Spectrophotometric Determination of Acidity Constants of Some Recently Synthesized Anthraquinones in Methanol + Water

Dariush Almasifar,[†] Ali Forghaniha,[‡] Zahra Khojasteh,[‡] Jahanbakhsh Ghasemi,[†] Hashem Sharghi,[‡] and Mojtaba Shamsipur*[,†]

Department of Chemistry, Razi University, Kermanshah, Iran, and Department of Chemistry, Shiraz University, Shiraz, Iran

The acidity constants of 14 recently synthesized derivatives of 9,10-anthraquinone in methanol + water at 25 °C and an ionic strength of 0.1 M have been determined spectrophotometrically. A linear inverse relationship between the pK_a of all acids and the mole fraction of methanol in the solvent mixtures is observed. The influence of substituents in the molecular structure on the ionization constants is discussed.

Introduction

The accurate determination of pK_a values is often required in various chemical and biochemical areas. These are of vital importance in understanding the distribution, transport behavior, binding to receptors and mechanism of action of certain pharmaceutical preparations (Frey et al., 1971; Rochester, 1970). The acidity constants of organic reagents play a very fundamental role in many analytical procedures such as acid−base titration, solvent extraction, and complex formation.

9,10-Anthraquinones as the largest group of naturally occurring quinones are of importance both in industry and in medicine (Thomson, 1971). In addition to a wide variety of chemical and industrial applications (Dadfarnia et al., 1993; Lucker, 1984; Qureshi et al., 1979; Thomson, 1971), recently the synthetic derivatives of anthraquinones, as well as naturally occurring derivatives, have been used for medical purposes (Arcamone, 1984; Lowe et al., 1984; Lucker, 1984).

This work was undertaken to determine the acidity constants of some anthraquinone derivatives, recently synthesized in this group (Khojasteh, 1994; Sharghi and Forghaniha, 1995, 1996), in various methanol + water mixtures at 25 °C using a spectrophotometric method.

Experimental Section

HPLC grade methanol (MeOH, Merck) and reagent grade perchloric acid (Merck) and ammonia (BDH) were used as received. Triply distilled deionized water was used throughout. Reagent grade sodium hydroxide (BDH), succinic acid (Merck), oxalic acid (BDH), lithium hydroxide (Merck), and sodium perchlorate (Merck) were of the highest purity available and used without further purification except for vacuum-drying over P_2O_5 for 72 h.

1-Hydroxy-9,10-anthraquinone (A1), 1-hydroxy-2-(methyl)-9,10-anthraquinone (A2), 1-hydroxy-2-(methoxymethyl)-9,10-anthraquinone (A3), 1-hydroxy-2-(ethoxymethyl)-9,10-anthraquinone (A4), 1-hydroxy-2-(propoxymethyl)-9,10-anthraquinone (A5), 1-hydroxy-2-(butoxymethyl)-9,10-anthraquinone (A6), 1-hydroxy-2-(amyloxymethyl)-9,10-anthraquinone (A7), 1-hydroxy-2-(bromomethyl)-9,10-anthraquinone (A8), 1-hydroxy-2-(dibromomethyl)-9,10-anthraquinone (A9), 1-hydroxy-2-(formyl)-9,10-anthraquinone (A10), 1-hydroxy-2-(hydroxymethyl)-9,10-anthraquinone (A11), bis[(1-hydroxy-9,10-anthraquinone)-2-methyl]sulfide (A12), 1,8-dihydroxy-2-(1-propenyl)-9,10-anthraquinone (A13), and 1,8-dihydroxy-2-allyl-9,10-anthraquinone (A14) were synthesized (Khojasteh, 1994; Sharghi and Forghaniha, 1995, 1996) and used after recrystallization from pure heptane and vacuum-drying. The structures of the anthraquinone derivatives used are shown in Figure 1.

The electronic spectra were recorded on a GBC 911 microprocessor-controlled UV−vis spectrophotometer, and the absorbance measurements at fixed wavelengths were carried out with a Metrohm 662 probe type photometer at (25.0 ± 0.2) °C. Measurements of pH were made with a Metrohm 692 pH meter using a combined electrode. In all experiments, the ionic strength of the solutions used was kept constant at 0.1 M using sodium perchlorate as the supporting electrolyte.

