J. Chem. Eng. Data **2003,** *48,* 911−915

Acidity Constants and Thermodynamic Parameters of Some Phenol Derivatives in Methanol + Water Systems Using Potentiometry and Spectrophotometry Methods

A. Abbaspour,* M. A. Kamyabi, A. Khalafi-Nezhad, and M. N. Soltani Rad

Chemistry Department, Shiraz University, Shiraz 71454, Iran

The acidity constants of four phenol derivatives, 4-methyl-2,6-bis(hydroxymethyl)phenol, 4-fluoro-2,6-bis(hydroxymethyl)phenol, 4-chloro-2,6-bis(hydroxymethyl)phenol, and 4-bromo-2,6-bis(hydroxymethyl)-phenol, were determined using potentiometric and spectrophotometric methods at 0.10 M tetraethylammonium bromide (TEAB) as supporting electrolyte in different ratios of methanol + water mixtures. In the spectrophotometric method, only the acidity constant of the hydroxy group that directly attached to the aromatic ring (phenolic group) was determined, whereas, by the potentiometric method, the acidity constants of all three hydroxy groups could be determined. The results show that the acidity constants K_{a1} decrease as the percent of methanol in the solvent mixture increases, but K_{a2} and K_{a3} do not show similar behavior. Thermodynamic parameters of these compounds in $x_1 = 0.2$ for methanol (1) + water (2) were determined in the temperature range (15 to 55) °C.

4-Halo-2,6-bis(hydroxymethyl)phenols are one of the significant precursors for synthesis of an important series of compounds such as phloroglucid analogues, polyphenol resins, and calixarenes. Applications of these compounds are published in the literature.[1−6] To our knowledge, there is no any report about the determination of the acidity constants of these compounds. For this reason, in this research, the acidity constants of four phenol derivatives, 4-methyl-2,6-bis(hydroxymethyl)phenol, 4-fluoro-2,6-bis-(hydroxymethyl)phenol, 4-chloro-2,6-bis(hydroxymethyl)-phenol, and 4-bromo-2,6-bis(hydroxymethyl)phenol, were obtained potentiometrically in methanol (1) + water (2) at $x_1 = 0.1$, 0.2, 0.3, 0.4, 0.5, 0.6, and 0.7 using the PKAS computer program.[7] In the spectrophotometric method, the acidity constants of these four phenol derivatives were determined in methanol (1) + water (2) at $x_1 = 0$ and 0.2 using the EQUISPEC program.[8]

The thermodynamic parameters of the above 4-halo-2,6-bis(hydroxymethyl)phenols were determined at $x_1 = 0.2$ in the temperature range (15 to 55) °C. For 4-methyl-2,6-bis-(hydroxymethyl)phenol, because of its low solubility, these parameters were obtained in $x_1 = 0.6$ in the same temperature range.

Experimental Section

Reagents. All reagents were of analytical grade from Merck except KOH, which was from Fluka. These reagents were used without further purification. The KOH solution was standardized by potassium hydrogen phthalate. Triply distilled water was used in the preparation of all solutions. Four phenol derivatives, 4-methyl-2,6-bis(hydroxymethyl)-phenol, 4-fluoro-2,6-bis(hydroxymethyl)phenol, 4-chloro-2,6-bis(hydroxymethyl)phenol, and 4-bromo-2,6-bis(hydroxymethyl)phenol, were synthesis according to the literature.[5] The synthesized ligands were purified by short column chromatography, and their purities were identified by means of ^{1}H NMR (DMSO-d_6, 250 MHz) and FT-IR (Shimadzue, 8300).

The NMR characteristics of these compounds are as follows:

4-Chloro-2,6-bis(hydroxymethyl)phenol. ^{1}H NMR (DMSO-d_6, 250 MHZ) δ: 8.73 (s, 1H, 1 phenolic OH exchangeable with D_2O), 7.17 (s, 2H, aromatic ring), 5.09 (s, 2H, 2 benzylic OH exchangeable with D_2O), 4.52 (s, 4H, $2CH_2$).

4-Bromo-2,6-bis(hydroxymethyl)phenol. ^{1}H NMR (DMSO-d_6, 250 MHZ) δ: 8.86 (s, 1H, 1 phenolic OH), 7.30 (s, 2H, aromatic ring), 5.33 (s, 2H, 2 benzylic OH), 4.52 (s, 4H, $2CH_2$).

