Anal. Chem. **2002,** *74,* 3312−3320

Chromium(III) Porphyrin as a Selective Ionophore in a Salicylate-Selective Membrane Electrode

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The construction, potentiometric response properties, and applications of a novel ion-selective electrode with high selectivity toward salicylate are described. Chromium(III) tetraphenylporphyrin chloride was used as ion carrier into plasticized PVC membrane. This ionophore is capable of serving as both a positively charged and neutral carrier, depending on the pH of the sample solution. The influence of several variables was investigated to optimize the potentiometric response and selectivity of the electrode. The resulting electrode demonstrates a near-Nernstian response over a wide range of salicylate concentration (10^{-6}−10^{-1} M). This electrode has a fast response time and micromolar detection limit and could be used over a wide pH range (3−9). The proposed electrode showed very high selectivity for salicylate over a number of common inorganic and organic anions. The specific interaction of salicylate with the central metal of porphyrin is described based on UV−visible absorption spectra. The electrode was successfully applied to the determination of salicylate in pharmaceutical preparations and clinical samples.

Carrier-based ion-selective electrodes (ISEs) have found widespread use for the direct determination of various ionic species in complex matrix samples.[1,2] Their response characteristics including fast response time, wide linear dynamic range, low detection limit, and good selectivity make these suitable for direct and rapid analytical detection of trace amounts of chemically and biologically important compounds.

A very interesting development in the field of ISEs is the construction of electrodes that can chemically recognize specific anions and offer potentiometric responses that differ from classical anion exchanger-based membranes. One of the most important recognition elements that can be utilized in the development of anion-selective electrodes involves specific metal−ligand interactions.[3] For the development of a truly anion-selective electrode, a relatively strong interaction between the ionophore and the anions is required in order to complex anions in a selective fashion. Some lipophilic organometallic compounds,[4−6] metalloporphyrins,[7−10] metallophthalocyanines,[11−16] as carriers for anions, have been observed to show such specific metal−ligand interactions and induce anion selectivity in the membranes that significantly differ from the Hofmeister selectivity pattern for conventional anion exchangers.

Salicylate, acetylsalicylate, and its derivatives are widely used as antimicrobial agents in several pharmaceutical preparations. The bactericide and fungicide actions of salicylate have been used as both oral and topical forms. Salicylate is the main metabolite resulting from hydrolysis of acetylsalicylate and its amounts in the blood of patients who are treated with medicine containing salicylate derivatives must be determined because levels higher than 2.2 mM salicylate are regarded as toxic for the patients.[17] The determination of salicylate in dermatological preparations, pharmaceuticals, and foods, where it has long been used for preservation, is also very important. In recent years, the electrochemical properties and preparations of several new salicylate-selective electrodes have been reported by using a variety of ion carriers.[18−22] The development of a suitable salicylate-selective sensor would enable the detection of free salicylate in samples and could help researchers in studying the pharmaceutical role of this drug. The main aim of the present work was the development of a highly selective membrane electrode for salicylate based on PVC membranes containing Cr^{III}TPP as ion

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10.1021/ac020099n CCC: $22.00
Published on Web 06/06/2002

Table 1. Composition of Membranes and Their Potentiometric Response Characteristics of Salicylate-Selective Electrodes Based on CrTPPCl, Measured in Phosphate Buffer Solutions (pH 4.0)

electrode	%(w/w) of various components					slope (±SD) (mV/decade)	linear range (M)	detection limit (M)
	PVC	plasticizer	CrTPPCl	TOMACl[e]	NaTPB[e]			
A	33.2	64.6	2.2			−48.7 (±1.7)	1×10^{-5}–1×10^{-1}	4.0×10^{-6}
B	31.7	63.3	5.0			−54.3 (±1.7)	5×10^{-6}–1×10^{-1}	1.9×10^{-6}
C	31.2	62.9	4.8	1.1		−55.0 (±1.7)	5×10^{-6}–1×10^{-1}	2.8×10^{-6}
D	31.1	61.9	4.9	2.1		−54.6 (±1.6)	5×10^{-6}–1×10^{-1}	3.5×10^{-6}
E	31.3	61.8	3.9	3.0		−52.4 (±1.7)	1×10^{-5}–1×10^{-1}	6.2×10^{-6}
F	31.8	61.5	5.1		1.6	−56.9 (±1.8)	5×10^{-6}–1×10^{-1}	3.5×10^{-6}
G	32.5	63.2		4.3		−51.5 (±1.9)	1×10^{-5}–1×10^{-1}	8.0×10^{-6}

carrier. The prepared membrane electrode displays a low detection limit and high selectivity and sensitivity to salicylate determination and is promising for measurements of salicylate in biological samples.

EXPERIMENTAL SECTION

Reagents. Cr(III) tetraphenylporphyrin chloride (CrTPPCl) was prepared and purified as described before.[23] Poly(vinyl chloride) (PVC) of high molecular weight was used as received from Fluka. Bis(2-ethylhexyl) phthalate (BEHP), trioctylmethylammonium chloride (TOMACl), sodium tetraphenylborate (NaTPB), tetrahydrofuran (THF), sodium salicylate, and other chemicals were of the highest purity available from Merck and were used without further purification, except THF, which was distilled before use. All aqueous solutions were prepared with deionized, distilled water.

A stock solution of 0.10 M salicylate was prepared by dissolving appropriate amounts of sodium salicylate in water. Solutions of anionic interferences, for selectivity studies, were prepared from sodium salts in water. Working solutions were buffered using of 0.05 M buffer solutions of phosphate and acetate.

