

# A Simple Continuous Titration Technique for Determining $pK$ Values of Protonated Ligands\*

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The dissociation constants of protonated ligands are dependent on parameters like dielectric constant and temperature of the system. A systematic study of these constants by varying either of these parameters requires a set of titrations to be carried out, followed by tedious calculations. A simplified quick method which can reduce all this labour and yet give equally reliable results is proposed and verified experimentally. The ligands chosen for this purpose are (i) benzoic acid and its *o*-amino, *p*-amino, *m*-amino, *p*-nitro, 2-methoxy, 4-methoxy, 2,3-dimethoxy, 2,4-dimethoxy, 2,6-dimethoxy, 2,4,5-trimethoxy and 2,4,6-trimethoxy derivatives and (ii) amino acids such as  $\alpha$ -alanine,  $\beta$ -alanine, glycine and  $\alpha$ -aminobutyric acid. In this method the pH of ligand solution is fixed equal to its  $pK$  value and then the dielectric constant or temperature of the system is varied as desired.

THE  $pK$  value of a protonated ligand (HL) is equal to pH of the solution when half the initial [ligand] has been neutralized<sup>1</sup>. This point can be approached systematically by potentiometric titration technique of Irving and Rossotti<sup>2</sup>. In general potentiometric titrations are carried out using alkali. In such titrations ionic strength effect is usually negligible and hence ignored. If the titration is arrested at this pH and only the dielectric constant or temperature of this isolated system (isolated with regard to its colligative property) is varied continuously, one should be able to get the  $pK$  values at different dielectric constants or temperatures in one experiment. The results reported in this paper are based on such an experimentation. The  $pK$  values thus obtained have been compared with those obtained using conventional method. Similar preadjustment of the pH of the solution was envisaged by Eigen, in T-jump technique<sup>3</sup>.

## Materials and Methods

All the chemicals used were of AR grade (Merck or Fluka). Dioxane was purified by method described by Vogel<sup>4</sup>. Conductivity water was used for preparing the solutions. An Elico model LI-10 pH meter (accuracy 0.02 pH unit) was used and calibrated against standard buffers.

The experimental procedure of Irving and Rossotti<sup>2</sup> involved potentiometric titrations of the following thermostated solutions under nitrogen atmosphere and  $\mu = 0.1M$  ( $NaClO_4$ ): (i) free  $HClO_4$  ( $1.0 \times 10^{-2}M$ ) and (ii) free  $HClO_4$  ( $1.0 \times 10^{-2}M$ ) + ligand ( $2.0 \times 10^{-3}M$ ) against standard carbonate-free NaOH. Such titrations were carried out in different dioxane-water mixtures.

## Results and Discussion

(i) *Effect of varying dielectric constant*— In the method developed by us the solution used for studying the effect of varying dielectric constant of the medium contained the requisite amounts of ligand,  $HClO_4$ ,  $NaClO_4$  and NaOH (and dioxane if necessary) as for conventional titration, keeping the ionic strength constant by adding 2.0M  $NaClO_4$  solution. The pH of this solution was adjusted to the  $pK$  value of the ligand, which was already determined by conventional Irving and Rossotti technique<sup>2</sup>. The total volume of this solution was 20 ml at the start. The  $pK$  values obtained by the two techniques for various substituted benzoic acids are given in Tables 1 and 2. The  $pK$  values obtained are the practical values.

The agreement of  $pK$  values of various ligands (Tables 1 and 2) is fairly good. The solution appears to have been significantly diluted because of the addition of dioxane. However, the change in pH around the half neutralization point is sluggish.

TABLE 1 — PRACTICAL  $pK$  VALUES OF BENZOIC ACID IN WATER-DIOXANE MIXTURES

[(i)  $HClO_4$  ( $1.0 \times 10^{-2}M$ ); (ii) benzoic acid ( $7.5 \times 10^{-3}M$ ); (iii) ionic strength 0.1M  $NaClO_4$ ; (iv) total initial volume 20 ml]

Dioxane added (ml)	2M $NaClO_4$ added (ml)	Dioxane (% v/v)	pH observed	Practical $pK$ reported <sup>7</sup>
0	0.0	0	4.01*	4.01
5	0.25	20	4.60	4.64
14	0.70	40	5.34	5.33
33	1.65	60	6.16	6.15
100	5.00	80	6.80	6.80

\*Initially adjusted pH.

