A theoretical study of metal-stabilised rare tautomers stability: N4 metalated cytosine (M=Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+}) in gas phase and different solvents

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Ab initio calculations are applied in order to explore metalation of the exocyclic amino group of cytosine by the elements of group IIA (Be, Mg, Ca, Sr and Ba).

Keywords: cytosine, metalated cytosine, *ab initio* calculation, solvent effects

The structure and property of DNA depends on metals. Metal ions can interact with many sites in DNA.[1-3] Interactions of mono- and bivalent metals have been studied.[4-7] 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.[8] Metalation can change the probability of the formation of rare (minor) tautomers of bases and could affect the ability of the nucleobase to be protonated or deprotonated.[9] Formation of rare nucleobase tautomers can occur under the influence of a metal entity. With replacing of a hydrogen atom of the N4 amino group of cytosine by a metal entity,[10-12] the N3 position is protonated to produce a metalated form of the rare iminooxo-tautomers of this base. Alkali cations, at high concentration, interact with the nucleic acid bases, destroying the base pair hydrogen bonding and, consequently, compromise the structure integrity of the nucleic acid polymer.[13,14] Furthermore, the presence of these ions in the cell nucleus has an inhibitory effect on the chain initiation process by RNA polymerase.[13] So the alkali ions affect syntheses, replication, structure integrity, and cleavage of nucleic acids. For these reasons, knowledge of the thermochemical and structure features that govern the interaction between alkali cations and nucleic acid bases gives an insight into their interactions with more complex nucleic acid polymers.

Not only monovalent alkaline cations interact exclusively with the phosphate group of the backbone, but also, the divalent alkaline cations (Mg^{2+},Ca^{2+},Ba^{2+}) interact mostly with the phosphate group.[1-3] This does not mean that interaction with bases is excluded. For example, a high resolution X-ray study of Z-DNA hexamer shows a barium cation bridging two side-by-side Z-DNS helices in the crystal by simultaneously coordination to the O and N of two guanines. This cation is, at the same time, coordinated to four water molecules.[15]

The solvent dependency of tautomeric equilibria has been the subject of many studies.[16-18] The tautomeric equilibria of hydroxyl pyridines has been studied theoretically owing to their relevance to the oxo-amino–hydroxy-amino tautomerism of nucleic acids.[19-21] It has been well established that solvents with large dielectric constants favor the more polar tautomers. The solvent effect is taken into account via the Self-Consistent Reaction field (SCRF) method. This method is based on Onsager reaction field theory of electrostatic solvation. In this model, the solvent is considered as a uniform dielectric with a given dielectric constant. The solute is placed into a cavity within the solvent. SCRF approaches differ in how they define the cavity and the reaction field. Tomasi's Polarised Continuum Model (PCM)[22,23] defines the cavity as a union of a series of interlocking atomic spheres. The effect of polarisation of the solvent continuum is represented numerically. PCM has proved useful in describing the effects of the solvent on some characteristics of the molecule in solution.[24] All PCM calculations in this report have been performed using this formalism as implement in GAUSSIAN 98.[25] Therefore, in this paper by using *ab initio* calculations and a quantum chemical approach, we analyse the energy of the formation of metal-assisted tautomers upon metalation of the amino groups of the base in gas and solution phases.

The calculations of systems contain C, H, N, O are described by the standard 6-31+G* basis set.[26] For other elements (Be, Mg, Ca, Sr and Ba) standard LANL2DZ basis sets are used[27] and Mg, Ca, Sr and Ba are described by effective core potential (ECP) of the Wadt and Hay pseudopotential[25,27b] with a doublet-ξ valence using the LANL2DZ set. All systems have been optimised at the Hartree-Fock level. In all cases, the steady-state nature (minimum on the potential energy surface) of the optimised complexes has been confirmed by calculating the corresponding frequencies at the same computational level. For the optimised geometries the correlation energies were calculated by Becke3LYP density functional theory (DFT). The calculations have been performed using the GAUSSIAN 98 suite of programs.[27]

The Natural Bond Orbital (NBO)[28] analyses were performed by using the NBO as implement in the GAUSSIAN98. NBO calculations have been done at the Hartree–Fock level. The second-order perturbative estimates of donor-acceptor (bond-antibond) interactions have been done on the NBO basis. This is carried out by examing all possible interactions between filled (donor) Lewis type NBOs and empty (acceptor) non Lewis NBOs and estimating their energetic importance by second-order perturbation theory. Since these interactions lead to loss of occupancy from the localised NBOs of the idealised Lewis structure into the empty non Lewis orbitals (and thus to departures from the idealised Lewis structure description) they are referred to as delocalisation corrections to the zeroth order natural Lewis structure. For each donor NBO (i) and acceptor NBO (j) the stabilisation energy E(2)associated with delocalisation (2e-stabilisation) i→ j is estimated as:

$$E(2) = \Delta E_{ij} = q_i / [F(i, j)^2 (\varepsilon_j - \varepsilon_i)]$$

Where q_i is the donor orbital occupancy, ε_i , ε_j are diagonal elements (orbital energies) and $F(i, j)$ is the off diagonal NBO Fock matrix element.

