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Theoretical Investigation of the Tautomerism of Isoorotic Acid in Gaseous and Aqueous Phases

SEUNG JOO CHO,[1] ADEL A. MOHAMED,[2] SHAABAN A. K. ELROBY[3]

[1]*Life Science Division, Korea Institute of Science and Technology, Seoul, South Korea*
[2]*Department of Chemistry, Faculty of Science, Helwan University, Egypt*
[3]*Department of Chemistry, Faculty of Science, Beni-Seuf University, Egypt*

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ABSTRACT: In the present investigation, the tautomeric and conformational equilibrium of isoorotic acid have been studied using Møller–Plesset second-order (MP2) and density functional theory (DFT) methods in the gas phase and aqueous solution (ε = 78.5) using the IPCM model. The relative energies of these tautomers have been calculated at the two levels of theory using 6-311++G** basis set. Energetics and relative stabilities of the tautomers were compared and analyzed in both the gaseous and aqueous phases. The results indicate that the diketo tautomer (**iso**) is the most stable form in the gas phase and water. The carboxylic substitution in the uracil ring does not alter its relative stability order of the tautomers. The proton affinity of the oxygen atoms and the deprotonation enthalpy of the NH bonds of isoorotic acid have been compared with recent data of uracil. The relative stability of both syn- and anti-conformations was investigated and the syn form was found to be more stable by 17.65 kcal/mol. It was determined in ab initio calculations that an electron can attach to isoorotic acid, forming a stable anion better than uracil.
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Key words: MP2; DFT calculations; tautomerism; isoorotic acid; IPCM

Introduction

Tautomers are structural isomers that are conceptually related by the shift of hydrogen and one or more π bonds. Aldehydes and ketones, which have at least one hydrogen atom, are in equilibrium with an isomer called enol, and this type of equilibrium between constitutional isomers is called tautomerism. For the past two decades, there has been considerable interest in studying the tautomerism of heterocyclic compounds to identify the influence of tautomerism on chemical and biological properties of molecules. The phenomenon of tautomerism is related to aromaticity and lone pair–

Correspondence to: S. A. K. Elroby; e-mail: sha_kamel@yahoo.com

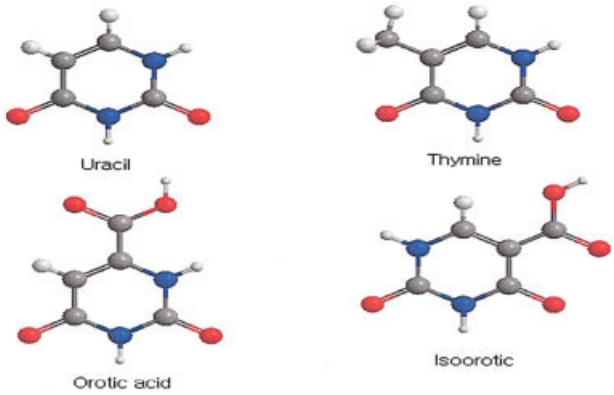

FIGURE 1. Schematic structures of uracil, thymine, orotic acid, and. isoorotic acid. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

lone pair repulsions. The experimental studies on tautomerism are still a challenging problem in chemistry and molecular biology. Most tautomers are not observed in the experimental studies because of their low concentration. A detailed analysis of the structure and changes in geometrical and energetic parameters caused by the migration of hydrogen atom would enable us to understand the different properties of tautomers. Knowledge of the relative stabilities of tautomeric forms of heterocycles as well as the conversion from one tautomeric form to another is important from the point of view of structural chemistry.

Pyrimidine derivatives constitute a very important class of compounds because they are components of the biologically important nucleic acids and have been shown to exert a pronounced physiological effect. Isoorotic acid (5-carboxyuracil) (Fig. 1); some of its metallic complexes are biologically and pharmacologically interesting compounds that exhibit antibacterial, antitumor, and antihypertensive activity [1].

The tautomers of uracil have been extensively studied by both experiments [nuclear magnetic resonance (NMR), ultraviolet (UV), and Raman and infrared (IR) spectra] and various theoretical levels [2]. The results show that the 2,4-dioxo-dilactam form is the predominant and stable one in gas phase, solution, and solid state. It is well known that the equilibrium between tautomers is largely influenced by the attachment of particular substituents on the molecules. The effect of substituent on the conformational, structure, and tautomerization process of uracil has been investigated, e.g., 6-propyl [3], 1- or 5-methyl [4], 5-fluoro [5], or 6-carboxylic (orotic acid) [6]. Hilal and colleagues [6] undertook a theoretical study of the electronic structure of orotic acid (6-carboxylic uracil) and all its tautomers and zwitterions at the gaseous and aqueous phases. The keto form has been shown to be the most stable one both in solution and in gas phases.

