Inorganica Chimica Acta, 76 (1983) L209–L212

Quantum Chemical Investigations on Group IA and IIA Metal Ion–DNA Base Complexes

KRITSANA P. SAGARIK and BERND M. RODE

Institut für Anorganische und Analytische Chemie, Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

Received December 6, 1982

In previous papers [1, 2] we have investigated the influence of metal ions on the hydrogen bonds of the Watson-Crick DNA base pairs, finding that metal ions can either stabilize or destabilize the donor–acceptor interaction of the hydrogen bonds connecting the purine or pyrimidine structures.

In addition to these results we now have obtained information about the interaction of various metal ions with adenine, thymine, guanine and cytosine. For these studies we have again used *ab initio* MO SCF calculations with minimal GLO basis set. The exponents of this basis set [3, 4] have been used successfully in previous investigations [1, 2].

The geometries of purine and pyrimidine base were taken from the experimental data presented by Spencer [5] and kept constant throughout the calculations, as it is known that the minimal basis set is suitable for the optimization of the inter- although not for intramolecular geometrical parameters [6]. The molecular structures of the bases and their reactive sites suitable for metal ion binding are illustrated in Fig. 1. Metal ions selected in this study are Li^+, Na^+, Mg^{2+} and Ca^{2+}. These metal ions are considered to be of special interest in relation to nucleic acid biology [7, 8]. The orientations of the metal ions in the field of the bases were selected only in the molecular plane according to the electrostatic molecular potential maps for nucleotide bases presented by Bonaccorsi *et al.* [9]. The energy optimized geometrical param-

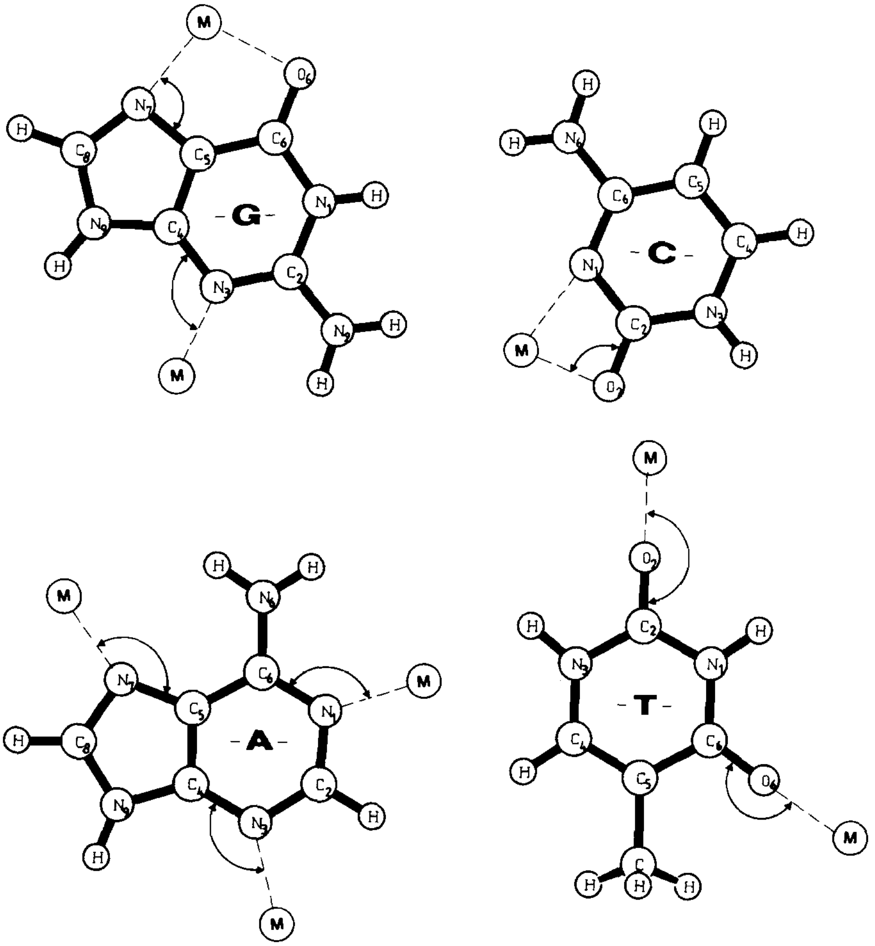

Fig. 1. Molecular structures of guanine(G), cytosine(C), adenine(A) and thymine(T). M = Reactive site suitable for metal ion binding.

