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Effect of the H-Bonding on Aromaticity of Purine Tautomers§

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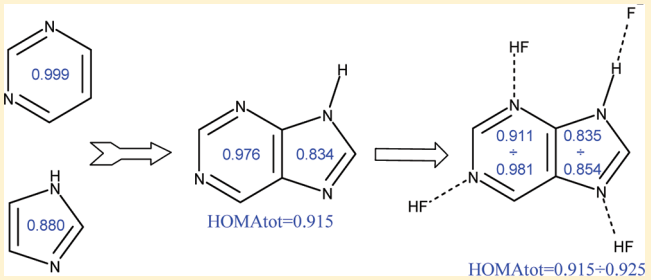
Supporting Information

ABSTRACT: Four tautomers of purine (1-H, 3-H, 7-H, and 9-H) and their equilibrium H-bonded complexes with F^- and HF for acidic and basic centers, respectively, were optimized by means of the B3LYP/6-311++G(d,p) level of theory. Purine tautomer stability increases in the following series: 1-H < 3-H < 7-H < 9-H, consistent with increasing aromaticity. Furthermore, the presence of a hydrogen bond with HF does not change this order. For neutral H-bonded complexes, the strongest and the weakest intermolecular interactions occur (−14.12 and −10.49 kcal/mol) for less stable purine tautomers when the proton acceptor is located in the five- and six-membered rings, respectively. For 9-H and 7-H tautomers the order is reversed. The H-bond energy for the imidazole complex with HF amounts to −14.03 kcal/mol; hence, in the latter case, the fusion of imidazole to pyrimidine decreases its basicity. The ionic H-bonds of $N^-\cdots HF$ type are stronger by ∼10 kcal/mol than the neutral N···HF intermolecular interactions. The hydrogen bond $N^-\cdots HF$ energies in pyrrole and imidazole are −32.28 and −30.03 kcal/mol, respectively, and are substantially stronger than those observed in purine complexes. The aromaticity of each individual ring and of the whole molecule for all tautomers in ionic complexes is very similar to that observed for the anion of purine. This is not the case for neutral complexes and purine as a reference. The N···HF bonds perturb much more the π-electron structure of five-membered rings than that of the six-membered ones. The H-bonding complexes for 7-H and 9-H tautomers are characterized by higher aromaticity and a much lower range of HOMA variability.



INTRODUCTION

Purine is a heterocyclic system built up of fused pyrimidine and imidazole rings. It exists in four tautomeric N-H forms. Purine is a mother frame for many biologically important compounds: adenine, guanine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, and many others.[1−3] Adenine and guanine are the most important organic molecules for life because they are the building blocks of DNA, RNA, and ATP systems.[4]

In the majority of cases, purines and their derivatives exist as 9-H or 7-H tautomers.[5] In the crystalline state, the 7-H tautomer is dominant,[6] but in the gas phase and in solutions, the problem of whether the H atom is located at the N7 or N9 position of the imidazole ring still remains to be solved. Modeling the geometry of 9-H and 7-H purine tautomers by means of ab initio MP2 and DFT computations[7] led to the conclusion that, due to a strong intermolecular interaction in the crystalline state, the molecular geometry of purines is not representative for molecules in the gas phase or in solutions. Therefore, various methods were applied to investigate the geometric structure of purine tautomers and their derivatives in solutions,[8] and in argon matrixes where the analysis of the influence of polar media on the shifts of the tautomeric equilibria[9] was performed. An excellent monograph related to these topics has recently been published by Collins and Caldwell.[2] Substituent and solvent effects on the ^{13}C and ^{15}N NMR chemical shifts have also been studied for 6-substituted purines[10] and purine derivatives.[11] Another possible use of purine derivatives as a material of high energy density has recently been pointed out.[12] It was found that the substituent effect on bond dissociation energies in nitro and amino purine derivatives is strongly dependent on the substituent position.

Aromaticity is one of the most interesting and useful concepts for the characterization of chemical compounds.[13,14] The commonly used criteria of aromaticity can be broadly divided into four groups: structural,[15] energetic,[16] magnetic,[17] and reactivity-related ones.[14] Only these first three criteria can be represented by numerical characteristics named as aromaticity indices. In the past decade, new electron structure indices were introduced.[18] They mainly serve to describe the properties of ring systems with π electrons, among which the most interesting are the heteroaromatic ring systems.[19] Furthermore, it was found that the π-electron delocalization plays an essential role in tautomeric systems and affects tautomeric preferences.[20] The aromaticity of nucleic acid bases was characterized by magnetic and structural properties as well as by indices based on electron delocalization.[11,21,22] However, the greatest interest is focused on purine derivatives, such as adenine and guanine.[20,23,24] Very recently, π-electron delocalization in all purine tautomers (four NH type and five CH type) was studied,[25] showing that the CH tautomers can be

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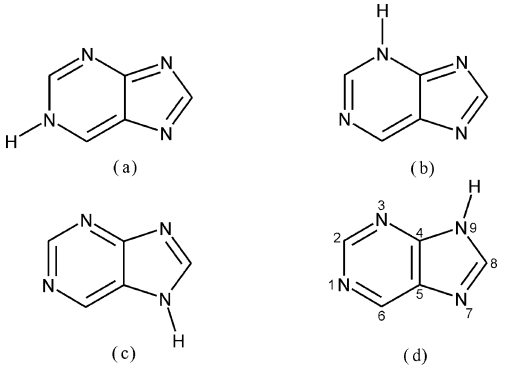
neglected in the tautomeric mixture of neutral purine. For this reason, only NH tautomers, presented in Scheme 1, will be the object of this study.

Scheme 1. Four Tautomeric Forms of Purine: (a) 1-H Purine, (b) 3-H Purine, (c) 7-H Purine, and (d) 9-H Purine with Labeling of Atoms



In the case of acid/base characteristics, the greatest interest is concentrated not on purines themselves but on their derivatives, such as adenine and guanine[26] or other nucleobases.[27] Undoubtedly, acid/base properties of adenine and guanine originating from their interactions in the Crick−Watson pairs are of great importance.[28] It should be stressed that, independent of the object of the investigations, determination of the acidic or basic character of a given center in a molecular system of interest is often very difficult to perform experimentally,[29] if even possible.[30] However, computational studies allow one to estimate these properties for appropriate parts of the molecule.[26,31]

As stated above, purine tautomers are much less frequently the subject of detailed investigations than their derivatives. Nevertheless, as a mother template of important nucleobases, they are good model systems to study such properties of these systems as π-electron delocalization or interactions with acidic or basic partners. They contain the centers of both acidic (NH group of the pyrrole type) and basic character (nitrogen atoms of the pyridine type), as shown in Scheme 1.

