

# Hydrogen Bond-Based Macrocyclic and Tripodal Neutral Ionophores for Highly Selective Polymeric Membrane Sulfate-Selective Electrodes

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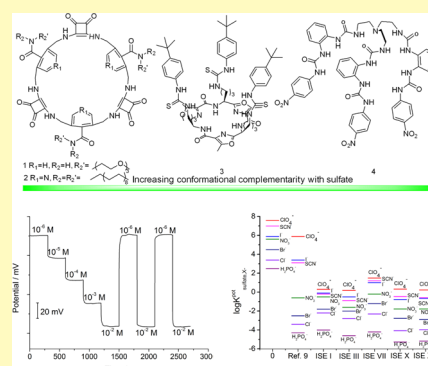
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Supporting Information

**ABSTRACT:** Four hydrogen bond-based macrocyclic and tripodal neutral receptors with increasing conformational complementarity with sulfate were used for the first time as ionophores to develop polymeric membrane sulfate-selective electrodes. Optimizing the membrane composition such as ionophores, lipophilic additives, and plasticizers yielded ISEs which showed Nernstian response to sulfate with the best selectivity so far and improved detection limits (a slope of  $-29.8$  mV/dec in the linear range of  $1 \times 10^{-6}$ – $1 \times 10^{-1}$  M with a detection limit of  $5 \times 10^{-7}$  M), which led to the success of the determination of sulfate in drinking water samples and neomycine tablets. The anion–ionophore complex constants in the membrane phase were determined and correlated with the selectivity sequence of the ISEs. Studies on the influence of pH of the sample solution demonstrated that the developed ISEs can be operated in a wide pH range of 3–8 with fast response and rapid (in 1 min) and long lifetime. The success of these ionophores represents a feasible strategy for overcoming the “Hofmeister series” by employing a combination of complementarity and hydrogen bonds.

**KEYWORDS:** polymeric membrane electrode, sulfate, macrocyclic, tripodal, ionophore



Benefiting from the advent of host–guest chemistry, polymeric membrane ion-selective electrodes (ISEs) fabricated with various ionophores have experienced exponential success in recent years owing to their routine application in clinical, industrial, and environmental fields.<sup>1–3</sup> It is well established that the performance of ISEs could be predicted by inspecting the binding affinity and selectivity of the ionophores to target ions and interfering ones.<sup>4–6</sup> Actually, the development of ionophores to selectively complex anions out of aqueous solutions is very challenging, owing to their diverse geometries, larger sizes, pH-dependent structures, low charge densities, and often inherently high hydration energies, especially for the anions (for example, sulfate) at the end of Hofmeister series (organic anions  $> \text{ClO}_4^- > \text{SCN}^- > \text{I}^- \approx \text{salicylate} > \text{NO}_3^- > \text{Br}^- > \text{Cl}^- > \text{HCO}_3^- > \text{HPO}_4^{2-} \approx \text{F}^- \approx \text{SO}_4^{2-}$ ).<sup>7–10</sup> Sulfate is among the most abundant and important macronutrients in cells and human plasma and is involved in the biosynthesis and detoxification of many endogenous/exogenous compounds. Also, a sulfate ion has been regarded as an end product of the metabolic process of sulfur-containing amino acids. Moreover, high concentrations of inorganic sulfate in drinking water might be related to diarrhea.<sup>11,12</sup> Therefore, there is an urgent need for sulfate determination in clinical, environmental, and pharmaceutical fields.

Several kinds of interactions or functional groups such as Lewis acid–base interactions, electrostatic forces, hydrogen-bonding (HB), and halogen-bonding (XB) have been employed in anion recognition chemistry to develop anion receptors.<sup>13–16</sup> However, only a part of these receptors have been proved to be good ionophores for polymeric membrane anion-selective electrodes, indicating that it is not so straightforward to correlate the binding data in a simple solvent directly with the performance the ISEs.<sup>17,18</sup> First, bis(thiourea) and bis(guanidinium) derivatives with a xylene spacer were used as ionophores for potentiometric sulfate detection; although the interference of several lipophilic anions was significantly reduced, the reported selectivity coefficients were not satisfactory for real-life application.<sup>19,20</sup> Learning from the recognition site of the sulfate-binding protein, a tripodal receptor molecule was synthesized by anchoring three urea groups on a tris(2-aminoethylamine) scaffold; sulfate complexation could be achieved through H-bonds in a three-

