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Aromaticity-Controlled Tautomerism and Resonance-Assisted Hydrogen Bonding in Heterocyclic Enaminone−Iminoenol Systems

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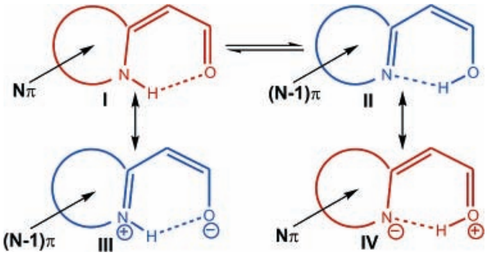

The contribution of aromaticity and intramolecular hydrogen bonding to relative stability, for a set of (1*H*-azahetero-2-ylidene)-acetaldehyde and 2-azahetero-2-yl-ethanol tautomeric pairs, has been investigated by means of quantum chemical DFT and ab initio methods up to the MP4(SDTQ)/AUG-cc-pVDZ and MP2/AUG-cc-pVTZ levels of theory. It is found that the relative energy of the tautomers is governed by the change in the degree of heterocycle aromaticity upon intramolecular hydrogen transfer. An analysis of geometrical parameters of a hydrogen-bonded system reveals a clear relationship between the aromaticity of the heterocycle, the conjugation in a resonant spacer, and the strengths of the intramolecular hydrogen bonds. This allows the conclusion to be drawn that intramolecular N−H···O and O−H···N hydrogen bonds formed are found to be resonance-assisted and their strength is dependent on the π-donating/accepting properties of the heterocycle. On the basis of the results of the calculations, a simple model describing the mechanism of resonance assistance of hydrogen bonding has been suggested.

Introduction

Hydrogen bonding, aromaticity, and tautomerism occupy a prominent position in modern heterocyclic chemistry.[1] They significantly influence the structure, relative stability of tautomers (or isomers), reactivity, and character of intramolecular interactions of various organic molecules. Therefore, these phenomena have been the subject of numerous experimental and theoretical studies (see refs 2 and 3 and references therein). One of the most interesting topics, especially in heterocyclic compounds, is the relationship between aromaticity of the heterocycle, the position of tautomeric equilibrium, and the strength of intramolecular hydrogen bonds. For example, amide−iminol tautomeric equilibrium occurs in hydroxypyridines, which is controlled by the aromaticity of the heterocycle, the substituent effects, and intra- or intermolecular hydrogen bonding.[4]

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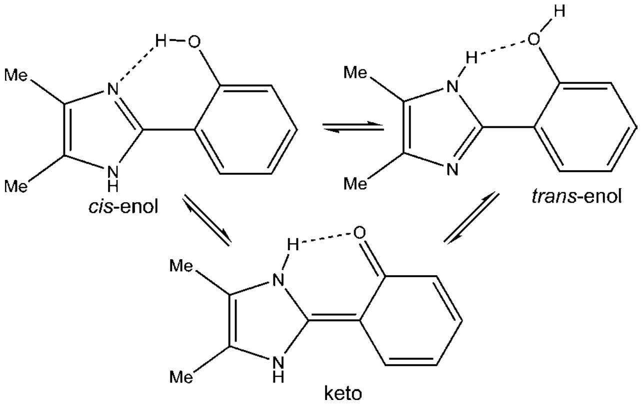
The most significant changes in the properties of a molecule are observed in systems with very strong hydrogen bonds. A comprehensive classification of hydrogen bonds, both intra- and intermolecular, was introduced by Gilli and co-workers[5] on the basis of an extended crystal structure data set. They have demonstrated several major factors that assist in the formation of really strong $O-H\cdots O$ bonds. The first factor corresponds to the presence of a surplus charge on the hydrogen bond. The so-called negative or positive charge-assisted hydrogen bond (±CAHB) has a proton-donor···proton-acceptor distance (described as the distance between non-hydrogen atoms) in the range of approximately 2.3−2.5 Å. They are well-exemplified by very short intermolecular $[RCOOH\cdots OOCR]^-$ bonds between carboxylic acids and carboxylates, $[O_nXOH\cdots OXO_n]^-$ bonds between inorganic oxoacids and their conjugate bases, $[O\cdots H\cdots O]^+$ bonds between two identical molecules (H_2O, R_2O, Me_2SO, pyridine N-oxide, etc.) with a bridging hydrogen atom donated by a strong acid, or by short intramolecular H-bonds formed in hydrogen maleate. Another class of strong H-bonds is represented by resonance-assisted hydrogen bonds (RAHB). This type of H-bond is observed in systems where two oxygen atoms are connected by a conjugated spacer containing single and double bonds, such as carboxylic acid dimers or β-enolones, with $O\cdots O$ distances of 2.39−2.55 Å. A positive synergism between hydrogen-bond strength and the efficiency of resonance in a conjugated spacer has been found.[6] Recently,[7,8] it was demonstrated that that basicity can be significantly enhanced by formation of the resonance-assisted H-bond in the corresponding conjugate acids.

The same conclusion generally is true for heteronuclear ($N-H\cdots O$, $N-H\cdots S$, etc.) H-bonds, although they are usually weaker than homonuclear H-bonds. It might be explained in terms of an electrostatic-covalent H-bond model (ECHBM).[5,9] This model assumes that strong hydrogen bonds have a partially covalent nature. Therefore, such bonds can only be formed if the proton affinities (PA) of proton donor and proton acceptor atoms have close values. In this situation, two wave functions corresponding to $X-H\cdots Y$ and $X\cdots H-Y$ tautomeric forms are isoenergetic and can mix to a greater extent, providing the possibility for strong hydrogen bonding. This implies one more necessary condition for the formation of strong H-bonds−the condition of minimum proton affinity difference (ΔPA) between H-bond donor and acceptor atoms. In the case of intramolecular H-bonds, this rule can be reformulated in terms of a minimum energy difference between two tautomeric forms related by an intramolecular proton transfer.

From this point of view, the hydrogen bonding and tautomerism represent closely related topics. The intrinsic weakness of heteronuclear bonds, in particular $N-H\cdots O/O-H\cdots N$ bonds, can be explained by the difference of inherent PA values of the nitrogen and oxygen atoms. The nitrogen atom has an intrinsically greater PA, as compared to the oxygen atom.[10] Therefore, the strongest $N-H\cdots O/O-H\cdots N$ bonds are formed in systems where the PA of the nitrogen atom is reduced by electron-withdrawing substituents or the PA of the oxygen atom is increased by electron-donating substituents. For example, Gilli at al.[6] have demonstrated the same differences in intramolecular H-bonding and tautomeric properties of 1-(4-F-phenylazo)2-naphthol and 1-(2-F-phenylazo)2-naphthol in variable-temperature X-ray crystallographic studies.

CHART 1



Another way of equalizing the energy of two tautomers in the case of RAHB is provided by inclusion of a resonant spacer between the proton donor and acceptor into a cyclic conjugated system.[11] This may result in a different distribution of formally single and double bonds within the ring and thus cause different aromaticity of the cyclic conjugated system in two tautomeric forms. The influence of aromaticity on the tautomeric properties of different heterocyclic systems has been extensively reviewed (see, for example, ref 1 and references therein). Numerous investigations have been devoted to the study of hydroxy, amino, and other substituted pyridines and related molecules.[12]

An example of aromaticity-controlled tautomerism is provided by 2-(2-hydroxyphenyl)azoles containing intramolecular hydrogen bonds. In particular, 4,5-dimethyl-2-(2-hydroxyphenyl)-imidazole[13] can exist in three tautomeric forms (Chart 1). In the gas phase, the cis-enol and trans-enol forms are more stable than the keto form (by 5−6 and 9−10 kcal/mol, respectively). It has been demonstrated that the stability order is determined primarily by the aromatic character of the benzene ring in these three isomers. However, the role of aromaticity of the imidazole ring has not been considered.