Isoorotic acid (5-carboxylic uracil), the structural isomer of orotic acid, is also expected to exhibit biological and pharmaceutical activity. It is well known that this biological and pharmaceutical activity depends on the substituents at the C_5 position [5]. Therefore, it is important to study and analyze its structural features, viz. the possible syn- and anti-orientations of the carboxylic group, barrier to internal rotation about the ring—COOH bond and the amine–imine and keto–enol tautomerism. This tautomerization process involves a 1,3-proton shift, where a proton is transferred from the nitrogen atom to the more electronegative oxygen atom, which is common to all pyrimidines. This may very well underlie the biological activity of pyrimidines.

The comparison between the structures of the two isomers is so important from the point of view of structural chemistry. Heterocyclic tautomerism has been studied extensively for the past two decades due to its biological importance and highly solvent-dependent nature. It has been shown that solute–solvent interactions can determine the relative stability of the tautomeric forms [7, 8]. In addition, knowing how the tautomerization energies change in different environments can provide insight into the influence of solvent effects on molecular stability. Theoretical treatments of solvent effects on tautomeric energies of heterocyclic systems are of general interest to organic chemists and, in particular, to medicinal chemists. Extensive experimental and theoretical studies of such tautomeric equilibria are available in Refs. [9–11]. Heterocyclic tautomeric equilibria are highly sensitive to environmental effects such as solvent polarity [12–19]; interactions between the solute and solvent molecules are responsible for the variations of physical and chemical properties of solute.

The proton affinity (PA) of the different proton acceptor sites (O_7, O_8) and the deprotonation energy of the two NH bonds of isoorotic acid are computed using density functional theory (DFT) calculation and compared with the results of the parent uracil.

The present investigation has been undertaken with the aim of achieving the following goals for the isoorotic acid and its tautomers: (i) study the conformational preference of isoorotic acid and its barrier to internal rotation about the ring—COOH bond; (ii) investigate the energetics of isoorotic acid tautomers and their relative stability in the gas phase and water; (iii) compare the two isomers with respect to their structure and tautomerization ability; and (iv) explore the effect of 5-COOH group on the structure, tautomerization, protonation, and deprotonation ability of uracil.

Computational Methods

The molecular orbital calculations were carried out using the Gaussian 98W program [20]. All geometries were fully optimized using the Becke-3LYP [21] with the 6-311++G** basis set. In addition, single-point MP2/6-311++G**//B3LYP/6-311++G** calculations were accomplished to compare the two electron correlation methods. The use of B3LYP method is due to its properly prediction of the higher stability of imino tautomers and reproduces very well the energy differences obtained by the conventional ab initio methods [5]. It was suggested that it is necessary to choose the basis sets included the polarized *p*-orbital function added to hydrogen atom for relative energy calculations [22, 23]. The vibrational frequency calculations were performed for all the studied tautomers to check the structure stabilities that correspond to the minima in the potential energy surface.

The solute–solvent effect was taken into account by using the isodensity polarized continuum model (IPCM) [24]. This method calculates the electric field analytically instead of numerically and the cavity in the solvent is defined upon an isosurface of the total electron density calculated at the B3LYP/6-311++G** level. The solvent effect in IPCM is derived from the interaction of the potential surfaces with the dielectric continuum. Because of the limitation in IPCM calculations, only single-point calculations are possible with this method. Therefore, the gas phase molecular geometries optimized at the B3LYP/6-311++G** level were used for the IPCM calculations and we assumed that the structures are not changed from gas phase to solutions [25,26]. The solvation free energies were taken as the difference between the energies in solution and gas phase.

Results and Discussion

CONFORMATIONAL PREFERENCE OF ISOOROTIC ACID

The way in which the energy of a molecule changes with rotation about its single bonds is of considerable interest. In the present work, the internal rotation of the carboxylic group around the single bond (C5—C12) has been investigated for isoorotic acid. The internal rotations were performed at the B3LYP/6-311++G** level with complete geometry optimization, unless otherwise stated. The rotated bond is designated as the rotamer and the rest of the molecule as the framework. The total torsion angle K is the angle between the rotamer and plane of the framework (Fig. 1).

