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Absolute Calculations of Acidity of C-Substituted Tetrazoles in Solution

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The CBS-QB3 method was used to calculate the gas-phase free energy difference between nine tetrazole derivatives and their anions, and the DPCM and CPCM continuum solvation methods were applied to calculate the free energy differences of solvation. The calculations were performed on both gas-phase and solvent-phase optimized structures. Absolute pK_a calculations using the CPCM method and the gas-phase optimized structures yielded mean unsigned error of 0.4 pK_a unit. The calculations were made with the routine settings implemented in *Gaussian 98*. The study is as accurate as the best reported so far for six carboxylic acids and phenols and, to our knowledge, the best reported for the acidities of heterocyclic compounds in solution.

Introduction

Proton transfer reactions are very important in chemistry and biology: for example, most pharmaceuticals are weak acids or bases. Many reactions of biological and technological relevance take place in aqueous solutions. The tendency of a molecule to lose its hydrogen atom as an acidic proton is quantified as pK_a.

The tetrazolic acids, R−CN_4H, are the full nitrogen analogues of carboxylic acids. The acidic properties of 5-substituted tetrazoles have resulted in the use of −CN_4H as a replacement for −COOH in a wide range of biologically active molecules. Although the tetrazole system does not occur in nature, it is applied very widely in pharmaceutical chemistry.[1] The pK_a values of tetrazole and 5-substituted tetrazoles are comparable with those of carboxylic acids. A considerable amount of theoretical investigation has been devoted to the acidity of carboxylic acids or phenols in solution,[2−20] while the acidity of heterocyclic compounds has been explored to a lesser extent.[14,17,21−27] Therefore, it seemed interesting to us to study acidities of substituted tetrazoles both in aqueous solutions, for which minimal experimental data could be found in the literature,[28−34] and in the gas phase, where experimental data are entirely lacking.

The absolute acidity calculations in the gas phase are much simpler, while the methodology is well-established. Such calculations have been shown to be accurate to within 0.8−1.5 kcal/mol when compared to the most accurate experimental data for the gas-phase deprotonation reaction.[35]

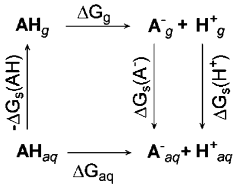
However, it is well-documented that a solvent can exert considerable influence on acid and base strength by differential solvation. For example, for simple alcohols, the order of gas-phase acidity is completely reversed from that in aqueous solution.[36] Inversion of the acidity of haloacetic acids on transition from gas phase to solution has also been reported.[20,36] Several theoretical models for the computational treatment of solvent effects and for the calculation of pK_a values in solution have been proposed.[37−39]

Among those, the continuum models are fairly popular. In such models, the solute molecule is placed in a cavity surrounded by a polarizable continuum whose reaction field modifies the energy and the properties of the solute. In the polarizable continuum model (PCM), the cavities are of molecular shape, and the reaction field is described in terms of polarization charges.[6,40,41] In this investigation, two PCM versions were applied: DPCM, the polarizable dielectric model, and CPCM, the polarizable conductor calculation model.[39]

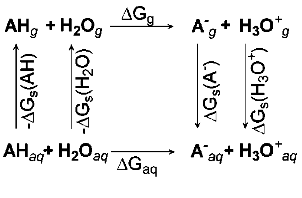
As for carboxylic acids, despite the difficulties resulting from the need for proper evaluation of the energy of solute−solvent interactions, very accurate results have recently been reported. The best results encompass those of Liptak and Shields (for six carboxylic acids)[10] and of Liptak et al. (for phenols).[13]

For heterocyclic compounds, the absolute pK_a determination produced results which do not match experimental data to a satisfactory extent.[24,26] Perhaps the best results have been obtained for substituted imidazoles with mean unsigned error (m.u.e.) equal 0.8 pK_a unit.[21] Thus, one may expect the expansion of the theoretical pK_a studies toward heterocyclic compounds with the same degree of accuracy as has been attained for carboxylic acids or phenols. The present investigation has been performed with this goal in mind. It may seem a straightforward task with methodology developed in the course of research into the acid−base equilibria conducted so far. Nevertheless, some problems emerge here regarding the choice of proper methodology. In fact, several different thermodynamic cycles and calculation variants have been proposed.

Cycle A



Cycle B



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The thermodynamic cycle A was successfully used in refs 4, 10, 13, 25, and 42. Cycle B was applied in refs 6−8 and 16.

In these cycles, ΔG_{gas} constitutes the free energy difference of the dissociation reaction in the gas phase, ΔG_{aq} means free energy of the dissociation reaction in water, $\Delta G_s(AH)$ and $\Delta G_s(A^-)$ denote the free energies of solvation of the acid and its anion, respectively, and $\Delta G_s(H^+)$ denotes free energy of the proton solvation. The performance of the two cycles was compared for phenols[13] and acids,[10] and the first appeared to be better for those groups of compounds.

