



Determination of the pK_a of hydroxy-benzophenones in ethanol–water mixtures. Solvent effects

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Abstract

Benzophenones are compounds of great importance due to their biological and physicochemical properties. The purpose of the present work was to determine by a UV–Visible spectroscopic method, the pK_a of 4(OH)benzophenone, 2(OH)benzophenone and 2(OH),4(CH₃O)benzophenone in ethanol–water solutions, varying solvent permittivity in the interval 61–72, at constant ionic strength (0.050) and temperature (25.0 ± 0.1 °C). The pK_a values of the compounds increase when the polarity–polarizability and solvation abilities of the reaction medium decrease. Correlations were established between the pK_a values and solvation parameters of the solvents, such as the relative permittivity, the α parameter of Taft the solvatochromatic polarity–polarizability parameter π^* , and the parameter *Acity*. Excellent linear equations were obtained from which pK_a values were determined in pure water. The structures of all the chemical species involved in the acid–base dissociation equilibria studied were calculated at the RHF/6-31G(d) level of theory, in ethanol and water. Considering the theoretical pK_a values, the conclusions obtained match our experimental determinations.

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1. Introduction

Benzophenones (BPs) exhibit structural, chemical and biological properties of great interest. One of their most important properties is the ability to absorb and dissipate ultraviolet radiation [1,2]. Of a group of 12 BPs, 2(OH),4(CH₃O)BP (also known as BP-3) is the major active ingredient in most sunscreen lotions and cosmetic that are used

extensively in medicine for protecting the skin from ultraviolet rays [3,4]. Other hydroxy-BP derivatives have been used as antioxidants, platelet aggregation inhibitors and they have been reported as potent xanthine oxidase inhibitors [5,6]. As part of a program aimed at investigating new physicochemical properties of BPs, the UV solvatochromic shifts [7] and the metal complexing capability [8] of *o*-hydroxy-BP in primary alcohols were recently studied. Now, considering that the pK_a of a compound is fundamental for explaining its acid–base properties, and these are decisive for

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the performing of chemical and biological studies such as those related to chemical stability and preformulation of pharmaceuticals, the values of pK_a of three hydroxy-BPs were determined.

BPs are practically insoluble in water, but they are soluble in organic solvents, like methanol, ethanol, dimethylsulfoxide and dimethylformamide. If a substance is virtually insoluble in water the determination of its pK_a in an aqueous solution can be difficult and problematic. Many methods for determination of pK_a have been offered: determination by liquid–liquid partition [9], by high-pressure liquid chromatography [10,11], and methods that involve potentiometric titration or spectrophotometry determination in mixtures of solvents, when the pK_a is determined by extrapolation in mixtures of methanol, ethanol and dimethylsulfoxide [12,13]. The determination of ionization constant by UV–Vis spectrophotometry is more time-consuming than by potentiometry. However, spectroscopy is an ideal method when a substance is too insoluble for potentiometry or when its pK_a value is particularly low or high [14].

For the above reasons, in this paper the acid–base dissociation constants of 4(OH)BP (1), 2(OH)BP (2), and 2(OH),4(CH₃O)BP (3) were determined in ethanol–water solutions by UV–Vis spectroscopy, varying solvent permittivity between 61 and 72, at 25.0 ± 0.1 °C and constant ionic strength. Also, diverse correlations are proposed between the pK_a values and solvation parameters of the medium, which permit to calculate the pK_a of the compounds in pure water. Besides, the structures of the ionized and non-ionized hydroxy-BPs in ethanol and water were calculated with *ab initio* methods.

2. Experimental

2.1. Reagents

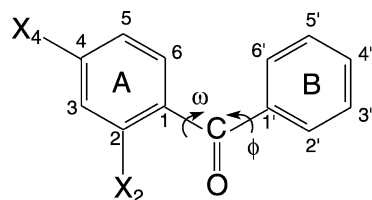
The structure and chemical numbering system of the hydroxy-BPs studied are shown in Fig. 1. These compounds from Sigma were purified by repeated crystallization from ethanol–water. The purity control was performed determining its melting point [15] (mp (1) = 132.5 °C, mp (2) = 40.0 °C, mp (3) = 65.5 °C) and its TLC chromatographic properties [16].

The buffer solutions employed were: (a) HCl–KCl, pH 2.0; (b) NaOH–KCl, pH 12.0; (c) NaPO₄H₂–Na₂PO₄H 5.0×10^{-3} M, covering the pH range from 7.00 to 8.00, each 0.20 ± 0.01 pH units and (d) NaCO₃H–Na₂CO₃ 0.01 M, from pH 9.00 to 10.0.

All these buffer solutions were prepared with the same ionic strength (0.050, adding KCl), using as solvent five w/w ethanol–water mixtures (12.1, 16.2, 20.3, 24.7, and 29.0%). The permittivity (D) of these solvents at 25.0 ± 0.1 °C is 71.61, 69.19, 66.78, 64.19, and 61.66, respectively [17]. Corrected pK_a values for ionic strength of 0.050 were used to perform the necessary calculations for preparation of buffer solutions [18]. The used drugs were purchased from Merck. Ethanol (spectroscopic grade) was used to prepare all the solutions.

