International Journal of Pharmaceutics, 42 (1988) 181–191
Elsevier

IJP 01424

Electrostatic and non-electrostatic free energy contributions to acid dissociation constants in cosolvent–water mixtures

Joseph T. Rubino

School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514 (U.S.A.)

(Received 19 May 1987)
(Modified version received 31 August 1987)
(Accepted 7 September 1987)

Key words: Dissociation constant; Cosolvent; Born equation; Estimation; Linear free energy approach

Summary

Thermodynamic pK_a values were determined for barbituric acid and several derivatives in solvents containing 0–50% ethanol in water. The data were analyzed using a model which accounts for electrostatic and non-electrostatic contributions to the pK_a changes as a function of solvent composition. The Born equation was used to calculate pK_a changes due to electrostatic effects and the difference between observed and calculated pK_a changes was attributed to non-electrostatic effects. The non-electrostatic effect was not constant for a given solvent system as suggested by previous investigations. When compounds possessing a different acidic group are analyzed by this approach, it becomes apparent that the type of hydrophilic functional group has a large influence on the non-electrostatic effect. The original model was thus extended such that the non-electrostatic effect was divided into a lipophilic and hydrophilic component, where the hydrophilic component was determined from the pK_a data of the parent compound of each series. The lipophilic non-electrostatic effect was found to correlate well with the hydrophobic surface area and log octanol–water partition coefficient of the solute. These results indicate that a linear free energy approach can be used to estimate pK_a changes for weak organic electrolytes in cosolvent–water mixtures.

Introduction

The prediction of acid dissociation constants of weak electrolyte drugs is important in estimating their physical and biological activity. Semiaqueous solvent systems are often used in the preparation of liquid dosage forms of weak electrolyte drugs, in liquid chromatographic analysis and in the estimation of relative dissociation constants of poorly water soluble compounds. As a general rule, weak electrolytes become even weaker as water is replaced by a non-aqueous solvent. Few theories have been capable of adequately estimating the influence of solvent composition on the behavior of weak electrolytes of organic compounds. In addition, many previous studies have dealt with relatively simple molecules containing only a single polar function group while drug molecules may be considerably more complex.

The change in the acid dissociation constant of a weak organic electrolyte with solvent composition has been described in terms of the medium effect. The medium effect γ_i is defined as the ratio of the activity of a chemical species in water to the activity in a non-aqueous or semi-aqueous solvent (Benet and Goyan, 1967). The difference in the

Correspondence: J.T. Rubino, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514, U.S.A.

pK_a between the non-aqueous or semi-aqueous solvent, s, and pure water, w, is therefore defined for a monoprotic weak acid as:

$$\Delta pK_a = pK_{a_s} - pK_{a_w} = \log \frac{\gamma_{HA}\gamma_A}{\gamma_{HA}} \quad (1)$$

The medium effect represents the free energy of transfer of each species from water to mixed solvent. It has been suggested in previous reports (Sager et al., 1964; Alfenaar and Deligny, 1967; Rubino and Berryhill, 1986) that the free energy of transfer between mixed solvent and water for a particular species can be divided into electrostatic, *el*, and non-electrostatic, *n*, contributions:

$$\frac{\log \gamma_{H^+}\gamma_A}{\gamma_{HA}} = \frac{\log \gamma_H^{el}\gamma_A^{el}}{\gamma_{HA}^{el}} + \frac{\log \gamma_H^{n}\gamma_A^{n}}{\gamma_{HA}^{n}} \quad (2)$$

The electrostatic contribution for a given charged species has been estimated using the Born equation (Sager et al., 1984; Alfenaar and Deligny, 1967; Rubino and Berryhill, 1986):

$$\log \gamma^{el} = \frac{Ne^2Z^2}{4.606rRT}\left(\frac{1}{\epsilon_s} - \frac{1}{\epsilon_w}\right) \quad (3)$$

where N is Avogadro's number, e is the electronic charge, Z is the charge on the ion, r is the ionic radius and ϵ is the dielectric constant of the medium, R is the universal gas constant and T is the absolute temperature.

The non-electrostatic effect has been estimated by the difference between observed ΔpK_a values and those predicted by the Born equation (Sager et al., 1964; Rubino and Berryhill, 1986). It has been shown previously that this effect correlates well with measures of solvent basicity for some benzoic acid derivatives (Rubino and Berryhill, 1986). For large ions, the non-electrostatic effect should be constant for a particular solvent mixture:

$$\gamma_A^n = \gamma_{HA}^n \quad (4a)$$

and

$$\Delta pKa^n = \log \gamma_{H^+}^n \quad (4b)$$

Sager et al. (1964) compared the non-electrostatic effects for two bases and two acids in methanol–water and found them to be relatively constant for a particular solvent mixture. However, a consistent method for choosing ionic radii was not used and a very small radius had to be chosen for the acetate ion in order to bring all the results into agreement.

For practical purposes the estimation of acid dissociation constants in mixed solvent systems requires that a reliable set of parameters be used in the estimation procedures. In the present study the acid dissociation constants of a series of barbituric acid derivatives were measured in ethanol–water mixtures and the observed ΔpKa values were compared to those estimated by the Born equation. Values of the molecular radii were estimated from molar volumes using the methods of Bondi (1968). The barbituric acids were selected as a representative group of drugs possessing a combination of polar and non-polar moieties. The results of this group of compounds were compared with the results of a series of carboxylic acids taken from the literature (Grunwald and Berkowitz, 1951; Sugunan, 1983) in order to examine the relationship between groups of compounds with widely different structures and polarities.

