

Ab Initio Calculations of Absolute pK_a Values in Aqueous Solution II. Aliphatic Alcohols, Thiols, and Halogenated Carboxylic Acids

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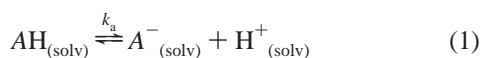
Received: June 23, 1999; In Final Form: October 15, 1999

A thermodynamical cycle is proposed to calculate absolute pK_a values for Brønsted acids in aqueous solution. The polarizable continuum model (PCM) was used to describe the solvent, and absolute pK_a values were computed for different classes of organic compounds: aliphatic alcohols, thiols, and halogenated derivatives of carboxylic aliphatic acids. The model furnishes pK_a values in good agreement with the experimental results for some classes of compounds. For the cases where appreciable deviations are observed, we have tried to establish a correlation among the neglected components of ΔG_{solv} resulting from the model adopted, the level of calculation employed, and the pK_a deviations relative to the experimental results.

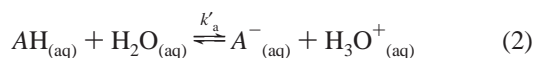
1. Introduction

The knowledge of the pK_a of a compound that can be characterized as a Brønsted acid is very important if its reactivity is under study. Many biological systems use proton-transfer reactions to perform communication between the extracellular and intracellular media and the rate of the proton-transfer reactions depend, among many other factors, on the degree of dissociation of the species involved. A detailed discussion of the importance of pK_a in chemistry, as well as the role of the proton in organic chemistry can be found in the papers by Schüürmann¹ and Stewart,² respectively.

The pK_a quantity can also be seen as a measure of the solute–solvent interaction. Depending on how strong the solvent is, interaction with the associated (AH) and dissociated (A^-) forms, the equilibrium can be shifted toward the acid or the conjugate base side:



To better represent the role played by the solvent we rewrite reaction 1 explicitly considering the solvent, to show that it does not simply provide a passive environment where chemical reactions can take place, but that it effectively interacts with the species in solution all of the time:



Thus, as a consequence of this interaction, the pK_a of a substance depends on the medium chosen to conduct the experiments.

Due to its importance, water is the solvent used in this work. Surely, it is the most studied solvent, but also one of the less structurally understood. Acid–base equilibrium studies in water can furnish very useful information related to many chemical processes, and so far the main source of this information comes from experimental work. All of the available pK_a data have been determined through very well established experimental tech-

niques,³ such as spectroscopy, potentiometry, conductimetry, competitive reactions, etc. But water is also a protic solvent. Therefore, its self-ionization may interfere in pK_a measurements, depending on the Brønsted acid being studied. In the case of small aliphatic organic acids (formic, acetic, propanoic, for instance), the dissociation constants are all higher than that of the pure water (k_w) by a factor of approximately 1×10^9 . Thus, all of the H_3O^+ species present in solution and detected by the experiment can be undoubtedly attributed to the Brønsted acid (AH) ionization. But for a similar study involving aliphatic alcohols, whose dissociation constants have values near the pure water self-ionization constant (for ethanol, $k_a = 1.26 \times 10^{-16}$ and $k_w = 1.82 \times 10^{-16}$),² some artifices have to be introduced to ensure that the experimental measurements are related to the H_3O^+ species coming from the alcohol and not from the water self-ionization.

Indeed, the experimental pK_a measurements of those classes of compounds always involve some artifice and approximations, which will be later presented and discussed. Thus, especially for the cases where the dissociation constant of the solvent is close to that of the solute, a theoretical model capable of properly describing this property can represent a unique way of obtaining reliable data. Moreover, the theoretical description not only furnishes an alternative way to obtain pK_a values, beyond the experimental technical limitations, but also may help the understanding of processes at the molecular level.

Several theoretical models to calculate pK_a values of compounds in solution have been proposed^{1,4–11} mainly due to the development of continuum models to describe the solution phase, and some recent results can be found in the literature. However, they all furnish pK_a values which differ, in a greater or lesser extent, from the experimental results. The degree of deviation depends on the model itself and also on the size and class of compounds. Also, depending on the model adopted, the deviations can be larger for a given class of compounds or affect almost equally all studied compounds. In some cases^{10,11} the authors briefly attempted to provide an explanation for the observed disagreement.

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The use of continuum models can lead to very interesting results since, under certain limitations, they allow a detailed description of the changes suffered by the solute molecule due to its interaction with the solvent. The appropriate description of these changes forms the cornerstone of the pK_a studies in solution phase. While for gas-phase calculations the theoretical methodology is very well established,^{12–14} the same is not true for the solution phase for which the challenge resides exactly in a proper description of the solute–solvent interactions and the structural changes promoted by these interactions.

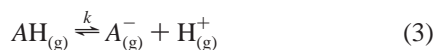
In this paper we discuss the most recent theoretical works on the subject, comparing them with the model here adopted. We try to establish a correlation between the neglected components of ΔG_{solv} resulting from the models adopted and the pK_a deviations relative to the experimental values. It is shown that, for certain classes of compounds, the neglected components may preclude the prediction of reliable pK_a values. It is important to mention that there is no solvation model, to the best of our knowledge, complete enough to ensure the proper description of this sensitive quantity, although some models can be clearly better than others, furnishing precise pK_a values for some classes of compounds.

