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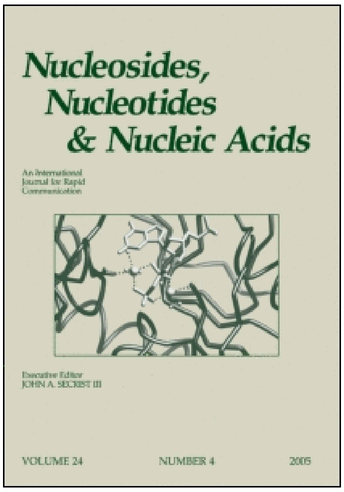

Nucleosides, Nucleotides and Nucleic Acids

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NMR Study on The Tuning of North South Equilibrium in Nucleos(t)ides by Metal Ion Interactions

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NMR STUDY ON THE TUNING OF NORTH ⇄ SOUTH EQUILIBRIUM IN NUCLEOS(T)IDES BY METAL ION INTERACTIONS

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ABSTRACT: The NMR study on the interactions of dG*p*Me (**1**), Me*p*dG (**2**) and dG (**3**) with Mg^{2+}, Zn^{2+} and Hg^{2+} ions in D_2O solution has shown that binding of softer metal ions to N7 shifts N ⇄ S pseudorotational equilibrium towards N-type conformations. At the same time the population of the *anti* conformers is slightly increased.

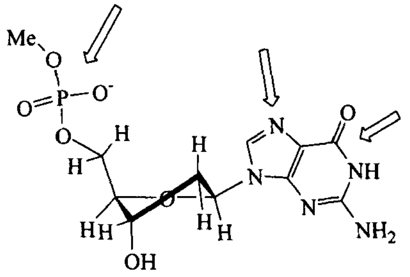
INTRODUCTION

Studies on the interaction of divalent metal ions to nucleosides and nucleotides have shown that soft metal ions bind to N7 of guanine.[1,2] Little is however known in the literature about how the metal ion promoted redistribution of π-electron density alters the anomeric effect of the constituent nucleobase and affects the conformational degrees of freedom along sugar-phosphate backbone. Two simple model compounds, Me*p*dG (**1**) and dG*p*Me (**2**), consist of all the essential structural elements of DNA to which metal ions can interact: β–*D*–2'-deoxyribofuranose, phosphodiester fragment and heterocycle. In the present study, the drive of North (N, ≈C3'-*endo*) ⇄ South (S, ≈C2'-*endo*) pseudorotational equlibrium[3,4] and the conformational changes across glycosyl bond in Me*p*dG (**1**) and dG*p*Me (**2**) were analysed in relation to parent dG (**3**)[5] as the affinity of Mg^{2+}, Zn^{2+} and Hg^{2+} aqua-ions for base complexation versus phosphate binding increases.

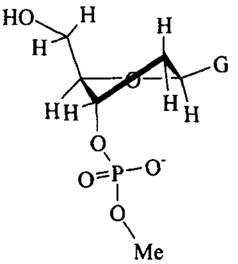
RESULTS AND DISCUSSION

The concentrations of Mg^{2+}, Zn^{2+} or Hg^{2+} ions have been gradually increased by titration of aqueous solutions of Me*p*dG (**1**), dG*p*Me (**2**) and dG (**3**). The ^1H, ^{13}C, ^{15}N and

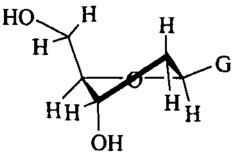
^{31}P NMR chemical shift changes showed that hard Mg^{2+} ions interact preferentially with the phosphate oxygens in Me*p*dG (**1**), whereas in the case of dG*p*Me (**2**) the interaction of Mg^{2+} ions with the phosphate oxygens competes with the interaction to C6=O carbonyl group. Softer Zn^{2+} and Hg^{2+} ions were found to show strong binding affinity to N7 in both Me*p*dG (**1**) and dG*p*Me (**2**).



