

Calculations of pK_a values of carboxylic acids in aqueous solution using density functional theory

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Abstract

With the specific aim of calculating the acidity equilibrium constant (K_a) of carboxylic acids in aqueous solution we investigated the solute–solvent interactions of these acids and their corresponding anions. The pK_a ($-\lg K_a$) values have been calculated using density functional theory (DFT). The polarized continuum model (PCM) is used to describe the solvent. Using these methods, we successfully predicted the pK_a s of 66 carboxylic acids in aqueous with the average error of 0.5 in pK_a units. Two different thermodynamic cycles have been studied. The theoretical values are in better agreement with the experimental results for those acids with moderate strength of acidity with the pK_a value higher than 3.

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1. Introduction

The pK_a of a compound is an important property in both the life sciences and chemistry, since the propensity of a compound to donate or accept a proton is fundamental to understanding many chemical and biochemical processes [1–3]. The pK_a value of a molecule also determines the amount of protonated and nonprotonated forms at a specific pH and shows the equilibrium state of the chemical system [4]. Depending on the extent of solvent interactions with the associated and dissociated forms, the equilibrium can be shifted toward the acid or the conjugate base side [5]. In biochemistry, the information about the pK_a values of ionizable groups in a protein is essential for understanding its functional mechanism at molecular level [6]. Many biological systems use proton-transfer reactions to perform communication between the extra cellular and intracellular media and the rate of the proton-transfer reaction depend, among many other factors, on the pK_a value of the species involved [5].

Not all chemical species such as reaction intermediates are readily amenable to experimental characterization [3]. Also, the experimental determination of acidity of a specific part of a large biological molecule such as a protein is not a straightforward task. Besides, in some cases where theoretical acidities showed deviation from experimental values, the experimental estimates were generally found to be associated with large uncertainties [7]. For these reasons and many others, there is widespread interest in developing methods to calculate acidity from theoretical approaches. The quantum chemical methods can provide reliable results for calculation of thermodynamic state functions such as Gibbs free energy. These methods can also provide reliable results for calculation of acidity of small molecules in the gas phase with equivalent or greater accuracy than that obtained experimentally [3]. However, due to the difficulty of calculating solvation energies, the situation is less satisfactory in solution. Nevertheless, the theoretical calculation of pK_a of acids in solution phase continues to arouse a considerable amount of interests and there has been a large number of papers published in this area [1–20]. For instance, calculation of Gibbs free energy and pK_a calculations can be found in papers which published by Shields

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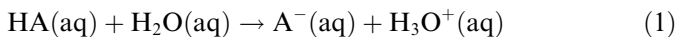
[18,19], Chipman [16], Yates [1,2] and Liu [3] and their coworkers.

We recently reported the calculated pK_a of a limited number of carboxylic acids (28) in aqueous solution [20,21]. The calculated pK_a values were obtained by employing ab initio calculations at the level of Hartree–Fock and density functional theories. The theoretical pK_a s were compared with the experimental values and the results were found to have small discrepancy for the majority of studied acids. Some questions have been raised: Is the presented theoretical model is sufficient for a larger number of carboxylic acids? Which type of carboxylic acids can present better results? Does different thermodynamic cycle present different results?

In the present article, these questions are under study by calculating the pK_a values of a larger number of carboxylic acids (66) in the aqueous phase by employing density functional theory at the level of B3LYP/6-31+G(d,p) [22]. In this article, besides the thermodynamic cycle presented in our previous papers [20,21], another cycle has been employed to calculate the pK_a values and a comparison has been made between results.

2. Methods and theoretical considerations

It is possible in principle to calculate pK_a value for dissociation of an acid using the change of free energy for the following reaction [3,18]:



$$\Delta G^\circ = -2.303RT \lg(K_a/[\text{H}_2\text{O}]) \quad (2)$$

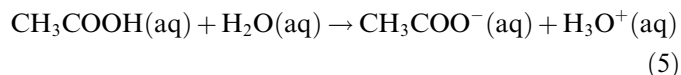
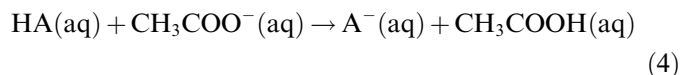
or

