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Metal-stabilized rare tautomers: N4 metalated cytosine ($M = Li^+$, Na^+, K^+, Rb^+ and Cs^+), theoretical views

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Ab initio **calculations indicate that metalation of the exocyclic amino group of cytosine by the elements of Group IA (Li, Na, K, Rb and Cs) induces protonation of a nucleobase ring nitrogen atom, and hence causes a proton shift from an exocyclic to an endocyclic nitrogen atom. Thus, this metal-assisted process leads to the generation of rare nucleobase tautomers. The calculations suggest that this kind of metalation increases the protonation energies of the aromatic ring of the nucleobase. The present study reports the quantum chemistry analysis of the metal-assisted tautomerization. The calculations clearly demonstrate that metalation of the exocyclic amino group of the nucleobase significantly increases the protonation energy of the aromatic rings of the nucleobase. Also, absolute anisotropy shift, molecular orbital and natural bond orbital calculations are compatible with these results. Copyright © 2003 John Wiley & Sons, Ltd.**

KEYWORDS: cytosine; *ab initio* calculation; tautomers; metalated cytosine; nonmetalated cytosine

INTRODUCTION

The structure and properties of DNA depend on metals. Metal ions can interact with many sites in DNA, such as a[1–3] phosphate group, a sugar moiety, as well as the DNA bases. Interactions of mono- and bi-valent metals have been studied.[4,5] The relative stability of tautomers of the pyrimidine base cytosine is very important in the structure of DNA. The occurrence of rare tautomers has been put forward as a possible mechanism of spontaneous mutation.[6] Metalation can change the probability or the formation of rare (minor) tautomers of bases and could influence the ability of nucleobases to be protonated or deprotonated.[7] The formation of rare nucleobase tautomers can occur under the influence of a metal entity. Upon replacement of a hydrogen atom of the N4 amino group of cytosine by a metal entity,[8–12] the N3 position is protonated to produce a metalated form of the rare iminooxo tautomers of this base. Therefore, in this paper, by using *ab initio* calculations and a quantum chemical approach, we analyze the energy of the formation of metal-assisted tautomers upon metalation of the amino groups of the base. Also, absolute anisotropy shift, molecular orbital and natural bond order (NBO) calculations are compatible with these results.

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COMPUTATIONAL DETAILS

The calculations for systems containing carbon, hydrogen, nitrogen and oxygen are described by the standard 6-31+G* basis set.[13] For other elements (lithium, sodium, potassium, rubiclium and cesium), the standard LANL2DZ basis set is used,[14–17] and sodium, potassium, rubiclium and cesium are described by the effective core potential (ECP) of the Wadt and Hay pseudopotential[15,18] with a doublet-ξ valence using the LANL2DZ basis set. All systems have been optimized at the Hartree–Fock level, because one imaginary frequency was found at the density functional theory (DFT) level. In all cases, the steady-state nature (minimum on the potential energy surface) of the optimized complexes has been confirmed by calculating the corresponding frequencies at the same computational level. For the optimized geometries the correlation energies were calculated by Moller–Plesset second-order perturbation theory (MP2) and Becke3LYP DFT. The calculations were performed using the GAUSSIAN 98 suite of programs.[18]

The NBO[19–23] analyses were performed using the NBO as implemented in GAUSSIAN98.

NMR shielding tensors were computed with the continuous set of the gauge independent atomic orbital (GIAO) method.[24–27]

The interaction energies E_I were determined as the difference between the optimized energy of the base···metal cation systems $E(B\cdots M^{n+})$ and the sum of the energies of the base $E(B)$ and the metal cation $E(M^{n+})$:

$$E_I = E(B\cdots M^{n+}) - [E(B) + E(M^{n+})] \quad (n = 1)$$

The final interaction energies $E_{I+BSSE}(B\cdots M^{+})$, were been calculated as the difference between the energy of the complex and the sum of the energy of the monomers, and have been corrected from the inherent basis set superposition error (BSSE), which is calculated using the Boys–Bernardi counterpoise technique:

$$E_{I+BSSE}(B\cdots M^{+}) = E(B\cdots M^{+})_{BM} - [E(B)_B + E(M^{+})_M] + [E(B')_B - E(B')_{BM} + E(M')_M - E(M')_{BM}]$$

where $E(B\cdots M^{+})_{BM}$ represents the energy of the complex, $E(B)_B$ is the energy of the isolated monomer B with its basis set, $E(B')_B$ is the energy of B in its geometry within the complex calculated with its basis set, and $E(B')_{BM}$ is the energy of B in its geometry within the complex with the complete basis set of the complex $(B\cdots M^{+})$.[28]

The absolute anisotropy shift, molecular orbital and NBO calculations were done at the Hartree–Fock level.

