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Acid Dissociation Constants of Melamine Derivatives from Density Functional Theory Calculations

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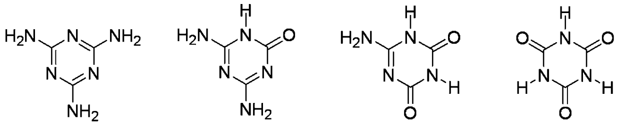
Melamine and its hydrolysis products (ammeline, ammelide, and cyanuric acid) recently attracted great attention as major food contaminants. Developing analytical tools to quantify them requires exact knowledge of their acid dissociation constants (pK_a values). Herein, we calculated the pK_a values of these melamine derivatives in water, using a density functional theory quantum mechanical method [B3LYP/6-311++G(d,p)] in combination with the Poisson−Boltzmann continuum solvation model. The excellent agreement of the calculated values with the experimental ones shows that our method can be used to predict such properties of other food contaminants.

1. Introduction

Since the recent incident of infant illness due to intentionally contaminated milk-based infant formula, melamine has attracted global attention as a serious contaminant in food. Melamine (1,3,5-triazine-2,4,6-triamine or 2,4,6-triamine-*s*-triazine) and its hydrolysis products or metabolites such as ammeline, ammelide, and cyanuric acid (Scheme 1) have also been found as hazardous contaminants in pet food formulated with wheat gluten.[1,2] Reliable and prompt detection and quantification of melamine residues and other potentially toxic contaminants in food (particularly in milk products and infant formula) immediately became a very important safety issue. Liquid chromatography (LC), gas chromatography (GC), and capillary electrophoresis (CE) are promising analytical tools for this purpose. In CE and LC, the charge of an analyte is one of the major factors determining the migration time and the retention time. Thus, knowing exactly the protonation states of melamine and its derivatives at given conditions should be critical to develop the optimum separation conditions (see refs 3−5, for example). However, the acid−base properties of melamine and its derivatives are rather complicated due to the presence of multiple protonation sites (the amine groups and the triazine ring) leading to several different tautomers.[6] In addition, precise measurements of the acid dissociation constants (pK_a values) of some melamine derivatives (ammeline and ammelide) can be hampered by their low solubility in water.[7] In this case, an alternative to determine the pK_a values would be a theoretical investigation. We have developed a protocol based on a density functional theory (DFT) quantum mechanics method to understand the keto−enol and amino−imino tautomeric equilibrium of normal and damaged DNA bases in various environments and to calculate their pK_a values in water.[8−13] DNA bases and melamine derivatives have similar chemical structures. Thus, in this study, we used the same method to calculate the relative tautomeric stabilities and the pK_a values of melamine, ammeline, ammelide, and cyanuric acid, and compared them to the experimental pK_a values. Because some experimental pK_a values have been known only from old literature sources, we also carried out spectrophotometric measurements of the pK_a values.

SCHEME 1: Melamine Derivatives



melamine (0) **ammeline (1)** **ammelide (13)** **cyanuric acid (135)**

2. Determination of pK_a Values

2.1. Tautomers. The tautomers considered in this study are shown in Figure 1. It is well-known that melamine (**0**) exists predominantly as an amino form,[7,14] which is quite symmetric (~C_{3v}; Figure 1a). The first protonation of melamine can occur either on one of the three equivalent nitrogens on the triazine ring (N1, N3, or N5) to form $\mathbf{1}^+$ or on one of the three equivalent amine groups (N2, N4, or N6) to form $\mathbf{2}^+$. Because the protonation at any of three different sites results in the same tautomer, we can say that such tautomers, $\mathbf{1}^+$ and $\mathbf{2}^+$, have a 3-fold degeneracy ($n = 3$). On the other hand, the deprotonation of melamine would occur from one of the three equivalent amino groups to form $\mathbf{Im0}^-$ in an imino form. With a subsequent proton transfer, it can also transform to $\mathbf{Im1}^-$. Both tautomers have a 3-fold degeneracy.

Ammeline and its conjugate acid (Figure 1b) can exist as a keto form (**1** and $\mathbf{13}^+$) or an enol form (**2** and $\mathbf{12}^+$). We can say that **1** and $\mathbf{12}^+$ have 2-fold degeneracy because positioning the proton on either N1 or N3 in the triazine ring would produce the same compound.