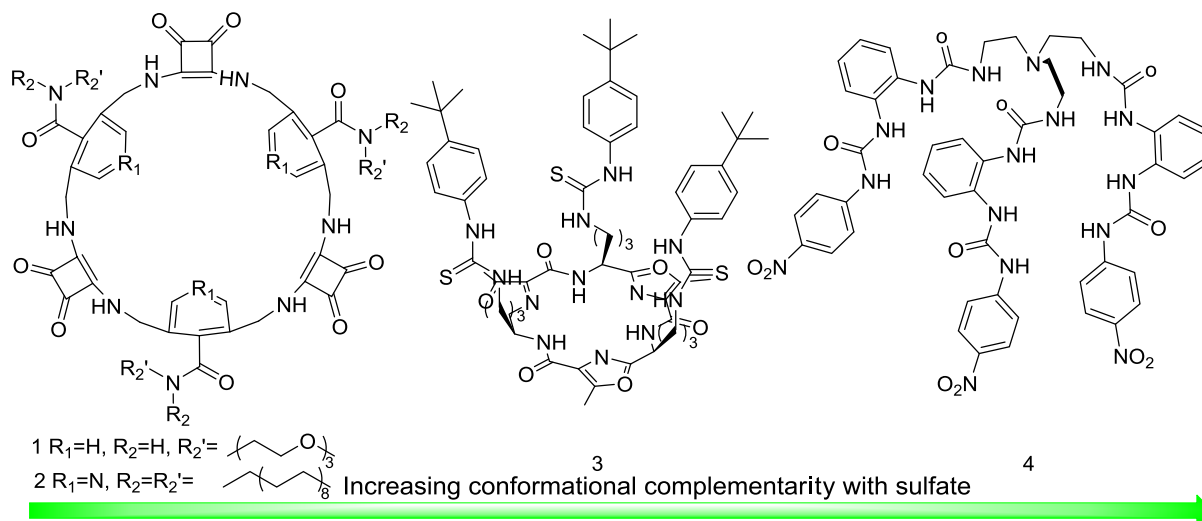
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Scheme 1. Structures of the Ionophores Used for Polymeric Membrane Sulfate Electrodes in This Work



dimensional cavity.<sup>20</sup> There is no doubt that molecules with the same tris(2-aminoethylamine) scaffold and more acidic squaramide legs also work well for sulfate recognition.<sup>9</sup> Although polymeric membrane sulfate-selective electrodes formulated with urea or squaramide-based tripodal ionophores showed an anti-Hofmeister response, and the latter electrodes have been used for sulfate determination in drinking water and cell lysates, it should be noticed that the interference from lipophilic ions is still significant.<sup>9,20</sup>

Besides the method mentioned before, more strategies can be envisioned by manipulating the topology of the ionophores. Macrocyclic compounds (see 1 and 2 in Scheme 1) containing alternating aryl spacers and squaramides have been synthesized by Elmes and proved to be sulfate-selective receptors with high association constants ( $>10^4 M^{-1}$  in organic/aqueous solutions), which can be ascribed to the matched size and shape of sulfate with the preorganized cavity.<sup>21–23</sup> It has been reported that tripodal urea or squaramide-based ionophores encapsulate tetrahedral sulfate in a 2:1 (host/guest) fashion, in which one of the ligands is a conformational complement with the three edges, but the other one faces the vertices of the bottom triangular plane of the tetrahedron.<sup>24,25</sup> It is obvious that complementarity for the sulfate is not optimal in this case, and calculations have demonstrated that the optimal saturated coordination mode for sulfate is binding in a complementary tetrahedral cavity with 12 optimally arranged hydrogen bonds along the edges.<sup>25</sup> Along this line, on the one hand, by substituting the tris(2-aminoethylamine) scaffold of the tripodal ionophores with cyclic peptide, Jolliffe developed a shielding cavity with high sulfate affinity (see 3 in Scheme 1).<sup>26</sup> On the other hand, Wu extended the three monourea legs of the tris(2-aminoethylamine) scaffold to an *ortho*-phenyl bridged bisurea to produce a hexaurea ligand that shows saturated coordination of a sulfate ion (see 4 in Scheme 1).<sup>27</sup> Competitive experiments with other competitive anions demonstrated that this tripodal hexaurea could selectively bind sulfate with an association constant larger than  $10^4 M^{-1}$  in DMSO/25%  $H_2O$ , and almost quantitative extraction of sulfate ions from an aqueous to an organic phase could be achieved.<sup>27</sup>