$$\Delta G^\circ (\text{kcal/mol}) = 1.36pK_a + 2.36 \quad (3)$$

where ΔG° here is the free energy change for the dissociation reaction at 298 K with standard state corresponding to a concentration of 1 mol/L. The values of 1.36 and 2.36 are $-2.303 RT$ and $2.303RT \lg(55.56)$, respectively. The free energy change for the dissociation reaction can be computed using gas phase free energies and solvation energies [16]. The gas phase Gibbs free energies are computed based on a standard state of one atmosphere. The internal electronic energies can be converted to Gibbs free energies by considering thermal corrections arising from translational, rotational and vibrational nuclear motions,

together with entropies and taking into account the calibrations [22]. Solvation energies can be calculated using a continuum model of solvation such as PCM [23]. Change of standard states for the gas phase ($P^\circ = 1 \text{ atm}$) and solution phase ($c^\circ = 1 \text{ mol} \cdot \text{L}^{-1}$) has been taken into account. In the present study, we have used two thermodynamic cycles (TC) in order to calculate pK_a values.

TC A: Thermodynamic cycle A, as shown in figure 1(A), is used to combine the isodesmic reaction (4) and the dissociation of acetic acid (5) as a reference molecule [20,21], for calculation of ΔG° for reaction (1):



The Gibbs free energy of dissociation reaction of acid HA in aqueous solution, ΔG° , can be written as a sum of changes of Gibbs free energy of reactions (4) and (5):

$$\Delta G^\circ = \Delta G_4^\circ + \Delta G_5^\circ \quad (6)$$

ΔG_5° can be obtained by equation (3) and considering the experimental value of pK_a , 4.76 [20]. Figure 1 shows two thermodynamical cycles proposed to calculate the ΔG_4° . From the cycle A, ΔG_4° is given by the following expression:

$$\Delta G_4^\circ = \Delta G_4^\circ (\text{gas}) + \Delta G_4^\circ (\text{solv})$$

in which $\Delta G_{4,\text{gas}}^\circ$ is the gas-phase Gibbs free energy of reaction (4) and $\Delta G_{4,\text{solv}}^\circ$ is the net solvation energy of reaction (4) and are defined as follows:

$$\Delta G_{4,\text{gas}}^\circ = \Delta G^\circ(\text{A}^-, \text{gas}) + \Delta G^\circ(\text{CH}_3\text{COOH}, \text{gas}) - \Delta G^\circ(\text{HA}, \text{gas}) - \Delta G^\circ(\text{CH}_3\text{COO}^-, \text{gas}) \quad (7)$$

$$\Delta G_{4,\text{solv}}^\circ = \Delta G^\circ(\text{A}^-, \text{solv}) + \Delta G^\circ(\text{CH}_3\text{COOH}, \text{solv}) - \Delta G^\circ(\text{HA}, \text{solv}) - \Delta G^\circ(\text{CH}_3\text{COO}^-, \text{solv}) \quad (8)$$

TC B: Thermodynamic cycle B as shown in figure 1 (B), presents a more direct method in order to calculate the Gibbs free energy of reaction (1). For the calculation of Gibbs free energy of this reaction, Gibbs free energies of H_2O and H_3O^+ in solution have been also calculated. The gas phase Gibbs free energies of H_2O and H_3O^+ have been calculated to be -76.43107 and -76.69160 in atomic units, Hartree. The solvation energies of H_2O and H_3O^+ have been obtained as -28.6 and -461.9 kJ/mol , respec-

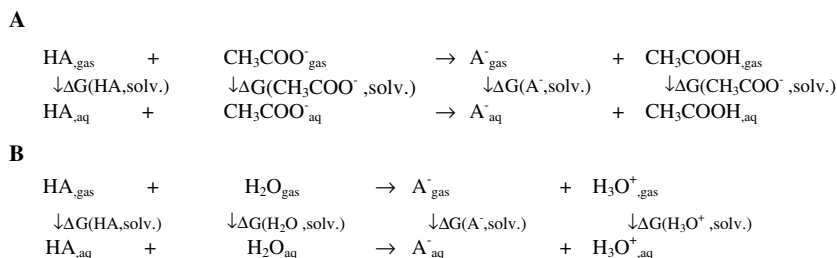


Fig. 1. (A) Thermodynamic cycle for the studied isodesmic reaction (TC A). (B) Thermodynamic cycle for the direct dissociation of acid (TC B).

tively. These energies are in agreement with those reported in a recent report [13] which were -6.77 and -106.61 kcal/mol (or -28.3 and -446.1 kJ/mol). Pliego and Riveros published the value of -110.4 kcal/mol (-461.9 kJ/mol) for free energy of solvation of H_3O^+ [24]. The latter is in more agreement with the value we calculated. Using these values together with the Gibbs free energies of HA_{aq} and its corresponding anion, A_{aq}^- , the total Gibbs free energy of the dissociation reaction (1) and therefore, the $\text{p}K_{\text{a}}$ values can be calculated (equation (2)).

