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DEVELOPMENT OF QUINHYDRONE ELECTRODE IN CHLOROFORM. APPLICATION TO THE DETERMINATION OF EQUILIBRIUM CONSTANTS OF ACID–BASE REACTIONS AND POTENTIOMETRIC TITRATION OF SOME AMINE DRUGS

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Summary—The optimum conditions for the functioning of quinhydrone electrode as acid indicator in chloroform was determined by voltammetric and potentiometric studies. This electrode was used for the determination of equilibrium constants of acid–base reactions and the potentiometric determination of the end point of acidimetric titrations of some amine drugs such as phenothiazinic derivatives in pharmaceutical preparations, after extraction into chloroform. The relative standard deviations of 20 mg of aliphatic amines, piperidine and piperazine substituted phenothiazines were 0.5, 0.7 and 1% respectively.

The quinhydrone electrode is an important secondary acid indicator electrode. This electrode is simple to construct, comes to equilibrium more rapidly than the hydrogen electrode. It is applicable in aqueous and likewise non-aqueous media.[1–4]

In spite of high dissolving power and extracting property of chloroform against natural products, organic and pharmaceutical compounds having acid or base properties, the potentiometry has not been used for the detection of end points of acid–base titrations in this solvent due to the low dielectric constant, high resistance of medium and lack of an acid–base indicator electrode.

Recently the use of potentiometry was reported for the detection of end points of oxidimetric titrations of phenothiazinic compounds by bromine solution in chloroform.[5]

The obtained results from our previous studies on the electrochemical behaviour of *p*-benzoquinone at Hg and Pt disk electrodes in chloroform,[6,7] suggest that the quinhydrone electrode may be available and used as acid indicator electrode in chloroform.

The aim of the present work was to study the possibility of functioning the quinhydrone electrode in chloroform and also its use in potentiometric detection of end points of acid–base titrations and determination of their equilibrium constants.

EXPERIMENTAL

Reagents

The solvent used was chloroform G.R. from E.Merck or Fluka. Tetrabutylammonium perchlorate(TBAP) and methanesulfonic acid (d = 1.485 p > 98%) were from Fluka. Pure phenothiazine compounds were from local sources. Other chemicals were P.A grade from E.Merck or Fluka. A stock solution of methanesulfonic acid ($1M$) was prepared by dilution of a required volume of pure methanesulfonic acid in chloroform. This solution was diluted 100 times, standardized and used as titrant. A $4 \times 10^{-3}M$ quinhydrone ($C_Q = C_{H_2Q} = 4 \times 10^{-3}M$) + $0.5M$ TBAP solution in chloroform was used as electrolyte in the potentiometric titration of phenothiazines. The standard solutions of *N*-substituted phenothiazines were prepared by dissolving accurately weighted amount of each pure phenothiazine (as its hydrochloride, dried according to the U.S. Pharmacopeia[8]) in 10 ml of $1M$ NaOH, then extracting three times with 10,10 and 5-ml portions of chloroform.

Apparatus

A Potentiograph E 536 equipped with an E 578 titration stand from Metrohm was used

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to plot the normal and differential forms of the titration curves.

The reference electrode, Ag/AgI (satd) 0.05*M* TBAI + 0.5*M* TBAP in chloroform, was used in a separated compartment with a dense ceramic plug in the bottom. A polished Pt disk electrode was immersed in electrolyte solution and used as acid indicator electrode (quinhydrone electrode). The experiments were carried out at 22 ± 0.2°.

Procedures

Standardization of methanesulfonic acid solutions. A 10-ml portion of standard strychnine solution (45 mg in 50 ml $CHCl_3$) was pipetted into the reaction cell and titrant solution added at 1 ml/min. The potential ranges from 250 to 700 mV *vs.* the reference electrode.

