Nonaqueous Titration of Barbiturates in Tetramethylurea

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Abstract □ Tetramethylurea was evaluated as a solvent for the nonaqueous titration of barbiturates and several of their dosage forms and combinations. Tetrabutylammonium hydroxide and sodium methoxide in benzene–methanol were used as titrants. Titrations were performed visually and potentiometrically with a titrimeter equipped with a glass–calomel electrode system. Comparison was made with the solvent dimethylformamide.

Keyphrases □ Barbiturates—nonaqueous titration in tetramethylurea □ Tetramethylurea, solvent evaluation—nonaqueous titration of barbiturates □ Titration, nonaqueous—barbiturates in tetramethylurea

The physical properties of tetramethylurea were described by Luttringhaus and Dirksen (1), who noted that tetramethylurea is an excellent solvent for a wide variety of organic compounds. Salts and polar compounds, in general, show a lower solubility in this solvent. It is stable, inert, and practically odorless; it has a low toxicity and is commercially available at moderate cost. It can be prepared in a high state of purity and essentially anhydrous. Tetramethylurea has not been studied to any great extent for its use as a nonaqueous titration solvent.

Culp and Caruso (2) titrated potentiometrically several phenols and carboxylic acids using tetrabutylammonium hydroxide as the titrant. The authors concluded that tetramethylurea is a useful solvent for titrating very weak to strong acids. Differentiation of benzoic acid and phenol was unsuccessful. In a subsequent paper, these authors (3) found thymol blue, phenolphthalein, and azo violet as useful indicators for the visual titration of acids in tetramethylurea. Azo violet proved the most useful for very weak acids.

In the present study, tetramethylurea was compared with dimethylformamide as a solvent for the titration of a series of barbiturates and a number of their dosage forms using tetrabutylammonium hydroxide as the titrant.

EXPERIMENTAL

Apparatus—Titrations were performed visually or potentiometrically with a titrimeter[1] equipped with microattachment accessories including a microcalomel[2] and glass[3] electrode system.

A 10-ml. buret, graduated in 0.02-ml. increments and equipped with a Teflon stopcock and a Teflon delivery tip tapered to a small bore, was used to deliver the titrants. Titrations were performed in a 10-ml. beaker, and stirring was effected with a magnetic stirrer using a 1-cm. length nail encased in Teflon as the stirring bar.

[1] Fisher model 35.
[2] Fisher No. 13-639-79.
[3] Fisher No. 13-639-77.

Reagents—Tetramethylurea was obtained commercially[4]. Sodium methoxide, 0.1 *N*, in benzene–methanol (10:1) was prepared and standardized as described earlier (4). Tetrabutylammonium hydroxide, 0.1 *N*, was prepared and standardized as reported by Cundiff and Markunas (5) or was purchased[5] as a 25% solution in methanol. The titrant solution was prepared by diluting 25 ml. to 200 ml. with dry benzene and was then standardized. The barbiturates and their dosage forms were obtained from commercial sources. Thymol blue indicator solution was 0.3% in anhydrous methanol, and phenolphthalein indicator was 1.0% in anhydrous methanol. Other chemicals and all solvents used in this study were reagent grade and were employed without further purification.

General Procedure for Free Barbiturates—About 50 mg. of each barbiturate, accurately weighed into a 10-ml. beaker, was dissolved in 5 ml. of tetramethylurea or dimethylformamide. The solution, magnetically stirred, was titrated potentiometrically with 0.1 *N* tetrabutylammonium hydroxide or 0.1 *N* sodium methoxide. During the titration, the tip of the buret was immersed into the titration solution. The end-point in the titration curve was determined from the inflection in the titration curve obtained by plotting volume (milliliters) of titrant added *versus* millivolt readings. Typical titration curves are shown in Fig. 1, and analysis data are recorded in Table I. The feasibility of a visual titration was investigated by adding two drops of thymol blue or phenolphthalein indicator solution to the titration solution prior to a potentiometric titration. The appropriate color change at the end-point in the titration was determined by comparing the color change with the graphic end-point. For all visual titrations, a blank determination was conducted and the necessary corrections were made.