To calibrate the pH meter in various binary methanol + water mixtures used, the 0.01 M solutions of oxalate and succinate buffers were employed. The reference values of pH of these buffer solutions in different methanol + water mixtures have been reported previously (Bates, 1973).

A modified form of the procedure introduced by Ausero et al. (Ausero et al., 1986) was used to determine the acidity constants. In this procedure, the absorbance of a solution of fixed concentration of the anthraquinones in a given solvent mixture (2.0×10^{-5} M to 4.0×10^{-4} M) was first measured in highly acidic and basic solutions. Then the absorbance measurements at λ_{max} of the basic forms vs pH of the solution were made, while the anthraquinone solution was titrated with a concentrated sodium hydroxide solution in the same solvent mixture, using a precalibrated micropipet. All pH values are expressed in terms of activity.

The acidity constants were evaluated from the computer fitting of the absorbance−pH data to the equations that resulted from substituting the pH and absorbance values in the mass balances (Ausero et al., 1986). The resulting equations for monoprotic and diprotic acids are given in eqs 1 and 2, respectively:

$$A = (A_0 + A_1[H^+]/K_1)/(1 + [H^+]/K_1) \quad (1)$$

$$A = (A_0 + A_1([H^+]/K_2) + A_2([H^+]^2/K_1K_2))/(1 + [H^+]/K_2 + [H^+]^2/K_1K_2) \quad (2)$$

In these equations, A is the observed absorbance at each titration point, A_0, A_1, and A_2 are the absorbances of the basic form, monoprotonated form, and diprotonated form, respectively, and K_1 and K_2 are the first and second acidity

[†] Razi University.
[‡] Shiraz University.

S0021-9568(97)00091-5 CCC: $14.00 © 1997 American Chemical Society

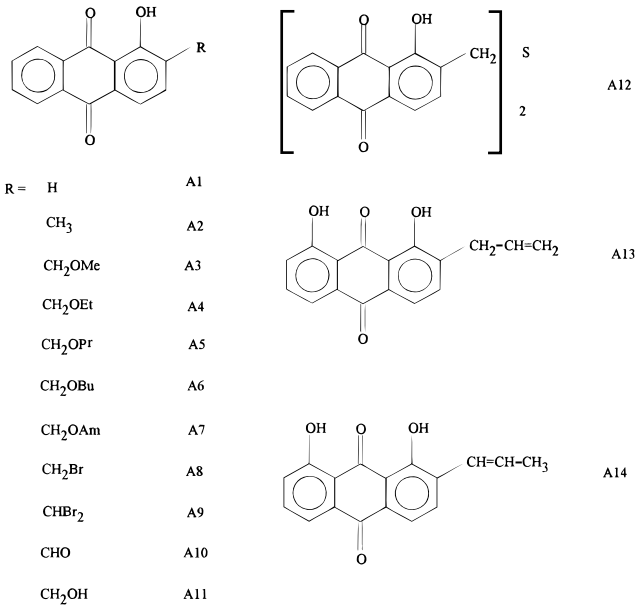

Figure 1. Structures of the anthraquinone derivatives used.

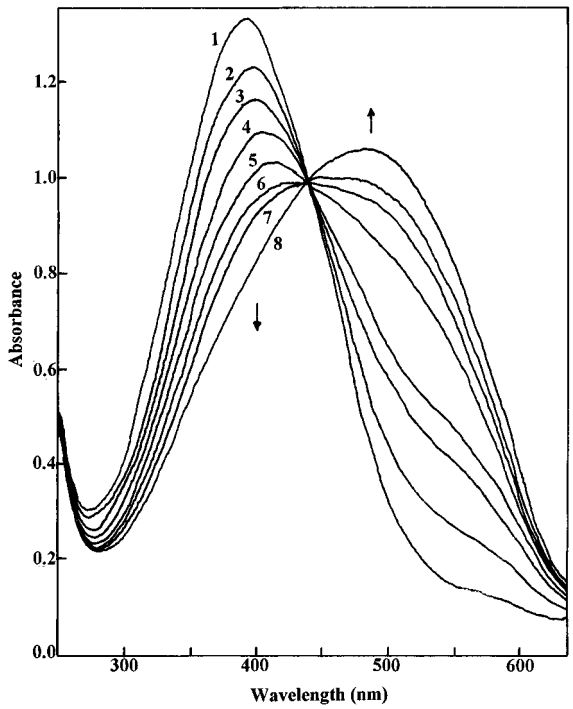

Figure 2. Absorption spectra of A3 in methanol solution at different pH values: (1) acidic, (2) 11.35, (3) 11.89, (4) 12.14, (5) 12.69, (6) 13.17, (7) 13.17, and (8) basic.

