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DETERMINATION OF SOME THIOBARBITURATES  
WITH ION-SELECTIVE MEMBRANE ELECTRODES

KEY WORDS: Ion-selective electrodes, thiobarbiturates,  
direct potentiometry, IR spectra.

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ABSTRACT

A liquid membrane  $\text{Ag}^+$ -selective electrode of our construction and a commercial solid membrane  $\text{Ag}^+/\text{S}^{2-}$ -selective electrode were used for the determination of thiobarbiturates by potentiometric titration with  $\text{AgNO}_3$  solution or by direct potentiometry. The potentiometric data correlated with IR spectra allowed the elucidation of the reaction mechanism.

## INTRODUCTION

The sodium salts of 5,5'-disubstituted thiobarbituric acid derivatives have been widely used for surgery anaesthesia. The 2-thiobarbituric acid (2-TA) and its 5,5'-disubstituted derivatives have been previously determined by different analytical methods: titrimetric<sup>1-3</sup>, spectrophotometric<sup>4-9</sup>, fluorimetric<sup>10</sup>, polarographic<sup>11,12</sup>, gas-chromatographic<sup>13,14</sup>, etc.

We now report a new method, using ion-selective membrane electrodes which permits the direct determination of 2-TA and of its 5,5'-disubstituted derivatives by direct potentiometry or by potentiometric titration using  $\text{AgNO}_3$  solution as titrant.

## EXPERIMENTAL

### Apparatus

E.m.f. measurements were made with a MV-87 digital pH-meter (Präcitronic, East Germany) and the potentiometric titration were carried out using automatic equipment for titration consisting of an ABU 12 Autoburette, TTT2 Titrator and SBR2c recorder (Radiometer). As indicator electrodes, the  $\text{Ag}^+$ -selective membrane electrode developed by us was used as well as an Orion Model 94-16A solid membrane sulfide electrode. A Radiometer saturated calomel electrode, type K401, was used as reference electrode, connected to the sample solution by a saturated potassium nitrate bridge. The IR spectra were recorded on a Zeiss UR 10 spectrophotometer in potassium bromide pellets.

### Reagents

Stock solutions of  $10^{-1} \text{M}$   $\text{AgNO}_3$  were made by diluting an appro-

riate Titrisol (Merck) with distilled water. 2-TA (Australanal) was standardized using titrimetric method proposed by Wojahn<sup>1</sup>. The 5,5'-disubstituted thiobarbiturates (5-ethyl,5' (1-methyl-butyl)-2-thiobarbituric acid, Thiopental-H, and its sodium salt, Thiopental-Na, and 5-ethyl,5' (1-methyl-propyl)-2-thiobarbituric acid, Inactin-H, and its sodium salt, Inactin-Na) were commercial grade.

#### Construction of the $Ag^+$ -selective membrane electrode

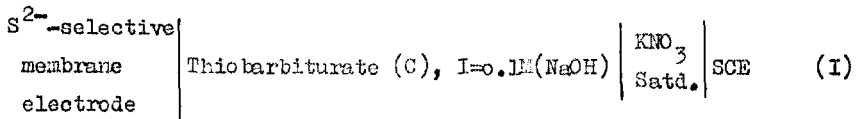
The construction of the electrode has been described previously<sup>15,16</sup> and consists of impregnating the support material (a graphite rod, 15 mm long, 6.5 mm diameter, made water-repellent) attached to the end of the teflon tube, with liquid exchanger consisting of  $Ag^+$  diethyldithiophosphate extracted in  $CCl_4$ . The internal reference electrode was eliminated by using a stainless steel wire introduced into the graphite rod.

#### Procedure

##### a) Direct potentiometry

In this case the  $S^{2-}$ -selective membrane electrode was used as indicator electrode for 2-TA, Thiopental (H- or Na- forms) and Inactin (H- or Na-forms). We prepared stock solutions of  $10^{-2}M$  concentration from those substances. The solutions of  $10^{-3}$ - $10^{-6}M$  concentrations have been obtained by successive dilutions from the above stock solutions. All solutions have been prepared in  $10^{-1}M$  NaOH.

The e.m.f. measurements were made using the following electrochemical cell:



were C represents the concentration of thiobarbiturate varying in the  $10^{-2}$ - $10^{-6}$ M domain. The solutions were stirred during establishment of a constant value of the potential.

