Highly Fluorinated Cyclodextrins and their Host-Guest Interactions

Maria M. Becker and Bart Jan Ravoo

Organic Chemistry Institute, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

E-Mail: b.j.ravoo@uni-muenster.de
Synthesis

**Synthesis of 6-chloro-6-deoxy-cyclodextrins 1a – 1c**

The synthesis of perchlorinated cyclodextrins was accomplished as described by Guillo et al.\(^1\) To a solution of 1 eq of cyclodextrin dissolved in DMF, 5.2 eq methylsulfonyl chloride per gly cose unit of the cyclodextrin is added and stirred at 65 °C for 4 d. The solution is concentrated, the residue is dissolved in methanol and neutralized with 3 M sodium methoxide. The product was precipitated in ice water, filtered out and washed with methanol. The product was vacuum-dried at 55 °C and was obtained as white solid.

**Hexakis-(6-chloro-6-deoxy)-\(\alpha\)-cyclodextrin 1a**

Cyclodextrin **1a** was synthesized as described above with \(\alpha\)-cyclodextrin (10.52 g, 10.81 mmol) and methylsulfonyl chloride (26.01, 335.6 mmol).

Empirical formula (MW in g/mol): \(C_{36}H_{54}O_{24}Cl_6\) (1083.52)

Yield: 78 % (9.19 g, 8.48 mmol)

MS (ESI, MeOH): 560.04 \([M + Ca]^{2+}\), 1103.10 \([M + Na]^+\), 2183.22 \([2 M + Na]^+\)

\(^1H\) NMR (400 MHz, DMSO) \(\delta\) 5.76 (d, \(J = 5.4, 1\)H, 2-OH), 5.59 (s, 1H, 3-OH), 4.92 (d, \(J = 3.2, 1\)H, 1-H), 4.13 – 3.89 (m, 2H, 5-H, 3-H), 3.90 – 3.71 (m, 2H, 4-H, 2-H), 3.44 (t, \(J = 8.9, 1\)H, 6a-H), 3.36 (s, 2H, 6b-H).

\(^13C\) NMR (101 MHz, DMSO) \(\delta\) 101.92 (1-C), 83.60 (4-C), 72.65 (3-C), 71.64 (2-C), 70.83 (5-C), 45.30 (6-C).

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Heptakis-(6-chloro-6-deoxy)-β-cyclodextrin 1b

Cyclodextrin 1b was synthesized as described above with β-cyclodextrin (10.04 g, 8.81 mmol) and methylsulfonyl chloride (24.8, 230 mmol).

Empirical formula (MW in g/mol): C₄₂H₆₃O₂₈Cl₇ (1264.10)
Yield: 89 % (9.86 g, 7.80 mmol)

¹H NMR (300 MHz, DMSO) δ 6.00 (d, J = 6.6, 1H, 2-OH), 5.85 (d, J = 1.5, 1H, 3-OH), 4.96 (d, J = 3.5, 1H, 1-H), 4.13 – 4.02 (m, 1H, 5-H), 3.91 – 3.70 (m, 2H, 3-H, 4-H ), 3.60 (dt, J = 8.5, 6.9, 1H, 6a-H), 3.42 – 3.29 (m, 3H, 2-H, 6b-H).

¹³C NMR (75 MHz, DMSO) δ 102.08 (1-C), 83.62 (4-C), 72.48 (3-C), 72.02 (2-C), 71.21 (5-C), 45.00 (6-C).

Octakis-(6-chloro-6-deoxy)-γ-cyclodextrin 1c

Cyclodextrin 1c was synthesized as described above with γ-cyclodextrin (10.11 g, 7.79 mmol) and methylsulfonyl chloride (25.28, 325.78 mmol).

