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Indirect Nonaqueous Titration of Hydrochlorides of Nitrogenous Bases

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Abstract □ An indirect nonaqueous titrimetric method was devised for the determination of the hydrochlorides of nitrogenous bases. The chloride-ion interference was prevented without the use of a mercuric acetate reagent. The method depends on the treatment of a solution of the hydrochloride of the organic base with an excess of standard aceteous perchloric acid solution and the hydrogen chloride displaced is removed by boiling. Residual excess perchloric acid is determined by titration against the basic titrant sodium acetate in glacial acetic acid, using either potentiometric or visual end-point detection with a crystal violet indicator. The proposed method was applied successfully to the determination of several hydrochlorides of nitrogenous bases. The mean percent recoveries obtained indicate that the proposed method is equivalent in accuracy and precision to the nonaqueous titrimetric method most commonly used by official compendia for this determination. Potentiometric titrations showed that the point of the maximum inflection in the titration curves coincided with the appearance of the violet color of the indicator.

Keyphrases □ Nitrogenous bases, hydrochlorides—indirect nonaqueous titration, method compared to compendial methods □ Nonaqueous titration, indirect—hydrochlorides of nitrogenous bases, compared to compendial methods □ Titrations, indirect nonaqueous—hydrochlorides of nitrogenous bases, compared to compendial methods

Many titrimetric methods have been developed for the determination of nitrogenous bases in aqueous solutions, and some have been accepted by various compendia. However, titrations of the nitrogenous bases in nonaqueous media allow much more accurate results and are quite simple. The nitrogenous bases may be extracted from an aqueous solution by a nonpolar solvent and determined directly without further isolation.

In the titration of the hydrochlorides of the nitrogenous bases in nonaqueous media, perchloric acid displaces hydrochloric acid from its salt. In an acetic acid medium, hydrogen chloride is only a little less acidic than perchloric acid, which makes the displacement reaction not quantitative and renders the method unsuitable for quantitative determination. Therefore, in the titration of the hydrochlorides of nitrogenous bases, there must be some specific technique to avoid the difficulty arising from the presence of the chloride ion.

Some procedures have been suggested to overcome this difficulty. An extraction titration method (1) was developed to determine a number of alkaloid hydrochlorides. Some hydrochlorides of nitrogenous bases were determined (2) by the titration of their acidic components against standard sodium methoxide solution in anhydrous pyridine.

A limited number of the hydrochlorides of organic bases and some alkali metals and ammonium halides were titrated directly in boiling glacial acetic acid against aceteous perchloric acid solution, using different indicators (3). The titrated solution had to be boiled to remove the hydrogen halides displaced during titration. However, no attempt was made to obtain extremely accurate quantitative results; rather, information was sought as to how some anions may influence analytical results.

An ingenious method was developed (4) for determining the hydrochlorides of nitrogenous bases in which the halide interference was prevented by using excess mercuric acetate reagent. The investigators used standard perchloric acid in dioxane as the titrant, with either potentiometric or visual end-point detection. This method has proved to be efficient for eliminating halide-ion interference and, therefore, has been adopted by many official compendia for the determination of the hydrochlorides of nitrogenous bases. The method has also been applied to the determination of some alkaloid halides (5, 6), using 0.01 *N* perchloric acid solution as the titrant and crystal violet as the indicator, and the hydrochlorides of several antihistamines (7) by potentiometric titration against standard tosylic acid solution in chloroform. The hydrochlorides of some phenothiazine derivatives were also determined (8) either in acetone using a mercuric acetate reagent or in a mixture of hexane and acetone after extracting the base from an aqueous potassium hydroxide solution.