Analysis of Barbiturate Tablets—Twenty tablets, accurately weighed, were triturated to a fine powder. An aliquot of the powder

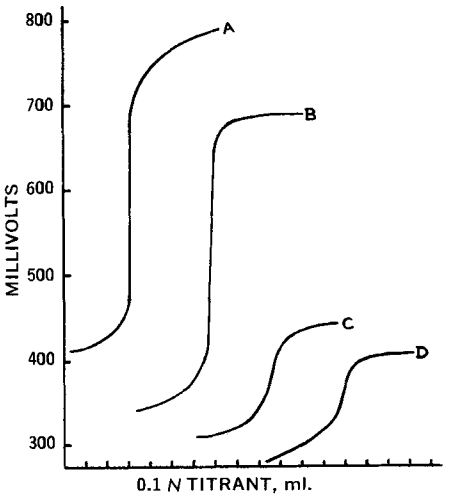

Figure 1—*Typical titration curves for free barbiturates. Curves A and B represent titrations in tetramethylurea and dimethylformamide, respectively, using tetrabutylammonium hydroxide as the titrant. Curves C and D represent titrations in tetramethylurea and dimethylformamide, respectively, using sodium methoxide as the titrant.*

[4] Ott Chemical Co., Muskegon, Mich.
[5] Eastman.

Table I—Analysis Data for Free Barbiturates

Powder	Recovery, %: TBAH[a] TMU[c]	TBAH[a] DMF[d]	SMO[b] TMU	SMO[b] DMF
Amobarbital	101.27 ± 0.41[e]	102.82 ± 0.20	96.03 ± 1.14	99.16 ± 0.33
Barbital	100.99 ± 0.33	100.49 ± 0.41	98.69 ± 0.10	99.35 ± 0.47
Hexobarbital	97.96 ± 1.69	98.60 ± 1.27	97.13 ± 0.23	98.61 ± 0.11
Phenobarbital	100.50 ± 0.16	100.30 ± 0.31	99.41 ± 0.39	99.25 ± 0.90
5-Allyl-5-ethylbarbituric acid	100.21 ± 1.08	102.73 ± 0.60	97.43 ± 0.11	98.87 ± 0.07
5-Ethylbarbituric acid	99.69 ± 0.13	99.25 ± 0.84	97.77 ± 0.43	98.69 ± 0.23
Ethylbenzylbarbituric acid	102.67 ± 0.28	102.11 ± 0.53	95.30 ± 0.41	98.44 ± 1.49
Ethylisoamylthiobarbituric acid	100.76 ± 0.11	101.94 ± 0.36	95.16 ± 0.50	95.06 ± 0.58
2-Hydroxypropyl-*n*-hexyl-thiobarbituric acid	102.21 ± 0.45	97.53 ± 2.14	98.77 ± 0.47	96.30 ± 0.06
5-Isopropylbarbituric acid	100.10 ± 0.38	99.67 ± 0.80	99.29 ± 0.31	99.17 ± 0.04

[a] Tetrabutylammonium hydroxide. [b] Sodium methoxide [c] Tetramethylurea. [d] *N,N*-Dimethylformamide. [e] Standard deviation is based on at least three determinations.

mass equivalent to about 50 mg. of barbiturate was accurately weighed into a 10-ml. beaker and dissolved in 5 ml. of tetramethylurea or dimethylformamide. The solution, magnetically stirred, was titrated potentiometrically with 0.1 *N* tetrabutylammonium hydroxide. The feasibility of a visual titration was explored. The data are recorded in Table II.

Extent of Interference by Water—The extent to which water interferes with the determination and detection of the potentiometric and visual end-points, respectively, was studied by titrating phenobarbital in tetramethylurea and dimethylformamide containing increasing percentages of water. Two series of stock solutions were prepared, the first containing 1–10% of water (v/v) in tetramethylurea, and the second containing 1–60% water (v/v) in dimethylformamide. About 50 mg. of phenobarbital, accurately weighed, was dissolved in 5 ml. of the stock solution in a 10-ml. beaker, and the solution was titrated visually or potentiometrically with 0.1 *N* tetrabutylammonium hydroxide as described previously. Typical titration curves are shown in Fig. 2.

