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Fluorous Bulk Membranes for Potentiometric Sensors with Wide Selectivity Ranges: Observation of Exceptionally Strong Ion Pair Formation

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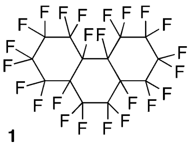
Chemical sensors based on receptor-doped polymeric membranes have been developed for over 60 analytes.[1] They are routinely used in clinical chemistry for well over a billion measurements per year. Recent improvements in the design of these sensors have lowered detection limits into the picomolar concentration range,[2] and novel receptors that allow the selective detection of new analytes continue to be reported frequently. Unfortunately, biofouling[3] can seriously limit the lifetime of these sensors. In this study, we explore the use of fluorous sensing membranes with a view to reduce biofouling. We describe the first use of fluorous membranes for potentiometric sensors and show fluorous membranes with remarkable potentiometric selectivity. Notably, the fluorous character of these membranes explains the formation of ion pairs of unprecedented strength.

The adsorption of lipids and proteins onto the sensing membranes of ion-selective electrodes (ISEs) or bulk membrane optodes may affect response times[4] but does not impair the equilibrium responses of these sensors. However, if the layer adsorbed to a sensor surface becomes thick, the sensor responds to the concentration of the analyte within this adsorbed layer instead of its concentration in the sample. To overcome this problem, chemical modification of sensor surfaces was suggested.[5] Moreover, NO-releasing membranes were shown to reduce blood platelet adhesion and the formation of fibrous tissue around sensors.[6]

However, while biofouling has long been suspected to be related to adsorption effects, it was only recently shown that drifts and a gradual loss of selectivity can also result from the extraction of synthetic nonionic surfactants[7] and naturally occurring hydrophobic sample components,[8,9] such as lipids and proteins, into sensing membranes. Examples for the latter are the decrease in selectivities of a H^+-selective ISE by up to 4 orders of magnitude upon exposure to cheese[8] and the 6-fold increase in Na^+ interference of the commercially highly successful valinomycin-based K^+ ISE upon exposure to urine.[9] The potential of fluorous phases to reduce this type of biofouling by limiting the extraction of electrically neutral sample components into sensing membranes results from their extraordinarily low polarity. For example, on the π^* scale of solvent polarity, water has a π^* value of 1, cyclohexane defines 0, and perfluorooctane has the value of -0.41.[10] Indeed, many alkanes are too polar to be miscible with perfluoroalkanes, and most lipids are poorly soluble in perfluorocarbons.[11,12] To emphasize the differences between common organic and perfluorocarbon phases, the term "fluorous" was coined.[13,14] This investigation shows that the use of fluorous membranes for electrochemical sensors not only is very promising but also tests the very limits of electrochemistry in phases of low polarity.

For this study, solutions of a fluorophilic salt in perfluoroperhydrophenanthrene, **1** (bp 215 °C), were used as fluorous cation-selective potentiometric sensing phases. The selection of an appropriate salt was difficult, since only a very small number of salts with solubility in fluorous solvents have been reported in the literature.[15] Preliminary results showed that highly hydrophobic tetraphenylborate salts commonly used in ISEs are insufficiently soluble in fluorous phases. Not even lithium perfluorotetraphenylborate and potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate dissolved appreciably in fluorous solvents. Ultimately, sodium tetrakis[3,5-bis(perfluorohexyl)phenyl]borate, **2**, was chosen. The colorless salt **2** was synthesized according to a modified literature procedure[15] in two steps from 1,3,5-tribromobenzene and was found to have a solubility in **1** of 1.4 mM.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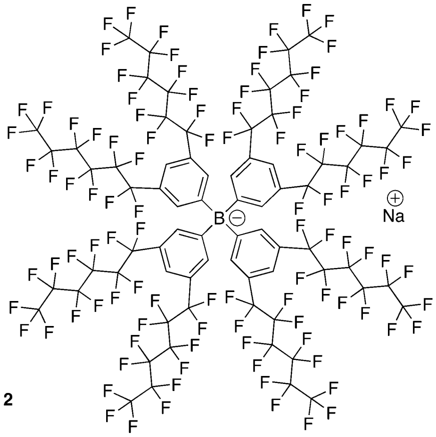
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The eight perfluorohexyl groups of **2** result in a fluorine content of 67.5% (w/w) and cause the high solubility of this salt in **1**, which itself has a fluorine content of 73.1%. In view of the exceptionally low polarity of fluorous solvents, a high tendency of **2** to form ion pairs was expected. To explore this possibility, the concentration dependence of the molar conductivity of **2** was determined in an electrochemical cell. For this purpose, porous Teflon filters[16] were impregnated with solutions of **2** in **1**. Since Teflon is not swelled by these solutions, it is an inert support for the liquid fluorous phase. The fluorous membranes prepared in this way were mounted into an electrode body custom-made from poly(chlorotrifluoroethylene),[17] and this body was equipped with an inner Ag/AgCl reference and internally filled with a 1 mM NaCl solution. An electrochemical cell was obtained by immersion of the thus fabricated electrode and an external reference electrode of the double junction type (saturated KCl as inner solution and 1 M LiOAc as bridge electrolyte) into a NaCl sample solution. A plot of the EMF of this cell as a function of the logarithm of the Na^+ concentration shows a Nernstian response slope, confirming that the Na^+ remains in the fluorous membrane. The resistances of the fluorous membranes were then determined with the known shunt method.[18] Ion pair formation constants, K_{ip} (M^{-1}), were obtained from the concentration dependence of the membrane resistance, as described in the literature.[19] In brief, molar conductivities, Λ, calculated from the measured resistances, were fitted with