Empirical formula (MW in g/mol): C₄₈H₇₂O₃₂Cl₈ (1444.69)
Yield: 84 % (9.49 g, 6.57 mmol)
MS (ESI, MeOH): 743.07 [M + 2 Na]²⁺, 1467.13 [M + Na]⁺

¹H NMR (300 MHz, DMSO) δ 6.01 (s, 2H, 2,3-OH), 4.98 (d, J = 3.7, 1H, 1-H), 4.02 (d, J = 9.9, 1H, 6a-H), 3.91 – 3.74 (m, 2H, 5-H), 3.60 (t, J = 9.2, 1H, 3-H), 3.37 (dd, J = 10.0, 7.8, 2H, 6b-H).

¹³C NMR (101 MHz, DMSO) δ 102.04 (1-C), 83.00 (4-C), 72.36 (3-C), 72.22 (2-C), 71.14 (5-C), 45.01 (6-C).
**Synthesis of fluorinated cyclodextrins 2a – 2c**

The synthesis of the 2,2,2-trifluoroethanethio-substituted cyclodextrins 2a – 2c from perchlorinated cyclodextrins 1a – 1c was performed according to the following procedure: 3 eq 2,2,2-trifluoroethanethiol per glucose unit of the cyclodextrin was dissolved in dry DMF at 0 °C and treated with 3 eq of a 60% dispersion of sodium hydride in mineral oil. After stirring for 30 min a solution of 1a – 1c in the minimal amount of DMF was added dropwise. The solution was stirred for 5 d at 70 °C. The solvent is concentrated and poured on water. The precipitation was collected by centrifugation, dissolved in DMF again and precipitated two times from diethyl ether. The product was vacuum-dried at 60 °C and obtained as light beige solid.

**Hexakis-(6-deoxy-6-trifluoroethanethio)-α-cyclodextrin 2a**

Cyclodextrin 2a was synthesized as described above with 2,2,2-trifluoroethanethiol (0.15 mL, 1.69 mmol), 60 % sodium hydride suspension in mineral oil (67 mg, 1.66 mmol) and 1a (0.11 g, 0.10 mmol).

![Chemical structure of 2a](image)

Empirical formula (MW in g/mol): C_{48}H_{66}O_{24}F_{18}S_{6} (1516.38)

Yield: 57 % (90 mg, 0.058 mmol)

MS (ESI, MeOH): 800.08 [M + Ca]^{2+}, 1583.19 [M + Na]^{+}

Elemental analysis (C_{48}H_{66}O_{24}F_{18}S_{6})

Calculated [%]: C, 36.92; H, 4.26; N, 0.0

Determined [%]: C, 36.62; H, 4.18; N, 0.0

^1H NMR (300 MHz, DMSO) δ 5.74 (d, J = 6.1, 1H, 2-OH), 5.58 (s, 1H, 3-OH), 4.90 (s, 1H, 1-H), 3.88 (s, 1H, 5-H), 3.72 (d, J = 6.6, 1H, 3-H), 3.60 – 3.29 (m, 4H, 4, 7, 2-H), 3.16 (d, J = 12.7, 1H, 6a-H), 3.01 (d, J = 6.3, 1H, 6b-H).

^13C NMR (75 MHz, DMSO) δ 126.42 (q, J = 266.3, 1C, 8-C), 101.80 (1-C), 84.60 (4-C), 72.78 (3-C), 71.69 (2-C), 71.31 (5-C), 34.13 – 33.31 (6,7-C).

^19F NMR (282 MHz, DMSO) δ -65.52 (t, J = 10.4, 3F).
**Heptakis-(6-deoxy-6-trifluoroethanethio)-β-cyclodextrin 2b**

Cyclodextrin 2b was synthesized as described above with 2,2,2-trifluoroethanethiol (3.7 mL, 41.5 mmol), 60 % sodium hydride suspension in mineral oil (1 g, 41.5 mmol) and 1b (2.5 g, 1.98 mmol).