In the following section we present the model employed in this paper to calculate pK_a values in solution, for different classes of compounds, some of the models previously used,^{8–10} and also the sources of experimental pK_a values. The understanding of the experimental conditions and limitations under which the pK_a values are determined is extremely important in order to ensure a proper comparison between experiment and theory. Next we present and discuss the results obtained for this paper, for the different classes of compounds studied, and analyze the possible sources of deviation from the experimental values.

2. Methods

The Model. Theory. The model used was discussed in detail in a previous publication¹¹ and only a brief review will be presented.

The equilibrium dissociation constant for reaction 3



is related to the variation of the standard Gibbs free energy through the expression

$$\Delta G^0 = -2.303RT \log k = 2.303 RT \text{p}K_{\text{a}}^{\text{gas}} \quad (4)$$

The equivalent equation for the process in aqueous solution, described by eq 2, is

$$\Delta G^0 = -2.303 RT \log \left(\frac{k_{\text{a}}}{[\text{H}_2\text{O}_{(\text{aq})}]} \right) \quad (5)$$

or

$$\Delta G^0 \text{ (kcal/mol)} = 1.36 \text{p}K_{\text{a}} + 2.36 \quad (6)$$

where ΔG^0 is the standard variation of the Gibbs free energy related to the process taking place in water at 298.15 K, with $R = 1.98 \text{ kcal/mol.K}$. It was assumed that all of the H_3O^+ species present in solution came from the generic AH Brønsted acid dissociation and therefore one can write

$$k'_{\text{a}} = \frac{k_{\text{a}}}{[\text{H}_2\text{O}_{(\text{aq})}]} = \frac{[\text{A}_{(\text{aq})}^-][\text{H}_3\text{O}_{(\text{aq})}^+]}{[\text{AH}_{(\text{aq})}][\text{H}_2\text{O}_{(\text{aq})}]} \quad (7)$$

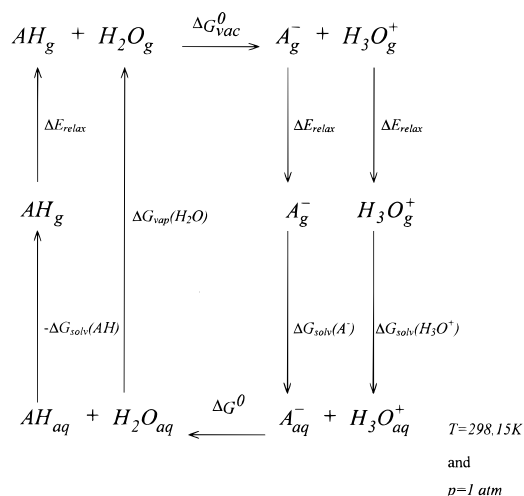


Figure 1. Thermodynamical cycle.

Figure 1 shows the thermodynamical cycle proposed to calculate the ΔG^0 . From this cycle, ΔG^0 is given by the following expression:

$$\Delta G^0 = -\Delta G_{\text{solv}}(\text{AH}) + \Delta E_{\text{relax}}(\text{AH}) + \Delta G_{\text{vap}}^0(\text{H}_2\text{O}) + \Delta G_{\text{vac}}^0 + \Delta E_{\text{relax}}(\text{A}^-) + \Delta G_{\text{solv}}(\text{A}^-) + \Delta E_{\text{relax}}(\text{H}_3\text{O}^+) + \Delta G_{\text{solv}}(\text{H}_3\text{O}^+) \quad (8)$$

In eq 8 the ΔG_{solv} components are the solvation energies, obtained when the molecule is transferred from gas phase to solution phase, keeping constant the temperature, pressure, and geometry.¹⁵ The ΔE_{relax} energy components are obtained when the geometrical constraint imposed is removed. It represents the change in energy when the geometry of the solute is allowed to relax after the molecule is transferred from one phase to another. This step was introduced in order to ensure a more realistic description of the phenomenon, since in solution the system must assume a different geometry from that in gas phase.

The $\Delta G_{\text{vap}}^0(\text{H}_2\text{O})$ component is the standard Gibbs free energy of vaporization of water, at 298.15 K and 1 atm. In the case of the solvent (water) itself, the use of the thermodynamic definition of solvation energy (in Ben Naim's sense) is not appropriate because once in solution the solvated molecule would be indistinguishable from any other water molecule. Also, if we were to compute ΔG for transferring a molecule of water from one phase to the other, to be consistent with all the other steps of the TC, one should optimize its geometry in both phases. Thus, it would be more appropriate to identify the transformation involving the water molecule in the TC with the vaporization process. As previously discussed,¹¹ the choice of the H_3O^+ species to represent the hydrated proton in the TC is the best one consistent with the PCM model, as following this model the parameterization of the cavity already takes into account the solute first solvation shell. Finally, ΔG_{vac}^0 is the standard variation of Gibbs free energy of the proton transfer process in gas phase (see Figure 1). This step of the thermodynamical cycle should not be confused with the deprotonation process represented by eq 3, used to define absolute gas-phase acidities.

