Ionization Constants by Curve Fitting: Application to The Determination of Partition Coefficients

FRANK H. CLARKE

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Abstract □ A multiparametric curve-fitting technique for pK_a calculation has been adapted for use with a programmable calculator or microcomputer. This method provides for the convenient and accurate determination of the ionization constant in aqueous solution and of the apparent ionization constant in the presence of octanol. From these parameters, partition coefficients and apparent partition coefficients are easily calculated and agree with data reported using the shaker technique or HPLC. The curve-fitting method has been applied to the differential titration technique in which the solvent curve is subtracted from the solution curve before calculations are begun. This method has been applied to the potentiometric titration of aqueous solutions of the salts of bases with a very low solubility in water.

Keyphrases □ Partition coefficients—octanol–water, determination by a multiparametric curve-fitting technique, adaptation to a programmable calculator/microcomputer □ Curve fitting—multiparametric, octanol–water partition coefficient and pK_a determination, adaptation to a programmable calculator/microcomputer □ Differential titration—use with curve-fitting technique for the determination of pK_a and octanol–water partition coefficients, programmable calculator/microcomputer

Partition coefficients (P or log P), important physical properties of drugs, are useful for studies of quantitative structure–activity relationships (1, 2). For compounds that are ionized at physiological pH, the apparent partition coefficient (P′ or log P′) may be a more appropriate parameter (3). The variation of the apparent partition coefficient with pH has been used in various ways to measure the partition coefficient of the un-ionized compound (4–9). The method described by Kaufman *et al.* (9) is one of the simplest of these procedures. In this method the ionization constant (pK_a) and the apparent ionization constant (pK_a') are first obtained from the results of two potentiometric titrations, one without and one with the presence of octanol, respectively. The log P is calculated from the difference between the pK_a and pK_a' values and the volumes of water and octanol. The log P′ for any desired pH is calculated from the same data. We have modified this titration method and have shown it to be rapid and convenient and to provide reproducible results (10) which agree with those obtained using the shaker technique (1, 2) or HPLC (11–13). Recently, this modified titration method has been used successfully in other laboratories (14, 15) and its advantages described (15). Calculated aqueous–octanol titration curves are very similar to experimental curves (10) and lend support to the general application of the method (Fig. 1).

Since the measurement of partition coefficients by potentiometric titration depends on the ability to calculate the pK_a and pK_a' values from the titration curves, it is important to have a general procedure that is applicable in most instances. For strong acids or strong bases, for instance, there may be no inflection at one end of the aqueous titration curve. In these cases, when there is an appreciable difference between the pK_a and the pK_a', the two titration curves may be used together to provide the equivalent volume (10) (Fig. 1). Other methods of determining the end point in a potentiometric titration have been reviewed (16).

The method of Meites and his associates (17–20) uses a multiparametric curve-fitting technique involving an iterative computer program to compare the calculated pH with the experimental value for each point on a titration curve. Parameters are varied until the standard deviation (σ) of the difference between calculated and experimental values is a minimum. Using this criterion, the optimum equivalent volume (V_e) and the starting titrant volume (V_s) are located, and the mean pK_a is calculated using these values. Briggs and Stuehr (21) and Meites *et al.* (27) described a similar procedure in which the σ of the ionization constant (K_a) is minimized. The latter method has been characterized as being less reliable although it has the advantage of requiring less computer time (22). The method of Meites has been used to provide accurate results in automatic titrations (23, 24) using an on-line or laboratory computer.

We have modified the method of Briggs and Stuehr (21) so that the σ of the pK_a values is minimized and have adapted it for use with a programmable calculator (10). Originally only V_e was optimized (10), but now it has been found that the results are improved if optimization is carried out for both V_e and V_s. Running time is 1–2 h on the calculator, but equivalent results are obtained in a few minutes when a similar program is run on a microcomputer. With this iterative method of calculation, pK_a and pK_a' values are easily determined and the calculator or computer printout provides P, log P, P′, and log P′ as well as pertinent parameters used in the calculation.

