518. *The Dissociation Constants of Some* p-*Alkoxybenzoic Acids.*

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The dissociation constants for a series of *p*-alkoxybenzoic acids have been determined by pH measurements with a glass electrode on buffered solutions of the acid with its sodium salt in aqueous organic solvents. Extrapolation of these values gives K_a values comparable with those obtained by other methods. Acetone has been found to be the most suitable solvent for this purpose.

The determination of the dissociation constants for weak organic acids which are only slightly soluble in water presents several problems. The common method, namely, measurement of the pH of a partly neutralised solution of the organic acid in water, is not reliable when the acid is very slightly soluble. The conductimetric method gives good results with very slightly soluble acids when suitable precautions are taken. The solubility of *p*-methoxybenzoic acid is 0·2 g./1000 ml. at 25°, and reasonable values being assumed for the ionic mobilities, the specific conductance of a saturated solution is 60×10^{-6} reciprocal ohms per c.c.; as the conductivity of water is of the order of 10^{-6} reciprocal ohms per c.c., corrections for carbon dioxide and impurities in the water must be carefully considered. Dippy (*Chem. Reviews*, 1939, **25**, 151) has discussed this problem and has shown that excellent results can be obtained by the conductivity method, particularly for reasonably soluble acids; however, it is often desirable to have a less elaborate method for general use.

The solubility of these acids may be increased considerably by the addition of organic solvents such as acetone or alcohol to the aqueous solution; a decrease in the thermodynamic activity of the hydrogen ion occurs, but as a rule the enhanced solubility more than offsets this decrease. Use has been made of this fact by several workers to measure K_a values by determining the apparent pH of an equimolecular solution of a weak organic acid (or base) and its salt in 50% aqueous methanol or ethanol. Mizutani (*Z. physikal. Chem.*, 1925, **118**, 318, 327) measured the apparent p*K* values for many acids and bases in different mixtures of methanol–water and ethanol–water, and although he showed that in 50% methanol the correction varied for different acids and bases, several workers have adopted the procedure of adding 0·5 p*K* unit to the value so obtained to get an approximate p*K* value in water. The validity of this correction is very limited; Table I shows that in the present investigation a correction of more than 1 p*K* unit is necessary, and it varies with different acids. Little systematic work has been reported on pH measurements in non-aqueous and mixed solvents; for references to this and related work Dippy's review (*loc. cit.*) should be consulted.

Table I.

p*K* *Values for benzoic and* p-*hydroxybenzoic acids in mixed solvents.*

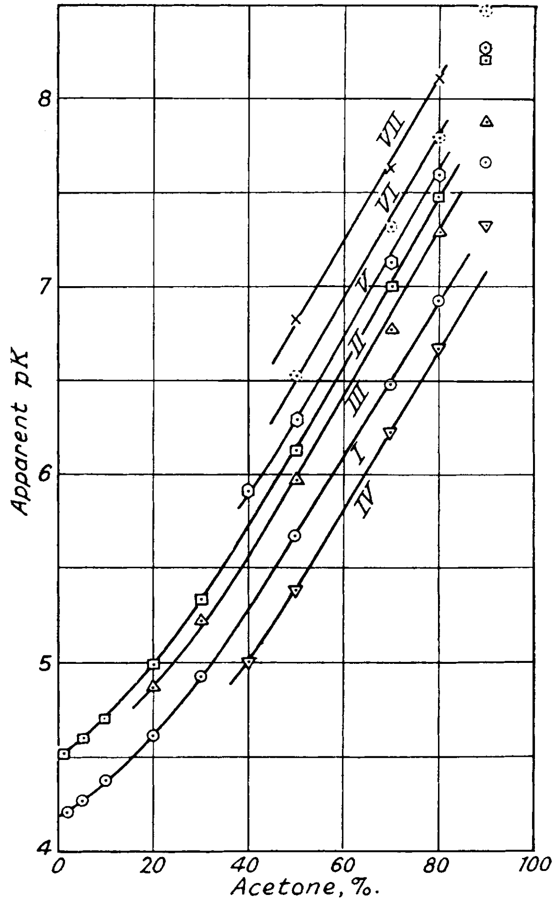
Acid.	p*K* Value in water.	p*K* Value in 50% solvent: Methanol.	Ethanol.	*n*-Propanol.	Acetone.	Dioxan.
Benzoic	4·17	5·22	5·49	5·68	5·67	6·07
Δp*K*	—	1·05	1·32	1·51	1·50	1·90
Hydroxybenzoic	4·49	5·60	5·96	6·13	6·12	6·58
Δp*K*	—	1·11	1·47	1·64	1·63	2·09