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TABLE 2 — PRACTICAL  $pK$  VALUES OF SUBSTITUTED BENZOIC ACIDS IN WATER-DIOXANE MIXTURE

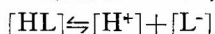
Benzoic acid	$pK$ values in dioxane (% v/v)					Ref.
	20	40	60	76	80	
2-Methoxy-	4.60(A) (4.60)	5.36 (5.41)	6.16 (6.17)	6.70 (6.73)	—	7
2,3-Dimethoxy-	4.11(A) (4.11)	4.90 (4.92)	5.70 (5.75)	6.29 (6.31)	—	7
2,6-Dimethoxy-	4.09(A) (4.09)	4.95 (5.03)	5.82 (5.87)	6.38 (6.43)	—	7
2,4,6-Trimethoxy-	4.49(A) (4.49)	5.35 (5.40)	6.20 (6.21)	6.75 (6.79)	—	7
<i>o</i> -Amino-	5.00(A) (5.00)	5.70 (5.76)	6.50 (6.56)	—	7.20 (7.23)	*
<i>m</i> -Amino-	4.77(A) (4.77)	5.40 (5.48)	6.20 (6.26)	—	6.86 (6.79)	*
<i>p</i> -Amino-	5.35(A) (5.35)	6.16 (6.10)	7.05 (7.01)	—	7.76 (7.81)	*
<i>p</i> -Nitro-	3.80(A) (3.80)	4.35 (4.32)	5.10 (5.10)	—	5.74 (5.75)	*

(A) refers to the initially adjusted  $pH$ . Values in brackets are obtained by conventional titration technique, using  $2 \times 10^{-3}M$  initial ligand concentration.

\*Taken from Jahagirdar *et al.* of our Department.

Some sort of buffer action seems to have been imposed at this stage, since the system consists of a weak acid and its sodium salt. A buffer of this type can tolerate the addition of reagent which can change  $pH$  equivalent to  $\pm 1.0$  unit\*<sup>10</sup>. The buffer capacity of these solutions seems to be appreciable as revealed by the flatness of the potentiometric titration curve near  $pK$  value (in our experiment, however, no acid or base has been added; the solution has only been diluted).

During the conventional titration of ligand with base by Irving-Rossotti technique in 0/100 and 80/20 dioxane-water media the following equilibrium (if the initial starting concentration of HL were  $2 \times 10^{-3}$ ) at half-neutralization, could be written,



$[10^{-a}] = [10^{-pK_{80}}] + [10^{-a}]$  in 0/100 dioxane-water and

$[10^{-a}] = [10^{-pK_0}] + [10^{-a}]$  in 80/20 dioxane-water where  $pK_0$  and  $pK_{80}$  are the values in 0 and 80% dioxane-water medium respectively.

In our method of continuous titration,  $pH$  is adjusted to  $pK_0$  initially, which changes to the same  $pK_{80}$  obtained by conventional method, on addition of dioxane, indicating that  $[H^+]$  has changed from  $10^{-pK_0}$  to  $10^{-pK_{80}}$ .

On the addition of dioxane, the dielectric constant of the medium decreases which facilitates the combination of  $H^+$  with  $L^-$  forming undissociated HL. The new concentration of the HL and  $L^-$  in 80/20 dioxane-water solution will thus be

$$[HL] = 10^{-a} + (10^{-pK_0} - 10^{-pK_{80}})$$

and

$$[L^-] = 10^{-a} - (10^{-pK_0} - 10^{-pK_{80}})$$

where  $a < pK_0 < pK_{80}$ .

\*In this particular case, benzoic acid gets six-fold diluted. This should bring about a change in  $[H^+]$  to 1/6th of the initial concentration and in  $pH$  of log 6 units, i.e. 0.8  $pH$  units, if the system is not buffered.

The new ratio would thus be

$$\frac{[HL]}{[L^-]} = \frac{10^{-a} + (10^{-pK_0} - 10^{-pK_{80}})}{10^{-a} - (10^{-pK_0} - 10^{-pK_{80}})} \neq 1$$

The above ratio could still be brought very close to unity by making  $10^{-pK_0} - 10^{-pK_{80}}$  very small (as is possible in the case of  $10^{-pK_0} - 10^{-pK_{20}}$ ). The dissociation constants are, however, beyond our control. If  $pK_{80}$  is large,  $10^{-pK_{80}}$  will be small as compared to  $10^{-a}$  and  $10^{-pK_0}$  which may, therefore, be neglected. Thus,

$$\frac{[HL]}{[L^-]} = \frac{10^{-a} + 10^{-pK_0}}{10^{-a} - 10^{-pK_0}} \neq 1$$

$$\therefore 1 + \frac{2 \times 10^{-pK_0}}{10^{-a} - 10^{-pK_0}} \neq 1$$

The ratio  $[HL]/[L^-]$  deviates from unity by this amount which may be put equal to  $C$ .