2.2. Procedure

(a1) A stock solution of 4(OH)BP 6.64×10^{-3} M was prepared in ethanol. Standard solutions were



(1)	$X_4=OH$	$X_2=H$	4(OH)benzophenone
(2)	$X_2=OH$	$X_4=H$	2(OH)benzophenone
(3)	$X_2=OH$	$X_4=CH_3O$	2(OH),4(CH ₃ O)benzophenone

Fig. 1. Structure of the hydroxy-benzophenones studied.

prepared adding $50.0 \pm 0.1 \mu\text{l}$ of stock solution at $5.00 \pm 0.02 \text{ ml}$ of phosphate buffers (pH between 7.00 and 8.00) with $D = 71.61$. The same procedure was used with the pH 2.0 and 12.0 buffer solutions. The analytic concentration of these standard solutions was $6.57 \times 10^{-5} \text{ M}$. Series of similar standard solutions were prepared using phosphate buffers at the same pH interval, with $D = 69.19, 66.78, 64.19,$ and 61.66 . All these series of standard solutions were placed in UV cells, hermetically closed and thermostated at $25.0 \pm 0.1 \text{ }^\circ\text{C}$ for 15 min. After this, the UV–Vis spectra were recorder on a Shimadzu UV 160 A double beam spectrophotometer, between 200 and 450 nm. Simultaneously, the corresponding absorbance values were determined at 348 nm.

(a2) A stock solution of 2(OH)BP $2.70 \times 10^{-2} \text{ M}$ was prepared in ethanol. Then, $50.0 \pm 0.1 \mu\text{l}$ of this solution were mixed with $5.00 \pm 0.02 \text{ ml}$ of six carbonate buffers (pH between 9.00 and 10.00) and buffers pH 2.0 and 12.0, with $D = 71.61$. The analytic concentration of these standard solutions was $2.67 \times 10^{-4} \text{ M}$. Similar solutions were prepared at the same pH interval, with $D = 69.19, 66.78, 64.19,$ and 61.66 . All the standard solutions were maintained at $25.0 \pm 0.1 \text{ }^\circ\text{C}$ for 15 min and the UV–Vis spectra were recorder. The absorbance values were also determined at 382 nm.

(a3) For 2(OH),4(CH₃O)BP, the procedure described under (a2) was followed. In this case, the stock solution in ethanol was $1.61 \times 10^{-2} \text{ M}$ and the

analytic concentration of standard solutions was $1.59 \times 10^{-4} \text{ M}$.

(a4) The pH values of the phosphate and carbonate buffer solutions prepared in the ethanol–water mixtures of different permittivities were determined. The pH original values in aqueous medium suffer slight variations when the percentage of EtOH is increased. The pH measurements were performed on an Orion SA 520 pH-meter. The pH-meter was standardized against aqueous buffers prepared from standard samples. Subsequently, the methodology proposed by Van Uiter et al. [19,20] was followed, which is based on pH measurement of buffer solutions prepared in aqueous media and in ethanol mixtures (%ethanol w/w from 12.1 to 29.0) at $25 \text{ }^\circ\text{C}$. Relations were obtained between the effective pH in pure water (pH_w) and the corresponding pH in ethanol–water ($\text{pH}_{\text{ol-w}}$) of the following type:

$$\text{pH}_{\text{ol-w}} = \text{intercept} + \text{slope} \times \text{pH}_w$$

Table 1 reports the intercept and slope values obtained when linking the pH of phosphate buffer solutions in water with the corresponding ones in ethanol–water. These equations are valid within the pH_w 7.0–8.0 range, which matches the $\text{pH}_{\text{ol-w}}$ 7.2–8.7 range, depending on the percentage of ethanol in the mixture. Also, the values of the determinations performed in carbonate buffer are given. These expressions are valid within the pH_w 9.0–10.0 range, which matches the $\text{pH}_{\text{ol-w}}$ 9.5–11.0 range.

Table 1

Relations between pH in aqueous solutions and in ethanol–water mixtures, using $\text{NaPO}_4\text{H}_2\text{--Na}_2\text{PO}_4\text{H}$ $5.0 \times 10^{-3} \text{ M}$ and $\text{NaCO}_3\text{H--Na}_2\text{CO}_3$ 0.01 M at $25 \text{ }^\circ\text{C}$

% EtOH w/w	Buffer phosphate solutions ^a			Buffer carbonate solutions ^b		
	Slope	Intercept	R	Slope	Intercept	R
12.1	0.9487	0.563	0.996	0.9619	0.854	0.999
16.2	0.9242	0.910	0.999	0.9842	0.744	0.999
20.3	0.8988	1.193	0.996	1.0120	0.585	1.000
24.7	0.9143	1.230	0.999	1.0314	0.563	0.991
29.0	0.9357	1.200	0.999	1.0624	0.424	0.997

R: correlation coefficient; equation: $\text{pH}_{\text{ol-w}} = \text{intercept} + \text{slope} \times \text{pH}_w$; pH_w : pH in aqueous solution; $\text{pH}_{\text{ol-w}}$: apparent pH in the ethanol–water mixture.

^a These equations are valid within the range $\text{pH}_{\text{ol-w}}$ 7.2–8.7.

^b These equations are valid within the range $\text{pH}_{\text{ol-w}}$ 9.5–11.0.