The general method described above applies to most acids or bases which may be titrated in aqueous solution. However, it fails when the un-ionized compound precipitates early in the titration. For many drugs, such as chlorpromazine, the UV method (25) also fails because there is no change in the UV spectrum on ionization. The solubility method (26, 27) is cumbersome as are the methods involving nonlogarithmic linear titration curves (28) or titrations in solvent mixtures (16, 29–31). On the other hand, the differential potentiometric titration method (32) is applicable for very dilute solutions when the pK_a is in the range of 4–10 (33). In this method the titration curve obtained with solvent alone is subtracted from that of the solution. We have found that the iterative method gives excellent results when applied to the difference curve.

THEORETICAL

Equations—In the equations derived below, the following assumptions are made:

1. Only un-ionized compounds are soluble in octanol.

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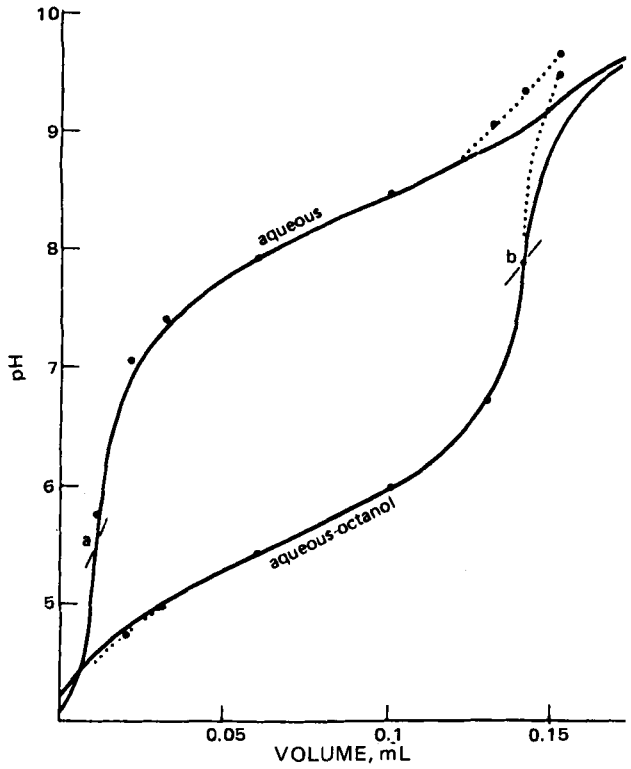

Figure 1—*Titration of an organic base in aqueous solution and in the presence of octanol. Inflections at a and b locate initial values of the starting titrant volume, V_s, and of the equivalent titrant volume, V_e. Key: (●) calculated values.*

2. All solutions are dilute (0.001 M) and the ionic strength is nearly constant (with added sodium chloride), so that it not necessary to consider activities.
3. Titrant volumes are small compared with the volume of titrated solution, so that the aqueous volume is considered constant for the calculation of the partition coefficient following a two-phase titration.

Concentration terms are indicated by square brackets, and the subscripts o and w refer to octanol and water phases, respectively. The following symbols are used: (M) molar amount of titrated compound; (m) molar amount of added titrant; (V_e) volume of titrant at the equivalence point; (V_i) volume of added titrant at the ith point; (V_w) total aqueous volume; (V_o) volume of octanol; (P) partition coefficient; (P′) apparent partition coefficient (at a given pH); (K_a) ionization constant; (K') apparent ionization constant (in the presence of octanol); (f) partition factor.

Consider the titration of the salt of a weak acid with a strong acid in the presence of octanol:

$$Na^+A^- + H^+Cl^- \rightleftarrows HA + Na^+ + Cl^- \qquad \text{(Eq. 1)}$$

By definition:

$$K_a = [H^+][A^-]/[HA] \qquad \text{(Eq. 2)}$$

$$P = \frac{[HA]_o}{[HA]_w} = \frac{HA_o \cdot V_w}{HA_w \cdot V_o} \qquad \text{(Eq. 3)}$$

$$P' = [HA]_o/([HA]_w + [A^-]_w) \qquad \text{(Eq. 4)}$$

Let f be a partition factor such that:

$$f = \frac{V_o \cdot P}{V_w} + 1 \qquad \text{(Eq. 5)}$$

Then, combining Eqs. 3 and 5:

$$HA_o + HA_w = f \cdot HA_w \qquad \text{(Eq. 6)}$$

At any point during the titration, material balance is maintained so that:

$$M = HA_o + HA_w + A^- \qquad \text{(Eq. 7)}$$

Table I—Raw Data for Computer Program [a] to Calculate pK_a and Log P

Symbol	Description
A$	Name of compound
B$	Source of compound
C$	Date
T$	Titrant: acid or base (A or B)
TX	Titrant increment
N	Normality of titrant
VI	Initial aqueous volume (mL)
VE	Estimated equivalent volume (mL)
Z$	Two-phase titration? (Y or N)
C	Volume of octanol (mL)
P$	Is the ion protonated? (Y or N)
A3	pK_a (when log P is calculated)
W$	Complete title? (Y or N) [b]
VI	First titrant volume
M	Number of data points
V(I)	Titrant volume at ith point
P(I)	pH at ith point

[a] A simplified, calculator version of the program is provided in Ref. 10. [b] A$, B$, and C$ are not repeated if both pK_a and log P results are printed at the same time.

Therefore:

$$M = f \cdot HA_w + A^- \qquad \text{(Eq. 8)}$$

Division by the aqueous volume converts amounts in the aqueous phase into concentration terms so that, after rearranging:

$$[HA]_w = \frac{1}{f}\left(\frac{M}{V_w} - [A^-]\right) \qquad \text{(Eq. 9)}$$

For ionic balance in the aqueous solution:

$$[H^+] + [Na^+] = [Cl^-] + [A^-] + [OH^-] \qquad \text{(Eq. 10)}$$

Since $[Na^+] = M/V_w$ and $[Cl^-] = [m]$ we may write:

$$[A^-] = \frac{M}{V_w} - [m] + [H^+] - [OH^-] \qquad \text{(Eq. 11)}$$

Hence:

$$K_a = f\left(\frac{[H^+]\left(\frac{M}{V_w} - [m] + [H^+] - [OH^-]\right)}{[m] - [H^+] + [OH^-]}\right) \qquad \text{(Eq. 12)}$$

$$K_a = f \cdot K', \quad pK_a = \log f + \log pK' \qquad \text{(Eq. 13)}$$

In the absence of octanol, $f = 1$ and:

$$pK_a = pH + \log\left(\frac{[m] - [H^+] + [OH^-]}{[M] - [m] + [H^+] - [OH^-]}\right) \qquad \text{(Eq. 14)}$$

In the presence of octanol:

$$pK' = pH + \log\left(\frac{[m] - [H^+] + [OH^-]}{\frac{M}{V_w} - [m] + [H^+] - [OH^-]}\right) \qquad \text{(Eq. 15)}$$

It can also be shown that:

$$P = \frac{V_w}{V_o}(10^{pK' - pK_a} - 1) \qquad \text{(Eq. 16)}$$

and:

$$P' = \frac{P}{1 + 10^{pH - pK_a}} \qquad \text{(Eq. 17)}$$

Corresponding expressions may be derived in an analogous fashion for the titration of the salt of a weak base with a strong base. In this case:

$$K_a = K'/f \qquad \text{(Eq. 18)}$$

$$pK_a = pH - \log\left(\frac{[m] + [H^+] - [OH^-]}{[M] - [m] - [H^+] + [OH^-]}\right) \qquad \text{(Eq. 19)}$$

Table II—Ionization Constants, Partition Coefficients, and Apparent Partition Coefficients

