Preparation of Spherically Agglomerated Crystals of Aminophylline

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Abstract □ The spherically agglomerated crystals of aminophylline (theophylline-ethylenediamine complex) can be compounded directly into pharmaceutical formulations without further processing, *e.g.*, granulation. Such crystals were prepared by mixing theophylline and ethylenediamine in a partially miscible solvent system, *i.e.*, organic solvent-ethanol-water. The organic solvents used were chloroform, 1-hexanol, isopropyl acetate, isobutyl acetate, isoamyl acetate, benzene, toluene, *n*-hexane, or *n*-heptane. Spherical crystallization depended upon the solubility of theophylline in the solvent mixture. The resultant agglomerated crystals were identical with the theophylline-ethylenediamine complex by IR, X-ray, and differential scanning calorimetry analyses, and was the α-, β-, or γ-form when the water of crystallization was ≤0.5, 1.0, and 2.5 mol, respectively. When the amount of ethylenediamine used was <1.1 mL (0.0165 mol), the resultant agglomerated crystals were converted to anhydrous theophylline by washing with ethanol. When water was added to the system (≥0.3 mL, *i.e.*, 0.0167 mol), water was occluded in the resultant agglomerates as water of crystallization. Ethylenediamine content in the agglomerated crystals could be controlled by changing the amount of ethylenediamine added in the crystallization solvent.

Keyphrases □ Aminophylline—preparation from spherically agglomerated crystals of theophylline and ethylenediamine □ Spherical crystallization—aminophylline, theophylline, ethylenediamine

In previous papers (1-3), we described a method for the direct agglomeration of crystals during the crystallization process. In this process, a partially miscible mixture, *e.g.*, water-ethanol-chloroform, was used as the crystallization solvent. By selecting the proper ratio, a small amount of water or chloroform was liberated which acted as the collecting liquid and preferentially wetted the resulting crystals and transformed them into a spherical shape. This technique was termed "spherical crystallization" (1) due to the spherical form of the resultant crystals. Sodium theophylline monohydrate crystals, produced by salting out, were directly agglomerated into spheres in a mixture of an ethylenediamine solution of theophylline, an aqueous sodium chloride solution, ethanol, and chloroform (2, 3). Needle-like salicylic acid crystals simultaneously formed and agglomerated into spheres in a mixture of water, ethanol, and chloroform (1).

The present study describes the preparation of spherically agglomerated crystals of the theophylline-ethylenediamine complex (aminophylline) by the spherical crystallization technique, and also describes the crystallization behavior and the physicochemical properties of the resultant agglomerated crystals.

EXPERIMENTAL SECTION

Spherical crystallization process—*Method 1*—A mixture of organic solvent (60 mL), ethanol (12 mL), and water (0.13-10 mL) was used as the crystallization solvent. The amount of water added to the solvent was adjusted so that the resulting spherically agglomerated crystals were ~1 mm in diameter. The organic solvents used were chloroform, 1-hexanol, isopropyl acetate, isobutyl acetate, isoamyl acetate, benzene, toluene, *n*-hexane, or *n*-heptane. All organic solvents were reagent grade and were used as received. Ethylenediamine[1] (3.0 mL) and theophylline[1] (6.0 g) were dissolved in the mixture and agitated at 500 rpm with a paddle type agitator with four blades. Fine white crystals formed and agglomerated simultaneously into spheres. After 2 h, the agglomerated crystals were separated and dried. When using 1-hexanol and isopropyl acetate, 6-7 h of agitation were required.

Method 2—Spherical crystallization was carried out using the crystallization solvent with various amounts of ethylenediamine (1.0-3.5 mL) and water (0.15-0.9 mL), added to alter the ethylenediamine content in the resultant agglomerated crystals. The crystallization solvent, without water, was also used. The aforementioned experimental procedure was followed.

For reference, the theophylline-ethylenediamine complex (aminophylline), without agglomeration, was prepared by a conventional method, referred to as JP(X) (4). To a solution of absolute ethanol (100 mL) and ethylenediamine (9.2 mL) was added theophylline (24.7 g). The mixture was stirred vigorously for 5-6 h, during which time white crystals formed. These were washed with ethanol and dried.