Ammelide and its conjugate acid and base can also exist as a keto form (**13**, $\mathbf{135}^+$, $\mathbf{1}^-$, and $\mathbf{3}^-$) or an enol form (**24**, $\mathbf{124}^+$, and $\mathbf{2}^-$). We also considered the conjugate base in an imino form ($\mathbf{Im13}^-$) (Figure 1c).

It is well-known that cyanuric acid exists predominantly as a keto form (**135** with ~D_{3h} symmetry; Figure 1d) rather than an enol form (**246**).[15] The first protonation would occur at one

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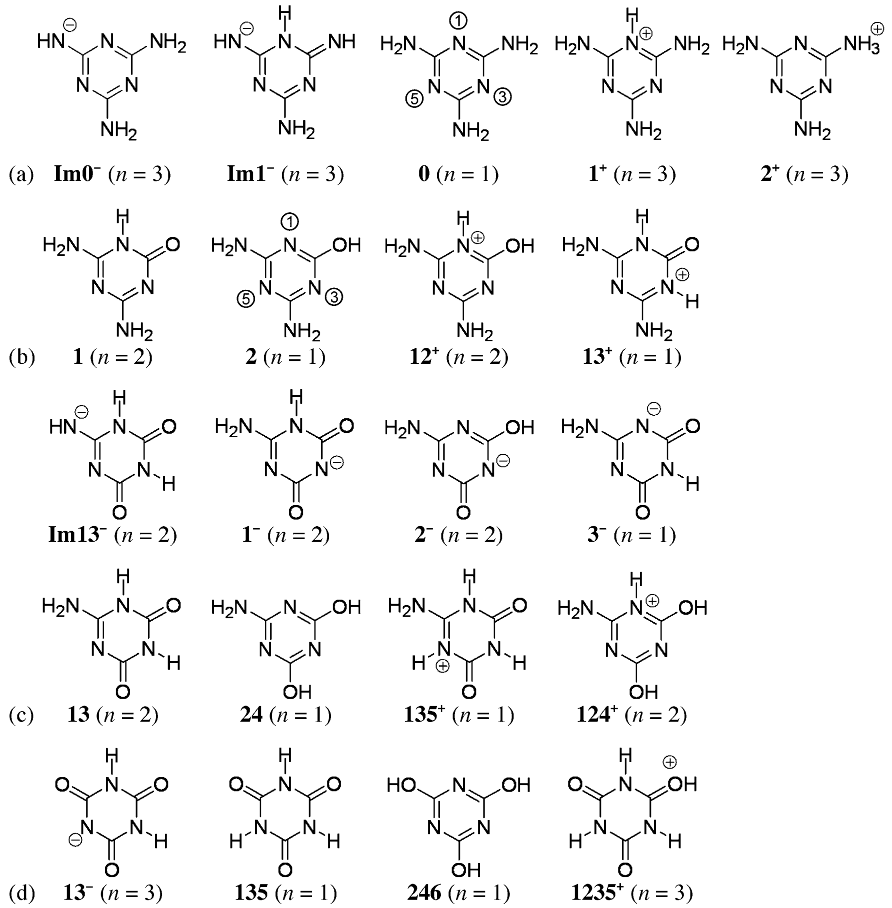

Figure 1. Tautomers of conjugate acids and bases of (a) melamine, (b) ammeline, (c) ammelide, and (d) cyanuric acid. The name of each compound designates the molecular charge (−1, 0, or 1) and the numbers of atoms where the nonamino protons are attached. [$\mathbf{1}^+$, for example, is positively charged and has a nonamino proton attached to N1.] Degeneracy n shown together denotes the symmetry of a tautomer. [The degeneracy of $\mathbf{1}^+$, for example, is 3 because placing the nonamino proton (currently at N1) at one of three sites (N1, N3, or N5) would result in the same compound.]

of the three equivalent oxygens ($\mathbf{1235}^+$ with a 3-fold degeneracy), while the first deprotonation would occur from one of the three equivalent nitrogens ($\mathbf{13}^-$ with a 3-fold degeneracy).

