

Conductometric and Potentiometric Determination of the Solubility Products of Some Distigmine Ion Recognition Species

Y. M. Issa^{1*}, M. A. El Ries^{2*}, and A. Khorshid²

¹Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt;

²NODCAR – National Organization for Drug Control and Research, Giza, Egypt.

Abstract: A conductometric method is proposed to determine the sparingly soluble ion-associate of *Distigmine*. A comparison between conductometric and ISEs values has shown that the conductometric method is suitable, rapid, and easy-to-perform. The *Distigmine*-ISE is successfully used for the determination of solubility products of different sparingly soluble salts of *Distigmine* of the Ds_3PM_2 , Ds_3PT_2 , Ds_2SM , Ds_2ST , $DsTPB_2$, $DsRein_2$ and $DsPi_2$ stoichiometry. The solubility products determined by Ds-ISE were found to be in good agreement with the values obtained by conductometric method. Finally, the solubility products for Ds_3PM_2 , Ds_3PT_2 , Ds_2SM , Ds_2ST , $DsTPB_2$, $DsRein_2$, and $DsPi_2$ were found to be 4.92×10^{-25} , 5.61×10^{-25} , 2.27×10^{-28} , 4.71×10^{-28} , 3.11×10^{-14} , 5.91×10^{-15} , and 6.40×10^{-14} , respectively.

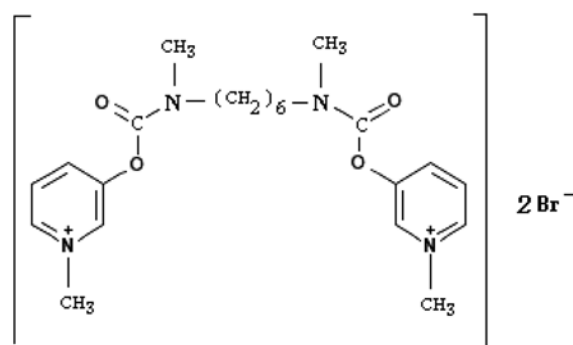
Key words: Potentiometry and conductometry; Ion-selective electrodes; *Distigmine*, Sparingly soluble salts; Solubility products.

* Authors for correspondence. E-mails: "yousrymi@yahoo.com" & "Mohamedelries@hotmail.com"

Introduction

Distigmine is a quaternary ammonium compound, where the quantitative analysis of quaternary ammonium salts $[N^+(R)_4]X^-$, is a difficult analytical problem. When the fragment "R" — i.e., an alkyl radical — is a long hydrocarbon chain or an aromatic system, and "X" is generally a halogen, quaternary ammonium salts are less soluble in water and often organophilic.

Recently, many quaternary ammonium salts have been widely used for several applications [1-4]. In designing pharmaceutical dosage forms the interaction between large organic anions and cations is an important factor in determining the physiochemical characteristics, compatibility, stability and availability of drug substances. Distigmine bromide is one of several drugs that have been used in the prevention and treatment of postoperative gastrointestinal atony; i.e., decreased gastrointestinal motility [5]. Distigmine bromide (aka "Bispyridostigmine bromide"; see Scheme 1) is a para-sympathomimetics quaternary ammonium compound for the treatment of *Myasthenia gravis* that is a reversible inhibitor of cholinesterase activity with actions similar to those of *Neostigmine*, but with more prolonged preventing the breakdown of acetylcholine.



Scheme 1. The chemical structure of *Distigmine* bromide

$$M(C_{22}H_{32}Br_2N_4O_4) = 576.3 \text{ g mol}^{-1}$$

Ion-selective electrodes (ISEs) are electrochemical sensors based on a thin selective membrane or a film, allowing us the potentiometric determination of the activity of certain ions in the presence of other ions in the sample solution. In recent years, ISEs have also been used for the determination of solubility products of different sparingly soluble salts [6-9]. In spite of successful progress in the design of highly selective electrodes for various ions, there has not been any report on the development of selective and sensitive sensors for *Distigmine*. The present paper reports on the determination of solubility products of different sparingly soluble distigmine salts based on ISEs fabricated in the laboratory. The present results were compared with the solubility products determined by conductometric / conductimetric method.

