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ORIGINAL PAPER

Consequences of one-electron oxidation and one-electron reduction for 4-aminopyrimidine—DFT studies

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Abstract The consequences of one-electron oxidation and one-electron reduction were studied for 4-aminopyrimidine (**4APM**), which displays prototropic tautomerism. Since experimental techniques are incapable of detecting less than 0.1% of minor tautomers, quantum-chemical calculations [DFT(B3LYP)/6-311+G(d,p)] were carried out for all possible tautomers of neutral **4AMP** and its redox forms, **4APM** $^{+\bullet}$ and **4APM** $^{-\bullet}$. Four tautomers were considered: one amine and three imine tautomers (two NH and one CH form). Geometric isomerism of the exo=NH group was also taken into account. One-electron oxidation (**4APM** − e → **4APM**$^{+\bullet}$) has no significant effect on the tautomeric preferences; it influences solely the composition of the tautomeric mixture. The amine tautomer is favored for both **4APM**$^{+\bullet}$ and **4APM**. An interesting change in the tautomeric preference occurs for **4APM** $^{-\bullet}$. One-electron reduction (**4APM**+e → **4APM** $^{-\bullet}$) favors the C5 atom for the labile proton. The preference of the imine CH tautomer in the tautomeric mixture of **4APM** $^{-\bullet}$ may partially explain the origin of CH tautomers in nucleobases.

Keywords 4-Aminopyrimidine · NH and CH tautomers · Effects of one-electron oxidation · Effects of one-electron reduction · DFT

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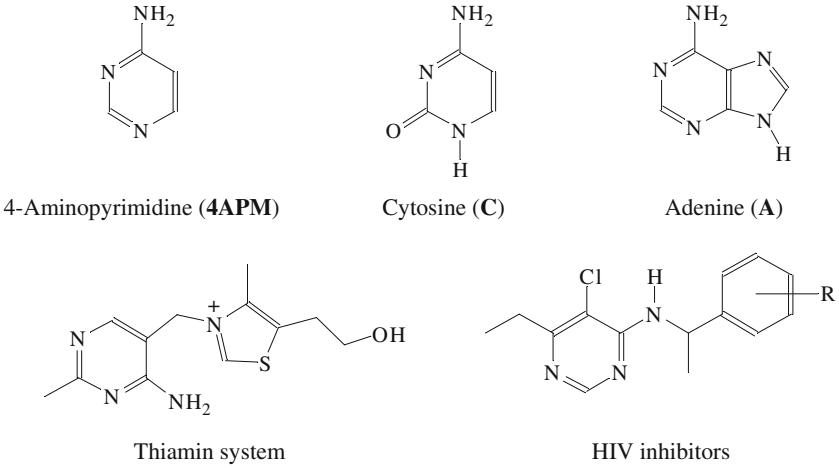
Introduction

Prototropic tautomerism is one of the most common investigated forms of isomerism for nucleobases [1–5]. Various prototropic conversions, such as keto–enol, amide–iminol, amine–imine, and enamine–imine tautomerism have been analyzed for nucleobases as well as for their convenient models. However, literature data are incomplete even for model compounds [5], with minor tautomers very frequently having been omitted. Investigations limited to the favored form(s) do not give a complete picture of the structure of nucleobases and their chemical and biochemical properties. Understanding the mechanisms of many important chemical and biochemical transformations, including ion-radical reactions, first requires an understanding of tautomerization for model compounds. In this paper, we chose a simple compound, 4-aminopyrimidine (**4APM**), which is a convenient model for the nucleobases cytosine and adenine (Scheme **1**). **4APM** is also a building block of the vitamin B_1 thiamin molecule [6] and of novel HIV inhibitors of unknown molecular target [7].

4-Aminopyrimidine contains one exo NH_2 group and two endo N-aza groups. Their positions in the six-membered ring are the same as those for nucleobases cytosine and adenine, and for the more complex thiamine system and HIV inhibitors. **4APM** possesses one labile proton that can move from the exo NH_2 group to the endo N or C atom. Four tautomers are thus possible for **4APM** (Scheme 2), one amine form (**1**) with the labile proton at the exo N atom, and three imine forms (**2**–**4**) with the labile proton at the endo N and C atoms. For all of them, the intramolecular proton transfer is accompanied by migration of π-electrons. Due to the geometric isomerism of the exo=NH group, two isomers are possible for **2**–**4**, one with the imine H atom synperiplanar to the ring N3 atom (**a**), and the other with the imine H atom antiperiplanar to the ring N3 atom (**b**).

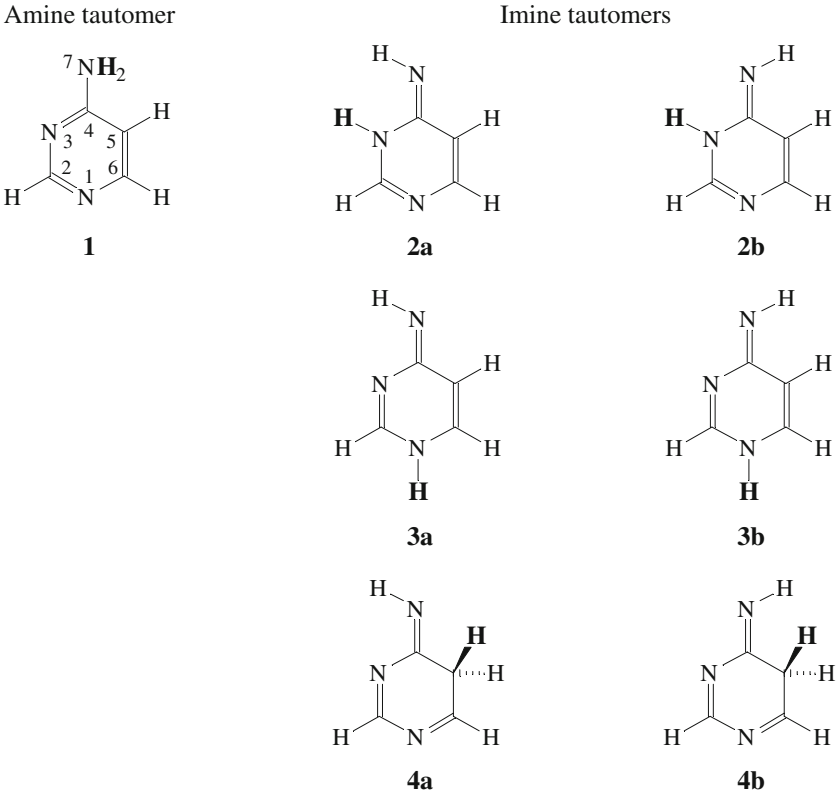
Scheme 1 4-Aminopyrimidine (**4APM**) and its biologically active derivatives



