pKa Determinations Utilizing Solutions of 7-(2-Hydroxypropyl)theophylline

H. V. MAULDING and M. A. ZOGLIO*

Abstract □ A method exhibiting applicability in the evaluation of ionization constants of certain difficultly soluble compounds by potentiometric titration is submitted. The neutral xanthine derivative, 7-(2-hydroxypropyl)theophylline, is employed as an aid in dissolution of poorly soluble molecules, allowing their subsequent titration with acid or base in the usual manner. The procedure has been found suitable for compounds belonging to widely diversified chemical and structural classes. The success with which it has been used seems dependent on the tendency of 7-(2-hydroxypropyl)-theophylline to interact in aqueous solutions with compounds leading to their dissolution. This effect is reminiscent of the co-solvent properties of water-miscible agents such as ethanol. Examples of the utility of this treatment are given and pertinent data included as they apply to several structural prototypes.

Keyphrases □ 7-(2-Hydroxypropyl)theophylline solutions—pKa determinations □ pKa determinations—7-(2-hydroxypropyl)theophylline solutions □ Ionization-constant determination—using 7-(2-hydroxypropyl)theophylline, potentiometric titrimetry

The observation that 7-(2-hydroxypropyl)theophylline[1] and several other xanthine analogs have a solubilizing effect on the proteinaceous ergot alkaloids has recently been reported (1–3). When pKa determinations of the ergot alkaloids by conventional methods were unsuccessful, it was decided to attempt utilization of the xanthine effect to keep the alkaloids in solution during titration. The most useful of the xanthine analogs for this purpose was found to be 7-(2-hydroxypropyl)-theophylline (4). This compound has a high degree of water solubility (55%, 25°), is neutral in solution, and exhibits cosolventlike properties.

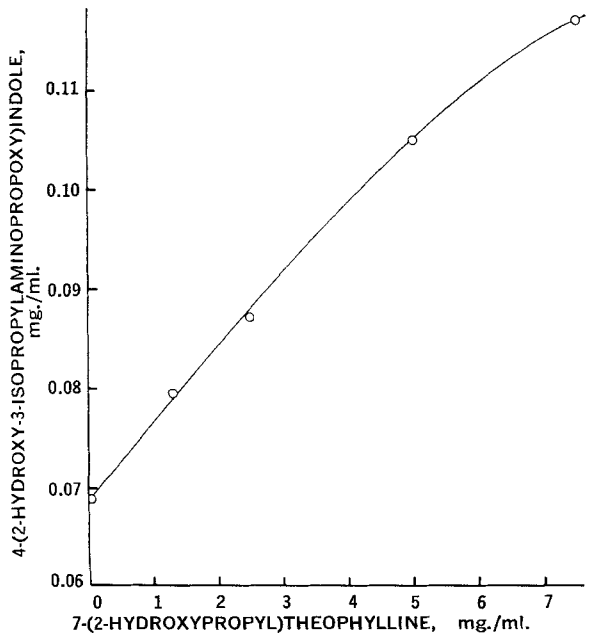

Figure 1—*Phase-solubility diagram for 4-(2-hydroxy-3-isopropylaminopropoxy)indole in distilled water at 30° for 24 hr. employing 7-(2-hydroxypropyl)theopylline as the solubilizing agent. Solubilities determined by the Van Urk procedure (12).*

[1] Referred to as 7-β-hydroxypropyltheophylline in previous reports.

Table I[a]—Approximate pKa Determination for 5-Allyl,5-isobutylbarbituric Acid[b] in 12% 7-(2-Hydroxypropyl)theophylline at 24°

Titrant, ml. (0.1 *N* KOH)	pH	Approximate pKa[c]
0.0	5.25	—
0.5	6.90	7.85
1.0	7.25	7.87
1.5	7.48	7.85
2.0	7.68	7.85
2.5	7.85	7.85
3.0	8.02	7.84
3.5	8.22	7.85
4.0	8.47	7.87
4.5	8.90	7.95
5.0	9.70	—

[a] These data are for titration of itobarbital in the neutral form (HA) with KOH as opposed to titration of the salt form as shown in Fig. 3. [b] 0.005 *M*. [c] Calculated from pKa = pH + log HA/A$^-$.

Several ergot alkaloids were successfully titrated, employing solutions of this xanthine, and their approximate pKa's were determined (4). Although it was assumed that this solubilizing effect was specific for ergot alkaloids, it was later observed that 7-(2-hydroxypropyl)theophylline can interact with a variety of structural types. These include not only compounds containing the lysergic acid nucleus but also derivatives of indole, derivatives of imidazothiazole, molecules containing the barbiturate nucleus, and perhaps others yet to be examined.

