A Substituted Tetraazaporphyrinogen as an Electroactive Component for a Polymeric Membrane Anion-Selective Electrode

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Abstract. A novel anion-selective electrode has been prepared by using tetraazaporphyrinogen as the electroactive component and *o*-nitrophenyloctyl ether as the plasticizer. The electrode exhibits almost Nernstian response characteristics for Pic^-, ReO_4^-, SCN^-, ClO_4^- and TPB^-. The linear response ranges towards the above-mentioned anions are $10^{-6} \sim 10^{-2}$, $10^{-5} \sim 10^{-2}$, $10^{-5} \sim 10^{-2}$, $10^{-5} \sim 10^{-1}$, and $10^{-5} \sim 10^{-2}$ mol/L and the corresponding slopes are -56.8, -57.1, -56.3, -56.1, and -59.9 mV/decade with correlation coefficients of -0.99978, -0.99987, -0.99999, -0.99998, and -0.99998, respectively. The electrode shows an anti-Hofmeister selectivity sequence: $Pic^- > SCN^- > ReO_4^- > ClO_4^- > I^- > Br^- > BF_4^- > Sal^- > NO_3^- > Cl^-$. The unusual response mechanism of the novel anion-selective electrode was investigated by experimental observations and calculation with the MNDO method. The electrode was used as a TPB^- and a Pic^- sensitive electrode, respectively, and applied to the assay of levamisole hydrochloride tablets by potentiometric titration and Gran's methods. The results obtained are in excellent agreement with that determined by the standard pharmacopoeia method based on nonaqueous titration.

Key words: tetraazaphorphyrinogen, anion-selective electrode.

1. Introduction

Considerable interest has focused on employing crown ethers or biscrown ethers as cation-sensitive electroactive materials during recent years. An exploration of the use of aza macrocycles as electroactive components of the cation-selective electrodes has been performed [1]. Tarrago et al. [2] have demonstrated that tetraazaporphyrinogens like crown ethers, can not only be used to extract, transport, and release alkali cations but also form stable complexes with transition metal cations. Therefore the utilization of a substituted tetraazaporphyrinogen (STAPPG, see Figure 1) as the electroactive material for cation-selective electrodes has been attempted in this paper. However, it is interesting to note that the STAPPG-based electrodes using 2-nitrophenyloctyl ether (*o*-NPOE), dibutylphthalate (DBP) and dioctylphthalate (DOP) as plasticizers show unusual anionic responses. The PVC

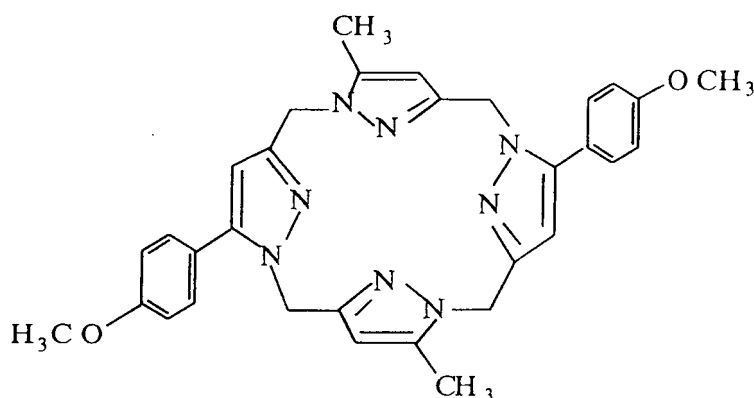⋆ Author for correspondence. E-mail: wyj@mail.zzu.edu.cn; Fax: (86) 0371-7979408.

Figure 1. Structure of STAPPG.

membrance electrode containing STAPPG and *o*-NPOE displays almost Nernstian slopes for Pic^-, ReO_4^-, SCN^-, ClO_4^-, and TPB^-. It is well known that conventional anion-selective electrodes are usually prepared using the classical anion exchangers such as quaternary ammonium or phosphonium salts as the electroactive components, whose applications are limited because they always show the same Hofmeister selectivity series [3]. Thus, during recent years the electroactive materials used for the anion-selective electrodes, such as metalloporphyrins [4–14], schiff base complexes of cobalt(II) [15], derivatives of vitamin B_{12} [16–17], cobalt phthalocyanine derivatives [18], metallocenes [19], palladium organophosphine complex [20], and mercury organic compounds [21–22], which all induce anti-Hofmeister selectivity series in membranes have been exploited extensively. To our knowledge, however, none of the STAPPG-type macrocycles has been reported to be an anion sensing component for polymeric membrane electrode. In this paper, we first report the anion response characteristics and response mechanism of the novel anion-selective electrode doped with STAPPG as the membrane active component and *o*-NPOE as the plasticizer. The electrode has been applied to the assay of levamisole hydrochloride and satisfactory results are obtained as compared with that of the standard pharmacopoeia method [23]. The study presented in this paper not only reveals a new binding property of the STAPPG-type macrocycles but also provides a promising application of the compounds.

