

The influence of secondary interactions on complex stability and double proton transfer reaction in 2-[1H]-pyridone/2-hydroxypyridine dimers

Borys Ośmiałowski · Robert Dobosz

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Abstract The 2-[1H]-pyridone/2-hydroxypyridine tautomeric pair and its 6-substituted complexes have been studied with the use of DFT(M05) method. The intermolecular interaction energy has been calculated and discussed in the light of secondary interaction concept. The attractive secondary interactions of O/NH and O/OH type and OH/NH and OH/OH repulsions have been analyzed in terms of stabilizing or destabilizing influence on intermolecular behavior. The transition states of the double proton transfer reaction have been found and the energy of activation has been determined. The activation energy of the proton transfer reaction, geometry of the complexes and transition states show NH₂ and/or OH groups influence the properties of complexes and transition states. The HOMA index of aromaticity was applied to describe the π -electron delocalization in the heterocyclic rings.

Keywords Hydrogen bond · 2-hydroxypyridine · Proton transfer · 2-[1H]-pyridone · Self-association · Transition state

Introduction

Chemical structures held together by hydrogen bonding, which is recognized as moderately strong and directional interaction, are very common [1, 2]. Sophisticated

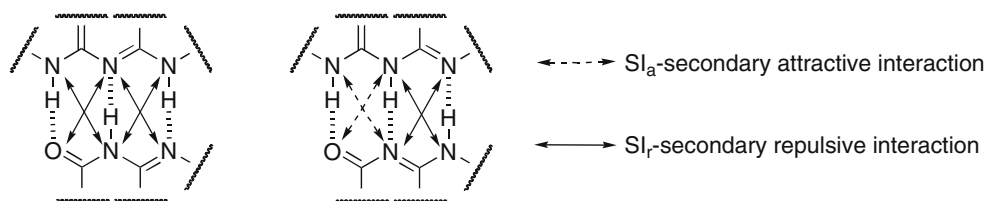
aggregates such as non-covalent polymers, blends [3, 4] and molecular sensors [5–7] often become the subject of contemporary studies. The hydrogen bond strength depends on a few factors. In general, the more electronegative atoms are, the stronger the hydrogen bonds [8]. Thus, the NH \cdots OC hydrogen bond is stronger than NH \cdots N. Among the plethora of structures stabilized by hydrogen bonding, the NH \cdots OC interaction is most common [9–13]. This type of hydrogen bond is met in amides [14–17] and DNA [18, 19]. Beside its natural occurrence, this type of hydrogen bonding may also be used to control the solvent dependent photoreaction [20] or in organocatalysis [21]. Apart from the strength of hydrogen bonding, there are other factors that may influence the stability of aggregate. One of them is secondary interaction (SI) present in multiple hydrogen-bonded complexes [22]. These interactions (Fig. 1) act as stabilizing or destabilizing forces in complexes with adjacent hydrogen bonds and play a crucial role in dimerization [23–26]. The character of secondary interaction depends on hydrogen-bonding pattern, *i.e.* the order of hydrogen bonds donors and acceptors [22]. As a consequence, the secondary interactions can be of attractive (SI_a) or repulsive (SI_r) character. These two interactions are the main driving forces that influence the stability of hydrogen-bonded associates.

2-[1H]-Pyridone [27, 28] is considered as the most stable doubly hydrogen-bonded dimer known so far [29]. However, the substituents in heterocyclic ring may influence the properties of the said dimer [30]. According to Yang [31], the NH \cdots OC hydrogen bond distance in 2-[1H]-pyridone is equal to 1.78 Å. The N-O distance is equal to 2.75 Å according to Held and Pratt [32] in the gas phase. This value is in agreement with MP2 optimized distance equal to 2.74 Å [29]. The respective

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B. Ośmiałowski (✉) · R. Dobosz
Faculty of Chemical Technology and Engineering,
University of Technology and Life Sciences,
Seminaryjna 3,
PL-85-326 Bydgoszcz, Poland
e-mail: borys.osmialowski@utp.edu.pl

Fig. 1 Secondary interactions in triple hydrogen bonded systems



hydrogen bond length in dimer of 5-nitro-2-[1*H*]-pyridone [30] is 1.88 Å. The mentioned X-ray data shows that the substituent is responsible for changes of hydrogen bond geometries of pyridone dimers. Taking into account the SI concept, the substituent in the 6 position, as being in the interacting part of molecule, of the 2-[1*H*]-pyridone should influence the intermolecular interactions.