Acetylsalicylic acid tablet samples (all purchased from the local pharmacies) were prepared by directly dissolving the samples in 50 mL of 0.5 M NaOH. The mixture was heated over a boiling water bath for 1 h. The resulting solution was diluted to 250 mL in a volumetric flask and used for determination of salicylate content by potentiometric and spectrophotometric methods. For preparation of serum samples, 5 mL of phosphate buffer (pH 6.0) was added to 5 mL of a serum sample obtained from Razi Institute of Serum and Vaccine in Tehran and the resulting solution was diluted to 50 mL with water. The salicylate content in serum samples was determined directly by a potentiometric calibration method, and the results were compared with those obtained using spectrophotometry. These samples were spiked with known amounts of salicylate for recovery studies.

Preparation of Electrodes. The general procedure to prepare the PVC membrane was mixing of various amounts of the ionophore (CrTPPCl) together with appropriate quantities of BEHP (as plasticizer) and PVC to give a total mass of 200 mg in 5 mL of THF. TOMACl and NaTPB as lipophilic cationic and anionic additives were also incorporated in some of the membranes. The resulting mixture was transferred into a glass dish of 2-cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube (6-mm i.d.) was dipped into the mixture for ~5 s so that a nontransparent membrane of ~0.3-mm thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for ~1 h. The tube was then filled with internal filling solution (0.01 M sodium salicylate and 0.01 M NaCl). The prepared electrodes were finally conditioned by soaking in a 0.01 M salicylate solution, which was adjusted to the working pH by using of H_3PO_4 and KOH, for 24 h.

Potential Measurements. The potential measurements were carried out at 25 ± 1 °C with a CyberScan pH/Ion meter 2500 (Eutech Instruments), by setting up the following assembly:

SCE || test solution | membrane | salicylate (0.01 M), NaCl (0.01 M) | AgCl | Ag

UV–Visible Spectra. Spectra of 1×10^{-4} M CrTPPCl solutions in dichloromethane were recorded on a Cary Bio UV–visible spectrophotometer (Varian Co.). This instrument was applied for the spectrophotometric determination of salicylate content in the pharmaceutical and physiological samples.

RESULTS AND DISCUSSION

Potentiometric Response Properties of Salicylate Electrodes. The response properties of membrane-selective electrodes based on ion carriers are strongly influenced by the membrane composition, especially ionic sites.[1,24] In the case of ISEs based on neutral carriers, ionic sites with a charge sign opposite to that of the primary ions is necessary for obtaining a Nernstian response, to decrease the membrane resistance, reduce the co-ion interferences, and improve the detection limit and optimization of selectivity. In ISEs based on electrically charged carriers, on the other hand, the use of ionic sites with the same charge sign as the primary ions can significantly improve the response properties and selectivity of the sensor.

The effect of membrane composition on the potentiometric response of the electrodes was investigated by varying the proportions of the ion carrier (CrTPPCl) and ionic additives. Table 1 presents the compositions of several typical membranes, along with their response characteristics. The potential response of all the membrane sensors was studied in the concentration range 1×10^{-7}–1×10^{-1} M salicylate. Figure 1 shows the potentiometric calibration curves for the salicylate electrodes, which obtained in buffered solutions at pH 4.0. As can be seen, an increase in the

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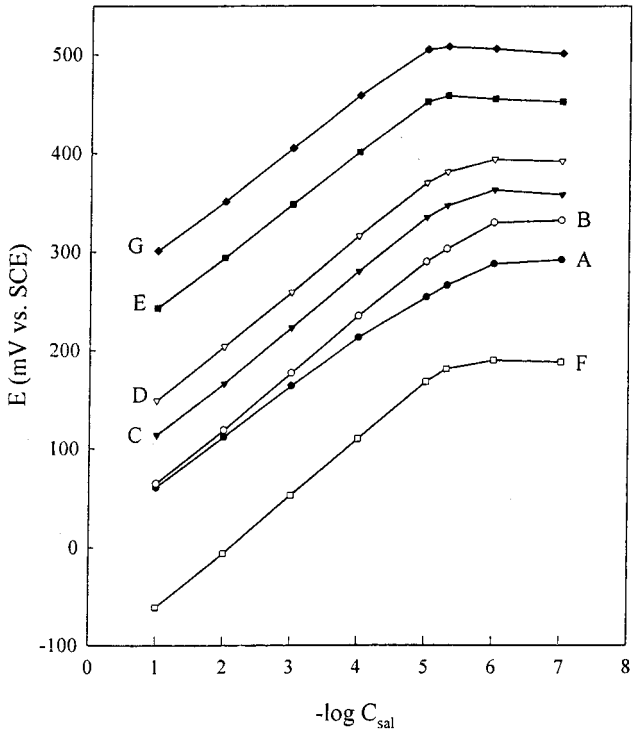

Figure 1. Potentiometric response properties of different electrodes based on the CrTPPCl as ionophore, in buffered solutions of salicylate (pH 4.0). Compositions of the electrodes are summarized in Table 1.

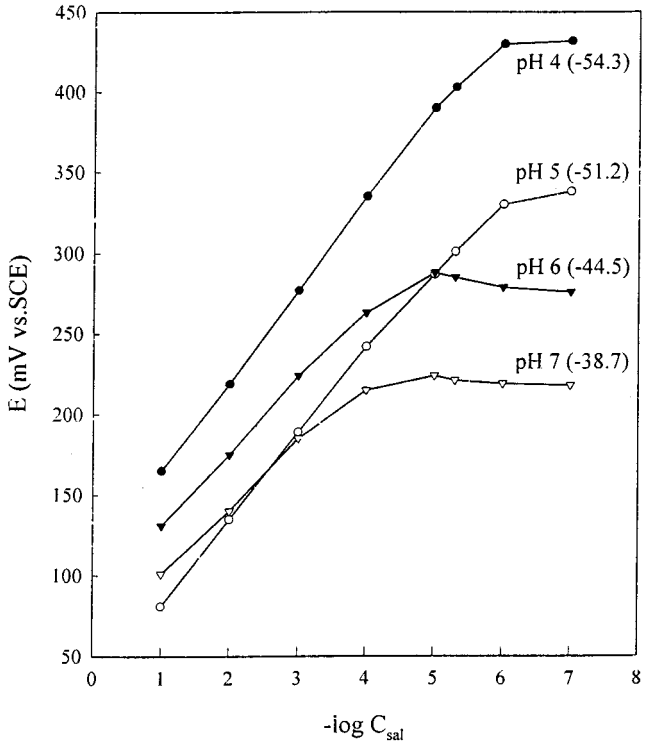

Figure 2. Potentiometric calibration curves of electrode B (Table 1) in a buffered solution of salicylate with various pHs. Values in parentheses represent the slope of calibration curves in terms of mV/decade.

