Computational and Theoretical Chemistry 1031 (2014) 56–63

Contents lists available at ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

Effects of positive and negative ionization for 2-aminopyrimidine in the gas phase and in water solution

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ARTICLE INFO

Article history:
Received 30 November 2013
Received in revised form 9 January 2014
Accepted 9 January 2014
Available online 21 January 2014

Keywords:
2-Aminopyrimidine
Prototropy
Effects of ionization
HOMED
DFT
PCM

ABSTRACT

Quantum-chemical calculations were performed for neutral 2-aminopyrimidine (**2APM**) and for its ionized forms (**2APM** – e → **2APM**$^{+\cdot}$ and **2APM** + e → **2APM**$^{-\cdot}$) in the gas phase {DFT(B3LYP)/6-311+G(d,p)} and in water solution {PCM(water)//DFT(B3LYP)/6-311+G(d,p)}. For calculations, the complete tautomeric mixture containing the amino and imino forms was considered. Geometric isomerism of the exo=NH group for the imino forms was also taken into account. There is a good correlation between prototropy and electron delocalization for the neutral isomers of **2APM**. The aromatic amine NH_2 tautomer is favored for neutral and ionized **2APM** in the gas phase and in water solution. Positive and negative ionization increase the stability of the imine NH isomers containing the labile proton at the endo N-aza atom that their contribution cannot be neglected in the positively and negatively ionized tautomeric mixture. Ionization influences also electron delocalization. For the major and minor forms of **2APM**, the exo N atom may lose preferentially one of the non-bonding electrons, and the pyrimidine ring may gain one excess electron. The adiabatic ionization potential and the adiabatic electron affinity change when going from the gas phase to water solution by ca. 2 eV.

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1. Introduction

Prototropic tautomerism, called prototropy is one of the most frequently occurred and studied form of isomerism for natural products, particularly for the nucleic acid bases [1–7]. This intramolecular proton-transfer between the conjugated tautomeric sites, accompanied by migration of π-electrons, dictates the structure of the pyrimidine and purine bases, their acid–base properties, hydrogen bond formation, solvent interactions, and other physicochemical properties. Consequently, it influences the structure of nucleic acids, their replication and point mutation. To understand and to explain the mechanisms of these processes for the nucleic acid bases, the tautomeric conversions for their parent systems and convenient models are frequently studied [1,4–7].

2-Aminopyrimidine (**2APM**, Fig. 1) is a model compound for isocytosine (**iC**) – a building block of the nucleobase guanine (**G**) and some drugs such as folic acid (**FA**) and acyclovir (**ACV**). It contains three functional groups, one exo NH_2 group and two endo N-aza groups which are n–π and π–π conjugated with the endo >C=C< group. One labile proton can move from the exo NH_2 group to the endo N or C atom. Two types of the tautomeric conversions are possible: amine–imine tautomerism {—NH—C(R)=N— → —N=C(R)—NH—} from the exo to endo N atom or from one endo to the other endo N atom, and enamine–imine tautomerism {>C=C(R)—NH— → >CH—C(R)=N—} from the exo or endo N atom to the endo C atom. Combinations of these two types of the tautomeric conversions lead to six tautomeric equilibria between four tautomers (Scheme 1), one amine NH_2 form with the labile proton at the exo N atom (**2APM1**), and three imine forms with the labile proton at the endo N and C atoms for the NH (**2APM2** and **2APM3**) and CH (**2APM4**) tautomers, respectively. Due to geometric isomerism of the exo=NH group in the imine NH tautomers, two isomers are possible for **2APM2** and **2APM3**, one **a** with the imine H atom synperiplanar to the ring NH group and the other one **b** with this atom antiperiplanar to the ring NH group. The structures **2APM2a** and **2APM3a**, and also **2APM2b** and **2APM3b** are identical for 2-aminopyrimidine, and thus the tautomeric equilibrium constants *K* for the conversions **2APM2a** → **2APM3a** and **2APM2b** → **2APM3b** are equal to unity. However, to well estimate the composition of the tautomeric mixture, all isomers (**2APM1**–**2APM4**) should be considered for 2-aminopyrimidine.

To our knowledge, the ionized forms of **2APM** (radical cations and radical anions) and the effects of positive and negative ionization (called also one-electron oxidation and one-electron reduction) have not yet been considered in the literature. Solely, the spectroscopic properties, the electronic structure, and the natural