On account of their selectivity and the relatively high binding constants of receptors 1–4 with sulfate in solution-phase measurements, we herein evaluated their performance as

new ionophores for polymeric membrane sulfate-selective electrodes. Different membrane components such as plasticizers and lipophilic additives were optimized to improve the detection sensitivity and selectivity. Binding constants of the ionophore–sulfate complexes in the membrane phase were determined by a segmented sandwich membranes method and correlated with the selectivity coefficients. Finally, the proposed polymeric membrane sulfate-selective electrode was applied for sulfate determination in real-life samples.

## EXPERIMENTAL SECTION

**Reagents.** All ionophores were supplied by Qingdao Zhongke Chemicals, prepared as described in the literature.<sup>21–23,26,27</sup> High molecular weight poly(vinyl chloride) (PVC), 2-nitrophenyl octyl ether (*o*-NPOE), bis(2-ethylhexyl) sebacate (DOS), and tridodecylmethylammonium chloride (TDMACl) were purchased from Sigma. 2-Fluorophenyl 2-nitrophenyl ether (FPNPE) was acquired from Heowns (Tianjin Heowns Biochem LLC). Other reagents were purchased from Sinopharm Group Co., Ltd. All chemicals were of selectophore or analytical reagent grade. Aqueous solutions were prepared with fresh deionized water (18.2 M $\Omega$  cm specific resistance) obtained using a Pall Cascada laboratory water system.

**Membrane and Electrode Preparation.** Polymeric membrane electrodes were prepared using a solvent casting technique according to established procedures reported elsewhere.<sup>6</sup> Briefly, specific amounts of the ionophores, TDMACl, and DOS, NPOE, or FPNPE plasticizers were dissolved in THF to prepare membrane cocktails. After transferring the membrane cocktail to a glass ring fixed on a glass plate and evaporation of the tetrahydrofuran overnight, a uniform polymeric liquid membrane (ca. 200  $\mu$ m in thickness) was obtained. Subsequently, the as-formed membrane was cut into small disks of 7 mm diameter using a cork borer to install onto Philips IS-561 electrode bodies. A solution of HEPES (20 mM, pH = 7.0) buffer with the addition of  $Na_2SO_4$  (10 mM) was used as the internal filling solution except otherwise mentioned. Membranes were conditioned in the internal filling solution overnight before evaluating the potentiometric performance. To prepare the sandwich membranes, a set of disks from membranes with or without ionophores were conditioned separately for 2 days in  $1 \times 10^{-2}$  M solution of specific anions prepared with HEPES (20 mM, pH = 7.0) buffer. After drying with filter paper, the sandwich membrane was then assembled by attaching the membrane with the ionophore to the ionophore-free membrane. The sandwich membrane was then mounted immediately in the electrode body.

**Potentiometric Measurements.** Potentiometric measurements were carried out using a CHI 660C electrochemical station (Shanghai

**Table 1. Compositions of the Membranes, Selectivity Coefficients and Characteristics of the Potentiometric Response toward Sulfate for Electrodes with PVC/Plasticizer (1:2) Membranes Containing 1 wt % Ionophores and TDMACl (mol %)**