2.2. Calculation Methods. The standard free energy of each tautomer in water was calculated as the sum of the gas-phase free energy and the free energy of solvation in water:[9−12]

$$\Delta G^\circ_{\text{aq}} = \Delta E_0 + \text{ZPE} + \Delta G_{0\rightarrow 298} + \Delta G^\circ_{\text{solv}} - RT \ln n \tag{1}$$

The total energy of the solute at 0 K (ΔE_0) was calculated using the density functional theory (DFT) at the B3LYP/6-311++G(d,p) (that is, B3LYP/6-311++G**) level with the final geometry optimized at the B3LYP/6-311G(d,p) (that is, B3LYP/6-311G**) level. The zero-point energy (ZPE) and the free energy change from 0 to 298 K ($\Delta G_{0\rightarrow 298}$) were calculated from the vibration frequencies obtained at the B3LYP/6-311G(d,p) level with the ideal gas approximation for the translational and rotational free energy contributions.

The standard free energy of solvation (ΔG_{solv}) was calculated using the Poisson−Boltzmann (PB) continuum solvation approach[16−19] at the B3LYP/6-311G(d,p) level. The atomic radii used to build the solute envelope were taken from our previous studies:[9−12] 1.88, 1.41, 1.46, and 1.08 Å for C, N, O, and H, respectively (6% reduction from Marten and co-workers' radii).[19] As will be shown below in section 3.2, the pK_a values calculated with this set of radii show an excellent agreement with experiment for melamine ($C_3H_6N_6$) but significant errors for other oxygen-containing compounds ($C_3H_{6-x}N_{6-x}O_x$; $x = 1$, 2, and 3 for ammeline, ammelide, and cyanuric acid), and the errors increase systematically with the increasing number of oxygen atoms in a compound (x). Therefore, for a better match with experiments, the radius for O was reoptimized to an increased value of 1.76 Å, as will also be shown in section 3.2. All calculations used the Jaguar v6.5 quantum chemistry software (Schrödinger Inc., Portland, OR, 2005).

Because the highly symmetric melanine derivatives have multiple equivalent protonation sites leading to each conjugate acid (n-fold degeneracy; $n = 3$ for $\mathbf{1}^+$, for example), extra stabilization in free energy due to the configurational entropy ($-RT \ln n$) was added, where R is the gas constant and T is the temperature (298.15 K).

From these standard free energies of tautomers, the free energy of deprotonation leading an acid HA into its conjugate base A$^-$ is given as

$$\Delta G^\circ_{\text{deprot,aq}} = \Delta G^\circ_{\text{aq}}(\text{A}^-) + \Delta G^\circ_{\text{aq}}(\text{H}^+) - \Delta G^\circ_{\text{aq}}(\text{HA}) \tag{2}$$

The corresponding pK_a value is given by[20,21]

$$\text{p}K_a = \Delta G^\circ_{\text{deprot,aq}}/2.303RT \tag{3}$$

TABLE 1: Relative Free Energies (kcal/mol) of Tautomers in a Vacuum and in Water[a]

	(a) melamine				(b) ammeline				(c) ammelide								(d) cyanuric	
	base		acid		neutral		acid		base				neutral		acid		neutral	
	Im0$^-$	**Im1**$^-$	**1**$^+$	**2**$^+$	**1**	**2**	**12**$^+$	**13**$^+$	**Im13**$^-$	**1**$^-$	**2**$^-$	**3**$^-$	**13**	**24**	**135**$^+$	**124**$^+$	**135**	**246**
$\Delta\Delta G°$(g)	3.4	0	0	19.3	1.1	0	4.2	0	3.5	18.2	16.8	0	0	9.0	0	7.0	0	29.4
$\Delta\Delta G°$(aq)[b]	0	3.7	0	9.5	0	7.4	9.0	0	7.4	4.9	11.8	0	0	16.7	0	18.1	0	29.9
$\Delta\Delta G°$(aq)[b]	0	3.7	0	9.5	0	5.7	9.4	0	6.6	6.0	10.6	0	0	14.1	0	17.1	0	25.1

[a] Free energies relative to the most stable tautomer of each compound at each state. [b] Calculated with O radius (r_O) values of 1.46 (upper) and 1.76 Å (lower), respectively.

