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**Tautomerisation of thymine acts against the Hückel 4N+2 rule.
Effect of metal ion and H-bond complexations on the electronic structure of thymine.**

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Dedicated to our friend, Professor Jacek Lipkowski of Guelph University, on the occasion of his 70th birthday.

TOC – graphical abstract
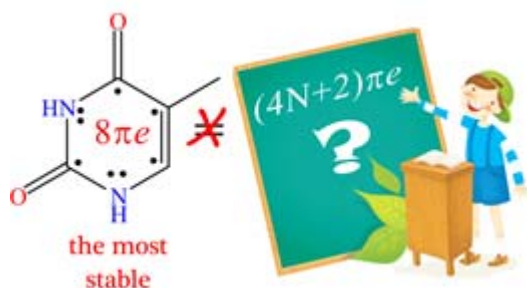
Abstract

Stability and aromaticity of thirteen known thymine tautomers were studied in the gas phase at the B3LYP/6-311++G(2d,2p) computational level. It was found that they do not follow the Hückel 4N+2 rule when the energetic criterion is considered, but they follow it when aromaticity indices, such as NICS, HOMA and the sum of the Wiberg bond indices, are applied. It was shown that the stability of a given tautomer is strongly dependent on the number of C=O groups attached to the ring. The most stable tautomer *i.e.* that with two carbonyl groups exhibits low π-electron delocalization (HOMA=0.490, NICS(0)= -1.5). Its stability results from specific interactions between $N^{\delta-}H^{\delta+}$ and $C^{\delta+}O^{\delta-}$ bond dipoles. A qualitative rule, which implies an increase in stability and loss of aromaticity with increasing number of C=O groups, holds in the case of thymine tautomers. Effects of intermolecular interactions (H-bonding and metal ion complexation) on the geometry and π-electron structure were analyzed for the five most stable tautomers with the following partners: HF/F^- and $Li^+/Na^+/K^+$. The magnitude of these effects strongly depends on the site and type of intermolecular interactions. Electronic structure of the

most aromatic tautomers is more weakly influenced by such external perturbations as H-bonding and almost entirely resistant to metal complexation.

Introduction

The aromatic sextet concept has been widely applied in organic chemistry as a convenient tool for explaining distinctly different chemical behavior of cyclic molecules containing six electrons.[1,2,3,4,5,6] Hückel Molecular Orbital[7,8] and Free Electron Molecular Orbital[9] theories clearly explain higher stability of the cyclic π-electron molecules containing six electrons rather than eight or four. The Hückel rule[10,11,12] states that cyclic π-electron systems are more stable when they consist of 4N+2 π-electrons than those with 4N π-electrons. A great advantage of its application in organic chemistry was presented in Streitwieser's monograph.[13] Currently it is considered as the leading rule in the studies of cyclic π-electron systems. As it has been recently shown this rule can be deduced on the basis of graph-topological considerations.[14] Typical application of this rule is presented for annulenes,[15,16] where the resonance energy of 4N+2 systems is always greater than that for 4N ones. A similar picture is found when the reactivity-based aromaticity index KK[17] is applied.[18] In reference (18) a classification of the cyclic π-electron systems was proposed, which showed that both 1,2- and 1,4-benzoquinone are much less aromatic than 4N annulenes: cyclobutadiene and cyclooctatetraene. Thus, double-bonded substituents attached to the ring dramatically decrease its aromatic character. Similar effects appear in some tautomers of thymine, deciding about their stability and aromaticity.

Thymine is a six-membered heterocyclic molecule which can exists in a form of 13 tautomers/rotamers. The 1H,3H-diketo tautomer, which contains two C=O groups and two N-H groups constituting inherent parts of the ring, is the most stable in the gas phase, solution and the solid state[19,20] which was confirmed by a series of theoretical[21,22,23] and experimental works.[24,25,26] Generally, this diketo tautomer exists as the main form in the double helix,[27] interacting with adenine *via* two H-bonds. A–T pairs with other tautomers of thymine are significantly less stable than the Watson-Crick pair comprising the canonical forms.[28] If thymine forms pairs with other bases, the regular DNA structure is disrupted and inadvertent mutations arise. The most frequent damage is the formation of thymine dimers induced by UV radiation.[29,30] They inhibit the enzymes carrying out DNA replications and