ISEs	ionophore	TDMACl (mol %) <sup>a</sup>	plasticizer	slope (mV/dec)	detection limit (M)	$\log K_{\text{sulfate}, X}^{\text{pot},b}$						
						$\text{ClO}_4^-$	$\text{I}^-$	$\text{SCN}^-$	$\text{NO}_3^-$	$\text{Br}^-$	$\text{Cl}^-$	$\text{H}_2\text{PO}_4^-$
0		1 wt %	<i>o</i> -NPOE	18.1	$1 \times 10^{-3}$	7.6	5.9	7.0	5.6	4.5	3.4	2.5
I	1	30%	<i>o</i> -NPOE	28.7	$1 \times 10^{-6}$	0.3	-0.1	-0.2	-0.5	-1.8	-2.2	-4.0
II	2	10%	<i>o</i> -NPOE	25.6	$4 \times 10^{-7}$	0.3	-0.4	-0.6	-1.3	-1.6	-2.6	-4.2
III	2	30%	<i>o</i> -NPOE	29.5	$5 \times 10^{-7}$	0.2	-0.5	-0.9	-1.6	-2.0	-2.8	-4.6
IV	2	50%	<i>o</i> -NPOE	27.4	$1 \times 10^{-6}$	0.4	-0.6	-0.7	-1.3	-1.8	-2.6	-4.3
V	2	30%	DOS	23.2	$5 \times 10^{-6}$	0.6	-0.1	0.3	-0.2	-1.4	-2.0	-4.0
VI	3	10%	<i>o</i> -NPOE	22.6	$8 \times 10^{-7}$	1.4	1.6	1.4	-0.1	-0.7	-2.0	-4.0
VII	3	30%	<i>o</i> -NPOE	28.2	$1 \times 10^{-6}$	1.5	1.0	1.2	-0.2	-1.2	-2.3	-4.2
VIII	3	50%	<i>o</i> -NPOE	25.3	$3 \times 10^{-6}$	1.8	1.6	1.5	-0.1	-0.5	-2.4	-4.0
IX	4	30%	FPNPE	28.5	$3 \times 10^{-7}$	0.6	-0.3	-0.1	-1.5	-2.5	-3.7	-4.6
X	4	50%	FPNPE	29.8	$5 \times 10^{-7}$	0.3	-0.8	-0.5	-1.8	-2.8	-4.1	-5.3
XI	4	70%	FPNPE	25.2	$1 \times 10^{-6}$	3.5	-0.4	-0.3	-1.3	-2.1	-3.8	-4.1
XII <sup>c</sup>	3	30%	FPNPE	28.0	$1 \times 10^{-6}$	1.4	0.8	1.1	-0.2	-1.4	-2.3	-4.4
XIII <sup>c</sup>	4	50%	FPNPE	29.5	$5 \times 10^{-7}$	0.2	-0.7	-0.6	-1.8	-2.9	-4.0	-5.2

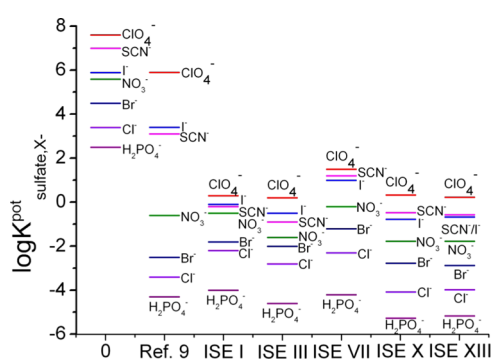
<sup>a</sup>Relative to the ionophore. <sup>b</sup>Separated solution method, theoretical slopes. <sup>c</sup>Polyurethane/FPNPE (1:1) membranes.

Chenhua Apparatus) at room temperature with Ag/AgCl (3 M KCl) as a reference electrode in the galvanic cell: Ag/AgCl|3.0 M KCl||1.0 M  $\text{CH}_3\text{COOL}$ |sample solution|ISE membrane|inner filling solution|Ag/AgCl. The selectivity coefficients were determined by a separated solution method, the potentials in two separate solutions (each containing a salt of the determined ion only) were recorded, and the values obtained at the highest examined concentrations were used to calculate the selectivity coefficient assuming theoretical slopes.<sup>28</sup> The complex formation constants were determined by the method described by Bakker.<sup>29</sup>

## RESULTS AND DISCUSSION

As shown in Scheme 1, four receptors with three different kinds of topology and increasing conformational complementarity with sulfate were used as ionophores here. Macrocyclic compound 1 was obtained by organizing aryl spacers and squaramides in an alternating fashion to match the size and shape of sulfate, which can sit comfortably in the cavity of the macrocycle.<sup>21</sup> Further preorganization and thus improved binding affinity and selectivity were achieved when benzene spacer units were replaced by pyridines (2 in Scheme 1), owing to the formation of intramolecular hydrogen bonds between the pyridine nitrogen and amide protons.<sup>22,23</sup> Considering the success of using tris(2-aminoethylamine) scaffold-based ionophores for potentiometric sulfate detection, it is reasonable that compound 3 with similar topology but more functional cyclic peptide amide hydrogen bond donors should also work well.<sup>26</sup> Last but not most important, compound 4 could reposition its *ortho*-phenyl bridged bisurea legs to accommodate the tetrahedral sulfate with perfect conformational complementarity and might be the only receptor reported to date that displays saturated coordination to sulfate by a single molecule.<sup>27</sup> In general, ionophores 1–2 are cyclic molecules favoring planar complexation of sulfate, while ionophores 3–4 are tripodal hosts that can provide cavities to accommodate sulfate with anchored functional groups in three dimension, this is true especially for collapsible legs bearing ionophore 4.

