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Original Scientific Article

Metal Complexation and H-bonding Effects on Electronic Structure of Cytosine Studied in the Gas Phase†

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Abstract. The influence of H-bonding and complexation with cations (probed by HF, F^-, Li^+, Na^+ and K^+) on structural and π-electron changes in the six most stable cytosine tautomers has been studied in the gas phase using the B3LYP/6-311++G(2d,2p) computational level. The presence of two *exo*- groups (amino/imino and carbonyl/hydroxyl) in cytosine tautomers significantly increases their sensitivity to structural changes due to intra- and intermolecular interactions. These interactions induce large changes in aromaticity of the rings and in the CX (X = N, O) bond lengths of exocyclic groups. Three types of H-bonds, considering their strength, could be distinguished: (i) charge-assisted $X^-\cdots HF$, X = N or O, as the strongest, (ii) neutral X···HF, where X is the nitrogen atom of the ring or imino group or the keto form oxygen atom and (iii) also neutral X···HF, where X being either amino N or alternatively hydroxylic O. Hydrogen bond energy decreases approximately twice in the above listed sequence of interactions. Structural consequences of H-bonding and metal complexation have been observed not only in the immediate region of the interaction but also in other parts of the molecule (the shape of the amino group, changes in CO and CN bond lengths). Complexation of the cytosine tautomers with cations leads to monotonic changes in aromaticity in line with an increase of their ionic radii.

Keywords: H-bonding, aromaticity, cytosine, tautomer, metal complexation

INTRODUCTION

Electronic structure of molecules is of crucial importance for the knowledge of their chemical, physical and biochemical properties,[1–5] and is usually considered in terms of π- and σ- electron structures.[3,5] It is assumed that the former is more sensitive towards various types of perturbations and hence it usually is responsible for intra- and intermolecular interactions and the resulting changes in molecular properties. The sigma core is assumed to be less flexible, but also may contribute to these changes. In the case of π-electron systems, changes in the molecular geometry are usually considered as solely caused by modifications of the π-electron structure, but this approach is still a subject of vivid disputation.[6–8] Aromaticity as an electronic structure dependent property of π-electron systems[9,10] is well described for families of similar molecules by geometric,[11] magnetic[12] and energetic[13] characteristics. However, for a more differentiated set of molecular systems, no good correlation between these different parameters is found.[14]

A parallel can be drawn here with the substituent effects in organic chemistry, where the main contributions are related to resonance or field/inductive effects.[15–17] The numerical characteristics (so-called substituent constants)[18,19] do not always work for systems being significantly different from those for which they were estimated. Numerous interpretations of a variety of chemical and physicochemical properties are present in modern handbooks on organic chemistry.[20–22]

There are many factors, which may affect the electronic structure of the molecules. Among them two kinds of complexation, by metal ions or *via* H-bonding, are the most important interactions for biological systems. The influence of these interactions on the electronic structure of DNA and RNA bases have been a subject of wide and intensive investigations.[23–29]

Cytosine, like adenine, has 14 possible tautomers. Results of theoretical calculations suggest that in the solid state as well as in aqueous solutions only the canonical 1H keto-amino form is present.[30] However, experimental studies have proven that in the gas phase two rotamers of the 2H enol form and the 1H keto-amino form are the most stable.[31,32] Moreover, experiments on cytosine in Ar matrices (and irradiated

† Dedicated to Dr. Mirjana Eckert-Maksić on the occasion of her 70th birthday.
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with monochromatic UV laser light) allowed to identify the presence of keto-imino isomers in the tautomeric mixture.[33,34]

It follows from these studies that the occurrence of tautomers depends on the surroundings in a different way, *i.e.* on intermolecular interactions which differ for various environments of the molecules. In this work we have undertaken a systematic study how H-bonding and metal complexation of the six most stable cytosine tautomers in the gas phase influence their geometric and π-electron structures. For this purpose, we have selected the following partners: HF/F^- and M^+ (M = Li, Na, K), which lead to the strongest intermolecular interactions. This approach allows us to observe the greatest possible changes in the electronic structure of cytosine and to estimate their short- and long-distance structural consequences.

