Synthesis, Structural Characterization, and Alkali-Metal Complexation of the Six Possible (1,3)- and (1,2)-Bridged *p-tert*-Butylcalix[4]crown-5 Conformers Bearing α-Picolyl Pendant Groups

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Complementary synthetic strategies leading to the six possible regioisomers and conformational isomers of bis[(α-picolyl)oxy]-*p-tert*-butylcalix[4]crown-5 (**1**−**6**) are reported. The overall conformation of **1**−**6** was deduced by NMR spectroscopy and further proven by single-crystal X-ray analysis for (1,3)-bridged cone and (1,2)-bridged 1,2-alternate conformers **1** and **6**. Compounds **1**−**6** form 1:1 complexes with alkali-metal cations. The complexation sites and solution structures for Na^+ and K^+ complexes have been determined by ^1H NMR titration experiments. The binding affinities of ligands **1**−**6** for alkali-metal ions have been assessed by phase transfer and stability constant measurements using spectrophotometric, potentiometric, and calorimetric techniques. All 1,3-bridged calixcrowns **1**−**3** show a strong affinity for K^+ (partial cone **2** and 1,3-alternate **3** also for Rb^+), conformer **3** being slightly more selective than the naturally occurring ionophore valinomycin. Conversely, 1,2-bridged calixcrowns **4**−**6** are less efficient and their selectivities vary from K^+ for cone **4** to both K^+ and Rb^+ for partial cone **5** and to Cs^+ for 1,2-alternate conformer **6**.

Introduction

Calixcrowns are macrobicyclic molecules in which a monocyclic calixarene structure[1] is linked—via its phenolic oxygens—to a cyclic polyether moiety. The earliest example of this family, i.e. (1,3)-*p-tert*-butylcalix[4]-crown-6-diol, was reported in 1983,[2] and since then the synthetic strategies for the attainment of calixcrowns have developed very fast,[3] owing to their proclivity to selectively bind alkali- and alkali-earth-metal cations. Nowadays selective polyether bridging at the lower rim of calixarenes is feasible not only for the smallest calix-[4]arene members but even for the larger calix[*n*]arenes (n = 5,[4] 6,[5] and 8[6]).

Complexation studies of calixcrowns with alkali-metal cations have mainly been focused on dialkylated (1,3)-bridged calix[4]crown ethers. Crown-4 derivatives in a fixed cone or partial cone conformation show the highest ($>10^5$) Na^+/K^+ selectivity,[7] while the larger (1,3)-*p-tert*-butylcalix[4]crown-5 derivatives in a partial cone conformation show a reverse K^+/Na^+ selectivity.[8] For the analogous crown-5 derivatives devoid of *p-tert*-butyl substituents, and locked in the 1,3-alternate conformation, the K^+/Na^+ selectivity is even higher than that of valinomycin.[9] Besides, conformationally locked 1,3-alternate calix[4]crown-6 derivatives exhibit very high ($>10^5$) Cs^+/Na^+ selectivity.[10]

Notably, very little is known about the ligating ability of the corresponding (1,2)-bridged regioisomers,[11] probably because they are more difficult to synthesize.[12] The only complexation data so far reported in the literature refer to a (1,2)-calix[4]bis(crown-5)[13] and to inherently chiral mono-*O*-alkylated (1,2)-*p-tert*-butylcalix[4]crowns.[14]

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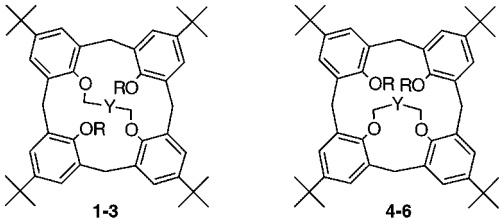
The introduction of (poly)pyridino side arms into diazacrown ethers has been shown to enhance, in comparison with the parent crown ethers, their cation binding ability toward "hard" metal cations via side arm participation, despite the notorious preference of the heterocyclic ring nitrogen for "soft" metal cations.[15] These observations sparked our interest in the design and synthesis of calix[4]crown ethers bearing *N*-heterocyclic pendant groups and in the investigation of their coordination behavior toward alkali-metal ions.

In this paper we report the synthesis, conformational features, and binding properties of the six possible bis-[(α-picolyl)oxy]-*p-tert*-butylcalix[4]crown-5 isomers **1**−**6**,



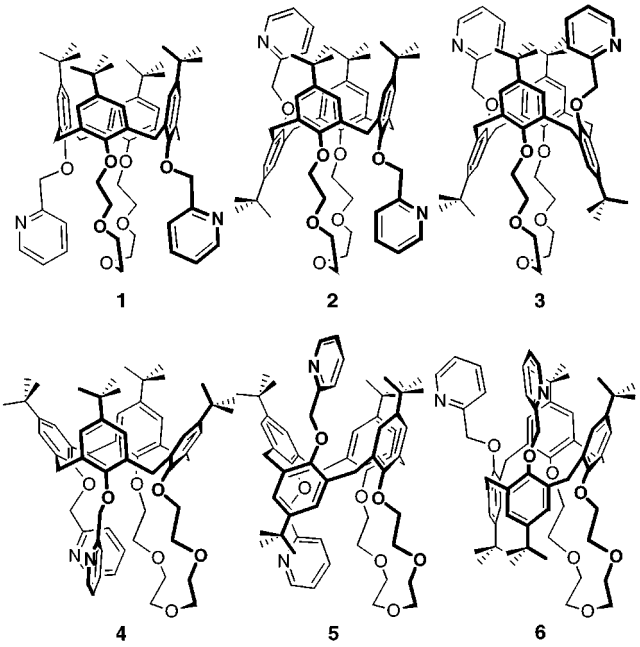
R = α-picolyl; Y = $(CH_2OCH_2)_3$

differing in the position of the bridge [(1,2)- or (1,3)-] and conformation [cone, partial cone, (1,2)- or (1,3)-alternate] of the calix[4]arene skeleton (Chart 1). Solution structures of Na^+ and K^+ complexes with **1**−**6** have been investigated by NMR spectroscopy. The binding affinities of these new ligands for alkali-metal ions and their thermodynamic parameters of complexation have been determined by two-phase solvent extraction, UV spectroscopy, potentiometric, and calorimetric studies.

