Spectrophotometric Titration of Sulfonamides with Bromate-Bromide Solution

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Abstract □ A spectrophotometric titration procedure for the analysis of sulfanilic acid and a number of sulfonamide drugs is described. The drug dissolved in a mixture of concentrated hydrochloric acid and glacial acetic acid (2:8) is titrated with a 0.1 *N* bromate–bromide mixture. The end-point is determined spectrophotometrically at 345 nm. Quantitative recoveries are reported for 10 sulfonamides. Good agreement between the proposed and the official procedure is obtained.

Keyphrases □ Sulfanilic acid, sulfonamides—determined by spectrophotometric titration using bromate–bromide solution, comparison with official method □ Sulfonamides, sulfanilic acid—determined by spectrophotometric titration using bromate–bromide solution, comparison with official method □ Bromine solution—used as titrant in analysis of sulfanilic acid and sulfonamides □ Spectrophotometric titration—analysis of sulfonamides and sulfanilic acid □ Titration, spectrophotometric—analysis of sulfonamides and sulfanilic acid

Sulfonamides, derivatives of sulfanilamide, are commonly employed in antimicrobial therapy. Numerous methods for their analysis have been suggested. Pastor (1) reviewed the literature on sulfonamide determination. Volumetric procedures include diazotization, bromination, and titration in nonaqueous media either with perchloric acid or alkali metal alkoxides. Argentometric (2) and complexometric (3) methods also have been reported. Methods utilizing UV and IR spectrophotometry have been developed. Analysis of sulfonamide mixtures by NMR spectrometry was suggested by Hammer and Joseph (4). Chromatographic procedures are widely employed for the separation, identification, and estimation of these drugs. Stahl (5) reviewed the literature on such methods employing TLC.

The bromination methods generally involve addition of excess bromine and back-titration of unreacted reagent. Direct titration with a bromate–bromide mixture (Koppeschaar's reagent) is also possible when the sulfonamide is dissolved in an acetic acid–hydrochloric acid mixture (6). The end-point is determined potentiometrically or with an indicator such as methyl red. The color change of the indicator during these titrations is generally not sharp. A coulometric procedure for the titration of several sulfonamides utilizing bromination with electrolytically generated bromine was reported by Ejima *et al.* (7). *N*-Bromosuccinimide (8) and, more recently, 1,3-dibromo-5,5-dimethylhydantoin (9) have also been utilized as brominating agents in the determination of certain sulfonamides.

Spectrophotometric titration with bromine has been reported for phenols (10) and for aromatic amines (11). Tanase and Shimomura (12) determined sulfanilamide and sulfacetamide by spectrophotometric titration with nitrous acid. In the present paper, we report a spectrophotometric titration procedure for the determination of sulfonamides with a bromate–bromide reagent. The procedure is simple, rapid, and accurate.

EXPERIMENTAL

Apparatus—Spectrophotometric titrations were performed utilizing either a Unicam SP 500 spectrophotometer or a Carl Zeiss model PMQ II spectrophotometer equipped with titration cell (silica, 18 × 35 mm.), cell carriage, and magnetic stirrer. For the latter, a special cell cover was provided which permitted the introduction of the buret tip through a small aperture in the cover (13). A 10-ml. buret (Technicon) graduated in 0.02 ml. was employed for the delivery of titrant.

Materials—Pure drug samples (listed in Table I) were obtained from commercial sources. Reagent grade potassium bromate, potassium bromide, acetic acid, hydrochloric acid, and sulfanilic acid were used[1].

Preparation of 0.1 *N* Bromine—Potassium bromate, 2.7842 g., and potassium bromide, 9.92 g., were dissolved in sufficient water to make 1 l.

Method—The following two titration procedures were employed depending upon the instrument used.

Method A—The titration procedure was performed with a Unicam SP 500 spectrophotometer. No modification of the instrument was involved. A stock solution was prepared by transferring 200 mg., accurately weighed, sulfonamide powder to a 100-ml. volumetric flask. The powder was dissolved in 20 ml. of concentrated hydrochloric acid, and glacial acetic acid was added to volume. Five-milliliter aliquots were transferred to each of nine 50-ml. volumetric flasks. Except for the first flask, the titrant was added to each succeeding flask in increasing volumes, differing by 0.5 ml. This was followed by sufficient glacial acetic acid to bring the volume to the mark. After bromination was complete (10 min. or less), the absorbance was measured at 345 nm. against 2% v/v concentrated hydrochloric acid in glacial acetic acid (slit 0.2–0.3). The intersection of the

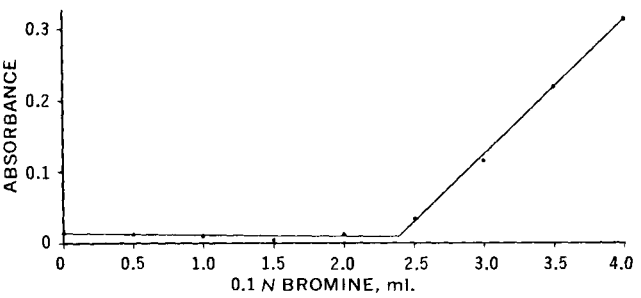

Figure 1—*Spectrophotometric titration curve for sulfanilamide with standard bromate–bromide solution at 345 nm.*

[1] British Drug House.

