

Influence of Intermolecular Hydrogen Bonds on the Tautomerism of Pyridine Derivatives

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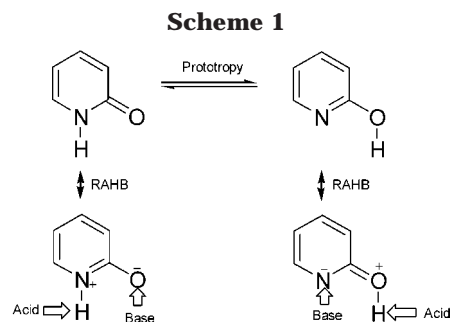
The effect of the dimerization, by hydrogen-bond (HB) complexation, on the tautomerism of 2-hydroxypyridine and a series 2-aminopyridines has been carried using ab initio methods. The results obtained for 2-hydroxypyridine fit satisfactorily with the experimental data and show that the 2-pyridone/2-pyridone homodimer complex is the most stable. For 2-aminopyridines, the effect of the substituent on the amino group has been investigated. For the monomers studied, the most favorable tautomer is the 2H; however, with electronegative substituents, the 1H/1H homodimers are more stable than the corresponding 2H/2H ones. The atom in molecule methodology has been used to characterize the HBs formed. Exponential relationships have been found between the electron density and its laplacian at the HB critical point vs the HB distance.

Introduction

The relationship between tautomeric equilibrium constants and intramolecular hydrogen bonds (IMHB) is well documented.^{1,2} As expected, an IMHB stabilizes the tautomer that presents it in comparison with other tautomers without IMHB. On the other hand, the information about the effect of intermolecular hydrogen bonds on the thermodynamic aspect of tautomerism is scarce. These HBs are of paramount importance in the solid state; in solution, the situation is more complicated because there are several possible associations that exist in dynamic equilibria.

On the other hand, intermolecular HBs play a fundamental role in the kinetic aspects of tautomerism. For example, we have demonstrated that the tautomerism of pyrazoles cannot occur intramolecularly (from one N atom to its neighbor) but needs the assistance of two water molecules.³ The same happens for other heterocycles in the ground and the excited states.^{2,4}

The 2-pyridone/2-hydroxypyridine tautomerism both for the isolated isomers and the possible dimers have been studied by several authors.^{5–9} Experimental data on the geometry of the most favorable dimer as well as low frequencies of the 2-pyridone/2-pyridone and 2-py-



ridone/2-hydroxypyridine dimers provides a basis to validate the computational method used.^{7–9}

The notion of resonance-assisted hydrogen bonds (RAHB)¹⁰ formulated by Gilli suggested that strong hydrogen bonding is facilitated by charge flow through the system of conjugated double bonds.^{11,12} All heteroaromatic tautomers have the required structure to form RAHB.¹⁰ This can be illustrated by the typical example of the pyridone/hydroxypyridine prototropic tautomeric equilibrium represented in Scheme 1.

Both tautomers have resonance forms that make them suitable to form strong HBs, although the RAHB model does not predict which will be the strongest. In some cases, the HB strength has been analyzed on the basis of the acidity of the proton donor and the basicity of the proton acceptor.¹³ Even though a number of exceptions have been described,¹⁴ it can be a useful approach in some situations. Tautomers that act simultaneously as HB donors and acceptors have in common the protonated and deprotonated species, and thus, the less stable one shows

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simultaneously the larger basicity and acidity. This characteristic of tautomeric structures is known as the Gustafsson paradox.¹ Thus, the less stable one, in principle, should provide the strongest HBs.

In the present paper, the influence of autoassociation by HBs of 2-hydroxypyridine and several 2-aminopyridines has been computed in the gas phase. The results obtained have been compared with experimental data when available.

Methods

The geometry of the monomers and complexes has been fully optimized with the Gaussian-98 package.¹⁵ The 6-31+G** basis sets¹⁶ have been used at the hybrid HF-DFT, B3LYP,¹⁷ computational level. The minimum nature of the monomers and dimers has been confirmed by frequency calculations.