In the solid state, **4APM** exists in the amine form **1** [8]. This form has been usually considered for free and associated **4APM** [9–15]. The amine–imine conversions **1→2** and **1→3** have been analyzed with various experimental and theoretical methods solely for the thiamine system and convenient related models [16–21]. To our knowledge, there is no report on prototropy for redox forms of **4APM**. For this reason, we studied all possible tautomers and all possible conversions for neutral, oxidized, and reduced 4-aminopyrimidine. For our investigations, we chose quantum-chemical methods, because experimental techniques are incapable of detecting less than 0.1% of minor tautomers. We applied the DFT method [22] with the B3LYP functional [23, 24] and the 6-311+G (d,p) basis set [25]. The DFT method has been applied successfully to proton transfer reactions, including tautomeric conversions in the gas phase that model apolar environments [26–34].

We considered various oxidation states for **4APM**: the neutral state (**4APM**), the radical cation (**4APM** − e → **4APM**$^{+\bullet}$), and the radical anion (**4APM**+e → **4APM**$^{-\bullet}$). We studied the consequences of one-electron oxidation and one-electron reduction when proceeding from neutral **4APM** to its redox forms. The redox forms can be formed in the presence of oxidizing or reducing agents [35, 36]. They can

Scheme 2 Tautomers of **4APM** (labile proton marked in *bold*)



also be generated electrochemically, photochemically, or in various types of mass spectrometers during positive or negative ionization [37–39]. Transfering an electron from or to a tautomeric molecule may change the stabilities of individual tautomers. Consequently, electron transfer may influence tautomeric equilibria and change the composition of tautomeric mixtures. Changes in tautomeric preferences may affect the mechanism of ion-radical reactions.

Computational details

Geometries of all neutral and redox isomers of **4APM** were fully optimized without symmetry constraints employing the DFT(B3LYP) method [22–24] and the 6-311+G(d,p) basis set [25]. All calculations were performed using the Gaussian 03 program [40]. For all neutral, oxidized, and reduced isomers, the DFT minima were found and thermodynamic parameters such as the energy (E), enthalpy ($H=E+pV$), entropy (S), and Gibbs energy ($G=H-TS$ for $T=298.15$ K) were calculated using the same level of theory. For the tautomeric conversions, the relative thermodynamic parameters (ΔE_T, ΔH_T, $T\Delta S_T$, and ΔG_T), the tautomeric equilibrium constants (as $pK_T=\Delta G_T/2.303RT$), and the percentage contents of individual forms $\{x=K_T/(1+K_T)\}$ were estimated. For oxidation and reduction processes, the corresponding thermodynamic parameters of oxidation (ΔE_{ox}, ΔH_{ox}, $T\Delta S_{ox}$, and ΔG_{ox}) and reduction (ΔE_{red}, ΔH_{red}, $T\Delta S_{red}$, and ΔG_{red}) were also calculated. The ΔG values include the changes in electronic energy, in zero-point energy (ZPE), and in thermal corrections to energy and entropy (vibrational, rotational, and translational).

Results and discussion

Geometries

For all isomers of neutral, oxidized, and reduced **4APM** (Scheme 2), the minima with all real frequencies were found at the DFT(B3LYP)/6-311+G(d,p) level. First perusal of the calculated geometric parameters shows that the loss or gain of one electron does not alter the geometric parameters very much. The exo NH_2 group is planar solely for the radical cation. For the radical anion, this group takes a pyramidal conformation similar to the neutral form [10, 16]. Due to the presence of the C-sp3 atom (C5), structures **4a** and **4b** lose the planarity of the ring. Other imine isomers (**2a**, **2b**, **3a**, and **3b**) are planar or almost planar. Transfer of the proton to the endo N atom only slightly affects the planarity of the ring (except radical anion isomers).

The CC and CN bond lengths, calculated for the neutral and redox isomers of **4APM**, are given in Table 1. For neutral isomers **1–3**, they are close to those calculated by Balci and Akyuz [10], and by Kitamura et al. [16] at the B3LYP/6-31++G(d,p) and/or B3LYP/6-311++G(d,p) levels. Differences in bond lengths are not larger than 0.02 Å. Generally, the CC bond lengths vary from 1.34 to 1.52 Å for neutral isomers, from 1.38 to 1.54 Å for oxidized isomers, and from 1.35 to 1.54 Å for reduced isomers. Variations in the CN bond lengths are as follows: 1.27–1.42, 1.25–1.43, 1.30–1.43 Å, respectively. Comparison of the CC and CN bond lengths for the neutral isomers of **4AMP** to those for fully delocalized aromatic systems, benzene (1.39 Å) and 1,3,5-triazine (1.33 Å), computed at the B3LYP/6-311+G(d,p) level [32], leads to the following conclusions. The CC (1.38-1.41 Å) and CN (1.33–1.36 Å) bond lengths for **1** are not very different from those calculated for benzene and *s*-triazine. This indicates that the amine tautomer **1** is aromatic. However, transfer of the labile proton to the endo N atom causes larger variations of the CC (1.34–1.47 Å) and CN (1.28–1.42 Å) bond lengths. Consequently, aromaticity of the imine NH tautomers **2** and **3** decreases. The imine CH isomers completely lose their

Table 1 The CC and CN bond lengths (in Å) calculated at the DFT (B3LYP)/6-311+G(d,p) level for all possible isomers of neutral 4-aminopyrimidine (**4APM**) and its charged radicals