This study is concerned with this phenomenon and the scope of its applicability in the measurement of ionization constants of acidic and basic substances of pharmaceutical importance.

EXPERIMENTAL

Crystalline substances to be evaluated were dried 24 hr. at 40–50°, 1 mm. Hg. Solutions were constituted from freshly boiled distilled water (50 or 100 ml.) to which was added 7-(2-hydroxypropyl)theophylline (amounts of 2.5 to 30% w/v) along with 0.005 mole of the compound under study.

Solutions of acidic substances were prepared from 0.005 mole acid[2] in the form of its sodium or potassium salts. Sodium salts were obtained commercially, and potassium salts were produced *in situ* by addition of 5.0 ml. 0.1 *N* KOH to 0.005 mole acid. Amines were dissolved by addition of 0.5 ml. 1 *N* HCl to an equimolar quantity of amine by means of a micropipet.[3]

Titrations of amine hydrochlorides were carried out with 10 equal increments (0.5 ml.) of carbonate-free 0.1 *N* KOH (5). Ten equal portions of 1 *N* HCl (0.05 ml.) were employed in the case of sodium or potassium salts of acids (5). The pH was read initially and after

[2] In several cases, 0.01 *M* was used as well as 0.005 *M*.

[3] Ultraprecision micrometer syringe, Roger Gilmont Instruments, Inc., Great Neck, NY 11021

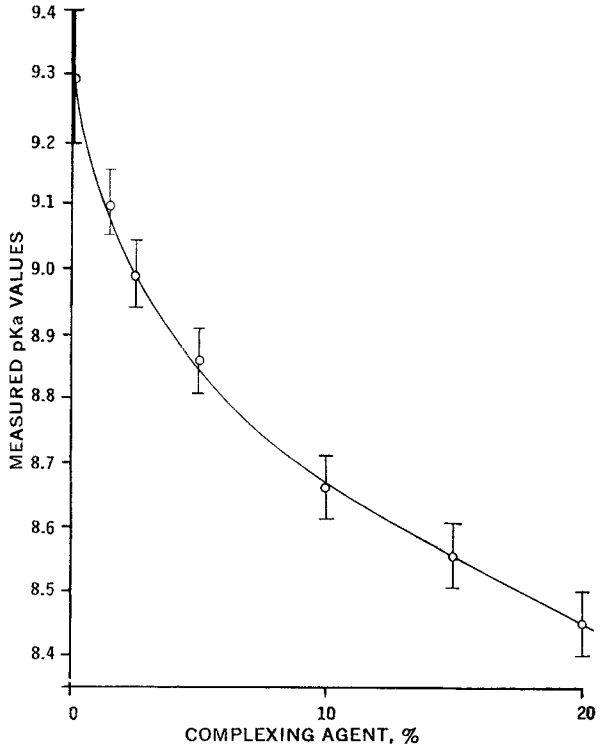

Figure 2—*Plot of pKa values* versus *percentage complexing agent [7-(2-hydroxypropyl)theopylline] for 3-(p-chlorophenyl)-5,6-dihydro-2-ethylimidazo[2,1-b]thiazole at 24°. The thermodynamic pKa value at zero xanthine concentration was determined spectrophotometrically.*

each portion of titrant. Nine values for the ionization constant were calculated.

The pH values were measured on a Metrohm pH meter using electrodes[4] standardized on 0.05 *M* potassium hydrogen phthalate (pH 4.0, 24°) and 0.05 *M* sodium borate (pH 9.20, 24°). Measurements were made at 24°. Electrodes were checked periodically with tris(hydroxymethyl)aminomethane (5).

MATERIALS

Itobarbital, 5-allyl,5-isobutylbarbituric acid,[5] was twice recrystallized from methanol–water and dried 24 hr. (1 mm. Hg), m.p. 137–138°. Phenobarbital[6] was twice recrystallized from methanol–water, m.p. 173–177°, following drying. 8-Bromotheophylline,[7] m.p. 320° dec., was not recrystallized prior to use. 7-(2-Hydroxypropyl)-theophylline,[8] m.p. 135–138°, was used in the form obtained. Tris(hydroxymethyl)aminomethane (THAM), primary standard,[9] was employed as a pKa standard; pKa = 8.18, 20° (5).

Other compounds studied were either analytically pure or used in the condition obtained from the manufacturer.

