Aqueous-phase pK_a of the methyl group in acetic acid

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The gas-phase acidity of the α-hydrogens of acetic acid and the aqueous-phase pK_a of ethyl acetate are combined with other literature values in a thermodynamic cycle to provide the aqueous-phase pK_a of the methyl group of acetic acid as 22.7 ± 1.0 and the pK_a of the enol of acetic acid as 3.3 ± 1.0.

Enolate anions of carboxylic acids are postulated as intermediates in a number of biologically important reactions that include addition,[1] racemization[2] and elimination processes.[3] Despite their importance and the attempts to understand how such energetic species could be stabilized,[4] little is known about α-C–H acidities in carboxylic acids including the prototypical acetic acid itself. Arguable exceptions are limited to compounds with special structural features that provide kinetic or thermodynamic stabilization[5,6] or those that can be generated as products from the decay of reactive intermediates produced by laser flash photolysis.[7]

An alternative strategy for determining an aqueous phase pK_a is to translate a gas-phase acidity into its condensed-phase counterpart by using an appropriate thermochemical cycle such as that for acetic acid shown in Scheme 1.[8] Knowing any four of the five parameters in Scheme 1 allows one to obtain the missing thermochemical value. This approach has been used to determine hydration enthalpies of alkyl ammonium[9] and aliphatic carboxylate ions,[8,10] and takes advantage of recently determined, accurate gas-phase basicities[11,12] or acidities.[13]

Several distinct advantages over conventional approaches are realized for pK_a determinations *via* Scheme 1. First, gas-phase acidities can be accurately determined across the full range of acidities, and in a well-defined common environment (*i.e.* the gas-phase), while condensed-phase values are easily and accurately determined only in water. Second, all gas-phase acidities, by their very nature, are for the direct ionization process depicted in the top equation of Scheme 1 and do not require any consideration for ion-pairing or other aggregation effects. Third, the control accessible to modern gas-phase ion chemistry techniques allows nearly equal ability to measure absolute acidities of two or more different types of protons in the same molecule, a process more difficult to address in the condensed-phase.

Recent determinations of the gas-phase acidity of the α-C–H of acetic acid[14,15] and the pK_a of ethyl acetate as a carbon acid in aqueous solution[16] can now be combined with other calorimetric data from the literature, as described below, to provide a direct evaluation of the aqueous phase pK_a of the less acidic proton in acetic acid. Inspection of Scheme 1 provides the necessary equation with which to evaluate the aqueous-phase ionization energy of acetic acid as a carbon acid,

$\Delta G^{aq}_{acid}\{CH_3CO_2H\}$ [eqn. (1)]. (All thermochemical values are summarized in Table 1.)

$$\Delta G^{aq}_{acid}\{CH_3CO_2H\} = \Delta G^{g}_{acid}\{CH_3CO_2H\} - \Delta G^{g \to aq}_{solv}\{CH_3CO_2H\} + \Delta G^{g \to aq}_{solv}\{H^+\} + \Delta G^{g \to aq}_{solv}\{H_2C=C(O^-)OH\} \quad (1)$$

Several years ago we discovered that gas-phase deprotonation of acetic acid by hydroxide and other bases led to competitive proton abstraction from the O and C sites;[14] bracketing studies in both directions led to the determination that $\Delta G^{g}_{acid}\{CH_3CO_2H\} = 361.2$ kcal mol^{-1} (1 cal = 4.184 J). Additional proton abstraction studies of the monoenolate anion of acetic acid prepared by a fluorodesilylation reaction are entirely consistent with this value.[15]

Free energies of hydration of many neutrals are available in the literature[17–19] and simple unknown values can be estimated to within an accuracy of better than 0.25 kcal mol^{-1}.[19] For acetic acid, $\Delta G^{g \to aq}_{solv}\{CH_3CO_2H\}$ is -6.70 kcal mol^{-1}, an experimental value reproduced to within 0.1 kcal mol^{-1} by group contributions.[19]