The ΔG_{vap}^0 component can be written as

$$\Delta G_{\text{vap}}^0 = \Delta H_{\text{vac}}^0 + T\Delta S_{\text{vac}}^0 \quad (T = 298.15 \text{ K and } p = 1 \text{ atm}) \quad (9)$$

and since the entropic variation at room temperature is very small when compared to the enthalpic one (for instance, at room

temperature, for acetic acid, $\Delta H = 348.48$ kcal/mol while $T\Delta S = 0.64$ kcal/mol) we have

$$\Delta G_{\text{vac}}^0 \approx \Delta H_{\text{vac}}^0 = \Delta E_{\text{vac}}^0 + \Delta(pV) \\ (T = 298.15 \text{ K and } p = 1 \text{ atm}) \quad (10)$$

Assuming ideal behavior, $\Delta(pV) = \Delta n(RT)$, and since $\Delta n = 0$, we may write

$$\Delta H_{\text{vac}}^0 \approx \Delta E_{\text{vac}}^0 = \Delta E_{\text{vac},0\text{K}} + \Delta ZPE + \Delta E_{298.15\text{K}}^{\text{rot}} + \\ \Delta E_{298.15\text{K}}^{\text{vib}} + \Delta E_{298.15}^{\text{trans}} \quad (11)$$

Also, assuming that the rotational, translational and vibrational corrections are very similar for products and reactants, the last three terms in eq 11 can be neglected and the final expression is

$$\Delta G_{\text{vac}}^0 \approx \Delta H_{\text{vac}}^0 \approx \Delta E_{\text{vac}}^0 \approx \Delta E_{\text{vac},0\text{K}} + \Delta ZPE \quad (12)$$

where $\Delta E_{\text{vac},0\text{K}}$ is the difference between the total energy for products and reactants, at 0 K, and ΔZPE is the difference between the total zero point energy for the products and of the reactants.

Computational Details. A continuum dielectric model was used to compute the ΔG_{solv} and ΔE_{relax} energies. A version of the polarizable continuum model^{16,17} (PCM) was kindly supplied to us by Professor Jacopo Tomasi and his group. The supplied version allowed us to perform geometry optimizations in solution, at the Hartree–Fock level, using analytical energy first derivatives. Other levels of description, including electronic correlation energy, were not available, except single-point MP2 calculations.¹⁸ Also present in this version was the integral equation formalism methodology¹⁹ (IEF/PCM), which furnishes a better description for the system in solution, since it minimizes the numerical errors always present in apparent surface charge models.²⁰

The cavity model used in the calculations was the united atom topological model²¹ (UATM), which was parameterized to reproduce solvation energies as well as possible.

In this continuum model, the solvation energy can be decomposed in five different contributions:

$$\Delta G_{\text{solv}} = \Delta G_{\text{electr}} + \Delta G_{\text{cav}} + \Delta G_{\text{rep}} + \Delta G_{\text{disp}} + \Delta G_{\text{Mm}} \quad (13)$$

The electrostatic component to the solvation energy (ΔG_{electr}) is the most important one, and it is obtained self-consistently together with the solute wave function. The solute–solvent interaction is explicitly included in the Hamiltonian of the system, being represented by an interaction potential describing the perturbation of the solute by the (dielectric) medium. The cavitation²¹ (ΔG_{cav}), repulsion (ΔG_{rep}), and dispersion²² (ΔG_{disp}) contributions were computed using semiempirical formulations. The molecular motion contributions (ΔG_{Mm}) are normally considered very small and thus are generally neglected. Although the vibrational contribution to ΔG_{Mm} could have been estimated by computing vibrational frequencies using finite differences of gradients (analytical second derivatives have also been incorporated to PCM), this contribution was neglected.

The gas-phase calculations were performed using the *Gaussian 94* program²³ with the 6-31G+** basis set, and in order to use the same level of description for both phases, all of the calculations were performed at the Hartree–Fock level. The zero-point energy corrections were scaled by a factor of 0.9181, as suggested for the used basis set and level of calculation.²⁴ A more detailed description of the procedure adopted to calculate

the solvation and relaxation energies can be found in our previous work.¹¹

Recent Studies. Schüürmann and co-workers¹⁰ have very recently discussed a theoretical approach to pK_a values also based on the PCM model, but concluded that the level of their computation was not sufficiently accurate to predict absolute acidity. Alternatively, they suggested the use of linear regression relationships for estimating pK_a values, since their data have shown good correlation. In a previous publication,¹¹ we have pointed out that the way the solvent (water) was treated was most probably the main reason for the discrepancy between the pK_a values calculated by those authors and the experimental ones. However, in light of our present analysis (see section 3), it is now clear that two other factors might have contributed to the disagreement observed in ref 10. If one compares the pK_a values for carboxylic acids, the results obtained by Schüürmann et al.¹⁰ are always much larger than the ones obtained from our calculations.¹¹ In both cases the ΔG_{Mm} component was neglected, but as previously discussed¹¹ (see also section 3), except for formic acid, neglecting this component should not drastically affect the pK_a values. However, by using the gas-phase HF optimized geometries to describe the species in both gas and solution phases, the ΔE_{relax} components, which reduce ΔG^0 and consequently the pK_a value, are neglected. Also, those same HF optimized geometries were used to compute the electronic correlation contribution at the MP2 level, to the ΔG_{vac} component (eq 8). This is certainly not a convenient way of computing this contribution,^{25–28} and most probably this effect, which also generally reduces ΔG_{vac}^0 , was not fully recovered.

