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Calculation of the pK$_a$ of 1-(*o*-Hydroxyphenyl) Imidazole Carboxylic Esters Using the *ab initio*, DFT and PCM–UAHF models

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The acidity of different classes of imidazole esters in aqueous solution has been calculated. The calculation are carried out at SCF and B3LYP level with inclusion of entropic and thermo chemical correction to yield free energies of dissociation, using the basis sets 6-31G** and the recently parameterized continuum-solvation method PCM-UAHF for the solvation contribution. The model furnishes pK$_a$ values in relatively in good agreement with experimental data. Scaling different parts of solvation energies provides a significant improvement in results and signifies the importance of balance of individual contributions from electrostatic, cavity, dispersion and repulsion interactions.

Key Words: pK$_a$, Acidity, 1-(*o*-Hydroxyphenyl) imidazole carboxylic esters, Solvation energy, Polarized continuum model, *Ab initio*, DFT.

INTRODUCTION

The acidity of compounds in solution phase is also of interest since many reactions occur practically and experimentally in solution phase. Many biological systems use proton-transfer reactions to perform communication between the extra cellular and intra cellular media and rate of these reactions depends on degree of dissociation of species[1]. Determination of pK$_a$ values is of special interest to many chemists in all branches of chemistry and life sciences[2,3].The structure and ionization of hydroxy acid derivatives has been the subject of several theory investigations[4-6]. As part of a research program aimed at investigating the stereochemical characteristics of 1-(*o*-hydroxyphenyl) imidazole carboxylic esters of biological importance, we recently investigated the structure and dipole moment in 1-(*o*-hydroxyphenyl)imidazole carboxylic esters solvents[7]. Considering that knowledge of the acid dissociation constants (pK$_a$) becomes essential for the development of new compounds with biological activity[8-14]. There are a number of ways that pK$_a$ values can be estimated, included by direct calculation *via* quantum mechanical simulations. There are reasons for taking a more empirical approach to the problem. For example, while some efforts for direct calculation of pK$_a$ values for small acid molecule *via* quantum mechanical methods have been reasonably successful.

The basic idea of the method is that the free energy of an acid dissociation reaction can be broken down as follows:

$$\Delta G_a^0 = \Delta G_{int}^0 + \Delta G_{elec}^0 = \Delta G_{chem}^0 + \Delta G_{elec}^{0*} + \Delta G_{elec}^0$$

where ΔG_{elec}^0 is the electrostatic work of proton removal from a charged surface or particle with an idealized geometry and ΔG_{int}^0 is the intrinsic energy of proton removal, meaning the free energy contribution of everything other than the idealized electrostatic work term. Further, ΔG_{int}^0 can be divided between ΔG_{chem}^0, which is the energy of bond-making and bond-breaking and ΔG_{elec}^{0*}, which represents the electrostatic work of proton removal not accounted for by the geometrically over simplified electrostatic treatment used to obtain ΔG_{elec}^0. We assert that ΔG_{chem}^0 can be predicted *via* a valence-based parameter, and ΔG_{elec}^{0*} can be predicted from the iconicity of (Me-O) bonds and the overall molecular shape involved. Together, these can be used to predict pKa values.

In this paper, the overlapping pK_a values of resorcinol in water is determined. Moreover, with the objective of explaining the pK_a values obtained, the molecular conformations and solute-solvent interactions of the resorcinate anions, by means of *ab initio* and density functional (DFT) methods are investigated. In the present study, the pK_a values of the imidazole carboxylic esters in aqueous phase have been calculated by employing Hartree fock and density functional theory using the HF and B3LYP functional and a large basis set, 6-31G**.

EXPERIMENTAL

The dissociation of an acid AH in aqueous solution[15],

$$AH_{aq} + H_2O_{aq} \rightleftharpoons A_{aq}^- + H_3O_{aq}^+ \quad (1)$$

is governed by the equilibrium constant K, which is related to the dissociation constant K_a according to

$$K = \frac{[A_{aq}^-][H_3O^+]}{[AH_{aq}][H_2O_{aq}]} = \frac{K_a}{[H_2O_{aq}]} \quad (2)$$

(It is assumed that concentrations can be used instead of the activities).

