Homonuclear versus Heteronuclear Resonance-Assisted Hydrogen Bonds: Tautomerism, Aromaticity, and Intramolecular Hydrogen Bonding in Heterocyclic Systems with Different Exocyclic Proton Donor/Acceptor

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Tautomerism and resonance-assisted hydrogen bonding have been analyzed on the basis of the results of ab initio calculations at the MP2/AUG-cc-pVDZ level of theory for the series of molecules containing different heterocycles connected with resonance spacer and containing different exocyclic proton donor/acceptor atoms. It is demonstrated that the position of tautomeric equilibrium is controlled mainly by two factors: aromaticity of heterocycle, which could be different for two tautomers, and relative proton affinities of two heteroatoms forming a hydrogen bond. Replacement of exocyclic proton donor/acceptor atom results in change of an aromaticity degree of heterocycle leading to alteration of relative stability of tautomers. Comparison of structure and properties of *E* and *Z* conformers of molecules demonstrates resonance-assisted character of intramolecular hydrogen bond. Application of the NBO theory reveals that the π-component of the electron density within resonant spacer plays the primary role for determination of characteristics of hydrogen bond while σ-skeleton only reflects the π-polarization. An analysis of strength of intramolecular hydrogen bond using geometrical, energetic, and AIM and NBO parameters indicates that the homonuclear N···H−N hydrogen bond is considerably weaker than heteronuclear N···H−O and N···H−S hydrogen bonds in the case of the XH tautomers.

Introduction

Hydrogen bonding plays an important role in modern chemistry, biology, and material science.[1] This especially concerns the chemistry of heterocyclic compounds because of the ability of heteroatoms to serve as very efficient proton donating/accepting sites. Formation of hydrogen bonds very often is responsible for stabilization of particular conformers and tautomers of heterocyclic systems.[2] The most significant influence on structure, energetic characteristics, and reactivity of heterocyclic compounds is observed in the case of strong intramolecular hydrogen bonds. Formation of such H-bonds usually results in significant polarization of molecule. This creates conditions for intramolecular proton transfer leading to tautomeric transitions. Therefore, investigation of nature and strength of intramolecular hydrogen bonds is a subject of numerous experimental and theoretical studies (for reviews, see refs 3−5).

It is worth mentioning that "classic" weak, moderate, and even strong hydrogen bonds have predominantly electrostatic nature.[1,6,7] On the other hand, it is generally believed that very strong hydrogen bonds possess a substantial covalence degree.[8−12] Gilli at al.[13,14] introduced the electrostatic-covalent hydrogen bond model (ECHBM), which states that weak hydrogen bonds have electrostatic nature but become increasingly covalent with increasing strength and very short H-bonds represent in principle three-center-four-electron covalent bonds. Therefore, taking into consideration dual electrostatic and covalent nature of the H-bonds, it is possible to assume three feasible ways to increase their strength: addition of an electron to the hydrogen-bonded bridge, its removal, or π-electron delocalization.[15] The first two methods lead to formation of so-called negative (or positive) charge-assisted hydrogen bonds (±CAHB). These H-bonds are formed in systems having positively charged proton donor (PD) or negatively charged proton acceptor (PA). In the case of resonance-assisted hydrogen bonds (RAHB), the PD and PA atoms are linked by the set of conjugated single and double bonds. Because of resonance within this spacer, proton donor and acceptor atoms acquire partial opposite charges and thus strengthening of H-bond occurs.

According to ECHBM, because of partially covalent character of strong hydrogen bonds the strongest H-bonds must be homonuclear (X−H···X) and symmetrical at both sides of the H-bond. Only in this situation two wave functions corresponding to X−H···X and X···H−X resonance forms are isoenergetic and can mix to a greater extent.[13,16,17] This argumentation was introduced to explain the fact that the strongest hydrogen bonds are formed most commonly between the same (or very close elements) of the periodic table. The most typical cases of CAHB are strong hydrogen bonds found between carboxylic acids and carboxylates, inorganic oxoacids and their conjugated bases, and very short intramolecular H-bond in hydrogen maleate.[18−20] The most well established cases of RAHB include inter- and intramolecular H-bonds in β-diketone enols and β-enaminones.[21−24]

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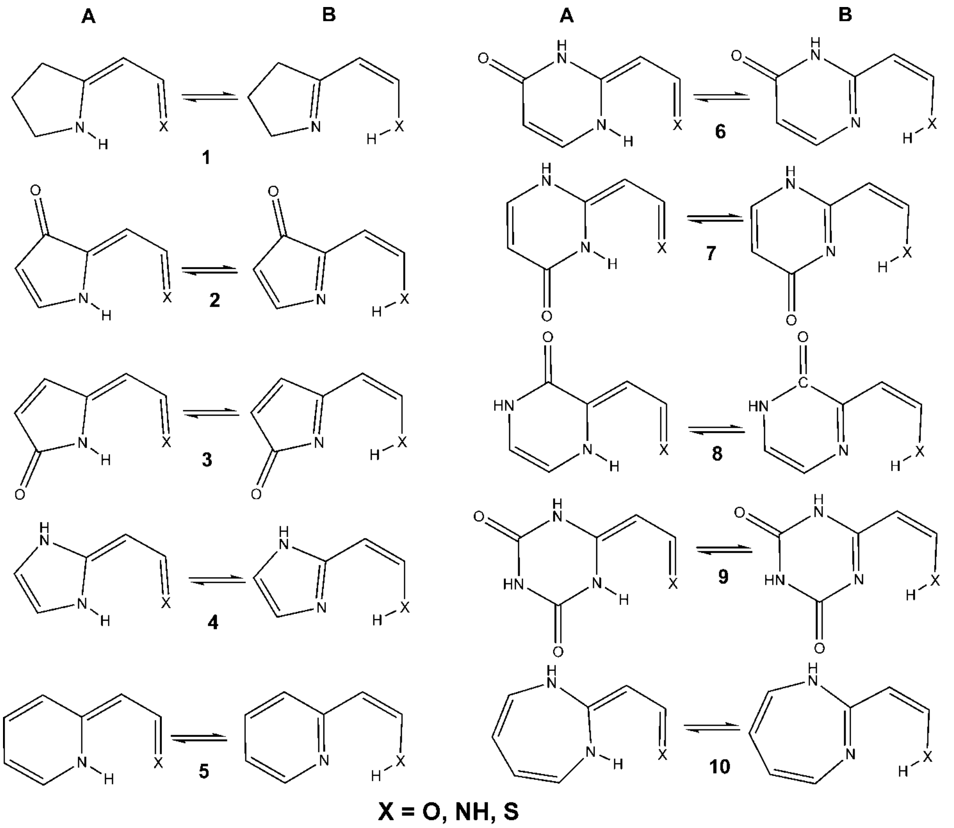
CHART 1



Therefore, investigations of systems with strong intramolecular resonance-assisted hydrogen bonds usually are limited to the oxygen- and nitrogen-containing molecules. However, it was demonstrated on the basis of structural data that hydrogen bonds in monothio-β-diketones possess similar features, as for oxygen analogues, and therefore could also be considered as RAHB.[25] An estimated O−H···S hydrogen bond strength in thiomalonealdehyde is also very close to that for malonaldehyde.[26−28] A high-level computational study of dimethylsulfide methanol and dimethylether methanol complexes also demonstrated that sulfur is nearly as capable as oxygen to act as a hydrogen bond acceptor. It was even suggested that in some cases the O−H···S bonds could be stronger than the O−H···O.[29] On the other hand, it has been generally believed for years that hydrogen bonds involving sulfur found, for example, in proteins are weak in nature.[30] Therefore, it is interesting to investigate hydrogen bonds involving a sulfur atom within the series of molecules with variable H-bond strengths.

