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# Synthesis and Host Properties of (1,3)-*p-tert*-Butylcalix[5]crown-6 Derivatives Incorporating the 1,1′-Binaphthalene-2,2′-dioxy Subunit

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**Abstract.** Alkylation of *p-tert*-butylcalix[5]arene (**1**) with 2,2′-bis(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-binaphthalene ((±)-**2**) in the presence of CsF affords selectively racemic 1,3-bridged calix[5] crown-6-triol **3**, along with very small amounts of the (1,2)-bridged regioisomer **4**. Compound **3** has been converted into tri-methoxy and tri-$\alpha$-picolyloxy derivatives **5** and **6**, respectively, by exhaustive alkylation with the appropriate electrophile and base. The direct separation of the enantiomers of racemates **3** and **6** was achieved by HPLC, using a chiral stationary phase (Chiralpak AD). Hosts **5** and **6** are able to selectively form 1 : 1 *endo*-cavity complexes with the linear $RNH_3^+$ ions.

**Key words:** Chiral calixarene crown ethers, separation of enantiomers, molecular recognition, $RNH_3^+$ inclusion complexes.

## 1. Introduction

Calixarenes [1, 2], termed by Shinkai ‘the third generation of supramolecules’ [3, 4], offer a broad range of possible chemical modifications, including the preparation of calixarenes endowed with chiral groups at the upper or lower rim [5], as well as inherently chiral calixarenes [6]. To date, only a few examples have been reported on the use of binaphthyl reagents to introduce axial chirality into calixarene host molecules, these studies being confined to calix[4]arenes. Earlier Kubo *et al*. have described the synthesis and colorimetric recognition properties of chromogenic 1,1′-binaphthyl-derived calix[4]crown ethers [7, 8], and more recently Stibor *et al.* have reported the synthesis of upper or lower rim binaphthyl-bridged calix[4]arenes as potential chiral hosts for molecular recognition and catalysis [9, 10].

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Following our previous studies on the creation of molecular asymmetry by modulation of the substitution pattern at the lower rim of calix[*n*]crown ethers [11–14], we wish to report here the synthesis, HPLC resolution and host properties of some *p-tert*-butylcalix[5]crown-6 derivatives incorporating a 1,1′-binaphthalene-2,2′-dioxy unit into the crown ether moiety. (1,3)-*p-tert*-Butylcalix[5]crown-6 derivatives chronologically represent the first host molecules capable of strongly discriminating between linear and branched butylammonium ions *via endo*-cavity complexation [15–17].

## 2. Experimental

### 2.1. GENERAL

Melting points were determined on a Kofler or 'Electrothermal' melting point apparatus and are uncorrected. The $^{1}$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were obtained on a Varian Gemini 300 BB spectrometer in $CDCl_3$ with $Me_4Si$ as the internal standard at room temperature. The multiplicity of the $^{13}$C signals was determined with the APT technique. FAB (+) mass spectra were recorded on a Kratos MS 50 double-focusing mass spectrometer, using *m*-nitrobenzyl alcohol as the matrix. All chemicals were reagent grade and were used without further purification. Anhydrous DMF, THF and MeCN were purchased from Fluka. *p-tert*-Butylcalix[5]arene (**1**) [18] and 2,2′-bis(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-binaphthalene ((±)-**2**) [19] were prepared according to literature procedures.

The HPLC system consisted of a Varian 5060 liquid chromatograph with Valco 10 $\mu$L sample loop, a Jasco Uvidec III UV spectrophotometric detector operating at 265 nm, and a Varian CDS 401 Data System. The column (250 × 4.6 mm) was packed with Chiralpak AD (amylose tris-3,5-dimethylphenylcarbamate, from Daicel, Tokyo) coated on 10 $\mu$m silica gel. Column void time ($t_0$) was measured by injection of tri-*tert*-butylbenzene as a nonretained sample [20]. Retention times were mean values of two replicate determinations. All separations were carried out at room temperature. Chromatographic parameters are given as usual [21].

### 2.2. SYNTHESIS

#### 2.2.1. *Reaction of p-tert-butyl-calix[5]arene (***1***) with ditosylate* (±) **2**

A suspension of **1** (0.81 g, 1 mmol) and CsF (0.76 g, 5 mmol) in anhydrous MeCN (50 mL) was refluxed for 1 h. Then a solution of (±)-**2** (0.847 g, 1.1 mmol) in MeCN (50 mL) was added dropwise over 8 h. The mixture was refluxed for an additional 20 h before the solvent was removed. The product was partitioned between water and $CH_2Cl_2$. The organic layer was washed with 0.1 N HCl, then with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by

column chromatography [($SiO_2$, a gradient of $Et_2O$ in petroleum ether (40–60°)] to afford two main fractions.