Empirical formula (MW in g/mol): $C_{56}H_{77}O_{28}F_{21}S_7$ (1820.23)

Yield: 88 % (3.17g, 1.74 mmol)

MS (ESI, MeOH): $930.10 \ [M + Ca]^{2+}$, 1843.22 $[M + Na]^+$

Elemental analysis (C$_{56}$H$_{77}$O$_{28}$F$_{21}$S$_7$)

Calculated [%]: C, 36.92; H, 4.26; N, 0.0

Determined [%]: C, 36.57; H, 4.11; N, 0.0

$^1$H NMR (600 MHz, DMSO) $\delta$ 5.98 (d, $J = 6.8$, 1H, 2-OH), 5.86 (d, $J = 1.9$, 1H, 3-OH), 4.93 (d, $J = 3.2$, 1H, 1-H), 3.89 – 3.77 (m, 1H, 5-H), 3.61 (t, $J = 9.1$, 1H, 3-H), 3.50 – 3.39 (m, 3H, 4-, 7-H), 3.39 – 3.34 (m, 1H, 2-H), 3.17 (d, $J = 12.3$, 1H, 6a-H), 3.00 (dd, $J = 14.2$, 7.2, 1H, 6b-H).

$^{13}$C NMR (151 MHz, DMSO) $\delta$ 126.33 (q, $J = 276.45$, 8-C), 102.05 (1-C), 84.22 (4-C), 72.38 (3-C), 72.06(2-C), 71.49 (5-C), 34.32 – 33.71 (6-, 7-C).

$^{19}$F NMR (564 MHz, DMSO) $\delta$ -65.70 (t, $J = 10.5$, 3F).
Octakis-(6-deoxy-6-trifluoroethanethio)-γ-cyclodextrin 2c

Cyclodextrin 2c was synthesized as described above with 2,2,2-trifluoroethanethiol (0.15 mL, 1.66 mmol), 60 % sodium hydride suspension in mineral oil (40 mg, 1.66 mmol) and 1c (98 mg, 0.068 mmol).

Empirical formula (MW in g/mol) C_{64}H_{88}O_{32}F_{24}S_{8} (2080.26)
Yield: 82 % (0.12 g, 0.055 mmol)
MS (ESI, MeOH): 1060.11 [M + Ca]^{2+}, 2103.25 [M + Na]^{+}
Elemental analysis (C_{64}H_{88}O_{32}F_{24}S_{8})
Calculated [%]: C, 36.92; H, 4.26; N, 0.0
Determined [%]: C, 36.91; H, 4.22; N, 0.0

$^1$H NMR (300 MHz, DMSO) δ 5.97 (s, 2H, 2,3-OH), 4.96 (d, $J = 3.0$, 1H, 1-H), 4.01 – 3.72 (m, 1H, 5-H), 3.57 (t, $J = 9.2$, 1H, 3-H), 3.43 (dd, $J = 14.7$, 6.9, 4H, 4,7,2-H), 3.17 (d, $J = 12.4$, 1H, 6a-H), 2.99 (dd, $J = 13.7$, 7.1, 1H, 6b-H).

$^{13}$C NMR (75 MHz, DMSO) δ 102.09 (1-C), 83.91 (4-C), 72.31 (3-C), 72.13 (2-C) 71.63 (5-C), 33.91 (6+7-C).

$^{19}$F NMR (282 MHz, DMSO) δ -65.63 (t, $J = 10.4$, 3F).
**Synthesis of fluorinated cyclodextrins 3a – 3c**

Fluorinated cyclodextrins 3a – 3c were synthesized according to the following procedure: cyclodextrin 2a – 2c was solved in dry DMF and treated with 1.5 eq sodium hydride per glycoside unit of the cyclodextrin. After stirring for 1 h at room temperature, 3 eq triethylene glycol toluenesulfonate ester per glycoside unit was added dropwise. The mixture was stirred for 2 d at room temperature. The solvent was removed and the raw product purified by size exclusion chromatography on a Sephadex LH-20 column. The product was dried at 60 °C in vacuum and obtained as brown highly viscous oil.