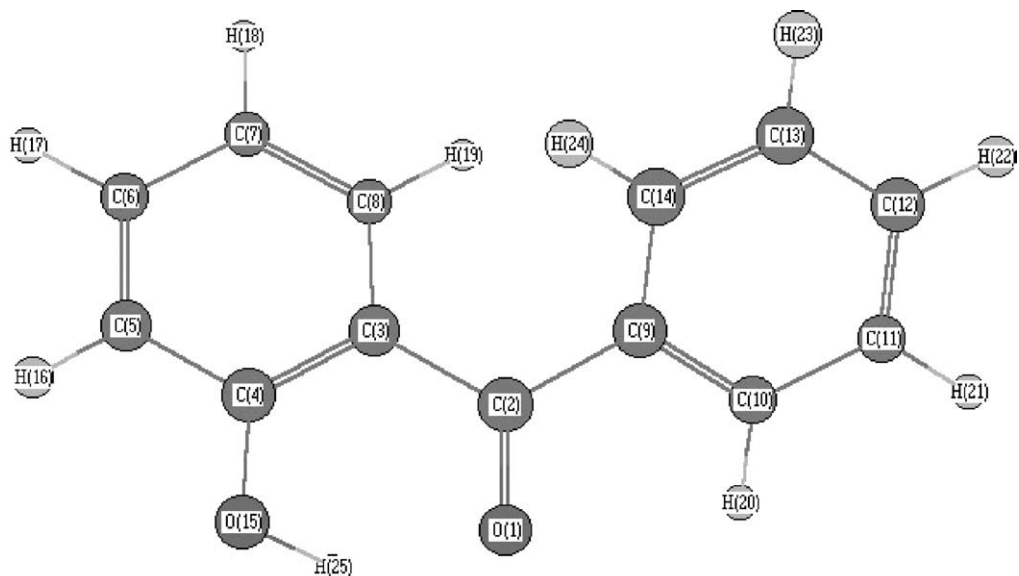


Fig. 2. Practical numbering system adopted in the calculations.

3. Calculations

Fig. 2 shows the practical numbering system adopted for performing the calculations, which were carried out following known procedures

[21]. In this way, the initial geometries of the molecules were modeled using the AM1 method included in the program CS Chem3D version 5.0 [22]. Afterwards, these geometries were optimized with the GAUSSIAN98 [23] program packages, using

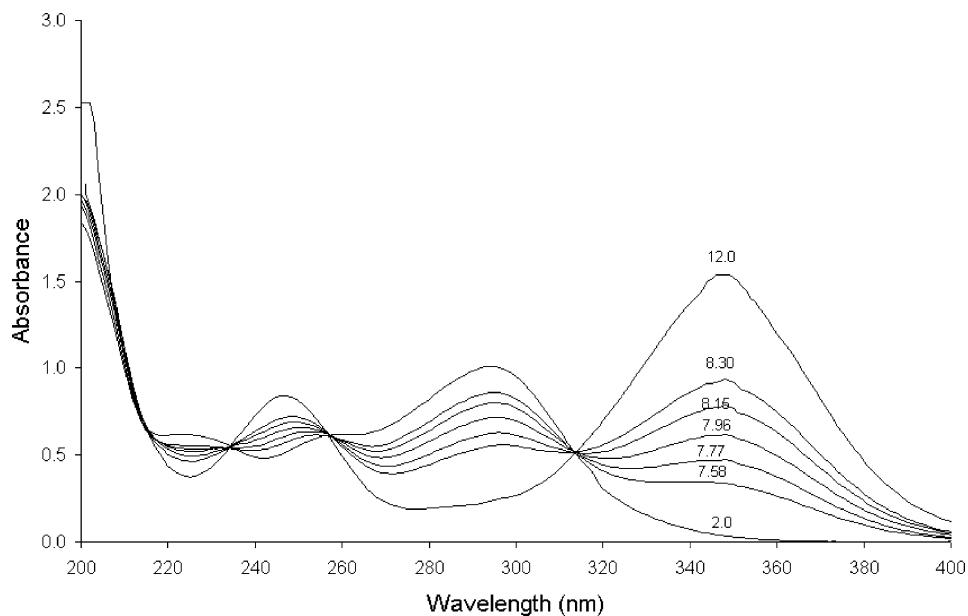


Fig. 3. UV–Vis spectra of 4(OH)benzophenone at different pH in ethanol–water mixtures 12.1% ($D = 71.61$). Numbers on spectra indicate the pH apparent ($\text{pH}_{\text{ol-w}}$).

basis sets at the level of theory RHF/6-31G(d). The calculations were performed on Intel Pentium IV 1.4 GHz CPU with 512 MB of RAM.

To analyze the solvent effects on the ionized and non-ionized forms of the hydroxy-BPs the COSMO method [24] was used.

4. Results and discussion

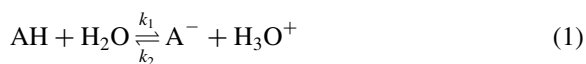
4.1. Choice of an analytical wavelength suitable to determine the pK_a

The determination of ionization constants by UV–Vis spectrophotometry depends upon the direct determination of the ratio of molecular species (neutral molecule) to ionized species in a series of non-absorbing buffer solutions (whose pH values are either known or measured). For this purpose, a wavelength is chosen at which the greatest difference between the absorbencies of the two species is observed. Fig. 3 shows a series of spectra for 4(OH)BP to pH extreme 2 and 12, and in buffers phosphate spaced at approximate intervals of 0.2 pH units, when the solvent permittivity was 71.61. The greatest difference between their absorbencies was seen to be at 348 nm, and hence this was selected as the analytical wavelength.

Fig. 4 shows the UV–Vis spectra of 2(OH),4(CH₃-O)BP in buffer solutions with permittivity equal to 66.78. It can be observed that the molecular and ionized species of this compound show maximum absorption at 288 and 371 nm, respectively. The absorption band of ionized species (371 nm) exhibits a small plateau so that λ_{max} does not change with solvent permittivity. It can also be observed that at 288 nm the absorption of ionized species is not negligible. On the other hand, at 371 nm the absorption of molecular neutral is practically null. It is therefore clear that the wavelength at 371 nm is the most suitable one to determine the pK_a value. The general characteristics of the spectra of 2(OH)BP are similar to those described for 2(OH),4(CH₃O)BP. In this case, the absorption band of ionized species was found at 382 nm.