Me*p*dG (**1**)



dG*p*Me (**2**)



dG (**3**)

The analysis of solution conformation of 2'-deoxyribofuranosyl moiety in **1** - **3** is based on five proton-proton coupling constants ($^3J_{1'2'}$, $^3J_{1'2''}$, $^3J_{2'3'}$, $^3J_{2''3'}$ and $^3J_{3'4'}$) acquired at several M^{2+} concentrations from $R(=[M^{2+}]/[\text{Nucl.}])=0.1$ to 2.0. The interpretation of $^3J_{HH}$ coupling constants of **1** - **3** in terms of a two-state N $\rightleftarrows$ S pseudorotational equilibrium[3-9] resulted in the geometries of the minor N-type conformers characterised by the puckering intermediate between C1'-*endo*–C2'-*exo* twist and C2'-*exo* envelope canonical forms ($-32° < P_N < -20°$, $33° < \Psi_m^N < 38°$), whereas the major S conformers are characterised by C2'-*endo* puckering ($159° < P_S < 167°$, $37° < \Psi_m^S < 40°$). At 298 K the populations of C2'-*endo* pseudorotamers in metal-free aqueous solutions of Me*p*dG (**1**), dG*p*Me (**2**) and dG (**3**) are 68%, 75% and 66%, respectively (FIG. 1). Titration of **1** - **3** with Mg^{2+} ions caused only minor (<1 unit %) shift of N $\rightleftarrows$ S pseudorotational equilibrium towards N. On the other hand, the shift of N $\rightleftarrows$ S pseudorotational equilibrium towards N–type conformers upon addition of two molar equivalents of Zn^{2+} was five unit % for Me*p*dG (**1**), three unit % for dG*p*Me (**2**) and one unit % for dG (**3**). As the Hg^{2+} concentration was increased above R=0.2 precipitation prevented extraction of individual $^3J_{HH}$ coupling constants. The shift of N $\rightleftarrows$ S pseudorotational equilibrium towards N–type conformers upon addition of 0.2 molar equivalents of Hg^{2+} was one unit % for both Me*p*dG (**1**) and

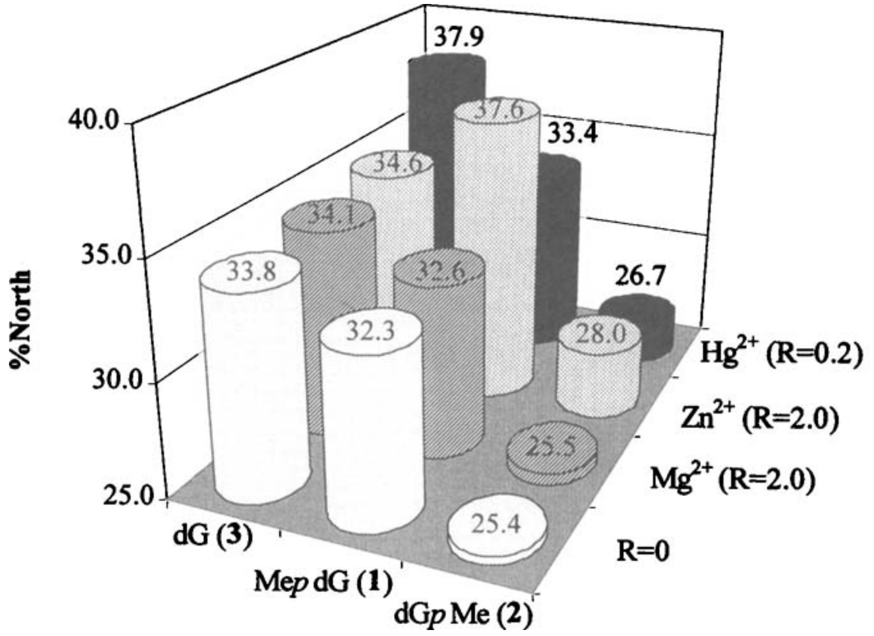


FIG. 1. The shift of N ⇄ S equilibrium in **1** – **3** upon the interaction with M^{2+} ions

Table 1. The change in the population of *syn* rotamers* in **1-3** with the nature of M^{2+} ions