Krygowski and co-workers[14,15] analyzed the influence of the strength of an intramolecular hydrogen bond on the degree of π-electron delocalization for the set of various substituted Schiff bases. They did not find any correlation between the $N\cdots O$ distance and the delocalization index for the $O-C-C-C-N$ hydrogen-bonded ring. On this basis, it was suggested that the considerable impact on the degree of delocalization is provided by the effects of the substituents attached to the aromatic ring and by the bond that is part of the spacer. The largest degree of

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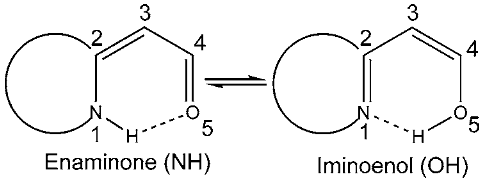
CHART 2



delocalization is observed in the case of substituents interacting strongly with the OH or C═N groups of the spacer.

Previous studies were mainly concentrated on systems where the hydrogen donor and acceptors are not part of cyclic conjugated system. Meanwhile, even a first glance at Chart 1 indicates that the degree of aromaticity of the imidazole ring may be responsible for the higher stability of the cis-enol tautomer despite the lower PA of the oxygen atom. Nevertheless, as far as we know, the role of heterocycles containing a proton donor/acceptor site for RAHB remains unclear up to now.

In this paper, we demonstrate the significant influence of the electronic nature of the heterocycle on the relative stability of tautomers and the characteristics of intramolecular resonance-assisted hydrogen bonds in molecules where a proton donor or proton acceptor fragment is part of the heterocyclic ring. We have analyzed the series of enaminone−iminoenol tautomers shown in Chart 2, which differ by the type of the heterocyclic ring. Our results indicate that the aromaticity of the heterocyclic conjugated system is the major factor determining the tautomeric equilibrium position and the characteristics of RAHB.

Computational Details

The geometries of molecules having the structures presented in Charts 3 and 4 (1−10 and 1M−10M) were optimized at the MP2/AUG-cc-pVDZ level of theory using the NWChem program.[16] The character of the stationary points on the potential energy surface (minimum or transition state) was confirmed by calculation of the Hessian matrix at the same level of theory within the harmonic approximation. The zero-point vibration energy from these calculations were used for computation of Gibbs free energy differences between the pair of tautomers at 0 K. Also, single-point energy calculations at the MP2/AUG-cc-pVTZ and MP4(SDTQ)/AUG-cc-pVDZ levels using the PC GAMESS program[17] were performed.

To estimate the change of heterocyclic aromaticity upon intramolecular proton transfer, the aromaticity indexes of the cyclic conjugated system for both tautomeric forms were calculated. Up to now, many aromaticity indexes were proposed.[18] All of them may be divided into three groups, structural (based on bond lengths and order nonuniformity), magnetic, and energetic indexes. In general, the latest (for example, aromatic stabilization energy or ASE) should be the most suitable for description of aromatic stabilization. However, it is difficult to suggest a correct and transferable scheme for calculations of ASE values especially in the case of substituted heterocyclic molecules. Therefore, it was demonstrated[19,20] that ASE values in many cases are less reliable as compared to structural and magnetic indexes.

Two independent approaches for calculating the aromaticity indexes were used: magnetic based on shielding of the induced magnetic field (nucleus-independent chemical shifts, NICS[21]) and structural based on bond orders nonuniformity (structural aromaticity index of Bird, SAIB[22,23]). While the original Schleyer's approach defines NICS as negative one-third of the trace of the magnetic shielding tensor (or its isotropic value), it was demonstrated[24] that there is no direct interrelation between this value and the diatropicity of the ring current. Therefore, the NICS values cannot be successfully applied for the study of aromaticity of the set of very different heterocycles. In the present study, the component of the NICS tensor corresponding to the principal axis perpendicular to the ring plane calculated at the point located 1 Å above the ring center ($\mathrm{NICS(1)_{zz}}$) was used as a more reliable aromaticity index.[24,25] The $\mathrm{NICS(1)_{zz}}$ values were calculated using the GIAO method[26] implemented in the Gaussian 03 program[27] for the B3LYP/AUG-cc-pVDZ//MP2/AUG-cc-pVDZ wave function.

For SAIB calculations, the Wiberg bond indexes[28] in the Natural Atomic Orbitals basis produced by the NBO 5.0 program[29] were calculated using the MP2/AUG-cc-pVDZ wave function. To estimate the degree of delocalization within the conjugated spacer between the proton donor and acceptor atoms, the I_3 delocalization index defined by the standard SAIB approach was applied:

$$I_3 = 100\left(1 - \frac{V}{V_\mathrm{k}}\right) \qquad V = \frac{100}{n}\sqrt{\frac{\sum(N_\mathrm{i} - \bar{N})}{n}}$$

where N_i is the bond order (Wiberg bond index); $\bar{N}$ is the arithmetic mean bond order; n is the number of bonds; and V and V_k are a measure of bonds nonuniformity for the real (localized) and idealized Kekülе structure with the completely localized single and double bonds. It should be noted that I_3 was used only as an index of delocalization within the exocyclic C═C−C═O fragment in the case of the NH tautomer and within the C−C═C−OH fragment in the case of the OH tautomer in molecules 1−10.

The total numbers of π-electrons ($\mathrm{N}\pi_\mathrm{a}$) within the separated fragments of molecules 1−10 and 1M−10M were estimated using