PCM reaction field calculation was performed by using the polarisable dielectric model.[29–31] The PCM cavity is defined by using the Pauling radius for each solute atom.[25] The model chemistry used for calculations is based on the B3LYP method. This corresponds to the approximation method that makes use of Becke–Style parameters density functional theory [32] with the Lee-Yang-Paar correlation functional.[33]

The interaction energies (E_I) were determined as the difference of the optimised energy of the base…metals cation

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[E (B…M $^{n+}$)] systems and the sum of the energies of the base [E (B)] and the metal cation [E (M $^{n+}$)]:

$$E_I = E\ (\text{B…M}^{n+}) - [E\ (\text{B}) + E\ (\text{M}^{n+})]\ (n = 2)$$

The final interaction energies (E_I), E_{I+BSSE} (B…M$^+$), have 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, by using the Boys-Bernardi counterpoise technique:

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

Where E (B…M $^+$)$_{BM}$ represents the energy of the complex, E (B)$_B$ the energy of the isolated monomer B with its basis set, E(B')$_B$ the energy of B in its geometry within the complex calculated with its basis set, and E(B')$_{BM}$ the energy of B in its geometry within the complex with the complete basis set of the complex (B…M$^+$).[34]

Metal ion affinity (MIA) was assumed as the negative of the enthalpy variations (ΔH) for the process:

$$B + M^{2+} \rightarrow BM^{2+}$$

In other words the MIA corresponds to the dissociation energy of the B–M^{2+} bond.

The variations in zero point energies were considered in the calculations together with thermochemical analysis at 298 K in order to obtain the entropic (ΔS) and free energy (ΔG) variation for the considered process.

Result and discussion

Protonation energies and tautomeric equilibria of N4-metalated cytosine.

Gas phase: The computed energies of the amino-oxo, imino-tautomer, protonated imino-tautomer and transition state of rearrangement of amino-oxo tautomer to imino-tautomer for nonmetalated and metalated cytosine are compared by HF and DFT methods (Table 1, Figs 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, while the neutral imino-tautomer of nonmetalated cytosine is destabilised by only 0.89 kcal mol $^{-1}$ with respect to the amino-oxo form, the neutral imino-tautomer of metalated-cytosine is stabilised with respect to the amino-oxo form, this energy difference upon metalation increases for Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} to 32.17, 14.73, 7.74, 5.82, 4.49 kcal mol $^{-1}$ (with the HF method), respectively. See Fig. 2. On the other hand, metalation of cytosine markedly enhances its basicity since the protonated form has been found more stable in the metalated complex than in the nonmetalated molecule. Also, these values show that the results depend on the metal. The

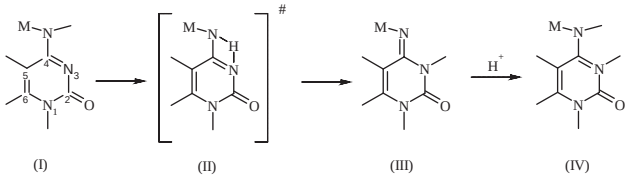

Fig. 1 Structures of cytosine: (I)Cytosine major (amino-oxo) form; (II)Transition state for transformation of major form to imino-form; (III) Neutral rare imino-form; (IV) N3-protonated cytosine structures.

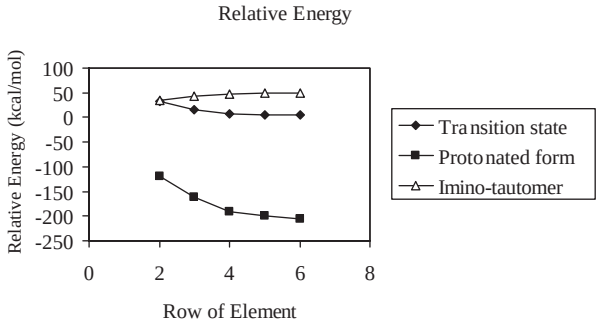

Fig. 2 Variation of relative energies (kcal mol^{-1}) of imino-tautomer, protonated cytosine and transition state with respect to amino-oxo tautomer for metalated speces.

stability of imino- and amino-tautomers is greater for electropositive metals, but the stability of the transition state is less for electropositive metals (Table 1).

Solution phase: The effect of solvent on stabilisation of tautomers shows interesting results. The standard approach of the PCM (without any explicit solvent molecules), as is used here, appears to be a good first step in the theoretical investigation of the effect of solvent. In the first instance, regular variations were observed concerning relative energy versus dielectric constant (Figs 3 and 4). For the nonmetalate- and metalated-cytosine with the decrease of dielectric constants of solvent the imino-tautomer is stabilising with respect to the amino-tautomer (Table 2, Fig. 3). This shows that the imino-tautomer is less polar, that it is compatible with the dipole moment of tautomers: amino>transition state>imino (Table 3). Also, the stability of the transition state is influenced by solvent. The stability of the transition state increases with decrease of the dielectric constant. The stability of the imino-tautomer and the transition sate decrease when the atomic number of metal is larger (Table 2, Figs 3 and 5). Also, calculations show that metalation causes the protonation energies of the aromatic ring of the nucleobase to increase (Table 3). The protonation energy increases as the dielectric constant of the solvent decreases. This result shows that the basicity of metalated cytosine increases.