4-Fluoro-2,6-bis(hydroxymethyl)phenol. ^{1}H NMR (DMSO-d_6, 250 MHZ) δ: 8.92 (s, 1H, 1 phenolic OH), 7.33 (s, 2H, aromatic ring), 5.36 (s, 2H, 2 benzylic OH), 4.56 (s, 4H, $2CH_2$).

4-Methyl-2,6-bis(hydroxymethyl)phenol. ^{1}H NMR (DMSO-d_6, 250 MHZ) δ: 8.46 (s, 1H, 1 phenolic OH), 7.11 (s, 2H, aromatic ring), 5.30 (s, 2H, 2 benzylic OH), 4.45 (s, 4H, $2CH_2$), 2.20 (s, 3H, CH_3.

The FT-IR characteristics of these compounds are as follows:

4-Chloro-2,6-bis(hydroxymethyl)phenol. υ_{max} 3600−3100 (br, OH), 3100 (m, C−H, aromatic), 2890 (m, CH_2−H, aliphatic), 1600 (s, C−C, aromatic), 1250−1150 (m, C−O, aromatic, aliphatic), 750 (s, C−Cl) cm^{-1}.

4-Bromo-2,6-bis(hydroxymethyl)phenol. υ_{max} 3600−3100 (br, OH), 3100 (m, C−H, aromatic), 2890 (m, CH_2-H, aliphatic), 1600 (s, C−C, aromatic), 1250−1150 (m, C−O, aromatic, aliphatic), 667 (s, C−Br) cm^{-1}.

4-Fluoro-2,6-bis(hydroxymethyl)phenol. υ_{max} 3600−3100 (br, OH), 3100 (m, C−H, aromatic), 2890 (m, CH_2−H, aliphatic), 1600 (s, C−C, aromatic), 1350 (s, C−F), 1250−1150 (m, C−O, aromatic, aliphatic) cm^{-1}.

4-Methyl-2,6-bis(hydroxymethyl)phenol. υ_{max} 3600−3100 (br, OH), 3100 (m, C−H, aromatic), 2890 (m, CH_2−H, aliphatic), 1600 (s, C−C, aromatic), 1250−1150 (m, C−O, aromatic, aliphatic) cm^{-1}.

Apparatus. The absorption spectra were recorded on a Shimadzu UV-160 1PC spectrophotometer, containing a thermoelectrically temperature-controlled cell holder (TB-

10.1021/je0256380 CCC: \$25.00

85 Thermo Bath Shimadzu) in the wavelength range (200 to 400) nm using 1 cm matched silica cells. The pH measurements were carried out with a 654 Metrohm pH-meter (Metrohm Ltd, CH-9100-Hersau Switzerland) using a combined glass electrode. Temperature was maintained at each specific temperature ($t \pm 0.1$) °C by circulation of thermostated water through the jacket. Nitrogen purge gas was used to remove CO_2. A 100 μL Eppendorf micropipet (±0.6%) was used for the addition of a standard base to the solution.

Procedure for Determination of K_w in Different Methanol + Water Systems. Before each experiment, it is necessary to calibrate[9−11] the pH meter and electrode system in terms of pH. For determination of K_w in various methanol + water mixtures,[10−11] at ionic strength 0.10 M TEAB and $t = 25.0$ °C, the cell was charged with 5.0 mL of 0.10 M HCl, the appropriate amount of TEAB (to have 0.10 M TEAB in 50.0 mL of solution), and the appropriated volumes of methanol and water until the total volume was equal to 50.0 mL. The cell was capped (letting inert gas flow), equilibrated until pH drifts < 0.001 unit/5 min (usually between 5 min and 0.5 h), and titrated with standard KOH (which is prepared in a given percentage of methanol). The ion product ($K_w = [H^+][OH^-]$) was determined in various percentages of mixture by several series of [OH] and pH measurements (The pH was measured from the pH meter, while $[OH^-]$ was calculated from the amount of base added to solution). K_w and then pK_w were calculated. The pK_w values that were obtained were 13.83, 13.87, 13.92, 13.97, 14.02, 14.06, 14.11, and 14.16 for 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 mole fraction methanol, respectively.