The syn form was shown to be more stable by 17.65 kcal/mol over the anti-conformation. In our previous work [6], the relative stability of both the syn- and anti-conformations for orotic acid was investigated at the B3LYP/6-311G** level. The difference in energy is only 1.58 kcal/mol, while the rotational barrier value is 7.66 kcal/mol. Consequently, orotic acid behaves as a free rotor about C6—C12 bond region and syn- and anti-conformations were equally probable. The two conformers of isoorotic acid are planar and have nearly the same geometrical parameters; the maximum difference in various bond lengths is only 0.02 Å. The stability of the syn form is attributed to the possibility of the existence of two H-bonds, viz. O10—H15 and O13—H11 where the calculated distances are 2.24 and 1.78 Å, respectively (see Fig. 2). The second reason is the repulsion between the two negatively charged oxygen atoms (O10$\cdots$O13) in the case of anti form. This result is in agreement with the experimental data [27], which indicates that the carboxylic group is oriented in syn orientation ($\theta = 0$).

RELATIVE STABILITY OF TAUTOMERS

The different tautomeric forms of the isoorotic acid are the diketo form (**iso**), dihydroxy form (**iso2**), 4-keto-2-hydroxy (**iso1**), and 2-keto-4-hydroxy (*iso3*). The tautomer *iso3* may exist in four structural forms; the syn-isomer **iso3A**, the anti-isomer **iso3C** and their rotamers **iso3D** and **iso3B**, respectively. The optimized molecular arrangements of these forms are shown in Figure 3. Geom-

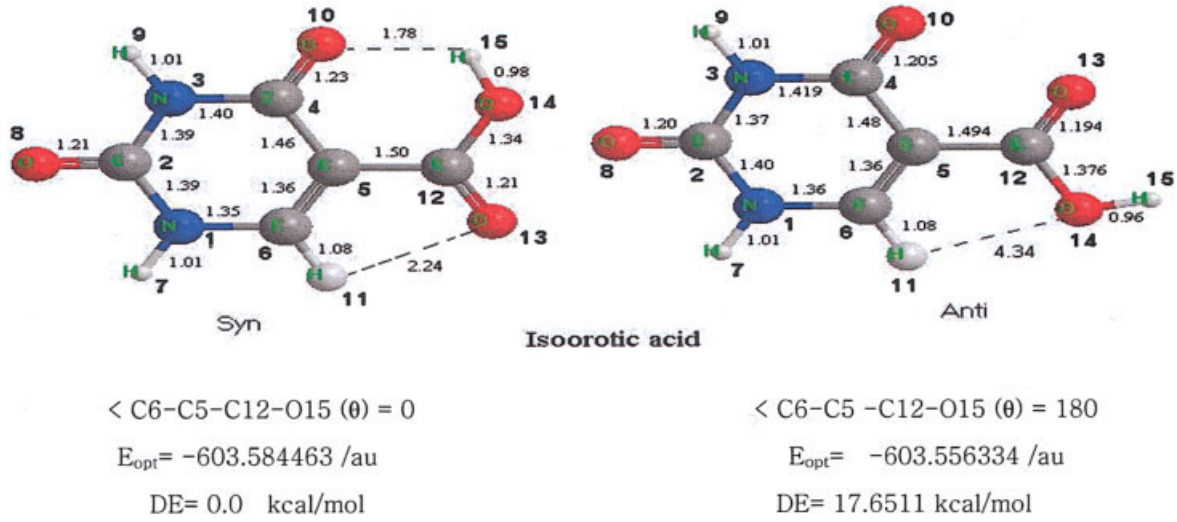

FIGURE 2. B3LYP/6-311++G** optimized geometry and optimized energy of the syn and anti-configurations of iso orotic acid. Bond lengths are in Å. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