Prior uses of the thermochemical cycle in Scheme 1 have variously considered the free energy of hydration of the proton[20,21] to be well established,[22] at -259.5 kcal mol^{-1}, as well as the 'object of much dispute',[8] at -262.4 kcal mol^{-1}. While this value is critical for determining absolute energies of solvation for anions, as previously demonstrated, it is completely unimportant herein because the value appears in eqn. (1) and in estimating $\Delta G^{g \to aq}_{solv}\{H_2C=C(O^-)OH\}$ and therefore cancels. Thus, while the value used by Wilson and co-workers[8] is adopted for Table 1, it is important to recognize that changing this solvation energy will have no effect on the pK_a that is derived.

To date, the major hindrance in using Scheme 1 to estimate pK_a values has been the lack of reliable anion hydration energies; this is the situation for the monoenolate anion of acetic acid. Scheme 1, therefore, is most commonly used when both gas and aqueous-phase acidities are known, to derive ion energies of hydration.[8,10,22] By using Scheme 1 to determine the free energy of hydration of the enolate anion for methyl acetate, and using this value to estimate the energy of hydration of the monoenolate anion of acetic acid, one can overcome two problems at once: namely, the uncertainty in the absolute hydration energy of the proton and the unknown hydration energy of the monoenolate anion of acetic acid.

Rearranging eqn. (1) for methyl acetate and to determine an anion hydration energy, requires: p$K_a\{CH_3CO_2CH_3\} = 25.6$ (assumed to be identical to ethyl acetate[16]) or $\Delta G^{aq}_{acid}\{CH_3CO_2CH_3\} = 34.9$ kcal mol^{-1};
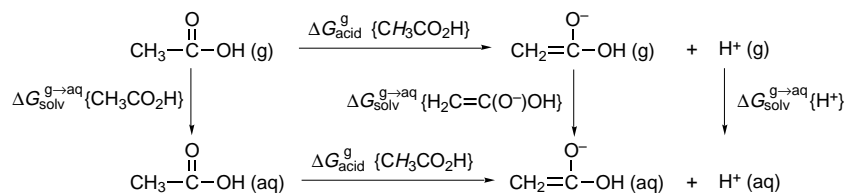
Scheme 1

$\Delta G^{\mathrm{g}}_{\mathrm{acid}}\{CH_3CO_2CH_3\}$ = 365.1 kcal mol^{-1} and[13] $\Delta G^{\mathrm{g}\rightarrow\mathrm{aq}}_{\mathrm{solv}}\{CH_3CO_2CH_3\}$ = -3.32 kcal mol^{-1}.[19] Combining these values with the hydration energy of the proton provides $\Delta G^{\mathrm{g}\rightarrow\mathrm{aq}}_{\mathrm{solv}}\{H_2C=C(O^-)OCH_3\}$ = -71.1 kcal mol^{-1}. If we assume the hydration energy of the monoenolate anion of acetic acid is equal to that of the enolate anion of methyl acetate plus a correction term for the mutation of a methyl group into a hydrogen, then the hydration energy of the proton drops out of consideration for the p$K_a\{CH_3CO_2H\}$ determination.

The remaining question concerns the correction term. Inspection of Table 1 reveals that CH_3CO_2H has a more negative solvation free energy than $CH_3CO_2CH_3$ by 3.4 kcal mol^{-1}. Likewise, literature data[19] for propanoic acid *vs.* methyl propanoate, butanoic acid *vs.* methyl butanoate and methanol *vs.* dimethyl ether shows that mutating a methyl into a hydrogen enhances solvation free energy in each case by 3.42 $\pm$ 0.15 kcal mol^{-1}. Using this value as the correction term therefore allows us to predict $\Delta G^{\mathrm{g}\rightarrow\mathrm{aq}}_{\mathrm{solv}}\{H_2C=C(O^-)OH\}$ = -74.54 kcal mol^{-1}. Using this latter value, the aqueous C–H acidity of acetic acid thus derived (Scheme 1, Table 1) is p$K_a\{CH_3CO_2H\}$ = 22.7. More complex corrections might have been required if the monoenolate anion of acetic acid possessed an internal hydrogen bond in the gas-phase. However, high level *ab initio* calculations clearly demonstrate the lack of such an interaction.[15,23]