level of CrTPPCl in the membrane causes an increase of the slope of the calibration curve (compare electrodes A and B). Membrane B with ~5 wt % ionophore shows a near-Nernstian slope of −54.3 mV/decade in a wide range of salicylate concentrations between 5×10^{-6} and 1×10^{-1} M in buffered solutions of pH 4.0.

The influence of a lipophilic ionic additive to the membranes is also dependent on the pH of the measuring solution and mechanism of the response of the carrier in the membrane (charged or neutral carrier mechanism). Porphyrins with a metal(III) center as ionophore can act as either a neutral or a charged carrier, depending on the charge sign of the axial ligands that precoordinated to the central metal of porphyrins.[25] Results in Table 1 and Figure 1 show that, in conditioning and measuring solutions at pH 4.0, the addition of $TOMA^+$ as a cationic additive in molar ratios less than 1 relative to the ionophore had no significant effect on the slope and dynamic range of the calibration graph (by comparing membranes B−D). On the other hand, addition of NaTPB to the CrTPP-based membranes (electrode F with 64% molar ratio respect to ionophore) causes a slight increase in the slope of the calibration graph, which approached the Nernstian behavior (~ −57 mV/decade). These results revealed that CrTPP in the membrane acts as a positively charged carrier in acidic solutions. In anion-selective electrodes based on positively charged carriers, ionic sites with the same charge sign as the primary ion are not required to obtain a Nernstian response.[1] Instead, it was recently shown that, for primary and interfering ions of equal charge and complexes of equal stoichiometry, the use of ionic sites with the same charge sign as the primary anion could significantly improve response slope and selectivity of the electrode.[1,26]

Previous studies have shown that the relatively low concentrations of the anionic sites that are present in plasticized PVC membranes as impurities of the matrix and plasticizer[1,27] may be sufficient to obtain the best possible potentiometric response properties (e.g., slope nearest to Nernstian response and lower detection limit) for charged carrier-based ISEs. Addition of a higher concentration of the sites with the same charge as the parent ion may increase leaching of the primary anion (salicylate) from the membrane to the sample solution at the interface of the two phases, and under these conditions, a flux of the primary ion is generated across the membrane. Therefore, higher concentrations of anionic sites can increase the detection limit of salicylate-selective membrane electrode. It can be seen in Table 1 that in the membrane containing NaTPB (electrode F) in comparison to the electrode without an ionic additive (electrode B), the lower detection limit slightly increased.

By increasing the pH in conditioning and also in test solutions, the effect of $TOMA^+$ in improvement of the potentiometric response of electrodes becomes more significant. As can be seen in Figures 2−4 for the electrodes B, D, and F, by increasing the pH of the solutions, the addition of $TOMA^+$ causes a significant increase in the slope and a lowering the lower detection limit. It seems that CrTPP acts as a neutral carrier in higher pHs (>6). In neutral carrier-based ISEs, the addition of a specified amount

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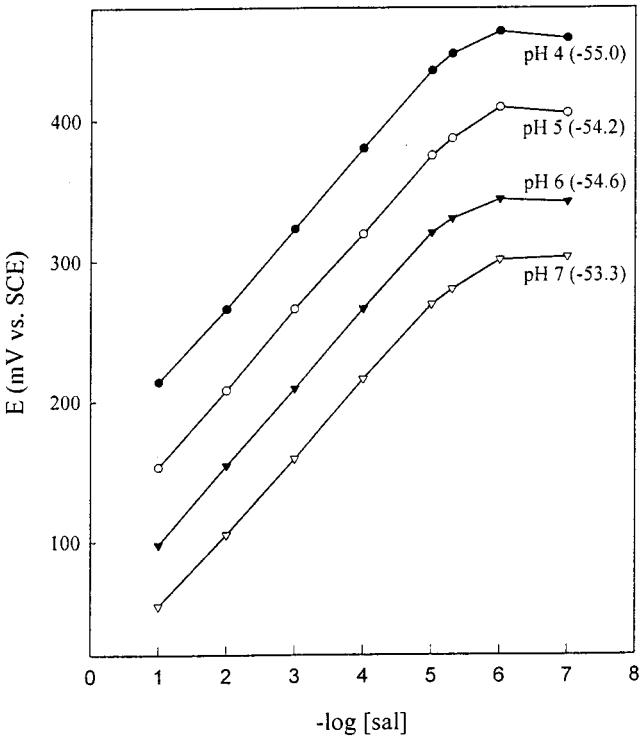

Figure 3. Potentiometric calibration curves of electrode D (Table 1) in a buffered solution of salicylate with various pHs. Values in parentheses represent the slope of calibration curves in terms of mV/decade.