Fraction A gave a trace amount of racemic (1,2)-bridged calix[5]crown-6-3,4,5-triol **4** (<1%): $R_f$ 0.65 (petroleum ether–$Et_2O$, 3 : 1); $^1$H NMR: $\delta$ 0.70, 1.07, 1.21, 1.26, 1.29 (9 H each, s, $C(CH_3)_3$), 3.28, 3.33, 3.37, 3.41, 3.42 (d, 1 H each, $J$ = 13.5–15.3 Hz, *exo*-$ArCH_2Ar$), 3.46–4.57 (m, 16 H, polyether chain), 3.94, 3.99, 4.15, 4.38, 4.54 (d, 1 H each, $J$ = 13.5–15.3 Hz, *endo*-$ArCH_2Ar$), 6.56, 6.59 (ABq, 2 H, $J$ = 2.5 Hz, ArH), 6.95 (s, 2 H, ArH), 7.08–7.32 (m, 13 H, ArH and BinaphH), 7.35 (bs, 1 H, OH), 7.48, 7.55 (d, 1 H each, $J$ = 9.0 Hz, 3,3′-BinaphH), 7.58 (bs, 1 H, OH), 7.70 (d, 1 H, $J$ = 7.9 Hz, 5-BinaphH), 7.75 (d, 1 H, $J$ = 9.0 Hz, 4-BinaphH), 7.76 (d, 1 H, $J$ = 7.9 Hz, 5′-BinaphH), 7.86 (d, 1 H, $J$ = 9.0 Hz, 4′-BinaphH), and 8.57 (bs, 1 H, OH); $^{13}$C NMR: $\delta$ 29.4, 29.65, 29.69 (×2), 30.7 (t, $ArCH_2Ar$), 30.9, 31.3, 31.4, 31.5, 31.6 (q, $C(CH_3)_3$), 33.7 33.80, 33.84, 33.87, 34.0 (s, $C(CH_3)_3$), 69.0, 69.7, 69.9, 70.3, 70.4, 70.9, 71.8, 72.8 (t, $OCH_2$), 115.3, 116.6 (d), 119.9, 121.0 (s), 123.4, 123.6, 124.3, 124.6, 125.0, 125.1, 125.2, 125.26,125.34, 125.5, 125.6 (d), 125.9 (s), 126.2 (×2) (d), 126.29 (s), 126.34 (d), 126.6, 126.7, 127.0, 127.2 (s), 127.8, 128.0, 129.2 (d), 129.3, 129.5 (s), 129.6 (d), 132.6, 133.1, 133.50, 133.54, 133.9, 134.0 (s), 142.3, 142.7, 142.9, 145.9, 146.4 (s, $C_{sp2}$–$C(CH_3)_3$), 147.8, 148.2, 149.2, 151.6 (×2), 153.9, and 154.5 (s, $C_{sp2}$–O); FAB (+) MS, $m/z$ 1237 ($MH^+$, 100).

Fraction B afforded racemic (1,3)-bridged calix[5]crown-6-2,4,5-triol **3** (0.89 g, 72%): mp 173–177 °C (abs EtOH); $R_f$ 0.43 (petroleum ether–$Et_2O$, 3 : 1); $^1$H NMR: $\delta$ 1.06, 1.16, 1.20, 1.32, 1.33 (s, 9 H each, $C(CH_3)_3$), 2.97 (bd, 1 H, $J$ = 11.7 Hz, $OCH_2CH_2O$), 3.27–3.43 (partly overlapped d, 5 H, $J$ = 13.4–13.8 Hz, *exo*-$ArCH_2Ar$), 3.6–4.5 (m, 15 H, $OCH_2CH_2O$), 4.03, 4.25, 4.39, 4.47, 4.56 (d, 1 H each, $J$ = 13.4–13.8 Hz, *endo*-$ArCH_2Ar$), 7.01, 7.08, 7.13 (d, 1 H each, $J$ = 2.4 Hz, ArH), 7.14–7.34 (m, 11 H, ArH and BinaphH), 7.28 (bs, 1 H, OH), 7.37, 7.40 (d, 1 H each, $J$ = 2.4 Hz, ArH), 7.47, 7.58 (d, 1 H each, $J$ = 9.0 Hz, 3,3′-BinaphH), 7.68 (bs, 1 H, OH), 7.80, 7.86 (d, 1 H each, $J$ = 7.9 Hz, 5,5′-BinaphH), 7.89 (d, 1 H, $J$ = 9.0 Hz, 4-BinaphH), 7.97 (d, 1 H, $J$ = 9.0 Hz, 4′-BinaphH), and 8.13 (bs, 1 H, OH); $^{13}$C NMR: $\delta$ 27.7, 28.4 (t, $ArCH_2Ar$), 31.2, 31.3, 31.4, 31.67, 31.73 (q, $C(CH_3)_3$), 33.9, 34.12, 34.13, 34.14, 34.18 (s, $C(CH_3)_3$), 69.9 (×3), 70.4, 70.5, 70.9, 74.5, 74.8 (t, $OCH_2$), 114.8, 115.8 (d), 120.1, 120.7 (s), 123.5, 123.6, 124.9, 125.2, 125.3, 125.41, 125.44, 125.48, 125.53 (d), 125.8 (s), 125.9, 126.0 (d), 126.2 (s), 126.3, 126.35 (d), 126.40 (s), 126.6 (d), 126.7, 126.8, 127.1 (s), 127.7, 127.9, 129.2 (d), 129.26, 129.28, 129.31 (s), 129.5 (d), 131.7, 132.3, 132.4, 133.2, 134.17, 134.22 (s), 141.2, 141.7, 142.9, 146.8, 147.0 (s, $C_{sp2}$–$C(CH_3)_3$), 148.0, 149.88, 149.94, 150.29, 150.32, 154.2, and 154.6 (s, $C_{sp2}$–O); FAB (+) MS, $m/z$ 1237 ($MH^+$, 100). *Anal. Found*: C, 80.21, H, 7.70. *Calc*. for $C_{83}H_{96}O_9$: C, 80.55; H, 7.82.

