# Synthesis, Optical Resolution and Complexation Properties of Inherently Chiral Monoalkylated *p-tert*-Butyl-(1,2)-calix[4]crown Ethers

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Reaction of mono-*O*-alkylated calix[4]arenes **2** with tri- to pentaethylene glycol ditosylates and $K_2CO_3$ affords asymmetrical (1,2)-calix[4]crown ether derivatives **3** as the main product, along with minor amounts of calix[4]arene dimers **4** and mixed syn-distal di-*O*-alkylated calix[4]arenes **5**. A reaction mechanism for the formation of **3**−**5** is proposed, and the NMR spectral features of these products are briefly discussed. Evidence of the chirality of **3** was provided by diastereomeric interaction with enantiopure alkylammonium salts. The enantiomeric resolution of racemates **3** was achieved by direct HPLC separation, using chiral stationary phases. A screening of the complexing abilities of pyridino-(1,2)-calix[4]crown ethers **3a**−**c** by extraction studies from water into $CH_2Cl_2$ showed a low extraction level of alkali, alkaline earth, and heavy metal picrates, while up to 25% extraction was found for $Ag^+$. UV and pH-metric measurements of **3a**−**c** with silver picrate in THF indicate the formation of 1:1:1 (metal:ligand:picrate) species, with log *K*'s in the range 3.1−3.7.

## Introduction

Calix[4]arenes have become very popular as three-dimensional molecular platforms for the design of artificial molecular receptors, owing to the ready availability of native calix[4]arenes and their ability to provide different stereochemical arrangements of binding sites.[1]

The quest for receptors with chiral discriminating ability has led to interest in chiral calix[4]arenes. Chiral calixarenes can be obtained by simply attaching chiral residues at the upper[2] or lower rim.[3] However, a more challenging approach to introducing chirality is to make the calixarene "inherently" chiral by exploiting the nonplanarity of the molecule in conjunction with an asymmetric substitution of the macrocycle (creation of molecular asymmetry). The basic concepts and methods available for the synthesis of atropisomeric inherently chiral calixarenes have been recently reviewed.[4] Among other possibilities,[5] mono- and 1,2-di-*O*-alkylated calix[4]arenes have been shown to provide a useful source of inherently chiral derivatives: these precursors possess only one plane of symmetry, which is lost by appropriate lower rim functionalization.[6]

In a preliminary paper we reported that the reaction of mono-*O*-alkylated calix[4]arenes with oligoethylene glycol ditosylates affords inherently chiral (1,2)-calix[4]-crown ethers.[7] Here we report the synthesis and characterization of these racemates and their enantiomeric resolution by enantioselective HPLC. Owing to the lack of information about the coordinating behavior of (1,2)-calix[4]crown ethers,[1c] the binding properties of the pyridino derivatives toward a variety of metal cations have also been explored.

## Results and Discussion

**Syntheses**. A two-step synthesis of racemic calix[4]-crown ethers **3** is depicted in Scheme 1. The pivotal mono-*O*-alkylated calix[4]arenes **2** were prepared in 23−50% yield by direct alkylation of *p-tert*-butylcalix[4]arene **1** with 1 equiv of the appropriate electrophile and 1 equiv of NaH [2 equiv in the case of the hydrochloride salts of 2-(chloromethyl)pyridine or 2-(chloromethyl)quinoline] in anhydrous toluene at 70 °C. The $^1$H NMR spectra of **2** display for the calixarene skeleton the expected symmetry for a monoalkylated derivative in a fixed cone conformation, i.e. two AX systems ($J = 13.4 \pm 0.4$ Hz) for $ArCH_2Ar$ protons, two singlets and an AB quartet (ratio 1:1:2) for the aromatic protons, and two sharp singlets for OH groups (ratio 2:1) (a broad singlet for calixarenes **2a** and **2e**) at very low field (9.1−10.0 ppm).

Subsequent reaction of **2** with the appropriate oligoethylene glycol ditosylate (1 equiv) was carried out in

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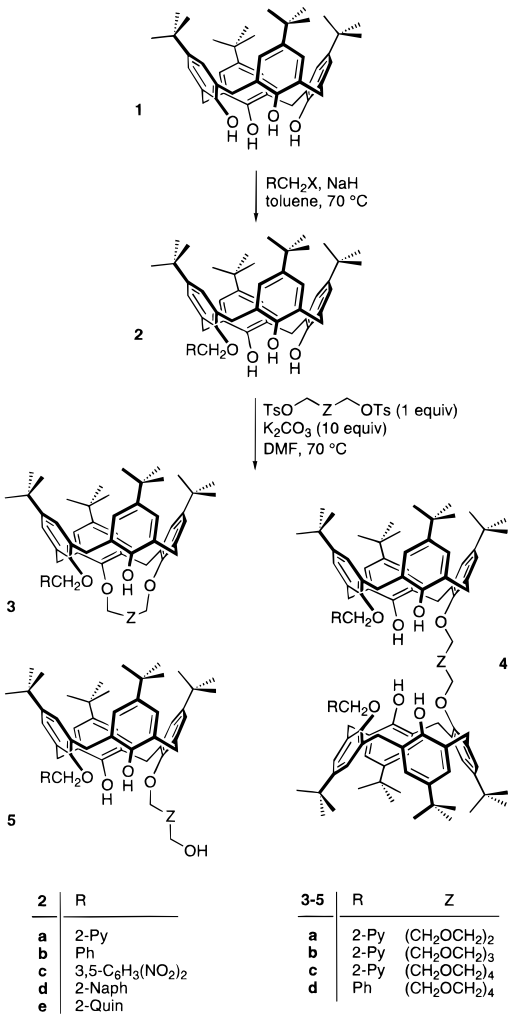
**Scheme 1**



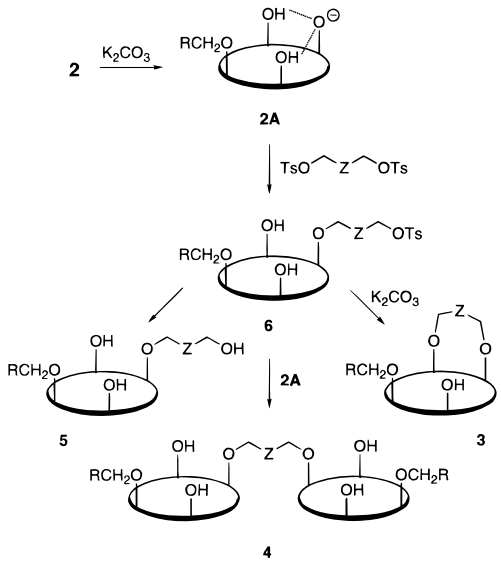

| 2 | R |
|---|---|
| a | 2-Py |
| b | Ph |
| c | 3,5-$C_6H_3(NO_2)_2$ |
| d | 2-Naph |
| e | 2-Quin |

| 3-5 | R | Z |
|---|---|---|
| a | 2-Py | $(CH_2OCH_2)_2$ |
| b | 2-Py | $(CH_2OCH_2)_3$ |
| c | 2-Py | $(CH_2OCH_2)_4$ |
| d | Ph | $(CH_2OCH_2)_4$ |

anhydrous DMF in the presence of a large excess of $K_2CO_3$ (10 equiv) for 48 h at 70 °C. After careful column chromatography of the reaction mixture, inherently chiral (1,2)-calix[4]crown ethers **3** were isolated as the main product (30−41%), along with minor amounts of calix[4]arene dimers **4**, mixed syn-distal calix[4]arenes **5**, and unreacted **2** (20−25%) (Scheme 1). Attempts to synthesize by the same strategy analogous (1,2)-calix[4]-crown ethers endowed with larger (3,5-dinitrobenzyl, 2-naphthylmethyl, or 2-quinolylmethyl) pendant groups failed, probably due to the deleterious role played by these bulky substituents during the crucial crown ether cyclization step.