#### b) Potentiometric titrations

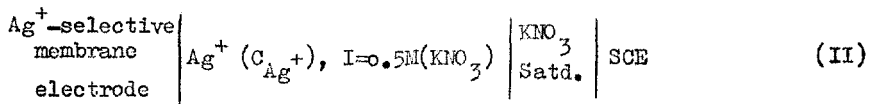
The weighed amounts of 2-TA, Thiopental-H and Inactin-H, respectively, were dissolved in 5 ml MeOH and 45 ml  $\text{H}_2\text{O}$ . For Thiopental-Na and Inactin-Na, addition of MeOH was not necessary. The electrodes ( $\text{Ag}^+$ - or  $\text{S}^{2-}$ -selective membrane electrode and SCE) were immersed into the solution and the sample was titrated with  $10^{-2}$ M  $\text{AgNO}_3$  solution.

### RESULTS AND DISCUSSION

#### Characteristics of $\text{Ag}^+$ -selective membrane electrode

The basic characteristics of the  $\text{Ag}^+$ -selective membrane electrode of our construction are presented in Table 1.

To establish the electrode function, the following electrochemical cell was used:



where  $\text{C}_{\text{Ag}^+}$  represents the  $\text{Ag}^+$  concentration in the range  $10^{-1}$ - $10^{-6}$ M. The e.m.f. of the cell (II) is given by the equation:

$$E = E_0 + 0.0595 \log [\text{Ag}^+] \quad (1)$$

were  $E_0$  represents the conditional standard potential of the electrode in the conditions of use of the electrochemical cell of type (II).

Table 1

The Basic Characteristics of the  $\text{Ag}^+$ -Selective Membrane Electrode

Membrane	Silver diethyldithiophosphate in $\text{CCl}_4$
Concentration of $\text{Ag}^+$ in membrane	$5 \times 10^{-4} \text{M}$
Linear response domain to $\text{Ag}^+$	$10^{-1} - 10^{-5} \text{M}$
Slope	59.5 mV/decade of concentration
Effect of pH	is function of the concentration of $\text{Ag}^+$ in the sample (e.g., pH=1-6 for $10^{-3} \text{M} \text{Ag}^+$ )
Response time	Few seconds in concentrated solutions and approx. 3-4 min. in diluted solutions
Selectivity	The selectivity coefficients, calculated by the separate solutions method have shown that only $\text{Hg}^{2+}$ interferes

#### Potentiometric titrations

The use of  $\text{Ag}^+$ -selective membrane electrode in potentiometric titration of thiobarbiturates give similar results as the commercial  $\text{S}^{2-}$ -selective membrane electrode.

Table 2

Results of the Determination of Thiopental-Na with  
 $\text{Ag}^+$ -Selective Membrane Electrode

No.	Taken (mg)	Found (mg)	Error (%)
1.	4.76	4.77	0.21
2.	7.14	7.20	0.84
3.	9.52	9.60	0.84
4.	11.90	11.94	0.33
5.	14.28	14.13	0.70
6.	19.04	19.03	0.05
7.	23.80	23.72	0.33

Since 2-TA, Thiopental-H and Inactin-H are not soluble in water, for their determination the appropriate solvent for the potentiometric titration as well as the pH of the solution have been taken into account. As the membrane of the  $\text{Ag}^+$ -selective electrode is liquid, the measurements in organic solvents cannot be performed. The potentiometric determinations proceed with good results for a methanol-water ratio equal to 1 : 10. For the Thiopental-Na or Inactin-Na the potentiometric titrations were carried out in distilled water.

Typical titration curves for the titration of Thiopental-H and Thiopental-Na using  $\text{Ag}^+$ - and  $\text{S}^{2-}$ -selective membrane electrodes are presented in Figs. 1 and 2, and the results of the determinations of Thiopental-Na are given in Table 2.

Similar potentiometric curves were obtained for 2-TA or Inactin (H- or Na-forms). It can be seen on the Figs. 1 and 2 that

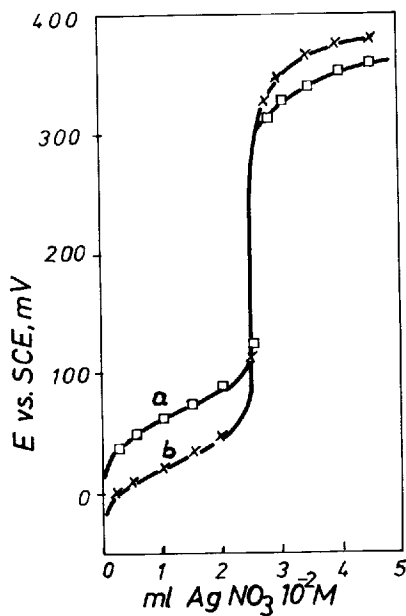


Fig. 1 Potentiometric titration of Thiopental-H (6.00 mg; solvent: MeOH: H<sub>2</sub>O, 1 : 10) a) Ag<sup>+</sup>-selective electrode b) S<sup>2-</sup>-selective electrode