The interaction energies of metalated cytosine: Table 4 shows the interaction energies of metalated cytosine. The interaction energies of the metalated cytosine systematically increase with atomic number of M. This increase is due to larger dipole

Table 1 Relative energies (kcal mol^{-1}) for structures (I), (II), (III) and (IV) in gas phase with DFT (B3LYP) and Hartree-Fock (HF) levels [a]

M $^{2+}$	HF				B3LYP			
	I	II	III	IV	I	II	III	IV
-	0.00	58.4	0.89	-238.71	0.00	45.08	2.06	-233.79
Be	0.00	35.42	-33.17	-118.71	0.00	23.59	-31.65	-110.79
Mg	0.00	43.50	-14.72	-161.80	0.00	30.44	-11.90	-155.55
Ca	0.00	47.91	-7.74	-190.32	0.00	35.18	-5.22	-182.64
Sr	0.00	48.90	-5.82	-198.53	0.00	36.24	-3.45	-191.44
Ba	0.00	49.48	-4.49	-205.88	0.00	36.49	-3.29	-199.03

[a]Relative energy of structures (II),(III),(IV) calculated respect to structure(I).

Table 2 Relative energies (B3LYP) (kcal mol^{-1}) for structures (II), (III) and (IV) in various solvent [a]

		Solvent						
M^{2+}	Structure	DMSO	$MeNO_2$	Acetone	CH_2Cl_2	THF	$CHCl_3$	Cyclohexane
	II	49.13	49.07	48.89	48.53	48.39	47.98	46.70
	III	5.36	5.34	5.21	4.83	4.76	4.37	3.34
	IV	-277.14	-276.89	-275.92	-273.29	-272.36	-269.22	-256.52
Be	**II**	-11.75	-11.90	-12.66	-14.76	-15.43	-17.49	-24.48
	III	36.25	36.14	35.62	34.34	33.87	32.56	28.05
	IV	-268.33	-367.71	-264.96	-257.10	-254.55	-245.48	-208.12
Mg	**II**	8.25	8.08	7.22	4.91	4.20	2.00	-5.14
	III	47.46	47.32	46.71	45.14	44.60	43.03	37.56
	IV	-287.08	-286.51	-284.04	-276.89	-274.53	-266.16	-231.49
Ca	**II**	11.77	11.64	10.96	9.11	8.52	6.74	0.77
	III	48.85	48.73	48.19	46.52	46.36	45.00	40.44
	IV	-293.29	-292.79	-290.59	-284.28	-282.18	-274.85	-244.42
Sr	**II**	13.02	12.89	12.24	10.47	9.90	8.21	2.51
	III	50.28	50.16	49.61	48.20	47.73	46.34	41.72
	IV	-295.25	-294.76	292.64	-286.56	-284.53	-277.52	-248.48
Ba	**II**	15.44	15.31	14.56	12.57	11.96	15.44	15.31
	III	51.45	51.32	50.69	49.13	48.59	47.11	42.13
	IV	-298.04	-297.59	-295.61	-289.89	-287.96	-281.26	-253.46

[a]Relative energy of structures (II),(III) and (IV) calculated respect to structure (I).