RESULTS AND DISCUSSION

Protonation energies and tautomeric equilibria of N4-metalated cytosine

The computed energies of the three forms (Fig. 1, **I**–**VI**) of nonmetalated and of metalated cytosine are compared in Tables 1 and 2. Their relative stabilities are markedly influenced by the metalation. The first major difference can be found in the relative stabilities of the neutral amino and imino tautomers of free and metalated cytosine; whereas the neutral imino tautomer of nonmetalated cytosine is destabilized by only 0.89 kcal mol^{-1} with respect to the major form, this energy difference upon metalation increases for Li^+, Na^+, K^+, Rb^+ and Cs^+ to 7.84 kcal mol^{-1}, 11.50 kcal mol^{-1}, 13.48 kcal mol^{-1}, 114.52 kcal mol^{-1}, 15.22 kcal mol^{-1} respectively (with HF method). On the other hand, metalation of cytosine markedly enhances its basicity, since the protonated form has been found to be more stable in the metalated complex than in the nonmetalated molecule. Also, these values show that the results are dependent on the metal and that the stability increases with its electropositivity. Therefore, these calculations clearly suggest that the observed proton shift is a direct result of the metalation. Table 3 shows the values of the BSSE and E_{I+BSSE} for structures **IV**, **V** and **VI**. Clearly, for all the complexes **VI** with M = Li, the values of the BSSE are rather small. Therefore, for these cases, the BSSE is negligible. For the other structures the values of the BSSE are positive.

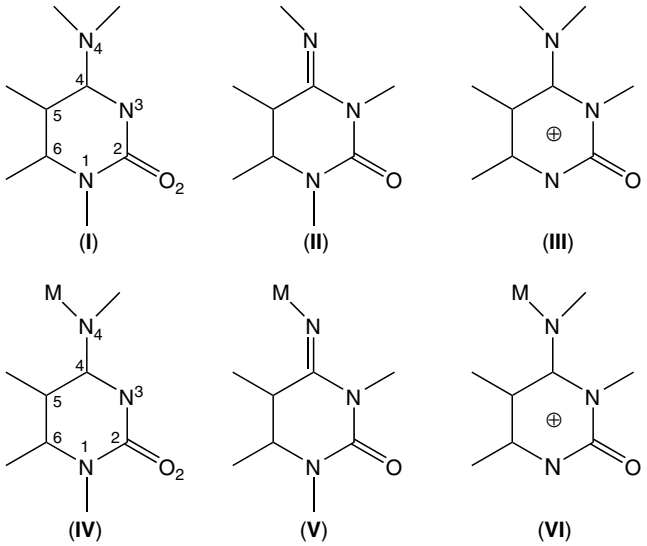

Figure 1. Structures of cytosine: (**I**) cytosine major (amino-oxo) form; (**II**) neutral rare imino form; (**III**) N3-protonated cytosine; structures (**IV**) and (**V**) represent the corresponding forms of the N-metalated cytosine.

From an analysis of the atomic charges evaluated by the NBO method, it was found that the charge of N3 in metalated cytosine is more than that in the nonmetalated form (Tables 1 and 4). The increases in dipole moments (Fig. 2, Table 1) and highest occupied molecular orbital (HOMO) energies (Table 2, Fig. 3) and the decreases in absolute anisotropy shift of the metalated cytosine (Table 1, Fig. 4) show that N3 is more basic in metalated cytosine.

As shown above, metalation of the amino tautomer strongly influences the electronic structure of the amino tautomer, and this leads to energetic destabilization of the structure. Therefore, the increasing N3 basicity of the metalated cytosine (M = Na, K, Rb, Cs) can be attributed to the relative destabilization of the neutral amino tautomer and the increased stability of the protonated form.

Interaction energies of metalated cytosine

Table 3 shows the interaction energies of the metalated cytosine, increased systematically with the atomic number of M. This increase is due to the larger dipole moments for metalated cytosine with heavy atoms (Fig. 2).