In addition to various thermodynamic approaches, the authors consider various theoretical levels (HF, DFT, MP2) and different basis sets in addition to such variants of the PCM models as RS (realistic solvation simulation) and RI approximation.[17] A hybrid approach that combines a continuum method with the addition of explicit solvent molecules has been proposed.[14,43] This discrete/continuum model considers the ion solvated by some explicit solvent molecules forming a rigid cluster. Chipman used the SSC(V)PE method, which is based on dielectric continuum theory for long-range electrostatic interactions using various isodensity contours.[3]

Because comparisons of the performance of the said theory implemented with the above-mentioned or other characteristics are rarely quoted, the choice of optimum approach is far from trivial. Application of A or B thermodynamic cycles requires calculation of the absolute pK_a in the gas phase. Here, one can use the results of a comparison of the ultimate results for the carboxylic pK_a's when the gas-phase step is calculated by CBS-QB3, CBS-APNO, and G2 models,[35] considered state-of-the art models for accurate thermochemistries. Of these, the CBS-QB3[44] model used for the calculation of ΔG_{gas} combined with solvation models gave the most accurate pK_a values.

Very good results have been reported by Klamt et al. for 64 organic and inorganic acids (12 heterocyclic compounds among them),[17] yet the authors did not calculate their pK_a's from the free energy difference of the dissociation reaction in solution, ΔG_{aq}, but from the regression of the experimental data on the ΔG_{aq} values. If they had calculated the pK_a values on the basis of their free energy differences in solution, they would have gotten, in many cases, far larger values than those from the regression applied.

Methods

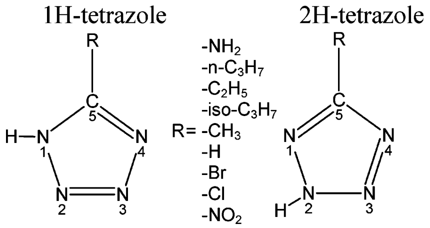
The pK_a values were calculated from eq 1 derived with the use of the thermodynamic Cycle A.

$$pK_a = \Delta G_{aq}/2.303RT = [G(A^-_{gas}) - G(AH_{gas}) + \Delta G_s(A^-) - \Delta G_s(AH) - 269.0]/1.3644 \quad (1)$$

Equation 1 was derived in ref 10 using a value of −264.61 kcal/mol for $\Delta G_s(H^+)$ combined with a value for $G_{gas}(H^+)$ of −6.28 kcal/mol taken from the experimental data (see Discussion section).

To predict the absolute free energy of dissociation for a molecule, ΔG_{aq}, the statistical average over all possible conformations was calculated. The tetrazole ring can take one of two tautomeric forms: The experimental[45,46] and theoretical[47−49] results for tetrazole itself and for its ten C-substituted derivatives show the 2H tautomer to occur predominantly in the gas phase, whereas the 1H form is the stable one in the crystal state[50] and in polar solvents.[48] Chart 1 shows the 1H and 2H tautomers of the tetrazoles dealt with in the present work. Out of seven of the acids, only the two aforementioned tautomeric forms should be taken into consideration (dissociation of the two tautomers produced the same anion). On the grounds of the calculated free energy difference between the two acid tautomers in water, the mole percentages of both forms were calculated. Two of the investigated molecules involved more complex conformational issues which required more than one conformation for each tautomer to be considered. For those molecules, the mole percentages of all forms were calculated. Then, using thermodynamic cycle A, $\Delta G_{aq}(C)$ was calculated for each form, using eq 1 applied for each conformation

CHART 1



$$\Delta G_{aq}(C) = G(A^-_{gas}) - G(AH_{gas}) + \Delta G_s(A^-) - \Delta G_s(AH) - 269.0 \quad (2)$$

where $\Delta G_{aq}(C)$ stands for the dissociation free energy for a particular tautomer and conformation.

Next, for all the acids, the statistical average of ΔG_{aq} was calculated—a value which was used for the final evaluation of pK_a. For that purpose, the following formula was applied:

$$\exp[-\Delta G_{aq}/RT] = \sum P_C \exp[-\Delta G_{aq}(C)/RT] \quad (3)$$

where P_C is the equilibrium mole fraction of conformation C in water.

Equation 3 was used in the calculation of the average free energy of solvation for a conformer mixture.[51]

Calculation of pK_a for carboxylic acids produced very accurate results with a mean unsigned error of 0.4 kcal/mol.[10] Nevertheless, it was striking that the authors used highly accurate methods for the gas-phase calculations, yet the solvation energies were computed at the Hartree−Fock (HF) level with a moderately large basis set, namely 6-31+G*. Values of ΔG_s of the acids and the anions were obtained with the geometry optimization in water. In their next paper on the absolute pK_a determination for substituted phenols, the authors compared the results obtained with the CPCM calculation performed with the HF/6-31+G* and HF/6-31G* basis set using gas-phase or solvated-phase geometry (after geometry optimization in water). The second procedure produced far better results than the calculations using the gas-phase geometries.