The aim of this paper is to study how the H-bond formation affects the π-electron structure of particular purine tautomers and to estimate the acidity/basicity of all of their individual centers. For this purpose, modeling of equilibrium H-bond formation of the types N···HF and NH···F$^-$ is used.[32] Estimation of quantitative characteristics of these kinds of H-bonding allows us to evaluate the acidity or basicity of particular centers for all tautomeric forms of purine. The obtained structural parameters give deep insight into the influence of H-bond formation on the π-electron structure of these moieties.

METHODOLOGY

The geometry optimization was performed on the basis of potential energy surface (PES), applying the hybrid functional of Becke[33] with Lee, Yang, and Parr gradient correction[34] in conjunction with the 6-311++G(d,p) basis set,[35] B3LYP/6-311++G(d,p). This level of theory was chosen on the basis of our previous studies.[36]

Two types of equilibrium H-bonded complexes were analyzed: (i) without constrains (fully relaxed complex) and (ii) assuming a linearity of the X−H···Y hydrogen bond. In the latter case, the modeled structures were also calculated as a result of the energy minimization for the fixed distances between heavy atoms involved in the intermolecular H-bonding ($d_{X\cdots Y}$ equals the equilibrium value increased by 0.5, 1.0, and 1.5 Å) and the geometry optimization of the remaining internal degrees of freedom.

To confirm that the obtained systems correspond to the minima on the potential energy surface, the frequency analysis was performed. In the case of simulated complexes ($d_{X\cdots Y} = d_{X\cdots Y,eq} + i0.5$ Å, i = 1, 2, 3), only one imaginary frequency was found, indicating the proper route of the proton path realized by H-bonding of the system under consideration.

The energy of the hydrogen bond, E_{HB}, (also known as the binding energy or the total energy of interaction) was calculated as the difference between the energy of the complex and the sum of the energies of its components (assuming geometries obtained during the optimization procedure of the complex and the monomers, respectively), taking into account the basis set superposition error (BSSE).[37]

Additionally, the total energy was decomposed into the deformation and the interaction components.[32b] The deformation energy component is always positive because it determines the energy required to reshape monomers A and B from their equilibrium structure to their geometry in the A···B complex

$$E_{def} = E_A(basis_A; opt_{A\cdots B}) - E_A(basis_A; opt_A) + E_B(basis_B; opt_{A\cdots B}) - E_B(basis_B; opt_B) \quad (1)$$

where $E_A(basis_A; opt_{A\cdots B})$ 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, $opt_{A\cdots B}$, and for the optimized monomer A, opt_A, respectively, using the basis of A monomer, $basis_A$, in both cases. An analogous definition stands for E_B.

The interaction energy component, corrected by the BSSE,[37] was calculated as follows

$$E_{int} = E_{A\cdots B}(basis_{A\cdots B}; opt_{A\cdots B}) - E_A(basis_{A\cdots B}; opt_{A\cdots B}) - E_B(basis_{A\cdots B}; opt_{A\cdots B}) \quad (2)$$

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

Calculations were carried out using the Gaussian 09 series of programs.[38]

Geometry parameters of the purine rings (CC and CN bond lengths) were used to estimate the π-electron delocalization by applying the aromaticity index HOMA (harmonic oscillator model of aromaticity),[39] which reads

$$HOMA = 1 - \frac{1}{n}\sum_{j=1}^{n} \alpha_i (R_{opt,i} - R_{i,j})^2 \quad (3)$$

where n is the number of bonds taken into account when carrying out the summation and i denotes the type of bond (CC or CN), α_i is a normalization constant (for CC and CN bonds, α_{CC} = 257.7 and α_{CN} = 93.52) fixed to give HOMA = 0 for a model nonaromatic system and HOMA = 1 for the system with all bonds equal to the optimal value $R_{opt,i}$ assumed to be realized for full aromatic systems (for CC and CN bonds,

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Table 1. Relative Energies, ΔE_{rel}, and Aromaticity Indices (HOMA and NICS) for Four Tautomers of Purine, Pyrimidine, Imidazole, Purine Anion, and Their H-Bonded Complexes

complexes	ΔE_{rel}/kcal/mol	HOMA5[a]	HOMA6[b]	$HOMA_{per}$[c]	$HOMA_{tot}$[d]	NICS5[a]	NICS6[b]
1-H purine	13.09	0.667	0.665	0.916	0.778	−9.908	−7.480
$N1^-$···HF		0.801	0.855	0.967	0.892	−11.241	−8.542
N3···HF		0.661	0.672	0.916	0.779	−9.758	−7.639
N7···HF		0.749	0.731	0.927	0.824	−10.394	−7.701
N9···HF		0.712	0.718	0.920	0.807	−10.242	−7.722
3-H purine	9.88	0.772	0.819	0.924	0.854	−10.516	−7.993
N1···HF		0.751	0.805	0.922	0.844	−10.387	−8.073
$N3^-$···HF		0.819	0.877	0.971	0.905	−11.392	−8.687
N7···HF		0.850	0.856	0.950	0.897	−11.076	−8.229
N9···HF		0.827	0.882	0.933	0.891	−10.966	−8.296
7-H purine	3.97	0.832	0.966	0.925	0.914	−11.670	−9.407
N1···HF		0.835	0.957	0.930	0.914	−11.534	−9.489
N3···HF		0.849	0.969	0.935	0.924	−11.816	−9.552
$N7^-$···HF		0.850	0.912	0.968	0.922	−11.864	−8.723
N9···HF		0.850	0.973	0.930	0.923	−11.926	−9.519
9-H purine	0.00	0.834	0.976	0.920	0.915	−11.662	−8.857
N1···HF		0.835	0.971	0.923	0.915	−11.560	−8.952
N3···HF		0.851	0.979	0.929	0.925	−11.827	−8.924
N7···HF		0.854	0.981	0.926	0.925	−12.051	−9.057
$N9^-$···HF		0.841	0.911	0.964	0.918	−11.679	−8.624
anion		0.817	0.880	0.967	0.904	−11.457	−8.491
pyrimidine			0.999				−6.508
N···HF			0.999				−6.687
imidazole		0.880				−13.959	
N···HF		0.885				−14.324	
N^-···HF		0.940				−13.335	

[a]Calculated for five-membered ring. [b]Calculated for six-membered ring. [c]Calculated for perimeter. [d]Calculated for the whole molecule.