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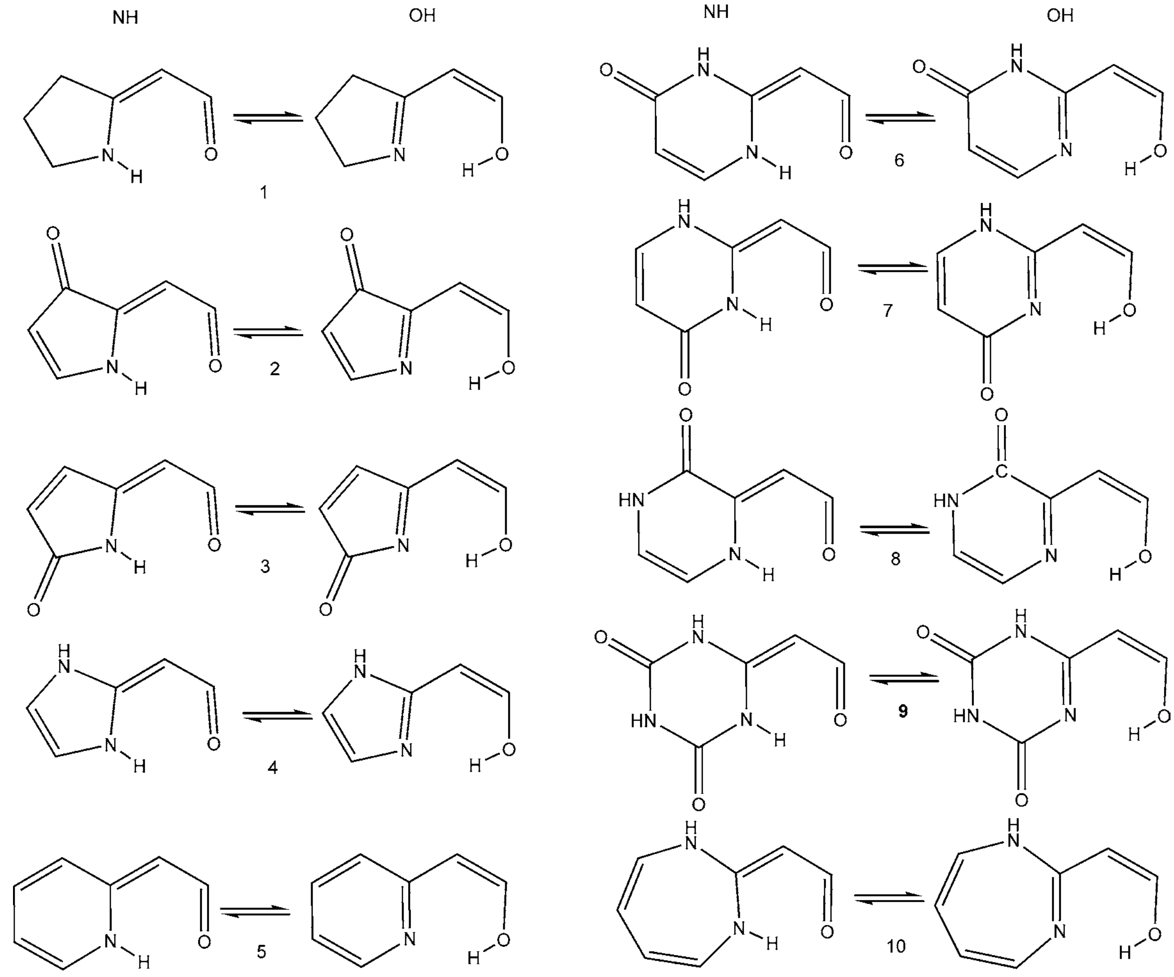
CHART 3



the Natural Bond Orbitals (NBO) theory[30] as a sum of the contributions from natural hybrid orbitals (NHOs) centered on the atoms of the considered fragment into π-type natural localized molecular orbitals (NLMOs). It is not entirely justified to use the correlated wave function for such an analysis because the electron population on the occupied molecular orbitals in this case is a non-integer and a small portion of the electrons on the unoccupied orbitals are disregarded. Therefore, the B3LYP/AUG-cc-pVDZ//MP2/AUG-cc-pVDZ wave functions were used, which account for the electron correlation effects but have an integer number of electrons on the occupied orbitals.

Results and Discussion

Relative Stability of Tautomers. As can be seen from the chemical formulas of molecules 1−10, the heterocycle has different electronic structures in the NH and OH tautomers. The formal number of π-electrons within the heterocycle decreases by one due to the intramolecular proton transfer from the nitrogen atom (which is part of the heterocyclic system) to the exocyclic oxygen atom. This is a general rule and does not depend on the structure of the heterocycle. In the NH tautomer, there are two π-electrons on the lone-pair of the amide nitrogen atom and one on the exocyclic C=C bond, for a total of three π-electrons that formally and exclusively belong to cyclic conjugated system of the heterocycle. In the OH form, only two such electrons remain on the endocyclic N=C bond. Thus, in the case of the presence of a conjugated system within the heterocyclic ring, the distinctions between two tautomers mentioned above can result in differences in their aromaticity.

As one may expect, the calculated relative stability of the NH and OH tautomeric forms of the set of molecules 1−10 significantly depends on the nature of the heterocycle. The relative energies of the tautomers vary in the wide range 3−13 kcal/mol (Table 1). In addition to the MP2/AUG-cc-pVDZ data, single-point energies with a larger atomic basis set (MP2/AUG-cc-pVTZ) and with a more accurate account of electron correlation effects (MP4(SDTQ)/AUG-cc-pVDZ) were calculated. Our results demonstrate that the MP2/AUG-cc-pVTZ method predicts stabilization of the OH form of tautomers 1−9 by 0.05−0.34 kcal/mol, as compared to MP2/AUG-cc-pVDZ. On the contrary, the MP4 method for most of the molecules (except for 2, 3, and 9) gives greater stability to the NH forms (up to 1.42 kcal/mol). Nevertheless, the relative energies for the set of tautomers of 1−10 computed by these three methods correlate well with each other with the linear correlation coefficients being approximately 0.999. Moreover, all of the trends that will be discussed in the present paper are the same regardless of the method that was used for the energy calculations. Therefore, one can conclude that the MP2/AUG-cc-pVDZ level of theory is sufficient for at least a qualitatively correct description of the electronic structure and relative stability of the considered molecules 1−10.

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CHART 4

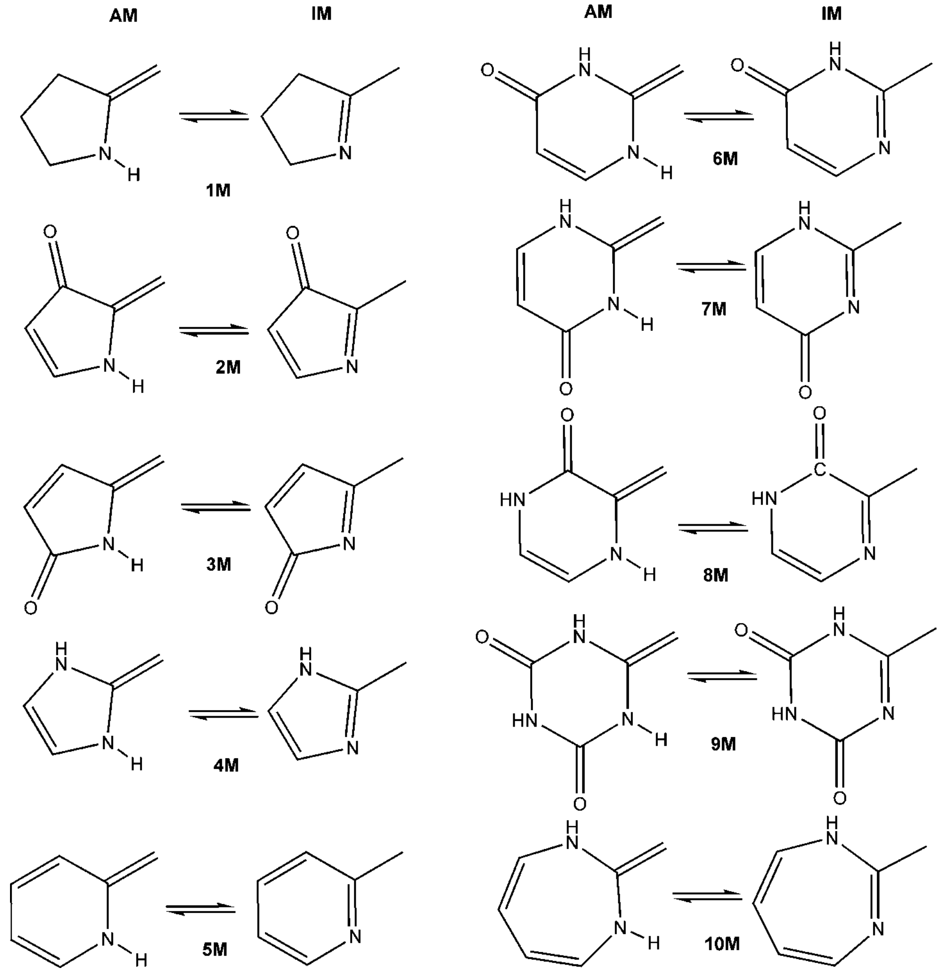

TABLE 1. Formal ($N\pi_f$) and Actual ($N\pi_a$) Numbers of π-Electrons within the Heterocycle for Molecules 1−10, Relative Gibbs Free Energies at 0 K (ΔG^0) of the NH Tautomeric Form with Respect to OH (kcal/mol), and Change of Relative Stability of the NH Tautomers ($\Delta\Delta G°$) with Respect to Molecule 1 (kcal/mol)