### 2.2.1. *Triether* **5**

A mixture of **3** (0.185 g, 0.15 mmol) and NaH (0.096 g, 4 mmol) in anhydrous THF (10 mL) was stirred for 30 min at room temperature. MeI (1.42 g, 10 mmol) was then added, and the mixture was stirred at room temperature for 15 h. The reaction was cautiously quenched by addition of MeOH (2 mL), poured into 0.5 N HCl (30 mL), and extracted with $CHCl_3$. The organic extract was washed with aqueous $Na_2S_2O_3$ and dried ($MgSO_4$). Evaporation of the solvent gave almost pure **5** (0.15 g, 80%), which was further purified by recrystallization from abs EtOH; mp 264–268 °C; $^1$H NMR: $\delta$ 1.07, 1.09, 1.12, 1.19, 1.28 (s, 9 H each, $C(CH_3)_3$), 2.66, 2.69, 2.93 (s, 3 H each, OMe), 3.14, 3.31 (d, 1 H each, $J$ = 13.9 Hz, *exo*-$ArCH_2Ar$), 3.40–4.25 (m, 23 H, $OCH_2CH_2O$ and *exo*-$ArCH_2Ar$), 4.65 (d, 1 H, $J$ = 13.9 Hz, *endo*-$ArCH_2Ar$), 6.87, 6.90 (d, 1 H each, $J$ = 2.4 Hz, ArH), 6.96 (t, 2 H, $J$ = 2.9 Hz, ArH), 6.99 (d, 1 H, $J$ = 2.4 Hz, ArH), 7.05–7.32 (m, 11 H, ArH and BinaphH), 7.36, 7.41 (d, 1 H each, $J$ = 9.0 Hz, 3,3′-BinaphH), 7.61, 7.89 (d, 1 H each, $J$ = 9.0 Hz, 4,4′-BinaphH), 7.74, 7.84, (d, 1 H each, $J$ = 8.1 Hz, 5,5′-BinaphH); $^{13}$C NMR: $\delta$ 29.5, 29.7, 29.9 (t, $ArCH_2Ar$), 31.3, 31.39, 31.42, 31.5, 31.6 (q, $C(CH_3)_3$), 33.97, 33.99, 34.04, 34.11 (s, $C(CH_3)_3$), 60.1, 60.28, 60.33 (q, $OCH_3$), 69.7, 70.1 (×2), 70.59, 70.62, 70.9, 73.0, 73.2 (t, $OCH_2$), 116.2, 117.3 (d), 120.66, 120.73 (s), 123.4, 123.5, 125.0, 125.29, 125.35, 125.40, 125.5, 125.6, 125.9, 126.0, 126.1, 126.2, 127.70, 127.73, 129.2 (d), 129.4, 129.5, 133.36, 133.44, 133.51, 133.66, 133.73, 133.75, 133.78, 133.90, 133.93, 134.06, 134.08 (s), 144.8, 144.9 (×2), 145.1, 145.2 (s, $C_{sp2}$–$C(CH_3)_3$), 152.2, 152.4, 154.1, 154.3, 154.5 (×2), and 154.8 (s, $C_{sp2}$—O); FAB (+) MS, $m/z$ 1279 ($MH^+$, 100). *Anal. Found*: C, 80.57; H, 8.16. *Calc*. for $C_{86}H_{102}O_9$: C, 80.71; H, 8.03.

### 2.2.2. *Triether* **6**

A stirred mixture of **3** (0.124 g, 0.1 mmol), 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl, 0.164 g, 1 mmol) and anhydrous $K_2CO_3$ (0.28 g, 2 mmol) in dry DMF (10 mL) was heated at 70 °C for 24 h under $N_2$. After cooling, the mixture was poured into water (50 mL) and the precipitate obtained was collected by suction filtration, dissolved in $CH_2Cl_2$ and dried ($MgSO_4$). The solution was concentrated to a small volume, and passed through a short alumina column, by eluting with a gradient of AcOEt in cyclohexane, to afford the desired tri-picolyl derivative **6** (0.097 g, 64%); mp 157–160 °C (EtOH); $^1$H NMR: $\delta$ 0.42, 1.00, 1.11, 1.33 (s, 45 H, ratio 1 : 1 : 1 : 2, respectively, $C(CH_3)_3$), 2.83–2.89 (m, 1 H, $OCH_2CH_2O$), 3.15, 3.17, 3.22, 3.27, 3.40 (d, 1 H each, $J$ = 13.3–14.7 Hz, *exo*-$ArCH_2Ar$), 3.12–4.30 (m, 15 H, $OCH_2CH_2O$), 4.41, 4.44, 4.53, 4.57, 4.70 (d, 1 H each, $J$ = 13.3–14.7 Hz, *endo*-$ArCH_2Ar$), 4.77 and 4.94 (ABq, 2 H, $J$ = 12.8 Hz, $OCH_2Py$), 4.83 and 4.92 (ABq, 2 H, $J$ = 12.1 Hz, $OCH_2Py'$), 4.94 and 5.04 (ABq, 2 H, $J$ = 12.8 Hz, $OCH_2Py''$), 6.21, 6.28 (ABq, 2H, $J$ = 2.3 Hz, ArH), 6.72 (ddd, 1 H, $J$ = 7.6, 4.9, and 0.9 Hz, 5-PyH), 6.89 (ddd, 1 H, $J$ = 7.6, 4.9, and 0.9 Hz, 5-Py′H), 6.92 (d, 1 H, $J$ = 2.8 Hz, ArH), 6.96–7.43 (m, 11 H, ArH, PyH and BinaphH), 7.26, 7.42