Experimental

Reagents and Materials

All reagents used were chemically pure grade. Doubly distilled water was used throughout all the experiments. *Distigmine* bromide (DsBr_2 , cat. No. 15876-67-2; M.wt = 576.3), and its pharmaceutical preparations (*Ubretid*[®]; tablets, 5 mg/tablet) were provided by Arab Drug Company, Cairo-A.R.E. under License of NYCOMED-Austria. Phosphomolybdic acid (PMA), phosphotungstic acid (PTA), silicomolybdic acid (SMA), silicotungstic acid (STA), sodium tetraphenylborate (NaTPB), ammonium reineckate (Amm.Rein), and picric acid (PiH), dioctylphthalate (DOP), poly (vinyl chloride) (PVC) of high relative molecular weight, acetonitrile, dimethylformamide (DMF) and tetrahydrofuran (THF) were obtained from Aldrich. The ion-exchangers, distigmine phosphomolybdate ($\text{Ds}_3\text{-PM}_2$) (greenish yellow powder), distigmine phosphotungstate ($\text{Ds}_3\text{-PT}_2$) (white powder), distigmine silicomolybdate ($\text{Ds}_2\text{-SM}$) (buff powder), distigmine silicotungstate ($\text{Ds}_2\text{-ST}$) (white powder), distigmine tetraphenylborate (Ds-TPB_2) (white powder), distigmine Reineckate (Ds-Rein_2) (magenta powder), and distigmine picrate (Ds-Pi_2) (yellow powder) were prepared by addition of 50 ml of 0.01 ± 0.001 M distigmine bromide (DsBr_2) solution to 100 ml of each of the following: 0.0033 ± 0.001 M PMA, 0.0033 ± 0.001 M PTA, 0.0025 ± 0.001 M SMA, 0.0025 ± 0.001 M STA, 0.01 ± 0.001 M NaTPB , 0.01 ± 0.001 M AmmRein, and 0.01 ± 0.001 M PiH.

The obtained precipitates were washed thoroughly with distilled water, until negative reaction to bromide (as tested with acidic solution of AgNO_3) then filtered and dried at room temperature and ground to fine powder. The chemical composition of the ion-exchangers as identified by elemental analysis was found to be 3:2 for ($\text{Ds}_3\text{-PM}_2$) and ($\text{Ds}_3\text{-PT}_2$), 2:1 for ($\text{Ds}_2\text{-SM}$) and ($\text{Ds}_2\text{-ST}$), 1:2 for (Ds-TPB_2), (Ds-Rein_2) and (Ds-Pi_2) respectively.

Electrochemical System

The potentiometric measurements mode was carried out with a Jenway 3510 digital pH/mV meter. A WTW packed saturated calomel electrode (SCE) was used as an external reference electrode. The conductometric measurements were carried out with a conductivity meter Model (644) Metrohm, provided with a conductivity cell of 1.000 cell constant.

Conductometric Determination of the Solubility Products for Ion-Exchangers

(according to [5])

A series of solutions of different concentrations (C) was prepared for each of DsBr₂, PTA, PMA, STA, SMA, NaTPB, AmmRein, and PiH. The conductivities of these solutions were measured at 25°C and the specific conductivities (λ_o), corrected for the effect of dilution, were calculated and used to obtain the equivalent conductivities (λ) of these solutions. Straight line plots of λ vs. $\sqrt[3]{C}$ were constructed and λ_o DsBr₂, λ_o PMA, λ_o PTA, λ_o SMA, λ_o STA, λ_o NaTPB, λ_o AmmRein and λ_o PiH were determined from the intercept of the respective line with the λ -axis. The activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute, the values of $\lambda_{o(Ds-PM)}$, $\lambda_{o(Ds-PT)}$, $\lambda_{o(Ds-SM)}$, $\lambda_{o(Ds-ST)}$, $\lambda_{o(Ds-TPB)}$, $\lambda_{o(Ds-Rein)}$, and $\lambda_{o(Ds-Pi)}$ were calculated using Kohlrausch's law of independent migration of ions [10].