Since the results in refs 10 and 13 have been the best theoretical pK_a results reported until now, we decided to adopt the methodology presented therein. Thus, CBS-QB3 was used to obtain the values for the free energies $G(A^-_{gas})$ and $G(AH_{gas})$. However, we also explored other means of calculating the solvation energy. The geometry in the gas phase was also determined at the HF level, using 6-31+G* and 6-311++G** basis sets. Then, solvation energies $\Delta G_s(A^-)$ and $\Delta G_s(AH)$ were calculated by applying CPCM and DPCM methods, using the same level and basis set which were used for geometry determination in the gas phase. The calculations were made both without and with geometry optimization. Namely, solvation energies were calculated using the CPCM/HF(6-31+G*)//HF(6-31+G*), CPCM/HF(6-311++G**)//HF(6-311++G**), CPCM/B3LYP(6-31+G*)//B3LYP(6-31+G*), and CPCM/

TABLE 1: Free Energies of 5-Substituted Tetrazole Derivatives in the Gas Phase Calculated Using CBS-QB3 Method

R	acid[a]	anion	ΔG_{gas}, kcal/mol
NH_2	−313.198815	−312.673275	329.78
	−313.203669		332.82
n-C_3H_7	−375.611328	−375.085130	330.19
	−375.613901		331.80
C_2H_5	−336.382166	−335.858113	328.84
	−336.385274		330.79
iso-C_3H_7	−375.612478	−375.088110	329.04
	−375.615858		331.16
CH_3	−297.154091	−296.628744	329.65
	−297.157580		331.84
H	−257.915182	−257.393199	327.54
	−257.918806		329.82
Br	−2830.196126	−2829.689348	318.00
	−2830.199377		320.04
Cl	−717.071784	−716.565237	317.86
	−717.076256		320.66
NO_2	−462.191942	−461.704599	305.81
	−462.195958		308.33

[a] Energies of two tautomers are given: 1H (upper lines) and 2H (lower lines). For ethyl and *n*-propyl tetrazoles, only the lowest conformer of each tautomer is shown.

B3LYP(6-311++G**)//B3LYP (6-311++G**) procedures, as well as using similar procedures differing according to the solvation model used (i.e., DPCM instead of CPCM). During the study, the *Gaussian 98*[52] suite of programs was used without any special adjustments to atomic radii or other parameters, which take the default values: the scaling factors of acidic hydrogens and the parameters used in the construction of the cavity, which is defined as a set of intersecting van der Waals spheres centered on atoms—that is number of the tessera on each sphere and area of the tesserae. The default methods were also used to normalize the polarization charge in order to achieve the value predicted by Gauss's law.

Results

Calculated Gas-Phase Acidities. The experimental pK_a data have been found for eleven tetrazole derivatives (water, 25 °C). Calculations were made for all the compounds for which the experimental data were given in refs 28−34, except for the J-tetrazole for which the calculations could not be performed using the same procedure. Because tetrazoles can exist as 1H and 2H tautomers, the energies were calculated for both. For two compounds, ethyl tetrazole and *n*-propyl tetrazole, more than one conformer was found for each tautomer: two for the former and three for the latter. Solvation energies were averaged for all forms, as explained in the Methods section. All gas-phase free energies were calculated at the CBS-QB3 level. It appeared that, for the anion of CF_3 tetrazole, one of the frequencies was negative; this fact suggests that the anion may be unstable, so as a consequence, this compound was omitted in further considerations. No compound has been removed from the data set for other reasons.

The CBS-QB3 gas-phase free energies for the acids and their corresponding anions are displayed in Table 1. For ethyl and *n*-propyl tetrazoles, only the lowest-energy conformer of the two tautomers is shown.

Acidities in Solution. Solvation energies were calculated using the eight procedures as described in the Methods section. Values of ΔG_s were calculated for the gas-phase and water-solution geometry. Tables 2 and 3 display results of the pK_a calculations using the thermodynamic cycle A and the eight solvation procedures. Table 2 shows the results using HF, whereas Table 3 shows those obtained with B3LYP. Inspection of the tables leads to several conclusions:

(1) The CPCM continuum model is superior to the DPCM, except for the pK_a's calculated at HF/6-31+G* and B3LYP/6-31+G* for gas-phase geometry.

(2) The pK_a values obtained using the HF method are better than those calculated using B3LYP.

(3) There is no significant difference in the quality of results obtained with the 6-31+G* and with 6-311++G** basis sets using CPCM, at HF and B3LYP levels.

(4) In the CPCM model with both basis sets and in DPCM with the 6-31+G* basis set, geometry optimization in water leads to greater discrepancies between the calculated and experimental pK_a values than the application of the gas-phase geometry.

(5) There is a marked tendency for the calculated values to be higher than the experimental ones. The mean difference between the calculated and experimental data, being positive in 15 of 16 cases, reflects a considerable bias. In other words, in the 15 cases, the theoretical pK_a values are overestimated.