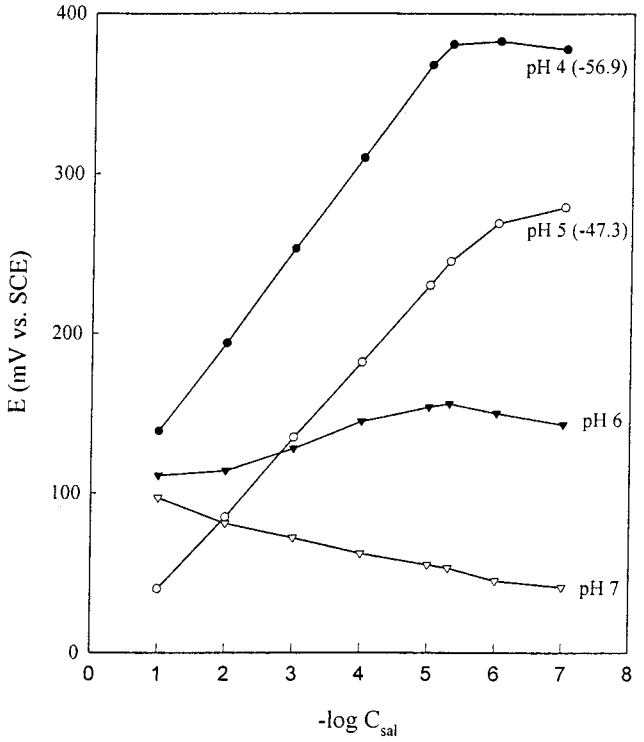

Figure 4. Potentiometric calibration curves of electrode F (Table 1) in a buffered solution of salicylate with various pHs. Values in parentheses represent the slope of calibration curves in terms of mV/decade.

of a salt of lipophilic cations is necessary for the decrease in co-ion interferences and improvement of dynamic range and sensitivity, and also for optimization of the selectivity. To date, such a

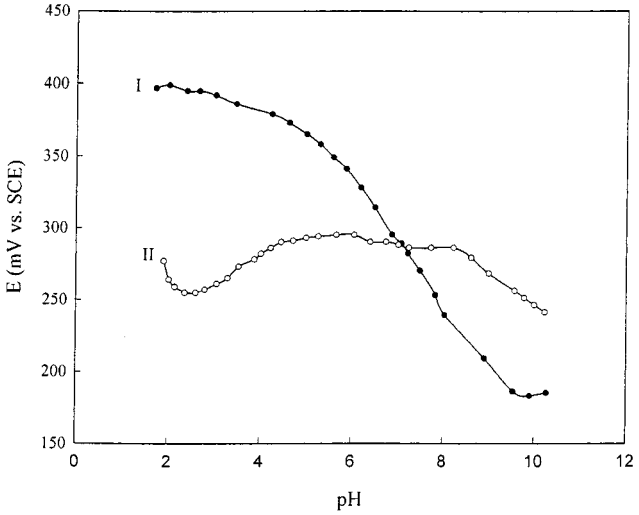

Figure 5. pH response of CrTPPCl-based membrane electrode B: (I) freshly prepared electrode in the absence of salicylate; (II) conditioned electrode in the presence of 0.01 M salicylate.

dual behavior has not been observed for other metal(III) porphyrin-based anion-selective membrane electrodes. An analogous system is reported for the calcium-selective electrodes based on dialkylphosphonates[28] that a carrier can act as both a neutral and a charged carrier, depending on the pH of the sample solution and protonation of ionophore.

The potentiometric response of membrane electrodes based on CrTPP was found to be sensitive to the pH changes. Figure 5(I) shows a typical pH response curve for the freshly prepared metalloporphyrin-based membrane electrode B, which was obtained by titration of 0.1 M phosphoric acid with sodium hydroxide. Such a potentiometric pH response can be ascribed to the coordination of water molecules as axial ligands to the central metal of porphyrin complex.[29] Upon increasing the pH, the axial water molecules can readily lose a proton to the solution, yielding hydroxide-coordinated porphyrin as following type,

$$\mathrm{CrTPPCl} + 2\mathrm{H_2O} \rightarrow [\mathrm{CrTPP(H_2O)_2}]^{+}\mathrm{Cl}^{-}_{\mathrm{org}} \quad (1)$$
"charged carrier"

$$[\mathrm{CrTPP(H_2O)_2}] \rightarrow [\mathrm{CrTPP(H_2O)(OH)}]_{\mathrm{org}} + \mathrm{H}^{+} + \mathrm{Cl}^{-} \quad (2)$$
"neutral carrier"

These results in response to pH are analogous to that resulting from anion coordination at the same axial sites. The mechanism of pH response appears to be similar in nature to those found with the membranes doped with porphyrin, phthalocyanine, and Schiff base complexes of various metallic cations as ionophore in the membrane electrodes.[21,22,30,31] On the other hand, when the same membrane electrode is conditioned in 0.01 M salicylate solution (for ~24 h), the response of the electrode is hardly affected by the change in pH in the range of about 3.5−8.5 (Figure

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5(II)). The behavior of the electrode at higher pHs can be explained in terms of the increased interference from hydroxide ions.

The following mechanisms may be proposed for the potentiometric response of CrTPP-based membrane electrode toward salicylate at different pHs:

charged carrier-based mechanism

$$Na^+Sal^- + [CrTPP(H_2O)_2]^+Cl^-_{org} \rightarrow [CrTPP\ (H_2O)Sal]_{org} + Na^+ + Cl^- + H_2O \quad (3)$$

neutral carrier-based mechanism

$$Na^+Sal^- + [CrTPP(H_2O)(OH)]_{org}, R^+Cl^-_{org} \rightarrow [CrTPP(OH)Sal]^-, R^+_{org} + Na^+ + Cl^- + H_2O \quad (4)$$

The working pH range over which the electrodes can be used (3.5−8.5) covers physiological conditions (7.2−7.6).

For analytical applications, the response time of a sensor is an important factor. The response time of the electrodes tested by measuring the time required to achieve a steady-state potential (within ±0.5 mV), was ≤1 min for solutions with salicylate concentration in the linear range (1×10^{-6}−1×10^{-1} M). The stability and reproducibility of the electrodes were also tested. The potential remained almost constant for ~10 min (drift ≤0.5 mV), after which, a very slow divergence was observed. The standard deviation of the potential readings of electrodes, for 10 identical measurements over a period of 30 min, was about ±1.1 mV. The detection systems are very stable and can be used over a period of 2 months without observing any considerable change in their response characteristic. The reproducibility of the slope of calibration curves was within ±1.2 mV/decade over a period of 2 monthes ($n = 6$).