In the present investigation, an indirect nonaque-

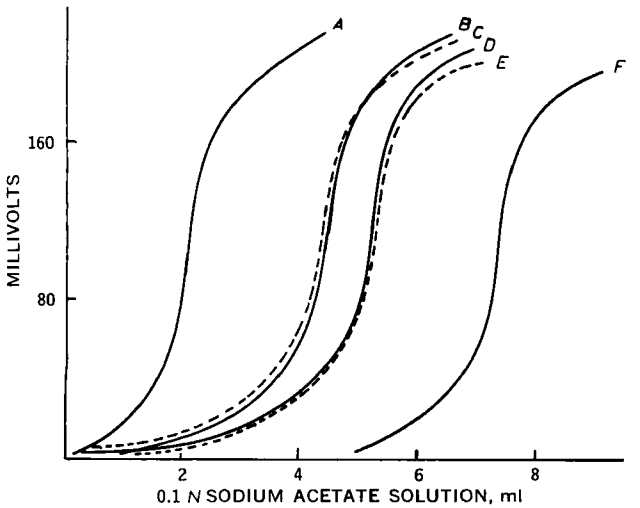

Figure 1—*Potentiometric titration of the hydrochlorides of the nitrogenous bases in glacial acetic acid by the proposed method. Key: A, quinine hydrochloride; B, ephedrine hydrochloride; C, phenylephrine hydrochloride; D, diphenhydramine hydrochloride; E, papaverine hydrochloride; and F, chlorpromazine hydrochloride.*

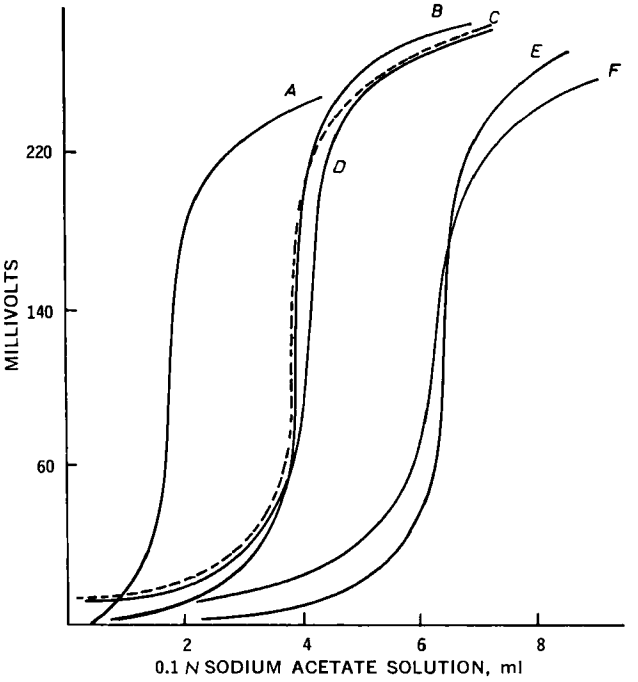

Figure 2—*Potentiometric titration of the hydrochlorides of the nitrogenous bases in dioxane–glacial acetic acid mixture by the proposed method. Key: A, quinine hydrochloride; B, ephedrine hydrochloride; C, diphenhydramine hydrochloride; D, phenylephrine hydrochloride; E, papaverine hydrochloride; and F, chlorpromazine hydrochloride.*

ous titrimetric method was devised for the determination of the hydrochlorides of nitrogenous bases in which the basic titrant sodium acetate was used. The difficulty arising from chloride ions was overcome without the use of a mercuric acetate reagent.

EXPERIMENTAL

Apparatus and Materials—The following were used: a suitable titrimeter[1] equipped with a combination electrode[2], a magnetic stirrer, a microburet (capacity 10 ml) graduated to 0.02 ml, glacial acetic acid[3], acetic anhydride[3], dioxane[4], 70% perchloric acid[5], mercuric acetate[5], ascorbic acid[6], sodium acetate[7], potassium acid phthalate[8], chlorpromazine hydrochloride[8], papaverine hydrochloride[9], ephedrine hydrochloride[9], quinine hydrochloride[10], diphenhydramine hydrochloride[11], and phenylephrine hydrochloride (BP grade).