Extraction and separation of phenothiazines from pharmaceutical preparations. Transfer an accurately measured volume of syrup, injection solution or weighed portion of finely powdered tablets equivalent to about 50 mg of phenothiazine drugs (as their hydrochlorides) to a 125-ml separate funnel, add 10 ml of 1*M* NaOH, mix and extract with three 20-ml portions of chloroform, shaking gently for 3 min to avoid emulsion formation. Combine the extracts in a 100-ml volumetric flask.

Potentiometric titration of acids HA(CH_3SO_3H, CCl_3COOH...) with bases B (Bu_3N, $BuNH_2$...) for the determination of equilibrium constants of occurred reactions. To prevent intervening of various ion-pair reactions with unknown equilibrium constants in a thermodynamic analysis of the potential changes of quinhydrone electrode in order to determine the equilibrium constants, the conductive medium was provided by a related BH^+A^- ion-pair, during the potential measurements in chloroform. This may be carried out by preliminary neutralization of 0.1*M* HA in chlorofrom with a 0.2*M* chloroformic solution of B. Plots of the well-defined potentiometric titration curves were obtained by introducing a new 10-ml aliquot of 0.1*M* HA solution in this medium. Note that all potentiometric titrations pursued by means of quinhydrone electrode (quinhydrone concentration in assayed solution was about $10^{-3}M$).

Potentiometric titration of phenothiazines. Pipette 40 ml of combined chloroform extracts onto the reaction cell, add 10 ml of electrolyte solution, titrate with 0.01*M* methanesulfonic acid and plot the titration curve with the potentiograph. Quantitative determination of phenothiazines is achieved in one of the following ways.

(i) A standardized solution of methanesulfonic acid is used as a titrant in potentiometric titrations.

(ii) Another titration is carried out with a second 10-ml aliquot of a standard solution of *N*-substituted phenothiazines. The quantity of phenothiazine is calculated by comparison of the volumes of titrant used in two titrations.

Equations of titration curves

The titration curves of acids HA with bases B and vice versa may be plotted by potential measurement using quinhydrone electrode as acid indicator in the presence of a related HB^+A^- ion-pair as conductive electrolyte, according to the described procedure.

The electrode potential on the two sides of the equivalence point can be expressed as follows.

(1) Before the equivalence point:

In the presence of strong acid (HA), *p*-benzoquinone (Q) is found as $(HA)_2Q$ species in chloroform[7] and the *p*-benzoquinone/hydroquinone redox system can be shown as follows:

$$Q(HA)_2 + 2e \rightleftharpoons H_2Q + 2A^-$$

at 22°:

$$E_{eq} = E_1^\circ + \frac{0.058}{2}\log\frac{[Q(HA)_2]}{[H_2Q][A^-]^2} \qquad (1)$$

or

$$E_q = E_1^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_H + \frac{0.058}{2}\log\frac{[HA]^2}{[A^-]^2} \qquad (2)$$

with:

$$Q(HA)_2 \rightleftharpoons Q + 2HA \quad K_H = \frac{[Q][HA]^2}{[Q(HA)_2]} \qquad [2(a)]$$

During the formation of HB^+A^- in solution according to the titration reaction (b) and dissociation of the formed HB^+A^- according to equilibrium (c), relationship (2) can be rewritten as relationship (3):

$$HA + B \rightleftharpoons HB^+A^- \quad K_T = \frac{|HA|\,|B|}{|HB^+A^-|} \qquad [2(b)]$$

$$HB^+A^- \rightleftharpoons HB^+ + A^-$$

$$K_d = \frac{[HB^+][A^-]}{[HB^+A^-]} = \frac{[A^-]^2 \text{ or } [HB^+]^2}{[HB^+A^-]} \qquad [2(c)]$$

$$E_{eq} = E_1^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_H K_d + \frac{0.058}{2}\log\frac{|HA|^2}{|HB^+A^-|} \quad (3)$$

or

$$E_{eq} = E_1^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_H K_d + \frac{0.058}{2}\log C_0 + \frac{0.058}{2}\log\frac{A(1-x)^2}{(x+1)} \quad (4)$$

with:

$$x = \frac{\text{add titrant}}{C_0}, \quad [HA] = C_0 - xC_0,$$

$$|HB^+A^-| = C_0 + xC_0 \quad \text{and} \quad \frac{V_0}{V_0+v} = A$$

where C_0 is the initial concentration of HA or preformed HB^+A^- an electrolyte (see experimental procedures) and V_0, v are the initial volumes of assayed solution and added titrant respectively.