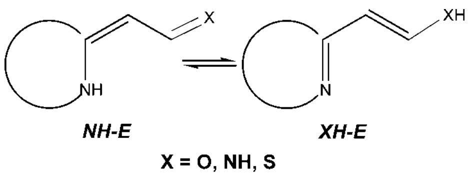
Recent analysis of mechanisms of heterocycle aromaticity effect on intramolecular RAHB in enaminone/iminoenol systems[31] (Chart 1, X = O) revealed that increase of hydrogen bond strength was observed in the case of enhancement of contribution from zwitterionic resonant structures into total structure of molecule. It was demonstrated that this contribution is mainly regulated by the aromaticity degree of the heterocycle. However, taking into account close relations between aromaticity of heterocycle and delocalization within conjugated spacer, it is possible to assume that in such systems not only the characteristics of heterocycle can influence the properties of hydrogen bonds, but also the type of heteroatom located on another side of the spacer affects these properties. Moreover, if the proton donor/acceptor atom is a part of the heterocyclic system, this provides additional possibilities for regulation of strength of intramolecular hydrogen bonds. Involvement of the heteroatom in conjugation interactions within the heterocycle allows changing its proton affinity, leading to change of characteristics of the H-bond.[32,33] Therefore, it is possible to suggest that under some conditions heteronuclear hydrogen bonds may become stronger than homonuclear bonds.

Thus, the main aim of the present work is twofold. First is to establish the possible effect on the properties of heterocycle resulting from the change of exocyclic PD/PA atom. Taking into account close relations between relative stability of tautomers, change of aromaticity of heterocycle on the one hand, and delocalization degree within resonant spacer and characteristics of RAHB on the other hand,[31] one could expect that alteration of character of exocyclic donor/acceptor group may lead to considerable changes of properties of such heterocyclic systems. The second focus of this work is to establish the properties of RAHB formed by different pairs of heteroatoms in the presence of a heterocycle, which has an effect on delocalization within the spacer and thus controls RAHB formation. Special attention is paid to comparison of characteristics of homonuclear and heteronuclear resonance-assisted hydrogen bonds.

Computational Details

The computational study of molecules **1−10** presented in Charts 1 and 2 with X = O was previously reported.[31] Therefore, we used the same computational methods for the analogous molecules **1−10** with X = NH and S. The molecular geometries were optimized at the MP2/AUG-cc-pVDZ level of theory. Earlier,[31] it was demonstrated that this level of theory provides accurate enough data on geometrical parameters and relative stability of tautomers of compounds under consideration. The character of the stationary points on the potential energy surface (minimum or transition state) was confirmed by calculation of

CHART 2



the Hessian matrix at the same level of theory within the harmonic approximation. The zero-point vibration energy from these calculations was used for computation of Gibbs free-energy differences at 0 K between the pair of tautomers. All calculations were performed using the Gaussian 03 program.[34]

Two independent approaches for estimation of aromaticity of heterocycles were used on the basis of bond order nonuniformity (structural aromaticity index of Bird,[35,36] SAIB) and the values of shielding of the induced magnetic field (nucleus-independent chemical shift,[37] NICS). There are many geometry-based aromaticity indexes, for example, Bird, Pozharsky, HOMA, and so forth. In general, there is a good correlation among predicted values of these indexes. We used the Bird index because it is based on bond order values instead of bond lengths and its calculation does not require application of some empirical constants that are necessary for calculation of the HOMA index. In the case of SAIB calculations, the Wiberg bond indexes[38] in the natural atomic orbitals basis predicted by the NBO 5.0 program[39] were calculated using the MP2/AUG-cc-pVDZ wave function. NICS values were calculated using the GIAO method[40] for B3LYP/AUG-cc-pVDZ//MP2/AUG-cc-pVDZ wave function at 1 Å above the ring center and the *zz* component of the NICS tensor was used (NICS(1)*zz*).

To estimate the degree of delocalization within the conjugated spacer between the proton donor and acceptor atoms, the I_3 delocalization index[31] defined by the standard SAIB approach was applied:

$$I_3 = 100\left(1 - \frac{V}{V_k}\right) \qquad V = \frac{100}{n}\sqrt{\frac{\sum (N_i - \bar{N})}{n}}$$

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 bond nonuniformity for the real (delocalized) and idealized Kekülе structure with the completely localized single and double bonds.

The total numbers of π-electrons within the fragments of molecules **1**−**10** were estimated using the natural bond orbitals (NBO) theory as a sum of the contributions of natural atomic orbitals (NAOs) centered on the atoms of the considered fragment into π-type natural localized molecular orbitals (NLMOs).[31] One-electron B3LYP/AUG-cc-pVDZ//MP2/AUG-cc-pVDZ wave function was used for this analysis to obtain strictly integer occupations of molecular orbitals.

Results and Discussion

Relative Stability of Tautomers. Recently, it was demonstrated[31] that, in the case of molecules **1**−**10** with X = O, the difference in aromaticity of the heterocycle in NH and XH tautomers represents the main factor governing relative stability of tautomers. A comparison of the chemical formulas of molecules **1**−**10** presented at Chart 1 clearly indicates that the heterocycle has different electronic structures in the NH and XH tautomers. In all compounds under consideration, the formal number of π-electrons within the heterocyclic ring decreases by one because of tautomeric transition from the NH to the XH tautomer. 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, a total of three π-electrons that formally and exclusively belong to the cyclic conjugated system of the heterocycle. In the XH tautomer, only two such electrons remain on the endocyclic N=C bond. Therefore, tautomeric transition between NH and XH tautomers results in a change of aromaticity of the heterocycle.