(6) The CPCM/HF(6-31+G*)//HF(6-31+G*) and CPCM/HF-(6-311++G**)//HF(6-311++G**) methods do not fare equally well for all functional groups. For the bulky ones, such as *n*-propyl, isopropyl, and NO_2, the results are evidently poorer than for the rest.

In accordance with these inferences, the best agreement between the calculated and experimental data with mean unsigned error equaling 0.4 is obtained using the CPCM/HF-(6-31+G*), CPCM/HF(6-311++G**), and DPCM/HF(6-31+G*) solvation models for the single-point calculation (on gas-phase geometries) determined at the same level/basis set.

The experimental data for pK_a's of tetrazoles are rather scarce, and for most, only one experimental value is reported. Only for the unsubstituted (parent) tetrazole, as many as five values are reported (Table 2). Their mean value is 4.83 ± 0.23, while the error is calculated at the significance level of 0.05. That is, with 95% probability, the experimental value lies between the limits 4.60−5.06. A comparison of experimental accuracy with our mean unsigned error of 0.4 and with the best results for that compound, 4.70 and 4.67 ((CPCM/HF(6-31+G*) and (CPCM/HF(6-311++G**)), indicates that the accuracy of the calculated values is not far removed from that of the experimental results.

Solvation Energies. It is not possible to predict reliable pK_a's using the thermodynamic cycles unless the corresponding solvation free energies ΔG_s can be accurately calculated. According to Klamt et al.,[17] typical values for the solvation of neutral polar molecules are −8 kcal/mol and even up to −120 kcal/mol for ions. Quoting some exemplary values calculated presently can therefore be informative. They are given in Table 4. In the interest of brevity, the values for only two procedures are provided. Comparison of the values shows that the differences between the results produced by the two procedures are not high: For neutral solutes, they are lower than 1 kcal/mol (except for the 2H tautomer of NO_2 tetrazole, for which the difference amounts to 1.5 kcal/mol). For anions, the differences do not exceed 2 kcal/mol. There is a general trend for the solvation free energies in which those calculated at the HF level are higher than those calculated at the B3LYP level. It can be seen that the solvation free energy of an anion is several times greater than the values for the neutral forms (and is greater for the tautomer having the larger dipole moment), as could be expected.

TABLE 2: ΔpK_a (pK_a Calculated Using HF Method−Experimental pK_a)

		CPCM				DPCM			
		gas-phase geometry		geometry optimized in water		gas-phase geometry		geometry optimized in water	
R	pK_a exptl	6-31+G*	6-311++G**	6-31+G*	6-311++G**	6-31+G*	6-311++G**	6-31+G*	6-311++G**
NH_2	5.96[a]	0.32	0.34	0.66	0.66	0.21	−0.37	0.30	0.33
n-C_3H_7	5.61[b]	1.34	1.08	1.19	1.17	0.52	2.13	1.98	2.02
C_2H_5	5.59[b]	−0.15	−0.21	−0.11	−0.07	−0.56	1.62	0.18	0.27
iso-C_3H_7	5.55[b]	0.65	0.66	0.91	0.89	0.26	2.70	1.48	1.83
CH_3	5.56[c]	0.02	−0.02	0.16	0.14	−0.46	1.30	0.16	0.23
H	4.83[d]	−0.13	−0.16	0.06	0.06	−0.27	−0.88	0.00	0.09
Br	2.13[e]	0.25	0.26	0.42	0.41	−0.49	1.97	2.33	2.43
Cl	2.07[e]	−0.01	0.20	0.18	0.40	−0.24	−0.87	0.96	1.75
NO_2	−0.83[f]	0.59	0.59	0.90	0.92	0.81	1.61	2.13	2.27
m.u.e.		0.38	0.39	0.51	0.52	0.42	1.49	1.06	1.25
mean error		0.32	0.30	0.49	0.51	−0.22	1.02	1.06	1.25

[a] Mean valuew of 5.93,[28] 5.95,[29] and 6.[30] [b] Taken from ref 30. [c] Mean values of 5.56,[30] 5.50,[31]and 5.63.[33] [d] Mean values of 4.70,[29] 4.79,[30] 4.86,[31] 4.89,[32] and 4.90.[33] [e] Taken from ref 32. [f] Taken from ref 31.