The gas phase Gibbs free energies and solvation energies have been determined from the density functional theory at the level of B3LYP [22]. Solvation energies, $\Delta G_{\text{i,solv}}^\circ$, have been calculated using polarizable continuum model (PCM) [23]. By default, the PCM method builds up the cavity using an united atom (UA) model, i.e. by putting a sphere around each solute heavy atom. We have used UA0 radii (United Atom Topological Model). The electrostatic scaling factor of 1.2 by which the sphere radius is multiplied, has been used. The default value is 1.2 [25,26]. The Mulliken charges have been used for all calculations of solvation energies. In PCM model, the solvation energy is partitioned into two components: electrostatic energies (ΔG_{elec}) and non-electrostatic energies (ΔG_{nelec}). The cavity, dispersion and repulsion energies form non-electrostatic interactions between solute and solvent.

The diffuse basis set of 6-31+G(d,p), has been chosen since it is recommended for anions and molecules with lone pair electrons [25] and by considering the size and type of studied molecules. All of the structures were fully optimized without any symmetry limitation using B3LYP with 6-31+G(d,p) basis set. Gaussian 98 have been employed for all DFT calculations [26].

3. Results and discussion

We chose a large number of carboxylic acids whose experimental $\text{p}K_{\text{a}}$ values were available to us. Table 1 shows the list of studied acids in which a variety of substituted acids can be seen. The list consists of a wide range of acids with the $\text{p}K_{\text{a}}$ values in the range of 2.50 to 5.05. Inspecting substitutions and the experimental $\text{p}K_{\text{a}}$ values and also to be consistent with the other study [21], the studied acids have been partitioned into three classes. Class I: acids with $\text{p}K_{\text{a}}$ values higher than 4.00. There are 36 acids in this class. Among these acid, the weakest is $(\text{CH}_3)_3\text{CCOOH}$ with $\text{p}K_{\text{a}}$ value of 5.05 and the strongest acid is $\text{CH}_3\text{CHClCH}_2\text{COOH}$ with $\text{p}K_{\text{a}}$ value of 4.05. Class II: strong acids with $\text{p}K_{\text{a}}$ values between 3.00–4.00, consisting of acids with hydroxyl and methoxy groups as well as *ortho* and *para* halogenated phenyl. There are 22 acids, which has been classified in this group. Among these acid, the weakest is *p*- $\text{ClC}_6\text{H}_4\text{COOH}$ with $\text{p}K_{\text{a}}$ value of 3.99 and the strongest acid is *o*- $\text{ClC}_6\text{H}_4\text{OCH}_2\text{COOH}$ with $\text{p}K_{\text{a}}$ value of 3.05. Class III: strong acids with $\text{p}K_{\text{a}}$ values less than 3.00. One can see that the acids in this class have strong electron-withdrawing substitutions. There are eight acids in this class. We did not

study acids with $\text{p}K_{\text{a}}$ less than 2.50 in this work since our previous studies showed that there were large sources of errors for very strong acids such as strong inter hydrogen bonding and dimerization effects. The present solvation models have deficiency to take into account all different parts of solvation energies for such strong solute–solvent interactions.

Table 2 shows the calculated gas phase energy and solvation energy of each acid and its corresponding anion together with the standard Gibbs free energy of reaction (1), ΔG° . Comparison of the calculated solvation energies with the available experimental values shows that the PCM results are consistent with the experimental values, though they are slightly overestimated. For instance, the experimental solvation energies of acetic acid, propanoic acid and butanoic acid are -28.0 , -27.1 , -26.6 kJ/mol, respectively [28]. Calculated solvation energies of these acids, which are presented in table 2, are -29.7 , -28.7 and -25.6 kJ/mol. However, the trend of the calculated solvation energies is the same as the trend for the experimental values.

