(5) "Organic Solvents Hand Book," 1st ed., Organic Synthesis Chemistry Association Japan, Ohm Co., Tokyo, 1981, p. 294.

ACKNOWLEDGMENTS

The authors thank Prof. A. Otsuka, Meijo University, Nagoya, Japan, for the use of the X-ray diffractometer. This paper is part VII of a series on spherical crystallization.

A part of this research was supported by a grant-in-aid (Project No. 59490023) for scientific research, Ministry of Education, Culture and Science, Japan.

Determination of the Ionization Constants of Compounds which Precipitate During Potentiometric Titration Using Extrapolation Techniques

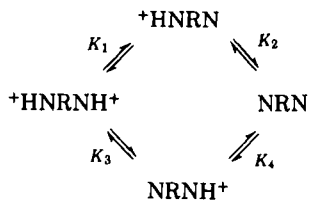
WILLIAM H. STRENG ˣ and M. A. ZOGLIO

Received December 12, 1982, from the *Merrell Dow Research Institute, Merrell Dow Pharmaceuticals, Inc., Subsidiary of The Dow Chemical Co., Cincinnati, OH 45215.* Accepted for publication October 11, 1983.

Abstract □ It is shown that the ionization constants of diacidic compounds can be determined by utilizing potentiometric titration data, even when a precipitate forms during the titration. The two methods presented are particularly useful for compounds for which the pK_a values are close together. A third method is presented which can be used with monoacidic compounds or compounds for which the pK_a values are far apart and form a precipitate during the titration. Four symmetrical diacidic compounds were studied which had similar pK_a values, and one compound was studied which had pK_a values that were far apart. Comparison of the second pK_a of the latter compound with that previously reported determined by a spectrophotometric procedure showed excellent correlation.

Keyphrases □ Ionization constants—determination, compounds which precipitate during potentiometric titration □ Potentiometric titration—determination of ionization constants

A method for determining the microionization constants of zwitterionic compounds is described in which potentiometric data are combined with spectrophotometric data (1). This method should be restricted, however, to well-behaved systems, *i.e.*, those which do not form precipitates or degrade during the course of the experiment. For sparingly soluble compounds, Maulding and Zoglio (2) and Levy and Rowland (3) have presented two techniques. Weak complexing agents were used by Maulding and Zoglio, whereas the method of Levy and Rowland required determining the solubility of the sparingly soluble component. In addition, these methods were only developed for monoprotic compounds or those polyprotic compounds for which pK_a values were sufficiently far apart (about 4 pK_a units) to be considered monoprotic. This study describes a method to determine the macroionization constants of compounds which precipitate during titration and which have similar pK_a values. The type of compounds considered form diacid salts, *i.e.*, there are two nitrogen atoms which can be protonated on each molecule and which undergo the equilibrium shown in Scheme I.



Scheme I

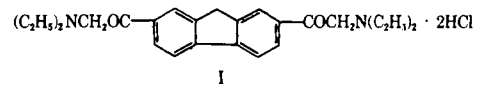
The microionization constants K_1, K_2, K_3, and K_4 are related to the macroionization constants by:

$$K_{13} = K_1 + K_3 \qquad \text{(Eq. 1)}$$

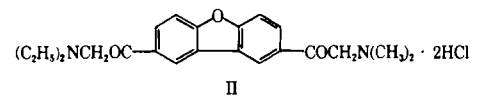
$$\frac{1}{K_{24}} = \frac{1}{K_2} + \frac{1}{K_4} \qquad \text{(Eq. 2)}$$

Utilizing potentiometric titration data, the macroionization constants K_{13} and K_{24} were determined for diprotic compounds in which species solubilities were exceeded and, therefore, which precipitated during the titration. This was accomplished by preparing the appropriate plots, as discussed below.

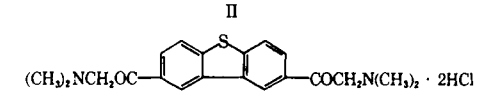
Measurements were made on four diacid salts in which the pK_a values were similar: 1,1′-(9*H*-fluorene-2,7-diyl)bis[2-diethylamino)ethanone]dihydrochloride (I); 1,1′-(2,8-dibenzofurandiyl)bis[2-(dimethylamino)-1-ethanone]dihydrochloride (II); 1,1′-(2,8-dibenzothiophendiyl)bis[2-(dimethylamino)-1-ethanone]dihydrochloride (III); 2,7-bis[2-(diethylamino)ethoxy]fluoren-9-one dihydrochloride (IV). Measurements were also made on one diacid salt for which the pK_a values were far apart: 10,11-dihydro-*N*-methyl-5*H*-dibenz[b,f]azepine-5-propanamine hydrochloride (V) (desipramine).