The inherent basis set superposition error (BSSE) of the energy has been evaluated using the full counterpoise method proposed by Boys and Bernardi.¹⁸ Thus, the uncorrected E_i and corrected interaction energies E_{i+BSSE} can be evaluated for each complex from the corresponding values of the tautomeric forms involved in the interaction using eqs 1–3.

$$E_i = E_{AB} - E_A^A - E_B^B \quad (1)$$

$$BSSE = (E_{A'}^{AB} - E_{A'}^A) + (E_{B'}^{AB} - E_{B'}^B) \quad (2)$$

$$E_{i+BSSE} = E_i + BSSE \quad (3)$$

where E_A^A represents the energy of the minimum geometry of the isolated tautomeric form of molecule A calculated with its basis set and $E_{A'}^{AB}$ corresponds to the calculated energy of the tautomer of molecule A with its geometry in the AB complex using the basis function of the AB complex.

To characterize the intermolecular HB and other contacts, an analysis of the electron density has been carried using the atoms in molecules (AIM) methodology¹⁹ and the AIMPAC programs.²⁰

Results and Discussion

2-Hydroxypyridina vs 1H-2-Pyridone [2-Pyridinol vs 2(1H)-Pyridinone]. The tautomerism of 2-hydroxypyridine/1H-2-pyridone (Scheme 1) has been widely studied both experimentally and theoretically.^{1,5–9,21–23}

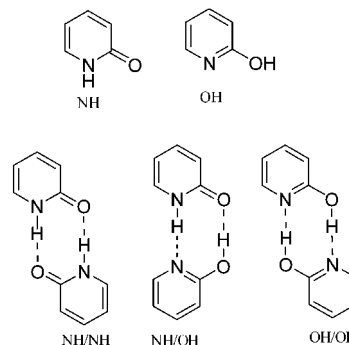
It has been found that DFT methods predict incorrectly that in the gas phase the NH tautomer is more stable than the OH one.^{22,24,25} Field and Hillier's 3-21G calcula-

Table 1. Relative Energy E_{rel} and Interaction Energies E_i and E_{i+BSSE} (kcal/mol) and Geometrical Parameters (Å, deg) of the HBs of the Monomers and Dimers of the 2-Hydroxypyridine Tautomers

system	E_{rel}	E_i	E_{i+BSSE}	HB distance (H...X)	Y–H distance	HB angle (Y–H...X)
NH	0.00				1.013	
OH	0.47				0.971	
NH/NH	0.00	–19.90	–19.18	1.724	1.044	179.4
NH/OH	4.68	–16.15	–15.33	1.866 ^a	1.042 ^a	174.0 ^a
				1.628 ^b	1.006 ^b	171.5 ^b
OH/OH	4.65	–16.18	–15.21	1.698	1.013	174.6

^a NH...N interaction ^b OH...O interaction.

Chart 1



tions also find the 2-pyridone tautomer more stable than the 2-hydroxypyridine by 3.3 kcal mol^{–1}.⁵ Only methods that include high electron correlation effects are able to reproduce the experimental findings.²⁶ Our result, Table 1, is 0.47 kcal mol^{–1} in favor of the NH-tautomer. The study of the tautomeric equilibria in the gas phase, using UV and IR spectroscopies, has shown that the major tautomer is the hydroxy form. The determined K_T constants [NH/OH] were 0.4 ± 0.25 (by UV) or 0.5 ± 0.3 (by IR),²⁴ which correspond to an approximate energy difference of 0.6 ± 0.3 kcal mol^{–1}. Thus, the absolute error at the B3LYP/6-31+G** level is only 1.1 kcal mol^{–1}. This discrepancy can be imputed to the fact that the OH form has two isomers in gas phase and is therefore stabilized by an entropic contribution up to $R \ln 2$, 1.38 kcal/mol.

Three possible dimers, presenting two HBs, are possible by combination of the previously mentioned tautomers (Chart 1). The energetic results (Table 1) indicate that the most stable dimer corresponds to that formed by the combination of two pyridones (NH/NH) in agreement with the experimental gas-phase results.^{8,9} The calculated stabilization energy by the double HB formation, E_{i+BSSE} , is -19.18 kcal mol^{–1}, which is almost identical to the one obtained at the B3LYP/6-311++G-(2d,2p) level (-18.45 kcal mol^{–1}).⁷ The stabilization of the other two dimers is about 3.7 kcal mol^{–1} less than that of the NH/NH one mentioned previously. Even assuming an error of 1.1 kcal mol^{–1} in the estimation of the relative

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Table 2. Relative Energy E_{rel} (kcal/mol) of the Tautomeric Form of the 2-Aminopyridines Studied at the B3LYP/6-31+G Level^a**