A possible reaction pathway to explain the formation of compounds **3**−**5** is shown in Scheme 2. Deprotonation of the distal OH group of **2** by the weak base $K_2CO_3$, followed by reaction of the resulting monoanion **2A** with the bifunctional electrophile, produces the key monotosylated intermediate **6**.[8] Subsequently, **6** undergoes (*i*) intramolecular cyclization (with $K^+$ acting as a template) to afford crown ethers **3** as the main product, (*ii*)

**Scheme 2**



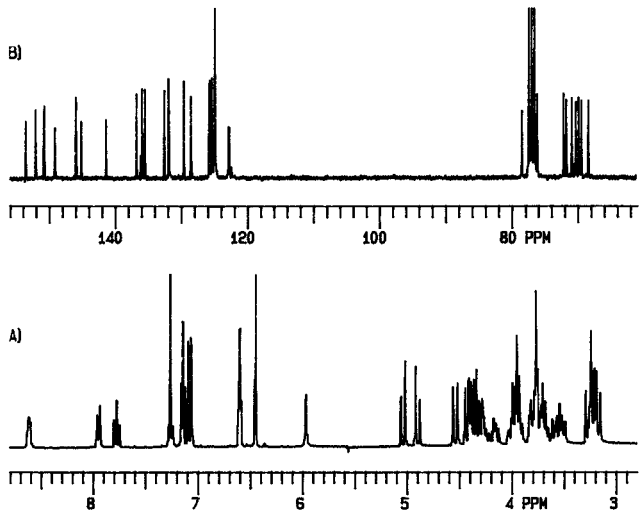




**Figure 1.** Aromatic and oxymethylene regions of (a) $^1$H NMR ($CDCl_3$, 300 MHz) and (b) BB decoupled $^{13}$C NMR spectra ($CDCl_3$, 75.5 MHz) of **3b**.

nucleophilic displacement by the monoanion **2A** to give calix[4]arene dimers **4**, or alternatively (*iii*) hydrolysis to produce **5**. The product distribution is in full agreement with the general mechanism of stepwise alkylation of calix[4]arenes with weak bases (only the phenoxyde anion stabilized by hydrogen bonding with the two flanking OH is formed).[9] Furthermore, the complete absence, in the reaction mixtures, of the achiral regioisomeric (1,3)-calix[4]crown ethers confirms the mechanism proposed.

**NMR Studies**. The absence of symmetry elements in compounds **3** is evident from their complex NMR spectra, which show characteristic line patterns for the chiral calix[4]arene skeleton and the groups attached to it. The NMR spectra of **3** are quite uniform and here we will discuss the $^1$H and $^{13}$C NMR spectra of crown-5 derivative **3b**, typical of this class of compounds.

The $^1$H NMR spectrum of **3b** shows (Figure 1a) four singlets for *tert*-butyl groups (not shown), four partly overlapping AX systems ($J$ = 12.6−13.5 Hz) for the

(8) Although **6** was not detected in the reaction mixtures, it was possible to isolate and characterize compound **6a** [Z = $(CH_2OCH_2)_2$] during an alkylation of **2a** with a limited amount of triethylene glycol ditosylate. **6a**: $^1$H NMR $\delta$ 0.93, 0.95, 1.29 (s, ratio 1:1:2, 36 H), 2.41 (s, 3 H), 3.29, 4.29 (d, $J$ = 13.3 Hz, 4 H), 3.30, 4.32 (d, $J$ = 13.1 Hz, 4 H), 3.54−4.15 (m, 12 H), 5.13 (s, 2 H), 6.77, 6.79, 7.05 (s, ratio 1:1:2, 8 H), 7.06 (m, 1 H), 7.16 (s, 2 H), 7.29, 7.75 (d, $J$ = 7.7 and 8.4 Hz, respectively, 2 H each), 7.84 (td, $J$ = 7.7, 1.7 Hz, 1 H), 8.18 (d, $J$ = 7.7 Hz, 1 H), and 8.59 (dt, $J$ = 4.7, 0.9 Hz, 1 H); FAB (+) MS, $m/z$ 1026 (100, $MH^+$).

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bridging methylenes, a complex pattern for the polyether chain in the range 3.4−4.4 ppm, an AB system ($J$ = 12.3 Hz) for the diastereotopic protons of the $OCH_2Py$ group, an upfield resonance for the residual OH group at $\delta$ 5.96 ppm, three AB systems ($J$ = 2.4−2.5 Hz) and a (pseudo) singlet for the aromatic protons of the calix[4]arene skeleton, and a four-spin system for the 2-substituted pyridine ring. A chemical shift difference ($\Delta\delta$) >1 ppm between the four pairs of signals due to the bridging methylene protons ($CH_{exo}$ and $CH_{endo}$) is suggestive of a cone conformation for **3b**.[1a]

The cone structure for **3b** is further confirmed by the $^{13}C$ NMR spectrum (Figure 1b), which shows resonances around 31 ppm (partly buried under the *t*-Bu signals) for the $ArCH_2Ar$ carbons, considered of diagnostic value for such a conformation.[10] Due to the greater dispersion of the $^{13}C$ scale as compared to that of $^1H$, very often the number of observed resonances coincide with those expected, as can be seen for the nine lines of roughly equal intensity present in the oxymethylene region (68−78 ppm) and for the eight-line pattern for the bridgehead carbons in the range 128−136 ppm (Figure 1b). The NMR spectra of the other inherently chiral calix[4]crown ethers show a similar trend (see Experimental Section), so that these compounds are believed to adopt a fixed cone conformation as well.

The NMR analysis of the achiral byproducts **4** and **5** is much more straightforward, owing to the persistence of at least one plane of symmetry in the molecule after derivatization of **2**. Their spectra show the presence of three resonances for the *tert*-butyl groups and for the aromatic protons in the ratio 1:1:2, respectively, and two AX systems for the bridging methylenes. Also in this case a $\Delta\delta$ > 1 ppm for the geminal $ArCH_2Ar$ protons of **4** and **5** is suggestive of a cone conformation. The NMR pattern for the polyether bridge is symmetrical for calix[4]arene dimers **4** and quite complex for mixed syn-distal di-*O*-alkylated calix[4]arenes **5**, due to the presence of an asymmetrical glycolic chain. Compounds **5a** and **5b** were isolated as DMF solvates with stoichiometry 1:1 (NMR and elemental analyses).

Evidence of chirality for asymmetrical (1,2)-calix[4]-crown ethers synthesized was provided by titration experiments of $CDCl_3$ solutions of **3 (**containing one drop of $CD_3OD$) with both (*R*)- and (*S*)-α-methylbenzylammonium picrates. Whereas the $^1H$ NMR spectra of crown-4 and crown-5 derivatives **3a** and **3b** did not show any appreciable change upon titration with 1 equiv of the chiral salt, splitting and doubling of signals occurred in *every region* of the spectra of crown-6 derivatives **3c** and **3d** from the addition of the first aliquot (0.25 equiv) of each chiral salt. Illustrative regions of the $^1H$ NMR spectrum of receptor **3c**, without and with increasing amounts of the (*R*)-salt, are shown in Figure 2. The spectra did not change further by adding an excess of the salt, suggesting that the diastereomeric 1:1 complexes had formed. These results confirm that a crown-6 moiety is likely to be a prerequisite for anchoring the $NH_3^+$ group of the primary ammonium cation into its crown ether-cavity via N−H···O hydrogen bonds.[11] It is worth noting that the signals due to the diastereomeric complexes show comparable intensities, even by performing the

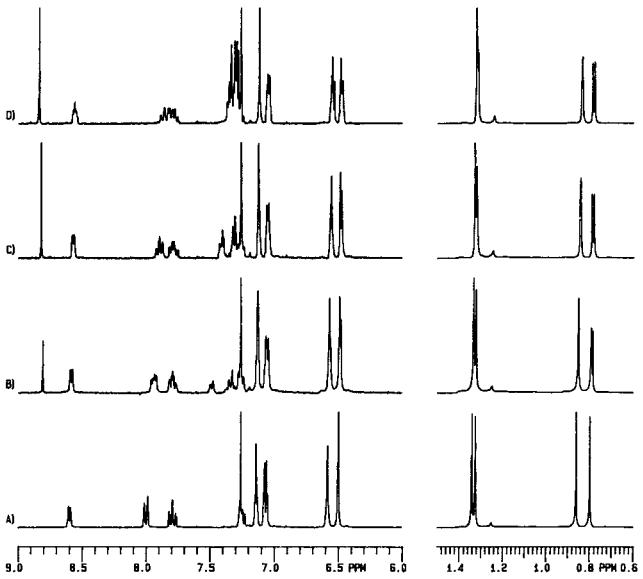


**Figure 2.** Aromatic and *tert*-butyl regions of the $^1H$ NMR spectrum ($CDCl_3$, 300 MHz) of **3c** (a) and spectral changes upon addition of (b) 0.25, (c) 0.5, and (d) 1 equiv amount of (*R*)-α-methylbenzylammonium picrate. The two regions are plotted in different scales.

experiment at low temperatures (223 K), suggesting that no discrimination between the two enantiomers is taking place. On the other hand, compounds **3c** and **3d** do not give any diastereomeric interaction with the more encumbered (*R*)- or (S)-α-methyl-*o*-methoxybenzylammonium picrates, which presumably cannot approach the crown ether portion in a favorable manner from either side (vide infra).