**Hexakis-(2-O-(2-(2-hydroxyethoxy)ethoxy)ethyl), 6-deoxy-6-trifluoroethanethio)-α-cyclodextrin 3a**

Cyclodextrin 3a was synthesized as described above with 2a (0.2 g, 0.13 mmol), sodium hydride (46 mg, 1.18 mmol) and triethylene glycol toluenesulfonate ester (0.95 g, 3.14 mmol).

Empirical Formula (MW in g/mol): C_{84}H_{138}F_{18}O_{42}S_{6} (2354.33)

Yield: 100 % (0.31 g, 0.13 mmol)

MS (ESI, MeOH): 1397.93 \([\text{M} + 2\text{Na}]^{2+}\), 1331.90 \([\text{M} + 2\text{Na}]^{2+}\), 1265.86 \([\text{M} + 2\text{Na}]^{2+}\), 1199.32 \([\text{M} + 2\text{Na}]^{2+}\), 1133.28 \([\text{M} + 2\text{Na}]^{2+}\), 1067.24 \([\text{M} + 2\text{Na}]^{2+}\)

Elemental analysis

Calculated [%]: C, 42.85; H, 5.91; N, 0.0

Determined [%]: C, 43.05; H, 5.75; N, 0.0

\(^1\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 4.90 (d, J = 22.9, 1H, 1-H), 4.82 – 4.55 (m, 1H, 3-OH), 4.02 (dd, J = 18.0, 9.8, 2H, 3-H, 5-H), 3.92 – 3.71 (m, 2H, 2-H, 14-H), 3.56 (dd, J = 18.7, 6.4, 11H, 9-H, 10-H), 3.45 – 3.30 (m, 2H, 2-H, 4-H), 3.20 (dd, J = 27.2, 18.0, 4H, 6a-H, 7-H), 2.90 (dd, J = 14.7, 5.3, 1H, 6b-H).

\(^13\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 126.09 (q, J = 276.1, 8-C), 101.00 (1-C), 86.17 (4-C), 80.54 (2-C), 77.65 – 70.39 (9-C, 10-C, 11-C, 12-C, 13-C), 61.65 (14-C), 35.39 – 34.36 (6-C, 7-C).

\(^19\text{F} \text{NMR} (282 \text{ MHz, CDCl}_3) \delta -66.38 (t, J = 9.9, 3F).
**Heptakis-(2-O-(2-(2-hydroxyethoxy)ethoxy)ethyl), 6-deoxy-6-trifluoroethanethio-β-cyclodextrin 3b**

Cyclodextrin 3b was synthesized as described above with 2b (95 mg, 0.052 mmol), sodium hydride (13.2 mg, 0.55 mmol) and triethylene glycol toluenesulfonate ester (0.45 g, 1.46 mmol).

Empirical Formula (MW in g/mol): C_{98}H_{161}F_{21}O_{49}S_{7} (2744.78)

Yield: 108% (0.14 g, 0.06 mmol)


Elemental analysis (C_{98}H_{161}O_{49}F_{21}S_{7})

Calculated [%]: C, 42.85; H, 5.91; N, 0.0

Determined [%]: C, 42.63; H, 6.12; N, 0.0

^1H NMR (300 MHz, CDCl3) δ 4.99 (d, J = 3.2, 1H, 1-H), 4.91 (s, 1H, 3-OH), 4.11 (dd, J = 7.4, 3.6, 2H, 3-H, 5-H), 3.84 (dd, J = 17.9, 9.9, 5H, 14-H), 3.74 – 3.50 (m, 20H, 9-H, 10-H, 11-H, 12-H, 13-H), 3.40 (dt, J = 12.8, 6.4, 3H, 2-H, 4-H), 3.20 (dd, J = 17.2, 7.6, 6H, 6a-H, 7-H), 2.93 (dd, J = 14.1, 6.7, 1H, 6b-H).