Another interesting publication has recently discussed the problem of computing pK_a values. Richardson⁸ and co-workers explored the use of a finite-difference electrostatic method to solve the Poisson–Boltzmann equation to compute the reaction potential, together with a DFT description of the solute molecule in gas phase. Those authors used a different thermodynamical cycle where the solvent (water) was not explicitly included. Thus, the bare proton appeared in their treatment and its solvation energy value was estimated from experimental measurements of the absolute potential of the standard hydrogen electrode. Moreover, while the solvation energy of the neutral species was calculated using the above methodology, the solvation energy for the anions was obtained from a combination of experimental data which includes the compound pK_a value itself. Therefore, their procedure cannot be considered a fully theoretical approach to calculate absolute pK_a values in aqueous solution and in principle can only be used to predict unknown pK_a values through correlation charts. However, although these authors used experimental data to compute the theoretical pK_a values, the results of Schüürmann et al.¹⁰ show a much better correlation with experimental pK_a values.

Considering all of the papers mentioned in this section^{8,10,11} concerning pK_a studies in solution, it is clear that the problem of calculating electronic correlation energy in solution phase has not yet been properly taken into account.

Experimental Results. As mentioned before, the compounds can be divided into two main groups, with regard to their pK_a values: compounds whose equilibrium constants are far from that of the solvent itself (considering protic solvents, as water, for instance) and those whose equilibrium constants are close to such value.

Aliphatic carboxylic acids, halogenated carboxylic acids, and thiols are examples of the first class of compounds for which reliable pK_a values can be found in the literature.^{2,29} For those compounds, irrespective of the methodology employed, reliable

TABLE 1: pK_a Values

compound	ref 10 ^a	ref 8	this work	experiment
(1) MeOH		22.5	20.14	15.5 ^b ; 16 ^c
(2) EtOH			18.84	15.9 ^b ; 18 ^c
(3) n-PrOH			19.37	16.1 ^b ; 18 ^c
(4) i-PrOH			20.56	17.1 ^b ; 18 ^c
(5) MeSH		9.3	5.81	10.33 ^b
(6) EtSH			6.15	10.61 ^b
(7) H ₂ O		16.4	16.77	15.74 ^b
(8) HCOOH	6.87	1.5	2.92	3.75 ^d
(9) CH ₃ COOH	8.17	4.9	4.32	4.76 ^d
(10) CH ₃ CH ₂ COOH	9.21		4.76	4.87 ^d
(11) CH ₃ (CH ₂) ₂ COOH			4.59	≈ 4.82 ^d
(12) (CH ₃) ₃ CCOOH	10.15		5.42	5.05 ^d
(13) FCH ₂ COOH	5.25		1.14	2.66 ^d
(14) ClCH ₂ COOH	5.18	0.8	1.57	2.86 ^d
(15) BrCH ₂ COOH	5.37		0.63	2.86 ^d

^a Values obtained as shown in ref 11. ^b Reference 2. ^c Reference 30. ^d Reference 31.

values can be obtained mainly because interfering effects which arise from the solvent self-ionization are not present.

On the other hand, when aliphatic alcohols are considered, the measurements are more difficult to make once their equilibrium constants are very close to that of pure water. Although their pK_a values are generally presented in the same tables containing the pK_a values for compounds of the first class, quite different experimental procedures are used for alcohols and the obtained pK_as are subjected to much higher uncertainties.

There are not too many experimental studies for alcohols,^{30–34} and the methods used to measure their acidities often give conflicting results. Their pK_a values have been obtained either by addition of some hydroxide to shift the chemical equilibrium in the desired direction (which introduces some approximations) or by following the competitive reaction of a solution of the alkoxides of two alcohols with an alkyl-halide, in the presence of an excess of the alcohols.

In conclusion, there exists a great deal of uncertainty in the pK_a values for aliphatic alcohols available in the literature. Therefore, a theoretical model which is capable of producing reliable pK_a values for these compounds would be extremely useful. In fact, if one considers the quality of our results for carboxylic acids,¹¹ one could say that the pK_a values for alcohols presented in this paper should be more reliable than the available experimental results.

3. Results and Discussion

The pK_a values calculated in this work are shown in Table 1 where they are compared with those obtained from the theoretical calculations previously discussed, as well as with the experimental values. For the sake of comparison, we also included the values for some of the acids previously studied.¹¹

To take full advantage of the proposed thermodynamic cycle to obtain pK_a values, one should be able to take into account the electronic correlation effects, in both phases, and the ΔG_{Mm} component for all of the species. However, due to the reasons already presented, our calculations did not consider any changes in molecular motion as the species were transferred from gas to solution phase (ΔG_{Mm} in eq 13). Neglecting this term is equivalent to assuming that the neutral system (AH) and its conjugate base (A⁻) exhibit similar motions in solution. This is, of course, a simplification which should affect more drastically the smaller systems (formic acid, methanol), as previously discussed.¹¹

As mentioned before, to take full advantage of the TC one should also consider the correlation effects in both gas and liquid

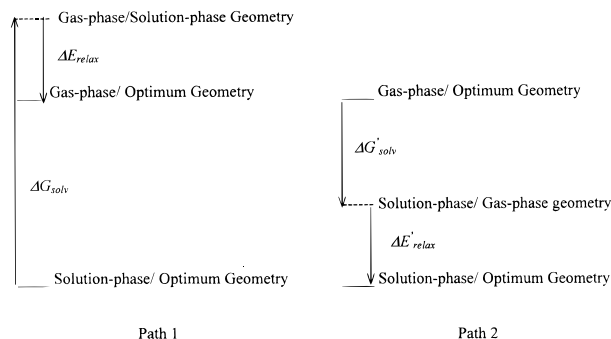


Figure 2. Equivalent ways of transferring a solvaton between phases.

phases. However, the fact that the TC includes geometry relaxation precludes the use of the PCM model to compute ΔG_{solv}, as one could not perform geometry optimization in solution at any correlated level of calculation. Thus, to treat both phases consistently, the correlation effects, in both phases, were neglected. Despite that, the proposed TC should be able to provide reliable pK_a values for compounds for which the differential correlation effects along the TC are minimal. This is the case when the TC proton transfer steps become isodesmic reactions. Thus one expects the differential correlation effects to be minimal for alcohols, carboxylic acids,¹¹ and other compounds for which an O–H bond is broken as another HO–bond is being formed (H₃O⁺).