transcription, and are the main source of carcinogenic mutation known as melanoma.[31] Another factor which can cause a mismatch in the base pairing is the metalation of nucleobases.[32] Metal cations contribute to the stabilization of rare nucleobase tautomers[23,33] and increase the probability of gene mutations.[34,35,36] Such interactions of thymine with alkali metal ions are well described by theoretical[23,37,38,39] and experimental[40,41,42,43] methods. It was found that metal cations in all types of complexes studied preferentially bind to the oxygen at C4 atom of thymine as well as in uracil. However, an influence of metal binding on aromaticity of the thymine ring has not yet been investigated. It is also interesting to compare the effect of metal binding and another important interactions of the nucleobases – hydrogen bonds, on their π-electron structure. Along with the studies of conventional H-bonds formed between nucleobase pairs an interest in interactions of DNA with anions has recently aroused.[44,45,46] Based on extensive survey of the Nucleic Acid Database (NDB), Auffinger *et. al.*[44] concluded that anions (mostly Cl^- and SO_4^-) do intrude the first hydration shell of nucleic acids and bind to electropositive amino, imino, and hydroxyl groups. Two types of such complexes formed by H-bonding of the most stable thymine tautomer with anions have recently been studied. It was found that the complexes with N1H centers are stronger and more stable than those with N3H ones. Additionally, a correlation between the interaction energy and the proton affinity for these complexes was established.

The purpose of this work was to undertake a systematic study of the electron structure of the five most stable thymine tautomers and to evaluate the effect of two types of intermolecular interactions caused by different environments (HF/F$^-$ and metal cations) on geometric and π-electron structures of these tautomers in the gas phase. In particular, all these changes were elucidated by the use of the structural aromaticity index HOMA.[47,48] It should be stressed that the gas phase computational results indicate stronger interactions than those in which solvent effect is taken into account.[49,50] Therefore, in order to be able to observe a tendency in the changes of thymine electronic structure the influence of these stronger intermolecular interactions on structural properties of thymine tautomers was investigated.

Methodology

All geometry optimizations of the studied systems, without any symmetry constraints, were performed using the Gaussian 09 series program[51] at the B3LYP/6-311++G(2d,2p) computational level. To prove that the obtained structures are minima on the potential energy

surface frequencies were calculated at the same level of theory. Justification of the theoretical method choice is given in our previous work.[52]

Geometry-based index of aromaticity HOMA[47,48] was used as a measure of π-electron delocalization in the ring. It is defined as:

$$\mathrm{HOMA} = 1 - \frac{1}{n}\sum_{j=1}^{n}\alpha_i\left(R_{\mathrm{opt},i} - R_j\right)^2$$

(1)

where n is the number of bonds taken into the summation; α_i is a normalization constant (for CC and CN bonds $\alpha_{CC} = 257.7$ and $\alpha_{CN} = 93.52$) fixed to give HOMA = 0 for a model non-aromatic system and HOMA = 1 for the system in which all bonds are equal to the optimal value $R_{\mathrm{opt},i}$ assumed to be realized for fully aromatic systems (for CC and CN bonds $R_{\mathrm{opt,CC}} = 1.388$ Å and $R_{\mathrm{opt,CN}} = 1.334$ Å, respectively) and R_j denotes bond lengths taken into calculation.

For free tautomers the following Nucleus Independent Chemical Shifts (NICS) were calculated: (i) in the center of the ring,[53] NICS(0); (ii) 1 Å above the center,[54] NICS(1); and (iii) the component of the tensor perpendicular to the molecular plane,[55,56] NICS(1)zz. Calculations of the NICS's were performed with Gaussian 09 program at HF/6-31+G(d) level of theory (following recommendation given in Ref. 53) using the GIAO method.

As an additional tool for the electronic structure description, Natural Bond Orbitals (NBO) analysis[57] was applied to study atomic charges distribution and carry out a population analysis. Additionally, the sum of the Wiberg bond indices[58] of all bonds in the ring was taken as a numerical characteristic of aromaticity, WBI_Σ.