There are two basic centres in hydroxypyridine anion that compete for one proton. However, the proton transfer (tautomerism) may be observed not only in isolated molecules but also in complexes. The tautomerism in 2-[1*H*]-pyridone/2-hydroxypyridine was the subject of many publications [33–39]. Also, the aminopyridines [40–43] were studied with the use of experimental and theoretical methods [29, 40, 44]. The 2-[1*H*]-pyridone has also been considered as hydrogen-bonded counterpart for DNA bases [45, 46], 2-aminopyridine [47], azaindole [48]. The hydrogen bonding of 2-[1*H*]-pyridone is strong enough to allow transferring the energy between said molecule and DNA bases in the excited state [46], thus it has been used by Müller et al. as a probe chromophore [45].

The ab initio calculations suggest that MP2 [49] method is accurate enough to describe hydrogen bonded dimer geometry [50]. Recently improved DFT methods are alternative to MP2, especially when a large system is considered. The DFT functionals by Zhao and Truhlar take the long distance interactions into account, thus they are useful in describing non-covalent interactions [51–53]. Moreover, the DFT method is much less time demanding than the MP2 one.

Figure 2 shows the studied structures and atom numbering.

The hydrogen-bonded dimers of studied structures may exist in equilibrium passing through the transition state. The double proton transfer leads to change in the type of hydrogen bonds stabilizing the dimer ($\text{NH}\cdots\text{O} \rightarrow \text{OH}\cdots\text{N}$) and secondary interaction(s) ($\text{SI}_a \rightarrow \text{SI}_r$) (Scheme 1). The question arises: what is the structure of the transition state? It is worth noting that the OH and NH_2 substituents are expected to influence complex properties in different way. Thus, apart from the fact that type of SIs changes in double proton transfer reaction depending on presence/absence of substituent(s) at 6/6'

position(s), also the strength of SIs depends on substituent type (OH or/and NH_2). According to the SIs model, the attractive SI present in one constituent of the complex should lower the intermolecular/interatomic distances at the side of its presence. Reverse situation is expected for repulsive SI.

The aim of this work is to describe the energetic preferences of 2-hydroxy/2-oxo-[1*H*]-6-substituted pyridines/ones in the hydrogen-bonded complex and double proton transfer (tautomerism) reaction within complexes.

Methods

The 6-311+G(d,p) basis set was suggested for calculations of molecules involved in hydrogen bonding where the cooperativity of interactions was observed [54–57]. Structure optimizations were unrestricted. Although the triple- ζ basis set with diffuse and polarization functions was suggested for similar system, the basis set study was performed. The geometry of 2-[1*H*]-pyridone dimer was taken for tests (see [Supplementary material](#)). The best agreement of X-ray data with calculated geometries was obtained for calculations with 6-311+G(2d,p) basis set. Consequently, this basis set was used for calculations of monomers, complexes and transition states. All calculations were performed with the use of GAMESS [58] and Gaussian [59] software. For all optimized geometries (M05/6-311+G(2d,p) level), the frequency