Isomer	N1C2	C2N3	N3C4	C4C5	C5C6	C6N1	C4N7
Neutral **4APM**							
1	1.33	1.33	1.34	1.41	1.38	1.34	1.36
2a	1.29	1.36	1.42	1.45	1.35	1.39	1.28
2b	1.30	1.36	1.41	1.45	1.36	1.38	1.28
3a	1.37	1.28	1.42	1.46	1.34	1.39	1.28
3b	1.38	1.28	1.42	1.47	1.34	1.38	1.28
4a	1.42	1.28	1.41	1.51	1.50	1.28	1.27
4b	1.42	1.28	1.41	1.52	1.51	1.28	1.27
Oxidized **4APM**$^{+\bullet}$							
1	1.36	1.31	1.36	1.43	1.39	1.33	1.33
2a	1.32	1.34	1.40	1.42	1.40	1.34	1.32
2b	1.33	1.33	1.39	1.41	1.40	1.34	1.32
3a	1.37	1.30	1.37	1.42	1.38	1.35	1.34
3b	1.37	1.30	1.37	1.42	1.38	1.35	1.34
4a	1.43	1.26	1.43	1.52	1.51	1.26	1.25
4b	1.43	1.26	1.41	1.54	1.51	1.26	1.25
Reduced **4APM**$^{-\bullet}$							
1	1.32	1.39	1.34	1.39	1.44	1.35	1.42
2a	1.33	1.43	1.43	1.42	1.42	1.34	1.31
2b	1.33	1.42	1.41	1.42	1.42	1.34	1.31
3a	1.35	1.30	1.41	1.46	1.35	1.36	1.30
3b	1.36	1.30	1.41	1.47	1.35	1.36	1.30
4a	1.35	1.34	1.37	1.53	1.50	1.33	1.30
4b	1.35	1.34	1.36	1.54	1.50	1.33	1.31

aromatic character. π-Electrons are only slightly delocalized. The CC bond lengths (1.50–1.52 Å) for **4a** and **4b** are close to that for ethane (1.53 Å), and their CN bond lengths (1.41–1.42 Å and 1.27–1.28 Å) are close to those for methylamine (1.46 Å) and methylimine (1.27 Å). All bond lengths for ethane, methylamine, and methylimine were calculated at the B3LYP/6-311+G(d,p) level [32].

When proceeding from the neutral isomers to their 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 isomers. This means that one-electron oxidation causes some decrease of π-electron delocalization for $\mathbf{1}^{+\bullet}$, $\mathbf{4a}^{+\bullet}$, and $\mathbf{4b}^{+\bullet}$. On the other hand, variations in the CC and CN bond lengths are smaller for the charged imine NH isomers ($\mathbf{2a}^{+\bullet}$, $\mathbf{2b}^{+\bullet}$, $\mathbf{3a}^{+\bullet}$, and $\mathbf{3b}^{+\bullet}$), indicating some increase of π-electron delocalization. A different situation occurs when going from the neutral isomers to their radical anions. Small variations of the CC and CN bond lengths for the charged imine CH isomers ($\mathbf{4a}^{-\bullet}$ and $\mathbf{4b}^{-\bullet}$) demonstrate that one-electron reduction causes an exceptional increase of π-electron delocalization for these isomers. Delocalization of π-electrons also slightly augments for the charged imine NH isomers ($\mathbf{2a}^{-\bullet}$, $\mathbf{2b}^{-\bullet}$, $\mathbf{3a}^{-\bullet}$, and $\mathbf{3b}^{-\bullet}$), and slightly decreases for the charged amine tautomer ($\mathbf{1}^{-\bullet}$).

HOMED indices

To quantitatively measure delocalization of n- and π-electrons for all isomers of 4-aminopyrimidine and its redox forms, the geometry-based HOMED (harmonic oscillator model of electron delocalization) index [32, 41–45] can be applied. This index, based on the original HOMA (harmonic oscillator model of aromaticity) idea [46, 47] describes well the various types of conjugations (π-π, n-π, and σ-π) possible in heteroatomic systems. The reformulated HOMA index [48] is not appropriate for π-electron delocalized systems containing heteroatoms [32, 41–45]. The main reason is a use of different measures of π-electron delocalization for the reference CC and CX bonds. The HOMA index can be employed solely for homoaromatics. Its application to heteroaromatics leads to artificial values that have nothing common with real π-electron delocalization [42].

The HOMED procedure has been described in details in [42] and applied to various cyclic and acyclic π-electron compounds containing heteroatoms [32, 41–45]. The HOMED index can be estimated on the basis of the theoretically derived bond lengths using the following equation: $\mathrm{HOMED} = 1 - [\alpha \cdot \Sigma(R_o - R_i)2] : n$ [41, 42]. This equation is similar to that for the reformulated HOMA index [48], but the values of its parameters are different. 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. The following R_o values (in Å), calculated at the B3LYP/6-311+G(d,p) level [32, 42–44], were used here: 1.394 (benzene) and 1.334 (1,3,5-triazine) for CC and CN bonds, respectively. Similarly, as in the case of aniline [32] and other heteroaromatic compounds [42], normalization α constants equal to 88.09 (CC) and 91.60 (CN) were used for the ring (six atoms), and 80.90 (CC) and 84.52 (CN) for the whole tautomeric system (seven atoms). The α constants differ from those employed for the HOMA index, because of the use of a simple, only slightly delocalized, reference CC (ethane and ethene [42] instead of 1,3-butadiene [48]) and CN bonds (methylamine and methylimine [42, 48]), and different procedures for the even and odd number of bonds in the system [32, 42, 43].

The HOMED indices, estimated for the neutral isomers (Table 2), are close to unity for the amine tautomer **1**. When going from the ring (six atoms) to the whole tautomeric system (seven atoms) the HOMED indices decrease due to the cross π-π and n-π conjugations possible in the whole tautomeric system, i.e., conjugation of n-electrons of the exo NH_2 group with π-electrons of the ring. Transfer of the proton to the endo N and C atom decreases the HOMED indices by 0.2–0.3 and 0.5–0.8 units, respectively. The imine NH isomers (**2a**, **2b**, **3a**, and **3b**) are less delocalized than the amine tautomer (**1**), but more delocalized than the imine CH isomers (**4a** and **4b**). The N1 and N3 atoms taking the labile proton retain their planarity due to n-π conjugation,

Table 2 Density functional theory (DFT)-estimated HOMED (harmonic oscillator model of electron delocalization) indices for isomers of **4APM**

Isomer	Neutral form	Radical cation	Δ[a]	Radical anion	Δ[b]
For the ring (six atoms)					
1	0.991	0.950	-0.04	0.904	-0.09
2a	0.737	0.924	0.19	0.712	-0.02
2b	0.707	0.938	0.23	0.775	0.07
3a	0.664	0.917	0.25	0.777	0.11
3b	0.663	0.921	0.26	0.773	0.11
4a	0.346	0.122	-0.22	0.557	0.21
4b	0.170	0.106	-0.06	0.470	0.30
For the whole tautomeric system (seven atoms)					
1	0.981	0.960	-0.02	0.843	-0.14
2a	0.756	0.936	0.18	0.767	0.01
2b	0.736	0.949	0.21	0.818	0.08
3a	0.701	0.934	0.23	0.805	0.10
3b	0.702	0.936	0.23	0.804	0.10
4a	0.435	0.226	-0.21	0.640	0.20
4b	0.297	0.210	-0.09	0.574	0.28