Procedure for Determination of pK_a via Potentiometry. The acidity constants were determined as in a pervious work[12] by titrating 50.0 mL of (2.00×10^{-3} to 2.00×10^{-2}) M analyte with KOH in each medium, and the ionic strength of the solution was adjusted by 0.10 M TEAB. The temperature was maintained at each specific temperature ($t \pm 0.1$) °C by circulation of thermostated water through the jacket. Before doing each titration, the solution was allowed to equilibrate until pH drifts < 0.001 unit/5 min were obtained at each specific temperature. N_2 gas was pumped through the solution to remove CO_2. During the titration the pumping of N_2 was continued above the solution (except at 55 °C, since it is not necessary). To obtain each pK_a value, at least three titrations were made, and each titration had almost 44 points (in the pH range 5.5 to 11.5). It took 1−2 min to reach the equilibrium at each titration point, but around the equivalent point it took a longer time to reach to the equilibrium. In the present study, Martell's computer[7] program has been used to calculate the acidity constants (in different media) of the four phenol derivatives 4-methyl-2,6-bis(hydroxymethyl)phenol, 4-fluoro-2,6-bis(hydroxymethyl)phenol, 4-chloro-2,6-bis(hydroxymethyl)phenol, and 4-bromo-2,6-bis(hydroxymethyl)phenol.

Procedure for Determination of pK_a via Spectrophotometry. In the spectrophotometric method the acidity constant of the hydroxy group that is directly attached to the aromatic ring was determined, because only this group causes a change in the spectrum by changing the pH. Phenol derivative solutions (16−20 solutions for each phenol derivative) having the concentration 1.0×10^{-4} M with pH varying from 2.5 to 11.5 were prepared at constant the ionic strength 0.10 M TEAB. The spectra (baseline corrected) of the samples were recorded from (200 to 400) nm at 0.2 nm intervals. Since the methyl derivative does not dissolve in water, its spectrum was obtained in 60% mole fraction methanol. The EQUISPEC program[8] was used for determination of the acidity constants. The EQUISPEC program is a computer program using the matrix based Matlab environment for second-order global analysis of spectrophotometric equilibrium data.

Table 1. Acidity Constants of 4-Fluoro-2,6-bis(hydroxymethyl)phenol at 0.1 M TEAB in Methanol + Water Mixture Solvent by the Potentiometry Method

x_{mole}	pK_{a1}	pK_{a2}	pK_{a3}
0.1	9.32 (±0.03)	10.89 (±0.02)	12.90 (±0.04)
0.2	9.41 (±0.03)	10.74 (±0.05)	12.55 (±0.03)
0.3	9.52 (±0.04)	10.59 (±0.04)	12.05 (±0.04)
0.4	9.61 (±0.05)	10.52 (±0.05)	11.69 (±0.05)
0.5	9.70 (±0.03)	10.63 (±0.04)	11.75 (±0.04)
0.6	9.79 (±0.04)	10.75 (±0.04)	12.10 (±0.06)
0.7	9.87 (±0.03)	10.85 (±0.05)	12.90 (±0.04)

Table 2. Acidity Constants of 4-Chloro-2,6-bis(hydroxymethyl)phenol at 0.1 M TEAB in Methanol + Water Mixture Solvent by the Potentiometry Method

x_{mole}	pK_{a1}	pK_{a2}	pK_{a3}
0.1	8.93 (±0.02)	10.99 (±0.03)	13.80 (±0.02)
0.2	9.04 (±0.03)	10.81 (±0.03)	13.05 (±0.03)
0.3	9.15 (±0.03)	10.66 (±0.04)	12.25 (±0.03)
0.4	9.24 (±0.04)	10.59 (±0.03)	11.80 (±0.04)
0.5	9.32 (±0.03)	10.72 (±0.03)	12.10 (±0.03)
0.6	9.41 (±0.03)	10.85 (±0.02)	12.72 (±0.02)
0.7	9.49 (±0.04)	11.03 (±0.04)	14.00 (±0.03)