The solubility (S) and solubility product (K_{sp}) values of a particular ion associate were calculated using the following equations;

$$S = K_S \times 1000 / \lambda_{o(\text{ion-associate})}, \quad (1)$$

$$K_{SP} = S^2 \quad \text{for 1:1 ion-pairs}, \quad (2a)$$

$$K_{SP} = 108 S^5 \quad \text{for 3:2 ion-associates}, \quad (2b)$$

$$K_{SP} = 4 S^3 \quad \text{for 2:1 or /and 1:2 ion-associates}, \quad (2c)$$

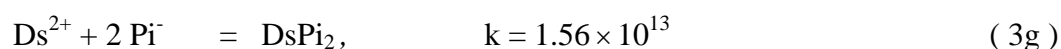
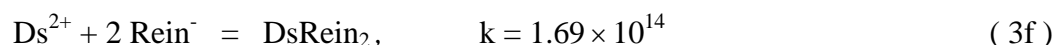
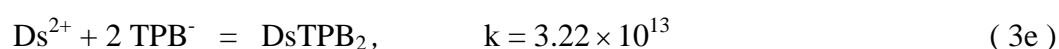
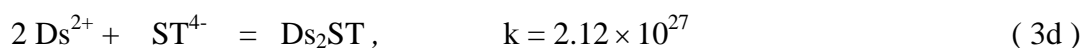
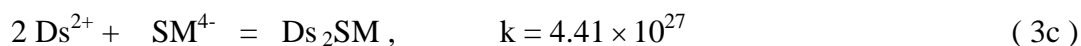
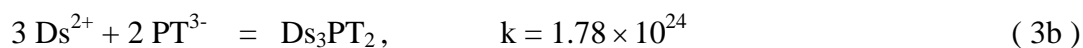
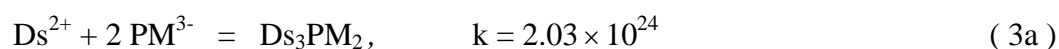
where, " K_s " are the specific conductivity of the saturated solution of the ion associate, determined at 25°C and corrected for the dilution effect. About 0.5 g portion of each ion-associates Ds₃PM₂, Ds₃PT₂, Ds₂SM, Ds₂ST, DsTPB₂, DsRein₂, and DsPi₂ was added to 50 ml distilled water. The solutions were shaken for about 24 h at 25°C and left to stand for a week to attain a stable equilibrium before measuring the conductivities. Then, each saturated solution was decanted to a dry beaker and the equilibrium concentration of drug ion present was determined potentiometrically using the corresponding electrodes by the standard additions method, and hence the solubilities and the solubility product constants of the ion associates were calculated.

Results and Discussion

Determination of the Solubility-Product Constants of the Ion-Associates

Ion-associates formation is the main controlling factors in many chemical reactions, such as precipitation reactions, where the degree of feasibility of titration depends on the degree of completeness of the precipitation reaction. The solubility product (K_{SP}) of the formed ion-associates were determined conductometrically [11] as described under the experimental part, the equilibrium constant of the precipitation reaction (K) is inversely proportional to the solubility product (K_{SP}), whereas the smaller the solubility product of the formed ion-associate, the sharper the end point of the corresponding titration curve.

The solubility products values by conductometric measurements of the investigated ion-associates for Ds_3PM_2 , Ds_3PT_2 , Ds_2SM , Ds_2ST , $DsTPB_2$, $DsRein_2$ and $DsPi_2$ are found to be 4.92×10^{-25} , 5.61×10^{-25} , 2.27×10^{-28} , 4.71×10^{-28} , 3.11×10^{-14} , 5.91×10^{-15} and 6.40×10^{-14} respectively. Consequently, the equilibrium constants of the ion-associate formation reactions are calculated and presented as follows by conductometric measurements:



The respective equilibrium constant values are very high, which indicates the high degree of completeness of the ion-associate formation reactions. At equilibrium, the solubility of the non-dissociated ion-associates in water (the intrinsic solubility) was omitted as this term makes a negligible contribution to the total solubility because the ion-associates are sparingly soluble in water and their saturated solutions are therefore very dilute [12].