Selectivity and Response Mechanism of Salicylate-Selective Electrodes. The selectivity is clearly one of the most important characteristics of a potentiometric sensor, which represents the preference of a sensor for response to a primary ion over other ions (interfering ions) that are present in the measuring solution. For environmental and clinical applications, these selectivities determine the accuracy of analytical measurements. The modified separate solution method (MSSM) was used for the calculation of potentiometric selectivity coefficients ($k^{pot}_{I,J}$).[32] In this method, the potentiometric calibration curves are obtained for primary (I) and interfering ions (J) and values of $E°$ for J ions and I are determined by extrapolating the response functions to 1 M activities. Equation 5 can be used for the

$$k^{pot}_{I,J} = \frac{a_I}{a_J^{1/z_J}} \exp\left[\frac{E_I - E_J}{RT}F\right] = \exp\left[\frac{E°_I - E°_J}{RT}F\right] \quad (5)$$

determination of selectivity coefficients by this method. A typical selectivity pattern of salicylate-selective electrodes for salicylate compared to the other common carboxylic acids and inorganic anions is shown in Figures 6 and 7 for electrode F. These results show that the response of the potentiometric sensor toward various interfering ions deviates significantly from Nernstian behavior, revealing that not only the interfering ion (J) but also

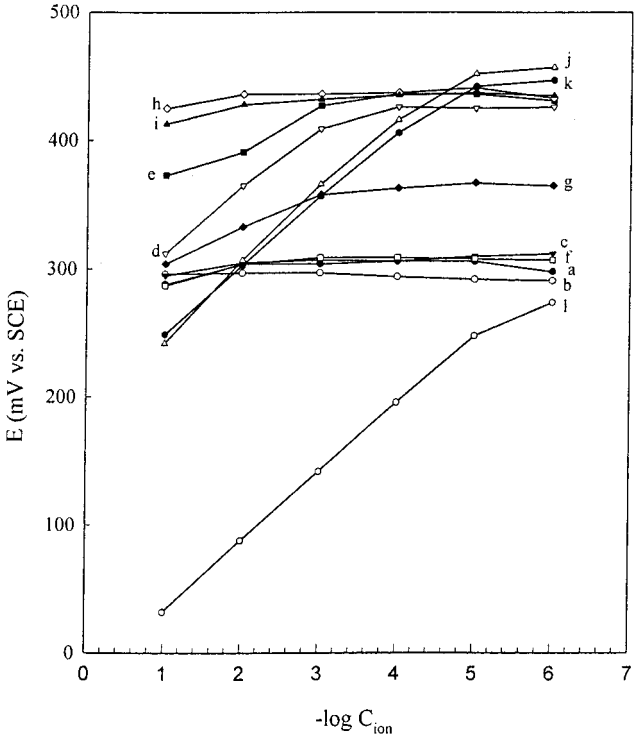

Figure 6. Selectivity pattern of electrode F for common inorganic anions with respect to salicylate: (a) F^-, (b) Cl^-, (c) Br^-, (d) I^-, (e) NO_2^-, (f) NO_3^-, (g) CO_3^{2-}, (h) $H_2PO_4^-$, (i) SO_4^{2-}, (j) SCN^-, (k) ClO_4^-, and (l) salicylate. All measurements were performed in solutions containing 0.01 M phosphate buffer, pH 4.0.

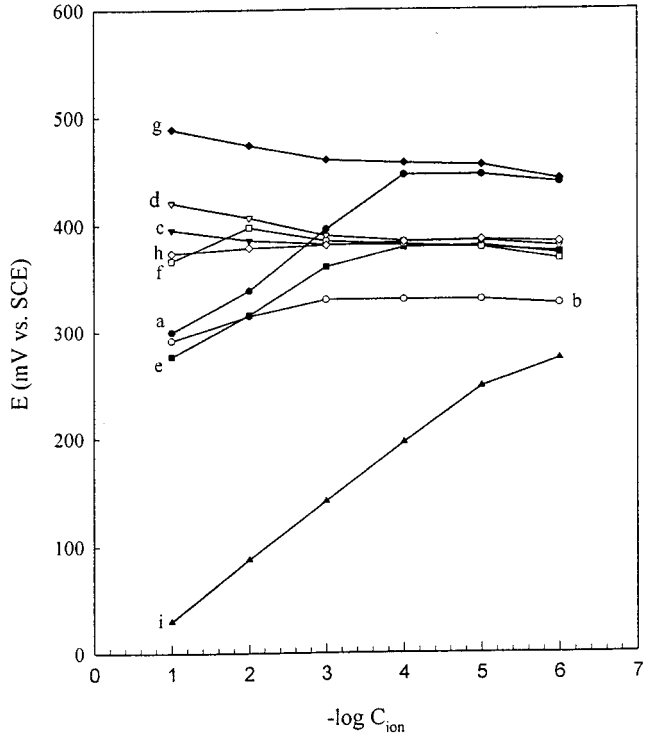

Figure 7. Selectivity pattern of electrode F for organic carboxylate anions with respect to salicylate: (a) phthalate, (b) nicotinate, (c) lactate, (d) tartrate, (e) maleate, (f) oxalate, (g) citrate, (h) acetate, and (i) salicylate. All measurements are performed in solutions containing 0.01 M phosphate buffer, pH 4.0.

