The Influence of Small Monovalent Cations on the Hydrogen Bonds of Base Pairs of DNA

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The influence of small monovalent metal ions on the multiple hydrogen bonds of Watson-Crick DNA base pairs has been theoretically studied, using ab initio *calculations with minimal GLO basis set, and combined with the Boys-Bernardi counterpoise method to eliminate the basis set superposition error. The results were compared with the available experimental data. Only metal ion binding to N3 or N7··O6 of guanine seems to lead to a hydrogen bond stabilization of the G–C pair, whereas in the case of A–T pair no such effect could be observed.*

Introduction

The reported studies on the stability of the helical structure of DNA indicate that the helix stability arises as a consequence of at least four factors: solvent effects, backbone conformations, hydrogen bonds and stacking of the aromatic bases. The last two factors seem to play the most important role [1].

The presence of metal ions at various reactive sites of DNA should also influence the physical properties and chemical reactivity of the polynucleotide chains, which are the fundamental units of the biological systems [2]. Experimental investigations on such effects is restricted by the complexity of the measured thermodynamic quantities. In such cases, quantum chemical methods provide a helpful tool for investigation.

Coordination of transition and some divalent metal ions of the main group elements to DNA have been intensively studied. Several reviews pertaining to this subject have been published previously [3, 4]. However, direct binding of small monovalent cations such as Li^+ to the bases and base pairs has not yet been systematically studied by experimental or theoretical methods.

Some calculations on DNA bases and base pairs have been reported using various techniques, ranging from semiempirical [5, 6] and *ab initio* [7–9] to Monte Carlo methods [10].

In previous papers, theoretical studies on the influence of Li^+ on neighbouring N··H–O and O··H–N–C=O hydrogen bonds have been reported [11, 12]. The results of these *ab initio* calculations showed a considerable enhancement of the donor–acceptor interaction in such hydrogen-bonded systems, due to metal influence.

In this work, we have focused our attention on the effect of small metal ions on the hydrogen bonds linking base pairs of DNA, using Li^+ ion and the Watson-Crick complementary base pairs guanine–cytosine (G–C) and adenine–thymine (A–T) as model systems for the *ab initio* calculations.

Method

In the view of *ab initio* methods, chemical systems as considered here are considerably large. We had to use therefore a minimal GLO basis set with the exponents as given in ref. 13. This basis set has been used successfully in previous investigations on similar systems, and comparison with the results obtained from larger basis set calculations have shown that relative changes are reflected correctly in all cases [11, 12].

The standard experimental geometries of A, T, G and C were taken from ref. 14 and kept constant throughout the calculations. The molecular structures of DNA bases are illustrated in Fig. 1.

Although there are many possibilities of DNA base pair formations, the complementary ones proposed by Watson and Crick, A–T and G–C, were selected for model calculations since these forms are believed to be the most favourable ones in nature [1]. The planar orientation of a pair of bases is described by the distance L (see Fig. 2), which corresponds to the distance between C_1' and C_1 of the deoxyribose rings, and by the angles θ_1 and θ_2. These parameters were optimized, starting from experimental values given in Table I, for the base pairs as well as for the Li^+/base pair complexes.

In order to gain more information about the cation binding sites, all possible coplanar orientations of the cation around the bases and base pairs were investigated systematically, namely at N1, N3 and N7 of adenine, N3, N7 and O6 of guanine, N1 and O2 of cytosine and O2 and O6 of thymine. In the