Three types of complexes of thymine tautomers were studied: (i) neutral (with HF), (ii) anionic (with F$^-$) and (iii) cationic (with M$^+$, M=Li, Na, K). In order to estimate the energy of the intermolecular interaction, the difference between the energy of the complex A$\cdots$B and the sum of the energies of its components (A and B) was used. The basis set superposition error (BSSE)[59] was taken into account. In the next stage of the used approach, the total energy of interaction was decomposed into deformation (E_{def}) and interaction (E_{int}) components:

$$E_{\mathrm{tot}} = E_{\mathrm{def}} + E_{\mathrm{int}}$$

(2)

The first term of the above equation represents the amount of energy required to deform the

equilibrium geometries of both fragments (E_A^0 and E_B^0) into their geometries in the complex (E_A and E_B).

$$E_{def} = (E_A-E_A^0) + (E_B-E_B^0) \tag{3}$$

The second term of eq. 2 corresponds to the actual energy change when the two distorted fragments are combined in the final structure. The interaction energy was estimated using a calculation procedure described elsewhere.[60]

It should be stressed that the above methodology has already been used for a series of nucleobases.[52,61,62]

Results and discussion

For clarity, the results are discussed in three sections dealing with (i) stability and aromaticity of free tautomers, (ii) their intermolecular interactions *via* H-bonding, and (iii) their complexation with metal ions.

Stability and aromaticity of free thymine tautomers

To find the most stable tautomers of thymine the energies of all 13 tautomers were calculated. The resulting order of their stability is consistent with previous findings based on DFT calculations. It slightly differs from that obtained by MP2 one[20,21] (Table S1). However, the set of five most stable tautomers, whose relative energies are within 15 kcal/mol, is the same for all mentioned above calculations. In the subsequent part of the paper only these five tautomers will be subject to deeper analysis. Their chemical structures are shown in Fig. 1, whereas their main characteristics (stability and aromaticity data) are presented in Table 1. Additionally, numbers of π-electrons in the ring, N, obtained from the formal approach and from NBO calculations are given in Table 1 (for details see Table S2). Some differences arise when comparing the formal number of π-electrons in the ring and the number obtained by NBO calculations. This can be explained by the fact that the formal approach counts electrons at atoms, which are not interacting with each other, in contrast to the NBO method, which counts the occupations at interacting atoms in real molecule by taking into account their electronegativity and resonance/inductive/field interactions between particular parts of the molecule.
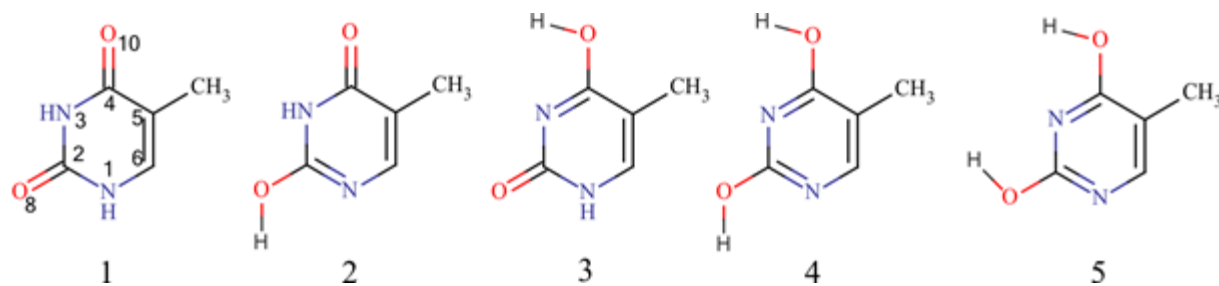
Fig. 1 Structures of the most stable thymine tautomers.

Table 1 The main characteristics of thymine tautomers (N – number of $2p_z$ electrons in the ring, formal and from NBO; relative energy, E_{rel}; HOMA, NICS's and WBI_Σ as aromaticity indices).

Tautomer	N_{formal}	N_{NBO}	E_{rel} /kcal/mol	HOMA	NICS(0)	NICS(1)	NICS(1)zz	WBI_Σ
thy1	8	6.98	0.00	0.490	-1.5	-2.2	-2.1	7.07
thy2	7	6.63	10.83	0.629	-2.8	-4.3	-8.2	7.64
thy3	7	6.69	12.38	0.718	-2.7	-4.2	-7.5	7.62
thy4	6	6.24	13.02	0.984	-7.2	-8.8	-20.9	8.28
thy5	6	6.29	14.17	0.987	-7.3	-8.9	-21.1	8.19