[a] Δ = HOMED(radical cation) - HOMED(neutral form)

[b] Δ = HOMED(radical anion) - HOMED(neutral form)

which is similar to that for the N1 atom in the five membered ring (pyrrole, pyrazole, imidazole, etc.), whereas the C5 atom (C-sp3), taking the labile proton, loses its planarity and aromatic character. For the imine CH isomers, π-electrons of the π-π conjugated −C=N−C=N−C=NH fragment are cross hyperconjugated with σ-electrons of the CH_2 group. σ-π Hyperconjugation leads usually to smaller electron delocalization than π-π and n-π conjugations [42]. One-electron oxidation and also one-electron reduction decrease the HOMED indices for **1**, and increase them for **2** and **3**, but to different degrees. Interestingly, for **4**, one-electron oxidation decreases the HOMED indices, whereas one-electron reduction increases them.

Spin densities

For charged forms of **4APM**, the distribution of the unpaired spin density, calculated at the DFT/B3LYP/6-311+G(d,p) level may give some additional information on delocalization of one unpaired electron. Table 3 summarizes the total atomic spin densities for heavy atoms in tautomers of the 4-aminopyrimidine radical cation (**4APM**$^{+\bullet}$) and its radical anion (**4APM**$^{-\bullet}$). As expected, the spin density exists on all atoms of the **4APM** charged radicals. For the **4APM**$^{+\bullet}$ tautomers, most of the density is carried by the N1, N3, C5, and N7 atoms. On the C2, C4, and C6 atoms, a spin population also exists, but is negative. In the case of the **4APM**$^{-\bullet}$ tautomers, the distribution of the spin density depends on the position of the labile proton. Most of the density is carried by the C2, C4, C6, and N3 atoms for **1**$^{-\bullet}$, by the C2, C5, and C6 atoms for **2**$^{-\bullet}$, by the C4, C5, C6, and N1 atoms for **3**$^{-\bullet}$, and by the C2, C6, and N7 for **4**$^{-\bullet}$. On the other atoms, a spin density also exists, but is considerably lower (positive or negative). Unfortunately, there is no experimental data for the distribution of the unpaired spin density for **4APM** charged radicals and no comparison can be made. In the case of pyrimidine nucleic bases (thymine, uracil, cytosine, and their methyl derivatives), DFT spin density data have been found to be in good agreement with experimental FT EPR results [49].

Table 3 Atomic spin populations for heavy atoms in tautomers of **4APM**$^{+\bullet}$ and **4APM**$^{-\bullet}$ calculated at the DFT(B3LYP)/6-311+G(d,p) level

Isomer	N1	C2	N3	C4	C5	C6	N7
Oxidized **4APM**$^{+\bullet}$							
1	0.446	-0.038	0.120	-0.044	0.364	-0.156	0.335
2a	0.162	-0.008	0.110	-0.205	0.374	-0.033	0.647
2b	0.182	-0.035	0.116	-0.202	0.380	-0.064	0.668
3a	0.168	-0.086	0.158	-0.169	0.242	0.013	0.716
3b	0.144	-0.071	0.135	-0.159	0.216	-0.001	0.775
4a	0.365	-0.047	0.467	-0.066	0.116	-0.060	0.172
4b	0.273	-0.058	0.467	-0.050	0.143	-0.057	0.240
Reduced **4APM**$^{-\bullet}$							
1	-0.119	0.319	0.224	0.206	-0.038	0.569	-0.106
2a	-0.118	0.577	0.103	-0.052	0.307	0.234	0.024
2b	-0.118	0.577	0.103	-0.052	0.307	0.234	0.024
3a	-1.336	0.079	0.019	1.107	2.238	-1.416	-0.041
3b	-1.331	0.126	-0.010	1.124	2.022	-1.255	-0.028
4a	-0.083	0.283	0.092	0.014	-0.087	0.628	0.137
4b	-0.072	0.262	0.090	-0.025	-0.078	0.655	0.151

Relative stabilities

The relative energies (ΔE_T, including ΔZPE), relative enthalpies (ΔH_T), relative entropy terms ($T\Delta S_T$), relative Gibbs energies (ΔG_T), tautomeric equilibrium constants (as pK_T), and percentage contents (x) of all individual neutral and charged tautomers, estimated at the B3LYP/6-311+G(d,p) level, are summarized in Table 4. As expected [9–15], the amine tautomer **1** with the labile proton at the exo N atom has the lowest energy for neutral **4APM**. Aromaticity of the six-membered ring seems to be one of the most important factors dictating the high stability of **1** and its tautomeric preference in the gas phase. The imine NH tautomers **2** and **3** possessing the labile proton at the endo N atoms have larger energies than **1** by 10–20 kcal mol^{-1}. Energetically favorable and energetically unfavorable interactions possible for the structures **a** and **b** of the imine NH tautomers differentiate their energies by only 3–4 kcal mol^{-1}. A similar energy difference (4 kcal mol^{-1}) occurs for the structures **a** and **b** of the imine CH tautomer **4**. However, transfer of the labile proton to the endo C atom exceptionally decreases stabilities of **4a** and **4b**. Their energies are larger than that of **1** by more than 30 kcal mol^{-1}. The percentage contents of all imine NH and CH tautomers (**2**–**4**) are very low (< $1{\cdot}10^{-8}$ %). Indeed, they cannot be detected experimentally for neutral **4APM** [10].

