Thermodynamic cycles and the calculation of pK_a

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Abstract

A theoretical equation for the calculation of pK_a based on a proton transfer reaction between the acid and one water molecule is derived using the general chemical equilibrium relationship. The present result is compared with two equations recently used that were based on thermodynamic cycles, but predict different pK_a's. It is shown that one thermodynamic cycle is wrong, and its better performance when compared with the correct cycle is due to an erroneous value used for the solvation free energy of the H_3O^+ ion. In addition, this analysis indicates that the PCM-UAHF solvation model is inconsistently parametrized.
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1. Introduction

In several recent reports [1–11] on the theoretical calculation of pK_a, Eq. (1) is extensively used

$$HA \rightarrow A^- + H^+ \tag{1}$$

However, this approach has a serious drawback. The *free* proton is not a *species* suitable for theoretical calculation of the solvation free energy. The usual approach is to make use of the experimental absolute solvation free energy of the proton, a value that presents considerable experimental uncertainty [12], even considering that recent work [13] has provided an important contribution to resolve this issue. In order to overcome this problem, relative pK_a calculations can be done or Eq. (2) can be used

$$HA + H_2O \rightarrow A^- + H_3O^+ \tag{2}$$
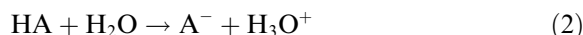
This equation was applied by Schuurmann et al. [14] in the theoretical calculation of pK_a of several carboxylic acids. Based on Eq. (2) and the thermodynamic cycle 1 (Fig. 1), the calculation of pK_a can be done through Eqs. (3) and (4)

$$\Delta G_{sol} = \Delta G_g + \Delta G_{solv}(A^-) + \Delta G_{solv}(H_3O^+) \\ - \Delta G_{solv}(HA) - \Delta G_{solv}(H_2O), \tag{3}$$

$$pK_a = \frac{\Delta G_{sol}}{1.364} - \log[H_2O]. \tag{4}$$

Following this approach, da Silva et al. [15,16] have applied Eq. (2) for calculating pK_a of carboxylic acids, alcohols and thiols. However, due to the presence of a water molecule in the chemical equation, da Silva et al. has questioned the use of the solvation free energy of water in the thermodynamic cycle 1. Rather, they have defended the use of the vaporization free energy of water as shown in cycle 2 (Fig. 1). Using this cycle, the calculation of pK_a was done through Eqs. (4) and (5)
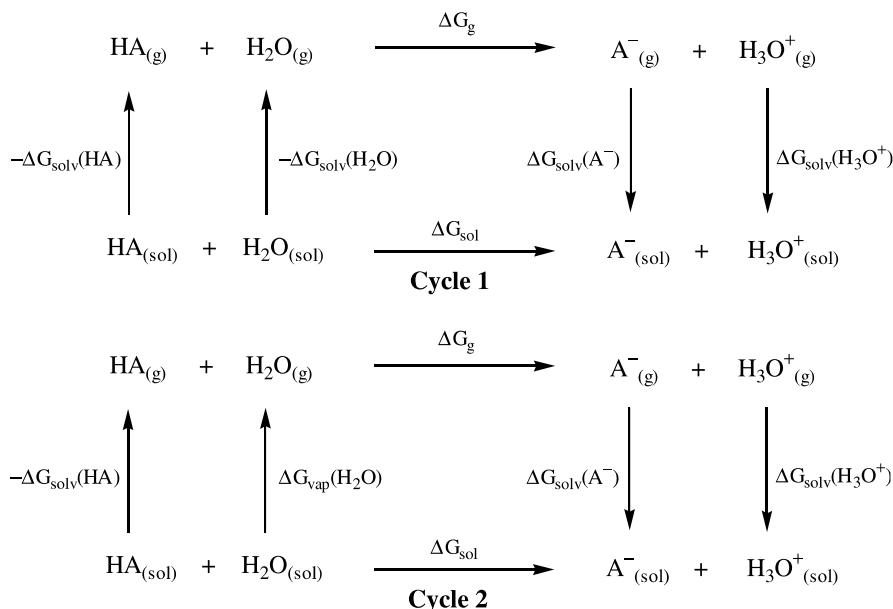
E-mail address: josef@qmc.ufsc.br.

Fig. 1. Thermodynamic cycles used in the calculation of pK_a.

$$\Delta G_{\text{sol}} = \Delta G_{\text{g}} + \Delta G_{\text{solv}}(\text{A}^-) + \Delta G_{\text{solv}}(\text{H}_3\text{O}^+)$$
$$- \Delta G_{\text{solv}}(\text{HA}) + \Delta G_{\text{vap}}(\text{H}_2\text{O}). \qquad (5)$$

The difference in the pK_a calculated by these two cycles amount to pK_a (cycle 1) $- pK_a$ (cycle 2) $= 3.1$ units if we use experimental values of solvation and vaporization free energy of water. This is an unacceptable situation because the final result can not be dependent on a particular thermodynamic cycle. As a consequence, one of the cycles is not correct.