Methodology

Since this study is a continuation of our research on the effects of H-bonding and complexation with metal ions on structural properties of the nucleobases, all further calculations were performed in the same way as described in our previous papers,[35,36] using the Gaussian 09 series program[37] at the B3LYP/6-311++G(2d,2p) computational level to compare the obtained results. The absence of imaginary frequencies confirmed that the obtained geometries correspond to the minima on the potential energy surface and consequently to the equilibrium structures.

The energy of the intermolecular interaction was calculated as the difference between the energy of the complex A···B and the sum of the energies of its components for geometries obtained during the optimization procedure of the A···B, A and B systems. The basis set superposition error (BSSE)[38] was taken into account in these calculations. For energetically stable complexes the estimated total energy of interaction, E_{tot} (E_{HB} in the case of H-bonding), is negative.

The total energy of interaction was decomposed into deformation (E_{def}) and interaction (E_{int}) components. The first term represents the amount of energy required to change the geometries of two fragments into one in the complex:

$$E_{def} = E_A\left(basis_A;opt_{AB}\right) - E_A\left(basis_A;opt_A\right) + E_B\left(basis_B;opt_{AB}\right) - E_B\left(basis_B;opt_B\right) \quad (1)$$

where $E_A(basis_A;opt_{AB})$ and $E_A(basis_A;opt_A)$ are the energies of the A molecule for its geometries obtained during the optimization procedure of the A···B complex, opt_{AB}, and the monomer A, opt_A, respectively. An analogous definition stands for E_B.

Interaction energy, corrected by the BSSE, was calculated as follows:

$$E_{int} = E_{AB}\left(basis_{AB};opt_{AB}\right) - E_A\left(basis_{AB};opt_{AB}\right) - E_B\left(basis_{AB};opt_{AB}\right) \quad (2)$$

where $E_A(basis_{AB}; opt_{AB})$ is the energy of molecule A, calculated using the basis of the A···B complex, named $basis_{AB}$, and its geometry obtained during the optimization procedure of the complex, opt_{AB}. The other terms in Equation 2 should be understood in the same way.

The π-electron delocalization of the ring was characterized using structural parameter of aromaticity HOMA (Harmonic Oscillator Model of Aromaticity)[39,40] and magnetic indices NICS (Nucleus independent chemical shifts).[41–44] NICS's were calculated at HF/6-31+G(d) level of theory using the GIAO method.

The shape (pyramidalization) of amino group was characterized by the angle φ estimated as a difference between 360° and the sum of the bond angles for bonds linking the nitrogen atom to two H atoms and to the carbon; for the planar NH_2 group $\varphi = 0°$.

RESULTS AND DISCUSSION

To make this section more clear the results are discussed in two parts dealing with (i) free tautomers and their interactions *via* H-bonding and (ii) by complexation with metal ions.

Cytosine and Their H-bonded Complexes

The six most stable tautomers of cytosine are schematically shown in Figure 1, whereas their characteristics (stability and aromaticity data) are presented in Table 1.

The most indicative information resulting from the data collected in Table 1 is a lack of any correlation between the relative energy, E_{rel}, of free tautomers and their aromaticity indices HOMA, NICS(0), NICS(1) and NICS(1)zz. The coefficients of determination for linear regressions between them are always very low ($R^2 \leq 0.1$). It can be interpreted as an indication that cytosine tautomers do not form a family of molecules with a similar electronic structure.[45] At variance, the mutual correlations between all aromaticity indices in Table 1 are excellent ($R^2 \geq 0.9$). Two tautomers, cyt2 and cyt3, are highly aromatic, since their ring is of 4N+2 π-electron type and hence well fulfills the Hückel rule. In tautomers with one carbonyl group, *i.e.* cyt1 and cyt6, aromaticity is lower since it is well known that double-bonded groups attached to the ring decrease its π-electron delocalization.[46] Cyt4 and cyt5 have the lowest aromaticity since two double-bonded groups are attached to the ring. Therefore, it can be concluded that such functional groups with double bond play a very important role in the electronic structure and aromaticity of the ring in cytosine tautomers. The protonation of these groups (as in cyt2 and cyt3) substantially increases aromaticity of the ring.

