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Geometric and energetic consequences of prototropy for neutral and ionized 4-aminopyrimidine in water solution

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Quantum-chemical calculations were performed for the major, minor, and rare tautomers of neutral and ionized 4-aminopyrimidine (**4APM**, **4APM+●**, and **4APM-●**) in water solution at the PCM(water)//DFT(B3LYP)/6-311+G(d,p) level. Four tautomers were considered, one amine and three imine forms. Geometric isomerism of the exo =NH group was also taken into account. Ionization strongly influences the relative stabilities (ΔE) of the amino and imino forms in water solution. The amine tautomer is favored for **4APM**, whereas the imine ones have the lowest energies for the charged radicals, that is, the imine form with the labile proton at the endo N1 atom for **4APM+●** and the imine form with the labile proton at the endo C5 atom for **4APM-●**. The geometric parameters (HOMED - harmonic oscillator model of electron delocalization) estimated in water solution correlate well with those found in the gas phase {B3LYP/6-311+G(d,p)} for all tautomers of **4APM**, **4APM+●**, and **4APM-●**. A good relation also exists between the HOMED and ΔE values for the neutral and positively ionized forms in water solution. For the radical anions, the HOMED/ΔE relation is more complex. The electron affinity seems to be a more important factor than aromaticity, and dictates the tautomeric preference.

Key words: 4-Aminopyrimidine, Tautomers, Ionization Effects, Relative stabilities, HOMED indices, DFT, PCM

INTRODUCTION

Prototropy and electron delocalization (particularly aromaticity) are well known phenomena that infuence the structure and properties of many chemical compounds, natural products, and drugs [1-6]. Electron delocalization is a concept introduced for molecules (e.g., butadiene, benzene, guanidinium cation, pyridine, pyrimidine, etc.) displaying an exceptional stability, for which a single arrangement of atoms cannot be represented by one Lewis electronic structure, and the resonance hybrid has been proposed [7-9]. Prototropy is a concept introduced for chemical compounds (e.g. phenols, hydroxyazines, imidazoles, purines, nucleobases, etc.) displaying a particular case of isomerism of functional groups [1-6, 10]. It refers to a compound existing in an equilibrium between two or more isomers (tautomers) which differ by their constitution, i.e., by the positions of the labile proton(s). Consequently, tautomers differ by the positions of the double bond(s), and their structures can be explained by the resonance hybrids. A relation between prototropy and electron delocalization has been signaled more than fifty years ago by Pauling [10]. For example, phenol favors its enol form because of a complete electron delocalization (aromaticity) in the ring, whereas cyclohexanone takes preferentially the keto form [11, 12]. 2-aminopyridines prefer more aromatic amino than imino forms [13].

In the case of 4-aminopyrimidine (**4APM**), prototropy and electron delocalization have been recently discussed for isolated systems [14]. Since **4APM** is a convenient model for the nucleobases cytosine [15], vitamin B_1 thiamine molecules [16], and novel HIV inhibitors [17], investigations in water solution were undertaken in this paper. Four tautomers (Scheme 1): one amine form (**1**) and three imine forms (**2-4**) are possible for **4APM**. One proton can move between the exo NH_2 group and the endo N and C atoms. Due to geometric isomerism of the exo =NH group, two isomers can be considered for **2-4**, one with the imine H atom synperiplanar to the ring N3 atom (**a**) and the other one with this atom antiperiplanar (**b**). In the solid state, neutral **4APM** exists in the amine form **1** [18]. This form has been also found for isolated and associated neutral **4APM** [14, 19-25]. The ionized forms of **4APM** have been solely investigated by us in the gas phase [14]. Since ionization changes tautomeric equilibria [14], the complete tautomeric mixture of **4APM** was studied here in water solution.

