

# THE DIRECT ESTIMATION OF THE BASE CONTENTS OF ALKALOIDAL HALIDES

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Received June 3, 1952

It is well known that acetic acid is a suitable solvent for acidimetric titration of bases too weak to be titrated in aqueous solution. The titrations are usually carried out with perchloric acid which is the strongest acid known in this solvent. The method generally used has recently been discussed by Ekeblad<sup>1</sup> who introduced some new indicators. A complete review of the literature on the method is given by Riddick.<sup>2</sup>

This "acetous perchloric acid method" also permits a direct titration of many organic and inorganic salts. Even salts of such strong acids as nitric and phosphoric can be titrated in this way and sulphates can be titrated to acid sulphates. Recently, work on this line has been published by Higuchi and Concha.<sup>3</sup>

The hydrogen halides in acetic acid, however, are too strong acids to allow a direct titration of their salts. Two different ways have been proposed to overcome this difficulty.

Higuchi and Concha<sup>4</sup> boiled the solutions during the titration in order to remove the undissociated hydrogen halide, a method analogous to the accurate titration of carbonates in aqueous solution. However, this method offers difficulties in practice, and many organic compounds are decomposed during the heating.

Pifer and Woolish<sup>5</sup> converted the halide salts into acetates by adding an excess of mercuric acetate dissolved in acetic acid. The mercuric acetate and the mercuric halides are practically undissociated in acetic acid solution and do not react with the perchloric acid. The authors titrated the halide salts in acetic acid solution but a 0.1N solution of perchloric acid in dioxan was used for the titration. The end-points were usually indicated potentiometrically. In some cases visual end-point determinations with crystal violet were possible.

This method *inter alia* permits a rapid estimation of the base content in samples of alkaloidal halides without previous separation of the base. As the procedure described by Pifer and Woolish requires rather large quantities of the solvents and as the solution of perchloric acid in dioxan has to be standardised daily, a modified method has been worked out in this laboratory which permits the titration to be made with a solution of perchloric acid in acetic acid. With this method most alkaloidal halides can be titrated visually with the indicator Blue BZL previously proposed.<sup>1</sup>

## TITRATIONS WITH 0.1N PERCHLORIC ACID

### *Reagents used.*

*Anhydrous acetic acid.* Acetic acid of pharmacopœia quality and containing less than 0.15 per cent. of water when determined by the Karl

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Fischer method. The water in the commercial acetic acid is readily removed by the freezing-out method.

*0.1N acetous perchloric acid.* 14.3 g. of 70 per cent. aqueous perchloric acid is diluted with 200 ml. of anhydrous acetic acid. 31 g. of acetic anhydride is added and the solution diluted with anhydrous acetic acid to 1 l. After 1 day the solution should contain less than 0.05 per cent. of water, determined by the Karl Fischer method. If not, more acetic anhydride must be added. 1 g. of water is equivalent to 5.7 g. of acetic anhydride. If the solution contains no titratable amount of water, 0.02 per cent. of water must be added and a new water determination is made after 1 day. Even a slight excess of acetic anhydride can interfere with the titration of primary and secondary amines.

*Blue BZL solution.* Dissolve 0.5 g. of blue BZL (a dye from Ciba, Basle, catalogue number CIBA 22062 S), in 100 ml. of anhydrous acetic acid.

*Crystal violet solution.* Dissolve 0.5 g. of crystal violet, hexamethyl-*p*-rosaniline chloride, in 100 ml. of anhydrous acetic acid.

*Acetous mercuric acetate solution.* 3 per cent. w/v solution of reagent grade mercuric acetate in anhydrous acetic acid. The solution can easily be prepared without heating. The solution should comply with the following test:—to 10 ml. of acetous mercuric acetate solution add 2 drops of Blue BZL solution; not more than 0.02 ml. of 0.1N acetous perchloric acid should be needed to change the colour from blue to violet or red.

The acetous mercuric acetate solution is approximately 0.2N and can be used as solvent for the salts being titrated. Usually the salts are dissolved in such proportion that the solution is 0.1N with respect to the salt. About 50 per cent. of the mercuric acetate is thus converted into the mercuric halide.