R	tautomer	symmetry	E_{rel}	dipole moment
Me	1H	C_s	14.88	2.51
Me	2H	C_1	0.00	2.07
H	1H	C_s	14.14	2.99
H	2H	C_1	0.00	2.04
F	1H	C_s	5.61	5.33
F	2H	C_1	0.00	2.51
Cl	1H	C_s	6.23	5.09
Cl	2H	C_1	0.00	2.08
NO ₂	1H	C_s	7.73	9.34
NO ₂	2H	C_1	0.00	4.71
CN	1H	C_s	2.56	9.02
CN	2H	C_s	0.00	4.01
SO ₂ H	1H	C_1	4.26	7.60
SO ₂ H	2H	C_1	0.00	4.73

^a The symmetry of the minimum structure and its dipole moment (debye) are indicated.

energy of each monomer, the method used here still predicts that the NH/NH homodimer will be the more stable one.

The experimental and calculated structures of the NH/NH dimer correspond in both cases to a C_{2h} symmetry. The available experimental data [N(H)⋯O distance = 2.77 ± 0.03 Å, C=O⋯(H)N angle = $121.8 \pm 0.5^\circ$]⁹ and the corresponding calculated ones (2.767 Å and 123.7° , respectively) are in excellent agreement.

In total, four different HBs are present in these dimers. The ones where OH acts as HB donor are shorter than those with NH, and in the same way, the oxygen as HB acceptor provides shorter HB than nitrogen. The values of these HBs are 1.628, 1.698, 1.724, and 1.866 Å for OH⋯O, OH⋯N, NH⋯O, and NH⋯N, respectively. It is significant that the shortest HB distance does not correspond to the more favorable interaction.

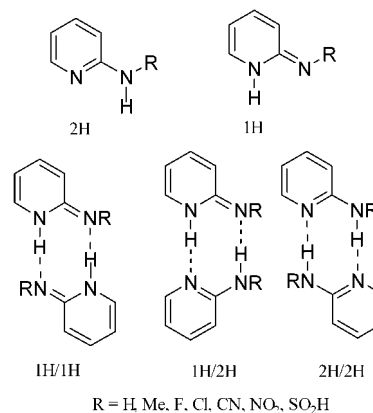
The dimer formation produces an important red shift of the OH and/or NH stretching bands. The corresponding values for the symmetrical stretching in the NH/NH, OH/NH, and OH/OH dimers are 3018, 3018, and 2849 cm^{-1} , respectively, while in the monomers their values are 3604 and 3771 cm^{-1} for the NH and OH tautomers, respectively.

The excellent results obtained for this system provide confidence on the application of the same methodology for the study of 2-aminopyridines.

Aminopyridines. The energy results of the 2-aminopyridines (Table 2) indicate that, in all the cases considered here, the 2H tautomer is the most stable one in the gas phase. As the electronegativity of the group attached to the amino moiety (R in Chart 2) increases, the relative energy of the 1H tautomer decreases. Thus, while the relative energy of the 1H tautomer for R = Me is 14.8 kcal mol^{-1} , that for R = CN is 2.6 kcal mol^{-1} .

In all examples, the dipole moments of 1H tautomers are larger than those of the 2H tautomers. The differences are very pronounced in the case of electronegative substituents, indicating that probably in polar media the difference between tautomers would be smaller or even that the 1H tautomer would become the most stable.

Regarding the geometry of 2-aminopyridines, the 1H tautomer shows C_s symmetry in all cases, and the 2H tautomer shows C_1 symmetry due to the nonplanarity of the amino group. As the electronegativity of the R group increases, the amino group tends to be more planar, and

Chart 2**Table 3. Relative Energy E_{rel} and Interaction Energies E_{I} and $E_{\text{I+BSSE}}$ (kcal/mol) of the 2-Aminopyridine Tautomers Dimers Calculated at the B3LYP/6-31+G** Level**