RESULTS AND DISCUSSION

The use of ethanol as an aqueous cosolvent was first reported by Mizutani (6) and has been utilized since in numerous cases with somewhat dubious success (5). Cellosolves (7) and other mixed solvent systems have been investigated and employed for certain purposes.

The solubilizing effect of xanthines on indole-containing molecules was observed in this laboratory (1–3). It was subsequently shown the dissociation constants could be determined for several

[4] Corning triple-purpose glass electrode No. 476020 and calomel electrode No. 476002, Corning Glass Works, Medfield, MA 02052
[5] Ganes Chemical Works, Inc., New York. N. Y.
[6] Mallinckrodt.
[7] Chemical Procurement Labs., Inc., College Point, NY 11356
[8] Ganes.
[9] Fisher Scientific Co.

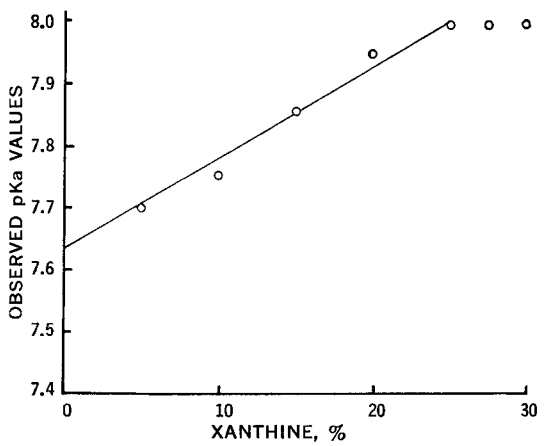

Figure 3—*Plot of pKa values against 7-(2-hydroxypropyl)theophylline concentrations for the titration of itobarbital (0.01 M) in 60-ml. volume at 24°.*

insoluble ergot alkaloids possessing the characteristic cyclic tripeptide moiety by addition of a xanthine for solubilization (4). This procedure has now been found suitable for several other types of compounds.

This method only offers a route toward approximation of ionization constants. The quantities of complexing agent which, of necessity, are added preclude evaluation of thermodynamic constants due to interference with activities of the species in solution.

The basic principle allowing these determinations is increased solubility of the acidic or basic substance in the presence of a complexing agent or cosolvent. The solubility effect as utilized in this procedure is illustrated in Fig. 1, where an almost twofold elevation of 4-(2-hydroxy-3-isopropylaminopropoxy)indole solubility occurs in the presence of 7-(2-hydroxypropyl)theophylline. These phenomena are indicative of an affinity between the two components. The exact chemical nature of this interaction has yet to be defined, but it appears to be a general one between xanthine and other relatively planar molecules.

Ionization constants were evaluated by titration of the hydrochloride salts of amines and sodium or potassium salts of acids in aqueous solutions (0.005–0.010 *M*) containing 7-(2-hydroxypropyl)-theophylline following the outline of Albert and Sergeant (5). The pKa values were calculated using the general Eqs. 1 and 2:

$$\text{pKa} = \text{pH} + \log \frac{\text{BH}+}{\text{B}} \qquad \text{(Eq. 1)}$$

$$\text{pKa} = \text{pH} + \log \frac{\text{HA}}{\text{A}-} \qquad \text{(Eq. 2)}$$

where BH+ and B are concentrations of amine salt and free base, respectively, and HA and A^- are concentrations of undissociated

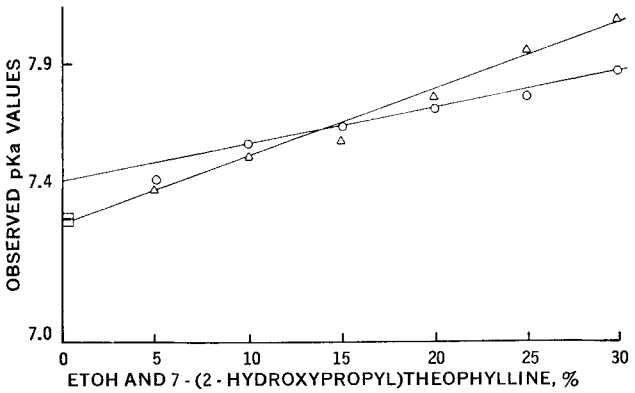

Figure 4—*The observed pKa values are plotted against the percentages of xanthine and ethanol employed for phenobarbital (0.005 M) in the form of the sodium salt titrated with 1.0 N HCl (titrated in 50-ml. volume). Key: O, 7-(2-hydroxypropyl)theophylline; and Δ, ethanol. Actual pKa is 7.41 (9).*