$$\therefore \frac{2 \times 10^{-pK_0}}{10^{-a} - 10^{-pK_0}} = C$$

On solving

$$10^{pK_0 - a} = \frac{2+C}{C} = 2/C + 1$$

Obviously as the difference between  $pK_0$  and  $a$  increases, deviation of  $C$  from unity becomes smaller and smaller. Thus the difference in the starting concentration of HL and  $pK_0$  (the initially adjusted dissociation constant) should be higher for the usefulness of continuous titration. In order to check this the continuous titrations have been carried out with initial [ligand] =  $6 \times 10^{-3}$ ,  $2 \times 10^{-3}$  and  $0.75 \times 10^{-3}M$ . The results agree well in the case of solutions with higher initial [ligand] and show deviation at lower initial concentration, i.e.  $0.75 \times 10^{-3}M$  (Table 3).

In some representative cases where deviation from  $pK$  was large their  $pK$ 's have been found by

TABLE 3 — PRACTICAL  $pK$  VALUES BY CONTINUOUS TITRATION TECHNIQUE[Initial ligand conc. =  $0.75 \times 10^{-3}M$ ]

Benzoic acid	$pK$ values in dioxane (% v/v)					
	0	20	40	60	76	80
Benzoic acid	4.01(A) (4.01)	4.48 (4.64)	5.15 (5.33)	5.91 (6.15) [6.13]	—	6.69 (6.80)
2-Methoxy-	—	4.60(A) (4.60)	5.31 (5.41)	6.10 (6.17)	6.64 (6.73)	—
2,3-Dimethoxy-	—	4.11(A) (4.11)	4.80 (4.92)	5.59 (5.75) [5.73]	6.19 (6.31)	—
2,6-Dimethoxy-	—	4.09(A) (4.09)	4.85 (5.03) [5.00]	5.66 (5.87) [5.87]	6.25 (6.43)	—
2,4,6-Trimethoxy-	—	4.49(A) (4.49)	5.29 (5.40) [5.40]	6.12 (6.21)	6.70 (6.79)	—
<i>o</i> -Amino-	—	5.00(A) (5.00)	5.68 (5.76)	6.49 (6.56) [6.56]	—	7.20 (7.23)
<i>m</i> -Amino-	—	4.77(A) (4.77)	5.39 (5.48)	6.20 (6.26)	—	6.95 (6.79)
<i>p</i> -Amino-	—	5.35(A) (5.35)	6.16 (6.10)	7.06 (7.01)	—	7.79 (7.81)
<i>p</i> -Nitro-	—	3.80(A) (3.80)	4.21 (4.32)	4.85 (5.10) [5.10]	—	5.80 (5.75)

$pK$  values in circular brackets from Tables 1 and 2 for comparison.  $pK$  values in square brackets from representative runs found by conventional method using  $0.75 \times 10^{-3}M$  ligand. (A) refers to the initially adjusted  $pH$ .

TABLE 4 — PRACTICAL  $pK$  VALUES BY BACK TITRATION

Benzoic acid	$pK$ in dioxane (% v/v)				
	80	76	60	40	20
Benzoic acid	6.80(A) (6.80)	—	6.16 (6.15)	5.49 (5.33)	4.80 (4.64)
2-Methoxy-	—	6.73(A) (6.73)	6.23 (6.17)	5.47 (5.41)	4.76 (4.60)
2,3-Dimethoxy-	—	6.31(A) (6.31)	5.76 (5.75)	4.98 (4.92)	4.27 (4.11)
2,6-Dimethoxy-	—	6.43(A) (6.43)	5.90 (5.87)	5.10 (5.03)	4.30 (4.09)
2,4,6-Trimethoxy-	—	6.79(A) (6.79)	6.31 (6.21)	5.50 (5.40)	4.65 (4.49)
<i>o</i> -Amino-	7.23(A) (7.23)	—	6.55 (6.56)	5.75 (5.76)	5.11 (5.00)
<i>m</i> -Amino-	6.79(A) (6.79)	—	6.09 (6.26)	5.31 (5.48)	4.74 (4.77)
<i>p</i> -Amino-	7.81(A) (7.81)	—	7.15 (7.01)	6.25 (6.10)	5.46 (5.35)
<i>p</i> -Nitro-	5.75(A) (5.75)	—	5.09 (5.10)	4.44 (4.32)	4.09 (3.80)

(A) refers to the initially adjusted  $pH$ . Values in brackets are obtained by conventional technique from Tables 1 and 2 for comparison.

conventional technique using low [ligand] ( $0.75 \times 10^{-3}M$ ). These  $pK$  values do not deviate from the values reported earlier proving thereby the limitations of the continuous titration method.