	$N\pi_f$		$N\pi_a$		MP2/AUG-cc-pVDZ		MP2/AUG-cc-pVTZ[a]	MP4(SDTQ)/AUG-cc-pVDZ[a]
molecule	NH	OH	NH	OH	ΔG^0(NH)	$\Delta\Delta G^0$(NH)	ΔG^0(NH)[b]	ΔG^0(NH)[b]
1	3	2	2.49	2.18	−3.27	0	−2.93	−3.54
2	6	5	5.41	4.95	−10.55	−7.28	−10.22	−10.39
3			5.32	4.94	−13.32	−10.05	−13.00	−13.12
4	7	6	6.31	6.07	7.00	10.27	7.13	6.04
5			6.39	6.12	4.75	8.02	5.01	4.06
6	8	7	6.96	6.65	0.79	4.06	0.98	0.44
7			7.01	6.71	−2.95	0.32	−2.64	−3.33
8			7.08	6.68	1.44	4.71	1.49	0.02
9	9	8	7.53	7.21	−3.06	0.21	−2.75	−2.99
10			8.46	8.14	−3.47	−0.20	−3.68	−4.06

[a] Single-point calculations for MP2/AUG-cc-pVDZ geometry. [b] ZPVE correction from the MP2/AUG-cc-pVDZ calculations.

It is possible to assume several important factors that influence the relative energy of tautomers 1−10. The first factor is, as was stated above, the electronic nature of the heterocyclic moiety, particularly its aromaticity. One can suggest that a more stable tautomer should possess a more aromatic cyclic conjugated system. The second essential factor is the presence of a conjugated spacer between the proton donor and the proton acceptor. Efficiency of conjugation within this spacer can vary up to some degree, resulting in a different decrease in energy for a particular tautomer. Finally, the third factor is the presence of an intramolecular hydrogen bond, which presumably has resonance-assisted nature. This means that the degree of conjugation in a resonant spacer is correlated with the strength of the H-bond. Moreover, electron density redistribution due to conjugation within the spacer and due to formation of a resonance-assisted H-bond (RAHB) can result in changes in the properties of a heterocyclic ring.

While discussing the influence of aromaticity of molecules 1−10 on their tautomeric properties, it is convenient to use molecule 1 as reference point. This molecule does not contain a cyclic conjugated system within the heterocycle. Therefore, the relative stability of NH and OH tautomers results in a difference in the intrinsic stability of the enaminone and iminoenol forms, the −NH−C═C−C═O and the −N═C−C═C−OH fragments. According to our computational data, the 1NH tautomer is more stable than the 1OH tautomer (by 2.93−3.54 kcal/mol (Table 1)). This result agrees well with the higher proton affinity of the nitrogen atom, as compared to the oxygen and also with the known experimental results for simple enaminones.[31]

The calculated energy differences between the NH and OH tautomers of 2−10 can be fairly rationalized on the basis of the change of the formal π-electron number within the heterocycle and the consequent change in the degree of aromaticity, according to the $(4n+2)$ Hückel rule.[32] Yet to obtain additional quantitative descriptions, we have also calculated the actual total number of π-electrons within the heterocycle (Table 1) as a sum of atomic contributions into π-type localized molecular orbitals.

In compounds 2 and 3, the NH form becomes considerably more stable as compared to the stability pattern in 1. These molecules formally have 6 π-electrons within the heterocycle in the NH form and, thus, can be considered to be aromatic according to the Hückel rule. In the OH form, this number decreases to 5, and the molecules become formally nonaromatic. Therefore, we can suggest that the stabilization of the NH tautomeric form occurs due to the greater degree of aromaticity of the heterocycle as compared to the OH form. The same suggestion results from the actual total number of π-electrons within the heterocycle (Table 1). In the OH form, these molecules have about 5 π-electrons, so this tautomer really has nonaromatic character. In the NH tautomer, the heterocycle has more π-electrons (5.4 and 5.3 π-electrons for 2 and 3, respectively), and their number is closer to 6. In molecules 4 and 5, an opposite trend occurs. The NH tautomer is no longer more stable because the aromatic stabilization is observed for the OH form where the heterocycle formally contains 6 π-electrons (Table 1).

In molecules 6−8 and 9−10, the formal $8\pi \rightarrow 7\pi$ and $9\pi \rightarrow 8\pi$ transitions, within the heterocycle, occur during the NH → OH intramolecular proton transfer. However, in contrast to molecules 2−5, the effect on the relative stability of tautomers is less pronounced. Nevertheless, the change of relative stability of the tautomers (using molecule 1 as reference point) is in accord with the change in the actual number of π-electrons within the ring. The OH tautomer of molecules 6−8 is stabilized as compared to molecule 1. This means that relative stability of this tautomer in molecules 6−8 is higher as compared to molecule 1 (Table 1). In the case of 9, it is less aromatic (as compared to the nearly anti-aromatic NH tautomer). The opposite situation occurs in molecule 10 in which the OH tautomer is destabilized due to its anti-aromaticity.

Thus, the relative stability of the whole set of molecules 2−10 seems to be controlled by the change of aromaticity characteristics of the heterocycle that take place during the intramolecular proton transfer. However, one can argue that the total π-electron numbers within the ring cannot be considered as aromaticity indexes because these values do not take into account the effects of cyclic electron delocalization. To estimate the aromaticity of the heterocycles in a more direct way, we have calculated magnetic NICS$(1)_{zz}$ and structural SAIB aromaticity indexes for the NH and OH tautomers of molecules 1−10 (Table 2). Our results indicate that, in general, the number of π-electrons correctly predicts the aromaticity of most of the heterocycles in the series of molecules 2−10. Two plots display the presented changes of NICS$(1)_{zz}$ and the SAIB indexes with the change of the total π-electron number of heterocycles (Figure 1). Both plots show sharp extrema at the region near 6 π-electrons (minimum for NICS$(1)_{zz}$ and maximum for SAIB) that correspond to the aromatic state of the heterocycle. The extrema at the region near 8 π-electrons are not so well-defined. This can be explained as follows. The only species in the set that has about 8 π-electrons within the heterocycle is molecule 10. In contrast to molecules 2−9, the diazepine ring of 10 is noticeably nonplanar in both tautomers. The hydrogen-bonded nitrogen atom (N_a) in the NH tautomer has an almost planar configuration, while the other nitrogen atom (N_b) is considerably pyramidal. The sum of bond angles centered on this atom changes from 343.0° in the NH tautomer to 331.2° in the OH tautomer. The ring has a nearly perfect boat conformation including the N_b−C−N_a−C and N_b−C−C−C fragments, which are approximate planar, while the C−C−N_b−C and C−N_a−C−C torsion angles are 59.3° and 38.4° (NH), and 66.8° and 39.4° (OH), respectively. The greater degree of nonplanarity of the OH tautomer as compared to the NH tautomer is probably caused by its higher degree of anti-aromaticity according to the total number of π-electrons.