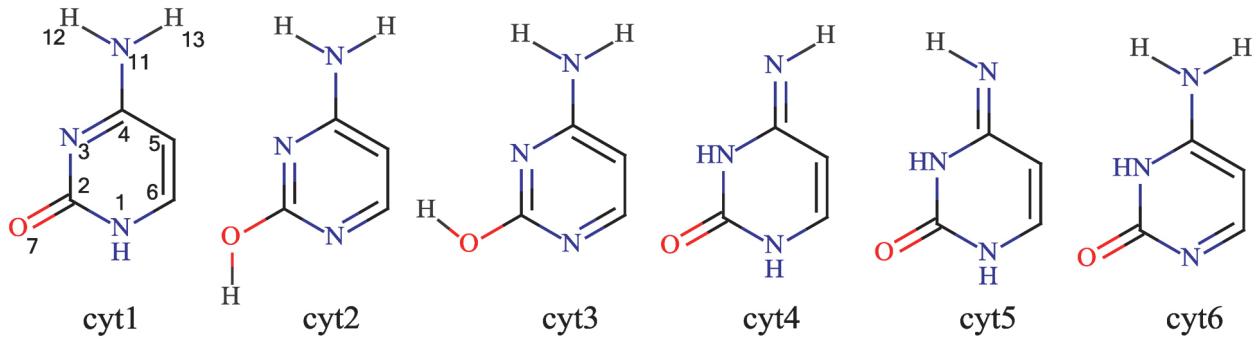

Figure 1. The most stable cytosine tautomers.

Table 1. Main characteristics for free cytosine tautomers

Tautomer	E_{rel} / kcal mol^{-1}	HOMA	NICS(0)	NICS(1)	NICS(1)zz
cyt1	0.00	0.699	–1.3	–3.3	–5.7
cyt2	0.54	0.976	–5.3	–7.5	–18.1
cyt3	1.29	0.981	–5.4	–7.6	–18.3
cyt4	1.81	0.534	–0.6	–1.2	+0.5
cyt5	3.56	0.512	–0.6	–1.2	+0.4
cyt6	6.97	0.800	–1.8	–3.6	–6.7

The double bond loses some part of its "doubleness" as a result of H-bonding or cation complexation, therefore, in complexes of the cytosine tautomers substantial changes in aromaticity are observed (see Table 2). It follows from previous studies[28,47] that H-bonding in the guanine-cytosine (G-C) Watson-Crick base pair does not change the aromaticity of the cytosine ring (cyt1) in any significant way (HOMA = 0.7). However, intermolecular interactions of the G-C pair with metal cations can increase the aromaticity of this ring up to 0.8 HOMA unit.[28]

There are two kinds of characteristics of molecules involved in intra- or intermolecular interactions: the energetic and structural ones. Table 2 presents full characteristics of H-bonded complexes of cytosine tautomers, including interaction (E_{int}) and deformation (E_{def}) energies as well as energy of H-bond formation (E_{HB}). Additionally, important structural patterns, mentioned above, are also presented: the CN (C4N11, see Figure 1) and CO bond lengths as well as geometry-based aromaticity index HOMA describing a degree of π-electron delocalization of the ring. It should be noted that in some cases the formation of intermolecular H-bond leads to a proton transfer. As a result, these systems become negatively charged and absolute values of their E_{HB} are much greater than those calculated for all other cases. Such H-bonding is also associated with greater values of the deformation energy. Another important observation is a strong dependence of the π-electron delocalization, visualized by HOMA index, on the site of H-bonding and on its type – with or without proton transfer.

To make the data of Table 2 clear, let us consider all possible H-bonds, which may be formed as a result of fluoride (F^-) or hydrofluoric acid (HF) approach to the acidic or basic centers of the discussed cytosine tautomers. It is well known that a stronger acid is a better proton donor, and a stronger base is a better proton acceptor, but increasing acidity has a certain limit, since eventually proton transfer may take place.[48,49] Therefore, the following "reactions" should be formally taken into account:

1. O + HF → O···HF
2. OH + F^- → OH···F^-
3. OH + F^- → O^-···HF
4. N + HF → N···HF
5. NH + F^- → N^- ···HF
6. NH + F^- → NH···F^-

Almost all of these interactions occur in the studied complexes, including those with proton transfer. Their structural and energetic effects are summarized in Table 3. Structural changes in the region of H-bonding and their long-distance consequences depend on the type of intermolecular interactions.