The present investigation was designed to determine whether p*K* values comparable with those obtained by other methods could be derived by extrapolation of a curve of pH against % of organic solvent for the solution of a half-neutralised organic acid. Two series of experiments were undertaken: (1) Using benzoic and *p*-hydroxybenzoic acids, for which p*K* values are known with accuracy, the curve of apparent pK_a (pK_a') against % of organic solvent was determined to compare the effects of the various solvents and indicate a suitable one for the purposes of extrapolation: solvents used were methanol, ethanol, *n*-propanol, acetone, and dioxan. (2) Using acetone as a suitable solvent, the K_a values of certain slightly soluble *p*-alkoxybenzoic acids were measured. These acids were chosen initially because their K_a values were required in connection with an investigation of their fungistatic activity, to be reported later.

The E.M.F. measurements with a glass electrode were carried out on buffered solutions of the organic acid together with its sodium salt to obtain figures of " apparent pH " (pH′) from which an extrapolation to zero concentration of the organic acid was made. It must be emphasised that no theoretical meaning is attached to these values of apparent pH in mixed solvents, as the electrode had not been standardised under the same conditions; they are required only for the purposes of obtaining an extrapolated pH in water.

FIG. 1.

pK_a' *of the* p-*alkoxybenzoic acids in aqueous acetone.*



The results are shown in Figs. 1 and 2 and in Tables I, II, and III. Fig. 1 shows that for similar acids the decrease in the apparent pK values with increasing amount of organic solvent is of the same order, and of the solvents tried, parallelism is best for acetone. Methanol and ethanol were considered unsatisfactory as they do not give a sufficient increase in solubility of the acid; *n*-propanol was considered undesirable because anomalous behaviour at a concentration of 30% of solvent made extrapolation doubtful. Acetone was better than dioxan,

TABLE II.

pK' *of benzoic acid in partly aqueous solvents.*

Solvent, %.	MeOH.	EtOH.	PrOH.	$COMe_2$.	$C_4H_8O_2$.
0·0 *	4·21	4·21	4·21	4·21	4·21
0·0	4·17	4·17	4·17	4·17	4·17
0·5	4·18	—	—	4·18	—
1·0	4·18	4·17	4·17	4·19	4·18
2·0	4·20	4·18	4·18	4·21	4·21
5·0	4·25	4·21	4·22	4·27	4·26
10·0	4·30	4·27	4·32	4·38	4·43
15·0	—	—	4·47	—	—
20·0	4·46	4·48	4·65	4·62	4·78
25·0	—	—	4·90	—	—
30·0	4·66	4·77	5·10	4·94	5·14
40·0	—	—	5·42	—	—
50·0	5·22	5·49	5·68	5·67	6·07
70·0	5·84	6·20	6·27	6·48	7·12
80·0	—	6·54	6·62	6·92	7·64
90·0	6·54	6·90	7·10	7·66	8·18

* Corrected values.

TABLE III.

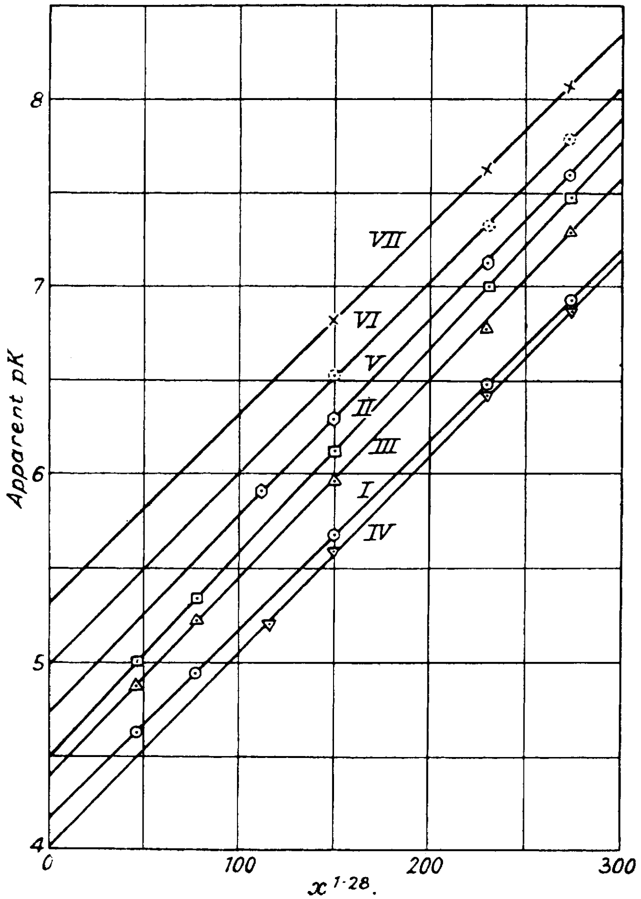
p*K'* *of* p-*hydroxybenzoic acid in partly aqueous solvents.*