Geometry parameters

Intermolecular parameters

All the intermolecular distances M–N4 for metalated cytosine are longer than the distance of H–N4 in nonmetalated cytosine. This can be explained by the fact that the atomic radius of M is larger than for hydrogen. The intermolecular M–N4 distance increases with the atomic number for the

Table 1. Relative energies (HF, MP2, DFT), dipole moment (Debye), charge and absolute anisotropy shift of N3 for structures **I**, **II** and **III**

Structure	Relative energy (kcal mol^{-1})			Dipole moment (D)	Charge of N3[a]	Absolute anisotropy shift of N3
	HF	MP2	DFT			
I	0.00	0.00	0.00	7.39	−0.714	256.78
II	0.89	1.85	2.06	5.45	−0.694	29.34
III	−238.71	−229.50	−233.79	5.88	−0.695	65.63

[a] Atomic charges (in *e*) on N3 of structures **I**, **II** and **III** and obtained by NBO method.

Table 2. Relative energies (HF, MP2, DFT)[a] and HOMO energy for structures **IV**, **V** and **VI**

	Relative energy (kcal mol^{-1})											
	HF			MP2			DFT			HOMO energy (Hartree)		
M^+	**IV**	**V**	**VI**	**IV**	**V**	**VI**	**IV**	**V**	**VI**	**IV**	**V**	**VI**
Li	0.00	7.84	−268.41	0.00	7.65	−258.08	0.00	7.85	−261.19	−0.31	−0.29	−0.49
Na	0.00	11.50	−277.71	0.00	11.51	−266.99	0.00	12.49	−270.71	−0.29	−0.27	−0.47
K	0.00	13.48	−285.61	0.00	13.29	−275.07	0.00	14.27	−277.66	−0.27	−0.25	−0.46
Rb	0.00	14.52	−288.50	0.00	14.35	−277.89	0.00	15.24	−280.37	−0.27	−0.25	−0.45
Cs	0.00	15.22	−291.31	0.00	15.07	−280.74	0.00	15.85	−283.26	−0.26	−0.24	−0.45

[a] The calculations for systems containing C, H, N, O are described by the standard 6-31+G* basis set. For other elements (Li, Na, K, Rb and Cs) the standard LANL2DZ basis set is used.

Table 3. Interaction energies E_I, BSSE and E_{I+BSSE} for structures **IV**, **V** and **VI**[a]

	E_I (HF) (kcal mol^{-1})			BSSE (HF) (kcal mol^{-1})			E_{I+BSSE} (HF) (kcal mol^{-1})		
M^+	**IV**	**V**	**VI**	**IV**	**V**	**VI**	**IV**	**V**	**VI**
Li	−139.9	−161.2	−50.5	−0.5	−0.7	−0.5	−140.4	−161.9	−51.0
Na	−114.1	−131.7	−34.0	32.6	44.5	−0.7	−81.5	−87.1	−34.7
K	−94.4	−110.1	−22.2	32.4	44.3	−0.6	−62.0	−65.8	−22.8
Rb	−88.0	−102.7	−18.7	32.2	44.1	−0.7	−55.8	−58.5	−19.4
Cs	−82.1	−96.0	−15.6	32.0	44.0	−0.7	−50.1	−52.0	−16.3

[a] The calculations for systems containing C, H, N, O are described by the standard 6-31+G* basis set. For other elements (Li, Na, K, Rb and Cs) the standard LANL2DZ basis set is used.

Table 4. Atomic charges (in *e*) on selected atoms of metalated cytosine obtained using the NBO method

	M			N3			O		
M^+	**IV**	**V**	**VI**	**IV**	**V**	**VI**	**IV**	**V**	**VI**
Li	0.966	0.967	0.981	−1.216	−1.199	−1.067	−0.768	−0.773	−0.671
Na	0.972	0.980	0.987	−1.143	−1.111	−0.996	−0.781	−0.786	−0.681
K	0.990	0.996	0.996	−1.113	−1.074	−0.953	−0.791	−0.794	−0.690
Rb	0.991	0.997	0.997	−1.097	−1.053	−0.935	−0.795	−0.797	−0.694
Cs	0.995	1.000	0.998	−1.086	−1.039	−0.919	−0.798	−0.799	−0.786

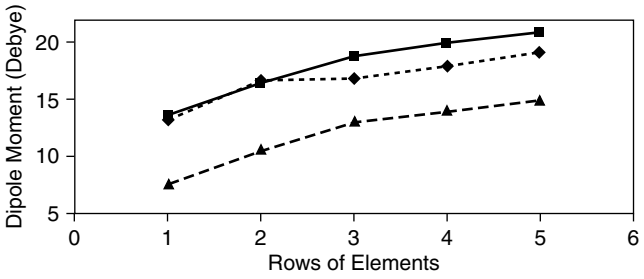

Figure 2. Dependencies of dipole moments on the atomic number of the metals of Group IA. Solid line with symbols ■ indicates structure **IV**, dotted line with symbols ▲ indicates structure **V** and dotted line with symbols ♦ indicates structure **VI**.