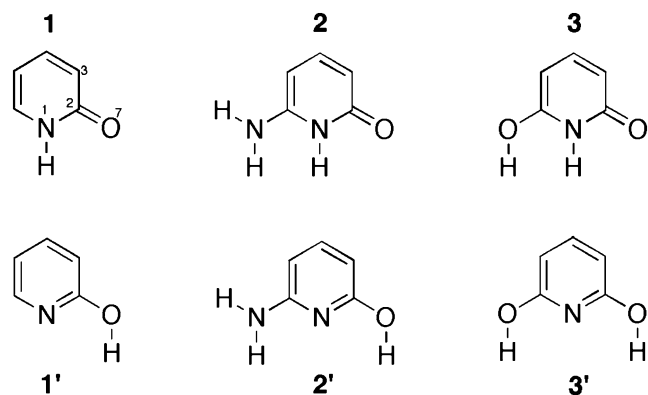
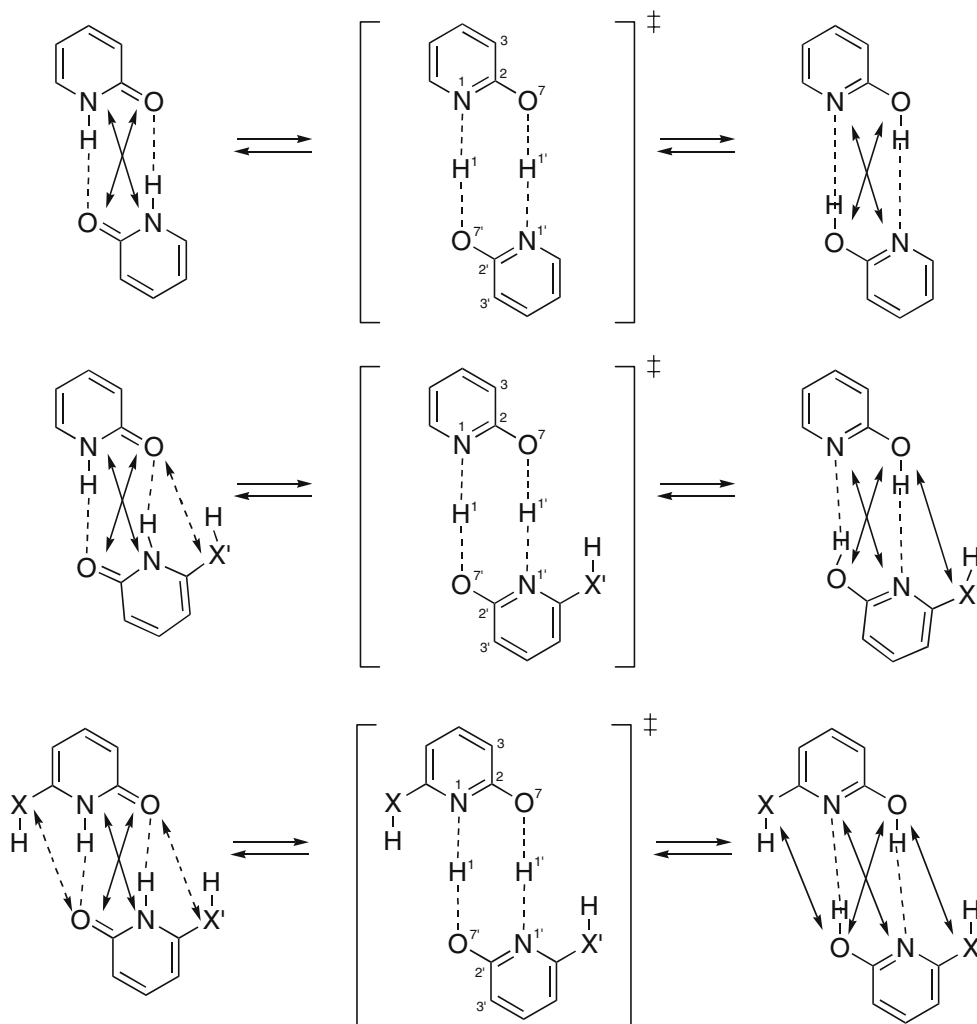


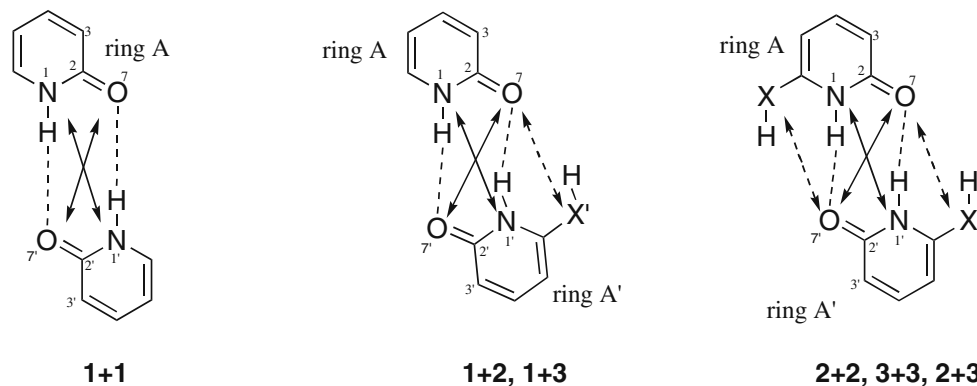
Fig. 2 The compounds studied and atom numbering



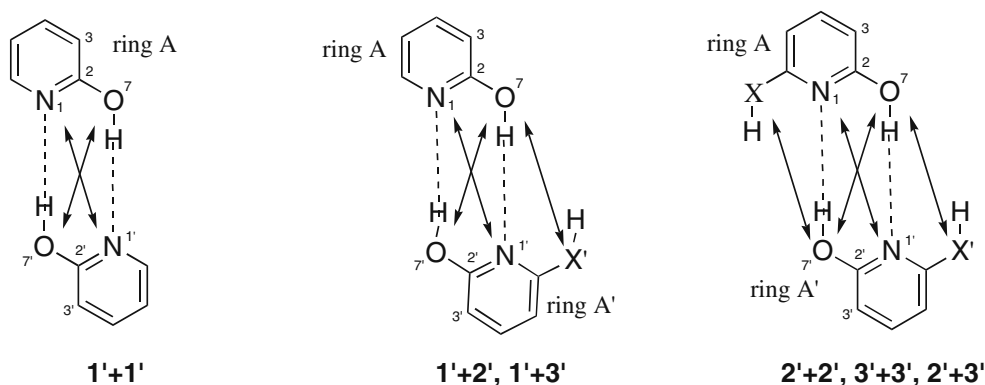
Scheme 1 The transition state (TS) for double, intermolecular proton transfer reaction

