THE NON-AQUEOUS TITRATION OF PHENOLIC COMPOUNDS

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The published methods for the titration of very weak acids are reviewed and the choice of a suitable solvent, electrode system and titrant discussed. Ethylenediamine as a solvent is rejected for routine purposes because it is toxic and unpleasant in use. Dimethylformamide is a suitable solvent for phenolic substances and gives a titration curve with a step at the end point of at least 75 mV. This is nearly the bottom limit of practicability, using tetrabutylammonium hydroxide in benzene and methanol as titrant. The electrode system preferred for its reliability is a glass indicator electrode and a saturated calomel half cell, slightly modified, as reference electrode.

THE volumetric determination of very weak acids by titration in non-aqueous solvents has been investigated by a number of workers, the earliest successful method being that of Moss, Elliott and Hall[1] in 1948 using ethylenediamine as solvent and a solution of sodium aminoethoxide in ethylenediamine as titrant. Since that time, a number of different solvents and titrants have been proposed and the use of various electrode systems has been reported.

The purpose of this paper is to present a procedure for the potentiometric determination of very weak acids that is simple, convenient and sufficiently reliable for routine use. No attempt has been made to use visual indicators because the change in e.m.f. at the end point of the average titration is considered to be too low to give a sharp colour change.

Electrodes

The choice of a suitable electrode system presents difficulties when ethylenediamine is used. Moss, Elliott and Hall[1] used an antimony indicator electrode with a second antimony electrode immersed in the titrant stream, electrical connection being maintained by allowing the tip of the burette jet to dip below the surface of the solution being titrated. A hydrogen indicating electrode was also found to be satisfactory with the antimony reference electrode, while a calomel reference electrode was considered to be less convenient. The glass electrode does not respond to changes in acidity in ethylenediamine in the presence of sodium ions and in fact, Katz and Glenn[2] have used it as a reference electrode under these conditions, with antimony or platinum as indicating electrode. Sprengling[3] found difficulty in obtaining reproducible curves with the antimony indicating electrode using ethylenediamine and benzene with *iso*propyl alcohol as solvents, while Gran and Althin[4] reported that they had been unable to obtained good indication of end points with either the antimony or the platinum electrodes systems used by Moss, Elliott and Hall.

We have found the antimony:antimony system unreliable and the observed variability does not appear to be dependent on the solvent or titrant chosen, replicates of the same titration often giving different titration curves.

In a suitable solvent system, the glass electrode as indicating electrode is the most stable and reproducible of those examined and, in our hands, the saturated calomel electrode is the most convenient and reliable reference electrode. Gran and Althin[4] devised a non-aqueous "calomel electrode" for use as a reference in titrations in ethylenediamine with bright platinum as indicating electrode. This employed ethylenediamine saturated with mercurous chloride and lithium chloride in place of the usual aqueous potassium chloride. We have used an electrode prepared on similar lines, but found in a variety of titrations that the curves showed shallower steps than with a conventional sleeve-type calomel electrode. This latter type of reference electrode has been used throughout the work described in this paper and for routine application it is useful to separate the ground sleeve from the main bulk of potassium chloride in the body of the electrode vessel with a plug of Gooch asbestos drawn into the capillary by suction.

Solvent

Ethylenediamine is the solvent of choice for the titration of very weak acids but for routine use, its highly unpleasant nature makes it desirable to find a satisfactory alternative. *n*-Butylamine and dimethylformamide are less basic than ethylenediamine, but dimethylformamide in particular seems suitable for the titration of all but the most weakly acidic phenols. In addition, it appears to be a better solvent than either ethylenediamine or *n*-butylamine for phenolates; many of the phenols examined give a precipitate during titration in ethylenediamine, even with an ammonium type base as titrant. Purification of ethylenediamine by distillation before use is essential, and should be repeated weekly. Dimethylformamide is more stable and can be treated as later described.