In recent work, Liptak and Shields [1] have tested Eq. (2) and the thermodynamic cycles 1 and 2. They found that the thermodynamic cycle that uses vaporization free energy predicts a more accurate pK_a for carboxylic acids than the cycle that uses solvation free energy. However, they have questioned the soundness of the da Silva et al. cycle and suggested that the good results are fortuitous. On the other hand, they were not able to provide an explanation for these contradictory numbers.

The aim of this work is to resolve the presented inconsistencies. To attain this objective, we use the general chemical equilibrium relationship to derive the correct equation for the calculation of pK_a and compare it with the equations derived from the thermodynamic cycles. The incorrect cycle is identified and its flaw is discussed. Further, we present the source of error in the calculation of pK_a by Liptak and Shields using the thermodynamic cycle 1.

2. Algebraic derivation of an equation for the calculation of pK_a

A point that deserves attention and many authors do not consider carefully is the question of the standard state used to describe a thermodynamic process. Ignoring this can lead to thermodynamically inconsistent equations. The use of an algebraic approach instead of a thermodynamic cycle avoids missing terms that make important contributions to the total process. Thus, let us write the chemical potential of a species X in solution as

$$\mu_{\text{sol}}(\text{X}) = \mu_{\text{g}}^*(\text{X}) + \Delta G_{\text{solv}}^*(\text{X}) + RT \ln[\text{X}], \qquad (6)$$

where we are using the $*$ symbol for a standard state of 1 mol l^{-1}. The first term on the right side is the chemical potential of X in gas phase, considered to be an ideal gas at 1 mol l^{-1} of concentra-

tion. The second term is the solvation free energy as defined by Ben-Naim [17,18], which corresponds to lead the solute from a fixed position in gas phase to a fixed position in solution. The last term is related to the concentration of X in solution. The reader should note that it is not needed to explicitly include the activity coefficient, because all physically relevant solute–solvent interaction is included in the solvation free energy ($\Delta G^*_{\mathrm{solv}}(X)$) term. Eq. (6) is correct for either species, whether solute or solvent. Considering the Eq. (2), we can write the chemical equilibrium relationship as

$$\mu_{\mathrm{sol}}(A^-) + \mu_{\mathrm{sol}}(H_3O^+) - \mu_{\mathrm{sol}}(HA) - \mu_{\mathrm{sol}}(H_2O) = 0. \tag{7}$$

Substituting Eq. (6) for each species in Eq. (7) leads to

$$\Delta G^*_{\mathrm{sol}} = -RT \ln \frac{[A^-][H_3O^+]}{[HA][H_2O]} \tag{8}$$

and $\Delta G^*_{\mathrm{sol}}$ is given by

$$\Delta G^*_{\mathrm{sol}} = \Delta G^*_{\mathrm{g}} + \Delta\Delta G^*_{\mathrm{solv}}, \tag{9}$$

$$\Delta G^*_{\mathrm{g}} = \mu^*_{\mathrm{g}}(A^-) + \mu^*_{\mathrm{g}}(H_3O^+) - \mu^*_{\mathrm{g}}(HA) - \mu^*_{\mathrm{g}}(H_2O), \tag{10}$$

$$\Delta\Delta G^*_{\mathrm{solv}} = \Delta G^*_{\mathrm{solv}}(A^-) + \Delta G^*_{\mathrm{solv}}(H_3O^+) - \Delta G^*_{\mathrm{solv}}(HA) - \Delta G^*_{\mathrm{solv}}(H_2O). \tag{11}$$

Eq. (8) can be rewritten as

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} = e^{-\Delta G^*_{\mathrm{sol}}/RT}[H_2O]. \tag{12}$$

Taking $-\log$ on each side, we can obtain ($T = 298.15$ K)

$$pK_a = \frac{\Delta G^*_{\mathrm{sol}}}{1.364} - \log[H_2O]. \tag{13}$$

Eqs. (9)–(11) and (13) provide an exact relation between the gas phase process, the solvation free energy of the involved species and the pK_a. Now, considering the relations $\Delta G^*_{\mathrm{solv}} = \Delta G_{\mathrm{solv}}$ and $\Delta G^*_{\mathrm{g}} = \Delta G_{\mathrm{g}}$, a direct comparison of Eqs. (9)–(13) with Eqs. (3)–(5) permit us to conclude that the thermodynamic cycle 1 is correct, while the cycle 2 is not. The failure of the thermodynamic cycle 2 is twofold: first, by using the vaporization free en-

ergy in order to describe the transfer of water from liquid phase to gas phase, the reference state of water as a reactant species become the liquid state, with $[H_2O] = 55.5$ mol l^{-1}. Thus, the correction for water concentration through Eq. (4) should not be used in cycle 2 in order to avoid a double count. Second, the solvation free energies calculated for other species is based on Ben-Naim's definition, which leads the reactant species from solution to gas phase at 1 mol l^{-1} concentration. Thus, cycle 2 leads to a mixture of standard states in gas phase. The HA, A$^-$ and H$_3$O$^+$ species staying in a standard state of 1 mol l^{-1} while H$_2$O stays in standard state of 1 atm. This analysis indicates that the better result obtained with the thermodynamic cycle 2 is indeed fortuitous, as previously suggested by Liptak and Shields [1]. The next section shows the source of error in the calculation of pK_a through cycle 1.