4.2. Determination of pK_a

The acid–base equilibria studied in aqueous solution were represented with the general equation,



where AH is **1** (**2** or **3**); A[−] is the anion of **1** (**2** or **3**), and k_1 , k_2 are the rate constants for the forward and reverse reaction rates, respectively.

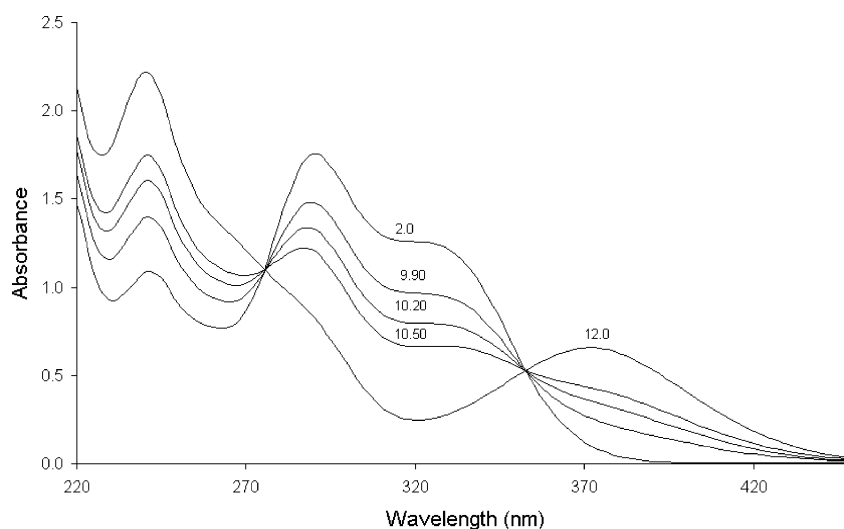


Fig. 4. Absorption spectra of 2(OH),4(CH₃O)benzophenone at different pH in ethanol–water mixtures 20.03% ($D = 66.78$). Numbers on spectra indicate the pH apparent (pH_{ol-w}).

Thus, the Henderson–Hasselbach equation becomes useful for obtaining the pK_a value of a compound, by measuring the absorbance of species A^- and AH (at a determined wavelength), in media of variable pH, which is formulated as:

$$pH_{ol-w} = pK_a + \log \frac{A - A_a}{A_b - A} \quad (2)$$

where A_a is the absorbance of the acid form (AH); A_b is the absorbance of the conjugate form (A^-); A is the absorbance due to the presence of species A^- and AH in the buffer solution; and pH_{ol-w} is the apparent pH in the ethanol–water mixture.

4.3. Data from a typical experiment

The absorbance values of the dissociated and neutral molecular forms, together with the absorbance due to the presence of both species at the different pH values, for each of the analyzed permittivities were determined at 348, 382 and 371 nm for compounds **1**, **2** and **3**, respectively. The results obtained for the determination of pK_a of these compounds, in a 12.1% w/w ethanol–water mixture ($D = 71.61$) at 25 °C, are given in Table 2. Fig. 5 shows the graphic representation of Eq. (2) for the three compounds. By linear regression, the pH_{ol-w} vs. $\log(A - A_a)/(A_b - A)$ data were adjusted, obtaining the following values:

4(OH)BP

Intersection = $pK_{a_{ol-w}} = 7.98$ (sd = 0.00578)
Slope = 0.988 (sd = 0.01688)

$N = 5$

SSR = 0.00031

$R^2(1 - SSR/(N - 1)/\text{Var}(Y)) = 0.99913$

$R^2(Y, \text{Pred}(Y)) = 0.99913$

2(OH)BP

Intersection = $pK_{a_{ol-w}} = 9.82$ (sd = 0.00775)
Slope = 1.067 (sd = 0.02289)

$N = 6$

SSR = 0.00111

$R^2(1 - SSR/(N - 1)/\text{Var}(Y)) = 0.9982$

$R^2(Y, \text{Pred}(Y)) = 0.9982$

2(OH),4(CH₃O)BP

Intersection = $pK_{a_{ol-w}} = 9.94$ (sd = 0.00623)
Slope = 1.060 (sd = 0.02051)

$N = 6$

SSR = 0.00090

$R^2(1 - SSR/(N - 1)/\text{Var}(Y)) = 0.9985$

$R^2(Y, \text{Pred}(Y)) = 0.9985$

where N is the number of data; SSR, sum of square residual; R , multiple correlation coefficient; $\text{Var}(Y)$, total variation of Y ; and $\text{Pred}(Y)$, predicted Y .

Table 2

Data for determination of pK_a of hydroxy-benzophenones, in ethanol–water 12.1% w/w ($D = 71.61$) at 25 °C

4(OH)BP ^a			2(OH)BP ^b			2(OH),4(CH ₃ O)BP ^c	
pH_{ol-w}	$A_{348 \text{ nm}}$	$\log(A - A_a/A_b - A)$	pH_{ol-w}	$A_{382 \text{ nm}}$	$\log(A - A_a/A_b - A)$	$A_{371 \text{ nm}}$	$\log(A - A_a/A_b - A)$
7.39	0.339	-0.600	9.53	0.378	-0.271	0.342	-0.393
7.58	0.474	-0.390	9.71	0.442	-0.119	0.408	-0.204
7.77	0.611	-0.213	9.90	0.535	0.092	0.474	-0.033
7.96	0.786	-0.009	10.09	0.606	0.259	0.543	0.144
8.15	0.938	0.167	10.28	0.672	0.432	0.599	0.295
			10.45	0.720	0.582	0.664	0.498

A_a = absorbance of the acid form (AH); A_b = absorbance of the conjugate form (A^-); A = absorbance due to the species A^- and AH in the buffer solution; and pH_{ol-w} is the apparent pH in the ethanol–water mixture.

