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Solvation Of Monoacidic Conjugate Bases And Calculation Of Acidity Constants In Aqueous Solutions

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ABSTRACT

With the specific aim of analyzing the interactions of monoacidic conjugate bases with the solvent, equations that describe several reactions and equilibria of ionization were proposed. Furthermore, to prove the validity of these acid-base equations we calculate the pKa values in aqueous solutions of monohydroxylic phenols, benzoic acids and acetic acids, by means of a DFT method that makes use of Tomasi's model. The B3LYP/6-311++G(d,p)//HF/6-311++G(d,p) method was used for performing the calculations that permitted to describe the molecular conformations of the compounds and of their corresponding conjugate bases. Diverse ionization reactions and equilibria in water, which possesses a high hydrogen-bond-donor capability, were proposed. It was considered that the solvation of monoacidic conjugate bases occurs by means of intermolecular hydrogen bonds that involve one molecule of the base and one molecule of water. The very good agreement between the calculated acidity constants and the experimental pKa values reported in the literature constitutes a good support for the reactions and equilibria of ionization proposed in this paper. Moreover, the use of the acid-base equations proposed, together with the selected DFT method and Tomasi's model, permitted to develop a procedure potentially suitable for calculating with reasonable accuracy the acidity constants of diverse compounds in aqueous solutions.

KEYWORDS

Acidity constants;
Intermolecular hydrogen bonds;
pKa prediction;
DFT calculations.

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INTRODUCTION

It is well-known that diverse experimental[1-4] and theoretical[5-7] procedures are used for the determination of acidity constants. Recently, have been developed diverse procedures to perform excellent studies on the solvation of ions[8] and the determination of the pKa of compounds of varied nature[9-13]. Moreover, it must be pointed out that important software has been developed for the calculation of pK_a values[14,15]. However, there exist few studies dealing with the molecular structures and acid-base properties of monoacidic compounds in aqueous solutions[16-18].

As part of a research program aimed at investigating acid-base molecular properties in aqueous solutions, we study the interactions of monoacidic conjugate bases with the solvent by means of equations that describe several reactions and equilibria of ionization. In addition, to prove the validity of the acid-base equations proposed in this paper, we calculate the acidity constants of monohydroxylic phenols, benzoic acids and acetic acids using a DFT method with the Tomasi's model.

Methods

The following compounds were studied: **(1)** phenol; **(2)** 3-chlorophenol; **(3)** 4-chlorophenol; **(4)** 3-methoxyphenol; **(5)** 3-formylphenol; **(6)** benzoic acid; **(7)** 4-methylbenzoic acid; **(8)** 4-chlorobenzoic acid; **(9)** acetic acid; **(10)** fluoroacetic acid; **(11)** chloroacetic acid and **(12)** bromoacetic acid. Calculations were performed following procedures used in previous works[16,18,19]. The initial molecular geometries of the conjugate acids were modeled by the AM1 method included in the CS Chem3D program version 5.0[20]. On the other hand, the initial structures of monoacidic conjugated bases solvated (by means of H-bonds) with one water molecule, $(H_2O)AO^-$, were obtained simulating the reaction of partial neutralization,

$$HAO + OH^- \rightleftharpoons (H_2O)...AO^-$$

using the MM+ method included in the HyperChem programs package[21,22]. Afterwards, all the initial geometries were optimized with the Gaussian 98[23] programs package. The final optimization of all the molecular structures was performed with the B3LYP/6-311++G(d,p)//HF/6-311++G(d,p) method. To compute solvation free energies of the optimized structures in gas-phase of all the species involved in the proposed ionization reactions, the PCM model of Tomasi et al.[24-26] with radii of Pauling[27] was used. We do not carry out any type of modification in the PCM works, i.e. that always was used the standard PCM method included in the Gaussian 98 (Revision A.9). In all the calculations the default convergence criteria were used.