calculations were run to check if the geometry was in energy minima (no negative frequencies were obtained). The optimized transition states were also characterized by the frequency calculations (one imaginary frequency was

obtained). The interaction energies corrected to the BSSE (basis set superposition error) were calculated with the use of counterpoise method implemented in Gaussian with default settings.



Scheme 2 The structure and atom numbering in pyridone complexes. Solid and dashed double-headed arrows show the attractive and repulsive interactions, respectively



Scheme 3 The structure and atom numbering in hydroxypyridine complexes. Solid double-headed arrows show the repulsive interactions

Results and discussion

The structures of studied complexes are exemplified in Schemes 2 and 3 (substituents X and X' are explained in Tables 1 and 2 that follow the respective schemes). Tables 1 and 2 also show the selected geometric data of complexes of **1-3** and **1'-3'** and energy of interaction (*E*). The molecules in optimized complexes converged to planar geometries including the OH and NH₂ groups unless otherwise stated in the following tables.

The geometry data of optimized complexes shows that in most structures, NH...O intermolecular hydrogen bonds are shorter than respective OH...N hydrogen bonds. The opposite situation is realized for H1...O7'

hydrogen bond in **1+1**, **1+2** and **1+3** comparing to **1'+1'**, **1'+2'** and **1'+3'**. The presence of X(X')H groups in the complex makes the intermolecular hydrogen bond shorter in complexes containing **1**, **2** or **3** and longer in that of **1'**, **2'** or **3'**. The N1–N1' distance is smaller in complexes of pyridones in comparison to hydroxypyridines. On the other hand, the O7–O7' distance is higher in pyridone than in hydroxypyridine complexes. This suggests that the presence of the X(X')H substituent increases the SI_a and SI_r interactions energy in complexes of pyridone and hydroxypyridine, respectively. This, in turn, results in variation of the O–N distances in the complexes. Interestingly, the C2–C2' distance in **1+1** and **1'+1'** complexes is the shortest in both series, *i.e.* the presence of X(X')H

Table 1 The hydrogen bond lengths, interatomic distances [Å] and angles [°] and energy of interaction (*E*) [kcal mol⁻¹] in the complexes of pyridones **1-3**

	Complex						
	1+1	1+2	1+3	2+2	3+3	2+3	
X	-	-	-	NH	O	O	
X'	-	NH	O	NH	O	NH	
<i>E</i>	-17.57	-20.12	-21.64	-23.12	-26.05	-24.76	
H1...O7'	1.785	1.773	1.796	1.781	1.750	1.735	
H1'...O7	1.785	1.782	1.736	1.781	1.750	1.802	
N1–C2'	3.635	3.627	3.622	3.585	3.529	3.534	
N1–O7'	2.816	2.808	2.830	2.804	2.773	2.757	
N1'–C2	3.635	3.610	3.565	3.585	3.529	3.574	
N1'–O7	2.816	2.806	2.761	2.804	2.773	2.823	
C2–C2'	4.108	4.127	4.121	4.151	4.125	4.138	
N1–N1'	3.660	3.606	3.564	3.513	3.431	3.466	
O7–O7'	3.583	3.617	3.640	3.696	3.727	3.719	
O7–X'	-	3.410	3.351	3.315	3.270	3.321	
O7'–X	-	-	-	3.315	3.270	3.247	
C2–O7–N1'	122.8	121.3	121.1	119.6	117.8	117.7	
C2'–O7'–N1	122.8	122.5	120.7	119.6	117.8	119.1	
C3–C2–C2'	174.9	173.9	174.3	171.0	169.9	169.3	
C3'–C2'–C2	174.9	172.5	171.4	171.0	169.9	170.5	

Table 2 The hydrogen bond lengths, interatomic distances [Å] and angles [°] and energy of interaction (E) [kcal mol⁻¹] in the complexes of hydroxypyridines **1**'-**3**'