Materials and Methods

pK_a values were determined by potentiometric titration or UV spectrophotometric analysis (Albert and Serjeant, 1984) when the compounds were too insoluble for potentiometric methods. For the potentiometric determinations, standardized potassium hydroxide was used as the titrant. The concentration of titrant was 100-fold larger than the concentration of solute so that a total volume change of less than 1% occurred by the end of the titration. It was necessary to keep the volume of titrant small in order to avoid dilution of the cosolvent during pK_a determinations in mixed solvent systems. All titrations were performed at $25 \pm 0.5\,^{\circ}C$ under nitrogen gas. The

pK_a changes were determined from the well-known relationship:

$$Z = C_0 - (1/K_a)Z[H^+]$$

where $Z = [H^+] + [K^+] - [OH^-]$ at each point in the titration and C_0 is the initial concentration of drug. The calculations of Z and $Z[H^+]$ as well as linear regression of the data were performed on an Apple computer using a program written in Microsoft Basic. The hydrogen ion concentration at each point in the titration in the mixed solvent systems was corrected for liquid junctions errors using 10^{-3} M HCl according to a modification of the methods of Van Uitert and Haas (1953). All pK_a values were adjusted for solvent and concentration effects using the appropriate form of the Debye Huckel equation (Martin et al., 1983).

5-Ethyl 5-(3-nitrophenyl) barbituric acid was synthesized by nitration of phenobarbital as described previously (Bousquet and Adams, 1930). The product was recrystallized twice from hot methanol and dried in a vacuum oven. The melting point of the dried crystals was 284°C. All other barbiturates were used as received from Sigma Chemicals [1].

Molar volumes were estimated using the group contribution approach of Bondi (1968). The radii of the various anions were estimated from molecular volumes, assuming spherically shaped molecules. A radius of 0.111 nm was used for the hydrogen ion in each calculation. Surface areas of lipophilic groups (Ah) were determined from the same source. Octanol/water partition coefficients (log PC) of the neutral molecules were taken from the listing of Leo et al. (1971) or calculated as described therein. Dielectric constant values for ethanol–water mixtures were estimated from the algebraic sum of the values for pure ethanol and water (Eastman Kodak, 1975) adjusted for the volume fraction of each solvent.

Results and Discussion

Table 1 presents the list of compounds studied, the log PC, radii and hydrophobic surface areas. Table 2 lists the observed pK_a values, the ΔpK_a values predicted by the Born equation and the residual ΔpK_a values, ie. the pK_a change due to non-electrostatic effects. Measured pK_a values for the barbiturates in water were in agreement with previously published data by a factor of 0.05 units or less (McKeown, 1980). The ΔpK_a values due to non-electrostatic effects were determined from the difference between the observed and calculated ΔpK_a values. In order to compare the influence of solvent composition on the pK_a values of the various compounds, plots of ΔpK_a vs. $(1/\epsilon_s - 1/\epsilon_w)$ were constructed and the slopes of these plots compared for each compound and each series of compounds. These plots were linear, as expected (Benet and Goyan, 1967). The results of a linear regression of ΔpK_a vs. $(1/\epsilon_s - 1/\epsilon_w)$ are reported in Table 3.

It might also be expected that the more lipophilic species would show larger ΔpK_a values, as measured by the slopes of the ΔpK_a vs. $(1/\epsilon_s - 1/\epsilon_w)$ plots. Fig. 1 illustrates a plot of these slopes vs. log PC for the compounds studied. It can be observed that the slopes increase with increasing log PC for a given series of compounds, but the values of the slopes do not fall on a single line for members of different homologous series.

Surprisingly, some of the carboxylic acid derivatives show larger pK_a changes than the more lipophilic barbiturates. It is also significant that the parent compound in each series, barbituric acid and formic acid, behaved differently as the fraction of ethanol in the solvent was increased; the pK_a of barbituric acid remained practically invariant as the fraction of ethanol increased while the pK_a of formic acid increased with the fraction of ethanol as seen in Table 2.

The residual ΔpK_a values for each series are plotted in Figs. 2 and 3 for easy comparison. The residual ΔpK_a values are not constant for a particular solvent composition as predicted by Eqn. 4b. Upon comparing the residual ΔpK_a values of the barbiturates with the carboxylic acids it is seen that the residual values are much smaller for the former series of compounds than for the latter. Conversely, the residual values for the parent compounds, barbituric acid and formic acid, demonstrate the opposite trend, with barbituric acid

[1] Sigma Chemicals Co., P.O. Box 14508, St. Louis, MO 63178, U.S.A.