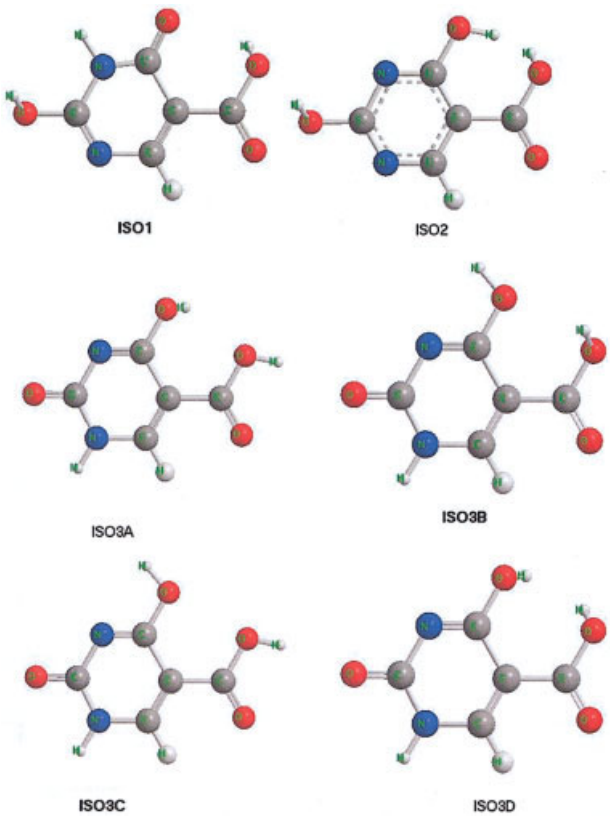

FIGURE 3. Molecular structures of tautomers of isoorotic acid. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

etry optimizations for all species were carried out at the B3LYP/6-311++G** level of theory. Additional single-point MP2/6-311++G**//B3LYP/6-311++G** calculation was also performed. The selected optimized geometrical parameters of these tautomers in the gas phase are given in Table I, while their energies and relative stabilities are presented in Table II.

The calculated harmonic vibrational frequencies using analytical second derivative at the B3LYP/6-311++G** level of theory indicated that all these optimized structures are at stationary points. Careful inspection of the data given in Tables I and II reveals the following:

1. The most significant changes in geometry accompanied the keto-enol tautomerization in isoorotic acid are the C2—N1 and C4—N3 bond lengths (~0.14 Å), and the C—O bond lengths (~0.12 Å). The changes of the other bond lengths including the carboxylic group are negligible. This is due to the week interaction between the uracil ring and the —COOH group (cross-conjugation). The corresponding changes found in case of the unsubstituted uracil molecule were 0.12 and 0.10 Å, respectively at the B3LYP/6-31+G* level [2]. The two nitrogen atoms of the ring have negative charges in all forms. Consequently, the stable conformers of the enolic forms are

TABLE I

Bond lengths (Å) and the charge densities for the optimized form of the studied tautomers of isoorotic acid calculated at the B3LYP/6-311++G level.**

	iso	iso1	iso2	iso3a	iso3b	iso3c	iso3d
			Bond lengths (Å)				
R(1,2)	1.399	1.297	1.335	1.442	1.431	1.433	1.439
R(1,6)	1.360	1.358	1.326	1.333	1.340	1.338	1.336
R(2,3)	1.387	1.363	1.333	1.367	1.378	1.372	1.372
R(2,8)	1.207	1.337	1.334	1.209	1.208	1.210	1.208
R(3,4)	1.396	1.412	1.324	1.301	1.298	1.306	1.296
R(4,5)	1.457	1.440	1.414	1.456	1.434	1.442	1.449
R(4,9)	1.227	1.229	1.343	1.333	1.352	1.333	1.348
R(5,6)	1.358	1.374	1.400	1.375	1.372	1.373	1.373
R(5,13)	1.500	1.501	1.482	1.467	1.496	1.479	1.481
R(13,14)	1.336	1.341	1.197	1.372	1.344	1.345	1.378
R(13,15)	1.207	1.205	1.386	1.207	1.206	1.213	1.200
			Charge densities				
N1	−0.350	−0.215	−0.160	−0.299	−0.303	−0.308	−0.289
C2	0.317	0.203	0.108	0.232	0.213	0.230	0.254
N3	−0.416	−0.292	−0.190	−0.251	−0.246	−0.248	−0.218
C4	0.101	0.034	−0.289	−0.095	0.107	0.149	−0.260
C5	0.501	0.645	0.929	0.507	0.533	0.181	0.783
C6	0.061	−0.151	−0.216	−0.085	−0.168	−0.160	0.015
O8	−0.307	−0.156	−0.170	−0.310	−0.317	−0.327	−0.308
O10	0.250	−0.359	0.247	0.247	0.250	0.254	0.237
C12	−0.193	−0.406	−0.243	−0.308	−0.203	−0.186	−0.198
O13	−0.321	−0.201	−0.200	−0.315	−0.315	−0.320	−0.262
O14	0.359	−0.304	0.314	0.348	0.356	0.352	0.352

those where OH group orients toward the nitrogen lone pair of electrons (Fig. 2).