$R_{opt,CC}$ = 1.388 Å and $R_{opt,CN}$ is equal to 1.334 Å), and $R_{i,j}$ denotes bond lengths taken into calculation.

Nucleus-independent chemical shifts (NICSs) estimated in the center of the ring,[40] NICS, and 1 Å above the center of the ring,[41] NICS(1), as well as the component of the tensor being perpendicular to the molecular plane,[42] NICS(1)zz, were calculated at the HF/6-31+G(d) level of theory using the GIAO method.

A detailed analysis of electron density distribution in H-bonds was performed within the framework of Bader's Quantum Theory of Atoms in Molecules (QTAIM).[43] Such parameters as the electron density in bond critical points (BCPs), ρ_{BCP}, its laplacian, $\nabla^2\rho_{BCP}$, density of the total electron energy in BCP, H_{BCP}, and its two components, potential and kinetic electron energy densities, V_{BCP} and G_{BCP}, were taken into account. In the case of rings, QTAIM parameters at ring critical points (RCPs) were applied as the aromaticity characteristics.[44]

RESULTS AND DISCUSSION

Tautomers of purine exhibit both acidic and basic character, and both of their rings are aromatic, as presented in Scheme 1. In describing chemical properties of purines and their derivatives, the role of H-bonding formation and its effect on the π-electron delocalization in each particular ring and in the molecule as a whole seem of crucial importance. For these reasons, the main goal of this paper is to elucidate these effects.

The results are presented in two separate parts: (i) for free purines and (ii) for complexes formed by intermolecular interaction of NH parts with fluoride and of N interacting with hydrofluoric acid. The analysis of the relation between the characteristics for free molecules with those for H-bonded complexes is then presented. For convenience, Scheme 1d presents the labeling of atoms.

Aromaticity of Free Tautomers of Purine. Table 1 presents the energetic data and aromaticity indices of all four purines. As we can see, differences in energy (ΔE_{rel}) between tautomers are not large: the range of variability is 13.09 kcal/mol. It is interesting to note that tautomers with the NH group located in the six-membered ring are less stable (mean value ∼ 11.5 kcal/mol) than those in which NH is found in the five-membered ring (mean value ∼ 2.0 kcal/mol).

The six-membered rings with no NH group (7-H and 9-H) exhibit higher aromaticity (mean HOMA6 is equal to 0.971), whereas for 1-H and 3-H tautomers, the aromaticity is lower (mean HOMA6 = 0.742). To the contrary, in the five-membered rings, the presence of NH favors aromaticity since the HOMA index calculated for 7-H and 9-H tautomers (mean HOMA5 = 0.833) is higher than the corresponding HOMA value obtained for 1-H and 3-H (mean HOMA5 = 0.720). Similar trends are observed for NICS values. These findings are easy to explain: six-membered rings without the NH group and five-membered rings with the NH group contain six π electrons each. Moreover, the six-membered rings without the NH group resemble the aromatic pyrimidine ring whose protonation leads to a quinoid-like π-electron structure that reduces their aromatic character; see Scheme 1a,b. As it can be concluded from the data presented in Table 1, fusion of the imidazole and pyrimidine rings into one molecule reduces their aromaticity. Moreover, the decrease in the HOMA5 index, calculated for the least-stable tautomer (1-H), is stronger than in the case of the electron-accepting group for N-substituted imidazole derivatives.[45]

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An approximately linear correlation can be found between the HOMA values of five- and six-membered rings as well as the whole molecule and the relative stability energy (see Figure 1).

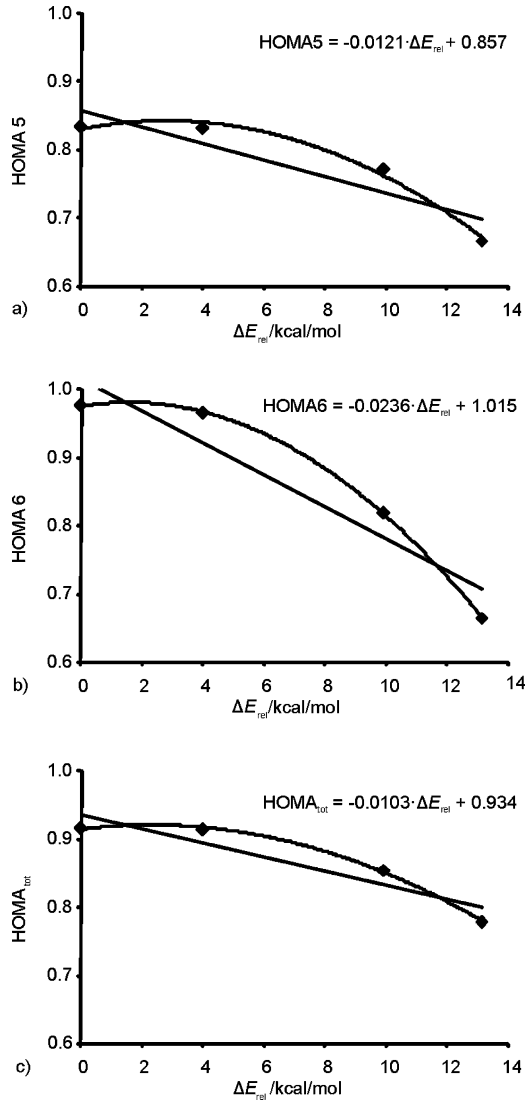

Figure 1. HOMA values for (a) five-membered, HOMA5, and (b) six-membered, HOMA6, rings and (c) for the whole cyclic system, $HOMA_{tot}$, plotted against relative energy of tautomers, ΔE_{rel}. Correlation coefficients $cc = -0.907$, -0.947, and -0.929, respectively; for quadratic relationships $R^2 > 0.988$.

Therefore, the observed stability augmentation is associated with an increase of the ring aromaticity. Moreover, the slopes of the curves obtained for five- and six-membered rings are significantly different; the sensitivity of the HOMA changes in five-membered rings is around half of that observed for six-membered rings: the slopes are −0.0121 and −0.0236, respectively. Note also that quadratic approximation for these regressions leads to an excellent value of the determination coefficients ($R^2 > 0.988$). This indicates a much stronger decrease of aromaticity with a decrease of the relative stability of the molecule than predicted by the linear regression. In other words, the less stable the system is, the more pronounced is the loss of aromaticity.