	Complex					
	1 '+ 1 '	1 '+ 2 '	1 '+ 3 '	2 '+ 2 '	3 '+ 3 '	2 '+ 3 '
X	-	-	-	NH	O	O
X'	-	NH ^a	O	NH	O	NH ^a
E	-13.73	-13.33	-12.37	-13.05	-11.11	-12.26
H7...N1'	1.775	1.760	1.786	1.796	1.821	1.792
H7'...N1	1.775	1.815	1.812	1.796	1.821	1.825
N1–C2'	3.529	3.575	3.579	3.577	3.610	3.604
N1–O7'	2.769	2.802	2.800	2.781	2.799	2.803
N1'–C2	3.529	3.544	3.567	3.577	3.610	3.582
N1'–O7	2.769	2.750	2.769	2.781	2.799	2.777
C2–C2'	4.105	4.128	4.138	4.149	4.169	4.161
N1–N1'	3.407	3.442	3.459	3.455	3.501	3.474
O7–O7'	3.771	3.744	3.744	3.735	3.724	3.732
O7–X'	-	3.359	3.432	3.398	3.485	3.394
O7'–X	-	-	-	3.398	3.485	3.482
C2–O7–N1'	114.5	116.4	116.5	116.5	117.4	117.1
C2'–O7'–N1	114.5	115.3	115.7	116.5	117.4	116.7
C3–C2–C2'	177.7	178.2	179.1	178.9	179.3	178.4
C3'–C2'–C2	177.7	177.4	178.3	178.9	179.3	178.2

a – amino group is tetrahedral

substituent(s) increases the C2–C2' distance. The intermolecular C2–O7–N1' angle decreases in pyridones and increases in hydroxypyridine series as the X(X')H substituent changes. Thus, besides the change in the relative position (*shift*) of molecules, the *twist* of one molecule against another is observed. Taking into account symmetric dimers, the change of N1–N1' and O7–O7' distances (due to X(X')H presence) are larger in pyridone than in hydroxypyridine series. This suggests that SI_as are stronger than SI_ss (for numerical values see Table 3).

Table 3 collects the stabilization and destabilization energies (ΔE) of studied complexes upon substitution of H by OH and/or NH₂ in 6 and/or 6' position in the

complex. The non-substituted complexes, **1**+**1** and **1**'+**1**', were used as references.

Comparison of ΔE values given in Table 3 shows that the secondary interaction energies are not additive, *i.e.* two attractive interactions stabilize the complex more than two separate interactions of the same type. The same is realized for repulsions. This type of group like behavior is called cooperativity [60] and is based on the principle stating that in supramolecular chemistry "1+1 is more than 2" [1]. The cooperativity is also observed in geometry of complexes. For example, the difference in O7–O7' distance (Table 1) between **1**+**1** and **1**+**2** is 0.034 Å (one attraction is present in **1**+**2**), while the same difference in distance between **1**+**2**

Table 3 The influence of NH₂ and OH groups on stabilization (negative values)/destabilization (positive values) of the complexes^a

Pyridone series	No. of NH ₂ Groups	No. of OH groups	ΔE
1 + 2	1	0	-2.5
1 + 3	0	1	-4.0
2 + 2	2	0	-5.5
2 + 3	1	1	-7.2
3 + 3	0	2	-8.5
Hydroxypyridine series			ΔE
1 '+ 2 '	1	0	0.4
1 '+ 3 '	0	1	1.3
2 '+ 2 '	2	0	0.6
2 '+ 3 '	1	1	1.4
3 '+ 3 '	0	2	2.6

