DFT Studies of the Lithium Complexes of DNA Bases

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The H^+ and Li^+ interactions with DNA bases have been studied by a variety of experimental and theoretical method.[1-6] It is known that the coordinated metal ions play a significant role in the biological action of nucleic acids. Metal cations interact with the DNA bases, destroying the hydrogen bonding between the base pairs, especially. Therefore, the structure of DNA is changed.[7,8] So, the metal cations affect syntheses, replication and cleavage of DNA. Cerda and Wesdemiotis[9] have reported the interaction of Li^+, Na^+ and K^+ with DNA bases by a modified version of the kinetic method, but they do not show the information on the coordination site of the metal. Del Bene[10] have reported the results of a study for the Li^+ complexes of the DNA bases by *ab initio* calculations with the STO-3G basis sets to determine the optimized structures and stabilization energies. However the results are not reliable because calculations have been done at low level. Actually, we can not locate the structures for the some complexes which are optimized by him. Instead the some new bridging complexes have been found.

In this study, we focus our attention on the association sites, association energies and optimized structures for the Li^+ complexes of DNA bases to describe the structural and energetic features of these complexes. DFT calculations are carried out at B3LYP level[11] of theory with the 6-31G(d,p) basis sets using the Gaussian98 series of program.[12] The geometry of all structures are fully optimized using energy gradient method[13] without any constraint. Vibration frequencies are also calculated at B3LYP level to confirm that all the stationary points correspond to true minima on the potential energy surface. All frequency calculations are performed using numerical second derivatives and verified that all structures are true minima by frequency analysis and obtained all positive Hessian eigenvalue. Zero-point corrections are included in association energies, however, a basis set superposition errors (BSSE) are not considered because the BSSE for alkali metal complexes of DNA bases are small, as in other paper[6] on K^+ and H^+ complexes with BSSE of about 1 and 2 kcal/mol, respectively. The lithium cation association energies are calculated as the difference of the optimized energy of the base-Li^+ complex[$E(B\text{-}Li^+)$] and the sum of the energies of the base[$E(B)$] and lithium cation[$E(Li^+)$] for the reaction

$$B + Li^+ \rightarrow B\text{-}Li^+$$

The optimized geometrical structures for Li^+ complexes of DNA bases are shown in Figure 1. All optimized structures in Figure 1 have C_s symmetry without C_1 of the A1 and C2.

The selected geometrical parameters for the optimized DNA bases and Li^+ complexes of these bases are summarized in Table 1. And the computed lithium cation association energies are shown in Table 2.

As shown in Figure 1, there are three distinct complexes of Li^+ with adenine. The most stable complex of the adenine with Li^+ is the bridging complex in which Li^+ forms a five-membered ring, interacting with both N_6 and N_7. The lithium cation association energy of this complex is -56.23 kcal/mol as shown in Table 2. The bicoordination of lithium cation yields the more stable adenine-Li^+ complex.

Association of adenine with Li^+ is accompanied by structural changes within the pyrimidine ring as can be seen in Table 1. When Li^+ binds at both N_1 and N_6, the N_1-C_2 distance increases by 0.012 Å, whereas the C_5-C_6 bond length of 1.411 Å is reduced to 1.386 Å in the complex. The notable change in bond lengths is an increase of 0.086 Å in the C_6-N_6 distance. The two dihedral angles of -10.0 and -170.1° by amino hydrogens in adenine change to 133.6 and -110.4° in N_1-N_6 complex, respectively. This is due to the repulsion between the Li^+ and amino hydrogen on the N_1 side of the C_6-N_6 bond. The amino hydrogens rotate to reduce this repulsion. The N_1-Li^+ and N_6-Li^+ distances are calculated to be 1.990 and 2.066 Å, respectively. When Li^+ binds at N_3 (A2 in Figure 1), the N_1-C_2 bond length decreases by 0.027 Å. The C_2-N_3 and N_3-C_4 distances increase by 0.025 and 0.021 Å. The N_3-Li^+ distance is 1.910 Å. All other bond distance and bond angle changes are small. For the bridging complex in which Li^+ forms a five-membered ring (A3 in Figure 1), the N_7-Li^+ distance is 1.991 Å and the N_6-Li^+ is 2.094 Å. The $C_5C_6N_6$ angle changes notably, decreasing by 4.7°. This large change is associated with bridging nature of the complex caused by interaction of Li^+ with both N_6 and N_7.