(d, 1 H each, $J$ = 9.0 Hz, 3,3′-BinaphH), 7.66, 7.71 (d, 1 H each, $J$ = 7.8 Hz, 3-PyH and 3-Py′H), 7.84–7.91 (m, 5 H, 3-Py″H and 4,4′,5,5′-BinaphH), 8.31 (dt, 1 H, $J$ = 4.9, 0.9 Hz, 6-PyH), 8.38 (ddd, 1 H, $J$ = 4.9, 1.8, 0.9 Hz, 6-Py′H), and 8.52 (ddd, 1 H, $J$ = 4.9, 1.8, 0.9 Hz, 6-Py″H); $^{13}$C NMR: $\delta$ 28.0, 28.4, 29.0, 30.2, 30.7 ($ArCH_2Ar$), 30.8, 31.3, 31.4, 31.62, 31.64 ($C(CH_3)_3$), 33.68, 34.02, 34.07, 34.10, 34.12 ($C(CH_3)_3$), 68.0, 68.39, 69.41, 69.5, 69.8, 71.3 (×2), 71.7 ($OCH_2$), 76.2, 77.48, 77.52 ($OCH_2Py$), 115.0, 115.4, 119.9, 120.0, 121.8, 122.48, 122.53, 122.56, 122.62, 123.3, 123.5, 124.0, 124.2, 124.9, 125.1, 125.3, 125.51, 125.52, 126.25, 126.28, 126.6, 126.8, 127.1, 127.3, 127.82, 127.86, 128.95, 129.1, 129.19, 129.21, 132.5, 133.14, 133.16, 133.5, 133.7, 133.8, 133.9, 134.1, 134.3, 134.5, 134.9, 136.4, 136.6, 136.9, 145.0, 145.17, 145.23, 145.40, 145.43, 151.2, 151.5, 151.7, 152.4, 152.8, 153.8, 154.3, 157.3, 157.6, and 158.0; FAB (+) MS, $m/z$ 1510 ($MH^+$, 100). *Anal. Found*: C, 80.44; H, 7.56; N, 2.71. *Calc.* for $C_{101}H_{111}N_3O_9$: C, 80.28; H, 7.40; N, 2.78.