As shown in Table 1 and Figure 1, polymeric membrane electrodes formulated with all of the four ionophores 1–4 exhibit Nernstian/near-Nernstian response toward sulfate and selectivity patterns significantly different from the Hofmeister series, confirming the strong ionophore properties and high binding affinity of sulfate to ionophores. The nature of the



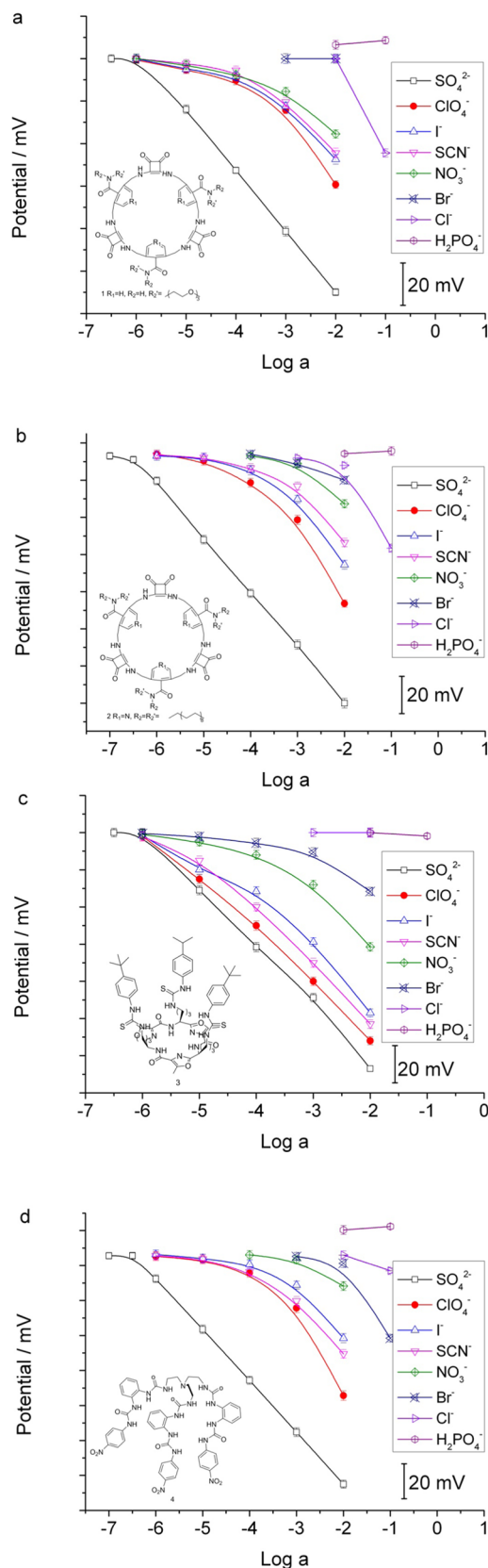
**Figure 1.** Potentiometric selectivity coefficients of tripodal squaramide ionophore-based electrodes from ref 9, ISE I, ISE III, ISE VII, ISE X, and ISE XIII toward sulfate over different anions.

plasticizers exerts a significant influence on the dielectric constant of the membrane and the mobility of the ionophore. A higher dielectric constant increases the polarity and decreases the electrical resistance of the membrane.<sup>6</sup> Since ionophores 3 and 4 had poor solubility in DOS ( $\epsilon = 4.8$ ) and/or *o*-NPOE ( $\epsilon = 24$ ), more polar *o*-NPOE and FPNPE ( $\epsilon = 50$ ) were chosen for ionophores 3 and 4, respectively. The results showed that DOS-plasticized electrodes demonstrated lower slopes, higher detection limits, and poor selectivity than those plasticized with NPOE (see ISE III and V in Table 1, which have the same composition but different plasticizer).