2. Experimental

2.1. REAGENTS AND APPARATUS

1, 6, 11, 16-tetraaza-2, 12-dimethyl-7, 17-di(*p*-methoxyphenyl) porphyrinogen (STAPPG) was synthesized according to the literature method [24]. *o*-NPOE was prepared as reported [25]. Tetrahydrofuran (THF) (dried by sodium and distilled prior to use), DBP of analytical-reagent grade, DOP of chemical-reagent grade, and poly(vinylchloride) (PVC) of high molecular mass were obtained from Shanghai

Chemical Co. Levamisole hydrochloride tablets were supplied by Henan Institute of Drug Control. All solutions were prepared with analytical grade reagents. Doubly-distilled deionized water was used throughout. A standard solution of sodium tetraphenylborate (NaTPB) was standardized by the literature method [26] and stored in the dark. Standard sodium picrate solution was standardized by the method described by Hadjiioannou et al. [27].

Potentials were measured by using an ISE-Computer Analyzer (New Technology Co., Zhengzhou Univ.). Measurements of pH values were carried out on a pH-meter of model PHS-2C (Leici Analytical instrument, Shanghai).

2.2. PREPARATION OF ELECTRODES

STAPPG (6.76 mg) and plasticizer (500 mg, o-NPOE, DOP or DBP) were dissolved in 5% (wt%) PVC-cyclohexanone solution (containing 170 mg PVC). The solution was uniform and transparent and was poured into a glass ring with a 42 mm diameter. The solvent was allowed to evaporate and a tough flexible membrane was obtained. Then, the membrane was cut and sealed onto the end of the Ag/AgCl electrode barrel with a 5% THF solution of PVC (wt%).

An internal reference electrode (Ag/AgCl) and an internal solution of 1 mol/L NaCl were used. Prior to potentiometric measurement, the electrode was conditioned over night in a 1.0×10^{-2} mol/L sample solution.

A Hg/Hg_2Cl_2 double-junction reference electrode with an outer chamber filling solution of 0.1 mol/L LiAc was used throughout the experiment.

Cell assemblies of the following type were used: Ag-AgCl/internal solution/PVC membrane/sample solution//reference electrode.

2.3. PROCEDURES

Direct potentiometry. Standard solutions ($10^{-3} \sim 10^{-7}$ mol/L or $10^{-2} \sim 10^{-7}$ mol/L) were prepared by successive dilution of a 10^{-2} mol/L (for NaTPB, NaPic, $KReO_4$, $NaBF_4$) or of a 10^{-1} mol/L sample solution. The PVC membrane electrode in conjunction with the reference electrode was immersed in the stirred sample solution. In the order from low to high concentrations, the emf values were tested and recorded. A plot of emf (mv) against log[c] was made and then the unknown sample concentration was gained from the calibration graph using the ISE-Computer Analyzer.

Electrode selectivity. Selectivity coefficients, log $K^{pot}_{Cl^-, X^-}$, were obtained by the separate solution method [4] in 1.0×10^{-2} mol/L solutions of the corresponding sodium or potassium salts. Concentrations of test anions were used and all sample solutions contained 0.1 mol/L Na_2SO_4 as an ionic strength buffer.

Content assay of levamisole hydrochloride tablets. Thirty levamisole hydrochloride tablets were weighed and finely powdered. Then, two assay methods were used. (1) A portion of the powder, equivalent to about 7.2 mg of levamisole

hydrochloride, was weighed accurately and transferred to a 50 mL beaker, and then dissolved in a 30 mL solution of 0.1 mol/L Na_2SO_4 by stirring adequately. The electrode in conjunction with the reference electrode was immersed in it. The end-point of titration was determined potentiometrically using the standard solution of 1.08×10^{-2} mol/L NaTPB as the titrant. (2) A portion of the powder, equivalent to about 103.6 mg of levamisole hydrochloride, was weighed accurately and transferred to a 50 mL beaker and then dissolved in a 15 mL solution of 0.1 mol/L Na_2SO_4. The same process as in part (1) was carried out, but using Gran's titration the potential end-point was determined using a 4.37×10^{-2} mol/L NaPic standard solution as the titrant.