It would be very instructive if one could find ways of establishing the relative importance of the correlation effects and the neglect of the ΔG_{Mm} component to the final pK_a values for the different classes of compounds.

We now proceed in analyzing the different compounds, or classes of compounds, for which large deviations from the experiments were observed, in an attempt at establishing the effect of the neglected components of ΔG_{solv} on the final pK_a results. The main deviations were observed for methanol, the thiols, and halogenated carboxylic acids. The case of methanol requires a special analysis due to the uncertainties in the available experimental values.

Let us start our analysis, discussing the solvation process adopted in this work, and comparing it against the standard solvation energy definition. The standard solvation energy definition¹⁵ is associated with the process where the solvaton (species under study) is transferred from gas phase to solution phase, keeping fixed its geometry, which is supposed to be optimum in the gas phase.

The solvation energies (ΔG_{solv}) calculated in this paper cannot be compared to those standard values, because we started from the optimum geometry in solution, and the solvaton was transferred to the gas phase, keeping its geometry fixed. An additional geometry relaxation step was introduced in the thermodynamical cycle to obtain the optimized geometry in the gas phase and the so-called relaxation energy (ΔE_{relax}) (see Path 1, in Figure 2). The opposite way could have also been adopted, starting from the optimized geometries in gas phase, transferring the solvaton to solution phase (ΔG'_{solv}), and letting it relax its geometry according to its new environment (ΔE_{relax}). The solvation energy values (ΔG'_{solv}) obtained from this calculation are comparable to the standard ones.

The two equivalent paths are shown in Figure 2. Either ΔE_{relax} or ΔE'_{relax} can be considered an indirect but quantitative way to estimate by how much the geometry of a compound changes when it is phase transferred. If a solvaton has a large value of ΔE_{relax}, it means that its geometry has changed appreciably when it was phase transferred, and a corresponding large ΔG_{Mm} value

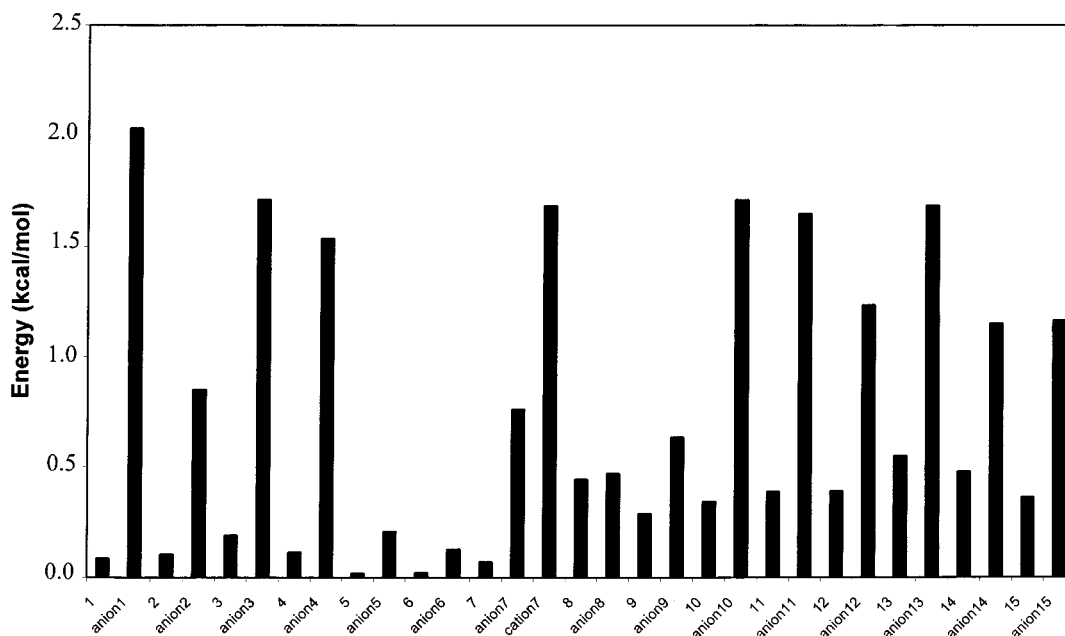
Relaxation Energy ($|\Delta E_{relax}|$)

Figure 3. $|\Delta E_{relax}|$ energies (kcal/mol).

can be expected for this compound. Thus, it seems reasonable to use ΔE_{relax} to estimate how important the ΔG_{Mm} contribution is to ΔG_{solv} .

Based on this assumption, Figure 3 was constructed, showing $|\Delta E_{relax}|$ for all of the neutral and charged species studied. In this figure, the compounds are numbered according to the order of their appearance in Table 1.

Methanol. Energy solvation calculations for the methoxy ion usually show large deviation from the experimental values, whose origin is still unknown^{8,34} but always in the direction of producing larger pK_a values for methanol.