R	dimer	symmetry	E_{rel}	E_{I}	$E_{\text{I+BSSE}}$
Me	1H/1H	C_{2h}	20.37	-18.75	-17.93
Me	1H/2H	C_1	11.07	-13.17	-12.48
Me	2H/2H	C_2	0.00	-9.36	-8.82
Me	2H/2H	C_i	0.03	-9.33	-8.79
H	1H/1H	C_{2h}	16.78	-20.72	-19.79
H	1H/2H	C_1	9.69	-13.67	-12.93
H	2H/2H	C_2	0.00	-9.95	-9.39
H	2H/2H	C_i	0.02	-9.93	-9.37
CN	1H/1H	C_{2h}	-1.51	-20.20	-19.36
CN	1H/2H	C_s	3.02	-13.11	-12.32
CN	2H/2H	C_{2h}	0.00	-13.57	-12.81
Cl	1H/1H	C_{2h}	2.79	-19.86	-18.70
Cl	1H/2H	C_1	3.86	-12.56	-11.58
Cl	2H/2H	C_2	0.00	-10.20	-9.33
Cl	2H/2H	C_i	2.38	-7.82	-6.94
F	1H/1H	C_{2h}	2.25	-19.05	-18.32
F	1H/2H	C_1	3.51	-12.19	-11.43
F	2H/2H	C_2	0.00	-10.09	-9.33
F	2H/2H	C_i	3.94	-6.15	-5.42
NO ₂	1H/1H	C_{2h}	-0.68	-29.89	-28.55
NO ₂	1H/2H	C_1	9.94	-11.54	-10.39
NO ₂	2H/2H	C_2	0.00	-13.75	-12.47
NO ₂	2H/2H	C_i	0.04	-13.70	-12.48
SO ₂ H	1H/1H	C_2	-3.11	-25.23	-23.13
SO ₂ H	1H/2H	C_1	4.94	-12.92	-11.27
SO ₂ H	2H/2H	C_2	0.00	-13.60	-11.94
SO ₂ H	2H/2H	C_i	-0.11	-13.71	-12.04

thus, the CN derivative is planar and the NO₂ and SO₂H ones are only slightly nonplanar.

As previously, three different dimers with two HB are possible (Chart 2). However, in this case and due to the C_1 symmetry of the 2H tautomer, two different 2H/2H complexes with C_2 and C_i symmetry can be built up, except for the CN derivative whose 2H tautomer is planar.

In all the cases studied here, the interaction of the 1H/1H dimer is larger than the rest of the configurations (Table 3). The values obtained are in all cases approximately -18 kcal mol^{-1} , except for the NO₂ and SO₂H derivatives where additional contacts are observed between those groups and the C-H group in position 6 of the pyridine ring, which increase the interaction energy up to -29.9 and -25.2 kcal mol^{-1} , respectively.

The interaction energy of the 2H/2H dimers range between -9.4 and -13.8 kcal mol^{-1} for the C_2 symmetry ones and -6.2 and -13.7 kcal mol^{-1} for the C_i ones. In all cases, the C_2 symmetry complexes are more stable than the corresponding C_i ones, since the disposition of

Table 4. Geometrical Parameters of the Intermolecular HBs (Å and deg) of the 2-Aminopyridine Tautomers Dimers Calculated at the B3LYP/6-31+G Level**

R	dimer	symmetry	HB distance (H...X)	Y-H distance	HB angle (Y-H...X)	addnl contacts
Me	1H/1H	C_{2h}	1.762	1.059	177.0	
Me	1H/2H	C_1	1.918 ^a	1.038 ^a	175.7 ^a	
			1.925	1.033	175.8	
Me	2H/2H	C_2	2.042	1.024	174.5	
Me	2H/2H	C_i	2.038	1.024	174.4	
H	1H/1H	C_{2h}	1.756	1.051	179.5	
H	1H/2H	C_1	1.916 ^a	1.038 ^a	176.8 ^a	
			1.898	1.034	178.4	
H	2H/2H	C_2	2.021	1.025	178.9	
H	2H/2H	C_i	2.020	1.025	177.3	
CN	1H/1H	C_{2h}	1.830	1.044	178.9	
CN	1H/2H	C_s	1.877 ^a	1.042 ^a	177.4 ^a	
			1.865	1.042	179.9	
CN	2H/2H	C_{2h}	1.849	1.044	177.2	
Cl	1H/1H	C_{2h}	1.806	1.045	179.0	
Cl	1H/2H	C_1	1.900 ^a	1.039 ^a	178.0 ^a	
			1.864	1.040	176.6	
Cl	2H/2H	C_2	1.939	1.036	177.4	
Cl	2H/2H	C_i	1.992	1.032	164.7	
F	1H/1H	C_{2h}	1.848	1.039	174.0	
F	1H/2H	C_1	1.921 ^a	1.037 ^a	175.1 ^a	
			1.912	1.039	168.0	
F	2H/2H	C_2	1.955	1.038	176.8	
F	2H/2H	C_i	2.072	1.030	156.4	
NO ₂	1H/1H	C_{2h}	1.847	1.045	180.0	2.359 ^b
NO ₂	1H/2H	C_1	1.848 ^a	1.044 ^a	172.4 ^a	
			1.929	1.038	171.1	
NO ₂	2H/2H	C_2	1.898	1.040	178.4	2.406 ^b
NO ₂	2H/2H	C_i	1.900	1.040	178.5	2.407 ^b
SO ₂ H	1H/1H	C_2	1.872	1.041	176.5	2.302 ^c
SO ₂ H	1H/2H	C_1	1.918 ^a	1.036 ^a	175.4 ^a	2.165 ^d
			1.940	1.042	176.7	
SO ₂ H	2H/2H	C_2	1.909	1.042	176.4	2.420 ^c
SO ₂ H	2H/2H	C_i	1.918	1.042	176.8	2.370 ^c