Sensitivity of Procedure—The sensitivity of the titration procedures in tetramethylurea and dimethylformamide was evaluated by titrating decreasing sample weights of phenobarbital with 0.01 *N* tetrabutylammonium hydroxide. The 0.01 *N* tetrabutylammonium hydroxide was prepared by diluting 0.1 *N* tetrabutylammonium hydroxide with benzene–methanol (10:1) and standardizing the solution against primary standard benzoic acid. A series of stock solutions was prepared which contained 1–10 mg. of phenobarbital/5 ml. of solution. A 5-ml. aliquot of each solution was transferred by pipet to a 10-ml. beaker and was titrated visually or potentiometrically as described previously.

RESULTS AND DISCUSSION

Since tetramethylurea is an excellent solvent for most classes of organic compounds and is completely miscible with water, and since it is not reactive, it seems to be a solvent worth investigating as a titration medium. To date, little interest has been shown in tetramethylurea for this purpose, as is reflected in the dearth of publications appearing in the literature.

A series of barbiturates and typical dosage forms were studied here because they are weak organic acids of pharmaceutical importance and have been the subject of numerous studies involving titration in nonaqueous solvents. These were noted earlier (6). Sodium methoxide and tetrabutylammonium hydroxide were used as titrants, and comparisons were made between tetramethylurea and dimethylformamide as titration solvents. The similarity in the potentiometric titration curves is shown in Fig. 1. While millivolt changes and the overall inflection in the titration curves are essentially the same for both solvents, tetrabutylammonium hydroxide produces significantly greater millivolt changes at the end-point than does sodium methoxide. Analysis data shown in Table I indicate quantitative recoveries for eight barbiturates in the four systems studied. While the data were calculated on the basis of the potentiometric end-points, satisfactory end-points were also obtainable with thymol blue indicator. Color changes (yellow to blue) were equally sensitive in both dimethylformamide and tetramethylurea. The phenolphthalein end-point was less satisfactory and appeared consistently prior to the graphic end-point. Thymol blue indicator permitted detection of the end-point with a single drop of titrant addition in either solvent with both titrants.

A series of tablet dosage forms containing barbiturates was analyzed by potentiometric titration using tetrabutylammonium hydroxide as titrant and tetramethylurea and dimethylformamide as the titration solvent. The analysis data are recorded in Table II. Essentially the same results were obtained in either solvent. A high recovery is reported for hexobarbital tablets in both solvents. Since the tablets were not pretreated to isolate the barbiturate from the excipients in the tablet, other acidic components in the formulation may have interfered in the titration. If this was the case, the pKa value for the interfering acid must have approximated that of the barbituric acid, since only one inflection in the titration curve was noted. On the other hand, the high recovery may indicate a high barbiturate content in the tablet. The analysis data for all other dosage forms appear reasonable and within acceptable limits of barbiturate content.

The dosage forms were titrated only with tetrabutylammonium hydroxide because it produced greater millivolt changes at the end-

Table II—Analysis Data for Barbiturate Dosage Forms

Tablet	Dosage Size, mg.	Recovery, %: TMU[a]–TBAH[b]	DMF[c]–TBAH
Amobarbital	100	96.66 ± 0.39[d]	96.24 ± 0.49
Barbital	325	100.33 ± 1.28	100.58 ± 0.99
Hexobarbital	250	106.75 ± 0.71	107.12 ± 0.16
Mephobarbital	32	104.45 ± 0.09	103.82 ± 0.25
Mephobarbital	100	104.88 ± 0.65	101.82 ± 0.20
Mephobarbital	200	100.95 ± 0.32	101.00 ± 0.55
Phenobarbital	15	94.74 ± 0.44	95.53 ± 0.18
Phenobarbital	30	99.35 ± 0.99	99.15 ± 0.17
Phenobarbital	60	97.74 ± 0.17	99.19 ± 0.30
Phenobarbital	100	99.73 ± 0.66	99.30 ± 0.43

[a] Tetramethylurea. [b] Tetrabutylammonium hydroxide. [c] *N,N*-Dimethylformamide. [d] Standard deviation is based on at least three determinations.

