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POTENTIOMETRIC TITRATION OF ORGANIC CATIONS WITH SODIUM TETRAPHENYLBORATE AND A LIQUID-MEMBRANE TETRAPHENYLBORATE ION-SELECTIVE ELECTRODE

T. K. CHRISTOPOULOS, E. P. DIAMANDIS and T. P. HADJIIOANNOU*
Laboratory of Analytical Chemistry, University of Athens, Athens (Greece)
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SUMMARY

Simple potentiometric titrations are described for the determination of various organic cations (usually 5—25 μmol) with 0.01 M sodium tetraphenylborate. A liquid-membrane electrode with tetrapentylammonium tetraphenylborate dissolved in 4-nitro-*m*-xylene as liquid ion-exchanger is used successfully in the semi-automatic titration of quaternary ammonium compounds, cationic surfactants, alkaloids and other substances of pharmaceutical importance which are precipitated by tetraphenylborate. Analysis of pharmaceutical preparations gave satisfactory results.

Sodium tetraphenylborate has been used extensively for the determination of univalent cations, various alkaloids, cationic surfactants, quaternary ammonium compounds and amines. These methods are based on the formation of sparingly soluble tetraphenylborate salts. Classically, gravimetric and titrimetric methods were used. In some methods, an excess of sodium tetraphenylborate solution is added to the sample solution, and the excess of reagent in the filtrate is titrated with silver nitrate or cetylpyridinium chloride using adsorption indicators [1, 2]. Organic cations precipitated by tetraphenylborate can also be determined by two-phase titration using various dyes as indicators; the dye moves from one phase to the other at the end-point [3—5].

Ion-selective electrodes have been applied successfully to various titrations in which tetraphenylborate served as titrant [6—14]; early work in this area has been reviewed by Vytras [15].

In this paper, a liquid-membrane electrode which can be used in potentiometric precipitation titrations with sodium tetraphenylborate is described. The liquid ion-exchanger is tetrapentylammonium tetraphenylborate dissolved in 4-nitro-*m*-xylene. This electrode exhibits near-Nernstian response to the tetraphenylborate anion in the range 5×10^{-6}—3×10^{-4} M. It can be used in the semi-automatic potentiometric titration of a large number of organic cations (including quaternary ammonium compounds, cationic surfactants, alkaloids and other substances of pharmaceutical importance) which are precipitated by tetraphenylborate(TPB^-). The proposed methods

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are simple, accurate and sensitive. Satisfactory results were obtained for several organic cations in pharmaceutical preparations.

EXPERIMENTAL

Apparatus

The tetraphenylborate-sensitive electrode was used with a double-junction silver—silver chloride reference electrode (Orion Model 90-02-00). The outer chamber of the reference electrode was filled weekly with a 10% (w/v) sodium nitrate solution. E.m.f. values were measured with a Corning Model 12 Research pH/mV meter. The cell potential was recorded with a Heath-Schlumberger system, which consisted of a pH/pIon electrometer (EU-200-30), a potentiometric amplifier (EU-200-01), a d.c. offset module (EU-200-02) and a strip-chart recorder (EU-205-11). The titrant was added with a multi-speed constant-rate burette (Radiometer Model ABU12). Titration rates were kept constant at 0.36 ml min^{-1}. pH values were measured with a Metrohm pH meter (Model E350B). All solutions were titrated at ambient temperature (22 ± 2°C) with constant magnetic stirring.

Reagents

All solutions were prepared with deionized distilled water from reagent-grade materials.

Standard 0.010 M sodium tetraphenylborate solution. Dissolve 3.422 g of sodium tetraphenylborate (Merck) in water and dilute exactly to 1 l with water. Let the solution stand for 24 h and filter through Whatman No. 42 paper. This solution is standardized by potentiometric titration with tetraphenylarsonium chloride as described below.

Standard 0.001000 M tetraphenylarsonium chloride solution. Dissolve 0.4188 g of anhydrous tetraphenylarsonium chloride (Merck) in water and dilute exactly to 1 l with water. The purity of the dry substance is checked by gravimetry [16].

Standard solutions of organic cations. The organic cationic compounds used were of the highest purity available and were used without further purification. Generally, 0.00100 M solutions were prepared, by dissolving the appropriate amount of substance, or its hydrochloric, phosphate or sulfate salt, in water. Organic bases were dissolved by the addition of small amounts of hydrochloric acid (brucine, cinchonine) or sulfuric acid (quinaldine). In some cases 0.0100 M solutions of organic cations were used (for amphetamine sulfate).