The DFT calculations performed for all unpaired cationic isomers of **4APM**$^{+\bullet}$ show clearly that one-electron oxidation has no significant effect on the tautomeric preference in the gas phase (Table 4). The amine tautomer **1**$^{+\bullet}$ has the lowest energy. However, oxidation changes the relative energies for the imine tautomers, and consequently, also changes the composition of the tautomeric mixture. For the imine NH tautomers, the relative energies decrease even to 1–2 kcal mol^{-1} for **2b**$^{+\bullet}$ and **3a**$^{+\bullet}$ with energetically favorable configurations and to 5–6 kcal mol^{-1} for **2a**$^{+\bullet}$ and **3b**$^{+\bullet}$ with energetically unfavorable configurations, whereas they increases for the imine CH isomers **4a**$^{+\bullet}$ and **4b**$^{+\bullet}$ to more than 40 kcal mol^{-1}. The decrease in the relative energies for the NH tautomers augments their

Table 4 DFT-calculated relative thermodynamic parameters (ΔE_T, ΔH_T, $T\Delta S_T$, ΔG_T, and pK_T) and the percentage contents (x in %) for neutral isomers of **4APM** and its charged radicals

Isomer	Charge	ΔE_T [a,b]	ΔH_T [b,c]	$T\Delta S_T$ [b,c]	ΔG_T [b,c]	pK_T [c]	x
Neutral **4APM** [d]							
1	0	0.0	0.0	0.0	0.0	0.0	100
2a	0	16.1	16.0	-0.2	16.2	11.8	$1\cdot10^{-10}$
2b	0	13.2	13.0	-0.2	13.3	9.7	$2\cdot10^{-8}$
3a	0	18.3	18.3	0.1	18.2	13.3	$5\cdot10^{-12}$
3b	0	22.4	22.4	0.2	22.2	16.2	$6\cdot10^{-15}$
4a	0	32.4	32.4	0.2	32.2	23.6	$2\cdot10^{-24}$
4b	0	37.0	36.9	0.1	36.8	27.0	$1\cdot10^{-25}$
Oxidized **4APM**$^{+\bullet}$ [e]							
1$^{+\bullet}$	1	0.0	0.0	0.0	0.0	0.0	88.3
2a$^{+\bullet}$	1	4.8	4.6	-0.2	4.8	3.6	$3\cdot10^{-2}$
2b$^{+\bullet}$	1	1.4	1.2	-0.3	1.5	1.1	7.3
3a$^{+\bullet}$	1	1.7	1.6	-0.2	1.8	1.3	4.4
3b$^{+\bullet}$	1	6.0	5.6	-0.6	6.2	4.6	$3\cdot10^{-3}$
4a$^{+\bullet}$	1	42.7	42.9	0.5	42.4	31.1	$8\cdot10^{-30}$
4b$^{+\bullet}$	1	43.4	43.6	0.5	43.0	31.6	$3\cdot10^{-30}$
Reduced **4APM**$^{-\bullet}$ [f]							
1$^{-\bullet}$	-1	5.0	5.5	0.6	4.9	3.6	$3\cdot10^{-2}$
2a$^{-\bullet}$	-1	9.5	9.8	0.3	9.5	7.0	$1\cdot10^{-5}$
2b$^{-\bullet}$	-1	6.4	6.6	0.3	6.4	4.6	$2\cdot10^{-3}$
3a$^{-\bullet}$	-1	19.0	18.9	-0.3	19.2	14.1	$9\cdot10^{-13}$
3b$^{-\bullet}$	-1	22.8	22.7	0.2	22.9	16.8	$2\cdot10^{-15}$
4a$^{-\bullet}$	-1	0.0	0.0	0.0	0.0	0.0	99.9
4b$^{-\bullet}$	-1	4.6	4.6	0.0	4.6	3.4	$4\cdot10^{-2}$

[a] ΔZPE included

[b] In kcal mol^{-1}

[c] At 298.15 K

[d] Thermodynamic parameters relative to those for **1**

[e] Thermodynamic parameters relative to those for **1**$^{+\bullet}$

[f] Thermodynamic parameters relative to those for **4a**$^{-\bullet}$

contributions in the tautomeric mixture. The percentage contents of **2b**$^{+\bullet}$ and **3a**$^{+\bullet}$ are exceptionally large (7.3 and 4.4 %, respectively), and thus, they cannot be neglected in the tautomeric mixture of **4APM**$^{+\bullet}$. This means that at least three isomers, **1**$^{+\bullet}$, **2b**$^{+\bullet}$, and **3a**$^{+\bullet}$, should be considered in electron-transfer reactions in which **4APM** loses one electron. The percentage contents of **4a**$^{+\bullet}$ and **4b**$^{+\bullet}$ are very low (ca. $1\cdot10^{-30}$ %). As very rare isomers, they may be neglected in the tautomeric mixture of the **4APM** radical cation.

Contrary to one-electron oxidation, which stabilizes **1**$^{+\bullet}$ with the labile proton at the exo N atom, preferred also for neutral **4APM** (**1**), one-electron reduction changes the tautomeric preference dramatically. For reduced **4APM**, the imine CH isomer **4a**$^{-\bullet}$ with the labile proton at the endo C5 atom has the lowest energy (Table 4). Since this isomer may decide the product formed, it should be considered for electron-transfer reactions in which 4-aminopyrimidine gains one electron. The isomer **4b**$^{-\bullet}$ with unprofitable configuration has greater energy than **4a**$^{-\bullet}$ by ca. 5 kcal mol^{-1}. Two other reduced isomers **1**$^{-\bullet}$ and **2b**$^{-\bullet}$ have energies close to that of **4b**$^{-\bullet}$. The contents of the three isomers **1**$^{-\bullet}$, **2b**$^{-\bullet}$, and **4b**$^{-\bullet}$ are 0.03, 0.002, and 0.04%, respectively. Structures **3a**$^{-\bullet}$ and **3b**$^{-\bullet}$ have the largest energies. Their percentage contents are lower than $1\cdot10^{-10}$ %.

The relative entropy terms ($T\Delta S_T$) for the neutral and redox forms of **4APM** are not larger than ±1 kcal mol^{-1}. This may suggest that all tautomeric conversions are isoentropic in the gas phase and do not depend on the oxidation or reduction state of the molecule. Generally, there are no large structural changes during tautomerization. Some exceptions are those resulting from loss of the ring planarity for **4**. The relative thermal corrections (from zero to 298.15 K) are close to zero, and thus, $\Delta E_T \approx \Delta H_T \approx \Delta G_T$. All these observations suggest that the relative thermodynamic parameters do not depend much on temperature (thermal corrections and entropy terms cancel out), and thus the percentage contents of the same order of magnitude may be expected for individual tautomers in jet-cooled experiments.