Curve No.	Compound	pK_a Found[a]	pK_a Lit.	pK_a Δ	Log P Found[a]	Log P Lit.	Log P Δ	Log P pH	Log P Found	Log P Lit.	Log P Δ
1	Pyridine	5.16	5.23[b]	0.07	0.63	0.65[c]	0.02	7.4	0.63		
2	*p*-Aminobenzoic Acid	4.71	4.67[d]	0.04	0.83	0.83[d]	0.00	7.4	0.83	0.85[e]	0.02
3	Benzoic Acid	4.08	4.17[b]	0.09	1.87	1.87[f]	0.00	7.4	1.87		
4	*p*-Toluic Acid	4.26	4.37[b]	0.11	2.34	2.27[f]	0.07	7.4	2.34		
5	Adamantanamine	10.49	10.63[g]	0.14	2.54	2.44[g]	0.10	7.4	−0.55		
6	*p*-Chlorobenzoic Acid	3.85	3.98[b]	0.13	2.66	2.65[f]	0.01	7.4	2.65		
7	Pyrilamine	8.91	8.85[h]	0.06	3.27	3.15[h]	0.12	7.4	1.74		
8	Chlorpheniramine	9.09	9.16[i]	0.07	3.39	3.38[j]	0.01	7.4	1.69	1.38[k]	0.31
9	Triprolidine	9.25	9.50[h]	0.25	3.87	3.92[h]	0.05	7.4	2.02		
10	Cyproheptadine	8.87			4.69			7.4	3.20	3.20[h]	0.00
										3.11[i]	0.09
11	Chlorpromazine	9.20	9.22[l]	0.01	5.25	5.32[h]	0.07	7.4	3.44	3.25[o]	0.19
			9.3[m]	0.1		5.55[n]	0.30	8.1	4.11	4.19[h]	0.08
								7.0	3.04	2.93[p]	0.11

[a] Mean value, $SD \pm 0.1$. [b] Ref. 1. [c] Ref. 2. [d] J. K. Seydel and W. Butte, *J. Med. Chem.*, **20**, 489 (1977). [e] H. P. A. Illing and D. Benford, *Biochim. Biophys. Acta*, **429**, 768 (1976). [f] T. Fugita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964). [g] J. G. Henkel, J. T. Lane, and G. Gianutsos, *J. Med. Chem.*, **25**, 51 (1982). [h] Ref. 1. [i] N. G. Lordi and J. E. Christian, *J Am. Pharm. Assoc. Sci. Ed.*, **45**, 300 (1956). [j] By HPLC Ref. 1. [k] By HPLC, S. H. Unger and G. H. Chiang, *J. Med. Chem.*, **24**, 262 (1981). [l] By extrapolation from aqueous-alcohol titrations, L. G. Chatten and L. E. Harris, *Anal. Chem.*, **34**, 1495 (1962). [m] By solubility method Ref. 19. [n] By potentiometric titration with large octanol-water ratio Ref. 8. [o] J. Krieglstein, W. Meiler and S. Staab, *Biochem. Pharmacol.*, **21**, 985 (1972). [p] M. Frisk-Holmberg and E. Kleijn, *Eur. J. Pharmacol.*, **18**, 139 (1972).

$$pK' = pH - \log\left(\frac{[m] + [H^+] - [OH^-]}{\frac{M}{V_w} - [m] - [H^+] + [OH^-]}\right) \quad \text{(Eq. 20)}$$

$$P = \frac{V_w}{V_o}(10^{pK_a - pK'} - 1) \quad \text{(Eq. 21)}$$

$$P' = \frac{P}{1 + 10^{pK_a - pH}} \quad \text{(Eq. 22)}$$

Curve Fitting—In the curve-fitting technique, the raw data and descriptive information (Table I) are entered into the calculator or computer as requested by the program. The calculator program has been described (10). In the case of the microcomputer[1] the raw data may be saved on a diskette. The program plots the titration curve on the monitor, locates one or two inflection points using the Kolthoff method (34), indicates these with vertical lines on the graph, and then makes a hard copy of the graph with the printer.

Iteration then begins. First V_e is varied systematically until the standard deviation (σ) is a minimum. Then, this V_e value is maintained and V_s is varied until σ is again minimized. Naturally an increment added to or subtracted from V_s must be added to or substracted from each V_i. The two-stage iterative process is repeated until successive σ values do not differ by more than 0.001. When this condition is met, iteration is complete if $SD < 0.008$.

If σ at this point exceeds 0.008, residuals are calculated for each pK_a value and compared (in absolute magnitude) with 2σ. Points at the beginning or end of the curve which do not meet this test are excluded and the entire iteration is repeated with the reduced number of points. This test approximates exclusion of points which lie outside the 95% confidence interval since $tS = X^* - \overline{X}$ and $t = 2.09$–2.13 for 15–20 DF (35).

When iteration is complete, a summary of titration conditions and results is printed together with a table of raw data and calculated pK_a values.