Solutions—The following reagents were prepared in glacial acetic acid: 0.1 *N* perchloric acid solution, 0.1 *N* sodium acetate solution, 5% (w/v) mercuric acetate solution, and 0.2% (w/v) crystal violet indicator solution.

The perchloric acid solution was standardized by potentiometric titration against potassium acid phthalate, previously dried at 110° for 2 hr, in glacial acetic acid.

For comparison, the hydrochlorides of the nitrogenous bases investigated were determined by the method of Pifer and Wollish (4), where mercuric acetate was used to liberate the base. All investigated compounds behaved as monoacidic bases, taking up 1 equivalent of acid/mole, except quinine hydrochloride where 2 equivalents were taken up.

Determination of Hydrochlorides of Nitrogenous Bases by Proposed Indirect Method—The accurately weighed sample (50.0–400.0 mg) was placed in a 150-ml erlenmeyer flask with 40 ml of glacial acetic acid. The sample was allowed to dissolve with the aid of gentle heat, if necessary. A known excess of 0.1 *N* aceteous perchloric acid solution (10–20 ml) was added, and the flask was placed on a hot plate at 100–120° for 30 min. The solution was cooled, 2 drops of crystal violet indicator solution were added, and the titration was performed against 0.1 *N* aceteous sodium acetate solution to the first violet color change.

Potentiometric titrations were carried out in a 250-ml beaker. The solution, prepared as described and magnetically stirred, was titrated against standard aceteous sodium acetate solution. The end-point was determined from the inflection in the titration curve. The appearance of the violet color was found to coincide with the maximum change in millivolts reading. Potentiometric titrations were also performed in a glacial acetic acid–dioxane solvent system by adding an equal volume of dioxane to the contents of the beaker just before titration.

Determination of Chlorpromazine Hydrochloride—An accurately weighed sample of chlorpromazine hydrochloride (55.0–300.0 mg) was dissolved in 30 ml of glacial acetic acid. Standard aceteous perchloric acid solution was added and the solution was heated as mentioned previously. Ten milliliters of glacial acetic acid and enough ascorbic acid (1.0–3.0 g) to decolorize the developed red color (9) were added. The solution was titrated against standard aceteous sodium acetate solution using crystal violet indicator as mentioned.

RESULTS AND DISCUSSION

The most commonly used method for the determination of the hydrochlorides of nitrogenous bases is that of Pifer and Wollish (4). This method has been adopted by official compendia such as USP XVIII (10), BP 1968 (11), and NF XIII (12) for the determination of many hydrochlorides of organic bases. According to this method, the use of mercuric acetate, which binds the halide ion present, thus liberating the nitrogenous base, is necessary to make the acid–base reaction between perchloric acid and the hydrochloride of the organic base quantitative. The resulting mercuric halide and the excess mercuric acetate, both being nonionized, do not interfere with the determination.

However, in the proposed method the liberation of the base (B) from its hydrochloride salt is achieved by heating the salt under investigation with an excess of 0.1 *N* aceteous perchloric acid solution, whereby the base perchlorate and hydrogen chloride are

[1] Pye model 79.
[2] Pye catalog No. 461 E07, series No. 546022.
[3] El-Nasr Pharmaceutical Chemicals Co., A.R.E.
[4] VEB Laborchemie Apolda, Germany.
[5] Merck.
[6] Roche.
[7] British Drug Houses Ltd., England.
[8] Rhone-Poulenc, France.
[9] Chemishe Fabriken, Ludwigshafen am Rhein.
[10] Carnegies of Welwyn Ltd., England.
[11] Kongo Chemicals Co., Japan.