When relative energies, E_{rel}, are considered (see Table 1), it appears that the most stable tautomer (thy1) contains formally 8 π-electrons, next two less stable ones – 7 π-electrons, and the least stable tautomers – 6 π-electrons. This is opposite to the Hückel rule. Important to note that the Hückel rule was formulated for cyclic unsaturated hydrocarbons. In our case such functional groups as NH, CO and COH interfere and induce additional interactions, which may significantly affect the stability of thymine tautomers. However, when the aromaticity indices are concerned, particularly NICS(1)$_{zz}$ and HOMA, it can be noticed that π-electron delocalization follows well the Hückel rule. It is worth mentioning that HOMA and NICS(1)zz are well correlated (see Fig. S1, cc= -0.982). The same kind of correlation was found between the sum of Wiberg bond indices, WBI_Σ, and HOMA (cc = 0.976) as well as NICS(1)zz (cc= -0.976). The values of Wiberg bond indices for the most stable thymine tautomers are shown in Fig. S2. Values of HOMA and NICS(1) are very close to those reported previously.[63] Figure 2 shows the dependence of HOMA on E_{rel} of the tautomers. Three groups of thymine tautomers can be distinguished: (i) very aromatic (HOMA is close to 1.0); (ii) the least aromatic (HOMA < 0.4) and (iii) with intermediate aromaticity (in this case an increase of aromaticity is connected with a decrease of stability). From structural point of view, the most stable tautomer (thy1) may also be

included into the second group for its quinoid-like structure. A very similar dependence was found by Raczynska *et al.* for uracil tautomers.[64]
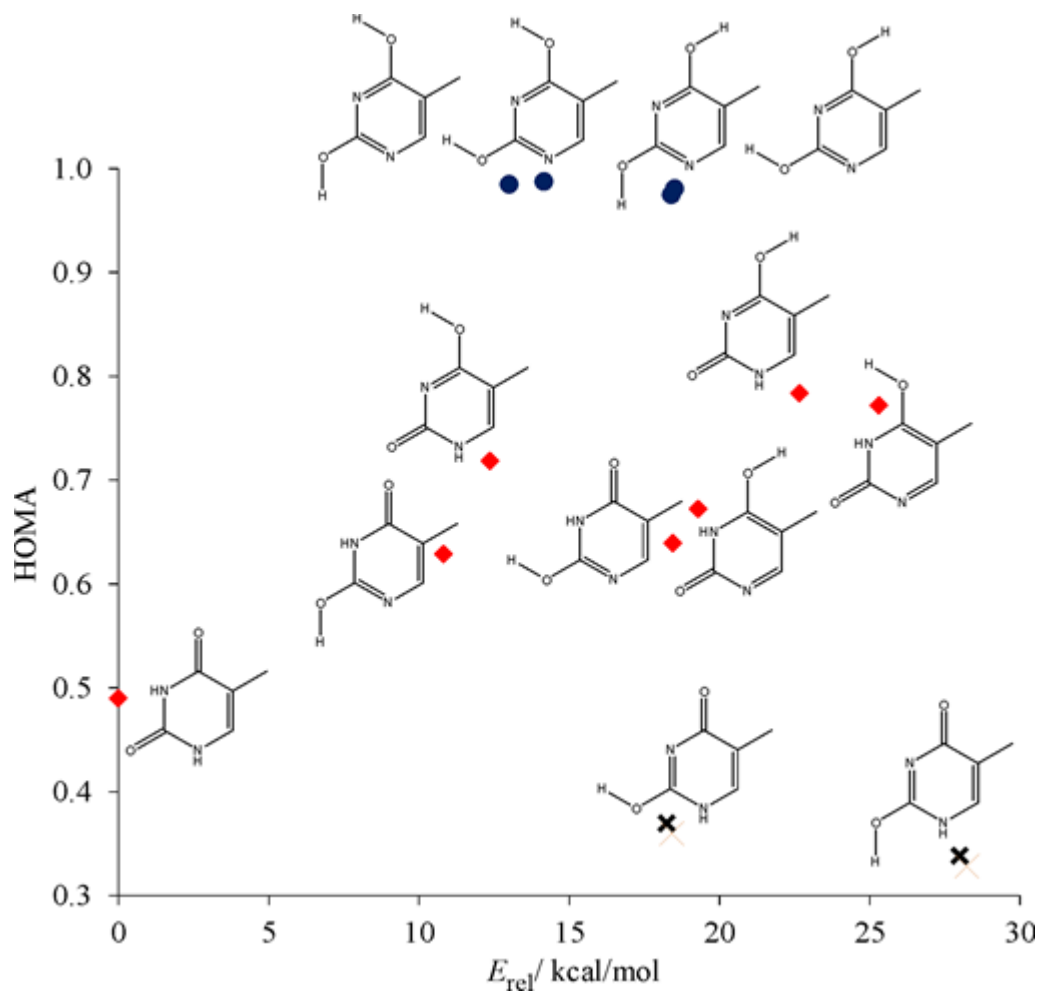

Fig. 2 Dependence of HOMA on relative energy, E_{rel}, for thymine tautomers. Group (i) blue circles, group (iii) crosses, and (ii) red diamonds.