### *Procedure.*

*Standardisation of the acetous perchloric acid.* The perchloric acid is standardised against potassium acid phthalate. 0.4000 g. of potassium acid phthalate is dissolved by heating in 20 ml. of anhydrous acetic acid. When acetic acid solutions are heated silica gel tubes must always be used to prevent adsorption of moisture from the air. After cooling, 1 drop of crystal violet solution is added and the solution is titrated with the perchloric acid. The first colour change from violet to blue is the end-point. The equivalent weight of potassium acid phthalate is 204.2.

*Titration of halide salts.* The accuracy of the method is demonstrated in Table I by two titrations on pure sodium chloride (the argentimetric standard substance of Ph. Suec. Ed. XI). The sodium chloride was dissolved by boiling in 20 ml. or 10 ml. of the acetous mercuric acetate solution. After cooling to room temperature and adding 2 drops of the Blue BZL solution, the solutions were titrated with the acetous perchloric acid.

In Table II are listed results from titrations of some alkaloidal salts. The results are expressed in percentage of anhydrous salt found. In those cases

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TABLE I  
TITRATION OF SODIUM CHLORIDE

Amount weighed mg.	0.0989N perchloric acid ml.	Amount recovered mg.
101.6	17.59	101.7
57.2	9.91	57.3

where the samples contained water it was determined by the Karl Fischer method. Amounts corresponding to approximately 10 ml. of 0.1N acetous perchloric acid have been used. The salts were first dissolved or suspended in 2 to 5 ml. of anhydrous acetic acid. When 10 ml. of the acetous mercuric acetate solution was added most of the samples insoluble in acetic acid dissolved rapidly. In a few cases gentle heating was required to obtain complete solution. 2 drops of the Blue BZL solution were used. Generally, this indicator gives a distinct colour change from blue to red at the end-point. In some cases, however, especially when precipitation occurs, the colour change may not be sharp. In these cases the titrations have been carried out to an intermediate reddish violet colour. Even in these cases (e.g., morphine hydrochloride) the accuracy of the results is sufficient for practical purposes.

TABLE II

Sample	Amount g.	Perchloric acid		Anhydrous salt per cent.	Water (Karl Fischer) per cent.	Anhydrous salt + water per cent.
		ml.	normality			
Æthylmorphine hydrochloride.	0.4660	12.18	0.0989	90.45	90.5	9.7
	0.4606	12.05	0.0989	90.53		
	0.3826	9.50	0.1041	90.44		
" "	0.3997	9.97	0.1041	90.86	90.7	9.4
	0.3814	9.50	0.1042	99.74		
	0.4193	10.45	0.1042	99.80		
Atropine methobromide.	0.3814	9.50	0.1042	99.74	99.8	---
	0.4193	10.45	0.1042	99.80		
Carbacholum.	0.2344	12.28	0.1041	99.61	99.7	---
	0.2159	11.34	0.1041	99.87		
Cocaine hydrochloride.	0.3460	9.66	0.1041	98.76	98.7	0
	0.3987	11.12	0.1041	98.66		
" "	0.3530	9.89	0.1041	99.10	99.1	0
	0.3469	9.71	0.1041	99.01		
Ephedrine hydrochloride.	0.1785	8.46	0.1041	99.53	99.7	---
	0.2006	9.54	0.1041	99.87		
" "	0.2146	10.19	0.1041	99.70	99.7	---
	0.1830	9.69	0.1041	99.71		
Hyoscine hydrobromide.	0.3513	7.66	0.1041	87.2	85.9	11.7
	0.4106	10.50	0.1042	85.75		
Morphine hydrochloride.	0.4177	10.72	0.1042	86.06	85.9	14.2
	0.4497	9.66	0.0989	95.58		
Narcotine hydrochloride.	0.4605	9.91	0.0989	95.75	95.7	3.9
	0.3961	9.78	0.0988	85.84		
Oxicon hydrochloride (Eukodal).	0.3595	8.84	0.0988	85.49	85.7	14.6
	0.3686	8.64	0.1041	85.85		
" "	0.3503	8.25	0.1041	86.25	86.1	13.8
	0.4467	11.35	0.1041	99.41		
Papaverine hydrochloride.	0.3574	9.11	0.1041	99.73	99.6	---
	0.4061	10.38	0.1041	100.00		
" "	0.3725	9.53	0.1041	100.10	100.1	---
	0.2709	10.59	0.1040	99.49		
Pilocarpine hydrochloride.	0.2537	9.93	0.1040	99.61	99.6	---
	0.2830	11.06	0.1040	99.46		
" "	0.2547	10.00	0.1040	99.92	99.7	---
	0.2090	9.76	0.1041	99.95		
Pyridoxine hydrochloride.	0.2028	9.51	0.1041	100.37	100.2	---