^a N(1)-H...N(1) HB. ^b Intermolecular NO...HC contact. ^c Intermolecular SO...HC contact. ^d Intermolecular SO...HS contact.

the HBs is more adequate in the former case than in the latter, where the pyridine rings are almost in the same plane and the amino groups do not point so efficiently to the nitrogen. The only exception is the SO₂H derivative, where the secondary interaction is closer in the C_i symmetry.

The 1H/2H dimers show the effect of locating in proximity the R groups of the two interacting molecules. Thus, for groups strongly repulsive and nearby in the complexes (R = NO₂ and SO₂H), their interaction is smaller than those of the 2H/2H dimers, while in the rest of the cases is intermediate between the ones obtained for the 1H/1H dimer and the 2H/2H ones.

The large difference observed in the stabilization in the 1H/1H dimers due to the complexation compared to the rest of the dimers studied overcome the energy difference of the individual tautomers toward the 2H dimers in several of the cases studied (R = CN, NO₂, and SO₂H). A search in the CSD²⁸ shows that the 2-(nitramino)pyridine, R = NO₂ (refcode: TOQMUH01), is present in the solid phase as a 1H/1H dimer. In addition, three SO₂R derivatives (refcodes: BEWKUJ, BULFOD, and SENCIX) are present as 1H structures, forming the last two 1H/1H dimers.

The geometry of the calculated 1H/1H dimer of the NO₂ derivative resembles the structure found in the CSD. The experimental value for the HB is 2.89 Å [N(H)...N]

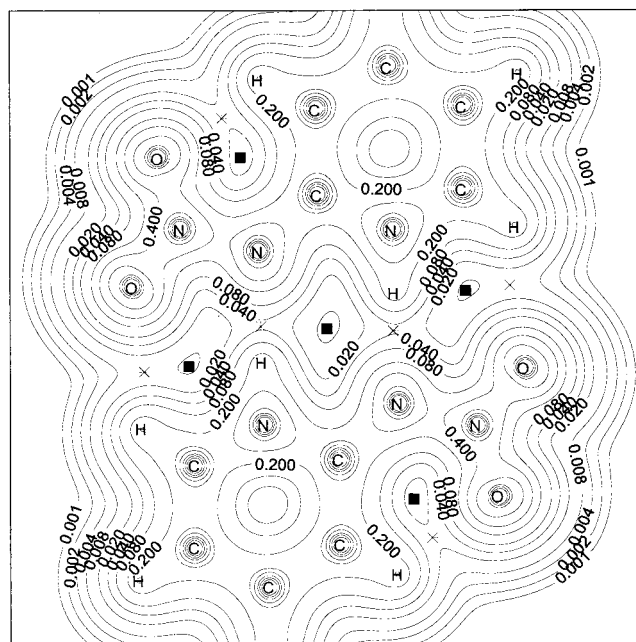


Figure 1. Electron density map of the 1H/1H dimer of the NO₂ derivative. The HB critical points (four intermolecular and two intramolecular) are shown with stars and the ring critical points generated by them with squares.

and the calculated value 2.891 Å. In the same way, the intermolecular distance between the NO₂ group and the CH in position 6 is 3.16 Å [C(H)...O] experimentally and 3.154 Å at the B3LYP/6-31+G** level.

The distance of the HB formed ranges between 1.76 and 2.08 Å and the bond angles are close to linearity (Table 4). For each substituent, the shortest HB is found in the 1H/1H dimer. In general, for each substituent, the HB distance provides an idea of the strength of the complex. Those with shorter HB are the stronger ones. However, an attempt to find a correlation in all the cases studied here only yields a poor R^2 .