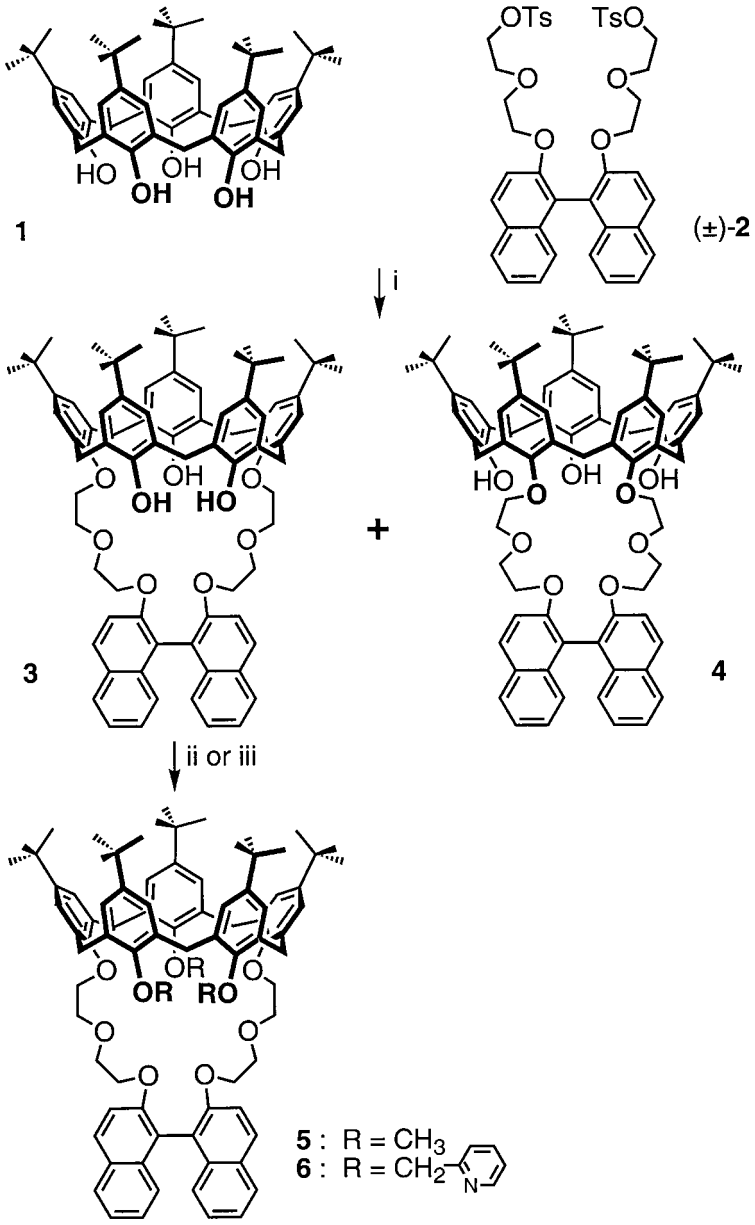
## 3. Results and Discussion

### 3.1. SYNTHESIS, STRUCTURE AND CONFORMATION OF CALIX[5]ARENE HOSTS

The synthesis of hosts **3**-**6** is illustrated in Scheme 1. Racemic (1,3)-*p-tert*-butyl calix[5]crown-6-2,4,5-triol **3** was selectively obtained in 72% yield by reacting *p-tert*-butylcalix[5]arene (**1**) and 2,2′-bis(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-binaphthalene (**2**) under Böhmer's conditions [22] (refluxing $CH_3CN/CsF$). Trace amounts of the (1,2)-bridged regioisomer **4** were also isolated. The exhaustive alkylation of triol **3** with an excess of $CH_3I/NaH$ in THF or $PicCl{\cdot}HCl/K_2CO_3$ in DMF smoothly afforded triether derivatives **5** (80%) and **6** (64%), respectively.

The formation of regioisomeric mono crown ethers **3** and **4** and triether derivatives **5** and **6** was proven by their FAB (+) mass spectra, which show very prominent parent peaks. Structure assignment and conformation of **3**–**6** was further achieved by their $^1$H and $^{13}$C NMR spectra. The distinction between (1,3)- and (1,2)-bridging of the polyether chain to the calixarene was made by comparison of phenolic OH resonances in the $^1$H NMR spectra of **3** and **4** (see Figure 1). Due to the axial chirality of the binaphthyl unit, both isomers show a set of three signals of equal intensity for the OH groups. However, in the less abundant compound one of the three OH groups resonates at much lower field ($\delta$ 8.57 ppm), as compared to those of the major regioisomer ($\delta$ in the range 7.28–8.13 ppm), strongly indicating the (1,2)-bridged structure **4**, in which the central OH group is involved in a continuous row of intramolecular hydrogen bonded OH groups. Similar arguments have recently been used for structure assignments of a number of (poly)hydroxylated calix[$n$]arenes [22–25].

The overall cone conformation of **3**–**6** is corroborated by the presence of five pairs of doublets of equal intensity for $ArCH_2Ar$ protons, with a $\Delta\delta_H$ separation between geminal protons around 1 ppm and the pertinent methylene carbon res-




*Scheme 1.* Synthesis of hosts **3**–**6**. Reagents and conditions: (i) (±)–**2** (1.1 equiv), CsF (5 equiv), $CH_3CN$, reflux, 28 h; (ii) NaH (25 equiv), $CH_3I$ (66 equiv), THF, 15 h, 80%; (iii) PicCl·HCl (10 equiv), $K_2CO_3$ (4 equiv), DMF, 70 °C, 24 h, 64%.

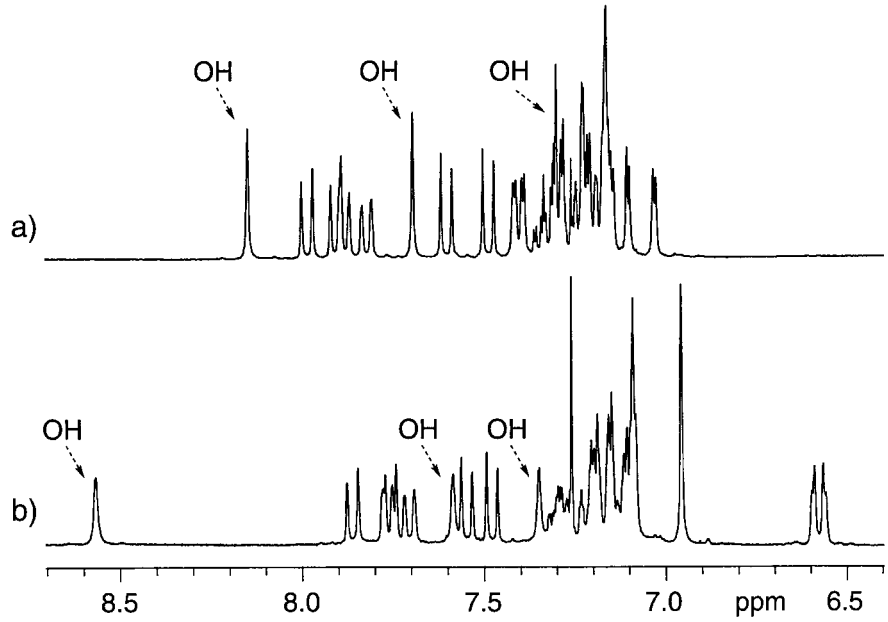



*Figure 1.* The aromatic region in the $^1$H NMR spectra (300 MHz, $CDCl_3$) of (a) **3** and (b) **4**. The position of OH signals was proven by exchange with $D_2O$.

