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Dissociation constants of phenols in methanol–water mixtures

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Abstract

A preferential solvation model that relates solute properties with solvent composition in binary mixtures has been applied to the dissociation pK_a values of a set of 28 substituted phenols in methanol–water mixtures. The parameters of the model allow estimation of the pK_a value of each phenol for any methanol–water composition. Moreover, it is demonstrated that the pK_a values of the whole set of phenols at any methanol–water composition are linearly related to the pK_a values of the phenols in water. Equations that relate the correlations' slope and intercept values with the solvent composition have been derived and tested with the set of phenols. The general parameters obtained for these equations allow an accurate calculation of the pK_a value of any phenol, even of those not included in the original set, at any methanol–water composition solely from the pK_a value of the phenol in water. These calculated pK_a values can be used for quantitative structure–HPLC retention relationships. The method is tested by comparison of the calculated pK_a values with the HPLC determined pK_a values of 26 phenols in a polymeric column with a 50% methanol as mobile phase.

Keywords: Dissociation constants; Preferential solvation; Phenols; Methanol–water mixtures

1. Introduction

Methanol–water mixtures are widely used as solvents in analytical chemistry. Typical uses involve acid-base pK determination, titrimetric analysis [1], and HPLC separations [2–4].

In previous studies, we have demonstrated that the rigorous pH determination in the mixed solvent used as mobile phases for an HPLC separation of ionizable compounds is needed to get correct retention-mobile phase pH relationships [3–5]. In fact, the IUPAC has remarked on the importance of the knowledge of the pH values of buffers in mixed solvents in order to achieve complete and effective pH standardization in these media [6–8]. The establishment of reference pH values of buffers in mixed solvents requires the determination of the acid-base pK values of the acids and bases that compose the buffer in the mixed solvent. We have determined the pK values of different acids in several mixed solvents and we have proposed models that relate the pK value with the solvent composition [5,9–12]. The relationships obtained allow calculation of the pK value of the acid for any solvent composition. The relationships have been used in the calculation of the pH values of reference buffers [3–5], for quantitative structure–HPLC retention relationships [13,14], and for the estimation of the aqueous pK values of pharmaceutical drugs sparingly soluble in water [12,15].

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In this paper, we analyze the available literature p*K* data of phenols in methanol–water mixtures and relate it with the solvent composition through a model previously developed [16–20] that take into account the preferential solvation of the phenol by any of the components of the solvent mixture. The equations developed allow the calculation of the p*K* value of the phenols studied for any methanol–water mixture. The similar behaviour in preferential solvation of the phenols allows also to relate the p*K* values in any methanol–water mixture with the p*K* value in pure water. This lead to the establishment of equations to estimate the p*K* value of any phenol, even for those not included in the studied data set, at any methanol–water mixture from its p*K* value in water.

2. Theory

2.1. Relationships between pK and solvent composition in binary solvents

We have developed several models that consider the solute–solvent and solvent–solvent interactions in binary solvent mixtures to relate a microscopic solute property with the solvent composition [16–20]. The models were initially derived for the transition energy (E_T) of solvatochromic indicators, which is a microscopic property that depends on the composition and properties of the solvation sphere of the solute used as indicator [21]. Some of the models were also applied to dissociation p*K* values of acids in binary solvents [5,9–12], since the p*K* is another microscopic property that depends on the composition of the solute solvation sphere.

An extensive analysis of the transition energy of solvatochromic indicators in more than 70 binary solvents [16–20] has shown that the most appropriate model is based on the two solvent exchange processes:

$$\mathrm{I(S1)_2} + 2\mathrm{S2} \Leftrightarrow \mathrm{I(S2)_2} + 2\mathrm{S1}$$
$$\mathrm{I(S1)_2} + \mathrm{S2} \Leftrightarrow \mathrm{I(S12)_2} + \mathrm{S1}$$

where S1 and S2 are the two solvents that constitute the solvent mixture (e.g. water and methanol) and $\mathrm{I(S1)_2}$ and $\mathrm{I(S2)_2}$ refer to the solute solvated by these solvents. $\mathrm{I(S12)_2}$ refers to the solute solvated by a mixed solvent S12 formed by interaction of S1 and S2. By convention we shall refer S1 to water and S2 to methanol. Therefore, $\mathrm{I(S1)_2}$ is the solute solvated by water, $\mathrm{I(S2)_2}$ the solute solvated by methanol, and $\mathrm{I(S12)_2}$ is the solute solvated by methanol and water which interact to form a hydrogen bonding complex, with different properties. The model is equivalent to that developed by Skwierczynski and Connors [22], except for that we consider the hydrogen bonding complex to have different properties than the simple average of the properties of water and methanol [16–18].

The constants of the processes are the preferential solvation parameters $f_{2/1}$ and $f_{12/1}$ that measure the tendency of the solute to be solvated by solvent S2 (methanol) or S12 (methanol–water) in reference to solvent S1 (water).

$$f_{2/1} = \frac{x_2^s / x_1^s}{(x_2/x_1)^2} \tag{1}$$

$$f_{12/1} = \frac{x_{12}^s / x_1^s}{x_2/x_1} \tag{2}$$

In Eqs. (1) and (2), x_1^s, x_2^s, and x_{12}^s are the mole fractions of solvents S1, S2, and S12 solvating the solute (i.e. water, methanol, and methanol–water, respectively) and x_1 and x_2 the mole fractions of solvent S1 and S2 mixed. Taken into account that the addition of the three mole fractions is the unit,

$$x_1^s + x_2^s + x_{12}^s = 1 \tag{3}$$

the composition of the sphere of solvation of the solute can be derived

$$x_1^s = \frac{x_1^2}{x_1^2 + x_2^2 f_{2/1} + x_1 x_2 f_{12/1}} \tag{4}$$

$$x_2^s = \frac{x_2^2 f_{2/1}}{x_1^2 + x_2^2 f_{2/1} + x_1 x_2 f_{12/1}} \tag{5}$$

$$x_{12}^s = \frac{x_1 x_2 f_{12/1}}{x_1^2 + x_2^2 f_{2/1} + x_1 x_2 f_{12/1}} \tag{6}$$

