Correlation of aqueous $pK_a$ values of carbon acids with theoretical descriptors: A DFT study

I.E. Charif $^a$, S.M. Mekelleche $^{a,*}$, D. Villemin $^b$, N. Mora-Diez $^c$

$^a$ Département de Chimie, Faculté des Sciences, Université A. Belkaid, B.P.119, Tlemcen 13000, Algeria
$^b$ ENSICAEN, Université de Caen, LCMT, UMR 6507 CNRS, 6, Bd Maréchal Juin, Caen 14050, France
$^c$ Department of Chemistry, Thompson Rivers University, Kamloops, BC, Canada V2C 5N3

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Abstract

Theoretical calculations are carried out to predict gas- and aqueous-phase acidities of a series of 21 carbon acids with $pK_a$ values varying from $-6.20$ to 50. Acceptable linear correlations ($R^2 > 0.93$, SD < 4) are obtained between calculated deprotonation Gibbs free energy changes and experimental $pK_a$ values (measured in water). Solvent effects are taken into account by means of the polarizable continuum model (PCM). Our calculations also show that the high acidity of $\alpha$-proton carbonyl compounds and electron-withdrawing substituted methanes can be related to the strong increase in the vicinal charge interactions $n_c \pi^*\pi$ in anion species. Calculations are performed at the B3LYP/6-311++G(d,p) level of theory.

$^*$ Corresponding author.
E-mail address: sm_mekelleche@mail.univ-tlemcen.dz (S.M. Mekelleche).

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1. Introduction

The deprotonation energies of organic acids and the proton affinities of the corresponding conjugate bases are widely used for the prediction of gas-phase and aqueous-phase Brønsted acidities [1–8]. Strong acids have small values of deprotonation energy (i.e., the release of the proton is easier) while strong bases have large values of proton affinity (i.e., the binding to the proton is stronger). Several works on the prediction of the acidity of organic and inorganic acids can be found in the literature. For instance, Smith and Radom [9,10] have shown that the G2 and G2(MP2) methods provide excellent results for both deprotonation enthalpies and proton affinities of small molecules. Catalan and Palomar [11] have investigated gas-phase acidities of a number of species and have shown that calculations at the B3LYP method with 6-311+G(d) and 6-311+G(3df,3pd) basis sets correlate well with the experimental data. Good correlations have been obtained between experimental $pK_a$ values of a wide range of organic Brønsted acids and their calculated gas-phase deprotonation enthalpies [12]. Correlations between theoretical descriptors and gas-phase acid-base equilibrium constants of organic compounds have been reported for amines, alcohols and thiols [13–15]. An excellent correlation was obtained between the aqueous-phase acidity calculated with the HF/3-21G(d) method and experimental $pK_a$ values for a series of nitrogen bases [16].

Recently, various theoretical descriptors were used to investigate their correlation with the carbon acidity of compounds having the CHR$\_1R_2R_3$ structure. A reasonable correlation was obtained between the deprotonation energies of the compounds calculated at the HF/3-21G and B3LYP/6-31G(d) levels of theory and their aqueous $pK_a$ values [17,18]. The ability to predict acidity using a coherent, well-defined theoretical approach, without external approximation or fitting to experimental data, would be very useful to chemists. Thanks to the rapid development
of computational chemistry, the acidity of small molecules in the gas phase can be calculated with equivalent or greater accuracy than can be obtained experimentally. However, the current situation is less satisfactory in solution, mostly due to the difficulty of calculating solvation energies with adequate accuracy.

The aim of this work is to establish a correlation model for determining the aqueous pKₐ values of carbon acids at 298.15 K by working with a series of 21 compounds (Fig. 1) that exhibit pKₐ values from −6.2 to 50.0 (see Table 1) [18–21]. In addition, the second-order charge-transfer energies, calculated using the natural bond orbital (NBO) method [22–26], are used to explain the high acidity of the dicarbonyl compounds and the electron-withdrawing substituted methanes included in this study.

2. Computational details

2.1. Gas-phase acidity calculations

Calculations are preformed with the Gaussian 98W software package [27]. The geometries of the neutral and deprotonated species are fully optimized at the B3LYP/6-311++G(d,p) level of theory. Frequency calculations are performed at the same level of theory to characterize the stationary points obtained. The gas-phase Gibbs free-energy change (ΔG°ₐₕ) of Scheme 1 is calculated using Eq. (1). For G°ₐₕ(H⁺) the experimental value of −6.28 kcal/mol is used [28].

\[
ΔG°ₐₕ = G°ₐₕ(A⁻) + G°ₐₕ(H⁺) - G°ₐₕ(AH) \tag{1}
\]

2.2. Aqueous-phase acidity calculations

Solvent effects are taken into account by means of the polarizable continuum model (PCM) [29–31] through single-point energy calculations at the B3LYP/6-311++G(d,p) level of theory (using the gas-phase optimized geometries). The PCM calculations, using Gaussian 98W, employ the UAHF atomic radii when constructing the solvent cavity for the calculation of the Gibbs free-energy of solvation. A common practice to calculate the

AH(gas)→A'(gas)+H'(gas)

Scheme 1.