TABLE 1

List of compounds and physical properties

Compound	Ionic radius (nm)	Ah (10^9 cm^2/mol)	Log *PC*
Barbituric acid	0.291	–	−1.47
Barbital	0.344	6.94	0.65
5,5-Diallylbarbituric acid	0.359	8.58	1.19
Aprobarbital	0.362	9.10	1.24
Butabarbital	0.366	9.63	1.89
Phenobarbital	0.367	8.80	1.42
Amobarbital	0.375	10.98	2.07
5-Ethyl-5-(3-nitrophenyl)barbituric acid	0.383	–	1.14
Formic acid	0.195	–	−0.54
Acetic acid	0.225	2.12	−0.17
Propionic acid	0.249	3.47	0.33
Butyric acid	0.269	4.82	0.79
Isovaleric acid	0.287	6.16	1.13
Benzoic acid	0.289	5.33	1.87
Ethyl H-terephthalic acid	0.341	11.00	2.98
n-Propyl H-terephthalic acid	0.352	12.35	3.48
Isobutyl H-terephthalic acid	0.363	13.89	3.78

showing much larger negative deviations from the Born equation than formic acid. It should be noted that the ionization of barbituric acid involves a different chemical group, the C-5 methylene, compared to the 5,5-disubstituted analogs. However, this fact does not explain the difference between the two series of compounds which is evident from Fig. 1 and is based only on the solute partition coefficient.

It is again surprising that the barbiturates demonstrate such relatively small residual ΔpK_a values compared to the carboxylic acids. These ob-

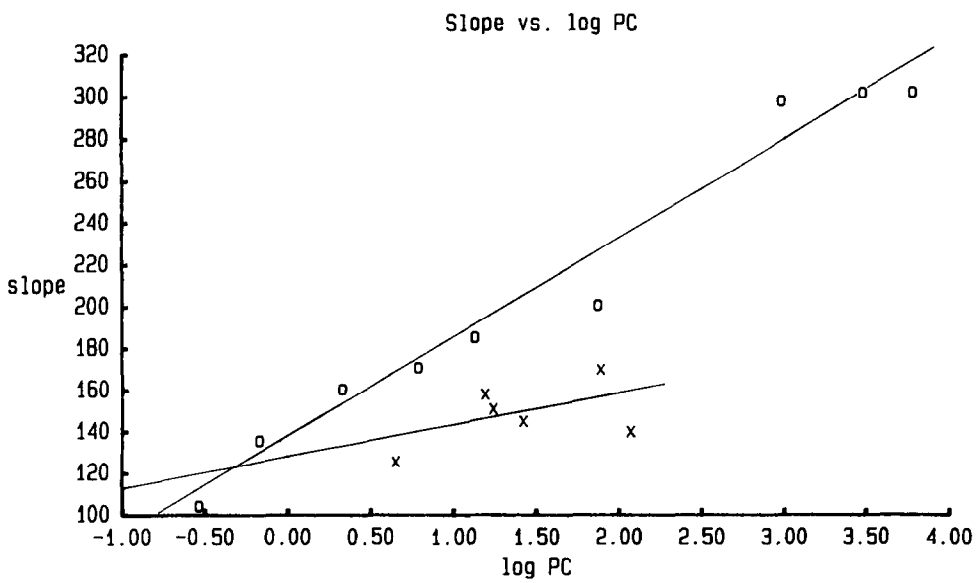

Fig. 1. Slope (see Table 3) vs. log *PC*. ○, carboxylic acids; ×, barbituric acids.

servations are apparently not related to molecular size since the acid phthalates are of a comparable size to the barbiturates, yet they demonstrate larger deviations from the Born equation. It thus appears that the acid dissociation constants of the barbiturates in ethanol–water mixtures are estimated fairly well by the Born equation, while the those of the carboxylic acids are not. In practice, it would not be known whether the pK_a values for a given series of compounds can or cannot be estimated by the Born equation without experimental data. Therefore an approach which unifies the pK_a estimation of different series of compounds in mixed solvent systems would be useful.

It seems reasonable to suspect that the hydrophilic portion of the molecules, represented by barbituric acid and formic acid, plays a major role in determining the influence of solvent composition on the changes in the pK_a of the molecule. With this thought in mind, the residual ΔpK_a can be written:

$$\frac{\log \gamma_A^n}{\gamma_{HA}^n} = \frac{\log \gamma_A^h}{\gamma_{HA}^h} + \frac{\log \gamma_A^p}{\gamma_{HA}^p} \qquad (5)$$

where the superscripts h and p refer to the lipophilic and hydrophilic portions of the molecule, respectively. Based upon Eqn. 5, the residual pK_a of each parent compound was subtracted from each member of the series. These plots are presented in Figs. 4 and 5. These residual plots, referred to as the liporesidual plots, demonstrate the expected trend in mixed solvent systems, i.e., the more lipophilic compounds are affected to a larger extent than less lipophilic compounds. These liporesidual values for the barbiturates are much greater than the residual values in Table 2 due to the large deviation of the parent compound, barbituric acid, from the Born equation. The plots of the liporesidual pK_a vs f, the volume fraction of cosolvent, are reasonably linear and the slopes were tabulated. The results of a linear regression of the liporesidual pK_a vs. f are listed in Table 4 for each compound.

