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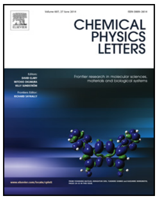

Acidity constants and its dependence on solvent selection from first-principles calculations using cluster-continuum models

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ABSTRACT

Dissociation constants of selected carboxylic acids in aqueous and organic solvents were calculated at quantum chemical level. We considered cases in which trace quantities of water may be present, as well as cases in which water was entirely absent. In the latter cases, alternative proton acceptors need to be considered. For aqueous solvent, short-range solvation effects are considered by adding explicit water molecules as the first solvent shell. In the absence of water, corresponding organic solvents are used directly as the proton acceptors and the resulted pK_a are quite comparable to those obtained from previous case of aqueous solvent.

1. Introduction

The strength of an acid in solution is quantified by its tendency to dissociate into constituent ions, which is in general measured by the logarithm of the acid dissociation constant, pK_a. This is usually expressed relative to the parent acid's behavior in aqueous solution, but the question emerges as to its capability to be applied to other solvents. The acidity of chemical compounds is a prerequisite in understanding many fundamental phenomena in chemistry, biological science and medicine, and the knowledge of this thermodynamic property finds applications in control of many industrial processes, including chemical and pharmaceutical manufactures [1,2]. The dissociation constants of carboxylic acids in aqueous solution can be experimentally obtained by measurements of conductance [3,4], calorimetry [5], potentiometry [6–9] and spectroscopy [10]. In some cases, the experimental methods can be restricted, for instance, to a certain range of temperatures, pH and pK_a. These measurements are also complicated when substance's solubility in solution is low or when the surrounding environment is complex [1,11,12].

The pK_a of a given acid can be usefully calculated using a quantum chemical method. Many studies on dissociation constants of organic compound in solution have been recently reported [1,13–21]. Computational techniques and methods have been recently reviewed and it was shown that the accuracy of obtained pK_a values could be highly subjected to the choice of thermodynamic cycles and solvation models, including direct methods, proton exchange scheme, cluster-continuum model and implicit–explicit models [22–24]. The equilibrium of acid dissociation into a proton and the associated conjugated base can be simply described in the following equation:

$$HA \rightarrow H^+ + A^- \tag{1}$$

The equilibrium constant of the acid dissociation process, K_a, is defined as:

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

The pK_a is then obtained by

$$pK_a = -\log_{10} K_a \tag{3}$$

where HA denotes the parent acid, A^- is the conjugate base and H^+ is the proton. Several authors have directly employed this thermodynamic cycle in their theoretical investigations [11,15,16]. The limitation of this approach is that solvation energy of a free proton is not a calculable quantity quantum chemically, since it has no electrons. The commonly used workaround is to use the experimentally derived absolute solvation free energy of the proton. Although this process has been shown to work well for acids in aqueous solution, it is clearly inappropriate for other solvents since the solvation free energy will not commonly be available. A more often and recently used approach suggests to recast the dissociation process to involve an explicit water molecule. The proton is now represented by the hydronium ion, H_3O^+:

$$HA + H_2O \rightarrow H_3O^+ + A^- \tag{4}$$

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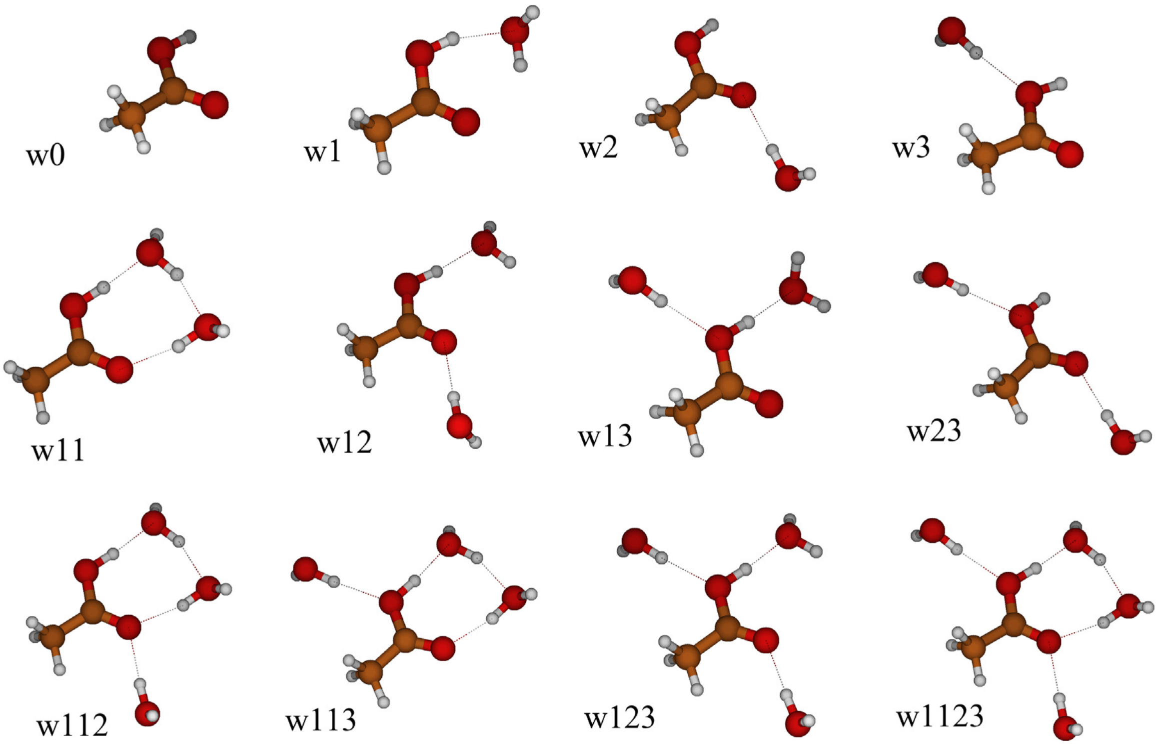