2. There were no significant differences in the ring structure of the tautomers **iso3a–d**.
3. Energetically, it is interesting to note that the diketo forms and the one keto form of isoorotic acid were found to be the most stable forms than the total hydroxy form in both DFT and MP2. The total keto form (**iso**) of isoorotic acid is the most stable form and represents the global minima in the potential energy curve of isoorotic acid. The same find-

TABLE II

Total energy *E* (in Hartree), relative energy *DE* (in kcal/mol) and, dipole moment (in Debye), for tautomers of isoorotic acid in the gas phase calculated at MP2 and B3LYP by implementing the 6-311++G basis set.**

	MP2			B3LYP		
	E_{opt}	*DE*	*DM*	E_{opt} (au)	E_{Rel} (kcal/mol)	*DM*
iso	−602.0466	0	4.51	−603.5845	0	4.16
Iso1	−602.0145	−20.18	8.52	−603.5509	−21.06	7.95
Iso2	−602.0069	−24.97	2.79	−603.5367	−29.94	3.17
Iso3a	−602.0206	−16.36	6.47	−603.5574	−16.95	5.82
Iso3b	−602.0219	−15.53	0.55	−603.5579	−16.64	0.64
Iso3C	−602.0225	−15.17	3.09	−603.5582	−16.47	3.012
Iso3D	−602.0033	−27.22	3.81	−603.5376	−29.38	3.33

ings were also found for the unsubstituted uracil [2–6] at various levels of theory.

4. The B3LYP/6-311++G** level has predicted the order of stability of tautomers in gas phase as **iso** > **iso3c** > **iso3b** > **iso3a** > **iso1** > **iso3d** > **iso2**. While the MP2/6-311++G** level has predicted the order to be **iso** > **iso3c** > **iso3b** > **iso3a** > **iso1** > **iso2** > **iso3d**.
5. The two tautomers **iso3c** and **iso3b** have nearly equal total energies. The difference between their stabilities is only 0.17 and 0.26 kcal at the two levels of calculation, while **iso3a** is less stable by 1.48 and 1.20 kcal/mol, respectively. The least stable form of **iso3** is **iso3d** is with 12.09 and 12.06 kcal/mol less than the **iso3c** one. The nonbonding interactions between the hydroxyl groups of the enolic ring and the carboxylic group control the stability of the **iso3a-d** tautomers.
6. The greater stability of **iso3c** over the tautomer **iso1** indicates the difference in proton acidity between N1 and N3 protons.

DIPOLE MOMENT AND SOLVENT EFFECT

Probably one of the most crucial factors determining the tautomer distribution in the biological material is the environment. The study of interaction between solute and solvent is normally a complicated process. However, the self-consistent reaction field (SCRF) theory can be employed to examine the solvent effect on the tautomerism. A continuum model like SCRF theory allows one to take into account long-range interactions and allows the molecular geometry and dipole moment of the solute to be adjusted to reflect the interaction of the polar medium. In addition to this, the SCRF model is simple to implement and is computationally efficient for the prediction of general structural and stability trends in aqueous phase. The magnitude of the dipole moment is strongly related to the tautomeric stability in polar environment. The calculated dipole moments of the studied tautomers are listed in Tables II and III. The gaseous diketo form **iso** has a dipole moment value of 4.16 and 4.51 D at the B3LYP and MP2 levels. In the gas phase, the highest value of dipole moment is found in case of **iso1** (7.95 and 8.52 D) while the lowest dipolar one is **iso3b** form (0.64 and 0.55 D). The dipole moment order in gas phase is **iso1** > **iso3a** > **iso** > **iso3d** > **iso2** > **iso3c** > **iso3b**.

