Salicylate-Selective Electrodes Based on Tripodal Tris-thiourea Derivatives

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A new highly salicylate-selective PVC membrane electrode based on tripodal tris-thiourea derivatives, L^1 and L^2, as neutral carriers is described. The electrodes display an excellent potentiometric response to salicylate ions and an anti-Hofmeister selectivity sequence in the following order: Salicylate$^-$ > ClO_4^- > Benzoate$^-$ > I$^-$ > NO_3^- > NO_2^- > Maleate$^-$ > Acetate$^-$ > Lactate$^-$ > Fumarate$^-$. It also exhibited a near-Nernstian potential in a linear range of 5.0×10^{-5} - 1.0×10^{-1} M with a detection limit of 9.0×10^{-5} mol/L and a slope of -59.9 mV/decade at a pH of 7.0 in a saline buffer solution at 25 °C. The stability constant (log K_S) of the anions-ionophore complex was also determined at 25 °C by a conductometric titration in DMSO solution.

Key Words : Salicylate-selective electrode, Tripodal tris-thiourea derivatives, Anti-Hofmeister selectivity

Introduction

The interest in ion-selective electrodes has grown over recent years as they are easy-to-use devices that allow rapid and accurate analytical determination of chemical species at relatively low concentrations with a reasonable selectivity and at low cost[1-3] Salicylic acid is one of the common metabolites of acetylsalicylic acid (aspirin), widely used as an analgesic and inflammatory agent as well as recently as a preventive of heart attacks.[4] Aspirin is easily hydrolyzed to salicylic acid, which circulates in blood in the ionized form. Monitoring the plasma salicylate concentration is important for controlling the dose and frequency of aspirin administrations.[5]

In recent years, the electrochemical properties and preparations of several new salicylate-selective membrane electrodes have been reported by using a variety of ion carriers.[6-10]

The thiourea group as a hydrogen bond donor has drawn much interest as a functional group for neutral receptors to recognize various anions. The relatively high acidity of the NH thiourea protons is correlated with a strong hydrogen bonding donor capability already exploited in the design of efficient anion receptors. Thus, thiourea segments embedded into a tripodal amine structure may provide efficient anchoring points for the hydrogen bonding recognition of complementary functional groups, such as carboxylate, phosphate or sulfonate, in a specific and predictable fashion.[11-14]

The study of the complexes formed between aromatic carboxylates such as salicylate, benzoate, etc. and tripodal tris-thiourea with lipophilic substituents that form hydrogen bonds and have appropriate spaces for holding analyte has attracted us. It is, in general, assumed that thioureas bind to carboxylates through double hydrogen bonds, shown in Scheme 1.[15-20]

In this paper, we have synthesized tripodal tris-thiourea derivatives containing alkyl (L^1) or phenyl group (L^2) appended to the thiourea units (see Figure 1) and evaluated them as ionophores for salicylate ions in plasticized PVC membrane electrodes. The proposed membrane electrodes based on tripodal tris-thiourea derivatives, L^1, displayed high selectivity, sensitivity and low detection limit for the salicylate determination. The interaction of L^1 with salicylate and other anions also studied in DMSO solution using conductometry

Experimental

Reagents: Tridodecylmethylammonium chloride (TDMACl), *o*-nitrophenyl octyl ether (*o*-NPOE) and high molecular mass poly(vinyl chloride) (PVC) were obtained from Fluka AG (Buchs, Switzerland). Tris(2-aminoethyl)amine, 1-octyl-thiocyanate, phenylthiocyanate, acetonitrile, bis(2-ethylhexyl)adipate) (BEHA), tris(2-ethylhexyl) phosphate (TEHP), tetrahydrofuran (THF) and dimethylsulfoxide (DMSO) were obtained from Aldrich (Milwaukee, WI). All orther chemicals were of the highest purity available from Merck (Darmstadt, Germany) and were used without further purification, except for THF, which was distilled before use. A 0.1 M stock solution of salicylate and other interferences was prepared by dissolving an appropriate amount of each compound, usually their sodium salts, in water. Working solutions were prepared by successive dilutions with water. All of the working solutions were buffered at a pH of 7.0, using a saline buffer solution.[21]