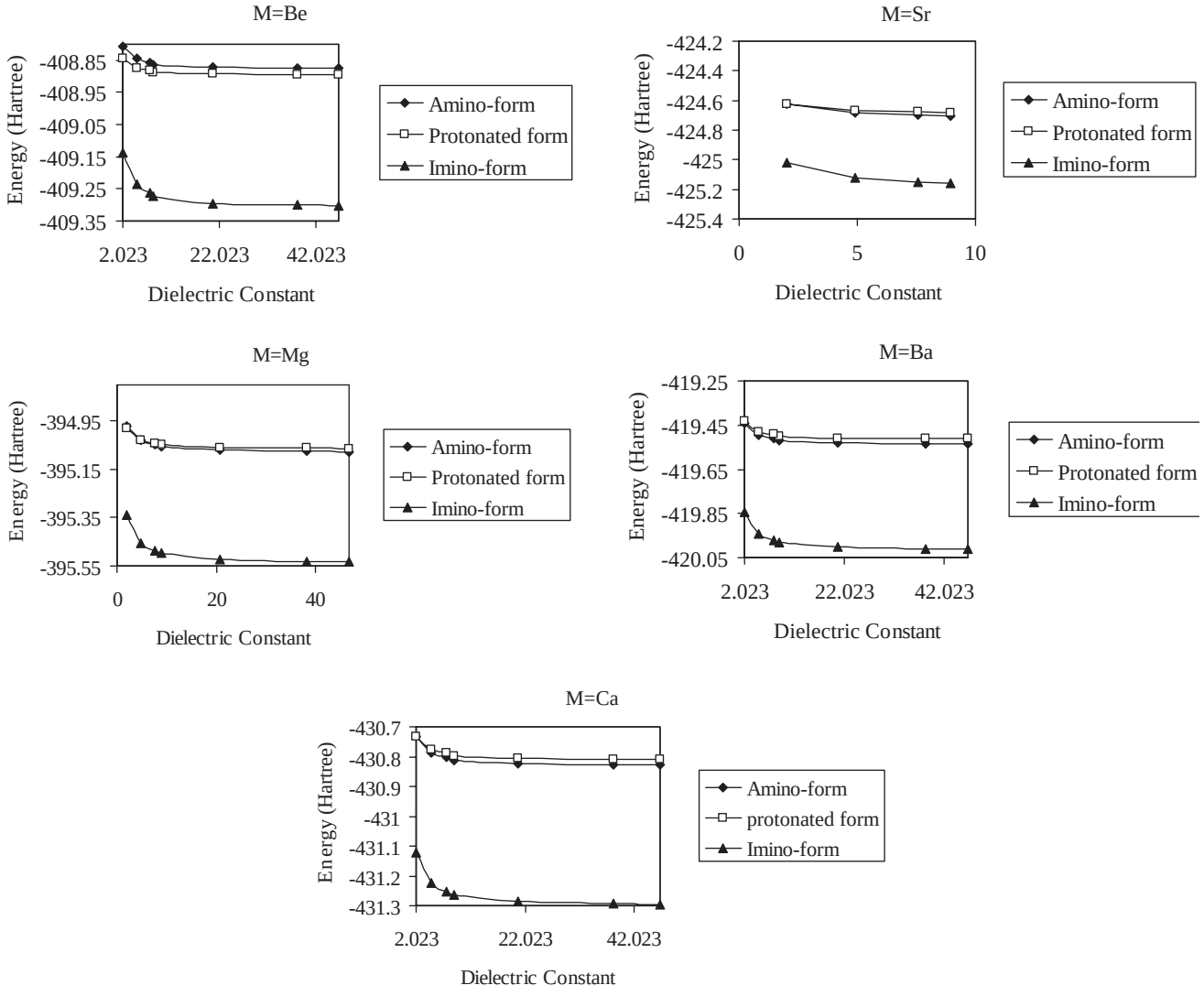

Fig. 3 Variation of energy (Hartree) with dielectric constant for amino-oxo tautomer, and imino-tautomer and protonated form.

Table 3 Dipole moment (debye) for structures (I), (II), (III) and (IV) in gas phase and various solvent in B3LYP level

			Solvent						
M^{2+}	Structure	Gas	DMSO	$MeNO_2$	Acetone	CH_2Cl_2	THF	$CHCl_3$	Cyclohexane
-	**I**	7.39	8.5158	8.5011	8.4350	8.2551	8.2019	8.0216	7.4337
	II	6.43	7.1195	7.1093	7.0625	6.9356	6.8978	6.7688	6.3412
	III	5.45	6.0352	6.0263	5.9857	5.8749	5.8423	5.7309	5.3623
	IV	5.88	6.6417	6.6338	6.5976	6.4983	6.4686	6.3663	6.0045
Be	**I**	15.71	21.65	21.61	21.47	21.05	20.93	20.50	18.94
	II	13.52	17.34	17.31	17.19	16.85	16.74	16.39	15.17
	III	11.19	13.78	13.76	13.68	13.46	13.39	13.15	12.30
	IV	19.84	22.37	22.34	22.21	21.87	21.77	21.41	20.20
Mg	**I**	19.82	27.26	27.22	27.05	26.56	26.41	25.90	23.99
	II	17.09	24.16	24.12	23.92	23.44	23.29	22.77	20.76
	III	16.43	21.35	21.32	21.20	20.85	20.74	20.34	18.86
	IV	27.64	25.93	25.90	25.75	25.34	25.21	24.79	23.30
Ca	**I**	24.05	30.56	30.53	30.38	29.95	29.83	29.37	27.68
	II	20.68	26.67	26.65	26.52	26.16	26.04	25.65	24.06
	III	20.25	24.56	24.54	24.46	24.22	24.14	23.86	22.75
	IV	29.00	27.28	27.25	27.12	26.77	26.6	26.29	25.03
Sr	**I**	23.45	29.19	29.15	29.01	28.61	28.49	28.06	26.48
	II	19.71	24.84	24.82	24.70	24.38	24.28	23.92	22.53
	III	19.44	22.91	22.90	22.82	22.60	22.53	22.28	21.30
	IV	30.98	22.51	22.48	22.35	22.00	21.90	21.54	20.34
Ba	**I**	23.75	28.88	28.85	28.70	28.29	28.17	27.74	26.24
	II	19.67	23.92	23.90	23.79	23.49	23.39	23.07	21.85
	III	18.98	22.06	22.04	21.97	21.75	21.69	21.45	20.52
	IV	33.11	19.63	19.60	19.48	19.14	19.04	18.69	17.52

Table 4 E_I (interaction energies), BSSE and E_{I+BSSE} (kcal mol^{-1}) for structures (I), (III) and (IV) in HF level

M^{2+}	E_I			BSSE			E_{I+BSSE}		
	I	III	IV	I	III	IV	I	III	IV
Be	–437.9	–500.2	–232.0	–0.32	–0.58	–0.21	–438.2	–500.78	–232.21
Mg	–317.4	–361.3	–136.1	–0.50	–0.68	–0.49	–317.90	–361.98	–136.59
Ca	–242.7	–279.6	–82.9	0.11	0.05	–0.01	–242.59	–279.55	–82.91
Sr	–223.1	–258.0	–69.6	–0.43	–0.54	–0.51	–223.53	–258.54	–70.11
Ba	–205.4	–239.0	–57.9	–0.28	–0.37	–0.36	–205.68	–239.37	–58.26

Table 5 Optimised bond distances of M–N4, C4–N4 and C4–N3 (Å) for structure (I), (II) and (III) in gas phase in HF level

M^{2+}	M-N4			C4-N4			C4-N3		
	I	II	III	I	II	III	I	II	III
-	0.99	1.00	0.99	1.34	1.25	1.31	1.29	1.39	1.34
Be	1.468	1.383	1.514	1.409	1.290	1.374	1.275	1.356	1.334
Mg	1.85	1.764	1.91	1.377	1.268	1.339	1.286	1.380	1.341
Ca	2.240	2.155	2.34	1.354	1.255	1.318	1.290	1.401	1.350
Sr	2.385	2.296	2.512	1.349	1.253	1.313	1.304	1.408	1.353
Ba	2.537	2.443	2.707	1.344	1.251	1.307	1.307	1.413	1.357