RESULTS AND DISCUSSION

Recently it has been reported[16-18] that the autoprotolysis of water takes place according to the following reaction,

$$3H_2O \rightleftharpoons (H_2O)H^+ + (H_2O)OH^- \quad (1)$$

In the above reaction, (H_2O) indicates the water molecules of solvation of the H^+ and OH^- ions. This is to say that the proposed reaction considers that both H^+ and OH^- ions are hydrated with one water molecule. It must be noted that H_3O^+ or $(H_2O)H^+$ will be used to represent the hydronium ion. The equilibrium constant (K_N) of the reaction described by Eq. (1) is,

$$K_N = \frac{[(H_2O)H^+][(H_2O)OH^-]}{[H_2O]^3} \quad (2)$$

Taking into account that the value of the K_W constant (ionic product of water) is,

$$K_W = [(H_2O)H^+][(H_2O)OH^-] = 1.008 \times 10^{-14}\ (298.15\,K) \quad (3)$$

and also that the molarity of water is 55.3 (298.15 K), from Eq. (2) it is inferred that,

$$K_N = \frac{K_W}{[H_2O]^3} = 5.961\ \ 10^{-20}\ (298.15\,K) \quad (4)$$

It must be remarked that Eq. (1) together with other acid-base equations different to the proposed in this paper, have been used to determine the overlapping pK_a values of resorcinol with a B3LYP/6-31+G(d) method[17]. In the referred study, it was considered that in alkaline aqueous solutions the monoanion and dianion of resorcinol are solvated with two and four molecules of water, respectively. On the other hand, it should also be pointed out

that Eq. (1) has been strongly supported[18] by means of B3LYP/6-311++G(d,p) calculations that involve the solvation of OH^- ions, and the solvation parameters α and β of the water, which measure its high hydrogen-bond-donor ability (HBD capability) and considerable hydrogen bond acceptor ability (HBA capability).

In aqueous solutions an acid takes part in the following proton transfer equilibrium[28],

$$HAO + H_2O \rightleftharpoons AO^- + H_3O^+ \quad (5)$$

Where, AO^- is the conjugate base of monoacidic acid HAO. The above reaction represents the proton-donating ability of HAO, which is characterized by the ionization equilibrium constant (K_i), conventionally defined as,

$$K_i = \frac{aAO^- aH_3O^+}{aHAO\, aH_2O} \quad (6)$$

In this equation, aAO^-, aH_3O^+, aHAO and aH_2O are the activities of the species in equilibrium. To simplify the discussion we shall make the approximations of replacing the activities in ionization constants by the numerical values of the molar concentrations. Consequently,

$$K_i = \frac{[AO^-][H_3O^+]}{[HAO][H_2O]} \quad (7)$$

It is well-known that Eqs. (5)-(7) are widely used in studies of acid-base equilibria in aqueous medium. Besides, that hydrogen bonding in protic solvents plays an important role in solvating anions. Thus, the solvation of anions is effective in protic solvents as water, because hydrogen bonds may be formed between the proton of the solvent and the lone pairs of electrons of the anion[29a]. The stabilization of the anion by formation of hydrogen bonds implies a decrease of its free energy[29b] and a higher thermodynamic stability. For these reasons we believe that the reaction described by Eq. (5) should be improved (see Eq. (10)), considering the solvation of the conjugate base involved in the ionization reaction. Therefore, we consider that in alkaline aqueous solutions, it is appropriate to represent the partial neutralization reaction of monoacidic compounds, in the following way,

$$HAO + (H_2O)OH^- \rightleftharpoons (H_2O)AO^- + H_2O \quad (8)$$

In this reaction, HAO represents to monohydroxylic phenols (P), benzoic acids (B) and acetic acids (Ac) while $(H_2O)AO^-$ represents the corresponding conjugate bases solvated with one water molecule. It must be noted that this fact, i.e. the solvation of the conjugate bases with one water molecule, implies the formation of intermolecular hydrogen bonds (IHBs) between the O^- atom of the conjugate bases and the H atom of water molecules, which exert their high HBD capability[30]. Moreover, it should also be observed that the reaction described by Eq. (8) is characterized by the equilibrium constant K_C, which is defined by the following equation,