The associated free energy change ΔG can be written for 1 M solutions at 298 K as

$$\Delta G_{(kcal/mol)} = -2.3\ RT \log K = 1.39\ pK_a + 2.36 \quad (3)$$

and correspondingly, the solution-phase dissociation constant pK_a is given by

$$pK_a = 0.735\ \Delta G - 1.735 \quad (4)$$

where ΔG is the standard change in the Gibbs free energy for the process in water at 298.15 K.

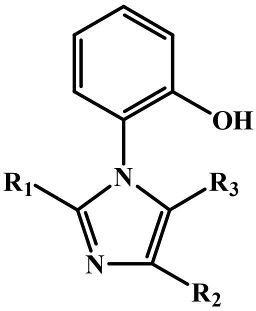
For the free energy of proton transfer in the gas phase, ΔG, computational models with high accuracy like the G2 model[16,17] and complete basis set (CBS)[18] approaches would be typical methods of choice. For practical reasons, the following simplified approach was selected. The *ab initio* calculations have been performed at the level of Hartree-Fock. The zero-point energies and thermal corrections together with entropies have been used to convert the internal energies to the Gibbs energies at 298.15 K. A medium-size basis set, 6-31(d,p) has been chosen by considering the size of studied molecules. Higher level of theory was not justified because of hardware limitations and the significant length of time of computations. GAUSSIAN98[19] have been employed for all *ab initio* calculations.

RESULTS AND DISCUSSION

The molecular structures of N-hydroxy phenyl-functionalized imidazole esters **1-3** derivative are shown in Fig. 1 and their acidity constants are represented in Table-1. As seen, the pK_a value[7] of this compound varies between 4.05-7.86.

TABLE-1
GIBBS FREE ENERGY OF EACH MOLECULE AND ITS ANION IN THE GAS AND AQUEOUS PHASE TOGETHER WITH CHANGE OF GIBBS ENERGY ΔG_{gas}, ΔG_{sol} IN THE GAS PHASE AND SOLVATION PHASE

Compd.	G_{gas} (a.u.)		G_{sol} (a.u.)		ΔG_{gas}	ΔG_{sol}
	Acid	Base	Acid	Base	kcal/mol	
HF/6-31G**						
A1	-756.025259	-755.655018	-756.296358	-755.845335	-0.3702	-0.4510
A2	-755.655018	-755.123502	-755.845335	-755.381090	-0.5315	-0.4642
B1	-756.056226	-755.689862	-756.331755	-755.884760	-0.3664	-0.4470
B2	-755.689862	-755.156231	-755.884760	-755.12949	-0.5336	-0.4718
C1	-794.641976	-794.673651	-794.930646	-794.890873	-0.0317	-0.0398
C2	-794.673651	-794.164508	-794.890873	-794.453682	-0.5091	-0.4372
D1	-529.448652	-529.078537	-529.688156	-529.227339	-0.3701	-0.4608
D2	-529.078537	-528.536733	-529.227339	-528.755089	-0.5418	-0.4723
B3LYP/6-31G**						
A1	-760.553492	-760.182670	-760.803431	-760.353055	-0.3708	-0.4504
A2	-760.182670	-759.661699	-760.353055	-759.894834	-0.5210	-0.4582
B1	-760.574357	-760.208438	-760.826899	-760.379058	-0.3659	-0.4478
B2	-760.208438	-759.684376	-760.379058	-759.918538	-0.5241	-0.4605
C1	-799.632021	-799.480911	-799.918281	-799.675369	-0.1511	-0.2429
C2	-799.480911	-798.969944	-799.675369	-799.232173	-0.5110	-0.4432
D1	-532.729540	-532.361803	-532.954577	-532.494580	-0.3677	-0.4600
D2	-532.361803	-531.829319	-532.494580	-532.030370	-0.5325	-0.4642



A: $R_1 = CO_2Me$, $R_2 = R_3 = H$ B: $R_1 = R_3 = H$, $R_2 = CO_2Me$
C: $R_1 = R_3 = H$, $R_2 = CO_2Et$ D: $R_1 = R_2 = R_3 = H$

Fig. 1. Structures of 1-(*o*-hydroxyphenyl)imidazole carboxylic esters

Two well distinguished steps can be observed, which have been correlated to the two dissociation events: between pH 5 and 7, is corresponded to dissociation of the imidazolium species (Fig. 2a) and between pH 7 and 9, is corresponded to transformation of the neutral phenol to the phenolate (Fig. 2b).