Opposite to the relative energies, a very limited range of variability (0.019 units of HOMA) is observed for HOMA values calculated for only the perimeter bonds ($HOMA_{per}$). The obtained values for all tautomers are between the HOMA indices of pyrimidine and imidazole (Table 1). However, if all bonds are taken into consideration, the range of the HOMA index is much larger, 0.137 units (for $HOMA_{tot}$). In this case, the substantial variability is caused by the central CC bond length, which is strongly dependent on the location of the NH group. The obtained $HOMA_{tot}$ values for the most stable tautomers (7-H and 9-H, in which the NH group is in the five-membered ring) are between those calculated for pyrimidine and imidazole, whereas the $HOMA_{tot}$ values of the remaining tautomers (1-H and 3-H) indicate that they are less aromatic than imidazole (see Scheme S1, Supporting Information).

H-Bonded Complexes of Purine Tautomers. To study the acidic and basic character of NH and N centers in all tautomers, a procedure described in detail elsewhere was applied.[32a] As a result of approaching fluoride and hydrofluoric acid to the acidic and basic centers, respectively, the H-bonded complexes are formed for which the H-bond characteristics are analyzed in this section. Figures 2−5 and Table S1 (Supporting Information) and Table 2 present the optimized geometries of the equilibrium complexes as well as HOMA and energetic characteristics, and QTAIM parameters of H-bonds.

The observed intermolecular interactions are almost linear, except for the N9···HF hydrogen bond for 3-H purine and the N3···HF one for 9-H purine. The E_{HB} differences between full equilibrium complexes and with linearity of H-bonding assumed (Table S3, Supporting Information) are 2.06 and 1.26 kcal/mol, respectively. These differences result from the interaction between hydrofluoric acid and the NH group of the neighboring ring in the complex.

Important information can be extracted from the data collected in Table S1 (Supporting Information). First, in the case of NH···F^- interactions, a proton is transferred to fluoride and hydrofluoric acid is formed. Thus, in the resulting complex, a negatively charged purine moiety interacts with hydrofluoric acid via the nitrogen atom. Therefore, in all intermolecular H-bonds presented in Table S1 (Supporting Information), the nitrogen atom of the purine ring (or of its anion ring) acts as a proton acceptor and hydrofluoric acid acts as a proton donor. In this case, two types of H-bonds should be distinguished: (i) conventional (classical),[32b] N···HF, and (ii) charge-assisted,[46] N^-···HF. In the latter case, all three energetic characteristics, E_{int}, E_{def}, and E_{HB}, have extreme values, indicating the strongest H-bond, which is in line with expectations. In addition, the calculations yield the greatest energy associated with the deformation of the free molecule to its geometrical shape in the H-bonded complex.

For N···HF interactions, the values of E_{int}, E_{def}, and E_{HB} are much smaller (in modulo); that is, H-bonds are weaker, and the deformation energy is smaller. While looking at the energies of all N···HF equilibrium complexes, presented in Table S1 (Supporting Information), one finds out immediately that complexes, in which N···HF interactions involve the six-membered rings, are less stable (with the mean value of total H-bond energy, E_{HB}, equal to −11.57 kcal/mol) than those with five-membered rings participating in H-bonding (mean energy equal to −13.26 kcal/mol). A similar picture is found for NH···F^- → N^-···HF interactions. The complexes with interactions in five- and six-membered rings have mean H-bond energies of −24.40 and −22.23 kcal/mol, respectively (Table S1, Supporting Information). For all N···HF interactions in a particular purine tautomer, the greatest basicity (and, thus, the

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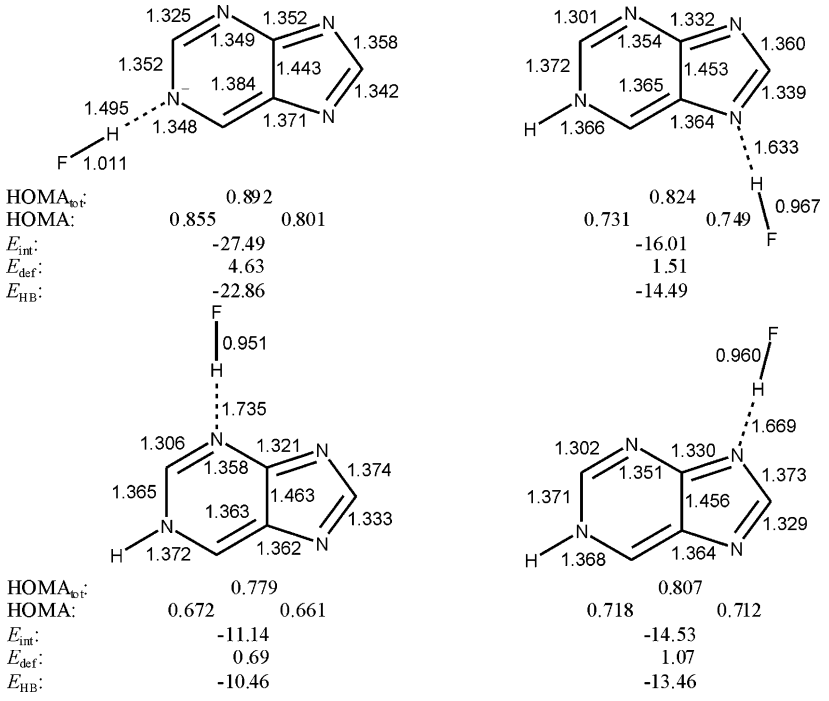

Figure 2. H-bonded complexes of 1-H purine. HOMA values for the free molecule are $HOMA_{tot}$ = 0.778, HOMA6 = 0.665, and HOMA5 = 0.667; energies in kcal/mol.