The high sensitivity of the present electrodes which are enough to determine distigmine as low as $0.5 \mu\text{g/ml}$ Ds-PM, $2.5 \mu\text{g/ml}$ Ds-PT, $1.0 \mu\text{g/ml}$ Ds-SM, $5.0 \mu\text{g/ml}$ Ds-ST, $0.5 \mu\text{g/ml}$ Ds-TPB, $0.45 \mu\text{g/ml}$ Ds-Rein and $0.1 \mu\text{g/ml}$ Ds-Pi enabled us to use these

electrodes in the determination of the solubility of the employed ion-exchangers and hence to calculate their solubility products. The solubility product constant values were confirmed by conductometric method gathered in Table I and illustrated in Figs. 2 and 3. It is noteworthy to mention that the solubility of an ion-exchanger is one of the main factors controlling the sensitivity of the ion-selective electrode incorporating this ion-exchanger as the electroactive material. This is confirmed by the values of solubilities given in Table I showing that the ion-exchangers of the least solubilities have the lowest detection limits. This is in good agreement with conclusions given by Pungor and Tóth [13] who have postulated that the solubility products of the precipitates contained in the membranes of ion-selective electrodes are in direct relation with the LODs of precipitate(s)-based electrodes.

Table I. Solubility product constants of ion-associates

Ion-associates (denotation)	Solubility S [mol·L ⁻¹]	K _{SP}		LOD (3σ) [mol·L ⁻¹]	Life- time [days]	K = 1 / K _{sp}
		potentiometric	conductometric method			
Ds₃PM₂	5.39×10 ⁻⁶	3.56×10 ⁻²⁵	4.92×10 ⁻²⁵	5.0×10 ⁻⁷	70	2.80×10 ²⁴
Ds₃PT₂	5.53×10 ⁻⁶	4.72×10 ⁻²⁵	5.61×10 ⁻²⁵	2.5×10 ⁻⁶	63	2.11×10 ²⁴
Ds₂SM	7.78×10 ⁻⁶	1.09×10 ⁻²⁸	2.27×10 ⁻²⁸	1.0×10 ⁻⁶	63	9.17×10 ²⁷
Ds₂ST	8.84×10 ⁻⁶	2.48×10 ⁻²⁸	4.71×10 ⁻²⁸	5.0×10 ⁻⁶	56	4.03×10 ²⁷
DsTPB₂	1.98×10 ⁻⁵	1.25×10 ⁻¹⁴	3.11×10 ⁻¹⁴	5.0×10 ⁻⁷	77	8.00×10 ¹³
DsRein₂	1.14×10 ⁻⁵	3.78×10 ⁻¹⁵	5.91×10 ⁻¹⁵	4.5×10 ⁻⁷	63	2.64×10 ¹⁴
DsPi₂	2.52×10 ⁻⁵	5.23×10 ⁻¹⁴	6.40×10 ⁻¹⁴	1.0×10 ⁻⁷	42	1.91×10 ¹³

Abbreviations and symbols used: LOD ... limit of detection; K ... equilibrium constant.