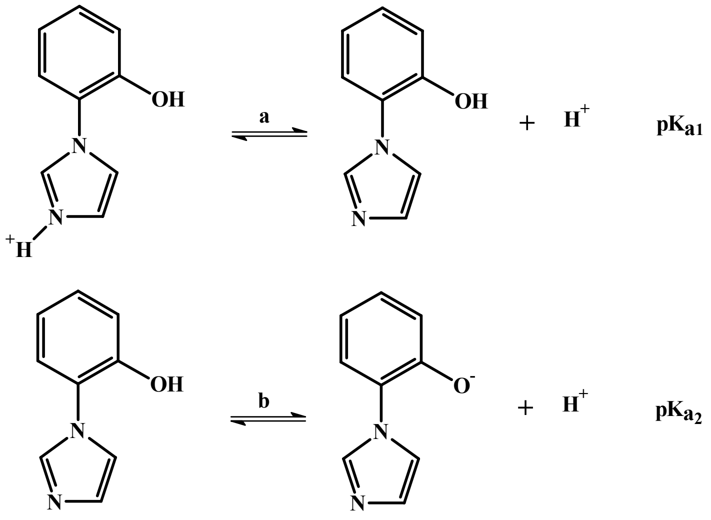


Fig. 2. Dissociation equilibrium of imidazole compound

The aim of present work is to provide a consistent and reliable set of gas phase and solvation phase acidities for N-hydroxy phenyl-functionalized imidazole esters **1-3** derivative using at the Hartree Fock and density functional level of theory and 6-31 G** basis set and salvation energies obtained by PCM model.

In this work, after optimization of all components the frequency calculations were carried out using HF/6-31g** and B3LYP/6-31g** in order to obtain the Gibbs free energies. The result of the calculated gas-phase energy and solvation energy of each acid and its corresponding anion together with the change of total standard Gibbs energy of reaction ($HA \rightarrow A^- + H^+$) is shown in Table-1. The change of Gibbs energy of deprotonation might be of theoretical interest, but only the differences between the most stable species can have physical meaning and can be compared with experiments. The result show that the acidities of acids in solvation phase is stronger than gas-phase.

Using the total Gibbs free energies, the pK_a values have been calculated using eqn. 4 and the results are shown in Table-2 where they are compared with those obtained from the experimental values. The calculated pK_a for acids are in relatively good agreement with the experimental values.

TABLE-2
GAS-PHASE AND SOLVATION ENERGIES AND THE pK_a VALUES CALCULATED IN THIS WORK USING PCM MODEL

Compd.	ΔG_{1gas}	ΔG_{1sol}	$pK_{a,cal}$	$pK_{a,exp}$[a]
		HF/6-31G**		
A1	75.828346	75.761075	4.13	4.05
A2	75.747564	75.828346	6.51	6.58
B1	75.823765	75.761945	4.57	4.25
B2	75.743134	75.823765	6.49	6.80
C1	75.801441	75.729489	4.61	4.30
C2	75.729993	75.801441	6.55	6.89
D1	75.869861	75.800307	6.39	6.12
D2	75.779159	75.869861	7.52	7.86
		B3LYP/6-31G**		
A1	75.848278	75.785528	4.67	4.05
A2	75.768724	75.848278	6.38	6.58
B1	75.848043	75.784501	4.75	4.25
B2	75.766121	75.848043	6.62	6.80
C1	75.824205	75.756434	4.18	4.30
C2	75.732403	75.824205	6.63	6.89
D1	75.885886	75.817612	6.23	6.12
D2	75.793626	75.885886	7.80	7.86

[a]The experimental values are taken from Ref. 18.

Different salvation algorithms have been employed in order to calculate solvation energies. These models have been dielectric-PCM (DPCM)[20], Conductor-PCM (CPCM)[21] and Integral equation formalism-PCM (IEFPCM)[22]. These methods are different in their modeling of the cavity created in solvent in order to place the solute molecules. The iso density surface, which is employed in the recent version of PCM methods, is a natural shape for the cavity and it corresponds to the reactive shape of molecules. The solvation energy of each molecule and its anion calculated using DPCM, CPCM and IEFPCM models are shown in Tables 3-5 as well as four components of solvation energies from the electrostatic interaction, cavity term, dispersion and repulsion energies. Examination of the calculated values shows that electrostatic interactions between anions and solvent are much greater than interaction of neutral molecules and solvent (seven to ten times for formic acid derivatives and two to three times for silanoic acids derivatives). Dispersion and repulsion energies of anions are also greater than acids because of the extra net charge on anions. Cavity energies of acids are slightly greater than anions because of the extra hydrogen atom.