Table 3. Acidity Constants of 4-Bromo-2,6-bis(hydroxymethyl)phenol at 0.1 M TEAB in Methanol + Water Mixture Solvent by the Potentiometry Method[a]

x_{mole}	pK_{a1}	pK_{a2}	pK_{a3}
0.2	8.88 (±0.03)	10.87 (±0.03)	13.63 (±0.03)
0.3	8.98 (±0.04)	10.70 (±0.03)	12.50 (±0.04)
0.4	9.08 (±0.03)	10.65 (±0.03)	11.90 (±0.04)
0.5	9.17 (±0.03)	10.78 (±0.03)	12.25 (±0.03)
0.6	9.26 (±0.04)	10.90 (±0.04)	13.00 (±0.04)
0.7	9.34 (±0.03)	11.09 (±0.04)	14.50 (±0.03)

[a] Ar−Br is not soluble in 0.1 mole fraction methanol.

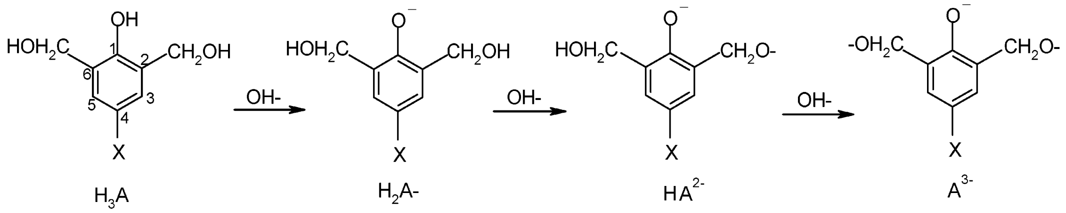
Table 4. Acidity Constants of 4-Methyl-2,6-bis(hydroxymethyl)phenol at 0.1 M TEAB in Methanol (1) + Water (2) Systems by the Potentiometry Method

x_1	pK_{a1}	pK_{a2}	pK_{a3}
0.55	8.73 (±0.05)	11.23 (±0.05)	15.51 (±0.04)
0.6	8.77 (±0.04)	11.30 (±0.04)	15.98 (±0.05)
0.7	8.85 (±0.04)	11.41 (±0.03)	17.06 (±0.03)
0.8	8.94 (±0.03)	11.52 (±0.04)	18.27 (±0.04)

Results and Discussion

The pK_a values of four phenol derivatives, 4-methyl-2,6-bis(hydroxymethyl)phenol, 4-fluoro-2,6-bis(hydroxymethyl)phenol, 4-chloro-2,6-bis(hydroxymethyl)phenol, and 4-bromo-2,6-bis(hydroxymethyl)phenol, were calculated in methanol + water mixture solutions. The results using the potentiometry method are given in Tables 1−4. The unexpected pK_{a1} values' order in each mole fraction of methanol for corresponding phenols ($pK_{a1}(Ar-F) > pK_{a1}(Ar-Cl) > pK_{a1}(Ar-Br) > pK_{a1}(Ar-Me)$) can be explained by the stronger intramolecular hydrogen bond which is formed in H_2A^- when the electronegativity of the substituent group is lower. In another words, the stability of the H_2A^- (see Scheme 1) anion is in the order Ar−Me > Ar−Br > Ar−Cl

Scheme 1



X= F, Cl, Br and Methyl

> Ar−F. This anion stability order is because the inductive effect causes hydrogen bond formation between $-CH_2OH$ groups with $C(1)O^-$ to diminish, as we can see from Scheme 1, when the electronegativity of the substituent at carbon number 4 increases.

In the case of pK_{a2} and pK_{a3}, the reverse order of pK_{a1} was observed. The main factor which can assist stabilization in these anions (HA^{2-} and A^{3-}) is the inductive effect of electronegative substituents. In this case, as the electronegativity of the substituent increases, the negative charge density in the anion will decrease and the anion will become more stable; therefore, the relative acidity of H_2A^- and HA^{-2} will increase (i.e. pK_{a2} and pK_{a3} decrease) as in the following order.