The standard Gibbs free energy of reaction (1), ΔG° , presented in table 2, have been obtained by two methods (two thermodynamic cycles) described earlier. By using these energies, one can calculate the $\text{p}K_{\text{a}}$ values according to equation (2). The theoretical values of $\text{p}K_{\text{a}}$ which are obtained by both methods together with the experimental values for comparison, have been shown in table 3. A comparison between the theoretical and experimental values reveals that there is small discrepancy between theory and experiment. For instance, for $(\text{CH}_3)_3\text{CCOOH}$, molecule 1, the experimental $\text{p}K_{\text{a}}$ is 5.05, the theoretical values which are obtained by methods 1 and 2 are 5.10 and 5.07, respectively. For all acids in class I, the average error which has been defined as mean absolute deviations (MAD) is only 0.42 in $\text{p}K_{\text{a}}$ unit for both cycles, which is very small compare with those results reported previously (for example see Ref. [5]). The theoretical values of $\text{p}K_{\text{a}}$ for acids in Class II are also consistent with the experimental values. For this class of acids, the average error is 0.44 for the cycle A and 0.45 for cycle B. Finally, for the strong acids with $\text{p}K_{\text{a}}$ less than 3, which are assigned in Class III, the theoretical $\text{p}K_{\text{a}}$ values are more deviated from the experimental results, although for some cases the theoretical values are good enough (see figure 2). For example, for *o*- $\text{ClC}_6\text{H}_4\text{COOH}$, the experimental $\text{p}K_{\text{a}}$ is 2.88 whereas the theoretical $\text{p}K_{\text{a}}$ s are 2.25 and 2.23 achieved by TC A and TC B, respectively. The average error for acids in this class is 0.86 and 0.88 for two cycles. The average error for all 66 acids studied in this work is the same and is only 0.48–0.49 for both methods. This average error can be considered to be small in comparison with those reported recently, for instance for those organic acids in DMSO solution, the precision of theoretical $\text{p}K_{\text{a}}$ was reported to be 1.7–1.8 $\text{p}K_{\text{a}}$ units [3]. The present results are also satisfactory compared to the results of Shields and his co-workers [4]. Table 4 summaries the mean absolute deviations and standard deviations of errors for the different studied classes and all 66 acids. Although these two methods present similar

TABLE 1

The wide range of carboxylic acids studied in this work and their experimental pK_a taken from reference [27]