Titrant

Alkali methoxides have been widely used as basic titrants in non-aqueous solvents, the sodium, potassium or lithium methoxides dissolved in the minimum of methanol and diluted with a neutral solvent such as benzene, being usually chosen. Cundiff and Markunas[5] have discussed the disadvantages of these titrants, one of which is the formation of gelatinous precipitates during a titration which obscure the end point. Sodium aminoethoxide was recommended by Moss Elliott and Hall[1] but this is troublesome to prepare and uses ethylenediamine as solvent. Deal and Wyld[6] recommended the use of tetrabutylammonium hydroxide to overcome the problem of precipitation, but this use was not strictly non-aqueous, since an *iso*propyl alcohol and water mixture was used as solvent. Harlow, Noble and Wyld[7] extended the work of Deal and Wyld, but still retained *iso*propyl alcohol as solvent. Cundiff and Markunas[5]

investigated the potentialities of this titrant quite extensively, using benzene as solvent with the addition of sufficient methanol to keep the quaternary base in solution. Recently van der Heijde and Dahmen[8] used tetrabutylammonium hydroxide in pyridine, and found it necessary to store it at −20° to avoid decomposition of the solution due to the Hoffmann degradation. We find that dimethylformamide is a good solvent for the base, but, after an induction period of about 2 hours decomposition takes place at room temperature. Any other conditions of storage are out of the question for a titrant for general use and, therefore, we have employed the solution of tetrabutylammonium hydroxide in benzene and methanol described by Cundiff and Markunas[5]; this is stable if stored so as to minimise the absorption of carbon dioxide.

Apparatus

The titration vessel comprises a 50 or 100 ml. tallform beaker closed with a cork shive; rubber is attacked by dimethylformamide. Three holes in the shive take respectively the two electrodes and the tip of the burette. Magnetic stirring is employed. When working on N/25 scale or weaker it is advisable to flush the vessel and contents with nitrogen; no elaborate precautions to exclude moisture or carbon dioxide during the course of the titration are necessary when using solutions stronger than N/50. The burette is conveniently a 10-ml. micro burette graduated to 0·05 ml. In our experiments, the cell e.m.f. was measured with a Pye direct reading pH meter with a glass and calomel electrode system. The calomel half cell used is described above and the conventional glass electrode was immersed in dimethylformamide for 24 hours before use. One electrode should be kept for this type of work exclusively and stored in dimethylformamide.

Reagents

Dimethylformamide. The pure grade of this solvent should be neutralised to the blue colour of azo violet and it is then suitable for immediate use if the titration is carried out on the deci-normal scale. The blank titration on an average sample should not exceed 0·8–1·0 ml. 0·1N base per 100 ml. For use in smaller scale titrations, the dimethylformamide should be shaken occasionally during 24 hours with barium oxide and redistilled; after this treatment the solvent can be stored in a well filled glass-stoppered bottle for some weeks without development of more than a trace of acidity.

Benzene Analar grade used without further treatment.

Methanol B.P.C. is distilled from sodium metal.

Tetrabutylammonium hydroxide is prepared from the iodide by the method of Cundiff and Markunas[5]. A solution so prepared is approximately 0·1N and can be standardised by titrating a known weight of pure dry benzoic acid dissolved in dimethylformamide using a glass:calomel electrode system, the end point being indicated by a large increase in e.m.f. (about 500 mV. on the addition of about 0·1 ml. of tetrabutylammonium hydroxide solution).

Harlow, Noble and Wyld[7] have stated that the quaternary hydroxide may be prepared from the iodide by passing a methanol solution of the latter through a strongly basic exchange resin in the form of its free base. We have experienced difficulty in obtaining reasonable yields by this method; also the resin could not be regenerated.

General Method

Dissolve an accurately weighed quantity of the compound in neutralised dimethylformamide in a volumetric flask and dilute to volume. Transfer a suitable aliquot, equivalent to about 0·5 mg. equivalent of the phenol, to the titration vessel and dilute to about 25 ml. with neutralised dimethylformamide. Titrate potentiometrically with 0·1N tetrabutylammonium hydroxide in benzene and methanol, stirring constantly and plot the

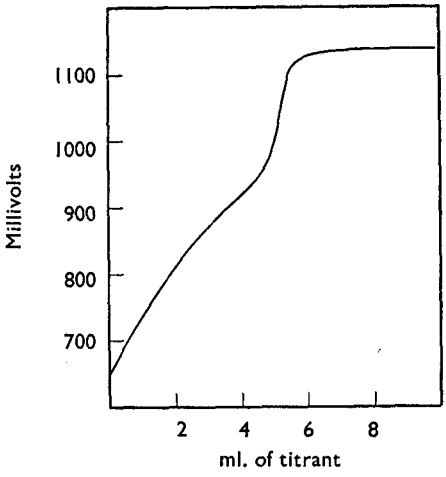

FIG. 1. Titration curve of phenol.