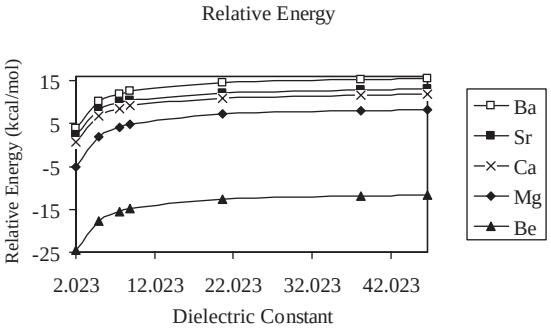

Fig. 4 Variation of relative energy of imino-tautomer (kcal mol^{-1}) respect to amino-tautomer with dielectric constant. Be, Mg, Ca, Sr and Ba.

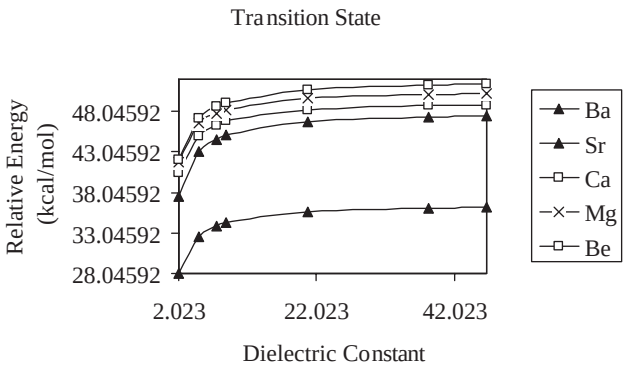

Fig. 5 Variation of relative energy of transition state (kcal/mol) respect to amino-tautomer with dielectric constant. Be, Mg, Ca, Sr and Ba.

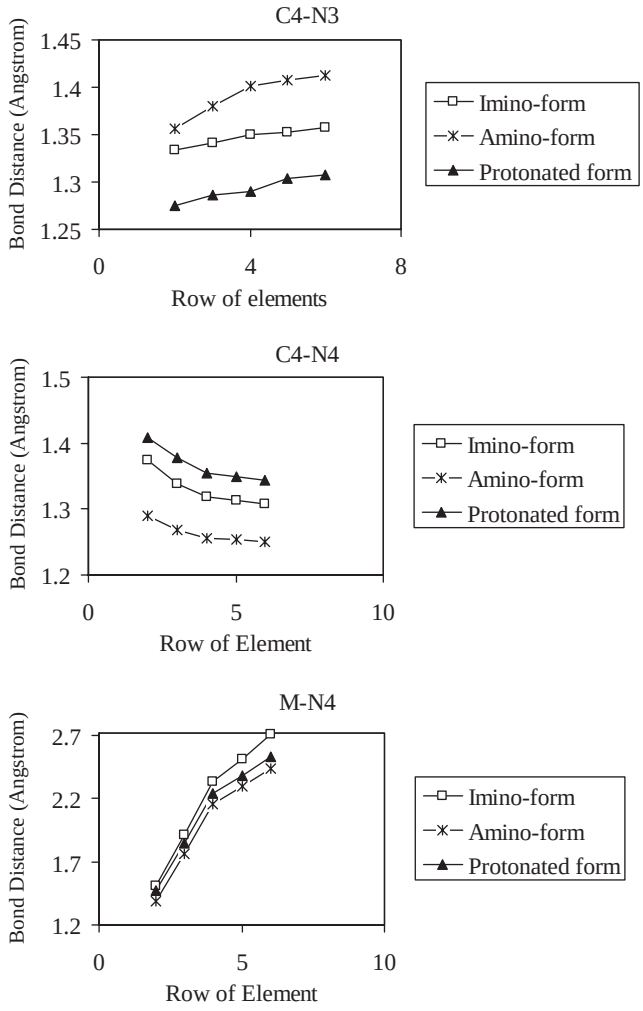

Fig. 6 Dependencies of C4–N3, C4–N4, M–N4 distances on the atomic number of the metal for amino-tautomer, imino-tautomer and N3- protonated cytosine.

moments for metalated cytosine with heavy atoms (Table 3). Table 4 shows the value of BSSE and E_{I+BSSE} for the structures V and VI. Clearly for the all complexes, values of BSSE are rather small. Therefore, for these cases BSSE is negligible.

Geometry parameters

Intermolecular parameters: All the intermolecular distances M–N4 for metalated cytosine are longer than the distance of H–N4 in nonmetalated cytosine (Table 5). This can be explained by the fact that the atomic radius of M is larger than H. The intermolecular M–N4 distance monotonically increases with the atomic number for the metals of alkaline earths (Table 5, Fig. 6). This increase is more pronounced where this difference is more than 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 (Table 5).

Intramolecular parameters: Distances of C4–N4 and C4–N3 are shown in Table 5. In protonated forms the N4–C4 distances decrease while 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 (Fig. 6). Therefore we conclude that the double bond characterisation of C4–N4 bond and single bond characterisation of the C4–N3 bond increase in the following order: amino< protonated< imino. The single bond characterisation of the C4–N3 bond is compatible with the results of NBO calculations. Hybridation coefficients for this bond have been given in Table 6 and 11.NBO calculation shows the π-bonding contribution in the C4–N3 bond of the amino-tautomer. All the intramolecular distances C4–N3 for metalated cytosine are larger than nonmetalated. The intramolecular C4–N3 distances increase with atomic number of the alkaline earth metals (Table 5, Fig. 6). This increase is not pronounced, where this difference is more than 0.032 Å (for Be^{2+} to Ba^{2+}). On the other hand, all the intramolecular distances C4–N4 for metalated cytosine are larger than nonmetalated. The intramolecular C4–N4 distances decrease with atomic number of the alkaline earth metals (Table 5, Fig. 6). This decrease is not pronounced, where this difference is more than 0.06 Å (for Be^{2+} to Ba^{2+}).