Differential Titration—The differential titration technique (32) succeeds in providing the pK_a of an aqueous solution for compounds with a very low solubility in water which form water-soluble salts. In this case, the titration curve of water is subtracted from that of the compound before the calculations are carried out. The equation is then a simple one:

$$pK_a = pH \pm \log\left(\frac{V_i}{V_e - V_i}\right) \quad \text{(Eq. 23)}$$

where V_i is the difference in titrant volumes for solution and solvent at each pH; the log term is added for an acid titrant and subtracted for a base titrant. The experiment is performed so that the conditions for the titration in solvent alone are as close as possible to those of the solution. The equation does not include concentration terms, so that neither the solution volume nor the titrant normality need to be known precisely provided conditions for the two titrations are the same. Impurities in the water, such as carbon dioxide, do not interfere. This is an important advantage for extremely dilute solutions.

EXPERIMENTAL

Apparatus—Potentiometric titrations were carried out with an automatic titrator[2], titration assembly[3], and an autoburet[4]. The titration assembly was fitted with a 40-mL water-jacketed sample cell kept at a constant temperature of 25°C with circulating water. A calomel reference electrode and a porous pin liquid junction electrode were used.

Aqueous solutions (10 mL) were titrated with 0.1 M standard HCl or NaOH delivered from a 0.25-mL microburet. Stirring was provided with a medium-size mechanical stirrer which emulsified two-phase octanol–water systems (15 mL and 10 mL, respectively). The solvents were boiled, deionized water and commercial-grade octanol[5]. Air was displaced from above the sample with a slow stream of nitrogen for a few minutes before stirring was begun, and the nitrogen stream was maintained during the titration.

Procedure—In a typical titration, water (9.0 mL), 0.02 M aqueous NaCl (0.5 mL), and a 0.5-mL aliquot of a stock solution containing 0.02 mM of the compound to be titrated were added to the titration vessel. For two-phase titrations, octanol (15 mL) was added. Aqueous and two-phase titrations were carried out in the same manner. Stirring and titrant addition were continuous while the titration curve was recorded on the servograph. The equilibrium titration mode provided smoother titration curves, especially for very dilute solutions, but the calculated results were equivalent without the step procedure, indicating that equilibrium is very rapid in the homogenized two-phase system.

Usually, the total volume of the stock solution was calculated from the sample weight and equivalent weight so that a 0.5-mL aliquot would require 0.2 mL of titrant. When the sample was available as its salt, a 20% excess of acid or base was added. Because the calculation finds both ends of the titration curve, it was not assumed that the original compound was exactly a 1:1 salt of acid and base. Weak bases were converted to their hydrochloride salts and weak acids to their sodium salts wilth a 20% excess of 0.1 M HCl or 0.1 M NaOH, respectively. Organic salts such as the maleate salt of a weak base or the dicyclohexylamine salt of a weak acid were converted to their hydrochloride or sodium salts, respectively, by passing the aqueous solution through a short column of an appropriate ion-exchange resin. Excess acid or base was added to the eluate before dilution to an appropriate volume in a volumetric flask. In these cases, the aliquot volume was calculated to require 0.2 mL of titrant and sufficient water was added to make the total aqueous volume of the titrated solution 10.0 mL.

An approximate value of one end of the titration curve may usually be obtained as the point along the curve where the slope changes sign [using parallel lines (10), the mathematical equation of Kolthoff (34), or the first

[1] Apple II Plus with 48K memory, disk drive, monitor, and Silentype printer; Apple Computer Inc., Cupertino, Calif.

[2] TTT60; Radiometer, Copenhagen, Denmark.
[3] TTA60; Radiometer, Copenhagen, Denmark.
[4] ABU 12; Radiometer, Copenhagen, Denmark.
[5] Aldrich Chemical Co., Milwaukee, Wis.