TABLE 1: Relative Stability of NH Tautomer with Respect to XH (ΔG°(NH), kcal/mol) and with Respect to Relative Stability of NH Tautomer in Molecule 1 (ΔΔG°(NH), kcal/mol) for Molecules 1−10

	X = O[a]		X = NH		X = S	
	ΔG° (NH)	ΔΔG° (NH)	ΔG° (NH)	ΔΔG° (NH)	ΔG° (NH)	ΔΔG° (NH)
1	−3.27		3.36		−5.62	
2	−10.55	−7.28	−4.11	−7.48	−11.06	−5.45
3	−13.32	−10.05	−6.69	−10.06	−14.62	−9.01
4	7.00	10.27	15.15	11.78	3.75	9.36
5	4.75	8.02	11.44	8.07	1.12	6.74
6	0.79	4.06	8.14	4.77	−1.46	4.16
7	−2.95	0.32	4.37	1.01	−4.93	0.69
8	1.44	4.71	7.25	3.89	−1.74	3.88
9	−3.06	0.21	4.57	1.21	−4.41	1.21
10	−3.47	−0.20	3.12	−0.24	−5.27	0.35

[a] Data from ref 31.

According to the formal number of π-electrons within the heterocyclic ring and on the basis of the classical Hückel's rule, molecules **2**−**10** can be divided into several groups. In the case of molecules **2** and **3**, there are six π-electrons within the ring in the NH tautomer and five π-electrons in the XH tautomer. Therefore, one can expect aromatic stabilization of the former tautomer. In molecules **4** and **5**, an opposite trend should be observed. The NH tautomer has seven π-electrons and thus might be regarded as nonaromatic, while aromatic stabilization is possible in the XH tautomer having six π-electrons. According to Hückel rule, the NH tautomer of molecules **6**−**8** should possess an antiaromatic nature, and thus nonaromatic XH tautomer having seven π-electrons should be more favorable. An opposite situation is observed for molecules **9** and **10**, which have a nonaromatic NH tautomer with nine π-electrons and an antiaromatic XH tautomer with eight π-electrons. Therefore, on the basis of the formal π-electron numbers one can expect a wide range of aromaticity variation within the set of considered molecules **2**−**10**.

It is very convenient to use compound **1** as a reference point for the analysis of relative stability of tautomers since it does not contain a cyclic conjugated system within the heterocycle. Therefore, the relative stability of its tautomers is determined mainly by intrinsic properties of the N−C−C−C−X fragment and the natural proton affinities of PD and PA atoms.

Recently,[31] for the enaminone/iminoenol pair of tautomers (X = O), it was demonstrated that the NH tautomer is more stable than XH by more than 3 kcal/mol (Table 1). This fact agrees well with known experimental and theoretical results for simple enaminones. In the case of the enaminthione/iminothienol system (X = S), the difference in relative stability is even larger. This finding also reflects a lower proton affinity of the sulfur atom, as compared to that of oxygen. For example, according to quantum-chemical calculations of thiomalonaldehyde[26] at the G2(MP2) level of theory, the tautomer containing the O−H···S hydrogen bond is more stable, by 0.2 kcal/mol. On the basis of the proton affinities, one can expect that, in the case of X = N,

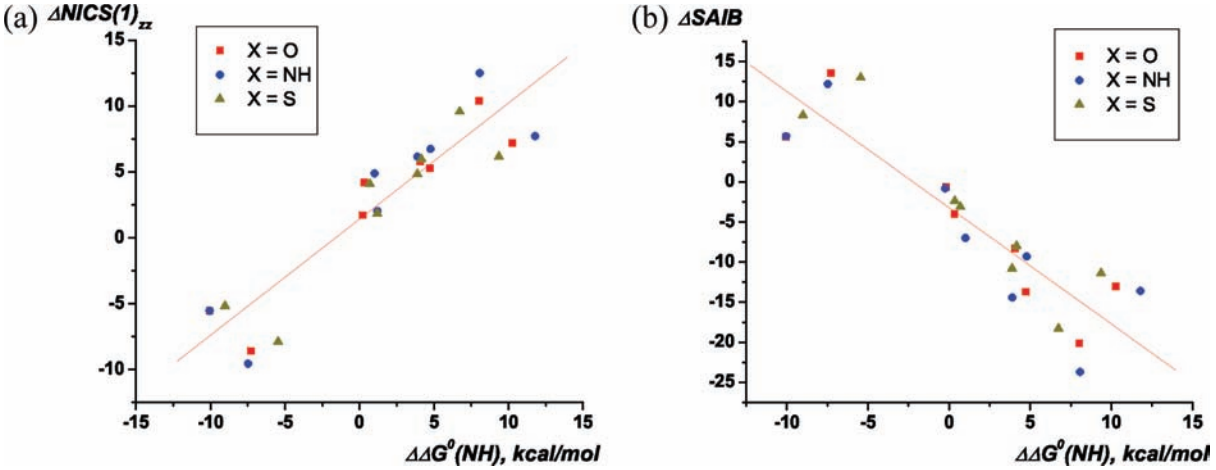


Figure 1. Dependence of relative stability of tautomers of molecules **2**−**10** from the variation of NICS (a) and SAIB (b) aromaticity indexes.

the stabilities of two tautomers of **1** should be very close. However, the calculation results demonstrate that the XH tautomer of this molecule containing an exocyclic amino group is considerably more stable (Table 1). Therefore, it is possible to conclude that proton affinities of cyclic and exocyclic nitrogen atoms are considerably different despite the absence of a cyclic conjugated system within the heterocycle. It should also be noted that the energy difference between NH and XH tautomers is also determined by differences in energy of chemical bonds, namely, the N−C and C═X in the NH tautomer and N═C and C═X in the XH form.

A difference in intrinsic properties of endocyclic and exocyclic nitrogen atoms should be taken into account for analysis of the influence of the conjugated system of the heterocycle on characteristics of compounds **2**−**10**. The values of relative energy of tautomers (Table 1) contain two main contributions derived from the difference in properties of the nitrogen atom in two tautomers and from conjugation within the heterocycle. The contribution of each type of heterocycle into stabilization of either the NH or XH tautomer can be estimated using the $\Delta\Delta G°$(NH) values (Table 1). These values provide the difference in relative stability of tautomers of a molecule with a particular heterocycle and relative stability of tautomers in molecule **1**. In this case, change of relative stability of tautomers reflects only effect introduced by the cyclic conjugated system of the heterocycle because the influence of different energies of chemical bonds is the same for all compounds under consideration. Regardless the significant differences in the $\Delta G°$(NH) values for three sets of molecules, the $\Delta\Delta G°$(NH) values are rather similar despite the nature of the exocyclic heteroatom (Table 1). In particular, a presence of formally aromatic heterocycles in the NH tautomers of molecules **2** and **3** results in significant stabilization of these tautomers (by 5.5−10.0 kcal/mol), as compared to **1**. An opposite situation is observed for molecules **4** and **5** where an aromatic heterocycle is formed in the XH tautomer, providing stabilization by 6.8−11.8 kcal/mol. Stabilization of the XH tautomer in compounds **6**−**8** is caused by existence of a formally antiaromatic cyclic conjugated system in the NH tautomer. Small effects of the conjugated system of the heterocycle on relative stability of tautomers of molecules **9** and **10** result from rather small changes of π-electron density within the heterocycle as discussed earlier.[31] Thus, the replacement of the heteroatom involved into the intramolecular hydrogen bond does not change qualitatively the previously reported[31] general trend of heterocycle effect on the relative stability of tautomers.