onances in the range 29.2 ± 1.5 ppm [26]. The correlation of these five pairs of doublets in **3** was resolved with the aid of 2D COSY $^1$H NMR spectroscopy, as shown in Figure 2. The $\Delta\delta$ values of the five pairs of doublets are 1.27, 1.13, 0.98, 0.83 and 0.61 ppm, respectively. Since the $\Delta\delta$ for a regular cone conformation is ca. 0.9 ppm [27–29], one of the phenyl units is flattened while the four remaining phenyl units adopt a more regular cone-like conformation. Similarly, the high field resonances of methoxy groups in trimethyl ether **5** ($\delta$ 2.66, 2.69 and 2.93 ppm) are suggestive of a *cone-out* (flattened cone) conformation [30], with methoxy groups pointing into the ring cavity and relevant *p-tert*-butyl substituents directed away from it. In contrast, triol **4** and tripicolyl ether **6** adopt preferentially a *cone-in* conformation, with a *p-tert*-butylphenyl moiety (the "isolated" one in **6**) canted inward in the calix cavity, as substantiated by the upfield resonances of relevant *tert*-butyl and aryl protons [$\delta$ 0.70 (s, 9 H) and 6.56 and 6.59 (ABq, 2 H, $J$ = 2.5 Hz) in **4** (see Figure 1), and 0.42 (s, 9 H), 6.21 and 6.28 (ABq, 2 H, $J$ = 2.3 Hz) in **6**].

### 3.2. CHROMATOGRAPHIC ENANTIOSEPARATION

The enantiomeric pairs of **3** and **6** were resolved by HPLC using an enantioselective column (Chiralpak AD). The chromatographic results are presented in Table I and Figure 3. The best separation factor ($\alpha$) was obtained for compound **3**, while only a

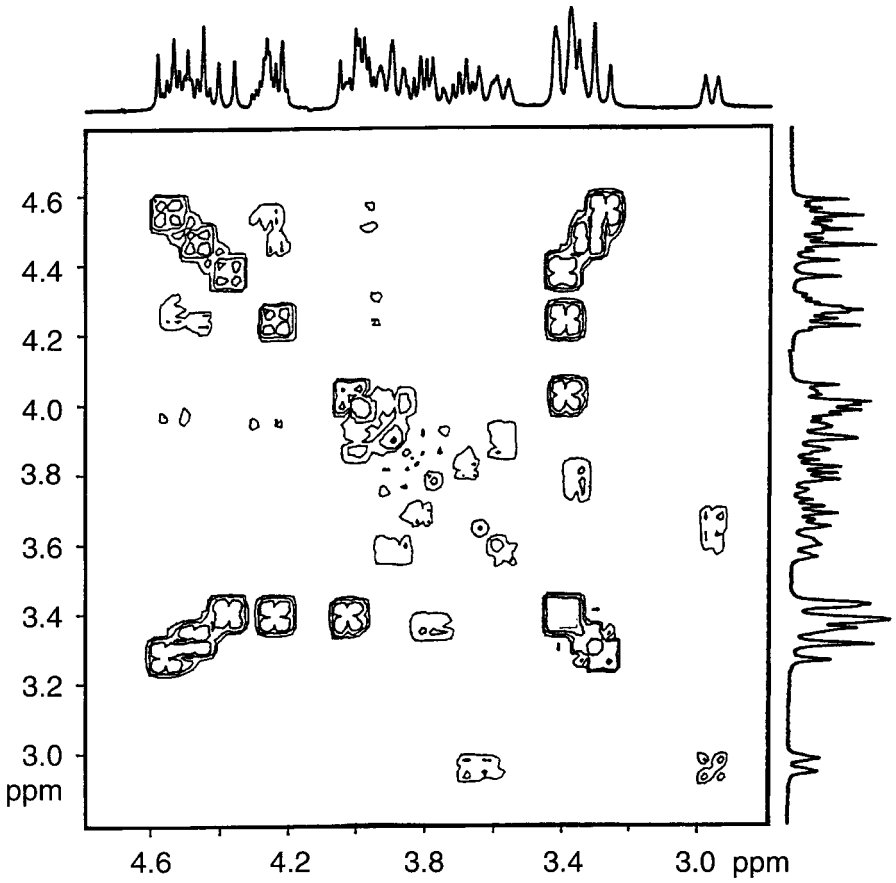



*Figure 2.* The 2.8–4.8 ppm region in the COSY spectrum of **3**.

single peak with a shoulder was obtained for compound **5** at a lower polarity of the mobile phase. The chromatographic behaviour of **3** can be attributed to the presence of three hydroxyl groups, that are able to interact *via* hydrogen bond(s) with the carbamate moiety of the chiral stationary phase (CSP). Similarly, compound **6** can interact with the CSP through its pendant electron-poor picolyl moieties and accordingly shows a good enantiomeric separation. In contrast trimethoxy derivative **5**, which is unable to form H bonds with CSP, is weakly adsorbed on the stationary phase ($k_1' = 0.293$) and consequently is not resolved. Similar behaviour has previously been observed for other chiral calix[4]arenes [12, 31].