From Figure 3 one sees that ΔE_{relax} has its maximum value exactly for the methoxy ion. In fact, if the geometries in both phases are compared, a decrease of ≈ 0.02 Å is observed in all the C–H bonds when passing from gas to solution phase. This value is much higher than that observed for the equivalent geometrical parameters of methanol. Following our assumption, neglecting the ΔG_{Mm} component in the energy expression for ΔG_{solv} (eq 13) will affect the methoxy ion description much more than that of other species, as previously suggested.¹¹ Thus, according to our assumption, to obtain the correct theoretical description for this compound, the ΔG_{Mm} component must be taken into account. In fact, to better evaluate the relative effect of ΔG_{Mm} , one should compute differences of relaxation energies, $\Delta|\Delta E_{relax}|$, between the anions (conjugate basis) and the respective neutral species (acids), since they are both involved in the dissociation process which defines the pK_a value. The values of $\Delta|\Delta E_{relax}|$ are shown in Figure 4, where the species are numbered as indicated in Table 1. As it can be seen from Figure 4, methanol is the most affected compound when the ΔG_{Mm} component is neglected.

However, if one compares our pK_a value for methanol (Table 1) with the one obtained by Richardson et al.⁸ (Table 1), one sees that their value is two pK_a units larger than ours. Both calculations neglected the ΔG_{Mm} component, but Richardson et al.⁸ included electronic correlation effects only in the gas phase, which is inconsistent with the use of a TC as discussed

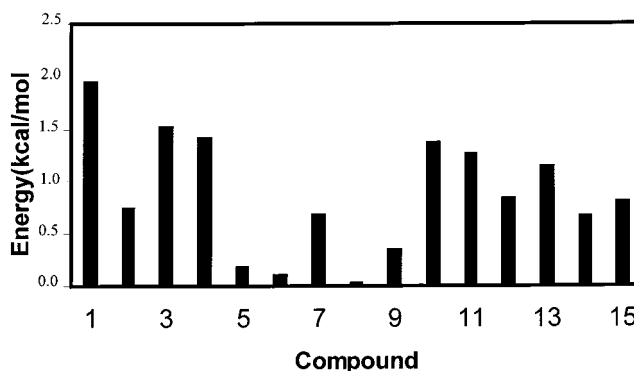
Relaxation Energy Difference ($\Delta|\Delta E_{relax}|$)

Figure 4. Difference between $|\Delta E_{relax}|$ for the pair acid/conjugate base.

above. Assuming for a minute that $pK_a = 16$ is the correct value for methanol, one could attribute our better description to the fact that we have consistently treated the differential correlation effects. However, as previously discussed, the uncertainties in the measurement raise some doubts about the accuracy of the experimental value. On the other hand, it seems reasonable to take $pK_a = 20.14$ as an upper limit to the methanol pK_a value. We believe that once ΔG_{Mm} and electronic correlation effects are taken into account, the proposed TC will be able to provide the most accurate pK_a value for methanol.

In Table 2 the values of $|\Delta E_{relax}|$ and $|\Delta E'_{relax}|$ for some compounds are compared. In some cases they are very similar, but in others they differ appreciably. Of course, since they are related to different processes, there is no reason they should be equal for a given compound.

Thiols. For methanethiol and ethanethiol the pK_a values calculated with our model are in very poor agreement with the experimental ones. In addition, methanethiol is the only compound for which a large discrepancy was observed between

TABLE 2: $|\Delta E'_{\text{relax}}|$ and $|\Delta E_{\text{relax}}|$ Values (kcal/mol)

compound	$ \Delta E_{\text{relax}} $	$ \Delta E'_{\text{relax}} $
MeOH	0.088	0.058
MeO ⁻	2.036	2.149
EtOH	0.106	0.076
EtO ⁻	0.851	1.448
HCOOH	0.444	0.263
HCOO ⁻	0.470	0.553
CH ₃ COOH	0.290	0.238
CH ₃ COO ⁻	0.634	0.947
H ₂ O	0.070	0.633
H ₃ O ⁺	1.685	0.997
OH ⁻	0.761	0.034

TABLE 3: Comparison between HF and MP2 Descriptions of the Systems in Gas Phase^a

compound	ΔE^0_{HF}	ΔE^0_{MP2}	$\Delta E^0_{\text{HF}} - \Delta E^0_{\text{MP2}}$
HCOOH	180.73	176.31	4.42
CH ₃ COOH	184.74	180.28	4.46
CH ₃ CH ₂ COOH	184.42	179.67	4.75
MeOH	223.93	218.65	5.28
EtOH	221.46	214.72	6.74
n-PrOH	220.91	214.06	6.85
MeSH	187.32	192.00	-4.68
EtSH	186.07	188.91	-2.84
FCH ₂ COOH	174.21	169.11	5.10
ClCH ₂ COOH	171.66	168.16	3.50
BrCH ₂ COOH	170.99	166.86	4.13

^a Energy values are in kcal/mol.

our pK_a value and that from ref 8. Comparing our description with the one employed by those authors, we both neglected the ΔG_{Mm} component, but Richardson et al.⁸ included correlation effects in gas phase by optimizing the geometries at the DFT level, and also indirectly in solution phase by making use of some experimental data to compute ΔG_{solv} for the anions. Thus, for the case of methanethiol the correlation effects were more consistently treated by Richardson et al.⁸