Two potential explanations could be postulated:

(i)   some kind of resonance effect between the electron-rich NH and the electron attracting CO groups;

(ii) stabilization/destabilization effects due to bond dipole interactions between $N^{\delta-}H^{\delta+}$ and $C^{\delta+}O^{\delta-}$ as well as with the lone pair of the aza-type nitrogen atom.

The first reason implies a substantial change in the CO bond length. However, in thymine tautomers the CO bond lengths for carbonyl groups are between 1.213 Å and 1.219 Å, which is comparable to the values obtained for 1,4-benzoquinone (1.219 Å), acetone (1.211 Å) and urea (1.216 Å). Additionally, the obtained values of Wiberg bond indices for thymine tautomers (Fig. S2) confirm that in thy1 the resonance effect does not occur. Thus, this hypothesis seems should most likely be excluded. The next (ii) explanation assumes stabilizing interactions between charges at $H^{\delta+}$ and $O^{\delta-}$ of NH and CO groups as well as destabilizing interactions between the nitrogen lone pairs and CO bond dipole in COH groups.
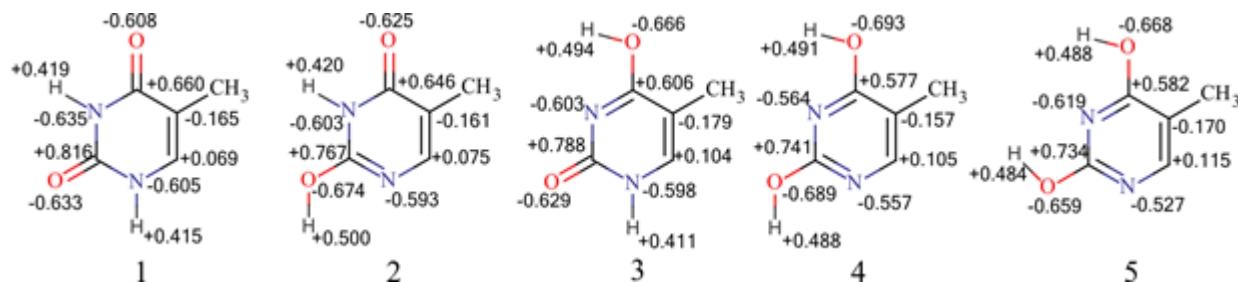

Fig. 3 NBO atomic charges for free tautomers of thymine.

Such assumption is confirmed by the NBO charge distribution in thymine tautomers (Fig. 3), which indicates that for thy1 stabilizing interactions between NH and CO groups are the strongest, for thy2 and thy3 they are weaker, for thy4 and thy5 they are essentially non-existent. A negative charge localized at aza-type nitrogen atoms is provided by the lone pairs located in the plane of the molecules. Therefore, interactions of these lone pairs with CO bond dipole of COH groups lead to the destabilization of such systems. To put these problems into a wider perspective a few demonstrative examples will be presented.

First, to estimate the magnitude of the repulsive energy between two identical bond dipoles CF in *ortho*- and *para*- positions, the energies of homodesmotic reactions for 1,2- and 1,4-difluorobenzene were calculated (see Fig 4). The difference between their energies amounts

to *ca.* 3 kcal/mol that indicates the destabilization of 1,2-difluorobenzene in comparison to the 1,4- isomer.
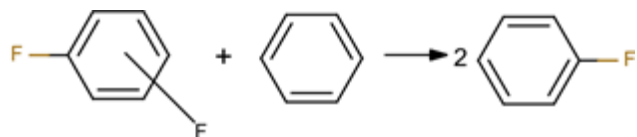
ortho- ΔE=-4.5 kcal/mol

para- ΔE=-1.4 kcal/mol

Fig. 4 Homodesmotic reaction for 1,2- and 1,4-difluorobenzenes.

