Neutral Anion Receptors: Synthesis and Evaluation as Sensing Molecules in Chemically Modified Field Effect Transistors

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A new class of anion selective receptors is based on the neutral uranyl-salenophene building block as Lewis acidic binding site. Additional hydrogen bond accepting or donating moieties near the anion binding site offer the possibility of varying the binding selectivity. Field effect transistors chemically modified with such receptors exhibit anion selectivities that strongly deviate from the classical Hofmeister series favoring phosphate or fluoride anions, depending on the structure of the uranyl-salenophenes. The phosphate selective chemically modified field effect transistors (CHEMFETs) detect phosphate with high selectivity over much more lipophilic anions, such as nitrate (log $K_{\text{PONO}_3^{-}} = -1.3$), and [H$_2$PO$_4^{-}$] $\geq$ 6.3 $\times$ 10$^{-4}$ M. CHEMFETs modified with salophenes with amido substituents result in a high fluoride selectivity; even in the presence of 0.1 M chloride, fluoride can be detected at $[F^{-}] \geq 6 \times 10^{-4}$ M (log $K_{\text{FCl}}^\text{tot}$ = -2.0).

Introduction

Compared with synthetic neutral receptors for cations, such receptors for anions have only recently received the attention they deserve. Both in membrane transport and anion sensing, such receptors will be required in order to obtain sufficient selectivity. The wide variety of anion-exchange membranes, e.g. nitrate, phosphate, and halides, or in clinical chemistry, e.g. chloride and sulfate, stimulate our work on highly selective sensors. Sensors for lipophilic anions, like nitrate, can be obtained with anion-exchange membranes that introduce a selectivity following the relative hydration energies of the anions (i.e., the so-called Hofmeister series). Most sensors described in the literature for the detection of hydrophilic ions contain organonitro derivatives or metalloporphyrins as the receptor in the ion-selective membrane to selectively bind the target anion. A drawback of the organonitro receptors is their limited stability, and furthermore with both types of receptors, tuning of the selectivity by introducing additional binding sites is difficult.

Previously, we have reported a number of uranyl-salenophene derivatives which show selective binding of anions in organic solvents. In these neutral receptors four of the five equatorial coordination sites of the uranyl cation are occupied by the salophene, and the fifth site is available for anion binding. The binding of anions can be further influenced by functionalization of the uranyl-salenophene with additional binding sites that can form hydrogen bonds. Recently these receptors have been used successfully in combination with cation receptor molecules to selectively transport salts through supported liquid membranes.

This paper describes the synthesis of a second generation of uranyl-salenophene derivatives which show high selectivity for phosphate and fluoride, together with their application as sensing molecules in membrane sensors. These novel uranyl-salenophenes all have dodecyl chains in order to increase the lipophilicity, and in addition they have hydrogen bond accepting methoxy or hydrogen bond donating acetamido groups in close proximity to the anion coordination site. The additional binding sites tune the selectivity with respect to individual anions.

Results and Discussion

Synthesis

The salophenes were prepared by condensation of 1,2-phenylenediamine with 2 equiv of the appropriate salicylaldehyde derivative. To increase the lipophilicity of the salophene derivatives, the 1,2-phenylenediamine moiety was substituted with two dodecyl ether groups. Alkylation of catechol 1 gave, after nitration, 1,2-dinitro-4,5-bis(dodecylxyloxy)benzene (2) that was reduced to the diamine 3 in an overall yield of 60% (Scheme 1).

Diamine 3 was used to synthesize the lipophilic uranyl-salenophene derivatives 7, 8, 9, and 13. The parent salophene 7 and the methoxy-substituted salophenes 8 and 9 were prepared in 45-50% yield by reaction of 3 with 2 equiv of the appropriate salicylaldehyde (respectively 4, 5, and 6) and 1 equiv of UO$_2$(OAc)$_2$$\cdot$2H$_2$O in methanol (Scheme 2).


The acetamido-substituted salophene 13 was obtained under similar conditions in 30% yield, starting from salicyl aldehyde derivative 12. Compound 12 was obtained by reaction of 4-tert-buty1-2-aminophenol (10) with acetic acid anhydride, followed by formylation with hexamethylenetetramine (HMTA) in trifluoroacetic acid (Scheme 3).