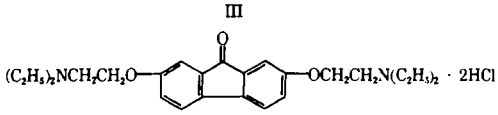
I



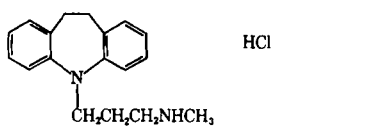
II



III



IV



V

0022-3549/84/1000-1410$01.00/0

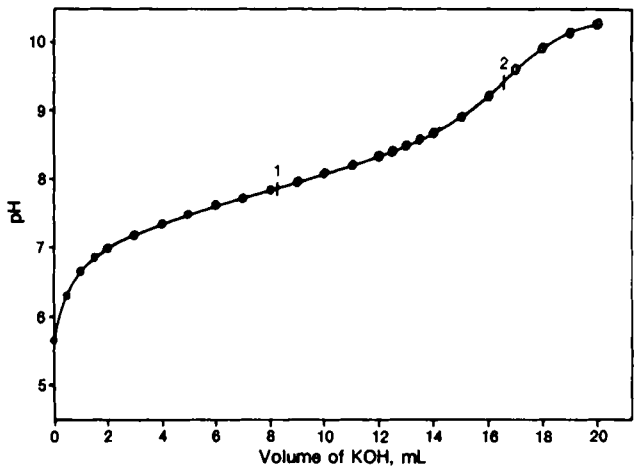


Figure 1—*Titration curve for compound II. Key: (1) first equivalence point; (2) second equivalence point.*

EXPERIMENTAL SECTION

Apparatus and Equipment—Potentiometric measurements were made with the apparatus previously described (1). For compounds I–IV, the apparatus was placed in a constant temperature bath and maintained at 25 ± 0.05°C, whereas the titration of V was done at room temperature (~24°C). Instead of the 50-mL buret used for I–IV, a syringe microburet was used for V.

Solution Preparation—Solutions of I–IV were prepared in the concentration range 3×10^{-4}–19×10^{-4} M. These solutions were titrated with 0.01 M potassium hydroxide, which was standardized with potassium acid phthalate. A solution of V with a concentration of 7×10^{-3} M was prepared, and an excess of 0.10 M hydrochloric acid standardized with potassium hydroxide was added to protonate both nitrogen atoms. This solution was titrated with 0.16 M potassium hydroxide standardized with potassium acid phthalate. All solutions were made with distilled water, boiled to remove oxygen and carbon dioxide, and saturated with nitrogen.

Table I—pK_{13} and pK_{24} Values for Compounds I–V

Compound	pK_{13}	pK_{24}
I[a]	8.16	8.89
II[b]	7.54	8.27
II[a]	7.54	8.24
III[a]	7.42	8.15
IV[a]	8.73	9.35
V[b,c]	1.51	10.24
V[c,d]	—	10.2

[a] Obtained by Method II. [b] Obtained by Method I. [c] The value of S_0 for compound V, obtained in this study was 60.8 μg/mL; the value obtained by Green (9) was 58.6 μg/mL. [d] Spectrophotometric method of Green (9).

THEORETICAL SECTION

In the following equations, { }, [ ], Y, and K represent activity, concentration, activity coefficient, and equilibrium constants on a molar scale, respectively. The total concentration of base added as titrant, halide, and acid being titrated are represented by $[B]$, $[X]$, and $[A]$, respectively.