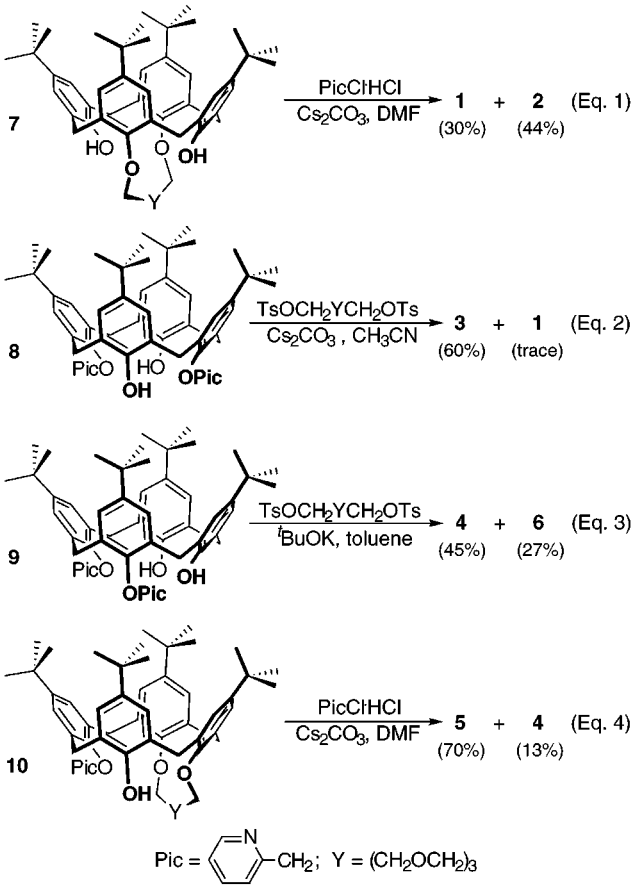
Results and Discussion

Synthesis and Conformational Features of Ligands 1−**6**. The four complementary synthetic strategies leading to the different bis[(α-picolyl)oxy]-*p-tert*-butylcalix-[4]crown-5 conformers **1**−**6** are shown in Scheme 1. The known[8a,16] (1,3)-*p-tert*-butylcalix[4]crown-5-diol precursor **7** was obtained in 50% yield by reaction of *p-tert*-butylcalix[4]arene with tetraethylene glycol ditosylate (TGD, 1 equiv) and K_2CO_3 in refluxing CH_3CN, by adapting a procedure described by Shinkai for the synthesis of the (1,3)-*p*-H-calix[4]crown-4 homologue.[17] Exhaustive alkylation of **7** with an excess of 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl) and Cs_2CO_3 in dry *N*,*N*-dimethylformamide (DMF) at 70 °C afforded dialkylated cone **1** (30%) and partial cone **2** (44%) conformers (eq 1). On the other hand, the 1,3-alternate conformer **3** was obtained in 60% yield by reacting *distal* bis[(α-picolyl)oxy]-*p-tert*-butylcalix[4]arene (**8**)[18] with TGD (1 equiv) and Cs_2CO_3 (10 equiv) in refluxing CH_3CN (eq 2).

Chart I



Scheme 1



The 1,2-bridged conformers **4** and **6** were synthesized according to eq 3. Thus, treatment of *proximal* bis[(α-picolyl)oxy]-*p-tert*-butylcalix[4]arene (**9**)[18a,19] with TGD (1.1 equiv) and ^{t}BuOK (2.2 equiv) in dry toluene at 70

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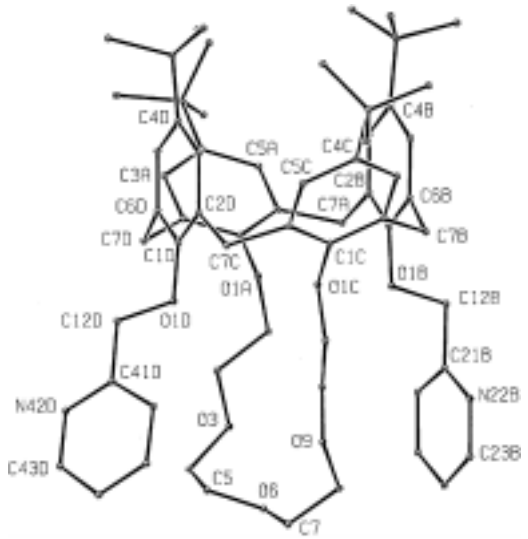

Figure 1. General view of **1** with an indication of our numbering scheme. The atoms are shown as spheres of an arbitrary size and H atoms are omitted.

°C produced dialkylated cone **4** (45%) and 1,2-alternate **6** (27%) conformers.[20] For the synthesis of the remaining inherently chiral partial cone conformer **5** we resorted to the Cs_2CO_3-catalyzed alkylation of mono[(α-picolyl)oxy]-(1,2)-*p*-*tert*-butylcalix[4]crown-5 (**10**)[14,21] with PicCl·HCl in DMF (eq 4). The reaction afforded the desired partial cone **5** in 70% yield, along with cone **4** (13%).

Stereochemical assignments of the six isomers have been made on the basis of distinctive ^{1}H and ^{13}C NMR spectral patterns arising from conformation[1a,22] and from 1,2- or 1,3-bridging of the polyether chain to the calixarene skeleton. The conformations of **1** and **6** have been further proven by single-crystal X-ray analyses.

As expected on the basis of symmetry considerations, (1,3)- and (1,2)-cone regioisomers **1** and **4** show one and three AX systems (ratio 1:1:2), respectively, for the $ArCH_2Ar$ groups, with a $\Delta\delta$ separation > 1 ppm between the *exo* and *endo* geminal protons, and resonances for the pertinent carbon atoms close to 31 ppm. In **1**, the position of the singlets due to the aromatic (6.44 and 7.10 ppm) and ^{t}Bu (0.81 and 1.33 ppm) protons is suggestive of a distorted C_{2v} cone conformation in solution, with the alkylated rings (those bearing the picolyl groups) lying in roughly parallel planes and enjoying mutual diamagnetic shieldings. In contrast, in **4** the aromatic protons (m, 6.79−6.83 ppm) and the two singlets of the ^{t}Bu groups (1.087 and 1.091 ppm) are very close to one another, suggesting a regular cone conformation.

The solid-state structure of **1** is shown in Figure 1. The molecule has a cone conformation with aryl rings A and C (which are linked via the polyether chain) essentially normal to one another (interplanar angle 88.2(3)°); in agreement with ^{1}H NMR observations, aryl rings B and D (which carry the pyridyl substituents) are parallel to one another (interplanar angle 0.2(7)°). The O−C−C−N torsion angles which define the orientation of the pendant pyridyl ring systems are O1B−C12B−C21B−N22B −98(1)° and O1D−C12D−C41D−N42D −147(11)°. In the solid state, the molecules are separated by normal van der Waals contacts.

The partial cone conformation of **2** is substantiated by the presence of three singlets (ratio 2:1:1) for the ^{t}Bu groups, one AB system and two singlets for the aromatic protons (ratio 2:1:1), one AX and one AB system (ratio 1:1) for the $ArCH_2Ar$ groups (with relevant carbon resonances at 30.8 and 39.0 ppm), two singlets (4.25 and 5.13 ppm) for the picolyloxy protons, and two four-spin systems for the *anti*-positioned pendant pyridyl protons (henceforth the abbreviations Py will refer to the pyridine ring adjacent and *syn* to the crown ether moiety and Py′ to the inverted one). The dramatic upfield shifts experienced by one set of the heteroaromatic protons (in particular H3-Py′, resonating at 4.53 ppm in $CDCl_3$) are a clear indication that the inverted picolyl substituent is deeply accommodated inside the hydrophobic cavity generated by the three remaining phenol units, with the ring nitrogen atom *exo* to the calix cavity, in a sort of "self-inclusion" complex. Self-inclusion phenomena of inverted heteroaromatic substituents have been shown to be very common in atropisomeric partial cone calix[4]arenes.[23] Owing to the inherently chiral nature of partial cone regioisomer **5**, the ^{1}H NMR spectral patterns are more complex. At 300 MHz, the spectrum shows four resonances for the ^{t}Bu groups, two well-resolved AX systems and two AB systems (partly buried under the signals of the polyether chain) in the ratio 1:1:1:1 for the $ArCH_2Ar$ groups (with pertinent carbon resonances at 30.7, 30.9, 38.4, and 38.8 ppm), an AB system (4.74 and 4.99 ppm, J = 13.4 Hz) and a pseudosinglet (4.53 ppm) for the picolyloxy protons, and two four-spin systems for the Py and Py′ substituents, partly superimposed on the signals of the aromatic protons of the calixarene skeleton. The assignment of the signals of the heteroaromatic protons to the pertinent pyridine ring required the aid of a COSY spectrum. From a comparison of the spectra of the two partial cone regioisomers in $CDCl_3$, it turned out that, contrary to **2**, in **5** the Py′ substituent is nestled, but not included, into the hydrophobic calix cup. However, in $CDCl_3$−CD_3OD (1:1, v/v) solution the chemical shift of H3-Py′ in **5** moves upfield ($\Delta\delta \cong 1.7$ ppm), strongly suggesting that in polar media the self-inclusion process is more favored, owing to the MeOH solvation of picolyl substituents and enhanced hydrophobic interactions with the calix cavity. Single-crystal X-ray analyses of tetrakis[(α-picolyl)oxy]calix[4]arenes have shown the tendency of the pyridine nitrogen to coordinate MeOH of solvation via hydrogen bonding.[19a]