$$pK_{a3}(Ar-F) < pK_{a3}(Ar-Cl) < pK_{a3}(Ar-Br) < pK_{a3}(Ar-Me)$$

Similarly

$$pK_{a2}(Ar-F) < pK_{a2}(Ar-Cl) < pK_{a2}(Ar-Br) < pK_{a2}(Ar-Me)$$

The spectra of these phenol derivatives were obtained in water and in an $x_1 = 0.2$ methanol (1) + water (2) mixture except for the case of 4-methyl-2,6-bis(hydroxymethyl)phenol, whose spectrum was obtained in $x_1 = 0.6$, because its solubility was low. Figure 1 shows the UV spectra of the phenol−F derivative. The electronic absorption spectra of these phenol derivatives show mainly two bands. The shorter wavelength band, appearing at low pH values (pH < 6), represents absorption of the nonionized species, whereas the longer wavelength band, observed at higher pH's (>8.5), is due to the absorption by ionized species. On increasing the pH of the medium, the absorbance of the former band decreases while that of the latter band increases, where a fine isobestic point is achieved, denoting existence of an equilibrium of the type

$$H_3A \rightarrow H_2A^- + H^+$$

In other words, since a phenolic group possesses an absorbance in the vicinity of 280 nm, while the conjugate phenolate group absorbs at around 305 nm (i.e. ∼25 nm longer in wavelength), the UV probe is responsive only to the phenol to phenolate conversion. The first acidity constants of the four derivatives were determined spectrophotometrically,[8] and the results are given in Table 5. The values obtained for the first acidity constant by both techniques (potentiometry and spectrophotometry) are in good agreement.

As Tables 1−4 show, pK_{a1} values increase as the mole fraction of methanol increases (Figure 2). The solvating ability and relative permittivity play a fundamental role in dissociation reactions. The energy required to separate the opposite charges of an acid in a solvent is inversely proportional to the relative permittivity of the solvent. This energy requirement can be supplied by solvation of the ions, and in addition, the proton transfer from acid to the solvent molecule also supplies some energy. Since the relative permittivity and solvating ability of the mixture decrease as the percentage of methanol increases ($\epsilon_{H_2O} = 78.36$ and $\epsilon_{MeOH} = 32.6$), the energy required for separation of charges will increase and thus the extent of the dissociation constant will be lowered. This explains that the pK_{a1} value of each acid will increase as the mole fraction of methanol

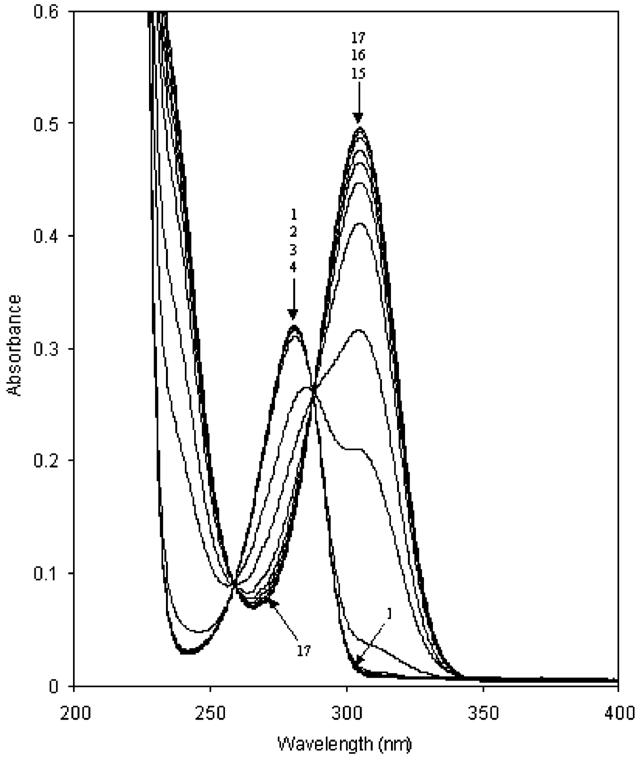


Figure 1. UV spectra of 4-fluoro-2,6-bis(hydroxymethyl)phenol at 0.1 M TEAB. pH values are as follows: 1, 2.630; 2, 3.083; 3, 3.643; 4, 4.157; 5, 5.893; 6, 6.917; 7, 7.255; 8, 8.095; 9, 9.262; 10, 9.593; 11, 10.005; 12, 10.293; 13, 10.519; 14, 10.726; 15, 11.033; 16, 11.390; 17, 11.877.