The equilibria to be considered are not those for the microionization constants given by Scheme I, but rather the equilibria for the macroionization constants given by:

$$(NRN)H_2^{2+} \overset{K_{13}}{\rightleftharpoons} (NRN)H^+ + H^+ \qquad \text{(Eq. 3)}$$

$$(NRN)H^+ \overset{K_{24}}{\rightleftharpoons} NRN + H^+ \qquad \text{(Eq. 4)}$$

for which

$$K_{13} = \frac{\{(NRN)H^+\}\{H^+\}}{\{(NRN)H_2^{2+}\}} \qquad \text{(Eq. 5)}$$

$$K_{24} = \frac{\{NRN\}\{H^+\}}{\{(NRN)H^+\}} \qquad \text{(Eq. 6)}$$

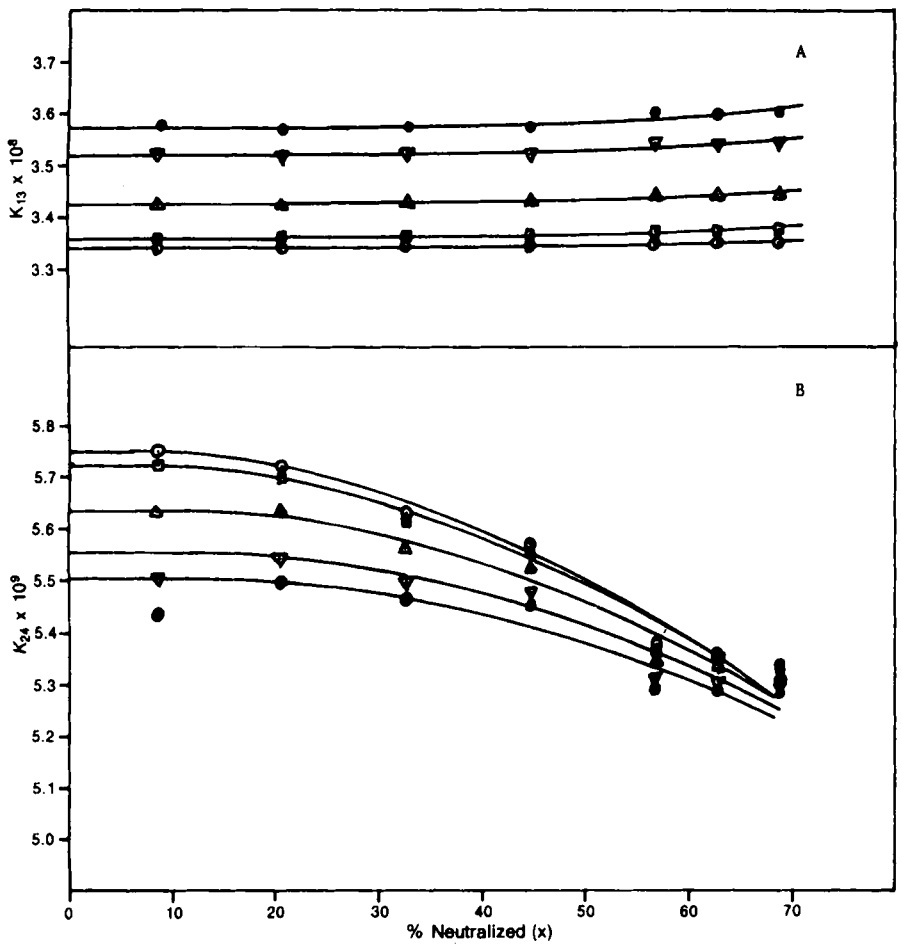


Figure 2—*(A)* K(*n,x*) versus *percent neutralized (x) for* K_{13} *of compound II. Key: the percent neutralized n is (⊙) 12; (⊡) 18; (▲) 24; (▼) 36; (●) 48. (B)* K(*n,x*) versus *percent neutralized (x) for* K_{24} *of compound II.*