The ΔG^0 of dissociation of the acid in the mixed solvent can be considered as an average of the ΔG^0 in pure solvents S1, S2, and S12, according to the mole fractions of these solvents that solvate the acid

(x_1^s, x_2^s, and x_{12}^s). Since the acid-base pK is directly related with the ΔG^0, we can write:

$$pK = x_1^s pK_{(S1)} + x_2^s pK_{(S2)} + x_{12}^s pK_{(S12)} \quad (7)$$

where $pK_{(S1)}$, $pK_{(S2)}$, and $pK_{(S12)}$ are the acidity pK values of the acid in solvents S1 (water), S2 (methanol), and S12 (methanol–water hydrogen bond complex). Replacing Eqs. (4)–(6) in Eq. (7), the following equation, which relates the pK value of the acid with the mole fraction of methanol in the mixture (x_2), is obtained:

$$pK = \frac{(1 - x_2)^2 pK_{(S1)} + x_2^2 f_{2/1} pK_{(S2)} + (1 - x_2) x_2 f_{12/1} pK_{(S12)}}{(1 - x_2)^2 + x_2^2 f_{2/1} + (1 - x_2) x_2 f_{12/1}} \quad (8)$$

2.1.1. Relationships between pK values in different media

Eq. (8) allows to estimate the pK value of a particular compound at any solvent composition provided that the $pK_{(S1)}$, $pK_{(S2)}$, $pK_{(S12)}$, $f_{2/1}$, and $f_{12/1}$ parameters are known. These parameters depend on the solute–solvent interactions and therefore a particular set of parameters is, in principle, required for each compound.

Another approach is to relate the pK values of a series of compounds (e.g. phenols) in a particular solvent (e.g. methanol) with the pK values of the same compounds in another solvent (e.g. water). The basis of this approach is the theory proposed by Izmailov [23,24] to explain the dissociation of an acid in a solvent. When the dissociation pK values of the acid in two different solvents (S and S′) are compared, the following equation is derived:

$$pK_{(S)} = a\, pK_{(S')} + b \quad (9)$$

The most simplified theory predicts the slope *a* of the equation to be the unity, and the intercept *b* to have the same value for any compound family. However, it has been demonstrated that consideration of the specific solvation effects (other than electrostatic effects) leads to equations with slopes *a* different from unity, but constant for each family of compounds (e.g. phenols) and intercepts *b* different for each family, but constant for the compounds of the family [24]. In fact, the value of the slope *a* measures the ‘‘resolution of acid strength’’ [25] of the family of compounds in the solvent S in reference to the solvent S′. The approach has been well established for the pK values of families of compounds in pure solvents in reference to the pK values in water [23–25]. However, application to the pK values in solvent mixtures is doubtful because the preferential solvation can act in a different degree for the different compounds of the family. In spite of that, the approach has been applied successfully to a particular dimethyl sulfoxide/water mixture [26].

On behalf of the application to solvent mixtures, it can be argued that Eq. (9) assumes that the specific solvation effects are similar for all the compounds belonging to the same family. In this instance, one may expect that all these compounds will show similar preferential solvation in the same mixed solvent. This implies that the preferential solvation parameters $f_{2/1}$ and $f_{12/1}$ should be constant for all the compounds and therefore Eq. (8) could be written as

$$pK = k_1 pK_{(S1)} + k_2 pK_{(S2)} + k_{12} pK_{(S12)} \quad (10)$$

where k_1, k_2, and k_{12} are constants for a particular solvent composition x_2.

If the equation is applied to binary systems of water (S1) and methanol (S2), it has been already demonstrated that for phenols $pK_{(S2)}$ is linearly related to $pK_{(S1)}$ [24]

$$pK_{(S2)} = a_{S2} pK_{(S1)} + b_{S2} \quad (11)$$

S12 is an hypothetical ‘‘pure’’ solvent formed by the hydrogen bonding between methanol and water [18] and therefore one may assume that there is also a linear relationship between the $pK_{(S12)}$ and the $pK_{(S1)}$ values.

$$pK_{(S12)} = a_{S12} pK_{(S1)} + b_{S12} \quad (12)$$

Replacing Eqs. (11) and (12) in (10), the following equation, that predicts a linear relationship between the pK values of the compounds at any methanol–water mixture (pK) and the pK values of the compounds in water ($pK_{(S1)}$), is obtained

$$pK = a\, pK_{(S1)} + b \quad (13)$$

The slope *a* and the intercept *b* of the equation depend on the particular solvent composition (x_2)