Lipophilic sites could compensate the charges of the anion–ionophore complex at high concentrations and improve the sensitivity, and thus the influence of a lipophilic additive on the performance of the electrodes containing different ionophores was evaluated.<sup>5</sup> Although little differences in the slopes of ISEs IX–XI were observed when changing the amount of additives, the amount of TDMACl does have a significant influence on the slopes of ionophore 2 and 3-based ISEs. For ionophores 2–4-based membranes, modest contents of TDMACl are necessary to obtain optimal slopes, and selectivity (30 mol % for ionophores 1–3 and 50 mol % for ionophore 4, ISEs I, III, VII, and X), and lower or higher contents may deteriorate the performance. Unfortunately, electrodes with optimized sulfate selectivity (ISE III, VII, and X) did not show the best detection

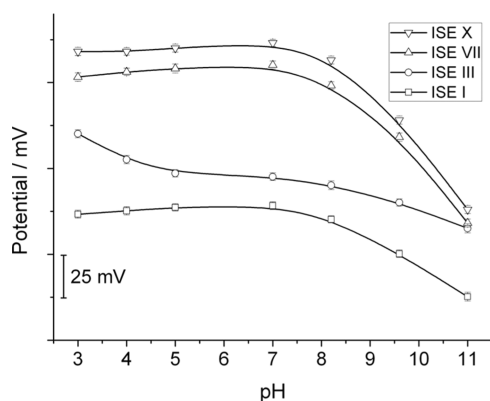
limits (ISE II, VI, and IX). Similar anti-Hofmeister selectivity pattern ( $\text{ClO}_4^- > \text{SO}_4^{2-} > \text{I}^- \approx \text{SCN}^- > \text{NO}_3^- > \text{Br}^- > \text{Cl}^- > \text{H}_2\text{PO}_4^-$ ) was observed for the ISEs developed with ionophores 1, 2, and 4, while ISEs fabricated with ionophore 3 prefer lipophilic anions ( $\text{ClO}_4^- > \text{I}^- \approx \text{SCN}^- > \text{SO}_4^{2-} > \text{NO}_3^- > \text{Br}^- > \text{Cl}^- > \text{H}_2\text{PO}_4^-$ ), and it is interesting to find that the performance sequence of the ionophores follow the trend  $4 > 2 > 1 > 3 >$  squaramide-based tripodal ionophore (see Figure 1). These results are counterintuitive considering more conformational complementary properties and additional hydrogen bond donating ability of ionophore 3, compared with ionophores 1–2 and squaramide-based tripodal ionophore (from ref 9), respectively. However, these results are consistent with the observation that ionophore 2 and tripodal squaramide showed high bulk liquid membrane and lipid bilayer sulfate transport activity, while ionophore 3 did not work under similar conditions.<sup>23,30</sup> Moreover, solvation of the ionophores and anions, as well as aggregation of ionophores, may play major roles in this process. Apparently, the best selectivity values for our proposed ISE over  $\text{H}_2\text{PO}_4^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{NO}_3^-$ ,  $\text{SCN}^-$ ,  $\text{I}^-$ , and  $\text{ClO}_4^-$  are  $-5.3$ ,  $-4.1$ ,  $-2.8$ ,  $-1.8$ ,  $-0.5$ ,  $-0.8$ , and  $+0.3$ , which are 1.0, 0.7, 0.3, 1.2, 3.6, 4.2, and 5.6 units better than previously reported best selectivity (the best selectivity coefficients of sulfate-selective sensors over  $\text{H}_2\text{PO}_4^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{NO}_3^-$ ,  $\text{SCN}^-$ ,  $\text{I}^-$ , and  $\text{ClO}_4^-$  are  $-4.3$ ,  $-3.4$ ,  $-2.5$ ,  $-0.6$ ,  $+3.1$ ,  $+3.4$ , and  $+5.9$ , respectively).<sup>9</sup> It is obvious that although the improvement in selectivity over hydrophilic anions is not significant, interference from lipophilic anions such as  $\text{SCN}^-$ ,  $\text{I}^-$ , and  $\text{ClO}_4^-$  is reduced largely, which are the most relevant ions for sulfate detection in environmental and clinical samples. It should be mentioned that the selectivity coefficients were determined by a separate solution method, which makes it possible to selectivity coefficient compare data of the new ionophores with those of the previously reported ionophores. In parallel, potentiometric response curves toward various anions are also illustrated (see Figure 2).