TABLE 3: ΔpK_a (pK_a Calculated Using B3LYP Method−Experimental pK_a)

		CPCM				DPCM			
		gas-phase geometry		geometry optimized in water		gas-phase geometry		geometry optimized in water	
R	pK_a exptl	6-31+G*	6-311++G**	6-31+G*	6-311++G**	6-31+G*	6-311++G**	6-31+G*	6-311++G**
NH_2	5.96	1.10	1.10	1.41	1.41	1.22	0.17	1.21	1.06
n-C_3H_7	5.61	1.51	2.26	2.21	1.99	1.67	3.70	3.09	3.18
C_2H_5	5.59	0.51	0.40	0.61	0.76	0.53	1.46	0.74	0.76
iso-C_3H_7	5.55	1.72	1.60	1.88	1.85	1.30	4.14	2.71	2.86
CH_3	5.56	0.80	0.70	0.94	0.87	0.38	2.10	1.15	1.14
H	4.83	−0.49	−0.66	−0.34	−0.49	−0.31	1.46	−1.18	−1.32
Br	2.13	0.43	0.66	0.86	0.85	0.19	2.45	3.17	3.18
Cl	2.07	0.90	0.66	0.87	0.82	1.16	2.36	2.28	2.35
NO_2	−0.83	0.74	0.67	0.92	0.92	0.86	1.81	2.19	2.05
m.u.e.		0.91	0.97	1.12	1.11	0.85	2.18	1.97	1.99
mean error		0.80	0.82	1.04	1.00	0.78	2.18	1.71	1.70

TABLE 4: Solvation Free Energies of Tetrazolic Acids and Their Corresponding Anions at Two Calculation Levels (upper entries). The Nonelectrostatic Contributions to Them Are Given in Parentheses

	CPCM/HF/6-31+G* gas-phase geometry			CPCM/B3LYP/6-31+G* gas-phase geometry		
	acid (two tautomers)		anion	acid (two tautomers)		anion
R	1H	2H		1H	2H	
NH_2	−21.29	−17.25	−73.19	−21.04	−16.79	−71.84
	(−0.21)	(−0.34)	(0.16)	(0.01)	(−0.12)	(0.39)
n-C_3H_7 [a]	−14.39	−11.25	−65.74	−13.47	−10.74	−63.58
	(1.47)	(1.30)	(1.55)	(1.69)	(1.51)	(1.87)
C_2H_5 [a]	−15.76	−12.35	−67.69	−14.99	−11.89	−65.87
	(0.43)	(0.06)	(0.34)	(0.57)	(0.23)	(0.56)
iso-C_3H_7	−14.92	−11.79	−66.19	−14.29	−11.26	−64.12
	(0.93)	(0.63)	(1.03)	(1.12)	(0.99)	(1.35)
CH_3	−15.46	−12.23	−68.18	−14.75	−11.69	−66.44
	(0.27)	(0.13)	(0.44)	(0.45)	(0.31)	(0.62)
H	−16.42	−13.05	−68.23	−15.43	−12.43	−67.80
	(0.05)	(−0.09)	(0.26)	(0.22)	(0.09)	(0.28)
Br	−12.94	−11.85	−59.35	−12.27	−11.22	−58.10
	(0.72)	(0.57)	(0.86)	(0.91)	(0.77)	(1.01)
Cl	−12.54	−11.55	−59.96	−12.01	−10.91	−58.08
	(0.89)	(0.75)	(1.07)	(1.08)	(0.96)	(1.27)
NO_2	−14.13	−16.53	−55.80	−13.23	−14.98	−54.05
	(1.32)	(1.21)	(1.57)	(1.63)	(1.56)	(1.95)

[a] Values for the lowest-energy conformer are given.

Electrostatic and Nonelectrostatic Contributions. In both solvation models used among those implemented in the *Gaussian 98* software, the free energy of solvation is given as the sum of the free energies of the electrostatic and nonelectrostatic interactions. The first is calculated as a sum of the solute polarization energy and the polar solute−solvent interaction energy. The nonelectrostatic interaction energy is composed of the energy of cavity formation in the continuum medium, dispersion interactions, and repulsion interactions. It seemed interesting to us to compare the electrostatic and nonelectrostatic terms. It has been expected that the solvation free energies for anions, being charged species, would be dominated by the electrostatic component. The comparison is given in Table 4 where the sums of the nonelectrostatic contributions are given as the entries in parentheses. The electrostatic contributions equal the difference between the two entries in every cell. The somewhat unexpected result is that, in every case, the electrostatic term is strongly dominant over the nonelectrostatic one. More thorough inspection into the nonelectrostatic terms shows that the individual components are much larger than their sum and that the cavitation and repulsion terms on one hand and dispersion terms on the other hand have opposite signs. What follows is a high degree of cancellation. This suggests that errors in the components may result in a sizable error of the sum.

Discussion

The results of the calculation of pK_a's for unsubstituted 1H and 2H tetrazoles were reported previously.[26] There, the solvation energies were calculated by applying four different methods: (1) the semiempirical quantum mechanical method SM5.42R/A (based on AM1 Hamiltonian), (2) the iLP (iterative Langevin dipole), (3) the integral equation formulation version of PCM (IEF-PCM), and (4) the solution of the Poisson−Boltzmann equation. The results were highly divergent; the best, calculated using the fourth method, were 2.31 for 1H tetrazole and 1.33 for 2H tetrazole; the average value lies somewhere between the two (eq 3), whereas the average experimental value for tetrazole is 4.83. In view of the comparison of our results with those on tetrazole[26] and other heterocycles (e.g., histamine[24]), we consider our results very satisfying. They are as accurate as the best results reported so far for carboxylic acids and phenols.[10,13]

