

Quantum mechanics investigation of acid dissociation constant of carboxylic acids in aqueous solution

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ABSTRACT

According to the Bronsted definition, any compound which has a hydrogen atom is an acid, since it may be lost as a proton. A thermodynamical cycle is proposed to calculate absolute pK_a values for Bronsted acids in aqueous solution. The equilibrium of dissociation of a Bronsted acid depends on the interaction of the acid and its conjugate base with solvent molecules. Therefore the pK_a value depends on the solvent medium. The polarizable continuum model (PCM) was used to describe the solvent, and absolute pK_a values were computed for different compounds: HCOOH, CH₃COOH, C₆H₅COOH, FCH₂COOH and CH₃CH₂COOH. The model of furnishes pK_a values was in good agreement with the experimental results for some classes of compounds. The quantum Mechanics (QM) calculations were carried out with the GAUSSIAN 98 program based on HF/6-31+G** level.

Keywords: pK_a ; Acid dissociation constants; Free energy; Gas phase; Solution; Thermodynamic cycles; Deprotonation

INTRODUCTION

Acid dissociation constants, also known as pK_a values, are essential for understanding many fundamental reactions in chemistry and biochemistry. Oftentimes pK_a values can be measured quite easily experimentally; however, many times chemists are interested in the pK_a values of molecules that have not been synthesized or for which experiments are not straightforward. For instance, amino acids, a part of a polypeptide chain, have pK_a values that vary based on their local environment, which are difficult to determine. Therefore, the ability to computationally calculate these pK_a values accurately is important for scientific

advancements in biochemistry and other fields.

Methods other than thermodynamic cycles are often used to calculate acid dissociation constants. Previous publications implement the theoretical relationship between pK_a and structural property [1], bond valence methods and bond lengths [2], pK_a correlations with highest occupied molecular orbital (HOMO) energies and frontier molecular orbitals [3], and artificial neural networks [4] to predict pK_a values. In addition much work has been done using physical properties as quantitative structure-activity relationship (QSAR) descriptors, and regression equations with such descriptors to yield accurate pK_a values for specific classes of molecules [5-16].

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Therefore, in this work we will focus on the use of various thermodynamic cycles in the calculation of acid dissociation constants.

The gas-phase free energy calculation is the lowest source of error in pK_a calculations. With today's computers and focusing on small molecules, CCSD (T) calculations extrapolated to the complete basis set limit can give gas-phase free energies as accurate as the experiment. The problem, however, is producing accurate results without using such computationally expensive levels of theory [17]. Combinations of different methods, such as model chemistries, density functional theories (DFTs), and ab initio theories, and different basis sets have been used in an attempt to achieve an accurate but less computationally demanding method. The largest source of error in pK_a calculations is the change in free energy of solvation calculation for the reaction, which is based on the type of solvation model used and the specific level of theory [18-21]. The basic problem is that experimental free energies of solvation for ions have error bars of roughly 2–5 kcal/mol, and so models that have been developed to reproduce experimental values have the same inherent uncertainty. It is not possible to improve a particular solvation model by simply increasing the basis set, as one can when calculating ab initio quantum mechanical gasphase values.

Explicit solvation methods include the addition of solvent molecules directly in the calculation. This method is advantageous because specific solute–solvent interactions are taken into account. These multiple interactions, however, make it more difficult to find a global minimum for the complex [22, 23]. The number of necessary solvent molecules included in the reaction also comes into question, leading to the problem of balancing accuracy with computational expense. In addition, conformational effects can be daunting; it is difficult to know how many different ion–water configurations

are necessary to get a conformationally averaged result.

COMPUTATIONAL DETAILS

An acid dissociation constant, K_a is a quantitative measure of the strength of an acid in solution. It is the equilibrium constant for a chemical reaction known as dissociation in the context of acid-base reactions. The equilibrium can be written symbolically as:



where HA is a generic acid that dissociates by splitting into A^- , known as the conjugate base of the acid, and the hydrogen ion or proton, H^+ , which, in the case of aqueous solutions, exists as a solvated hydronium ion. The dissociation constant is usually written as a quotient of the equilibrium concentrations (in mol/L), denoted by $[HA]$, $[A^-]$ and $[H^+]$:

$$K_a = \frac{[A^-][H^+]}{[HA]} \quad (2)$$

Due to the many orders of magnitude spanned by K_a values, a logarithmic measure of the acid dissociation constant is more commonly used in practice. The logarithmic constant, pK_a , which is equal to $-\log_{10} K_a$, is sometimes also (but incorrectly) referred to as an acid dissociation constant:

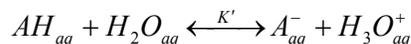
$$pK_a = -\log_{10} K_a \quad (3)$$

Equilibrium constant is related to the standard Gibbs energy change (ΔG_g°) for the reaction, so for an acid dissociation constant:

$$\Delta G_g^\circ = -2.303RT \log K$$

$$\text{Or } \Delta G_g^\circ = 2.303RT \log pK_a^{gas}$$

The equivalent process in aqueous solution may be written as:



with

$$K' = \frac{[A_{aq}^-][H_3O_{aq}^+]}{[AH_{aq}][H_2O_{aq}]} \quad (4)$$

Since all of the H_3O^+ species in this model come from H^+ solvated by one water molecule ($[H_3O_{aq}^+] = [H_{aq}^+]$), K is related to K' by the equation

$$K' = \frac{K}{[H_2O_{aq}]} \quad (5)$$

Thus, the relationship between the Gibbs standard free energy changes (ΔG°) and pK_a in aqueous solution, becomes:

$$\Delta G^\circ = -2.303RT \log \left(\frac{K}{[H_2O_{aq}]} \right) \quad (6)$$

If R and T are taken equal 1.98 cal/mol.K and 298.15 K respectively:

$$\Delta G^\circ (kcal/mol) = 1.36 pK_a + 2.36 \quad (7)$$

To make use of eq (7), it is necessary to calculate a thermodynamical quantity, the Gibbs standard free energy changes (ΔG°). But since ΔG° is a state property. It is completely determined by the initial and final states of the system and is independent of the path connecting them. In another words, it is almost always possible to propose a set of thermodynamical intermediate steps for the whole process, as long as the final and initial states are the same as the process being decomposed.

One of the many possible alternatives is the following Born-Haber thermodynamical cycle (TC), shown in Fig 1. From Fig 1, ΔG° is given by:

$$\Delta G^\circ = -\Delta G_{solv}(AH) + \Delta G_{vap}(H_2O) + \Delta G_{vac}^\circ + \Delta G_{solv}(A) + \Delta G_{solv}(H_3O^+) \quad (8)$$

where the ΔG_{vac}° is the standard Gibbs free energy change for the process in a vacuum, $\Delta G_{vap}(H_2O)$ is the Gibbs free energy change related to the vaporization process and ΔG_{solv} are the solvation energy quantities where computed from equation:

$$\Delta G_{solv} = G_{solv} - G_g \quad (9)$$

RESULTS AND DISCUSSION

The geometry of HCOOH, CH₃COOH, C₆H₅COOH, FCH₂COOH and CH₃CH₂COOH have been optimized at HF method with 6-31+G** basis set. The quantum Mechanics (QM) calculations were carried out with the GAUSSIAN 98 program [24]. Table 1 shows optimized energies of different carboxylic acids and its conjugate base in various phases.

The Gibbs free energy change of solvation and vaporization process, zero point energy and relaxation energy of different carboxylic acids and its conjugate base have been reported in Table 2, and Table 3 shows $\Delta E_{vac,0^\circ k}^\circ$, $\Delta ZPE_{vac,0^\circ k}^\circ$, ΔG_{vac}° , $\Delta E_{relax(tot)}$, ΔG_{tot}° values. Where $\Delta E_{vac,0^\circ k}^\circ$ is the variation in the internal energy at $T = 0$ K, $\Delta ZPE_{vac,0^\circ k}^\circ$ is the difference between the total zero point energy correction for the products and that of the reactants and ΔG_{vac}° is the standard Gibbs free energy change for the process in a vacuum. When we include the zero point energy (ZPE) and statistical mechanics contributions to the Gibbs free energy, we obtain accurate free energies for successive deprotonations of carboxylic acid in aqueous solutions.

Theoretical and experimental pK_a values have been reported in Table 4. The pK_a values calculated using Eq (7). For

halogenated acid the deviations can be attributed to neglecting the molecular motion contributions term.