The highly symmetrical 1,3-alternate conformer **3** shows an AB quartet for the $ArCH_2Ar$ protons and a single resonance for the relevant carbons at 39.2 ppm. As a consequence of the conformation, the crown ether moiety is sandwiched between two facing phenoxy units, and a set of oxyethylene protons experiences a remarkable diamagnetic shielding, as shown by the triplet at 3.00 ppm. Besides, a mutual shielding between the Py′ groups and the flanking aryl units is observed, with H3-Py′ resonating at higher field ($\Delta\delta$ = 1.15 ppm) with respect to the corresponding protons in the cone conformer **1**. The less symmetrical 1,2-alternate regioisomer **6** displays two singlets for the ^{t}Bu groups, two AX

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Table 1. Selected Proton Chemical Shifts (δ, ppm) (300 MHz, $CDCl_3$−CD_3OD, 1:1 v/v, 25 °C) of Ligands 1−6 and Their Complexes with Alkali-Metal Thiocyanates

compd	^{t}Bu	crown unit	OCH_2Py	ArH	H3-Py	H4-Py	H5-Py	H6-Py
1	0.84, 1.35	3.59, 4.11	4.89	6.47, 7.14	7.82	7.91	7.40	8.54
1⊂Na^+	1.11, 1.19	3.95, 4.07, 4.15	5.34	7.04, 7.16	7.11	7.74	7.43	8.89
1⊂K^+	1.14, 1.17	4.02, 4.13	5.15	7.09, 7.11	7.06	7.75	7.45	8.84
2	0.80, 1.27, 1.50	3.57−4.10	5.18	6.58, 6.98, 7.10, 7.22	7.44[a]	7.71[a]	7.27[a]	8.43[a]
2⊂Na^+	0.70, 1.40, 1.51	3.71−4.10	5.20	6.61, 6.99, 7.29, 7.39	6.81[a]	7.66[a]	7.38[a]	8.73[a]
2⊂K^+	0.68, 1.41, 1.55	3.70−4.15	5.04	6.57, 6.99, 7.29, 7.48	6.64[a]	7.59[a]	7.36[a]	8.70[a]
3	0.83, 1.42	3.06, 3.38, 3.47, 3.67	4.70	6.72, 7.11	6.62	7.63	7.22	8.41
3⊂Na^+	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*
3⊂K^+	0.78, 1.41	3.59, 3.65, 3.78, 3.99	4.76	6.81, 7.31	6.49	7.71	7.34	8.52
4	1.111, 1.115	3.6−4.1	4.95	6.85−6.90	8.07	7.76	7.30	8.45
4⊂Na^+	1.159, 1.161	3.8−4.1	5.08, 5.14	7.06−7.12	7.27	7.76	7.39	8.75
4⊂K^+	1.157, 1.162	3.8−4.1	4.96, 5.11	7.07−7.14	7.10[c]	7.76	7.40	8.75
5	0.78, 0.84, 1.07, 1.36	3.3−4.2	4.73, 5.00	6.61, 6.64, 6.93, 6.95, 6.97, 7.18, 7.21, 7.24	7.66[a]	7.95[a]	7.31[a]	8.45[a]
5⊂Na^+	0.77, 0.82, 1.11, 1.37	3.3−4.1	4.67, 4.99	6.62, 6.64, 6.90, 6.97, 6.99, 7.21, 7.25, 7.28	7.59[a]	7.94[a]	7.34[a]	8.49[a]
5⊂K^+	0.69, 0.70, 1.44 (×2)	3.6−4.3	4.52, 5.57	6.52, 6.56, 6.62, 7.07, 7.12, 7.38, 7.41, 7.43	7.08[a]	7.82[a]	7.49[a]	8.77[a]
6	1.13, 1.40	2.82, 3.3−3.6	4.51, 4.59	6.80, 7.26, 7.16, 7.41	6.20	6.91	7.02	8.23
6⊂Na^+	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*
6⊂K^+	1.17, 1.38	3.6−4.1	4.28, 4.41	7.06, 7.41, 7.25, 7.47	5.91	7.30	7.16	8.30

[a] Pyridine ring adjacent and *syn* to the polyether chain. [b] The addition of NaSCN (up to 2 equiv) caused no spectral changes at all in the ligand. [c] Superimposed on the ArH protons.

systems and one AB system (ratio 1:1:2) for the $ArCH_2$-Ar protons and three resonances at 28.7, 29.8, and 38.8 ppm (1:1:2 ratio) for the pertinent carbon atoms, an AB system for the diastereotopic OCH_2Py' protons, and two AB systems for the aromatic rings. A comparison with the spectra of the cone conformer **4** reveals strong upfield shifts for a pair of symmetrical oxyethylene protons and for the Py′ protons of **6**, which are respectively exposed to the diamagnetic shielding effect of two pairs of aryl rings (one above and one below the mean methylene-containing plane). The dramatic upfield shift experienced by H3-Py′ ($\Delta\delta \cong 1.7$ ppm) and to a lesser extent by H4-Py′ ($\Delta\delta \cong 0.8$ ppm) further suggests that (i) the heteroaromatic pendant groups alternate in filling the pocket created by the two facing aryl rings and (ii) the ring nitrogen is *exo* to the calix cup and *anti* oriented with respect to the phenolic oxygen. The structure of 1,2-alternate conformer **6** has already been proven by single-crystal X-ray analysis.[20]

^{1}H NMR Titration Experiments. The topology of ligands **1**−**6** is such that cone and partial cone conformers are expected to behave as monotopic receptors, while 1,2- and 1,3-alternate conformers, at least in principle, may act as ditopic receptors, since they contain potential binding sites above and below the mean plane containing the four bridging methylenes. To afford precise insight into the binding sites, stoichiometry, and solution structures of the alkali−metal complexes, extensive ^{1}H NMR titration experiments of **1**−**6** with sodium and potassium thiocyanates (up to 2 equiv) were carried out in $CDCl_3$−CD_3OD (1:1, v/v). Two contrasting situations emerged when we examined the effect of adding incremental amounts of salt to 1,3-bridged calix[4]crowns **1**−**3**. Titration of **1**−**3** with KSCN showed that, with a salt/ligand ratio of less than 1, signals for both complexed and uncomplexed ligands were present in the spectrum, indicating that on the NMR time scale the exchange rate between the two species was slow at room temperature. Upon reaching a 1:1 ratio, all the signals for the free ligand disappeared and subsequent additions of salt produced no further spectral changes, suggesting a 1:1 ligand to metal stoichiometry. By contrast, titration of

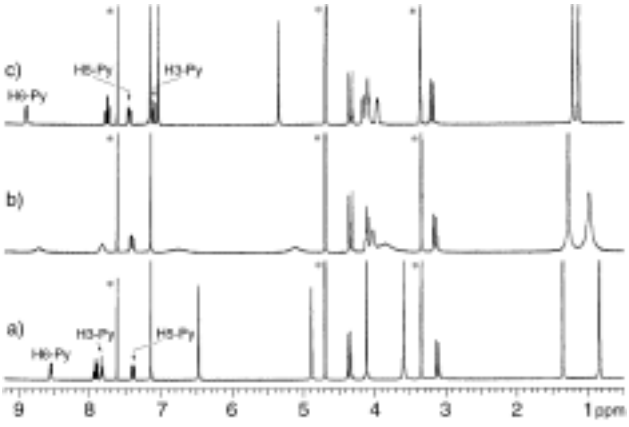

Figure 2. ^{1}H NMR spectrum (300 MHz, $CDCl_3$−CD_3OD, 1:1 v/v, 293 K) of **1** (a) and spectral changes upon addition of 0.5 (b) and 1 equiv (c) of NaSCN. The large CIS values observed for H3- and H6-Py provide evidence for the Na^+/Py interaction (asterisk indicates residual solvent peak).

