Synthesis of Tripodal Trifluoroacetophenone Derivatives and Their Evaluation as Ion-Selective Electrode Membranes

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New, C₃ symmetric, tripodal trifluoroacetophenone derivatives 1-3 have been synthesized as anion ionophores. Evaluation of their ion selectivity has been carried out through ion-selective electrode membranes. The selectivity coefficients for the carbonate electrode toward various anions are dependent on the composition of the membranes and the lipophilicity of the ionophores. The tripodal ionophore 1a showed an improved selectivity toward salicylate when 90 mol% of a lipophilic additive was used, compared to that of p-dodecyltrifluoroacetophenone.

Key Words: Tripodal ionophores, Trifluoroacetophenone, Carbonate anion, Ion-selective electrode

Recently selective recognition and sensing of anions by artificial receptors have attracted a considerable research interest in view of their potential applications in various areas. ¹ To develop an artificial receptor that is selective toward a specific analyte, multiple interactions between host and guest in a complementary fashion may be considered. We have been interested in C₃ symmetric tripodal receptors that provide multiple interaction sites toward given analytes. ² Among various anions, oxoanions such as carbonates, phosphates, or chlorates may participate in trigonal interactions with suitably designed tripodal receptors because these anions have trigonal or tetragonal structural features. ²d As a recognition motif, we were particularly interested in the trifluoroacetophenone group, which has been successfully used in the carbonate-selective electrode membranes. ³ Selective recognition and sensing of carbonate ions are of importance in clinical diagnostics, environmental monitoring, and industrial purposes. ⁴ It is known that trifluoroacetyl group reacts with carbonates (CO₃²⁻, HCO₃⁻) to generate carbonyl adducts. ⁵ Therefore, it may result in an ideal receptor system if we introduce three trifluoroacetyl (TFA) groups in the receptor positioned suitably to interact with the oxoanions of trigonal or tetrahedral guests. Herein, we wish to report the synthesis of C₃ symmetric trifluoroacetophenones 1-3 and their evaluation as recognition components in ion-selective electrode membranes.

Synthesis of the ionophores 1-3. The benzene-based tripodal receptor system has been designed based on the fact that three trifluoroacetophenone groups can have a conformational preference of “all-syn” conformer over others. ⁷ A molecular modeling study on the benzene-based tripodal trifluoroacetophenone receptors (BTTFAs) suggested that the position of TFA groups, meta and para, seems to affect the relative strain of the host-guest adducts depending on different guests. During the synthesis of receptors 1, we found that introduction of the TFA groups was problematic. After examining several routes, finally the TFA groups could be introduced through the addition of CF₃⁻ anion to the aldehyde function⁶ and subsequent oxidation. The established procedures for BTTFAs 1a and 1b are illustrated in Scheme 1. The synthesis of tris(1,3-dioxane) 6a was achieved by generation of the Grignard reagent from bromobenzene 4 and subsequent CuI-catalyzed coupling with tris(1,3,5-bromomethyl)-2,4,6-trimethylbenzene 5a at 60 °C in THF in 89% yield. ⁹ A lower yield (65%) was obtained in the synthesis of 6b from tribromide 5b, probably owing to increased steric strain. Regeneration of the aldehyde function gave 7a, and subsequent addition of “CF₃” followed by oxidation of the corresponding alcohol 8a with the Dess-
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**Scheme 1.** Reagents and conditions: (a) Mg, 15 mol% CuI, THF, 60 °C; (b)aq. HCl, acetone; (c) TMSCF$_3$, cat. CsF, DME, r.t.; (d) Dess-Martin periodinane, CH$_2$Cl$_2$, r.t.

Martin periodinane$^{10}$ afforded the final product $1a$. Also, $1b$ and a para analog $2$ were synthesized similarly. The tripodal receptors $1$ and $2$ exhibited C$_3$ symmetric structures by NMR analyses.