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http://dx.doi.org/10.1016/j.comptc.2014.01.007
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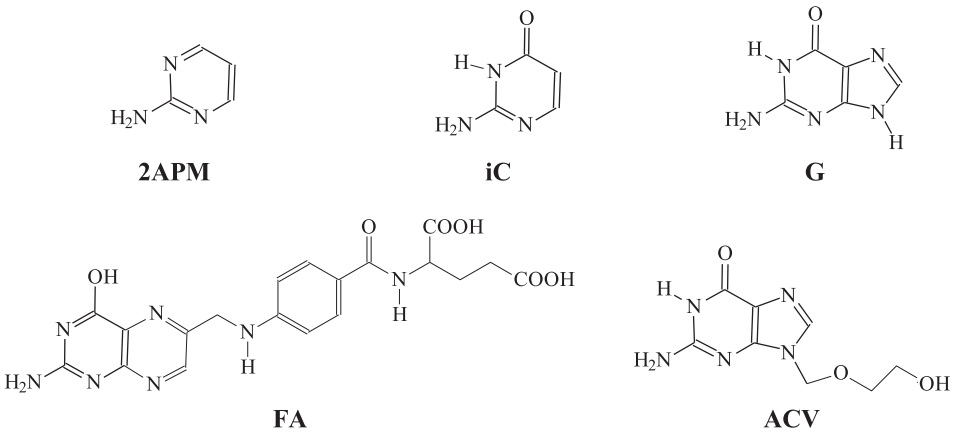
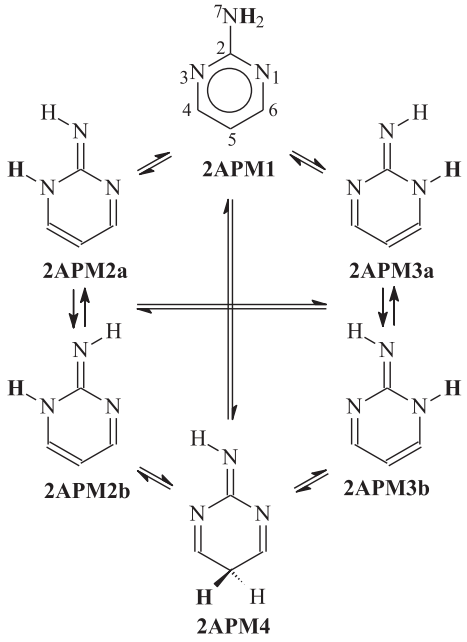


Fig. 1. Structures of 2-aminopyrimidine (**2APM**), isocytosine (**iC**), guanine (**G**), folic acid (**FA**), and acyclovir (**ACV**).



Scheme 1. Tautomeric equilibria for **2APM** (labile proton marked in bold).

bond analysis have been reported for the neutral amine NH_2 (**2APM1**) and imine NH tautomers (**2APM2/3**) of 2-aminopyrimidine [8,9]. The relative thermodynamic stabilities have been calculated for isolated neutral **2APM1** and **2APM2/3** [10], and for their complexes with water [11]. The photoinduced amino-imino conversion has been discussed for complexes of **2APM1** and **2APM2/3** with acetic acid [12]. 2-Aminopyrimidine exists preferentially in the amine tautomeric form **2APM1** in the solid state [13–15], in a Ne matrix [16], and in apolar solvents [17]. This form is favored for the free neutral molecule [9,10], and also for the associated dimers, trimers, polymers of 2-aminopyrimidine, including metal complexes [13,15,17–20]. In the literature, the CH tautomer has not been investigated for **2APM**. However, this type of pyrimidine tautomers has been well documented as intermediates in free-radical chemistry of the pyrimidine DNA bases [21]. The CH tautomers have been also characterized for the radicals and charged forms of nucleobases [22–28]. The CH tautomers dominate in the tautomeric mixture for the negatively ionized nucleobase models such as imidazole [29], purine [30], and 4-aminopyrimidine [31]. For these reasons, the complete tautomeric mixture was studied here for neutral and ionized **2APM**.

Since intramolecular proton-transfers are very fast and reversible processes, and it is difficult to separate and to study the individual tautomers [1,4–7], quantum-chemical methods were applied for neutral and ionized **2APM**. Application of spectroscopic techniques (UV, IR, NMR, MW, MS, etc.) to the tautomeric mixture gives solely some information for 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. As described previously [28], two methods were chosen to model the tautomeric equilibria for aminoazines, one method, DFT(B3LYP)/6-311+G(d,p), for investigations in the gas phase, and the other one, PCM(water)//DFT(B3LYP)/6-311+G(d,p), for investigations in aqueous solution. The application of the quantum-chemical methods gives the possibilities to study the effects of positive (**2APM** – e → **2APM**$^{+\cdot}$) and negative ionization (**2APM** + e → **2APM**$^{-\cdot}$) on the tautomeric mixture of **2APM**, and also to estimate the relative stability of the individual tautomers, the adiabatic ionization potential, and the adiabatic electron affinity. To investigate the variations of π-electron delocalization for the six-membered pyrimidine ring and for the whole tautomeric system (seven bonds), the geometric parameters for the neutral and charged forms of 2-aminopyrimidine, and the charges and the spin densities for heavy atoms in the ionized forms were also analyzed.

2. Computational details

In the gas phase, geometries of all neutral and charged isomers of 2-aminopyrimidine (Scheme 1) were fully optimized in their ground states without symmetry constraints employing the DFT(B3LYP) method [32–34] and the 6-311+G(d,p) basis set [35]. The restricted B3LYP functional was used for the neutral isomers, and the unrestricted B3LYP functional was applied for the charged radicals. For all isomers, frequencies were calculated to prove that the neutral and charged structures are minima at the level of theory applied here. 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 for all isomers using the same level of theory. For the tautomeric conversions, the relative thermodynamic parameters (ΔE, ΔH, $T\Delta S$, and ΔG), tautomeric equilibrium constants (as $pK = \Delta G/2.303RT$), and percentage contents of individual forms $\{x = K/(1 + K)\}$ were estimated. 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). The theoretical adiabatic ionization potential {IP = E(optimized radical cation) – E(optimized neutral)} and the theoretical adiabatic electron affin-

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