	M^{2+} free	Mg^{2+}	Zn^{2+}
Me*p*dG (**1**)	38	26	15
dG*p*Me (**2**)	69	71	40
dG (**3**)	45	58	50

*Calculated[10] from % H8 ↔ H1' 1D NOE enhancements for R=2.0.

dG*p*Me (**2**) and four unit % for dG (**3**). The increase in the population of N-type pseudorotamers upon binding of Zn^{2+} to Me*p*dG (**1**) is bigger than in the case of dG*p*Me (**2**) which suggests that neighbouring phosphodiester group is involved in the partial formation of chelate, which results in additional drive towards N-type pseudorotamers.

The binding of divalent metal ions to **1** - **2** causes a shift of *syn* ⇄ *anti* equilibrium towards *anti*, which is larger for softer Zn^{2+} than for harder Mg^{2+} ions (Table 1).

We can conclude that interactions of softer Zn^{2+} and Hg^{2+} ions with N7 of **1** - **3** result in the increased population of N-type pseudorotamers, which can be interpreted by strengthening of the anomeric effect (*i.e.* $n_{O4'} \rightarrow \sigma^*_{C1'-N9}$ delocalization is stabilised when imidazole moiety becomes less electron rich). Our results suggest that when a metal ion drug (*e.g.* cisplatin) binds to N7 of particular dG residue in DNA it locally results in a preferential drive towards N-type sugar thus bringing 5'-residue closer to 3'-residue.

EXPERIMENTAL SECTION

NMR spectra were recorded at 299.9 MHz on Varian Unity Plus and at 600.1 MHz on Varian Inova NMR spectrometers at the National NMR Center of Slovenia. Sample concentration was 10 mM in D_2O (99.9% D). The sample temperature (298K) was controlled to approximately ±0.5 K. Metal ion concentration was gradually raised by simple titration by nitrate salts to 0.1, 0.2, 0.5, 1.0 and 2.0 molar equivalents (R). 1D NOE experiments were run with saturation of individual lines within the multiplet and by internal subtraction of on– and off–resonance spectra.

The computer program PSEUROT[6] has been used for the conformational analysis of sugar moiety. The final convergence resulted in the global minima for each metal ion data set with root–mean–square error below 0.3 Hz and the maximum discrepancy between experimental and calculated coupling constants below 0.5 Hz.

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REFERENCES

1. *Interactions of Metal Ions with Nucleotides, Nucleic Acids, and Their Constituents*; Sigel, A.; Sigel, H. (Eds.) Vol. 32, M. Dekker Inc.: New York, **1996**; pp. 814.
2. (a) Marzilli, L. G.; de Castro, B.; Solorzano, C. *J. Am. Chem. Soc.* **1982**, *104*, 461-466. (b) Miller, S. K.; VanDerveer, D. G.; Marzilli, L. G. *J. Am. Chem. Soc.* **1985**, *107*, 1048-1055.
3. Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205-8212. *ibid* **1973**, *95*, 2333-2344.
4. Plavec, J.; Tong, W.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1993**, *115*, 9734-9746.
5. Polak, M.; Plavec, J. *Nucleosides & Nucleotides* **1998**, *17*, in press.
6. de Leeuw, F. A. A. M.; Altona, C. *J. Comp. Chem.* **1983**, *4*, 428-437.
7. Altona, C.; Francke, R.; de Haan, R.; Ippel, J. H.; Daalmans, G. J.; Westra Hoekzema, A. J. A.; van Wijk, J. *Magn. Reson. Chem.* **1994**, *32*, 670-678.
8. Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1996**, *61*, 266-286.
9. Luyten, I.; Thibaudeau, C.; Chattopadhyaya, J. *J. Org. Chem.* **1997**, *62*, 8800-8808.
10. Rosemeyer, H.; Toth, G.; Golankiewicz, B.; Kazimierczuk, Z.; Bourgeois, W.; Kretschmer, U.; Muth, H.-P.; Seela, F. *J. Org. Chem.* **1990**, *55*, 5784-5790.