The effects of pH (3–11) on macrocyclic and tripodal ionophore-based membrane electrodes (ISEs I, III, VII, and X) were investigated by recording the potential change in 1 mM sulfate solution prepared with deionized water, to which very small aliquots of 0.1 M NaOH or HCl was added to adjust the pH. As shown in Figure 3, the potential responses of ISEs I, VII, and X were independent of pH in the range of 3–8, further increasing the pH of the solution to a higher range of 8–11 resulted in a negative slope of 10–50 mV/pH. The negative potential responses in the pH range of 8–11 might be attributed to the binding of  $\text{OH}^-$  by the ionophores embedded in the membrane phase. It is interesting to find that ISE III displayed a positive potential response to  $\text{H}^+$  in the pH range of 3–5, and the surprising response might be ascribed to the protonation of the isonicotinamide units ( $\text{p}K_a = 3.3$ ) in the macrocycle, which could provide additional electrostatic interactions with the anion and thus increase the binding affinity.<sup>22</sup> An example of the dynamic response of representative ISE X to sulfate is presented in Figure 4. Although a little potential drift was observed when changing the concentration of sulfate, the response time was considerably shorter ( $<60$  s). To give more information about the reversibility, potential traces when switching sensors from high to low concentrations several times are also displayed in Figure 4. It seems that although strong complexation (see the ionophore–anion complex formation constants) with sulfate is observed, good reversibility is obtained, and similar phenomena have been

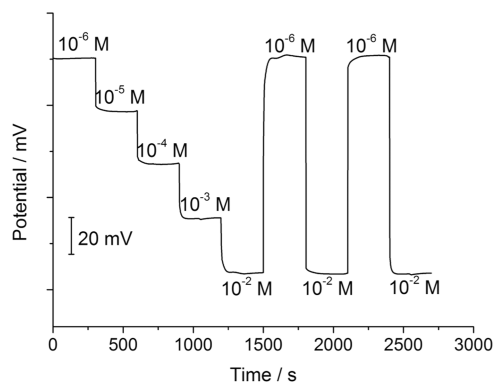


**Figure 2.** Potentiometric responses of ISE I (a), III (b), VII (c), and X (d) toward different anions.

reported in a previous work.<sup>31,32</sup> Moreover, the stability of ISEs I, III, VII, and X has been evaluated over a period of 2 months. While no significant changes in the slopes, detection limit, and



**Figure 3.** Effects of pH on the potential responses of ISEs I, III, VII, and X.



**Figure 4.** Dynamic sulfate EMF response of ISE X (HEPES buffer, pH = 7.0).

selectivity coefficients were observed for ISEs I and III, only 22 and 20 mV/dec responses were observed for ISEs VII and X, originating from the crystallization of the ionophores 3 and 4 in the membrane phase. To solve this problem, polymeric membrane electrodes have been fabricated by embedding the ionophores 3 and 4 in FPNPE plasticized polyurethane membrane. It is obvious that no significant changes in potentiometric responses were observed for ISEs XII and XIII in 2 months, demonstrating their satisfying stability (see Table S1 in the Supporting Information). Moreover, further structure refinement such as anchoring long lipophilic alkyl chains on the aromatic moieties of ionophore 4 is in progress in our lab.

It is well established that the binding affinity of ion–ionophore complexes have significant influence on the selectivity of the ISEs. However, translating the binding data in the solution-phase to the selectivity of the ionophore-based ISEs is not so straightforward. Herein, the formation constants