A consideration of the approach used to derive the pK_a shows that the error in the derived value is determined by the error in four terms. Relative gas-phase acidities are good to better[24] than 1.0 kcal mol^{-1} while relative solvation energies have an estimated error of 0.1 kcal mol^{-1}. The stated error for the pK_a of ethyl acetate is 0.5 pK_a units ($\pm$ 0.7 kcal mol^{-1}) and little extra error will result from the assumption of equivalent pK_a values for methyl and ethyl acetates. The standard deviation for the four sets of literature examples used to derive an average $\delta\Delta G^{\mathrm{g}\rightarrow\mathrm{aq}}_{\mathrm{solv}}$ for mutation of a methyl group into a hydrogen is 0.15 kcal mol^{-1}. Thus the best estimate is p$K_a\{CH_3CO_2H\}$ = 22.7 $\pm$ 1.0.

The pK_a value derived here is entirely consistent with the oft-cited value of 24 that is obtained from an extrapolation of a correlation of ionization rate to pK_as[25] and may be compared to the p$K_a\{CH_3COCH_3\}$[26] = 19.27, p$K_a\{\alpha$-hydroxy-α-phenyl-acetic acid$\}$[7] = 22 and p$K_a\{CH_3COSCH_2CH_3\}$[27] = 21.0. Combination of p$K_a\{CH_3CO_2H\}$ = 22.7 with pK_E = 19.4 (where K_E is the equilibrium constant for formation of the enol

from the keto tautomer)[28–30] leads to the prediction that p$K_a\{H_2C=C(OH)_2\}$ = 3.3 ($\pm$1.0).[16]

In summary, an approach has been outlined that allows one to determine pK_a values in aqueous solution by hydrating the reaction for the corresponding gas-phase value. This approach is limited by the availability and accuracy of the necessary thermochemical values. Even the simplest 'thermochemical literature history' reveals a constant refinement and improvement in accuracy as time and experimental methodologies progress. All values used in this work are, therefore, summarized in Table 1. In the event that one of the values used to derive this pK_a is refined in the future, one simply needs to replace that value in Table 1 and thereby derive the new and presumably more accurate pK_a. For comparison, the hydration energy of acetate ion and acetone enolate are also included in Table 1; these values were obtained using a method analogous to that in Scheme 1.

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Table 1 Free energies and pK_as (at 298 K) used and derived in this work^a

	$CH_3CO_2CH_3$	CH_3CO_2H	CH_3COCH_3	CH_3CO_2H
Gas-phase acid data^b	365.1	361.2^c	361.9	341.5
Neutral solvation data^d	-3.32	-6.70	-3.85	-6.70
H$^+$ Solvation data^e	-262.4	-262.4	-262.4	-262.4
Aqueous acidity data				
pK_a	25.6^f	22.7^g	19.27^i	4.76
$\Delta G^{\mathrm{aq}}_{\mathrm{acid}}$	34.91^g	31.0^b	26.28^g	6.49^g
Anion solvation data	-71.12^{h}	-74.52^{i}	-77.09^{h}	-79.3^{h}

^{a} All values except pK_a's are in kcal mol^{-1}. ^{b} All gas-phase acidities are obtained from ref. 13 unless noted. ^{c} Ref. 14. ^{d} All neutral free energies of hydration are obtained from ref. 19. ^{e} Derived from the ΔH and ΔS values cited in ref. 8. Note that while this value is crucial for deriving absolute solvation energies using gas- and aqueous-phase acidities, the pK_a derived for the methyl position of acetic acid is insensitive to this value as discussed in the text. ^{f} Assumed to the same as ethyl acetate and obtained from ref. 16. ^{g} Derived from $\Delta G = -RT\ln K_a$. ^{h} Derived from the other values in this Table and a consideration of Scheme 1. ^{i} Ref. 24. ^{j} See text.