The two association sites for Li^+ complex with thymine have been found, one at each carbonyl group, as shown in Figure 1. The lithium cations are nearly collinear with the C=O bonds, and the O-Li^+ distances are 1.730 and 1.725 Å in the O_2 and O_4 complex. Complexation with Li^+ leads to structural changes in the ring as shown in Table 1, the notable change is an increase in the internal angle of the ring at carbon of the carbonyl binding site, and increase in the carbonyl C=O bond lengths. The C=O bond distances increase upon complexation by 0.043 and 0.040 Å in the O_2 and O_4 complex, respectively. When Li^+ associates at the O_4, the C_4C_5 $C(CH_3)$ angle increases by 2.4° reducing the

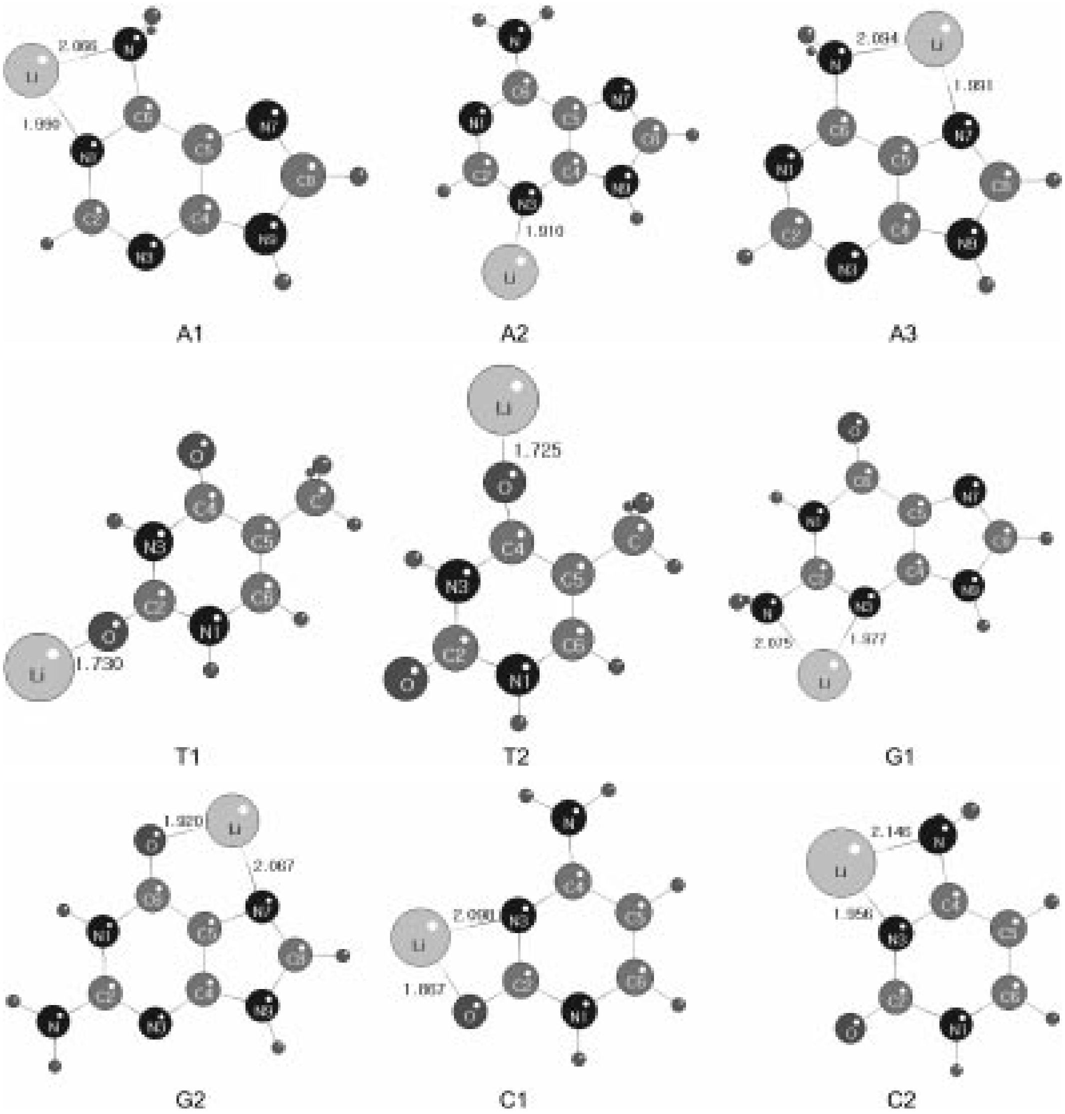

Figure 1. B3LYP-optimized structures for Li^+ complexes of A) adenine, T) thymine, G) guanine, and C) cytosine. Distances are in Å.

