A NOTE ON THE TITRATION OF SULPHONAMIDES IN NON-AQUEOUS SOLVENTS

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In analytical chemistry the use of non-aqueous solvents as media in which titrations can be performed is steadily increasing. Although Vorländer[1] in 1903 titrated aniline with a solution of anhydrous hydrogen chloride in benzene, using *p*-dimethylaminobenzene as indicator, the starting point for a general application of such methods is to be found in the publications of Conant, Hall and Werner[2,3,4,5]. The want of a general theory of the changes taking place during titrations in non-aqueous solvents was one reason that the applications of this method have been developed only in the last two or three decades. Besides the well-known electrolytic dissociation theory of Svante Arrhenius (1884), which could be applied only to aqueous solutions, three new concepts which apply to the acid-base relationship in solvents in general were introduced: the solvent-system concept (Franklin[6], Audrieth[7]), the protonic concept (Brönsted[8,9], Lowry[10]) and the electronic concept (Lewis[11]). There is no space to discuss these theories here. The application of the Brönsted-concept to titration methods in non-aqueous solvents is reviewed by Van Arkel[12].

Titration of Sulphonamides

Several authors have described the titrations of sulphonamides in glacial acetic acid with slightly differing results. These titrations, which are carried out with perchloric acid as the titrant are based on the proton-accepting (basic) properties of the sulphonamide molecule. The behaviour of sulphonamides when titrated in anhydrous acetic acid has been studied by Tomicek[13], who concluded that the stronger bases may be titrated with methyl violet as indicator, while the weaker ones are best titrated potentiometrically. Other workers have criticised the method and have suggested modifications (van Arkel and Kroonenberg[14], Per Ekeblad[15] Gautier and Pellerin[16]).

With the object of defining a method which would be suitable for pharmacopœial purposes the perchloric acid titration was tried with several sulphonamides by two methods: (*a*) solution of the sulphonamide in anhydrous acetic acid by boiling, followed by titration with 0·1 N perchloric acid, using crystal violet, α-naphtholbenzene or quinaldine red as indicator; (*b*) suspension of the sulphonamide in anhydrous acetic acid and titrating with 0·1 N perchloric acid with constant mechanical stirring. Both methods gave bad results.

These results indicate further that when the sulphonamides are heated with anhydrous acetic acid the basic properties of the molecule are

weakened, probably by acetylation of the free amino group. Ultraviolet absorption studies (Havinga and Veldstra[17]; Pestemer and Flaschka[18]) led to the expectation that heterocyclic derivatives of sulphanilamide could be titrated better as acids than as bases. A method involving solution in ethanol, addition of excess of 0·1N aqueous sodium hydroxide and back titration with 0·1N hydrochloric acid using thymolphthalein as indicator[19] has proved unsatisfactory[20]. Fritz and Keen[21], applying the more general method of Fritz and Lisicki[22], titrated sulphonamides, dissolved in dimethylformamide and butylamine, with 0·1N sodium methoxide in a mixture of benzene and methanol, using thymol blue as indicator. Vespe and Fritz[23] described a similar method.

Recommended Method

The method described below has been found to give satisfactory results which are in good agreement with those obtained by the nitrite method described in various pharmacopœias (Ph. I., 1951; U.S.P. XIV; B.P., 1953).

Reagents and Solutions—

Benzene, purified grade.

Benzoic acid, reagent purity.

Methanol, dried over calcium or calcium oxide and freshly distilled.

Benzene-methanol mixture. Mix 3 volumes of benzene with 1 of methanol.

Pyridine, reagent purity; neutralised immediately before use with sodium methoxide solution.

Thymol blue solution. Dissolve 0·1 g. of thymol blue in 100 ml. of methanol.

Sodium methoxide solution 0·1 to 0·2 N:

Dissolve about 3 g. of sodium, freshly cut or previously washed in methanol, in 50 ml. of methanol. Protect the solution from carbon dioxide while the sodium is dissolving and cool to prevent the reaction from becoming too violent. When all the sodium has reacted, add 100 ml. of methanol and 750 ml. of benzene, and store the reagent in borosilicate glassware, protected from carbon dioxide.