The standard free energy of the proton in water was chosen as −269.75 kcal/mol from the previous studies.[9−12]

2.3. Experimental Methods. Melamine was obtained from Aldrich (Milwaukee, WI, USA). Ammeline, ammelide, and cyanuric acid were obtained from TCI (Tokyo, Japan). The 10 mM acetate buffers were used for pH near 5, and 1.0 mM phosphate buffers were used for pH near 2 and 7. A solution of HCl was used as a buffer for pH below 2. KCl was added to each buffer to keep the ionic strength at 0.10 M. The pK_a value of an acid HA can be expressed as[22]

$$\mathrm{p}K_\mathrm{a} = -\log\left(\frac{\gamma_{\mathrm{A}^-}}{\gamma_{\mathrm{HA}}}\rho\right) + \mathrm{pH} \quad \text{with} \quad \rho = \frac{A_{\mathrm{HA}} - A}{A - A_{\mathrm{A}^-}}\frac{[\mathrm{A}^-]}{[\mathrm{HA}]} \tag{6}$$

where γ is the activity coefficient of the species denoted by the subscript. A_{HA} and A_{A^-} are the absorbance of fully protonated and fully deprotonated forms measured at pH much lower and higher than pK_a, respectively. The activity coefficients at the ionic strength of 0.1 M were calculated using the Davies equation.[23] From log ρ measured at several wavelengths near the UV peak as a function of pH, the pK_a value of HA was determined. All four compounds were insoluble or slightly soluble, and the saturated solution of each compound was filtered and used without determining the actual concentration because the pK_a values depend on the concentration ratios only.

3. Results and Discussion

3.1. Tautomers. Table 1 lists the relative free energies ($\Delta\Delta G°$) of the tautomers of melamine, ammeline, ammelide, and cyanuric acid at each protonation state. We see that the two different radii used for oxygen atoms in the solvation energy calculations (1.46 and 1.76 Å) did not change the tautomeric preferences. In most cases, the tautomeric preference is the same both in the gas phase and in the aqueous phase but reversed in some cases.

For melamine, the neutral state with the predominant amide−amino form **0** has the aqueous-phase structure (bond length CN = 1.344 and 1.347 Å; angle CNC = 115°, NCN = 125° and 118°, HNC = 120°; dihedral angle HNCN = 7°) that is very similar to the one reported from a single-crystal neutron diffraction study at 14 K.[14] Its conjugate acid has a predominant tautomer **1**$^+$ in both environments. That is, the nitrogens on the triazine ring are more basic than those in the amine groups. This was expected from the higher basicity of pyridine (C_5H_5N; pK_a 5.23) than that of aniline ($C_6H_5NH_2$; pK_a 4.87).[24] Moreover, the aromatic resonance character is more preserved and the symmetric structure is less distorted in **1**$^+$ (CN distance = 1.33−1.37 Å; CNC angle = 117−119°; NCN angle = 118−125°) than in **2**$^+$ (CN distance = 1.31−1.48 Å; CNC angle = 113−117°; NCN angle = 113−130°). The calculated planar structure of **1**$^+$ is very similar to the one observed in an X-ray crystallography study on a melaminium chloride salt at 210 K (CN distance = 1.32−1.38 Å, CNC angle = 116−120°; NCN angle = 117−126°).[25] As its conjugate base, **Im1**$^-$ with two imino groups and one proton on the triazine ring is predominant in the gas phase probably due to a favorable intramolecular hydrogen bond (HN$^-$···H−N1), but **Im0**$^-$ with one imino group becomes predominant in the aqueous phase.

For ammeline, the neutral state of the keto form **1** is slightly less stable than the enol form **2** in the gas phase ($\Delta\Delta G°$ = 1.1 kcal/mol) but significantly more stable than **2** in the aqueous phase ($\Delta\Delta G°$ = 6−7 kcal/mol). This is consistent both with an assignment of the enol form to gas-phase ammeline from an ab initio calculation at the HF/6-31G** level[26] and with an assignment of the keto form to aqueous-phase ammeline from a UV absorption spectroscopy study.[15] However, as its conjugate acid, the keto form **13**$^+$ is predominant in both phases. This is consistent with the assignment from a single-crystal X-ray diffraction and IR spectroscopy study on three ammelinium salts.[27] The aqueous-phase structure of **13**$^+$ (bond length CO = 1.21 Å, CN = 1.39, 1.37, 1.33, and 1.32 Å; angle CNC = 122° and 119°, NCN = 121°, 119°, and 114°) is in very good agreement with the one from the X-ray diffraction study, especially on an ammelium nitrate salt.[27]

For ammelide and cyanuric acid, the keto forms (**13**, **135**$^+$, **3**$^-$, and **135**) are always more stable than the corresponding enol forms (**24**, **124**$^+$, **2**$^-$, and **246**) in both environments. The neutral state with the predominant keto form **135** of cyanuric acid has the aqueous-phase structure (bond length CO = 1.21 Å, CN = 1.38 Å; angle CNC = 126°, NCN = 114°, NCO = 123°, CNH = 117°) that is very similar to the one reported from a single-crystal X-ray diffraction study at 100 K,[28] except for the NH bond length (1.02 Å from calculation and 0.90 Å from the diffraction study).