From our previous discussion, the results in Figures 3 and 4 indicate that the ΔG_{Mm} component is very small for both thiols and their conjugate bases. Although these results were obtained at the HF level, we believe that the same pattern would be found at a correlated level of calculation, otherwise the results of ref 8 would not show such a good agreement with the experiments since the authors also neglected the ΔG_{Mm} component. Thus, as for such compounds, the ΔG_{Mm} component seems to be negligible and correlation effects should most probably be responsible for the large discrepancy observed in the pK_a values. To put in evidence the TC capability of analyzing the results in terms of the different effects which could be contributing to the final pK_a values, we performed MP2 geometry optimization calculations in gas phase to quantify the effect of neglecting the electronic correlation in this phase. The results of these calculations are shown in Table 3 and in Figure 5, where the following notation was employed:

$$\Delta E^0_{\text{HF}} = \sum E^{\text{tot}}_{\text{PROD}} - \sum E^{\text{tot}}_{\text{REAC}} \quad (14)$$

$$\Delta E^0_{\text{MP2}} = \sum E^{\text{tot}}_{\text{PROD}} - \sum E^{\text{tot}}_{\text{REAC}} \quad (15)$$

where ΔE^0_{HF} is the difference between the HF total energies, at 0 K, for products ($\sum E^{\text{tot}}_{\text{PROD}}$) and reactants ($\sum E^{\text{tot}}_{\text{REAC}}$), with the geometries optimized at that level. The ΔE^0_{MP2} term represents the same difference, but at the MP2 level of calculation. The difference ($\Delta E^0_{\text{HF}} - \Delta E^0_{\text{MP2}}$) gives a quantitative measure of how important are the electronic correlation effects in the gas-phase step of the thermodynamical cycle.

Following our previous discussion, the differential correlation effect (δE_c), in any phase, should increase with the O–H bond strength of the acid. On the other hand, δE_c should become negative when the bond being broken in the acid is weaker than the O–H bond in H₃O⁺, as in the case of the thiols. But this is just what is shown in Figure 5, although the numbers there include all of the correlation effects (at the MP2 level) and not only the differential ones. From Figure 5, it is clear that exactly for the thiols, the consideration of electronic correlation in the gas phase would increase the ΔE^0_{vac} component, and consequently the pK_a values, in the direction needed to diminish the observed discrepancy. On the other hand, why is not the δE_c in gas phase being compensated by the fact that we are also neglecting correlation effects in the solution phase? This has to do with the fact that for thiols the enthalpy of ionization in aqueous solution is much smaller than in gas phase.^{29b} In fact, the order of acidity for these compounds, in gas and aqueous solution, changes more drastically than for the alcohols. As a result, one cannot have a good balance between the δE_c in the different phases. Thus, for this class of compounds one cannot expect to obtain reliable pK_a values unless electronic correlation effects are also introduced in the solution phase.

Halogenated Carboxylic Compounds. Considering the calculated pK_a values obtained for the halogenated compounds (Table 1), we observe that the disagreement with the experimental values gets worse as the size of the halogen atom increases.

The neglected ΔG_{Mm} component does not seem to be important for this class of compounds. At most it will contribute with the same weight as for the compounds for which the agreement between theory and experiment was satisfactory. Therefore, the observed deviations cannot be attributed to the neglect of the ΔG_{Mm} component.

A similar conclusion can be drawn from Figure 5, where the electronic correlation in gas phase seems to have approximately the same value as for the alcohols and organic acids, for which good pK_a values have been computed. Since there is no evidence that the differential correlation effects should differ appreciably from the gas to the solution phase, one should expect results of the same quality as the results obtained for the alcohols and nonsubstituted carboxylic acids.

Despite the fact that the solvation model employed takes into account the first solvation shell²¹ when defining the cavity, the implicit representation of the solvent molecules precludes their association with the solute molecules through hydrogen bond formation. Neglecting this effect could also contribute to the disagreement observed among the calculated and experimental pK_a values. In principle, this problem could be remedied by explicitly considering solvent molecules inside the cavity and redefining it. However, this association effect should also be present in the case of the carboxylic acids and alcohols for which good pK_a values were obtained. Besides, if this effect is responsible for the poor agreement observed for the halogenated acids, one should expect the larger deviations for the fluoroacetic acid, which forms stronger hydrogen bonds with water than do the chlorine or bromine equivalent compounds.

There is another factor that should be considered when analyzing the results for the halogenated acids. The cavity parameters in the PCM model were defined as to reproduce, as closely as possible, the experimental solvation energies.²¹ For molecules containing only first row atoms (with the exception of fluorine), many different compounds were used to calibrate the cavity parameters.²¹ However, only a few compounds containing halogens were investigated,²¹ and none of them could