^13C NMR (75 MHz, CDCl3) δ 126.14 (q, J = 276.1, 8-C), 101.37 (1-C), 85.76 (4-C), 81.08 (2-C), 73.17 – 70.49 (3-C, 5-C, 9-C, 10-C, 11-C, 12-C, 13-C), 61.78 (14-C), 35.51 – 34.29 (6-C, 7-C).

^19F NMR (282 MHz, CDCl3) δ -66.64 (t, J = 9.7, 3F).
Octakis-(2-O-(2-(2-hydroxyethoxy)ethoxy)ethyl), 6-deoxy-6-trifluoroethanethio-γ-cyclodextrin 3c

Cyclodextrin 3c was synthesized as described above with 2c (113 mg, 0.054 mmol), sodium hydride (15.6 mg, 0.65 mmol) and triethylene glycol toluenesulfonate ester (0.53 g, 1.74 mmol).

Empirical Formula (MW in g/mol): C_{112}H_{184}F_{24}O_{56}S_{8} (3139.11)

Yield: 78 % (133 mg, 0.04 mmol)


Elemental analysis

Calculated [%]: C, 42.85; H, 5.91; N, 0.0
Determined [%]: C, 42.81; H, 5.97; N, 0.0

$^1$H NMR (300 MHz, CDCl3) δ 5.05 (d, J = 3.4, 1H, 1-H), 4.93 (s, 1H, 3-OH), 4.19 – 3.99 (m, 1H, 3-H), 3.99 – 3.48 (m, 13H, 5-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H), 3.41 (s, 3H, 2-H, 4-H), 3.19 (dd, J = 18.9, 9.4, 3H, 6a-H, 7-H), 3.00 – 2.89 (m, 1H, 6b-H).

$^{13}$C NMR (101 MHz, CDCl3) δ 126.12 (dd, J = 552.6, 276.7, 8-C), 100.99 (1-C), 84.81 (4-C), 81.27 (2-C), 72.94 - 70.31, 61.67 (14-C), 35.36 - 34.18 (6-C, 7-C).

$^{19}$F NMR (282 MHz, CDCl3) δ -66.67 (t, J = 9.7, 3F).
Isothermal Titration Calorimetry

Isothermal titration calorimetry (ITC) was performed on a Nano-Isothermal Titration Calorimeter III (Model CSC 5300) made by Calorimetry Sciences Corporation (USA). Analyte solutions for ITC measurements were prepared with distilled and deionized water and degassed for 20 min at room temperature. The guest solution (10-fold excess) was titrated into the cyclodextrin solution. 20 injections of 10 µL were performed with an interval of 300 s. The stirring rate was 300 rpm. The data were fitted to a 1:1 model (2:1 in case of diflunisal and 3c) using a spreadsheet method.²

Table S1: Analyte solutions for ITC with α-cyclodextrin 3a.

<table>
<thead>
<tr>
<th>compound</th>
<th>M [g/mol]</th>
<th>n [mmol]</th>
<th>m [mg]</th>
<th>c [mM]</th>
</tr>
</thead>
<tbody>
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<td>CD 3a</td>
<td>2354,33</td>
<td>0,0551</td>
<td>129,7</td>
<td>5,509</td>
</tr>
<tr>
<td>p-fluorophenol</td>
<td>112,1</td>
<td>0,275</td>
<td>31</td>
<td>55,09</td>
</tr>
<tr>
<td>p-trifluoromethylphenol</td>
<td>162,11</td>
<td>0,275</td>
<td>44,8</td>
<td>55,09</td>
</tr>
<tr>
<td>m-trifluoromethylphenol</td>
<td>162,11</td>
<td>0,275</td>
<td>44,7</td>
<td>55,09</td>
</tr>
<tr>
<td>phenol</td>
<td>94,11</td>
<td>0,25</td>
<td>23,4</td>
<td>50</td>
</tr>
<tr>
<td>p-cresol</td>
<td>108,14</td>
<td>0,275</td>
<td>29,7</td>
<td>55</td>
</tr>
</tbody>
</table>

Figure S1: ITC of 3a with p-fluorophenol.