repulsion between the Li^+ and two methyl hydrogens. The association energy of this complex is -55.44 kcal/mol and is slightly preferred to O_2 complex, which is -52.82 kcal/mol.

The two distinct complexes of Li^+ with guanine have been found as shown in Figure 1. One is the four-membered bridging complex in which Li^+ interacts with both N_2 and N_3, the other is the complex in which Li^+ forms a five-membered ring with both O_6 and N_7. As shown in Table 2, the Li^+ association energies of these complexes are -45.86 and -80.25 kcal/mol. The five-membered ring formation is about 34.4 kcal/mol more stable than the four-membered ring formation. This result shows that the five-membered ring formation is favored with respect to formation of four-membered ring because of the minor annular strain.[14] The O_6-N_7 five-membered ring complex is the strongest of the Li^+ complexes with the DNA bases as seen in Table 2. This is consistent with the result obtained by Del Bene,[10] and it is shown that the imino nitrogen is preferred over the amino one.

In five-membered ring complex, the N_1-C_6 and C_5-C_6 bond distances decrease by 0.049 and 0.033 Å, respectively, while the C_6-O_6 distance increases by 0.035 Å. The $C_5C_6O_6$ angle decreases notably by 6.9°. This large change is also associated with the bridging nature of complex. The O_6-Li^+ and N_7-Li^+ distances are found to be 1.920 and 2.067 Å, respectively. On the other hand, the two N-Li^+ distances in four-membered ring complex are found to be 2.075 and 1.977 Å.

The two bridged complexes have been found in the cytosine molecular plane in which Li^+ forms four-membered ring with O_2-N_3 and N_3-N_4 as shown in Figure 1. The more stable is the bridging complex formed with both O_2 and N_3. This result is shown that the carbonyl oxygen is preferred over the amino nitrogen. In the O_2-N_3 complex, notable changes occur in bond distances and angles from N_1 to C_4 as shown in Table 1. The N_1-C_2 distance decreases by 0.051 Å and $N_1C_2O_2$ angle increases by 2.9°. These results lead to enhancement of the simultaneous interaction of Li^+ with O_2

Table 1. Selected geometrical parameters for the optimized bases and base-Li$^+$ complexes(bond lengths in and bond angle in degree)

Parameter	Adenine				Thymine			Guanine			Cytosine		
	Base	A1	A2	A3	Base	T1	T2	Base	G1	G2	Base	C1	C2
N_1-C_2	1.344	1.356	1.317	1.354	1.390	1.354	1.393	1.371	1.346	1.395	1.430	1.379	1.422
C_2-N_3	1.337	1.329	1.362	1.340	1.386	1.352	1.405	1.312	1.316	1.324	1.373	1.364	1.395
N_3-C_4	1.339	1.330	1.360	1.326	1.407	1.435	1.370	1.358	1.374	1.343	1.320	1.343	1.320
C_5-C_6	1.411	1.386	1.415	1.388	1.352	1.350	1.366	1.441	1.448	1.408	1.359	1.357	1.377
N_1-C_6	1.345	1.346	1.358	1.322	1.380	1.396	1.363	1.440	1.468	1.391	1.355	1.366	1.345
C_6-N_6	1.356	1.442	1.333	1.453									
C_2-O_2					1.218	1.261	1.206				1.220	1.252	1.207
C_4-O_4					1.222	1.210	1.262						
C_6-O_6								1.218	1.204	1.253			
R		1.990^{b}	1.910^{c}	1.991^{f}		1.730^{g}	1.725^{g}		1.977^{c}	2.067^{j}		1.867^{g}	1.956^{l}
$N_1C_2N_3$	128.9	126.2	128.8	127.6	112.5	115.5	111.7	123.6	124.2	123.7	116.1	119.4	113.9
$C_2N_3C_4$	111.1	113.4	111.6	112.7	128.2	126.8	127.2	112.5	113.6	113.5	120.3	119.9	121.4
$C_5C_6N_6$	122.3	126.6	122.9	117.6									
$C_5C_6O_6$								131.4	132.2	124.5			
C_4C_5 C(CH_3)					117.7	117.5	120.1						
$N_3C_4C_5$					114.5	114.0	117.4						
$N_1C_2O_2$					123.2	121.8	124.7				118.2	121.1	121.5
$N_3C_4N_4$											116.9	118.4	111.2
Θ		90.8^{b}	111.7^{c}	96.9^{f}		174.5^{h}	174.6^{i}		91.6^{c}	91.8^{j}		91.9^{k}	95.5^{m}
$N_1C_6N_6H^{a}$	-10.0	133.6	0.0^{d}	56.3									
	-170.1	-110.4	180.0^{e}	-56.3									
$N_1C_2N_2H^{a}$								169.9	60.0	180.0			
								34.3	-60.0	0.0			
$N_3C_4N_4H^{a}$											9.8	0.0	-95.7
											164.5	180.0	145.4