2- and 3-hydroxypyrroles can be considered as additional instructive examples. The results of their optimization show that 2-hydroxypyrrole is more stable than 3-hydroxypyrrole by 2.1 kcal/mol. Total charge distribution in 2-hydroxypyrrole, presented in Fig. 5, clearly confirms the stabilizing interactions between the NH and CO(H) dipoles.
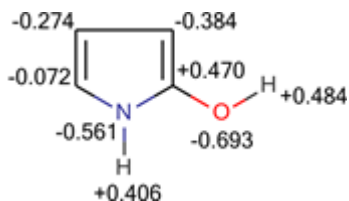

Fig. 5 NBO charge distribution for 2- hydroxypyrrole.

Finally, one more example, illustrating repulsive interactions between nitrogen lone pairs, comes from a comparison of energies of pyridazine and pyrimidine, where the intramolecular interactions are of 1,2- and 1,3- types, respectively. The difference in energy between them is 22.61 kcal/mol which indicates a substantial destabilization of the system in the case of 1,2-interactions as compared to 1,3- ones, see Table S3.

Taking into account these illustrative data, we can find good qualitative arguments for the earlier mentioned assumption (ii) that the reasons of anti-Hückel properties of thymine tautomers originate from specific intramolecular interactions between bond dipoles of NH, lone pairs of aza-nitrogen atoms and two forms of CO bonds. This interpretation differs from that applied to uracil. In that case it has been suggested that such interactions play a rather secondary role and stability of the functional groups is the main factor responsible for the observed tautomeric preference. Important to note that due to the presented above conclusive remarks the

H-bonding and metal complexation may play crucial role in the stability and π-electron delocalization of thymine complexes.

H-bonded complexes of thymine tautomers

Energetic and structural characteristics of H-bonded complexes of the discussed thymine tautomers are collected in Table S4, data for free tautomers are added for comparative reasons. Relationships between the strength of intermolecular interactions and the H-bond distance, shown in Fig. 6, resemble those obtained for cytosine complexes. Also in this case, three types of H-bonds can be distinguished: (i) charge-assisted, (ii) classical X···HF with sp^2 hybridized X, X= O or N, and (iii) also X···HF with sp^3 hybridized X, X= O of the hydroxyl group. It is found that their strength decreases approximately twice in a given sequence. Since the range of the H-bond lengths is not large and intermolecular interactions are less diversified than in the case of cytosine, the E_{HB} vs. d_{HB} dependences can be described by linear equations. The obtained slopes (Table S5) are almost three times greater for O···H interactions than for N···H ones (see Fig. 6) both for neutral and for charge-assisted H-bonds. This agrees with the expectation that for the O···H and N···H bonds of the same energy the latter should be longer.[65, 66]
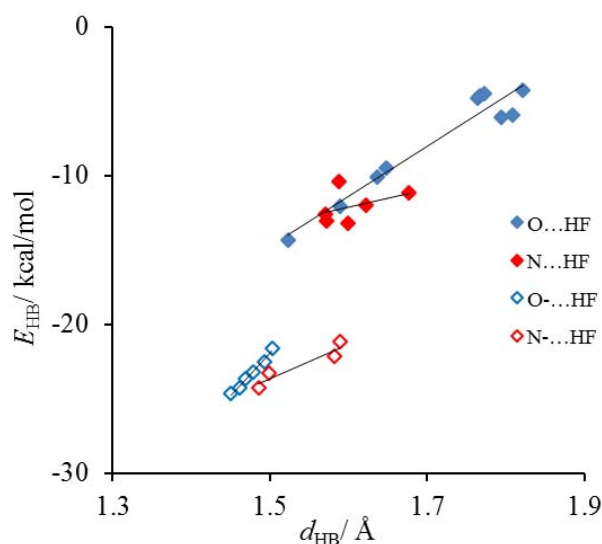

Fig. 6 Dependences of H-bond energy on H-bond length for H-bonded complexes of thymine tautomers.

Almost all types of H-bonding induce significant structural changes in the region of interactions and in more distant parts of the complex (so called long-distance consequences of

the H-bond formation). The magnitude of these changes depends on the site and type of intermolecular interactions (see Table 2).