To prove that complexation occurs inside the hydrophilic pocket generated by the substituents attached at the lower rim of the calix[4]arene, a $CDCl_3$ solution of pyridino compound **3c** was protonated with $CF_3COOH$ (1.2 equiv) to give the corresponding pyridinium salt **3c**·$H^+$ (as supported by a significant to large downfield shift experienced by the pyridinyloxy protons; see experimental section for the $^1H$ NMR spectrum of **3c**·$H^+$). Upon titration with 1 equiv of the (*R*)-salt, the chemical shifts of most protons remained unvaried, with the exception of the *tert*-butyl region, which underwent some changes. The two downfield resonances coalesced to a broad singlet, while the remaining two singlets split into two doublets. The invariability of the other signals in the spectrum suggests that the $R-NH_3^+$ cation is impeded from entering the hydrophilic pocket of **3c**·$H^+$ (*internal approach*), due to a strong electrostatic repulsion with the pendant pyridinium group (complexation is switched off by protonation); therefore, the interaction with the crown ether moiety necessarily occurs on the side exterior to the hydrophilic cavity (*external approach*).

**Chromatographic Enantioseparation**. Racemic calix[4]crown ethers **3a**−**d** were resolved on at least one of the chiral stationary phases (CSPs), as shown in Table 1. The Chiralpak AD CSP [amylose tris(3,5-dimethylphenylcarbamate)] was effective in the enantiomeric resolution of all compounds, while the Chiralcel OD [cellulose tris(3,5-dimethylphenylcarbamate)] gave no resolution for compounds **3a** and **3c**. The difference in chiral recognition of cellulose and amylose derivatives is probably due to the different chiral environment around the carbamate residue and to the wider and more

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**Table 1. HPLC CSP Resolution of Inherently Chiral Calix[4]crown Ethers 3a−d and 7**

| compd | column | *A* (%)[a] | FR[b] | $k'_1$[c] | *a* | Rs |
|---|---|---|---|---|---|---|
| **3a** | AD | 10 | 0.5 | 0.113 | 3.57 | 2.9 |
| | AD | 5 | 0.5 | 0.239 | 3.49 | 4.5 |
| | AD | 5 | 1 | 0.320 | 2.65 | 3.3 |
| | OD | 10 | 0.5 | 0.173 | NS[d] | |
| **3b** | AD | 10 | 0.5 | 0.214 | 2.60 | 3.0 |
| | AD | 5 | 0.5 | 0.437 | 2.55 | 4.7 |
| | AD | 5 | 1 | 0.425 | 2.46 | 3.8 |
| | OD | 10 | 0.5 | 0.164 | 1.80 | 1.0 |
| **3c** | AD | 10 | 0.5 | 0.286 | 1.20 | 0.7 |
| | AD | 5 | 0.5 | 0.473 | 1.24 | 1.1 |
| | AD | 5 | 1 | 0.669 | 1.21 | 0.9 |
| | OD | 10 | 0.5 | 0.322 | NS[d] | |
| **3d** | AD | 10 | 0.5 | 0.196 | 1.20 | 0.8 |
| | AD | 5 | 0.5 | 0.336 | 1.35 | 1.3 |
| | AD | 5 | 1 | 0.437 | 1.26 | 1.1 |
| | OD | 10 | 0.5 | 0.379 | 1.32 | 0.6 |
| **7** | AD | 10 | 0.5 | 0.147 | 1.99 | 1.9 |
| | AD | 5 | 0.5 | 0.252 | 1.98 | 2.5 |
| | AD | 5 | 1 | 0.254 | 1.97 | 2.4 |
| | OD | 10 | 0.5 | 0.150 | NS[d] | |

[a] Percentage of 2-propanol in *n*-hexane. [b] Flow rate (mL/min); FR = 1, $t_0$ = 3.4 min; FR = 0.5, $t_0$ = 7.1 min. [c] Capacity factor of the first-eluted enantiomer. [d] Not separated.

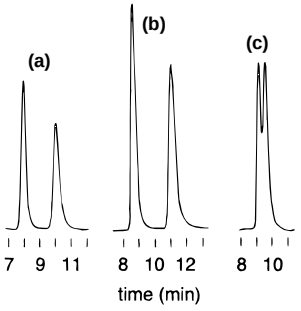
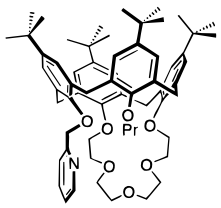



**Figure 3.** HPLC separation on Chiralpak AD (mobile phase *n*-hexane/2-propanol 9:1 at 0.5 mL/min) of the enantiomeric pairs of (a) **3a**, (b) **3b**, and (c) **3c**.

compact helix of the amylose derivative. Zugenmaier et al., in fact, proposed left-handed 3/2 and 4/1 helical structure for cellulose tris(phenylcarbamate)[12] and amylose tris(phenylcarbamate),[13] respectively. Comprehensive surveys on chiral discrimination by using polysaccharide derivatives have recently appeared.[14]

The separation factors (α) and resolution factors (Rs) with Chiralpak AD (Table 1) are much better for **3a** than for **3b**−**d**, indicating a possible influence of the size of the crown ether moiety on the chiral recognition mechanism. An increase of the polarity of the mobile phase has a detrimental effect on Rs, whereas a decrease in the flow rate of the mobile phase has a beneficial effect on α. Moreover, the very low capacity factor ($k'_1$) and good α and Rs values may allow a semipreparative-scale isolation of the single enantiomers of **3a** and **3b**. Figure 3 shows typical chromatograms of the resolution of racemic crown ethers **3a**−**c**. In the absence of the diode array detector, the area ratio of the peaks was measured (in a number of different experiments) with the UV detector set at different wavelengths (240, 265, and 280 nm). As expected for an enantiomeric pair, these area ratios were equal.[15]

When the OH group in **3b** was replaced by a propoxy substituent as in **7** (obtained in 70% yield by reaction of **3b** with *n*-propyl iodide and NaH in dry THF), chiral discrimination with Chiralpak AD was less effective, while no separation at all occurred with the less efficient Chiralcel OD phase (Table 1). Similar behavior has previously been observed for other chiral calix[4]arenes.[16]




**7**

**Complexation Studies with Alkali Metal Cations.** As shown in Table 2, compounds **3a**−**c** do not significantly extract alkali picrates from water into $CH_2Cl_2$. Under our experimental conditions, the highest extraction percentage (%*E*) obtained is hardly higher than 2 (i.e., $K^+$ and **3c**).

However, complexation of a number of alkali cations could be detected from spectrophotometric measurements in MeOH with ligands **3b** and **3c**. Analysis of the UV spectra showed the formation of 1:1 species (Table 3). The results indicate a low level of complexation—$\beta$ values never exceeding 2.2 log units—in comparison with other calixarene-based receptors[17] and, more specifically, with 1,3-dialkoxy calix[4]-crowns[18] and calix[4]-bis-crowns.[19] The crown-5 derivative **3b** appears to be selective for $K^+$ (log $\beta$ = 2.2): it is not efficient for the smaller $Li^+$ and $Na^+$ cations, with which no spectral modifications were recorded, or for the larger $Rb^+$ and $Cs^+$ cations, which produced only small and uninterpretable spectral changes. The crown-6 derivative **3c** is less discriminating as it accommodates the three cations $Na^+$, $K^+$, and $Rb^+$ to the same extent. Little or no complexation is again observed for $Li^+$ and $Cs^+$ with this ligand. No data could be obtained with **3a** due to solubility limitations in MeOH.