**Anion Selectivity.** The anion selectivity of the uranyl salophenes was evaluated by application of these receptors as the sensing molecule in potentiometric anion sensors, in analogy with the experiments previously reported for calix[4]arene-based cation receptors. Plasticized PVC membranes (plasticized with 65 wt % of o-nitrophenyl n-octyl ether (o-NPOE), and containing 1 wt % of uranyl salophene receptor and 20 mol % tacryctylamonium bromide with respect to the receptor) were cast on chemically modified field effect transistors (CHEMFETs). The anion-binding selectivity of the parent salophene 7 is governed by the character of the electron-accepting uranyl center. The incorporation of receptor 7 in the membrane renders the sensor sensitive and selective for the hydrophilic monovalent dihydrogen phosphate anion. Figure 1 shows that even in the presence of a large excess of chloride (0.1 M) the sensor starts responding to the dihydrogen phosphate ions at concentrations $\geq 6 \times 10^{-4}$ M with a close to Nernstian response of $-53$ mV/decade at concentrations $\geq 3.2 \times 10^{-3}$ M. This sensor is selective for dihydrogen phosphate over many other and much more lipophilic anions (Table 1). Even in the presence of the lipophilic nitrate anion, the sensor is 20 times more sensitive for phosphate ($\log K_{H_2PO_4}^{7}$ $= -1.3$). This remarkable selectivity deviates strongly from the Hofmeister selectivity commonly observed with ion-exchange membrane sensors. Such ion-exchange membrane sensors have usually a $10^{4}$-to-$10^{6}$ higher selectivity for nitrate over phosphate, indicating that the sensor with receptor 7 increases the phosphate selectivity with a factor of $2 \times 10^{2}$ to $2 \times 10^{4}$.

When the o-methoxy-substituted salophene derivative 8 was incorporated in the sensing membrane, a distinct change in the sensor characteristics was observed (Table 1). The detection limit for phosphate is further lowered to $1.6 \times 10^{-4}$ M, and also the selectivity in the presence of halides and sulfate is further enhanced by a factor of 3–10 ($\log K_{H_2PO_4}^{8}$ $= -1.8$ and $-2.3$ respectively for 7 and 8, and $\log K_{H_2PO_4}^{8}$ $= -2.3$ and $-3.3$). The favorable effect on the phosphate sensitivity, reflected in the improved detection limit, is most likely due to additional hydrogen bond formation of a dihydrogen phosphate anion coordinated to the Lewis acidic uranyl center, with the hydrogen bond accepting methoxy groups of the receptor. Previously we have reported X-ray crystal structures that indeed show that hydrogen bonds

![Figure 1](image_url)

**Figure 1.** Phosphate response of CHEMFET with receptor 7 in the presence of 0.1 M NaCl (0.01 M MES, pH 4.5).

**Table 1.** Sensor Characteristics of Phosphate Selective CHEMFETs with Receptors 7–9

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Detection Limit (mM)</th>
<th>$K_{H_2PO_4}^{7}$ (mV/decade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>$3.8 [-56]$</td>
<td>$-1.3 [-50]$</td>
</tr>
<tr>
<td>8</td>
<td>$3.8 [-50]$</td>
<td>$-1.7 [-56]$</td>
</tr>
<tr>
<td>9</td>
<td>$3.8 [-50]$</td>
<td>$-2.0 [-30]$</td>
</tr>
</tbody>
</table>

Notes:
- $K_{H_2PO_4}^{7}$ is the dissociation constant of dihydrogen phosphate.
- The dissociation constant of dihydrogen phosphate is $K_{H_2PO_4}^{7} = -1.3$.
- The dissociation constant of dihydrogen phosphate is $K_{H_2PO_4}^{8} = -2.3$. 
- The dissociation constant of dihydrogen phosphate is $K_{H_2PO_4}^{9} = -3.3$.
are formed between dihydrogen phosphate bound to an o-methoxy-substituted uranylarsalophene and adjacent methoxy groups. An additional effect of the presence of the methoxy substituents near the uranyl binding center will be the reduction of the size of the binding cleft and the increased electrostatic repulsion with the relatively large interfering halide ions. The presence of the electron-donating methoxy substituents furthermore reduces the electronphilicity of the uranyl center, thereby affecting its anion binding strength. This electronic effect causes the reduced selectivity of the “hard” phosphate over the “softer” nitrate anion of receptor 8 as reflected in CHEMFETs with the p-methoxyarylarsalophene derivative 9. The methoxy groups of 9 should have approximately the same effect on the charge density of the uranyl center as in 8, but cannot form additional hydrogen bonds with phosphate. This results in a reduced phosphate over nitrate selectivity (log $K_{P(O)}^{nit}$ = -0.2 with receptor 9 vs -1.3 with receptor 7, Table 1). Compared with receptor 9 the phosphate over nitrate selectivity of receptor 8 is increased due to the additional hydrogen bond formation of phosphate.