$$\Lambda = \lambda_o K_{ip}^{-1/2}(c^{-1/2} + 2K_t\, c^{1/2}/3)$$

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Table 1. Ion Pair Formation Constants in Perfluoroperhydrophenanthrene Containing Tetrakis[3,5-bis(perfluorohexyl)phenyl]borate and Various Cations

ion	Li^+	Na^+	Cs^+	NH_4^+	H_3O^+
$\log K_{ip}$	20.36 ± 0.17	20.57 ± 0.95	20.29 ± 0.02	20.11 ± 0.23	20.73 ± 0.20

Table 2. Potentiometrically Determined Logarithmic Selectivity Coefficients, $\log K^{pot}_{Cs,J}$, Referenced to Cs^+ for Fluorous, Nonfluorous Ion Exchanger, and Ionophore-Based ISE Membranes

	$\log K^{pot}_{Cs,J}$ (separate solution method)					
membrane type	Ca^{2+}	Li^+	Na^+	K^+	$N(Pr)_4^+$	$N(Bu)_4^+$
I (Fluorous, **2**)	−4.35	−4.01	−3.75	−2.59	+9.08	+11.41
II (chloroparaffin, KFPB)	−0.69	−1.07	−0.99	−0.65	+5.88	+6.91
III (*o*NPOE, **2**)	−3.85	−3.66	−2.85	−1.06	+4.76	+4.33
IV (*o*NPOE, KClPB)	−3.79	−3.66	−2.90	−1.07	+5.48	+4.41
ionophore[22a]	−3.39	−4.20	−3.87	−2.68		
ionophore[22b]	−6.03	−5.69	−5.53	−3.74		

where c is the total concentration of the fluorophilic salt, λ_o is its limiting molar conductivity, and K_t is the triple ion formation constant. To obtain K_{ip} values for other cations, membranes were equilibrated with solutions of the chloride salt of different cations of interest. Successful ion exchange was confirmed by resistance measurements and Nernstian responses of these membranes.

Table 1 shows $\log K_{ip}$ values for several cations. They all fall into the relatively narrow range of 20.11 to 20.73, excluding the possibility of very specific cation−anion interactions. These are the first reported K_{ip} values for ion pair formation in a fluorous solvent. To the best of our knowledge, these K_{ip} values exceed previously reported ones by at least 5 orders of magnitude. For example, for tetraoctylammonium chloride in 98:2 toluene−nitrobenzene, a $\log K_{ip}$ of 14.9 was determined,[19b] and for tetrakis(decyl)ammonium tetraphenylborate in cyclohexane, a $\log K_{ip}$ of 14.2 was found.[19c] Notably, the K_{ip} values reported here also considerably exceed constants reported for ion pair formation in α,α,α-trifluorotoluene, which takes an intermediate role between hydrocarbons and fluorous solvents, since it is miscible with both. While α,α,α-trifluorotoluene is, to date, the "most fluorous" solvent for which electrochemistry has been reported, its dielectric constant, ϵ, of 9.2 is relatively high and the $\log K_{ip}$ of 5.4 for tetrabutylammonium tetrafluoroborate is rather low.[20]

In view of chemical sensing, the potentiometric selectivities of the electrodes described above are of particular interest. Selectivity coefficients of fluorous and conventional receptor-free ISE membranes are compared in Table 2. The Cs^+ ion serves as the common reference point.

While the selectivities of the fluorous membranes span a remarkably wide range of more than 16 orders of magnitude, the selectivity range for membranes prepared from poly(vinyl chloride), the plasticizer chloroparaffin, and the lipophilic anion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (KFPB, membrane type II) is limited to only 8 orders of magnitude. Notably, the perfluorohexyl-substituted anion of **2** does not appear to interact with appreciable specificity with alkali metal ions, as a comparison of the selectivities of type III and type IV membranes shows. Both types were prepared with *o*-nitrophenyl octyl ether (*o*NPOE) as plasticizer, but the latter contained potassium tetrakis(4-chlorophenyl)borate (KClPB) instead of **2** as the lipophilic anion. Nevertheless, their selectivities do not differ substantially.[21]

Surprisingly, the selectivities of fluorous membranes not only compare well with those of receptor-free membranes but also are in the range of those of ionophore-based Cs^+ selective electrodes[22] (see Table 2). Since the high selectivities of the fluorous membranes are the result of the low extent of solvation of interfering ions, we expect that similarly receptor-based fluorous membranes will be much more selective than corresponding nonfluorous ones. Experiments to show this for ISEs based on fluorophilic receptors are in progress.

In summary, these results show that potentiometry with fluorous sensing membranes exhibits extraordinarily high selectivities. The exceptionally low polarity of these sensing membranes is evidenced by unprecedented strong ion pair formation, and the low solubility of lipids in fluorous phases is of great promise in view of the reduction of biofouling.

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Supporting Information Available: Experimental preparation of **2** and details of electrochemical measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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