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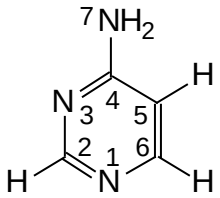
It is well known that tautomeric conversions are very fast and reversible processes, and it is difficult to separate and to study the individual tautomers [1-6]. For this reason, quantum-chemical calculations were performed for all seven isomers of neutral, positively, and negatively ionized forms of 4-aminopyrimidine (**4APM**, **4APM**$^{+\bullet}$, and **4APM**$^{-\bullet}$) in water solution at the PCM(water)//DFT(B3LYP)/6-311+G(d,p) level. This level of theory has been chosen previously for investigations of the favored and rare tautomers of adenine in water solution [26]. The computations give the possibilities to study the variations of geometric and energetic consequences of prototropy for all possible tautomers when proceeding from the gas phase {B3LYP/6-311+G(d,p)} to water solution {PCM(water)//B3LYP/6-311+G(d,p)}.

Spectroscopic techniques (e.g., UV, IR, NMR, MW, MS, etc.) were not applied here to the tautomeric mixture, because their application gives solely an information on the major tautomers, signals of which have significant intensities. The minor and rare tautomers cannot be detected when their amounts are too small (< 0.1%) and their signals are in the background.

Amine NH_2 tautomer



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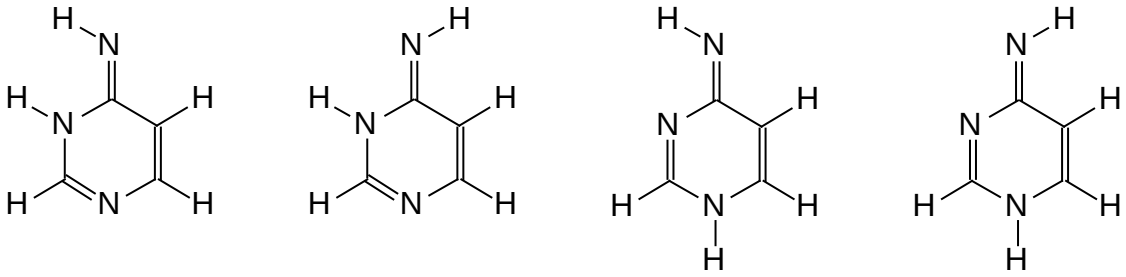
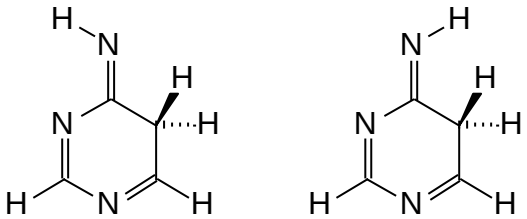
Imine NH isomers



2a **2b** **3a** **3b**

Imine CH isomers



4a **4b**

Scheme 1. Prototropic tautomers of 4-aminopyrimidine.

METHODS

Geometries of all seven neutral and charged isomers of 4-aminopyrimidine in their ground states were fully optimized without symmetry constraints employing the DFT(B3LYP) method [27-29] and the 6-311+G** basis set [30]. The restricted and unrestricted B3LYP functionals were used for the neutral and ionized forms, respectively. The solvent effect was studied with the PCM method [31, 32] applied to water as solvent. Geometries of all isomers were re-optimized at the PCM(water)//B3LYP/6-311+G(d,p) level, and the relative energies calculated. All calculations were performed using the Gaussian 03 program [33]. The adiabatic ionization potential (IP) and the adiabatic electron affinity (EA) were estimated using equations (1) and (2), respectively, where *E*s are the total electronic energies of the optimized charged (**4APM**$^{+\bullet}$ and **4APM**$^{-\bullet}$) and neutral isomers (**4APM**) of 4-aminopyrimidine. The geometry-based HOMED (harmonic oscillator model of electron delocalization) indices [34, 35] were estimated for the neutral and charged isomers optimized at the PCM//DFT level using equation (3) as described previously for purine [36]. In this equation, α is a normalization constant, R_o is the optimum bond length (assumed to be realized for fully delocalized system), R_i are the running bond lengths in the system, and n is the number of bonds taken into account. Equation (3) is the same as that for the original [37] and reformulated [38] HOMA (harmonic oscillator model of aromaticity) indices. Similarities and differences between HOMED and HOMA were described in details in refs [35, 36].