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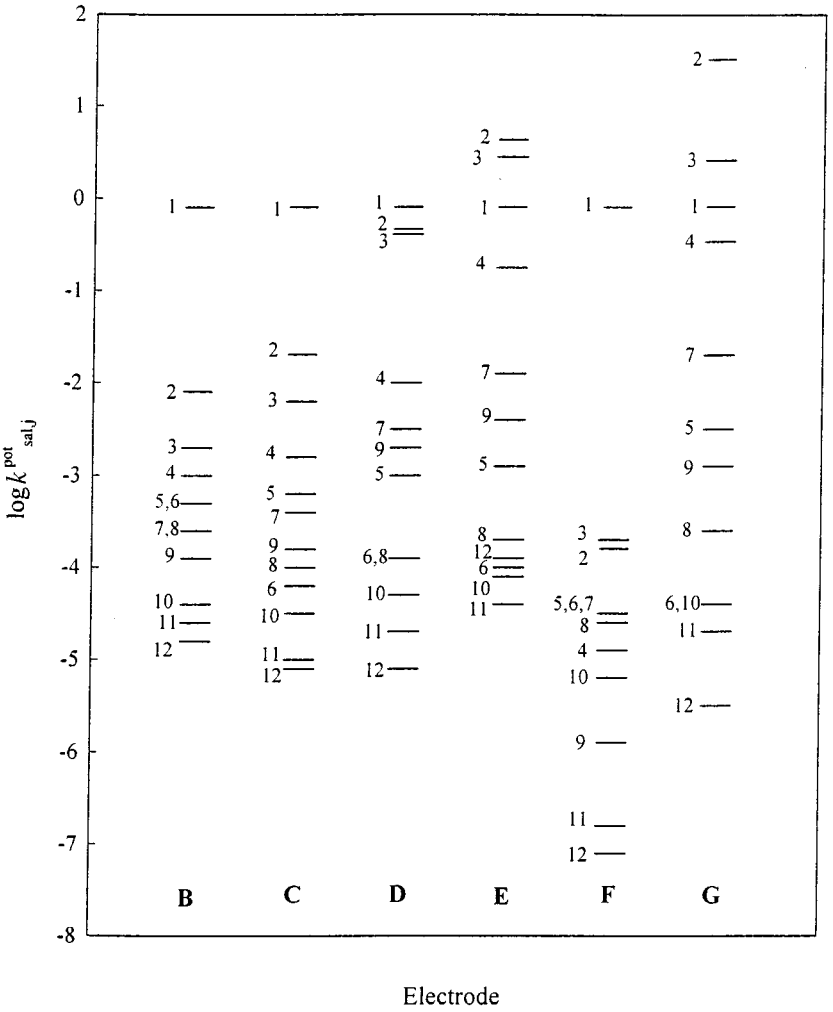

Figure 8. Potentiometric selectivity coefficients, log $k^{pot}_{I,J}$, of different salicylate-selective electrodes based on CrTPPCl measured in buffered solutions of common inorganic anions (pH 4.0): (1) salicylate, (2) ClO_4^-, (3) SCN^-, (4) I^-, (5) Br^-, (6) F^-, (7) NO_3^-, (8)Cl^-, (9) NO_2^-, (10) HCO_3^-, (11) $H_2PO_4^-$, and (12) SO_4^{2-}.

the primary ion leaching (I) from the membrane is potential determining. In this case, maximum limiting values of $k^{pot}_{I,J}$ were calculated from the potential measurements at the highest activity of the interfering ion (by extrapolation of the response curve to 1 M activity with a Nernestian slope).

The results of the potentiometric selectivity coefficients for different salicylate-selective electrodes, based on CrTPPCl as ionophore, are summarized in Figures 8 and 9. These values of selectivity coefficients are obtained in solutions buffered to pH 4.0 using phosphate buffer (0.01 M). The potentiometric selectivity patterns clearly indicate that the electrodes based on CrTPP as carrier are highly selective toward salicylate over a number of other anions. A typical selectivity pattern for a series of anions presented by electrode B is as follows:

salicylate ≫ phthalate > perchlorate > thiocyanate > maleate > iodide > bromide > chloride > nitrate ∼ fluoride > acetate > nitrite > lactate > nicotinate > oxalate > carbonate > phosphate > sulfate > citrate > tartrate

The selectivity of the CrTPP-based membranes for salicylate over highly lipophilic anions such as perchlorate, thiocyanate, iodide, and nitrate clearly shows a deviation from the conventional Hofmeister anion response pattern and suggests that salicylate is directly interacting with the metalloporphyrin as an axial ligand. The hard metal center in the ionophore endows oxophilic character on the complex and interacts with the carboxylate group of salicylate, which acts as a hard base.

To obtain a clue about the interaction mechanism of CrTPP with salicylate, the UV−visible spectra of 1×10^{-4} M CrTPPCl in THF were obtained with and without the presence of salicylate and the results are shown in Figure 10. The Soret peak in the CrTPPCl involves one band at 450 nm. The origin of this band is similar to that predicted by Bruice et al. for meso(tetrakis(2,6-dibromophenyl)porphinato)chromium(III) chloride ($(Br_8TPP)Cr^{III}Cl$).[33] A comparison between the two spectra in Figure 10 reveals that, upon interaction with salicylate ion, the Soret band of CrTPPCl shifts to 430 nm and also a new band appears at 390 nm (the precision of the spectrophotometer is of the order of 0.01 nm). Studies on $(Br_8TPP)Cr^{III}(Cl)$ show a Soret band at 449 nm and two weaker bands at 366 and 393 nm. Upon interaction with