3.2. pK_a Values. The pK_a values were calculated for the deprotonation involving the most stable tautomer at each state in the aqueous phase: (**1**$^+$ → **0**) for melamine's pK_{a1}, (**13**$^+$ → **1**) for ammeline's pK_{a1}, (**135**$^+$ → **13**) and (**13** → **3**$^-$) for ammelide' pK_{a1} and pK_{a2}, respectively, and (**1235**$^+$ → **135**) for pK_{a2} of cyanuric acid. The calculated pK_a values are listed in Table 2.

Table 2 also lists the experimental pK_a data obtained from our spectrophotometric measurements and those collected from

TABLE 2: pK_a Values of Melamine Derivatives in Water

	(a) melamine	(b) ammeline	(c) ammelide	(d) cyanuric
pK_{a1} ($H_2A^+ \rightarrow HA$)				
calc (r_O 1.46 Å)	4.9	3.6	0.2	
calc (r_O 1.76 Å)	4.9	4.4	1.3	
experimental	5.0	4.5	1.8	
literature[a]	5.0−5.1	4.4−4.5	1.8	
pK_{a2} ($HA \rightarrow A^-$)				
calc (r_O 1.46 Å)			5.7	4.6
calc (r_O 1.76 Å)			7.2	6.9
experimental			6.9	6.9
literature[a]			6.9	6.4−6.9

[a] See the text (section 3.2) for the references.

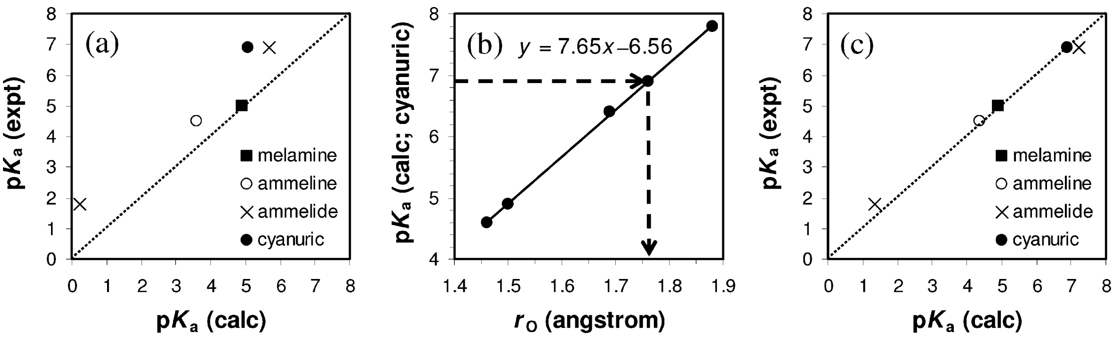

Figure 2. (a) pK_a values of melamine derivatives calculated with an oxygen solvation radius r_O of 1.46 Å, which are compared to the spectrophotometric measurements. (b) Optimization of r_O from r_O-dependent pK_a values of cyanuric acid. (c) pK_a values calculated with the optimized r_O of 1.76 Å showing excellent agreement with the experimental values.

the literature. Except for cyanuric acid, the literature values, both old and new, agree well with our measurements within 0.1 pK_a unit. For melamine, our measurement gave the pK_{a1} value of 5.0, while previous titration[24,29] and UV absorption[15,29] works had given similar values of 5.0 and 5.1, respectively. For ammeline, the pK_{a1} value was measured as 4.5 from our work, and this is again in good agreement with the values of 4.5 and 4.44, which had been measured by UV absorption[15] and capillary electrophoresis[6] studies, respectively. For ammelide, our measurements gave the same pK_{a1} (1.8) and pK_{a2} (6.9) values as those previously measured using UV absorption.[15] In the case of cyanuric acid, our measurement (6.9) agrees with the recent compilation (6.88; ref 24) better than the old experiment [6.5 (UV absorption, ref 15); 6.78, 6.74, and 6.42 (titration, ref 30 and references therein)]. Thus, the following discussions are based on this newly measured value (6.9).