Table 2. Characteristics of H–bonded complexes of cytosine tautomers.Bolded values concern properties of free tautomers

Tautomer	Interaction	d_{HB} / Å	E_{int} / kcal mol^{-1}	E_{def} / kcal mol^{-1}	E_{HB} / kcal mol^{-1}	d_{CN}[(a)] / Å	d_{CO} / Å	HOMA
cyt1						**1.361**	**1.216**	**0.699**
	N1H···F$^-$ [(b)]	1.473	–30.91	5.98	–24.94	1.405	1.231	0.836
	N3···HF	1.610	–16.36	2.22	–14.15	1.345	1.213	0.720
	N11···HF	1.789	–6.93	1.31	–5.61	1.398	1.212	0.724
	NH12···F$^-$ [(b)]	1.468	–32.35	6.09	–26.26	1.317	1.236	0.480
	NH13···F$^-$ [(b)]	1.359	–40.82	12.76	–28.06	1.316	1.237	0.548
	O···HF	1.505	–18.11	2.99	–15.12	1.353	1.240	0.781
cyt2					**1.364**	**1.346**	**0.976**	
	N1···HF	1.555	–16.35	3.12	–13.22	1.356	1.331	0.956
	N3···HF	1.630	–14.57	1.87	–12.70	1.348	1.340	0.966
	N11···HF	1.776	–7.33	1.23	–6.11	1.400	1.341	0.992
	NH12···F$^-$ [(b)]	1.453	–33.80	6.81	–27.00	1.317	1.371	0.795
	NH13···F$^-$ [(b)]	1.363	–40.65	8.51	–32.14	1.316	1.372	0.821
	O···HF	1.789	–6.91	0.31	–6.60	1.359	1.358	0.967
	OH···F$^-$ [(b)]	1.457	–28.73	3.98	–24.75	1.406	1.259	0.919
cyt3					**1.366**	**1.346**	**0.981**	
	N1···HF	1.664	–13.02	1.11	–11.90	1.357	1.339	0.969
	N3···HF	1.563	–14.44	2.74	–11.70	1.359	1.333	0.982
	N11···HF	1.775	–7.24	1.16	–6.08	1.400	1.341	0.995
	NH12···F$^-$ [(b)]	1.440	–34.82	7.41	–27.41	1.318	1.370	0.818
	NH13···F$^-$ [(b)]	1.373	–39.64	11.49	–28.15	1.317	1.372	0.832
	O···HF	1.801	–6.67	0.29	–6.38	1.361	1.358	0.974
	OH···F$^-$ [(b)]	1.449	–29.27	4.26	–25.02	1.404	1.260	0.921
cyt4					**1.278**	**1.214**	**0.534**	
	N1H···F$^-$ [(b)]	1.489	–28.99	5.10	–23.89	1.300	1.230	0.730
	N3H···F$^-$ [(b)]	1.580	–25.70	3.14	–22.56	1.301	1.234	0.428
	N11···HF	1.566	–16.87	2.63	–14.24	1.289	1.210	0.608
	NH13···F$^-$	1.656	–29.08	3.09	–25.98	1.265	1.230	0.363
	O···HF	1.581	–14.00	1.71	–12.29	1.276	1.234	0.558
cyt5						**1.278**	**1.216**	**0.512**
	N1H···F$^-$ [(b)]	1.489	–28.97	5.13	–23.85	1.299	1.231	0.708
	N3H···F$^-$ [(b)]	1.489	–29.20	5.56	–23.64	1.296	1.235	0.467
	N11···HF	1.614	–15.23	1.67	–13.56	1.285	1.212	0.577
	O···HF	1.588	–13.61	1.61	–11.99	1.275	1.234	0.537
cyt6						**1.369**	**1.214**	**0.800**
	N1···HF	1.663	–13.48	1.17	–12.31	1.360	1.210	0.825
	N11···HF	1.800	–5.30	0.91	–4.39	1.400	1.210	0.760
	NH12···F$^-$ [(b)]	1.437	–31.51	7.07	–24.44	1.315	1.231	0.809
	NH13···F$^-$ [(b)]	1.460	–30.89	6.10	–24.79	1.314	1.234	0.796
	O···HF	1.498	–18.91	3.40	–15.51	1.360	1.240	0.892

[(a)] C4N11, see Figure 1.
[(b)] Proton transfer takes place.