However, a more detailed analysis of the $\Delta\Delta G°$ values reveals the effect of exocyclic proton donor/acceptor on the relative stability of tautomers. This effect is most pronounced for molecules **2**−**5** where influence of the heterocycle on relative stability is the most vital. The values of $\Delta\Delta G°$ in these molecules are reduced in the series X = NH > O > S. Therefore, one can conclude that there is an inter-relation between heterocycle effect on the relative stability of tautomers and exocyclic substituent effect.

The heterocycle effect on the relative stability, as noted above, is provided mainly because of its different aromaticity in two tautomeric forms. This is also confirmed by correlation between relative stability of the NH tautomer and differences in aromaticity indexes of two tautomers (Figure 1). The correlations are almost the same regardless of the type of heteroatom. However, again, the range of variation of aromaticity indexes is the smallest in the case of X = S. This may indicate that the discussed above exocyclic heteroatom effect on the relative stability of tautomers is provided through its influence on aromaticity of the heterocycle.

An influence of exocyclic proton donor/acceptor on conjugation and aromaticity within heterocycle can be estimated on the basis of the formal number of π-electrons within the cyclic conjugated system as suggested earlier.[31] Analysis of these data reveals that the number of π-electrons within the heterocycle is systematically reduced in the series of compounds with X = N > O > S (Table 2). It should be noted that the same situation is observed for both tautomers. Taking into account the character of exocyclic C═X/C−XH groups, one can conclude that π-electron-withdrawal properties are decreased in the series C═S > C═O > C═N in NH tautomers and electron-donating properties are increased in the series $C-NH_2 \geq C-OH > C-SH$ in XH tautomers. A change of π-electron-donating/withdrawal properties of exocyclic fragment results in corresponding variations of aromaticity degree of conjugated system of the heterocycle. The presence of the strongest electron acceptor (the C═S group) in the NH tautomer or the weakest electron donor (the C−SH group) in the XH tautomer leads to decrease of aromaticity degree in molecules where heterocycle formally contains six and nine π-electrons and increase of heterocycle aromaticity in molecules with formally seven and eight π-electrons in the cyclic conjugated system (Table 2).

According to these data, one could make a somewhat controversial conclusion that the sulfur atom is effectively more electronegative compared to the oxygen and nitrogen atoms. Probably, this fact could be explained on the basis of the "resonance-induced electronegativity" concept proposed by Allen et al.[41] for thioamide fragments. It was demonstrated that the $R_1R_2C{=}S$ group is an effective proton acceptor only when

TABLE 2: Calculated Number of π-Electrons within the Heterocycle (Nπ), NICS(1)*zz* Values, and SAIB Aromaticity Indexes for Molecules 1−10

	X = O[a]			X = N			X = S		
	Nπ	NICS(1)*zz*	SAIB	Nπ	NICS(1)*zz*	SAIB	Nπ	NICS(1)*zz*	SAIB
				NH Tautomer					
1	2.49			2.53			2.43		
2	5.41	2.6	37.8	5.46	2.2	40.1	5.39	3.6	36.2
3	5.32	−3.2	29.4	5.36	−3.4	30.9	5.31	−2.0	30.8
4	6.31	−20.7	53.3	6.34	−20.0	52.6	6.26	−22.3	57.0
5	6.39	−12.9	68.3	6.46	−10.3	64.3	6.35	−14.7	71.2
6	6.96	−1.1	45.0	7.00	−0.3	45.4	6.92	−1.5	45.1
7	7.01	−0.3	42.1	7.06	0.4	42.8	6.98	−0.8	43.0
8	7.08	−4.5	45.0	7.13	−3.6	44.2	7.03	−4.9	48.3
9	7.53	1.5		7.57	1.7		7.51	1.6	
10	8.46		30.7	8.53		31.8	8.42		30.5
				XH Tautomer					
1	2.14			2.15			2.09		
2	4.95	11.9	24.2	4.99	11.8	27.9	4.92	11.5	23.3
3	4.94	2.3	23.8	4.96	2.2	25.2	4.92	3.2	22.5
4	6.07	−27.9	66.3	6.07	−27.7	66.2	6.03	−28.5	68.4
5	6.12	−23.3	88.4	6.13	−22.8	88.0	6.08	−24.2	89.5
6	6.65	−6.9	53.3	6.66	−7.0	54.6	6.62	−7.5	53.1
7	6.71	−4.5	46.1	6.71	−4.5	49.8	6.67	−4.9	46.1
8	6.68	−9.8	58.7	6.70	−9.7	58.6	6.64	−9.7	59.1
9	7.21	−0.2	56.6	7.21	−0.3	57.3	7.17	−0.2	52.9
10	8.14		31.3	8.15		32.6	8.10		32.9

[a] Data from ref 31.

R_1 and R_2 can form an extended delocalized system with C═S. As a result, resonance-induced electronegativity of the C═S in thioamides could be even higher than electronegativity of ketonic C═O in $(C_{sp3})_2C{=}O$.

Thus, in agreement with the previous data the main factor governing relative stability of tautomers in heterocyclic systems with resonance-assisted hydrogen bond is the difference in aromaticity of the conjugated system of the heterocycle. However, the degree of influence of this factor may be tuned by adjustment of character of exocyclic proton donor/acceptor atom. Generally, a replacement of the exocyclic heteroatom leads to variations of aromaticity degree of the heterocycle.

Resonance-Assisted Hydrogen Bonding. Although the concept of RAHB was introduced about 20 years ago,[42] it is still under debate. Originally, a positive synergism between hydrogen bonding and π-delocalization within the spacer was assumed.[42,43] However, a recent computational study of the series of different enols of β-diketones and their nitrogen counterparts,[21] *N*-formylformimidic acid, *N*-(hydroxymethyl)formamide, and related compounds,[44] containing both saturated and unsaturated spacers led its authors to the conclusion that stronger hydrogen bonds formed in the case of an unsaturated spacer are the consequence of the σ-skeleton structure that keeps PD and PA atoms coplanar and close to each other. A comprehensive analysis of electron density distribution in malonaldehyde under nonequilibrium conditions (varied donor, acceptor distance) leads to the conclusion that π-electron density redistribution within the spacer is only reaction to the hydrogen bond formation.[45] Since the H-bond is inherently a σ-type interaction, the π-electron framework serves as a spectator to H-bond formation. However, these conclusions were built on the basis of analysis of a series of molecular structures perturbed by σ-type effects: saturation of the spacer and/or constraining donor−acceptor distance. From this point of view, it is interesting to investigate resonance-assisted hydrogen bonding in the group of molecules **1−10**, in which heterocycle clearly provides π-type perturbation to the H-bond.