^a Analytic concentration of 4(OH)BP = 6.57×10^{-5} M; A_a at 348 nm = 0.034; A_b at 348 nm = 1.554.

^b Analytic concentration of 2(OH)BP = 2.67×10^{-4} M; A_a at 382 nm = 0.109; A_b at 382 nm = 0.880.

^c Analytic concentration of 2(OH),4(CH₃O)BP = 1.59×10^{-4} M; A_a at 371 nm = 0.145; A_b at 371 nm = 0.829.

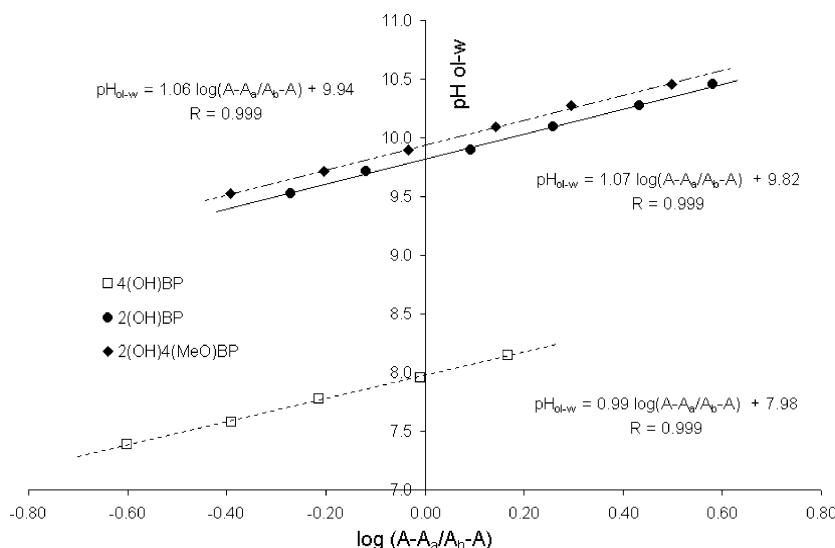


Fig. 5. Determination of the pK_a of hydroxy-benzophenones in ethanol–water 12.1% w/w ($D = 71.61$) at 25 °C. Graphic representation of Eq. (2).

In the determination of the pK_a values at the different permittivities good correlation coefficients and slope values close to one were obtained in all cases, as established by the Henderson–Hasselbach used.

4.4. Solvent effects

Table 3 shows the pK_a values determined for **1**, **2** and **3** at 25 °C, in diverse ethanol–water solutions. It is known that one of the most important factor determining the equilibrium constants (or reaction rates) is the reaction medium; and it can be observed that the pK_a values of the compounds increase when the permittivity of the reaction medium decreases.

The influence of the solvent upon the specific rate of ion–ion, ion–dipole or dipole–dipole reactions can be analyzed using the expression by Kirkwood [25,26].

$$\ln k = \ln k_0 + \frac{e^2}{2DkT} \left[\frac{Z_A^2}{r_A} + \frac{Z_B^2}{r_B} - \frac{(Z_A + Z_B)^2}{r_{\neq}} \right] + \frac{3}{4DkT} \left[\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_{\neq}^2}{r_{\neq}^3} \right] \quad (3)$$

In this equation k_0 and k are the reaction specific rates for media with infinite and D relative permittivity; e is the unit of electric charge; k is Boltzmann's constant; T is the absolute temperature; Z_A and Z_B are the charges of the two ions; r is the radius of the involved species; μ stands for the dipolar moments while that the symbol \neq refers to the activated complex.

We used Kirkwood's equation to obtain a relationship between the pK_a of a compound and the D of the medium. It is evident that in the acid–base dissociation equilibrium of Eq. (1), the forward reaction involves to two dipolar molecules, AH and H_2O , while the reverse reaction involves the A^- and

Table 3
Values of pK_a of hydroxy-benzophenones at 25 °C in ethanol–water solutions

EtOH (%w/w)	D (25 °C)	$pK_{a,ol-w}$		
		4(OH)BP	2(OH)BP	2(OH),4(CH ₃ O)BP
12.1	71.61	7.98	9.82	9.94
16.2	69.19	8.17	9.99	10.11
20.3	66.78	8.37	10.16	10.31
24.7	64.19	8.61	10.34	10.52
29.0	61.66	8.86	10.55	10.70

H_3O^+ ions. Consequently, applying Kirkwood's equation to these two reactions in equilibrium, Eq. (4) was obtained

$$\text{p}K_{\text{a}} = \text{p}K_{\text{a}}^0 + \frac{1}{2.303} \left[\frac{e^2}{2kT} \left(\frac{1}{r_{\text{A}^-}} + \frac{1}{r_{\text{H}_3\text{O}^+}} \right) + \frac{3}{4kT} \left(\frac{\mu_{\neq}^2}{r_{\neq}^3} - \frac{\mu_{\text{AH}}^2}{r_{\text{AH}}^3} - \frac{\mu_{\text{H}_2\text{O}}^2}{r_{\text{H}_2\text{O}}^3} \right) \right] \frac{1}{D} \quad (4)$$