Despite many difficulties and approximations related to the conduct of the calculations in water, the best results of the gas-phase acidity calculations are not significantly better than the latter. For example, in the paper devoted to evaluation of a high-precision gas-phase acidity scale, for 16 reference species with accurately known experimental acidities, the mean absolute error was 0.36 kcal/mol at the CCSD(T)/aug-cc-pVDZ//B3LYP/aug-cc-pVDZ level.[53] In another calculation of the gas-phase acidities, a high-quality basis set and inclusion of correlation were also required.[54]

When the continuous medium is involved, taking electron correlation into consideration does not always improve the results. Comparison of different procedures performed during the pK_a investigation concerning phenols in water showed that the most accurate results were obtained at the HF level, while the B3LYP method gave the worst results.[13] This effect was mentioned by Barone and Cossi and explained as resulting from underestimation of the solvent reaction field at the second-order Møller-Plesset (MP2) and DFT levels.[40] Here, the results with B3LYP were poorer than at the HF level for the gas-phase geometry and for the geometry optimized in water. However, in another study, the absolute pK_a values were very close to the experimental ones, but only when the solutes were treated at the correlated ab initio level.[21] Results of the calculation of the two first steps of deprotonation of histamine obtained with HF were much poorer than those obtained using B3LYP for five different basis sets.[24]

Our findings that, for DPCM calculations, the larger basis set (6-311++G**) produces poorer (too high) results than the smaller (6-31+G*) one in three cases out of four can be attributed to larger basis sets allowing more solute charge to escape the cavity. Or, it may well be that the solvation energies are overestimated at the HF/6-311++G** level. However, the effect is absent in our CPCM results (Tables 1 and 2). Chipman calculated pK_a values in water using HF/6-31+G* and B3LYP/aug-cc-pVTZ levels, but the results were only slightly better for the latter.[3] He was of the opinion that the HF/6-31+G* method works reasonably well for gas-phase acidity because of a partial cancellation of the errors from neglect of the electron correlation and inadequate basis-set completeness. In a solution, similar cancellation may take place. The best results for carboxylic acid and phenols were also obtained using the 6-31+G* basis set.[10,13] In another study on carboxylic acids, it was also reported that better results were obtained with the 6-31+G** basis set than with 6-311G(2d,2p) and 6-311+G(2d,2p) ones.[6]

The solvation free energies can be calculated with gas-phase geometry (without geometry optimization in water) or with water-optimized geometry. Here, in seven cases out of eight, the best results have been obtained for the first case. However, for phenols, it was stated that the solvated-phase optimized structures of anions are absolutely critical to obtain a high level of accuracy (0.4 pK_a units).[13] The authors concluded that, for any molecules that allow significant charge delocalization, geometry optimization in solution will be vital. The optimization was not crucial for carboxylic acids, because there are no ring systems available to diffuse the charge. In the course of methylamine basicity calculations, it was observed that geometry optimization of the molecular solute does not produce important changes in molecular geometry or in energetic terms.[55]

Calculation of acidity according to cycles A and B has been termed "absolute" in the literature. Nevertheless, there are two terms which are not calculated but usually derived experimentally: $G_{gas}(H^+)$ and $\Delta G_s(H^+)$. The two values have been taken from the literature. $G_{gas}(H^+)$ is consistently adopted as -6.28 kcal/mol.[10,16,21,23,25] The second value is not known to high precision, however. It can be estimated on the basis of the absolute potential of the standard hydrogen electrode, which is itself only known to several kilocalories per mole accuracy, and the $\Delta G_s(H^+)$ values thus obtained range from -254 to -261 kcal/mol.[4] It has also been determined on the basis of cluster ion solvation data, resulting in two values: -263.9 ± 0.2[56] and -263.7 ± 0.2[57] kcal/mol. The calculated value ranged from about -160 to -262.4 kcal/mol.[58−61] Changes in this value will shift absolute pK_a value but will not affect relative ones. The values used in the pK_a calculation were found to fall within the -258.32 to -264.61 kcal/mol range. The first value was chosen in order to minimize the root-mean-square (rms) deviation between the calculated and experimental pK_a values for the 5-substituted uracils;[25] the last was calculated from the experimental thermodynamic cycle of acetic acid.[10] The difference in $\Delta G_s(H^+)$ is enough to make the error in calculated absolute pK_a as substantial as 5 pK_a units.