For the purpose of predicting pK_a values in mixed solvent systems, it is necessary to express the slope of the liporesidual vs f plots as a function of some physical property of the solute. The slopes from Table 4 were found to correlate well with the hydrophobic surface area of each solute. A plot of the slopes listed in Table 4 vs the surface areas of the hydrophobic groups is presented in

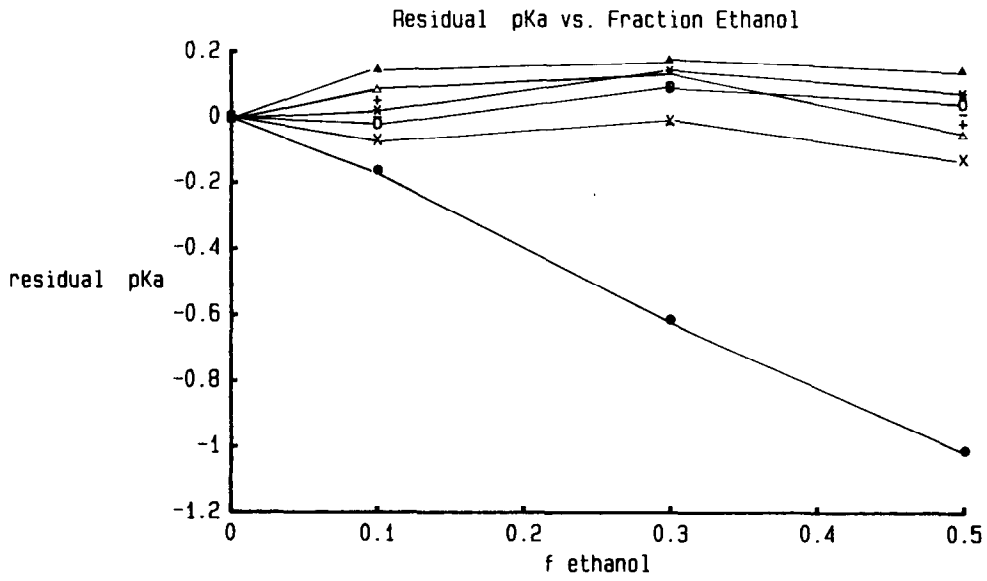

Fig. 2. Residual pK_a vs. volume fraction ethanol for barbituric acids and derivatives. ●, barbituric acid; ×, barbital; ○, aprobarbital; +, phenobarbital; –, amobarbital; *, 5,5-diallylbarbituric acid; ▲, butabarbital; △, 5-ethyl-5-(3-nitrophenyl) barbituric acid.

TABLE 2

Observed, predicted and residual ΔpK_a values

Compound	f ethanol	pK_a	ΔpK_a (obs.)	ΔpK_a (Born)	ΔpK_a (resid.)	ΔpK_a (SA) *	ΔpK_a (PC) **
Barbituric acid							
	0.00	4.06	0.00	0.00	0.00		
	0.10	4.03	−0.03	0.13	−0.16		
	0.30	3.95	−0.11	0.50	−0.61		
	0.50	4.06	0.00	1.01	−1.01		
Barbital	0.00	7.97	0.00	0.00	0.00		
	0.10	8.03	0.06	0.13	−0.07	0.14	0.13
	0.30	8.43	0.46	0.47	−0.01	0.36	0.35
	0.50	8.80	0.83	0.96	−0.13	0.79	0.77
5,5-Diallybarbituric acid							
	0.00	7.73	0.00	0.00	0.00		
	0.10	7.88	0.15	0.13	0.02	0.17	0.17
	0.30	8.34	0.61	0.47	0.14	0.46	0.45
	0.50	8.75	1.02	0.95	0.07	0.95	0.93
Aprobarbital	0.00	8.00	0.00	0.00	0.00		
	0.10	8.11	0.11	0.13	−0.02	0.18	0.17
	0.30	8.56	0.56	0.47	0.09	0.50	0.46
	0.50	8.99	0.99	0.95	0.04	1.00	0.94
Butabarbital	0.00	7.95	0.00	0.00	0.00		
	0.10	8.22	0.27	0.13	0.14	0.19	0.21
	0.30	8.59	0.64	0.47	0.17	0.53	0.58
	0.50	9.04	1.09	0.95	0.14	1.06	1.14
Phenobarbital	0.00	7.48	0.00	0.00	0.00		
	0.10	7.66	0.18	0.13	0.05	0.18	0.18
	0.30	8.04	0.56	0.47	0.09	0.48	0.49
	0.50	8.41	0.93	0.95	−0.02	0.97	1.00
Amobarbital	0.00	7.94	0.00	0.00	0.00		
	0.10	8.06	0.12	0.12	0.00	0.21	0.21
	0.30	8.39	0.45	0.47	−0.02	0.61	0.61
	0.50	8.89	0.95	0.94	0.01	1.19	1.18
5-Ethyl-5(3-nitrophenyl) barbituric acid							
	0.00	6.99	0.00	0.00	0.00		
	0.10	7.20	0.21	0.12	0.09		
	0.30	7.58	0.59	0.46	0.13		
	0.50	7.88	0.89	0.94	−0.05		
Formic acid [a]							
	0.00	3.75	0.00	0.00	0.00		
	0.24	4.02	0.27	0.42	−0.15		
	0.41	4.24	0.49	0.84	−0.35		
	0.56	4.60	0.85	1.37	−0.52		
Acetic acid [a]							
	0.00	4.76	0.00	0.00	0.00		
	0.24	5.13	0.37	0.40	−0.03	0.41	0.39
	0.41	5.43	0.67	0.80	−0.13	0.73	0.69
	0.56	5.84	1.08	1.30	−0.22	1.16	1.11
Propionic acid [a]							
	0.00	4.87	0.00	0.00	0.00		
	0.24	5.33	0.46	0.39	0.07	0.47	0.45
	0.41	5.68	0.81	0.78	0.03	0.82	0.80
	0.56	6.13	1.26	1.26	0.00	1.28	1.24