Table 1
Parameters for pK_a values of phenols in methanol–water mixtures

Phenol	$pK_{(S1)}$	$pK_{(S2)}$	$f_{2/1}$	$pK_{(S12)}$	$f_{12/1}$	SD	n[a]	Reference
2,6-Dibromo-4-nitrophenol	3.508	7.310	0.10	4.278	1.46	0.01	6	[27]
2,6-Dichloro-4-nitrophenol	3.552	7.400	0.26	4.242	2.70	0.01	6	[27]
2,6-Dinitrophenol	3.730	7.700	0.10	4.763	1.20	0.06	53	[27–31]
2,4-Dinitrophenol	4.099	7.818	0.11	4.878[b]	1.10	0.07	24	[27,29,31]
2,3-Dinitrophenol	5.235	9.433	0.16	6.186[b]	1.67	0.06	9	[29]
2,5-Dinitrophenol	5.242	8.933	0.55	5.596	4.23	0.05	24	[27,29,32]
3,4-Dinitrophenol	5.424	9.464	0.09	6.405[b]	1.03	0.05	9	[29]
2,6-Di-*tert*.-butyl-4-nitrophenol	6.617	10.890	0.12	8.011	1.42	0.04	12	[33]
3,5-Dinitrophenol	6.723	10.289	0.14	7.508	1.65	0.05	12	[33]
4-Nitrophenol	7.150	11.236	0.08	8.633	0.97	0.05	30	[29,34,35]
2-Nitrophenol	7.238	11.524	0.24	8.352	2.07	0.06	25	[29,33,36]
4-Hydroxybenzaldehyde	7.577	12.033	0.16	8.882	1.80	0.04	12	[34]
3,5-Dichlorophenol	8.192	12.104	0.49	8.970	3.68	0.03	12	[33]
Salicylaldehyde	8.372	12.820	0.05	10.381	0.92	0.02	12	[33]
3-Nitrophenol	8.429	12.400	0.09	9.814	1.16	0.04	25	[29,33,37]
2-Chlorophenol	8.530	12.830	0.09	10.481	1.38	0.02	12	[33]
2-Fluorophenol	8.701	12.941	0.12	10.444	1.65	0.03	12	[33]
3-Chlorophenol	9.089	13.097	0.17	10.400	1.49	0.05	12	[33]
4-Bromophenol	9.330	13.627	0.17	10.670	2.20	0.03	11	[34]
4-[(*E*)-2-(4-Nitrophenyl)-1-ethenyl]phenol	9.360	13.110	0.09	10.940[b]	1.08	0.06	6	[35]
1-Naphthol	9.364	13.910	0.10	11.357	1.97	0.02	12	[33]
2-Methoxyphenol	9.943	14.483	0.35	11.506	3.98	0.05	12	[33]
Phenol	9.969	14.324	0.11	11.634	2.02	0.05	25	[29,34]
3-Methylphenol	10.043	14.482	0.18	11.675	2.78	0.06	12	[33]
3,5-Dimethylphenol	10.147	14.622	0.19	11.824	3.02	0.04	12	[33]
4-*tert*.-Butylphenol	10.215	14.521	0.14	11.792	2.10	0.03	11	[34]
4-Methylphenol	10.258	14.540	0.14	11.857	1.98	0.03	12	[34]
2-Methylphenol	10.258	14.901	0.13	12.107	2.59	0.05	12	[33]

[a] n: number of pK points analyzed excluding those of the pure solvents water and methanol (i.e. number of solvent mixtures analyzed).
[b] $pK_{(S12)}$ calculated from Eq. (20).

and on the constancy of the preferential solvation parameters $f_{2/1}$ and $f_{12/1}$ for the different compounds, according to

$$a=\frac{(1-x_2)^2+x_2^2 f_{2/1}a_{S2}+(1-x_2)x_2 f_{12/1}a_{S12}}{(1-x_2)^2+x_2^2 f_{2/1}+(1-x_2)x_2 f_{12/1}} \tag{14}$$

$$b=\frac{x_2^2 f_{2/1}b_{S2}+(1-x_2)x_2 f_{12/1}b_{S12}}{(1-x_2)^2+x_2^2 f_{2/1}+(1-x_2)x_2 f_{12/1}} \tag{15}$$

or

$$a=\frac{1+a_1x_2+a_2x_2^2}{1+a_3x_2+a_4x_2^2} \tag{16}$$

$$b=\frac{b_1x_2+b_2x_2^2}{1+b_3x_2+b_4x_2^2} \tag{17}$$

where a_1, a_2, a_3, a_4, b_1, b_2, b_3, and b_4 are fitting parameters constant for all phenols at all methanol–water mixtures. Similar equations can be derived if the solvent mixture composition is measured in concentration units other than mole fraction. For instance, volume fractions (v_2) and weight fractions (w_2) are related with mole fraction according to

$$x_2=\frac{v_2V_{M1}}{(1-v_2)V_{M2}+v_2V_{M1}} \tag{18}$$

$$x_2=\frac{w_2M_1}{(1-w_2)M_2+w_2M_1} \tag{19}$$

where V_{M1} and V_{M2} are the molar volumes of water and methanol, respectively (18.07 and 40.7 cm^3 mol^{-1} at 25°C), and M_1 and M_2 the molecular weighs of water and methanol, respectively (18.01

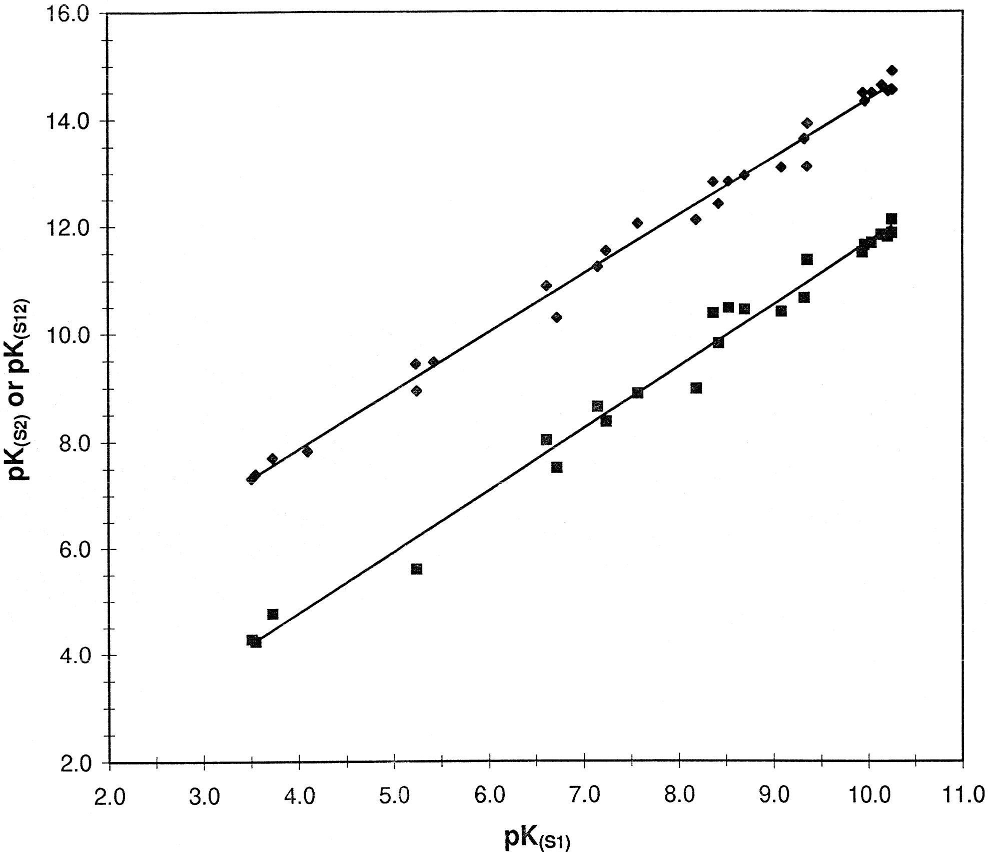

Fig. 1. Linear relationships between the pK parameters of the preferential solvation model: (◆) p$K_{(S2)}$ (pK_a of the phenol in pure methanol) and (■) p$K_{(S12)}$ (pK_a of the phenol in pure methanol–water hydrogen bonded complex) versus p$K_{(S1)}$ (pK_a of the phenol in pure water).

and 32.04 g mol^{-1}). Substituting Eqs. (18) or (19) in Eqs. (16) and (17), equations of the same type, with different fitting parameters, are obtained. Same type of equations are also obtained if the solvent composition is measured in volume percentage (V% = 100 v_2) or weigh percentage (W% = 100 w_2).