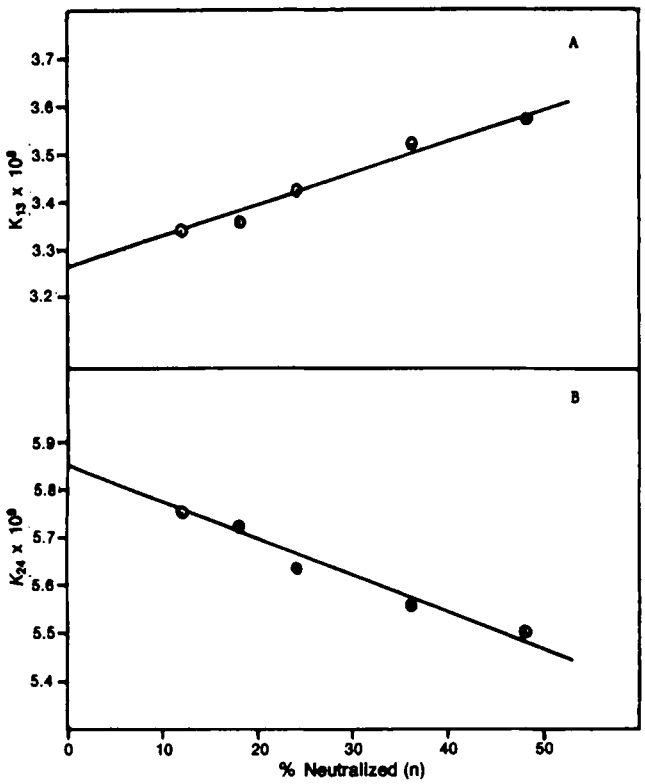


Figure 3—K(*n*,E) versus *percent neutralized (n) for* K_{13} *of compound II. (B)* K(*n*,E) versus *percent neutralized (n) for* K_{24} *of compound II.*

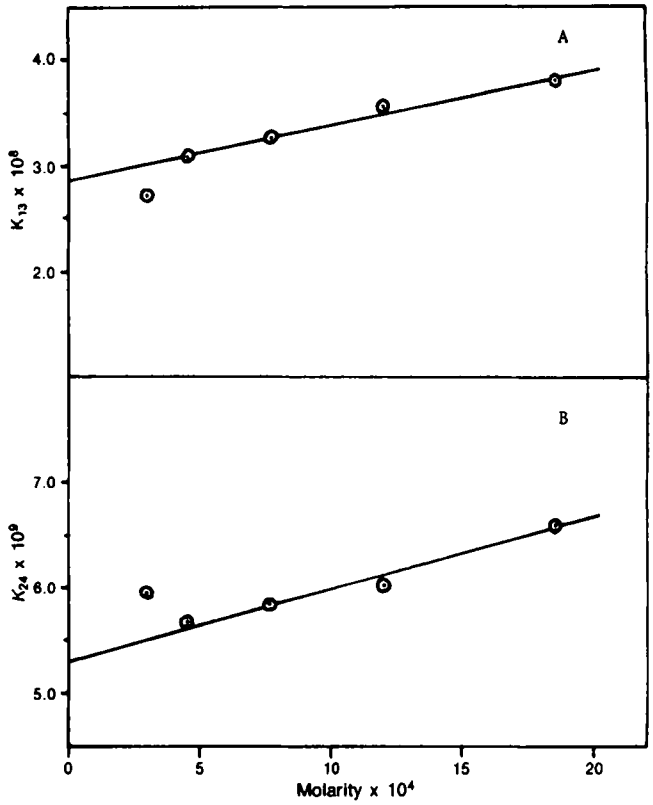


Figure 4—K(*0*,E) versus *molarity for* K_{13} *of compound II. (B)* K(*0*,E) versus *molarity for* K_{24} *of compound II.*

The equations used to determine the equilibrium constants in Eqs. 5 and 6 have been reported by many authors since the late 1800s (4–7) and will not be derived here. The derivation results in:

$$\alpha = \beta K_{13} + \gamma K_{13} K_{24} \qquad \text{(Eq. 7)}$$

where:

$$\alpha = [B]\{H^+\}^3 + \frac{\{H^+\}^4}{Y_{H^+}} - \frac{K_w\{H^+\}^2}{Y_{OH^-}} \qquad \text{(Eq. 8)}$$

$$\beta = \frac{Y_{(NRN)H^+}}{Y_{(NRN)H^+}}\left([A]\{H^+\}^2 - [B]\{H^+\}^2 - \frac{\{H^+\}^3}{Y_{H^+}} + \frac{K_w\{H^+\}}{Y_{OH^-}}\right) \qquad \text{(Eq. 9)}$$

$$\gamma = \frac{Y_{(NRN)H^+}}{Y_{NRN}}\left(2[A]\{H^+\} - [B]\{H^+\} - \frac{\{H^+\}^2}{Y_{H^+}} + \frac{K_w}{Y_{OH^-}}\right) \qquad \text{(Eq. 10)}$$

$$K_w = \{H^+\}\{OH^-\} \qquad \text{(Eq. 11)}$$

Conventional methods (4–7) can be used to determine K_{13} and K_{24} for well-behaved systems. Either of the two sets of experimental data can be combined according to Eqs. 12 and 13, or a plot of α/γ *versus* β/γ can be prepared, and the values for K_{13} and K_{24} determined from the slope and intercept:

$$K_{13} = \frac{\alpha_n\gamma_x - \alpha_x\gamma_n}{\beta_n\gamma_x - \beta_x\gamma_n} \qquad \text{(Eq. 12)}$$

$$K_{24} = \frac{\alpha_x\beta_n - \alpha_n\beta_x}{\alpha_n\gamma_x - \alpha_x\gamma_n} \qquad \text{(Eq. 13)}$$

where the subscripts n and x refer to two different sets of data. Modifications of these approaches can be made to determine the constants in systems in which precipitates are formed.