1 and **2** with NaSCN produced initial broadening of several signals, followed by sharpening at the equivalence, indicating that the exchange rates for Na^+ with **1** and **2** were faster than those for K^+. Analogous studies on 1,2-bridged calixcrown conformers **4** and **5** have shown fast exchange rates in all cases, irrespective of the cation used. Remarkably, no hint of spectral changes was detected with 1,3- and 1,2-alternate conformers **3** and **6** and NaSCN, even in the presence of an excess of salt. Diagnostically important spectral changes of ligands **1**−**6** induced by Na^+ and K^+ complexation are collected in Table 1.

The ^{1}H NMR spectral changes upon titration of **1** with NaSCN are illustrated in Figure 2. Complexation affects all the proton chemical shifts in the ligand, in particular those of the OCH_2Py groups, the aromatic protons of the alkylated rings, H3- and H6-Py, which move up or downfield with complexation induced shifts (CIS) in the range 0.35−0.71 ppm (Table 1).

$CDCl_3$ solutions of the parent *p-tert*-butylcalix[4]arene at room temperature (where the cone conformation is

fixed on the ^{1}H NMR time scale) show a singlet for the ArH protons at 7.05 ppm and a singlet for the ^{t}Bu groups at 1.15 ppm.[24] In $CDCl_3-CD_3OD$ (1:1), the corresponding signals of ligand **1** appear as singlets at 6.47 and 7.14 ppm (ArH) and 0.84 and 1.35 ppm (^{t}Bu), respectively. These signals upon Na^+ complexation undergo upfield and downfield shifts (7.04 and 7.16 ppm for ArH and 1.11 and 1.19 ppm for ^{t}Bu groups) and reappear in a range similar to that of *p-tert*-butylcalix[4]arene. The changes in chemical shifts observed for the complexation of Na^+ can be interpreted in terms of a C_{2v} symmetry in the free ligand and a pseudo-4-fold symmetry (C_{4v}) in the complex. Besides, the shifts experienced by H3-Py (upfield, $\Delta\delta$ = 0.71 ppm) and H6-Py (downfield, $\Delta\delta$ = 0.35 ppm), and the invariance of H5-Py strongly suggest the participation of the pyridine ring nitrogens in the formation of the complex (Figure 2). Coordination of the pyridine rings takes place by rotation around the C12D−C41D and C12B−C21B linkages (see Figure 1), with changes in the orientation of the O and N heteroatoms of the OCH_2Py groups from anti to syn.[25] Comparable spectral changes are observed for K^+ complexation (Table 1). Therefore, Na^+ and K^+ cations are believed to be encapsulated into the ionophoric cavity defined by the phenoxy and crown ethereal oxygens, and bis-capped by the two pyridine nitrogens, for a total of nine binding sites.

The different trend in the titration experiments with NaSCN and KSCN (fast vs slow exchange rate) clearly shows that the dimensions of the ionophoric cavity in **1** are best adapted for the K^+ cation but still allow the inclusion of the smaller Na^+ cation, by a change in the tilt angle of the aromatic rings and an inward flexing movement of the pendant picolyl groups. The resulting contraction of the ionophoric cavity is energetically expensive and leads, in relative terms, to a destabilization of the complex, as indicated by the broadening of the spectra in defect of NaSCN. These observations are in agreement with the results of stability constant measurements of alkali-metal complexes by UV spectroscopy (vide infra).

The broadening in the spectra of Na^+ and K^+ complexes with the regioisomer **4** clearly indicates some conformational reorganization of the ligand upon complexation (with $\Delta\delta$ up to 0.25 ppm for $ArCH_2Ar$ resonances) and confirms the participation of both picolyl substituents in the stabilization of the complexes (Table 1).

The titration experiment of the partial cone **2** with KSCN, shown in Figure 3, provides a typical example of slow exchange rate between complexed and uncomplexed species. Doubling of the signals is observed from the addition of the first aliquot (0.5 equiv) of salt. The ligand seems to be highly preorganized for the complexation of the K^+ cation, since only small shifts are observed for most protons of the calixarene skeleton. However, a close scrutiny of the spectral changes upon K^+ complexation shows that the aromatic protons of the alkylated rings undergo significant downfield shifts ($\Delta\delta$ = 0.19 and 0.26 ppm), whereas those of the aryl rings holding the polyether chain are almost unaffected. These features point to the occurrence of strong K^+/π interactions with the inverted aromatic moiety.[26] It is interesting to note

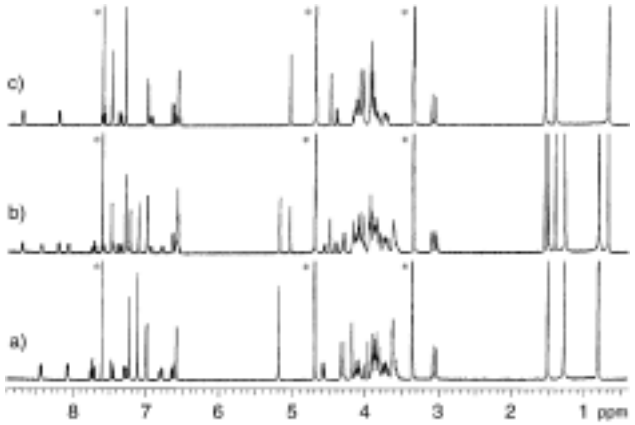

Figure 3. ^{1}H NMR spectrum (300 MHz, $CDCl_3-CD_3OD$, 1:1 v/v, 293 K) of **2** (a) and spectral changes upon addition of 0.5 (b) and 1 equiv (c) of KSCN. The doubling of all signals in trace b shows that the exchange between the free ligand and the complex is slow (asterisk indicates residual solvent peak).

that in the Na^+ complex with **2** such a cation/π interaction is less effective, as suggested by a lower shift of pertinent protons ($\Delta\delta$ = 0.17 ppm). The assistance of the Py moiety in the uptake of K^+ is demonstrated once again by the usual upfield ($\Delta\delta$ = 0.8 ppm) and downfield ($\Delta\delta$ = 0.27 ppm) shifts experienced by H3- and H6-Py, respectively. Therefore, one can conclude that the cation is tightly encapsulated inside the three-dimensional ionophoric cavity defined by the crown ether ring, the picolyloxy group, and the inverted aryl ring. The geometry of **2**⊂K^+ complex is believed to be quite similar to that found in the solid state for the K^+ picrate complex with 1,3-diisopropoxy-*p-tert*-butylcalix[4]crown-5 fixed in the partial cone conformation.[27]