The first postulate of the RAHB model is that hydrogen bond strength depends on the resonance degree within the spacer. This effect for molecules **1−10** can be readily established from the correlation between delocalization index I_3 calculated for three exocyclic bonds of the spacer and proton donor−acceptor distance (Figure 2). It should be noted here that molecules containing different exocylic PD/PA atoms show different delocalization degree within the spacer. This can be explained by different π-electron donating/accepting strengths of heteroatoms, as discussed above. Another reason can be the difference(s) in polarizability of the conjugated system containing different heteroatoms.

In molecules **1−10**, a heterocycle acts as an external to the hydrogen bond factor influencing the resonance within the spacer. It was demonstrated above that different heterocycles possess different aromaticities, which depend on the number of π-electrons within the ring. This provides the variation of π-electron donating/accepting properties of heterocycles within the set of molecules **1−10**. The correlation of delocalization degree within the spacer and π-charge of this fragment calculated within the NBO framework (Figure 3) provides the evidence for the fact that resonance and thereby hydrogen bonding is also related to π-electron donating/accepting properties of the heterocycle. In the case of both NH (having negative Q_π within the spacer) and XH (positive Q_π) tautomers, the delocalization degree is reduced while absolute values of π-charges converge to zero.

Finally, to dismiss any doubts about which subsystem σ or π plays the primary role in RAHB systems we also calculated σ-charges within the spacer (Figure 4). Regardless of the type of heterocycle and exocyclic PD/PA atom, the absolute value of σ-charges is several times smaller than corresponding π-charges and always has an opposite sign. This fact provides the evidence that π-charge redistribution within the spacer is the dominant effect. Most likely, that σ-framework adjusts its polarization to compensate up to some degree this π-charge redistribution.

On the other hand, the RAHB concept implies that hydrogen bonding increases resonance degree within the spacer. To prove this assumption for molecules **1−10**, we calculated a series of *E* conformers containing the same set of heterocycles (Chart 2). These molecules do not contain hydrogen bonds. Therefore, the changes in molecular structure between *E* and *Z* conformers can be associated mainly with hydrogen bond effects. The delocalization indexes I_3 for both *Z* and *E* conformers are listed in the Table 3. It is clearly seen from these data that for all molecules and both NH and XH tautomers the delocalization is weaker in *E* conformers. Therefore, it is possible to conclude that formation of the hydrogen bonds in molecules **1−10** supports resonance within the spacer.

A comparison of relative stabilities of tautomers for *Z* and *E* conformers also provides the evidence for hydrogen bond effect on the relative stability of tautomers. One can conclude from the $\Delta\Delta G°$(NH) values for *Z* (Table 1) and *E* conformers (Table 4) that in the case of *E* conformers the values of relative energy of tautomers exhibit a much wider range of variation. Similarly to the set of *Z* conformers, $\Delta\Delta G°_E$(NH) values are rather close for molecules having the same heterocycle with different exocyclic PD/PA atoms. It was demonstrated earlier[31] that the spacer can act as a soft buffer that influences heterocycle aromaticity. A polarization of the spacer can change the number of π-electrons within the less aromatic form of the heterocycle leading to its stabilization and decrease in the difference in energy between tautomers. Therefore, one can conclude that the hydrogen bond effect on relative stability of tautomers is

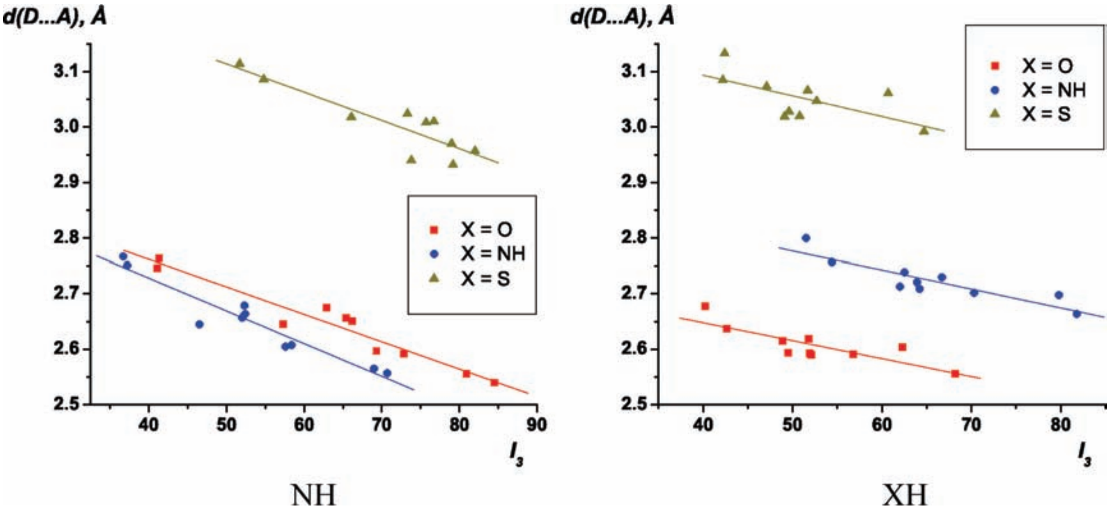


Figure 2. Correlation between spacer delocalization index I_3 and proton donor–acceptor distance for NH and XH tautomers of molecules **1**–**10**.

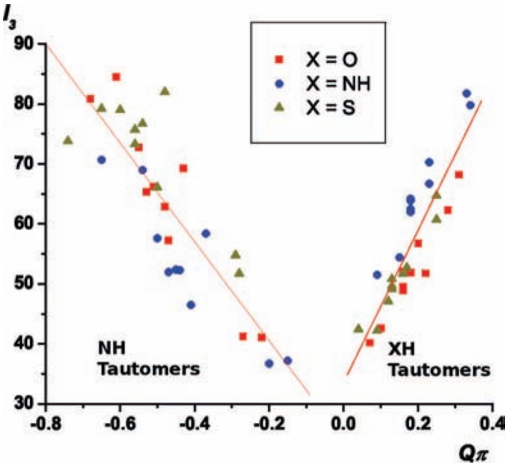


Figure 3. Dependence of the π-charges on the delocalization within the spacer.