Table I—Analysis of Sulfonamides by Spectrophotometric Titration with 0.1 *N* Bromine

Sulfonamide	Molecular Weight	Equivalents of Bromine Consumed	Bromination Time, min.	Proposed Method Recovery, %	Official Method Recovery, %
Sulfanilic acid	173.84	4	10	99.33 ± 1.47[a]	99.12[b]
Sulfanilamide	172.21	4	5	101.23 ± 1.47	99.02
Sulfacetamide	214.24	4	10	100.30 ± 1.35	99.64
Sulfaguanidine	232.26	4	10	99.62 ± 1.27	98.00
Sulfamethizole	270.33	4	5	101.48 ± 1.18	100.52
Sulfamethazine	278.33	4	(1)[c]	100.81 ± 0.30	99.68
Sulfisoxazole	267.31	6	5	100.57 ± 0.88	99.87
Sulfadimethoxine	310.33	6	10	99.96 ± 0.80	99.60
Sulfamerazine	264.31	6	5	98.43 ± 0.58	99.28
Sulfathiazole	255.32	6	10	99.27 ± 0.49	100.38
Sulfadiazine	250.28	6	(1)[c]	100.28 ± 0.21	98.95

[a] Standard deviation based on at least four analyses. [b] Average of two determinations by the official procedure. See *Reference 14*. [c] Method B was followed. The absorbance was measured 1 min. after each addition of the titrant.

two straight-line segments obtained by plotting absorbance *versus* volume of the titrant corresponded to the end-point of the titration. A typical titration curve obtained is shown in Fig. 1.

Method B—The titration procedure was performed with a modified Carl Zeiss model PMQ II spectrophotometer. A stock solution of sulfonamide was prepared as already described. Seven milliliters of this solution was placed in the titration cell. The instrument was set at a wavelength of 345 nm. (slit 0.6). The absorbance was read initially and after each addition of successive 0.1-ml. portions of the titrant. The solution was magnetically stirred throughout the titration. After correcting the absorbance of the solution for dilution, the treatment of data was similar to that described under *Method A*.

RESULTS AND DISCUSSION

The results of the analysis of sulfanilic acid and 10 sulfonamides by spectrophotometric titration with 0.1 *N* bromine are shown in Table I. The results are compared with those obtained when the materials were analyzed by the official procedure (14). In all cases, good agreement between the two procedures is realized. The bromination time is the time interval allowed to elapse between the titrant addition and absorbance measurement, which required no longer than 10 min. Sulfaethidole, structurally similar to the successfully analyzed sulfamethizole, could not be determined because of poor solubility. Solution could not be effected when the hydrochloric acid concentration was increased to 40% v/v and even when the mixture was warmed on a water bath. Except for this particular instance, the mixture of concentrated hydrochloric acid and acetic acid was found to be suitable for all sulfonamides studied. Initially, the solvent mixture consisting of methanol, hydrochloric acid, and potassium bromide, as suggested by Sweetser and Bricker (10) for the titration of phenols, was used; but as the titration progressed, a precipitate appeared which interfered with the absorbance measurements. The high concentration of acetic acid in the concentrated hydrochloric–acetic acid mixture is necessary to avoid similar precipitation problems. Sulfapyridine, sulfisomidine, sulfamethoxazole, and sulfamethoxypyridazine did not yield reproducible results.

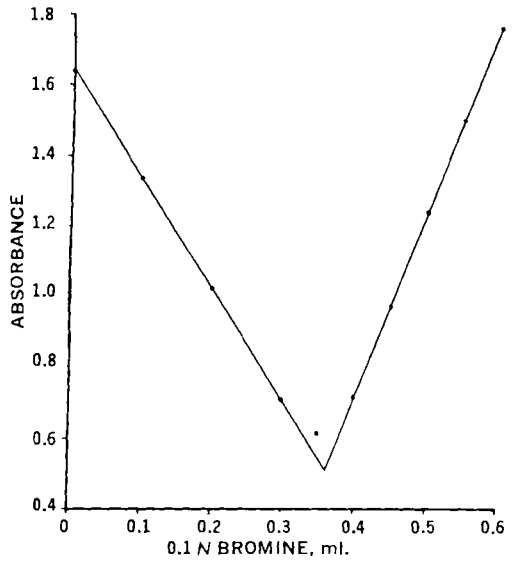

Figure 2—*Spectrophotometric titration curve for sulfadiazine with standard bromate–bromide solution at 345 nm.*