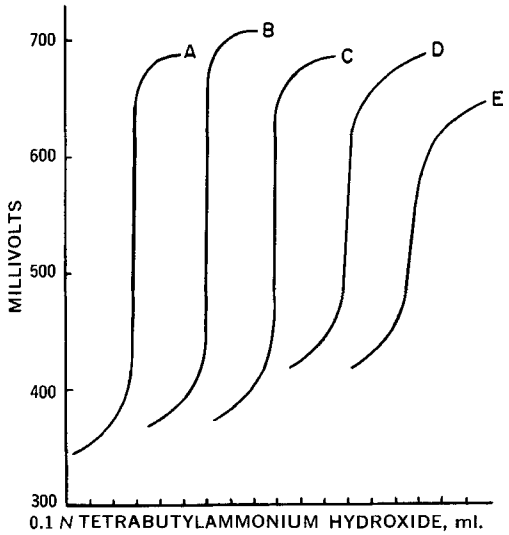

Figure 2—*Effect of water on the titration of phenobarbital in dimethylformamide. Curves A, B, C, D, and E represent 0, 5, 10, 30, and 60% (v/v) of water in dimethylformamide, respectively. The curves have been displaced to show the effect of water on the nature of the titration curve. The actual end-point was not affected.*

point than did sodium methoxide. Preliminary studies with the latter indicated that there was considerable drifting of the titrimeter scale needle as the end-point was approached and, in general, the titration was less satisfactory. Visual titration of the dosage forms was unsuccessful because of interference of the excipients with detection of the end-point color change due to the turbidity of the solution.

The presence of water did not apparently interfere in the titration when dimethylformamide was the solvent. A series of titration curves is shown in Fig. 2 where phenobarbital is titrated in dimethylformamide containing increasing concentrations of water. When the water content was 30% or higher (Curves D and E), the titration mixture separated into two layers[6] which became emulsified through rapid stirring. This did not interfere with the potentiometric titration. When significant amounts of water were present (20% or more), the visual end-point became obscure and visual titration was not possible. At water concentrations over 60%, titrations were not possible because of the insolubility of the barbiturate in the solvent mixture.

In tetramethylurea, water concentrations as low as 1% caused considerable drifting in the titrimeter needle as the end-point was approached and did not permit a satisfactory potentiometric titration. Because of the difficulty in end-point detection in the presence of water, percent recoveries were not determined. Visual titrations did not produce reproducible end-points in the presence of water. It is apparent that tetramethylurea must be anhydrous when used as a solvent for nonaqueous titrations.

[6] The upper layer is apparently benzene from the titrant solvent being thrown out by the water in the titration mixture.

Table III—Sensitivity of Potentiometric Titration Procedure for Phenobarbital

Phenobarbital Weight Taken, mg.	Recovery, % in DMF[a]	Recovery, % in TMU[b]
50[c]	100.50 ± 0.16[d]	100.30 ± 0.31
10	104.93 ± 0.25	103.66 ± 0.22
5	102.93 ± 0.25	103.95 ± 1.90
1	99.84 ± 1.01	98.29 ± 2.24

[a] *N,N*-Dimethylformamide. [b] Tetramethylurea. [c] 0.1 *N* titrant used for this sample size. [d] Average deviation is based on at least three determinations.

The sensitivity of potentiometric titrations in tetramethylurea and dimethylformamide was studied by titrating phenobarbital over the concentration range of 1–50 mg., using 0.01 *M* tetrabutylammonium hydroxide as titrant. Recovery data are shown in Table III. At low concentrations of phenobarbital, titrations appear to be more successful in dimethylformamide than in tetramethylurea. Visual end-points were not readily detectable in either system.

Tetramethylurea appears to be a useful solvent for titrating weak acids, free and combined in tablet dosage forms. Further studies will be required to determine whether it is as widely applicable as dimethylformamide, dimethyl sulfoxide, and methyl isobutyl ketone as a nonaqueous titration solvent. Such studies are currently in progress.

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