constants. The A_0, A_1, A_2, K_1, and K_2 values were calculated by computer fitting of the absorbance−pH data to either eq 1 or eq 2 (depending on the number of acidic protons of the anthraquinones) by using a nonlinear least-squares program written on the basis of the Gauss−Newton algorithm (Hamilton, 1964).

Results and Discussion

The visible absorption spectra of anthraquinone derivatives A1−A14 in different binary methanol + water mixtures at various pH values were recorded. Sample spectra for monoprotic derivative A3 at varying pH values in pure methanol are shown in Figure 2. The shorter wavelength band (405 nm) that appears at low pH values is due to the acid form, and the longer wavelength band (505 nm)

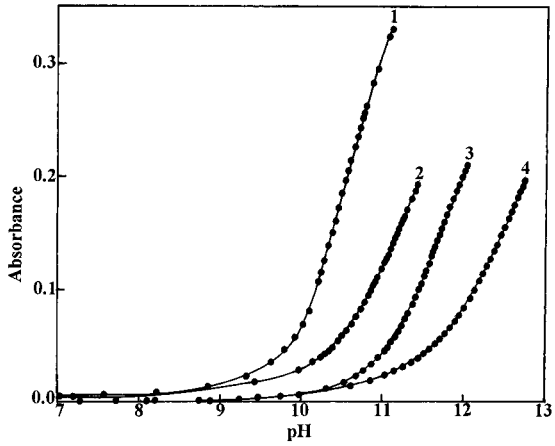

Figure 3. Absorbance−pH plots of A4 in different methanol−water mixtures. Weight percent of methanol in the binary mixture is (1) 70, (2) 80, (3) 90, and (4) 100.

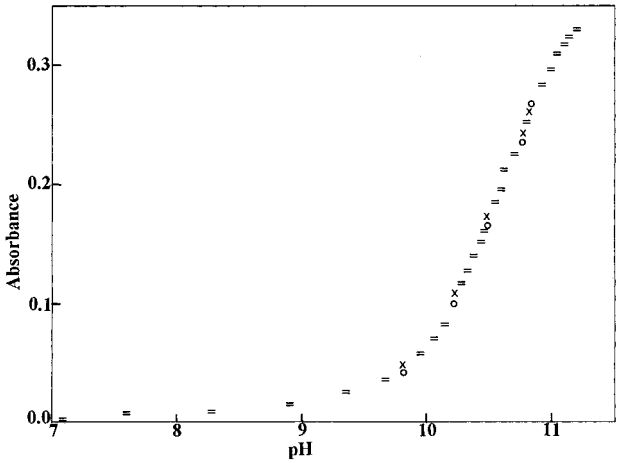

Figure 4. Computer fit of the absorbance−pH data for A4 in 70% methanol solution: (×) experimental point; (○) calculated point; (=) experimental and calculated points are the same within the resolution of the plot.

represents the absorption by the basic form of the molecule. The occurrence of a clear isosbestic point in the resulting spectra indicates that only two species (i.e., A^- and HA) are in equilibrium under the experimental conditions.

The acidity constants of molecules A1−A14 were investigated in four different methanol + water mixtures at 25 °C spectrophotometrically. Sample absorbance−pH plots for molecule A5 in different solvent systems are shown in Figure 3. The acidity constants of all anthrquinone derivatives studied were evaluated by computer fitting of the corresponding absorbance−pH data to the appropriate equations (i.e., eq 1 for monoprotic and eq 2 for diprotic acids). A sample computer fit of the absorbance−pH data is shown in Figure 4 and all the resulting pK_a values are summarized in Table 1.