Method I—To use Eqs. 12 and 13, one set of data should be obtained before the first equivalence point and one should be obtained after. In well-behaved systems, the constants calculated will be independent of the sets of data used. For those systems that are not well behaved, *e.g.*, due to the formation of a precipitate, the values calculated for K_{13} and K_{24} will be incorrect. Those equilibrium constants calculated with data obtained after precipitation started will not be the same. They will, however, change in a systematic manner. Extrapolation of the calculated values to regions in which there is no precipitation should result in the correct value. This procedure can be expressed by:

$$K_T = \lim_{C\to 0}(\lim_{n\to 0}[\lim_{x\to E}[K_c(n,x)]]) \qquad \text{(Eq. 14)}$$

where K_c is the calculated equilibrium constant, C is the concentration, and K_T is the thermodynamic equilibrium constant. In this equation, n and x are two data sets: x is taken between the first and second equivalence points, and n is taken up to the first equivalence point. The limits used are E, the first equivalence point, for data set x; zero base addition for data set n; and infinite dilution for C. Each data set is comprised of a volume of base added and the measured pH. By knowing the concentration of strong base and the number of moles of weak acid initially, the volume of strong base can be expressed as a percentage of the weak acid neutralized.

Values for K_c are calculated by using two sets of data. For each n, there will be a set of K_c values determined with a different value for x. A plot is then prepared of the calculated K_c values *versus* the percentage of the second equivalent neutralized (x) for each n. Each value of n will result in a separate curve. The extrapolated values of K_c at x = 0 are then plotted *versus* the percentage of the first equivalent neutralized (n). The extrapolated value of K_c at n = 0 should equal the correct value, excluding activity effects. A third