Oxidation and reduction energies

Direct comparison of the DFT calculated thermodynamic parameters for the same oxidized and neutral isomers of **4APM** indicates that one-electron oxidation is very endothermic process and requires ca. 200 kcal mol^{-1} (Table 5). There are no experimental data in the literature for the ionization energy of **4AMP** [50] and no comparison can be made. However, it should be mentioned here that the

Table 5 DFT-estimated energies of oxidation (ΔE_{ox}, ΔH_{ox}, and ΔG_{ox}) and entropy terms ($T\Delta S_{ox}$) for individual isomers of **4APM**

Oxidation	ΔE_{ox} [a,b]	ΔH_{ox} [b,c]	$T\Delta S_{ox}$ [b,c]	ΔG_{ox} [b,c]
1 − e → **1**$^{+\bullet}$	202.0	202.1	0.4	201.6
2a − e → **2a**$^{+\bullet}$	190.7	190.7	0.4	190.3
2b − e → **2b**$^{+\bullet}$	190.2	190.2	0.4	189.8
3a − e → **3a**$^{+\bullet}$	185.4	185.4	0.2	185.2
3b − e → **3b**$^{+\bullet}$	185.8	185.9	0.5	185.4
4a − e → **4b**$^{+\bullet}$	212.3	212.6	0.7	211.8
4b − e → **4b**$^{+\bullet}$	208.4	208.7	0.8	207.9

[a] ΔZPE included

[b] In kcal mol^{-1}

[c] At 298.15 K

Table 6 DFT-estimated energies of reduction (ΔE_{red}, ΔH_{red}, and ΔG_{red}) and entropy terms ($T\Delta S_{red}$) for individual isomers of **4APM**

Reduction	ΔE_{red} [a,b]	ΔH_{red} [b,c]	$T\Delta S_{red}$ [b,c]	ΔG_{red} [b,c]
1+e → **1**$^{-\bullet}$	10.7	11.2	1.3	9.8
2a+e → **2a**$^{-\bullet}$	-1.0	-0.5	1.2	-1.7
2b+e → **2b**$^{-\bullet}$	-1.2	-0.7	1.2	-2.0
3a+e → **3a**$^{-\bullet}$	6.3	6.3	0.3	6.0
3b+e → **3b**$^{-\bullet}$	6.1	6.1	0.3	5.8
4a+e → **4a**$^{-\bullet}$	-26.8	-26.7	0.5	-27.2
4b+e → **4b**$^{-\bullet}$	-26.7	-26.6	0.6	-27.1

[a] ΔZPE included

[b] In kcal mol^{-1}

[c] At 298.15 K

literature ionization energies for 4-aminopyridine (8.8 eV [51], 1 eV=23.06037 kcal mol^{-1}), 2-aminopyridine (8.5 eV [51]), and pyrimidine (9.3 eV [50]) are of the same order of magnitude as the DFT-estimated energy of oxidation for **4APM**.

For the favored amine tautomer **1**, the DFT-calculated oxidation Gibbs energy (ΔG_{ox}) for reaction **1** − e → **1**$^{+\bullet}$ is equal to 202 kcal mol^{-1}. For the imine NH isomers **2b** and **3a**, whose contribution to the tautomeric mixture cannot be neglected, the ΔG_{ox} values are lower than that of **1** by ca. 11 and 16 kcal mol^{-1}, respectively. Interestingly, a change in the configuration of the imine H atom from synperiplanar position to the ring N3 atom to antiperiplanar position has no significant effect on ΔG_{ox} values. This suggests that energetically favorable and energetically unfavorable interactions for neutral and oxidized isomers are similar. A different situation takes place for the imine CH isomers **4a** and **4b**. The ΔG_{ox} values are larger than that for **1** by 6–10 kcal mol^{-1}. Additionally, they differ by 4 kcal mol^{-1} between structures **a** and **b**. This difference indicates smaller intramolecular effects for the oxidized forms (with positive charge) than for the neutral ones.

Comparison of the DFT-calculated thermodynamic parameters for the reduced and neutral tautomers of **4APM** shows evidently that one-electron reduction is a more profitable process than one-electron oxidation, and requires lower energy (Table 6). This means that 4-aminopyrimidine may take one electron spontaneously from a reducing agent. For some isomers, reduction is even an exothermic process. The imine CH isomers (**4a** and **4b**) may be transformed more easily to the reduced forms than the imine NH isomers (**2a**, **2b**, **3a**, and **3b**) and the amine tautomer (**1**). The ΔG_{red} values are larger in the negative scale for **4a** and **4b** (ca. −27 kcal mol^{-1}) than for the other isomers (ca. −2 kcal mol^{-1} for **2a** and **2b**, 6 kcal mol^{-1} for **3a** and **3b**, and 10 kcal mol^{-1} for **1**). This trend confirms preference of the imine CH tautomer in the tautomeric mixture of **4APM**$^{-\bullet}$. A change in the position of the imine H atom from syn- to antiperiplanar to the ring N3 atom for isomers **a** and **b** has no large effect on the ΔG_{red} value. This suggests that energetically favorable and energetically unfavorable interactions for the neutral and reduced isomers are similar. There are no experimental data in the literature for the electron affinity of **4APM** and no comparison can be made. Interestingly, the literature electron affinity for unsubstituted pyrimidine is not very large (experimental EA>−0.24999 eV found using the electron transmission spectroscopy method [52], and calculated EA −4 kcal mol^{-1} at the G2MP2B3 level [53]).

The entropy terms for both the oxidation ($T\Delta S_{ox}$) and reduction ($T\Delta S_{red}$) reactions of **4APM** are not very large (0–1.3 kcal mol^{-1}), indicating that the electron-transfer processes, electron-loss (**4APM** − e → **4APM**$^{+\bullet}$) and electron-gain (**4APM**+e → **4APM**$^{-\bullet}$) are isoentropic in the gas phase for **4APM** similar to the proton-transfer interconversions for its neutral and redox forms. The relative thermal corrections are close to zero, and thus, $\Delta E_{ox} \approx \Delta H_{ox} \approx \Delta G_{ox}$ and $\Delta E_{red} \approx \Delta H_{red} \approx \Delta G_{red}$.

Tautomeric preferences

When oxidizing or reducing agents are present, neutral 4-aminopyrimidine in its favored amine form **1** may lose or gain one electron. Consequently, it may be transferred to its oxidized (**4APM** − e → **4APM**$^{+\bullet}$) or reduced (**4APM**+e → **4APM**$^{-\bullet}$) very reactive states. The mechanisms of chemical, anodic oxidations or cathodic reductions can be very complex and may depend on the conditions of reaction, such as solvent, reagent, catalyst, electrode, etc. [35–37, 54–56]. The oxidation and reduction processes may pass through different intermediates among which the charged forms, radical cation and radical anion are possible [57–60]. A simple one-electron loss or one-electron gain may be also

observed during positive or negative ionization in the mass spectrometer [39, 58].