TABLE-3
SOLVATION ENERGY AND ITS FOUR COMPONENTS (ELECTROSTATIC INTERACTION, CAVITY TERM, DISPERSION AND REPULSION ENERGIES) OF EACH MOLECULE AND ITS CORRESPONDING ANION CALCULATED USING DPCM MODEL (ALL VALUES ARE IN kcal/mol)

Compd.	ΔG_{ele}		ΔG_{cav}		ΔG_{dis}		ΔG_{rep}		ΔG_{solv}	
	Acid	Base	Acid	Base	Acid	Base	Acid	Base	Acid	Base
HF/6-31G**										
A1	-12.44	-53.95	26.86	27.09	-27.98	-28.10	4.46	4.37	-8.87	-50.59
A2	-62.53	-12.20	26.21	26.86	-27.96	-27.98	4.87	4.46	-59.41	-8.87
B1	-16.31	-57.96	27.48	27.47	-28.23	-28.69	4.41	4.63	-12.66	-54.55
B2	-63.45	-16.31	26.79	27.48	-28.28	-28.23	4.87	4.41	-60.08	-12.66
C1	-11.19	-50.34	28.86	28.83	-29.84	-31.87	4.85	5.84	-7.32	-47.54
C2	-69.04	-11.19	28.98	28.86	-29.53	-29.84	5.53	4.85	-64.06	-7.32
D1	-10.94	-58.73	20.63	20.77	-22.36	-22.75	3.71	3.83	-8.96	-56.88
D2	-63.07	-10.94	19.98	20.63	-22.33	-22.36	4.16	3.71	-61.26	-8.96
B3LYP/6-31G**										
A1	-10.50	-52.04	27.10	27.37	-28.01	-28.21	4.55	4.46	-6.86	-48.41
A2	-57.22	-10.50	26.53	27.10	-28.13	-28.01	5.02	4.55	-53.79	-6.86
B1	-11.92	-54.94	27.72	27.83	-28.26	-28.87	4.48	4.79	-7.97	-51.19
B2	-59.13	-11.92	26.85	27.72	-29.26	-28.26	5.69	4.48	-55.85	-7.97
C1	-9.0.9	-60.20	29.10	29.61	-29.89	-31.54	4.95	5.81	-4.93	-56.32
C2	-62.45	-9.09	28.87	29.10	-29.91	-29.89	5.95	4.95	-57.54	-4.93
D1	-9.06	-58.12	20.82	20.95	-22.38	-23.39	3.78	4.35	-6.85	-56.22
D2	-59.30	-9.06	19.97	20.82	-23.31	-22.38	4.98	3.78	-57.65	-6.85

TABLE-4
SOLVATION ENERGY AND ITS FOUR COMPONENTS (ELECTROSTATIC INTERACTION, CAVITY TERM, DISPERSION AND REPULSION ENERGIES) OF EACH MOLECULE AND ITS CORRESPONDING ANION CALCULATED USING CPCM MODEL (ALL VALUES ARE IN kcal/mol)