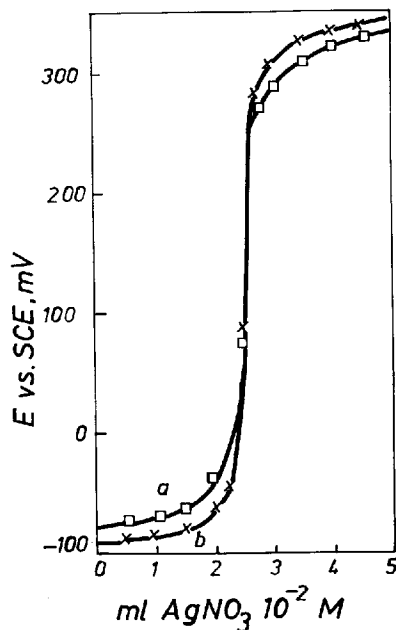


Fig. 2 Potentiometric titration of Thiopental-Na (6.61 mg; solvent: H<sub>2</sub>O) a) Ag<sup>+</sup> selective electrode; b) S<sup>2-</sup>-selective electrode

potential changes around the equivalence point are high enough that the location of the end-point titrant volume is easy. The potentiometric titrations carried out in alkali medium ( $10^{-1}$  or  $10^{-2}$  M NaOH) are doubtful due to the coprecipitation tendency of the silver oxide.

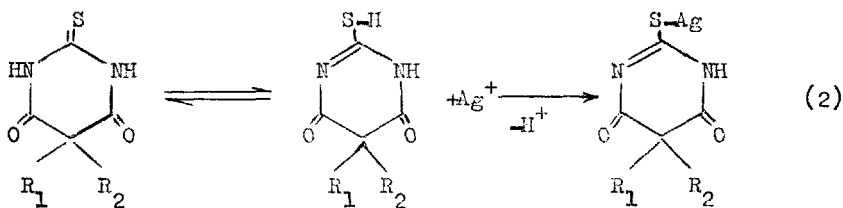
#### Identification of the products

In order to identify the products formed during the reactions,



the precipitates obtained after the titrations were filtered, washed with distilled water and dried at  $105^{\circ}\text{C}$  and their IR spectra were then recorded.

As an example we further discuss only the case of Thiopental-H and its silver salt respectively. Thiopental-H presents a characteristic stretching band at  $1535\text{ cm}^{-1}$  (the "thioureide band" which is due to a  $\nu_{\text{C-N}}$  mode<sup>17,18</sup>). This band completely disappears in Ag (I) salt obtained after titration with  $\text{AgNO}_3$ . The antisymmetric stretching modes of N-C-S function at  $1427$  and  $1220\text{ cm}^{-1}$ , respectively are also present in the Ag (I) salt spectrum shifted if they are compared with those of the original compound. The weakness and the broadening of the bands  $\nu_{\text{N-H}} = 3160$  and  $3053\text{ cm}^{-1}$ , ascribed to the N-H stretching vibrations as well as the fact that in the spectrum of the precipitate both carbonyl group frequencies ( $\nu_{\text{C=O}} = 1740$  and  $1680\text{ cm}^{-1}$ ) were present confirms that the reaction mechanism is that according to equation 2:



thione form

thiol form

( $\text{R}_1 = \text{CH}(\text{CH}_3)\text{-C}_3\text{H}_7$ ;  $\text{R}_2 = \text{C}_2\text{H}_5$  for Thiopental-H)

The potentiometric data also confirm the reaction mechanism given by eq. (2), since on the titration curve only one potential jump, corresponding to the 1 : 1 compound, is present.