To evaluate whether increasing lipophilicity of the receptor leads to an enhanced ISE performance of the membrane, we also synthesized receptor $3$. 1,3,5-Tribromo-2,4,6-tris(bromo-methyl)benzene $10$, prepared from 2,4,6-(tribromo)mesitylene$^{9,11}$ via radical bromination, was subjected to the CuI-catalyzed Grignard coupling to afford tribromide $11$, albeit in a lower yield. Introduction of a long lipophilic chain could be achieved by a direct nucleophilic substitution reaction with 1-dodecanethiol$^{13}$ via a thiolate anion. Because of steric hindrance, other attempts to introduce a long alkyl chain such as transition metal-catalyzed coupling reactions were not successful. From thioether $12$, BTTF A$^3$ was synthesized following the same reactions as described above (Scheme 2).

**Evaluation of BTTFAs 1-3 as ISE membranes toward various anions.** Evaluation of ion selectivity through ion-selective membrane electrodes has several advantages such as very short response time, independent behavior towards colored or turbid samples, simple preparation of the membranes, and lower cost compared to other methods. ISE membranes from the BTTFAs were prepared according to the established procedure$^{14}$ using 4.2 mg of a BTTF A (5.2 wt%), 30 mg of poly(vinyl chloride) (37.3 wt%) as the matrix, 46.3 mg of bis(2-ethylhexyl)adipate (57.5 mol%) as the plasticizer, and a varying amount of tridodecyl(methyl)-ammonium chloride (TDMACl) as the lipophilic additive (30-90 mol% with respect to that of the ionophore). Potential differences were measured between the ion-selective electrodes and a double junction Ag/AgCl reference electrode. The response slopes of the ISE membranes were evaluated in 0.1 M Tris-H$_2$SO$_4$, pH 8.6. As can be seen from Figure 1a, the BTTF A $1a$-doped membrane (with 90 mol% of the additive) shows a similar response behavior toward selected ions as that of $p$-dodecyltrifluoracetophenone (TFADB), a reference membrane. The membranes of other BTTFAs also showed similar response patterns. The pH response of BTTF A $1a$-doped membrane shows a relatively insensitive range pH 6-9, as observed in the case of TFADB (Figure 1b). The ion selectivity coefficients of the BTTF A-doped membranes under different composition were examined by using the separate solution method (IUPAC SSM II method) at an interfering ion concentration of 0.1 M, and the results are listed in Table 1. Anions other than oxoanions including salicylate (Sal$^-$) have been studied. Positive values mean higher response toward the ions compared to carbonate ions and negative values mean lower response. The relative ion selectivity in the case of BTTF A $1a$-doped membrane is as follows: Sal$^-$ > ClO$_4^-$ > SCN$^-$ > (CO$_3^{2-}$, HCO$_3^-$) > NO$_3^-$ > NO$_2^-$ > Br$^-$ > Cl$^-$ > HPO$_4^{2-}$. This trend has a correlation with

Scheme 2. Reagents and conditions: (a) cat. (PhCO$_2$)$_2$, NBS, CCl$_4$, reflux, 85%; (b) Mg, 15 mol% CuI, THF, 60 °C, 24%; (c) n-C$_3$H$_7$SH, NaH, N,N-dimethylimidazolidinone, reflux, 44%; (d)aq. HCl, acetone, 88%; TMSCF$_3$, cat. CsF, DME, r.t., 84%; Dess-Martin periodinane, CH$_2$Cl$_2$, 100%.
the lipophilicity of anions. The selective recognition involves a partition process of the anions into the organic solvent of the membrane phase, which is assisted by the lipophilic quaternary ammonium species, TDMACl. The trend of ion selectivity, however, is changed in the case of BTTFA 1b when the mol% of [TDMACl]/[1b] was 90%; in this case, the selectivity coefficients of lipophilic anions increased much, and perchlorate anion showed a larger selectivity coefficient than that of salicylate anion. Among the ionophores 1-3, the most lipophilic 3 shows increased selectivity toward more lipophilic anions and vice versa. Regarding to the carbonate selectivity toward the lipophilic anions, a better selectivity was observed in the case of BTTFA 1a with 90% of the additive, compared to that of the TFADB membrane. A considerable effort has been focused in the development of a carbonate-selective membrane, particularly that has selectivity toward the most interfering salicylate anion. The selectivity coefficient data of our tripodal TFA analogs suggests that in addition to multiple interactions other factors such as lipophilicity, steric and electronic factors have to be optimized as well as membrane properties. A significant progress has been made recently in the carbonate-selective membranes composed of three TFA groups, which augur for the development of new tripodal carbonate sensors.

