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

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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 α-proton carbonyl compounds and electron-withdrawing substituted methanes can be related to the strong increase in the vicinal charge interactions $n_c \rightarrow \pi^*$ in anion species. Calculations are performed at the B3LYP/6-311++G(d,p) level of theory.
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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 Brönsted acidities [1–8]. Strong acids have small values of deprotonotion 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 Brönsted 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

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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 pK_a values of carbon acids at 298.15 K by working with a series of 21 compounds (Fig. 1) that exhibit pK_a 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^{o}_{gas}) of Scheme 1 is calculated using Eq. (1). For $G^{o}_{gas}(H^+)$ the experimental value of −6.28 kcal/mol is used [28].

$$\Delta G^{o}_{gas} = G^{o}_{gas}(A^-) + G^{o}_{gas}(H^+) - G^{o}_{gas}(AH) \tag{1}$$

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
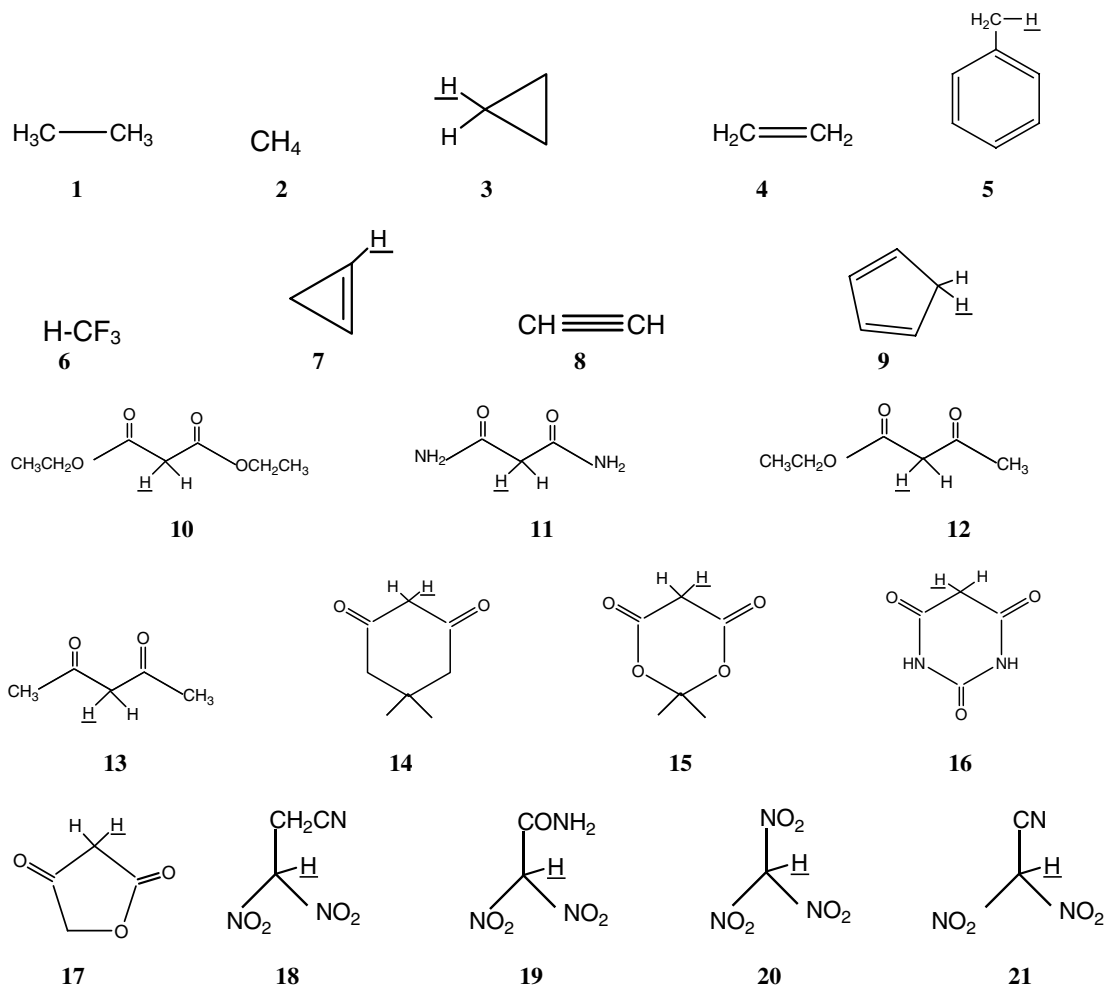
$$AH(gas) \rightarrow A^-(gas) + H^+(gas)$$
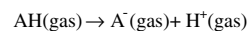
Scheme 1.