Direct potentiometry

We have investigated the potentiometric response of the  $\text{Ag}^+/\text{S}^{2-}$  crystal membrane electrode to the thiobarbiturate. If the electrode is introduced into a solution containing  $\text{Ag}^+$  ions on both sides of the membrane a potential difference is developed, given by equation:

$$E - E'_o = RT/F \ln a_{\text{Ag}^+} \quad (3)$$

where  $a_{\text{Ag}^+}$  is the activity of the silver ion at the sample solution - membrane interface. The  $\text{Ag}^+/\text{S}^{2-}$  crystal membrane electrode also responds to inorganic  $\text{S}^{2-}$  (the response slope for  $\text{S}^{2-}$  is one-half that observed for  $\text{Ag}^+$ , having an opposite sign):

$$E - E'_o = - RT/2F \ln a_{\text{S}^{2-}} \quad (4)$$

The response to  $\text{S}^{2-}$  is due to an equilibrium change in  $\text{Ag}^+$  activity at the membrane surface. When such an electrode is used for direct potentiometry determinations of sulfur-containing organic compounds<sup>19-22</sup>, it is assumed that the electrode functioning is the result of interactions between sulfur-containing functional groups and  $\text{Ag}^+$  from the membrane.

In the presence of thiobarbiturate ion (5,5'-disubstituted thiobarbiturates exists in two predominant forms in alkaline solution<sup>12</sup>), the reaction between  $\text{Ag}^+$  and the thiobarbiturate is given by the equation (2) and the electrode responds to thiobarbiturate ion according to eq. (5):

$$E - E'_o = S \log a_{\text{thiobarbiturate}} \quad (5)$$

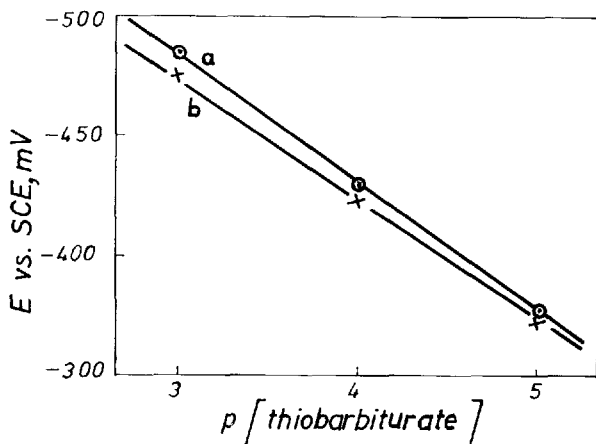


Fig.3

Response of the  $\text{Ag}^+/\text{S}^{2-}$  crystal membrane electrode to Thiopental (curve a) and Inactin (curve b)

were  $S$  is the slope of the electrode which should be  $-59.1 \text{ mV/decade}$  of concentration in this case according to a stoichiometry of interaction given by the equation (2), and  $a_{\text{thiobarbiturate}}$  represents the activity of thiobarbiturate ion.

Fig.3 shows the plots of  $E(\text{mV})$  vs.  $p$  [thiobarbiturate] for Thiopental-H and Inactin-H in  $10^{-1} \text{ M NaOH}$ . The linear response domain in both cases is about  $10^{-3}$  -  $10^{-5}$  thiobarbiturate with slopes which are in agreement with the corresponding value for a 1 : 1 silver-thiobarbiturate compound (51 mV for Inactin and 54 mV for Thiopental, respectively).

The electrode response time has to be taken into account when the electrode is used in direct potentiometry. Fig.4 shows the electrode response to different concentration of Thiopental.

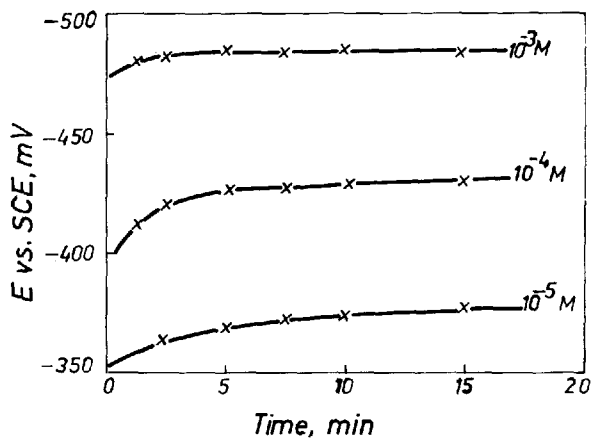


Fig.4

Response time of the  $\text{Ag}^+/\text{S}^{2-}$  crystal membrane electrode to different concentration of Thiopental in  $10^{-1}\text{M}$  NaOH

Similar response times have been found for Inactin too. In diluted solutions, however, response times in the range of 15 min. are too long for usual measurement. Therefore the potentiometric titration, showing good results up to  $5 \times 10^{-4}\text{M}$  thiobarbiturate is recommended.

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