Titration experiments of **5** with NaSCN under our standard conditions (up to 2 equiv of salt) have shown that the ^{t}Bu, ArH and Py resonances are scarcely affected by the addition of the salt, suggesting a low affinity of **5** for Na^+, and small spectral changes could only be detected with a large excess of NaSCN (> 5 equiv). The solution structure of alkali-metal complexes with **5** could be better deduced by a titration experiment with KSCN, whose interpretation required additional COSY and HETCOR experiments. Spectral changes suggest that the K^+ cation is bound, after considerable conformational reorganization of the ligand, inside the ionophoric cavity composed of the crown unit, the Py side arm, and the inverted aromatic ring. The accommodation of K^+ likely occurs by a flipping motion of the inverted aryl ring, which causes its ^{t}Bu substituent to move away from the crown ether portion of the molecule, to make room for the incoming cation. Consequently, the Py′ pendant group attached to it intrudes more deeply into the hydrophobic cavity, opposite to the coordination pocket, as strongly substantiated by the very upfield resonance of H3-Py′ (4.25 ppm). The occurrence of K^+/π interaction in **5**⊂K^+ complex is supported by the moderate downfield shift experienced by the relevant AB system for the ArH protons of the inverted aryl residue ($\Delta\delta$ = 0.2 ppm), and additional binding by the Py moiety is suggested by the usual CIS values for H3- and H6-Py (Table 1).

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

ligand	Li^+	Na^+	K^+	Rb^+	Cs^+
1	3.3 ± 0.2	8.5 ± 0.2	37.5 ± 0.8	7.2 ± 0.5	3.0 ± 0.4
2	5.2 ± 0.2	22.2 ± 0.3	75 ± 1	69 ± 1	11.2 ± 0.6
3	6.1 ± 0.1	5.9 ± 0.9	9 ± 2	7 ± 1	5.2 ± 1.2
4	9.3 ± 0.3	3.7 ± 0.2	10.8 ± 0.9	5.0 ± 0.8	6.4 ± 0.4
5	3.5 ± 0.1	1.5 ± 0.1	9.7 ± 0.2	8.3 ± 0.2	3.7 ± 0.2
6	3.2 ± 0.8	0.7 ± 0.1	3.5 ± 0.6	3.3 ± 0.3	5.7 ± 0.2

[a] Standard deviation σ_{n-1} on the mean of $n = 4$ experiments; $n = 2$ for Li^+.

Table 3. Protonation Constants of (1,3)- and (1,2)-Calix[4]crown-5 1−6 in MeOH at 25 °C, I = 0.1 M Et_4NCl

	log K_i[a]					
	1	**2**	**3**	**4**	**5**	**6**
$i = 1$	5.33	6.18	5.57	6.29	5.81	5.25
$i = 2$	4.64	4.70	2.98	3.23	4.03	2.66

[a] Corresponding to the equilibria $LH_{(i-1)}^{(i-1)+} + H^+ \rightleftharpoons LH_i^{i+}$.

Titration experiments of alternate regioisomers **3** and **6** with KSCN indicate that the cation is sitting inside the binding pocket constituted by the inverted aryl residues and the crown ether ring. In both cases the downfield shifts of the ArH protons of the inverted aryl residues ($\Delta\delta$ = 0.2 ppm in **3**⊂K^+, 0.15 and 0.26 ppm in **6**⊂K^+) are suggestive of the presence of cation/π interactions in solution, the best binding geometry for K^+ complexation being provided by the more preorganized ligand **3**.

Extraction Efficiency. The binding properties of compounds **1**−**6** were further investigated by two-phase extraction experiments of alkali-metal picrates from water into CH_2Cl_2. The results, given in Table 2, show that among the 1,3-bridged calixcrowns the partial cone conformer **2** is the best extractant with a peak selectivity for K^+ and Rb^+ (% E = 75 and 69, respectively). The cone conformer **1** is less efficient but still selective for K^+, whereas the alternate conformer **3** shows a low extraction level. The 1,2-bridged calixcrowns are much less efficient than their 1,3-bridged counterparts (maximum % $E \approx 10$). Conformer **4** is selective for K^+ and **5** for both K^+ and Rb^+, whereas **6** shows a slight preference for Cs^+.

UV and Potentiometric Titration Experiments. Complexation of alkali-metal cations could be followed in MeOH by spectrophotometric titrations of the ligands by the metal. Near neutrality (pH ∼ 8.5 in MeOH), the picolyl groups on the calixcrowns are unprotonated as can be inferred from the values of the protonation constants determined in this medium (Table 3). In addition, the high separation observed between the two constants (Δ (log K) = log K_1 − log K_2 > 2.5) for compounds **3**, **4**, and **6** suggests strong interaction between the nitrogens in these ligands. In compound **1**, however, for which Δ (log K) = 0.69, there is some independence of the two picolyl sites, due certainly to the presence of the crown moiety.

The UV spectral changes observed in the complexation of K^+ by **1** are shown in Figure 4 as an example. Substantial changes in the absorption spectrum of the ligand leading to isosbestic points indicate the presence of two absorbing species. In all cases, the analysis of the absorbance pattern was consistent with the formation of 1:1 complexes, in agreement with ^{1}H NMR complexation

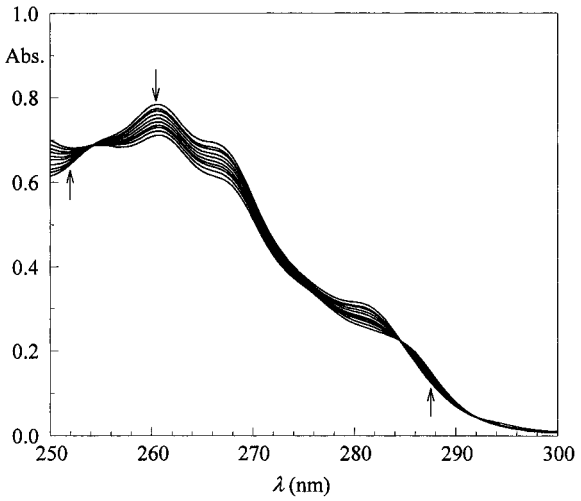

Figure 4. Changes in the UV absorption spectrum of ligand **1** upon addition of KCl in MeOH: $C_L = 8.0 \times 10^{-5}$ M, $0 \le R \le 2$, cells of 1 cm path length.

results in $CDCl_3/CD_3OD$. The corresponding stability constants (log β) are reported in Table 4.

In agreement with the extraction data, the 1,3-bridged calixcrowns **1** and **2** are poor binders for Na^+ and Cs^+ and especially for Li^+. In some instances, no significant spectral changes were observed even in the presence of a large excess of the metal salt. Therefore, it was impossible to determine precisely the stability constants and only an upper limit of 1 log unit could be given. In contrast, both ligands are selective for K^+, **2** having also a strong affinity for Rb^+. Although conformer **3** is a poor extractant, it proved to be quite efficient and also very selective for K^+ and Rb^+. The stability constants (Table 4) suggest that K^+ and Rb^+ fit very well into the 1,3-positioned crown ether moiety of compounds **2** and **3**. The lack of cation/π interactions in the cone conformer **1** accounts for the lower efficiency toward these cations. Li^+ and Cs^+ ions are respectively too small and too large to match the crown ether cavity. The sequences of stability follow the order **1** > **2** > **3** for Na^+ and **2** > **3** > **1** for K^+, Rb^+, and Cs^+.