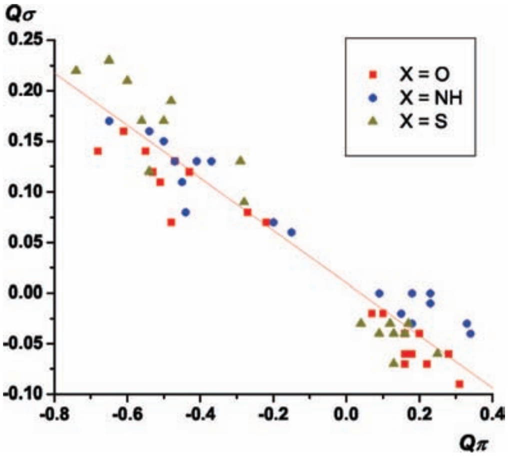


Figure 4. Correlation between σ- and π-charges within the spacer.

provided because of the resonance within the spacer, enhanced as the result of RAHB formation.

It is interesting to compare the strength of intramolecular hydrogen bonds formed in molecules **1**–**10** containing different combinations of heterocycles. The intramolecular hydrogen bond energy cannot be measured (or calculated) in a direct way as a difference between the energies of the complex and of the isolated molecules like in the case of intermolecular hydrogen bonds. Therefore, there are a number of approaches for estimation and/or comparison of the strength of such bonds based on geometrical criteria, electron density distribution parameters, orbital analysis, spectral properties, and so forth.

TABLE 3: Delocalization Indexes I_3 Calculated for the Exocyclic Part of the Spacer for *Z* and *E* Conformers of Molecules 1–10

	Z			*E*		
	X = O	X = NH	X = S	X = O	X = NH	X = S
			NH			
1	62.9	52.3	76.7	43.5	35.1	54.2
2	41.1	37.2	54.8	32.9	30.8	45.0
3	41.3	36.7	51.7	34.9	32.2	45.4
4	80.9	70.7	73.8	60.0	48.2	70.5
5	84.5	69.0	79.2	53.5	43.9	65.7
6	72.8	57.6	79.0	48.4	39.5	58.8
7	65.4	52.0	73.3	47.2	38.7	57.7
8	69.3	58.4	82.0	43.2	36.8	56.7
9	57.3	46.5	66.1	41.7	35.0	51.5
10	66.2	52.4	75.7	47.5	39.0	57.9
			XH			
1	49.5	62.0	49.1	29.6	44.1	34.4
2	62.3	79.8	60.7	39.4	61.4	44.5
3	68.2	81.8	64.7	40.3	63.8	44.3
4	40.2	51.5	42.4	28.1	40.0	34.6
5	42.6	54.4	42.2	28.7	42.0	34.0
6	48.9	62.5	47.1	32.5	49.3	36.7
7	51.9	64.2	49.6	31.9	48.5	35.6
8	51.8	66.7	51.7	34.4	51.1	39.4
9	56.8	70.3	52.7	36.2	57.4	39.3
10	52.1	63.9	50.8	31.2	47.1	36.0

The calculated geometrical parameters of the hydrogen bonds in molecules **1**–**10** are listed in Table 5. It is clearly seen that the characteristics of H-bonds depend on both the type of heterocycle and the nature of PA and PD atoms. It should be noted here that geometrical parameters of hydrogen bonds involving different heteroatoms should always be compared with care because of the differences in van der Waals radii of heteroatoms and optimal values of the C–X–H and C–X–Lp angles (Lp denotes position of hydrogen-accepting lone pair). Nevertheless, on the basis of the values of the H···X distances and the D–H···X angles it is possible to assume that the strength of the N–H···N hydrogen bonds in the NH tautomer is slightly greater as compared to that of the N–H···O bonds. This assumption is because both geometrical parameters of these

TABLE 4: Relative Stability of NH Tautomer with Respect to XH ($\Delta G°_E$(NH), kcal/mol) and with Respect to Relative Stability of the NH Tautomer in Molecule 1 ($\Delta\Delta G°_E$(NH), kcal/mol) for *E* Conformers, and Relative Stability of *E* and *Z* Conformers of Molecules 1−10 (MP2/AUG-cc-pVDZ)

	$\Delta G°_E$(NH)	$\Delta\Delta G°_E$(NH)	$\Delta G°_{E-Z}$(NH)	$\Delta G°_{E-Z}$(XH)
		X = O		
1	−7.06		−7.48	−11.27
2	−14.81	−7.76	−5.47	−9.73
3	−21.14	−14.08	−3.68	−11.50
4	9.27	16.33	−12.05	−9.79
5	9.83	16.89	−13.38	−8.30
6	2.30	9.36	−11.04	−9.53
7	−6.66	0.40	−7.58	−11.29
8	4.26	11.32	−11.43	−8.60
9	−5.48	1.57	−7.72	−10.14
10	−6.51	0.55	−8.04	−11.08
		X = NH		
1	3.54		−7.61	−7.43
2	−5.42	−8.97	−6.11	−7.42
3	−10.83	−14.37	−4.09	−8.23
4	22.19	18.64	−13.33	−6.28
5	20.76	17.22	−14.13	−4.80
6	14.40	10.86	−11.87	−5.61
7	5.21	1.66	−7.98	−7.14
8	14.10	10.55	−12.36	−5.51
9	6.86	3.32	−8.41	−6.12
10	4.81	1.26	−8.64	−6.95
		X = S		
1	−2.41		−8.51	−5.30
2	−10.91	−8.49	−5.05	−4.89
3	−17.39	−14.98	−3.03	−5.80
4	13.23	15.64	−14.05	−4.57
5	13.33	15.74	−14.64	−2.44
6	6.47	8.88	−11.15	−3.22
7	−2.43	−0.02	−7.22	−4.72
8	8.07	10.48	−12.34	−2.53
9	−1.30	1.11	−6.84	−3.73
10	−1.93	0.48	−8.10	−4.76

hydrogen bonds in molecules **1**−**10** and van der Waals radii of the nitrogen and oxygen atoms are very close (1.52 and 1.55 Å, respectively[46]). At the same time, in the XH tautomer the N−H···N hydrogen bonds seem to be weaker than the O−H···N bonds. This contradicts the assumptions of the ECHBM,[13,16] which states that homonuclear hydrogen bonds are intrinsically stronger than heteronuclear H-bonds.

The energy of the intramolecular RAHBs can also be estimated by comparing the energy of *Z* and *E* conformers (Table 4). However, it should be noted that this energy contains not only the "hydrogen bonding" term due to direct interaction between PA and PD groups through the hydrogen bond, but also the "resonance energy" component within the spacer. It was demonstrated above that the resonance degree is noticeably different in *Z* and *E* forms. Therefore, the resonance term probably provides an essential contribution and thus resulting energy difference cannot be regarded as pure "hydrogen bond" energy. On the other hand, in the case of the RAHB resonance and hydrogen bonding energy could not be separated in any direct way. On the basis of $\Delta G°_{E-Z}$ values, it is also possible to conclude that in the NH tautomer the N−H···O hydrogen bonds are somewhat weaker that the N−H···N bonds, regardless of the heterocycle type. In the XH tautomers of molecules **1**−**10**, N−H···N bonds are weaker than those of O−H···N. Thus, the strength of the N−H···O and N−H···N hydrogen bonds predicted by the $\Delta G°_{E-Z}$ values agrees with their geometrical parameters.