At the wavelength selected for the spectrophotometric titrations, most sulfonamides do not show appreciable absorption. The titration of sulfanilamide with 0.1 *N* bromine is shown in Fig. 1. Initially, there is no change in the absorbance as the titrant is added; but after the equivalence point is reached, the absorbance increases due to absorption by the excess bromine. With the exception of sulfadiazine, all other substances gave titration curves similar to that shown in Fig. 1. A V-shaped curve was obtained with sulfadiazine (Fig. 2). There is a gradual decrease in absorbance with the addition of titrant before the end-point followed by an increase in absorption due to bromine. Both Methods A and B are equally satisfactory; however, Method B is considerably quicker and employs less quantity of the solvent. The main advantage of Method A lies in the fact that modification of the spectrophotometer is not required and special equipment is not needed.

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TECHNICAL ARTICLES

Automated Drop Volume Apparatus for Surface Tension Measurement

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Abstract □ The drop volume method for surface tension measurements is ideal for new compounds since only a few milligrams are needed to obtain the CMC. However, the method is tedious and time consuming. An automated drop volume apparatus was constructed which provides sufficient accuracy with very little operator time. It is based on measurement of the average time between falling drops delivered from a constant-rate motorized syringe.

Keyphrases □ Surface tension measurement—automated drop volume apparatus □ Drop volume surface tension measurements—automated apparatus

Measurement of surface activity as a function of concentration usually requires upward of 500 mg. of compound when measured by the widely used du Nouy ring or Wilhelmy plate method. When the amount of test compound available is limited, the drop volume method is ideal since only a few milliliters of solution are required for accurate surface tension determination. However, this method is very tedious and time consuming. The present study was undertaken to automate the drop volume procedure so that very little operator time is involved while the minimum amount of test compound is used. Errors due to variation in operator technique also would be reduced. A prototype apparatus was built which fulfills these criteria.

An automatic drop counter was described by Nikita and Taubman (1). Refinements in the apparatus were made by others (2, 3). Essentially, it consists of a stalagmometer, photocell, light source, and appropriate electrical circuitry to count the *number* of drops formed from a measured volume. An apparatus has been constructed which automatically measures the *time* between drops at a constant delivery rate, permitting quick and direct calculation of surface tension.

APPARATUS

The essential features of the automated drop volume apparatus are shown in Fig. 1. It consists of a B-D syringe fitted with a special dispensing tip. The tip is a stainless steel cylinder which has a channel terminating at the lower end as a 26-gauge needle orifice. The lower end, upon which the droplets are formed, is machined flat and has a diameter of 0.6 cm. The syringe is held rigidly and discharged at a constant rate by a Harvard infusion pump.

A light source and photoelectric cell are fixed in a U-shaped metal holder so that an approximately 2 × 2-cm. light beam strikes the photocell. The photocell output is fed into a recorder[1] set for an input range of 10 mv.

After the syringe is filled with the test solution and it is installed in the pump, the motor is started and run continuously throughout the experiment. The combination of a $^1/_2$-r.p.m. motor and 2-ml. syringe gives a measured delivery rate of 0.0332 ml. min.$^{-1}$. Droplets form on the tip, growing to a size that is dependent on the solution surface tension, and then fall off. As each droplet grows, it intercepts a significant portion of the light impinging on the photo-

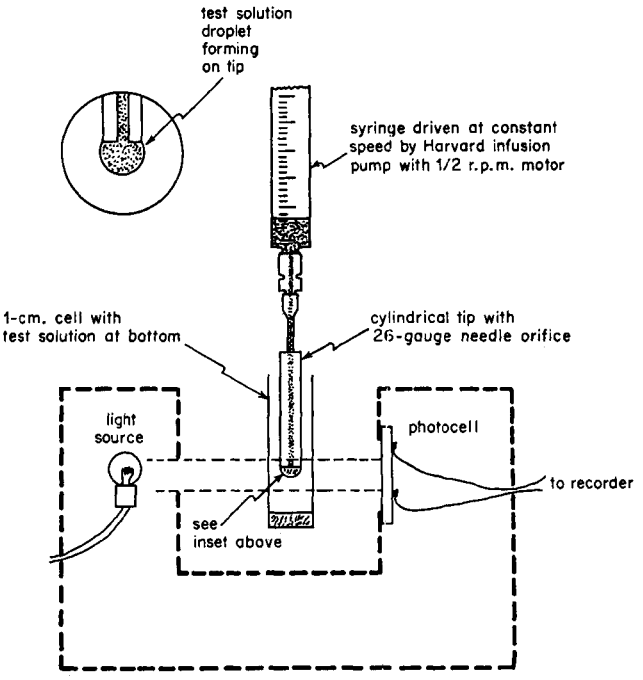

Figure 1—*Schematic of the essential features of the automated drop volume apparatus.*

[1] Sargent model SRL.