Compd.	ΔG_{ele}		ΔG_{cav}		ΔG_{dis}		ΔG_{rep}		ΔG_{solv}	
	Acid	Base	Acid	Base	Acid	Base	Acid	Base	Acid	Base
HF/6-31G**										
A1	-12.44	-54.87	26.86	27.09	-27.98	-28.10	4.46	4.37	-9.11	-51.51
A2	-60.79	-12.44	26.21	26.86	-27.96	-27.98	4.87	4.46	-57.67	-9.11
B1	-15.90	-58.81	27.48	27.47	-28.23	-28.69	4.41	4.63	-12.25	-55.40
B2	-62.35	-15.90	26.79	27.48	-28.28	-28.23	4.87	4.41	-58.97	-12.25
C1	-11.27	-51.08	28.86	28.83	-29.84	-31.87	4.85	5.84	-7.40	-48.28
C2	-66.92	-11.27	28.98	28.86	-29.53	-29.84	5.53	4.85	-61.93	-7.40
D1	-11.13	-59.09	20.63	20.77	-22.36	-22.75	3.71	3.83	-9.15	-57.24
D2	-61.65	-11.13	19.98	20.63	-22.33	-22.36	4.16	3.71	-59.85	-9.15
B3LYP/6-31G**										
A1	-10.55	-52.98	27.10	27.37	-28.01	-28.21	4.55	4.46	-6.92	-49.35
A2	-55.61	-10.55	26.53	27.10	-28.13	-28.01	5.02	4.55	-52.19	-6.92
B1	-12.09	-55.53	27.72	27.83	-28.26	-28.87	4.48	4.79	-8.14	-51.78
B2	-57.74	-12.09	26.85	27.72	-29.26	-28.26	5.69	4.48	-54.46	-8.14
C1	-9.21	-60.11	29.10	29.61	-29.89	-31.54	4.95	5.81	-5.05	-56.24
C2	-60.22	-9.21	28.87	29.10	-29.91	-29.89	5.95	4.95	-55.31	-5.05
D1	-9.28	-58.85	20.82	20.95	-22.38	-23.39	3.78	4.35	-7.06	-56.22
D2	-57.82	-9.28	19.97	20.82	-23.31	-22.38	4.98	3.78	-56.17	-7.06

TABLE-5
SOLVATION ENERGY AND ITS FOUR COMPONENTS (ELECTROSTATIC INTERACTION, CAVITY TERM, DISPERSION AND REPULSION ENERGIES) OF EACH MOLECULE AND ITS CORRESPONDING ANION CALCULATED USING FPCM MODEL (ALL VALUES ARE IN kcal/mol)

Compd.	ΔG_{ele}		ΔG_{cav}		ΔG_{dis}		ΔG_{rep}		ΔG_{solv}	
	Acid	Base	Acid	Base	Acid	Base	Acid	Base	Acid	Base
HF/6-31G**										
A1	-12.30	-55.08	26.86	27.09	-27.98	-28.10	4.46	4.37	-8.96	-51.72
A2	-59.41	-12.30	26.21	26.86	-27.96	-27.98	4.87	4.46	-56.29	-8.96
B1	-15.68	-59.09	27.48	27.47	-28.23	-28.69	4.41	4.63	-12.03	-55.68
B2	-61.52	-15.68	26.79	27.48	-28.28	-28.23	4.87	4.41	-58.15	-12.03
C1	-11.16	-51.29	28.86	28.83	-29.84	-31.87	4.85	5.84	-7.29	-48.49
C2	-65.94	-11.16	28.98	28.86	-29.53	-29.84	5.53	4.85	-60.95	-7.29
D1	-11.02	-59.28	20.63	20.77	-22.36	-22.72	3.71	3.83	-9.04	-57.43
D2	-60.77	-11.02	19.98	20.63	-22.33	-22.36	4.16	3.71	-58.96	-9.04

Compd.	ΔG_{ele}		ΔG_{cav}		ΔG_{dis}		ΔG_{rep}		ΔG_{solv}	
	Acid	Base	Acid	Base	Acid	Base	Acid	Base	Acid	Base
B3LYP/6-31G**										
A1	-10.43	-53.25	27.10	27.37	-28.01	-28.21	4.55	4.46	-6.80	-49.62
A2	-54.30	-10.43	26.53	27.10	-28.13	-28.01	5.02	4.55	-50.87	-6.80
B1	-11.95	-56.03	27.72	27.83	-28.26	-28.87	4.48	4.79	-8.00	-52.28
B2	-56.82	-11.95	26.85	27.72	-29.26	-28.26	5.69	4.48	-53.54	-8.00
C1	-9.13	-60.38	29.10	29.61	-29.89	-31.54	4.95	5.81	-4.97	-56.51
C2	-59.15	-9.13	28.87	29.10	-29.91	-29.89	5.95	4.95	-54.24	-4.97
D1	-9.19	-59.10	20.82	20.95	-22.38	-23.39	3.78	4.35	-6.98	-57.20
D2	-56.78	-9.19	19.97	20.82	-22.31	-22.38	4.98	3.78	-55.13	-6.98

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