In this paper, we shall test the validity of the assumptions taken and the equations derived for the studied family of phenols in methanol–water mixtures.

3. Results and discussion

3.1. Analysis of literature pK_a data of phenols

A data set of pK values of 28 phenols (including 1-naphtol) in methanol–water mixtures have been analyzed by means of the proposed equations. The pK data were obtained from references [27–37]. Although most data are also given in the excellent compilation of Palm [38,39], the edition is nowadays exhausted and very difficult to consult. The pK data for each phenol were fitted to Eq. (8) and the parameters obtained are presented in Table 1. In this table, p$K_{(S1)}$ and p$K_{(S2)}$, obtained from the fits, refer in fact to the pK value of the phenol in pure water and methanol, respectively. There are small differences (in general less than 0.1 pK units) between the values reported in Table 1 and those reported for the same phenols in reference [24]. The reason is in reference [24] we averaged all the available pK data of the same phenol in pure water or methanol, whereas here we have preferred to use the data for pure water and methanol given by the same authors whose pK data in methanol–water were analyzed. When the series analyzed for a particular phenol in methanol–water mixtures did not included pK data for pure water and/or methanol, the data in reference [24] was used. The pK values of 2,6-dichloro-4-nitrophenol, 2,3-dinitrophenol, and 3,4-dinitrophenol in pure methanol were not available and we have estimated them from their pK values in water through Eq. (11) and the parameters obtained from Ref. [24], i.e. $a_{S2}=1.08$ and $b_{S2}=3.66$.

The p$K_{(S12)}$ values obtained have been plotted against the p$K_{(S1)}$ values and this plot is presented in Fig. 1 together with the plot of p$K_{(S2)}$ against p$K_{(S1)}$. A reasonable straight line is obtained in both cases, which confirms the validity of Eqs. (11) and (12). The correlations obtained are:

$$\mathrm{p}K_{(S12)} = 1.152\,\mathrm{p}K_{(S1)} + 0.159$$

$$n = 24 \quad r = 0.993 \quad \mathrm{SD} = 0.31 \quad F = 1482 \qquad (20)$$

$$\mathrm{p}K_{(S2)} = 1.084\,\mathrm{p}K_{(S1)} + 3.507$$

$$n = 28 \quad r = 0.996 \quad \mathrm{SD} = 0.23 \quad F = 3047 \qquad (21)$$

The slope and intercept of the correlation of the

Table 2
pK_a values of phenols at different methanol–water compositions calculated from Eq. (8) and the parameters of Table 1

Methanol contents											
x_2:	0.000	0.047	0.100	0.160	0.229	0.308	0.401	0.510	0.641	0.800	1.000
v_2:	0.000	0.100	0.200	0.300	0.400	0.500	0.600	0.700	0.800	0.900	1.000
w_2:	0.000	0.081	0.165	0.254	0.346	0.442	0.543	0.649	0.760	0.877	1.000
Phenol	pK										
2,6-Dibromo-4-nitrophenol	3.508	3.561	3.620	3.687	3.764	3.855	3.967	4.115	4.338	4.783	7.310
2,6-Chloro-4-nitrophenol	3.552	3.636	3.721	3.810	3.904	4.009	4.133	4.293	4.535	5.031	7.400
2,6-Dinitrophenol	3.730	3.789	3.856	3.934	4.025	4.137	4.276	4.463	4.742	5.276	7.700
2,4-Dinitrophenol	4.099	4.140	4.189	4.246	4.317	4.405	4.522	4.686	4.948	5.484	7.818
2,3-Dinitrophenol	5.235	5.309	5.391	5.482	5.586	5.707	5.855	6.049	6.336	6.896	9.433
2,5-Dinitrophenol	5.242	5.307	5.372	5.439	5.513	5.600	5.712	5.870	6.132	6.689	8.933
3,4-Dinitrophenol	5.424	5.473	5.529	5.597	5.678	5.780	5.913	6.096	6.383	6.951	9.464
2,6-Di-tert.-butyl-4-nitrophenol	6.617	6.710	6.813	6.928	7.059	7.210	7.391	7.616	7.929	8.482	10.890
3,5-Dinitrophenol	6.723	6.784	6.850	6.924	7.008	7.106	7.225	7.379	7.607	8.056	10.289
4-Nitrophenol	7.150	7.219	7.298	7.392	7.503	7.638	7.809	8.036	8.363	8.945	11.236
2-Nitrophenol	7.238	7.344	7.457	7.579	7.713	7.864	8.043	8.271	8.598	9.209	11.524
4-Hydroxybenzaldehyde	7.577	7.685	7.802	7.928	8.067	8.223	8.405	8.628	8.938	9.499	12.033
3,5-Dichlorophenol	8.192	8.316	8.434	8.551	8.670	8.798	8.947	9.137	9.424	9.988	12.104
Salicylaldehyde	8.372	8.460	8.561	8.678	8.817	8.982	9.186	9.446	9.799	10.366	12.820
3-Nitrophenol	8.429	8.505	8.591	8.690	8.805	8.941	9.107	9.320	9.619	10.141	12.400
2-Chlorophenol	8.530	8.655	8.794	8.947	9.118	9.312	9.537	9.805	10.147	10.678	12.830
2-Fluorophenol	8.701	8.834	8.977	9.132	9.301	9.487	9.698	9.945	10.260	10.763	12.941
3-Chlorophenol	9.089	9.180	9.282	9.397	9.528	9.682	9.867	10.104	10.440	11.035	13.097
4-Bromophenol	9.330	9.463	9.601	9.744	9.894	10.055	10.233	10.441	10.718	11.209	13.627
4-[(*E*)-2-(4-Nitrophenyl)-1-ethenyl]phenol	9.360	9.441	9.533	9.640	9.765	9.913	10.095	10.327	10.648	11.182	13.110
1-Naphthol	9.364	9.542	9.727	9.919	10.121	10.334	10.561	10.813	11.113	11.559	13.910
2-Methoxyphenol	9.943	10.204	10.435	10.646	10.841	11.028	11.217	11.424	11.691	12.170	14.483
Phenol	9.969	10.121	10.279	10.444	10.616	10.799	10.996	11.218	11.490	11.924	14.324
3-Methylphenol	10.043	10.242	10.436	10.625	10.813	11.001	11.195	11.407	11.667	12.100	14.482
3,5-Dimethylphenol	10.147	10.367	10.576	10.777	10.972	11.164	11.359	11.568	11.821	12.240	14.622
4-*tert*.-Butylphenol	10.215	10.365	10.519	10.680	10.849	11.028	11.223	11.446	11.728	12.194	14.521
4-Methylphenol	10.258	10.402	10.553	10.711	10.879	11.059	11.257	11.485	11.774	12.252	14.540
2-Methylphenol	10.258	10.469	10.677	10.882	11.086	11.291	11.501	11.725	11.989	12.399	14.901