Synthesis of L^1 and L^2. The structures of the tripodal receptors, L^1 and L^2, are shown in Figure 1. The procedures for the preparation of tripodal tris-urea derivatives, are
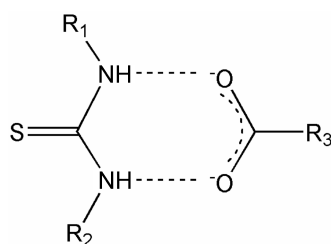
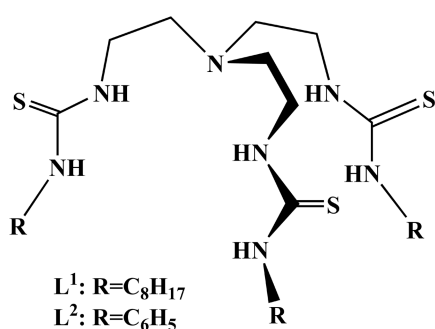**Scheme 1**. Y-type hydrogen bonding model of thiourea-carboxylate complex.

L^1: R=C_8H_{17}
L^2: R=C_6H_5

Figure 1. Structure of the ionophores, L^1 and L^2.

reported elsewhere.[22] We have modified the previous procedures for the synthesis of the tripodal tri-thiourea derivatives, L^1 and L^2, used in this study. The compounds characterized by mp, IR and NMR. The ^{1}H NMR spectra were recorded with a Bruker Advance-300 (300 MHz) NMR spectrometer using chloroform-*d* as a solvent and tetramethylsilane as an internal standard. IR spectra (KBr disk) were measured with a Shimadzu FT-IR 8100 spectrometer.

L^1: mp: 103.5 ℃; IR (KBr): 2853, 1557, 1466, 1358, 1282, 716 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$, ppm): δ 0.96 (t, 3H, CH$_3$), 1.24 (s, 2H, CH$_2$), 1.30 (s, 2H, CH$_2$), 2.61 (t, 2H, CH$_2$), 3.27 (s, 2H, CH$_2$), 3.47 (m, 2H, CH$_2$), 7.24 (s, 1H, NH), 7.51 (s, 1H, NH).

L^2: mp: 98.6 ℃; IR (KBr): 3219, 3053, 1595, 1495, 1449 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$, ppm): δ 2.71 (t, 2H, CH$_2$), 3.57 (t, 2H, CH$_2$), 7.08 (t, 1H, Ar), 7.39 (m, 4H, Ar), 7.62 (s, 1H, NH), 9.61 (s, 1H, NH).

Membrane Preparation. PVC-matrix ion-selective membranes were prepared by the method described elsewhere.[23,24] Membrane solutions were prepared by dissolving appropriate amounts of the ionophore (L^1 and L^2), plasticizer(*o*-NPOE, TEHP and BEHA) and PVC, to give a total mass of 180 mg, in 5 mL of THF. TDMACl as lipophilic cationic additives were also incorporated in some of the mixtures. The membrane compositions are listed in Table 1.