Table 3. Changes in the main characteristics of the H-bonded cytosine complexes with respect to the free tautomers. Arrows assign an increase or decrease of a given parameter

Interaction	d_{CN}	d_{CO}	E_{HB} / kcal mol^{-1}	Tautomer	HOMA
N(ring)···HF	↓	↓	–12 ÷ –14	keto	↓
				enol	↑
N$^-$(ring) ···HF	↑	↑	–23 ÷ –25	all	↑ (N1$^-$···HF)
					↓ (N3$^-$···HF)
N(amino)···HF	↑	↓	–4 ÷ –6	amino	↑ (except cyt6)
			–14	imino	↑
N$^-$(amino)···HF	↓	↑	–24 ÷ –32	all	↓ (except cyt6)
O···HF	↓	↑	–6 ÷ –7	enol	↓
			–12 ÷ –16	keto	↑
O$^-$···HF	↑	↓	–25	all	↓

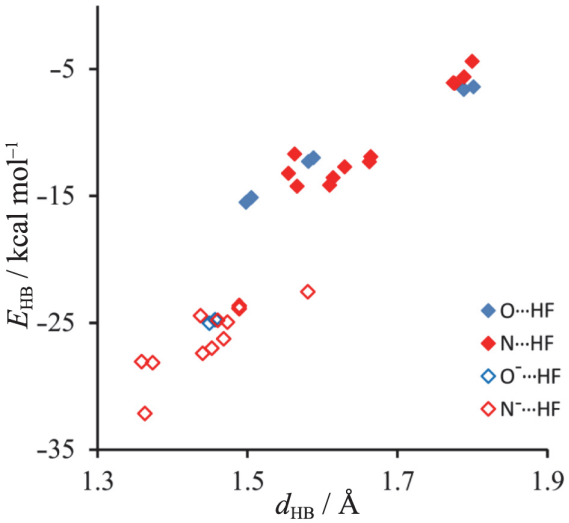

Figure 2. Relation between hydrogen bond energy, E_{HB}, and its length, d_{HB}, for the H-bonded complexes of cytosine tautomers. For all data points $R^2_{tot} = 0.8706$.

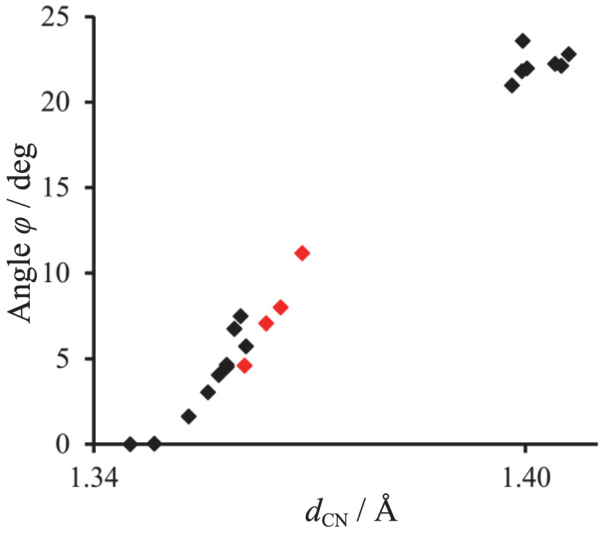

Figure 3. Correlation between pyramidality of the NH_2 group, φ, and the CN bond length, d_{CN}, for H-bonded complexes (black) and free tautomers of cytosine (red); $R^2 = 0.9843$.

Neutral N(amino)···HF and O···HF types of interactions cause lengthening of the CN and CO bonds, respectively. Additionally, shortening of the CO bond in the first case and the CN bond in the second one are observed. The opposite changes are observed for N$^-$(amino)···HF and O$^-$···HF hydrogen bonds. Thus in both cases the bonds, which are not directly involved in the H-bonding, are also sensitive to those interactions occurring in other parts of the molecule. Furthermore, participation of N(ring) in H-bonding also induces some long-distance consequences, pronounced by the changes in both CX bond lengths in one direction. Charge-assisted H-bonds result in CX bond lengthening, whereas for neutral interactions their shortening is found (Tables 2 and 3).

Considering strength of intermolecular interactions three type of H-bonds should be distinguished: (i) charge-assisted H-bonds X$^-$···HF (X = N and O) as the strongest, (ii) classical X···HF, X =N of the ring or imino group, or O of the keto form – sp^2 hybridized X, and (iii) also X···HF with X = N of the amino group or O of the hydroxyl group – sp^3 hybridized X. Hydrogen bond energy decreases approximately twice in a given sequence (Figure 2).