TABLE III

Total energy E_{opt} (in Hartree), relative energies DE (in kcal/mol), solvation energy (in kcal/mol), dipole moment (in Debye), for tautomers of isoorotic acid in aqueous phase using IPCM method calculated at B3LYP/6-311++G level of theory.**

	E_{opt}	E_{sol}	*DE*	*DM*
iso	−603.6196	22.0508	0	5.92
Iso1	−603.6046	33.7468	−9.36	11.44
Iso2	−603.5804	27.4055	−24.58	3.49
iso3a	−603.5964	24.4859	−14.52	7.56
iso3b	−603.5928	21.8965	−16.79	0.88
iso3C	−603.5923	21.4485	−17.07	5.15
iso3D	−603.5811	27.3200	−24.11	4.21

The influence of the polar environment on the relative stabilities of isoorotic acid tautomers can be easily identified by comparing their dipole moment values in both the gaseous and aqueous phases. The dipole moments change to higher values on going from gaseous state to the water phase, which is attributed to the sensitivity of the tautomers to the polarity of the medium. This is because the charge redistribution in the molecules.

The energetic parameters of the tautomeric forms in the aqueous phase ($\epsilon = 78.5$) calculated at the B3LYP/6-311++G** level of theory are listed in Table III. The calculated relative energy values indicate that the solvent interaction with the molecular system has increased the stability of the tautomers due to the solvent–molecule interaction. The order of stability changes in all cases from gas phase into solution, where the order of stability of tautomers in solution becomes **iso** > **iso1** > **iso3a** > **iso3b** > **iso3c** > **iso3d** > **iso2**. The most stable tautomer iso is more stable than the least stable tautomer form **iso2** by 24.58 kcal/mol.

The calculated dipole moments for the studied tautomers at the B3LYP/6-311++G** level in solution are given in Table III. The order of the dipole moment of tautomers in aqueous solution is **iso1** > **iso3a** > **iso** > **iso3c** > **iso3d** > **iso2** > **iso3d**. The three tautomers **iso3a-c** have small magnitude in total energy differences in gas phase and large dipole moments (Table II). This leads to the inversion of their order of stability in polar solvent.

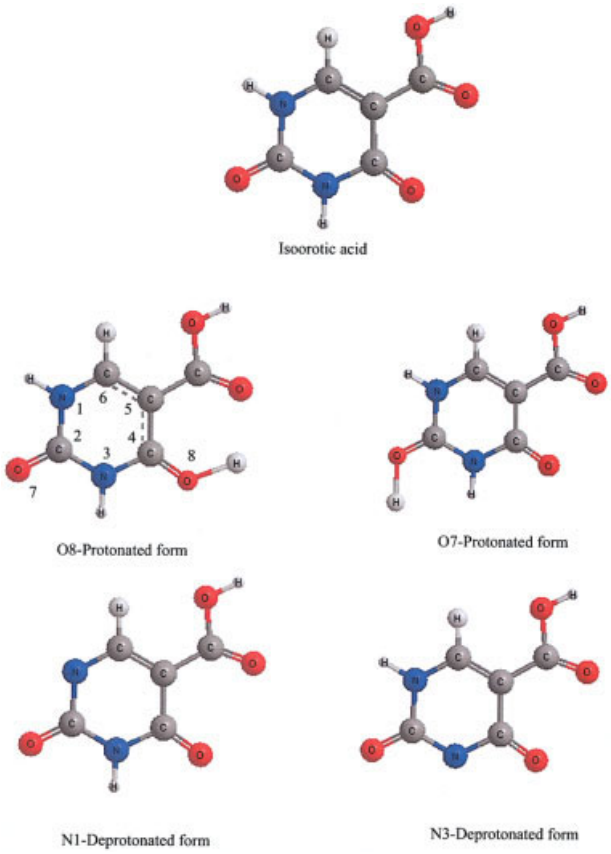

CHART I. Protonation and deprotonation forms of isoorotic acid considered in this work. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

PROTONATION AND DEPROTONATION ENERGIES OF ISOOROTIC ACID

The protonation affinity (PA) is defined as the negative of the enthalpy change associated with the gas phase protonation reaction $B + H^+ = HB^+$, while the deprotonation energy (DPE) is defined as the enthalpy change associated with the gas phase deprotonation reaction $AH = A^- + H^+$. In this section, we will discuss the PAs and DPEs of the atoms or bonds participating in the tautomerization process, i.e., the protonation of the carbonyl oxygen and the deprotonation of the carboxylic group and N—H bonds as well (Chart I). The differences between the tautomerization energies can be discussed as a function of the PA of the two O atoms and of the *N*-deprotonation enthalpies of the two NH bonds of isoorotic acid and compared with uracil, which are depicted in Table IV.