Table 5. First Acidity Constants of 4-Fluoro-2,6-bis(hydroxymethyl)phenol, 4-Chloro-2,6-bis(hydroxymethyl)phenol, and 4-Bromo-2,6-bis(hydroxymethyl)phenol (in 0.0 and 0.2 mole fraction Methanol) and 4-Methyl-2,6-bis(hydroxymethyl)phenol (in 0.6 mole fraction Methanol) at 0.1 M TEAB Using the Spectrophotometry Method

x_1	phenol-F	phenol-Cl	phenol-Br	phenol-Me
0.0	9.18 (±0.02)	8.80 (±0.01)	8.72 (±0.02)	
0.2	9.43 (±0.03)	9.01 (±0.02)	8.95 (±0.03)	
0.6				8.73 (±0.03)

Table 6. Thermodynamic Functions of 4-Methyl-2,6-bis(hydroxymethyl)phenol, 4-Fluoro-2,6-bis(hydroxymethyl)phenol, 4-Chloro-2,6-bis(hydroxymethyl)phenol, and 4-Bromo-2,6-bis(hydroxymethyl)phenol in 0.2 mole fraction Methanol (except for 4-Methyl-2,6-bis(hydroxymethyl)phenol in 0.6 mole fraction Methanol) at 0.10 M TEAB

		t/°C = 15	t/°C = 25	t/°C = 35	t/°C = 45	t/°C = 55	$-\Delta H$ (kJ mol^{-1})	$-\Delta S$ (J mol^{-1} K^{-1})	ΔG (kJ mol^{-1})
Ar−F	pK_{a1}	9.28	9.41	9.55	9.64	9.72	20.16 (±0.38)	247.8 (±1.2)	53.72 (±0.38)
	pK_{a2}	10.65	10.74	10.91	11.05	11.14	23.34 (±0.55)	284.5 (±1.8)	61.49 (±0.55)
	pK_{a3}	11.94	12.55	13.25	13.95	14.52	118.69 (±1.17)	639.5 (±3.8)	71.97 (±1.17)
Ar−Cl	pK_{a1}	8.90	9.04	9.10	9.20	9.27	16.34 (±0.40)	227.4 (±1.3)	51.46 (±0.40)
	pK_{a2}	10.70	10.81	10.90	11.00	11.12	18.61 (±0.30)	269.3 (±1.0)	61.68 (±0.30)
	pK_{a3}	12.55	13.05	13.70	14.30	14.85	105.77 (±1.38)	606.0 (±4.5)	74.92 (±1.38)
Ar−Br	pK_{a1}	8.80	8.88	9.00	9.05	9.11	14.35 (±0.40)	218.4 (±1.3)	50.75 (±0.40)
	pK_{a2}	10.80	10.87	10.98	11.08	11.18	17.51 (±0.37)	267.2 (±1.2)	62.15 (±0.37)
	pK_{a3}	12.70	13.63	14.72	15.60	16.40	169.74 (±1.27)	831.6 (±4.1)	78.22 (±1.27)
Ar−Me	pK_{a1}	8.58	8.77	8.95	9.10	9.25	30.79 (±0.33)	271.0 (±1.1)	50.00 (±0.33)
	pK_{a2}	11.09	11.30	11.45	11.72	11.87	35.81 (±0.75)	336.3 (±2.4)	64.47 (±0.75)
	pK_{a3}	14.40	15.98	17.30	18.80	20.20	260.91 (±2.02)	1180.3 (±6.6)	91.01 (±2.02)

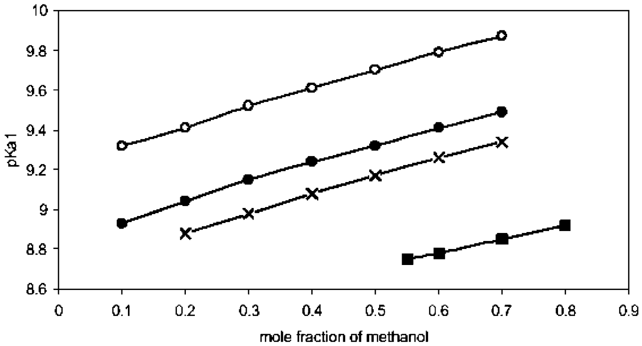


Figure 2. Relationship between pK_{a1} values of four phenol derivatives and the mole fraction of methanol in water: ○, Ar−F; ●, Ar−Cl; ×, Ar−Br; ■, Ar−Me.