As a result of the H-bond formations and the changes in the electronic structure, the modification of the shape of the amino group are also observed. As follows from previous studies[36,50] the more electron attracting moiety to which NH_2 is attached, the more planar is the amino group. Variety of electron attractive

Table 4. Main characteristics for metal complexes of cytosine tautomers. Energy is expressed in kcal mol^{-1}. Bolded HOMA values concern aromaticity of free tautomers

	Interaction	$E_{rel}(Li^+)$	$E_{rel}(Na^+)$	$E_{rel}(K^+)$	HOMA (Li^+)	HOMA (Na^+)	HOMA (K^+)	E_{def} (Li^+)	$E_{def}(Na^+)$	$E_{def}(K^+)$	$E_{int}(Li^+)$	$E_{int}(Na^+)$	$E_{int}(K^+)$	$E_{tot}(Li^+)$	$E_{tot}(Na^+)$	$E_{tot}(K^+)$
cyt1						**0.699**										
	$M^+\cdots$N3,N11	22.00	–	–	0.813	–	–	13.88	–	–	–61.81	–	–	–47.92	–	–
	$M^+\cdots$N3,O	0.00	0.00	0.00	0.812	0.803	0.795	3.19	1.75	1.27	–73.12	–53.59	–41.06	–69.93	–51.84	–39.79
cyt2						**0.976**										
	$M^+\cdots$N3,N11	23.53	21.70	–	0.992	0.998	–	15.17	8.54	–	–62.06	–39.29	–	–46.90	–30.75	–
	$M^+\cdots$N3,O	16.45	14.24	13.02	0.922	0.941	0.952	2.53	1.33	0.16	–56.60	–39.44	–28.20	–54.08	–38.11	–33.73
cyt3						**0.981**										
	$M^+\cdots$N3,N11	30.57	28.89	26.15	0.981	0.991	0.995	12.39	7.33	3.66	–53.07	–31.68	–18.62	–40.68	–24.35	–14.96
	$M^+\cdots$N3,O	11.94	9.70	8.60	0.907	0.925	0.933	2.60	1.38	0.95	–61.93	–44.84	–33.41	–59.33	–43.46	–32.46
cyt4						**0.534**										
	$M^+\cdots$N11	21.81	19.80	17.88	0.698	0.670	0.651	2.01	1.38	0.99	–52.17	–35.55	–24.76	–50.16	–34.17	–23.77
	$M^+\cdots$O	20.51	18.56	15.36	0.487	0.502	0.509	2.75	1.78	1.36	–54.16	–37.01	–27.64	–51.41	–35.24	–26.28
cyt5						**0.512**										
	$M^+\cdots$N11	21.74	20.15	18.64	0.691	0.663	0.643	2.02	1.38	1.03	–53.99	–36.98	–25.84	–51.97	–35.60	–24.82
	$M^+\cdots$O	24.27	22.28	19.03	0.449	0.466	0.475	2.68	1.72	1.32	–52.07	–34.98	–25.69	–49.39	–33.26	–24.37
cyt6						**0.800**										
	$M^+\cdots$N11	55.75	48.78	–	0.593	0.647	–	5.06	2.61	–	–26.33	–12.75	–	–21.27	–10.14	–
	$M^+\cdots$N1,O	4.73	4.29	4.36	0.929	0.916	0.905	3.78	2.27	1.68	–75.94	–56.78	–44.10	–72.16	–54.51	–42.42

abilities of cytosine tautomers leads to a classical linear regression as presented in Figure 3. In the case of $H_2N\cdots HF$ H-bonds, direct participation of the nitrogen atom in intermolecular interaction with a proton donating HF affects the shape of NH_2 in a more pronounced manner (φ > 21 deg, Figure 3) than in all other cases. Nevertheless, even in those cases (with the N atoms of the ring) H-bonding causes a substantial pyramidalization up to ~8 deg.

Interactions with Metal Cations (M^+)

Some important characteristics related to the $M^+\cdots$cytosine (M = Li, Na, K) tautomers interactions are collected in Table 4. There are two types of such interactions: (i) singular and (ii) bifurcated. In a singular coordination the cation interacts only with one atom containing a lone pair (O or N), whereas in the case of bifurcated coordination two neighboring atoms are involved in the interaction.