Table 6 Hybridation coefficient of C4–N3, C4–N4 bonds calculated by NBO method in HF level

M^{2+}		C4–N4		
		I	III	IV
Be	σ	$0.6111\ (sp^{2.74})_C + 0.7916\ (sp^{1.53})_N$	$0.6431(sp^{1.91})_C + 0.7658(sp^{0.82})_N$	$0.6266\ (sp^{2.32})_C + 0.7793(sp^{1.44})_N$
	π		$0.4352(p^{1.00})_C + 0.9003(p^{1.00})_N$	
Mg	σ	$0.6309\ (sp^{2.37})_C + 0.7759\ (sp^{1.58})_N$	$0.6536(sp^{1.69})_C + 0.7569\ (sp^{0.96})_N$	$0.6399(sp^{2.05})_C + 0.7685(sp^{1.44})_N$
	π		$0.5113(p^{1.00})_C + 0.8594(p^{1.00})_N$	
Ca	σ	$0.6385\ (sp^{2.17})_C + 0.7696\ (sp^{1.54})_N$	$0.6546\ (sp^{1.58})_C + 0.7560\ (sp^{0.99})_N$	$0.6446\ (sp^{1.92})_C + 0.7645(sp^{1.42})_N$
	π		$0.5623(p^{1.00})_C + 0.8269(p^{1.00})_N$	$0.4394(p^{1.00})_C + 0.8983\ (p^{1.00})_N$
Sr	σ	$0.6396\ (sp^{2.13})_C + 0.7687\ (sp^{1.53})_N$	$0.6547(sp^{1.56})_C + 0.7559\ (sp^{1.01})_N$	$0.6458\ (sp^{1.89})_C + 0.7635(sp^{1.42})_N$
	π		$0.5753\ (p^{1.00})_C + 0.8180\ (p^{1.00})_N$	$0.4533\ (p^{1.00})_C + 0.8914(p^{1.00})_N$
Ba	σ	$0.6398\ (sp^{2.11})_C + 0.7685\ (sp^{1.52})_N$	$0.6545(sp^{1.55})_C + 0.7561(sp^{1.03})_N$	$0.6467(sp^{1.87})_C + 0.7628\ (sp^{1.42})_N$
	π		$0.5852(p^{1.00})_C + 0.8109(p^{1.00})_N$	$0.4664\ (p^{1.00})_C + 0.8846(p^{1.00})_N$

M^{2+}		C4–N3		
		I	III	IV
Be	σ	$0.6440(sp^{1.89})_C + 0.7650(sp^{1.49})_N$	$0.6123\ (sp^{2.50})_C + 0.7906\ (sp^{1.67})_N$	$0.6212\ (sp^{2.28})_C + 0.7837\ (sp^{1.66})_N$
	π	$0.5795\ (p^{1.00})_C + 0.8150(p^{1.00})_N$	-	-
Mg	σ	$0.6433(sp\ 1.94)_C + 0.7656(sp^{1.52})_N$	$0.6064\ (sp^{2.65})_C + 0.7952\ (sp^{1.69})_N$	$0.6182\ (sp^{2.34})_C + 0.7860\ (sp^{1.65})_N$
	π	$0.5506\ (p\ 1.00)_C + 0.8348(p\ 1.00)_N$	-	-
Ca	σ	$0.6422\ (sp^{1.96})_C + 0.7665(sp^{1.55})_N$	$0.6006\ (sp^{2.75})_C + 0.7996\ (sp^{1.70})_N$	$0.6154\ (sp^{2.37})_C + 0.7882\ (sp^{1.65})_N$
	π	$0.5272(p^{1.00})_C + 0.8497(p^{1.00})_N$	-	-
Sr	σ	$0.6419\ (sp^{1.97})_C + 0.7668(sp^{1.56})_N$	$0.5989\ (sp^{2.78})_C + 0.8008\ (sp^{1.70})_N$	$0.6147\ (sp^{2.38})_C + 0.7888\ (sp^{1.66})_N$
	π	$0.5208(p^{1.00})_C + 0.8537(p^{1.00})_N$	-	-
Ba	σ	$0.6415(sp^{1.97})_C + 0.7672\ (sp^{1.57})_N$	$0.5977\ (sp^{2.80})_C + 0.8017(sp^{1.70})_N$	$0.6139\ (sp^{2.39})_C + 0.7893\ (sp^{1.66})_N$
	π	$0.5157(p^{1.00})_C + 0.8567(p^{1.00})_N$	-	-

Table 7 Enthalpy (ΔH=MIA, in kcal mol^{-1}), entropy ($T\Delta S$, in kcal mol^{-1} K), free energy (ΔG, in kcal mol^{-1}) and equilibrium constants(K) variations for the formation process of (I),(II) and (IV) complexes, at 298 K, computed at HF level of theory [a]