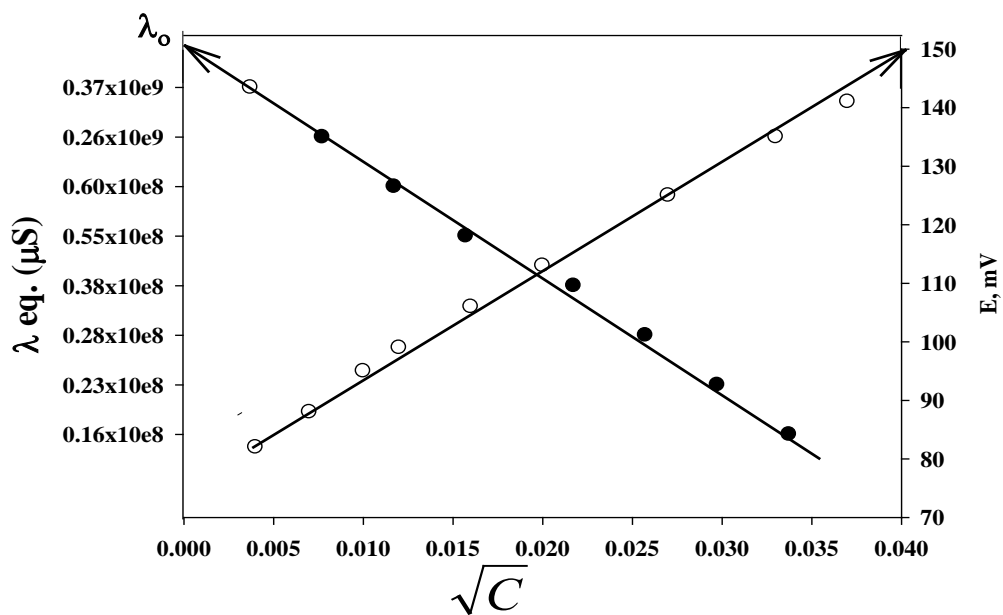


Figure 1. Equivalent conductance (λ_{eq}) vs. the square root of concentration and the corresponding potential measurement for $DsBr_2$

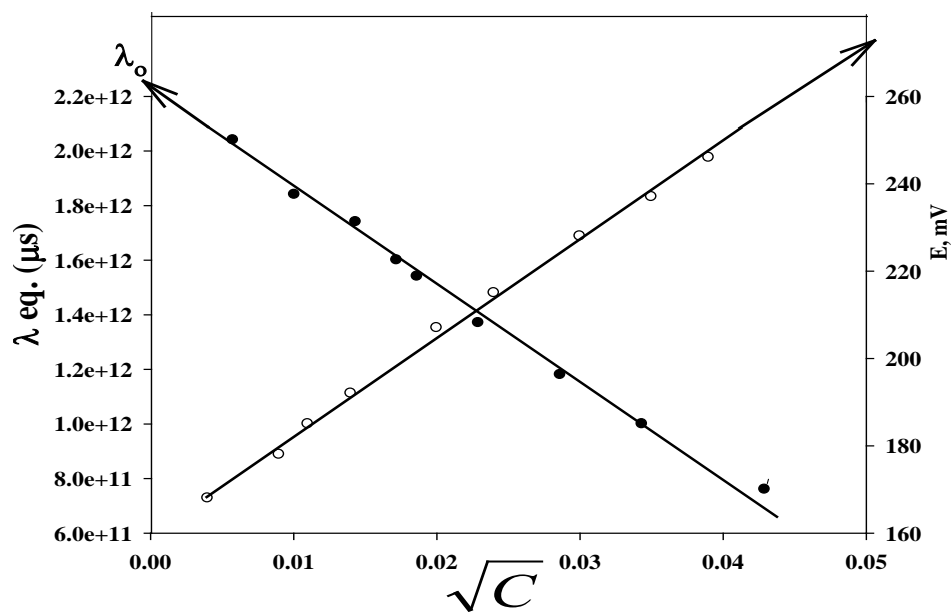


Figure 2. Equivalent conductance (λ_{eq}) vs. the square root of concentration and the corresponding potential measurement for STA

The reciprocal of the solubility product is approximately equal to the equilibrium constant (K) of the precipitation reaction employed in such titration:



where: "Aⁿ⁻" is the counter anion and "D" is the drug moiety, forming a cation involved in the precipitation process; number of experiments, n = 4.

Conclusion

It is clear that the very low solubility product values of the ion-exchangers, the potential break in the titration curves of acids were very high and sharp. This makes it being easy to detect the end points potentiometrically even when solutions of very low concentration of drug solution ($\sim 5.0 \times 10^{-7}$ M) were titrated with these reagents, PMA, PTA, SMA, STA, NaTPB, AmmRein and PiH and revealing that the electrodes constructed can be used successfully as indicator electrodes in potentiometric titrations of DsBr₂ in different samples with a very high recovery.

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