Standardisation of the sodium methoxide solution.—Dissolve about 0·250 g. of benzoic acid, accurately weighed, in 30 ml. of benzene-methanol-mixture. Add 4 drops of thymol blue solution and fit the flask with a 1-holed stopper through which the burette tip is passed. Titrate with sodium methoxide solution till the colour changes from yellow to blue, using a magnetic stirrer during the titration.

Procedure.—Suspend about 0·5 g. of the sulphonamide, accurately weighed, in 40 ml. of benzene-methanol mixture (or dissolve the same amount in 50 ml. of pyridine). Proceed as directed above in the "standardisation of the sodium methoxide solution", beginning with "Add 4 drops of thymol blue solution. . . .".

This procedure has been applied to sulphanilamide, sulphathiazole,

sulphadiazine, sulphamerazine, sulphadimidine and succinylsulphathiazole. All the substances were of pharmacopœial purity (Ph. I. I, 1951; sulfadimidine B.P. 1953). For sulphanilamide the method fails, the colour change taking place immediately after the first drops of sodium methoxide solution have been added. With the other drugs good results were obtained, which agreed with those obtained with the nitrite method (see Table I). The colour-change is sharper in pyridine solution, which is clear, than in the benzene-methanol mixture, which gives a turbid liquid. In assaying tablets the benzene-methanol solvent is unsuitable because the end-point is reached too early, also the titration must be carried out very slowly as otherwise the colour changes at once.

With tablets the nitrite method gives somewhat lower results than the sodium methoxide method. Of the common tablet excipients sugar and gelatin did not give a blank; talc and potato starch gave a small blank, but some trade products of magnesium stearate gave a blank of 0·05 ml. of 0·1N solution per 5 mg. With tablets containing 500 g. of sulphonamide, 5 mg. of magnesium stearate, 30 mg. of talc, 100 mg. of potato starch and some gelatin the results of the assay by the sodium methoxide method may be expected to be too high by as much as 0·4 per cent. When stearic acid or other acidic excipients are used, the results become, of course, much too high. Thus for assaying tablets the procedure should be used with caution.

TABLE I

COMPARISON OF RECOMMENDED METHOD WITH NITRITE METHOD

Method	Pure substances				
	Sulphathiazole per cent.	Sulphadiazine per cent.	Sulphamerazine per cent.	Sulphadimidine per cent.	Succinylsulphathiazole per cent.
Sodium methoxide + benzene methanol	99·8 99·8	101·5 101·3	100·0 99·7	101·7 101·4	— 90[3]
Sodium-methoxide + pyridine	100·0 100·1 100·6[1]	101·5 101·6 —	99·5 99·3 —	100·8 100·7 —	100·2[3] 99·8[3] —
Nitrite	99·6 99·8	101·5 100·8	99·5 99·1	101·4 101·7	100·5[4] 100·6[4]
	Tablets (trade-products)				
Sodium methoxide + pyridine	100·1 100·2	101·9 101·6	101·5 101·3	100·2 100·0	— —
Nitrite	97·5 97·6	98·6 98·7	98·7 98·8	98·8 99·0	— —

[1] Sulphathiazole 500 mg. + magnesium stearate 5 mg. + talc 30 mg. + potato starch 100 mg. + gelatin
[2] Colour changes too early; titration carried out very slowly.
[3] 1 equivalent of succinylsulphathiazole = 0·5 mol.
[4] 1 equivalent of succinylsulphathiazole = 1 mol.

SUMMARY

1. The titration methods of sulphonamides with visual indicators in non-aqueous solvents are shortly reviewed.

2. A method is recommended for assaying sulphathiazole, sulphadiazine, sulphamerazine, sulphadimidine and succinylsulphathiazole by

titrating in pyridine solution with sodium methoxide in benzene-methanol mixture 3:1; indicator, thymol blue in methanol.

3. The method is more convenient than the nitrite method and gives the same results.

4. When assaying tablets attention must be paid to excipients which have acidic properties, and cause high results.

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