Table III—Influence of an Impurity (pK_a 6.4) on the Accuracy of pK_a Calculations

Curve No.	I, mEq	Titrant	pK_a (calc.)	Δ pK_a	×1000 *SD*	V_e[a]	Xs[b]	n[c]
1	0	A	7.00	0.00	4.10	0.200	0.000	19
2	0	B	7.00	0.00	4.10	0.200	0.000	19
3	0.005	A	6.99	0.01	5.04	0.204	0.000	19
4	0.005	B	6.98	0.02	7.72	0.204	0.000	20
5	0.01	A	6.98	0.02	6.65	0.209	0.000	20
6	0.01	B	6.97	0.03	9.38	0.210	−0.001	19
7	0.02	A	6.96	0.04	4.67	0.216	−0.001	18
8	0.02	B	6.95	0.05	6.32	0.217	0.001	19
9	0.02	B	6.954	0.046	6.32	0.217	0.002	19
10	0.02	B	6.959	0.041	3.86	0.216	0.001	18
11	0.02	B	6.94	0.06	6.71	0.216	0.000	37
12	0.01	B	3.05	0.05	8.93	0.192	−0.002	16
13	0.01	A	4.01	0.01	3.96	0.200	0.008	17
14	0.01	A	5.01	0.01	5.05	0.203	0.000	17
15	0.01	A	6.02	0.02	4.32	0.210	0.000	19
16	0.01	A	6.98	0.02	4.86	0.208	0.000	19
17	0.01	A	7.99	0.01	4.17	0.202	0.001	18
18	0.01	A	9.00	0.00	5.55	0.200	0.000	19
19	0.01	A	10.00	0.00	3.04	0.200	0.000	19
20	0.01	A	11.00	0.00	5.39	0.200	0.000	19
21	0.01	A	11.99	0.01	22.9	0.200	−0.006	17
22	0.02	A	6.04	0.04	5.95	0.219	0.000	20

[a] Calculated equivalent titrant volume. [b] Displacement of the starting titrant volume. [c] Number of data points used in the calculation.

derivative]. However, this point may not provide the most accurate pK_a because of the undetected presence of CO_2 or of titrated impurities in the solution. It has been shown that the most accurate pK_a values are provided by curve-fitting techniques (17–20).

At least one end of the titration curve may lack an inflection point because of the contribution of the dissociation of water to the pH. Approximate values of the equivalent titrant volume, V_e, and of the initial titrant volume, V_s, may often be obtained in such instances by carrying out the titration using the same aliquot volume in the presence of a water-immiscible solvent (such as octanol) or a water-miscible solvent (such as isopropyl alcohol or dimethyl sulfoxide) (10). Values of V_e and V_s obtained in this manner serve as initial estimates for the multiparametric curve-fitting technique.

Differential Titration—When a precipitate forms during the titration, it is often possible to use the curve-fitting technique to calculate the pK_a from the portion of the curve which preceded precipitation (10). For very insoluble acids or bases with water-soluble salts, a differential titration is often successful.

For this pK_a determination, 0.5 mL of a solution containing 0.002 mM of compound in water was added to 8.0 mL of water and 0.5 mL of a solution of 0.02 M NaCl. The solution was acidified with 5 μL of 0.1 M HCl and titrated with 0.001 M NaOH. A blank titration was carried out in the same manner except that 0.5 mL of water replaced the solution of compound. The titration curves were recorded using an expanded pH scale from 8.1 to 8.8. Titrant volumes were measured at pH intervals of 0.05 for both curves, and the differences were recorded as values of V_i. Using a microcomputer program V_e and V_i were varied until the σ of the calculated pK_a values was minimized. In contrast to a normal titration, there may not be an inflection in titration curves recorded on such an expanded scale. Accordingly, the computer program was designed to facilitate the initial trial and error process that is required to obtain optimum values of V_e and V_s. The pK_a results obtained in this way may have a larger experimental error because usually only a portion of the titration curve is available before errors in the measurement of V_i become large.

RESULTS AND DISCUSSION

Table II summarizes the results of pK_a and log P measurements for a series of 11 acids and bases which span the log P range from 0.63 to 5.33. These results were reproducible to within ≤0.06 of a pK_a or log P unit. These results for log P are in very close agreement with data reported using the classical shaker method or by chromatography. Apparent partition coefficients (pH 7.4) are automatically calculated by the program and may be calculated easily for any desired pH (no. 11). Log P calculations by potentiometric titration involve differences between pK_a measurements and appear in Table II to be closer to literature values than the pK_a determinations. However, it should be noted that there is a wide variation for most pK_a results in the literature (36) reflecting different experimental conditions. The pK_a values for cyproheptadine and chlorpromazine were determined using differential titration.