$$K_C = \frac{[(H_2O)AO^-][H_2O]}{[HAO][(H_2O)OH^-]} \quad (9)$$

The K_C constant was theoretically determined using the relation, $\Delta G°_{reaction} = -RT\ Ln\ K_C$. On the other hand, considering that the AO^- and H^+ ions are hydrated, appearing predominantly as $(H_2O)AO^-$ and H_3O^+, the ionization reaction of monoacidic compounds in aqueous medium (Eq. (5)) is better represented by the following reaction,

$$HAO + 2H_2O \rightleftharpoons (H_2O)AO^- + H_3O^+ \quad (10)$$

The above reaction was obtained adding the reactions described by equations (1) and (8). It must be remarked that we are not affirming that the solvation of any anion involves only one water molecule. The reaction of Eq. (10) is one of the model reactions that we adopted to carry out our pKa calculations. The theoretical calculations for ΔG_{diss} in water performed by Klamt et al.,[10] are based on the reaction model,

$$AH + H_2O \rightarrow A^- \therefore H_3O^+$$

Considering the higher thermodynamic stability of $(H_2O)AO^-$ with respect to A^- (or AO^-)[8,18], it is evident that Klamt's reaction has a lower physicochemical significance that the reaction model of Eq. (10). On the other hand, taking into account the preceding comments, the following equation was proposed,

$$K_a = \frac{[(H_2O)AO^-][H_3O^+]}{[HAO]} \quad (11)$$

This equation defines the acidity constant ($K_{a\,Theo}$) of monoacidic compounds. Considering Eqs. (2), (9)

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TABLE 1: Calculated molecular parameters and properties whit the Tomasi's method at B3LYP/6-311++G(d,p) for water molecule (H_2O), monohydrated hydroxyl ion ((H_2O)(OH^-)), monohydroxylic phenols, benzoic acids, acetic acids and their conjugate bases solvated with one water molecule, in aqueous medium at 298 K.

Compounds	G^o_{sol}	dH_{water}-O^-	A-$O_wH_wO^-$
H_2O	-47988.1	------	------
(H_2O)(OH^-)	-95672.9	1.362	176.6
Phenol	-193001.8	------	------
(H_2O)···phenolate$^-$	-240694.2	1.661	171.2
3-Chlorophenol	-481418.2	------	------
(H_2O)···3-Chlorophenolate$^-$	-529112.4	1.691	172.8
4-Chlorophenol	-481418.4	------	------
(H_2O)···4-Chlorophenolate$^-$	-529112.3	1.673	171.6
3-Methoxyphenol	-264888.7	------	------
(H_2O)···3-Methoxyphenolate$^-$	-312582.6	1.653	172.4
3-Formylphenol	-264135.5	------	------
(H_2O)···3-Formylphenolate$^-$	-311829.2	1.708	176.5
Benzoic acid	-264154.0	------	------
(H_2O)···benzoate$^-$	-311854.6	1.698	171.0
4-Methylbenzoic acid	-288832.2	------	------
(H_2O)···4-Methylbenzoate$^-$	-336532.8	1.695	171.2
4-Chlorobenzoic acid	-552570.3	------	------
(H_2O)···4-Chlorobenzoate$^-$	-600271.1	1.699	172.3
Acetic acid	-143809.8	------	------
(H_2O)···acetate$^-$	-191509.6	1.724	161.4
Fluoroacetic acid	-206094.4	------	------
(H_2O)···Fluoroacetate$^-$	-253797.4	1.761	161.0
Chloroacetic acid	-432220.4	------	------
(H_2O)···chloroacetate$^-$	-479923.3	1.771	161.1
Bromoacetic acid	-1758729.8	------	------
(H_2O)···bromoacetate$^-$	-1806432.0	1.777	161.3