TABLE 2. NISC$(1)_{zz}$ (GIAO B3LYP/AUG-cc-pVDZ//MP2/AUG-cc-pVDZ) and SAIB[a] (MP2/AUG-cc-pDZ) Aromaticity Indexes for Molecules 1−10

		NICS$(1)_{zz}$	SAIB	ΔNICS$(1)_{zz}$	ΔSAIB
1	NH	−3.2		−0.3	
	OH	−3.5	29.9		
2	NH	2.6	37.8	−8.6	13.6
	OH	11.9	24.2		
3	NH	−3.2	29.4	−5.4	5.6
	OH	2.3	23.8		
4	NH	−20.7	53.3	7.2	−13.0
	OH	−27.9	66.3		
5	NH	−12.9	68.3	10.4	−20.1
	OH	−23.3	88.4		
6	NH	−1.1	45.0	5.8	−8.3
	OH	−6.9	53.3		
7	NH	−0.3	42.1	4.2	−4.0
	OH	−4.5	46.1		
8	NH	−4.4	45.0	5.4	−13.7
	OH	−9.8	58.7		
9	NH	1.5		1.7	
	OH	−0.2	56.6		
10	NH	11.5	30.7	9.1	−0.6
	OH	2.4	31.3		

[a] For the NH forms of 1 and 9, the SAIB index cannot be calculated because no bond order alternation is in the reference structure.

The fact that the relative stability of tautomers of 2−10 is mostly controlled by the difference in the heterocycle aromaticity in the two tautomers is also confirmed by correlation between the ΔNICS and ΔSAIB values with the relative stability of the tautomers of molecules 2−10 (Figure 2). The only point on the ΔNICS$(1)_{zz}$−ΔG^0 plot that corresponds to molecules 10 is an outlier. The most probable explanation of this fact is the nonplanarity of the heterocycle, which does not allow the center of the cyclic π-system to be correctly determined.

The other item of interest is the influence of the exocyclic resonant spacer and the intramolecular hydrogen bond on the relative energy of the tautomers. To ascertain this, we have calculated the relative energies of the series of aminomethyl-

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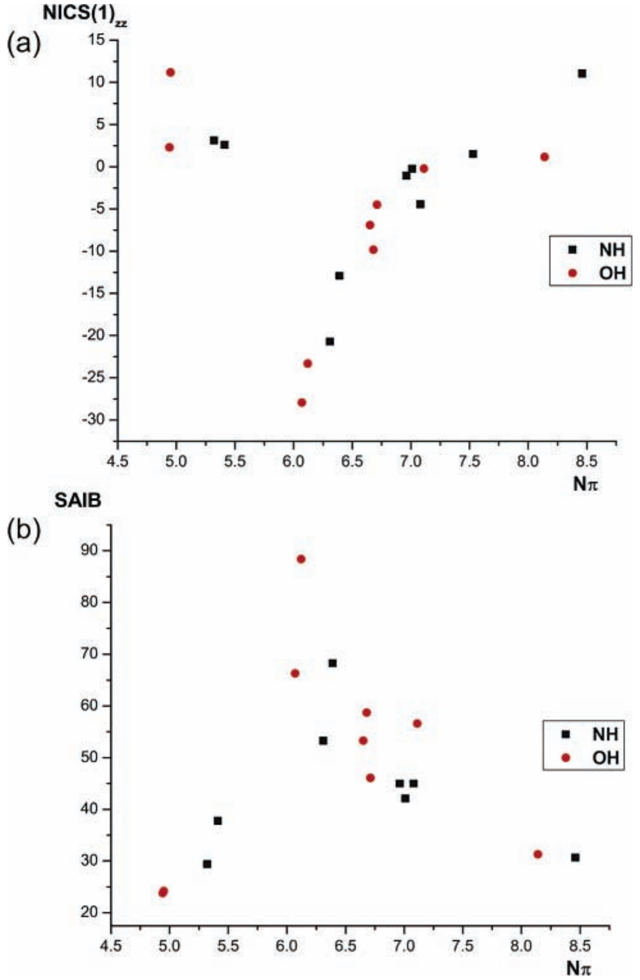

FIGURE 1. Dependence of NICS(1)$_{zz}$ (a) and SAIB (b) aromaticity indexes from the number of π-electrons within the heterocycle in molecules 2–10.

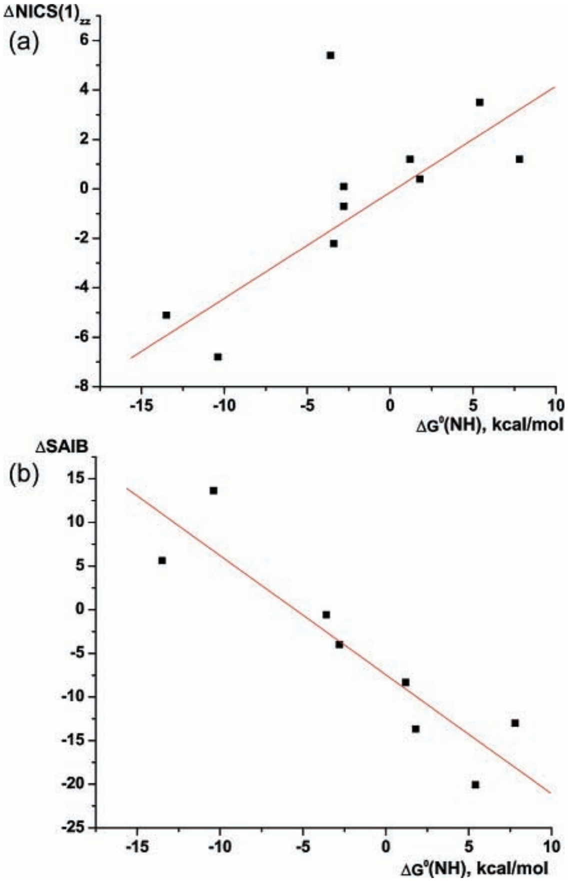

FIGURE 2. Correlations of differences of NICS(1)$_{zz}$ (a) and SAIB (b) aromaticity indexes with relative stability of the NH tautomer ΔG^0(NH) (MP2/AUG-cc-pVDZ data).

ene–iminomethyl tautomers 1M–10M (Chart 4), which have the same heterocycles as molecules 1–10 but do not contain resonant spacer and intramolecular hydrogen bonds. The substituent attached to the heterocycle is reduced to either the methyl (tautomer AM) or the methyene group (tautomer IM). In the case of molecules 1M–10M, all changes in relative stability of tautomers are caused only by changes of properties of heterocycle. Therefore, comparison of data for two sets of molecules 1–10 and 1M–10M allows one to estimate the contribution of resonant spacer and intramolecular hydrogen bonds into stabilization of NH or OH tautomers.