Fig. 1. Carbon acids considered in this study.

Table 1

Calculated gas- and aqueous-phase ΔG° values (in kcal/mol) of the acid dissociation and aqueous pK_a values of the compounds under study, together with the experimental aqueous pK_a values at 298.15 K

Compound number	Gas-phase		Aqueous-phase			
	ΔG°_{gas}	pK_a(calc)[a]	ΔG°_{aq}	pK_a(calc)[b]	pK_a(calc)[c]	pK_a(exp)
1	410.77	46.91	78.78	57.75	48.80	50[d]
2	409.25	46.24	53.56	39.26	32.62	48[d]
3	405.33	44.49	69.86	51.21	43.08	46[d]
4	398.98	41.66	58.28	42.72	35.65	44[d]
5	398.12	41.28	73.87	54.15	45.65	41[e]
6	365.67	26.83	36.84	27.01	21.89	32[e]
7	377.80	32.23	46.66	34.20	28.19	29[d]
8	368.83	28.24	28.95	21.22	16.82	25[d]
9	346.06	18.10	16.99	12.45	9.15	15[e]
10	336.62	13.90	16.38	12.01	8.76	13.30[f]
11	340.31	15.54	21.85	16.02	12.27	12.50[f]
12	331.50	11.62	13.06	9.57	6.63	10.70[f]
13	336.15	13.69	21.17	15.52	11.83	9.00[f]
14	325.46	8.93	12.14	8.90	6.03	5.25[e]
15	321.34	7.09	9.87	7.24	4.58	4.83[e]
16	316.57	4.97	10.12	7.42	4.74	4.01[e]
17	319.21	6.14	7.88	5.78	3.30	3.76[e]
18	301.18	−1.88	−2.47	−1.81	−3.34	2.27[f]
19	304.05	−0.60	−0.45	−0.33	−2.05	1.30[f]
20	290.84	−6.49	−6.74	−4.94	−6.08	0.06[f]
21	287.15	−8.13	−15.17	−11.12	−11.49	−6.20[f]

[a] Values calculated using the correlation equation between pK_a(exp) and ΔG°_{gas} (Eq. (6), see Fig. 2).
[b] Values calculated using Eq. (5).
[c] Values calculated using the correlation equation between pK_a(exp) and pK_a(cal) (Eq. (7), see Fig. 4).
[d] Ref. [18a].
[e] Ref. [21].
[f] Ref. [18b–20].

aqueous Gibbs free-energy change of an acid dissociation (ΔG°_{aq}, see Eq. (2)) is by combining the ΔG°_{gas} of the deprotonation process with the change in Gibbs free-energy of solvation ($\Delta\Delta G^{\circ}_{solv}$), using the thermodynamic cycle of Scheme 2 and Eq. (3). For $G^{\circ}_{solv}(H^+)$ the experimental value of −264.61 kcal/mol is used [28]. The aqueous pK_a is calculated according to Eq. (5). All the calculations and experimental data reported in this paper are at 298.15 K.

$$\Delta G^{\circ}_{aq} = G^{\circ}_{aq}(A^-) + G^{\circ}_{aq}(H^+) - G^{\circ}_{aq}(AH) \quad (2)$$

$$\Delta G^{\circ}_{aq} = \Delta G^{\circ}_{gas} + \Delta\Delta G^{\circ}_{solv} \quad (3)$$

$$\Delta G^{\circ}_{aq} = G^{\circ}_{gas}(A^-) + G^{\circ}_{gas}(H^+) - G^{\circ}_{gas}(AH)$$
$$+ \Delta G^{\circ}_{solv}(A^-) + \Delta G^{\circ}_{solv}(H^+)$$
$$- \Delta G^{\circ}_{solv}(AH) \quad (4)$$
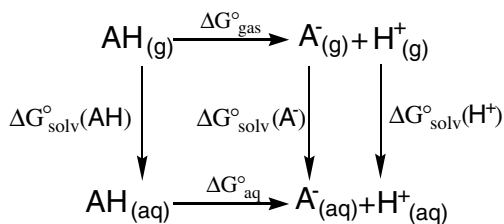
Scheme 2. $\Delta G^{\circ}_{solv}(X)$ represents the Gibbs free-energy of solvation of species X.