Complexation of K^+ by ligands **1** and **2** has also been followed by competitive potentiometric measurements with H^+. A titration curve of ligand **2** in the presence of 1 equiv of KCl is shown in Figure 5. The considerable pH lowering in comparison with the titration curve of the free ligand is characteristic of a high complexation level. In this case, an additional protonated species MLH^+ has been found besides the 1:1 complex in the more acidic region. This result is a strong argument in favor of the participation of the pyridine nitrogen(s) in complexation. The stability constants of the 1:1 complexes are in agreement with the values obtained from spectrophotometric measurements (Table 4).

Complexes of the 1,2-bridged calixcrowns are less stable than those of their 1,3-bridged counterparts, the highest stability constants being inferior to 4 log units. The selectivities of compounds **4**−**6** depend on their conformation: these vary from K^+ for the cone conformer **4**, to both K^+ and Rb^+ for the partial cone **5**, and to Cs^+ for the 1,2-alternate **6**. The selectivity of **6** for Cs^+ may be explained by better cation/π interactions.

Selectivity. The series of 1,3-bridged calixcrowns displays a strong affinity for K^+ or for both K^+ and Rb^+.

Table 4. Stability Constants (log $\beta \pm \sigma_{n-1}$)[a] of Alkali-Metal Complexes in MeOH at 25 °C, I = 0.01 M Et_4NCl

ligand	Li^+	Na^+	K^+	Rb^+	Cs^+
1	≤1	2.76 ± 0.02	4.81 ± 0.01 (4.86)[c]	3.15 ± 0.06	≤1[b]
2	≤1[b]	2.34 ± 0.01	6.6 ± 0.1 (6.98)[c,d]	6.3 ± 0.1	3.42 ± 0.04
3	≤1[b]	≤1[b]	5.62 ± 0.07[e]	5.74 ± 0.06	2.86 ± 0.01
4	≤1[b]	2.0 ± 0.1	2.70 ± 0.01	1.40 ± 0.01	≤1[b]
5	≤1[b]	≤1[b]	3.38 ± 0.01	3.46 ± 0.01	2.40 ± 0.06
6	1.2 ± 0.1	≤1[b]	1.74 ± 0.07[e]	2.89 ± 0.02	3.23 ± 0.04

[a] Mean of at least two different experiments; σ_{n-1} = standard deviation on the mean. [b] No significant spectral changes even in the presence of a large excess of metal ion. [c] Value from potentiometric measurements (1 experiment). [d] log β_{MLH} = 10.52. [e] One determination only.

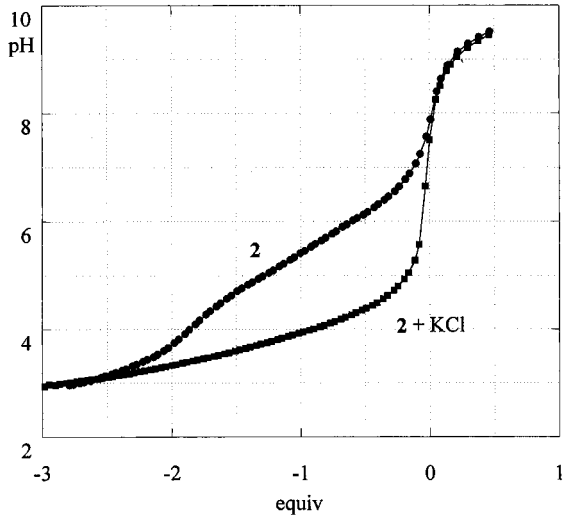

Figure 5. Potentiometric titration curves of ligand **2** in the absence ($C_L = 1.0 \times 10^{-3}$ M) or in the presence of KCl ($C_L = 8.8 \times 10^{-4}$ M, $C_M = 8.9 \times 10^{-4}$ M).

Table 5. M^+/Na^+ Selectivities[a] of Ligands 1−5 and Comparison with Valinomycin

selectivity	**1**	**2**	**3**	**4**	**5**	valinomycin
K^+/Na^+	100	1.8×10^4	4×10^4	**5**	$\geq 2.4 \times 10^2$	1.7×10^4
Rb^+/Na^+	2	9×10^3	5.2×10^4		$\geq 3 \times 10^2$	3.9×10^4

[a] $S(M^+/Na^+) = \beta(M^+)/\beta(Na^+)$. [b] From ref 28.

The partial cone derivative **2** is the most efficient, but the most selective is undoubtedly the 1,3-alternate derivative **3**. The latter shows K^+/Na^+ and Rb^+/Na^+ selectivities slightly higher than those reported for the naturally occurring valinomycin (Table 5).[28] Among synthetic ionophores, comparable or higher K^+/Na^+ selectivity has only been reported for structurally related 1,3-diisopropoxycalix[4]crown-5 conformers devoid of ^{t}Bu substituents at the upper rim.[29]

The 1,2-bridged series seems to be less selective, the best K^+/Na^+ selectivity (ca. 2.4×10^2) being observed for ligand **5**.

Thermodynamics of Complexation. Calorimetric studies were carried out for a better understanding of the complexation process. The thermodynamic parameters of complexation are given in Table 6. No values for **6** are reported due to the sparing solubility of this ligand in MeOH.

For 1,3-bridged calixcrowns **1**−**3**, the stabilization of the complexes is enthalpy controlled ($-\Delta H > 0$ and $T\Delta S < 0$). For a given cation (K^+, Rb^+, or Cs^+), the better efficiency of the partial cone **2** over the 1,3-alternate conformer **3** is due to higher values of $-\Delta H_c$ overcoming more negative, hence more unfavorable, entropy terms. $T\Delta S_c$ decreases on going from the cone to the partial cone and to the 1,3-alternate conformers. This trend is consistent with the increasing degree of preorganization of the ligand and the resulting smaller loss of freedom upon complexation. The highest $-\Delta H_c$ value is found for the partial cone derivative, indicating better interactions between the cation and this ligand, which offers the best compromise between preorganization of the binding sites, steric hindrance and cooperative effects of pyridine nitrogens, and cation/π interaction.

With ligands **2** and **3**, similar trends are observed along the series, i.e. the highest $-\Delta H_c$ value for Rb^+, consistent with appropriate size and optimized interactions, and a decrease of $T\Delta S_c$ values from K^+ to Rb^+ and Cs^+, consistent with the degree of cation solvation. The better affinity of ligand **1** for K^+ is explained by the more favorable enthalpy term overcoming a more unfavorable entropy term. This could result from the steric hindrance caused by the presence of the picolyl arms in the complexation of the larger Rb^+ ion and from the fact that this ligand is the least preorganized in the series.

With 1,2-bridged calixcrowns **4** and **5**, the stabilization of the complexes is also enthalpy driven. However, there are two main differences with respect to their 1,3-counterparts: (i) The entropy changes are close to zero or even positive for **5**⊂K^+ and, hence, more favorable. (ii) The enthalpy changes are much smaller indicating lower interaction with the cation. The case of **5**⊂K^+ and **5**⊂Rb^+ is particularly striking: Both complexes have almost the same stability, but their stabilization is quite different; with K^+ the enthalpy term is nearly half that observed for Rb^+ (11.5 instead of 21 kJ mol^{-1}), while the entropy term is much higher (7.8 instead of −1 kJ mol^{-1}).