Table 3
Parameters for the correlation between pK_a values of phenols at different methanol–water compositions and the pK_a values of the phenols in water (Eq. (13))

v_2	0.000	0.100	0.200	0.300	0.400	0.500	0.600	0.700	0.800	0.900	1.000	1.000[a]
a	1.000	1.019	1.038	1.055	1.071	1.086	1.099	1.109	1.113	1.103	1.084	1.08
b	0.000	−0.034	−0.056	−0.064	−0.052	−0.016	0.057	0.190	0.445	1.030	3.507	3.66
SD	–	0.038	0.069	0.093	0.113	0.127	0.137	0.143	0.145	0.148	0.230	0.30
r	–	0.9999	0.9996	0.9993	0.9990	0.9987	0.9985	0.9984	0.9984	0.9983	0.9958	0.991

[a] From Ref. [24] with $n=86$.

pK in pure methanol (p$K_{(S2)}$) with the pK in pure water (p$K_{(S1)}$) agree very well with the parameters obtained in Ref. [24] with a larger number of phenols ($n=86$, $a_{S2}=1.08$ and $b_{S2}=3.66$, see above). The slope of Eq. (20) is larger than the slope of Eq. (21) and we may conclude that the resolution of the acid strength in the hypothetical S12 solvent (methanol–water hydrogen bond complex) is better than in methanol (S2). In fact, the existence of solvent S12 was postulated in our model to explain the variation of transition energies of solvatochromic indicators in solvent mixtures [16–20]. However, experimental evidence of the existence of the methanol–water complex has been very recently reported

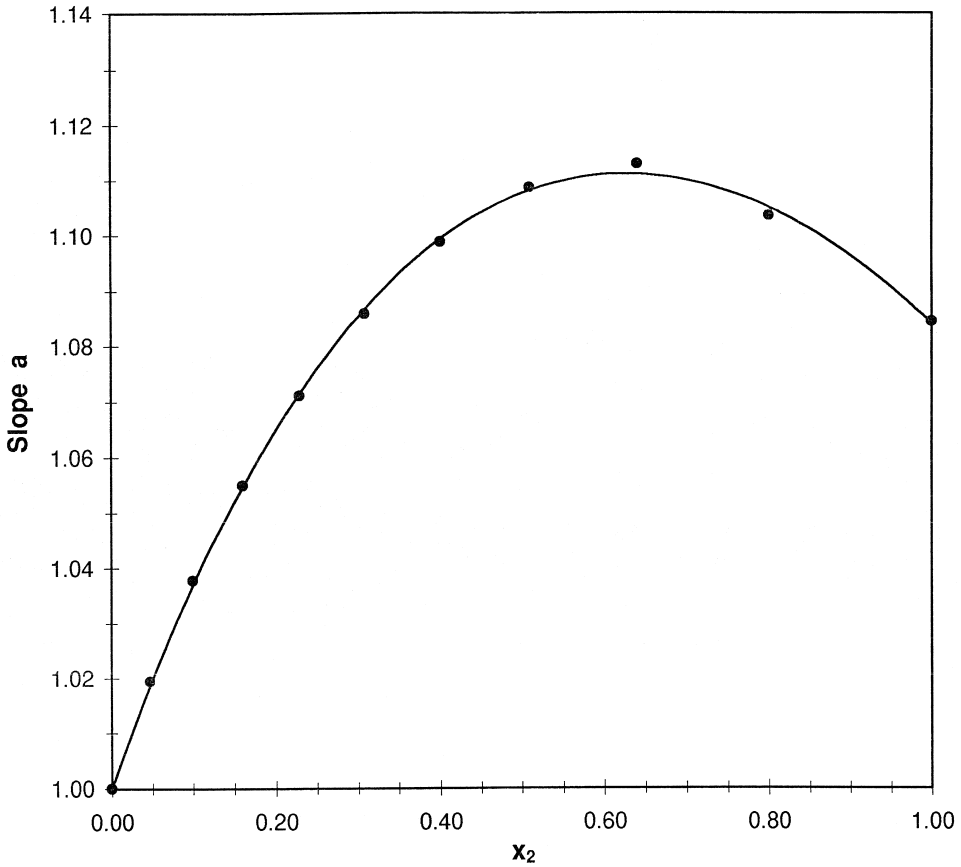

Fig. 2. Variation of the slope a of the correlations of the pK_a values of phenols in methanol–water mixtures versus pK_a in water (Eq. (13)) with solvent composition (in mole fraction of methanol): (●) a values of Table 3 fitted to Eq. (22) -continuous line-.

by Zhao and Malinowski [40] through factor analysis of FT-IR data.