As the uranyl center strongly binds low polarizable (hard) anions of high electron density, the receptors were also evaluated for their fluoride selectivity. Besides having a high electron density, fluoride is also a strong hydrogen bond acceptor, and this makes this ion very hydrophilic and difficult to extract into organic media. Selective measurement of fluoride anions with polymeric membrane sensors therefore requires the presence of extremely selective fluoride receptors in the membrane.

Incorporation of the parent salophene 7 in the sensor membrane introduces fluoride sensitivity with a detection limit of [F-] = 1.3 x 10^-4 M. The selectivity for fluoride with respect to the more lipophilic halide ions is ≥10, but nitrate ions significantly interfere when present at equal or higher concentrations (Table 2). The selectivity of the receptor for fluoride could be improved by optimization of the binding cleft for the specific characteristics of this ion. The data for salophene 8 in Table 2 show that already the reduction of the binding cleft by the presence of the o-methoxy substituents results in improved selectivity for fluoride over the larger chloride and bromide ions (e.g. log $K_{P(O)}^{Cl}$ = -1.3 and -1.9 respectively for salophene 7 and 8). The fluoride sensitivity, reflected in the detection limit and slope of the response curve of the sensor, is also slightly improved compared with 7 as the receptor. However, excellent fluoride sensitivity and selectivity was obtained only with sensors that contain the anion receptor 13, having hydrogen bond donating amide substituents in close proximity of the uranyl center, in the membrane. This receptor combines a reduced size of the cleft with the ability to donate hydrogen bonds to the fluoride anion. The slope of the response curve of ≈53 mV/decade is almost Nernstian, and the detection limit is in the sub-millimolar range. Sensors with ion receptor 13 have a 100-fold or higher selectivity (log $K_{P(O)}^{Cl}$ ≤ -2) for fluoride over the other halides, nitrate, and sulfate (Table 2). As is shown in Figure 2 even in the presence of a large excess of the very lipophilic perchlorate ion (0.1 M) it is possible to determine fluoride at the (sub)millimolar level (log $K_{P(O)}^{ClO_4}$ = -1.7). This implies an enhancement of the fluoride selectivity over perchlorate of at least 10^4 when compared with the Hofmeister selectivity observed in ion-exchange membrane sensors.

In summary, we have developed a new generation of lipophilic uranylarsalophene derivatives that can be applied as selective receptors in anion sensitive membrane sensors. It is very important that the anion selectivity can favorably be tuned by the introduction of additional binding sites close to the anion binding site of the neutral uranyl salophene binding site. Incorporation of these novel ion receptors in polymeric membranes on chemically modified field effect transistors enables the evaluation of their anion binding properties and the determination of the ion activity of the very hydrophilic dihydrogen phosphate and fluoride anions in aqueous solutions, even in the presence of an excess of very lipophilic ions such as nitrate and perchlorate.

**Experimental Section**

**General.** NMR spectra were recorded in CDCl3 unless stated otherwise, with TMS as internal standard at 250 MHz. Ion fast atom bombardment (FAB) mass spectra were obtained with m-nitrobenzyl alcohol as a matrix. Melting points are uncorrected. CHCl3 was distilled from CaCl2 and stirred over molecular sieves (4 Å). All commercially available chemicals were of reagent grade quality from Acros, Aldrich, or Merck and were used without further purification. 1,2-Bis(dodecyl)-oxybenzene (1) was made according to a literature procedure.12