No.		pK_a	No.		pK_a
<i>Class I</i>			<i>Class II</i>		
1	$(CH_3)_3CCOOH$	5.05	37	$p\text{-ClC}_6\text{H}_4\text{COOH}$	3.99
2	$trans\text{-CH}_3\text{CHCCH}_3\text{COOH}$	5.02	38	$\text{CH}_3\text{CHOHCOOH}$	3.87
3	$p\text{-NH}_2\text{C}_6\text{H}_4\text{COOH}$	4.92	39	$m\text{-BrC}_6\text{H}_4\text{COOH}$	3.86
4	$\text{C}_6\text{H}_5\text{COOH}$	4.90	40	HOCH_2COOH	3.83
5	$\text{CH}_3(\text{CH}_2)_5\text{COOH}$	4.89	41	$m\text{-ClC}_6\text{H}_4\text{COOH}$	3.82
6	$\text{CH}_3(\text{CH}_2)_8\text{COOH}$	4.89	42	$o\text{-C}_2\text{H}_5\text{C}_6\text{H}_4\text{COOH}$	3.77
7	$\text{CH}_3(\text{CH}_2)_4\text{COOH}$	4.88	43	$\text{HOCC}_6\text{H}_4\text{COOH}$	3.75
8	$\text{CH}_3\text{CH}_2\text{COOH}$	4.87	44	HCOOH	3.75
9	$(\text{CH}_3)_2\text{CHCOOH}$	4.86	45	$\text{C}_4\text{H}_9\text{OCH}_2\text{COOH}$	3.69
10	$m\text{-NH}_2\text{C}_6\text{H}_4\text{COOH}$	4.78	46	$\text{CH}_3\text{CHCH}_3\text{OCH}_2\text{COOH}$	3.69
11	CH_3COOH	4.76	47	$trans\text{-ClCHCHCOOH}$	3.65
12	$\text{C}_3\text{H}_7\text{COOH}$	4.76	48	$\text{C}_3\text{H}_7\text{OCH}_2\text{COOH}$	3.65
13	$\text{CH}_3\text{CHCHCOOH}$	4.69	49	$\text{C}_2\text{H}_5\text{COHCOOH}$	3.65
14	$p\text{-(CH}_3)_2\text{COC}_6\text{H}_4\text{COOH}$	4.68	50	$\text{C}_2\text{H}_5\text{OCH}_2\text{COOH}$	3.60
15	$\text{CH}_3\text{CHC}_6\text{H}_5\text{COOH}$	4.64	51	$\text{CH}_3\text{OCH}_2\text{COOH}$	3.54
16	$o\text{-ClC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{COOH}$	4.58	52	$m\text{-NO}_2\text{C}_6\text{H}_4\text{COOH}$	3.47
17	$p\text{-OHC}_6\text{H}_4\text{COOH}$	4.55	53	$\text{C}_6\text{H}_5\text{C}_6\text{H}_4\text{COOH}$	3.46
18	$p\text{-OC}_5\text{H}_{11}\text{C}_6\text{H}_4\text{COOH}$	4.55	54	$\text{C}_6\text{H}_5\text{COHCOOH}$	3.41
19	$p\text{-C}_4\text{H}_9\text{C}_6\text{H}_4\text{COOH}$	4.53	55	$p\text{-NO}_2\text{C}_6\text{H}_4\text{COOH}$	3.41
20	$\text{ClCH}_2\text{CH}_2\text{CH}_2\text{COOH}$	4.52	56	$\text{CHCCH}_2\text{COOH}$	3.32
21	$3,4\text{-(OH)}_2\text{C}_6\text{H}_3\text{COOH}$	4.48	57	$\text{C}_6\text{H}_5\text{OCH}_2\text{COOH}$	3.12
22	$p\text{-C}_3\text{H}_7\text{OC}_6\text{H}_4\text{COOH}$	4.46	58	$o\text{-ClC}_6\text{H}_4\text{OCH}_2\text{COOH}$	3.05
23	$p\text{-CH}_3\text{CH}_2\text{OC}_6\text{H}_4\text{COOH}$	4.45	<i>Class III</i>		
24	$trans\text{-C}_6\text{H}_5\text{CHCHCOOH}$	4.44	59	$o\text{-ClC}_6\text{H}_4\text{COOH}$	2.88
25	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COOH}$	4.37	60	$\text{CH}_3\text{CH}_2\text{ClCHCOOH}$	2.86
26	$p\text{-CH}_3\text{C}_6\text{H}_4\text{COOH}$	4.36	61	BrCH_2COOH	2.86
27	$p\text{-C}_2\text{H}_5\text{C}_6\text{H}_4\text{COOH}$	4.35	62	$o\text{-BrC}_6\text{H}_4\text{COOH}$	2.84
28	$\text{CH}_2\text{CHCH}_2\text{COOH}$	4.35	63	ClCH_2COOH	2.81
29	CH_2CHCOOH	4.26	64	$\text{CH}_3\text{CHClCOOH}$	2.80
30	$m\text{-C}_3\text{H}_7\text{OC}_6\text{H}_4\text{COOH}$	4.20	65	FCH_2COOH	2.66
31	$\text{C}_6\text{H}_5\text{COOH}$	4.20	66	$\text{CH}_3\text{COCOCH}_2\text{COOH}$	2.50
32	$\text{C}_7\text{H}_{10}\text{COOH}$	4.17			
33	$m\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4\text{COOH}$	4.17			
34	$p\text{-(CH}_3)_2\text{CHOC}_6\text{H}_4\text{COOH}$	4.15			
35	$\text{CH}_2\text{ClCH}_2\text{COOH}$	4.10			
36	$\text{CH}_3\text{CHClCH}_2\text{COOH}$	4.05			

results, there are some advantages and disadvantages for each method. The calculated pK_a based on TC A can be reliable since many inherent systematic errors in calculation of free energies will be cancelled in determination of the total change of Gibbs free energy of proton-transfer reaction. But, these results are reference-dependent. Naturally, the non-substituted acetic acid can be chosen as reference, however, one can change it in order to improve the results. TC B results are reference-independent since the water molecule is involved. Although this model is more compatible with experiment, the large uncertainty accompanied with Gibbs free energy of solvation of H_3O^+ can seriously affect the results [24,29].

In this study, we have showed that theoretical values for pK_a can be predicted with a relatively small error for those carboxylic acids, which are not very strong acid with the pK_a higher than 3.00. For strong acids with pK_a less than 3.00, extra care should be taken into account. We also found that both indirect and direct methods of calculations (two studied thermodynamic cycles) of pK_a studied in this

work, present similar results in terms of mean absolute deviations.