Additional extraction tests showed that these ligands were also inefficient for alkaline earth cations, as well as for $Zn^{2+}$, $Pb^{2+}$, and $Cd^{2+}$. Only $Ag^+$ is to some extent extracted by the three ligands, **3a** being the most efficient (%*E* = 25). The lower and comparable efficiencies shown by **3b** and **3c** are consistent with their log $\beta$ values (3.58 and 3.44, respectively), determined by spectrophotometric measurements in MeOH. The value for **3b** was confirmed by pH-metric measurements (Table 4). A very similar value of 3.28 was obtained with $Zn^{2+}$ and the same ligand, although no extraction could be detected in this case. With $Ag^+$ and especially with $Zn^{2+}$, titration curves (Figure 4) show that deprotonation of the phenol and/or solvolysis of the cation or the complex may occur at higher pH.

To compare the efficiencies of the three ligands toward $Ag^+$, spectrophotometric measurements were carried out

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**Table 2. Extraction Percentage (%*E*) of Metal Picrates from Water into $CH_2Cl_2$ by Compounds 3 at 20 °C[a]**

| ligand | $Li^+$ | $Na^+$ | $K^+$ | $Rb^+$ | $Cs^+$ | $Ca^{2+}$ | $Sr^{2+}$ | $Ba^{2+}$ | $Ag^+$ | $Zn^{2+}$ | $Pb^{2+}$ | $Cd^{2+}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | *b* | 0.9 | 0.4 | 0.5 | 0.4 | 0.1 | 0.1 | *b* | 25.0 | *b* | 0.5 | 0.2 |
| **3b** | 0.2 | 0.4 | 0.7 | 0.6 | 0.5 | 0.4 | 0.1 | 0.2 | 12.6 | *b* | 0.8 | 0.2 |
| **3c** | 0.8 | 1.0 | 2.1 | 1.8 | 1.4 | 0.6 | 0.6 | 0.6 | 11.4 | 0.8 | 0.5 | 0.6 |

[a] Standard deviation on the mean of several experiments: $\sigma_{n-1} \leq 0.7$. [b]Not detected.

**Table 3. Stability Constants (log $\beta$) of Metal Complexes of Compounds 3 in MeOH at 25 °C, $I = 0.01$ M ($Et_4NClO_4$ or $Et_4NCl$)[a]**

| ligand | $Li^+$ | $Na^+$ | $K^+$ | $Rb^+$ | $Cs^+$ | $Ag^+$ | $Zn^{2+}$ |
|---|---|---|---|---|---|---|---|
| **3b** | *b* | *b* | $2.20 \pm 0.06$ | $\leq 1$[c] | $\leq 1$[c] | $3.58 \pm 0.02$ (3.43)[d] | $2.9 \pm 0.4$ (3.28)[d] |
| **3c** | *b* | $2.18 \pm 0.05$ | $2.12 \pm 0.09$ | $2.09 \pm 0.01$ | $\leq 1$[c] | $3.44 \pm 0.01$ | $2.90 \pm 0.01$ |

[a] Spectrophotometric determinations; standard deviation $\sigma_{n-1}$ on the mean of two experiments. [b] No spectral changes. [c] Very small spectral changes. [d] pH-metric determinations.

**Table 4. Association Constants (log K) of $Ag^+Pic^-$ with Compounds 3a–c in THF and Bathochromic Shifts [$\Delta\lambda$ (nm)] vs $Ag^+Pic^-$**

| ligand | log $K$[a] | $\Delta\lambda$[b] |
|---|---|---|
| **3a** | $3.7 \pm 0.1$ | 11 |
| **3b** | $3.14 \pm 0.09$ | 11 |
| **3c** | $3.54 \pm 0.08$ | 2 |

[a] Standard deviation $\sigma_{n-1}$ on the mean of at least four experiments. [b] Precision: ±2 nm.

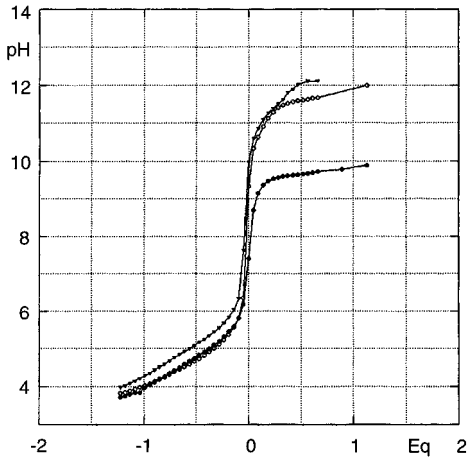


**Figure 4.** Titration curves of **3b** (▽), and **3b** in the presence of equimolar amounts of $Ag^+$ (○) and $Zn^{2+}$ (●).

in THF, where no solubility limitations were met. In such a low polarity solvent, complexation may lead to an increase in the interionic distance between the cation and the anion and to the conversion of a tight ion pair into a loose or ligand separated ion pair, as previously shown for alkali picrates with crown ethers[20] and calixarene derivatives.[21–23] The resulting bathochromic shift of the main absorption band of the metal picrate ion pair has been used as a measure of this separation. The three ligands are able to separate the tight silver picrate ($Ag^+Pic^-$) ion pair by forming 1:1:1 (metal:ligand:picrate) species only, as suggested by the observation of the spectra and the isosbestic points (Figure 5) and further confirmed by numerical treatment of the absorbances. The association constants of the loose ion pairs are given in Table 4 as well as the bathochromic shifts with respect to $Ag^+Pic^-$. Compounds **3a** and **3b** induce strong shifts ($\Delta\lambda = 11$ nm), indicating a significant but incomplete

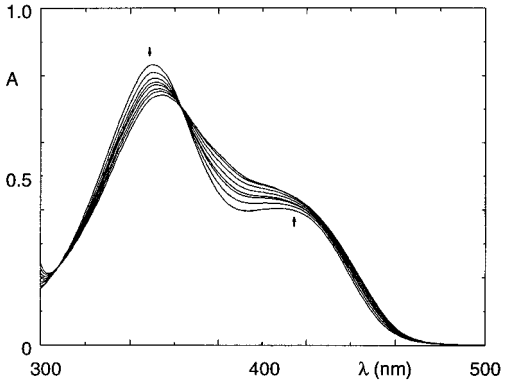


**Figure 5.** Spectral changes observed for $Ag^+Pic^-$ in the presence of increasing amounts of ligand **3a** in THF ($[Pic^-] = 1.0 \times 10^{-4}$ M, $0 \leq [Pic^-]/[L] \leq 4$).

separation of the ion pair. For comparison, $Ag^+Pic^-$ has been found to undergo a very large shift of 31 nm in the presence of calix[4]-bis-crown-5, corresponding to a fully separated ion absorbing at 380 nm.[23] On the other hand, ligand **3c** gives rise to a much smaller shift ($\Delta\lambda = 2$ nm), suggesting an external solvation of the ion pair by the ligand. The relatively high association constant found with **3a**, and the rather large $\Delta\lambda$ and %*E* values, demonstrate that this ligand is the best adapted for $Ag^+$. However, with the three ligands the picrate anion is involved in the complexation of $Ag^+$ in THF.

## Conclusions

In conclusion, we have developed a two-step synthesis of inherently chiral (1,2)-calix[4]crown ethers **3** starting from *p-tert*-butylcalix[4]arene **1**. All racemates have been resolved into their enantiomers by direct HPLC, using chiral stationary phases. The results obtained with Chiralpak AD are very promising for a fast semipreparative-scale separation of the pure enantiomers. This will make it possible to explore the chiral discrimination properties of this new class of calixarene-based chiral receptors. The complexing properties of **3** toward alkali, alkaline earth, and heavy metal cations, with the exception of $Ag^+$ and $Zn^{2+}$, appear to be modest in comparison with those of (1,3)calix[4]crown ethers.