Figure S2: ITC of 3a with p-trifluoromethylphenol.

Figure S3: ITC data of 3a with m-trifluoromethylphenol.

Figure S4: ITC of 3a with phenol.
Figure S5: ITC of 3a with p-cresol.

Table S2: Analyte solutions for ITC with β-cyclodextrin 3b.

<table>
<thead>
<tr>
<th>compound</th>
<th>M</th>
<th>n</th>
<th>m</th>
<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 3b</td>
<td>2744,78</td>
<td>0,055</td>
<td>151</td>
<td>5,5</td>
</tr>
<tr>
<td>p-fluorophenol</td>
<td>112,1</td>
<td>0,275</td>
<td>30,8</td>
<td>55</td>
</tr>
<tr>
<td>p-trifluoromethylphenol</td>
<td>162,11</td>
<td>0,275</td>
<td>44,7</td>
<td>55</td>
</tr>
<tr>
<td>CD 3b</td>
<td>2744,78</td>
<td>0,05</td>
<td>137,3</td>
<td>5</td>
</tr>
<tr>
<td>m-trifluormethylphenol</td>
<td>162,11</td>
<td>0,275</td>
<td>40,5</td>
<td>50</td>
</tr>
<tr>
<td>phenol</td>
<td>94,11</td>
<td>0,25</td>
<td>23,4</td>
<td>50</td>
</tr>
<tr>
<td>p-cresol</td>
<td>108,14</td>
<td>0,25</td>
<td>27,1</td>
<td>50</td>
</tr>
<tr>
<td>CD 3b</td>
<td>2744,78</td>
<td>0,008</td>
<td>22,9</td>
<td>1,67</td>
</tr>
<tr>
<td>4-(trifluoromethyl)cyclo-</td>
<td>196,17</td>
<td>0,25</td>
<td>49</td>
<td>16,7</td>
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<tr>
<td>hexanecarboxylic acid</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>CD 3b</td>
<td>2744,78</td>
<td>0,0096</td>
<td>26,4</td>
<td>1,6</td>
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<td>4-methylcyclo-</td>
<td>142,196</td>
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<td>hexanecarboxylic acid</td>
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<tr>
<td>CD 3b</td>
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<td>41,8</td>
<td>3</td>
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<tr>
<td>diflunisal</td>
<td>250,198</td>
<td>0,15</td>
<td>37,8</td>
<td>30</td>
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</tbody>
</table>

Figure S6: ITC of 3b with p-fluorophenol.
Figure S7: ITC of 3b with p-trifluoromethylphenol.

Figure S8: ITC of 3b with m-trifluoromethylphenol.

Figure S9: ITC of 3b with phenol.
Figure S10: ITC of 3b with p-cresol.

Figure S11: ITC of 3b with 4-(trifluoromethyl)cyclohexane carboxylic acid.

Figure S12: ITC of 3b with 4-methylcyclohexane carboxylic acid.
Figure S13: ITC of 3b with diflunisal in borate buffer at pH 9.

Table S3: Analyte solutions for ITC with γ-cyclodextrin 3c.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M [g/mol]</th>
<th>n [mmol]</th>
<th>m [mg]</th>
<th>c [mM]</th>
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</thead>
<tbody>
<tr>
<td>CD 3c</td>
<td>3139,11</td>
<td>0,01</td>
<td>31,4</td>
<td>1</td>
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<tr>
<td>diflunisal</td>
<td>250,198</td>
<td>0,15</td>
<td>37,9</td>
<td>30</td>
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</table>