The results of the calculation allow one to assume (Table 3) that the presence of a resonant spacer and RAHB is important for the stabilization of NH tautomer for compounds 1–10. The most drastic changes are observed for molecules 1M, 7M, 9M, and 10M, where the aminomethylene tautomer (NH form) becomes significantly less stable with respect to the iminomethyl tautomer corresponding to the OH forms in 1–10. The same trend is found for the other molecules. Only in the case of compounds 2M and 3M are the aminomethylene tautomers more stable (Table 3). The ΔG^0 values for molecule 1M reflect the intrinsic properties of the HN–C=C/N=C–CH fragment associated with the relative stability of the tautomer. Therefore, using 1M as a reference point, we can conclude that the presence of a cyclic conjugated system in molecules 2M–10M results in significant stabilization of the aminomethylene (2M, 3M, and 9M) or the iminomethyl (4M–6M, 8M) tautomer depending on the nature of the heterocycle.

Similar to molecules 1–10, one can assume that in molecules 2M–10M change in heterocycle aromaticity is the main factor determining the relative stability of the tautomers. The ΔG^0 values for this set of molecules correlate with the NICS(1)$_{zz}$ and SAIB aromaticity indexes in the same manner as for molecules 2–10. Yet the most interesting results follow from a comparison of the relative stability of the tautomers in molecules 1–10 and 1M–10M (Figure 3). An almost ideal correlation between ΔG^0 for the enaminone–iminoenol and aminomethylene–iminomethyl tautomer pairs is found. A similar correlation is obsrved also for values of aromaticity indexes changes in molecules 1–10 and 1M–10M (Figure 3). It should be noted that slopes of these lines are very close to 0.5. This means that the main factor controlling the position of tautomeric equilibrium in molecules 2–10 and 2M–10M should be the same. Taking into account that tautomeric properties of molecules 2M–10M are determined only by change of heterocycle, one can conlude that relative stability of tautomers in both sets of compounds is controlled mainly by change of aromaticity degree of heterocycle (Table 4). The hydrogen bond and resonant spacer present in molecules 1–10 may influence the aromaticity of the heterocycle changing the stability of the particular tautomer. Therefore, conjugation in the resonant spacer and formation of RAHB should be additional factors also

TABLE 3. Relative Energies of the Aminomethylene Form with Respect to Iminomethyl (kcal/mol) for Molecules 1M−10M

	MP2/AUG-cc-pVDZ	MP2/AUG-cc-pVTZ[b]	MP4(SDTQ)/AUG-cc-pVDZ[b]
molecule	ΔG^0(NH)[a]	ΔG^0(NH)[a]	ΔG^0(NH)[a]
1M	9.94	8.83	11.10
2M	−5.40	−6.97	−3.18
3M	−11.06	−12.64	−8.55
4M	31.98	30.46	30.89
5M	27.14	25.87	26.19
6M	18.23	16.67	18.83
7M	9.05	7.59	9.93
8M	16.74	14.98	16.13
9M	7.38	5.86	9.05
10M	9.86	8.18	10.98

[a] ZPVE correction from the MP2/AUG-cc-pVDZ calculations. [b] Single-point calculations for MP2/AUG-cc-pVDZ geometry.

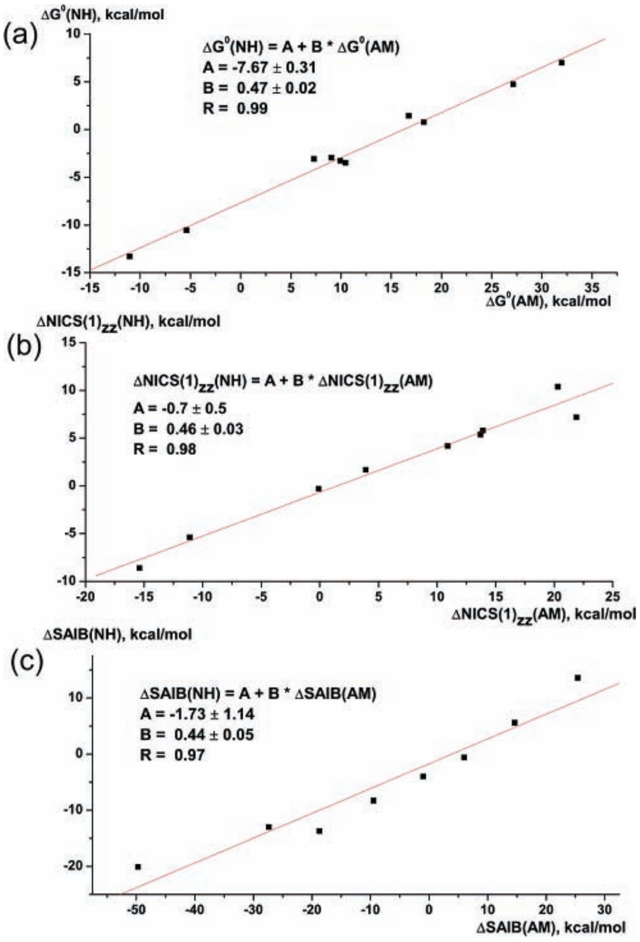

FIGURE 3. Correlations between the ΔG^0 (a), ΔNICS$(1)_{zz}$ (b), and ΔSAIB (c) values of the corresponding tautomer pairs from the 1−10 and 1M−10M sets.

TABLE 4. NISC$(1)_{zz}$ (GIAO B3LYP/AUG-cc-pVDZ//MP2/AUG-cc-pVDZ) and SAIB[a] (MP2/AUG-cc-pDZ) Aromaticity Indexes for Molecules 1M−10M

		NICS$(1)_{zz}$	SAIB	ΔNICS$(1)_{zz}$	ΔSAIB
1	AM	3.4		−0.1	
	IM	3.5	16.5		
2	AM	−2.8	39.2	−15.4	25.4
	IM	12.6	13.8		
3	AM	−6.7	29.5	−11.1	14.6
	IM	4.4	15.0		
4	AM	−7.3	36.3	21.9	−27.4
	IM	−29.2	63.7		
5	AM	−6.5	45.7	20.3	−49.7
	IM	−26.9	95.4		
6	AM	4.7	40.2	13.9	−9.5
	IM	−9.2	49.7		
7	AM	4.7	40.2	10.9	−1.0
	IM	−6.3	41.2		
8	AM	1.4	35.3	13.7	−18.7
	IM	−12.3	54.0		
9	AM	2.6		3.9	
	IM	−1.3	41.4		
10	AM	−0.7	33.8	−0.7	6.0
	IM	0.1	27.8		

[a] For the AM forms of 1 and 9, the SAIB index cannot be calculated because no bond order alternation is in the reference structure.

making some contribution to the relative stability of the tautomers in compounds 1−10.

Resonance-Assisted Hydrogen Bonding. Results of calculations indicate that the nature of the heterocycle in molecules 1−10 influences the characteristics of the hydrogen bonds (Table 5). The studied set of molecules shows considerable variation in the N−H⋯O hydrogen-bond strengths as estimated by the N⋯O distance. Taking into account that values of the N−H⋯O/N⋯H−O angles are varied in relatively small extents (Table 5), change of hydrogen-bond strength can be described using variations of the N⋯O distance. The corresponding N⋯O distances range from 2.54 Å for 5 (which can be classified as a strong H-bond[33]) to 2.76 Å for 3 (a moderate H-bond). At the same time, in the set of OH tautomers the variation of H-bond strength is somewhat smaller. The N⋯O distances for the O−H⋯N bonds are within 2.56−2.68 Å. This fact is in agreement with published observations that the proton-donor properties are more important in the formation of H-bonds than are the proton-acceptor properties.[34,35] A change in the heterocycle in molecules 1−10 certainly provides a more significant effect on the properties of the nitrogen atom, which itself is part of the heterocycle, rather than on the oxygen atom of the substituent.