Calculations which take advantage of cycle B meet with similar obstacles. There, the value that remains a controversial issue and subject to considerable uncertainty is $\Delta G_s(H_3O^+)$. When cycle B was used by Liptak and Shields for carboxylic acids instead of cycle A, the theoretical pK_a values have presented systematic deviation from experimental data.[16] For $\Delta G_s(H_3O^+)$, the authors used a value of -104.0 kcal/mol, which is the value most frequently cited.[60,62] Pliego and Riveros showed that using a value of -110.2 kcal/mol for the latter results in very accurate pK_a values.[63] However, this value seems to be fairly arbitrary. Other values quoted in the literature ranged between -99.53 and -108.3 kcal/mol.[27] The highest-level calculations of $\Delta G_s(H_3O^+)$ at the coupled cluster with single, double, and (triple) excitation (CCSD(T))/6-311+G(2df,p) level yield different values, depending on n, the number of water molecules in the hydronium-ion−water clusters: For example, for $n = 3$, it is -107.77 kcal/mol; for $n = 5$, it is -104.69 kcal/mol.[60] The value reported last is -103.4 kcal/mol.[64] What follows is the conclusion that presently there is no possibility of solving the question as to which of the two cycles is more favorable. To achieve this aim, the testified values of $\Delta G_s(H^+)$ and $\Delta G_s(H_3O^+)$ are needed, simultaneously derived in both experimental and theoretical manners. It may well be that neither of the cycles, A nor B, is the best of all possible ones, because there are results suggesting that the first hydration shell of the proton is composed of at least four water molecules.[60]

Conclusions

Despite the fact that, for solvation in polar liquids, the conductor-like model (CPCM) which imposes the total electrostatic potential to cancel out on the cavity surface is physically less founded than dielectric models, the conductor approach, in most cases, better-reproduced the tetrazole acidities in water than the dielectric (DPCM) approach.

Study of the gas-phase acidities in the gas phase is free from the perturbing influence of a solvent or counterions; still, water-phase acidity calculations approach the comparable accuracy of the gas-phase ones when confronted with the experimental data. Presently, we are not fully aware which calculation variants are inherently better for the purpose and which perform well because of the partial cancellation of errors.

To avoid the problem of establishing the precise value of proton solvation, the method of relative pK_a determination, based on the value characterizing a compound for which it is already known, has been applied.[24,27] However, we believe that the absolute pK_a determination is a task that entails the quest after answering a couple of important queries and is worth some effort.

Because the investigations are in rapid and continuing progress as far as both new software and its applications are considered, our present results are a snapshot of a certain stage of the evolution of acidity calculation.

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References and Notes

(1) Brigas, F. A. Tetrazoles. In *Five Membered Heteroarenes with Three or More Heteroatoms, Science of Synthesis*; Storr, R. C., Gilchrist, T. L., Eds.; Thieme Verlag: Stuttgart−New York, 2004; Vol. 13, p 863.

(2) Richardson, W. H.; Peng, C.; Bashford, D.; Noodleman, L.; Case, D. A. *Int. J. Quantum Chem.* **1997**, *61*, 207.

(3) Chipman, D. M. *J. Phys. Chem. A* **2002**, *106*, 7413.

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

(5) Himo, F.; Leif, A.; Eriksson, L. A.; Blomberg, M. R. A.; Siegbahn, P. E. M. *Int. J. Quantum Chem.* **2002**, *76*, 714.

(6) Schüürmann, G.; Cossi, M.; Barone, V.; Tomasi, J. *J. Phys. Chem. A* **1998**, *102*, 6706.

(7) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **1999**, *103*, 11194.

(8) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **2000**, *104*, 2402.

(9) Shapley, W. A.; Backsay, G. B.; Warr, G. G. *J. Phys. Chem. B* **1998**, *102*, 1938.

(10) Liptak, M. D.; Shields, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 7314.

(11) Toth, A. M.; Liptak, M. D.; Phillips, D. L. *J. Chem. Phys*. **2001**, *114*, 4595.

(12) Wiberg, K. B.; Ochterski, J.; Streitwieser, A. *J. Am. Chem. Soc*. **1996**, *118*, 8291.

(13) Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421.

(14) Adam, K. R. *J. Phys. Chem. A* **2002**, *106*, 11963.

(15) Namazian, M.; Heidary, H. *THEOCHEM* **2003**, *620*, 257.

(16) Liptak, M. D.; Shields, G. C. *Int. J. Quantum Chem*. **2001**, *85*, 727.

(17) Klamt, A.; Eckert, F.; Diedenhofen, M.; Beck, M. E. *J. Phys. Chem. A* **2003**, *107*, 9380.

(18) Himo, F.; Noodleman, L.; Blomberg, M. R.; Siegbahn, P. E. M. *J. Phys. Chem. A* **2002**, *106*, 8757.

(19) Schüürmann, G. *Quant. Struct.−Act. Relat.* **1996**, *15*, 121.

(20) Wiberg, K. B.; Clifford, S.; Jorgensen, W. L.; Frisch, M. J. *J. Phys. Chem. A* **2000**, *104*, 7625.

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

(22) Taagapera, M.; Summerhays, K. D.; Hehre, W. J.; Topsom, R. D.; Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1981**, *46*, 891.

(23) Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, J. B. *J. Phys. Chem. B* **1999**, *103*, 7302.

(24) De Abreu, H. A.; De Almeida, W. B.; Duarte, H. A. *Chem. Phys. Lett*. **2004**, *383*, 47.