M	$\Delta H^{298\ K}$			$T\Delta S^{298\ K}$			$\Delta G^{298\ K}$			K		
	I	III	IV	I	III	IV	I	III	IV	I	III	IV
-	353.02	379.63	234.03	6.33	7.59	1.51	346.69	372.04	232.52	1.78	1.86	1.48
Be	435.90	495.94	228.82	8.41	8.34	8.21	427.49	487.60	220.61	2.05	2.27	1.45
Mg	316.88	358.17	133.48	9.22	7.58	7.95	307.65	350.59	125.53	1.68	1.80	1.23
Ca	241.70	276.81	80.37	6.80	7.65	7.65	234.89	269.15	72.72	1.48	1.57	1.13
Sr	222.77	255.41	67.11	8.86	7.56	7.45	213.90	247.84	59.65	1.43	1.51	1.10
Ba	205.12	236.47	55.49	8.74	7.47	7.24	196.37	229.00	48.24	1.39	1.47	1.08

Thermochemical analysis: Thermochemical analysis is done for metalated and nonmetalated cytosine. The values of ΔH, ΔS and ΔG are reported in Table 7 in which the individual terms are referred to a temperature of 298 K. As can be seen, the ΔS values are quite similar for all complexes, although the relative difference of the ΔG are almost the same as the ΔH. The equilibrium constants of the all complexes are given in Table 7. This shows that the equilibrium constant is less for the more electropositive metals. This is compatible with a symbiosis effect.[35] Table 7 shows that with increasing metal ion radius the value of ΔG will decrease which shows complex stability decline. It sounds right, because as we have indicated previously, bond length will increase with increasing of radius of metals. As a result, the bonding strength will decrease. Stability constants in Table 7 prove this case. The reaction that can be considered is:

$$M + B \rightarrow MB$$

Since in this reaction two particles form one, ΔS should have a negative value.

Population analysis: Mulliken population analysis, like all atomic charge assignment schemes, is an arbitrary method for assigning atomic charges. Generally, changes in Mulliken population provide a reasonable estimation of changes in electron density within closely related molecules. Mulliken population analysis assigns atomic charges by dividing molecular orbital overlap evenly between each pair of atoms involved in a chemical bond. To identify any artifacts in the Mulliken population analysis, a natural bond orbital was also examined. The Mulliken charges for N3, O and N4 on cytosine and M, N3, O and N4 on metalated cytosine are given in Table 8. Also, analysis of the atomic charges is done by the natural bonding orbital (NBO) method. Atomic charges of selected atoms of metalated cytosine that participate in hydrogen bondings between DNA bases and N4 have are shown in Table 9. It was found that the charge on N4 in metalated cytosine is more than in nonmetalated cytosine (Tables 8, 9 and 10). Increased dipole moments of metalated cytosine show that N4 is more basic in metalated cytosine (Table 3). As shown above, metalation of the imino-tautomer strongly influences the electronic structure of the imino-tautomer, and this leads to energetic stabilisation of the structure. Therefore, the increasing N4 basicity of the metalated cytosine can be attributed to the relative stabilisation of the imino-tautomer and increased stability of the protonated form.

It is possible to identify principle delocalising acceptor orbitals associated with each donor NBO and their topological relationship to this NBO, *i.e.*, whether attached to the same atom (geminal), to an adjacent bonded atom (vicinal) or to a more remote site. These acceptor NBO's will generally correspond to the principle delocalisation tails of the non-Lewis molecular orbital (NLMO) associated with the parent donor NBO.

In the amino-tautomer the N1 lone pair is seen to be the lowest occupancy and highest energy Lewis NBO and to be primarily delocalised into antibonds, the vicinal $\pi^*_{C2\text{-}O2}$, $\pi^*_{C5\text{-}C6}$ NBOs. See Table 11. The Lewis NBOs in Table 11 describes percentage of the total density, with the remaining non Lewis density found primarily in the valence-shell antibonding. In the imino-tautomer the N3 lone pair is seen to be the lowest occupancy and highest energy Lewis NBO and to be primarily delocalised into antibonds, the vicinal $\pi^*_{C2\text{-}O2}$, $\pi^*_{C5\text{-}C6}$ NBOs. The same NBOs are used for the amino-tautomer and describe percentage of the total density.

Donor-acceptor interaction perturbation theory energy analysis: The localised orbitals in a best Lewis structure can interact strongly. A filled bonding or lone pair orbital can act as a donor and an empty or filled bonding, antibonding or lone pair orbital can act as an acceptor. These interactions can strengthen and weaken bonds. For example, a lone pair donor →antibonding acceptor orbital interaction will weaken the bond associated with the antibonding orbitals. Conversely, an interaction with a bonding pair as the acceptor will strengthen the bond. Strong electron delocalisation in a best Lewis structure will also show up as donor-acceptor interactions. Table 12 shows the interactions that give the strongest stabilisation.

Therefore in this paper we have shown:

(1) *Ab initio* calculations indicate that metalation of the exocyclic amino- group of cytosine by the elements of group IIA (Be, Mg, Ca, Sr, Ba) stabilise imino-tautomer respect to amino-tautomer.

(2) Metalation increases the protonation energy of the nucleobase ring nitrogen atom.

(3) The calculations suggest that this kind of metalation increases the transition state energy of the tautomerisation of the nucleobase.

(4) For the nonmetalated and metalated cytosine, with decrease of dielectric constant of solvent the imino-tautomer is stabilising respect to amino-tautomer.

(5) The strongest bonding interactions have been found for metalated cytosine with heavy metals.