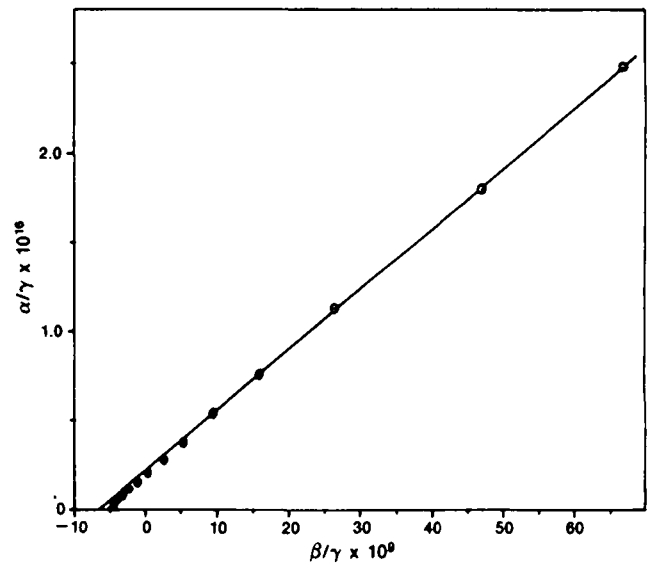


Figure 5—α/γ versus β/γ *for compound II.*

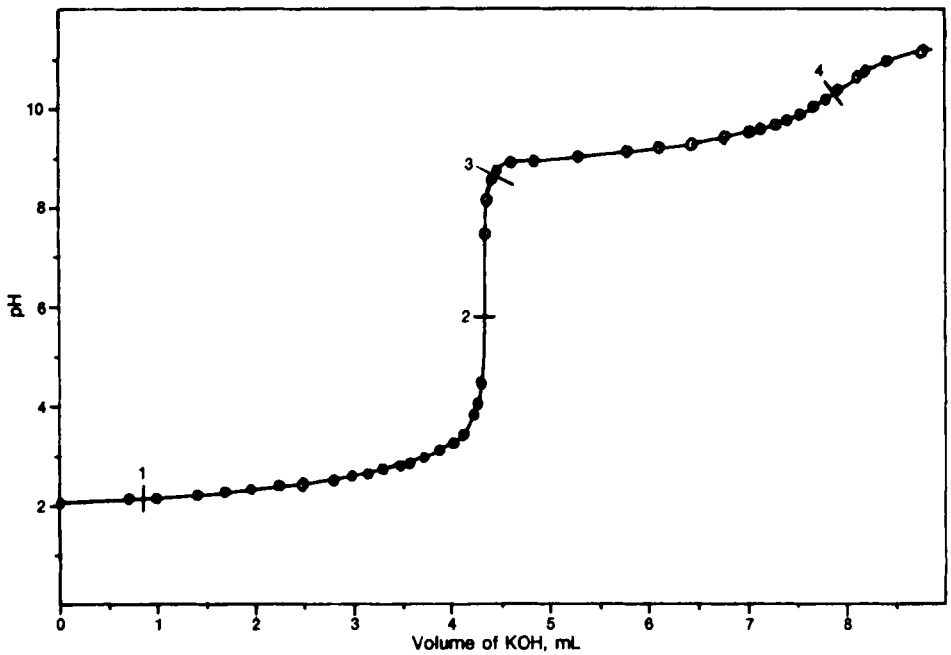


Figure 6—*Titration curve for compound V. Key: (1) starting point; (2) first equivalence point; (3) precipitate formed; (4) second equivalence point.*

plot of K_c *versus* concentration of weak acid will result in the thermodynamic value at infinite dilution.

Method II—A plot of α/γ *versus* β/γ from Eq. 7 will be linear until there is precipitation. Therefore, the determination of the slope of the linear segment and the linear extrapolation of this segment to the intercepts at α/γ and β/γ equal to zero enable the calculation of the equilibrium constants. The thermodynamic constants can be obtained from the infinite dilution value as described in method I.

RESULTS AND DISCUSSION

Figure 1 shows a typical titration curve for compounds I–IV. A precipitate formed during each titration, some of which formed prior to the first equivalence point. The data were treated by method I and/or method II. Approximations to the single ion activity coefficients were made by using the Davies equation (8):

$$-\log Y_i = AZ_i^2\left\{\frac{\sqrt{I}}{1+\sqrt{I}} - 0.2I\right\} \qquad \text{(Eq. 15)}$$

where Y_i is the single ion activity coefficient, A is a parameter for which the value at 25°C is 0.5092 on a molar scale, Z_i is the charge of ion i, and I is the molar ionic strength. The activity coefficients of the uncharged species were assumed to have a value of one.

According to method I, equilibrium constants were calculated with pairs of data; one set of data was from the region prior to the first equivalence point and the second set of data was from the region following the first equivalence point. These constants are written as K(n,x). For each data point designated by n, there was a set of equilibrium constants differentiated by the second data point used in the calculation and designated by x. The calculated values for K(n,x) can therefore be plotted *versus* x, and a separate curve can be obtained for each value of n. Typical plots of this type are shown in Figs. 2A and B for compound II. It can be seen that there is a separate curve for each data set n and that each curve approaches a constant value at x which corresponds to the first equivalence point. These values for K(n,E) are plotted *versus* n (Figs. 3A and B), and the curves obtained were extrapolated to an n value of zero. This value of n corresponds to zero base addition. There is a concentration dependency with these values of K(0,E) (Figs. 4A and B), and extrapolation of these curves to zero concentration will result in thermodynamic values. In Table I, the values obtained by this method for compound II are given.

By using method II, plots similar to those shown in Fig. 5 are obtained in which the deviation from linearity can be either negative or positive. This nonlinearity is due to either the formation of a precipitate during the titration and/or degradation. According to Eq. 7, the slope of the line from the linear segment will equal K_{13}, whereas the value of α/γ at the intercept at which

Table II—Microionization Constants for Compounds I–IV

Compound	$pK_1 = pK_3$	$pK_2 = pK_4$	K_{13}/K_{24}	K_1/K_2
I	8.46	8.59	5.37	1.35
II	7.84	7.94	5.01	1.26
III	7.72	7.85	5.37	1.35
IV	9.03	9.05	4.17	1.05