It is interesting to note that the hydrogen bonds involving a sulfur atom as proton acceptor show more pronounced dependence on the heterocycle type than the N−H···O and the N−H···N bonds. In the case of the weakest N−H···S hydrogen bonds formed in molecules **2** and **3**, the H-bond energy is lower compared to these molecules with first-row atoms acting as proton acceptors. The strongest H-bond in the NH tautomers according to $\Delta G°_{E-Z}$ values is formed in molecule **5** with X = S. In the XH tautomers, S−H···N hydrogen bonds are the weakest ones regardless of the type of heterocycle.

An electron density distribution analysis was found to be an important tool for exploration of various types of intra- and intermolecular interactions. It was demonstrated that parameters of the A···H (3,−1) bond critical points are connected with the properties of the considered bond. In particular, the values of electron density $\rho(\mathbf{r})$ and Laplacian of electron density $\nabla^2\rho(\mathbf{r})$ at this point correlate with energy of the H-bond.[4,15,47−52] The Laplacian of electron density indicates local charge concentration (negative value) or depletion (positive value), corresponding to the covalent (shared electron) or ionic (closed shell) interactions, respectively. Also, a sign of local electron energy density $H(\mathbf{r})$ at the bond critical point represents an index of the amount of covalency in the chemical interaction.[53,54] Therefore, this value is an important criterion for the hydrogen bond analysis.[8,9,55] It was demonstrated[51] that for weak hydrogen bonds both $\nabla^2\rho(\mathbf{r})$ and $H(\mathbf{r})$ values are positive, for medium H-bonds $H(\mathbf{r})$ values become negative, and in the case of very strong H-bonds both values are negative.

As seen in Table 6, according to the values of electron density at the hydrogen bond critical point, among the NH tautomers the N−H···N hydrogen bonds are the strongest. However, the N−H···S bonds demonstrate a greater covalence degree, as is evident from lower $\nabla^2\rho(\mathbf{r})$ and more negative $H(\mathbf{r})$ values. Within the set of the XH tautomers, the strongest H-bonds are observed in the molecules containing the O−H···N bonds. However, these bonds have the largest positive $\nabla^2\rho(\mathbf{r})$ values and also negative $H(\mathbf{r})$ values. These facts could indicate considerable contribution of both covalent and electrostatic component of H-bonds. The weakest N−H···N bonds have small positive $H(\mathbf{r})$ values, and therefore should be considered as pure electrostatic in nature.

The hydrogen bond interaction could be also expressed in terms of localized orbitals as donor−acceptor interaction.[31] The donor-accepting atom donates electron density from the lone pair to the antibonding orbital of the X−H bond ($n \rightarrow \sigma^*$ interaction). The strength of such an interaction could be estimated in terms of the NBO theory as $E(2)$ second-order orbital interaction energy, which is in proportion to the occupation of donor orbital and to the Fock matrix element between the orbitals, and in the inverse proportion to the energy gap between the orbitals. The values of $E(2)$ and also electron occupation of the antibonding X−H orbitals are listed in the Table 6. According to the $E(2)$ values, the strongest H-bond in the NH tautomers is formed in the case of the sulfur atom being the proton acceptor. This could be caused by the energetic proximity of the lone pair of the sulfur atom and antibonding orbital of the N−H bond. Taking into account the considerable amount of charge transfer through the H-bond in the N−H···S molecules indicated by large occupancy of the σ^*_{NH} orbital (up to 0.16e), it is possible to conclude the essential covalent nature of these bonds. In the XH tautomers, the NBO analysis predicts O−H···N bonds to be somewhat stronger than the S−H···O bonds, while the N−H···N bonds are the weakest.

TABLE 5: Hydrogen Bond Geometrical Parameters (Å, deg) for Molecules 1−10

	X = O[a]			X = NH			X = S		
	D···A	H···A	D−H···A	D···A	H···A	D−H···A	D···A	H···A	D−H···A
				NH Tautomer					
1	2.675	1.912	128.6	2.679	1.907	129.5	3.010	2.172	136.6
2	2.746	2.094	119.9	2.751	2.073	121.8	3.086	2.358	127.4
3	2.764	2.110	120.0	2.767	2.091	121.7	3.114	2.391	127.0
4	2.556	1.704	135.2	2.557	1.689	135.8	2.940	2.046	140.2
5	2.540	1.595	144.7	2.565	1.645	141.9	2.932	1.964	148.8
6	2.592	1.701	140.4	2.605	1.713	139.7	2.970	2.038	146.1
7	2.657	1.806	136.6	2.657	1.800	136.9	3.024	2.123	143.0
8	2.597	1.717	139.2	2.608	1.725	138.8	2.957	2.023	145.9
9	2.646	1.806	135.6	2.645	1.793	136.4	3.018	2.128	142.0
10	2.651	1.752	142.4	2.664	1.766	141.4	3.008	2.067	148.4
				XH Tautomer					
1	2.594	1.677	148.5	2.713	1.925	131.1	3.019	1.774	145.0
2	2.604	1.697	147.6	2.698	1.896	132.5	3.061	1.846	143.1
3	2.556	1.632	148.0	2.664	1.859	132.2	2.992	1.748	144.4
4	2.678	1.785	147.3	2.800	2.025	130.7	3.133	1.932	142.6
5	2.637	1.739	147.6	2.757	2.005	128.4	3.085	1.889	141.7
6	2.615	1.711	147.5	2.739	1.979	128.7	3.073	1.874	141.8
7	2.593	1.681	147.4	2.709	1.943	128.9	3.028	1.807	142.8
8	2.619	1.713	148.0	2.730	1.960	129.7	3.066	1.863	142.2
9	2.591	1.688	146.4	2.702	1.946	128.1	3.047	1.860	140.4
10	2.590	1.668	149.0	2.721	1.945	130.2	3.020	1.776	144.9

[a] Data from ref 31.