Liberation Test of the Aqueous Phase from the Crystallization Solvent—To a solution of *n*-hexane (10 mL) and ethanol (2 mL), ethylenediamine (0-6 mL) and water (0-0.9 mL) were added to give two phases.

Measurement of the Physicochemical Properties of the Agglomerated Crystals—The spherically agglomerated crystals and the aminophylline crystals, prepared by the conventional method, were photographed through an optical microscope[2] and a scanning electron microscope[3], respectively. The particle size of the agglomerated crystals was measured by sieve analysis, and the crystalline forms of the agglomerated crystals were analyzed by an X-ray diffractometer[4] and an infrared spectrophotometer[5]. The thermal degradation behavior of the agglomerated and conventional crystals was investigated with a differential scanning calorimeter with heating at a rate of 10°C/min. The contents of theophylline and ethylenediamine in the agglomerated crystals were measured spectrophotometrically at 275 nm and by a neutralization titration method with 0.1 M HCl, respectively. The water content was measured by the Karl Fischer method[6].

RESULTS AND DISCUSSION

Spherical Crystallization Behavior of Method 1—It was found that spherical crystallization was dependent upon the solubility of theophylline in the solvent mixture. When chloroform or 1-hexanol were used as the organic solvents, theophylline completely dissolved. When chloroform was used, the fine crystals changed into the spherically agglomerated crystals within a 1-2 h period. With 1-hexanol, 7 h were required to obtain acceptable spherically agglomerated crystals. The solubility of water in 1-hexanol (5) is relatively high when

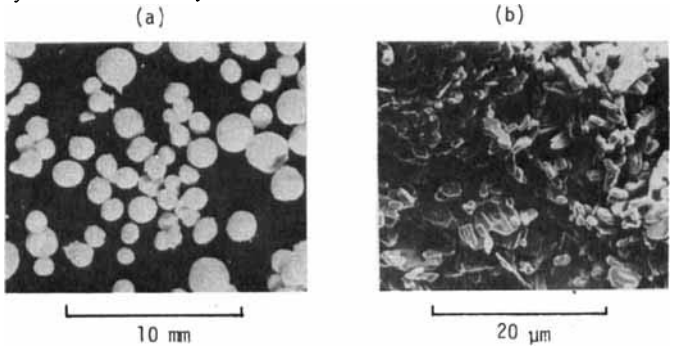

Figure 1—*Photographs of the agglomerated crystals and aminophylline crystals. (a) The spherical agglomerated crystals prepared in a mixture of chloroform-ethanol-water. (b) Aminophylline crystals prepared by a conventional method (4).*

[1] Nakarai Chemical Ltd., Japan.

[2] Olympas Optical Co., Ltd., JM, Japan.
[3] Nihon Denshi, JMS-SI, Japan.
[4] Nihon Denshi, JOX, Japan.
[5] Rigaku CN80852, Japan.
[6] Kyoto Electronics Manufacturing Co., Japan.

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Table I—Effect of Organic Solvents used on Spherical Crystallization

Organic Solvent	Water in the System, mL	Drug and Water Contents in the Agglomerate, %			Average Diameter of Agglomerate, mm	Solubility of Water[a]
		Theophylline	Ethylene-diamine	Water		
1-Hexanol	10.00	84.86	15.15	0.48	0.86	5.85
Isopropyl Acetate	3.75	82.82	16.43	5.78	1.55	1.66
Isobutyl Acetate	3.25	81.38	17.19	6.32	1.45	1.44
Isoamyl Acetate	2.25	84.30	15.74	5.28	1.30	—
Benzene	1.95	83.78	15.79	4.98	0.81	0.0385
Toluene	1.60	83.65	16.27	5.31	0.90	0.0373
n-Hexane	0.25	82.04	17.46	6.19	1.40	0.0073
n-Heptane	0.13	83.17	16.77	5.57	1.35	0.00897
Chloroform	4.00	85.13	15.47	8.31	1.35	0.0118[b]
Aminophylline[c]	—	83.39	14.39	4.21	5.52(μm)[d]	—