### 3.3. $^1$H NMR COMPLEXATION STUDIES

(1,3)-Calix[5]crown ethers **3**–**6** are potentially heteroditopic receptors, since they combine both a hydrophilic crown ether pocket at the lower rim and a preorganized hydrophobic cone-like cavity on the opposite side, the latter being well-suited for

*Table I.* HPLC behaviour of chiral calix[5]crown-6 derivatives on Chiralpak AD

| Compound | $A$(%)[a] | $k'_1$[b] | $\alpha$ | $R_s$ |
|---|---|---|---|---|
| **3** | 5 | 0.506 | 2.41 | 4.7 |
| **5** | 5 | 0.293 | NS[c] | |
| | 3 | 0.369[d] | NS[c] | |
| **6** | 5 | 1.370 | 1.20 | 1.2 |

[a]Percentage of 2-propanol in *n*-hexane at a flow rate of 0.5 ml/min, $t_o$ = 6.5 min.
[b]Capacity factor of the first eluted enantiomer.
[c]Not separated.
[d]Shoulder in the rising edge of the peak.

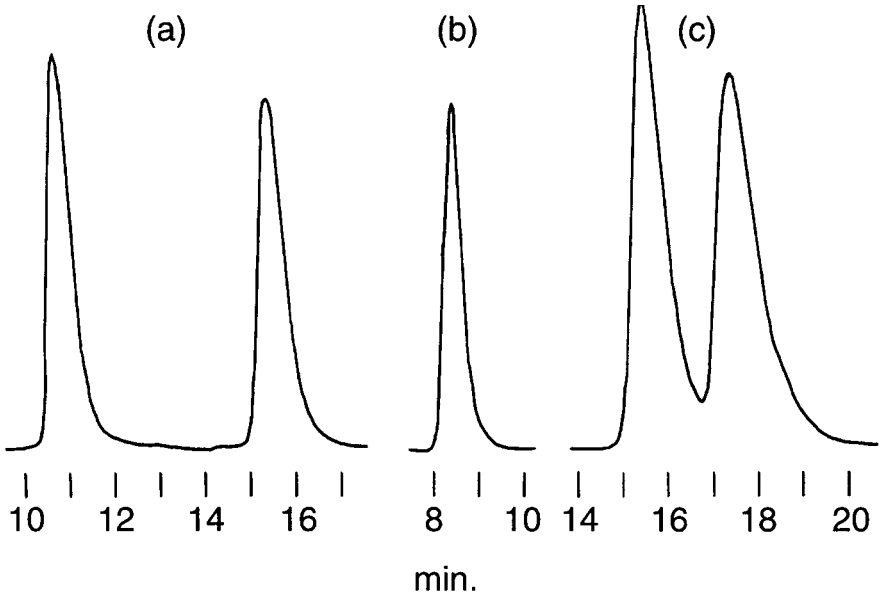



*Figure 3.* HPLC separation on Chiralpak AD (mobile phase: *n*-hexane/2-propanol 95 : 5, v/v; flow rate: 0.5 ml/min) of the enantiomeric pairs of (a) **3**, (b) **5** and (c) **6**.

cation-$\pi$ interactions [32, 33]. In order to prove complementary host-guest interactions and determine the preferred binding sites, $^1$H NMR titration experiments with a variety of organic ammonium ions were carried out in $CDCl_3$-$CD_3OD$ (9 : 1, v/v), by following the spectral changes upon addition of increasing amounts of salt. Accordingly, the addition of 1-10 equiv of *n*-$BuNH_3^+$, *i*-$BuNH_3^+$, *s*-$BuNH_3^+$ or (*R*)-$\alpha$-methylbenzylammonium picrate salts to a solution of **3** caused progressive up- or down-field shifts in every region of the spectrum. Moreover, in the case of the chiral salt distinct splitting of signals could be observed, notably of the doublets