for ionophores 1–4 and various anions in *o*-NPOE or FPNPE plasticized membranes are determined using the segmented sandwich method. As shown in Table 2, each ionophore formed its strongest complexes with sulfate, but the sequence of the formation constants of the anion–ionophore complex did not correlate well with the determined selectivity pattern of the ISEs, indicating that the difference between the formation constants for sulfate and other interfering anions cannot be translated equivalently to selectivity. Using ionophore 4 as an example, the difference between the formation constants for sulfate and perchlorate is 8.0, whereas the related best  $\log K_{\text{sulfate, anion}}^{\text{pot}}$  is 0.2. This difference could partly be ascribed to different thermodynamics of ions, and the ion flux across the membrane generated by coextraction and ion-exchange processes.<sup>17</sup> Actually, the ratio of the complex formation constants of an ionophore with various ions changes the selectivity pattern as compared to Hofmeister series. Although the determination was executed in a different plasticized membrane environment, it can be concluded that compound 4 was the most powerful ionophore, following which was ionophore 2, ionophore 1, and ionophore 3. Similar results have also been mentioned and discussed in the previous section, emphasizing the important roles of size matching (ionophores 1 and 2) and conformational complementarity (ionophore 4) played in anion binding. Determination of the binding affinity of ionophore 2 with sulfate at pH 3.0 gave a  $K_a$  of  $6.3 \times 10^{10}$  M ( $\log K_a = 10.8$ ), approximately double of that observed in a neutral environment ( $3.2 \times 10^8$  M,  $\log K_a = 10.5$ ), these data correlated well with the results obtained in binary H<sub>2</sub>O/DMSO solution.<sup>22</sup>

As described above, the performance (with a linear range of  $1 \times 10^{-6}$ – $1 \times 10^{-1}$  M and detection limit of  $5 \times 10^{-7}$  M) of ISE X suggests that it may be suited for real-life applications. Therefore, sulfate determination in drinking water samples and neomycine tablets were performed using the ISE X and turbidimetry method. As shown in Table 3, the results

**Table 3.** Analytical Results for the Determination of Sulfate in Drinking Water Samples and Neomycine Tablets ( $n = 3$ )

samples	added (mM)	ISE X (mM)	turbidimetry (mM)
drinking water 1	1.0	$0.92 \pm 0.03$	$0.98 \pm 0.02$
drinking water 2	2.0	$1.90 \pm 0.05$	$2.02 \pm 0.03$
neomycine tablet 1		$1.02 \pm 0.05$	$0.98 \pm 0.04$
neomycine tablet 2		$0.96 \pm 0.06$	$0.99 \pm 0.03$

obtained using the developed electrode are consistent with those obtained by the turbidimetry method, proving its reliability for sulfate detection in environmental and pharmaceutical fields.

**Table 2.** Ionophore–Anion Complex Formation Constants Determined in PVC/*o*-NPOE or FPNPE (1:2) Membranes<sup>a</sup>

ionophore (1 wt %)	plasticizer	formation constants ( $\log K_a$ )							
		SO <sub>4</sub> <sup>2-</sup>	ClO <sub>4</sub> <sup>-</sup>	I <sup>-</sup>	SCN <sup>-</sup>	NO <sub>3</sub> <sup>-</sup>	Br <sup>-</sup>	Cl <sup>-</sup>	H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>
1	<i>o</i> -NPOE	10.0	2.5	4.0	2.6	4.0	4.1	4.5	3.0
2	<i>o</i> -NPOE	10.5	2.6	4.1	2.6	4.1	4.3	4.7	3.2
	pH = 3.0	10.8	2.9	4.2	2.8	4.3	4.6	4.9	3.3
3	<i>o</i> -NPOE	9.9	3.2	4.2	3.2	4.3	4.4	4.5	3.4
4	FPNPE	11.7	3.7	4.5	3.6	4.6	4.8	4.9	4.1

<sup>a</sup>The measurement was operated in HEPES buffer (pH = 7.0) unless otherwise stated. The complex stoichiometry is 1:1.

## CONCLUSIONS

Four hydrogen bond-based macrocyclic and tripodal neutral receptors with increasing conformational complementarity with sulfate were used as ionophores to develop polymeric membrane sulfate-selective electrodes. By optimizing the membrane composition such as ionophores, lipophilic additives, and plasticizers, the proposed ISEs showed Nernstian response to sulfate with the best selectivity so far and improved detection limits (a slope of  $-29.8$  mV/dec in the linear range of  $1 \times 10^{-6}$ – $1 \times 10^{-1}$  M with a detection limit of  $5 \times 10^{-7}$  M), which led to the success of the determination of sulfate in drinking water samples and neomycine tablets. The anion–ionophore complex constants in the membrane phase were determined and correlated with the selectivity sequence of the ISEs. The success of the ionophores represents a feasible strategy for overcoming the “Hofmeister series” by employing a combination of complementarity and hydrogen bonds.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssensors.0c02231>.

Data for slopes, detection limits, and selectivity coefficients of ISEs XII and XIII in a period of 2 months (PDF)

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## Notes

The authors declare no competing financial interest.

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