[a] Solubility in the organic solvent (v/v %) at 20°C. [b] Solubility at 22°C. [c] Prepared by a conventional method (4). [d] Measured by a photographic counting method.

compared with the solubility of chloroform and the other solvents (Table I). Therefore, the liberation of the aqueous solution, which acted as the collecting liquid for the crystals, appeared to occur less readily from 1-hexanol than chloroform. When a small amount of additional water (*e.g.*, 0.05 mL) was added to the 1-hexanol mixture during crystallization, (*e.g.*, at 2 h) the crystals agglomerated within several minutes.

When isopropyl acetate, isobutyl acetate, isoamyl acetate, benzene, or toluene were used, a part of the theophylline crystals remained undissolved. Since only dissolved theophylline presumably complexes with ethylenediamine, it is assumed that the undissolved theophylline dissolves as the complex precipitates. When using isopropyl acetate, 5 h were required.

When *n*-hexane or *n*-heptane were used, the spherically agglomerated crystals of theophylline formed immediately: the resultant crystals disintegrated into dispersed particles, and the spherically agglomerated crystals of the complex formed.

Physicochemical Properties of Spherically Agglomerated Crystals Prepared by Method 1—The representative photographs of the spherically agglomerated crystals and the theophylline-ethylenediamine complex (aminophylline) crystals, prepared in the conventional manner, are seen in Fig. 1.

The X-ray diffraction patterns of the agglomerated crystals, shown in Fig. 2, indicate that the agglomerates have three different crystalline forms, described here as the α-, β-, and γ-forms. The β-form was identical with aminophylline, while the patterns of the α- and γ-forms were different. The IR spectra of all the agglomerates were identical with that of aminophylline. The above IR and X-ray diffraction analyses suggested that the α- and γ-form of the agglomerated crystals were theophylline-ethylenediamine complexes with different crystalline forms.

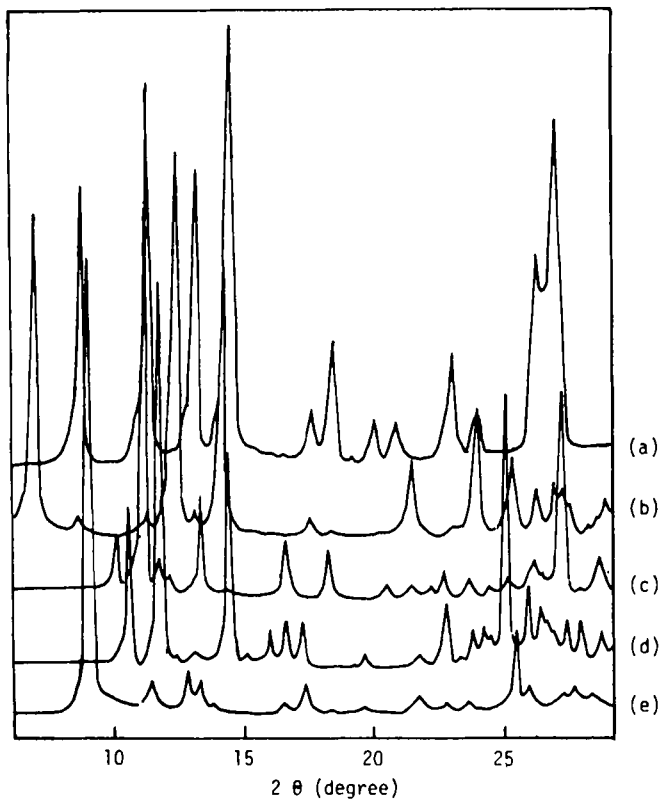

Figure 2—*X-ray powder diffraction patterns of agglomerates, anhydrous theophylline, theophylline monohydrate, and aminophylline. Key: (a) theophylline monohydrate; (b) anhydrous theophylline; (c) α-form of agglomerates; (d) β-form of agglomerates, aminophylline; (e) γ-form of agglomerates.*

The theophylline, ethylenediamine, and water content in the agglomerated crystals is tabulated in Table I. The water content in the agglomerates was classified in the following way: <0.5, 5-6, and 8-10%. Irrespective of the water content, the ratio of theophylline and ethylenediamine remained essentially the same. The water content of 4-6 and 8-10% correspond with ~1 and 2.5 mol of the water of crystallization, respectively, suggesting that the β- and γ-forms of the agglomerated crystals contained 1 and 2.5 mol of water of crystallization, respectively.