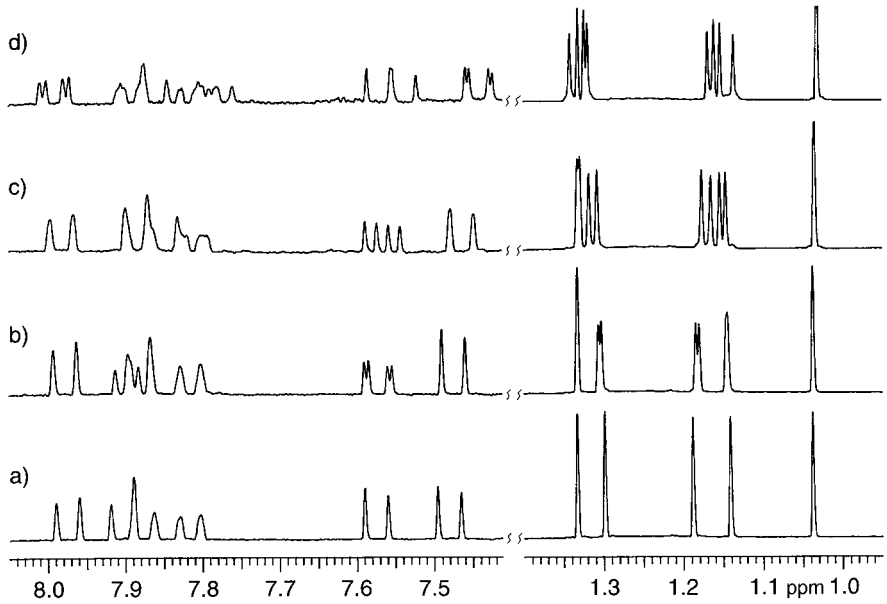



*Figure 4.* Selected regions (plotted on different horizontal and vertical scales) of the $^1$H NMR spectrum ($CDCl_3$–$CD_3OD$ 9 : 1, v/v) of host **3** (trace a), and spectral changes upon addition of 2.0 (trace b), 5.0 (trace c), and 10.0 equiv (trace d) of (*R*)-$\alpha$-methylbenzylammonium picrate.

due to the 4′- and 3(3′)-binaphthyl protons ($\delta$ 7.97, 7.57, and 7.48 ppm) and of four out of the five $^t$Bu singlets ($\delta$ 1.33, 1.30, 1.19, and 1.14 ppm) (Figure 4). This suggests that the interaction of **3** with alkylammonium ions occurs at the lower rim (*exo*-complexation [34]), in close proximity to the chiral binaphthyl unit and that the exchange rate between free and complexed species is fast on the NMR time scale. Only a very weak interaction (down-field shifts of the $^t$Bu groups) was detected in the case of *t*-$BuNH_3^+$ picrate.

Triethers **5** and **6** were also tested as potential hosts for the four isomeric butylammonium picrates. While a similar trend was apparent from the spectra of mixtures of these hosts and branched butylammonium guests, surprisingly *endo*-cavity complexation was clearly observed with *n*-$BuNH_3^+$. This is unambiguously substantiated by the dramatic upfield shifts ($\Delta\delta$ up to 3.87 ppm) experienced by the cavity included *n*-alkyl chain. The free and included *n*-$BuNH_3^+$ ion are in a slow exchange rate on the NMR time scale, as shown by the presence in the spectra of distinct signals for the free and complexed species. Consequently, the 1 : 1 host-guest stoichiometry and association constants ($K_a$) for the formation of *endo*-complexes could be deduced by direct $^1$H NMR analysis of equimolar solutions (ca. $5 \times 10^{-3}$ M) of host and guest in the stated solvent mixture. The $K_a$ values at 293 K for the *endo*-calix complexation of *n*-$BuNH_3^+$ with **5** and **6** are 65 and 48 $M^{-1}$, respectively. These results have provided the first direct evidence for the formation of $RNH_3^+$ *endo*-calix complexes with calix[5]arene systems in a

slow exchanging regime [15]. Mandolini *et al*., on the other hand, have recently reported that the cone-like cavity of (1,3)-bridged calix[5]arene crown ether triols is well suited, but rather unselective, for the inclusion of the larger quaternary ammonium salts. For these substrates fast complexation equilibria on the NMR time scale, and an adverse effect of the upper rim *tert*-butyl substituents on *endo*-cavity complexation have been noticed [35].

Inspired by previous work by Cram on the separation of aminoacid esters by binaphthyl-derived crown ethers [36], our studies were also extended to a series of aminoacid (Ala, Val, Phe, Hys) methylester hydrochlorides as potential chiral guests but to no avail. The spectra of hosts **3** and **5** ($CDCl_3$-$CD_3OD$ 9 : 1, v/v) were unaltered by addition of 1 equiv of the salt, while strikingly pyridino receptor **6** underwent the same spectral changes (broadening of every region of the spectrum, and downfield shifts of the signals due to the canted *tert*-butylphenyl moiety), irrespective of the aminoacid used. These spectral modifications are associated with host conformational changes from *cone-in* to *cone-out*, induced by protonation of the 'isolated' picolyl group and subsequent stabilization of the resulting pyridinium ion by the juxtaposition of the polyether chain. This conclusion is corroborated by the perfect matching of these spectra with those obtained by protonation of **6** with trifluoroacetic acid in the same solvent.

## 4. Conclusions

The synthesis and enantioselective HPLC separation of racemic (1,3)-bridged calix[5]arene crown ethers **3**–**6** have been achieved. $^1$H NMR titration experiments with a variety of organic ammonium ions have provided evidence that triether derivatives **5** and **6**, unlike triol precursor **3**, show a remarkable affinity for the primary unbranched $RNH_3^+$ ions, which are accommodated inside the hydrophobic cone-like cavity. These results confirm that the bulky *tert*-butyl substituents at the upper rim of calixarenes play a central role in the discrimination process between cationic organic guests, exploiting the $\pi$-basic cavity as the primary recognition site [37]. Structural modifications aimed at obtaining more efficient and selective calix[5]arene-based receptors for organic ammonium ions are in progress.

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