$$IP = E(\mathbf{4APM}^{+\bullet}) - E(\mathbf{4APM}) \quad (1)$$

$$EA = E(\mathbf{4APM}) - E(\mathbf{4APM}^{-\bullet}) \quad (2)$$

$$HOMED = 1 - \{\alpha\Sigma(R_o - R_i)^2\}/n \quad (3)$$

RESULTS AND DISCUSSION

Geometric Parameters

For the seven isomers of neutral and charged 4-aminopyrimidine (Scheme 1), the minima with all real frequencies were found in the gas phase at the DFT(B3LYP)/6-311+G** level [14]. The PCM model with water as solvent does not change very much the geometries optimized in the gas phase. In water solution, the exo NH_2 group is planar solely for the radical cation (**1**$^{+\bullet}$). For the radical anion (**1**$^{-\bullet}$), this group takes the pyramidal conformation similar to the neutral form (**1**).

The transfer of the labile proton to the endo N atom in the structures **2a**, **2b**, **3a**, and **3b** (imine NH isomers) does not destroy the planarity of the ring for the neutral and ionized forms in water solution. Due to presence of the C-sp^3 atom (C5), the structures **4a** and **4b** (imine CH isomers) lose the planarity of the ring at each oxidation state.

Table 1. Comparison of the HOMED indices estimated for the seven isomers of neutral and ionized 4-aminopyrimidine in water solution with those in the gas phase

(a) gas phase {B3LYP/6-311+G(d,p)} [14]

	Neutral form		Radical cation		Radical anion	
Isomer	HOMED6	HOMED7	HOMED6	HOMED7	HOMED6	HOMED7
1	0.991	0.981	0.950	0.960	0.904	0.843
2a	0.737	0.756	0.924	0.936	0.712	0.767
2b	0.707	0.736	0.938	0.949	0.775	0.818
3a	0.664	0.701	0.917	0.934	0.777	0.805
3b	0.663	0.702	0.921	0.936	0.773	0.804
4a	0.346	0.435	0.122	0.226	0.557	0.640
4b	0.170	0.297	0.106	0.210	0.470	0.574

(b) water solution {PCM(water)//B3LYP/6-311+G(d,p)}

	Neutral form		Radical cation		Radical anion	
Isomer	HOMED6	HOMED7	HOMED6	HOMED7	HOMED6	HOMED7
1	0.979	0.981	0.937	0.949	0.867	0.841
2a	0.797	0.816	0.957	0.958	0.786	0.828
2b	0.813	0.828	0.954	0.961	0.806	0.844
3a	0.765	0.795	0.935	0.949	0.749	0.801
3b	0.766	0.797	0.934	0.948	0.749	0.802
4a	0.384	0.470	0.199	0.287	0.556	0.641
4b	0.406	0.486	0.211	0.308	0.580	0.658

In water solution, the CC (1.375-1.416 Å) and CN (1.333-1.354 Å) bond lengths for the neutral amine NH_2 tautomer **1** are not very different from those calculated for fully delocalized benzene (1.396 Å) and *s*-triazine (1.335 Å), respectively. The HOMED indices (Table 1) estimated for the six-membered ring (HOMED6 = 0.979) and for the whole tautomeric system including the exo NH_2 group (HOMED7 = 0.981) are close to unity, confirming the aromatic character of **1**. The transfer of the labile proton from the exo NH_2 group to the endo N atom induces larger variations of the CC (1.349-1.461 Å) and CN (1.295-1.412 Å) bond lengths for the neutral imine NH isomers (**2a**, **2b**, **3a**, and **3b**) than for **1**. Consequently, the HOMED indices (< 0.9) for **2a**, **2b**, **3a**, and **3b** are lower than those for **1**. The neutral imine CH isomers (**4a** and **4b**) completely lose their aromatic character. The CC bond lengths (1.498-1.512 Å) for **4a** and **4b** are close to that for ethane (1.531 Å), and their CN bond lengths (1.413-1.415 Å and 1.273-1.285 Å) are close to those for methylamine (1.469 Å) and methylimine (1.270 Å). Hence, the HOMED indices estimated for **4a** and **4b** are lower than 0.5. All bond lengths for simple compounds (ethane, methylamine, methylamine, benzene, and s-triazine) were calculated at the PCM(water)//B3LYP/6-311+G(d,p) level [36].