TABLE 6: Parameters Describing Hydrogen Bond Strength in Molecules 1−10: Electron Density at (3,−1) Hydrogen Bond Critical Point $\rho(\mathbf{r})$, Laplacian of the Electron Density $\nabla^2\rho(\mathbf{r})$, and Local Electron Energy $H(\mathbf{r})$ at This Point (au), $E(2)$ Energy in Kilocalories per Mole from NBO Analysis, and Occupation of Antibonding Proton-Donor Orbitals $N(\sigma^*)$ (e)

	NH					XH				
	$\rho(\mathbf{r})$	$\nabla^2\rho(\mathbf{r})$	$H(\mathbf{r})$	$E(2)$	$N(\sigma^*_{NH})$	$\rho(\mathbf{r})$	$\nabla^2\rho(\mathbf{r})$	$H(\mathbf{r})$	$E(2)$	$N(\sigma^*_{XH})$
					X = O					
1	0.0319	0.10	−0.0004	12.8	0.04	0.0554	0.14	−0.0081	32.7	0.09
2	0.0223	0.07	−0.0003	5.9	0.03	0.0517	0.14	−0.0059	29.6	0.08
3	0.0217	0.07	−0.0004	5.6	0.03	0.0611	0.14	−0.0123	38.6	0.10
4	0.0498	0.15	−0.0037	29.7	0.07	0.0421	0.12	−0.0015	21.9	0.06
5	0.0641	0.17	−0.0113	44.2	0.10	0.0490	0.13	−0.0043	27.0	0.07
6	0.0497	0.15	−0.0035	30.0	0.07	0.0519	0.14	−0.0059	29.8	0.08
7	0.0393	0.12	−0.0010	20.2	0.06	0.0563	0.14	−0.0087	33.6	0.09
8	0.0479	0.15	−0.0028	27.6	0.07	0.0518	0.14	−0.0058	29.0	0.08
9	0.0391	0.13	−0.0008	20.0	0.05	0.0544	0.14	−0.0074	31.9	0.08
10	0.0441	0.14	−0.0017	24.2	0.06	0.0581	0.14	−0.0098	34.8	0.09
					X = NH					
1	0.0341	0.11	0.0004	16.0	0.06	0.0326	0.10	0.0004	13.1	0.04
2	0.0247	0.08	0.0007	8.5	0.04	0.0339	0.11	0.0004	14.3	0.05
3	0.0240	0.07	0.0006	8.2	0.04	0.0371	0.11	−0.0001	16.8	0.05
4	0.0560	0.14	−0.0080	36.7	0.10	0.0261	0.08	0.0006	9.0	0.03
5	0.0613	0.14	−0.0113	42.1	0.11	0.0285	0.09	0.0004	9.7	0.03
6	0.0521	0.14	−0.0056	33.3	0.09	0.0299	0.09	0.0005	10.8	0.04
7	0.0428	0.12	−0.0016	24.5	0.07	0.0324	0.10	0.0003	12.3	0.04
8	0.0506	0.14	−0.0046	31.0	0.09	0.0312	0.10	0.0004	11.5	0.04
9	0.0434	0.13	−0.0018	25.1	0.07	0.0320	0.10	0.0005	11.9	0.04
10	0.0456	0.13	−0.0024	26.6	0.07	0.0323	0.10	0.0002	12.2	0.04
					X = S					
1	0.0332	0.07	−0.0022	27.5	0.09	0.0479	0.11	−0.0038	26.8	0.09
2	0.0231	0.06	−0.0003	14.0	0.06	0.0400	0.11	−0.0013	20.2	0.07
3	0.0217	0.05	−0.0002	12.5	0.05	0.0499	0.12	−0.0046	29.1	0.09
4	0.0441	0.07	−0.0065	44.7	0.14	0.0334	0.09	−0.0004	15.4	0.05
5	0.0520	0.07	−0.0108	57.2	0.16	0.0382	0.10	−0.0012	18.5	0.06
6	0.0440	0.07	−0.0064	44.8	0.13	0.0390	0.10	−0.0013	19.4	0.07
7	0.0365	0.07	−0.0033	33.3	0.11	0.0453	0.11	−0.0030	24.6	0.08
8	0.0455	0.07	−0.0070	45.9	0.14	0.0403	0.10	−0.0016	19.7	0.07
9	0.0360	0.07	−0.0031	32.7	0.10	0.0398	0.10	−0.0014	19.9	0.06
10	0.0408	0.07	−0.0049	38.5	0.12	0.0487	0.11	−0.0042	27.0	0.09

Summarizing, it is possible to compare hydrogen bond strength predicted by the different methods (Table 7). In general, in XH tautomers the differences in hydrogen bond strength between molecules with different X atoms are much more

TABLE 7: Hydrogen Bond Strength Order according to Different Descriptors

	NH	XH
$\Delta G°_{E-Z}$	S ≈ NH ≈ O	O > NH > S
$\rho(\mathbf{r})$	NH > S > O	O > S > NH
$E(2)$	S > NH > O	O > S > NH
$N(\sigma^*_{XH})$	S > NH > O	O > S > NH
d(H···X)	N > O	O > S > NH

pronounced than in the NH tautomers. Quite possibly, this is the consequence of the known fact that properties of a proton-donating group have more impact on the hydrogen bond parameters than properties of a proton-accepting group.[56,57]

Conclusions

Tautomerism and resonance-assisted hydrogen bonding have been analyzed for the series of molecules containing different heterocycles connected with resonance spacer and containing different exocyclic proton donor/acceptor atoms. These molecules could exist in two tautomeric forms, with hydrogen atom bonded either to the nitrogen atom of the heterocycle or to the exocyclic heteroatom. It was demonstrated that the position of tautomeric equilibrium is controlled mainly by two factors: aromaticity of the heterocycle, which could be different for two tautomers, and relative proton affinities of two heteroatoms forming a H-bond. In particular, the substituent containing thionyl group is more electronegative compared to the substituent containing carbonyl and imino groups. This fact is most probably caused by high "resonance-induced electronegativity" of the sulfur atom. As a result, in the molecules with X = S, the exocyclic heteroatom is the one that provides the greater effect on the properties of the heterocycle. In particular, this results in variations of heterocycle aromaticity leading to change of the relative stability of tautomers.

The hydrogen bonds in the molecules under consideration are proved to be resonance-assisted. In particular, this conclusion comes from the comparison of delocalization in E and Z conformers and also from the analysis of the charge distribution, divided onto σ- and π-components using the NBO technique. These data support existence of resonance assistance in hydrogen bonding, which was a subject of some discussion.[21,32,33,44] It was demonstrated that the π-component of the electron density plays the primary role upon formation of RAHB, while σ-skeleton only reflects the π-polarization.

Intramolecular hydrogen bond strength was estimated on the basis of geometrical, energetic, AIM, and NBO parameters. It is possible to conclude that in the case of the NH tautomers the N−H···O bonds are the weakest, while the N−H···N bonds are the strongest. In the XH tautomers, the homonuclear N−H···N bond appears to be considerably weaker compared to the O−H···N and the S−H···N bonds. Thus, heteronuclear hydrogen bonds may be considerably stronger as compared to homonuclear bonds because of influence of conjugation within the heterocycle on proton affinity of the cyclic nitrogen atom.

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