TABLE 2 *(continued)*

Compound	f ethanol	pK_a	ΔpK_a (obs.)	ΔpK_a (Born)	ΔpK_a (resid.)	ΔpK_a (SA) *	ΔpK_a (PC) **
Butyric acid [a]							
	0.00	4.82	0.00	0.00	0.00		
	0.24	5.31	0.49	0.38	0.11	0.53	0.51
	0.41	5.70	0.88	0.76	0.12	0.92	0.89
	0.56	6.15	1.33	1.23	0.10	1.40	1.37
Isovaleric acid [a]							
	0.00	4.78	0.00	0.00	0.00		
	0.24	5.29	0.51	0.38	0.13	0.59	0.56
	0.41	5.75	0.97	0.74	0.23	1.01	0.95
	0.56	6.22	1.44	1.21	0.23	1.54	1.46
Benzoic acid [a]							
	0.00	4.20	0.00	0.00	0.00		
	0.24	4.77	0.57	0.37	0.20	0.54	0.66
	0.41	5.24	1.04	0.74	0.30	0.94	1.14
	0.56	5.76	1.56	1.20	0.36	1.43	1.70
Ethyl H-terephthalate [b]							
	0.00	3.66	0.00	0.00	0.00		
	0.20	4.04	0.38	0.29	0.09	0.66	0.66
	0.50	5.73	2.07	0.97	1.10	1.78	1.77
n-Propyl H-terephthalate [b]							
	0.00	3.61	0.00	0.00	0.00		
	0.20	4.06	0.45	0.29	0.16	0.72	0.72
	0.50	5.69	2.08	0.95	1.13	1.90	1.90
Isobutyl H-terephthalate [b]							
	0.00	3.63	0.00	0.00	0.00		
	0.20	4.02	0.39	0.28	0.11	0.77	0.75
	0.50	5.73	2.10	0.95	1.15	2.06	1.99

[a] Data from Grunwald and Berkowitz (1951).
[b] Data from Sugunan (1983).
* Liporesidual ΔpK_a from Eqn. 6.
** Liporesidual ΔpK_a from Eqn. 7.

TABLE 3

Regression equations [a]*:* ΔpK_a *vs* $(1/\epsilon_s - 1/\epsilon_w)$

	Coeff. (S.E.M.)	r^2
Barbital	125.48 (5.61)	0.9880
5,5-Diallylbarbituric acid	158.07 (7.16)	0.9863
Aprobarbital	150.97 (5.38)	0.9920
Butabarbital	170.05 (10.85)	0.9699
Phenobarbital	145.06 (7.55)	0.9810
Amobarbital	140.01 (1.71)	0.9991
Acetic acid	135.68 (1.64)	0.9988
Propionic acid	160.53 (3.61)	0.9956
Butyric acid	170.87 (4.51)	0.9939
Isovaleric acid	185.35 (4.65)	0.9946
Benzoic acid	200.70 (5.30)	0.9940
Ethyl H-terephthalate	297.89 (24.00)	0.9766
n-Propyl H-terephthalate	302.15 (17.55)	0.9873
Isobutyl H-terephthalate	302.39 (23.92)	0.9774

Fig. 6. The results of the regression analysis are as follows:

$$\text{slope(lipo)} = 0.2067(0.0182)A_h + 0.2424(0.2250)$$
$$n = 14 \quad r^2 = 0.9151 \qquad (6)$$

For some solutes there may not be a clear distinction between hydrophilic and hydrophobic surface areas. In such cases, the partition coefficient may serve as a more convenient measure of solute polarity. The log octanol/water partition coefficient of each compound was adjusted for the contribution of its corresponding parent compound by subtracting the log *PC* for barbituric or

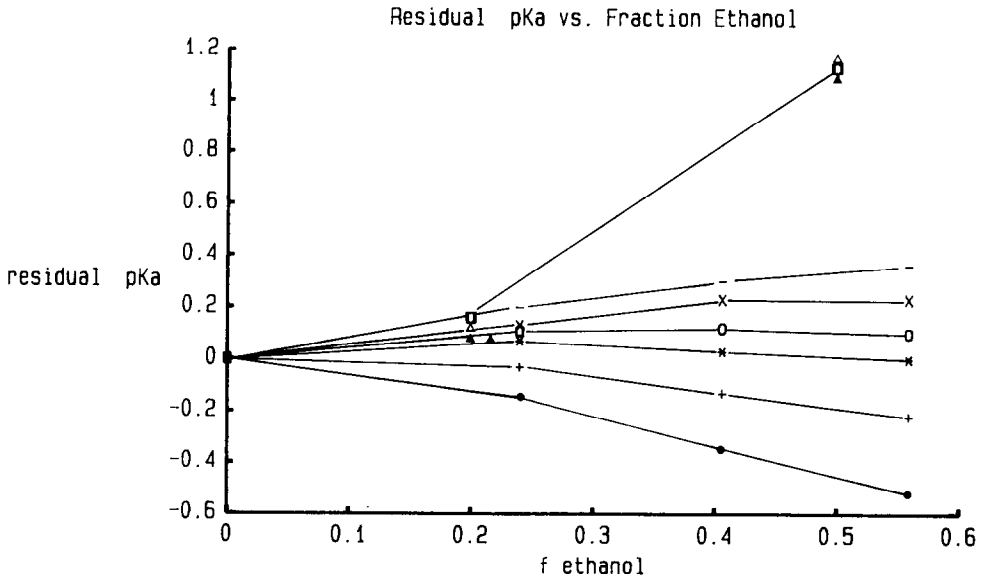

Fig. 3. Residual pK_a vs. volume fraction ethanol for carboxylic acids. ●, formic acid; +, acetic acid; *, propionic acid; ○, butyric acid; X, isovaleric acid; –, benzoic acid; ▲, ethyl-H-terephthalate; □, *n*-propyl-H-terephthalate; △, isobutyl-H-terephthalate.