When going from the neutral isomers of 4-aminopyrimidine to the radical cations, variations of the CC and CN bond lengths are greater for the charged amine ($\mathbf{1}^{+\bullet}$) and imine CH isomers ($\mathbf{4a}^{+\bullet}$ and $\mathbf{4b}^{+\bullet}$) than for the neutral ones. However, they are smaller for the charged imine NH isomers ($\mathbf{2a}^{+\bullet}$, $\mathbf{2b}^{+\bullet}$, $\mathbf{3a}^{+\bullet}$, and $\mathbf{3b}^{+\bullet}$) than for the neutral ones. Consequently, positive ionization decreases the HOMED indices for the amine NH_2 and imine CH isomers (by 0.03-0.04 and 0.18-0.20 HOMED units, respectively), and increases them for the imine NH ones (by 0.13-0.17 HOMED units). Quite a different situation takes place when proceeding from the neutral isomers to the radical anions of 4-aminopyrimidine for which resonance conjugations and variations of the CC and CN bond lengths are completely different. Negative ionization induces an exceptional increase of π-electron delocalization. Small variations of the CC and CN bonds are observed for the negatively ionized imine CH isomers ($\mathbf{4a}^{-\bullet}$ and $\mathbf{4b}^{-\bullet}$). For the charged imine NH isomers ($\mathbf{2a}^{-\bullet}$, $\mathbf{2b}^{-\bullet}$, $\mathbf{3a}^{-\bullet}$, and $\mathbf{3b}^{-\bullet}$), delocalization of π-electrons also changes. However, it decreases for the charged amine isomer ($\mathbf{1}^{-\bullet}$). Consequently, the HOMED indices increase for the imine CH tautomers (by ca. 0.17 HOMED units) and decrease for the amine NH_2 one (by 0.11-0.14 HOMED units). For the imine NH tautomers, the HOMED variations are not larger than ±0.02 units.

Generally, trends observed in water solution are similar to those in the gas phase [14], that is, the aromatic amine NH_2 and imine NH isomers are more delocalized than the non-aromatic imine CH ones. Solvent decreases slightly the HOMED values for **1** and it increases them for **2**-**4**, for both the neutral and ionized forms. Although these solvent effects are different for the individual isomers, there is a good linear relationship between the HOMED values estimated in water solution and those in the gas phase for the pyrimidine ring - six bonds, and also for the whole tautomeric system - seven bonds (Fig. 1). This indicates that the solvent does not affect very much the resonance conjugations possible for the neutral and ionized isomers of 4-aminopyrimidine. Electron delocalization in water solution is parallel to that in the gas phase.

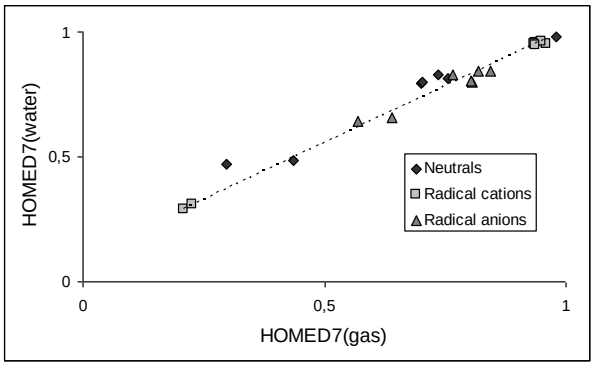


Fig. 1. Correlation between the HOMED7 values estimated in the gas phase and in water solution for the whole tautomeric system (seven bonds) of the neutral and ionized isomers of 4-aminopyrimidine