Potential Measurements. The potential differences between the ISEs and the reference electrode (Orion sleeve-type double junction Ag/AgCl reference electrode; model 90-02) were measured using a PC equipped with high-impedance input 16-channel analog-to-digital converter (KOSENTECH, Busan, Korea). The response of the sensor for salicylate ions was examined by measuring electromotive force (EMF) of the following electrochemical cell: Ag|AgCl|sat. KCl|sample solution||PVC membrane||10^{-2} M NaSal + 10^{-2} M NaCl solution|AgCl|Ag. Dynamic response curves and calibration plots were obtained through a step addition of standard solutions to 100 mL of background electrolyte at 25 ℃. The solutions were magnetically stirred while the records of all emf values. The selectivity coefficients, $K_{sal,j}^{pot}$, were determined by a separate solution method (SSM) using the reduced form of the Eisenman equation.[24]

$$\log K_{sal,j}^{pot} = (E_1 - E_2)/S - (n/z - 1) \log[a]$$

where, E_1 is the potential measured in 0.1 M solution of the interfering ion, E_2 is the potential measured in 0.1 M salicylate solution, S is the calibration slope, n and z are electrical charges of salicylate and interfering ions, respectively, and a is the concentration of the ions used (0.1 M). The detection limits of the electrodes were also estimated according to the method suggested in the IUPAC recommendation.[24]

Conductance Measurements. Conductance measurements at 298.15 K were carried out using a Metrohm model 660 conductivity bridge (Swiss) at a frequency of 2 kHz. The conductance cell was a Russell-type glass-bodied electrode with a cell constant of 0.769 cm^{-1}. Conductometric titrations were carried out as follows: a solution of the anion salt (concentration of 5.0 × 10^{-5} M) was placed in the conductometric cell in DMSO (7 cm^3) and titrated with a solution of the ionophore (concentration range from 5.0 × 10^{-4} to 4.0 of mole ratio, [L]/[Sal$^-$]) in the same solvent. The conductance was measured after each addition. Stability constants, log K_S, was calculated by fitting all conductometric curves with the KINFIT program.[25]

Results and Discussion

Response Characteristics of Electrodes. It is well known that the sensitivity, linear dynamic range, and

Table 1. Potentiometric response characteristics of electrodes based on L^1 and L^2 measured in a saline buffer solution at a pH of 7.0[*]

Electrode	Membrane mass composition / mg				Slope	Detection limit
	Plasticcizer	PVC	Ligand	TDMACl	(mV/decade)	(M)
1	NPOE(118.7)	59.5	–	0.7	−60.4	3.0 × 10^{-5}
2	NPOE(115.1)	59.3	L^1(1.8)	–	−54.6	7.0 × 10^{-5}
3	NPOE(118.8)	59.4	L^1(1.8)	0.6	−54.3	7.0 × 10^{-5}
4	TEHP(118.7)	59.5	L^1(1.8)	–	−53.6	7.0 × 10^{-5}
5	TEHP(119.2)	59.2	L^1(1.8)	0.6	−54.6	7.0 × 10^{-5}
6	TEHP(115.1)	59.4	L^1(5.6)	–	−50.7	2.0 × 10^{-4}
7	BEHA(119.3)	59.4	L^1(1.9)	–	−59.9	9.0 × 10^{-5}
8	BEHA(115.6)	59.4	L^1(1.9)	0.7	−59.3	4.0 × 10^{-5}
9	BEHA(118.1)	59.5	L^2(1.8)	–	−35.5	1.0 × 10^{-3}
10	BEHA(118.4)	59.7	L^2(1.8)	0.5	−49.3	5.0 × 10^{-4}
11	NPOE(118.6)	59.3	L^2(1.9)	0.5	−53.6	3.0 × 10^{-5}

[*]Inner filling solution: NaH$_2$PO$_4$ (0.1 M) + Na$_2$HPO$_4$ (0.1 M) + NaCl (0.01 M)

selectivity obtained for a given sensor depend significantly on the membrane composition[1,2,26] Therefore, the effect of membrane composition on the electrode performance was studied with various different ratios of the membrane active phase, ionphore (L^1, L^2), PVC and plasticizers (TEHP, BEHA, *o*-NPOE). Additionally, we prepared the membranes without or with TDMACl as a cationic additive. Table 1 presents the compositions of several typical membranes along with their electrochemical characteristics.