Tetrapentylammonium bromide and tetraheptylammonium bromide were purchased from Eastman Kodak Co., and tetraphenylphosphonium bromide, 4-nitro-*m*-xylene, *o*-nitrotoluene, nitrobenzene, tri-n-butyl phosphate and gelatine from Merck.

Acetate buffers (0.10 M, pH 3.3 or 5.0). Dissolve 6.0 g of anhydrous acetic acid in about 800 ml of water, adjust the pH to 3.3 or 5.0 with 6 M NaOH solution and dilute to 1 l with water.

Phosphate buffers (0.10 M, pH 7.0 or 10.2). Dissolve 13.8 g of sodium dihydrogenphosphate monohydrate in about 800 ml of water, adjust the pH to 7.0 or 10.2 with 6 M NaOH solution and dilute to 1 l with water.

Preparation of the liquid ion-exchanger. Precipitate tetrapentylammonium tetraphenylborate by mixing 10.0 ml of 0.010 M sodium tetraphenylborate solution with 1.0 ml of 0.10 M tetrapentylammonium bromide solution. Extract the salt with 10.0 ml of 4-nitro-*m*-xylene and wash the organic phase three times with water. Filter the organic phase through a filter paper, Whatman No. 42, containing 1—2 g of anhydrous sodium sulfate, to remove traces of water. The filtrate should be clear and yellow. This solution is approximately 0.010 M in tetrapentylammonium tetraphenylborate. It is stored in a dry glass bottle.

Procedures

Construction of the electrode. An Orion liquid-membrane electrode body (Model 92) was used as the electrode assembly with a Millipore LCWPO-1300 teflon membrane; the teflon membranes were cut to the appropriate size and a stack of four was used to avoid any leakage of the liquid ion-exchanger.

After the body has been assembled in the usual way, inject the internal solution and the liquid ion-exchanger through the appropriate ports in the electrode body. The internal aqueous reference solution is 0.010 M sodium tetraphenylborate—0.10 M NaCl. Condition the electrode by soaking in a stirred 0.01 M sodium tetraphenylborate solution for 1 h before use. When not in use, store the electrode in a 10^{-3} M sodium tetraphenylborate solution. The operative life of the electrode is about 3—4 months.

Preparation of the calibration curve. Pipet 30.00 ml of water into the measurement cell (a 50-ml beaker), immerse the electrodes into the solution, start stirring at the maximum speed at which air bubbles are not formed, and add 1.00 μl of 0.010 M sodium tetraphenylborate solution. Read the e.m.f. when it has stabilized to ± 0.1 mV (0.5—2 min). Continue with new additions of sodium tetraphenylborate solution to cover the concentration range 3.3×10^{-7}—5×10^{-3} M. Record the e.m.f. after stabilization in each case and plot E (mV) vs. log [TPB^-].

Standardization of the 0.01 M sodium tetraphenylborate solution. Pipet into a 50-ml beaker a 25.00-ml aliquot of the 0.001000 M tetraphenylarsonium chloride standard solution, start the stirrer, and after the potential has stabilized ($\approx$1 min), start simultaneously the burette and the recorder to obtain the titration curve. Calculate the titer of the sodium tetraphenylborate solution, preferably using the mean result from four titrations. The titer of the sodium tetraphenylborate solution should be checked weekly.

Titration of organic cations with standard 0.01 M sodium tetraphenylborate solution. For Method 1, pipet into a 50-ml beaker a 25.00-ml aliquot of the sample in the following concentration ranges: 4.00×10^{-5}—1.00×10^{-3} M for papaverine hydrochloride; 2.00×10^{-4}—1.00×10^{-3} M for tetraphenylarsonium chloride, tetrabutylammonium bromide, cetyltrime-

thylammonium bromide, cetylpyridinium bromide, trimethylphenylammonium bromide, tetraphenylphosphonium bromide, atropine sulfate, cocaine hydrochloride, cinchonine hydrochloride, brucine hydrochloride or novatropine; 4.00×10^{-4}—1.00×10^{-3} M for codeine phosphate and quinaldine sulfate; 6.00×10^{-4}—1.00×10^{-3} M for thiamine hydrochloride; 8.00×10^{-4}—1.00×10^{-3} M for morphine hydrochloride; 2.00×10^{-4}—6.00×10^{-4} M for quinine sulfate; and 1.00×10^{-3} M for acetylcholine hydrochloride. Adjust the volume to 30.00 ml by adding 5.00 ml of the appropriate buffer solution (see Tables) or water and add 3 ml of 0.02% (w/v) gelatine solution if required. Continue as in the procedure for the standardization of the sodium tetraphenylborate solution from the point of starting the stirrer.