G^o_{sol}=Total free energy in solution, kcal/mole; dH_{water}-O^-= Distance of the IHB between the indicated atoms, Å; A-$O_wH_wO^-$= H-Bond angle(°).

and (11), it is clear that the constants K_N, K_C and $K_{a\ Theo}$ are related by the equation,

$$K_{a\ Theo} = K_C\ K_N\ [H_2O]^2 \qquad (12)$$

The above equation was used to determine theoretically the $K_{a\ Theo}$ values of P, B and Ac in aqueous solutions. TABLES 1 and 2 summarize the optimized values of molecular properties of all the species involved in the reaction described by Eq. (8) for the compounds **(1-12)**. The experimental pK_a values (pK_{aExp})[9,31,32] of the compounds are also given in TABLE 2. From TABLE 1, it can be observed that the distances and angles that characterize the IHBs in compounds **(1-12)** indicate that they belong to the class of moderate IHBs[33]. To illustrate, figure 1 shows the monosolvated structure of the benzoate anion.

TABLE 2: Calculated acidity constants using the Tomasi's method at B3LYP/6-311++G(d,p) for monohydroxylic phenols and benzoic acids, in aqueous medium at 298 K.

	Compounds	K_C	$pK_{a\ Theo}$	$pK_{a\ Exp}$	pK_a[9]
1	Phenol	3.723 x 10^5	10.17	9.89[31]	9.95
2	3-Chlorophenol	7.767 x 10^6	8.85	8.85[31]	9.25
3	4-Chlorophenol	4.681 x 10^6	9.07	9.18[31]	-----
4	3-Methoxyphenol	4.761 x 10^6	9.06	9.65[32]	-----
5	3-Formylphenol	3.340 x 10^6	9.22	8.98[32]	-----
6	Benzoic acid	3.815 x 10^{11}	4.16	4.19[31]	3.49
7	4-Methylbenzoic acid	3.223 x 10^{11}	4.23	4.37[32]	4.25
8	4-Chlorobenzoic acid	4.517 x 10^{11}	4.08	4.00[32]	3.69
9	Acetic acid	8.352 x 10^{10}	4.82	4.76[32]	-----
10	Fluoroacetic acid	1.851 x 10^{13}	2.47	2.59[32]	-----
11	Chloroacetic acid	1.564 x 10^{13}	2.55	2.87[32]	-----
12	Bromoacetic acid	4.798 x 10^{12}	3.06	2.90[32]	-----

K_C= Equilibrium constant of Eq. (9); $K_{a\ Theo}$= Theoretical acidity constant of the compound in water, Eq. (12); $pK_{a\ Exp}$= Experimental pK_a values;[9,31,32] pK_a[9]= pK_a values calculated by Schmidt am Busch *et al.*

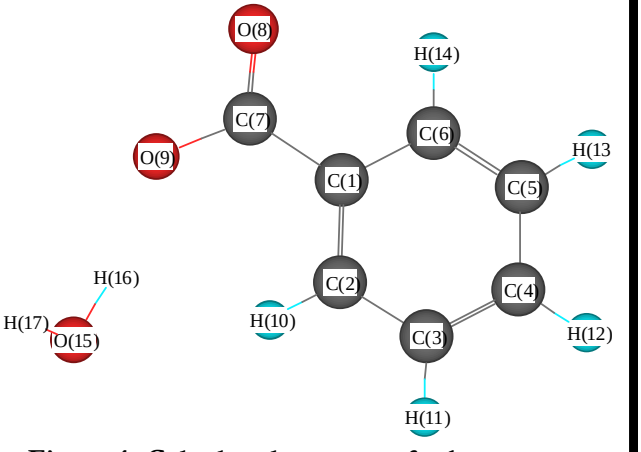

Figure 1: Calculated structure for benzoate anion solvated with one water molecule, at B3LYP/6-311++G(d,p) using the Tomasi's method, in aqueous solution at 298 K.