(6) The M–N4 and C4–N3 distances for metalated cytosine are larger than nonmetalated. But, the C4–N4 distances for metalated cytosine are smaller than nonmetalated.

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Table 8 Mulliken population of M, N3, O and N4 in metalated cytosine in HF level

M^{2+}	M			N3			O			N4		
	I	III	IV	I	III	IV	I	III	IV	I	III	IV
–	–	–	–	–0.62715	–0.37776	–0.35998	–0.637604	–0.639679	–0.519225	–0.071000	–0.340330	0.030730
Be	-0.16568	-0.48193	0.17830	–0.44781	–0.32874	–0.16438	–0.536168	–0.545170	–0.425894	0.698311	0.498361	0.502627
Mg	1.512479	1.465708	1.655473	–0.63701	–0.38932	–0.37667	–0.468254	–0.579218	–0.575485	–0.431623	–0.931803	–0.207814
Ca	1.899141	1.924065	1.939447	–0.66449	–0.36417	–0.40717	–0.599012	–0.609111	–0.493788	–0.83684	–1.282778	–0.233569
Sr	1.954846	1.979040	1.98155	–0.65816	–0.33515	–0.40745	–0.607658	–0.618013	–0.503100	–0.877391	–1.359014	–0.239864
Ba	1.922229	1.941759	1.949841	–0.64154	–0.30399	–0.40143	–0.615752	–0.624938	–0.511850	–0.880009	–1.340739	–0.246268

Table 9 Natural population of M, N3 O and N4 in metalated cytosine in HF level

M^{2+}	M			N3			O			N4		
	I	III	IV	I	III	IV	I	III	IV	I	III	IV
–	–	–	–	–0.71475	–0.74518	–0.71212	–0.72842	–0.73028	–0.62942	–0.88055	–0.78034	–0.82346
Be	1.79836	1.80432	1.85378	–0.64787	–0.71436	–0.69977	–0.65956	–0.6672	–0.57544	–1.46176	–1.62193	–1.39044
Mg	1.86762	1.90202	1.92313	–0.69301	–0.74488	–0.71435	–0.68491	–0.70152	–0.60133	–1.37274	–1.49816	–1.28207
Ca	1.95634	1.97633	1.98061	–0.72933	–0.76296	–0.72715	–0.71112	–0.72888	–0.62497	–1.33716	–1.41351	–1.20408
Sr	1.97232	1.99020	1.98799	–0.73883	–0.76665	–0.73067	–0.71937	–0.73621	–0.63201	–1.32070	–1.38477	–1.17206
Ba	1.98860	1.99961	1.99459	–0.74677	–0.76900	–0.73386	–0.72732	–0.74176	–0.63922	–1.31032	–1.36177	–1.14081

Table 10 Change in natural population of N4 after metalation

M^{2+}	Δ Population		
	I	III	IV
Be	–0.58121	–0.84159	–0.56698
Mg	–0.49219	–0.71782	–0.45861
Ca	–0.45661	–0.63317	–0.38062
Sr	–0.44015	–0.60443	–0.34860
Ba	–0.42977	–0.58143	–0.31735

Table 11 %Total Lewis, highest energy Lewis NBO lowest and lowest occupancy of N1, N3 in amino and imino-tautomer, respectively

M^{2+}	Amino-tautomer			Imino-tautomer		
	%Total Lewis	Lowest occupancy (N1)	Highest energy Lewis NBO(a.u) (N1)	%Total Lewis	Lowest occupancy (N3)	Highest energy Lewis NBO(a.u) (N3)
Be	98.0074	1.66150	-0.50975	97.8806	1.68043	–0.53886
Mg	97.9424	1.67429	-0.48594	98.0164	1.71335	–0.49829
Ca	97.8476	1.68582	-0.46167	98.0622	1.73140	–0.46419
Sr	97.8191	1.68944	-0.45392	98.0687	1.73489	–0.45464
Ba	97.7959	1.69330	-0.44612	98.0689	1.73698	–0.44687

Table 12 The stabilisation energy *E* (2) associated with delocalisation for interactions that to give the strongest stabilisation

M	Donor NBO			Acceptor NBO			E(2)(kcal mol^{-1})		
	I	III	IV	I	III	IV	I	III	IV
-	BD*(2) C 4- N3	LP (1)N 3	LP(1) N3	BD*(2) C2- O2	BD*(2) C2- O2	BD*(2) C4- N4	95.73	87.00	113.42
Be	BD*(2) C 5- C6	LP (1)N 3	LP(1) C2	BD*(2) C4- N3	BD*(2) C4- N4	BD*(2) C4- N3	268.53	104.38	245.95
Mg	BD*(2) C 5- C6	BD*(2) C4- N4	LP(2) N4	BD*(2) C4- N3	BD*(2) C5- C6	BD*(2) C4- N3	171.24	129.50	111.86
Ca	BD*(2) C 5- C6	LP (1)N 1	LP(1) N4	BD*(2) C4- N3	BD*(2) C2- O2	BD*(2) C4- N3	196.21	76.85	109.20
Sr	BD*(2) C 5- C6	BD*(2)C5- C6	LP(1) N4	BD*(2) C4- N3	BD*(2) C4- N4	BD*(2) C4- N3	230.93	117.65	105.00
Ba	BD*(2) C 5- C6	LP (1)N3	LP(1) N4	BD*(2) C4- N3	BD*(2) C2- O2	BD*(2) C4- N3	296.15	86.58	100.99

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