For Method 2, pipet into a 25-ml beaker a 3.00-ml aliquot of amphetamine sulfate (2.00×10^{-3}—1.00×10^{-2} M), adjust the volume to 5.00 ml by adding 2.00 ml of the appropriate buffer solution or water, and titrate as described above.

RESULTS AND DISCUSSION

Membrane material and optimal pH range

For the construction of the tetraphenylborate electrode, the liquid ion-exchangers examined were the tetraphenylborate salts of tetrapentylammonium, tetraheptylammonium and tetraphenylphosphonium, dissolved in 4-nitro-*m*-xylene, *o*-nitrotoluene, nitrobenzene or tri-n-butyl phosphate. The results indicated that the best combination was tetrapentylammonium tetraphenylborate dissolved in 4-nitro-*m*-xylene.

To check the pH dependence of the electrode potential, potential-pH curves at various tetraphenylborate concentrations were constructed. The pH of the initial solution was altered by addition of very small volumes of 18 M NaOH or 12 M HCl solution. The results showed that the potential is practically unaffected by pH in the range 3—12. Thus, the constructed electrode can be used in potentiometric titrations over this wide pH range.

Characteristics of the electrode

Calibration curve. A typical calibration curve for the tetraphenylborate electrode is shown in Fig. 1. The response is linear in the range 5.0×10^{-6}—3.0×10^{-4} M with a slope of about 51 mV/concentration decade, at 20°C. The slope of the calibration curve is stable during the operative lifetime of the electrode. The deviation from linearity at high tetraphenylborate concentrations may be due to micellar association.

Response time and stability. The electrode provides stable potential readings (±0.1 mV) within 3—10 s provided that the concentration of the measured solution is within the linear response range. In this range, the day-to-day reproducibility is within ±5 mV. Electrode stability is not a critical factor when the electrode is applied in potentiometric titrations only.

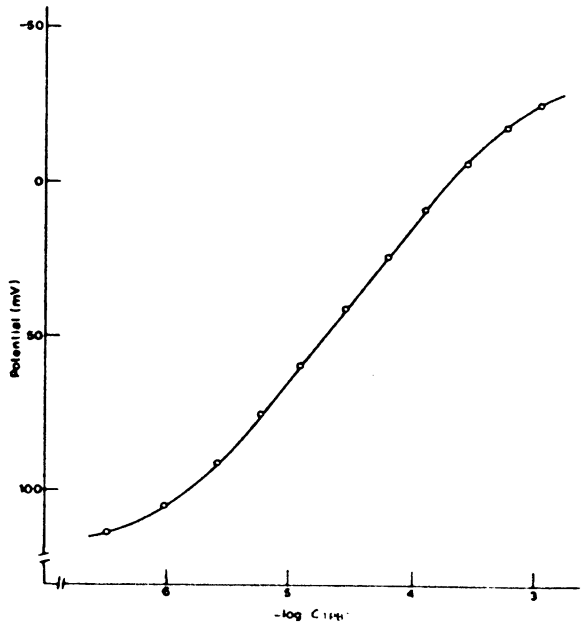

Fig. 1. Calibration curve for the tetraphenylborate-sensitive liquid membrane electrode in aqueous solutions.

Potentiometric titrations

Selig [8] and Vytras et al. [10] recommend the use of thallium(I) for the standardization of sodium tetraphenylborate solutions. Tetraphenylarsonium chloride was preferred here because it is commercially available in a very pure form, its purity can be checked by gravimetry [16] and its potentiometric titration with sodium tetraphenylborate yields large and sharp potentiometric breaks (≈430 mV) as shown in Fig. 2. The precision of such a titration is about 0.3%.