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TABLE 3: Properties calculated acidity constants using the Tomasi's method at B3LYP/6-311++G(d,p) for monohydroxylic phenols and benzoic acids, in aqueous medium at 298 K.

	AM	SD	Min	Max
$pK_{a\ Theo}$	5.9783	3.0040	2.47	10.17
$pK_{a\ Exp}$	6.0192	2.9859	2.59	9.89

AM= arithmetic mean; SD= standard deviation; Min= minimum value; Max= maximum value.

It was considered interesting to search a linear relationship between the pK_{aTheo} and pK_{aExp} values. TABLE 3 shows the characteristics of the input data while figure 2 illustrates the straight line and the regression parameters obtained. The corresponding linear equation is,

$$\mathbf{pK_{a\ Theo} = 1.0028\ pK_{a\ Exp} - 0.0576 \quad (r= 0.9967) \quad (13)}$$

Figure 3 illustrates the data of the function pK_{aTheo} vs. pK_{aExp} with a 95% confidence range. The statistical results obtained indicate that the $pK_{a\ Exp}$ values explain 99.35% of the variability of the pK_{aTheo} values. This fact implies, for example, that we would take only 0.01% risk when rejecting the hypothesis that a constant model would be better than the linear model proposed. Moreover, the Eq. (13) reveals that the algorithm proposed allows calculating $\Delta G°_{solvation}$ with quite accuracy.

The $pK_{a\ Exp}$ values of P and B (TABLE 2) increase as,

$$\mathbf{pK_{a\ Exp}(8)=4.00 < pK_{a\ Exp}(6)=4.19 < pK_{a\ Exp}(7)=4.37 < pK_{a\ Exp}(2)= 8.85 < pK_{a\ Exp}(5)= 8.98 < pK_{a\ Exp}(3)=9.18 < pK_{a\ Exp}(4)=9.65 < pK_{a\ Exp}(1)=9.89 \quad (14)}$$

On the other hand, the pK_a values calculated by us ($pK_{a\ Theo}$) increase in the following order,

$$\mathbf{pK_{a\ Theo}(8)=4.08 < pK_{a\ Theo}(6)=4.16 < pK_{a\ Theo}(7)=4.23 < pK_{a\ Theo}(2)= 8.85 < pK_{a\ Theo}(4)=9.06 \sim pK_{a\ Theo}(3)=9.07 < pK_{a\ Theo}(5)=9.22 < pK_{a\ Theo}(1)=10.17 \quad (15)}$$

Comparing Eqs. (14) and (15) it is inferred that the $pK_{a\ Theo}$ constants here obtained are in good agreement with the $pK_{a\ Exp}$ constants. The percentual deviations between the values of $pK_{a\ Theo}$ and $pK_{a\ Exp}$ for **(1-5)** and **(6-8)** compounds are 2.83%, 0.0%, -1.20%, -6.11%, 2.67% and -0.72%, -3.20%, 2.00%, respectively.

Recently, the pK_a values of **(1), (2), (6), (7)** and **(8)** were calculated by Schmidt am Busch et al.,[9] using DFT methods (Becke-half&half and B3LYP). The following pK_a values were obtained by these authors (last column of TABLE 2),

$$\mathbf{pK_a(6)=3.49 < pK_a(8)=3.69 < pK_a(7)=4.25 < pK_a(2)= 9.25 < pK_a(1)=9.95 \quad (16)}$$

The above pK_a values are in reasonable agreement with the experimentally determined ones (Eq. (14)). However, the pK_a values calculated by Schmidt am Busch et al. are more distant from the experimental pK_a values than those calculated by us.