## Experimental Section[24]

$^1H$ and $^{13}C$ NMR spectra were taken in $CDCl_3$ at 300 and 75.5 MHz, respectively. *p-tert*-Butylcalix[4]arene·toluene 1:1

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complex **1** was prepared by a literature procedure.[25] The HPLC system used for the enantiomeric separations has been previously described.[16] The columns (25 cm × 4.6 mm) were packed with Chiralpak AD or Chiralcel OD coated on 10 $\mu$m silica gel. Column void time ($t_0$) was measured by injection of tri-*tert*-butylbenzene as a nonretained compound.[26] Retention times for each pair of enantiomers ($t_1$ and $t_2$) are mean values of two replicate determinations. HPLC chromatographic parameters are given as usual.[27]

**Conversion of 1 into Mono-*O*-alkylated 2. General Procedure**. A slight modification of Shinkai's procedure was used.[28] A stirred mixture of **1** (4.44 g, 6 mmol), the appropriate electrophile $RCH_2X$ (1 equiv), and NaH (1 equiv) (2 equiv in the case of 2-(chloromethyl)pyridine or 2-(chloromethyl)quinoline hydrochlorides) in anhydrous toluene was heated at 70 °C for 7−12 h. The reaction was monitored by TLC (cyclohexane−AcOEt 5:1), and quenched by addition of MeOH (1 mL) as soon as the di-*O*-alkylated product(s) started to form. The solvent was evaporated in vacuo, and the residue was partitioned between 1 N HCl and $CHCl_3$. The organic extract was washed with water, dried ($MgSO_4$), and concentrated. The solid was treated with AcOEt (30−40 mL) to leave unreacted **1** as an insoluble material. The solution was concentrated to dryness and subjected to column chromatography on silica gel, by eluting with cyclohexane−$CH_2Cl_2$ 1:1 (to remove residual **1**), and then with $CH_2Cl_2$. The fractions containing **2** were further purified by recrystallization from an appropriate solvent.

***p-tert*-Butyl-25-[(3,5-dinitrobenzyl)oxy]-26,27,28-trihydroxycalix[4]arene (2c)**: 32% yield; mp 143−145 °C (MeOH); $^1$H NMR $\delta$ 1.21, (s, 36 H), 3.44, 4.22 (d, $J$ = 13.8 Hz, 4 H), 3.50, 4.25 (d, $J$ = 13.0 Hz, 4 H), 5.29 (s, 2 H), 7.00, 7.06 (ABq, $J$ = 2.4 Hz, 4 H), 7.04, 7.15 (s, 2 H each), 9.10 [m, 3 H], 9.14 and 9.66 (s, ratio 2:1, 3 H); FAB (+) MS, *m/z* 825 (100, $MH^+$). Anal. Calcd for $C_{51}H_{60}N_2O_8$: C, 73.89; H, 7.29; N, 3.38. Found: C, 73.86; H, 7.49; N, 3.60.

***p-tert*-Butyl-25-($\beta$-naphthylmethyloxy)-26,27,28-trihydroxycalix[4]arene (2d)**: 30% yield; mp 140−143 °C (2-propanol); $^1$H NMR $\delta$ 1.19, 1.20, 1.22 (s, ratio 2:1:1, 36 H), 3.38, 4.20 (d, $J$ = 13.7 Hz, 4 H), 3.41, 4.39 (d, $J$ = 12.9 Hz, 4 H), 5.33 (s, 2 H), 6.95, 7.04 (ABq, $J$ = 2.4 Hz, 4 H), 7.02, 7.12 (s, 2 H each), 7.5−8.1 (m, 7 H), 9.46, and 10.03 (s, ratio 2:1, 3 H); FAB (+) MS, *m/z* 785 (100, $MH^+$). Anal. Calcd for $C_{55}H_{60}O_4 \cdot 1.5H_2O$: C, 80.94; H, 8.27. Found: C, 81.17; H, 8.17.

***p-tert*-Butyl-25-[2-(quinolylmethyl)oxy]-26,27,28-trihydroxycalix[4]arene (2e)**: 38% yield; mp 170−173 °C (MeCN); $^1$H NMR $\delta$ 1.21, 1.23 (s, ratio 3:1, 36 H), 3.43 (bd, $J$ = 13.0 Hz, 4 H), 4.28, 4.63 (d, $J$ = 13.6 and 12.9 Hz, respectively, 2 H each) 5.52 (s, 2 H), 6.98, 7.09 (ABq, $J$ = 2.3 Hz, 4 H), 7.06, 7.12 (s, 2 H each), 7.59 (bt, $J$ = 7.2 Hz, 1 H), 7.75 (bt, $J$ = 6.9 Hz, 1 H), 7.90 (d, $J$ = 8.4 Hz, 2 H), 8.24 (d, $J$ = 8.4 Hz, 1 H), 8.34 (d, $J$ = 8.5 Hz, 1 H), and 9.95 (bs, 3 H); FAB (+) MS, *m/z* 786 (100, $MH^+$). Anal. Calcd for $C_{54}H_{59}NO_4 \cdot H_2O$: C, 81.63; H, 7.55; N, 1.76. Found: C, 81.76; H, 7.88; N, 1.92.

**Reaction of Monoalkylated Calix[4]arene 2a with Triethylene Glycol Ditosylate. General Procedure**. A solution of **2a** (0.44 g, 0.6 mmol) in DMF (20 mL) was slowly added to a stirred solution of triethylene glycol ditosylate (0.275 g, 0.6 mmol) in DMF (30 mL) in the presence of $K_2CO_3$ (0.83 g, 6 mmol). The mixture was kept at 60−70 °C under stirring for 2 days. After evaporation of the solvent, the residue was partitioned between water and $CH_2Cl_2$. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was redissolved in $CH_2Cl_2$ and column chromatographed on silica gel, by eluting with a gradient of AcOEt in cyclohexane to give compounds **3a**−**5a**.

**3-[2-(Pyridylmethyl)oxy]-*p-tert*-butylcalix[4]arene-(1,2)-crown-4 (3a)**: 38% yield; mp 278−281 °C (MeOH); $R_f$ = 0.34 (cyclohexane−AcOEt 5:1); $^1$H NMR $\delta$ 0.79, 0.88, 1.33, 1.34 (s, 9 H each), 3.17, 3.23, 3.29 (d, $J$ = 12.6, 13.4, and 13.4 Hz, respectively, ratio 2:1:1, 4 H), 3.57−4.35 (m, 12 H), 4.26, 4.31, 4.49, 4.50 (d, $J$ = 13.5, 12.7, 13.0, and 12.4 Hz, respectively, 1 H each), 4.94, 5.00 (ABq, $J$ = 11.9 Hz, 2 H), 5.84 (s, 1 H), 6.48 (s, 2 H), 6.58, 6.64 (ABq, $J$ = 2.4 Hz, 2 H), 7.05, 7.08 (ABq, $J$ = 2.4 Hz, 2 H), 7.14, 7.16 (ABq, $J$ = 2.5 Hz, 2 H), 7.27 (m, 1 H), 7.78 (td, $J$ = 7.6, 1.8 Hz, 1 H), 7.88 (d, $J$ = 7.7 Hz, 1 H), and 8.62 (d, $J$ = 4.1 Hz, 1 H); $^{13}$C NMR $\delta$ 30.36, 31.18, 31.51 (t), 31.02, 31.68 (q), 33.84, 34.14(s), 69.40, 69.77, 70.19, 71.34, 72.50, 75.31, 78.68 (t), 122.76, 123.04, 124.80, 125.12, 125.41, 125.62, 125.76 (d), 128.35, 129.53, 131.56, 131.89, 132.02, 132.71, 135.72, 135.93 (s), 136.64 (d), 141.50, 145.27, 145.85 (s), 149.20 (d), 150.45, 150.71, 151.64, 153.55, and 157.58 (s); FAB (+) MS, *m/z* 854 (100, $MH^+$). Anal. Calcd for $C_{56}H_{71}NO_6$: C, 78.74; H, 8.38; N, 1.64. Found: C, 79.14; H, 8.54; N, 1.79.

**Calix[4]arene dimer (4a)**: ca. 1% yield; $R_f$ = 0.31 (cyclohexane−AcOEt 2:1); $^1$H NMR $\delta$ 0.93, 0.96, 1.28 (s, ratio 1:1:2, 72 H), 3.26, 3.28 (d, $J$ = 13.2 and 13.1 Hz, respectively, 4 H each), 3.81 (s, 4H), 3.91 (t, $J$ = 4.5 Hz, 4H), 4.04 (dd, $J$ = 5.4, 3.6 Hz, 4H), 4.28, 4.30 (d, $J$ = 12.9 and 13.1 Hz, respectively, 4 H each), 5.11 (s, 4 H), 6.77, 6.78, 7.04 (s, ratio 1:1:2, 16 H), 7.19 (m, 2 H), 7.22 (s, 4 H), 7.83 (td, $J$ = 7.7, 1.7 Hz, 2 H), 8.20 (d, $J$ = 7.7 Hz, 2 H), and 8.55 (dt, $J$ = 5.0, 0.9 Hz, 2 H); $^{13}$C NMR $\delta$ 30.99, 31.71 (q), 31.52 (t), 33.81, 33.92 (s), 70.03, 70.51, 70.63, 71.04, 75.37, 78.21 (t), 121.63, 122.70, 125.03, 125.52, 125.54, 125.60 (d), 127.59, 127.76, 132.44, 132.51 (s), 137.13 (d), 141.42, 146.97, 147.01 (s), 148.89 (d), 149.50, 149.72, 150.60, and 157.48 (s); FAB (+) MS, *m/z* 1593 (100, $MH^+$). Anal. Calcd for $C_{106}H_{132}N_2O_{10}$: C, 79.86; H, 8.35; N, 1.76. Found: C, 59.61; H, 8.45; N, 1.80.