The potentiometric response of the plasticized PVC based membrane electrodes incorporating ionophores, L^1 and L^2, for salicylate in saline buffer solutions at a pH of 7.0 is shown in Figure 2 and 3, respectively. The potential response of the membrane sensors used in this study was studied in the concentration range of 1.0×10^{-6} - 1.0×10^{-1} M salicylate. As can be seen in Figure 2 and 3 and Table 1, the membrane composition of ~1.0% (~1.8 mg) ionophores, ~33% (~59.4 mg) PVC, ~66% (~118.8 mg) plasticizer was optimized for obtaining an electrode slope closer to that of the theoretical value. Further increase in the concentration level of the ionophore in membranes resulted in somewhat decrease in the slopes (see Table 1, E6). The influence of the plasticizer on the characteristics of the salicylate ion selective electrode was investigated by using three different plasticizers, including BEHA, TEHP and *o*-NPOE. As seen in Table 1, the electrodes based on TEHP and *o*-NPOE with and without additives have both a sub-Nernstian response to salicylate. Membranes based on the ionophore, L^1, and BEHA plasticizer with and without TDMACl resulted both near-Nernstian response to salicylate with detection limits of lower than 9.0×10^{-5} M (Table 1, E7 and E8). These near-Nerntian anionic responses to salicylate in the absence of the cationic sites in these membranes demonstrated that the tripodal tris-thiourea derivative, L^1, functioned as a neutral receptor for the salicylate ion. However, the ionophore-free TDMACl as anion-exchanger-based membranes exhibited Nernstian responses toward salicylate and a Hofmeister selectivity order (electrodes 1 in Table 1, column E1 in Figure 5). Comparing E2 with E3, E4 with E5 and E7 with 8 (in Table 1 and Figure 5), the incorporation of TDMACl as a
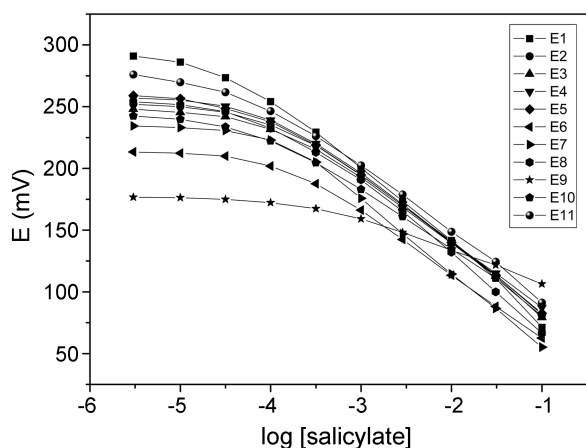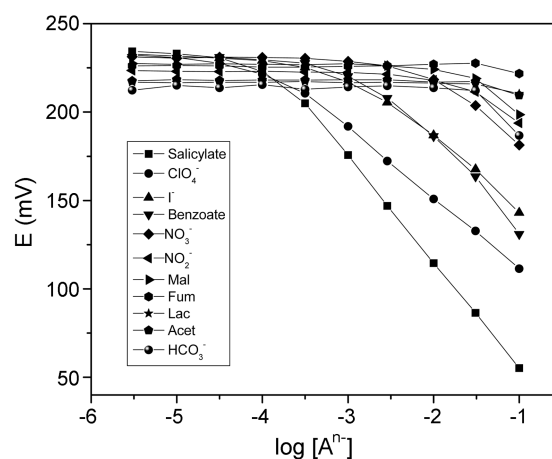