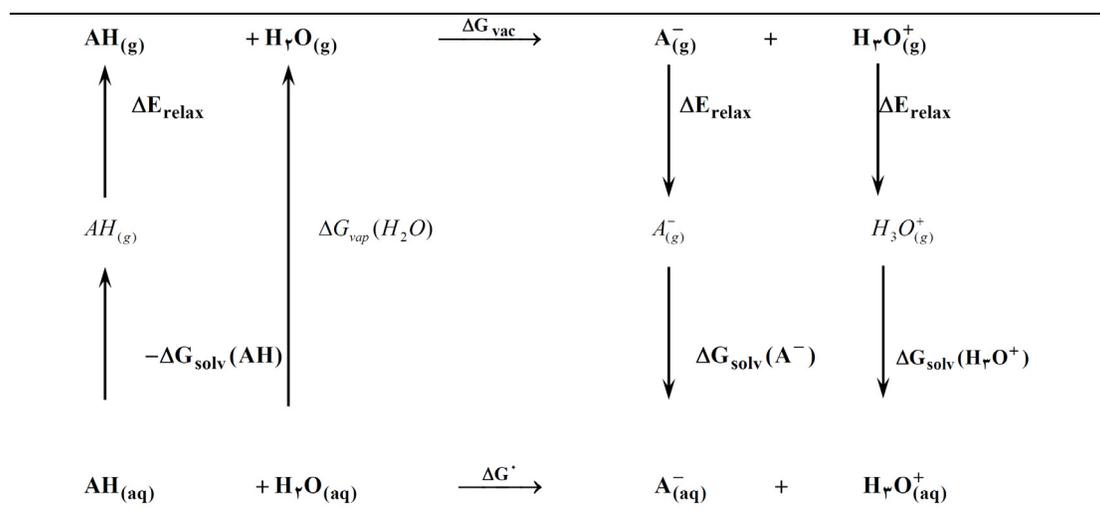


Fig. 1. A thermodynamical cycle is proposed to calculate absolute pK_a values for Bronsted acids in aqueous solution

Table 1. Optimized energies of different carboxylic acids and its conjugate base in various phases

Compound	Energy (Hartree)		
	Solution phase	Relaxation phase	Gas phase
	298.15 K	298.15 K	0 K
HCOOH	-188.7862851	-188.7679701	-188.7645659
HCOO ⁻	-188.3301261	-188.208823	-188.2063702
CH ₃ COOH	-227.8388949	-277.817207	-277.8144551
CH ₃ COO ⁻	-227.3749908	-227.2530036	-227.2509675
FCH ₂ COOH	-326.684734	-326.667705	-326.6680603
FCH ₂ COO ⁻	-326.2285742	-326.1145405	-326.1112758
C ₆ H ₅ COOH	-418.365042	-418.352182	-418.340602
C ₆ H ₅ COO ⁻	-417.896487	-417.787871	-417.7902435
CH ₃ C ₆ H ₄ COOH	-457.4058572	-457.3930009	-457.381404
CH ₃ C ₆ H ₄ COO ⁻	-456.9355268	-456.826398	-456.8288335
H ₂ O	-76.0454876		-76.303687
H ₃ O ⁺	-76.4826265	-76.3078511	-76.3099865

Table 2. The energy change of different carboxylic acids and its conjugate base

Compound	Energy (kcal/mol)			
	ZPE (kcal/mol) 0 K	ΔG_{solv}^0	ΔE_{relax}	ΔG_{vap}^0
HCOOH	21.2098211	11.4927737	-2.136167	
HCOO ⁻	12.802448819	-76.1188476	-1.539155	
CH ₃ COOH	39.21746122	13.609363	-4.86439	
CH ₃ COO ⁻	30.8897826	-76.5481268	-1.277672	
FCH ₂ COOH	34.9780070	10.68585	0.222954	
FCH ₂ COO ⁻	26.575027	-71.557230	-2.0486302	
C ₆ H ₅ COOH	77.71032	8.06977	-3.4465	
C ₆ H ₅ COO ⁻	68.73279	-68.15819	1.48876	
CH ₃ C ₆ H ₄ COOH	96.726365	8.06745	-4.139617	
CH ₃ C ₆ H ₄ COO ⁻	87.860479	-68.47935	1.528299	
H ₂ O	13.594365808			9.487253
H ₃ O ⁺	22.0525663585	-109.67297	1.339732	

Table 3. The standard energy change of different carboxylic acids and its conjugate base

Compound	Energy (kcal/mol)				
	$\Delta E_{vac,o^0k}^0$	$\Delta ZPE_{vac,o^0k}^0$	ΔG_{vac}^0	$\Delta E_{relax(tot)}$	ΔG_{tot}^0
HCOOH	174.80532	0.046665	174.85198	-2.33559	10.0402
CH ₃ COOH	178.1309335	0.11983232	178.2507658	-4.8023	15.1263
FCH ₂ COOH	173.92473	0.0506986	173.9754287	-0.48594	12.91833
C ₆ H ₅ COOH	169.8925	-0.476695	169.415805	-0.618	9.1416
CH ₃ C ₆ H ₄ COOH	171.2804	-0.37429	170.906	1.339732	10.308475

Table 4. Theoretical and experimental pK_a values

Compound	Energy (kcal/mol)	pK _a values	
	$\Delta G^0 + \Delta E_{relax}$	Theoretical	experimental
HCOOH	7.70461	3.92	3.77
CH ₃ COOH	10.32404	5.85	4.76
FCH ₂ COOH	12.432385	7.406	2.66
C ₆ H ₅ COOH	8.5235	4.53	4.82
CH ₃ C ₆ H ₄ COOH	9.036888	4.9	4.36

CONCLUSION

In this work HF level of theory at 6-31+G** basis set have been used to calculated pK_a

values. The model proposed in this work to calculate the Gibbs energies and pK_a values,

seems to be capable of predicting solute-solvent interactions. So the model proposed of calculations is likely to be useful in the prediction of pK_a values of other acids in aqueous solution. The model of furnishes pK_a values was in good agreement with the experimental results for some classes of compounds. But for halogenated acid the

deviations can be attributed to neglecting the molecular motion contributions term.

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