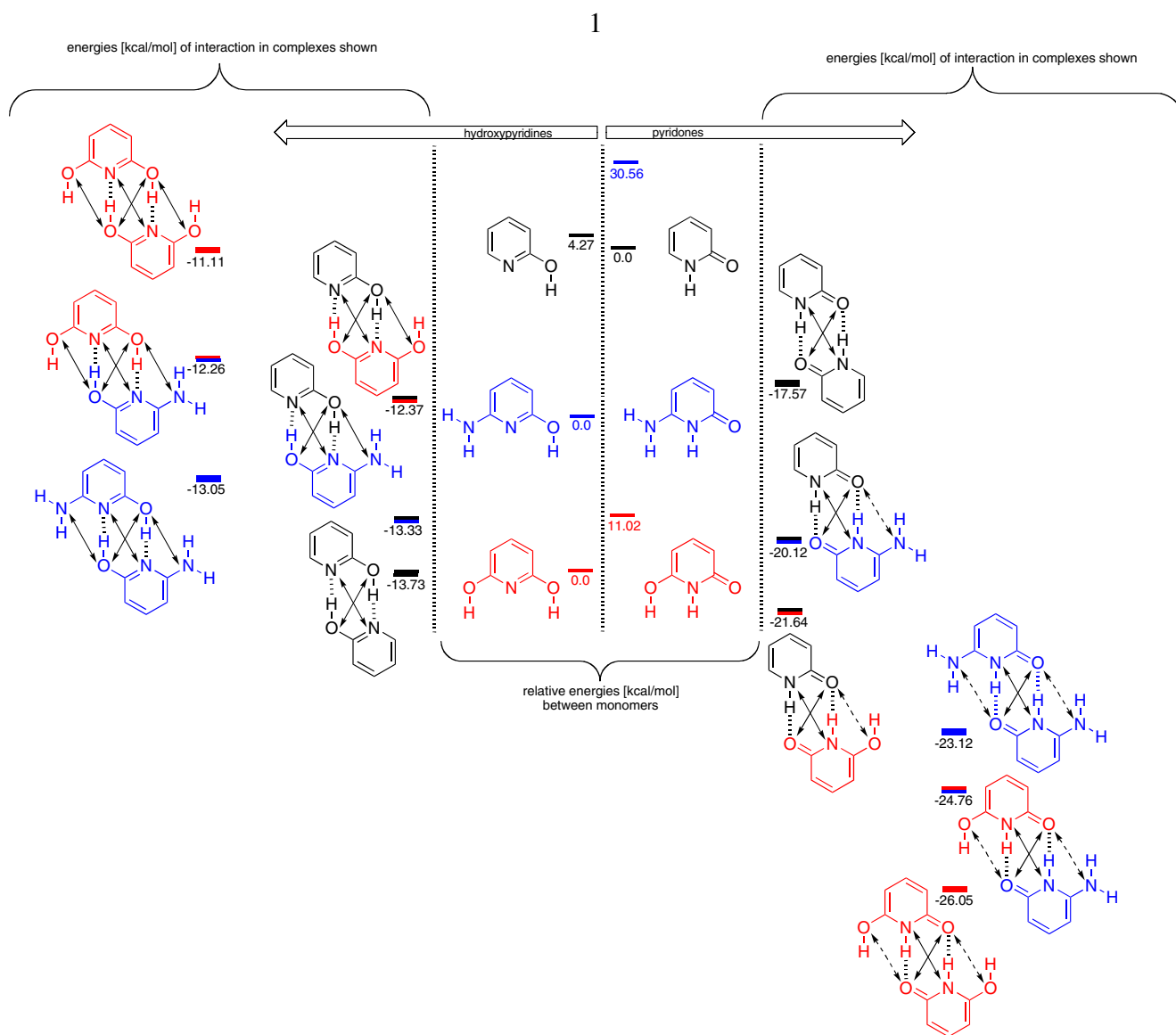
a – change in intermolecular interaction energy (ΔE , kcal mol⁻¹) related to **1**+**1** and **1**'+**1**'

and $2+2$ is 0.079 \AA (two attractions of the same type are present in $2+2$). Also, the $N1-N1'$ distance changes more (this distance decreases) when another secondary interaction is present. The similar situation is realized in the series $1'+1'$, $1'+2'$ and $2'+2'$ (Table 2). The $O7-O7'$ distance decreases, while $N1-N1'$ increases. In complexes containing only repulsive interactions, presence of the second SI_r results in smaller changes of interatomic distances ($O7-O7'$ or $N1-N1'$ in $2'+2'$ vs. $1'+2'$) rather than in complex containing one SI_r with respect to the complex without SI_r .

The E for pyridone and hydroxypyridine complexes is summarized in Scheme 4. The data shows that the complexes containing molecules **1-3** are, in general, more stable.

The most stable structure among all dimers studied here is $3+3$, while the least stable is $3'+3'$. The difference in interaction energy for these two complexes is $15.0\text{ kcal mol}^{-1}$. These dimers can exist in equilibrium by intermolecular, two proton exchange reaction that proceeds *via* the transition state. Thus, the transition states (Scheme 1) were optimized and the activation energy (E_a) of this process was calculated.

The transition state geometry parameters for studied double-proton transfer in the hydrogen-bonded complexes are summarized in Table 4. The superscript by the TS label gives the information about the reaction substrate and product (for example $^{(1+1,1'+1')}$ is related to the TS of $1+1 \rightarrow 1'+1'$ reaction).