In summary, we have synthesized a new type of C3 symmetric, tripodal trifluoracetophenone derivatives. The ion selectivity of the ionophores has been evaluated toward several anions through the corresponding ion-selective electrode membranes. The ion selectivity coefficients show that the selectivity is dependent on the composition of the membranes, particularly on the mol% of the lipophilic additive and the lipophilicity of ionophores. A better selectivity pattern as a carbonate-selective electrode membrane was observed in the case of BTTFA 1a with 90 mol% of the additive. A further structural optimization of the ionophores capable of multiple interactions is under investigation.

### Experimental Section

2-(3-Bromophenyl)-[1,3]-dioxane (4). To a mixture of 3-bromobenzaldehyde (2.33 mL, 20 mmol), 1,3-propanediol (1.9 mL, 26.0 mmol) and p-toluenesulfonic acid monohydrate (400 mg, 2.0 mmol), toluene (15 mL) was added. The reaction mixture was stirred for 3 h at reflux, and then the solvent was removed under reduced pressure. The residue was washed with water (20 mL) and dried under reduced pressure to give the product (4).

### Table 1. Selectivity coefficients of membrane electrodes of ionophores 1-3 toward various anions relative to carbonate ions

<table>
<thead>
<tr>
<th>Electrode-type</th>
<th>Selectivity coefficient</th>
<th>Slope (mV/dec.)</th>
<th>Detection limit (log[C])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt;</td>
<td>Br&lt;sup&gt;-&lt;/sup&gt;</td>
<td>NO&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;-&lt;/sup&gt;</td>
</tr>
<tr>
<td>TFADB - 13 mol%</td>
<td>4.4</td>
<td>-0.8</td>
<td>-0.47</td>
</tr>
<tr>
<td>BTTFA 1a-30 mol%</td>
<td>-2.77</td>
<td>-1.75</td>
<td>-1.06</td>
</tr>
<tr>
<td>BTTFA 1a-60 mol%</td>
<td>-2.68</td>
<td>-1.65</td>
<td>-1.00</td>
</tr>
<tr>
<td>BTTFA 1a-90 mol%</td>
<td>-2.33</td>
<td>1.30</td>
<td>-0.82</td>
</tr>
<tr>
<td>BTTFA 1b-30 mol%</td>
<td>-4.00</td>
<td>-3.34</td>
<td>-1.47</td>
</tr>
<tr>
<td>BTTFA 1b-60 mol%</td>
<td>-4.00</td>
<td>-1.74</td>
<td>-1.25</td>
</tr>
<tr>
<td>BTTFA 1b-90 mol%</td>
<td>-1.61</td>
<td>0.11</td>
<td>-0.13</td>
</tr>
<tr>
<td>BTTFA 2-30 mol%</td>
<td>-4.00</td>
<td>-1.46</td>
<td>-0.81</td>
</tr>
<tr>
<td>BTTFA 2-60 mol%</td>
<td>-4.00</td>
<td>-1.51</td>
<td>-0.94</td>
</tr>
<tr>
<td>BTTFA 2-90 mol%</td>
<td>-4.00</td>
<td>-1.59</td>
<td>-1.07</td>
</tr>
<tr>
<td>BTTFA 3&lt;sup&gt;+&lt;/sup&gt;</td>
<td>-2.45</td>
<td>-0.79</td>
<td>-0.44</td>
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</table>

The membrane electrodes were prepared using 4.2 mg of ionophore, 30 mg of PVC, 46.3 mg of the plasticizer, and 30-90 mol% of the additive. The mol% means that of the additive with respect to the ionophore. 8.3 mg of the ionophore and 1 mg of the additive were used.
hydrate (380 mg, 0.2 mmol) was added benzene (40 mL) and the reaction vessel was equipped with a Dean-Stark apparatus with reflux condenser. The reaction mixture was refluxed for 5 h with stirring. After being cooled to room temperature, the mixture was concentrated. Extractive workup with ethyl acetate and purification by column chromatography (hexane : EtOAc, 5 : 1) afforded 4 (5.6 g, 100%) as a colorless liquid: 1H NMR (300 MHz, CDCl3) δ 1.41 (m, 0.5H), 1.45-1.48 (m, 0.5H), 2.13-2.29 (m, 1H), 3.92-4.01 (m, 2H), 4.22-4.29 (m, 2H), 5.46 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.38-7.41 (m, 1H), 7.41-7.48 (m, 1H), 7.66 (t, J = 7.5 Hz, 1H), 9.96 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 141.5, 142.0, 137.3, 135.6, 131.4, 134.6, 129.8, 129.2, 128.4, 36.5, 17.5; MS (FAB) m/z: calced. for C33H32O3 475.22 [M+1]+, found 475.38.