However, the results show that the protonation on O_8 site is found to be strongly favored over the O_7-site for isoorotic acid as well as uracil and thymine. The PA of the O_7 atom is lower for isoorotic acid than for uracil and thymine, and the differences are small (~3–7 kcal/mol) because of the little withdrawing effect of carboxylic group on the O_7 atom. In contrast, the PA of the O_8 is higher for isoorotic acid than for thymine and uracil. The reason is probably that the O_8-protonated form of isoorotic acid is stabilized by a hydrogen bonding with C═O of adjacent carboxylic group. The results show that the two ion pairs of the O_7 and O_8 oxygen are not equivalent. A similar result has also been obtained for aliphatic amides, with the basicity of the lone pair in the *cis* position ~2.86 kcal/mol higher than that of the lone pair in the *trans* position [28]. This effect should be taken into account when considering the correlation between the energies or spectroscopic properties of the hydrogen bonds and the PAs. The DPE results in Table IV show that, the DPEs of the NH are much bigger than COOH (7.84 kcal/mol). The results in Table IV also indicate that the acidity of the two NH bonds of isoorotic acid is somewhat lower than that of the corresponding

TABLE IV

B3LYP/6-311++G proton affinities (PA(B)) and deprotonation enthalpies [DPE(A^-)] (kcal · mol^{-1}) of isorotic acid, uracil, and thymine.**

	PA(B)		PA(A^-)		
	O7	O8	N1	N3	COO^-
Isoorotic acid	191.00	214.75	334.66	352.40	7.84
Uracil[a]	194.78	202.91	332.45	345.83	—
Thymine[b]	198.37	204.34	334.12	346.31	—

[a] Energies are computed at B3LYP/6-31++G** level [30].
[b] Energies including ZPE computed at B3LYP/6-31++G** level [30].

bonds in uracil and thymine. It must be noticed that the NH bonds in both molecules are characterized by a relatively high intrinsic acidity, which is sensibly higher than that of formamide (358.50 kcal/mol), *N*-methylformamide (360.89 kcal/mol), *N*-methylacetamide (360.89 kcal/mol), and the biological NH donors of the peptide links (351.33–354.47 kcal/mol) [29]. According to the DFT calculations, the N_1 anion is more stable by 17.74 kcal/mol than the N_3 one. The reason for this low acidity of isoorotic acid compared with uracil is probably due to a strong localization of the negative charge over the $C{=}O_8$ and COOH parts of the molecule. Theoretical calculations of the electron affinities (EA) of larger biological molecules present a complicated task. Usually a significant electron correlation energy contribution mandates a treatment that goes beyond the Hartree–Fock model. Spatial expansion of the electron density for the anion requires additional diffused basis functions. The electron affinities of nucleic acid bases and related compounds in the gas phase are not well known, despite a significant interest in the mechanism for excess electron attachment to DNA [31].

Upon examining the results, one notices that the calculated electron affinity, of isoorotic acid is positive. This is mainly because the diffused orbitals in the basis set are included, which allowed an electron to attach to the molecular dipole. The phenomenon of electron attachment to a sufficient dipole should be applicable to all the DNA bases, since they all have significant dipoles. Thus, the electron affinities for all the DNA bases should be positive. The value of the electron attachment energy predicted for this process was equal to 0.04217 hartree for isoorotic acid. This value is very bigger than uracil (.00200).

Conclusion

Tautomers of isoorotic acid have been studied by using MP2 and DFT methods in the gas phase and in solution (IPCM). The following conclusions have been drawn from the present study:

1. All the optimized tautomers present at the stationary points are corresponding to local minima in the potential energy surface.
2. The diketo form **iso** was found to be the most stable form over than all enol forms in both MP2 and DFT methods in the gas phase and solution, which also the same situation for the unsubstituted uracil.
3. The tautomer **iso3c** is found to be the most stable one of the hydroxyketo forms in both MP2 and B3LYP using 6-311++G** basis set.
4. The influence of the polar environment substantially enhanced the dipole moment for all the tautomers in going from the gaseous to aqueous phase, which indicates that there is an increase in stability of the molecular system due to the solvent-molecule interaction and redistribution of the charge.
5. The greater stability of **iso3c** over the **iso1** tautomer indicates the difference in proton acidity between N_1 and N_3 protons and high the proton affinity of O_8 than O_7.

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