vs adjusted log *PC* is presented in Fig. 7. The results of this regression are reported as follows:

$$\text{slope(lipo)} = 0.6043\ (0.0505)\log PC + 0.3686\ (0.2148) \quad n = 14 \quad r^2 = 0.9312 \tag{7}$$

Estimated ΔpK_a values are listed in the last two columns of Table 2 for the barbiturates and the carboxylic acids. These were calculated from the sum of the liporesidual ΔpK_a, residual ΔpK_a of the parent compound (column 5) and the ΔpK_a

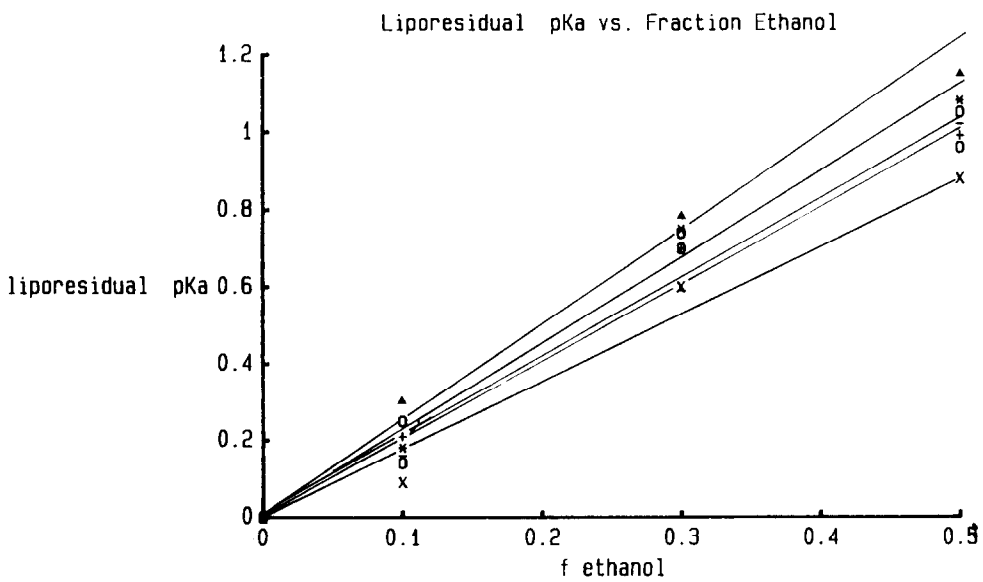

Fig. 4. Liporesidual pK_a vs volume fraction ethanol for barbituric acid and derivatives (see Fig. 2 for symbols).

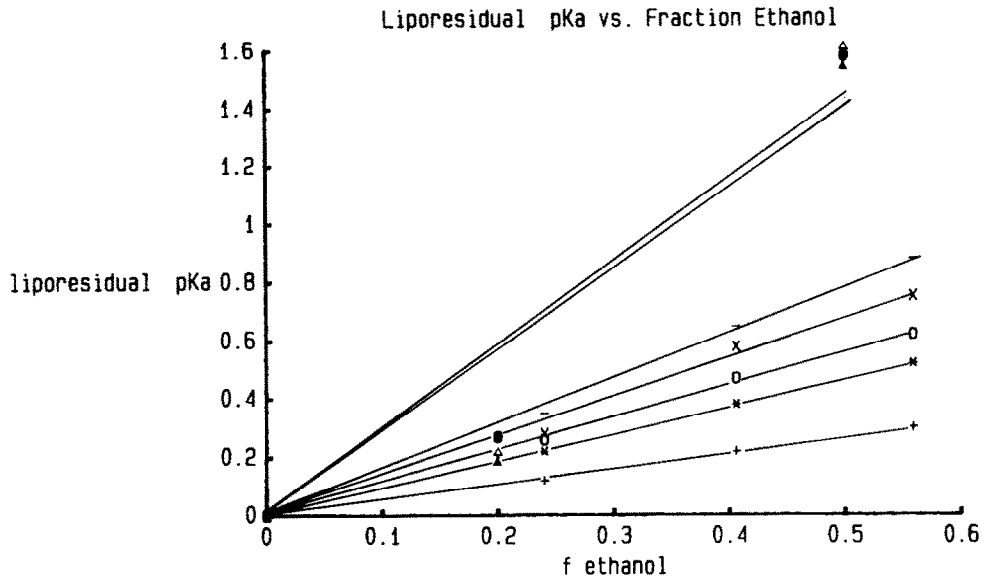

Fig. 5. Liporesidual pK_a vs volume fraction ethanol for carboxylic acids (see Fig. 3 for symbols).