Figure 2a shows the correlation between the calculated pK_a values and the corresponding experimental values obtained from our measurements. The agreement between the calculated pK_a values and the experiments is barely satisfactory with the root-mean-square (rms) deviation of 0.6 pK_a unit. The calculation for melamine (4.9) gives an excellent agreement with the experiment (5.0), but the calculation for ammeline (3.6) shows a discrepancy from the experiment (4.5), and the discrepancy is larger for ammelide [0.2 (pK_{a1}) and 5.7 (pK_{a2}) from calculation; 1.8 (pK_{a1}) and 6.9 (pK_{a2}) from measurement] and even larger for cyanuric acid (5.1 from calculation and 6.9 from measurement).

The quality of the pK_a calculation depends on a number of approximations and parameters involved in the calculation, such as DFT functional, basis set, implicit solvation model, and (empirical) atomic radii used to represent the solute in the implicit solvation model. The excellent agreement between our calculation and experiment in the case of melamine ($C_3H_6N_6$; $\Delta pK_a = 0.1$) and the systematic increase of errors with the increasing number of oxygen atoms in a compound (x) only after that [$\Delta pK_a = 0.9$ for ammeline ($C_3H_5N_5O$), 1.2 and 1.6 for ammelide ($C_3H_4N_4O_2$), and 1.8 for cyanuric acid ($C_3H_3N_3O_3$)] indicate that the problem in calculating the pK_a values should be specific to oxygen atoms. [We now note that we had also observed a similar kind, albeit in a smaller extent, of behavior in our previous study on purine DNA bases.[11]]

We therefore decided to keep our calculation method in general [B3LYP functional, 6-311++G(d,p)/6-311G(d,p) basis set, the PB solvation model, and the solvation radii for H, C, and N] and to fix the problem by changing an empirical parameter specific to oxygen atoms, that is, the radius used for oxygen atoms (r_O) in the solvation energy calculations. First, we employed several alternative values of r_O (1.50, 1.69, and 1.88 Å instead of the original 1.46 Å) to calculate the pK_a values of the most extreme case, cyanuric acid ($C_3H_3N_3O_3$). The calculated pK_a values show as a linear dependence on r_O, and thus from a linear regression a new value of r_O (1.76 Å) was chosen to give the best fit between the calculation and the experiment (pK_a = 6.9) [Figure 2b]. Indeed, the pK_a values calculated for all of the compounds with this new r_O parameter, 1.76 Å, are in excellent agreement with experiments, showing the rms deviation of 0.1 pK_a unit, as shown in Figure 2c. Interestingly, this new oxygen radius (1.76 Å) is very similar to the van der Waals (vdW) radii used for sp^2 oxygen atoms in the United Force Field (UFF; 1.75 Å)[31] and the United Atom Model for Hartree−Fock/Kohn−Sham (UAHF/UAKS; 1.68−1.82 Å, which was scaled up by 20% from the Pauling or Bondi radius 1.4−1.52 Å),[32] both of which are often employed in the Polarizable Continuum Model (PCM)[32] and other solvation calculations.[33] It is also close to the vdW radius used for sp^2 oxygen atoms in the Conductor-like Screening Model for Real Solvents (COSMO-RS; 1.72 Å).[34]

The effect of other parameters (such as the implicit solvation model and the atomic radii of H, C, and N) on the pK_a calculation was also studied and summarized in the Supporting Information.

4. Conclusions

Using a first principles quantum mechanical method combined with a continuum solvation model, we calculated the relative stabilities of tautomers of hazardous food contaminants (melamine, ammeline, ammelide, and cyanuric acid) and their conjugate acids and bases both in the gas phase and in water. In water, the keto−amino forms of tautomers are the most stable in all cases, but the enol and imino forms of tautomers of ammeline are the most stable in the gas phase. The pK_a values in water were calculated from the free energy differences during the acid dissociation processes between the most stable tautomers of conjugate acids and bases. We also carried out spectrophotometric measurements of the pK_a values to confirm the literature values. The calculated pK_a values are in excellent agreement with the newly measured values with the rms deviation of 0.1 pK_a unit. This result demonstrates that our first principles method can predict and explain acid−base properties of food contaminants and other potentially toxic compounds, which should help to develop the optimum conditions for the separation and quantification of those compounds.