**Caution:** Care should be taken when handling uranyl-containing compounds because of their toxicity and radioactivity.

1,2-Bis(dodecyl)-4,5-dinitrobenzene (2). To a cooled (15 °C) mixture of 4.5 g (0.01 mol) of 1 and 70 mL of glacial acetic acid in 70 mL of dichloromethane was slowly added 10 mL of concentrated nitric acid (65%), while keeping the temperature below 40 °C. After being stirred for 30 min, the

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Table 2. Sensor Characteristics of Fluoride Selective CHEMFETs with Receptors 7, 8, and 13

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Detection Limit (mV)</th>
<th>$\log K_{P(O)}^{ClO_4}$ (slope mV/decade)</th>
<th>$\log K_{P(O)}^{NO_3}$</th>
<th>$\log K_{P(O)}^{Cl}$</th>
<th>$\log K_{P(O)}^{SO_4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>-2.9 [-44]</td>
<td>-0.7 [-41]</td>
<td>-1.1 [-38]</td>
<td>-1.3 [-46]</td>
<td>-2.3 [-39]</td>
</tr>
<tr>
<td>8</td>
<td>-3.0 [-48]</td>
<td>-0.5 [-41]</td>
<td>-1.6 [-47]</td>
<td>-1.9 [-49]</td>
<td>-2.1 [-50]</td>
</tr>
</tbody>
</table>

* 0.01 M MES, pH = 6.0. 1[j] = 0.1 M in 0.01 M MES, pH = 6.0. 1’[NO3] = 0.01 M in 0.01 M MES, pH = 6.0.
solution was again cooled to 15 °C, 25 mL of fuming nitric acid (100%) was slowly added, and the mixture was stirred at room temperature for 3 days. The solution was poured into 250 g of ice water, and the resulting mixture was extracted six times with ether (3 x 100 mL). The ether layer was washed with 0.1 M HCl (3 x 150 mL), saturated NaHCO₃ solution (150 mL), and brine (150 mL). After the mixture was dried with MgSO₄, the solvent was evaporated. Recrystallization from acetone yields 4.0 g (78%) of mp 83–84 °C; 1H NMR δ 7.29 (2H, s), 4.10 (4H, t, J = 6 Hz), 1.87 (8H, m), 1.52–1.36 (36H, m), 0.98 (4H, t, J = 6 Hz), 0.75 (6H, m), 1.65 (158.1 s), 138.6 (s), 107.9 (t), 31.9 (t), 29.7 (t), 29.6 (t), 29.4 (t), 29.2 (t), 28.7 (t), 25.8 (t), 22.7 (t), 14.1 (q); MS-FAB m/z 538.1 (M + 2H)⁺, calcd 538.4. Anal. Calcd C₇H₁₃NO₆: C, 67.1; H, 9.8; N, 5.2. Found: C, 66.9; H, 9.9; N, 5.3.

1,2-Dicycloxy-4,5-dimethoxybenzene (3). To a solution of 1.8 g (5 mmol) of 2 in 50 mL of ethanol, 1 g of 10% Pd/C, and 6.3 mL (57 mmol) of hydrazine monohydrate were added. After 1 night of refluxing, the hot solution was filtered over Hyflo, while kept under N₂. After cooling, the white precipitate was filtered off and rinsed with cold, O₂-free methanol. Yield 1.9 g (90%); mp 73–74 °C; 1H NMR δ 6.38 (2H, s), 3.90 (4H, t, J = 6 Hz), 1.98 (8H, m), 1.62–1.25 (26H, m), 0.88 (6H, t, J = 6 Hz); 13C NMR δ 143.4 (s), 146.8 (s), 60.8 (t), 70.2 (t), 26.1 (t), 22.7 (t), 14.1 (q); MS-ES m/z 476.4 (M⁺, calcd 476.4).

N-(2-Hydroxy-4-tert-butylphenyl)acetamide (11). To a solution of 1.25 g (6 mmol) of 2-amino-4-tert-butylphenol in 40 mL of acetic anhydride was added dropwise 8.8 mmol (58 mmol) of acetic anhydride. The solution was stirred overnight, and after cooling, a white precipitate was collected; yield 1.5 g (80%); mp 169–171 °C; 1H NMR δ 5.89 (1H, s), 7.78 (1H, s), 7.14 (1H, d, J = 8.0 Hz), 6.99 (1H, s), 6.94 (1H, d, J = 8.4 Hz), 2.23 (3H, s), 1.25 (9H, s); 13C NMR δ 170.6 (s), 146.3 (s), 143.6 (s), 124.8 (s), 124.4 (d), 119.4 (s), 134.0 (s), 31.4 (q), 23.7 (q); MS-ES m/z 207.1 (M⁺, calcd 207.1). Anal. Calcd C₁₂H₁₄NO₂: C, 66.5; H, 8.2; N, 7.0.