3. Results and Discussion

3.1. Selection of the plasticizer

A series of PVC membrane electrodes based on STAPPG as the electroactive material and o-NPOE, DOP, or DBP as plasticizers, respectively, were examined. The results indicate that the o-NPOE-plasticized PVC membrane electrode doped with STAPPG exhibits superior response characteristics as compared with the DBP, or DOP-plasticized ones. Therefore, the properties of the electrode consisting of STAPPG as electroactive material and o-NPOE as plasticizer were studied in detail.

3.2. Response characteristics of the electrode

Figure 2 shows the calibration curves for potentiometric response toward eleven organic and inorganic anions of the PVC membrane electrode based on STAPPG and o-NPOE. The electrode exhibits almost Nernstian response characteristics for Pic^-, ReO_4^-, SCN^-, ClO_4^-, and TPB^- with linear response ranges of $10^{-6} \sim 10^{-2}$, $10^{-5} \sim 10^{-2}$, $10^{-5} \sim 10^{-2}$, $10^{-5} \sim 10^{-1}$, and $10^{-5} \sim 10^{-2}$ mol/L, the corresponding correlation coefficients of -0.99978, -0.99987, -0.99999, -0.99998, and -0.99998, and the corresponding slopes of -56.8, -57.1, -56.3, -56.1, and -59.9 mV/decade, respectively. Thus, the electrode is promising to be practically used as a general electrode sensitive to Pic^-, ReO_4^-, SCN^-, and ClO_4^-. On the other hand, it should be noted that, with an overnight conditioning in 1.0×10^{-2} mol/L NaTPB solution, the electrode becomes a specially TPB^--sensitive electrode which repeatedly displays excellent potentiometrical response characteristics toward TPB^- and has no obvious response for the others. This phenomenon is presumable due to the fact that TPB^- is a big and strongly lipophilic anion and seems to be able to exist very stably in the membrane phase and hinders other anions from being responded. Accordingly, in this case, the electrode becomes a special electrode of TPB^-.

On the basis of the solutions of Pic^-, ReO_4^-, SCN^-, ClO_4^-, and TPB^- as the tested solutions, the reproducibility, response time, and lifetime of the electrode were also investigated. Potential readings of the electrode dipped alternately three
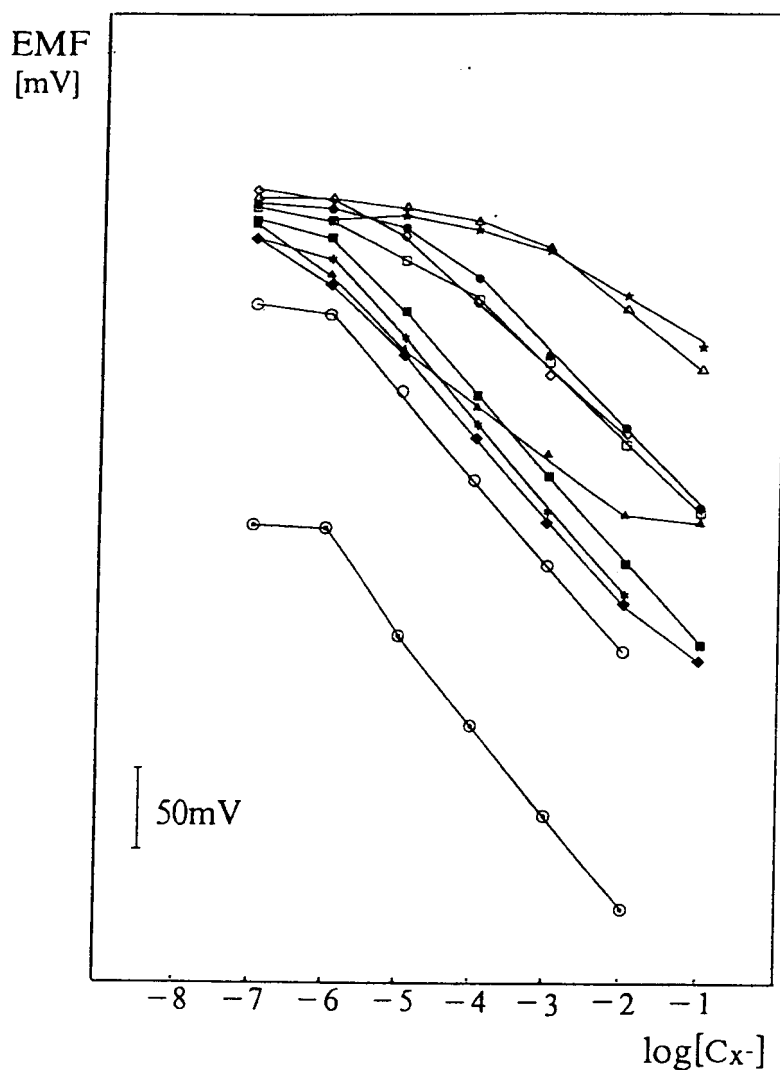
Figure 2. Potentiometric response curves of the PVC membrane electrode based on STAPPG and *o*-NPOE (($\odot$) TPB$^-$; ($\bigcirc$) Pic$^-$; ($\blacklozenge$) SCN$^-$; (*) ReO$_4^-$; ($\blacksquare$) ClO$_4^-$; ($\blacktriangle$) I$^-$; ($\square$) Br$^-$; ($\lozenge$) BF$_4^-$; ($\bullet$) Sal$^-$; ($\triangle$) NO$_3^-$; ($\bigstar$) Cl$^-$).