Results are presented in Table 1 for the potentiometric titration of aqueous solutions of various cations with sodium tetraphenylborate. In most cases the precision of the method is better than 1%. It is well known that in potentiometric semi-automatic precipitation titrations, there is frequently a blank which depends, among other factors, on the concentration of the sample and the titrant, the stirring rate, the titration rate, the adsorption of the titrant on the precipitate, and the reaction rate. All these factors can be kept constant except for adsorption and reaction rate, which depend on the individual compound. The blank effect can be eliminated by subtracting the appropriate blank volume from the end-point volume for each titration. This blank volume is estimated under constant experimental conditions, by titrating standard solutions of the compound of interest.

The optimum pH for each titration was found from tests with solutions buffered in the pH range 3—10 and with unbuffered solutions. The optimum pH value was chosen so as to achieve accuracy and precision, small blanks and steep potentiometric breaks near the equivalence point. For the quaternary ammonium, arsonium or phosphonium compounds, the pH dependence of the results was negligible. For the organic bases, the optimum pH was generally calculated from the expression $pH \leqslant 12 - pK_b$, where K_b is the dis-

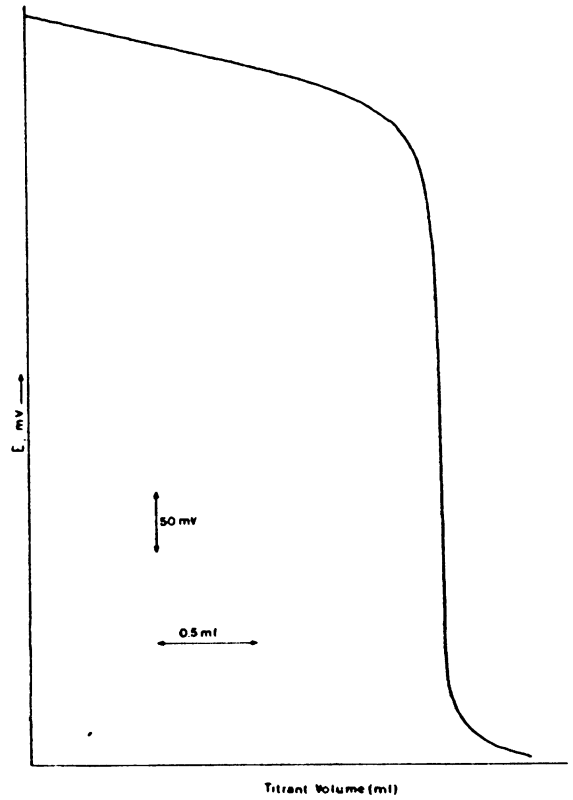

Fig. 2. Titration curve of 20.00 ml of 1.0×10^{-3} M tetraphenylarsonium chloride with 1.0×10^{-2} M sodium tetraphenylborate (other conditions as under Procedure).

sociation constant of the base, because at this pH value the base is quantitatively protonated. The optimum pH for the organic bases was always checked experimentally.

The optimum pH for thiamine is 7.0 (phosphate buffer); at pH 3—5 or in unbuffered solutions large positive errors occur (40—65%) and at pH 10 no titration curve is obtained. The titration of quinine at pH <5 yields large positive errors and unsatisfactory curves. Papaverine can be titrated at pH values <3.3; at pH 5, large positive errors occur (60%) because of the slow formation of papaverine tetraphenylborate and adsorption of the titrant on the precipitate. The titration of weak organic bases with sodium tetraphenylborate at pH values less than 2.5 is not feasible because the electrode is not useful in such acidic solutions and the titrant decomposes.

During the titration of mephentermine sulfate (see below), the precipitate formed affected the electrode, resulting in noisy response and erratic recording of titration curves. This difficulty was overcome by adding a small amount of a 0.02% (w/v) gelatine solution to the reaction mixture (see Procedures). Such quantities of gelatine do not affect the accuracy of the titration and help in obtaining a noise-free, steep titration curve.

Stirring rate is crucial in precipitation titrations. For best results, the maximum speed at which air bubbles are not formed must be used. In some cases, after a titration, the electrode exhibits sluggish response because of adherence of the precipitate to the membrane. In such cases, the membrane is rinsed thoroughly with water and cleaned with soft tissues.