Relative Stabilities

The relative energies (Δ*E*) calculated in water solution for all neutral and charged isomers can be compared with those in the gas phase (Table 2). As it could be expected [14, 19-25], the amine tautomer **1** has the lowest energy for neutral **4APM**. Aromaticity of the six membered ring seems to be one of the most important factor that dictates the high stability of **1** and its tautomeric preference (100%) in both environments. The imine NH tautomers (**2** and **3**) possess considerably larger energies than **1** (Δ*E* > 10 kcal mol^{-1}). They are lower in water solution (Δ*E* 10-12 kcal mol^{-1}) than in the gas phase (Δ*E* 13-22 kcal mol^{-1}). The

transfer of the labile proton to the endo C atom decreases exceptionally the stability of **4a** and **4b**. Their energies are larger than that of **1** by more than 30 kcal mol^{-1} in both environments. The intramolecular favorable and unfavorable interactions possible for the structures **a** and **b** of the imine NH and CH tautomers differentiate their energies in higher degree in the gas phase (3-5 kcal mol^{-1}) than in water solution (ca. 1 kcal mol^{-1}). However, these effects do not influence the tautomeric preference. The percentage contents of the imine NH and CH tautomers are very low (< 0.001 %). Indeed, they cannot be experimentally detected for neutral **4APM**, and thus they may be neglected in the tautomeric mixture.

Positive ionization changes the tautomeric preferences in water solution for **4APM**$^{+\bullet}$. Although the amine tautomer (**1**$^{+\bullet}$) has the lowest energy in the gas phase [14], the imine NH isomer (**3a**$^{+\bullet}$) dominates in water solution. Ionization and solvent also change the relative energies of the amine NH_2 (**1**$^{+\bullet}$) and imine NH tautomers (**2a**$^{+\bullet}$, **2b**$^{+\bullet}$, **3a**$^{+\bullet}$, and **3b**$^{+\bullet}$), and the compositions of the tautomeric mixture are different in both environments. They are as follows: 88.3% of **1**$^{+\bullet}$, 7.3% of **2**$^{+\bullet}$, and 4.4% of **3**$^{+\bullet}$ in the gas phase, and 1.5% of **1**$^{+\bullet}$, 27.0% of **2**$^{+\bullet}$, and 71.5% of **3**$^{+\bullet}$ in water solution. This difference should be considered in electron-transfer reactions in which 4-aminopyrimidine loses one electron. It should be also taken into account for positively ionized cytosine, vitamin B_1 thiamine molecules, and some HIV inhibitors. The Δ*E* values for the imine CH isomers (**4a**$^{+\bullet}$ and **4b**$^{+\bullet}$) are larger than 40 kcal mol^{-1} in both environments. Thus, their percentage contents are very low (< $1 \cdot 10^{-30}$ %). As exceptionally rare isomers, they may be neglected in the tautomeric mixture of **4APM**$^{+\bullet}$.

Negative ionization dramatically changes the tautomeric preference. For **4APM**$^{-\bullet}$, the imine CH isomer (**4a**$^{-\bullet}$) with the labile proton at the endo C5 atom has the lowest energy in water solution, as well as in the gas phase. Change of environment decreases solely the relative energies. In water solution, two tautomers should be considered in the tautomeric mixture of **4APM**$^{-\bullet}$: **1**$^{-\bullet}$ (1.3%) and **4**$^{-\bullet}$ (98.7%), whereas only one (**4**$^{-\bullet}$, 100%) in the gas phase. The amount of **1**$^{-\bullet}$ (0.03%) is very low in the gas phase. It may be considered as the rare tautomer. The imine NH tautomers (**2**$^{-\bullet}$ and **3**$^{-\bullet}$) possess considerably larger energies than **4**$^{-\bullet}$ (> 4 kcal mol^{-1}). They may be neglected in the tautomeric mixture of **4APM**$^{-\bullet}$ in both environments.