**Syn−distal *p-tert*-butyl-25-[(2-pyridylmethyl)oxy]-27-[(1-hydroxy-3,6-dioxaoct-8-yl)oxy]-26,28-dihydroxycalix[4]arene (5a)**: 11% yield; mp 111−113 °C; $R_f$ = 0.15 (cyclohexane−AcOEt 1:1); $^1$H NMR $\delta$ 0.93, 0.95, 1.29 (s, ratio 1:1:2, 36 H), 2.85, 2.89 (s, 3 H each), 3.31 (d, $J$ = 12.8 Hz, 4 H), 3.52 (m, 2 H), 3.61 (m, 2 H), 3.65 (m, 2 H), 3.75 (t, $J$ = 5.4 Hz, 1 H), 3.84 (dd, $J$ = 5.6, 3.7 Hz, 2 H), 3.99 (t, $J$ = 4.5 Hz, 2 H), 4.16 (dd, $J$ = 5.5, 3.5 Hz, 2 H), 4.32 (t, $J$ = 12.5 Hz, 4 H), 5.15 (s, 2 H), 6.78, 6.79, 7.06 (s, ratio 1:1:2, 8 H), 7.19 (s, 2 H), 7.28 (m, 1 H), 7.86 (td, $J$ = 7.7, 1.7 Hz, 1 H), 7.99 (s, 1 H), 8.18 (d, $J$ = 7.8 Hz, 1 H), and 8.61 (dt, $J$ = 4.9, 0.8 Hz, 1 H); FAB (+) MS, *m/z* 872 (100, $MH^+$). Anal. Calcd for $C_{56}H_{73}NO_7 \cdot C_3H_7NO$: C, 74.96; H, 8.53; N, 2.96. Found: C, 74.68; H, 8.45; N, 2.48.

**Reaction of 2a with Tetraethylene Glycol Ditosylate**. The reaction was carried out under the above-described procedure. Usual workup, followed by chromatography afforded the following components:

**3-[2-(Pyridylmethyl)oxy]-*p-tert*-butylcalix[4]arene-(1,2)-crown-5 (3b)**: 35% yield; mp 256−258 °C (MeOH); $R_f$ = 0.27 (cyclohexane−AcOEt 5:1); $^1$H NMR $\delta$ 0.77, 0.88, 1.33, 1.34 (s, 9 H each), 3.17, 3.20, 3.22, 3.26 (d, $J$ = 12.7−13.2 Hz, 1 H each), 3.48−4.34 (m, 16 H), 4.36, 4.39, 4.42, 4.53 (d, $J$ = 12.6, 12.7, 13.5, and 13.0 Hz, respectively, 1 H each), 4.90, 5.03 (ABq, $J$ = 12.3 Hz, 2 H), 5.96 (s, 1 H), 6.45 (s, 2 H), 6.59, 6.61 (ABq, $J$ = 2.5 Hz, 2 H), 7.06, 7.09 (ABq, $J$ = 2.4 Hz, 2 H), 7.13, 7.15 (ABq, $J$ = 2.5 Hz, 2 H), 7.26 (m, 1 H), 7.77 (td, $J$ = 7.7, 1.7 Hz, 1 H), 7.95 (d, $J$ = 7.8 Hz, 1 H), and 8.61 (d, $J$ = 4.5 Hz, 1 H); $^{13}$C NMR $\delta$ 30.92, 31.28 (t), 31.03, 31.68, 31.77 (q), 33.61, 33.76, 33.85, 34.15 (s), 68.41, 69.52, 69.81, 70.38, 70.95, 71.71, 72.15, 76.26, 78.51 (t), 122.62, 122.86, 124.76, 124.86, 124.94, 125.06, 125.37, 125.56, 125.80 (d), 128.47, 129.56, 131.67, 131.82, 131.87, 132.54, 135.58, 136.01 (s), 136.70 (d), 141.33, 145.10 145.85, 145.93, (s), 149.13 (d), 150.73, 150.81, 152.03, 153.61, and 157.97 (s); FAB (+) MS, *m/z* 898 (100, $MH^+$). Anal. Calcd for $C_{58}H_{75}NO_7$: C, 77.56; H, 8.42; N, 1.56. Found: C, 77.89; H, 8.61; N, 1.72.

**Calix[4]arene dimer (4b)**: 2% yield; mp 130−132 °C (MeOH); $R_f$ = 0.21 (cyclohexane−AcOEt 2:1); $^1$H NMR $\delta$ 097, 1.02, 1.27 (s, ratio 1:1:2, 72 H), 3.31 (t, $J$ = 12.3 Hz, 8 H), 3.70 (m, 8 H), 4.00 (dd, $J$ = 4.4, 4.0 Hz, 4 H), 4.17 (dd, $J$ = 4.4, 3.7 Hz, 4 H), 4.32, 4.34 (d, $J$ = 13.0 Hz, 4 H each), 5.17 (s, 4 H), 6.82, 6.89 (s, ratio 1:1, 4 H each), 7.03, 7.05 (ABq, $J$ = 2.4 Hz, 8 H), 7.28 (m, 2 H), 7.79 (s, 4 H), 7.85 (td, $J$ = 7.7, 1.8 Hz, 2 H), 8.10 (d, $J$ = 7.9 Hz, 2 H), and 8.61 (dt, $J$ = 4.9, 0.8 Hz, 2

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H); $^{13}$C NMR $\delta$ 28.69, 31.61 (t), 31.01, 31.05, 31.66 (q), 33.81 (s), 61.81, 69.81, 73.06, 75.07, 78.65 (t), 122.46, 122.71, 125.01, 125.27, 125.62, 125.73 (d), 127.41, 128.14, 132.67, 132.97 (s), 136.96 (d), 141.74, 146.89, 147.38 (s), 148.93 (d), 149.09, 150.10, and 157.16 (s); FAB (+) MS, *m/z* 1637 (100, $MH^+$). Anal. Calcd for $C_{108}H_{106}N_2O_{11}$: C, 79.18; H, 8.37; N, 1.71. Found: C, 77.57; H, 8.60; N, 1.78.

**Syn−distal *p-tert*-butyl-25-[(2-pyridylmethyl)oxy]-27-[(1-hydroxy-3,6,9-trioxaundec-11-yl)oxy]-26,28-dihydroxycalix[4]arene (5b)**: pale yellow oil, 8% yield; $R_f$ = 0.04 (cyclohexane−AcOEt 1:1); $^1$H NMR $\delta$ 0.94, 0.95, 1.29 (s, ratio 1:1:2, 36 H], 2.87, 2.94 (s, 3 H each), 3.31 (d, $J$ = 13.0 Hz, 4 H), 3.50−3.70 (m, 11 H), 3.83 (dd, $J$ = 5.6, 3.6 Hz, 2 H), 3.99 (t, $J$ = 4.6 Hz, 2 H), 4.16 (dd, $J$ = 5.7, 3.5 Hz, 2 H), 4.30, 4.34 (d, $J$ = 12.7 and 12.8 Hz, respectively, 2 H each), 5.14 (s, 2 H), 6.79, 7.06 (s, 4 H each), 7.21 (s, 2 H), 7.27 (m, 1 H), 7.87 (td, $J$ = 7.7, 1.8 Hz, 1 H), 8.01 (s, 1 H), 8.23 (d, $J$ = 7.9 Hz, 1 H), and 8.60 (ddd, $J$ = 4.9, 1.7, 0.9 Hz, 1 H); FAB (+) MS, *m/z* 916 (100, $MH^+$). Anal. Calcd for $C_{58}H_{77}NO_8 \cdot C_3H_7NO$: C, 74.05; H, 8.56; N, 2.83. Found: C, 73.82; H, 8.38; N, 2.53.