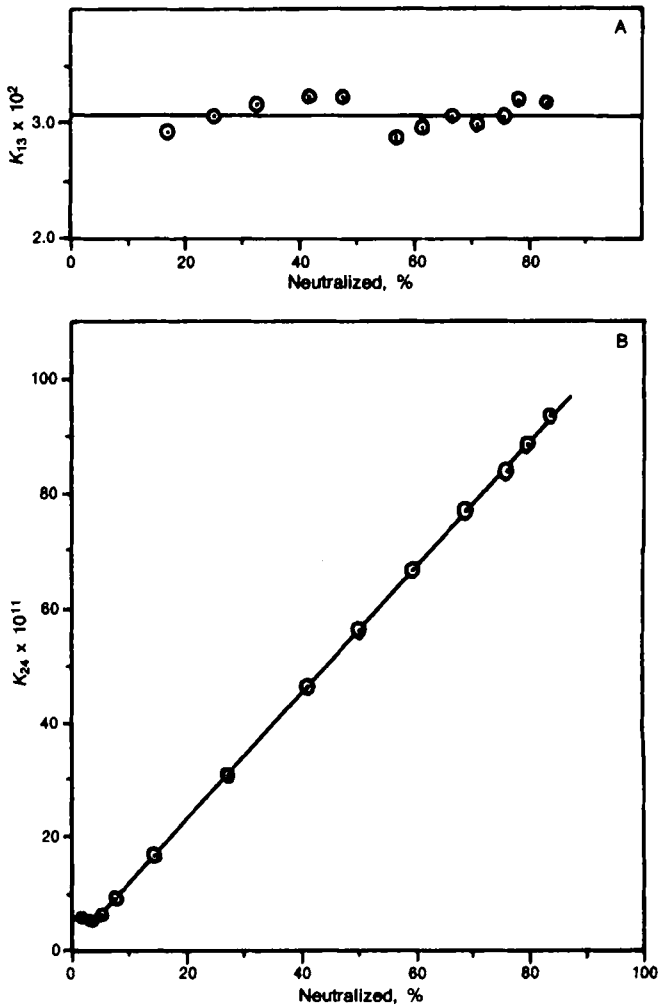


Figure 7—*(A)* K_{13} versus *percent neutralized for compound V. (B)* K_{24} versus *percent neutralized for compound V.*

$\beta/\gamma = 0$ is $K_{13}K_{24}$, and the value of β/γ at the intercept at which $\alpha/\gamma = 0$ is $-K_{24}$. These values of K_{13} and K_{24} have been found to be concentration dependent; therefore, plots similar to those shown in Figs. 4A and B were made to obtain the thermodynamic values. In Table I, the results of these calculations for compounds I–IV are given.

A modification of method I was used to obtain the values of K_{13} and K_{24} of compound V. Since the two pK_a values are far apart, the equilibria were assumed not to interact with each other; therefore, the equilibrium constants were determined by using the following expression for monoprotic compounds:

$$K_n = Z\frac{[H^+]([H^+] + [B] - [OH^-])}{[OH^-] + [A] - [H^+] - [B]} \qquad \text{(Eq. 16)}$$

where Z is the activity coefficient ratio $Y_{(NRN)H^+}/Y_{(NRN)H_2^{2+}}$ for K_{13} and $Y_{(NRN)}/Y_{(NRN)H^+}$ for K_{24}.

Figure 6 shows the titration curve obtained for compound V, and Figures 7A and B show the results of the calculated equilibrium constants *versus* percent neutralized. Precipitation was observed after the first equivalence point (Fig. 6), and therefore, consistent values should be obtained for K_{13} (Fig. 7A). Conversely, a change in the calculated value for K_{24} with respect to percent neutralized would be expected (Fig. 7B). The break in this latter curve at ~5% neutralization is due to the formation of a precipitate. The curve prior to precipitation should have a slope of zero (as in Fig. 7A), whereas the curve after precipitation will not necessarily be linear.

By knowing the value for K_{24} and the pH at which precipitation occurs, the solubility of the base (uncharged) species of compound V was determined by:

$$[NRN]_s = \frac{[A]K_{24}}{[H] + K_{24}} \qquad \text{(Eq. 17)}$$

In Table I, the results of the calculations for compound V are given, along with those values for K_{24} and $[NRN]_s$, as reported by Green (9) and determined by a spectrophotometric procedure. It can be seen there is excellent agreement among these data.

Since compounds I–IV are symmetrical molecules, it should be possible to calculate the microionization constants K_1, K_2, K_3, and K_4 of Scheme I. This is because K_1 should equal K_3, and K_2 should equal K_4. Furthermore, since the protonation sites are separated by large distances, it would be expected the K_2 and K_4 would be the same or only very slightly smaller than K_1 and K_3. The microionization constants were therefore calculated from Eqs. 1 and 2 and gave the results listed in Table II. It can be seen that there is very little difference in the calculated values, with K_2 and K_4 being slightly smaller.