(2) After the equivalence point:

In the presence of the produced acid (HB^+), the quinone/hydroquinone system can be presented as follows:

$$Q + 2HB^+ + 2e \rightleftharpoons H_2Q + 2B$$

$$E_{eq} = E_2^\circ + \frac{0.058}{2}\log\frac{|Q|\,|HB^+|^2}{|H_2Q|\,|B|^2} \quad (5)$$

or

$$E_{eq} = E_2^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_d + \frac{0.058}{2}\log\frac{[HB^+A^-]}{|B|^2} \quad (6)$$

or

$$E_{eq} = E_2^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_d + \frac{0.058}{2}\log C_0 + \frac{0.058}{2}\log\frac{2A}{(x-1)^2} \quad (7)$$

with:

$$|HB^+A^-| = 2C_0 \quad \text{and} \quad |B| = xC_0 - C_0$$

Equilibrium constants of reactions between acids and bases

The equilibrium constants of titration reactions of acids (HA) with bases (B) may be determined from intercepts of the plots E *vs.* $\log(A(1-x)^2)/(1+x)$ for $x < 1$ (a_1) and E *vs.* $\log(2A)/((x-1)^2)$ for $x > 1$ (a_2) using the related potentiometric titration curves as follows.

$$a_1 = E_1^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_d K_H + \frac{0.058}{2}\log C_0 \quad (8)$$

$$a_2 = E_2^\circ + \frac{0.058}{2}\log\frac{|Q|}{|H_2Q|} - \frac{0.058}{2}\log K_d + \frac{0.058}{2}\log C_0 \quad (9)$$

Substraction of (8) and (9) gives:

$$a_1 - a_2 = E_1^\circ - E_2^\circ + \frac{0.058}{2}pK_H$$

Taking into account that the equilibrium potentials (E_{eq}) of quinhydrone electrode according to relations (3) or (6) are the same, one can conclude that:

$$E_1^\circ - E_2^\circ = -\frac{0.058}{2}pK_H - 0.058\log\frac{|HA|\,|B|}{|HB^+A^-|}$$

hence for $pK_T = -\log(|HA||B|)/(|HB^+A^-|)$ we have:

$$pK_T = (a_1 - a_2)/0.058 \quad (10)$$

RESULTS AND DISCUSSION

Development of quinhydrone electrode

Voltammetric study. The results obtained from our previous studies on the electrochemical behaviour of quinones in the absence and presence of various types of proton donors at Pt and Hg electrodes,[6,7] show that the half-wave potential for the benzoquinone reduction wave varies with the type and concentration of added acid (Fig. 1) and functioning of quinhydrone electrode as acid indicator seems to be possible.

Potentiometric study. The potentiometric curve for the titration of 10 ml of 0.1*M* CH_3SO_3H (HA) in chloroform with 0.1*M* chloroform solution of Bu_3N (B) using quinhydrone electrode is shown in Fig. 2. The potential ranges from 0.850 to 0.300 volts *vs.* the reference electrode, with a large rise in the region of the equivalence point.