The $\text{p}K_{\text{a,ol-w}}$ values determined for **1**, **2** and **3** were plotted against $1/D$ according to Eq. (4), as is shown in Fig. 6. The following expressions were obtained:

$$\text{p}K_{\text{a,ol-w}}(\mathbf{1}) = 2.5231 + 390.67/D \quad (R = 1.0000) \quad (5)$$

$$\text{p}K_{\text{a,ol-w}}(\mathbf{2}) = 5.3444 + 321.03/D \quad (R = 0.9997) \quad (6)$$

$$\text{p}K_{\text{a,ol-w}}(\mathbf{3}) = 5.1767 + 341.76/D \quad (R = 0.9985) \quad (7)$$

Using the above equations, the following values were obtained in water at ionic strength 0.05 M and 25 °C:

$$\text{p}K_{\text{a,w}}(\mathbf{1}) = 7.51; \quad \text{p}K_{\text{a,w}}(\mathbf{2}) = 9.44; \quad (8)$$

$$\text{p}K_{\text{a,w}}(\mathbf{3}) = 9.54$$

Comparing the $\text{p}K_{\text{a,w}}$ of **1** with that of 4-hydroxy-chalcone ($\text{p}K_{\text{a,w}} = 8.13$) [13], it can be inferred that the greater ionization of the *p*-OH group of **1** is due to a greater π electronic delocalization of its benzoyl group. This suggests that the molecular

planarity of **1** is greater than that of 4-hydroxy-chalcone. The $\text{p}K_{\text{a,ol-w}}$ data of **2** and **3** indicate that the *o*-OH of **2** ionizes more easily than *o*-OH of **3**. This fact matches the electron-donating effect of the *p*-(CH₃O) group of **3**, which intensifies the strong intramolecular hydrogen bonding of compound [27] and, obviously, hinders the ionization of its *o*-OH group.

On the other hand, although the permittivity is an important physical property to measure the solvation abilities of solvents, we considered of great interest to relate the $\text{p}K_{\text{a,ol-w}}$ determined with other parameters of the solvents, which measure their specific interactions [28]. In this manner, to describe the solvent effects on the acid–base equilibria analyzed, we selected the parameter α [29] the solvatochromatic polarity–polarizability parameter π^* [29], and the solvation parameter *Acity* [30].

The empirical parameter α measures the hydrogen bond donating (HBD) ability of a solvent, and it is therefore very useful for describing interactions that involve solute–solvent intermolecular hydrogen bonds. The values of α determined for water and ethanol are [31] 1.17 and 0.86, respectively.

Several properties of binary hydroalcoholic mixtures can be calculated in an approximate fashion using expression [32],

$$P_{\text{MIXTURE}} = P_{\text{WATER}}X_{\text{WATER}} + P_{\text{EtOH}}X_{\text{EtOH}} \quad (9)$$

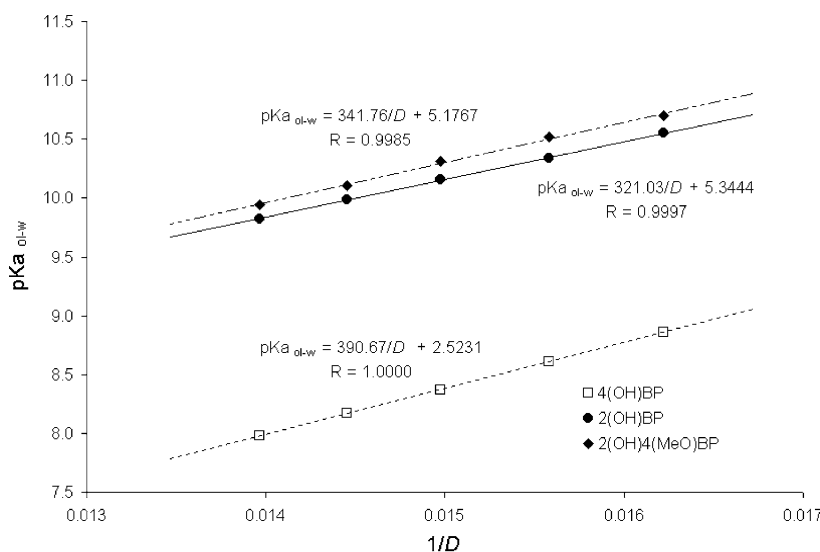


Fig. 6. Variations of the $\text{p}K_{\text{a,ol-w}}$ values hydroxy-benzophenones with the permittivity of ethanol–water solutions.

Table 4
Values of the empirical parameters α , π^* and *Acity* of the ethanol–water mixtures used as reaction media

Solution	Ethanol (%w/w)	Water (%w/w)	α	π^*	<i>Acity</i>	<i>D</i>
1	0.00	100.00	1.170	1.090	1.000	78.39
2	12.10	87.90	1.132	1.023	0.959	71.61
3	16.20	83.80	1.120	1.001	0.945	69.19
4	20.30	79.70	1.107	0.978	0.931	66.78
5	24.70	75.30	1.093	0.954	0.916	64.19
6	29.00	71.00	1.080	0.931	0.901	61.66
7	100.00	0.00	0.860	0.540	0.660	24.55

where *P* is the property of interest and *X* is the percentual fraction (w/w) of the components. For example, using equation

$$\alpha_{\text{MIXTURE}} = \alpha_{\text{WATER}}X_{\text{WATER}} + \alpha_{\text{EtOH}}X_{\text{EtOH}} \quad (10)$$

the values of α were obtained for the hydroalcoholic mixtures used. The values of the π^* and *Acity* parameters were calculated by the same procedure (Table 4).