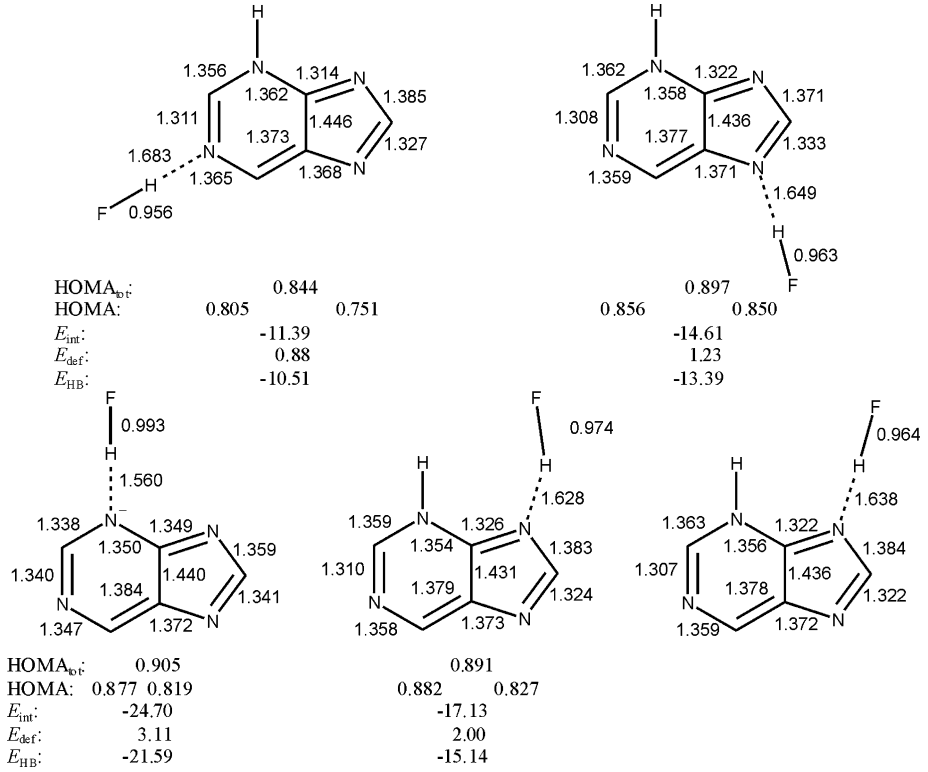

Figure 3. H-bonded complexes of 3-H purine. HOMA values for the free molecule are $HOMA_{tot}$ = 0.854, HOMA6 = 0.819, and HOMA5 = 0.772; energies in kcal/mol.

strongest H-bonding) is observed if basic and acidic centers belong to different rings. However, a deeper look at the stability of the purine monomers suggests dividing N···HF complexes into two groups: (i) with the NH group in a six-membered ring and (ii) with the NH groups in a five-membered ring.

The weakest hydrogen bonds are observed for 1-H purine complexes with HF, whereas the strongest one for 3-H purine complexes. The range of E_{HB} variability amounts to ~4.3 kcal/mol. For both tautomers, intermolecular interactions are stronger when the proton acceptor is a part

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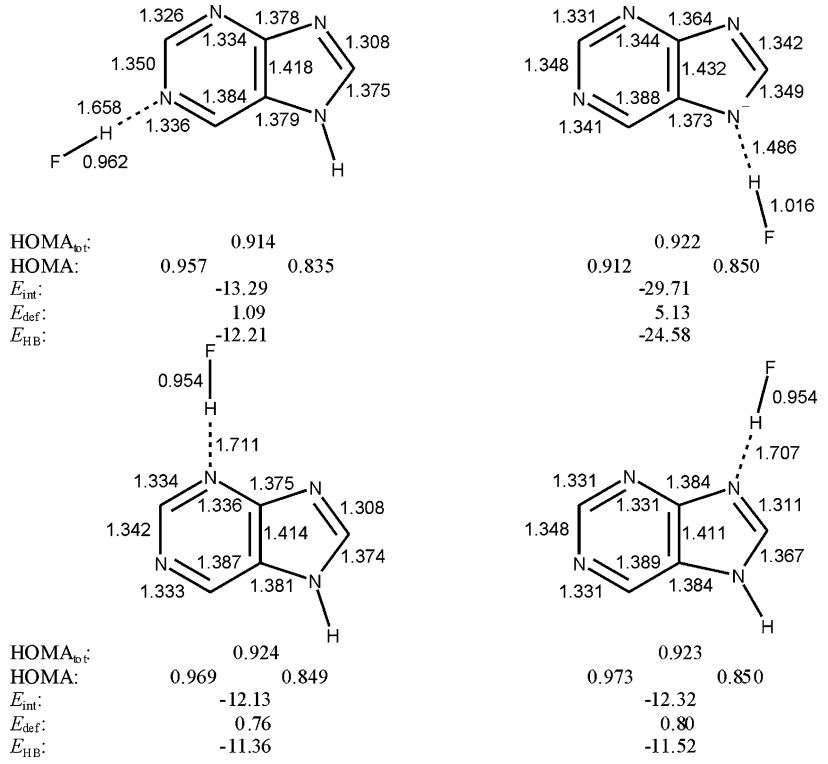

Figure 4. H-bonded complexes of 7-H purine. HOMA values for the free molecule are $HOMA_{tot}$ = 0.914, HOMA6 = 0.966, and HOMA5 = 0.832; energies in kcal/mol.

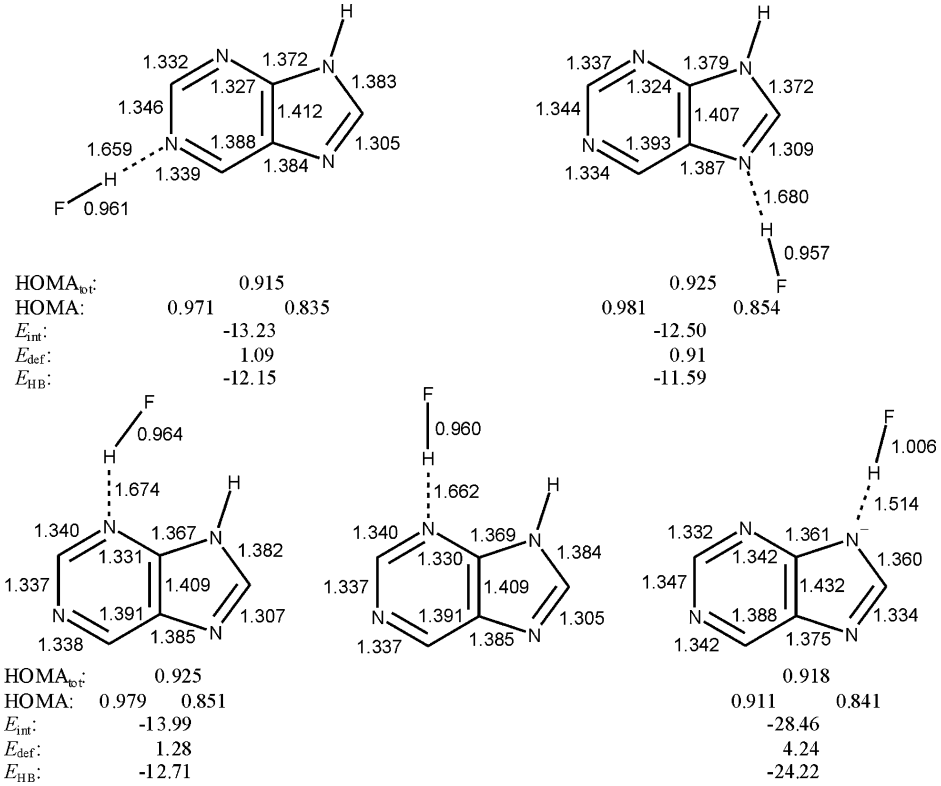

Figure 5. H-bonded complexes of 9-H purine. HOMA values for the free molecule are $HOMA_{tot}$ = 0.915, HOMA6 = 0.976, and HOMA5 = 0.834; energies in kcal/mol.