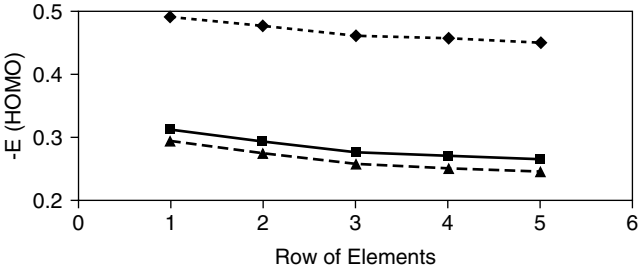

Figure 3. Dependencies of energy of HOMO on the atomic number of the metals of Group IA. Solid line with symbols ■ indicates structure **IV**, dotted line with symbols ▲ indicates structure **V** and dotted line with symbols ♦ indicates structure **VI**.

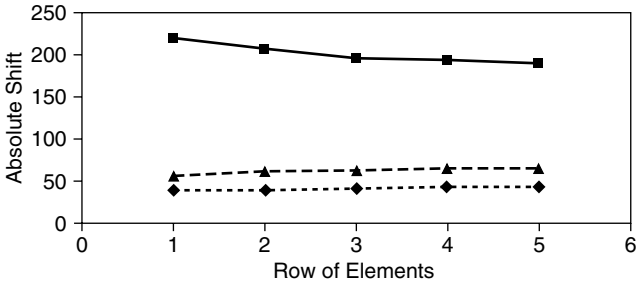

Figure 4. Dependencies of absolute anisotropy shift of N3 of metalated cytosine on the atomic number of the metals of Group IA. Solid line with symbols ■ indicates structure **I**, dotted line with symbols ▲ indicates structure **II** and dotted line with symbols ♦ indicates structure **III**.

alkali metals (Tables 5 and 6, Fig. 5). This increase is more pronounced, where this difference is about 1 Å.

A comparison of the M–N4 distances shows that the M–N bond in the protonated form is much weaker than the other two structures (Tables 5 and 6).

Table 5. Optimized bond lengths of M–N4, C4–N4 and C4–N3 for structures **I**, **II** and **III**

Bond	I	II	III
M–N4	0.99	1.00	0.99
C4–N4	1.34	1.25	1.31
C4–N3	1.29	1.39	1.34

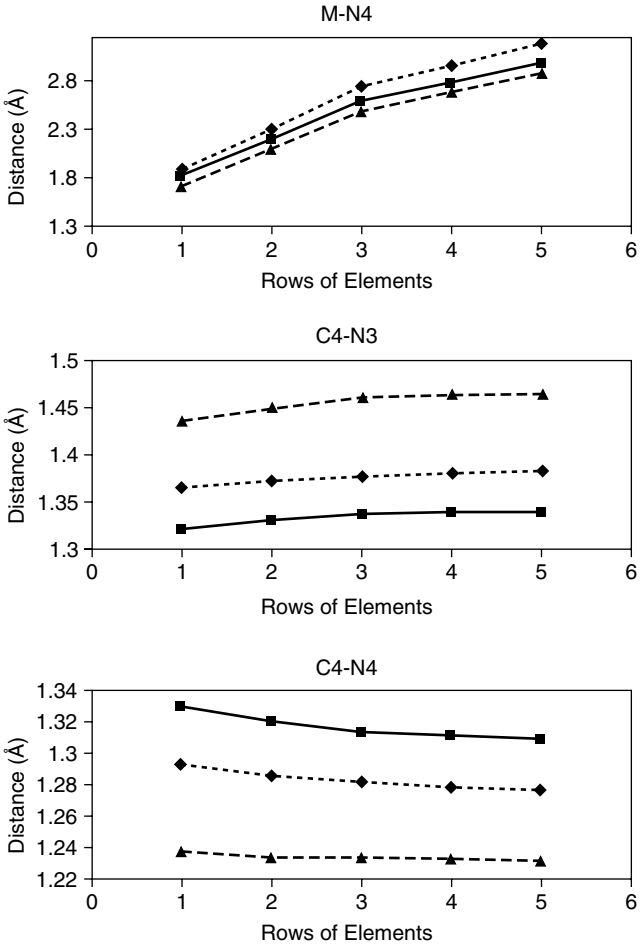

Figure 5. Dependencies of intermolecular and intramolecular distances on the atomic number of the metals of Group IA. Solid line with symbols ■ indicates structure **IV**, dotted line with symbols ▲ indicates structure **V** and dotted line with symbols ♦ indicates structure **VI**.