Scheme 4 Schematic representation of relative energies of monomers/complexes and secondary interactions influence on complex stability

Table 4 The optimized transition state geometry (hydrogen bond length, interatomic distances [\AA] and angles [$^\circ$])

Geometry parameter	Transition state					
	TS ^(1+1,1'+1')	TS ^(1+2,1'+2')	TS ^(1+3,1'+3')	TS ^(2+2,2'+2')	TS ^(3+3,3'+3')	TS ^(2+3,2'+3')
X	-	-	-	NH	O	O
X'	-	NH	O	NH	O	NH
H1...N1	1.232	1.322	1.265	1.228	1.205	1.291
H1'...N1'	1.232	1.196	1.188	1.228	1.205	1.186
H1...O7'	1.255	1.172	1.225	1.258	1.283	1.192
H1'...O7	1.255	1.295	1.300	1.258	1.283	1.311
N1-C2'	3.288	3.299	3.294	3.300	3.296	3.301
N1-O7'	2.486	2.492	2.489	2.483	2.485	2.480
N1'-C2	3.288	3.289	3.286	3.300	3.296	3.304
N1'-O7	2.486	2.488	2.484	2.483	2.485	2.494
C2-C2'	3.801	3.825	3.822	3.835	3.840	3.841
N1-N1'	3.296	3.280	3.278	3.284	3.274	3.282
O7-O7'	3.451	3.466	3.461	3.445	3.456	3.452
O7-X'	-	3.164	3.188	3.175	3.190	3.166
O7'-X	-	-	-	3.175	3.190	3.213
C2-O7-N1'	118.3	118.1	118.1	119.0	118.8	118.8
C2'-O7'-N1	118.3	118.3	118.5	119.0	118.8	119.0
C3-C2-C2'	175.9	175.9	175.6	175.4	174.7	175.2
C3'-C2'-C2	175.9	175.4	174.8	175.4	174.7	175.4

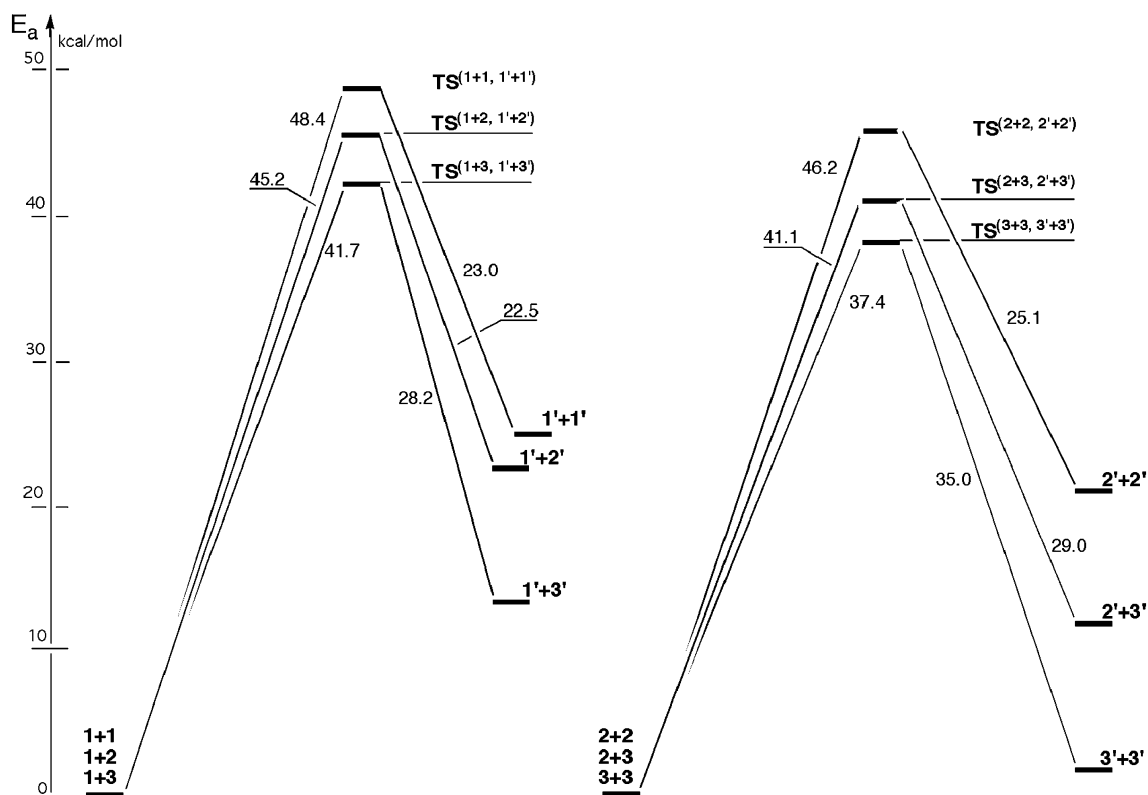
**Scheme 5** Schematic representation of E_a of double, intermolecular proton transfer reaction in complexes studied