The arguments apply equally well if the  $pH$  is fixed at  $pK_{80}$  and water containing  $0.1M$   $NaClO_4$  (to maintain the same ionic strength) is continuously added so as to decrease the dioxane percentage. In such a situation, the concentration of HL will

decrease and that of  $L^-$  will rise. The ratio of  $[HL]/[L^-]$  then will be

$$\frac{H[L]}{[L^-]} = \frac{10^{-a} - (10^{-pK_0} - 10^{-pK_{80}})}{10^{-a} + (10^{-pK_0} - 10^{-pK_{80}})} \neq 1$$

which is the reciprocal of the earlier ratio. The results of these so called back titrations are given in Table 4. The agreement among the  $pK$  values is not good particularly at lower dioxane percent-

TABLE 6 — PRACTICAL  $pK$  VALUES IN DIOXANE-WATER (76%, v/v) MEDIUM AT DIFFERENT TEMPERATURES

Temp. °C	$pK$ of benzoic acids					
	2-Methoxy	4-Methoxy	2,4-Dimethoxy	2,6-Dimethoxy	2,4,5-Tri-methoxy	2,4,6-Tri-methoxy
20	6.80 (6.82)	7.15 (7.12)	7.34 (7.35)	6.51 (6.52)	7.35 (7.35)	6.91 (6.90)
30	6.73(A) (6.73)	7.05(A) (7.05)	7.23(A) (7.23)	6.43(A) (6.43)	7.27(A) (7.27)	6.79(A) (6.79)
40	6.65 (6.67)	7.00 (6.99)	7.17 (7.16)	6.36 (6.34)	7.17 (7.16)	6.68 (6.67)
50	6.60 (6.61)	6.95 (6.93)	7.12 (7.10)	6.28 (6.30)	7.10 (7.09)	6.64 (6.62)

(A) refers is the initially adjusted  $pH$ .  $pK$  values in parentheses obtained by conventional titration technique.

 TABLE 5 —  $pK_2$  VALUES OF AMINO ACIDS AT DIFFERENT TEMPERATURES

Temp. °C	$\alpha$ -Alanine	$\beta$ -Alanine	Glycine	$\alpha$ -Amino-butyr-ic acid
15	10.15 (10.13)	10.54 (10.56)	10.05 (10.04)	10.14 (10.09)
25	9.90(A) (9.90)	10.29(A) (10.29)	9.81(A) (9.81)	9.86(A) (9.86)
40	9.54 (9.54)	9.96 (9.93)	9.40 (9.47)	9.40 (9.46)

The values in brackets are reported by Sharma *et al.*<sup>5</sup>. (A) refers to the initially adjusted  $pH$ .

ages. There is a difference in the two types of continuous titrations. During the addition of dioxane the solution is being diluted affecting the dissociation of HL, while the dielectric constant of the medium is being lowered, which has an opposite effect of facilitating association of  $H^+$  and  $L^-$ . Both these effects counteract each other. However, when water is added the effect due to dilution and increase in dielectric constant of the medium act in the same direction of promoting dissociation. One can yet, fix the  $pK$  at an intermediate percentage of dioxane and lower or raise the percentage using the continuous method advantageously.

Similar arguments apply equally well to the change of  $pK$  with temperature or with any other parameters for that matter.

*Effect of varying temperature* — The  $pH$  of the solution was adjusted to the reported  $pK$  value as above, in 50 ml total volume of solution which was thermostated. The temperature of the titration vessel was changed to the desired temperature, and  $pH$  of the solution was noted.

The amino acids investigated by Sharma *et al.*<sup>5</sup> were chosen because these show significant variation in the  $pK_2$  values with temperature. The changes

in  $pK_1$  were within the experimental error. The  $pK_2$  reported by Sharma *et al.*<sup>5</sup> are the corrected concentration values after taking in to consideration the activity coefficient. Since our method gives only the direct  $pH$ , their reported values were converted into the  $pH$ , i.e. the  $pH$  meter readings 'B' by using the relevant activity coefficients<sup>6</sup>. The results are given in Table 5 for comparison.

Table 6 compares the practical  $pK$  values of substituted methoxybenzoic acids in 76% dioxane-water (v/v) medium at different temperatures which we have investigated in this laboratory both by conventional and continuous titration technique<sup>7</sup>. There is good agreement in general.

The new method is advantageous because it gives  $pK$  values at any desired dioxane percentage or temperature within the smallest possible variation in either of the parameters. This work could be extended to other solvent systems. Further work on the effect of continuous change in the ionic strength on  $pK$  values and extension of the method to the determination of stability constants of metal complexes under varying conditions, is in progress.

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