HOMED/ΔE Relation

A parallelism of the Δ*E* and HOMED values for the neutral and positively ionized isomers indicates that some relation exists between prototropy and electron delocalization for 4-aminopyrimidine (Fig. 2). In water solution, the HOMED7 indices estimated for the neutral isomers of **4APM** correlate well with their Δ*E* values: HOMED7(water) = -0.014Δ*E* + 0.972, R = -0.999. Similar relationship is found in the gas phase: HOMED7(gas) = -0.017Δ*E* + 1.007, R = -0.977. The HOMD7/Δ*E* correlation is slightly better in water solution than in the gas phase. Solvent diminishes intramolecular interactions between the exo and endo functional groups, and influences the relative energies and the HOMED indices. The energetic effects are larger than the geometric ones. Electron delocalization (aromaticity) seems to be one of the main factors that influences the stability of the neutral forms. It is also an important factor for the radical cations. A good linear relationship between the HOMED7 and Δ*E* values is observed in water solution {HOMED7(water) = -0.013Δ*E* + 0.967, R = -0.999}. The parameters of this relationship do not differ very much from those found for the neutral isomers. Negative ionization differentiates the imine CH isomers from the family of other ones (NH_2 and NH). In this case, the HOMED/Δ*E* relation is more complex. The electron affinity seems to be more important factor than aromaticity and dictates the tautomeric preference.

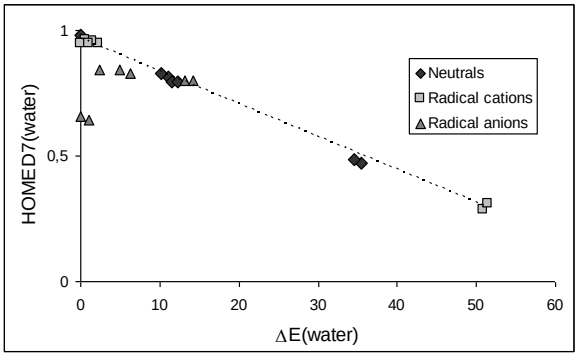


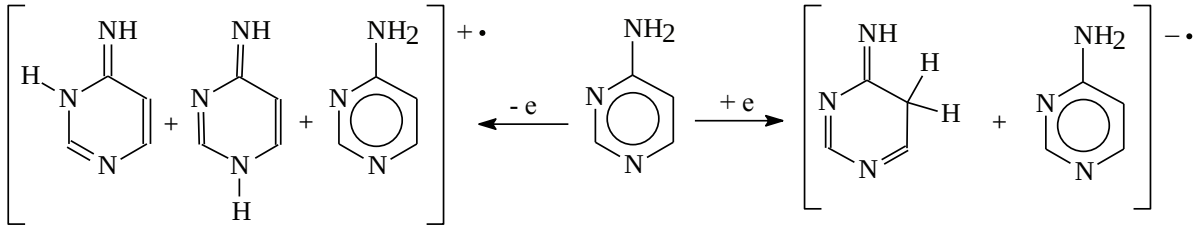
Fig. 2. HOMED7/Δ*E* plot for the neutral and ionized isomers of 4-aminopyrimidine in water solution.

Table 2. Comparison of the relative energies (in kcal mol^{-1} at 0 K) calculated for the seven isomers of neutral and ionized 4-aminopyrimidine in water solution with those in the gas phase

	Neutral form		Radical cation		Radical anion	
Isomer	Gas	Water	Gas	Water	Gas	Water
1	0.0	0.0	0.0	2.2	6.4	2.4
2a	16.1	11.0	4.5	1.5	10.2	6.3
2b	12.9	10.1	0.9	0.6	6.8	4.9
3a	18.3	11.5	1.4	0.0	17.7	13.2
3b	22.5	12.3	6.2	1.1	21.6	14.2
4a	37.8	35.5	45.4	50.9	4.8	1.0
4b	33.2	34.5	44.8	51.5	0.0	0.0

Table 3. The adiabatic ionization potentials (IP) and the adiabatic electron affinities (EA) estimated for all isomers of 4-aminopyrimidine in the gas phase and in water solution (in eV at 0 K, 1 eV = 23.06037 kcal mol^{-1})