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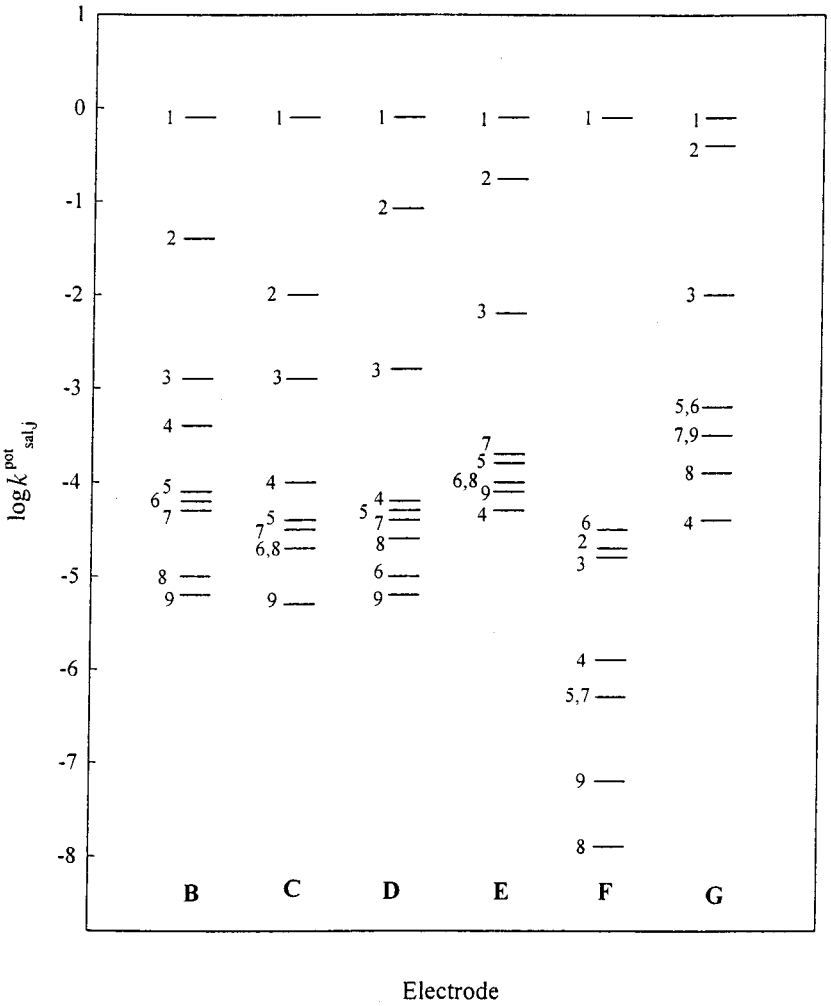

Figure 9. Potentiometric selectivity coefficients, log $k^{pot}_{i,j}$, of different salicylate-selective electrodes based on CrTPPCl measured in buffered solutions of some carboxylate anions (pH 4.0): (1) salicylate, (2) phthalate, (3) maleate, (4) acetate, (5) lactate, (6) nicotinate, (7) oxalate, (8) citrate, and (9) tartrate.

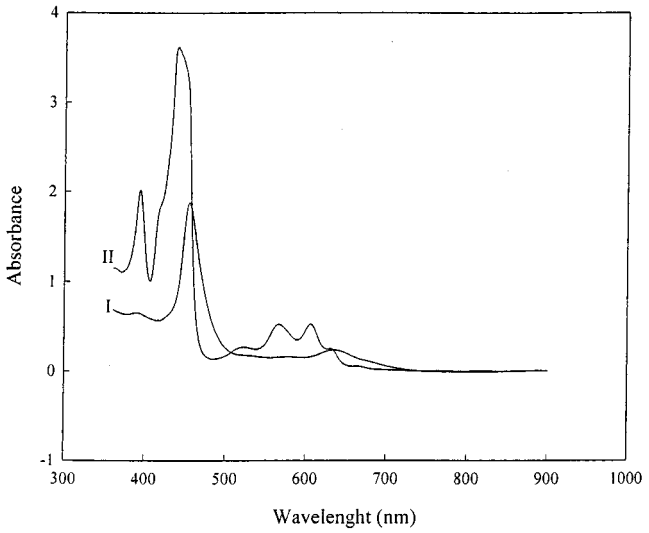

Figure 10. UV−visible spectra of 1×10^{-4} M CrTPPCl in THF solution in the absence (I) and presence (II) of salicylate.

oxygen, in $(Br_8TPP)Cr^{IV}(O)$, the Soret band shifts to 431 nm and only a weaker band appears at 375 nm. This conformity between the results obtained in this study and results from the previous work may be used to show the interaction of chromium in the center of the metalloporphyrin with the oxygen of the carboxylate group in salicylate anion.

Table 2. Comparison between the Results Obtained for Measurement of Salicylate Concentrations in Human Serum Samples by the Potentiometric and Spectrophotometric Methods

	concentration (M)	
serum sample	potentiometry (electrode C)[a]	spectrophotometry[a]
A	$3.12\ (\pm 0.17) \times 10^{-4}$	$2.98\ (\pm 0.12) \times 10^{-4}$
B	$3.44\ (\pm 0.22) \times 10^{-3}$	$3.73\ (\pm 0.18) \times 10^{-3}$
C	$2.92\ (\pm 0.16) \times 10^{-4}$	$3.13\ (\pm 0.15) \times 10^{-4}$

[a] Average of five determinations in serum solutions buffered to pH 6.0 by use of phosphate buffer solutions.

In the membrane ion sensors based on electrically neutral carriers, the presence of ionic sites with a charge sign opposite to that of the primary ions is necessary to establish the permselectivity of the membrane and, therefore, the resulting Nernstian response.[1] By adjusting the molar ratio of ionic sites to neutral ionophore, the selectivity of the electrode can be improved. On the other hand, it was recently shown that the use of ionic sites with the same charge sign as the primary ion can significantly

Table 3. Results of Accuracy Determination for Salicylate Added to the Human Serum Samples

	serum sample A		serum sample B		serum sample C	
amt added (mmol)	amt found[a] (mmol)	recovery (%)	amt found[a] (mmol)	recovery (%)	amt found[a] (mmol)	recovery (%)
0	0.0156		0.1720		0.0146	
0.0250	0.0263	105.2	0.0232	92.8	0.0240	96.0
0.0500	0.0515	103.0	0.0479	95.8	0.0501	100.2
0.1000	0.1046	104.6	0.1024	102.4	0.1014	101.4
0.1500	0.1472	98.1	0.1561	104.1	0.1580	105.3
0.2500	0.2431	97.2	0.2646	105.8	0.2580	103.2
0.3500	0.3384	96.7	0.3665	104.7	0.3600	102.9