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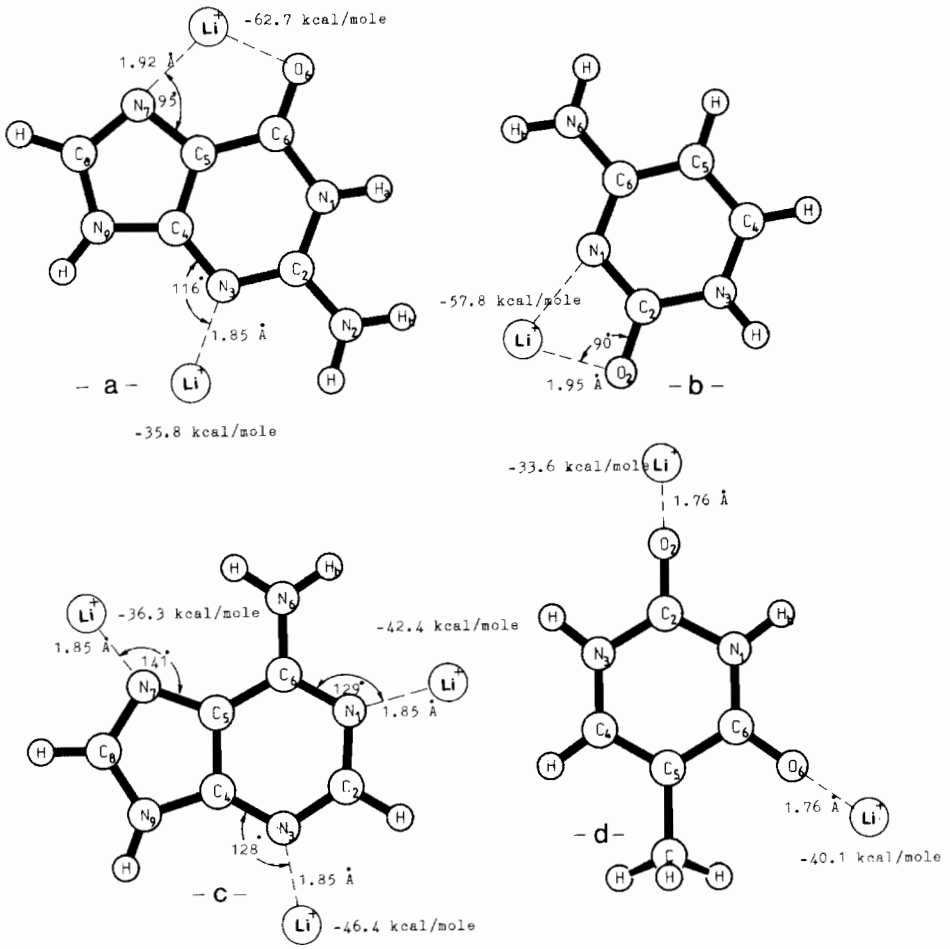

Fig. 1. Molecular structures of DNA bases, optimized metal coordination centers and corresponding binding energies obtained by *ab initio* calculations including the counterpoise correction. a) Li^+/guanine; b) Li^+/cytosine; c) Li^+/adenine; d) Li^+/thyminc.

Watson-Crick base pairs, only N3, N7 and O2 of A–T and N3 and N7 of G–C are available for metal ion coordinations.

TABLE I. Reported Hydrogen Bond Distances, L, θ_1, θ_2.

	Reported geometrical parameters in the solid state	
	Ranging from	to
N–H··O	2.68 Å	3.17 Å
N–H··N	2.94 Å	3.37 Å
L′	10.50 Å	11.50 Å
L	9.90 Å	10.90 Å (calculated from L′)
θ_1 and θ_2	42 deg.	59 deg.

Values taken from refs. 14, 17 and 18. L′ is the distance between C'_1 and C_1 of deoxyribose rings (in real system). L is a similar distance to L′ but carbons (C'_1 and C_1) are replaced by hydrogens.

The interaction energies computed with small basis sets are usually overestimated due to the basis set superposition error. To eliminate this error, the Boys-Bernardi counterpoise procedure [15] was employed in the final energy estimation. In this procedure, each molecule is computed in the presence of the 'empty' basis set functions of its partner in the system.

All calculations were performed at the CDC Cyber 170 computer of the Interuniversity Computer Center at the Technical University of Vienna. The program used here is discussed in detail in ref. 16.