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### TITRATIONS WITH 0·01N PERCHLORIC ACID

Procedures for titration of amines in acetic acid with 0·01N perchloric acid have been described by Keen and Fritz.<sup>6</sup> These authors use methyl violet for visual titrations, titrating to a clear blue colour. When titrating halide salts on this scale, the mercuric acetate solution may have a blank value of importance. As the colour change intervals of acid-base indicators in acetic acid are greatly affected by changes in the ionic strength, the correction obtained is not reliable even if a blank is run on the reagents. In the procedure described below, this difficulty is overcome by a previous "neutralisation" of the mercuric acetate solution at approximately the same ionic strength as in the titration.

#### *Reagents used.*

*0·01N acetous perchloric acid.* 1·43 g. of 70 per cent. aqueous perchloric acid is diluted with anhydrous acetic acid to 1 l. The water content is adjusted to less than 0·05 per cent. in the same manner as described above for the 0·1N acetous perchloric acid.

*Crystal violet solution.* A 0·05 per cent. solution in anhydrous acetic acid.

*Mercuric acetate—R.* To 100 ml. of the acetous mercuric acetate solution described above are added 10 ml. of a 0·1N triethylamine solution in anhydrous acetic acid\* and 5 ml. of the crystal violet solution. 0·1N acetous perchloric acid is added till the first change to green occurs in the intermediate blue colour.

#### *Procedure.*

*Standardisation of the acetous perchloric acid.* The 0·01N acetous perchloric acid is standardised against potassium acid phthalate (Table III). The weighed quantity of potassium acid phthalate is dissolved by heating in 2 ml. of anhydrous acetic acid. After cooling, 1 drop of the crystal violet solution is added, and the solution is titrated with 0·01N perchloric acid to a clear blue colour.

TABLE III  
STANDARDISATION OF THE 0·01N ACETOUS PERCHLORIC ACID AGAINST  
POTASSIUM ACID PHTHALATE

Amount weighed mg.	Perchloric acid used ml.	Normality found
35·17 40·54	16·58 19·09	0·010388 0·010400
Normality: 0·01039		

The standardisation was carried out at 21° C. As the coefficient of cubic expansion of acetic acid is about 0·001 per ° C. and the following titrations were carried out at 20° C., the normality was corrected to 0·01040.

*Titration of halide salts.* Aureomycin hydrochloride, diphenhydramine hydrochloride, terramycin hydrochloride, and tubocurarine chloride were

\* This solution is used in this laboratory as the standard base solution for back titrations in the acetous perchloric acid method.

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selected for testing the method on this scale. The following procedure was used. An amount corresponding to not more than 10 ml. of the 0.01N perchloric acid was weighed and suspended in 1 ml. of anhydrous acetic acid. 1 ml. of mercuric acetate R was added. The solution obtained was titrated to the first change to green in the intermediate blue colour. In the titration of terramycin hydrochloride it was necessary, due to the yellow colour of the compound, to add 2 drops of the crystal violet solution and titrate till no red tint could be seen in the green colour. Aureomycin hydrochloride failed to dissolve on the addition of mercuric acetate, and reproducible results were not obtained with this substance.

TABLE IV  
DIPHENHYDRAMINE HYDROCHLORIDE  
Equivalent weight: 291.8

Amount weighed mg.	0.01040N perchloric acid ml.	Found per cent.
29.78	9.78	99.7
32.49	10.70	99.9

TABLE V  
TERRAMYCIN HYDROCHLORIDE, CRYSTALLINE  
Molecular weight: 499 ( $\pm 5$ ).  
The sample contained 3.4 per cent. of water (Karl Fischer method)

Amount weighed mg.	0.01040N perchloric acid ml.	Equivalent weight found (calculated on anhydrous basis)
39.79	7.32	504.9
36.81	6.71	509.5

TABLE VI  
TUBOCURARINE CHLORIDE  
Equivalent weight of anhydrous salt: 347.8.  
The sample contained 6.0 per cent. of water (Karl Fischer method).

Amount weighed mg.	0.01040N perchloric acid ml.	Anhydrous salt found per cent.
31.49	8.25	94.8
29.28	7.59	93.8
Mean value 94.3		

My thanks are due to Dr. T. Canbäck, Head of this Laboratory, for valuable suggestions and discussions during the work.

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