**Reaction of 2a with Pentaethylene Glycol Ditosylate**. The reaction was carried out under the above-described procedure. Usual workup, followed by chromatography afforded the following components:

**3-[2-(Pyridylmethyl)oxy]-*p-tert*-butylcalix[4]arene-(1,2)-crown-6 (3c)**: 41% yield; mp 173−175 °C (MeOH); $R_f$ = 0.09 (cyclohexane−AcOEt 5:1); $^1$H NMR $\delta$ 0.80, 0.86, 1.33, 1.34 (s, 9 H each), 3.16, 3.20, 3.22, 3.29 (d, $J$ = 12.7, 12.4, 13.0, and 13.4 Hz, respectively, 1 H each), 3.30−4.21 (m, 20 H), 4.25, 4.40, 4.44, 4.47 (d, $J$ = 13.2, 13.0, 14.0, and 12.5 Hz, respectively, 1 H each), 4.91, 5.06 (ABq, $J$ = 12.6 Hz, 2 H), 5.67 (s, 1 H), 6.50 (s, 2 H), 6.58 (t, $J$ = 2.9 Hz, 2 H), 7.06, 7.08 (ABq, $J$ = 2.4 Hz, 2 H), 7.13, 7.15 (ABq, $J$ = 2.5 Hz, 2 H), 7.25 (m, 1 H), 7.79 (td, $J$ = 7.7, 1.8 Hz, 1 H), 8.00 (d, $J$ = 7.9 Hz, 1 H), and 8.60 (dt, $J$ = 4.8, 0.9 Hz, 1 H); $^{13}$C NMR $\delta$ 31.33, 31.48 (t), 31.01, 31.67, 31.74 (q), 33.65, 33.72, 33.86, 34.14 (s), 69.30, 69.69, 70.34, 70.59, 70.72, 71.06, 71.58, 74.93, 78.41 (t), 122.56, 124.87, 125.10, 125.26, 125.61, 125.66 (d), 128.73, 129.67, 131.54, 131.83, 132.08, 132.70, 135.65, 135.96 (s), 136.80 (d), 141.66, 145.35, 145.83 (s), 149.03 (d), 150.59, 150.80, 151.61, 153.59, and 157.94 (s); FAB (+) MS, *m/z* 942 (100, $MH^+$). Anal. Calcd for $C_{60}H_{79}NO_8$: C, 76.48; H, 8.45; N, 1.49. Found: C, 76.28; H, 8.62; N, 1.64.

**Pyridinium trifluoroacetate 3c·H$^+$**: $^1$H NMR ($CDCl_3$ with 1 drop $CD_3OD$) $\delta$ 0.80, 0.89, 1.30, 1.31 (s, 9 H each), 3.18, 3.19, 3.22, 3.31 (d, $J$ = 11.7, 13.1, 11.9, and 13.5 Hz, respectively, 1 H each), 3.4−4.2 (m, 20 H), 4.19, 4.31, 4.33, 4.47 (d, $J$ = 13.6, 12.9, 12.6 and 12.5 Hz, respectively, 1 H each), 5.02, 5.26 (ABq, $J$ = 14.3 Hz, 2 H), 6.50, 6.52 (ABq, $J$ = 2.5 Hz, 2 H), 6.63, 6.66 (ABq, $J$ = 2.4 Hz, 2 H), 7.03, 7.07 (ABq, $J$ = 2.4 Hz, 2 H), 7.11, 7.125 (ABq, $J$ = 2.4 Hz, 2 H), 7.55 (m, 1 H), 8.20 (td, $J$ = 7.9, 1.6 Hz, 1 H), 8.42 (d, $J$ = 7.8 Hz, 1 H), and 8.78 (dd, $J$ = 4.5, 0.9 Hz, 1 H).

**Calix[4]arene dimer (4c)**: 5% yield; mp 264−266 °C ($CH_2Cl_2$-MeOH); $R_f$ = 0.28 (cyclohexane−AcOEt 1:1); $^1$H NMR $\delta$ 0.94, 0.95, 1.28 (s, ratio 1:1:2, 72 H), 3.30, 3.31 (d, $J$ = 13.2 and 13.0 Hz, respectively, 4 H each), 3.49 (s, 4H), 3.58 (dd, $J$ = 5.6, 3.8 Hz, 4H), 3.79 (dd, $J$ = 5.6, 3.8 Hz, 4H), 3.97 (t, $J$ = 4.7 Hz, 4H), 4.14 (t, $J$ = 4.7 Hz, 4H), 4.29, 4.33 (d, $J$ = 13.0 Hz, 4 H each), 5.13 (s, 4 H), 6.79, 7.05 (s, 8 H each), 7.20 (s, 4 H), 7.26 (m, 2 H), 7.86 (td, $J$ = 7.7, 1.8 Hz, 2 H), 8.23 (d, $J$ = 7.9 Hz, 2 H), and 8.58 (dt, $J$ = 4.8, 0.8 Hz, 2 H); $^{13}$C NMR $\delta$ 30.99, 31.71 (q), 31.52 (t), 33.81, 33.92 (s), 70.03, 70.51, 70.63, 71.04, 75.37, 78.21 (t), 121.63, 122.70, 125.03, 125.52, 125.54, 125.60 (d), 127.59, 127.76, 132.44, 132.51 (s), 137.13 (d), 141.42, 146.97, 147.01 (s), 148.89 (d), 149.50, 149.72, 150.60, and 157.48 (s); FAB (+) MS, *m/z* 1703 (100, $MNa^+$). Anal. Calcd for $C_{110}H_{140}N_2O_{12} \cdot 1.5H_2O$: C, 77.29; H, 8.43; N, 1.64. Found: C, 77.15; H, 8.42; N, 1.82.

**Syn−distal *p-tert*-butyl-25-[(2-pyridylmethyl)oxy]-27-[(1-hydroxy-3,6,9,12-tetraoxatetradec-14-yl)oxy]-26,28-dihydroxycalix[4]arene (5c)**: pale yellow oil, 4% yield; $R_f$ = 0.05 (cyclohexane−AcOEt 1:1); $^1$H NMR $\delta$ 0.96, 0.97, 1.28 (s, ratio 1:1:2, 36 H), 3.31, 3.32 (d, $J$ = 13.2 Hz, 2 H each), 3.50−3.66 (m, 13 H), 3.70 (dd, $J$ = 5.4, 3.6 Hz, 2 H), 3.83 (dd, $J$ = 5.5, 3.7 Hz, 2 H), 3.99 (t, $J$ = 4.5 Hz, 2 H), 4.16 (dd, $J$ = 5.3, 3.8 Hz, 2 H), 4.30, 4.34 (d, $J$ = 13.0 Hz, 2 H each), 5.14 (s, 2 H), 6.82, 7.06 (s, 4 H each), 7.27 (s, 2 H), 7.29 (m, 1 H), 7.89 (td, $J$ = 7.7, 1.8 Hz, 1 H), 8.24 (d, $J$ = 7.7 Hz, 1 H), and 8.60 (d, $J$ = 4.0 Hz, 1 H); FAB (+) MS, *m/z* 960 (100, $MH^+$). Anal. Calcd for $C_{60}H_{81}NO_9$: C, 75.04; H, 8.50; N, 1.46. Found: C, 75.26; H, 8.34; N, 1.55.

**Reaction of 2b with Pentaethylene Glycol Ditosylate**. The reaction was carried out under the above-described procedure. Usual workup, followed by chromatography afforded the following components:

**3-(Benzyloxy)-*p-tert*-butylcalix[4]arene-(1,2)crown-6 (3d)**: 26% yield; mp 176−178 °C (MeOH); $R_f$ = 0.09 (cyclohexane−AcOEt 5:1); $^1$H NMR $\delta$ 0.81, 0.83, 1.33, 1.34 (s, 9 H each), 3.14, 3.15, 3.23, 3.26 (d, $J$ = 12.7, 12.6, 13.4, and 13.0 Hz, respectively, 1 H each), 3.18−4.17 (m, 20 H), 4.25, 4.34, 4.43, 4.44 (d, $J$ = 13.2, 12.5, 13.1, and 12.5 Hz, respectively, 1 H each), 4.81 (s, 2 H), 5.62 (s, 1 H), 6.51, 6.54 (s, 2 H each), 7.05, 7.07 (ABq, $J$ = 2.4 Hz, 2 H), 7.13 (t, $J$ = 2.8 Hz, 2 H), 7.30−7.42 (m, 3 H), and 7.55−7.58 (m, 2 H); $^{13}$C NMR $\delta$ 30.87, 31.34 (t), 31.00, 31.66, 31.74 (q), 33.65, 33.83, 34.12 (s), 69.14, 69.69, 70.35, 70.55, 70.68, 70.95, 71.56, 74.78, 78.14 (t), 124.71, 124.77, 124.93, 124.96, 125.03, 125.09, 125.55, 125.62, 127.91, 128.46, 128.95 (d), 128.86, 129.28, 131.82, 131.88, 132.19, 132.50, 135.80, 135.88, 137.52 (s), 141.45, 145.34, 145.52, 145.77, 150.61, 151.06, 151.37, and 153.84 (s); FAB (+) MS, *m/z* 941 (100, $MH^+$). Anal. Calcd for $C_{61}H_{80}O_8$: C, 77.83; H, 8.57. Found: C, 77.63; H, 8.58.