Results and Discussion

The favourable binding positions of Li^+ at various reactive sites of DNA bases and base pairs are shown in Figs. 1 and 2, respectively. The final energies computed from both the conventional *ab initio* method and that combined with the counterpoise

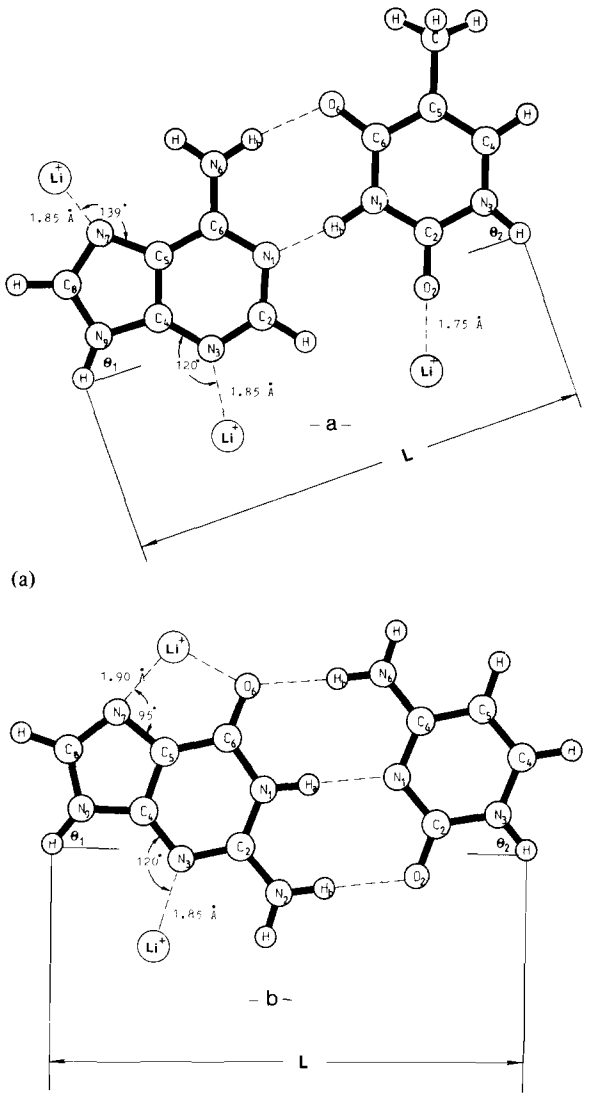

Fig. 2. Watson-Crick base pairs of DNA and optimized metal coordination centers. a) Li^+/A–T; b) Li^+/G–C.

correction of the basis set superposition error are presented in Table II. The optimized values of L, θ_1 and θ_2 and hydrogen bond distances and the hydrogen bond energies of both base pairs and Li^+/base pair complexes are summarized in Table III.

The Net Stabilization Energies (NSE), which are defined as the differences between hydrogen bond energies before and after complexing the metal ion, are also included in Table III.

The Bases and Base Pairs

Although the complementary base pairs of DNA were proposed in 1953 by Watson and Crick [17], there is still no reliable information other than X-ray data pertaining to the geometries of these pairs. The reported values are summarized in Table I.

Compared with our results (see Table I and III), the N–H··O, L, θ_1 and θ_2 values agree well but our N–H··N distances are slightly shorter. It should be emphasized, however, that the equilibrium geometries computed above correspond to the gas phase dimers for which a direct comparison to crystallographic data seems to be improper since it is known that substances containing both acidic and basic functional groups such as DNA, crystallize in a lattice involving very complex neighbour interactions.

Considering the final energies calculated from minimal GLO basis set including the counterpoise correction, G–C and A–T have hydrogen bond energies of 22.8 kcal/mol and 15.9 kcal/mol, respectively. Without corrections, the error results in overestimations of these energies (see Table II) up to 35 kcal/mol for G–C and 24 kcal/mol for A–T.