Table 5 The HOMA indexes of heterocyclic ring for monomers studied

Monomer	HOMA
2-[1 <i>H</i>]-pyridone (1)	0.64
6-amino-2-[1 <i>H</i>]-pyridone (2)	0.73
6-hydroxy-2-[1 <i>H</i>]-pyridone (3)	0.69
2-hydroxypyridine (1')	0.98
2-hydroxy-6-aminopyridine (2')	0.99
2,6-dihydroxypyridine (3')	0.99

The geometry of the TSs follows the concept of secondary interactions as it was previously shown for stable complexes (Tables 1 and 2). The N1–N1' distance is the biggest in $\text{TS}^{(1+1,1'+1')}$. The C2–C2' distance is the smallest in the same transition state. Due to the presence of X' substituent and associated secondary interaction, the H1...N1/H1'...N1' hydrogen bond in $\text{TS}^{(1+1,1'+1')}$ is shorter than H1...N1 in $\text{TS}^{(1+2,1'+2')}$ and $\text{TS}^{(1+3,1'+3')}$. On the other hand, the H1...N1/H1'...N1' hydrogen bond in $\text{TS}^{(1+1,1'+1')}$ is longer than H1'...N1' hydrogen bond in $\text{TS}^{(1+2,1'+2')}$ and $\text{TS}^{(1+3,1'+3')}$. The remaining intermolecular distances/hydrogen bond lengths are also in agreement with SIs concept. Intermolecular angles collected in Table 4 are practically constant.

In general, the substituent present in the 6 position of the studied structures makes the proton transfer reaction more probable by lowering the E_a (Scheme 5). It is worth mentioning that the lowest E_a is observed for $\text{TS}^{(3+3,3'+3')}$ and the relative energy of $3'+3'$ vs. $3+3$ is the smallest, too.

It has already been mentioned that the geometry of monomers, complexes and transition states is dependent on

Table 6 The HOMA indexes of heterocyclic rings in complexes

Complex	HOMA A	HOMA A'
1+1	0.74	-
1+2	0.77	0.86
1+3	0.79	0.84
2+2	0.87	-
3+3	0.87	-
2+3	0.85	0.88
1'+1'	0.98	-
1'+2'	0.98	0.99
1'+3'	0.98	0.99
2'+2'	0.99	-
3'+3'	0.99	-
2'+3'	0.99	0.99

Table 7 The HOMA indexes of heterocyclic rings in transition states

Transition state	HOMA A	HOMA A'
$\text{TS}^{(1+1,1'+1')}$	0.90	-
$\text{TS}^{(1+2,1'+2')}$	0.91	0.97
$\text{TS}^{(1+3,1'+3')}$	0.91	0.95
$\text{TS}^{(2+2,2'+2')}$	0.96	-
$\text{TS}^{(3+3,3'+3')}$	0.96	-
$\text{TS}^{(2+3,2'+3')}$	0.95	0.97

hydrogen bonding, tautomeric form and the secondary interactions. The HOMA [61] index based on the bond lengths is able to describe the degree of electron conjugation and thus the variances in molecular geometry. Tables 5, 6 and 7 collect the HOMA indexes calculated for heterocyclic rings in studied structures.

The HOMA index is practically constant in $1'-3'$, both in monomeric and hydrogen-bonded complexes containing $1'-3'$. The HOMA values are slightly higher for compounds **2** and **3** compared to **1** (Table 5). The HOMA index is increased in dimers (**1+1**, **2+2**, **3+3** - Table 6) compared the respective values for monomers (Table 5). It is interesting that HOMA for 2-[1*H*]-pyridone molecule raises when it forms complex with the 6-amino(hydroxy)-2-[1*H*]-pyridone (**2,3**), *i.e.* the substitution at 6' position of ring A' influences the π -electron conjugation in the ring A. All values of HOMA index for transition states are comparable (Table 7).

Conclusions

The intermolecular interactions in a classic 2-[1*H*]-pyridone/2-hydroxypyridine tautomeric pair are influenced by the substitution of the 6th position. The geometry and the energy of interaction follow the general trend of secondary interaction concept. The transition state of double proton transfer within the hydrogen-bonded complex is also affected by the type and number of secondary interaction present. The difference in E_a between the highest and the lowest lying transition state equals to 11 kcal mol⁻¹. In general, the pyridone form is more stable than the hydroxypyridine one. The HOMA index of aromaticity for heterocyclic rings changes only slightly showing no straightforward conclusions.

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