The results of the calculations reveal that the strength of the NH⋯O and O−H⋯N bonds in molecules 1−10 depends on the relative stability of the particular tautomer. Two curves in Figure 4 are shown that correspond to the NH and OH tautomers. These curves possess two interesting features. They have an intersection approximately at zero on the ΔG^0 scale, and they reflect inverse correlation between H-bond strength

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TABLE 5. Hydrogen-Bond Parameters (Å, deg) for Molecules 1−10

	NH form			
	N1−H6	O5···H6	N1···O5	N1−H6···O5
1	1.025	1.912	2.675	128.6
2	1.016	2.094	2.746	119.9
3	1.018	2.110	2.764	120.0
4	1.048	1.704	2.556	135.2
5	1.065	1.595	2.540	144.7
6	1.044	1.701	2.592	140.4
7	1.037	1.806	2.657	136.6
8	1.043	1.717	2.597	139.2
9	1.035	1.806	2.646	135.6
10	1.037	1.752	2.651	142.4

	OH form			
	O5−H6	N1···H6	N1···O5	N1···H6−O5
1	1.011	1.677	2.594	148.5
2	1.008	1.697	2.604	147.6
3	1.022	1.632	2.556	148.0
4	0.996	1.785	2.678	147.3
5	1.000	1.739	2.637	147.6
6	1.005	1.711	2.615	147.5
7	1.014	1.681	2.593	147.4
8	1.003	1.713	2.619	148.0
9	1.010	1.688	2.591	146.4
10	1.014	1.668	2.590	149.0

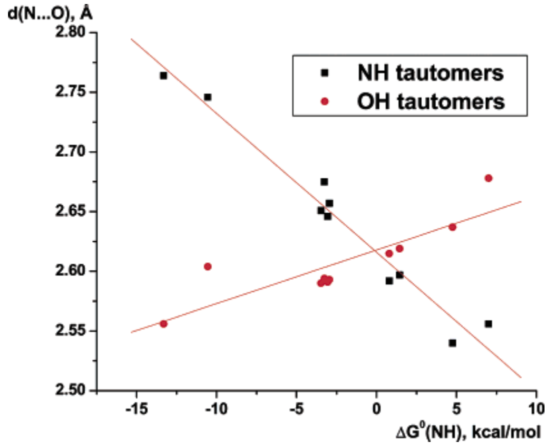

FIGURE 4. Correlations of hydrogen-bond strength estimated as the N···O distance for the NH and OH tautomers of molecules 1−10 with relative stability of the particular tautomer.

and relative stability for both tautomers. This result is in disagreement with the electrostatic-covalent hydrogen-bond model (ECHBM),[5,9] stating that the strongest H-bonds are formed when proton-donor and -acceptor atoms have close values of proton affinities. In other words, according to ECHBM, the strongest H-bonds are formed when two tautomeric forms have the same energy. According to our results, the strongest H-bonds are found in the least stable tautomers where the difference in energy between two tautomers is maximal. However, this disagreement can be easily resolved if we will limit our consideration only by experimentally observed tautomers. The ECHBM theory was formulated on the basis of the experimentally available results, while the geometrical parameters of unstable tautomers cannot be observed by experimental techniques because of the extremely low energetic barrier of the proton-transfer reaction, which is typical for hydrogen-bonded systems.[36] In the case of tautomers with negative ΔG values that may be detected in experiments, conclusions derived from our calculations and ECHBM theory are the same.

One of the most recognized features of resonance-assisted hydrogen bonds is significant delocalization of the electron density within the resonant spacer between the proton donor and acceptor. The existence of such resonance manifests itself in considerable elongation of formally double bonds and shortening of single bonds. The results of the calculations clearly demonstrate the presence of delocalization within the resonant spacer in molecules 1−10. The formally double C═C bond is systematically longer (Table 6) as compared to its average value of 1.32 Å.[37] The opposite situation is observed for single C−C bonds. Moreover, in some cases, the lengths of formally double and single C−C bonds become almost the same (for example, their values are 1.413 and 1.416 Å in the NH tautomer of molecule 4). This undoubtedly confirms the presence of very strong π-delocalization within the resonant spacer in molecules 1−10. The values of bond lengths within the spacer depend noticeably on the nature of the heterocycle and the tautomeric form. In the case of NH tautomers, a stronger H-bond is accompanied by longer C2═C3 and C4═O5 bonds and shorter C3−C4 bonds (for atom numbering see Chart 2), reflecting strong π-electron delocalization within this fragment. For molecules 4NH and 5NH, where the strongest N−H···O bonds are formed, the bond lengths of formally double C2═C3 and single C3−C4 bonds are almost equivalent. Variation of bond lengths within the spacer in the OH tautomers is considerably smaller as compared to the NH tautomers. Nevertheless, in the case of the strongest O−H···N bond in molecule 3, the C2═C3 and C3−C4 bond lengths differ only by 0.05 Å.

For a description of π-electron delocalization within the resonant spacer, we have used the I_3 index (Table 6) for the C2−C3−C4−O5 fragment. This index was calculated in the same way as the standard Bird aromaticity index for ring systems based on the values of bond orders. Like the Bird aromaticity index, the I_3 values reflect the degree of bond orders nonuniformity within the fragment under consideration. The results of the calculations demonstrate that the I_3 index correlates relatively well with the strength of the N−H···O and O−H···N hydrogen bonds (Figure 5). The positive synergism between the degree of delocalization and H-bond strength is typical for resonance-assisted hydrogen bonds (RAHB).[38,39] This means that higher value of delocalization index corresponds to stronger intramolecular hydrogen bond (Figure 5). It indicates that the H-bonds formed in both NH and OH tautomers of 1−10 can be classified as RAHB. Hence, π-electron conjugation and consequent charge transfer within the resonant spacer between the proton donor and acceptor atoms is a critical factor that influences the properties of H-bonds.

On the basis of the data plotted in Figure 5, one can conclude that the degree of delocalization within the −C═C−OH fragment in the case of OH tautomers is generally smaller than that within the ═C−C═O fragment in the case of NH tautomers.

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TABLE 6. Selected Geometrical Parameters (Å) for Molecules 1−10, Delocalization Index I_3 (see Text) for the C2−C3−C4−O5 Fragment, and Total Number of π-Electrons within the Exocyclic C−C−O Fragment

		N1−C2	C2−C3	C3−C4	C4−O5	I_3	$N\pi$ (CCO)
1	NH	1.352	1.388	1.439	1.256	62.9	3.48
	OH	1.315	1.449	1.373	1.339	49.5	3.84
2	NH	1.375	1.370	1.463	1.244	41.1	3.22
	OH	1.323	1.426	1.380	1.332	62.3	3.72
3	NH	1.378	1.374	1.464	1.242	41.3	3.27
	OH	1.330	1.427	1.385	1.322	68.2	3.69
4	NH	1.364	1.413	1.416	1.275	80.9	3.68
	OH	1.350	1.450	1.366	1.350	40.2	3.93
5	NH	1.380	1.413	1.418	1.277	84.5	3.61
	OH	1.368	1.459	1.369	1.348	42.6	3.90
6	NH	1.368	1.397	1.432	1.263	72.8	3.55
	OH	1.333	1.450	1.372	1.337	48.9	3.84
7	NH	1.369	1.393	1.437	1.256	65.4	3.53
	OH	1.326	1.450	1.374	1.332	51.9	3.82
8	NH	1.369	1.395	1.433	1.264	69.3	3.43
	OH	1.350	1.442	1.375	1.341	51.8	3.78
9	NH	1.373	1.383	1.446	1.252	57.3	3.47
	OH	1.325	1.443	1.377	1.328	56.8	3.80
10	NH	1.360	1.394	1.438	1.257	66.2	3.51
	OH	1.312	1.452	1.375	1.335	52.1	3.84