estimated from the Born equation (column 4) for a given solvent mixture. The liporesidual ΔpK_a was calculated from the liporesidual slope using Eqn. 6 or 7. In most cases, good agreement was obtained between the observed ΔpK_a values and those listed in columns 6 and 7. Calculated values for the hydrogen phthalates in 20% ethanol in water showed the worst agreement with experimental values, but the experimental values appeared to be anomalously low as seen in Fig. 3. The advantage of using hydrophilic and lipophilic residuals over the Born Eqn. alone is especially evident at higher

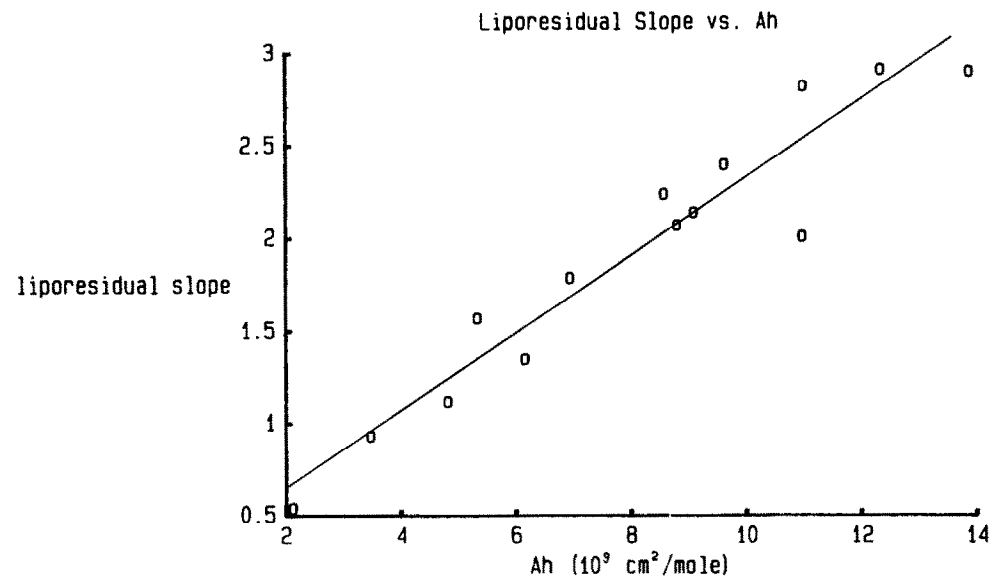

Fig. 6. Liporesidual slope vs hydrophobic surface area.

TABLE 4

Liporesidual ΔpK_a vs f

Compound	*X* Coeff. (S.D.)	r^2
Barbital	1.7971 (0.1073)	0.9770
5,5-Diallylbarbituric acid	2.2371 (0.0957)	0.9872
Aprobarbital	2.1400 (0.0938)	0.9872
Butabarbital	2.3971 (0.0961)	0.9875
Phenobarbital	2.0743 (0.0887)	0.9865
Amobarbital	2.0086 (0.0444)	0.9967
Nitrophenobarbital	2.0771 (0.1435)	0.9628
Acetic acid	0.5343 (0.0070)	0.9984
Propionic acid	0.9305 (0.0032)	0.9999
Butyric acid	1.1213 (0.0147)	0.9984
Isovaleric acid	1.3496 (0.0431)	0.9910
Benzoic acid	1.5700 (0.0234)	0.9980
Ethyl-H-terephthalate acid	2.8276 (0.7310)	0.8324
n-Propyl-H-terephthalate acid	2.9103 (0.6241)	0.8683
Isobutyl-H-terephthalate acid	2.9034 (0.7414)	0.8350

cosolvent concentrations, and this can be seen by comparing columns 3, 4, 6 and 7 at 50% ethanol in water mixtures.

In both Figs. 6 and 7 the barbiturates generally deviate from the regression line to a larger extent than the carboxylic acids. McKeown (1980) has presented evidence of steric hindrance to solvation of polar groups by alkyl moieties on barbituric acid molecules. Such an event would have the effect of decreasing the effective hydrophilic surface area or increasing the effective hydrophobic surface area in comparison to the calculated values. Steric effects might also result in changes in the entropy of dissociation where a larger entropy change would be expected in going from a less solvated, sterically hindered, neutral molecule to a highly solvated anion. These effects might be accounted for by inclusion of steric parameters in the regression equation.

An explanation for the observed correlations is difficult at the present time. It is obvious that Eqn. 4b is not valid for many solutes of the molecular size, shape and polarity studied. It would be expected that the ability to separate electrostatic and non-electrostatic effects would be more valid for larger molecules. This may be due to the fact that ions can induce solvent structuring in polar solvents. If these effects extend beyond the immediate region of the ionic portion of the molecule it would lead to $\gamma_A^n \neq \gamma_{HA}^n$ since the anion is surrounded by a solvent essentially different from that around the neutral molecule. It would be expected that such an event would be more significant for small molecules since the non-ionic portions of the molecule are closer in proximity to the