**2.4.6-Tris[3-(1,1,3-dioxan-2-ylmethyl)phenyl]-1,3,5-triethylbenzene (6a).** To a stirred solution of magnesium powder (183 mg, 7.5 mmol) in THF (5 mL) was added 4 (1.22 g, 5 mmol) and 1,2-dibromoethane (cat.) at room temperature under an argon atmosphere. The resulting mixture was stirred for additional 1 h. To this Grignard solution was added dropwise a THF (5 mL) solution of 1,3,5-tris(bromomethyl)mesitylene 5 (399 mg, 1.0 mmol) and copper iodide (19 mg, 0.1 mmol) at 60 °C. After being stirred for additional 12 h, the reaction mixture was allowed to cool to room temperature, and it was quenched with saturated aqueous NaHCO3 (10 mL) solution. The resulting solution was diluted with ethyl acetate (10 mL), washed with brine, dried over anhydrous MgSO4, and concentrated in vacuo. Purification of the residue by column chromatography (hexane : EtOAc, 3 : 2) afforded dioxane 6a (579.4 mg, 89%) as a white solid: mp 60-62 °C; 1H NMR (300 MHz, CDCl3) δ 1.41-1.46 (m, 3H), 2.01 (s, 9H), 2.12-2.28 (m, 3H), 3.97 (dt, J = 2.4, 12.2 Hz, 6H), 4.13 (s, 3H), 4.26 (dd, J = 4.9, 11.0 Hz, 6H), 5.46 (s, 3H), 6.83 (d, J = 7.5 Hz, 3H), 7.20 (t, J = 7.5 Hz, 9H), 7.31-7.36 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 141.5, 139.3, 135.5, 135.2, 129.1, 128.4, 126.3, 124.1, 102.5, 68.0, 36.8, 26.4, 17.5; MS (FAB) m/z: calcd. for C29H27BrO4 649.35 [M+1]+, found 649.35.

**2.4.6-Tris[3-(1,1,3-dioxan-2-ylmethyl)phenyl]-1,3,5-triethylbenzene (6b).** This compound was prepared following the same procedure as for 6a using dioxane 6b (324.5 mg, 0.5 mmol). Purification by column chromatography (hexane : EtOAc, 7 : 3) afforded 7b (142 mg, 55%) as a white solid: mp 125-127 °C; 1H NMR (300 MHz, CDCl3) δ 6.214 (s, 9H), 6.45 (s, 6H), 7.33 (d, J = 7.7 Hz, 3H), 7.45 (t, J = 7.6 Hz, 3H), 7.55 (s, 3H), 7.69 (d, J = 7.5 Hz, 3H), 9.96 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 193.2, 142.0, 137.3, 135.6, 131.4, 129.8, 129.2, 128.4, 36.5, 17.5; MS (FAB) m/z: calced. for C33H30O3 475.22 [M+1]+, found 475.38.

**2.4.6-Tris[(3-formyl)phenyl)methyl]-1,3,5-triethylbenzene (7a).** To an acetone (5 mL) solution of triis-[1,3]dioxane 6a (570 mg, 0.878 mmol) was added 2.5% aqueous HCl solution (1 mL) at room temperature. After being stirred for several hours, the mixture was treated with saturated aqueous NaHCO3 (15 mL) solution and diluted with ethyl acetate (15 mL). Extractive workup and purification by column chromatography (hexane : EtOAc, 3 : 2) afforded 7a (331.4 mg, 80%) as a white solid: mp 125-127 °C; 1H NMR (300 MHz, CDCl3) δ 6.214 (s, 9H), 4.25 (s, 6H), 7.33 (d, J = 7.7 Hz, 3H), 7.45 (t, J = 7.6 Hz, 3H), 7.55 (s, 3H), 7.69 (d, J = 7.5 Hz, 3H), 9.96 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 193.2, 142.0, 137.3, 135.6, 131.4, 129.8, 129.2, 128.4, 36.5, 17.5; MS (FAB) m/z: calced. for C33H30O3 475.22 [M+1]+, found 475.38.
mesitylene. The mixture of 2,4,6-tribromomesitylene was prepared from known 2,4,6-tribromo-