Figs. 7 and 8 show the linear relations obtained between the $pK_{a_{\text{ol-w}}}$ values and the α and π^* parameters, respectively. From Fig. 7 the following

equations were obtained:

$$pK_{a_{\text{ol-w}}}(\mathbf{1}) = 26.976 - 16.789\alpha \quad (R = 0.9988) \quad (11)$$

$$pK_{a_{\text{ol-w}}}(\mathbf{2}) = 25.451 - 13.807\alpha \quad (R = 0.9994) \quad (12)$$

$$pK_{a_{\text{ol-w}}}(\mathbf{3}) = 26.603 - 14.719\alpha \quad (R = 0.9996) \quad (13)$$

Considering that $\alpha(\text{H}_2\text{O}) = 1.17$ [31], the following data were obtained:

$$pK_{a_w}(\mathbf{1}) = 7.33; \quad pK_{a_w}(\mathbf{2}) = 9.30; \quad (14)$$

$$pK_{a_w}(\mathbf{3}) = 9.38$$

Similarly, from Fig. 8 it was obtained that:

$$pK_{a_{\text{ol-w}}}(\mathbf{1}) = 17.648 - 9.4627\pi^* \quad (R = 0.9988) \quad (15)$$

$$pK_{a_{\text{ol-w}}}(\mathbf{2}) = 17.779 - 7.7822\pi^* \quad (R = 0.9994) \quad (16)$$

$$pK_{a_{\text{ol-w}}}(\mathbf{3}) = 18.425 - 8.2961\pi^* \quad (R = 0.9995) \quad (17)$$

Considering that $\pi^*(\text{H}_2\text{O}) = 1.09$ [31], the following values of pK_{a_w} were obtained:

$$pK_{a_w}(\mathbf{1}) = 7.33; \quad pK_{a_w}(\mathbf{2}) = 9.30; \quad (18)$$

$$pK_{a_w}(\mathbf{3}) = 9.38$$

The pK_{a_w} values obtained using parameters α and π^* agree with each other and match well with those previously calculated using relative permittivities

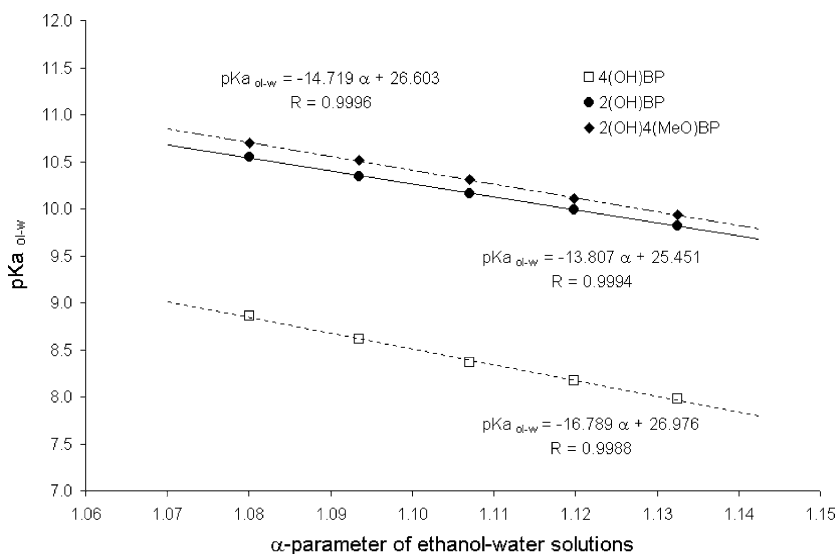


Fig. 7. Relationships between the $pK_{a_{\text{ol-w}}}$ of hydroxy-benzophenones and the α -parameter of ethanol–water solutions.

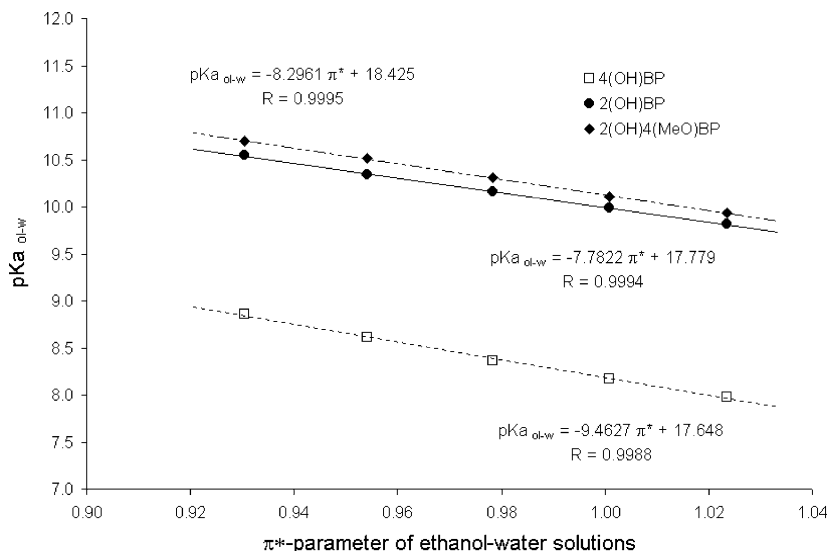


Fig. 8. Variations of the $pK_{a,ol-w}$ of hydroxy-benzophenones with the α -parameter of ethanol–water solutions.

(Eq. (8)). The *Acity* parameter developed by Swain [30], is useful as the α parameter of Taft for measuring the HBD ability of a solvent. In addition, excellent relations were obtained between the $pK_{a,ol-w}$ values determined and the *Acity* parameter of the reaction medium.