of the five-membered ring. Calculations give weaker interactions when the nitrogen atom belongs to the six-membered ring.

In the case of 7-H and 9-H purine complexes with HF, the range of E_{HB} variability is smaller (~1.0 kcal/mol) and stronger H-bonding is observed for complexes with the proton acceptor

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Table 2. QTAIM Characteristics of H-Bonding for Tautomers of Purine Complexes

complexes	$\rho_{BCP}\cdot10^2$/au	$\nabla^2\rho_{BCP}\cdot10$/au	$H_{BCP}\cdot10^2$/au
9-H purine			
N1···HF	5.70	1.16	−1.30
N3···HF	5.47	1.13	−1.20
N7···HF	5.26	1.18	−1.01
$N9^-$···HF	8.21	0.89	−3.16
7-H purine			
N1···HF	5.71	1.16	−1.30
N3···HF	4.91	1.14	−0.82
$N7^-$···HF	8.88	0.78	−3.73
N9···HF	4.88	1.16	−1.06
3-H purine			
N1···HF	5.32	1.16	−1.06
$N3^-$···HF	7.39	0.98	−2.52
N7···HF	5.70	1.18	−1.29
N9···HF	6.05	1.13	−1.59
1-H purine			
$N1^-$···HF	8.84	0.79	−3.68
N3···HF	4.62	1.13	−0.66
N7···HF	5.95	1.16	−1.47
N9···HF	5.39	1.17	−1.10

atom being a part of the six-membered ring, contrary to the previously discussed cases of 1-H and 3-H.

Obviously, and in agreement with well-known observations,[32b,47] the H-bond energy is correlated with its length. Because the range of variability of the H-bond length is rather narrow (∼0.3 Å), the linear regression was applied (cc = 0.974), as shown in Figure 6. However, if the scatter plots of particular

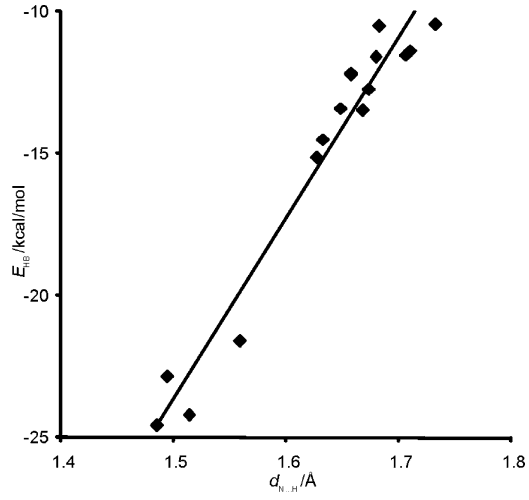

Figure 6. Dependences of H-bonding energy, E_{HB}, on N···H distance, $d_{N\cdots H}$; cc = 0.974.

tautomers are considered, the correlation coefficients are much better, and the observed slopes are different (see Table S2 and Figure S1 in the Supporting Information). This indicates a substantial role of the local structural environment in the relation between H-bonding energy and N···H distance.

The energy and geometry characteristics are in line with the QTAIM parameters collected in Table 2 for purine tautomers interacting via N···HF and N^-···HF.

As expected, the presence of atomic interaction paths with respective critical points, the first criterion,[48] was confirmed for all studied systems. The Popelier's criteria[48] were applied to the critical point describing H-bonding formation (N···H): the electron density at BCP at the hydrogen bridge was in the range of 0.002 ÷ 0.034 au (the second Popelier's criterion) while its laplacian was between 0.024 ÷ 0.139 au (the third Popelier's criterion). These criteria were fulfilled by all H-bonds for the studied complexes. Additionally, the nature and the strength of the interaction can be characterized by the total electron energy density, H_{BCP}.[47,49,50] Its negative value suggests a partly covalent character of the analyzed H-bond.[49f,51] Therefore, the nature of all studied H-bonds (Table 2) should be considered as partially covalent.

The geometric characteristic of H-bonds in tautomeric forms of purines, $d_{N\cdots H}$ (Table S1, Supporting Information), correlates well with QTAIM characteristics in BCPs, such as charge density, ρ_{BCP}; its laplacian, $\nabla^2\rho_{BCP}$; and density of the total electron energy, H_{BCP}, as illustrated in Figure 7. Noteworthy, all systems (neutral and charged) are included in these correlations. Note that the dependences for ρ_{BCP} and H_{BCP} should be exponential,[52] but for the short-range of the variability, a linear approximation can be applied. As expected, $\nabla^2\rho_{BCP}$ versus $d_{N\cdots H}$ is parabolic.

Similar scatter plots of QTAIM parameters in BCP versus H-bond energies are also observed, but with slightly worse correlation coefficients (see Figure S2 in the Supporting Information). The latter results from the fact that QTAIM parameters do not reflect directly the pure electrostatic contribution to the interaction energy.[53]

As mentioned above, the purine moiety may be considered as imidazole fused to pyrimidine. The question is posed: how much does this fusion affect the H-bonds and their properties? A comparison of H-bonding characteristics in purines with those in pyrimidine and imidazole is presented in Tables S1 and S5 (Supporting Information).