times into stirred tested solutions of 10^{-3} and 10^{-2} mol/L showed standard deviations within 0.6 mV. The response time is a few seconds at higher concentrations ($10^{-1} \sim 10^{-3}$ mol/L) and about $1 \sim 2$ minutes in diluted solutions. The electrode has demonstrated an effective lifetime of at least three months by a consecutive use of the electrode for the sample solutions studied.

Potentiometric selectivity coefficients, log K_{Cl^-,X^-}^{pot}, were obtained by the separate solution method in 1.0×10^{-2} mol/L solutions of the corresponding salts. The
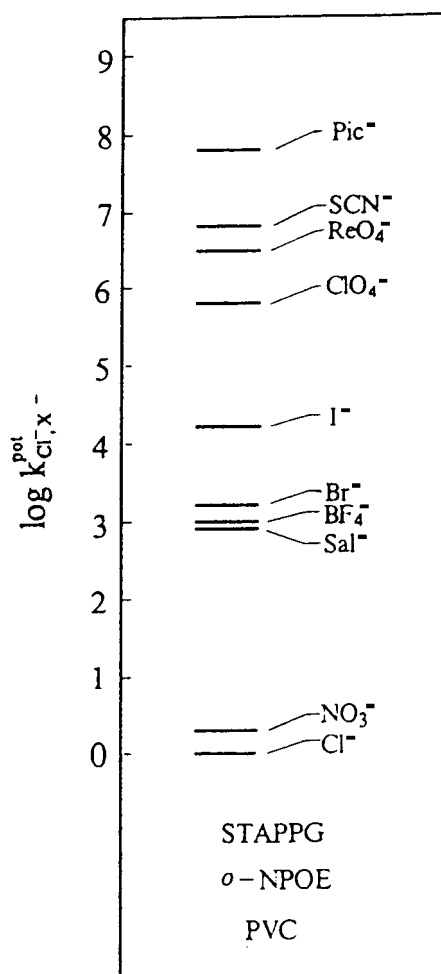
Figure 3. Potentiometric selectivity coefficients determined by the separate solution method for the PVC membrane electrode based on STAPPG and o-NPOE. (Apart from the potassium salts of thiocyanate, perrhenate, iodide and bromide, all the others are salts containing Na^+ cation.)

results presented in Figure 3 show that the potentiometric selectivity sequence* is as follows: $Pic^- > SCN^- > ReO_4^- > ClO_4^- > I^- > Br^- > BF_4^- > Sal^- > NO_3^- > Cl^-$. It is shown that the selectivity sequence of inorganic anions deviates from the so-called Hofmeister series.