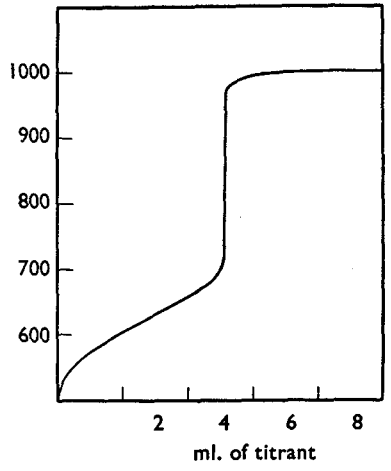

FIG. 2. Titration curve of vanillin.

titration curve. Determine the end point either by geometrical construction or by inspection. For routine purposes, the end point can be selected by calculating $\Delta E/\Delta V.$, or by plotting the differential curve.

Discussion

Figures 1–2 show typical titration curves. The rather steep slope of that part of the curves preceding the end point is characteristic of this solvent-electrode system. The height of the step in the e.m.f. to volume of titrant curve is about 100 to 150 mV. for most of the phenolic compounds examined. Some, like resorcinol give a step of about 75 mV., which is approaching the lower limit of practicability while for others the step height might reach 300 to 400 mV. Picric acid, a relatively strong acid, gives a potential change at end point over practically the whole range of the solvent, producing a step of nearly 1·5 V.

The superiority of tetrabutylammonium hydroxide as a titrant for phenolic compounds in dimethylformamide with the glass and calomel

electrode system is shown by the increased step height obtained compared with the more usual alkali methoxide solution. Thus, a number of compounds have been titrated with tetrabutylammonium hydroxide in benzene and methanol and with lithium methoxide in the same solvent with the results shown in Table I.

TABLE I

TITRATION OF PHENOLIC COMPOUNDS WITH TETRABUTYLAMMONIUM HYDROXIDE IN BENZENE AND METHANOL AND WITH LITHIUM METHOXIDE IN THE SAME SOLVENT

Compound	Step height, mV.	
	Tetrabutylammonium hydroxide	Lithium methoxide
Phenol	125	25
Resorcinol	75	10
n-Propyl *p*-hydroxybenzoate	300	50
Picric acid	1400	1200
Eugenol	100	15

Table II gives the step heights obtained with the phenolic oestrogens. Each of the three synthetic hormones, although dihydroxy compounds, give only one step, corresponding to the titration of a single phenolic group.

TABLE II

STEP HEIGHTS OBTAINED WITH PHENOLIC OESTROGENS

Compound	Step height, mV.
Stilboestrol	140
Hexoestrol	125
Dienoestrol	120
Oestradiol	100
Oestrone	160
Ethinyloestradiol	100

TABLE III

STEP HEIGHTS OF PHENOLIC COMPOUNDS SUCCESSFULLY TITRATED WITH TETRABUTYLAMMONIUM HYDROXIDE

Compound	Step height, mV.
Phenol	125
Cresol, mixed isomers	150
4-Chloro-3-cresol	180
4-Chloro-3 : 5-xylenol	200
Eugenol (4-allyl-2-methoxy-phenol)	110
Thymol	120
Vanillin	300
Resorcinol	75
Hexyl-resorcinol	80
Dithranol	450
Propyl gallate	280
n-Propyl *p*-hydroxy benzoate	300
Picric acid	1400
Dichlorophene	150

With oestradiol and ethinyloestradiol, the curve shapes are anomalous; the rather steep slope before the end point which is characteristic of the solvent and electrode system is repeated after the end point. Thus it is advisable to plot the differential curve when titrating these substances.