The DFT calculations performed here for **4APM** show that one-electron oxidation has no effect on the tautomeric preference, and the amine tautomer $\mathbf{1}^{+\bullet}$ is favored for oxidized **4APM** (radical cation). On the other hand, one-electron reduction favors the imine CH isomer $\mathbf{4a}^{-\bullet}$ in the tautomeric mixture of reduced **4APM** (radical anion). If we consider solely the favored neutral and redox forms of **4APM**, the following scheme of the redox reactions can be drawn (Scheme 3). This scheme can be compared with that previously found at the same level of theory for aniline [32].

Generally, the Gibbs energies for the favored oxidation and reduction reactions are almost of the same order of magnitude. However, the oxidation reaction for **4APM** requires more energy (by 28 kcal mol^{-1}), whereas lower energy (by 8 kcal mol^{-1}) is sufficient for the reduction reaction. When going from aniline to **4APM**, the two N-aza atoms included in the ring of **4APM** do not change the tautomeric preferences; only the compositions of the tautomeric mixture are different (see data in Table 4 and those in Table 4 in [32]). Moreover, the two N-aza atoms in **4APM** increase the HOMED indices in comparison to aniline [32] due to stronger n-π conjugation between the exo NH_2 group and the pyrimidine ring than between the exo NH_2 group and the phenyl ring in aniline.

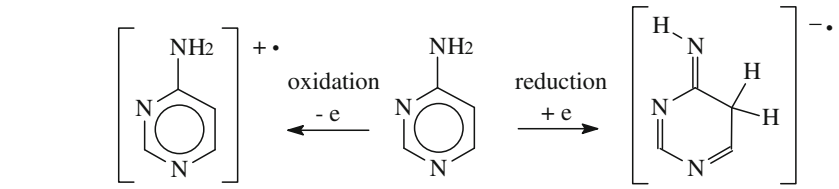
To obtain more information on the mechanism of one-electron oxidation and one-electron reduction processes, we also analyzed the Mulliken charges, calculated at the same level of theory for the neutral and redox forms of **4-APM**. For the favored tautomers, these charges are summarized in Table 7. When proceeding from the neutral amine tautomer **1** to its radical cation $\mathbf{1}^{+\bullet}$, the exo N atom and the endo N and C atoms lose part of their negative charge. This indicates a loss of one electron from the n-orbital of the N7 atom (Scheme 4) as well as from the π-orbital of the ring (Scheme 5). Larger variations in the Mulliken charges for the N1, N3, N7, and C5 atoms suggest that one electron may be taken preferentially from the n-orbital of the N7 atom. This is in good agreement with the distribution of the spin density for $\mathbf{1}^{+\bullet}$ (Table 3) For the radical anion isomer $\mathbf{4a}^{-\bullet}$, one-electron reduction

Table 7 DFT-calculated Mulliken charges for selected isomers of **4-APM**

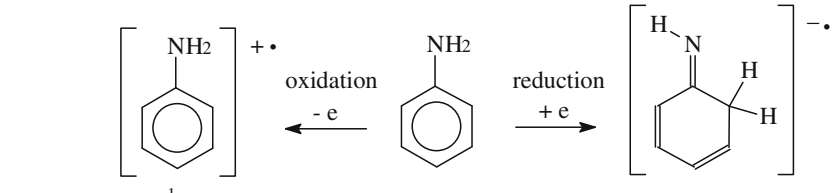
Reaction	Atom	Neutral form	Charged form	Δ*
$\mathbf{1} - e \rightarrow \mathbf{1}^{+\bullet}$	N1	-0.153	0.032	0.18
	C2	-0.032	0.025	0.06
	N3	-0.200	-0.105	0.10
	C4	-0.123	-0.131	-0.01
	C5	0.207	0.361	0.15
	C6	-0.245	-0.245	0.00
	N7	-0.342	-0.218	0.12
$\mathbf{4a} + e \rightarrow \mathbf{4a}^{-\bullet}$	N1	-0.102	-0.168	-0.07
	C2	-0.073	-0.186	-0.11
	N3	-0.109	-0.239	-0.13
	C4	-0.110	-0.163	-0.05
	C5	-0.240	-0.145	0.10
	C6	-0.026	-0.252	-0.23
	N7	-0.274	-0.421	-0.15

*Δ is the difference between the Mulliken charges in the charged and neutral forms

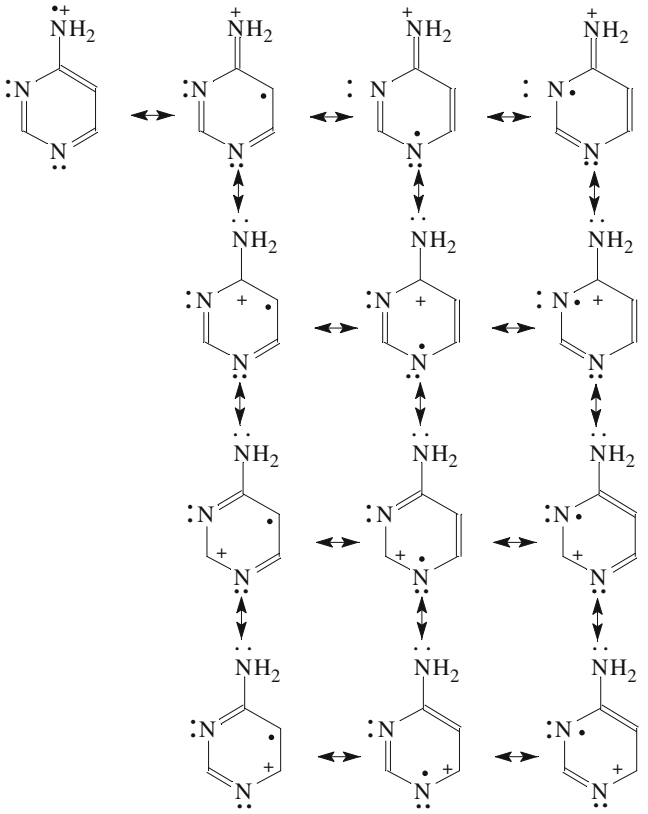
Scheme 3 Tautomeric preference for redox forms of **4APM** compared to that for aniline [32], both estimated at the B3LYP/6-311+G(d,p) level