$$pK_a = \frac{\Delta G^{\circ}_{aq}}{RT \ln 10} \quad (5)$$

3. Results and discussion

3.1. Gas-phase acidities

The calculated gas-phase ΔG° of the acid dissociation and the experimental aqueous pK_a 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°_{gas} values with the experimental aqueous pK_a values. A satisfactory linear correlation is obtained showing that the gas-phase Gibbs free-energy change of deprotonation generally increases when the acidity of these compounds decreases. For four of the 21 compounds studied (7, 11, 13 and 19) the calculated ΔG°_{gas} seems a bit higher than expected. The regression equation with the corresponding standard deviation (SD) and correlation coefficient (R^2) values are given in Eq. (6).

$$pK_a = 0.4453\Delta G^{\circ}_{gas} - 135.99 \ (R^2 = 0.969, \ SD$$
$$= 3.27) \quad (6)$$

If aqueous pK_a values are obtained from the calculated ΔG°_{gas} values using Eq. (6), the mean (MD) and mean absolute (AD) deviations between the experimental and
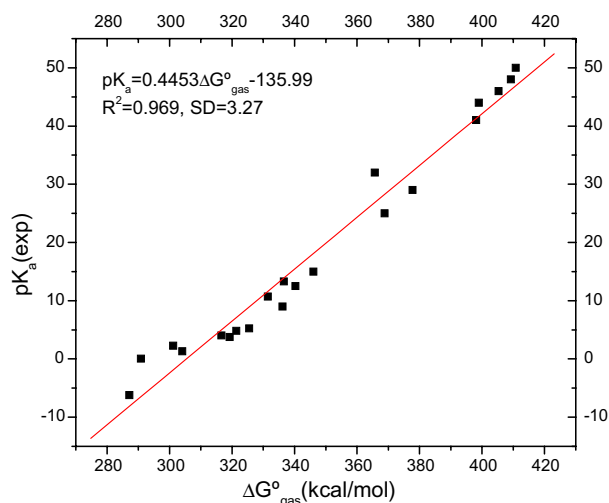
Fig. 2. Correlation of the experimental aqueous pK_a values of the carbon acids studied with the calculated (B3LYP/6-311++G(d,p)) gas-phase deprotonation Gibbs free-energy changes (ΔG^{o}_{gas}) at 298.15 K.

the calculated pK_a values are of -0.009 and 2.71 pK_a units, respectively. The largest AD values (greater than ± 5 pK_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 ΔG^{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 ΔG^{o}_{aq} versus ΔG^{o}_{gas} 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 ΔG^{o}_{gas} 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).

$$pK_a = 0.8755\ pK_a(calc) - 1.7563\ (R^2 = 0.934,\ SD = 4.80) \tag{7}$$

The MD and AD between the experimental and the calculated values are of -0.64 and 4.39 pK_a units, respectively. The largest AD values (greater than ± 5 pK_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 ΔG^{o}_{aq} values 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].
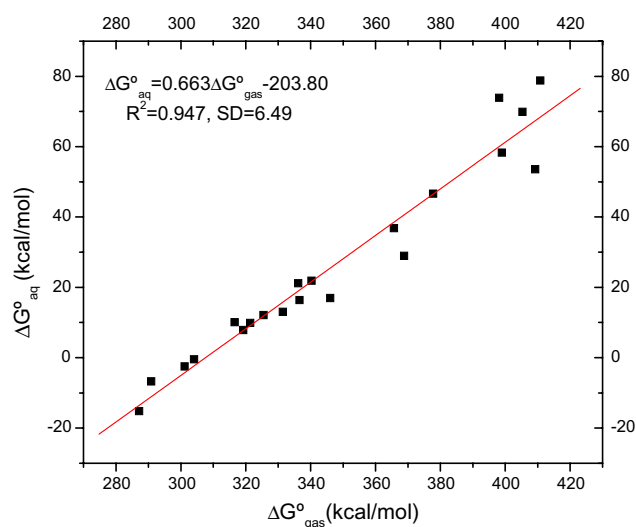