Table I—Nonaqueous Titration of Hydrochlorides of Nitrogenous Bases by Proposed Indirect Method and the Direct Method[a]

Proposed Indirect Method			Direct Method		
Weight, mg	Weight Found, mg	Recovery, %	Weight, mg	Weight Found, mg	Recovery, %
		Papaverine Hydrochloride			
404.0	401.4	99.36	403.2	399.1	98.98
299.7	301.1	100.47	198.5	196.9	99.19
200.4	201.1	100.35	142.5	142.0	99.65
154.9	155.6	100.45	89.9	89.4	99.44
95.7	95.7	100.00			
59.5	60.0	100.84			
Mean percent recovery (p' = 0.05) 100.24 ± 0.53			Mean percent recovery (p' = 0.05) 99.31 ± 0.47		
		Quinine Hydrochloride			
302.6	300.6	99.34	406.1	412.8	101.65
154.7	154.4	99.81	302.2	306.9	101.55
151.8	152.0	100.13	165.3	167.5	101.33
103.0	105.1	102.04	100.0	101.6	101.60
102.7	105.1	102.34	54.4	55.2	101.47
50.0	49.9	99.80			
Mean percent recovery (p' = 0.05) 100.58 ± 1.34			Mean percent recovery (p' = 0.05) 101.52 ± 0.15		
		Ephedrine Hydrochloride			
200.6	198.9	99.15	201.2	198.4	98.61
152.3	150.7	98.95	164.0	162.8	99.27
121.0	121.2	100.16	118.3	117.3	99.15
101.8	102.6	100.78	100.8	99.4	98.61
52.7	52.3	99.24	68.5	67.7	98.83
			51.0	50.8	99.62
Mean percent recovery (p' = 0.05) 99.66 ± 0.97			Mean percent recovery (p' = 0.05) 99.01 ± 0.42		
		Diphenhydramine Hydrochloride			
272.7	273.7	100.37	309.3	307.2	99.32
193.1	191.9	99.38	212.7	213.1	100.19
134.0	132.1	98.58	175.1	175.7	100.34
105.0	103.7	98.76	153.5	154.3	100.52
56.0	55.3	98.75	104.5	105.1	100.57
			76.5	77.1	100.78
Mean percent recovery (p' = 0.05) 99.17 ± 0.91			Mean percent recovery (p' = 0.05) 100.29 ± 0.54		
		Phenylephrine Hydrochloride			
300.0	299.7	99.90	272.3	271.2	99.60
198.8	197.2	99.19	211.3	210.2	99.67
158.7	157.2	99.05	162.5	161.5	99.38
121.3	121.6	100.25	125.6	125.6	100.00
100.0	99.3	99.30	80.2	79.9	99.62
			64.5	65.0	100.77
Mean percent recovery (p' = 0.05) 99.54 ± 0.64			Mean percent recovery (p' = 0.05) 99.84 ± 0.52		

[a] Pifer and Wollish method, Ref. 4.

formed (Scheme I).

$$BH^+Cl^- + HClO_4 \rightleftharpoons BH^+ClO_4^- + HCl$$

Scheme I

The thermodynamic activity of hydrogen chloride at any given concentration in glacial acetic acid is much higher than that in water (3) and, therefore, volatilization from such a nonaqueous solvent takes place more readily. Under the conditions of the proposed method, the liberated hydrogen chloride is readily removed by volatilization as it is formed, thus making the reaction between the base and the protonated acetic acid quantitative. The protonated acetic acid formed by the reaction of perchloric acid with this solvent (Scheme II) is a stronger acid than the conjugate acid of the titrated base, consequently acting effectively as a proton donor when titrated with standard sodium acetate solution.

$$CH_3COOH + HClO_4 \rightleftharpoons CH_3COOH_2^+ClO_4^-$$

Scheme II

An indicator that fulfills the requirement that its pK_1 value lies midway between the pKa values of the conjugate acids of the titrated bases and the protonated acetic acid will be suitable to effect titration of these bases visually (3).