When we compare H-bonding energies for N···HF interactions, then for pyridine-type nitrogen atoms in purines (Table S1, Supporting Information), the mean value for 1-H and 3-H purines is −10.49 kcal/mol, whereas for the most stable tautomers (7-H and 9-H) it amounts to −12.11 kcal/mol. In the case of the pyrimidine···HF complex, the obtained H-bond energy is in between the above-mentioned values (−11.60 kcal/mol; Table S5, Supporting Information). Thus, it may be concluded that the fusion of pyrimidine decreases or (and) increases, respectively, the basicity of the nitrogen atom. Interactions of the same kind in the fused imidazole are slightly different from those observed for the free imidazole. In this case, the mean value of H-bond energies for 1-H and 3-H purines is −14.12 kcal/mol; for 7-H and 9-H tautomers it amounts to −11.56 kcal/mol, whereas for the free imidazole interaction, the energy is −14.03 kcal/mol. Therefore, the fusion of imidazole leads to a decrease of H-bond energy in these parts of 7-H and 9-H purines.

The changes observed for N^-···HF interactions are more dramatic (Table S1, Supporting Information). Hydrogen bond energies in pyrrole and imidazole are equal to −32.28 and −30.03 kcal/mol, respectively, and are substantially stronger than those observed in 7-H and 9-H purines (−24.58 and −24.21 kcal/mol, respectively). Thus, the fusion of imidazole in purine reduces significantly the strength of N^-···HF interactions.

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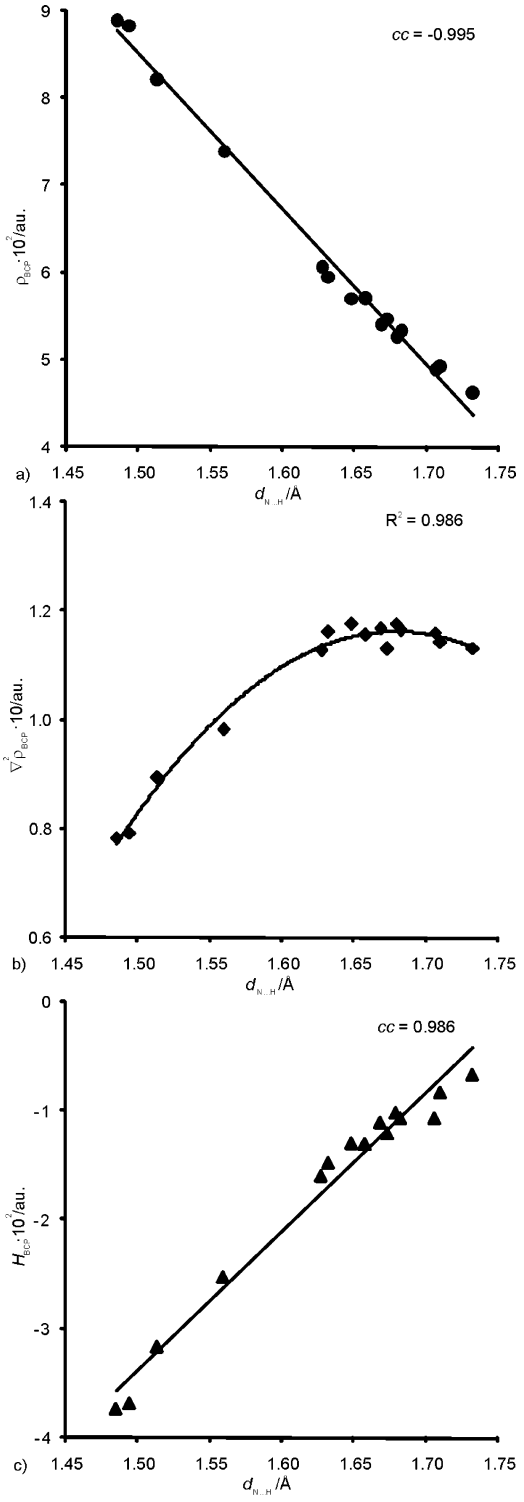
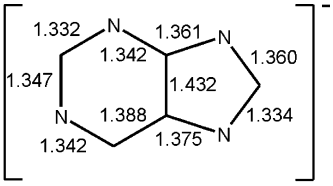


Figure 7. Dependence of (a) electron density, ρ_{BCP}, (b) electron density laplacian, $\nabla^2\rho_{BCP}$, and (c) density of the total electron energy in BCP, H_{BCP}, on H-bond distance, $d_{N\cdots H}$, for all considered H-bonded complexes.

Effect of H-Bond Formation on Aromaticity of the Rings in Tautomers of Purine. The question posed now is the following: to what extent do the H-bond formation and H-bond location affect π-electron delocalization in both rings of purine tautomers? Tables 1 and S6 (Supporting Information) present the HOMA and NICS aromaticity indices for all H-bonded systems.

In the case of $N^-\cdots HF$ interaction of purine tautomers, stronger H-bonds ($N7^-\cdots HF$ and $N9^-\cdots HF$) characterize an increase of all HOMA values (for both rings separately and for the whole molecule) with respect to the values obtained for the purine anion. When the six-membered ring participates in an intermolecular interaction, then H-bonding practically does not affect the aromaticity if the $N3^-\cdots HF$ interaction is involved, but a decrease of all HOMA indices is observed if the interaction is of the $N1^-\cdots HF$ type. For all anionic complexes, $HOMA_{tot}$ changes in the range between 0.892 and 0.922 (Table 1), whereas the value for the purine anion is equal to 0.904 (Scheme 2, Table 1). This shows a substantial similarity in

Scheme 2. Geometry and HOMA Values of Purine Anion



$HOMA_{tot}$: 0.904
HOMA: 0.880 0.817

π-electron structure between the complexes with $N^-\cdots HF$ interactions and that observed for the anion. Note that, in the anionic form, both rings of the purine moiety may contain six π electrons.

If the free purine tautomer (Scheme 1) is taken as a reference, then the $N7^-\cdots HF$ and $N9^-\cdots HF$ H-bond interactions reduce significantly the aromaticity of the six-membered ring, whereas the aromaticity of the five-membered ring is slightly increased. Therefore, long-distance consequences of intermolecular interaction are observed, because the six-membered ring does not participate directly in this intermolecular interaction.

For neutral complexes with the $N\cdots HF$ interaction, the picture is not so clear. As mentioned earlier, neutral H-bonds are weaker. A comparison of aromaticity in these types of complexes with the data obtained for free tautomers shows that the $HOMA_{tot}$ values are either slightly lower (one case in 3-H purine: $N1\cdots HF$) or higher. However, if a proton acceptor atom is in the five-membered ring, then the aromaticity of the H-bonded complex increases, in comparison with that of the free tautomer (Table S8, Supporting Information). In the cases of 1-H and 3-H purines (the strongest H-bonds, mean value $E_{HB} = -14.12$ kcal/mol), the changes in the HOMA values for the five- and six-membered rings and for the whole molecule are the highest. The same effect, but weaker, is observed for the analogous 7-H and 9-H purine complexes (with the proton acceptor atom in the five-membered ring, mean value $E_{HB} = -11.56$ kcal/mol). In both cases, the long-distance consequences of the hydrogen bond are observed.