Differential scanning calorimetry (DSC) thermograms of the agglomerated crystals are shown in Fig. 3. The endothermic peak due to the release of 1 mol of ethylenediamine appeared at ~120°C and was detected by thermal gravimetry. The water of crystallization in the agglomerated crystals was released in a different way, depending on the crystalline form of the agglomerated crystals. In Table I, the amount of water required for obtaining the acceptable crystals having an average diameter of 0.81-1.55 mm are listed for the various organic solvents used. It was found that decreasing the solubility of water in the solvent decreased the amount of water required for the agglomeration, except for chloroform. This was explained by the fact that the agglomerates prepared using chloroform had higher amounts of water of crystallization (2.5 mol) than the other agglomerated crystals.

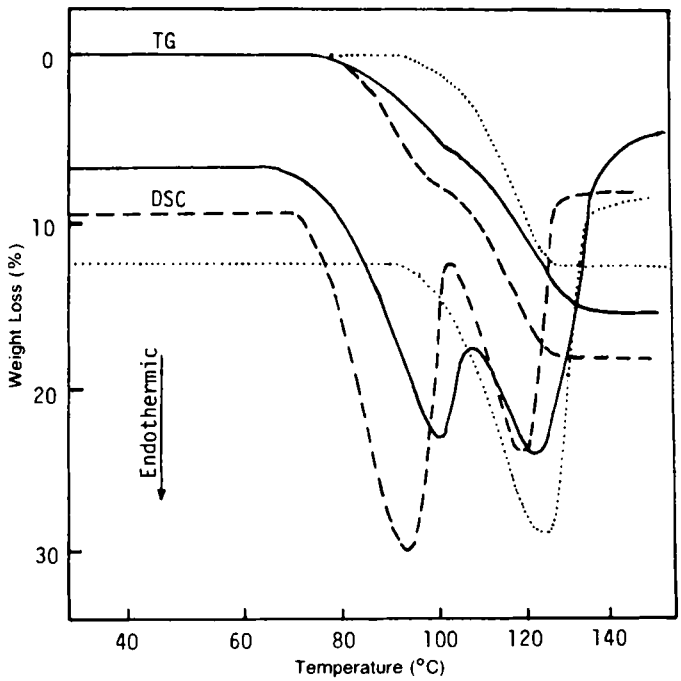

Figure 3—*DSC-TG thermograms of agglomerates and aminophylline. Key: (·····) α-form of agglomerates; (——) β-form of agglomerates, aminophylline; (- - -) γ-form of agglomerates.*

Table II—Effect of the Amounts of Ethylenediamine and Water on Theophylline and Ethylenediamine Contents in the Product

Ethylenediamine in the System, mL	Water in the System, mL	Drug and Water Contents in the Agglomerate, %			Average Diameter of Agglomerate, mm
		Theophylline	Ethylene-diamine	Water	
1.0	0.90	87.43	12.71	4.18	2.20
1.5	0.70	84.51	15.37	3.72	1.20
2.0	0.65	85.42	15.36	4.02	1.10
2.5	0.30	83.63	17.10	4.30	1.35
3.0	0.25	80.53	19.43	5.42	0.90
3.5	0.15	78.47	21.65	3.85	1.10

The theophylline and ethylenediamine content in the agglomerated crystals prepared using *n*-hexane, *n*-heptane, etc., in Table I, did not meet the specified values in JP(X), *i.e.*, 84–86% for theophylline and 14–15% for ethylenediamine. However, the theophylline and ethylenediamine contents in the resultant agglomerated crystals could be adjusted to the specified values in JP(X) by changing the amount of ethylenediamine used for the crystallization, as described below.