From the data given in Table 1, it is immediately obvious that the nature of solvent plays a fundamental role in the acid−base equilibria. In all cases, there is a drastic decrease in the acidity of the molecules by an increase in the mole fraction of methanol in the binary methanol−water mixtures. It is well-known that the energy required for the separation of charges in acid dissociation, which is inversely proportional to the dielectric constant of the medium, is compensated by the solvation of the resulting ions (Bates, 1973). Thus, due to much lower dielectric constant, ϵ, and lower solvating ability (as expressed by the Gutmann donor number, DN) (Gutmann, 1978) of

Table 1. Acidity Constants (pK_a) of Various Anthraquinone Derivatives in Different Methanol + Water Mixtures

acid		wt % methanol 70	80	90	100
		Monoprotic			
A1	pK_1	10.61 ± 0.02	11.03 ± 0.03	11.50 ± 0.03	12.08 ± 0.03
A2	pK_1	11.56 ± 0.05	11.71 ± 0.04	12.17 ± 0.05	12.55 ± 0.08
A3	pK_1	10.73 ± 0.02	11.23 ± 0.02	11.68 ± 0.02	12.19 ± 0.02
A4	pK_1	10.53 ± 0.02	11.29 ± 0.02	11.81 ± 0.02	12.56 ± 0.02
A5	pK_1	10.67 ± 0.02	10.87 ± 0.02	11.76 ± 0.02	12.66 ± 0.02
A6	pK_1	10.84 ± 0.02	10.89 ± 0.02	11.42 ± 0.02	12.55 ± 0.02
A7	pK_1	10.68 ± 0.02	10.94 ± 0.02	11.37 ± 0.02	12.47 ± 0.02
A8	pK_1	10.61 ± 0.02	10.81 ± 0.02	11.19 ± 0.02	12.38 ± 0.05
A9	pK_1	10.21 ± 0.02	10.69 ± 0.02	11.21 ± 0.02	11.73 ± 0.02
A10	pK_1	8.79 ± 0.02	9.49 ± 0.02	9.93 ± 0.02	10.78 ± 0.02
A11	pK_1	10.19 ± 0.07	10.29 ± 0.02	10.48 ± 0.12	10.65 ± 0.08
		Diprotic			
A12	pK_1	8.94 ± 0.09	9.61 ± 0.12	10.31 ± 0.03	11.22 ± 0.08
	pK_2	10.86 ± 0.03	11.11 ± 0.09	11.99 ± 0.12	12.76 ± 0.05
A13	pK_1	9.31 ± 0.03	9.46 ± 0.03	9.80 ± 0.15	11.02 ± 0.03
	pK_2	10.38 ± 0.04	10.50 ± 0.07	10.87 ± 0.08	11.92 ± 0.02
A14	pK_1	8.99 ± 0.02	9.15 ± 0.02	9.47 ± 0.06	10.54 ± 0.12
	pK_2	10.03 ± 0.03	10.25 ± 0.02	10.82 ± 0.03	11.85 ± 0.07

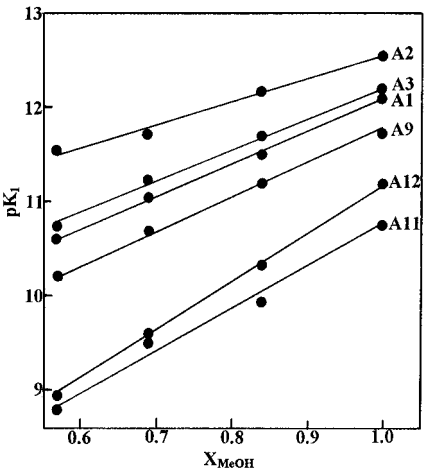

Figure 5. Variation of pK_1 values of some of the anthraquinone derivatives used with X_{MeOH} in the binary mixtures.

methanol (ϵ = 32.6 and DN = 19) than those of water (ϵ = 78.3 and DN = 33) (Erlish and Popov, 1971), it is not surprising to observe such a decrease in the extent of ionization of the acids by an increase in the amount of methanol in the solvent mixtures used.