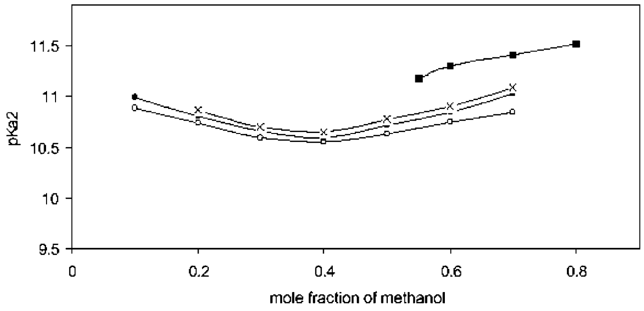


Figure 3. Relationship between pK_{a2} values of four phenol derivatives and the mole fraction of methanol in water: ○, Ar−F; ●, Ar−Cl; ×, Ar−Br; ■, Ar−Me.

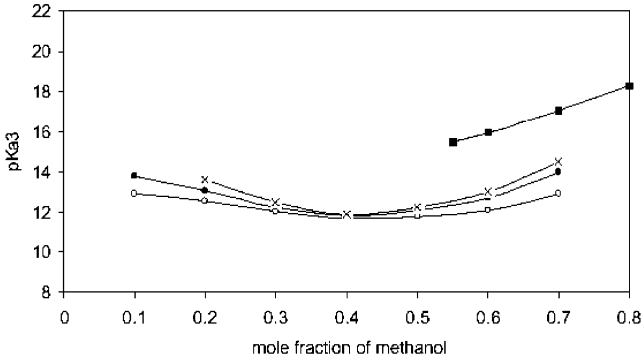


Figure 4. Relationship between pK_{a3} values of four phenol derivatives and the mole fraction of methanol in water: ○, Ar−F; ●, Ar−Cl; ×, Ar−Br; ■, Ar−Me.

in the mixture increases. The effect of the solvent itself upon the acidity constants of various compounds has been studied by several authors.[13,14] Robinson and Stokes[15] have developed a linear relationship based on Born's equation between the logarithm of the acid dissociation constant and the dielectric constant of the solvent.

The pK_{a2} and pK_{a3} values of all phenol derivatives have been plotted against the mole fraction of methanol in Figures 3 and 4. As these figures show, not only do the pK_{a2} and pK_{a3} values not have a linear relationship with mole fraction of methanol but their values also pass through a minimum (about 0.4 mole fraction of methanol).[16] Bates[17] has investigated solvent effects for the observation of a minimum in pK_a which corresponds to the dissociation of the charged acids such as ammonium and aniliums in a number of mixed solvent media. He concluded that the main factor is the marked preference of the H^+ for water and that it is this preference that causes an increase in the pK_a of all charged acids in solvent mixtures as the percentage of water becomes lower. At the end, the authors should mention that the precision and accuracy given for pK_a values are the ones that the computer program evaluated just on the basis of the variability among the three titrations made for each system.

The thermodynamic parameters are also listed in Table 6. Values of enthalpies and entropies of ionization were calculated using a Van't Hoff analysis. In all cases, plots of ln K_a versus $1/T$ were linear with good correlation coefficients. Values of Gibbs energy order for K_{a1} as ΔG(Ar−F) > ΔG(Ar−Cl) > ΔG(Ar−Br) > ΔG(Ar-Me), which is also the order of their acidity constants. The results which were obtained for Gibbs free energy values for second and third acidity constants were as follows: ΔG(Ar−F) < ΔG(Ar−Cl) < ΔG(Ar−Br) < ΔG(Ar−Me), which is also the order of their acidity constants.

Conclusions

In this work, we distinguish the behavior of acidity constants of phenol derivatives in different media and compare spectrophotometry and potentiometry methods for obtaining their acidity constants. Thermodynamic parameters of these phenol derivatives were obtained at five different temperatures ranging from (15.0 to 55.0) °C and at an ionic strength of 0.10 M TEAB.