TABLE 1

Results for the potentiometric titration of aqueous solutions of various cations with sodium tetraphenylborate [a]

Compound	Optimum pH	Amount of sample (μmol)	Av. error (%)	R.s.d. (%)	Av. potential break (mV)
Tetraphenylarsonium chloride	Unbuffered	5—20	1.3	0.3 (n=4)	400
Tetrabutylammonium bromide	Unbuffered	7—25	—	0.6 (n=3)	170
Cetyltrimethylammonium bromide	Unbuffered	5—20	0.9	0.6 (n=4)	380
Cetylpyridinium bromide	Unbuffered	10—20	1.0	1.3 (n=3)	470
Trimethylphenylammonium bromide	Unbuffered	10—20	1.6	0.4 (n=3)	80
Acetylcholine chloride	Unbuffered	25	1.6	0.4 (n=3)	65
Tetraphenylphosphonium bromide	Unbuffered	5—20	3.2	0.5 (n=3)	400
Atropine sulfate	3—7	5—25	1.5	1.3 (n=5)	55
Papaverine hydrochloride	3.3	5—25	1.6	1.3 (n=3)	150
Morphine hydrochloride	3—5	25	1.6	0.7 (n=4)	50
Codeine phosphate	3—7	25	—	0.6 (n=9)	65
Cocaine hydrochloride	3—5	5—25	2.0	0.4 (n=6)	120
Cinchonine hydrochloride	7	5—25	0.7	1.0 (n=7)	80
Brucine hydrochloride	2—7	5—25	2.1	0.6 (n=3)	120
Novatropine	3—7	5—25	2.2	0.3 (n=4)	120
Quinine sulfate	7	5—15	3.0	0.5 (n=3)	100
Quinaldine sulfate	2.7	12—31	1.7	1.0 (n=3)	65
Thiamine hydrochloride	7	15—25	1.5	0.4 (n=3)	80
Amphetamine sulfate	7	30	3.3	1.0 (n=3)	70

[a] All compounds except amphetamine sulfate were titrated by Method 1.

As is usual with liquid-membrane electrodes, some pre-conditioning is necessary before the first titrations of the day or in changing from one compound to another. For the present systems, one titration of a relatively concentrated sample proved to be sufficient for conditioning. For titrations of dilute solutions of substances which give small potentiometric breaks, 2—3 pre-titrations are needed for conditioning.

Generally, the potentiometric breaks and the steepness of the titration curve increase with increasing concentration of the substance titrated, with the exception of papaverine hydrochloride and cocaine hydrochloride. Representative curves are shown in Fig. 3. The titration curves for tetraphenylphosphonium bromide, tetrabutylammonium bromide, cetyltrimethylammonium bromide, cetylpyridinium bromide, papaverine hydrochloride, cocaine hydrochloride, and novatropine were similar to the sigmoidal curves obtained for tetraphenylarsonium chloride. The titration curves for morphine hydrochloride, codeine phosphate, cinchonine hydrochloride, brucine hydrochloride, quinine sulfate, thiamine hydrochloride and quinaldine sulfate were similar to those obtained for atropine sulfate (Fig. 3a). The titration curves for trimethylphenylammonium bromide were similar to those obtained for acetylcholine chloride (Fig. 3b).

In the titration curves for atropine sulfate (and for compounds with similar titration curves) and for amphetamine sulfate, the electrode potential drops initially because the tetraphenylborate added is not precipitated instantaneously; as the titration proceeds, the sigmoidal shape is regained.