2,4-Dinitrophenol, 2,3-dinitrophenol, 3,4-dinitrophenol, and 4-[(*E*)-2-(4-nitrophenyl)-1-ethenyl]-phenol were not included in correlation (20) because the estimation of $pK_{(S12)}$ and preferential solvation parameters $f_{2/1}$ and $f_{12/1}$ from p*K* data did not converge to reasonable values. In fact, Eq. (20) was used to estimate $pK_{(S12)}$ for these phenols and from them $f_{2/1}$ and $f_{12/1}$ parameters could be well estimated.

Table 1 shows that the preferential parameters $f_{2/1}$ and $f_{12/1}$ of the different phenols are rather constant, and therefore we can expect linear plots for the p*K* values of the phenols in methanol–water mixtures versus the p*K* values in water. This has been checked by calculation of the p*K* value of each phenol at different methanol–water mixtures from Eq. (8) and the parameters of Table 1. Table 2 presents the p*K* values calculated for the solvent mixtures studied. These p*K* values have been correlated for each mixture with the p*K* value in water and the parameters of the correlations are presented in Table 3. The statistical parameters indicate that the precision of the calculated data decreases with the increase in methanol contents of the mixture, as it is usual in measurements in water–organic solvent mixtures, but in no case the precision is worse than the precision obtained for phenols in Ref. [24], included in the Table.

The slopes and the intercepts presented in Table 3 have been plotted against the solvent composition and the plots are presented in Figs. 2 and 3. The slope of the correlations presents a maximum for an

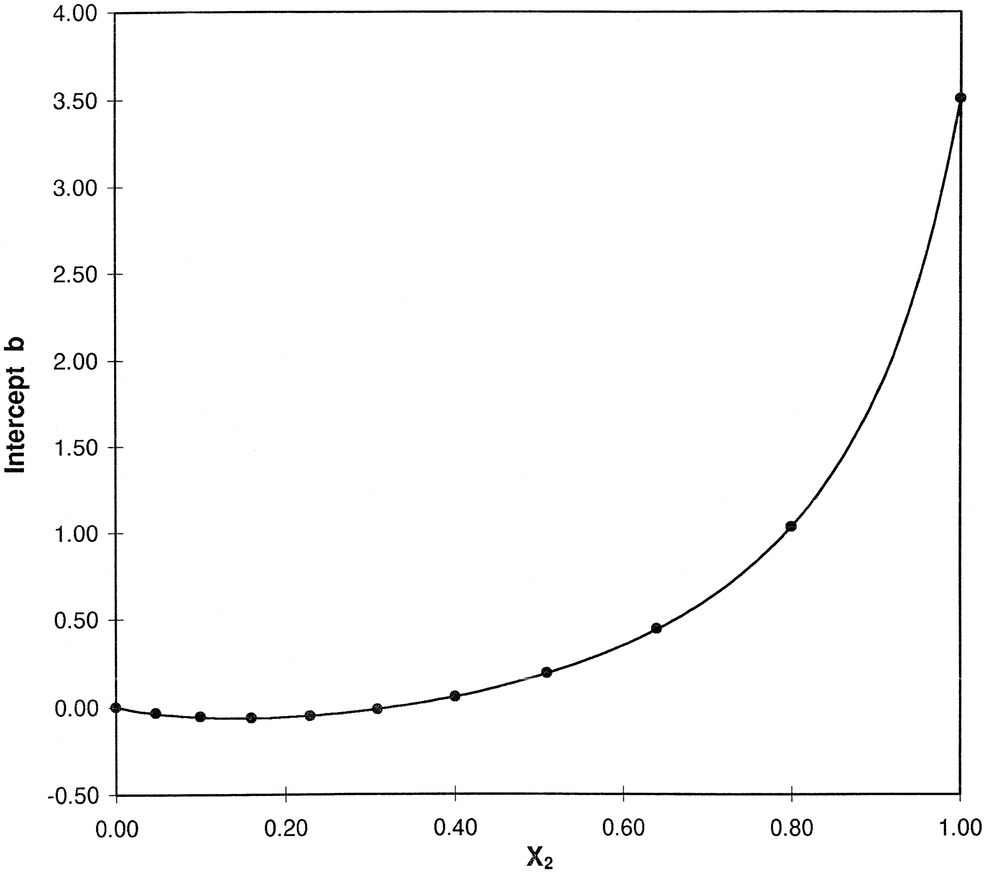

Fig. 3. Variation of the intercept *b* of the correlations of the pK_a values of phenols in methanol–water mixtures versus pK_a in water (Eq. (13)) with solvent composition (in mole fraction of methanol): (●) *b* values of Table 3 fitted to Eq. (23) -continuous line-.

80% (v/v) of methanol approximately ($x_2 = 0.64$), because the slope of the p$K_{(S12)}$ vs. p$K_{(S1)}$ correlations is larger than the slope of the p$K_{(S2)}$ vs. p$K_{(S1)}$ correlations (see Eqs. (20) and (21)). The intercepts show a small minimum for a 30% of methanol, although the value is not significantly different from zero. In fact the intercept practically does not change up to a mole fraction of methanol of 0.5. When methanol predominates in the mixtures, there is a large variation of the intercept with the methanol contents.