Conclusions

All possible bis[(α-picolyl)oxy]-*p*-*tert*-butylcalix[4]crown-5 atropisomers (**1**−**6**), differing in the position of the polyether bridge [(1,2)- or (1,3)-], have been obtained by four complementary synthetic routes. ^{1}H NMR titration experiments of **1**−**6** with Na^+ and K^+ thiocyanates have demonstrated the active role of the picolyl nitrogen(s) and/or π-electrons of the inverted aryl residue(s) in cation complexation. The binding efficiencies, selectivities, and thermodynamic parameters of complexation of **1**−**6** for alkali-metal cations have been determined by a combination of UV spectrophotometric, potentiometric, and calorimetric measurements. The results have shown that the efficiency and selectivity of our calix[4]crowns-5 depend on two main factors: (i) the position at which the crown part is attached to the calixarene and (ii) the conformation of the calixarene moiety. All 1,3-bridged calixcrowns

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Table 6. Thermodynamic Parameters of Complexation in MeOH at 25 °C [ΔG_c (kJ·mol^{-1}), ΔH_c (kJ·mol^{-1}), $T\Delta S_c$ (kJ·mol^{-1}), and ΔS_c (J·K^{-1} mol^{-1})][a]

	1		**2**			**3**			**4**	**5**	
ligand	K^+	Rb^+	K^+	Rb^+	Cs^+	K^+	Rb^+	Cs^+	K^+	K^+	Rb^+
$-\Delta G_c$	27.43 ± 0.06	18.0 ± 0.3	37.6 ± 0.6	35.9 ± 0.6	19.5 ± 0.2	32.0 ± 0.4	32.7 ± 0.3	16.31 ± 0.06	15.40 ± 0.06	19.28 ± 0.06	19.73 ± 0.06
$-\Delta H_c$	44 ± 4	31 ± 2	44 ± 3	46 ± 1	29 ± 4	32.8 ± 0.4	37 ± 2	19 ± 2	14 ± 1	11.46 ± 0.08	21 ± 2
$T\Delta S_c$	−17 ± 4	−13 ± 2	−6 ± 4	−10 ± 2	−10 ± 4	−0.8 ± 0.8	−4 ± 2	−3 ± 2	1 ± 1	7.8 ± 0.1	−1 ± 2
ΔS_c	−57 ± 13	−44 ± 7	−20 ± 13	−34 ± 7	−34 ± 13	−3 ± 3	−13 ± 7	−10 ± 7	3 ± 3	26.2 ± 0.3	−3 ± 7

[a] Standard deviation σ_{n-1} on the mean of at least 2 independent experiments.

present a high affinity for K^+ (**2** and **3** also for Rb^+), while the more rigid 1,2-bridged counterparts are less efficient and selective. The best ligand is the partial cone conformer **2**, which achieves the best compromise between preorganization, steric hindrance, and cooperative effects of cation/π and cation/Py interactions. However, the most selective is the 1,3-alternate conformer **3**, showing selectivity levels similar or even slightly better than valinomycin.[29]

Experimental Section

General Methods. Melting points were determined on a Kofler or "electrothermal" melting point apparatus and are uncorrected. Unless otherwise stated, the ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained in $CDCl_3$ using tetramethylsilane as the internal standard at room temperature. The multiplicity of the ^{13}C signals was determined by means of the APT technique. FAB (+) mass spectra were recorded using 3-nitrobenzyl alcohol as the matrix. All chemicals were reagent grade and were used without further purification. Anhydrous solvents (toluene, DMF, THF, and MeCN) and PicCl·HCl were purchased from Fluka. Tetraethylene glycol ditosylate,[30] *p-tert*-butylcalix[4]arene,[31] 25,27-bis[(2-pyridylmethyl)oxy]-*p-tert*-butylcalix[4]arene (**8**),[18] 25,26-bis[(2-pyridylmethyl)oxy]-*p-tert*-butylcalix[4]arene (**9**),[19] and [2-(pyridylmethyl)oxy]-(1,2)-*p-tert*-butylcalix[4]crown-5 (**10**)[14,21] were prepared according to reported procedures. All reactions were carried out under nitrogen atmosphere.

25,27-Dihydroxy-(1,3)-*p-tert*-butylcalix[4]crown-5 (7). A stirred mixture of *p-tert*-butylcalix[4]arene (toluene 1:1 complex, 0.74 g, 1 mmol), TGD (0.53 g, 1.05 mmol), and K_2CO_3 (0.29 g, 2.1 mmol) in dry CH_3CN (50 mL) was refluxed for 48 h. After evaporation of the solvent, the residue was acidified with 1 N HCl, extracted into CH_2Cl_2 (2 × 30 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography (SiO_2, *n*-hexane−AcOEt, 1:1), to give diol **7** (0.4 g, 50%) as a white solid: mp 245−247 °C (lit.[8a] mp 246−248 °C); ^{1}H NMR δ 0.91, 1.31 (s, 18 H each), 3.29, 4.37 (AX, J = 13.0 Hz, 8 H), 3.84, 3.97 (t, J = 5.5 Hz, 4 H each), 4.08 (s, 8 H), 6.75, 7.07 (s, 4 H each), and 7.18 (s, 2 H).

Alkylation of 7 with PicCl·HCl. A stirred mixture of **7** (0.61 g, 0.75 mmol), PicCl·HCl (0.49 g, 3 mmol), and Cs_2CO_3 (2.44 g, 7.5 mmol) in dry DMF (15 mL) was heated at 60−70 °C for 20 h. Evaporation of the solvent gave a solid, which was treated with water (15 mL) and stirred for 10 min. The solid was collected by filtration, dissolved in CH_2Cl_2, and dried ($MgSO_4$). Removal of the solvent gave a residue, which was purified by column chromatography (neutral Al_2O_3, *n*-hexane−AcOEt, 3:1), to afford two fractions.

2,4-Bis[(2-pyridylmethyl)oxy]-(1,3)-*p-tert*-butylcalix[4]-crown-5, partial cone conformer (2) (fraction A): 44% yield; mp 270−271 °C (CH_2Cl_2−MeOH); ^{1}H NMR δ 0.79, 1.25, 1.49 (s, 36 H, ratio 2:1:1, respectively), 2.96, 4.22 (AX, J = 12.0 Hz, 4 H), 3.54−4.09 (m, 20 H), 4.25 (s, 2 H), 4.53 (d, J = 8.0 Hz, 1 H), 5.13 (s, 2 H), 6.51 (td, J = 7.8, 1.9 Hz, 1 H), 6.56, 6.94 (ABq, 4 H, J = 2.5 Hz), 6.66 (m, 1 H), 7.03 (d, J = 7.7 Hz, 1 H), 7.06 (s, 2 H), 7.17 (ddd, J = 7.6, 4.9, 1.2 Hz, 1 H), 7.20 (s, 2 H), 7.55 (td, J = 7.6, 1.8 Hz, 1 H), 8.12 (dt, J = 4.8, 0.9 Hz, 1 H), 8.54 (ddd, J = 4.8, 1.8, 0.9 Hz, 1 H); ^{13}C NMR δ 30.8, 39.0 (t), 31.0, 31.5, 31.8 (q), 33.6, 34.1, 34.2 (s), 69.1, 70.1, 70.7, 71.0, 73.4, 78.3 (t), 119.4, 120.3, 122.4, 124.2, 124.3, 124.7, 124.8, 125.3 (d), 132.3, 132.9, 134.4, 135.0 (s), 135.6, 136.2 (d), 144.7, 145.1, 145.3, 147.0, 149.1, 157.5, 157.9 (s); MS, *m*/*z* 989 (100, MH^+). Anal. Calcd for $C_{64}H_{80}N_2O_7$: C, 77.70; H, 8.15; N, 2.83. Found: C, 77.92; H, 7.95; N, 2.78.