Table 2 Changes in the main characteristics of H-bonded thymine complexes with respect to free tautomers. Arrows indicate an increase or decrease of a given parameter

Interaction	d_{C2O8}	d_{C4O10}	E_{HB} /kcal/mol	Form	HOMA
N···HF	↓	↓	-10 ÷ -13	-	↓ (except N3 in thy3)
N⁻···HF	↑	↑	-23 ÷ -25	-	↑ (except N3 in thy1)
O8···HF	↑	↓	-4 ÷ -6	enol	↓
O8⁻···HF	↓	↑	-22 ÷ -25	-	↓ (except thy2)
O10···HF	↓	↑	-4 ÷ -5	enol	↑
O10⁻···HF	↑	↓	-21 ÷ -25	-	↓

Due to the formation of the neutral H-bonds with O8 or O10 atoms the CO bond participating in this interaction is elongated, whereas the other CO bond is shortened. In the case of charge-assisted H-bonds involving the same oxygen atoms an opposite tendency is observed. Nevertheless, the long-distance effect of H-bonding is 3-5 times smaller than in the immediate region of the interaction. In addition, some long-distance consequences were also observed for interactions with the nitrogen atoms. The neutral H-bonds N···HF induce shortening of both CO bonds, whereas N⁻···HF interactions lead to their lengthening. The above-presented consequences of H-bonding result in a significant variability of the π-electron structure in the thymine rings. It is confirmed by changes in HOMA indices describing aromaticity of studied systems (Table 2).

Interactions with metal cations (M⁺)

Two types of interactions between thymine and metal cation can be distinguished: (i) singular and (ii) bifurcated. The singular coordination, where cation interacts only with one atom containing a lone pair (O or N), occurs in all tautomers. However, the case of the bifurcated coordination is found only in thy3, thy4 and thy5, where the lone pair of nitrogen is located close to the lone pair of oxygen. Main characteristics of thymine interactions with M⁺ (M = Li, Na, K) are collected in Table S6.

In agreement with previous studies,[23,38] the most stable complexes of thymine tautomers with metal ions are found for thy1, where the cation interacts with O10 atom of the carbonyl group (M⁺···O10). The decrease of thymine complexes stability up to E_{rel}=10 kcal/mol (Table S6)

occurs in the following sequence: $M^+ \cdots N3,O8$ of thy3, $M^+ \cdots O8$ of thy1 and $M^+ \cdots O10$ of thy2. However, their stability is not associated with the strength of interactions, which weaken in order: $M^+ \cdots N3,O8$ of thy3, $M^+ \cdots O10$ of thy2, $M^+ \cdots O10$ of thy1 and $M^+ \cdots O8$ of thy1. It should be noted that bifurcated interactions ($M^+ \cdots N3,O8$ in thy3 complexes) are only slightly stronger (by ca. $8 \div 12$ kcal/mol for the above-mentioned complexes) than the singular ones. Only one exception to the above-presented stability order is found. The $K^+ \cdots N3,O8$ of thy3 complex is less stable than $K^+ \cdots O8$ of thy1 one, in a contrast to the systems with Li^+ and Na^+ ions. It can be explained by a large ionic radius of K^+, which tends to form singular coordination with O8 in thy1 (Table S6).

Structural consequences of the complexation by metal cation are similar to those observed in H-bonded systems. However, since the first interactions are stronger they cause greater structural changes. The most representative and interesting consequences are observed in complexes in which the cation interacts with the oxygen atom of the carbonyl group. The CO bond length becomes longer and both adjacent CN (or CN and CC) bonds shorten. Opposite changes are observed for the second CO group as a consequence of the long distance interactions: the CO bond becomes slightly shorter and the adjacent CN (or CN and CC) bonds lengthen. A comparison of the structural parameters found for $Li^+ \cdots O8$ and $Li^+ \cdots O10$ of thy1 complexes (the strongest singular interaction) with the free tautomer is presented in Fig. S3.

The formation of thymine complexes with cations is associated with changes in aromaticity of the rings (Table S6). Depending on the form of the oxygen atom, which participates in the interaction, π-electron delocalization of the ring, expressed by index HOMA, may increase or decrease as compared to the free tautomer. If the interaction takes place between the metal ion and the O atom of any carbonyl group, HOMA index is higher for the complex than for the free tautomer. Rationalization of this observation is based on elongation of the double CO bond participating in the intermolecular interactions which leads to an increase of the ring aromaticity. The only exception is $M^+ \cdots O8$ type of thy1 complex (see Fig. S3).

