relevance because this residue occurs widely in nature. It is the aim of this review to evaluate this role. We consider first several 9-methylpurine derivatives with amino and methyl substituents at various positions: the data indicate that substituents at C6 inhibit M^{2+} binding at both, the N1 and N7 sites. To separate these effects we use (i) *o*-amino(methyl)pyridines as models for the pyrimidine part of the adenine residue, i.e., for N1, and (ii) benzimidazole derivatives regarding the properties of N7. The inhibiting effects of *ortho*-amino and *ortho*-methyl groups on N1 of pyridines are identical, which agrees with the fact that such an amino group has no basic properties at all. This is different with 1-methyl-4-aminobenzimidazole (MABI) (=9-methyl-1,3-dideazaadenine) and 1,4-dimethylbenzimidazole (DMBI) (=6,9-dimethyl-1,3-dideazapurine) because the amino group in MABI still has some basic properties and thus, its steric inhibition is somewhat smaller than that of the methyl group in DMBI. It is suggested that the methyl group in DMBI mimics the steric effects of (C6)NH_2 upon (N7)-M^{2+} coordination in the adenine residue. The evaluation of the N1 versus N7 dichotomy for 2,9-dimethylpurine, 2-amino-9-methylpurine, and 6-amino-9-methylpurine (=9-methyladenine) reveals that the (N7)-M^{2+} isomer dominates. It is further suggested that the (C6)NH_2 adenine group may act as a proton donor and the O atom of a coordinated water molecule as acceptor. The metal ion-binding properties of the two acyclic nucleotide analogues 9-[(2-phosphonomethoxy)ethyl]adenine (PMEA) and 9-[(2-phosphonomethoxy)ethyl]-2-aminopurine (PME2AP), which are structural isomers due to the shift of the (C6)NH_2 group in PMEA to the C2 site in PME2AP, fit into the indicated coordination patterns. In the monoprotonated species $M(H;PMEA)^+$ and $M(H;PME2AP)^+$ the proton is located at the phosphonate group and M^{2+} at N7. However, the $M(H;PME2AP)^+$ complexes are considerably more stable than the $M(H;PMEA)^+$ ones: indeed, the steric effect on N1 is the same in both types of complexes, but the one on N7 has disappeared in $M(H;PME2AP)^+$. Furthermore, there is evidence that the (N7)-coordinated M^{2+} interacts with the $P(O)_2(OH)^-$ group in an outersphere manner leading to practically identical formation degrees of the macrochelates formed with Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} or Zn^{2+} [on average $65 \pm 15\%$ (3σ)]. The coordination chemistry of $PMEA^{2-}$ and $PME2AP^{2-}$ differs for the 3d ions as well, whereas for the alkaline earth ions, which are primarily coordinated (like all other M^{2+}) to the phosphonate group, 5-membered chelates form involving the ether O of the $-CH_2CH_2-O-CH_2-PO_3^{2-}$ residue. In contrast, Co^{2+}, Ni^{2+}, and Cu^{2+} form with $PMEA^{2-}$ a further isomer, which involves next to the ether O also N3; macrochelates involving N7 and the phosphonate-coordinated M^{2+} are minority species, but for Ni^{2+} and Cu^{2+} they occur and formation degrees of all four isomers could be determined. In the M(PME2AP) complexes a N3 interaction practically does not occur; macrochelate formation of the phosphonate-coordinated M^{2+} with N7, which is the dominating species for Co^{2+}, Ni^{2+}, Cu^{2+} or Zn^{2+} is important here. The possible interrelations between M^{2+} coordination and the antiviral activity of the two acyclic nucleotide analogues, PMEA being especially active, are discussed shortly.

1. Introduction

Altered nucleobases [1,2] or otherwise altered nucleotides [3–6] are nowadays commonly employed as probes. One of these compounds is 2-aminopurine, a structural isomer of adenine, in which the amino group is at C2 instead of C6 and as such it can form stable Watson–Crick-type base pairs with thymine [7]. In nucleic acid research it is often used as a molecular marker due to its excellent fluorescent properties [8], which are exploited in numerous studies in structural biology and biophysics [9,10], including charge transfer mechanisms in DNA [11,12]. Incorporation of 2-aminopurine also perturbs the dynamics and structure of DNA [13] and it modulates the minor groove properties in duplex RNA [14].

These few examples demonstrate the significant effect that the switch of the amino group from C6 to C2 has on the interaction of the purine residue with other molecules. How is the situation with metal ions? That metal ions interact with the adenine, or more generally, the purine residue, is well known [15–18], e.g., in nucleotides [19–25] or nucleic acids [23,25–30]. However, the quantitative effect of the amino group on metal ion binding at N1 and N7 of the adenine residue is not well described yet. The intrinsic basicities of the nitrogen sites decrease in the order N1 > N7 > N3 [17,31,32]; the corresponding micro acidity constants for monoprotonated adenosine are $pk_{a/(N1)H} = 3.63$, $pk_{a/(N7)H} = 2.15$, and $pk_{a/(N3)H} = 1.5$ [33]. Hence, all three nitrogen atoms are thus expected to coordinate metal ions. Clearly, N3 of the adenine residue is least prone to bind metal ions; indeed, (N3)-metal ion interactions are rare, but known [3,34–37] (see Section 7.6). Metal ion binding to N1 or N7 is common (e.g., [38]; see also Sections 5, 7.3, and 7.6), but a dichotomy of N1 versus N7 binding is expected [32,39].

N1 of the adenine residue is a pyridine-type nitrogen and studies with 2-aminopyridine derivatives showed that an *ortho*-amino group next to a N site hinders metal ion binding [40]. Similarly, N7 is an imidazole-type nitrogen [41] and based on benzimidazole derivatives [42] it is concluded that the (C6)NH_2 substituent also exercises some steric hindrance on metal ion coordination of the adenine N7 [43]. Hence, the question arises: to which extent are the different basicities of N1 and N7, and thus their metal ion affinities, possibly compensated by different dimensions of the steric effect of the (C6)NH_2 group on metal ion binding at N1 and N7? Tentatively one may expect that inhibition at N7 is somewhat smaller because it is one atom further away from the NH_2 group than N1.