Figure 1. Optimized structures of hydrated acetic acid clusters in aqueous solution, performed using the B3LYP/PCM/6-31+G(d,p) method.

the appropriate equilibrium constant is:

$$K' = \frac{[H_3O^+][A^-]}{[HA][H_2O]} \tag{5}$$

where we can relate this to K_a by

$$K' = \frac{K_a}{[H_2O]} \tag{6}$$

Clearly this model may work when water is the proton acceptor species, and, in many non-aqueous solvents, there is likely to exist some trace amount of water, at the part-per-million (ppm) level, for instance. In such cases, Eq. (6) could be usefully applied. In fact, numerous first-principles studies of deprotonation of organic and biochemical compounds in nonaqueous solutions were already presented [25–28]. The authors either used the direct thermodynamic cycle, as presented in Eq. (1), or used the supermolecule approach, in which a well-known compound is used as the reference for the pK_a estimation of the desired compound. The continuum model was then incorporated to account for the solvation effect from nonaqueous solvents implicitly. In this work, however, we consider the capability for other species (nonaqueous solvents) to accept proton, in the absence of water. Although a diversity of possible proton-accepting contaminants may exist, we herein constrain ourselves to consider the possibility for proton complexation by a variety of neat solvent molecules, including heptane, carbontetrachloride, benzene, chloroform, dichloroethane and acetone. This investigation spans a range of alkane, aromatic and halogenated solvents at the low end of dielectric constants (below 20). In such study we consider two possibilities. In the first case, the hydrogen cation binds to some number n solvent molecules. When we investigated these cases, we found that the proton in fact chemically adds to hydrocarbons to form carbocation:

$$RCOOH + nR' \rightarrow H^+[R']_n + RCOO^- \tag{7}$$

$$K_{a,solv} = \frac{[H^+][RCOO^-]}{RCOOH} \tag{8}$$

In other cases, the H^+ can bind to a basic functional group (B) in the solvent molecule, resulting in the elimination of BH and the formation of a carbocation via the reaction:

$$RCOOH + B\cdots R' \rightarrow BH + R' + RCOO^- \tag{9}$$

$$K_{a,solv} = \frac{[BH][R'^+][RCOO^-]}{[RCOOH]} \tag{10}$$

One of the less computationally expensive methods to account for the effect of the surrounding solvent medium, beyond such reaction centers, is by using the continuum model. This method is widely used by computational community due to its simplicity and broad physical meaning that allows the treatment of basic chemical properties in liquid phase, especially for neutral species [29]. However, the homogeneous continuum, while introduces an average effect induced by solvent medium (representing by internal properties such as dielectric constant and thermal expansion), does not capture all the details of the individual bonding interactions between solute and solvent molecules. This is even more challenging when dealing with ionic species due to its strong electrostatic interaction with the environment. As an attempt to overcome this drawback, several authors recently showed that the pK_a calculation could be improved by using a so-called cluster-continuum model [12,14,18,19]. In this extended method, the use of explicit solvent molecules is combined with surrounding continuum to account for the bulk solvent effects on dissociation products.

Some success has been obtained for pK_a calculations at normal conditions, utilizing all the techniques mentioned above. However, many industrial processes are carried out in environments other than aqueous. In this work, we report our attempt on theoretical calculations of dissociation constants for carboxylic acids in both aqueous solution and organic solvents. Section 2 will detail the theoretical and computational background, followed by our results and discussions in Section 3.