The plots of $\log(A(1-x)^2)/(1+x)$ against E for $0 < x < 1$ and $\log(2A)/((x-1)^2)$ against E for $x > 1$, gave the straight lines with slopes of

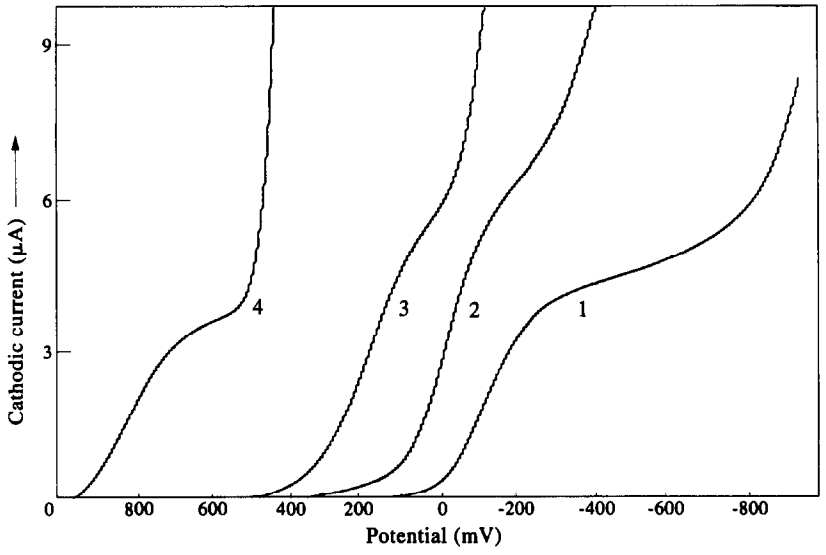


Fig. 1. Voltammogrammes of $5 \times 10^{-4}M$ p.benzoquinone at Pt disk electrode in $0.5M$ TBAP-chloroform solution. (1) In the absence of proton donor. (2) 1 + 25 mM piperidinium perchlorate (HB^+ type acid) (3) 2 + 25 mM acetic acid (HA type weak acid). (4) 3 + 25 mM methanesulfonic acid (HA type strong acid).

0.031 V (see Fig. 2). This agrees with the Nernst equation and therefore the potentiometric titration allows the equilibrium constant of the titration reaction and the end point to be determined.

Determination of equilibrium constants of acid–base reactions

The proposed potentiometric method was used for the determination of the equilibrium constants of acid–base reactions in chloroform. The calculated equilibrium constants of reactions between some acids and n-$BuNH_2$ using the relationship (10) are shown in Table 1. As can be seen, these values agree well with those obtained from spectrophotometric measurements.[13]

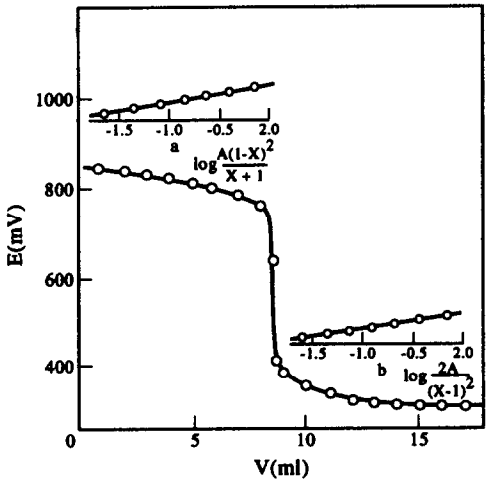


Fig. 2. Potentiometric titration of 10 ml $0.1M$ CH_3SO_3H in electrolyte solution ($0.1M$ preformed $CH_3SO_3^-$ H^+NBu_3 + $10^{-3}M$ quinhydrone) with $0.1M$ Bu_3N solution, (a) plot of E vs $\log(A(1-x)^2)/(1+x)$ (b) E vs $\log(2A)/((x-1)^2)$.