Table II—Ionization Constants[a] Determined by Titration Utilizing Solutions of 7-(2-Hydroxypropyl)theophylline

8-Bromotheophylline	5.45 (±0.1)
Theophylline	8.75 (±0.1)
3-(*p*-Chlorophenyl)-2-ethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thioazol-3-ol	7.68 (±0.1)
3-(*p*-Chlorophenyl)-5,6-dihydro-2-ethylimidazo[2,1-*b*]thiazole	9.30 (±0.1)
5-Allyl,5-isobutylbarbituric acid	7.63 (±0.1)
4-(2-Hydroxy-3-isopropylaminopropoxy)-indole	9.65 (±0.1)
5-Ethyl,5-phenyl barbituric acid	7.52 (±0.1)
Phenylbutazone	4.70 (±0.2)
8-Chlorotheophylline	5.31 (±0.1)

[a] All values presented are obtained by extrapolation to zero concentration of 7-(2-hydroxypropyl)theophylline.

acid and anion, respectively (5). Nine values were calculated when possible, and the precision was acceptable (usually ±0.05) when pure, dry compounds were used. Table I lists the data from a typical experiment on itobarbital.

Amines and acids were both used in the salt forms in hope of achieving an ease of initial solubilization. Complexation occurs with both ionized and neutral species (1–4). The xanthine prevents precipitation of the relatively insoluble neutral molecule, allowing complete titration. Either the salts were available or prepared *in situ* by addition of equimolar quantities of KOH or HCl. Frequently, warm or hot water was added to the salt along with the complexing agent to attain complete solution. This was especially necessary at the xanthine concentrations below 10%. Titrations were carried out as rapidly as possible to prevent precipitation of supersaturated solutions occurring at lower xanthine concentrations.

Figures 2–4 are plots of pKa *versus* concentration of 7-(2-hydroxypropyl)theophylline and show that both apparently straight and curved lines are obtainable in these experiments, depending on the structure being studied.

Figure 2 gives the limits of precision for a thiazole derivative on a plot of pKa against percent xanthine, while Figs. 3 and 4 illustrate a seemingly linear case with barbituric acid derivatives. Extrapolation of the lines to zero additive concentration should give an approximation of the actual pKa values and does in these cases, with the respective thermodynamic pKa's of Figs. 2–4 being 9.30 (8), 7.70–7.80 (9), and 7.42 (10).

When itobarbital in the form of its sodium salt (0.01 *M*) is titrated with HCl, the xanthine causes a leveling of the observed pKa above 25% concentration; but the lower portion of the data may be extrapolated, and the value obtained gives a good estimation of the actual value (9). The pKa of phenobarbital was previously studied as a function of ethanol percentage (9). Figure 4 gives a comparison of the results when ethanol is used as a cosolvent relative to 7-(2-hydroxypropyl)theophylline. The data are quite similar for the same percentages weight in volume ratio; however, this may be circumstance because the molar ratios of the two are quite dissimilar. Figure 4 indicates that the xanthine gives qualitatively results that are like those of ethanol of equal percentage weight in volume ratio.

Table II summarizes several compounds investigated by this method and gives the extrapolated values as well as the precision of the results. A diversified group of compounds are listed; this procedure lends itself reasonably well to most pKa approximations. Neither diphenylhydantoin or its sodium salt could be treated in this manner due to its failure to dissolve.[10] The same problem arose with alcohol, precluding its use with the hydantoin, although the pKa was reported spectrophotometrically as 8.31 (11).

SUMMARY

The compound, 7-(2-hydroxypropyl)theophylline, is an interesting case of a solid alkaloid substance displaying cosolventlike properties. Its high solubility is unique, and structure modifications might lead to other molecules with exceptional properties, although unusual compounds, with respect to properties, exist in all classes.

The use of this method should be considered for compounds resisting standard procedures for pKa evaluation and as a supplementary method to confirm data obtained by other methods. It is a relatively quick process and shows the ability of this xanthine to interact with a wide variety of substances. No attempt was made to study the scope of these phenomena, and doubtless many other structural types will complex in this manner.

The experimental results do not always extrapolate to zero xanthine concentration in a linear manner, as is seen in Fig. 2. This does not seem to be a limiting factor when enough points are available to describe the general curvature of the line, and acceptable values are produced in the cases examined.

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[10] Diphenylhydantoin sodium would dissolve only at 25% concentration of 7-(2-hydroxypropyl)theophylline.