Spherical Crystallization Behavior of Method 2—To adjust the theophylline and ethylenediamine contents in the resultant agglomerated crystals to those specified in JP(X), the spherical crystallization was carried out by changing the amount of ethylenediamine (1.0–3.5 mL) and water (0.15–0.9 mL) in the mixture of *n*-hexane (60 mL) and ethanol (12 mL) used as the solvent. It was found that >1.1 mL (0.0165 mol) of ethylenediamine was required to obtain the theophylline-ethylenediamine complex. This critical amount of ethylenediamine corresponded to the amount required to obtain the molecular complex with 6 g of theophylline (0.0333 mol). When the amount of ethylenediamine used was <1.1 mL, the resultant agglomerated crystals were converted to anhydrous theophylline by washing with ethanol. This indicated that ethylenediamine was adsorbed physically on the theophylline crystals. When the ethylenediamine used was >1.1 mL, less water was required to obtain the spherically agglomerated crystals with a 1–2 mm diameter. The excess of ethylenediamine, >1.1 mL, was consumed as the collecting liquid for the crystals and was occluded physically in the agglomerates. The action of ethylenediamine as the collecting liquid was proved by the fact that the agglomerated crystals were prepared in the *n*-hexane (or *n*-heptane) and ethanol mixture with theophylline by adding ethylenediamine alone to the system without water. When the amount of water was <0.3 mL (0.0167 mol of water of crystallization) for 6 g theophylline (0.0333 mol), the water acted only as the collecting liquid for the crystals. When >0.3 mL of water was used, the water was occluded as water of crystallization (1 mol) and acted as the collecting liquid in the agglomerated crystals.

The amounts of ethylenediamine and water required to obtain the acceptable agglomerated crystals for practical use are plotted in Fig. 4. The straight line in Fig. 4 represents a phase separation line. In the region below the line, the solvents were miscible, and no agglomerates formed; whereas, in the region above the line, phase separation occurred and an aqueous solution of ethylenediamine was liberated, which collected the crystals to form the agglomerated crystals. The corrected points, obtained by subtracting the amount of ethylenediamine (1.1 mL, *i.e.*, 0.0165 mol) required to form the complex with theophylline (6 g, *i.e.*, 0.0333 mol) from that of ethylenediamine actually added to the system, lay on the phase separation line when the amount of water used was <0.3 mL. When the amount of water used was >0.3 mL, the corrected points deviated from the phase separation line. This indicated that the water was occluded as the collecting liquid as well as water of crystallization in the agglomerated crystals.

The ethylenediamine and theophylline contents in the agglomerated crystals, prepared using various amounts of ethylenediamine and water, are tabulated in Table II. The average diameter of the resultant agglomerates are also shown in Table II. The water contents in the agglomerates were almost constant, irrespective of the amount of water in the solvent mixture. The ethylenediamine content in the agglomerates increased with increases in the amount of ethylenediamine used. A linear relationship was found between the ethylenediamine content in the agglomerates and the amount of ethylenediamine used, as shown in Fig. 5. This indicated that the ethylenediamine contents in the agglomerated crystals could be adjusted to that of aminophylline specified in JP(X) by changing the amount of ethylenediamine used. The ethylenediamine >14.3% in the agglomerated crystals (corresponding to 1 mol of ethylenediamine included in aminophylline) was released by drastic desiccation, since it was adsorbed only physically.