[a] Average of three determination by using of electrode C in samples containing 0.01 M phosphate buffer at pH 6.0.

improve response slope and selectivities of certain ISEs based on electrically charged carriers.[26] It was shown that, for singly charged anions with a 1:1 stoichiometry in the complex, an addition of ~60 mol % anionic additive seems to be optimum for an anion-selective electrode. As can be seen in Table 1 and Figure 1, for measurements in pH ~4.0, in which CrTPP acts as a charged carrier, the presence of a cationic additive does not improve the response properties of the electrode (compare electrode B with electrodes C−E). Instead, membrane F with 1.6 wt % NaTPB (0.64 molar ratio with respect to CrTPPCl) shows better sensitivity in the calibration curve. Results in Figures 8 and 9 show that in the presence of NaTPB (as anionic additive) selectivity for salicylate over other anions is significantly improved. Selectivities over the organic and inorganic anions studied in this work are better than those of other reported salicylate-selective sensors based on enzyme electrodes,[34] Nitron ionophore,[35] ion-exchanger membranes,[21,36,37] and membranes based on several metal complexes.[5,18,19,22] Therefore, for studies in mild acidic media, a membrane with an anionic additive (electrode F) has the optimum composition for obtaining the best potentiometric response and selectivity. But, for application in neutral conditions, in which CrTPP acts as a neutral carrier, a membrane with a cationic additive (electrode C) endows the optimum response and selectivity toward salicylate.

The results in Figures 7 and 8 show that, in certain electrodes, especially in the presence of anionic additives, the potential of the membrane electrode in very dilute solutions of interfering anions becomes ~100 mV more positive than that of the most dilute solution of salicylate. It was shown that in ion-selectve electrodes based on electrically charged carriers the lower detection limit, especially in the presence of ionic sites with the same charge sign as the primary ion, is significantly governed by the leaching of primary ion (salicylate) at the boundary of two phases.[38,39] In potential measuring in salicylate solutions, the concentration gradient through the interface of membrane/solution is smaller, but in the absence of salicylate, in solutions of interfering anions, which is highly discriminated by lipophilic anionic additive in the membrane, this concentration gradient become greater and may generate a greater ion flux of salicylate ion toward the sample solution. Therefore, phase boundary potential becomes more positive in dilute solutions of interfering ions with respect to the dilute solutions of salicylate.

Analytical and Clinical Applications. The high degree of salicylate selectivity exhibited by the CrTPP-based membrane electrode makes it potentially useful for monitoring the concentration levels of salicylate in physiological samples. In this regard, experiments were performed to determine the feasibility of using the electrode for measuring salicylate in human serum samples. The potentiometric calibration curve was used to estimate free salicylate concentration in 10-fold-diluted serum samples with a suitable buffer solution (phosphate buffer at pH 6.0). Because CrTPP in salicylate-selective electrodes in pHs near to physiological conditions (~7) acts as neutral carrier, the best Nernstian response can be observed only in the presence of cationic sites. In this regard, electrode C containing cationic sites was used for evaluation of salicylate amounts in human serum samples at a pH near to the physiological conditions (pH 6). The results obtained by the potentiometric method are in good agreement with the spectrophotometric procedure,[40] as shown in Table 2. The serum samples were spiked with known amounts of salicylate for determination of the accuracy for salicylate added using a calibration curve**.** Studies with salicylate-spiked serums yielded accuracies ranging from 92.8 to 105.8% as shown in Table 3.

Table 4. Results of the Analysis of Pharmaceutical Preparations

tablet sample	label value (mg of ASA/tablet)	potentiometry (electrode C)[a]	spectrophotometry[a]
I	100	92.8	89.4
II	325	319	307
III	500	416	438

[a] Average of five determinations.

The proposed electrodes were used for the determination of salicylate content of the different hydrolyzed pharmaceutical preparations. Tablets of different samples of aspirin were treated according to the procedure described above, and the resulting solutions were used for the determination of salicylate content by potentiometric and spectrophotometric methods. The results obtained by the membrane electrodes (Table 4) are in good agreement with the results from the spectrophotometric method.[41]

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CONCLUSIONS

The potentiometric method based on a membrane electrode containing CrTPPCl might provide an alternative means for the direct determination of salicylate. This ionophore, depending on the pH of the sample solution, can act as both a neutral and a positively charged carrier. In acidic solution, this compound acts as a charged carrier, and therefore, the sensitivity and selectivity for potentiometric response to salicylate can be optimized in the presence of lipophilic anionic sites. On the other hand, in neutral conditions, CrTPP shows a behavior similar to that of the neutral carrier, and in the presence of cationic sites, sensitivity approaches the Nernstian response. These electrodes are very easy to prepare and show high sensitivity and wide dynamic range (~6 orders of magnitude). High selectivity, very low detection limit, and rapid response make these electrodes suitable for measuring the concentration of salicylate in a wide variety of samples, including pharmaceutical preparations (aspirin tablets) and physiological samples such as the human serum, without need for preconcentration or pretreatment steps and without significant interaction from other anionic species that are present in the samples being measured. The mechanism of the response of electrodes and the effects of lipophilic ionic additives was studied in order to obtain optimum membrane composition of the salicylate membrane electrode.

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ACKNOWLEDGMENT

The authors express their appreciation to the Research Council of Sharif University of Technology for financial support of this work. The authors gratefully acknowledge Professor Mehdi Jalali Heravi (Head of Chemistry Department, Sharif University of Technology) for his helpful suggestions in this work.

Received for review February 12, 2002. Accepted April 30, 2002.

AC020099N