N-(3-Formyl-2-hydroxy-4-tert-butylphenyl)acetamide (12). A mixture of 1.6 g (7 mmol) of 11 and 1.01 g (7 mmol) of hexamethylenetetramine (HMTA) was dissolved in 150 mL of trifluoroacetic acid and refluxed for 3.5 d. After the mixture was cooled to 60 °C, 9 mL water was added, and the resulting mixture was stirred for 2.5 h. The mixture was dissolved in 150 mL of EtOAc, brought to neutral pH with NaHCO₃, and washed with 150 mL of brine. Evaporation yields the crude product, which could be purified using column chromatography (CH₂Cl₂/MeOH). Yield 1.7 g (70%); mp 109–110 °C; 1H NMR δ 9.30 (1H, t, J = 8.0 Hz), 6.92 (1H, s), 6.78 (1H, d, J = 2.2 Hz), 7.72 (1H, b), 7.25 (1H, d, J = 2.2 Hz), 2.24 (3H, s), 1.34 (9H, s); 13C NMR δ 197.0 (d), 168.5 (s), 147.9 (s), 145.4 (s), 127.1 (s), 124.7 (d), 123.4 (d), 119.1 (s), 34.5 (s), 31.2 (q), 24.9 (q); MS-ES m/z 235.1 (M⁺, calcd 235.1). Anal. Calcd C₁₄H₁₄NO₃: C, 66.4; H, 7.3; N, 6.0. Found: C, 66.5; H, 7.4; N, 6.0.

General Procedure for the Synthesis of UO₂ Salolophenes 7, 8, 9, and 13. A solution of 1.3 mmol of the appropriate aldehyde (salicyl aldehyde (4), 3-methoxyacetylaldehyde (5), 5-methoxyacetylaldehyde (6), or 12) and 0.3 g (0.55 mmol) of diamine 3 in 25 mL of methanol was refluxed for 3.5 d. Subsequently, 0.2 g (0.26 mmol) of O₃ was added, and refluxing was continued for another 1.5 h. The precipitate was filtered off and washed with methanol to yield 7, 8, 9, and 13 as an orange or red solid.


Medical Instruments, Enschede, The Netherlands). The developed membrane potential was compensated by an equal and opposite potential via the reference electrode. A saturated calomel electrode (SCE) was used as a reference, connected to the sample solution via a salt bridge filled with 1.0 M LiOAc. Small amounts of acetate that might leak from the salt bridge do not cause interference, as was checked in a separate experiment. For measurements, 10 CHEMFETs were placed in beaker with 26 mL of the sample solution (0.01 M MES and 0.1 M of the sodium salt of the interfering ion under investigation). Small amounts of primary ion sodium salt solution (stock solutions of 0.01 and 1.0 M for NaH₂PO₄ and 0.01 and 0.5 M for NaF) were added to the sample solution to obtain a series of measurements at primary ion activities (a) ranging from \( \log(a) = -6.1 \) to \(-1.1\), with steps of 0.2. Before and after the measurement series, the pH of the solution was measured and proved to be constant. The response of the CHEMFETs was monitored simultaneously, and the data were collected and analyzed using an Apple II GS microcomputer. The response times of CHEMFETs are on the order of a few hundred milliseconds and shorter than the measuring time.  

All equipment was placed in a dark and grounded metal box in order to eliminate any effects from static electricity and photosensitivity of the CHEMFETs. The potentiometric selectivity coefficients, \( K_j^{OY} \), were determined by the fixed interference method (FIM) according to IUPAC recommendations. All concentrations were converted to single-ion activities, and the mean activity coefficient was obtained by the extended Debye–Hückel equation. The measurements were performed at a temperature of 22 °C in an air-conditioned room.

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