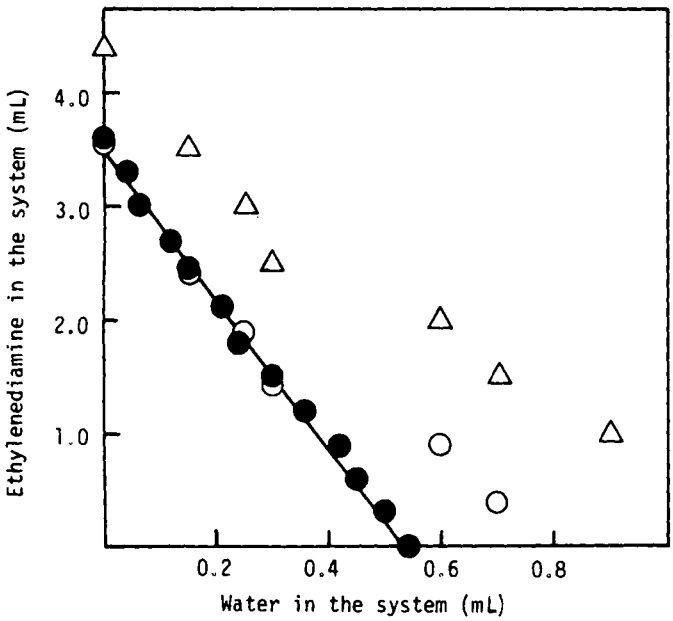

Figure 4—*Relationship between ethylenediamine and water in the system required for agglomeration and phase separation. Key: (△) agglomeration point; (●) phase separation point; (○) corrected point.*

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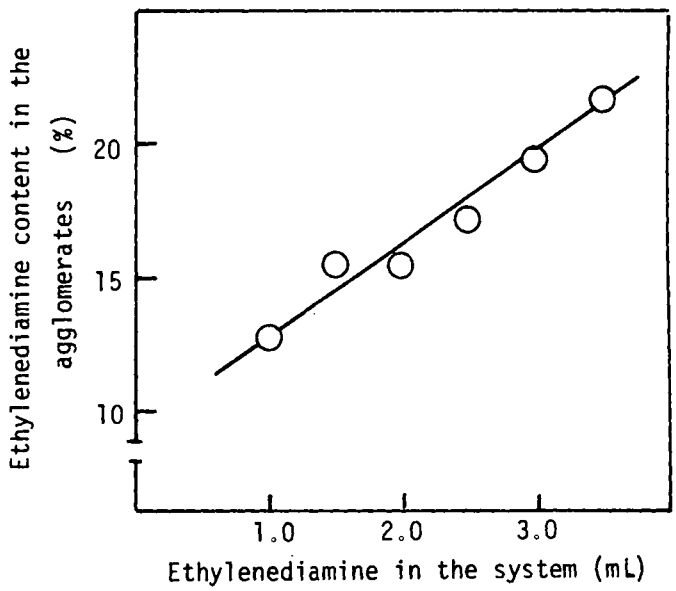

Figure 5—*Effect of the amount of ethylenediamine in the system on ethylenediamine content in the agglomerates.*

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

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

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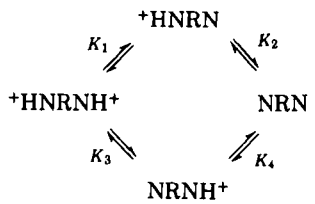
Abstract □ It is shown that the ionization constants of diacidic compounds can be determined by utilizing potentiometric titration data, even when a precipitate forms during the titration. The two methods presented are particularly useful for compounds for which the pK_a values are close together. A 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

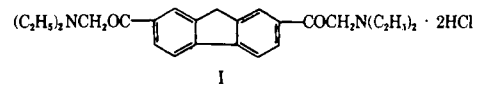
The microionization constants K_1, K_2, K_3, and K_4 are related to the macroionization constants by:

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

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

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).



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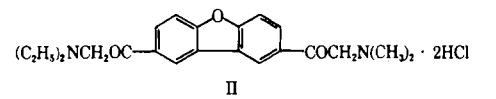

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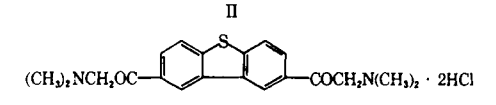

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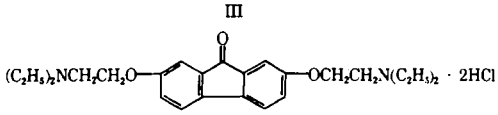

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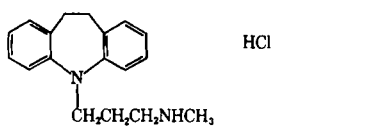

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