Solvent, %.	MeOH.	EtOH.	PrOH.	COMe$_2$.	$C_4H_8O_2$.	Solvent, %.	MeOH.	EtOH.	PrOH.	COMe$_2$.	$C_4H_8O_2$.
0·0 *	4·53	4·53	4·53	4·53	4·53	25·0	—	—	5·32	—	—
0·0	4·49	4·49	4·49	4·49	4·49	30·0	5·00	5·17	5·50	5·34	5·59
1·0	4·51	4·50	4·50	4·51	4·51	40·0	—	—	5·88	—	—
2·0	4·53	4·51	4·52	4·54	4·54	50·0	5·60	5·96	6·14	6·12	6·58
5·0	4·57	4·54	4·56	4·60	4·64	70·0	6·27	6·69	6·81	7·00	7·71
10·0	4·62	4·62	4·67	4·70	4·80	80·0	6·57	7·12	7·20	7·48	8·25
15·0	—	—	4·83	—	—	90·0	6·99	7·52	7·72	8·21	8·79
20·0	4·80	4·85	5·04	5·00	5·17						

* Corrected values.

FIG. 2.

*p*K$_a$*' of the* p-*alkoxybenzoic acids plotted against* $x^{1\cdot28}$, *where* x *is the percentage of acetone.*



Note to Figs. 1 and 2.—*As many of the lines in these diagrams would overlap, the values for some of the acids have been displaced vertically as shown :*

No.	*Acid.*	*Displacement.*	*Legend.*
I.	*Benzoic*	*Nil*	⊙
II.	p-*Hydroxybenzoic*	,,	⊡
III.	p-*Methoxybenzoic*	,,	△
IV.	p-*Ethoxybenzoic* (*Fig.* 1)	−0·6 *p*K *unit*	▽
	(*Fig.* 2)	−0·4 ,,	
V.	p-*Propoxybenzoic*	+0·3 ,,	⬡
VI.	p-*Butoxybenzoic*	+0·5 ,,	◌
VII.	p-*Amyloxybenzoic*	+0·8 ,,	×

as regards both increase in solubility and parallelism of curves. In Table I the difference between the apparent pK in water–solvent mixtures containing 50% of solvent and the pK in water is shown; for all the solvents used the correction exceeds 1 pK unit and for ethanol lies between 1·1 and 1·5. These figures show that the empirical correction of 0·5 pK unit is quite inapplicable to this series of acids. The figures in Tables II and III show that the less polar the solvent, the steeper is the pK_a–% of solvent curve. There is a progressive increase in pK_a at 70% of solvent as one passes along the series, methanol, ethanol, *n*-propanol, acetone, dioxan. This increase with decreasing polarity is not unexpected.

The results of measurements of pK_a values for the series of *p*-alkoxybenzoic acids in acetone are given in Figs. 1 and 2. All of the curves are parallel to within 0·1 pK unit and all obey an empirical equation of the type :

$$pK_a' = pK_a + nx^{1 \cdot 28}$$

where n is a constant for each acid and x is the percentage of organic solvent. The parallelism is shown best by Fig. 2, which gives a convenient method of obtaining pK_a for this series even when only three values of pK_a' are available at a fairly high percentage of solvent. The extrapolation is based on the assumption that the curves for the higher members of the series remain parallel at lower percentages of solvent. Justification for this assumption is provided by the excellent agreement obtained for the K_a of *p*-methoxybenzoic acid with K_a values measured by other methods. As an empirical rule the pK_a value can be obtained for any member of this series by adding 1·6 to the apparent pH of a 50% acetone solution. The pK_a values obtained are listed in Table IV, together with those obtained by other workers, for comparison. Some of these were obtained at 25° but all measurements quoted in this paper were carried out at 20°; the figures are comparable, however, for the variation of pK with temperature in this region is quite small. There is good agreement between the pK values obtained by each group of workers for benzoic, *p*-hydroxybenzoic, and anisic acids. However, our results for *p*-ethoxy- and *p*-*n*-propoxy-benzoic acids differ from those obtained by Jones and Speakman (*J.*, 1944, 19) and call for comment. On theoretical grounds one might not expect more than a slight increase in the pK_a values as one passes from the *p*-methoxy- to the higher *p*-*n*-alkoxy-benzoic acids. Such a trend, which is found in our results, has been observed for the *n*-alkoxyacetic acid series by Palomaa (*Chem. Zentr.*, 1912, **2**, 596).

TABLE IV.