The slope and intercept values have been fitted to equations of the type of Eqs. (16) and (17). As explained, the mixture composition can be measured in different concentration unities, and we have obtained for mole fraction (x_2), volume fraction (v_2) and weigh fraction (w_2) the following equations

$$a = \frac{1 + 1.016\,x_2 - 0.437\,x_2^2}{1 + 0.594\,x_2 - 0.138\,x_2^2} \tag{22}$$

$$b = \frac{-1.019\,x_2 + 3.090\,x_2^2}{1 + 2.445\,x_2 - 2.854\,x_2^2} \tag{23}$$

$$a = \frac{1 - 0.656\,v_2 - 0.030\,v_2^2}{1 - 0.844\,v_2 + 0.133\,v_2^2} \tag{24}$$

$$b = \frac{-0.454\,v_2 + 0.866\,v_2^2}{1 - 0.017\,v_2 - 0.865\,v_2^2} \tag{25}$$

$$a = \frac{1 - 0.305\,w_2 - 0.195\,w_2^2}{1 - 0.542\,w_2 + 0.002\,w_2^2} \tag{26}$$

$$b = \frac{-0.573\,w_2 + 1.227\,w_2^2}{1 + 0.498\,w_2 - 1.311\,w_2^2} \tag{27}$$

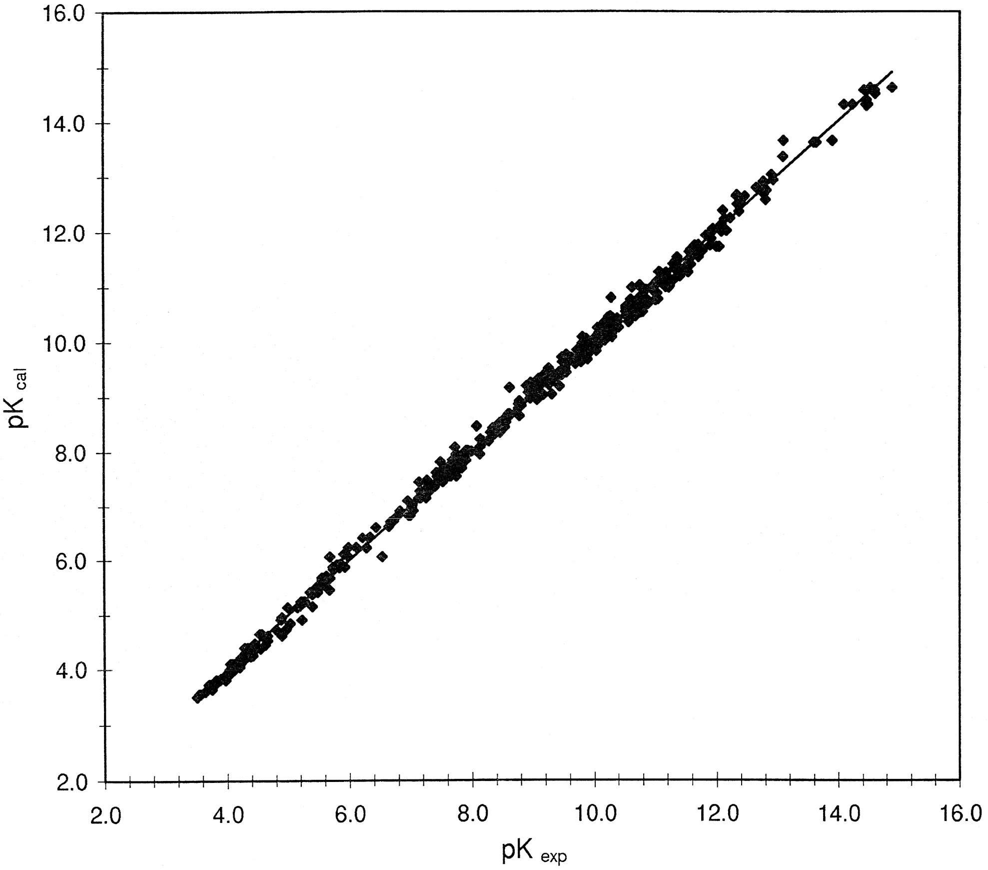

Fig. 4. Plot of pK_a calculated from Eqs. (13), (22), and (23) and the pK_a value in water (p$K_{(S1)}$ in Table 1) for the studied phenols in methanol–water versus pK_a experimental.

The statistics of the fits are: SD = 0.001 and $F = 4.1\times10^3$ for the slope a, and SD = 0.002 and $F = 6.0\times10^5$ for the intercept b.

Eqs. (22)–(27) allow to estimate the pK_a values of any phenol for any methanol–water mixture, only knowing the pK_a value of the phenol in pure water. We have checked this approach for the series of phenols analyzed by calculation of the pK_a value of each phenol at each solvent composition by means of Eqs. (22), (23) and (13) and the pK_a value of the phenol in pure water (p$K_{(S1)}$ reported in Table 1) and comparison with experimental pK_a data. The calculated pK_a values have been plotted against the experimental values and the plot is presented in Fig. 4. The agreement between calculated and experimental values is very good and this confirms the validity of the method to estimate pK_a values of phenols in methanol–water mixtures.

3.2. Comparison of calculated pK_a values with HPLC determined pK_a values

In fact, the equations should allow estimation of the pK_a of any phenol, even of those not included in the analyzed set, for any methanol–water mixture. We have tested this approach by calculation of the pK_a values of 26 phenols at 50% methanol which were previously studied by HPLC [14].

The slope and the intercept of Eq. (13) were calculated for 50% methanol ($v_2 = 0.5$) through Eqs. (24) and (25) and the values $a = 1.087$ and $b = -0.014$ were obtained, which agree very well with the original values of Table 3. Then, the pK_a value of each phenol at 50% methanol was calculated through Eq. (13) from its pK_a value in pure water (p$K_{(S1)}$) obtained from references [38,39,41]. Averaged pK_a values in water at 25°C were used when more than

Table 4

pK_a values of phenols in water (p$K_{(S1)}$) and in 50% methanol estimated from p$K_{(S1)}$ and Eqs. (13), (22) and (23) (pK_{cal}) and determined from chromatography (pK_{chrom})