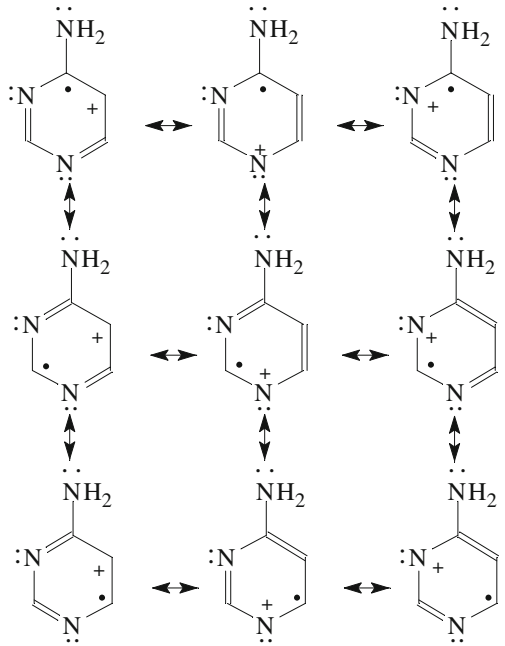
ΔG (in kcal mol^{-1})	201.6	9.6	
x (in %)	88.3	100	99.9
HOMED(6)	0.950	0.991	0.557
HOMED(7)	0.960	0.981	0.640



ΔG (in kcal mol^{-1})	173.7	17.1	
x (in %)	100	100	89.0
HOMED(6)	0.926	0.998	0.490
HOMED(7)	0.942	0.948	0.597



Scheme 4 Loss of one electron from n-orbital, and delocalization of electrons and positive charge for $\mathbf{1}^{+\bullet}$



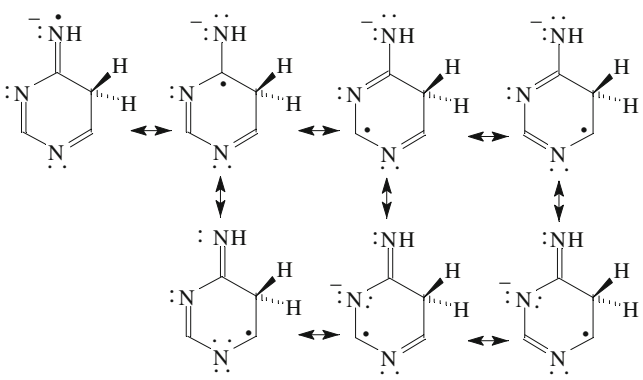
Scheme 5 Loss of one electron from π-orbital, and delocalization of electrons and positive charge for $\mathbf{1}^{+\bullet}$

increases the negative charge at the endo N and C atoms (except C5), and also at the exo N atom. This indicates that the π-π conjugated −C=N−C=N−C=NH fragment gains the excess electron (Scheme 6). Most of the spin density is carried by the C2, C6, and N7 for $\mathbf{4}^{-\bullet}$ (Table 3).

Conclusions

Quantum-chemical studies performed for all possible amine and imine tautomers of neutral **4APM** and its charged forms ($\mathbf{4APM}^{+\bullet}$ and $\mathbf{4APM}^{-\bullet}$) show greater changes in the tautomeric preference for the reduced ($\mathbf{4APM}^{-\bullet}$) than oxidized form ($\mathbf{4APM}^{+\bullet}$). At the DFT(B3LYP)/6-311+G(d,p) level, the order of stabilities for the radical cation isomers ($\mathbf{1}^{+\bullet}$, $\mathbf{2b}^{+\bullet}$, $\mathbf{3a}^{+\bullet}$, $\mathbf{2a}^{+\bullet}$, $\mathbf{3b}^{+\bullet}$, $\mathbf{4a}^{+\bullet}$, and $\mathbf{4b}^{+\bullet}$) is only slightly different from that for the neutral ones (**1**, **2b**, **2a**, **3a**, **3b**, **4a**, and **4b**). The amine tautomer $\mathbf{1}^{+\bullet}$ predominates for the oxidized mixture, similarly **1** as for the neutral molecule. Aromaticity seems to dictate the tautomeric preferences for both the neutral and oxidized forms. One-electron oxidation influences solely the composition of the tautomeric mixture. The neutral mixture of **4APM**, consists mainly of the amine tautomer **1** (100%), whereas the oxidized mixture of $\mathbf{4APM}^{+\bullet}$ consists of three tautomers: the amine tautomer $\mathbf{1}^{+\bullet}$ (88.3%), and the imine NH tautomers $\mathbf{2b}^{+\bullet}$ (7.3%) and $\mathbf{3a}^{+\bullet}$ (4.4%). The amounts of the rare imine CH radical cations $\mathbf{4a}^{+\bullet}$ and $\mathbf{4b}^{+\bullet}$ are exceptionally low ($8\cdot10^{-30}$ and $3\cdot10^{-30}$%) similar to those for **4a** and **4b** ($2\cdot10^{-24}$ and $1\cdot10^{-25}$%). All of them may be neglected in the tautomeric mixture.

The order of stabilities for the radical anion isomers ($\mathbf{4a}^{-\bullet}$, $\mathbf{4b}^{-\bullet}$, $\mathbf{1}^{-\bullet}$, $\mathbf{2b}^{-\bullet}$, $\mathbf{2a}^{-\bullet}$, $\mathbf{3a}^{-\bullet}$, and $\mathbf{3b}^{-\bullet}$) is completely different from those for neutral and oxidized **4APM**. A dramatic change takes place when proceeding from the neutral to the reduced form. The imine CH tautomer—a rare isomer for the neutral and oxidized molecule—



Scheme 6 Delocalization of electrons and negative charge for $\mathbf{4}^{-\bullet}$

becomes the favored isomer for the reduced **4APM**. The tautomeric mixture of **4APM** $^{-\bullet}$ consists mainly of the imine CH isomer **4a** $^{-\bullet}$ (99.9%). The amounts of the other CH isomer **4b** $^{-\bullet}$ (0.04%), the amine tautomer **1** $^{-\bullet}$ (0.03%), and the imine NH isomer **2b** $^{-\bullet}$ (0.003%) are considerably lower but are not negligible, and should be considered in the mechanisms of reduction reactions. The importance of the CH tautomer in the tautomeric mixture of **4APM** $^{-\bullet}$ may partially explain the origin of the CH isomers in the anionic states of nucleobases (cytosine and adenine) [61, 62].

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