Positive	IP		Negative	EA	
ionization	Gas	Water	ionization	Gas	Water
1 – e → $\mathbf{1}^{+\bullet}$	8.8	6.4	**1** + e → $\mathbf{1}^{-\bullet}$	-0.6	1.6
2a – e → $\mathbf{2a}^{+\bullet}$	8.3	5.9	**2a** + e → $\mathbf{2a}^{-\bullet}$	-0.1	1.9
2b – e → $\mathbf{2b}^{+\bullet}$	8.3	5.9	**2b** + e → $\mathbf{2b}^{-\bullet}$	-0.1	1.9
3a – e → $\mathbf{3a}^{+\bullet}$	8.1	5.8	**3a** + e → $\mathbf{3a}^{-\bullet}$	-0.3	1.6
3b – e → $\mathbf{3b}^{+\bullet}$	8,1	5.8	**3b** + e → $\mathbf{3b}^{-\bullet}$	-0.3	1.6
4a – e → $\mathbf{4a}^{+\bullet}$	9.3	7.0	**4a** + e → $\mathbf{4a}^{-\bullet}$	1.1	3.2
4b – e → $\mathbf{4b}^{+\bullet}$	9.1	7.0	**4b** + e → $\mathbf{4b}^{-\bullet}$	1.1	3.2



Scheme 2. The favored ionization reactions for 4-aminopyrimidine

Ionization Processes

A simple one-electron loss or one-electron gain may be observed during positive or negative ionization in the mass spectrometer. Consequently, 4-aminopyrimidine may be transformed to its positively (**4APM** – e → $\mathbf{4APM}^{+\bullet}$) or negatively ionized (**4APM** + e → $\mathbf{4APM}^{-\bullet}$) very reactive states. In the presence of oxidizing or reducing agents, neutral 4-aminopyrimidine may also lose or gain one electron. The mechanisms of chemical redox reactions, anodic oxidations or cathodic reductions of 4-aminopyrimidine, may be very complex and may depend on reaction conditions such as solvent, reagent, catalyst, etc.. The redox processes may pass through different intermediates among which the charged forms, $\mathbf{4APM}^{+\bullet}$ and $\mathbf{4APM}^{-\bullet}$, are possible.

A direct comparison of the energetic parameters for the ionized and neutral isomers of 4-aminopyrimidine suggests that one-electron loss is less endothermic process in water solution than in the gas phase, and one-electron gain is more profitable process than one-electron loss in both environments (Table 3). This means that 4-aminopyrimidine may take spontaneously one electron from a reducing agent. Interestingly, change of the position of the imine H atom vis-à-vis the ring N3 atom from synperiplanar to antiperiplanar has no important effect on the values

of the adiabatic ionization potential (IP) and of the adiabatic ionization affinity (EA). This suggests that favorable and unfavorable interactions possible for the neutral and ionized isomers are similar. However, the IP and EA values are different for the amine (NH_2) and imine (NH and CH) tautomers. The ionization mechanisms are not the same. An analysis of the distribution of the spin density and charge computed in the gas phase and in water solution shows evidently the differences. For the NH_2 and NH tautomers, the exo N atom may lose preferentially one of the non-bonding electrons, whereas the endo N atoms may participate in one-electron loss for the CH isomers. On the other hand, the pyrimidine ring may gain one excess electron for the NH_2 and NH tautomers, whereas the exo N atom may participate in one-electron gain. This tendency is similar in both environments. When going from the gas phase to water solution, the IP and EA values vary by ca. 2 eV.

If we consider solely the major and minor tautomers for neutral, positively, and negatively ionized 4-aminopyrimidine, the following ionization processes can be proposed (Scheme 2), and the following IP and EA values can be estimated for 4-aminopyrimidine in the gas phase and in water solution (ground states): IP 8.8 and 6.3 eV, EA -0.4 and 1.6 eV at 0K, respectively. The IP (8.5 and 6.3 eV) and EA values (-0.4 and 1.8 eV) found for 2-aminopyrimidine at the same levels of theory are of the same order of magnitude [39]. Unfortunately, there are no experimental data in the literature for the ionization potential (IP) and for the electron affinity (EA) of **4AMP** and no comparison can be made. However, it should be mentioned here that the IP values in the gas phase for pyrimidine (9.3 eV [40]), 2- and 4-aminopyridine (8.5 and 8.8 eV, respectively [41]) are of the same order of magnitude as the DFT-estimated IP for **4APM**. The literature EA value for unsubstituted pyrimidine is not very large in the gas phase (> -0.24999 eV [42]). The negative value suggests that the anion is not higher in energy than the corresponding neutral form, and hence unstable in the gas phase. However, the anion can be studied in water solution. The calculated EA value is positive for **4APM** in water solution. Similar tendencies on the IP and EA values in the gas phase and in water solution have been reported for nucleobases [26, 43, 44]. 4-Aminopyrimidine models well the redox properties of cytosine and adenine, containing the exo NH_2 group at the same position vis-à-vis the endo N atoms in the pyrimidine ring.