0020-1693/83/0000-0000/$03.00

eters describing the positions of the metal ion are the distances and angles shown in Fig. 1.

It is well known [10] that the intermolecular interaction energy obtained from the *ab initio* calculations with a minimal basis set is overestimated due to the basis set superposition error. To eliminate this error, the Boys–Bernardi counterpoise procedure [11] was employed in every final interaction energy calculation. In this procedure, each molecule is computed in the presence of the 'empty' basis set functions of its partner in the system. Therefore, the interaction energy in our study is defined as:

$$\Delta E = SCF^{\dagger} - [SCF(A) + SCF(B)]$$

where $SCF^{\dagger}$ = SCF energy of the whole system, SCF(A) = SCF energy of the subsystem A calculated with the basis set of the whole system, SCF(B) = SCF energy of the subsystem B calculated with the basis set of the whole system.

Following this approach, it has been shown that the computed binding energy with a small basis set can be improved, especially in large molecular systems such as the G–C and A–T base pairs [1, 2].

The calculations were performed partly on the CDC cyber 170/720 computer of the Interuniversity Computer Center at the Technical University of Vienna, and partly at the CDC cyber 74 computer of the University of Innsbruck. The program used is discussed in detail in ref. 12.

Results and Discussion

The energy optimized metal ion binding positions at various reactive sites of A, T, G and C, together with the corresponding binding energies, are listed in Table I.

In order to compare systematically the strength of metal ion–base interactions among various metal ions at various reactive sites of the bases, the binding energies are demonstrated graphically in Fif. 2 for all reactive sites.

The relative binding energy order of the metal ions binding with all bases investigated here is

$$Mg^{2+} > Ca^{2+} > Li^{+} > Na^{+}$$

Adenine Complexes

Neutral adenine has three reactive sites available for the metal ion, namely N_1, N_3 and N_7. Our results indicate that the ions of the first and second main group elements prefer to bind firstly at N_3 rather than at N_1 or N_7 (see Fig. 2).

Guanine Complexes

The reactive sites of guanine are N_3, N_7 and O_6. The simultaneous binding of metal ion to N_7 and O_6 is the most favourable form for all metal ions.

TABLE I. Energy Optimized Metal Ion Binding Positions at Various Reactive Sites of A, T, G and C, together with the Corresponding Binding Energies.

Adenine: metal ions at N_1 position

Metal Ion	M–N_1(Å)	M–$\hat{N}_1$–C_6 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.85	129	–42.4
Na^+	2.20	132	–28.6
Mg^{2+}	1.92	131	–110.9
Ca^{2+}	2.31	139	–69.8

Adenine: metal ions at N_3 position

Metal Ion	M–N_3(Å)	M–$\hat{N}_3$–C_4 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.85	128	–46.4
Na^+	2.20	130	–31.6
Mg^{2+}	1.92	128	–118.4
Ca^{2+}	2.31	135	–75.5

Adenine: metal ions at N_7 position

Metal Ion	M–N_7(Å)	M–$\hat{N}_7$–C_5 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.85	141	–36.3
Na^+	2.20	144	–23.0
Mg^{2+}	1.92	141	–99.9
Ca^{2+}	2.31	140	–59.5

Thymine: metal ions at O_2 position

Metal Ion	M–O_2(Å)	M–$\hat{O}_2$–C_2 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.76	180	–33.6
Na^+	2.10	180	–23.2
Mg^{2+}	1.80	180	–94.8
Ca^{2+}	2.18	180	–59.7

Thymine: metal ions at O_6 position

Metal Ion	M–O_6(Å)	M–$\hat{O}_6$–C_6 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.76	180	–40.1
Na^+	2.10	180	–29.2
Mg^{2+}	1.80	175	–109.9
Ca^{2+}	2.17	155	–73.4

Guanine: metal ions at N_3 position

Metal Ion	M–N_3(Å)	M–$\hat{N}_3$–C_4 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.85	116	–35.8
Na^+	2.20	116	–21.0
Mg^{2+}	1.90	114	–97.6
Ca^{2+}	2.28	108	–55.1

(continued)

TABLE I (continued)

Guanine: metal ions at $N_7\cdots O_6$ position

Metal Ion	M–N_7(Å)	M–$\hat{N}_7$–C_5 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.92	95	–62.7
Na^+	2.25	101	–50.3
Mg^{2+}	1.97	95	–166.1
Ca^{2+}	2.33	104	–120.9

Cytosine: metal ions at O_2 position

Metal Ion	M–O_2(Å)	M–$\hat{O}_2$–C_2 (degrees)	Binding Energy (Kcal/Mol)
Li^+	1.95	90	–57.8
Na^+	2.20	96	–45.6
Mg^{2+}	1.95	93	–146.5
Ca^{2+}	2.30	100	–104.9

Thymine Complexes

Thymine has only two atoms suitable for metal ions, namely O_2 and O_6. All metal ions prefer binding to O_6.