Determination of phenothiazinic derivatives

Several electroanalytical methods have been developed for the determination of phenothiazine derivatives in pharmaceutical preparations and biological media.[5,9–12] Since most of the employed methods follow a preliminary separation of compounds by solvent extraction, the direct application of a electroanalytical method in pure extract phases is simple, rapid and sensitive.[5,9]

In this work, acidimetric titration of phenothiazinic drugs has been achieved in chloroform, with a chloroformic solution of CH_3SO_3H, using quinhydrone electrode as indicator electrode for the potentiometric determination of the end point.

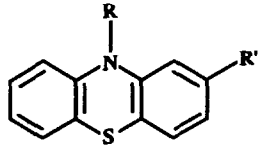
Phenothiazinic derivatives can be divided into three groups (see Table 2).

Table 1. The values of pK_T

Acids	Potentiometry	Spectrophotometry
Methanesulfonic acid	10.01 ± 0.50	9.65
Trichloroacetic acid	7.89 ± 0.95	7.20
Dichloroacetic acid	6.63 ± 0.62	6.22
Acetic acid	3.17 ± 0.40	2.95
Benzoic acid	3.61 ± 0.52	2.90

Table 2. Some phenothiazine derivatives

Phenothiazines*	R	R′	Groups
Phenothiazine	-H	-H	
Promethazine	$-CH_2-CH(CH_3)-N(CH_3)_2$	-H	A
Chlorpromazine	$-(CH_2)_3-N(CH_3)_2$	-Cl	A
Perphenazine	$-(CH_2)_3-N$ ⟨⟩ $N-(CH_2)_2-OH$	-Cl	B
Trifluoperazine	$-(CH_2)_3-N$ ⟨⟩ $N-CH_3$	$-CF_3$	B
Trifluopromazine	$-(CH_2)_3-N(CH_3)_2$	$-CF_3$	A
Flouphenazine	$-(CH_2)_3-N$ ⟨⟩ $N-(CH_2)_2-OH$	$-CF_3$	B
Thioridazine	$-(CH_2)_2-$ ⟨⟩ $N-CH_3$	$-SCH_3$	C

* 

A: Aliphatic amines substituted
B: Piperazine substituted
C: Piperidine substituted