The nine linear equations (5)–(7), (11)–(13) and (15)–(17) obtained, which have very good correlation coefficients ($R > 0.998$), indicate that when the polarity–polarizability and solvation abilities of

the ethanol–water solutions grow, the value of the acid–base dissociation constants also increases [33].

Table 5 summarizes the calculated magnitudes with the COSMO method at the RHF/6-31G(d) level of theory for the ionized and non-ionized forms of **1**, **2** and **3**, in ethanol and water. With the total free energy data in solution (G_{sol}^0) the pK_a in pure water ($pK_{a,w}$) were calculated according to Eq. (1), while the pK_a data in pure ethanol ($pK_{a,EtOH}$) were obtained with

Table 5

Calculated magnitudes using the COSMO method at the RHF/6-31G(d) level of theory, at 25 °C

Compound	Ethanol G_{sol}^0	ΔG_{solv}^0	Water G_{sol}^0	ΔG_{solv}^0
4(OH)BP	–647.853653	–6.44	–647.853423	–6.29
4(O [–])BP	–647.367907	–53.81	–647.369455	–54.78
2(OH)BP	–647.853409	–2.41	–647.852898	–2.09
2(O [–])BP	–647.359171	–59.72	–647.361360	–61.09
2(OH)4(CH ₃ O)BP	–761.739592	–2.99	–761.738943	–2.58
2(O [–])4(CH ₃ O)BP	–761.245801	–59.72	–761.247797	–60.97
Ethanol	–154.081155	–3.39	–	–
Ethanol-H ⁺	–154.497665	–69.34	–	–
H ₂ O	–	–	–76.024237	–8.46
H ₃ O ⁺	–	–	–76.440527	–94.88

G_{sol}^0 = total free energy in solution (Hartree); ΔG_{solv}^0 = free energy change of solvation (kcal mol^{–1}); 4(OH)BP = 4-hydroxy-benzophenone; 4(O[–])BP = 4-hydroxy-benzophenonate anion; 2(OH)BP = 2-hydroxy-benzophenone; 2(O[–])BP = 2-hydroxy-benzophenonate anion; 2(OH)4(CH₃O)BP = 2-hydroxy-4-methoxy-benzophenone; 2(O[–])4(CH₃O)BP = 2-hydroxy-4-methoxy-benzophenonate anion.

the acid–base dissociation equilibrium of Eq. (19),



The calculated $\text{p}K_{\text{a}_w}$ and $\text{p}K_{\text{a}_{\text{EtOH}}}$ values were:

$$\text{p}K_{\text{a}_w}(\mathbf{1}) = 31.13; \quad \text{p}K_{\text{a}_w}(\mathbf{2}) = 34.61; \quad (20)$$

$$\text{p}K_{\text{a}_w}(\mathbf{3}) = 34.43$$

$$\text{p}K_{\text{a}_{\text{EtOH}}}(\mathbf{1}) = 31.85; \quad \text{p}K_{\text{a}_{\text{EtOH}}}(\mathbf{2}) = 35.75; \quad (21)$$

$$\text{p}K_{\text{a}_{\text{EtOH}}}(\mathbf{3}) = 35.55$$

In absolute values, the calculated $\text{p}K_{\text{a}_w}$ differs very significantly from the one experimentally determined. Nevertheless, if the calculated $\text{p}K_{\text{a}_w}$ are analyzed comparatively, it is inferred that the ionization in the *p*-hydroxyl group of **1** is greater than in *o*-hydroxyl groups of **2** and **3**, which is coherent with experimental determinations. In addition, from Table 5 it is observed that the free energy change of solvation (ΔG_{sol}^0) of the hydroxy-benzophenonate anions in water are higher (in absolute value) than in EtOH. This suggests that the anions are specifically more solvated in water than in EtOH, according to the values of α -parameters of the solvents. On the other hand, Eqs. (20) and (21) show that $\text{p}K_{\text{a}_w} < \text{p}K_{\text{a}_{\text{EtOH}}}$. Taking into account these reasons, it is inferred that the ionization of **1**, **2** and **3** occurs more easily in water than in EtOH. This conclusion agrees with experimental observations that indicate that the acid–base equilibria are shifted towards the formations of ions when increases the polarity of the solvent [33].

5. Conclusions

The acid–base dissociation constants of hydroxy-BPs, water insoluble compounds, were determined in diverse ethanol–water solutions using a UV–Vis spectroscopic method based on the Henderson–Hasselbalch equation. The $\text{p}K_{\text{a}}$ values obtained in hydroalcoholic mixtures were correlated with solvation parameters of the solvents, such as relative permittivity, the α parameter of Taft, the solvatochromatic polarity–polarizability parameter π^* , and the solvation parameter *Acity*. Excellent linear equations were obtained from which the $\text{p}K_{\text{a}}$ values in pure

water were obtained. The results allowed proving that the *p*-OH group ionizes more easily than the *o*-OH group. It was also inferred that the $\text{p}K_{\text{a}}$ values of the compounds increase when the polarity–polarizability and solvation abilities of the reaction medium decrease. The structures of all the chemical species involved in the acid–base dissociation equilibria studied were calculated at the RHF/6-31G(d) level of theory, in ethanol and water. Considering the theoretical $\text{p}K_{\text{a}}$ values, conclusion were obtained that are coherent with the experimental determinations. The methodology presented in this paper, which basically includes the analysis of the solvent effect upon the ionization constant, permits to obtain their $\text{p}K_{\text{a}}$ values in pure water with enough accuracy. Consequently, this methodology is suitable for obtaining the $\text{p}K_{\text{a}}$ of compounds of low solubility in water such as the ones here studied.

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