Several experimental studies on hydrogen bonds involving O–H··O, N–H··O, N–H··N and N–H··F, *etc.* have been done on some small chemical systems in the gas phase [18, 19]. The values quoted for cyclic dimers (involving two hydrogen bonds) such as formamide, formic and trifluoroacetic acid dimers are about 14.5 kcal/mol. In the gas phase, acetic, trimethylacetic, butyric and heptanoic acid can form up to three hydrogen bonds, depending on temperature [18]. The corresponding experimental hydrogen bond energies are about 22.0 kcal/mol.

These experimental data seem to indicate that our computed hydrogen bond energies are reasonable.

The Lithium Complexes with Purines and Pyrimidines

The Lithium–Adenine Complex

The Li^+–N bond length seems to be equal for all binding sites (1.85 Å). The most favourable Li^+/adenine binding site is located at N3 of the six-membered aromatic ring, with a binding energy of 46.4 kcal/mol.

The Lithium–Thymine Complex

The computed Li^+–O distances are identical (1.76 Å). The binding energy for Li^+–O6 is about 6.5 kcal/mol higher than that to O2.

The Lithium–Guanine Complex

The simultaneous binding of Li^+ to N7 and O6 seems to be the most favourable form. The binding energy amounts to 62.7 kcal/mol, the Li^+–N7 distance is about 1.92 Å.

The Lithium–Cytosine Complex

The most preferential binding site is represented by a simultaneous binding of Li^+ to N1 and O2, with a stabilization energy of 57.8 kcal/mol. The Li^+–O2 distance is 1.95 Å.

TABLE II. Energy Values Calculated with *ab initio* Method Using Minimal GLO Basis Set Compared to those after the Counterpoise Correction for Energy Optimized Systems.

System	Â	B̂	SCF(Â)	SCF(Â)′	SCF(B̂)	SCF(B̂)′	SCF†	ΔE	ΔE′
Li^+/A:									
$-Li^+$ at N_1	Li^+	A	−6.4100	−6.4106	−394.1448	−394.1509	−400.6291	−46.6	−42.4
$-Li^+$ at N_3	Li^+	A	−6.4100	−6.4106	−394.1448	−394.1509	−400.6355	−50.6	−46.4
$-Li^+$ at N_7	Li^+	A	−6.4100	−6.4106	−394.1448	−394.1513	−400.6198	−40.8	−36.3
Li^+/T:									
$-Li^+$ at O_2	Li^+	T	−6.4100	−6.4105	−383.1872	−383.1949	−389.6590	−38.8	−33.6
$-Li^+$ at O_6	Li^+	T	−6.4100	−6.4105	−383.1872	−383.1953	−389.6697	−45.0	−40.1
Li^+/G:									
$-Li^+$ at N_3	Li^+	G	−6.4100	−6.4106	−457.7517	−457.7577	−464.2253	−39.9	−35.8
$-Li^+$ at N_7-O_6	Li^+	G	−6.4100	−6.4107	−457.7517	−457.7629	−464.2735	−70.1	−62.7
Li^+/C:									
$-Li^+$ at O_2-N_1	Li^+	C	−6.4100	−6.4106	−333.0977	−333.1080	−339.6107	−64.6	−57.8
A–T:	A	T	−394.1448	−394.1606	−383.1872	−383.2099	−777.3958	−40.0	−15.9
$Li^+/\{A-T\}$:									
$-Li^+$ at N_7(A)	Li^+/(A)	T	−400.6198	−400.6411	−383.1872	−383.2144	−783.8755	−43.0	−12.6
$-Li^+$ at N_3(A)	Li^+/(A)	T	−400.6355	−400.6567	−383.1872	−383.2144	−783.8871	−40.4	−10.0
$-Li^+$ at O_2(T)	A	Li^+/(T)	−394.1448	−394.1666	−389.6590	−389.6852	−783.8774	−46.2	−16.0
G–C:	G	C	−457.7517	−457.7782	−333.0977	−333.1267	−790.9412	−57.6	−22.8
$Li^+/\{G-C\}$:									
$-Li^+$ at N_3(G)	Li^+/(G)	C	−464.2253	−464.2496	−333.0977	−333.1267	−797.4367	−71.3	−37.9
$-Li^+$ at N_7-O_6(G)	Li^+/(G)	C	−464.2735	−464.2964	−333.0977	−333.1267	−797.4677	−60.6	−28.0