Figure S14: ITC of 3c with diflunisal in borate buffer at pH 9.
NMR Titration

**NMR titration of cyclodextrin 3b with p-trifluoromethylphenol**

NMR titration of β-cyclodextrin 3b with p-trifluoromethylphenol is characterized by a fast exchange of free and complexed guest relative to the NMR time-scale. The NMR spectrum displays an average (δ_{obs}) of the shift of free (δ_G) and complexed guests (δ_C):

\[
\delta_{obs} = \delta_G (1 - x) + x \delta_C
\]

\[
x = \frac{[C]}{[G]_0}
\]

The shift of complexed guest (δ_C) was obtained from NMR titrations and extrapolation. In view of the small shifts observed in ¹H-NMR, only ¹⁹F-NMR data (Table S4) were used to determine complex stoichiometry (Job’s Plot) and binding constant K_a. Once δ_C is known, the concentration of the complex in equilibrium can be determined and the equilibrium contact K can be calculated according to:

\[
K = \frac{[C]}{[G][CD]}
\]

\[
K = \frac{[C]}{([G]_0 - [C])([CD]_0 - [C])}
\]

(with [G]_0 = guest concentration and [CD]_0 = cyclodextrin concentration)
Table S4: $^{19}$F-NMR data for the titration of cyclodextrin 3b with $\text{p}$-trifluoromethylphenol.

<table>
<thead>
<tr>
<th>sample</th>
<th>$\Delta_{\text{guest}}$ [ppm]</th>
<th>$\Delta_{\text{host}}$ [ppm]</th>
<th>$\Delta \delta_{\text{guest}}$ [ppm]</th>
<th>$\Delta \delta_{\text{host}}$ [ppm]</th>
<th>n(G) [mmol]</th>
<th>n(H) [mmol]</th>
<th>n(G)/(n(G)+n(H))</th>
<th>ratio G:H</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>-66.81</td>
<td>0</td>
<td>0</td>
<td>0.0036</td>
<td>0.000</td>
<td></td>
<td>0.00:01</td>
</tr>
<tr>
<td>2</td>
<td>-60.72</td>
<td>-66.83</td>
<td>0.46</td>
<td>-0.02</td>
<td>0.0003</td>
<td>0.033</td>
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Figure S15: Determination of $\delta_C$.

The shift of the inclusion complex $\delta_C = -60.7$ is obtained from extrapolation of $^{19}$F-NMR data (Figure S15). A fit for 1:1 complexation gives a binding constant $K_a = 2.06 \times 10^3$ M$^{-1}$.
NMR titration of cyclodextrin 3a with p-trifluoromethylphenol

NMR titration of α-cyclodextrin 3a with p-trifluoromethylphenol was carried out as described for 3b.

Figure S16: $^{19}$F-NMR titration spectra of 2a with p-trifluoromethylphenol.
Table S5: $^{19}$F-NMR data for the titration of $\alpha$-CD 2a with $p$-trifluoromethylphenol.

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<th>$\Delta_{\text{host}}$ [ppm]</th>
<th>$\Delta \delta_{\text{guest}}$ [ppm]</th>
<th>$\Delta \delta_{\text{host}}$ [ppm]</th>
<th>n(G) [mmol]</th>
<th>n(H) [mmol]</th>
<th>n(G)/(n(G)+n(H))</th>
<th>G:H Ratio</th>
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The complex stoichiometry of 3a with $p$-trifluoromethylphenol was determined by plotting guest shift signals multiplied by molar amount against ratio of guest and host in a Job’s Plot (see Figure S1).

Figure S17: Job’s plot for the titration of 3a with $p$-trifluoromethylphenol.
Figure S18: Determination of $\delta_C$ by extrapolation of $^{19}$F-NMR data.

The $^{19}$F-NMR data of 3a were extrapolated to obtain $\delta_C = -59.72$ ppm (see Figure S18). A fit for 1:1 complexation gives a binding constant $K_a = 1.37 \times 10^2$ M$^{-1}$.

Figure S19: 1H-NMR titration of 3a with p-trifluoromethylphenol.