Figure 3. Potentiometric response of L^1/PVC/BEHA membrane electrodes without additive toward various interfering anion in saline buffer at a pH of 7.0.
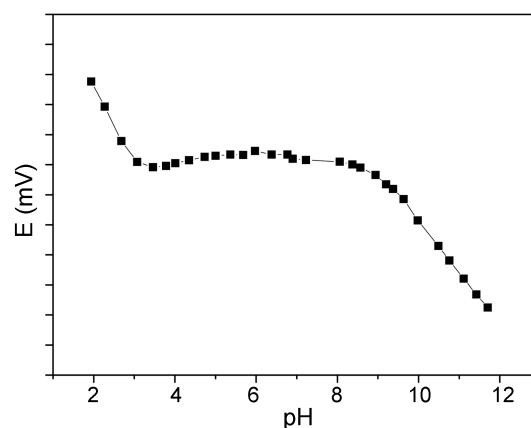

Figure 4. pH response of L^1-based membrane electrode in the presence of 0.01 M salicylate.

cationic additive to the membranes containing ionophores showed no significant effect on the slope of the calibration plots and detection limits for the L^1-based electrodes, however, the selectivity sequence changed back to the Hofmeister selectivity pattern. For the membrane containing thiourea tripodand, L^2, with and without TDMACl (in Table 1, electrode 9 and 10, in Figure 5, column E9 and E10), the slope of the calibration plot showed a sub-Nerntian response and worsened the selectivity over salicylate.

The detection limits defined as the concentration of salicylate obtained when extrapolating the linear region of the calibration curve to the baseline potential for the different electrodes are given in Table 1. As can be seen, electrodes 7 showed the lowest detection limits of about 9.0×10^{-5} M (the recommended therapeutic level of salicylate in biological fluids, *e.g.*, whole blood, plasma, serum and urine, is 1.5×10^{-4} M). The response time of the electrodes, tested by measuring the time required to achieve a steady-state potential (within 1 mV), was within ~30 s for the solutions with salicylate levels in the range 1×10^{-5} - 1×10^{-1} M.

The pH Response of the Electrodes. The potentiometric response of L^1 membrane electrodes was found to be

Figure 2. Potentiometric response of different electrodes based on L^1 and L^2. Compositions of electrodes are summarized in Table 1.
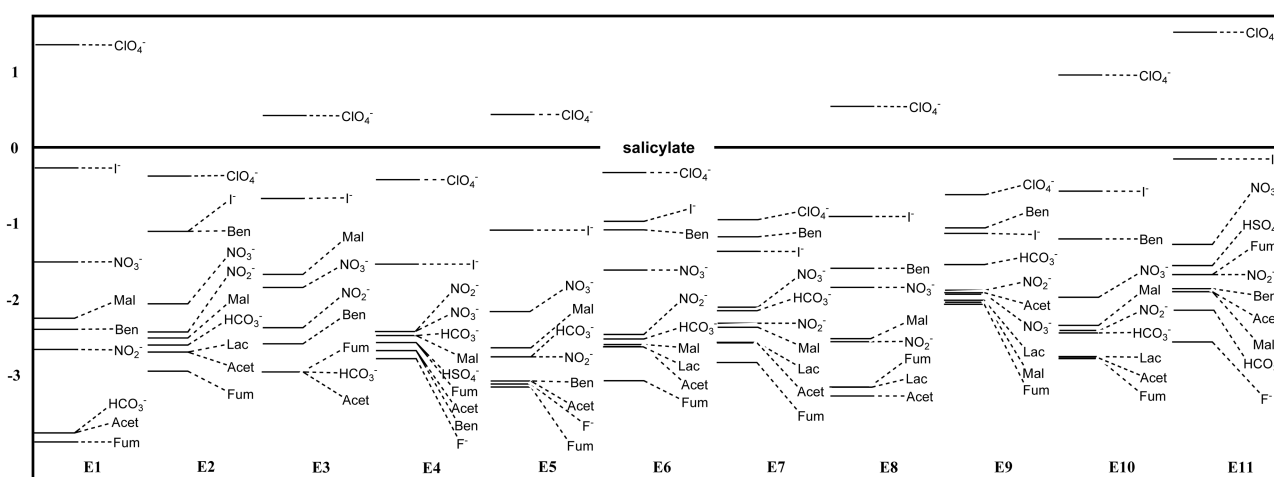
Figure 5. Potentiometric selectivity coefficients of the L^1 and L^2 membrane electrodes in Table 1.