Note that weaker $N\cdots HF$ interactions exist for the acceptor atom in the six-membered ring of 1-H and 3-H purines and cause both an increase and a decrease of aromaticity of this ring. Analogous H-bonds in 7-H and 9-H complexes decrease the aromaticity of the six-membered ring, which, in the free molecule, is highly aromatic (mean HOMA6 = 0.971, Table 1).

The influence of H-bond formation on the aromaticity of the ring in imidazole and pyrimidine complexes is weaker than the influence of the same interactions on these rings in purine.

Application of NICS values as an aromaticity indicator to both rings of H-bonded complexes of purine leads to similar

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conclusions, since there is an acceptable linear regression between NICS and HOMA, as shown in Figure 8. Nevertheless,

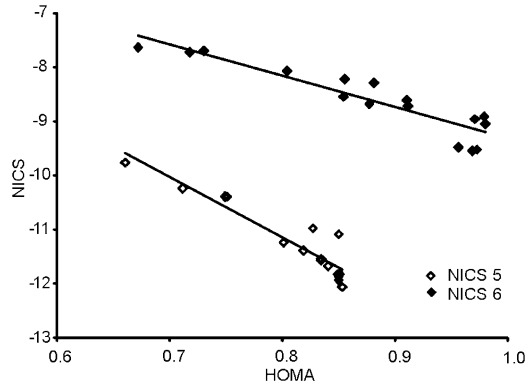

Figure 8. Dependence of NICS on HOMA for the five- and six-membered rings of H-bonded purine complexes (*cc* = −0.933 and −0.921, respectively).

in both cases (for the five- and six-membered rings), the deviating points toward more negative NICS values from the regression lines are observed for 7-H and 9-H purine tautomers. It should be noted that the NICS indices show higher aromaticity of the five-membered ring, whereas the HOMA ones of the six-membered ring (see Figure 8 and Table 1). This difference is associated with a difference of the area of the rings in question.

From other scatter plots, such as NICS(1) and NICS(1)zz versus HOMA, as well as densities of the potential, kinetic, and total energies in RCP versus HOMA, very poor relationships result, but they are always better for six-membered rings than for five-membered ones (for the values of indices, see Tables S6 and S7, Supporting Information).

CONCLUSIONS

The fusion of pyrimidine and imidazole moieties into purine units decreases the aromaticity of constituting rings. This resembles the case of naphthalene, in which both rings are less aromatic than benzene.

In agreement with earlier studies,[5,25,54] 9-H and 7-H purines' tautomers are more stable than 1-H and 3-H ones. The mean difference in energy is ∼9 kcal/mol. This is caused by the fact that, in 7-H and 9-H, the NH group is located in the five-membered ring, and hence, both rings contain (4n + 2) π electrons and fulfill the Hückel rule. Therefore, five- and six-membered rings of these tautomers are significantly more aromatic than the analogous rings in 1-H and 3-H tautomers, as documented by NICS and HOMA values. Note that the fusion of pyrimidine and imidazole changes substantially their π-electron properties, particularly in the case of less stable tautomers.

The ionic H-bonds, $N^-\cdots HF$, are stronger by ∼10 kcal/mol than the neutral ones. In the former case, the aromaticity of the whole molecule estimated by HOMA varies in the narrow range of 0.030 and is close to that obtained for the anion of purine ($HOMA_{tot}$ = 0.904, mean $HOMA_{tot}$ for the whole molecule = 0.909). Opposite to that, the aromaticity of both rings and of the whole molecule in neutral H-bonded complexes varies much more for 1-H and 3-H purines. In the latter case, the range of variability of HOMA for the five- and six-membered rings and the whole molecule is 0.099, 0.077, and 0.053, respectively (Table S8, Supporting Information). For more stable 9-H and 7-H tautomers, characterized by higher aromaticity of the monomers, H-bonding affects also π-electron delocalization, but in a much lower range of variability (about 5 times). This indicates that the N···HF bonds perturb much more strongly the π-electron structure of the five-membered rings than of the six-membered ones, and to the least extent, the purine moiety.

The energetic H-bond characteristics for particular intermolecular interactions of both rings in purine differ from those observed in the free imidazole and pyrimidine moieties. The fusion of pyrimidine and imidazole in purine does not change in a significant way the H-bond properties in the pyrimidine part; the basicity of the nitrogen atom slightly decreases or increases for less (1-H and 3-H) and more stable (7-H and 9-H) tautomers, respectively. However, it significantly lowers the strength of the N···HF interactions in the case of more stable tautomers and significantly decreases the strength of the $N^-\cdots HF$ interaction in the five-membered ring.

All H-bonds in the studied complexes are partially covalent, the ionic ones to a greater degree.

ASSOCIATED CONTENT

Supporting Information

Tables: The H-bond characteristics for optimal H-bonded complexes of purine tautomers (S1); statistics of linear regressions of H-bond energy vs its length for interactions of particular purine tautomers (S2); the H-bond characteristics for purine complexes with N···HF and $N^-\cdots HF$ interactions, linearity of H-bonding assumed (S3 and S4); the H-bond characteristics for pyrimidine and pyridine complexes with N···HF interactions as well as for pyrrole and imidazole with $N^-\cdots HF$ interactions (S5); indices of aromaticity [NICS, NICS(1), NICS(1)zz, HOMA, densities of the potential (V), kinetic (G), and total (H) energies at RCPs] for H-bonded complexes of purine tautomers (S6 and S7); the influence of H-bonding on the aromaticity of both rings and whole purine monomers (S8); Cartesian coordinates of equilibrium geometries for purine tautomers and their H-bonded complexes (S9 and S10). Scheme: HOMA index change of purine tautomers resulting from the fusion of the rings (S1). Figures: Dependences of H-bonding energy on the N···H distance for H-bonded complexes of purine tautomers (S1); the dependence of (a) electron density, (b) its laplacian, and (c) density of the total electron energy in BCP on H-bond energy (S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

[§]Dedicated to our friend, Professor Adam Proń, on the occasion of his 60th birthday.

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