For diprotic compounds with completely independent, equivalent sites of protonation, the ratio K_{13}/K_{24} will equal 4, and K_1/K_2 will equal 1. From these ratios (Table II), it can be seen that the values are very close to the theoretical values.

From these results, it can be concluded that the equilibrium constants of slightly soluble compounds can be determined potentiometrically by extrapolation procedures and give results which are consistent with those reported in the literature. It would be expected that method II would be better to use with those compounds that have equilibrium constants close together, whereas method I would be better to use with those compounds that have equilibrium constants farther apart.

REFERENCES

(1) W. H. Streng, H. E. Huber, J. L. DeYoung, and M. A. Zoglio, *J. Pharm. Sci.*, **65**, 1034 (1976).

(2) H. V. Maulding and M. A. Zoglio, *J. Pharm. Sci.*, **60**, 309 (1971).

(3) R. H. Levy and M. Rowland, *J. Pharm. Sci.*, **60**, 1155 (1971).

(4) A. A. Noyes, *Z. Physik. Chem.*, **11**, 495 (1893).

(5) C. Morton, *Trans. Faraday Soc.*, **24**, 14 (1928).

(6) W. R. Maxwell and J. R. Partington, *Trans. Faraday Soc.*, **31**, 922 (1935).

(7) J. C. Speakman, *J. Chem. Soc.*, 855 (1940).

(8) J. N. Butler, "Ionic Equilibrium a Mathematical Approach," Addison-Wesley Publishing Co., 1964, p. 437.

(9) A. L. Green, *J. Pharm. Pharmacol.*, **19**, 10 (1967).

Degradation of Fenprostalene in Polyethylene Glycol 400 Solution

DAVID M. JOHNSON ˣ **and WILLIAM F. TAYLOR**

Received March 14, 1983, from the *Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304.* Accepted for publiction October 26, 1983.

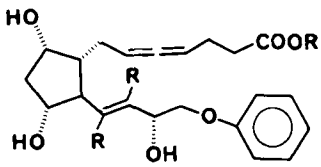
Abstract □ The kinetics of degradation of fenprostalene (I) in polyethylene glycol 400 solution was examined using HPLC. The degradation of I at 80°C was shown to depend on the presence of oxygen and a large number of polar products were produced, as evidenced by using ^3H-labeled I. Evidence that autoxidation of the polyethylene glycol 400 was concurrent with degradation of I was found from a drop in the apparent pH. Antioxidants were very effective in retarding the rate of degradation in the presence of oxygen. Degradation of I in polyethylene glycol 400 appears to arise from a reaction between the drug and reactive peroxide intermediates formed through air-oxidation of polyethylene glycol 400. This is supported by the finding that I reacts exclusively by a slow transesterification reaction in diethylene glycol, a solvent that is stable to autoxidation.

Keyphrases □ Degradation—fenprostalene in polyethylene glycol 400 □ Fenprostalene—autoxidation, degradation, kinetics □ Kinetics—fenprostalene in polyethylene glycol 400

Fenprostalene[1] (I), a PGF-type prostaglandin containing an aryloxy group at C-16 and an allene functionality at C-5 (1), is used as an abortifacient and for estrus synchronization in cattle (2). We have previously shown that in aqueous solution, I degrades exclusively through hydrolysis of the C-1 methyl ester under both acidic and basic conditions (3). No information is available, however, on the degradation of this family of prostaglandins in nonaqueous environments. Since an injectable formulation of fenprostalene (I) in polyethylene glycol 400 was chosen for development (4), we have investigated the chemical reactivity and degradation products of I in this solvent.

EXPERIMENTAL SECTION

Materials—The fenprostalene[1] (I) used was 99% pure (HPLC). The radiochemical purity of fenprostalene labeled with tritium at C-13 and C-14 was 98%. The acetonitrile used was glass-distilled HPLC-grade, and the water



I, R = H, R′ = CH_3
[^3H]I, R = ^3H, R′ = CH_3
II, R = H, R′ = $CH_2CH_2OCH_2CH_2OH$
III, R = R′ = H

[1] Fenprostalene is the generic name for methyl 7-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)cyclopentyl]-4,5-heptadienoate. Obtained from the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif. The synthesis of I is described in Ref. 1.

0022-3549/84/1000-1414$01.00/0