CONCLUSIONS

Quantum-chemical calculations performed for all possible amine and imine tautomers-isomers of neutral 4-aminopyrimidine (**4APM**) and of its charged forms (**4APM**$^{+\bullet}$ and **4APM**$^{-\bullet}$) show evidently important changes of the tautomeric preference when proceeding from the gas phase to water solution (Scheme 2). The neutral tautomeric mixture of **4APM** consists mainly of the amine NH_2 tautomer (100%). This is independent on environment. Positive and negative ionizations dramatically change the composition of the tautomeric mixture. The tautomeric preference for **4APM**$^{+\bullet}$ depends on the medium. In the gas phase, the amine NH_2 tautomer is favored for **4APM**$^{+\bullet}$, whereas the imine NH isomer with the labile proton at the N1 atom dominates in water solution. For **4APM**$^{-\bullet}$, the C5 atom takes preferentially the labile proton and the imine CH isomer is favored in the gas phase and also in water solution. Solvent has slight effect on the composition of the tautomeric mixture of **4APM**$^{-\bullet}$.

The geometric HOMED indices, which measure electron delocalization for the individual isomers, change little when proceeding from the gas phase to water solution. Larger variations take place for the relative energies (ΔE), which measure prototropic conversions. However, the HOMED and ΔE values correlate well for the neutral and positively ionized isomers of 4-aminopyrimidine (Fig. 2). Some discrepancies occur for the radical anions, for which the HOMED/ΔE relation seems to be more complex. In this case, two factors (electron affinity and aromaticity) influence the tautomeric conversions. For the favored ionization processes, the adiabatic ionization potentials and the adiabatic ionization affinities change by ca. 2 eV when proceeding from the gas phase to water solution. This solvent effect is similar to that reported for nucleobases [43, 44].

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ГЕОМЕТРИЧНИ И ЕНЕРГИЙНИ СЛЕДСТВИЯ ОТ ПРОТОТРОПИЯТА НА НЕУТРАЛЕН И ЙОНИЗИРАН 4-АМИНОПИРИМИДИН ВЪВ ВОДНИ РАЗТВОРИ

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(Резюме)

Извършени са квантово-химични пресмятания за тавтомерните форми (главни, малки, редки) на неутрален и йонизиран 4-аминопиримидин (**4APM, 4APM**+ и **4APM**$^-$) във водни разтвори на PCM(вода)//DFT(B3LYP)/6-311+G(d,p) ниво. Разгледани са четири тавтомери – една аминна и три иминни форми. Отчетен е и изометризмът на екзо =NH групите. Йонизацията силно влияе върху относителната стабилност (ΔE) на амино- и имино-формите във водни разтвори. Амино-тавомерите са предпочитани при **4APM**, докато иминните имат най-ниска енергия на натоварените радикали, т.е. имино-формите имат лабилен протон при ендо N 1 атома за **4APM**$^+$, а имино-формата е с лабилен протон при ендо C5-атом за **4APM.** Геометричните параметри (HOMED – модел на хармоничен осцилатор на електронна делокализация), оценени за воден разтвор се корелират добре с намерените за газова фаза {B3LYP/6-311+G(d,p)} за всички тавтомери - **4APM**, **4APM+ и 4APM**$^-$. Добра релация съществува между стойностите на HOMED и ΔE за неутрални и положително йонизираните форми във воден разтвор. Релацията HOMED/ΔE за анион-радикалите е по-сложна. Изглежда, че електронният афинитет е по-важен фактор и ароматната природа и определя предпочитането на тавтомерните форми.