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Supporting Information Available: Dependence of the pK_a calculation on the implicit solvation model and the atomic radii parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Dobson, R. L. M.; Motlagh, S.; Quijano, M.; Cambron, R. T.; Baker, T. R.; Pullen, A. M.; Regg, B. T.; Bigalow-Kern, A. S.; Vennard, T.; Fix, A.; Reimschuessel, R.; Overmann, G.; Shan, Y.; Daston, G. P. *Toxicol. Sci.* **2008**, *106*, 251.

(2) Filigenzi, M. S.; Puschner, B.; Aston, L. S.; Poppenga, R. H. *J. Agric. Food Chem.* **2008**, *56*, 7593.

(3) Schmitt, P.; Garrison, A. W.; Freitag, D.; Kettrup, A. *J. Chromatogr., A* **1996**, *723*, 169.

(4) Yuan, H.; Olesik, S. V. *Anal. Chem.* **1998**, *70*, 1595.

(5) Ali, M. S.; Rafiuddin, S.; Ghori, M.; Khatri, A. R. *Chromatograhia* **2008**, *67*, 517.

(6) Schmitt, P.; Poiger, T.; Simon, R.; Freitag, D.; Kettrup, A.; Garrison, A. W. *Anal. Chem.* **1997**, *69*, 2559.

(7) Bann, B.; Miller, S. A. *Chem. Rev.* **1958**, *58*, 131.

(8) Jang, Y. H.; Sowers, L. C.; Cagin, T.; Goddard, W. A., III. *J. Phys. Chem. A* **2001**, *105*, 274.

(9) Jang, Y. H.; Goddard, W. A., III; Noyes, K. T.; Sowers, L. C.; Hwang, S.; Chung, D. S. *J. Phys. Chem. B* **2003**, *107*, 344.

(10) Jang, Y. H.; Goddard, W. A., III; Noyes, K. T.; Sowers, L. C.; Hwang, S.; Chung, D. S. *Chem. Res. Toxicol.* **2002**, *15*, 1023.

(11) Rogstad, K. N.; Jang, Y. H.; Sowers, L. C.; Goddard, W. A., III. *Chem. Res. Toxicol.* **2003**, *16*, 1455.

(12) Jang, Y. H.; Hwang, S.; Chung, D. S. *Chem. Lett.* **2007**, *36*, 1496.

(13) Hwang, S.; Jang, Y. H.; Cho, H.; Lee, Y.-J. *Bull. Korean Chem. Soc.* **2008**, *29*, 539.

(14) Cousson, A.; Nicolai, B.; Fillaux, F. *Acta Crystallogr., Sect. E* **2005**, *61*, o222.

(15) Hirt, R. C.; Schmitt, R. G. *Spectrochim. Acta* **1958**, *12*, 127.

(16) Honig, B.; Sharp, K.; Yang, A.-S. *J. Phys. Chem.* **1993**, *97*, 1101.

(17) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honig, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875.

(18) Honig, B.; Nicholls, A. *Science* **1995**, *268*, 1144.

(19) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775.

(20) Lim, C.; Bashford, D.; Karplus, M. *J. Phys. Chem.* **1991**, *95*, 5610.

(21) Topol, I. A.; Tawa, G. J.; Burt, S. K.; Rashin, A. A. *J. Phys. Chem. A* **1997**, *101*, 10075.

(22) Patterson, G. S. *J. Chem. Educ.* **1999**, *76*, 395.

(23) Harris, D. C. *Quantitative Chemical Analysis*, 7th ed.; Freeman: New York, 2007.

(24) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, FL, 2006−2007.

(25) Athikomrattanakul, U.; Promptmas, C.; Katterle, M.; Schilde, U. *Acta Crystallogr., Sect. E* **2007**, *63*, o2154.

(26) Wang, Y.; Pittman, C. U.; Saebo, S. *J. Org. Chem.* **1993**, *58*, 3085.

(27) Lotsch, B. V.; Schnick, W. *Z. Anorg. Allg. Chem.* **2006**, *632*, 1457.

(28) Verschoor, G. C.; Keulen, E. *Acta Crystallogr., Sect. B* **1971**, *27*, 134.

(29) Dixon, J. K.; Woodberry, N. T.; Costa, G. W. *J. Am. Chem. Soc.* **1947**, *69*, 599.

(30) Redemann, C. E.; Lucas, H. J. *J. Am. Chem. Soc.* **1939**, *61*, 3420.

(31) Rappe, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.

(32) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

(33) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.

(34) Klamt, A.; Eckert, F. *Fluid Phase Equilib.* **2000**, *172*, 43.

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