There is actually a linear relationship between pK_a of the anthraquinone derivatives used and mole fraction of methanol, X_{MeOH}, in the binary mixtures. The resulting linear plots for some of the molecules used are shown in Figure 5. We have already observed the same linear behavior in the study of complexation equilibria of a number of metal ion−ligand systems (Khajesharifi and Shamsipur, 1995; Parham and Shamsipur, 1991; Rouhollahi et al., 1994; Saeidi and Shamsipur, 1990; Shamsipur and Ghasemi, 1995). It seems reasonable to assume that the preferential hydration of the conjugated bases is mainly responsible for such a monotonic dependence of pK_a upon the solvent composition.

It is well-known that the acidity of anthraquinone derivatives may be influenced by structural parameters such as inductive effect, mesomeric (hyperconjugation) effect, and steric hindrance of sidearms (March, 1968). Table 1 shows that the substitution of a $-CH_3$ group in the 2-position of 1-hydroxy-9,10-anthraquinone (A1), to form the A2 molecule, will lower its acidity strength considerably. This is obviously due to the donating inductive effect of the alkyl substituents on the A1 molecule. It is interesting to note that the replacement of the $-CH_3$ substituent by a $-CH_2OR$ group (with R varying from $-CH_3$ to $-C_5H_{11}$ to form A3−A7 molecules) will cause the acidity strength of A2 to increase to a value close to the mother molecule A1. This could be due to the withdrawing inductive effect of the −OR group, which compensates the opposite behavior of the $-CH_3$ group.

It is noteworthy that the acidity of the molecules bearing a $-CH_2OR$ group in their 2-position (i.e., molecules A3−A7) shows only a minor change by changing the −R group from $-CH_3$ to $-C_5H_{11}$. A further increase in the acidity constants of A8 and A9 molecules, as compared with those of acids A1−A7, can be interpreted on the basis of the foregoing discussion and the increased inductive effect of the bromide substituents. A comparison between the pK_1 values of molecules A2 and A11 makes it clear that the substitution of one of the $-CH_3$ protons by an −OH group increases the acidity constant very considerably (e.g., decreases pK_1 from 11.56 to 10.19 in 70% methanol). This is obviously not only due to the withdrawing inductive effect of the hydroxyl group but also to its intramolecular H-bonding with the $-O^-$ group in the 1-position via a 6-membered ring, which results in the increased stability of the conjugated base.

Comparison of the data given in Table 1 shows that, among different monoprotic anthraquinone derivatives studied, 1-hydroxy-2-(formyl)-9,10-anthraquinone (A10) possesses the highest acidity strength, in all solvent mixtures used. In this case, not only the withdrawing inductive effect but also the possible conjugation of the −CH═O group would participate in the stabilization of the resulting conjugated base and, therefore, results in the strongest acid in the series.

From Table 1, it is seen that, among the diprotic anthraquinone derivatives used, the acidity strength increases in the order A12 < A13 < A14. In acid A14 not only the steric hindrance but also the possible conjugation of the allyl sidearm seems responsible for the stabilization of the resulting conjugated base which, in turn, results in a pronounced increase in the acidity of the molecule. In the case of A13 it is the steric hindrance of the sidearm and its electron-releasing character that can influence the acidity constants of the molecule. Finally, the molecule A12 containing a withdrawing sulfur atom, which connects two anthrquinone molecules to each other, is expected to be the weakest acid in the series (March, 1968).

Literature Cited

Arcamone, F. Antitumor Anthracyclines: Recent Developments. *Med. Res. Rev.* **1984**, *14*, 153−188.

Ausero, A. G.; Navas, M. J.; Jimenez-Trillo, J. L. Spectrophotometric Methods for the Evaluation of Acidity Constants-I. *Talanta*, **1986**, *33*, 195−198.

Ausero, A. G.; Jimenez-Trillo, J. L.; Navas, M. J. Spectrophotometric Methods for the Evaluation of Acidity Constants-II. *Talanta* **1986**, *33*, 531−535.

Bates, R. G. *Determination of pH, Theory and Practice*; Wiley: New York, 1973.

Dadfarnia, S.; Shamsipur, M.; Tamaddon, F.; Sharghi, H. Extraction and Membrane Transport of Metal Ions by Some Synthetic 9,10-Anthraquinone Derivatives. A Selective System for Calcium Transport. *J. Membr. Sci.* **1993**, *78*, 115−121.