The effect of pH on the potentials of the electrode is shown in Figure 4 (all pH values of the tested solutions were adjusted with NaOH or HCl solution.). The results indicate no obvious pH dependence in the pH range from 1 to 12 for 10^{-4}

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* Owing to the strong interaction of TPB^- anion with the membrane phase of the electrode, there is no consideration about TPB^- in the selectivity sequence.
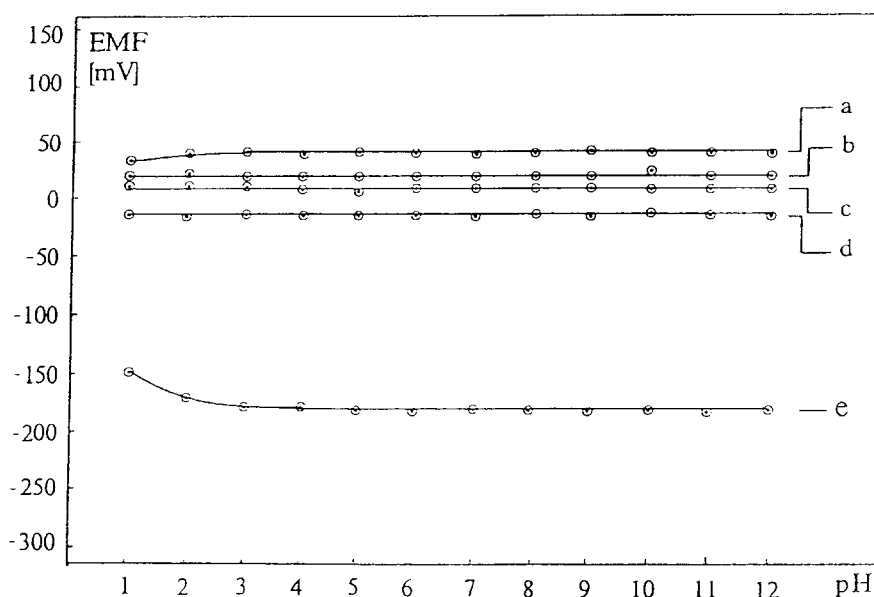
Figure 4. Effect of pH on the potentiometric response of the PVC membrane electrode based on STAPPG and *o*-NPOE in 10^{-4} mol/L sample solutions (a: ClO_4^-; b: ReO_4^-; c: SCN^-; d: Pic^-; e: TPB^-).

mol/L solutions of Pic^-, ReO_4^-, SCN^-, and ClO_4^-, and in the pH range from 3 to 12 for 10^{-4} mol/L TPB^- solution. However, when pH values of 10^{-4} mol/L TPB^- solution are lower than 3, the potential gradually increases with decreasing pH, which is ascribable to the instability of NaTPB in strongly acidic medium [28]. Therefore, good response characteristics of the electrode could be achieved in a wide working pH range.

3.3. STUDY OF THE RESPONSE MECHANISM

In order to elucidate the unusual response mechanism of the electrode, several experiments and quantum chemistry calculations have been designed and carried out.

In the light of the fact that *o*-NPOE has a high polarity ($\epsilon = 24$) whereas both DOP and DBP have a relatively low polarity ($\epsilon \approx 6$), it could be inferred that the *o*-NPOE-plasticized blank membrane electrode has stronger potentiometric responses toward lipophilic anions or cations than DOP- or DBP-plasticized ones via the classical ion-exchange mechanism. The following experiment provides evidence for this point. The blank membrane electrodes using *o*-NPOE, DOP or DBP as plasticizers, respectively, were prepared and tested. As expected, DOP-or DBP-plasticized blank membrane electrode has no appreciable potentiometric responses toward lipophilic ions (e.g. Pic^-, ReO_4^-, SCN^-, ClO_4^-, TPB^-, and $(CH_3)_4N^+$),

Table I. Potentiometric response characteristics of the *o*-NPOE-plasticized blank PVC membrane electrode.

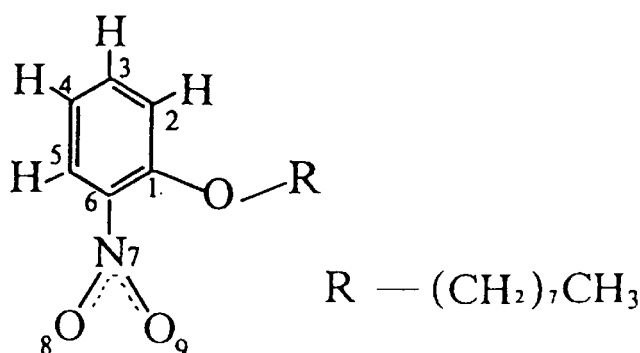| Tested ions	Slope (mV/log C)	Linear range (mol/L)	Correlation coefficients
TPB$^-$	−40.9	$10^{-6} \sim 10^{-3}$	−0.99818
Pic$^-$	−43.9	$10^{-6} \sim 10^{-2}$	−0.99901
SCN$^-$	−24.9	$10^{-5} \sim 10^{-1}$	−0.99992
ClO$_4^-$	−27.4	$10^{-6} \sim 10^{-1}$	−0.97151
ReO$_4^-$	−20.5	$10^{-5} \sim 10^{-1}$	−0.99963
(CH$_3$)$_4$N$^+$	47.1	$10^{-4} \sim 10^{-1}$	0.99685