Other Phenolic Substances

Table III gives the step heights of a number of phenolic compounds of pharmaceutical interest which have been successfully titrated with tetrabutylammonium hydroxide.

The polyhydric phenols resorcinol, hexyl-resorcinol, dithranol, propyl gallate and dichlorophene, give only one inflection point on the titration curve that is sufficiently well-marked to be used as an indication of the end point; thus, in each case, the equivalent is equal to the molecular weight.

Acknowledgement. The authors wish to express their thanks to Dr. R. E. Stuckey for his interest and encouragement.

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DISCUSSION

The paper was presented by MR. J. ALLEN.

The CHAIRMAN wondered to what extent the position of the step was a diagnostic character of a particular molecule; had one to depend upon the step height itself or were these only characteristic of a group of related substances?

MR. C. A. JOHNSON (Nottingham). Fritz and Yanamura had used triethylbutylammonium hydroxide which they regarded as more basic than tetrabutylammonium hydroxide. By their method, using acetone as a solvent he had not been able to observe any definite step comparable with the one now recorded. Would the authors comment on the basicity of the two materials and had they any experience with sulphonamides which had been titrated successfully by Fritz and Yanamura. Why did the authors use the calomel electrode in the way described?

MR. H. D. RAPSON (Dorking). Had the authors tried conductometric methods as these had certain advantages over potentiometric methods?

MR. S. G. E. STEVENS (London). Had the bubbling of nitrogen as a means of flushing and stirring been considered, and what was the source of the acidity which developed in the dimethylformamide previously treated with barium oxide, and presumably stored under nitrogen?

MR. H. B. HEATH (Sudbury). Had the authors any experience of the determination of eugenol in clove oil or phenolic bodies in ointment bases.

In reply, MR. J. ALLEN said that the basicity of quaternary ammonium hydroxides increased as the weight of the substituting radicals increased to a maximum at tetrabutyl, which was one of the reasons for choosing

this substance. A step height was obtained with phenol which it was not possible to obtain with other solvents. Acetone in certain electrode systems would depress the step and height. The solvent must not only possess intrinsic basic strength, but must also have a long basic range so that potential change at any particular addition was a steep one. Ethylenediamine was basic but it had a short range, pyridine which was less basic had a slightly longer range, and dimethylformamide was less basic but had a very long range. Since submitting the paper it had been possible to obtain with slight modification, two steps with dihydric phenols but there were no means of differentiating between two similar phenols having only one reactive group. They had had no great success in determining phenolic materials extracted from galenical preparations when there were also phenolic impurities in the extract. With dimethylformamide the junction potential between the electrode and the solvent was high, and even with a ground sleeve it was found that there was leakage and therefore Gooch asbestos had been used as a filler as it eliminated all leakage. High frequency conductivity methods had been tried but using the solvent system decided upon, the change of slope in the conductivity curve at the endpoint was small, and did not appear to give a sufficiently definite indication of the position of the endpoint for general routine purposes. The diagnostic properties of conductivity curves depend on the solvent. When water was used the curves could be useful, but in the case of non-aqueous solvents there was suppression of diagnostic characters of the conductivity curve. A nitrogen bubbler as stirrer had been used, but flushing with nitrogen was carried out only if using a weaker solution than N/25. The solution of tetrabutylammonium hydroxide was stored under nitrogen, but not the dimethylformamide. With reasonably pure dimethylformamide if using N/10 titrant it was only necessary to neutralise the acidity, but if N/50 were used it was necessary to resort to purification. It then probably remained stable under nitrogen, but if kept in a bottle a slight amount of acidity developed. However, it could then be used even with N/50 reagent if the acidity were first neutralised.

MR. STEVENS said it was surprising to hear that dimethylformamide did not seem to affect glass electrodes.

MR. ALLEN replied that glass electrodes could not be used with ethylenediamine because in that solvent the sodium ion gave a potential to the glass electrode, but in dimethylformamide that did not happen and an electrode stored in it for twelve months was still satisfactory. It was necessary first to separate the phenolic material to be determined from all other phenols; oils and fats would also interfere.