Erlish, R. H; Popov, A. I. Spectroscopic Studies of Ionic Solvation. X. A Study of the Solvation of Sodium Ions in Nonaqueous Solvents by ^{23}Na Nuclear Magnetic Resonance. *J. Am. Chem. Soc.* **1971**, *93*, 5620−5623.

Frey, P. A.; Kokesh, F. O.; Westheimer, F. H. A Reporter Group at the Active Site of Acetoacetate Decarboxylase I. Ionization Constant of the Nitrophenol. *J. Am. Chem. Soc.* **1971**, *93*, 7266−72.

Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*; Plenum Press: Now York, 1978.

Hamilton, W. C. *Statistics in Physical Science*; Roland Press: New York, 1964.

Khajesharifi, H.; Shamsipur, M. Spectrophotometric Study of the Thermodynamics of Complexation of Lithium and Sodium Ions with

Dibenzo-24-crown-8 in Binary Dimethylformamide-Acetonitrile Mixtures Using Murexide as a Metallochromic Indicator. *J. Coord. Chem.* **1995**, *35*, 289−297.

Khojasteh, Z. Investigation of Claisen Rearrangement of Some Allyloxy Anthraquinones with Tin/Acetic Acid as a New Catalyst; M.S. Thesis, Shiraz University, Shiraz, Iran, 1994.

Lowe, N. J.; Ashton, R. E.; Koudsi, H.; Verschoore, M.; Schaefer, H. Anthralin for Psoriosis: Short Contact Anthralin Therapy Compared with Topical Steroid and Conventional Anthralin. *J. Am. Acad. Dermatol.* **1984**, *10*, 69−75.

Lucker, M. *Secondary Metabolism in Microorganism, Plants and Animals*; Springer-Verlag: New York, 1984.

March, J. *Advanced Organic Chemistry: Reaction, Mechanisms, and Structure*; McGraw-Hill: New York, 1968.

Parham, H.; Shamsipur, M. Polarographic Study of Interaction Between Heavy Metal Ions and Some Macrocyclic Ligands in Binary Acetonitrile-Water Mixtures. *J. Electroanal. Chem.* **1991**, *314*, 71−80.

Qureshi, G. A.; Svehla, G.; Leonard, M. A. Electrochemical Studies of Strongly Chelating Anthraquinone Derivatives. *Analyst* **1979**, *104*, 705−722.

Rochester, G. H. *Acidity Functions*; Academic Press: London, 1970.

Rouhollahi, A.; Amini, M. K.; Shamsipur, M. NMR Study of the Stoichiometry, Stability and Exchange Kinetics of Complexation Reaction Between Pb^{2+} Ion and 18-Crown-6 in Binary Acetonitrile-Water Mixtures. *J. Solution Chem.* **1994**, *23*, 63−74.

Saeidi, M.; Shamsipur, M. Complex Formation Between Alkaline Earth Cations and 4-(2-Pyridylazo) resorcinol in Ethanol−Water Mixtures. *J. Coord. Chem.* **1990**, *22*, 131−137.

Shamsipur, M.; Ghasemi, J. Conductance Study of the Thermodynamics of Some Transition and Heavy Metal Cryptates in Binary Acetonitrile-Dimethyl sulfoxide Mixtures. *J. Inclusion Phenom.* **1995**, *20*, 157−171.

Sharghi, H.; Forghaniha, A. Efficient Synthesis of a Range of 1-Hydroxy-2-(1-alkyloxymethyl)-9,10-anthraquinone Derivatives. *Iran. J. Chem. Chem. Eng.* **1995**, 14, 16−22.

Sharghi, H.; Forghaniha, A. Synthesis of 1,1′-Dihydroxy-2,2′-(thiodimethylene)bis-9(10H)-anthrone. *J. Sci., Islamic Repub. Iran* **1996**, *7*, 89−91.

Thomson, R. H. *Naturally Occorring Quinones*; Academic Press: New York, 1971.

Received for review April 17, 1997. Accepted July 30, 1997.[⊗]

JE970091O

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.