Figure 5. Structure of *o*-NPOE.

whereas a *o*-NPOE-plasticized one has good responses for them (see Table I). Moreover, the anion selectivity sequence of *o*-NPOE-plasticized blank membrane electrode (i.e. TPB$^-$ > Pic$^-$ > ReO$_4^-$ = ClO$_4^-$ > SCN$^-$) is consistent with the so-called Hofmeister lipophilic series.

Because of the high polarity of *o*-NPOE, there are positively and negatively charged centers in the molecule of *o*-NPOE, which could interact with the counter-charged ions via electrostatic affinity. To gain further insight into the sites of both positively and negatively charged centers in the molecule of *o*-NPOE, the distribution of net charges of *o*-NPOE was calculated by using the most stable geometry configuration of *o*-NPOE obtained by the MNDO method. The results demonstrate that *o*-NPOE (see Figure 5) has high polarity (D = 6.3 Debye). O(8) and O(9) of the nitro-group of *o*-NPOE molecule, having −0.3651 and −0.3172 net negative charges, respectively, is the main negatively charged center of *o*-NPOE whereas both N(7) of the nitro-group and C(6) of the neighbouring phenyl ring, with +0.4956 and +0.2160 net positive charges, play the role of the main positively charged center of *o*-NPOE.

Considering of the ability of the substituted tetraazaporphyrinogens, like crown ethers, to form stable complexes with alkali cations [2], a possible response mechanism of a o-NPOE plasticized PVC membrane electrode doped with STAPPG may be proposed based on the above results. After the membrane of the electrode is conditioned overnight in the sample solution, some changes (as shown in Figure 6) have taken place in the organic membrane phase of the electrode. The cation existing in the given sample solution could freely permeate into the membrane phase accompanied with the counter anion species and then complexes to STAPPG via ion-dipole interaction, forming a cationic complex STAPPG-M^+($M^+ = K^+$ or Na^+). Since STAPPG-M^+ exhibits an approximately planar structure, the negatively charged center of o-NPOE could also interact with the center cation M^+ on each side of STAPPG-M^+ via ion-dipole interaction, forming a special response system as shown in Figure 6 (b). The formation of the special response system could certainly enhance the polarity of the o-NPOE molecule, which further leads to an increase of the electrostatic affinity of the positively charged center of o-NPOE to tested anions. Hence, the anionic response characteristics of the electrode are significantly improved as compared to those of the o-NPOE-plasticized PVC blank membrane electrode. If the tested electrode was plasticized with DBP or DOP, the anionic response characteristics were poor due to the low polarity of DBP and DOP that were not able to interact with STAPPG-M^+ to form such a synergistic response system as that existing in the membrane phase of the electrode based on STAPPG and o-NPOE.

The formation of the synergistic response system consisting of o-NPOE and STAPPG-M^+ strengthens the steric effect in the vicinity of the positively charged center of o-NPOE due to the approximately planar structure of STAPPG-M^+. As a result, the responses of the electrode towards nonlinear or big inorganic anions are reduced. This deduction is consistent with the experiment results (e.g. SCN^- is prior to ClO_4^- and Br^- is prior to NO_3^- in the selectivity sequence). Therefore, the selectivity sequence of the electrode toward inorganic anions is an anti-Hofmeister series whereas the selectivity sequence of o-NPOE-plasticized blank membrane agrees well with the Hofmeister series owing to no such steric effect as described above existing in the blank membrane phase. In the case of TPB^- and Pic^-, since the two organic anions are strongly lipophilic, their low hydration energy rather than the steric effect plays the predominant role in determining the selectivity sequence. Therefore, TPB^- and Pic^- anions are prior to all inorganic anions in the selectivity sequence.