**Calix[4]arene dimer (4d)**: 8% yield; mp 148−150 °C ($CH_2Cl_2$-MeOH); $R_f$ = 0.31 (cyclohexane−AcOEt 5:1); $^1$H NMR $\delta$ 0.96, 0.97, 1.27 (s, ratio 1:1:2, 72 H), 3.27 (d, $J$ = 13.0 Hz, 8 H), 3.51 (s, 4H), 3.55 (dd, $J$ = 5.6, 3.6 Hz, 4H), 3.75 (dd, $J$ = 5.6, 3.6 Hz, 4H), 3.91 (t, $J$ = 4.8 Hz, 4H), 4.11 (t, $J$ = 4.8 Hz, 4H), 4.30, 4.33 (d, $J$ = 12.7 and 13.0 Hz, respectively, 8 H each), 5.00 (s, 4 H), 6.78, 6.80, 7.03 (s, ratio 1:1:2, 16 H), 7.32 (s, 4 H), 7.36−7.44 (m, 6 H), and 7.64−7.67 (m, 4 H); $^{13}$C NMR $\delta$ 31.02, 31.71 (q), 31.57 (t), 33.79, 33.93 (s), 69.92, 70.44, 70.65, 71.08, 75.49, 78.21 (t), 124.95, 125.04, 125.47, 125.51, 127.91, 128.07, 128.50 (d), 127.71, 132.63, 132.69, 137.06 (s), 141.24, 146.81, 146.87, 149.63, 149.82, and 150.67 (s); FAB (+) MS, *m/z* 1701 (100, $MNa^+$). Anal. Calcd for $C_{112}H_{142}O_{12} \cdot 1.5H_2O$: C, 78.79; H, 8.56. Found: C, 78.65; H, 8.51.

**Syn−distal *p-tert*-Butyl-25-(benzyloxy)-27-[(1-hydroxy-3,6,9,12-tetraoxatetradec-14-yl)oxy]-26,28-dihydroxycalix-[4]arene (5d)**: 18% yield; pale yellow oil, which crystallizes on standing, mp 50−52 °C; $R_f$ = 0.15 (cyclohexane−AcOEt 1:1); $^1$H NMR $\delta$ 0.957, 0.959, 1.28 (s, ratio 1:1:2, 36 H), 2.85, 2.88 (s, 3 H each), 3.27 (d, $J$ = 13.2 Hz, 4 H), 3.53−3.80 (m, 17 H), 3.93 (t, $J$ = 4.6 Hz, 2 H), 4.12 (t, $J$ = 4.6 Hz, 2 H), 4.30, 4.32 (d, $J$ = 13.0 and 13.1 Hz, respectively, 2 H each), 5.01 (s, 2 H), 6.79, 6.80, 7.04 (s, ratio 1:1:2, 8 H), 7.32 (s, 2 H), 7.37−7.44 (m, 3 H), 7.67 (d, $J$ = 6.8 Hz, 2 H), and 7.99 (s, 1 H); FAB (+) MS, *m/z* 959 (100, $MH^+$). Anal. Calcd for $C_{61}H_{82}O_9 \cdot C_3H_7NO$: C, 74.46; H, 8.69; N, 1.36. Found: C, 74.58; H, 8.70; N, 1.26.

**3-[2-(Pyridylmethyl)oxy]-4-propoxy-*p-tert*-butylcalix-[4]arene-(1,2)crown-5 (7)**: A mixture of **3b** (90 mg, 0.1 mmol) and NaH (5 mg, 0.2 mmol) in anhydrous THF (5 mL) was stirred at rt for 0.5 h. *n*-Propyl iodide (34 mg, 0.2 mmol) was then added, and the reaction mixture was refluxed for 6 h. The excess NaH was destroyed by addition of MeOH (0.5 mL), and the solvent was evaporated. The residue was partitioned between water and $CH_2Cl_2$. The organic layer was washed with 1 N $Na_2S_2O_4$ and then with water, dried ($MgSO_4$), and evaporated. The crude product was passed through a short column (neutral alumina, eluent $Et_2O$). Evaporation of the solvent afforded propyl ether **7** (66 mg, 70%) as colorless crystals: mp 221−224 °C (hexane); $^1$H NMR $\delta$ 0.81 (t, $J$ = 7.5 Hz, 3 H), 1.044, 1.051, 1.139, 1.145 (s, 9 H each), 1.85 (m, 2 H), 3.12, 3.13, 3.14, 3.16 (d, $J$ = 12.3−12.7, 1 H each), 3.57−4.12 (m, 18 H), 4.37, 4.41, 4.45, 4.53 (d, $J$ = 12.3−12.7 Hz, 1 H each), 5.00, 5.07 (ABq, $J$ = 12.1 Hz, 2 H), 6.72−6.90 (m, 8 H), 7.28 (ddd, $J$ = 7.7, 4.8, 1.2 Hz, 1 H), 7.89 (td, $J$ = 7.7, 1.8 Hz, 1 H), 8.06 (d, $J$ = 7.9 Hz, 1 H), and 8.61 (dd, $J$ = 5.0, 1.0 Hz, 1 H); $^{13}$C NMR $\delta$ 10.11 (q), 22.96 (t), 30.69, 30.92, 30.96, 31.11 (t,), 31.37, 31.49 (q), 33.76, 33.78, 33.87 (s), 70.06, 70.37, 70.57, 70.66, 70.96, 71.03, 73.24, 73.72, 76.85, 78.37 (t), 122.45,

123.58, 124.74, 124.98, 125.00, 125.03, 125.05, 125.09, 125.23 (d), 133.13, 133.28, 133.34, 133.67, 133.90, 134.17, 134.20, 134.42 (s, bridgehead-C), 136.59 (d), 144.35, 144.45, 144.62, 144.68 (s), 149.13 (d), 152.80, 153.18, 153.36, 153.60, and 158.35 (s); FAB (+) MS, *m*/*z* 940 (100, $MH^+$). Anal. Calcd for $C_{61}H_{81}NO_7$: C, 77.92; H, 8.68; N, 1.49. Found: C, 77.55; H, 8.38; N, 1.60.

**Complexation Studies.** Extraction experiments were performed using the Pedersen method:[29] equal volumes (5 mL) of the aqueous phase ($2.5 \times 10^{-4}$ M metal picrate in bidistilled water) and the organic phase ($2.5 \times 10^{-4}$ M calixarene in $CH_2Cl_2$) were placed in stoppered glass tubes and shaken with a mechanical vibrator for 4 min and then stirred magnetically for 1 h. The percentages of cation extracted (%*E*) were calculated from the spectrophotometric determination at 355 nm of the concentration of picrate anion remaining in the aqueous phase after separation of the two phases. The experimental details and the preparation of the metal picrates have been described earlier.[30]

Stability constants $\beta$ in MeOH, referring to the equilibrium $M^{n+} + LH \rightleftharpoons MLH^{n+}$ (LH being the phenolic form of the ligand) were determined by UV absorption spectrophotometry or by pH-metry according to the procedures already described.[30,31] The ionic strength was maintained at 0.01 by using $Et_4NCl$ or $Et_4NClO_4$. The metal salts used were the alkali chlorides and silver and zinc perchlorates.

Association constants $K_a$ of ligands **3a**−**c** with $Ag^+Pic^-$ in THF, corresponding to the equilibrium $Ag^+Pic^- + LH \rightleftharpoons Ag^+LHPic^-$, were determined by following the change in the absorption spectra of solutions of the metal picrate in this solvent upon addition of increasing amounts of ligand.

Spectrophotometric and pH-metric data were treated with the program Sirko.[32]

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