In the direct titration of the hydrochlorides of nitrogenous bases, apart from the type of solvent and standard solution employed, the main factors influencing the shape of the potentiometric titration curve and hence the sharpness of the color change of the indicator are the strength and concentration of the base being titrated. Since the indirect proposed procedure involves the titration of excess standard perchloric acid against standard sodium acetate solution irrespective of the base titrated, the method has the advantage that the strength and concentration of the base play a minor role in determining the sharpness of the indicator color change as well as the magnitude of potential break in the titration curve.

The potentiometric titration curves of the compounds studied in glacial acetic acid and in dioxane–glacial acetic acid mixture are shown in Figs. 1 and 2, respectively. In glacial acetic acid solvent the magnitudes of the breaks at the end-point range from 200 to 250 mv/ml of titrant and the shapes of the curves are identical. In dioxane–glacial acetic acid mixture, however, the magnitudes are

Table II—Determination of Chlorpromazine Hydrochloride According to Proposed Indirect Method, Direct Method of USP XVIII, and BP 1968 Method

Number	Weight, mg	Weight Found, mg	Recovery, %	USP XVIII[a]	BP 1968[a]
1	299.5	297.9	99.46		
2	196.9	198.9	101.01		
3	139.6	138.8	99.43		
4	102.8	104.0	101.17		
5	57.2	56.7	99.12		
Mean percent recovery ($p' = 0.05$)		100.04 ± 1.20		100.70 ± 0.81	100.57 ± 1.05

[a] Mean percent recoveries were calculated from five determinations; data were reported by the authors in Ref. 9.

higher, ranging from 670 to 810 mv/ml, and the shapes are also almost identical. Such a narrow range of potential breaks and identical shapes of titration curves in each solvent system may support the fact that in the proposed method the shape of the curve, the magnitude of its break, and, hence, the sharpness of the indicator color change at the end-point are independent of the strength and the concentration of the base under investigation.

In addition, the proposed method has the advantage that it does not necessitate the use of mercuric acetate to liberate the base from its hydrochloride salt as in the Pifer and Wollish method (4). The repeated heating in the course of titration (3) has also been avoided.

The proposed method and the Pifer and Wollish (4) method were applied to the determination of the hydrochlorides of papaverine, quinine, ephedrine, diphenhydramine, phenylephrine, and chlorpromazine, which represent some general chemical structures having different pharmacological actions (Tables I and II). The mean percent recoveries ($p' = 0.05$) obtained by applying the proposed method to the determination of the hydrochlorides of papaverine, quinine, ephedrine, diphenhydramine, and phenylephrine were 100.24 ± 0.53, 100.58 ± 1.34, 99.66 ± 0.97, 99.17 ± 0.91, and 99.54 ± 0.64, respectively, compared with 99.31 ± 0.47, 101.52 ± 0.15, 99.01 ± 0.42, 100.29 ± 0.54, and 99.84 ± 0.52, respectively, when the Pifer and Wollish method was applied.

The determination of chlorpromazine hydrochloride was carried out according to the proposed method. However, ascorbic acid was used (9), as mentioned under *Experimental*, to prevent the formation of the red-colored semiquinoid free radical which interferes with the visual end-point detection. The data obtained are listed in Table II. A mean percent recovery of 100.04 ± 1.2 was obtained compared with 100.70 ± 0.81 and 100.57 ± 1.05 when the Pifer and Wollish method, adopted by the USP XVIII (10), and the BP 1968 method, respectively, were employed. Statistical analysis of the data listed in Tables I and II indicated that the proposed method is almost equivalent in accuracy and precision to the Pifer and Wollish method.

It is advisable that the number of equivalents of standard perchloric acid be twice that of the hydrochloride of the nitrogenous base to be determined. When the weights of the hydrochlorides of papaverine, quinine, and phenylephrine are larger than 400 mg, caution should be exercised not to exceed the 30-min heating time with perchloric acid; otherwise the titrated solution may develop a yellow color which may interfere with the visual detection of the end-point. However, in all cases the heating time should not be less than 15 min.

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