The dimerization produces a red shift in the symmetrical bond stretching of the NH groups involved in the HB that ranges between 300 and 900 cm⁻¹ depending on the system considered. In all cases, the smaller vibrational value is obtained for the 1H/1H dimer followed by the 1H/2H one and the largest ones correspond to the 2H/2H dimers, in accordance with the relative strength of the HB obtained.

The analysis of the electron density shows HB critical points characterized by electron density values in the range 0.05–0.02 e au⁻³ and positive values of the laplacian. The simultaneous HBs formed produce an eight-membered ring that shows a critical point with values of the electron densities approximately to 5 × 10⁻³ e au⁻³. In addition to the expected HB interactions, other contacts are observed in the case of the NO₂ and SO₂H derivatives between those groups and C–H moieties, both inter- and intramolecular, as many as six HB critical points in some of the dimers studied (see Figure 1). These intermolecular contacts are able to explain the extra stabilization energy observed for these dimers (Table 3).

Correlations between the electron density ρ and its laplacian $\nabla^2\rho$ at the HB critical point and the HB distance

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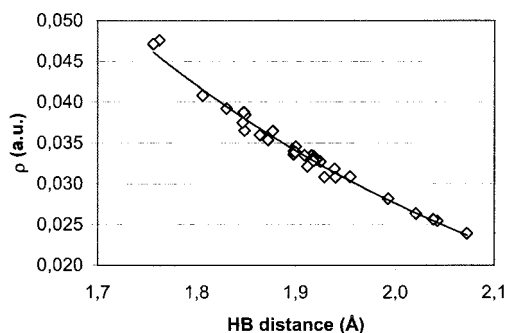


Figure 2. Electron density at the HB critical point vs HB distance. The fitted curve corresponds to the equation $\rho = 1.87 \exp(-2.11 \text{HB distance})$, $R^2 = 0.98$, $n = 34$. The linear correlation provides an $R^2 = 0.96$.

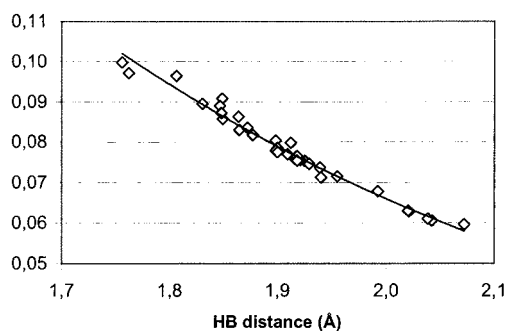


Figure 3. Laplacian of the electron density at the HB critical point vs HB distance. The fitted curve corresponds to the equation $\nabla^2\rho = 2.35 \exp(-1.79 \text{HB distance})$, $R^2 = 0.98$, $n = 34$. The linear correlation provides an $R^2 = 0.97$.

can be obtained (Figures 2 and 3). In both cases, the exponential correlation is statistically better than the linear ones. Previous reports with larger ranges clearly show the exponential behavior of these two electron density properties vs the HB distance.^{29,30}

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Conclusions

A theoretical study of the influence of dimerization by HB formation of 2-hydroxypyridine and 2-aminopyridine and their corresponding tautomers has been carried out at the B3LYP/6-31+G** level. The theoretical results with the 2-hydroxypyridine dimer properly predicts that the more stable structure corresponds to the 2-pyridine/2-pyridone one with a D_{2h} symmetry. The obtained geometrical parameters of these HB complexes are almost identical to the experimental one. In the case of 2-aminopyridines, the effect of the amino substitution in the tautomerism has been studied in detail. While in all the monomers the 2H tautomer is the most stable, the relative energy of the 1H tautomer decreases as the electronegativity of the substituent increases.

The interaction energy of the different dimers indicates that the 1H/1H dimers are the most favorable. In several of the compounds studied, the difference is enough to overcome the relative stability of the monomers and become the most stable dimer.

The atoms in molecule methodology has been used to characterize the HB interactions. In two cases ($R = \text{NO}_2$ and SO_2H), additional inter- and intramolecular HBs have been found. Exponential relationships have been found between the electron density and its laplacian at the HB critical points vs the HB distance.

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Supporting Information Available: Total energy and Cartesian coordinates of the optimized geometry of the monomers and dimers. Electron density and its laplacian at the bond critical points for all the dimers and frequencies of the symmetric bond stretching of the monomers and dimers are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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