Calculating accurate pK_a values is demanding, there are at least four sources of error in pK_a calculations. The first is the thermodynamic cycles used to calculate the total Gibbs free energies [18]. By the thermodynamic cycles, total change of Gibbs free energies are calculated considering gas-phase Gibbs free energies and the Gibbs free energies of solvation. Obviously, different chemical constituents (such as H_3O^+ or H^+) appear in employed cycles. Therefore, different cycles produce different values of pK_a . The second error come from the gas-phase energies. Different level of theories employed by ab initio calculations result in different gas-phase energies. The highest level of theory and the largest basis set are not practical for very large acids and for a numerous studied molecules from the computational point of view. The third error appears when we use different models of solvation in order to calculate the Gibbs free energy of solvation of species. Several versions of PCM and SM5 models have been frequently used for

TABLE 2

Gas phase Gibbs free energies, $\Delta G_{i,\text{gas}}^\circ$, and solvation energies, $\Delta G_{i,\text{solv}}^\circ$, for each acid and its anion together with the Gibbs free energies of reaction (5), ΔG° , based on methods 1 and 2

No. ^a	$\Delta G_{i,\text{gas}}^\circ/\text{Hartree}^b$		$\Delta G_{i,\text{solv}}^\circ/(\text{kJ/mol})$		$\Delta G^\circ/(\text{kJ/mol})$	
	Acid	Anion	Acid	Anion	Method 1	Method 2
1	−346.94046	−346.39872	−25.5	−291.8	38.9	38.7
2	−345.73819	−345.19304	−25.6	−295.6	44.2	43.9
3	−476.11948	−475.57729	−49.9	−317.6	38.7	38.5
4	−424.33388	−423.78892	−27.7	−302.3	39.1	38.9
5	−425.52622	−424.98095	−23.4	−301.1	36.7	36.5
6	−543.40171	−542.85461	−19.7	−296.5	42.5	42.2
7	−386.23564	−385.69062	−23.4	−301.0	36.2	36.0
8	−268.36133	−267.81532	−28.7	−308.9	36.1	35.9
9	−307.65325	−307.10701	−15.9	−303.1	42.0	41.7
10	−476.11948	−475.57729	−49.9	−317.6	38.7	38.5
11	−229.07158	−228.52331	−29.7	−315.1	37.0	36.8
12	−307.65386	−307.10699	−25.6	−302.5	41.8	41.6
13	−306.44361	−305.89696	−28.4	−308.6	37.9	37.7
14	−613.86482	−613.32319	−37.1	−303.8	38.2	38.0
15	−499.34896	−498.81239	−38.5	−289.9	40.3	40.1
16	−958.95707	−958.41872	−38.0	−294.2	40.1	39.9
17	−495.99671	−495.45728	−52.6	−318.3	33.4	33.2
18	−692.44500	−691.90367	−33.4	−301.8	35.8	35.6
19	−653.15317	−652.61167	−32.6	−298.6	38.6	38.3
20	−767.25827	−766.72234	−35.5	−290.2	35.3	35.0
21	−571.21945	−570.68074	−68.9	−326.0	40.2	40.0
22	−613.86212	−613.32083	−34.8	−302.5	36.3	36.1
23	−574.57103	−574.02971	−40.7	−305.1	39.7	39.5
24	−498.15047	−497.61164	−37.2	−303.8	31.0	30.8
25	−499.34971	−498.81038	−41.9	−305.9	34.9	34.6
26	−460.06957	−459.52999	−29.0	−298.9	29.6	29.4
27	−499.35912	−498.81972	−29.0	−296.6	31.5	31.3
28	−306.43834	−305.89766	−30.0	−292.7	39.7	39.4
29	−267.14759	−266.60436	−24.2	−299.4	33.9	33.7
30	−613.85940	−613.32038	−36.3	−303.1	31.3	31.1
31	−420.77173	−420.23367	−36.7	−299.1	32.6	32.4
32	−574.37985	−573.84534	−27.1	−278.7	34.6	34.4
33	−574.56817	−574.02903	−39.7	−305.1	32.9	32.7
34	−613.86185	−613.32253	−34.8	−302.9	30.8	30.6
35	−727.96636	−727.43590	−33.9	−274.9	34.6	34.4
36	−767.25981	−766.72339	−33.6	−287.1	37.7	37.5
<i>Class II</i>						
37	−880.37750	−879.84712	−28.7	−276.7	27.3	27.1
38	−343.57851	−343.05041	−42.4	−281.1	30.7	30.5
39	−2991.9094	−2991.3805	−31.9	−273.1	30.4	30.1
40	−304.28241	−303.75426	−47.2	−285.6	31.1	30.9
41	−880.37660	−879.84732	−34.3	−272.9	33.8	33.6
42	−499.35072	−498.81541	−25.8	−280.7	33.4	33.2
43	−534.09286	−533.56880	−40.1	−267.1	31.8	31.6
44	−189.76581	−189.22453	−31.5	−309.2	26.2	26.0
45	−422.14771	−421.60521	−46.0	−321.0	32.2	31.9
46	−461.43744	−460.89338	−33.8	−319.2	25.9	25.7
47	−726.75363	−726.22278	−26.4	−274.5	28.6	28.4
48	−422.14602	−421.60241	−35.4	−319.8	25.7	25.5
49	−382.86941	−382.34215	−35.1	−272.0	30.2	30.0
50	−382.85290	−382.31102	−47.6	−325.3	27.9	27.7
51	−343.55559	−343.01413	−51.7	−324.7	31.5	31.3
52	−625.28026	−624.76049	−42.6	−262.5	27.6	27.4
53	−651.76916	−651.23395	−38.3	−297.9	28.4	28.2
54	−535.27092	−534.75533	−57.4	−269.1	24.9	24.6
55	−625.27982	−624.76282	−34.1	−245.2	29.2	29.0
56	−305.20120	−304.66756	−35.0	−284.8	34.1	33.9
57	−535.26315	−534.73172	−52.8	−306.4	24.5	24.3
58	−994.86479	−994.33556	−47.6	−295.1	24.8	24.6