From TABLE 2, it can be observed that the pK_{aExp} values of the acetic acids analyzed, increase as,

$$\mathbf{pK_{a\ Exp}(10)=2.59 < pK_{a\ Exp}(11)=2.87 \sim pK_{a\ Exp}(12)=2.90 < pK_{a\ Exp}(9)= 4.76 \quad (17)}$$

While the pK_a values calculated by us ($pK_{a\ Theo}$) increase in the following order,

$$\mathbf{pK_{a\ Theo}(10)=2.47 < pK_{a\ Theo}(11)=2.55 < pK_{a\ Theo}(12)=3.06 < pK_{a\ Theo}(9)= 4.82 \quad (18)}$$

Comparing Eqs. (17) and (18) it is inferred that

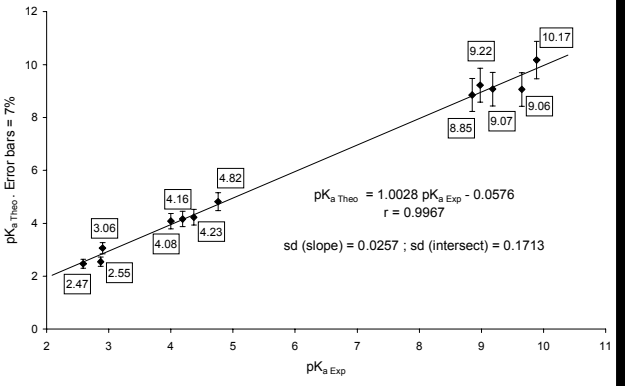

Figure 2: Plot of the calculated pKa values versus the experimental pKa values

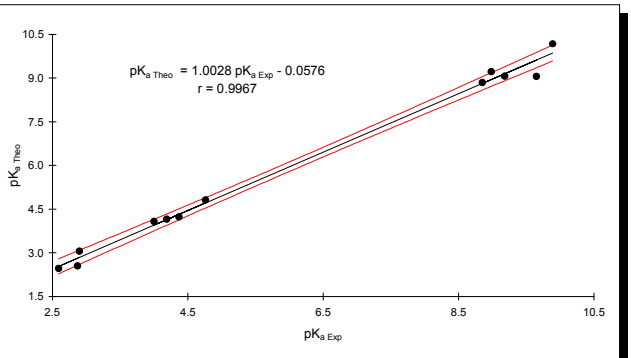

Figure 3: Data of the function pK_{aTheo} vs. pK_{aExp} with a 95% confidence range.

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the $pK_{a\ Theo}$ constants are in good agreement with the $pK_{a\ Exp}$ constants. The percentual deviations between the values of $pK_{a\ Theo}$ and $pK_{a\ Exp}$ for **(9)**, **(10)**, **(11)** and **(12)**, are 1.26%; -4.63%, -11.2% and 5.52%, respectively. The calculation of the ionization constants of **(9-12)** was also performed using the $CSpK_a$ predictor,[14] which is based on topological structure descriptors and was developed by the use of artificial neural networks. Using this software, the following pK_a values were obtained,

$$\mathbf{pK_a(10)=3.12 < pK_a(11)=3.18 < pK_a(12)=3.74 < pK_a(9)= 4.33} \quad \mathbf{(19)}$$

The above pK_a values are in reasonable agreement with the experimentally determined ones (Eq. (17)). Nevertheless, the pKa predicted with the $CSpK_a$ program differ from the $pK_{a\ Exp}$ values more than those obtained by us.

On the other hand, from TABLE 2 and according to Eq. (12) it is observed that the $pK_{a\ Theo}$ values increase when the K_C constants decrease. This result confirms that hydrogen bonding in protic solvents is essential in solvating anions[29]. We think that K_C constant is a good magnitude to measure the strength of IHBs, which determine the solvation of monoacidic conjugated bases.