R in $R \cdot C_6H_4 \cdot CO_2H$.	p$K_{therm.}$ (20°).	$K_{therm.} \times 10^5$.	pK found by other workers. (1) at 25°.	(2) at 20°.	(3) at 25°.
H	4·21±0·03	6·2	4·18	4·23	4·20
OH	4·53 ,,	3·0	4·54	4·62	—
OCH_3	4·43 ,,	3·7	4·44	4·52	—
OC_2H_5	4·45±0·1	3·5	—	4·80	—
OC_3H_7	4·46 ,,	3·5	—	4·78	—
OC_4H_9	4·53 ,,	3·0	—	—	—
OC_5H_{11}	4·55 ,,	2·8	—	—	—

(1) Branch and Yabroff, *J. Amer. Chem. Soc.*, 1934, **56**, 2568 (potentiometric).
(2) Jones and Speakman, *J.*, 1944, 19 (potentiometric).
(3) Dippy, *Chem. Reviews*, 1939, **25**, 151 (conductimetric).

Throughout this paper, pH and pH′ indicate pH values in water and mixed solvents, respectively, whilst pK_a and pK_a' refer to the corresponding pK values, where p$K_a = -\log K_a$. To obtain thermodynamic dissociation constants, $K_{\text{therm.}}$, a correction for the ionic strength of the solution is necessary. For the equilibrium of the acid in water, $HA \rightleftharpoons H^+ + A^-$, we have

$$K_{\text{therm.}} = a_{H^+}a_{A^-}/a_{HA} = a_{H^+}c_{A^-}f_{A^-}/c_{HA}$$

where f_{A^-} is the activity coefficient for the anion, the activity coefficient for the un-ionised acid HA being taken as unity. From the above expression,

$$pK_{\text{therm.}} = -\log K_a = pH - \log a_{A^-}/a_{HA} = pH - \log f_{A^-}$$

The activity correction is calculated from the simplified Debye–Huckel equation, $-\log f = 0{\cdot}502z^2\sqrt{I}$ at 20°, z being the valency of the ion and $I = \frac{1}{2}z^2c$ = ionic strength. For an M/200-solution of the sodium salt of a monobasic acid $I = 0{\cdot}005$; hence $-\log f = 0{\cdot}0357$, and to correct pK_a values obtained by extrapolation of pK_a' values it is necessary to add 0·036 to the figures so measured; then p$K_{\text{therm.}}$ = pK_a + 0·036.

EXPERIMENTAL.

Materials.—The *p*-hydroxybenzoic acid was obtained by prolonged alkaline hydrolysis of the methyl ester and was finally thrice recrystallised from distilled water. The benzoic and anisic acids, obtained from commercial sources, were similarly recrystallised before use. The preparation of the *p*-alkoxybenzoic acids has been described previously (Cavill and Gibson, *J. Soc. Chem. Ind.*, 1947, **66**, 274).

The solvents employed were first dried, the alcohols over calcium oxide, acetone over sodium hydroxide, and dioxan over sodium, then fractionated through ground-glass apparatus, care being taken to exclude moisture.

Solutions.—All measurements were made on solutions containing both the acid and its sodium salt at concentration M/200. Appropriate quantities of the organic acid dissolved in the organic solvent and standard sodium hydroxide were mixed with sufficient water to give the different concentrations of the solvent. In all cases the % of solvent is on a volume basis, *x* % of solvent meaning that *x* ml. of pure solvent were used, the solution being eventually made up to 100 ml. with water. A typical example was benzoic acid in 10% dioxan : 0·02N-benzoic acid (25 ml. aqueous), dioxan (5 ml.), and 0·05N-sodium hydroxide (5 ml.) were mixed, and distilled water added to a volume of 50 ml. at 20°. The concentration M/200 for the organic acid was chosen as the highest practicable concentration obtainable for the least soluble acid of the series in mixed solvent containing 30% of water.

Measurement of pH *Values.*—All measurements were taken at 20° by means of both a Cambridge Portable pH meter and a Leeds Northrup instrument. The instruments were calibrated against 0·05M-potassium hydrogen phthalate, the pH of which was taken as 4·00. The standardisation of the instrument was re-checked after each determination, and in no case was the drift greater than 0·01 pH unit. Three measurements were taken for each acid at each concentration and results agreed to within 0·01 pH unit. Temperature drift during measurements was less than 0·2° except with 90% acetone, for which it was as high as 0·8°. This was not serious, however, as a change in temperature of 1° caused a pH change of less than the minimum detectable sensitivity (0·01 pH unit). With the more volatile solvents, such as acetone, considerable difficulty was experienced when taking measurements in solutions containing 10% of water due to evaporation : such results tend to be slightly low.

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