(continued on next page)

TABLE 2 (continued)

No. ^a	$\Delta G_{f,\text{gas}}^\circ/\text{Hartree}^b$		$\Delta G_{f,\text{soln}}^\circ/(\text{kJ/mol})$		$\Delta G^\circ/(\text{kJ/mol})$	
	Acid	Anion	Acid	Anion	Method 1	Method 2
<i>Class III</i>						
59	−880.36782	−879.83521	−31.5	−290.0	22.8	22.5
60	−767.25219	−766.72341	−23.6	−274.6	20.3	20.1
61	−2800.1922	−2799.6642	−37.3	−285.5	21.1	20.8
62	−2991.9004	−2991.3701	−32.1	−279.2	27.9	27.7
63	−688.66718	−688.13944	−36.0	−281.7	22.7	22.5
64	−727.96159	−727.43262	−30.5	−280.0	22.1	21.9
65	−328.30662	−327.77553	−39.4	−300.0	16.6	16.4
66	−342.38555	−341.85432	−26.7	−287.3	17.0	16.8

^a See table 1 for the list of compounds.^b Energies are in atomic units, Hartree (1 Hartree = 627.5095 kcal/mol [25]).

TABLE 3

The theoretical $\text{p}K_{\text{a}}$ values based on two methods, which are described in the text along with the corresponding experimental values taken from reference [27]

No. ^a	$\text{p}K_{\text{a,calc}}$		$\text{p}K_{\text{a,exp.}}^d$	No.	$\text{p}K_{\text{a,calc}}$		$\text{p}K_{\text{a,exp.}}^d$
	TC A ^b	TC B ^c			TC A ^c	TC B ^b	
Class I				Class II			
1	5.10	5.07	5.05	37	3.06	3.03	3.99
2	6.01	5.99	5.02	38	3.65	3.62	3.87
3	5.06	5.03	4.92	39	3.59	3.56	3.86
4	5.12	5.09	4.90	40	3.72	3.69	3.83
5	4.71	4.68	4.89	41	4.20	4.17	3.82
6	5.72	5.69	4.89	42	4.12	4.09	3.77
7	4.62	4.59	4.88	43	3.84	3.82	3.75
8	4.60	4.57	4.87	44	2.87	2.84	3.75
9	5.63	5.60	4.86	45	3.91	3.88	3.69
10	5.06	5.03	4.78	46	2.81	2.79	3.69
11	4.76	4.73	4.76	47	3.28	3.25	3.65
12	5.60	5.57	4.76	48	2.78	2.75	3.65
13	4.92	4.89	4.69	49	3.56	3.54	3.65
14	4.97	4.94	4.68	50	3.16	3.13	3.60
15	5.33	5.30	4.64	51	3.79	3.76	3.54
16	5.31	5.28	4.58	52	3.11	3.08	3.47
17	4.12	4.10	4.55	53	3.25	3.22	3.46
18	4.54	4.51	4.55	54	2.62	2.60	3.41
19	5.03	5.00	4.53	55	3.38	3.35	3.41
20	4.45	4.42	4.52	56	4.25	4.22	3.32
21	5.32	5.29	4.48	57	2.56	2.53	3.12
22	4.63	4.60	4.46	58	2.61	2.58	3.05
23	5.24	5.21	4.45	Class III			
24	3.70	3.67	4.44	59	2.25	2.23	2.88
25	4.38	4.35	4.37	60	1.82	1.79	2.86
26	3.45	3.42	4.36	61	1.95	1.93	2.86
27	3.79	3.76	4.35	62	3.17	3.14	2.84
28	5.22	5.20	4.35	63	2.25	2.23	2.81
29	4.22	4.19	4.26	64	2.15	2.12	2.80
30	3.75	3.72	4.20	65	1.18	1.15	2.66
31	3.99	3.96	4.20	66	1.24	1.21	2.50
32	4.34	4.31	4.17				
33	4.04	4.01	4.17				
34	3.67	3.64	4.15				
35	4.33	4.31	4.10				
36	4.88	4.85	4.05				