Intramolecular parameters

Distances for C4–N4 and C4–N3 are shown in Tables 5 and 6. In the protonated forms the N4–C4 distances decrease, whereas the C4–N3 distances increase. A further decrease of the N4–C4 distances in the imino tautomer results in a surprisingly short N4–C4 bond, whereas the C4–N3 distances adopt an unusually high value. Therefore, we conclude that the double bond characterization of the N4–C4

Table 6. Optimized bond lengths of M–N4, C4–N4 and C4–N3 for structures **IV**, **V** and **VI**

	M–N4			C4–N4			C4–N3		
M^+	**IV**	**V**	**VI**	**IV**	**V**	**VI**	**IV**	**V**	**VI**
Li	1.80	1.72	1.89	1.328	1.236	1.292	1.320	1.435	1.365
Na	2.19	2.10	2.30	1.319	1.232	1.285	1.329	1.449	1.372
K	2.58	2.48	2.74	1.312	1.232	1.280	1.335	1.459	1.377
Rb	2.77	2.68	2.96	1.311	1.231	1.277	1.337	1.462	1.379
Cs	2.98	2.88	3.21	1.308	1.230	1.276	1.339	1.465	1.381

bond and the single bond characterization of the C4–N3 bond increase in the following order: amino < protonated < imino.

All the intramolecular distances C4–N3 for metalated cytosine are larger than for nonmetalated cytosine. The intramolecular C4–N3 distances increase with the atomic number of the alkali metals (Table 6, Fig. 5). This increase is not pronounced, where this difference is about 0.019 Å (for Li^+ to Cs^+). On the other hand, all the intramolecular distances C4–N4 for metalated cytosine are smaller than nonmetalated. The intramolecular C4–N4 distances decrease with atomic number of the alkali metals (Table 6, Fig. 5). This decrease is not pronounced, where this difference is about 0.02 Å (for Li^+ to Cs^+).

Analysis of wave function

NBO calculations

Atomic charges of selected atoms of metalated cytosine are presented in Table 4. The chosen atoms (with the exception of M) participate in hydrogen bondings between DNA bases. The amount of charge transfer (CT) between a base and an ion is easily determined as the difference between the charge of the isolated ion and the net atomic charge of the metal. For complexes of alkali metals, the smallest CT was found for cesium. The fact that the dependence of CT on the atomic number exhibits an extreme could be interpreted in terms of higher covalent contributions by cesium ion (compared with others). This point is briefly discussed in the next paragraph.

Molecular orbitals

The aim of the present analysis is to elucidate the above-mentioned behavior of energy, geometry and charge dependencies on the atomic number in the individual group metal studied. The wave function contains all the necessary information on the various system properties, including energies. Analysis of the molecular orbitals of alkali metal complexes revealed that this mixing of metal cation orbitals with the orbitals of the base in M = Li are smaller than for M = Na, K, Rb, Cs. For sodium, potassium, rubiclium and cesium, a slight mixing of ion (n-1) s and (1-n) p orbitals was detected in the molecular orbitals of the base with a main contribution of N4. All these elucidate the highly ionic character of the base$\cdots Li^+$ bonding and the increasingly covalent character of bonding when passing from Na^+ to Cs^+. The decreasing ionic character corresponds to an increasing interaction energy (Table 3).

CONCLUSIONS

1. *Ab initio* calculations indicate that metalation of the exocyclic amino group of cytosine by the elements of Group IA (lithium, sodium, potassium, rubiclium, cesium) induces protonation of a nucleobase ring nitrogen atom, and hence causes a proton shift from an exocyclic to an endocyclic nitrogen atom.
2. This metal-assisted process thus leads to the generation of rare nucleobase tautomers.
3. The calculations suggest that this kind of metalation increases the protonation energy of the aromatic ring of the nucleobase.
4. The calculated absolute anisotropy shift, the charges of the atom calculated using the NBO and the energy of the HOMO of metalated and nonmetalated cytosine suggest that metalation increases the basicity of N3.
5. The strongest bonding interactions were found for metalated cytosine with heavy metals.
6. The M–N4 and C4–N3 distances for metalated cytosine are larger than for nonmetalated cytosine, but the C4–N4 distances for metalated cytosine are smaller than for nonmetalated cytosine.

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