Finally, it must be remarked that the original acid-base equations shown in this section are very important because besides allowing the calculation of the pK_a of a compound, they facilitate the study of the nature of acid-base molecular interactions. The $pK_{a\ Theo}$ constants calculated show acceptable agreement with the $pK_{a\ Exp}$ constants. However, it is evident that in order to assure the reliability of a new method to calculate acidity constants of monoacidic compounds, it is necessary to consider a higher number of compounds than that considered in this work. Nevertheless, it was concluded that the use of the acid-base equations proposed, together with the selected DFT method and Tomasi's model, permitted to develop a procedure potentially suitable for calculating with reasonable accuracy the acidity constants of diverse compounds in aqueous solutions.

CONCLUSIONS

We have calculated the acidity constants of monohydroxylic phenols, benzoic acids and acetic acids in aqueous solution, based on the proposal of original equations to describe the acid-base properties of the solvent and the solutes. Thus, there were proposed a reaction for the partial neutralization of monoacidic compounds (Eq. (8)) that considers the solvation of the conjugate bases, as well as other equation (Eq. (11)) that defines the acidity constant $K_{a\ Theo}$ and that also take into account the solvation of the conjugate bases in water. On the other hand, in the model reactions described by Eq. (8) and Eq. (10), it was considered that the solvation of monoacidic conjugate bases occurs by means of intermolecular hydrogen bonds that involve one molecule of base and one molecule of water. The new acid-base equations proposed are very important because besides allowing the calculation of the pK_a of monoacidic compounds, they give the strength of the interactions involved in the solvation of the corresponding conjugate bases. The calculations were performed with the B3LYP/6-311++G(d,p) method and using Tomasi's model. The calculated ionization constants show acceptable agreement with the experimental constants. It was concluded that the use of the acid-base equations proposed, together with the selected DFT method and Tomasi's PCM model, permitted to develop a procedure potentially suitable for calculating with reasonable accuracy the acidity constants of monoacidic compounds in aqueous solutions. We are currently studying other compounds and have obtained quite acceptable results.

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REFERENCES

[1] S.M.C.Buckenmaier, D.V.McCalley, M.R.Euerby; J. Chromatogr.A, **1026**, 251-259 **(2004)**.

[2] V.Evagelou, A.Tsantili-Kakoulidou, M.Koupparis; J. Pharm.Biomed.Anal., **31**, 1119-1128 **(2003)**.

[3] M.Melouna, T.Syrový, A.Vrána; Talanta, **62**, 511-522 **(2004)**.

[4] G.T.Castro, O.S.Giordano, S.E.Blanco; J.Molec. Struct., Theochem, **626**, 167-178 **(2003)**.

[5] M.Remko, C.Von Der Lieth; Bioorg.Med.Chem., **12**, 5395-5403 **(2004)**.

[6] C.Ögretir, S.Yarlýgan, S.Demirayak, T.Arslan; J. Molec.Struct., Theochem, **666**, 609-615 **(2003)**.

[7] C.Alemán; J.Molec.Struct., Theochem, **528**, 65-73 **(2000)**.

[8] J.R.Pliego, J.M.Riveros; J.Phys.Chem.A, **105**, 7241-7247 **(2001)**.

[9] M.Schmidt am Busch, E.W.Knapp; ChemPhysChem, **5**, 1513-1522 **(2004)**.

[10] A.Klamt, F.Eckert, M.Diedenhofen, M.E.Beck; J.Phys. Chem.A, **107**, 9380-9386 **(2003)**.

[11] Y.Fu, L.Liu, R.Q.Li, R.Liu, Q.X.Guo; J.Am.Chem. Soc., **126**, 814-822 **(2004)**.

[12] U.A.Chaudry, P.L.A.Popelier; J.Org.Chem., **69**, 233-241 **(2004)**.

[13] E.Soriano, S.Cerdán, P.Ballesteros; J.Mole.Struct., Theochem, **684**, 121-128 **(2004)**.

[14] ChemSilico™, CSpKa™ Predictor, ChemSilico LLC, Tewksbury, MA 01876, USA **(2003)**.