Literature Cited

(1) Khalafi-Nezhad, A.; Soltani-Rad, M. N.; Hakimelahi, G. H. Synthesis of polyfunctional aromatic ring systems (ploroglucide analog) under microwave irradiation. Accepted for publication in *Helv. Chim. Acta*.

(2) Hwu, J. R.; Moshfegh, A. A.; Tsay, S.-C.; Lin, C. C.; Tsengg, W. N.; Azaripour, A.; Mottaghian, H.; Hakimelahi, G. H. Cephalosporin 3′-Phloroglucide Esters and 7-(Phloroglucidamido)cephalosporins as Novel Antibacterial Agents. *J. Med. Chem.* **1997**, *40*, 3434−3441.

(3) Moshfegh, A. A.; Hakimelahi, G. H. The Synthesis of Polyfunctional Aromatic Ring Systems. Structural Analogues of Phloroglucides, Aranciamycin, Cryptosporin and Terramycin. *Helv. Chim. Acta* **1981**, *64*, 599−609.
(4) Moshfegh, A. A.; Badri, R.; Hojjatie, M.; Kaviani, M.; Naderi, B.; Nazmi, A.; Ramezanian, M.; Roozpeiker, B.; Hakimelahi, G. H. The Synthesis of 4,11,18,25-Tetrachloro[1_4]metacyclophane-7,14,21,28-tetrol. Structural Analogues of Phloroglucides. *Helv. Chim. Acta* **1982**, *65*, 1221−1228.
(5) Moshfegh, A. A.; Mazandarani, B.; Nahid, A.; Hakimelahi, G. H. The Synthesis of Hetero-Halogenated Derivatives of Phloroglucide Analogues [1]. *Helv. Chim. Acta* **1982**, *65*, 1229−1232.
(6) Moshfegh, A. A.; Hakimelahi, G. H. Swiss Patent 003848, 1977; Swiss Patent 003849, 1977; Swiss Patent 007448, 1978.
(7) Motekaitis, R. J.; Martell, A. E. Program PKAS: a novel algorithm for the computation of successive protonation constants. *Can. J. Chem.* **1982**, *60*, 168−173.
(8) Dyson, R. M.; Kaderli, S.; Lawrence, G. A.; Maeder, M.; Zuberbühler, A. D. Second-order global analysis: the evaluation of series of spectrophotometric titrations for improved determination of equilibrium constants. *Anal. Chim. Acta* **1997**, *353*, 381−393.
(9) Meloun, M.; Havel, J.; Hogfeldt, E. *Computation of Solution Equilibria*; Wiley: New York, 1988.
(10) Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants*, 2nd ed; VCH Publishers: New York, 1992.
(11) Durust, N.; Abdulkadir Akay, M.; Durust, Y.; Kilic, E. Protonation Constants of Some N-Substituted Amidoximes in a 50% Ethanol−Water Mixture (v/v). *Anal. Sci.* **2000**, *16*, 825−827.
(12) Abbaspour, A.; Kamyabi, M. A. Acidity Constants and Thermodynamic Parameters of Barbituric and Diethylbarbituric Acids in Water, (Water + Tetrahydrofuran) and (Water + Triton X-100) System. *J. Chem. Eng. Data* **2001**, *46*, 623−625.
(13) Gunduz, T.; Kilic, E.; Canel, E.; Koseoglu, F. Protonation constants of some substituted salicylideneanilines in dioxan-water mixtures. *Anal. Chim. Acta* **1993**, *282*, 489−495.
(14) Gunduz, T.; Gunduz, N.; Kilic, E.; Kenar, A. Titrations in Nonaqueous Media. Part IV. Solvent Effects on Basicity of Aliphatic Amines. *Analyst* **1986**, *111*, 1345−1347.
(15) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*; Academic Press: New York, 1959.
(16) Koseoglu, F.; Kilic, E.; Canel, E.; Yilmaz, N. Protonation constants of some substituted salicylideneanilines in ethanol−water mixtures. *Anal. Chim. Acta* **1994**, *293*, 87−94.
(17) Bates, R. G. *Determination of pH, Theory and Practice*, 2nd ed.; Wiley: New York, 1973.

Received for review November 5, 2002. Accepted May 22, 2003. We gratefully acknowledge the support of this work by the Shiraz University Research Council.

JE0256380