Electronic Correlation Effects in Gas-Phase

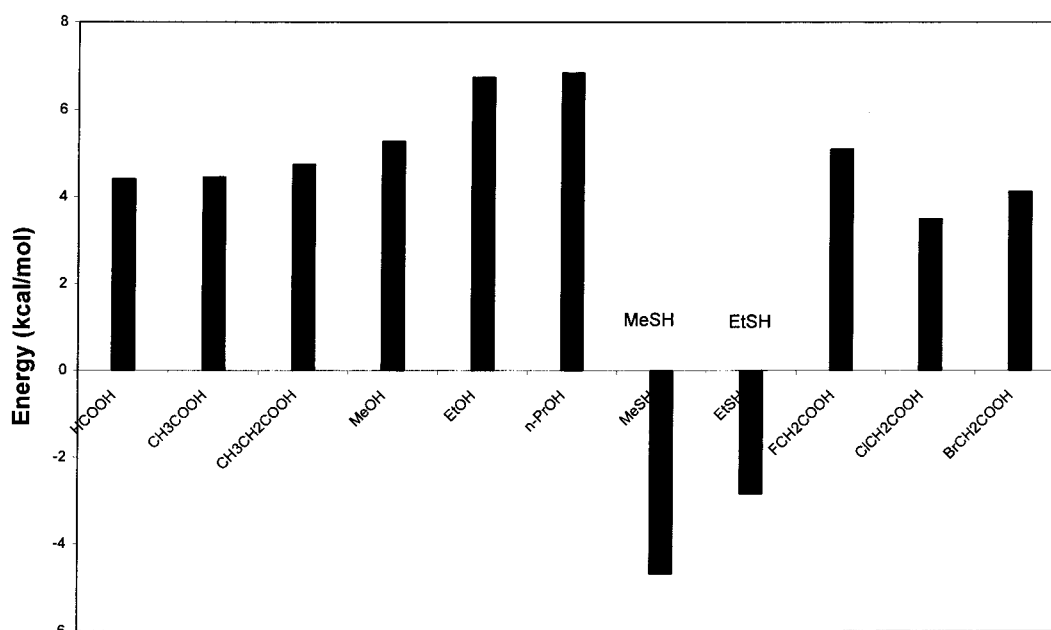


Figure 5. $\Delta E_{\text{HF}}^0 - \Delta E_{\text{MP2}}^0$ (kcal/mol).

be classified as bifunctional, as in the case of the halogenated carboxylic acids. On the other hand, the experimental solvation energies used for comparison³⁶ were, in fact, obtained from a scheme of group contributions. Following this scheme, for molecules containing more than one functional group (for instance, X = F, Cl, Br and Y = COOH), one correction parameter should be included when calculating the experimental property. However, no correction parameter is provided for the case of X = halogen and Y = COOH. Neglecting this correction we obtain the following results of solvation energy for the halogenated acids, from the group contribution scheme: ΔG_{solv} (X = F) = -8.50 kcal/mol; ΔG_{solv} (X = Cl) = -9.01 kcal/mol; and ΔG_{solv} (X = Br) = -9.13 kcal/mol. These results should be compared to the ones obtained with the PCM model: -11.55 kcal/mol, -10.40 kcal/mol, and -9.24 kcal/mol, for F, Cl, and Br, respectively. Thus, not only is the order reversed but also the differences between the experimental and PCM values are much larger than for the molecules which do not contain halogen atoms or even for those few molecules containing halogen atoms, which have been previously investigated.²¹ It is true that any errors in the cavity parameterization should affect both the acid and its conjugate bases. However, since the parameters were optimized to reproduce the experimental solvation energies, there is no guarantee that the parameters developed for monofunctional halogenated molecules should apply equally to bifunctional molecules. In conclusion, the discrepancy observed for the halogenated acids is most probably related to the fact that the parameters used to define the cavity for the halogen atoms are not appropriate for bifunctional molecules.

4. Conclusions

The $\text{p}K_{\text{a}}$ values obtained using the proposed thermodynamic cycle are in good agreement with the experimental results, for the majority of the studied compounds. Except for the thiols, the computed $\text{p}K_{\text{a}}$ values are those that show the best agreement with the available experimental data.

The good agreement between the theoretical and experimental $\text{p}K_{\text{a}}$ values, observed for some compounds, results from the fact that for these compounds the differential correlation effects, in both phases, are small and can compensate each other. Besides that, as the size of the molecule increases, the molecular motion component to the solvation energy can be also neglected.

Assuming that ΔG_{Mm} , the molecular motion component of ΔG_{solv} , should be larger for compounds which exhibit appreciable change of geometry when transferred from one phase to another, ΔE_{relax} can be used to estimate how important the ΔG_{Mm} contribution is to the solvation energy. According to this assumption, the correct prediction of the $\text{p}K_{\text{a}}$ value for methanol will require the inclusion of the ΔG_{Mm} component, as the methoxy ion changes its geometry considerably when transferred between phases. On the other hand, for the other compounds studied this component seems to be negligible.

For the thiols, the large discrepancy between the theoretical and experimental $\text{p}K_{\text{a}}$ values is most certainly due to the fact that the electronic correlation effects in gas and solution phases are not being compensated, as discussed in the text.

Regarding the halogenated derivatives of the carboxylic acids, the observed deviations cannot be attributed either to neglecting the ΔG_{Mm} component or to the electronic correlation effects. The fact that good $\text{p}K_{\text{a}}$ values were obtained for the nonhalogenated acids of the same size can be an indication that the halogen atoms may not be well represented by the PCM model. Although the differential electronic correlation effects, in solution and in the gas phase, are not exactly the same, it is quite improbable that the difference will be large enough to respond to the deviations observed for this class of compounds. Most probably, the cavity parameters used for the halogen atoms are not appropriate for the case of bifunctional molecules.

In conclusion, the proposed thermodynamic cycle, in conjunction with the PCM model to represent the solvent, can generate reliable $\text{p}K_{\text{a}}$ values. At the Hartree-Fock level, the methodology is expected to generate good results whenever the differential correlation effects, for the gas and solution phase

reaction steps of the TC, can compensate each other and the ΔG_{Mm} component can be neglected.

Acknowledgment. The authors thank CNPq, CAPES, FINEP, and FUJB for financial support. Very helpful discussion with Professor Jacopo Tomasi and the technical support given by Benedetta Mennucci and Maurizio Cossi are also acknowledged.

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