[15] Jaguar™ 4.2, Schrödinger, Inc., Portland, OR, USA **(1991-2002)**.

[16] S.E.Blanco, F.H.Ferretti; Internet Electron, C.Mol.Des. **(2004)**, IECMD 2004, http://www.biochempress.com.

[17] S.E.Blanco, M.C.Almandoz, F.H.Ferretti; Spectrochim. Acta Part A, **61**, 93-102 **(2005)**.

[18] S.E.Blanco, F.H.Ferretti; Chem.Phys.Lett., **403**, 400-404 **(2005)**.

[19] S.E.Blanco, M.C.Almandoz, M.I.Sancho; Physical Chemistry : An Indian Journal, **1**, 32-40 **(2006)**.

[20] C.S.Program, Chem3D 5.0, Molecular Modeling and Analysis, Cambridge Soft Corporation, MA, USA, **(2000)**.

[21] N.L.Allinger; J.Am.Chem.Soc., **99**, 8127-8134 **(1977)**.

[22] HyperChem™, Release 5.11 Pro, Hypercube, Inc., Gainesville, FL 32601, USA **(1999)**.

[23] Gaussian 98, Revision A.9, M.J.Frisch, G.W.Trucks, H.B.Schlegel, G.E.Scuseria, M.A.Robb, J.R. Cheeseman, V.G.Zakrzewski, J.A.Montgomery, Jr., R.E.Stratmann, J.C.Burant, S.Dapprich, J.M.Millam, A.D.Daniels, K.N.Kudin, M.C.Strain, O.Farkas, J.Tomasi, V.Barone, M.Cossi, R.Cammi, B.Mennucci, C.Pomelli, C.Adamo, S.Clifford, J.Ochterski, G.A. Petersson, P.Y.Ayala, Q.Cui, K.Morokuma, D.K. Malick, A.D.Rabuck, K.Raghavachari, J.B.Foresman, J.Cioslowski, J.V.Ortiz, A.G.Baboul, B.B.Stefanov, G. Liu, A.Liashenko, P.Piskorz, I.Komaromi, R. Gomperts, R.L.Martin, D.J.Fox, T.Keith, M.A.Al-Laham, C.Y.Peng, A.Nanayakkara, M.Challacombe, P.M.W.Gill, B.Johnson, W.Chen, M.W.Wong, J.L. Andres, C.Gonzalez, M.Head-Gordon, E.S.Replogle, J.A.Pople; Gaussian, Inc., Pittsburgh PA **(1998)**.

[24] S.Miertus, E.Scrocco, J.Tomasi; Chem.Phys., **55**, 117-129 **(1981)**.

[25] S.Miertus, J.Tomasi; Chem.Phys., **65**, 239-245 **(1982)**.

[26] M.Cossi, V.Barone, R.Cammi, J.Tomasi; Chem.Phys. Lett., **255**, 327-335 **(1996)**.

[27] B.H.Besler, K.M.Merz, P.A.Kollman; J.Comp.Chem., **11**, 431-439 **(1990)**.

[28] P.W.Atkins; 'Physical Chemistry', 6th Ed., Oxford University Press, England, 229 **(1998)**.

[29] F.Ruff, I.G.Csizmadia; 'Organic Reactions, Equilibria, Kinetics and Mechanism', Elsevier, London, 259-264 and 283 **(1994)**.

[30] Y.Marcus; Chem.Soc.Rev., **22**, 409-416 **(1993)**.

[31] D.R.Lide; 'Handbook of Chemistry and Physics', 78th Ed., CRC Press, New York, 8-43-51 **(1997-1998)**.

[32] A.Albert, E.P.Serjeant; 'The Determination of Ionization Constants', 3rd Ed., Chapman and Hall, New York, 139-145 **(1997-1998)**.

[33] G.A.Jeffrey; 'An Introduction to Hydrogen Bonding', Oxford University Press, Oxford, 11-12 **(1997)**.