[a]The hydrogen atoms are in amino group. [b]The N_1-Li$^+$ distance and C_6N_1Li$^+$ angle. [c]The N_3-Li$^+$ distance and C_2N_3Li$^+$ angle. [d]The amino hydrogen *cis* to N_1-C_6. [e]The amino hydrogen trans to N_1-C_6. [f]The N_7-Li$^+$ distance and C_5N_7Li$^+$ angle. [g]The O-Li$^+$ distance. [h]The C_2O_2Li$^+$ angle. [i]The C_4O_4Li$^+$ angle. [j]The N_7-Li$^+$ distance and C_5N_7Li$^+$ angle. [k]The C_2O_7Li$^+$ angle. [l]The N_3-Li$^+$ distance. [m]The C_4N_3Li$^+$ angle.

Table 2. Total energies (E in au) and lithium cation association energies (ΔE in kcal/mol) of DNA bases[a]

Base	Association site	E	ΔE
Adenine	N_1-N_6	-474.589477	-53.82
	N_3	-474.580929	-48.46
	N_6-N_7	-474.593323	-56.23
Thymine	O_2	-461.402456	-52.82
	O_4	-461.406625	-55.44
Guanine	N_2-N_3	-549.805841	-45.86
	O_6-N_7	-549.860645	-80.25
Cytosine	O_2-N_3	-402.247271	-75.27
	N_3-N_4	-402.212378	-53.37

[a]Zero-point corrections are included in energies.

and N_3. Similarly, the $N_3C_4N_4$ angle in the N_3-N_4 complex is reduced upon complexation to about 5.7°. In the O_2-N_3 complex, the O_2-Li$^+$ and N_3-Li$^+$ distances are 1.867 and 2.098 Å, respectively. The O-Li$^+$ distance in this complex is longer than the corresponding ones in the thymine complexes, whereas the N-Li$^+$ distance is longer than the corresponding ones in the adenine complexes. The association energy of this complex is -75.27 kcal/mol. On the other hand, the N-Li$^+$ distances in the N_3-N_4 complex are calculated to be 1.956 and 2.146 Å.

In conclusion, there are three distinguishable Li$^+$ complexes with adenine, two bridging complexes and the other an open structure at N_3. There are two Li$^+$ complexes with thymine, one at each carbonyl group. The two distinct complexes of Li$^+$ with guanine are found, one bridging guanine-Li$^+$ complex at N_2 and N_3, and the other at O_6 and N_7. For the cytosine-Li$^+$ complex, there are two bridging complexes, one at O_2 and N_3, and the other at N_3 and N_4.

The most stable of the Li$^+$ complexes with DNA bases are the bridging complexes with guanine and cytosine at both O and N. Among the open structures, those in which Li$^+$ associates with a carbonyl oxygen are more stable than those having Li$^+$ associated with a ring nitrogen. Thus, the Li$^+$ association energies with thymine are -52.82 and -55.44 kcal/mol, compare with the association energy of -48.46 kcal/mol in the N_3-Li$^+$ complex with adenine. In this study, it has been also found that complexation of Li$^+$ with the DNA bases leads to structural changes in the bases.

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