As an example, a very dilute solution of chlorpromazine [solubility of base, 6 μM (27)] was titrated with 0.001 M aqueous NaOH. An automatic titrator was used in which the pH scale was expanded so that no inflection appeared at either end of the titration curves. Application of the iterative procedure to the difference data optimized both V_e and V_s. The results of 9.20 and 5.33 for the pK_a and log P, respectively, are in close agreement with reported values of 9.22 (27) and 5.35 (1). In the calculation using this method, the solution volume and titrant normality are not involved and small amounts of carbon dioxide are compensated for by subtraction of the solvent curve.

The chlorpromazine value is unusual because the base is so insoluble that a potentiometric aqueous titration has been regarded as impossible (27). Previous results were obtained by extrapolation of results in aqueous–alcohol or by the solubility method (Table II).

Effect of Impurities—It was of interest to determine how an impurity such as carbon dioxide, with an effective pK_a of 6.4 (25), would affect the results of pK_a calculations by the curve-fitting method. Titration curves were calculated for mixtures of a major component and varying amounts (2.5, 5, and 10%) of an impurity (I) of pK_a 6.4 (to simulate carbon dioxide). In each case the solution volume was 10 mL, the titrant was 1 M acid or base, and the equivalent volume (V_e) of the major component was 0.2 mL. The data were used for calculations in the aforementioned manner. The raw data (19, 20, or 21 points, as appropriate) were entered into the computer and the program rejected points which failed to meet the standard criteria.

Table III provides the results of these calculations in which 5% of impurity (pK_a 6.4) was present. In these cases, the titration curves are smooth and do not indicate the presence of the impurity. Nevertheless the calculated pK_a is close to the theoretical value (the largest deviation is 0.06 pK unit). Furthermore, V_e is in error by ≤1% when the difference between the pK_a of the impurity and that of the major component is >2 pK_a units. When the difference between the two pK_a values is <2, the calculated V_e is closer to the sum of the two components. A similar calculation was performed for 10% of impurity. In these cases, the impurity is evident by an inflection in the curves when the pK_a values are quite different. However, in all cases the calculated pK_a is within 0.06 pK units of that of the major component. It is concluded from these results that curve fitting provides accurate data for the calculation of partition coefficients.

Raw data were calculated to four decimal places and rounded to two decimal places before entry into the computer. Curves 1 and 2 (Table III) for pure compounds show that a σ of 4.10×10^{-3} may be expected for data of such precision when there are no errors and no impurities. The maximum error in any of the curves is 0.06 pK_a unit. When the pK_a of the major component is close to that of the impurity (curves 3–8), the V_e reflects the sum of the two equivalent volumes, but the pK_a is very close to that of the major component. Curves 9 and 10 show that greater precision in the measurement of pH values (data rounded to three decimal places) does not increase the accuracy when there is titratable impurity present. Curve 11 shows that doubling the number of data points does

not improve the accuracy in the presence of an impurity. Curves 12 and 21 show that pK_a values of 3 and 12 are near the practical limits of this method of calculation. In fact, there was no convergence with curve 12 during the calculations when the titrant was an acid. When the impurity has a pK_a that is at least 2 pK_a units from the major component, this method of calculation will remove its influence completely. Curves 18–20 give the correct pK_a and the correct equivalent volume. Curve 22 has 10% of a titratable impurity and, although the V_e reflects both components, the pK_a is only 0.04 pK_a units in error.

CONCLUSIONS

It has been shown that the curve-fitting method for pK_a determination is easily adapted for the calculator and the microcomputer. The method provides a high degree of accuracy even in the presence of titratable impurity. When both the pK_a and the apparent pK_a are determined in this manner, accurate measures of the partition coefficient and the apparent partition coefficient are provided. It was surprising to find that pH measurement is so practical and convenient in emulsified aqueous–octanol mixtures and that equilibrium is reached so rapidly that titrant may be added continuously at a rate normal for an aqueous titration.

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