Fig. 1. Carbon acids considered in this study.
The experimental aqueous pKₐ values of the compounds under study, together with the experimental aqueous pKₐ values at 298.15 K, are shown in Table 1. All the calculations and experimental data reported in this paper are at 298.15 K. The raw data for these calculations are shown in Table S1 of the supplementary material. Fig. 2 shows the correlation of the ΔG°ᵦ values with the experimental aqueous pKₐ values. A satisfactory linear correlation is obtained showing that the gas-phase Gibbs free-energy change of deprotonation generally increases with the change in formula (Ångström) of the compounds decreases. For four of the 21 compounds studied (7, 11, 13 and 19) the calculated ΔG°ᵦ seems a bit higher than expected. The regression equation with the corresponding standard deviation (SD) and correlation coefficient (R²) values are given in Eq. (6).

\[ pK_a = \frac{\Delta G_{aq}^o}{RT \ln 10} \]

The calculated gas-phase ΔG° of the acid dissociation and the experimental aqueous pKₐ values (relative to water) at 298.15 K [18–21] are reported in Table 1. The raw data for these calculations are shown in Table S1 of the supplementary material. Fig. 2 shows the correlation of the ΔG°ᵦ values with the experimental aqueous pKₐ values. A satisfactory linear correlation is obtained showing that the gas-phase Gibbs free-energy change of deprotonation generally increases with the acidity of these compounds decreases. For four of the 21 compounds studied (7, 11, 13 and 19) the calculated ΔG°ᵦ seems a bit higher than expected. The regression equation with the corresponding standard deviation (SD) and correlation coefficient (R²) values are given in Eq. (6).

\[ pK_a = \frac{\Delta G_{aq}^o}{RT \ln 10} \]

Table 1

<table>
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<th>Compound number</th>
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<tr>
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<td>287.15</td>
<td>−8.13</td>
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</table>

\[ a \text{ Values calculated using the correlation equation between } pK_a(\text{exp}) \text{ and } \Delta G^{o}_{aq} \text{ (Eq. (6), see Fig. 2).} \]

\[ b \text{ Values calculated using Eq. (5).} \]

\[ c \text{ Values calculated using the correlation equation between } pK_a(\text{exp}) \text{ and } pK_a(\text{calc}) \text{ (Eq. (7), see Fig. 4).} \]

\[ d \text{ Ref. [18a].} \]

\[ e \text{ Ref. [21].} \]

\[ f \text{ Ref. [18b–20].} \]

\[ \Delta G^o \text{ represents the Gibbs free-energy of solvation of species X.} \]
the calculated $pK_a$ values are of $-0.009$ and $2.71 \text{ p}K_a$ units, respectively. The largest AD values (greater than $\pm 5 \text{ p}K_a$ units) are detected for compounds 6 and 20. Using the correlation Eq. (6) the predicted aqueous $pK_a$ values for compounds 6 and 20 would be $26.83$ (instead of $32$) and $-6.49$ (instead of $0.06$), respectively. It should be noted that very accurate aqueous $pK_a$ values (relative to water) can only be obtained for acids weaker than the hydronium ion ($pK_a = -1.74$) and stronger than water ($pK_a = 15.74$) [1].

The experimental aqueous $pK_a$ values of the very strong and very weak carbon acids listed in Table 1 must be regarded as approximate.

It is well known that in the gas phase, where solvation effects are completely or almost completely absent, acidity orders may be much different than in aqueous solution for certain families of compounds. Simple alcohols are an example of this: while tertiary alcohols are more acidic than secondary and primary alcohols in the gas phase, in aqueous solution the acidity order is completely reversed because the much bulkier tertiary anion is poorly solvated. A similar pattern is found in simple aliphatic carboxylic acids and when analyzing the basicity order of amines [1]. From the results we have obtained, we can infer that the aqueous-phase acidity order of the family of carbon acids studied is very similar to that in the gas phase. Hence, it might be possible to use gas-phase calculations to predict the aqueous $pK_a$ values of carbon acids. The predicted aqueous $pK_a$ values for the carbon acids under study using Eq. (6) are listed in Table 1.