Cytosine Complexes

The most preferential binding site for metal ions is at N_1 and O_2 simultaneously.

As one can see from Fig. 2, the binding features of monovalent and divalent metal ions with the bases are not qualitatively different. Guanine and cytosine are more suitable for all metal ions than adenine and thymine since the metal ions can form chelate complexes with them. The relative stability order for the metal ions binding to various reactive sites of the free bases of DNA can be written as:

$(N_7\cdots O_6)(G) > (N_1\cdots O_2)(C) > N_3(A) > N_1(A) >$

$O_6(T) > N_7(A) > N_3(G) > O_2(T)$

$(\cdots)$ denotes a chelate binding position.

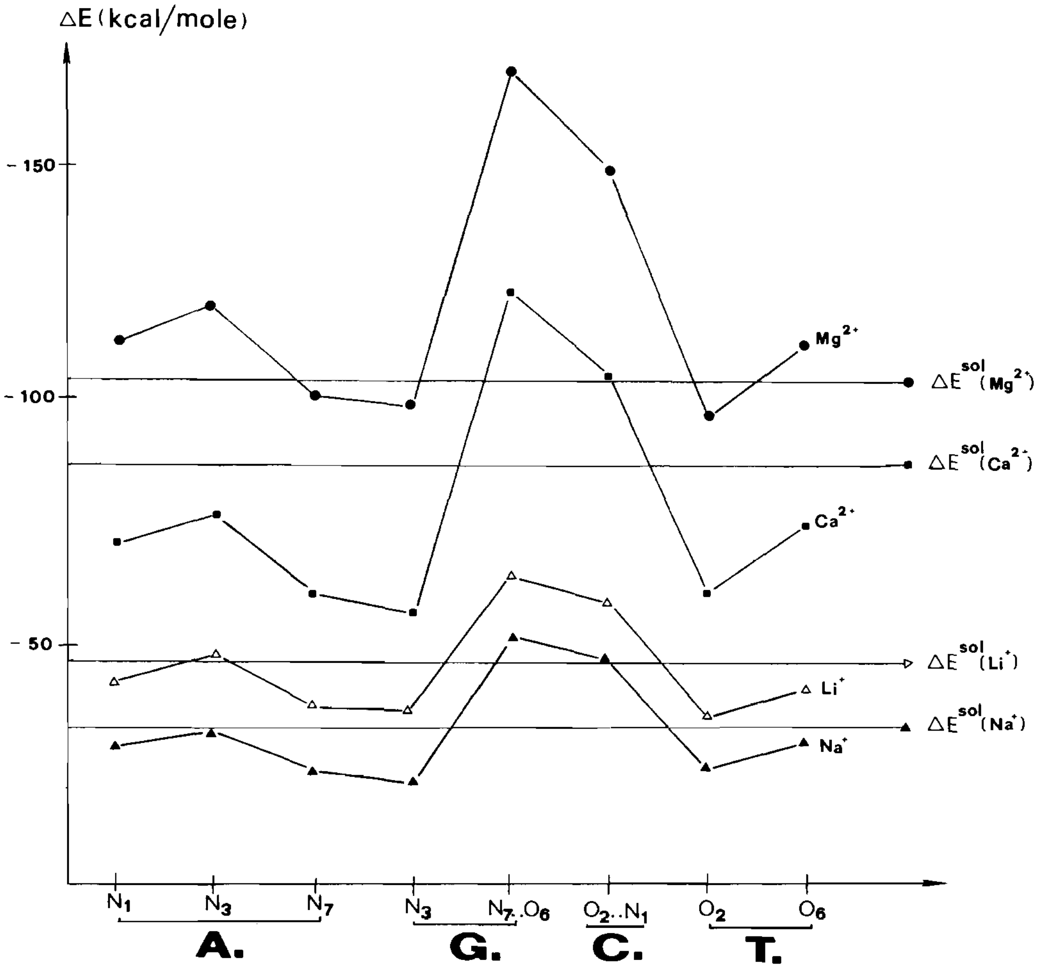

Fig. 2. Comparison of the strength of metal ion–DNA base interaction for various metal ions at the different reactive sites of the bases. The ΔE^{sol} values are given as reference lines as outlined in the text.