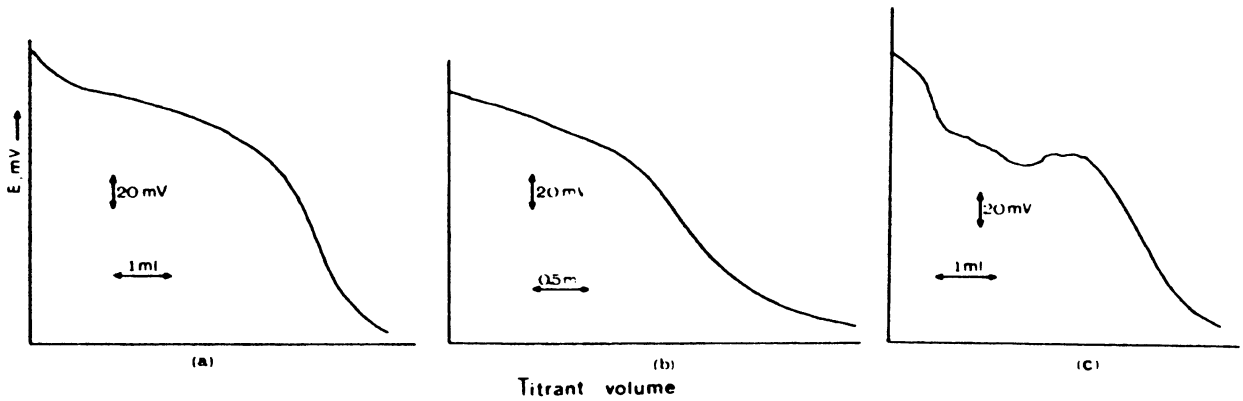

Fig. 3. Titration curves of organic cations with 1.0×10^{-2} M sodium tetraphenylborate: (a) 25.00 ml of 1.0×10^{-3} M atropine sulfate; (b) 25.00 ml of 1.0×10^{-3} M acetylcholine chloride; (c) 2.00 ml of 1.0×10^{-2} M amphetamine sulfate (other conditions as under Procedure).

Analysis of pharmaceutical preparations

Several pharmaceutical preparations which contain active substances precipitated by sodium tetraphenylborate were analyzed.

Mephentermine sulfate injection. The solution (6.00 ml) is diluted to exactly 50 ml with water, and 2.00-ml aliquots are titrated after addition of 3.00 ml of 0.02% (w/v) gelatine solution.

Thiamine hydrochloride tablets. Twenty tablets are powdered and dissolved in water, and the solution is adjusted to exactly 1 l. Aliquots (25.00 ml) of this solution are diluted to exactly 500 ml. Then 20.00-ml aliquots of this solution are mixed with 5.00 ml of buffer pH 7 for titration.

Atropine sulfate eye drops. A 4.00-ml portion of the solution is diluted to exactly 100 ml, and 20.00-ml aliquots are mixed with 5.00 ml of buffer pH 5 for titration.

Cetylpyridinium chloride in lozenges. Fifteen lozenges are powdered, 60 ml of water is added and the mixture is boiled for 5 min. The hot solution is filtered through a sintered glass crucible (G4) under suction, cooled and diluted to exactly 100 ml. For titration, 5.00-ml aliquots of this solution are diluted with 15.00 ml of water.

Amantadine hydrochloride capsules. Two capsules are added to 10 ml of water, and the mixture is heated to boiling until the capsules have completely melted. After cooling and dilution to exactly 50 ml, 2.00-ml aliquots of this solution are mixed with 6.00 ml of water and titrated.

Domiphen bromide in gargle solution. A 10.00-ml portion of the solution is diluted to exactly 250 ml with water, and 20.00-ml aliquots of this solution are titrated.

Results for the determination of organic compounds precipitated by tetraphenylborate in pharmaceutical preparations are shown in Table 2. There is fairly good agreement between the nominal values and the amounts of substance calculated from the titrimetric method. The titration curves for domiphen bromide were similar to those obtained for tetraphenylarsonium

TABLE 2

Potentiometric titration of organic compounds in pharmaceutical preparations with sodium tetraphenylborate

Compound	Content (mg)[a]		R.s.d. (%)	Potential break (mV)
	Nominal	Found		
Mephentermine sulfate injection	15[b]	15.3	0.7 (n=7)	110
Thiamine hydrochloride tablets	300	307.7	0.5 (n=6)	80
Atropine sulfate eye-drops	10	9.2	1.0 (n=6)	55
Cetylpyridinium chloride lozenges	2.5	2.3	1.0 (n=6)	470
Amantadine hydrochloride capsules	100	110	1.5 (n=4)	85
Domiphen bromide gargle solution	10	10.4	0.8 (n=4)	520

[a]Contents are given as mg ml^{-1} for liquid preparations, otherwise as mg per tablet, lozenge or capsule. [b]Expressed as base.

chloride. The titration curves of amantadine hydrochloride and mephendermine sulfate were similar to those obtained for atropine sulfate.

Conclusions

The tetraphenylborate-sensitive electrode described here is very easily constructed and is a useful sensor for the titration of many organic cations or bases with sodium tetraphenylborate. The proposed procedures are simple, accurate, precise and sensitive. The application of the electrode in the titration of active substances precipitated by tetraphenylborate in pharmaceutical preparations gave satisfactory results. It should be possible to extend the use of the electrode in titrations of drugs of major pharmaceutical importance such as phenothiazines, tricyclic antidepressants, etc.

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