### 3.2. Aqueous-phase acidities

The calculated aqueous-phase $\Delta G^o$ of the acid dissociation and $pK_a$ values of the compounds under study (using Eq. (5)) at 298.15 K are reported in Table 1. The plot of $\Delta G_a^o$ versus $\Delta G_g^o$ is displayed in Fig. 3. A satisfactory correlation is obtained between these two Gibbs free-energy changes ($R^2 = 0.947$) that might help explain the good correlation previously found between $\Delta G_g^o$ and the experimental aqueous $pK_a$ values. Fig. 4 shows the correlation between the experimental and calculated aqueous $pK_a$ values. The regression equation with the corresponding standard deviation (SD) and correlation coefficient ($R^2$) values are given in Eq. (7).

$$\text{pK}_a = 0.8755 \text{ pK}_a\text{(calc)} - 1.7563 \quad (R^2 = 0.934, \quad \text{SD} = 4.80)$$

(7)

The MD and AD between the experimental and the calculated values are of $-0.64$ and $4.39 \text{ p}K_a$ units, respectively. The largest AD values (greater than $\pm 5 \text{ p}K_a$ units) are detected in compounds 1, 2, 3, 5, 7 and 13. If Eq. (7) is used to predict what the aqueous $pK_a$ of compounds 6 and 20 should be, values of $21.89$ and $-6.08$ are obtained. The predicted aqueous $pK_a$ values for the carbon acids under study using Eq. (7) are listed in Table 1. The predicted values are smaller than those calculated with Eq. (5) which indicates that the calculated $\Delta G_a^o$ might be slightly overestimated.

The aqueous phase $pK_a$ calculation using gas-phase calculated data (by means of Eq. (6)) seems to be a more reliable approach for the family of organic acids considered since the AD obtained using the directly calculated aqueous $pK_a$ is almost twice as large as in the first approach described. The reasons for this should lie in the deficiencies of continuum solvation models to accurately calculate solvation energies since explicit solute–solvent interactions are ignored. The inclusion of continuum solvent effects in the geometry optimizations and frequency calculations might improve these results slightly [32].
bonyl compounds (10-17) the negative charge of the anions is conjugated with the two vicinal \( \pi \) bonds. Therefore, these anions are more stabilized by charge transfer delocalization. We note that these stabilizing effects are absent in compounds 1-6. For nitro and cyan-alkanes the following sequence of \( \Delta G^\circ_{\text{gas}} \) values is obtained.

19 \( \Delta G^\circ_{\text{gas}} = 304.05 \text{ kcal/mol} \) > 20 (290.84 \text{ kcal/mol}) > 21 (287.15 \text{ kcal/mol})

In these compounds, the contribution of resonance and inductive effects are important and the synergy of the two effects originates a remarkably high acidity. The stabilization energy of the anionic forms \( \left( \Delta E_{n\rightarrow\pi_{\text{N=O}}}^{(2)} \right) \), caused by the \( n_C \rightarrow \pi_{\text{N=O}} \) interaction, is very significant: 317.35 kcal/mol, for compound 20, and 345.02 kcal/mol for compound 21. Consequently, the negative charge on the acidic carbon of the anion is strongly delocalized over the whole molecule.

4. Conclusions

In the present work, we have shown satisfactory linear correlations between experimental aqueous \( pK_a \) values of a variety of carbon acids and theoretical gas- and aqueous-phase deprotonation Gibbs free-energy changes. The linear correlation using the gas-phase descriptor is slightly better \( (R^2 = 0.969, \text{SD} = 3.27) \) than using the aqueous-phase one \( (R^2 = 0.934, \text{SD} = 4.80) \). The correlation equation between the experimental aqueous \( pK_a \) values and the calculated gas-phase deprotonation Gibbs free-energy changes was used to predict better \( pK_a \) values for two of the compounds studied (HCF\(_3\) and HC(NO\(_2\))3). To assess the validity of the predictions in Table 1, further experimental work is required.

The difference in acidity of the compounds studied can be interpreted through inductive and resonance effects. The strong acidity of some carbon acids has been rationalized by calculating the \( n_C \rightarrow \pi^* \) charge transfer energy between the non-bonding orbital localized on the carbon atom of the base with the negative charge \( (n_C) \) and the vicinal unoccupied antibonding orbital \( \pi^* \) associated with the C=O, N=O or N=O groups. These molecular orbital interaction is called \( n_C \rightarrow \pi^* \) vicinal charge transfer. The stabilization energy of this interaction can be calculated by the NBO method using the second order perturbation theory as indicated by Eq. \( \left( 8 \right) \) \( \left[ 22-26 \right] \), where \( e_{n\pi} \), \( e_x \) are orbital energies and \( F_{n\rightarrow\pi^*} \) is the off-diagonal NBO Fock matrix element.

\[
\Delta E_{n\rightarrow\pi^*}^{(2)} = -2 \left( F_{n\rightarrow\pi^*} \right)^2 / (e_{n\pi} - e_{\pi^*}) \tag{8}
\]

For instance, the charge transfer energies \( \left( \Delta E_{n\rightarrow\pi^*}^{(2)} \right) \) in the conjugate bases of cyclopentadiene \( \left( 9 \right) \), acetyl acetone \( \left( 13 \right) \) and barbituric acid \( \left( 16 \right) \) are 75.72, 120.19, and 161.84 \text{ kcal/mol}, respectively (see Table S2 of the supplementary material). Therefore, the charge-transfer energy in these systems is remarkably important in explaining their acidity order. In the dicar-