Fig. 3. Correlation between the calculated (B3LYP/6-311++G(d,p)) aqueous (ΔG^{o}_{aq}) and gas-phase (ΔG^{o}_{gas}) deprotonation Gibbs free-energy changes of the carbon acids studied at 298.15 K.
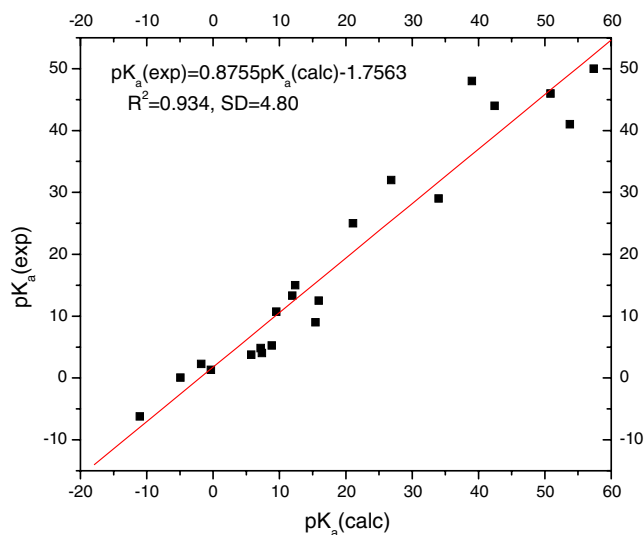
Fig. 4. Correlation between the experimental and calculated (B3LYP/6-311++G(d,p)-PCM(sp)) aqueous pK_a values of the carbon acids studied at 298.15 K.

The aqueous-phase acidity of the carbon acid series under investigation can be explained by the relative stabilities of their conjugate bases. The anions are stabilized by a combination of resonance and inductive effects [33]. Furthermore, it has been showed that delocalization is an important factor responsible for enhanced acidity [34–36]. However, inductive effects, produced by electron-withdrawing substitutents, have the same order of magnitude as delocalization effects. Acidity increases when the delocalization of the negative charge (in the carbanion) increases [34]. The values of intrinsic acidity (ΔG^o_{gas}) of the compounds **1–21** decrease with increasing delocalization effects. The charge delocalization (depletion of the negative charge) can be explained by the donor–acceptor interaction 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 π^* associated with the C=C, C=O or N=O groups. This molecular orbital interaction is called $n_C \to \pi^*$ 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. (8) [22–26], where ε_n, ε_{π^*} are orbital energies and $F_{n \to \pi^*}$ is the off-diagonal NBO Fock matrix element.

$$\Delta E^{(2)}_{n_C \to \pi^*} = -2(F_{n \to \pi^*})^2/(\varepsilon_n - \varepsilon_{\pi^*}) \tag{8}$$

For instance, the charge transfer energies $\left(\Delta E^{(2)}_{n_C \to \pi^*_{C=C}}\right)$ in the conjugate bases of cyclopentadiene (**9**), $\left(\Delta E^{(2)}_{n_C \to \pi^*_{C=O}}\right)$ acetyl acetone (**13**) and barbituric acid (**16**) are 75.72, 120.19, and 161.84 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-

bonyl compounds (**10–17**) the negative charge of the anions is conjugated with the two vicinal π 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 cyano alkanes the following sequence of ΔG^o_{gas} values is obtained.

19 (ΔG^o_{gas} = 304.05 kcal/mol]) > **20** (290.84 kcal/mol)

> **21** (287.15 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 $\left(\Delta E^{(2)}_{n_C \to \pi^*_{N=O}}\right)$, caused by the $n_C \to \pi^*_{N=O}$ 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 ($R^2 = 0.969$, SD = 3.27) than using the aqueous-phase one ($R^2 = 0.934$, 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 $n_C \to \pi^*$ 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 π^* associated with the C=C, C=O or N=O groups. These stabilization interaction energies are calculated by the NBO method using the second-order perturbation theory.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.theochem. 2007.04.037.

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