\( \delta \) 181.8, 181.4, 180.9, 180.4 (q, \( J = 34.6 \text{ Hz} \), -COF), 142.9, 142.5, 135.3, 134.0, 130.8, 130.0, 129.7, 128.7, 128.4, 123.1, 119.2, 115.4, 111.5 (q, \( J = 289.6 \text{ Hz} \), -C), 34.9, 24.4, 15.8; 19 F NMR (300 MHz, CDCl₃) \( \delta \) 5.02; HRMS (EI) \( m/z \): calculated for \( \text{C}_{39}\text{H}_{39}\text{Br}_3\text{O}_6 \) 841.03 \([\text{M}+1]^-\), found 841.15 \([\text{M}+1]^-\), 844.96 \([\text{Br} + 2 \text{ Br}]^-\), 846.87 \([3 \text{ Br}]^-\). 2,4,6-Tris[(4-[2,2,2-trifluoroacetyl]phenyl)methyl]-1,3,5-trimethylbenzene (2). This compound was prepared following the same procedure as for 1a: mp 160-163 °C; ¹H NMR (300 MHz, CDCl₃) \( \delta \) 2.14 (s, 9H), 4.26 (s, 6H), 7.24 (d, \( J = 8.3 \text{ Hz} \), 6H), 8.01 (d, \( J = 7.9 \text{ Hz} \), 6H); ¹C NMR (75 MHz, CDCl₃) \( \delta \) 181.8, 181.4, 180.9, 180.4 (q, \( J = 34.7 \text{ Hz} \), -COF), 149.7, 135.9, 134.7, 131.2, 129.2, 128.6, 123.2, 119.3, 115.5, 111.6 (q, \( J = 289.6 \text{ Hz} \), -C), 37.3, 17.6; ¹F NMR (300 MHz, CDCl₃) \( \delta \) 5.05; HRMS (EI) \( m/z \): calculated for \( \text{C}_{39}\text{H}_{33}\text{F}_9\text{O}_3 \) 720.2286 \([\text{M}]^+\), found 720.2288.

This compound was analytically pure and needs no further purification.

The reaction mixture was heated at 70-80 °C for 9 h. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL), and diluted with ethyl acetate (5 mL). Extractive workup and purification by column chromatography (hexane : EtOAc, 4 : 1) afforded 12 (124.5 mg, 44%) as a viscous oil; ¹H NMR (300 MHz, CDCl₃) \( \delta \) 0.88 (t, \( J = 6.9 \text{ Hz} \), 9H), 1.09-1.30 (m, 60H), 1.40-1.46 (m, 3H), 2.13-2.27 (m, 9H), 3.96 (dt, \( J = 2.3, 12.2 \text{ Hz} \), 6H), 4.24 (dd, \( J = 4.9, 10.7 \text{ Hz} \), 6H), 4.93 (s, 6H), 5.44 (s, 3H), 6.81 (d, \( J = 7.4 \text{ Hz} \), 3H), 7.17 (t, \( J = 7.6 \text{ Hz} \), 7.24-7.30 (m, 6H); ¹C NMR (75 MHz, CDCl₃) \( \delta \) 152.4, 142.4, 139.1, 137.5, 128.9, 128.6, 127.1, 123.8, 102.5, 68.0, 41.7, 38.3, 32.6, 30.3, 30.2, 30.0, 29.9, 29.6, 26.5, 23.4, 14.8; MS (FAB) \( m/z \): calculated for \( \text{C}_{50}\text{H}_{54}\text{F}_{10}\text{O}_8 \) 1206.78 \([\text{M}+1]^-\), found 1206.76.

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References