Aromaticity of a complex is, in turn, almost unchanged when the O atom of the hydroxyl group interacts with the cation. In such cases the intermolecular interaction can not change the nature of the single CO bond to a large extent and thus does not significantly influence the ring system. A substantial decrease of aromaticity was observed only for complexes of thy2 (from 0.6 to 0.4 units of HOMA). The reason of this decrease is non-planarity of such complexes, where

M^+ and the H atom of the OH group lie above and below the ring plane. This leads to a disturbance of conjugation between the lone pair at O8, which is almost coplanar with the ring plane and π-electron system of the ring. In all other cases the lone pairs are almost perpendicular to the ring and can effectively interact with the ring π-electron system. Another important observation is that bifurcated coordination induces larger changes in HOMA index than the singular one.

Additionally, correlations between ionic radii and HOMA values were found. The cation effect on the aromaticity changes is associated with the strength of the electrostatic interaction, which can play an important role in all discussed cases. The ionic radius increases in the following sequence of cations: Li^+, Na^+ and K^+. Hence the electrostatic interaction between the ion and thymine diminishes. This leads to a slight increase of π-electron delocalization of the ring, following the above order, for complexes with O(hydroxyl)$\cdots M^+$ interactions. Furthermore, a general rule should be noted – a decrease of aromaticity in the above-given sequence of the ionic radius takes place in complexes where intermolecular interaction results in an increase of π-electron delocalization in comparison with the free tautomer. An opposite relation is observed when the complexation induces a decrease of the ring aromaticity relative to the non-interacting tautomer.

In complexes of highly aromatic thymine tautomers (HOMA > 0.98) intermolecular interactions with metal cations essentially do not change the π-electron delocalization of the ring, in contrast with H-bonding that may result in aromaticity reduction by *ca.* 0.2 HOMA units. In the case of less aromatic but more stable tautomers both cation complexation as well as H-bonding may significantly increase or decrease the ring aromaticity.

Both kinds of the studied intermolecular interactions can be also characterized by the extent of charge transfer from thymine tautomer to HF or metal cation. Good correlation is observed only between the total energy of H-bonds and the transferred charge (*cc*=0.95), in the case of interactions with metal cations such correlation is significantly worse (*cc*=0.64), see Fig. S4a. However, the correlations between HOMA and CT (see Fig. S4b) do not exist.

Conclusions

(1) From the energetic viewpoint the tautomeric preference of thymine contradicts the Hückel rule. As a result, the most stable tautomer is not the most aromatic, as estimated by HOMA,

NICS and the sum of the Wiberg bond indices (for the ring). Aromaticity strongly depends on the number of C=O groups in the tautomer. The most aromatic systems are tautomers with two hydroxyl groups *i.e.* containing no carbonyl group. As it is known, the Hückel rule was formulated for cyclic π-electron hydrocarbons, and an addition of any functional groups to the cycle may affect the effectiveness of this rule, as earlier observed in benzoquinones.

(2) The main factor responsible for the stability of tautomers is their stabilization due to the extra interactions between $N^{\delta-}H^{\delta+}$ and $C^{\delta+}O^{\delta-}$ dipoles. Higher number of such interactions in the tautomer leads to its higher stability.

(3) Structural changes in the region of interactions and in its distant parts were found in all three types of the complexes of thymine tautomers studied: (i) neutral (with HF), (ii) anionic (with F^-), and (iii) cationic (with M^+, M=Li, Na, K). The magnitude of these geometrical and π-electron changes strongly depends on the site and type of the intermolecular interactions.

(4) H-bonding and metal complexation affect aromaticity of the ring in thy1 to a greater extent, whereas the most aromatic tautomers are resistant to the interactions with cations. To the contrary H-bonding may decrease their aromaticity.

Electronic supplementary information available: Tables: Relative energies for thymine tautomers in comparison with previous studies (S1); Natural atomic $2p_z$ orbital occupancies for thymine tautomers (S2); Energies of isomeric diazines, diazoles and triazoles (S3); The main characteristics for H-bonded complexes of thymine tautomers (S4); Statistics of linear regressions between the H-bond energy and length for H-bonded complexes of thymine tautomers (S5); The main characteristics for metal complexes of thymine tautomers (S6); Cartesian coordinates of equilibrium geometries for free tautomers of the thymine (S7), their H-bonded complexes (S8), and complexes with metal ions (S9). Figures: Correlations between aromaticity indices: NICS's, HOMA and WBI_Σ (S1), Wiberg bond indices for the most stable thymine tautomers (S2), Structural parameters of thy1 and its complexes with Li^+ (S3), Relationships the total energy of interactions and aromaticity index HOMA against the amount of charge transfer for the studied complexes of thymine (S4).

Acknowledgments

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