The Water–DNA Base Exchange Reaction

In order to predict correctly whether or not a complex is formed in aqueous solution, use of the metal–ligand interaction energy only is not sufficient, since the metal ion is strongly solvated. To form a complex in aqueous solution means to replace a water molecular in the first hydration shell by the approaching ligand.

It was pointed out [13] that in order to explain most of the properties of the hydrated ions correctly, one should consider at least two hydrations shells. From this information, we defined ΔE^{sol} as:

$$\Delta E^{sol} = \Delta E(I) + 2\Delta E(II)$$

where $\Delta E(I)$ and $\Delta E(II)$ are the calculated binding energies per water molecule of the first and second hydration shells, computed using the same basis set as in this work. ΔE^{sol}, $\Delta E(I)$ and $\Delta E(II)$ for the metal ions are shown in Table II and ΔE^{sol} is used as a criterion in determining whether the bases are able to approach the metal ions. The ΔE^{sol} values are seen as reference lines in Fig. 2. The metal ion is supposed to bind to the base whenever $\Delta E/\Delta E^{sol} > 1$.

Our results suggest that in aqueous solution, the ions will show a distinct preferential binding to the bases for the following positions (provided that the ion remains hydrated at the 'backside', *i.e.* the area not directed to the coordination center of the base): Li^+ at $(N_7 \cdot\cdot O_6)(G)$, $(N_1 \cdot\cdot O_2)(C)$ and $N_3(A)$; Na^+ at $(N_7 \cdot\cdot O_6)(G)$ and $N_1 \cdot\cdot O_2)(C)$; Mg^{2+} at $(N_7 \cdot\cdot O_6)(G)$, $(N_1 \cdot\cdot O_2)(C)$, $N_3(A)$, $N_1(A)$ and $O_6(T)$; Ca^{2+} at $(N_7 \cdot\cdot O_6)(G)$ and $(N_1 \cdot\cdot O_2)(C)$.

TABLE II. Calculated Binding Energies per Water Molecule of the First(I) and Second(II) Hydration Shell (assuming tetrahedral coordination). Values taken from ref. 13.

Ion	$\Delta E(I)$ (Kcal/Mol)	$\Delta E(II)$	ΔE^{sol}
Li^+	−25.7	−9.8	−45.3
Na^+	−17.3	−7.6	−32.5
Mg^{2+}	−59.4	−21.6	−102.6
Ca^{2+}	−47.1	−19.9	−86.9

Acknowledgement

Financial support by the Federal Ministry of Science and Research (Erl.Zi.18.854/6-10/81) is gratefully acknowledged.

References

1 K. P. Sagarik and B. M. Rode, *Inorg. Chim. Acta,* in press (B364).
2 K. P. Sagarik and B. M. Rode, *Inorg. Chim. Acta,* in press (B584).
3 B. M. Rode, *Mh. Chemie, 106,* 339 (1975).
4 B. M. Rode and K. H. Gstrein, *J. Chem. Soc. Faraday II, 74,* 889 (1978).
5 M. Spencer, *Acta Cryst., 12,* 59 (1959).
6 B. M. Rode and K. P. Sagarik, *Chem. Phys. Letters, 88,* 337 (1982).
7 G. I. Eichhorn (editor), 'Inorganic Biochemistry', Elsevier Scientific Publ. Co., Amsterdam (1973).
8 M. Daune, 'Interaction of Metal Ion with Nucleic Acid: Metal Ion in Biological System', *3,* 1 (1974).
9 R. Bonaccorsi, A. Pullman, E. Scrocco and J. Tomasi, *Theor. Chim. Acta (Berl.), 24,* 51 (1972).
10 E. Clementi, 'Lecture Notes in Chemistry 19, Computational Aspects for Large Chemical Systems', Springer-Verlag (1980).
11 S. F. Boys and F. Bernardi, *Mol. Phys., 19,* 553 (1970).
12 R. Ahlrichs, *Theor. Chim. Acta (Berl.), 33,* 157 (1974).
13 B. M. Rode, G. J. Reibnegger and S. Fujiwara, *J. Chem. Soc. Faraday II, 76,* 1268 (1980).