Compound	p$K_{(S1)}$ ± SD[a]	pK_{cal}	pK_{chrom}[b]	ΔpK
4-Chloro-2-nitrophenol	6.46±0.01	7.00	7.13	0.13
2,4,6-Trichlorophenol	6.18±0.63	6.70	7.46	0.76
2-Nitrophenol	7.24±0.02	7.85	7.77	−0.08
4-Nitrophenol	7.17±0.04	7.77	7.96	0.19
4-Hydroxybenzaldehyde	7.62	8.26	8.21	−0.05
2,4-Dichlorophenol	7.80±0.14	8.45	8.55	0.10
2-Chlorophenol	8.56	9.28	9.28	0.00
Vanillin	7.40	8.02	9.34	1.32
3-Bromophenol	9.03±0.02	9.79	10.11	0.32
2-Naphthol	9.51±0.04	10.31	10.38	0.07
4-Chlorophenol	9.40±0.03	10.19	10.45	0.26
4-Chloro-3-methylphenol	9.55	10.36	10.50	0.14
1-Naphthol	9.38±0.03	10.17	10.54	0.37
4-Hydroxybenzyl alcohol	9.82	10.65	10.60	−0.05
2-Aminophenol	9.72±0.05	10.54	10.92	0.38
3,5-Dimethylphenol	10.20	11.06	10.95	−0.11
3,4-Dimethylphenol	10.36±0.01	11.23	11.08	−0.15
m-Cresol	10.10	10.95	11.13	0.18
2,5-Dimethylphenol	10.38±0.05	11.26	11.14	−0.12
o-Cresol	10.33	11.20	11.16	−0.04
3-Aminophenol	9.90±0.08	10.74	11.17	0.43
Eugenol	10.00	10.84	11.18	0.34
4-Aminophenol	10.43±0.03	11.31	11.19	−0.12
Phenol	10.00±0.03	10.84	11.22	0.38
p-Cresol	10.27±0.01	11.14	11.39	0.25
2,6-Dimethylphenol	10.61±0.02	11.51	11.85	0.34

[a] pK_a in water from Refs. [38–40] at 25°C, data of different authors for the same phenol have been averaged and the mean and standard deviation are given.

[b] pK_a in 50% methanol from Ref. [14].

one pK_a literature data was available and the means and standard deviations of these values (p$K_{(S1)}$±s.d.) are given in Table 4. Table 4 also gives the calculated pK_a values for 50% methanol (pK_{cal}) and the values obtained for the same phenols after analysis of their retention in a polymeric column at different mobile phase pH values (pK_{chrom}). The plot of pK_{cal} against pK_{chrom} is given in Fig. 5. It can be observed that the agreement is quite good (in general ΔpK is less than 0.4 pK units), except for 2,4,6-trichlorophenol and vanillin. Vanillin was an outstanding outlier in the quantitative structure-retention relationships studied in reference [14] and the pK_{chrom} obtained is very doubtful. The literature reports several pK_a values for 2,4,6-trichlorophenol in water, ranging from 5.5 to 7.0. In fact, if the highest aqueous pK_a value is used (p$K_{(S1)}$=7.00), the pK_{cal} value obtained is 7.59 which is close to the pK_{chrom} value.

We may conclude that the presented equations allow an accurate estimation of the pK_a value of phenols for any methanol–water mixtures. Work is in progress in our lab to expand the equations to other sets of solutes, such as carboxylic acids and protonated amines and heterocyclic bases. The generalization of the pK estimation method to different families of acids and bases can be very valuable for some important analytical techniques, such as HPLC, CE or EC, that use mixed solvents and where the parameter of analytical interest, e.g. retention factor k, strongly depends on the pH of the medium and on the pK_a of the analyte [2–4,13,14]. Conversely, the same procedure can be applied to the estimation of the aqueous pK_a values of substances sparingly

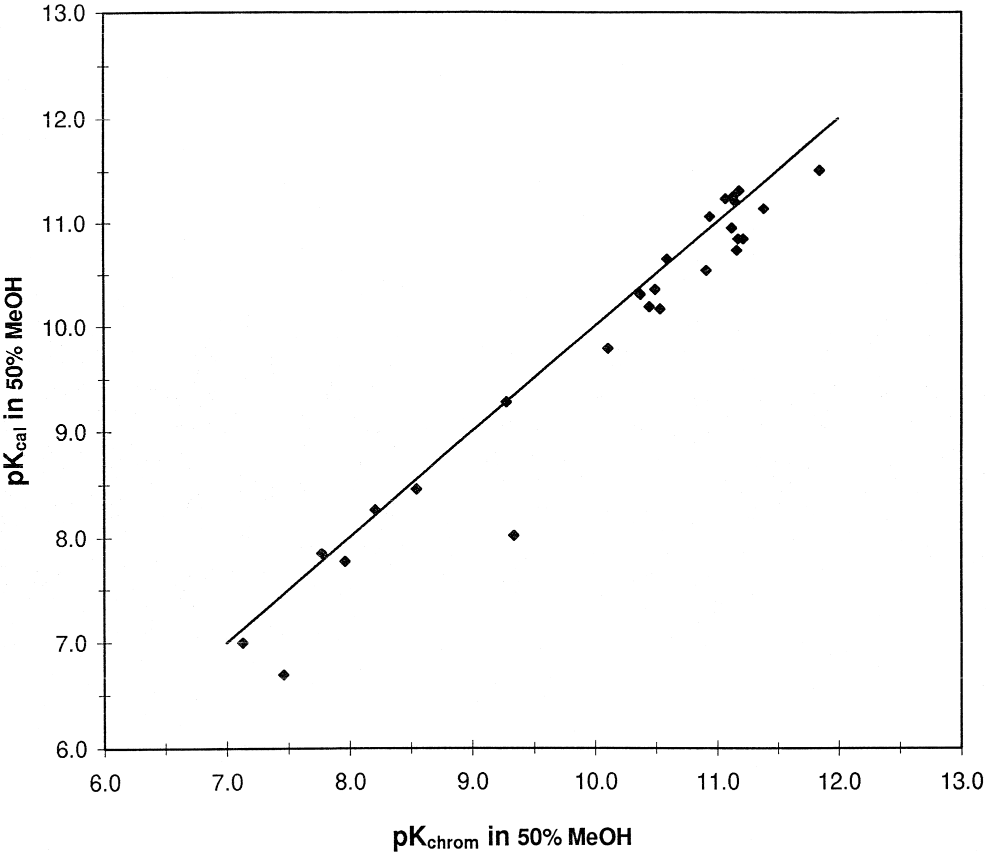

Fig. 5. Plot of pK_a calculated from Eqs. (13), (22), and (23) and the pK_a value in water versus pK_a determined from HPLC retention of phenols in a polymeric column with 50% methanol as mobile phase.

soluble in water, such as some pharmaceutical drugs, from the pK_a values of the substance in any methanol–water mixture [12,15,26].

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