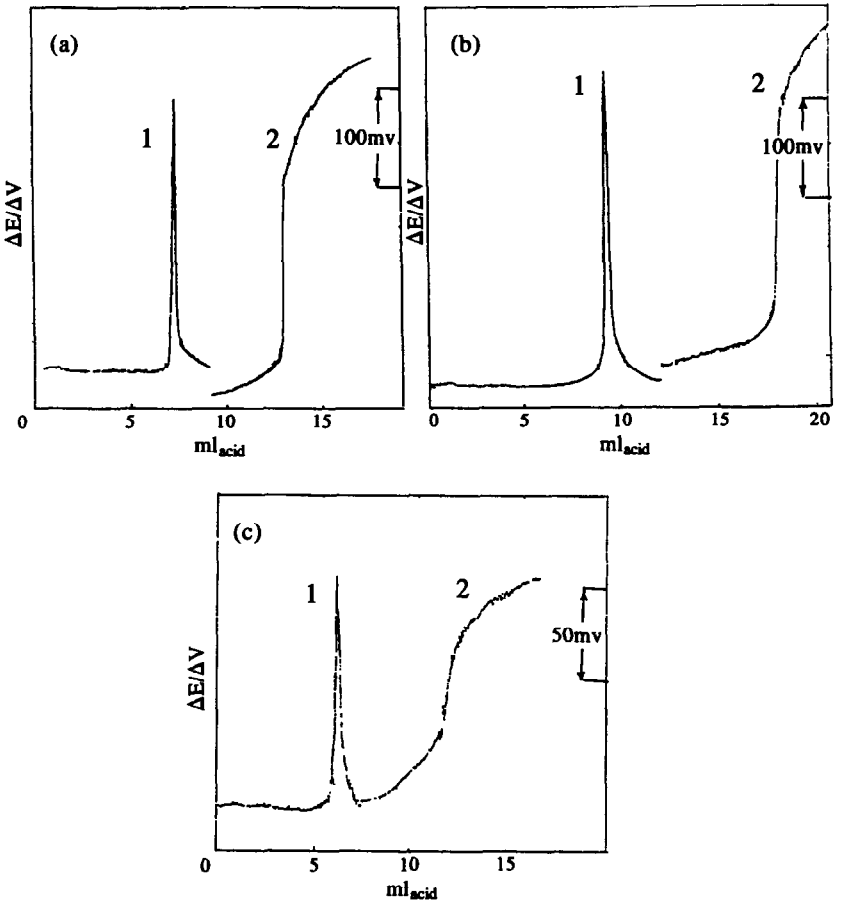


Fig. 3. Typical examples of titration curves of two successive 10 ml portions of chloroform extracts of phenothiazine derivatives related to the three groups listed in Table 2 with a 0.0095*M* solution of methanesulfonic acid (CH_3SO_3H) (a) 0.055 M chlorpromazine, (b) 0.0081*M* thioridazine, (c) 0.051*M* trifluoperazine (1) plots of $\Delta E/\Delta V_{acid}$ *vs* V_{acid} (2) plots of E *vs* V_{acid}.

Table 3. Determination of phenothiazinic drugs by potentiometric and U.S.P methods

Products	Nominal content	Found* Proposed method	U.S.P method
Chlorpromazine ampoul	50mg/2ml	50 ± 2	51 ± 1.6
Promethazine syrup	1mg/mm/ml	1 ± 0.2	1.1 ± 0.1
Thioridazine tablet	25mg/tab.	25 ± 1	25 ± 1.0
Fluophenazine tablet	100mg/tab.	100 ± 1	101 ± 103

Phenothiazines	Added mg	Found* mg	Recovery%
Chlorpromazine	50	50.3 ± 0.2	100.6
Trifluoperazine	50	50.2 ± 0.5	100.4
Thioridazine	50	50.1 ± 0.3	100.3
Promethazine	50	49.9 ± 0.2	99.8

*Mean of three determinations and 90% confidence interval of the mean.

Aliphatic amines substituted derivatives. The phenothiazines of this group are strongly basic and react with CH_3SO_3H, almost quantitatively. The potentiometric curve is shown in Fig. 3(a) for chlorpromazine.

Piperidine substituted derivatives. Dependents of this group are weaker bases than the first group. The potentiometric curve for thioridazine was shown in Fig. 3(b).

Piperazine substituted derivatives. Components of this group are weaker bases than two other group. The potentiometric curve is shown in Fig. 3(c) for trifluoperazine.

The values of the recovery obtained for 50 mg of pure phenothiazines (as their hydrochlorides) according to the procedure described in the experimental section were almost 100% (Table 3). The relative standard deviations for the determination of 20 mg of pure phenothiazine derivative of each group are 0.5, 0.7 and 1% respectively.

Analysis of pharmaceutical preparation

Several phenothiazinic drugs purchased from local sources in various forms (tablet, syrup and injection) were analysed by the proposed method. The results obtained for some typical pharmaceutical preparations by the proposed potentiometric method were compared with those obtained by the U.S.P. methods.[8] The results are given in Table 3. As can be seen, there was reasonably fair agreement between the present and standard U.S.P. methods.

CONCLUSION

On the basis of the results obtained from the voltammetric and potentiometric studies on the electrochemical behaviour of the Q/H_2Q redox couple in chloroform at Pt electrode the quinhydrone electrode can be used as indicator electrode for the potentiometric indication of acid-base titrations in chloroform. The equilibrium constants of acid-base reactions can be determined in this medium. The potentiometric titration curves of all substituted phenothiazines with CH_3SO_3H, show a sufficiently large potential rise in region of the equivalence point, and allow, rapid, accurate and precise determination of phenothiazines in pharmaceutical preparation, after their extraction into chloroform. The proposed method is rapid, general and versatile.

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