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

(26) Satchell, J. F.; Smith, B. J. *Phys. Chem. Chem. Phys.* **2002**, *4*, 4314.

(27) da Silva, C. O.; Nascimento, M. A. C. Computational Chemistry of Acids. In *Advances in Physical Chemistry*; Prigogine, I., Rice, S. A., Eds.; Wiley & Sons: New York, 2002; Vol. 123.

(28) Butler, R. N. *Tetrazoles* in *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 817.

(29) Borai, A. A. A. *J. Chem. Eng. Data* **2001**, *46*, 939.

(30) Mishima, J. S.; Herbst, R. M. *J. Org. Chem*. **1950**, *15*, 1082

(31) Ostrovskii, W. A.; Koldobskii, G. I.; Shirokova, N. P.; Poplavskii, W. S. *Khim. Geterotsikl. Soedin.* **1981**, 559.

(32) Lieber, E.; Patinkin, S.; Tao, H. H. *J. Am. Chem. Soc*. **1951**, *73*, 1792.

(33) Hansen, L. D.; Baca, E. J.; Scheiner, P. *J. Heterocycl. Chem.* **1970**, *7*, 991.

(34) Norris, W. P. *J. Org. Chem*. **1962**, *27*, 3248.

(35) Pokon, E. K.; Liptak, M. D.; Feldgus, S.; Shields, G. C. *J. Phys. Chem. A* **2001**, *105*, 10483.

(36) Smith, M. B.; March, J. *March*'s *Advanced Organic Chemistry*, 5th ed.; John Wiley and Sons, Ltd.: New York, 1985.

(37) Foresman, J. B.; Frisch, Æ. *Exploring Chemistry with Electronic Structure Methods*; Gaussian Inc, Pittsburgh, PA, 1996.

(38) Cramer, C. J. *Essentials of Computational Chemistry*; John Wiley & Sons, Ltd.: Chichester, U.K., 2003.

(39) *Gaussian 98 User's Reference*, 2nd ed.; Gaussian, Inc.: Pittsburgh, PA.

(40) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995.

(41) Cossi, M.; Barone, V.; Menucci, B.; Tomasi, J. *Chem. Phys. Lett*. **1998**, *286*, 253.

(42) Klicić, J. J.; Friesner, R. A.; Lin S.-Y.; Guido, W. C. *J. Phys. Chem. A* **2002**, *106*, 1327.

(43) Pliego, J. R.; Riveros, J. M. *J. Phys. Chem. A* **2002**, *106*, 7434.

(44) Montgomery, J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys*. **1999**, *110*, 2822.

(45) Rażyńska, A.; Tempczyk, A.; Maliński, E.; Szafran, J.; Grzonka, Z.; Hermann, P. *J. Chem. Soc., Perkin Trans. 2* **1983**, 379.

(46) Palmer, M. H.; Simpson, I.; Wheeler, J. R. *Z. Naturforsch*. **1981**, *36A*, 1246.

(47) Mazurek, A. P.; Osman, R. *J. Phys. Chem*. **1985**, *89*, 460.

(48) Mazurek, A. P.; Sadlej-Sosnowska, N. *Chem. Phys. Lett*. **2000**, *330*, 212.

(49) Sadlej-Sosnowska, N. *J. Org. Chem*. **2001**, *66*, 8737.

(50) Goddard, R.; Heinemann, O.; Krüger, C. *Acta Crystallogr., Sect. C* **1997**, *53*, 590.

(51) Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **1997**, *101*, 7147.

(52) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(53) Ervin, K. M.; DeTuri, V. F. *J. Phys. Chem. A* **2002**, *106*, 9947.

(54) Siggel, M. R. F.; Thomas, D. T.; Saethre, L. J. *J. Am. Chem. Soc*. **1998**, *110*, 91.

(55) Tuñón, I.; Silla, E.; Tomasi, J. *J. Phys. Chem*. **1992**, *96*, 9043.

(56) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coe, J. V.; Tuttle, T. R. *J. Phys. Chem. A* **1998**, *102*, 7787.

(57) Tuttle, T. R.; Malaxos, S.; Coe, J. V. *J. Phys. Chem. A* **2002**, *106*, 925.

(58) Mejías, J. A.; Lago, S. *J. Chem. Phys*. **2000**, *113*, 7306.

(59) Tuñón, I.; Silla, E.; Bertrán, J. *J. Phys. Chem*. **1993**, *97*, 5547.

(60) Tawa, G. J.; Topol, I. A.; Burt, S. K.; Caldwell, R. A.; Rashin, A. A. *J. Chem. Phys*. **1998**, *109*, 4852.

(61) Zhan, C.-G.; Dixon, D. A. *J. Phys. Chem. A* **2001**, *105*, 11534.

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

(63) Pliego, J. R.; Riveros, J. M. *Chem. Phys. Lett.* **2003**, *367*, 145.

(64) Palascak, M. W.; Shields, G. C. *J. Phys. Chem*. **2004**, *108*, 3692.