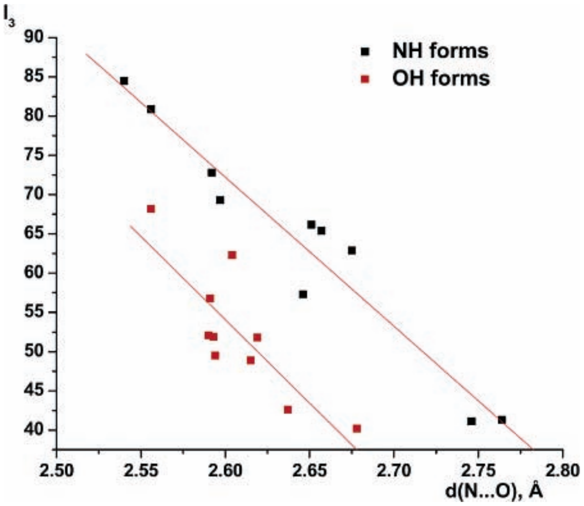


FIGURE 5. Correlations of the I_3 delocalization index within the exocyclic C−C−O fragment with the strength of the H-bond in the NH and OH tautomers of molecules 1−10 estimated as the N···O distance.

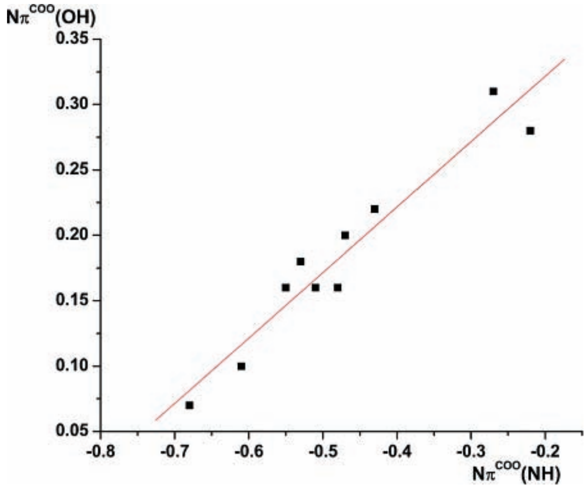
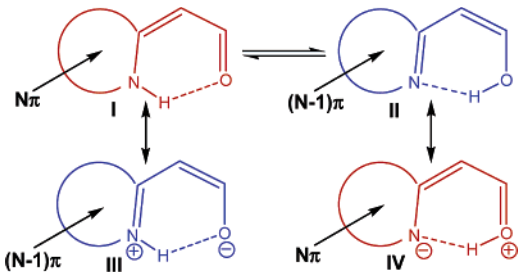


FIGURE 6. Correlation between the π-charges within the exocyclic CCO fragment in the NH and OH tautomers of molecules 1−10.

This fact might be explained by inherent electron affinity of the oxygen atom. Because of the strong electron-withdrawing properties of the carbonyl group, the =C−C=O fragment of the spacer can easily be turned into the −C=C−O$^-$ form. In contrast, the hydroxyl group is the weaker electron donor, and resonance between the −C=C−OH and =C−C=O$^+$H structures is less favorable. This is also confirmed by the calculated number of π-electrons localized within the exocyclic fragment of the spacer (Table 6). In the case of a lack of π-electron density redistribution, the NH tautomers of 1−10 should have 3 π-electrons, and the OH tautomers should have 4 π-electrons within this fragment. Hence, the π-charges within the exocyclic C−C=O fragment in the NH tautomers are negative and range from −0.22 for 2NH up to −0.68 for 4NH. In the case of OH tautomers, the π-charge of this fragment is positive. However, the range of its variation is smaller (from 0.07 for 2OH up to 0.31 for 3OH). One can ascertain from the data listed in Table 6 that a higher absolute value of the π-charge within the exocyclic fragment of the spacer is accompanied by a higher degree of bond length redistribution within this fragment.

This result demonstrates that the properties of the resonant spacer and, thus, the properties of the intramolecular hydrogen bonds in molecules 1−10 are controlled by the π-electron-donating or -withdrawing properties of the heterocycle. The results of our calculations demonstrate one more interesting feature of molecules 1−10. We have found that the π-charges within the exocyclic part of the resonant spacer in the NH and OH tautomers of this set of molecules are interrelated. It is clear from the data plotted in Figure 6 that, if a molecule has a large negative charge on the exocyclic part of the resonant spacer in the NH tautomer, it will have a small positive charge on this fragment in the OH tautomer and vice versa. The π-charge on the exocyclic COO fragment reflects the π-donor/acceptor properties of the heterocyclic moiety. Therefore, we can conclude that, in the set of molecules 1−10, the heterocycle acts as a strong donor (or acceptor) of π-electrons in either the NH or the OH tautomer but not in both forms. Since it was suggested above that the hydrogen bonds in molecules 1−10 are resonance-assisted and that their strength depends on the

CHART 5



π-charge on the exocyclic part of the spacer, we can conclude that the key factor that allows for the formation of strongest hydrogen bonds in the less stable tautomers is the electronic nature of the heterocycle.

Conclusions

A computational study of the set of heterocyclic enaminone−iminoenol systems demonstrates that the relative stability of tautomers varies in a wide range, favoring either the NH or the OH forms. It was found that the key factor determining the tautomeric equilibrium is the heterocycle aromaticity. The change in aromaticity of the heterocycle provides the main contribution to the relative energy of the tautomers. Some additional contribution is provided by the properties of the intramolecular H-bond and the resonant spacer between the proton donor and acceptor atoms. On the other hand, it was demonstrated that the hydrogen bonds in the studied systems are resonance-assisted. Their strength depends on the efficiency of resonance in the spacer, which in turn is controlled by the π-donating/accepting properties of the heterocycle. Hence, we can make the conclusion that the aromaticity of the heterocycle influences the properties of the intramolecular H-bond through the resonance in the spacer.

The nature of the heterocyclic moiety in molecules 1−10, its aromaticity, the strength of the intramolecular hydrogen bond, the degree of delocalization, and the acceptor spacer are closely related. The mechanism of such interplay can be illustrated by Chart 5. With the heterocycle in enaminone form I possessing N π-electrons within the heterocycle, it will consequently have $(N - 1)$ π-electrons in iminoenol form II. With the iminoenol II form being more aromatic, it exhibits greater stability. In such a case, it is favorable for enaminone form I to lose one π-electron and to convert itself into zwitterionic form III, giving rise to resonance assistance of hydrogen bonding. It is clear that for these conditions zwitterionic form IV will be unfavorable and that the hydrogen bond in the more stable tautomeric form will be weaker. Thus, molecules 1−10 during intramolecular proton transfer will transform either from structure I to structure IV or from structure II to structure III, depending on which form of the heterocycle containing N or $(N - 1)$ π-electrons is more aromatic.

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Supporting Information Available: Calculated total electronic and zero-point vibration energies (Tables S1 and S2), and optimized geometries of all molecules discussed in the paper (MOL). This material is available free of charge via the Internet at http://pubs.acs.org.

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