Ĉ = Â,B̂ denotes the corresponding subsystem. SCF(Ĉ) denotes the SCF energy of the subsystem Ĉ calculated with the basis set of this isolated subsystem, in hartrees. SCF(Ĉ)′ denotes the SCF energy of the subsystem Ĉ calculated with the basis set of the whole system, in hartrees. ΔE interaction energy computed with respect to energies of the isolated systems, in kcal/mol. ΔE′ interaction energy obtained after the counterpoise correction, in kcal/mol. SCF† SCF energy of the system, in hartrees.

The relative stability order for Li^+ binding to various reactive sites of the free bases of DNA is, therefore:

$$[N7\cdot\cdot O6](G) > [N1\cdot\cdot O2](C) > N3(A) > N1(A) > O6(T) > N7(A) > N3(G) > O2(T)$$

[··] denotes a chelate binding position

The interaction of Zn^{2+} and Na^+ with purine and pyrimidine bases has been studied [9, 20] using SCF LCAO *ab initio* calculations. It has been shown in these references, that the preferred binding sites of Na^+ and Zn^{2+} to guanine and cytosine are identical to ours for Li^+, although the relative stability series are different to some extent.

We can conclude, therefore, that the preferred binding positions of alkali metal ions, such as Na^+ and Li^+, to DNA bases are defined by the chelate bindings to N7··O6 of guanine and N1··O2 of cytosine.

The calculation of any DNA base with 'empty' lithium basis functions leads to a considerable decrease in the total energy (about 6.3 kcal/mol). On the other hand, only about 0.06 kcal/mol are gained when Li^+ ion is computed with the empty functions of the bases. Thus, the maximal basis set superposition error should amount to approximately 6 kcal/mol in all cases of Li^+/base complexes.

The Lithium Complexes with A–T and G–C

The NSE appeared in this section were deduced from the final interaction energies ΔE′ of base pairs and Li^+/base pair complexes (see Table III) including the correction. The results used for further discussion are listed in Tables II and III and Figs. 1 and 2.

The Lithium–G–C Complex

The Li^+ positions in this case are not much different from those in the Li^+/guanine complex. The Li^+–N3(G) and –N7(G) distances are 1.85 Å and 1.90 Å, respectively. Considering the Li^+ ion effect on the hydrogen bonds, Li^+ binding to N3 and N7··O6 of guanine gives rise to NSE values of 15.1 kcal/mol and 5.2 kcal/mol, respectively. Li^+ binding to these positions seems to give no change in the base pair orientation.

TABLE III. Optimized Values of L, θ_1, θ_2 and Hydrogen Bond Distances and Hydrogen Bond Energies of Both Base Pairs and Li^+/Base Pair Complexes.

System	L(Å)	θ_1 (degree)	θ_2 (degree)	Hydrogen Bond Energy (kcal/mol)	Hydrogen Bond Distance (Å)		NSE (kcal/mol)
A–T	10.10	51.0	59.2	15.9	$N_6-H_b\cdot\cdot O_6$	2.91	–
					$N_1\cdot\cdot H_b-N_1$	2.70	
Li^+–A–T:							
$Li^+-N_7(A)$	10.00	51.0	59.2	12.6	$N_6-H_b\cdot\cdot O_6$	2.81	−3.3
$Li^+-N_3(A)$	10.00	51.0	59.2	10.0	$N_1\cdot\cdot H_b-N_1$	2.60	−5.9
$Li^+-O_2(T)$	10.00	51.0	59.2	16.0			+0.1
G–C	10.16	51.0	51.0	22.8	$O_6\cdot\cdot H_b-N_6$	2.73	–
					$N_1-H_a\cdot\cdot N_1$	2.70	
					$N_2-H_b\cdot\cdot O_2$	2.79	
Li^+–G–C:							
$Li^+-N_3(G)$	10.16	51.0	51.0	37.9	$O_6\cdot\cdot H_b-N_6$	2.73	+15.1
$Li^+-N_7\cdot\cdot O_6$	10.16	51.0	51.0	28.0	$N_1-H_a\cdot\cdot N_1$	2.70	+5.2
					$N_2-H_b\cdot\cdot O_2$	2.79	