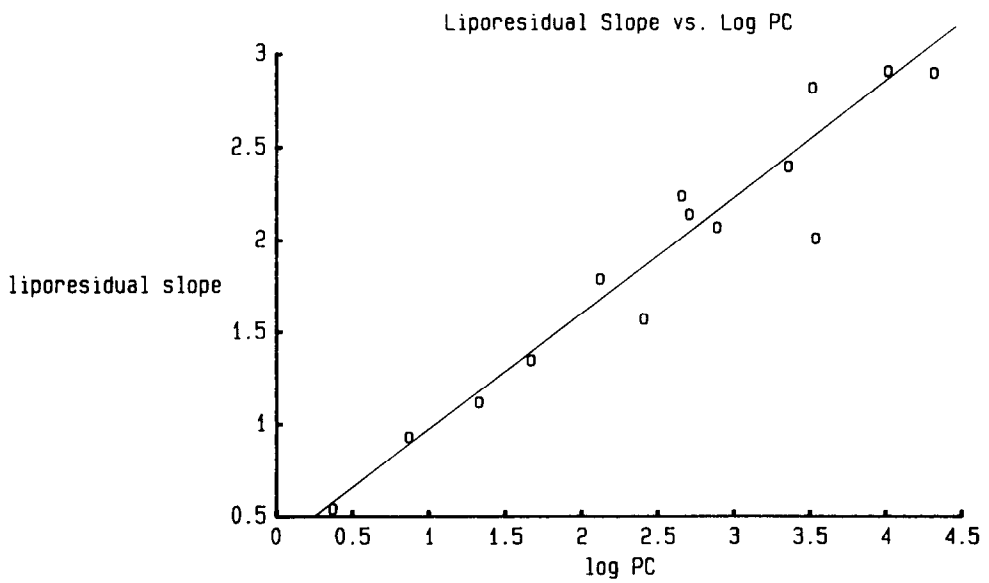

Fig. 7. Liporesidual slope vs log *PC* (adjusted for log PC of parent compound).

structure-inducing ionized group. The difference in the way in which each species interacts with the solvent would be expected to be proportional to the surface area of the molecule. In any case it is difficult to assign much physical significance to the calculated values of non-electrostatic and electrostatic effects.

Although the present investigation employed only a couple of representative groups of weak acids, the approach taken seems to hold promise for the estimation of acid dissociation constants of drugs in semiaqueous solvents. Thus, a consideration of both electrostatic and non-electrostatic effects can be combined in a linear free energy approach for the estimation of acid dissociation constants of weak electrolytes in semiaqueous solvents. Previous studies have developed methods for the estimation of the solubilities of unionized drugs in mixed solvents (Yalkowsky and Roseman, 1981; Rubino and Yalkowsky, 1987). A combination of past and present studies would allow both pK_a and solubility of weak electrolytes at various pH values to be estimated from physicochemical parameters of the solute and solvent.

References

Albert, A. and Serjeant, E.P., *The Determination of Ionization Constants*, 3rd edn., Chapman and Hall, New York, 1984.

Alfenaar, M. and DeLigny, A., Physical significance of activity coefficients of individual ions, *Rec. Trav. Chim.*, 86 (1967) 952–957.

Benet, L.Z. and Goyan, J.E., Potentiometric determination of dissociation constants, *J. Pharm. Sci.*, 56 (1967) 665–680.

Bondi, A., *Physical Properties of Molecular Crystals, Liquids and Glasses*, Wiley, New York, 1968.

Bousquet, E.W. and Adams, R., Substituted phenylethylbarbituric acids, *J. Am. Chem. Soc.*, 52 (1930) 224–229.

Eastman Kodak, *Physical Properties of Some Organic Solvents*, Eastman Kodak, Rochester, NY, 1975.

Grunwald, E. and Berkowitz, B.J., The measurement and correlation of acid dissociation constants for carboxylic acids in the system ethanol–water. Activity coefficients and empirical activity functions, *J. Am. Chem. Soc.*, 73 (1951) 4939–4944.

Leo, A., Hansch, C. and Elkins, D. Partition coefficients and their uses, *Chem. Rev.*, 71 (1971) 525–616.

Martin, A., Swarbrick, J and Cammarata, A., *Physical Pharmacy*, 3rd. edn. 1983, Chapt. 8.

McKeown, R.H., First thermodynamic dissociation constants of 5,5-disubstituted barbituric acids at 25 °C. Part 2. Structure reactivity relationships (SRR) linear free energy relationships which correlate C(5)-substituent effects with acid strength. *J. Chem. Soc. Perkins* II (1980) 515–522.

Rubino, J.T. and Berryhill, W.S., Effects of solvent polarity on the acid dissociation constants of benzoic acids, *J. Pharm. Sci.*, 74 (1986) 182–186.

Rubino, J.T. and Yalkowsky, S.H., Cosolvents and cosolvency. *Pharm. Res.*, 4 (1987) 220–230.

Sager, E.E., Robinson, R.A. and Bates, R.G., Medium effects on the dissociation of weak acids in methanol–water solvents, *J. Res. Natl. Bur. Stand.*, 68A (1964) 305–312.

Sugunan, S., Steric effects of alkyl groups. *Curr. Sci.*, 52 (1983) 124.

Van Uitert, L.G. and Has, C.G., Studies on coordination compounds. I. A method for determining thermodynamic equilibrium constants in mixed solvents. *J. Am. Chem. Soc.*, 75 (1953) 451–457.

Yalkowsky, S.H. and Roseman, T.J., Solubilization of drugs of cosolvents. In S.J. Yalkowski (Ed.) *Techniques of Solubilization of Drugs*, Dekker, New York, 1981, pp. 91–134.