The most stable complexes of cytosine tautomers with metal ions are found for cyt1, where the cation interacts with the oxygen atom of the carbonyl group and the nitrogen atom of the ring ($M^+\cdots$N3,O), which agrees with previous studies.[51] The relative stabilities of the other complexes with respect to the above described type of complexes are given in Table 4. Interestingly, the next stable systems are $M^+\cdots$N1,O complexes of the least stable tautomer cyt6 ($E_{rel} \approx 4$ kcal mol^{-1}), for which the least stable complexes with another active center are also observed ($M^+\cdots$N11, $E_{rel} > 48$ kcal mol^{-1}). It should be noted that in all studied cases the complexes with bifurcated interactions $M^+\cdots$N,O are more stable than those with $M^+\cdots$N, N ones. The resulting order of the stability of these complexes is consistent with previous findings.[23,52]

In all cases π-electron delocalization of the cytosine moiety is subject to substantial changes. There are two important variables influencing these changes: (i) the site of interaction and (ii) the type of the cation. Two types of interaction sites can be distinguished: with oxygen or nitrogen atoms.

The case of $M^+\cdots$O interactions will be first considered. In all cases in the sequence of cations: Li^+, Na^+ and K^+ the changes of HOMA are always either in increasing or in decreasing order – no chaotic behavior is observed. The changes are in the sequence of ionic radii increase. And hence the electrostatic interactions are decisive. When the HOMA value for a particular free tautomer is compared with those for complexed ones two trends are observed: the complexes exhibit either a higher π-electron delocalization (*i.e.* greater HOMA values) than their free tautomers or a lower one. An increase of the aromaticity is noticed only for complexes of cyt1 and cyt6 tautomers. It can be explained by lengthening of the double CO bond that leads to an increase of aromaticity of the rings in comparison to free tautomers. Moreover, in these cases a decrease of HOMA values in the sequence of cations: Li^+, Na^+, K^+ is observed. This effect of the cation nature on the aromaticity changes is also associated with CO bond lengthening. It decreases with weakening of the electrostatic interaction which diminishes in line with increasing ionic radii. For other tautomers totally opposite effects are found (Table 5).

Table 5. Changes in the main characteristics of the metal complexes with respect to the free tautomers. Arrows assign an increase or decrease of a given parameter.

Interaction	d_{CN}	d_{CO}	HOMA	↑ HOMA (Li^+, Na^+, K^+)	Tautomer
$M^+\cdots$O	↓	↑	↓	→	all
			↑	←	cyt1, cyt6
$M^+\cdots$N	↑	↓	↑(except cyt6)	→	amino
				←	imino

Slightly different changes are observed for complexes with $M^+\cdots$N interactions. In all tautomers, except cyt6, the complexation with the cation increases aromaticity of the ring. For cyt2, cyt3 and cyt6 this augmentation of aromaticity correlates with the increase of ionic radii, whereas in the case of cyt4 and cyt5 an oposite tendency is observed (Table 5).

CONCLUSION

(1) Different π-electron structure is a pronounced feature of cytosine tautomers. In particular, their aromaticity strongly depends on the number of double-bonded groups (C=O or C=NH). Tautomers without these groups (cyt2 and cyt3) are the most aromatic, whereas the presence of at least one of them significantly decreases aromaticity. Thus, the aromatic character of the tautomers decreases with the number of groups attached to the ring *via* a double bond.

(2) The strongest intermolecular interactions are observed for charge-assisted H-bonds of the amino group and for bifurcated coordination of the cation, which is located between N and O atoms.

(3) Effect of all intermolecular interactions on structural changes in a given tautomer is manifested both in the region of interaction and in the long-distant parts of the molecule. The latter depends on the type of interactions: charge-assisted H-bonds elongate the CX bond (X = N or O), whereas the neutral ones and interactions with a cation make them shorter.

(4) Both types of interactions, H-bonding and metal complexation, lead to substantial changes in aromaticity, mainly due to modifications of the double bond character of C=O or C=NH groups.

(5) Complexation of the cytosine tautomers with cations leads to monotonic changes in aromaticity in line with the increase of their ionic radii.

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