^a See table 1 for the list of acids.^b Calculated values based on *Thermodynamic Cycle A* as shown in figure 1(A).^c Calculated values based on *Thermodynamic Cycle B* as shown in figure 1(B).^d The experimental values have taken from reference [27].

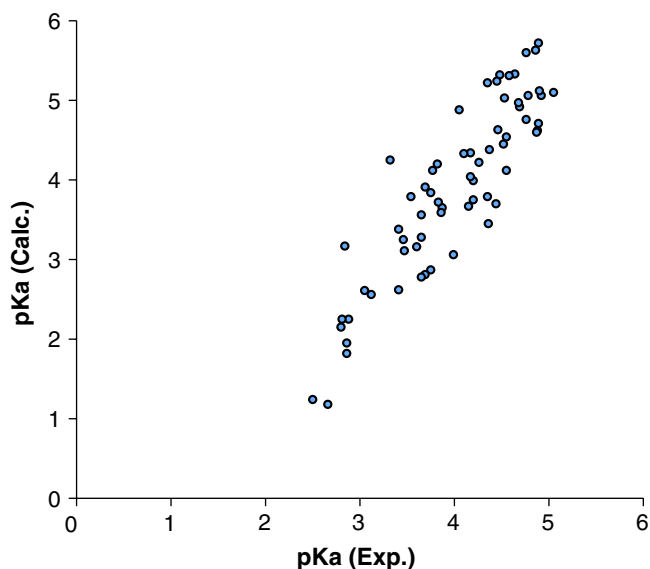


Fig. 2. The calculated pK_a values (by TC A) vs. experimental values for the studied acids. The R^2 value is 0.81. The thermodynamic cycle B (TC B) will present similar graph.

TABLE 4

Mean absolute deviations (MAD) of calculated pK_a values (for both thermodynamic cycles A and B) from the experimental data together with the standard deviations (STDEV) of errors for the three studied classes and all 66 acids in terms of pK_a units

	MAD		STDEV	
	TC A	TC B	TC A	TC B
Class I	0.42	0.42	0.32	0.31
Class II	0.44	0.45	0.30	0.31
Class III	0.86	0.88	0.39	0.40
Total	0.48	0.49	0.35	0.35

these calculations. This part of uncertainty is usually larger than for the gas-phase energies. Finally, the real chemistry of dissociation of acids should be taken into account. For example, some carboxylic acids are dimer in the gas phase and in solution phase, therefore the dimerism forms of the acid should be also considered.

4. Conclusions

In the present work, density functional theory at the level of B3LYP with the use of a diffuse basis set, has been employed in order to calculate the Gibbs energies and pK_a values for a large number of carboxylic acids. The average discrepancy between theory and experiment (MAD) was 0.5 in pK_a unit for whole acids whereas for acids with the moderate strength of acidity, the average error is even smaller (0.42 in pK_a unit depends on the class of acids and the employed methods). The proposed methods of calculations are likely to be useful in the prediction of pK_a values of other acids in aqueous solution. The inclusion of solvation energies, calculated by PCM model of solvation,

significantly improves the results and shows the capability of the model in prediction of solute–solvent interactions for molecules with low acidity in solution.

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