(NSE = Net Stabilization Energy, positive value = energy gain).

The Lithium–A–T Complex

All preferred binding positions of Li^+ to A–T are found to be unchanged compared to the Li^+–A and –T complexes. Li^+–N7 and Li^+–N3 distances are 1.85 Å, Li^+–O2 is 1.75 Å. Li^+ binding to O2 seems to give no effect, but directed to N3 and N7 it leads to a 'destabilization effect' (negative values of NSE) on the hydrogen bonds. In all cases only a slight decrease of the distance L is observed (about 0.1 Å). θ_1 and θ_2 are the same as in the optimized A–T pairs.

A comparative analysis of the hydrogen bond, X–A–H··B–Y with A and B being second row elements, done by Kollman and Allen [21] has indicated that upon hydrogen bond formation X, A and B gain electron density and H and Y lose it compared to the isolated XAH and BY molecules. These charge redistributions also lead to an increase of the polarities of the molecules.

Del Bene [22] has interpreted results from a series of calculations on hydrogen bonded systems in terms of an electrostatic effect so that the more electronegative X becomes, the more positive the proton becomes so that X–A–H becomes a better proton donor. The more electronegative Y is, the less electrons are located at B and the smaller is the H··B attraction.

According to these concepts, the metal binding to the proton donor side should decrease the hydrogen bond proton population according to the polarization effect and the increase in the proton donor ability of A.

$$M-\overleftarrow{X-A}-H\cdot\cdot\overleftarrow{B-Y}$$

On the other hand, metal binding at the Y atom should lead to a higher electron density at Y, and a lower density at B.

$$X-\overleftarrow{A-H}\cdot\cdot\overleftarrow{B-Y}-M$$

This can be regarded as a model for stabilization and destabilization effects of a metal ion on hydrogen bonded systems, which is also in agreement with Gutmann donor–acceptor concept [23].

In G–C and A–T systems, the situation seems to be more complicated due to the existence of multiple hydrogen bonds of different kinds. Moreover, each molecular fragment acts not only as proton donor but also as proton acceptor. However, the nearest neighbouring hydrogen bond to the metal binding position seems to experience a stronger effect than the others (see refs. 11 and 12, the examples of Li^+/water–ammonia and Li^+/formamide–water).

The Li^+ binding at N3(G) of G–C pair gives rise to the highest NSE value, since it can directly enhance the proton donor ability of both N1 and N2 of guanine, although some destabilization occurs at $O6\cdot\cdot H_b$–N6. Among all binding features, the Li^+–N3(A) seems to have the lowest NSE since the N1 atom experiences a direct destabilization effect from the Li^+ ion. Although the simultaneous binding of Li^+ to N7 and O6 of guanine is the most favourable one, it does not give rise to the highest value of NSE, since the destabilization of $O6\cdot\cdot H_b$–

N6 compensates for some of the stabilization of the other hydrogen bonds.

In general, the ability of metal ions to stabilize the DNA double helix is defined by the Tm, the melting temperature, or the temperature at which DNA unwinds to single strands [2]. This parameter is found to be increased linearly with the logarithm of the ionic strength. This phenomenon is believed to be a consequence of a compensation of electrostatic repulsion between adjacent phosphate groups and metal ions [2]. In addition our results indicate that metal ions, especially strongly binding small ions, can also stabilize the helical structure of DNA *via* the hydrogen bonds of the base pairs when they are bound to specific sites of the bases.

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