dependent on the pH. Figure 4 shows a typical pH response profile for the L^1-doped membrane, evaluated by titrating 0.1 M nitric acid and sodium hydroxide solution. The response remained unchanged over the 3.5-8.5 pH range which is in the physiological conditions (pH 7.2-7.6) for the salicylate determination.[27,28] The response of the electrode was therefore further studied using the saline buffer at a pH of 7.0. The behavior of the electrodes at a high pH can be explained in terms of the increased interference from the hydroxide ions. Protonation of salicylate anion may be the reason for potential changes at low pH values.

Selectivity. Potentiometric selectivity coefficients, $K^{pot}_{sal,j}$, describing the preference with the membranes for an interfering anion relative to salicylate were determined in 0.1 M solutions of the corresponding sodium salts by SSM.[29] Possible interferences from various monocarboxylates (benzoate, acetate, salicylate and lactate), di-carboxylates (maleate and fumarate) and inorganic anions (ClO_4^-, I^-, NO_3^- and NO_2^-) were studied. The potentiometric ion selectivity coefficients of the different electrodes, based on L^1 and L^2 membranes, are presented in Figure 5. The selectivity factors given as $K^{pot}_{sal,j}$ represented the membrane preferences for other anions relative to salicylate. Comparing column 1 with 2, and column 3 with 4 (in Figure 5), it shows that among mono- and di-carboxylate, even tested with lipophilic perchlorates, salicylate is the preferred ion for a long alkyl chain appended thiourea tripodand, L^1.

The electrodes incorporated only TDMACl as an ion-exchanger, *i.e* without neutral ionophore (Figure 5 column E1), exhibited a near-Nerntian slope and provided a Hofmeister selectivity pattern: ClO_4^- > Salicylate$^-$ > I^- > NO_3^- > Maleate$^-$ > Benzoate$^-$ > NO_2^- > HCO_3^- > Acetate$^-$ > Fumarate$^-$ > HSO_4^-, which is solely the order of lipophilicity of anions.[30-32] In Figure 5 column E7, the selectivity coefficients of the electrodes based on the ionophore L^1 only bearing more lipophilic substituents showed super selective to salicylate over all the tested anions even for the lipophilic anions such as perchlorate and iodide. The anti-Hofmeister selectivity pattern for a series of anions displayed by the sensor is: Salicylate$^-$ > ClO_4^- > Benzoate$^-$ > I^- >

NO_3^- > NO_2^- > Maleate$^-$ > Acetate$^-$ > Lactate$^-$ > Fumarate$^-$ > HSO_4^-. In contrast, the same plasticizerd PVC membrane containing both the ionophore and additive, TDMACl exhibited a more Hofmeister-like the selectivity (see the columns, E3, E5, E8 and E10 of Figure 5).

In the case of L^2 ionophore containing phenyl group, with the addition of the TDMACl to the L2-based membrane the slope and sensitivity were slightly improved.against over the only L^2-based membrane (see the electrode 9, 10 and 11 in Table 1). However, we have found that the sensitivity and selectivity of the membranes incoporated L^2 containing phenyl groups, in both the absence and presence of the cationic additive were still worse than those of L^1.

Although many new anion receptor-based electrodes offer a fairly good discrimination of hydrophilic anions, the significant interfering anions are still present such as, perchlorate, thiocyanate, and iodide. The L^1-based membrane electrodes showed a substantially improved selectivity for salicylate over several other anions. The high selectivity for salicylate over perchlorate and iodide clearly deviates from the conventional Hofmeister anion response.