In conclusion, the formation of the synergistic response system increases the electrostatic affinity between the positively charged center of o-NPOE and the tested anions, so the type of interaction is based on anion-exchange. However, as compared with the conventional anion-selective electrode, a special conformation of cationic sites composed of STAPPG and o-NPOE exists in the membrane of the electrode, which may induce the steric effect and lead to the anti-Hofmeister selective sequence of the electrode toward inorganic anions.
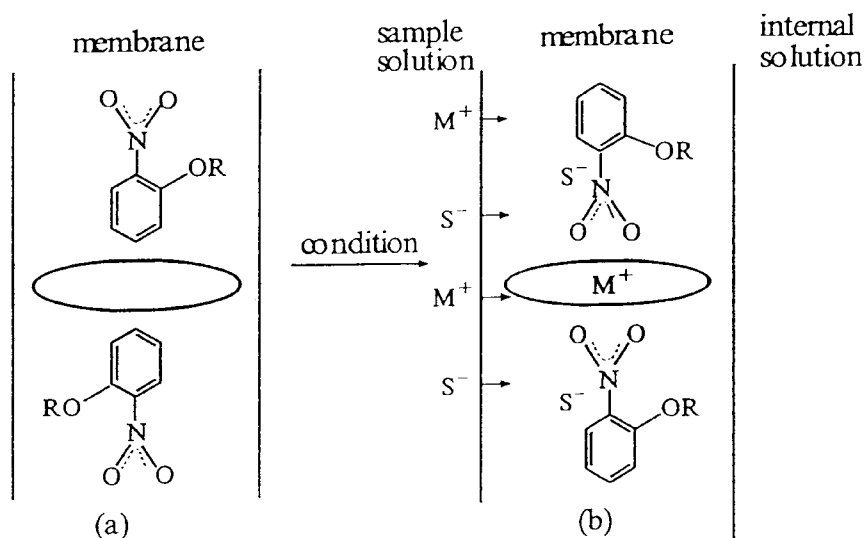
Figure 6. Proposed potentiometric response mechanism of the PVC membrane electrode based on STAPPG and *o*-NPOE; (a) Before conditioning. (b) After conditioning overnight in 10^{-2} mol/L sample solution.

Table II. Content assay of (YU 920830-2) levamisole hydrochloride tablets.

Method	Pharmacopoeia*	TPB$^-$-ISE**	Pic$^-$-ISE**
Mean (%)	94.1	94.3	93.9
Standard deviation (%)	0.13	0.46	0.34

* $n = 2$.
** $n = 6$.

3.4. APPLICATION TO PHARMACEUTICAL ASSAYS

Content assay of levamisole hydrochloride tablets (YU 920830-2) was carried out by using the methods described above ($n = 6$) with the new electrode serving as a TPB$^-$ or Pic$^-$-sensitive electrode, respectively. Both results from the electrode methods and from the pharmacopoeia procedure are shown in Table II. The significance tests (i.e. *t* test) were carried out by using the result obtained by the pharmacopoeia procedure as standard value. The results are as follows:

$$T_{Pic^-} = 1.44 < t\,(5; 0.05) = 2.57$$

$$T_{TPB^-} = 1.06 < t\,(5; 0.05) = 2.57$$

It shows that there are no significant differences between the results from the electrode methods and from the pharmacopoeia procedure.

4. Conclusions

The unusual response characteristics of the novel anion-sensitive electrode based on STAPPG as electroactive material and o-NPOE as plasticizer have been investigated. The results indicate that this electrode exhibits almost Nernstian response characteristics towards Pic^-, ReO_4^-, SCN^-, ClO_4^- and TPB^- in a wide range of concentrations and shows an anti-Hofmeister sequence: $Pic^- > SCN^- > ReO_4^- > ClO_4^- > I^- > Br^- > BF_4^- > Sal^- > NO_3^- > Cl^-$. The formation of the synergistic response system with STAPPG and o-NPOE rather than DBP or DOP for the elucidation of response mechanism has been proposed by means of experimental observations and the quantum chemistry calculation. The results obtained by using the electrode as the TPB^- and Pic^- sensitive electrode, respectively, to analyse levamisole hydrochloride tablets, agreed favourably with the standard pharmacopoeia method. The elucidation of the membrane response mechanism in this paper is only preliminary and the further unravelling of the response mechanism will be one of our research projects in the future.

Acknowledgements

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