3. Correcting the calculation of pK_a using cycle 1

Liptak and Shields [1] have reported high level ab initio quantum chemical calculations for reaction (2) that were applied for the calculation of pK_a of several carboxylic acids. The solvent effect was included by the conductor-like screening solvation model (CPCM). When the thermodynamically correct cycle 1 was used, the theoretical pK_a values have presented a systematic deviation from experimental data. Since the gas phase contribution was calculated very accurately, the sources of error are in the calculation of solvation free energies. Further, considering that the solvation free energy of ions is the most important contribution, the error should be in either $\Delta G^*_{\mathrm{solv}}(A^-)$ or $\Delta G^*_{\mathrm{solv}}(H_3O^+)$. The theoretical values of $\Delta G^*_{\mathrm{solv}}$ can be compared with a recent and reliable experimental result reported by Pliego and Riveros [19]. For HCOO$^-$ and CH$_3$COO$^-$, the experimental values of $\Delta G^*_{\mathrm{solv}}$ are -76.2 and -77.3 kcal mol^{-1}, while the theoretical values (CPCM/HF/6-31G(d) level) are -76.2 and -76.6 kcal mol^{-1}, respectively. However, Liptak and Shields have used a value of -104.0 kcal mol^{-1} for $\Delta G^*_{\mathrm{solv}}(H_3O^+)$, while the experimental value of Pliego and Riveros is -110.2 kcal mol^{-1}. Thus, the solvation free energy of

Table 1
Theoretical and experimental pK_a's for carboxylic acids

	pK_a (calculated)[a]	pK_a (corrected)[b]	pK_a (exp)[c]	Error
Acetic acid	9.37	4.82	4.75	0.07
Formic acid	7.50	2.96	3.75	−0.79
Cyanoacetic acid	6.36	1.82	2.45	−0.63
Chloroacetic acid	7.47	2.93	2.85	0.08
Oxalic acid	4.95	0.41	1.23	−0.82
Pivalic acid	9.63	5.09	5.03	0.06
RMS error	−	−	−	0.53

[a] Theoretical calculation from [1] at CBS-QB3 level for gas phase and at CPCM/HF/6-31G(d) level for solvation.
[b] Values corrected through Eq. (14).
[c] Values taken from [1].

H_3O^+ used by Liptak and Shields is the source of error in the calculation of pK_a through cycle 1. We can correct the Liptak and Shields calculation of pK_a using $\Delta G^*_{solv}(H_3O^+) = -110.2$ kcal mol^{-1}. Our results are in Table 1 and were obtained through Eq. (14)

$$pK_a \text{ (corrected)} = pK_a \text{ (calculated)} - 4.54. \quad (14)$$

As can be observed, the use of the most reliable solvation free energy of H_3O^+ leads to very accurate pK_a values for the six carboxylic acids, with a RMS error of only 0.53 pK_a units. In addition, the results show that there are no practical problems with the thermodynamic cycle 1.

The present Letter also points out that the PCM-UAHF [20] and CPCM [21] models, which use the same cavity, are inconsistently parametrized. Indeed, the solvation free energy of H_3O^+ ion predicted by the PCM-UAHF method is −105.3 kcal mol^{-1} (value taken from [20]), which can be compared with the experimental value of −110.2 kcal mol^{-1} [19]. Since the theoretical PCM-UAHF value is overestimated in relation to the experimental value by 4.9 kcal mol^{-1}, a look in Eqs. (9)–(13) indicates that a reliable calculation of pK_a would require that the theoretical ΔG^*_{solv} values for the anions would be underestimated in relation to the experimental values by ∼5 kcal mol^{-1}. This shift would be needed in order to compensate for the error in ΔG^*_{solv} of the H_3O^+ ion and to produce a correct $\Delta\Delta G^*_{solv}$ contribution in Eq. (9). However, for anions such as MeO$^-$, PhO$^-$, CH$_3$COO$^-$, HS$^-$ and PhS$^-$ the deviation of the theoretical ΔG^*_{solv} [20] from experimental data [19] is less than 2 kcal

mol^{-1}. As a consequence, it is not possible to predict accurate pK_a for these species through Eq. (2) using the PCM-UAHF solvation model. Rather, the calculated pK_a values will deviate systematically from experimental data, as observed in the case of carboxylic acids [1]. Thus, a new parametrization using more reliable and updated solvation data [19] would be necessary. By the way, a more realistic approach, such as the cluster–continuum model [22], could be undertaken. This discrete/continuum solvation model considers the ion solvated by some explicit solvent molecules, forming a rigid cluster. The complete system is then solvated by the dielectric continuum. This model was recently applied [23] in the calculation of pK_a of different organic species and has presented a very superior performance compared to the pure continuum methods PCM and SM5.42R.

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