Conductance Study for the Thiourea Tripoids-salicylate Complexation. The preferred response towards salicylate is believed to be associated with the coordination of salicylate with the thiourea tripodand. In order to investigate the interactions between anions and thiourea moiety, we employed conductometry which determined the stoichiometry and stability constants for the complexes formed between ionophore, L^1, and anionic guests. Figure 6 shows the plots of molar conductance, Λm, against the ionophore, L^1, *vs.* anion concentration ratio, $[L^1]/[Anion]$. The stability constants of the complexation between the ionophore and anions were determined by analysis of the molar conductance data using the KINFIT program.[25] Molar conductance, Λ_m, for salicylate increased with increasing concentration of ionphores, which can be fit adequately by the theoretical expression for 1:1 molar ratio between the ionophore, L^1, and salicylate. The best fitting curve for L^1-salicylate was obtained by a nonlinear least-square fitting procedure and the results are shown in Table 2. It is clear from data in Table
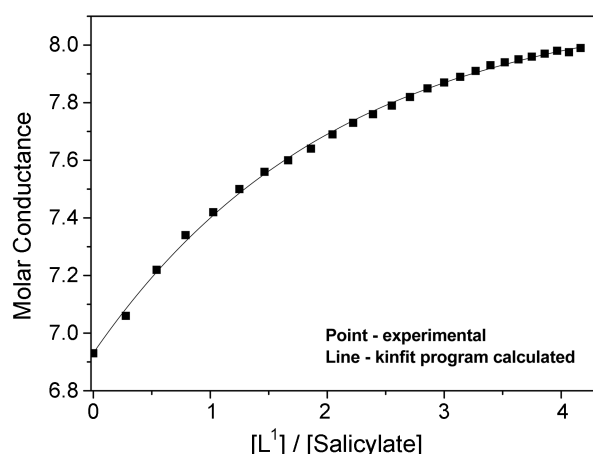
Figure 6. Conductometric curves for the titration of sodium salicylate with L^1 in DMSO at 25 °C.

Table 2. The Stability constants of the complexation of L^1 and anions in DMSO at 25 °C

Anions	Solvent	Log K_f
Sodium Salicylate		3.12
NaClO$_4$		3.09
NaNO$_3$		2.66
Sodium Benzoate	DMSO	2.82
Sodium L-lactate		1.84
NaNO$_2$		1.85
NaHSO$_4$		0.79

2 that the L^1 forms quite strong complexes with salicylate than any other anion studied even hydrophobic perchlorate. The order of stability constants is as follows; $Sal^- > ClO_4^- >$ Benzoate$^-$ ~$NO_3^- > NO_2^-$ ~Lactate$^- > HSO_4^-$, which is in accordance with the selectivity observed for the L^1-based salicylate selective electrode resulting in the anti-Hofmeister behavior.

Conclusions

Two tripodal tris-thiourea derivatives, L^1 and L^2, are prepared and incorporated in plasticized poly(vinyl chloride) membranes as sensor materials for the salicylate-selective electrode. The electrode compositions, 33% PVC, 66% plasticizer, BEHA and 1.0% ionophore, showed the best potentiometric response characteristics and displayed a linear log [sal$^-$] *vs.* EMF response over the concentration range of 1.0×10^{-6} - 1.0×10^{-1} M in phosphate buffer solutions at a pH of 7.0 with a Nernstian slope of -59.9 mV/ decade of salicylate concentration. The results of this study showed that the potentiometric method based on L^1 membrane PVC electrodes might provide an attractive alternative for the determination of salicylate. The strength of interaction between L^1 and salicylate, relative to other anions, dictates the observed selectivity pattern of the electrodes. The two hydrogen atoms of thiourea unit in tripodal ionophores endow a strong acidic character and interact strongly with the carboxylate group of salicylate by hydrogen bonds.

Stability constants of the various anions with the neutral ionophores, L^1, were measured by the conductometric method. The potentiometric selectivity coefficients correlate well with the thermodynamic stability constants for the complexation between ionophores and anions in polar solvents.

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