2,4-Bis[(2-pyridylmethyl)oxy]-(1,3)-*p-tert*-butylcalix[4]-crown-5, cone conformer (1) (fraction B): 30% yield; mp

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> 260 °C (CH_2Cl_2−MeOH); ^{1}H NMR δ 0.81, 1.33 (s, 18 H each), 3.08, 4.34 (AX, J = 12.6 Hz, 8 H), 3.56 (s, 8 H), 4.10 (m, 8 H), 4.90 (s, 4 H), 6.44, 7.10 (s, 4 H each), 7.25 (ddd, J = 7.4, 4.9, 1.2 Hz, 2 H), 7.65 (d, J = 7.8 Hz, 2 H), 7.77 (td, J = 7.6, 1.8 Hz, 2 H), 8.61 (ddd, J = 4.9, 1.7, 0.9 Hz, 2 H); ^{13}C NMR δ 31.0 (t), 31.1, 31.7 (q), 33.6, 34.1 (s), 70.0, 70.8, 71.7, 72.5, 78.8 (t), 122.6, 123.5, 124.6, 125.6 (d), 131.6, 135.2 (s), 136.7 (d), 144.4, 145.0 (s), 149.2 (d), 151.9, 154.8, 157.5 (s); MS, *m/z* 1011 (100, MNa^+), 989 (78, MH^+). Anal. Calcd for $C_{64}H_{80}N_2O_7$: C, 77.70; H, 8.15; N, 2.83. Found: C, 77.56; H, 8.26; N, 3.01.

2,4-Bis[(2-pyridylmethyl)oxy]-(1,3)-*p*-*tert*-butylcalix[4]-crown-5, 1,3-Alternate Conformer (3). A stirred mixture of **8** (0.5 g, 0.6 mmol), TGD (0.31 g, 0.6 mmol), and Cs_2CO_3 (1.97 g, 6 mmol) in CH_3CN (70 mL) was refluxed for 72 h. After cooling, the inorganic salts were filtered off, and the filtrate was concentrated to dryness. The residue was partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. Crystallization of the crude reaction mixture from CH_2Cl_2−MeOH afforded 1,3-alternate conformer **3** (60% yield) as colorless crystals: mp 153−155 °C; ^{1}H NMR δ 0.81, 1.41 (s, 18 H each), 2.97−3.65 (m, 16 H), 3.66, 3.83 (ABq, J = 17.3 Hz, 8 H), 4.69 (s, 4 H), 6.50 (d, J = 7.9 Hz, 2 H), 6.68, 7.07 (s, 4 H each), 7.10 (m, 2 H), 7.56 (td, J = 7.7, 1.8 Hz, 2 H), 8.46 (dt, J = 4.9, 0.9 Hz, 2 H); ^{13}C NMR δ 31.1, 31.9 (q), 33.5, 34.0 (s), 39.2 (t), 66.9, 70.4, 70.9, 72.7, 73.5 (t), 122.0, 122.4, 125.3 (×2) (d), 132.8, 132.9 (s), 136.8 (d), 144.6, 144.8 (s), 148.1 (d), 153.7, 153.8, 158.1 (s); MS, *m/z* 1011 (21, MNa^+), 989 (100, MH^+). Anal. Calcd for $C_{64}H_{80}N_2O_7$: C, 77.70; H, 8.15; N, 2.83. Found: C, 77.48; H, 8.36; N, 3.05.

Reaction of 9 with TGD. A solution of TGD (0.28 g, 0.55 mmol) in dry toluene (30 mL) was added dropwise over 3 h to a stirred mixture of **9** (0.41 g, 0.5 mmol) and ^{t}BuOK (0.12 g, 1.1 mmol) in dry toluene (50 mL) at 70 °C. The stirred mixture was kept at 70 °C for 24−36 h. Progress of the reaction could be monitored by following the disappearance of **9** by TLC analysis (neutral Al_2O_3, cyclohexane−AcOEt, 2:1). The solvent was evaporated in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (neutral Al_2O_3, *n*-hexane−AcOEt, 2:1 v/v), to give the following fractions.

3,4-Bis[(2-pyridylmethyl)oxy]-(1,2)-*p*-*tert*-butylcalix[4]-crown-5, 1,2-alternate conformer (6) (fraction A): 27% yield; mp 283−284 °C (CH_2Cl_2−MeOH); ^{1}H NMR δ 1.10, 1.45 (s, 18 H each), 2.82 (dt, J = 9.5, 7.0 Hz, 2 H), 3.18, 3.19 (d, J = 12.5 and 12.3 Hz, respectively, 1 H each), 3.28−3.65 (m, 14 H), 3.86, 3.89 (ABq, J = 17.7 Hz, 4 H), 4.13, 4.41 (d, J = 12.3 and 12.2 Hz, respectively, 1 H each), 4.53, 4.59 (ABq, J = 13.8 Hz, 4 H), 6.17 (d, J = 7.6 Hz, 2 H), 6.77 (d, J = 2.4 Hz, 2 H), 6.81 (td, J = 7.6, 1.9 Hz, 2 H), 6.88 (ddd, J = 7.5, 4.7, 1.3 Hz, 2 H), 7.12, 7.20, 7.38 (d, J = 2.4 Hz, 2 H each), 8.29 (dt, J = 4.7, 0.9 Hz, 2 H); ^{13}C NMR δ 28.7, 29.8, 38.8 (×2) (t), 31.4, 31.7 (q), 33.9, 34.1 (s), 68.7, 70.6, 71.0, 71.1, 74.5 (t), 121.2 (×2), 124.8, 125.6, 125.8, 125.9 (d), 132.1, 132.4, 133.7, 134.6 (s), 136.3 (d), 144.4, 145.0 (s), 147.8 (d), 153.58, 153.63, 158.0 (s); MS, *m/z* 1011 (44, MNa^+), 989 (100, MH^+). Anal. Calcd for $C_{64}H_{80}N_2O_7$: C, 77.70; H, 8.15; N, 2.83. Found: C, 77.65; H, 7.96; N, 2.98.

3,4-Bis[(2-pyridylmethyl)oxy]-(1,2)-*p*-*tert*-butylcalix[4]-crown-5, cone conformer (4) (fraction B): 45% yield; mp 252−255 °C (CH_2Cl_2−MeOH); ^{1}H NMR δ 1.087, 1.091 (s, 18 H each), 3.05, 3.10, 3.14 (overlapping d, 4 H), 3.57−4.13 (m, 16 H), 4.35, 4.36, 4.57 (d, J = 12.5 Hz, ratio 2:1:1, 4 H), 4.97, 5.02 (ABq, J = 13.1 Hz, 4 H), 6.79−6.83 (m, 8 H), 7.17 (td, J = 7.5, 4.9 Hz, 2 H), 7.63 (td, J = 7.7, 1.8 Hz, 2 H), 7.91 (d, J = 7.7 Hz, 2 H), 8.51 (dt, J = 4.9, 0.9 Hz, 2 H); ^{13}C NMR δ 30.5, 30.6, 30.9 (×2) (t), 31.4 (q), 33.8 (s), 69.9, 70.3, 71.0, 73.6, 78.0 (t), 122.2, 123.0, 125.0, 125.17, 125.21, 125.3 (d), 133.4, 133.5, 133.6, 134.2 (s), 136.7 (d), 144.6, 144.8 (s), 148.4 (d), 152.8, 153.0, 158.4 (s); MS, *m/z* 1011 (30, MNa^+), 989 (100, MH^+). Anal. Calcd for $C_{64}H_{80}N_2O_7$: C, 77.70; H, 8.15; N, 2.83. Found: C, 77.95; H, 8.06; N, 2.88.

Alkylation of 10 with PicCl·HCl. A mixture of **10** (0.54 g, 0.6 mmol) and Cs_2CO_3 (1.95 g, 6 mmol) in dry DMF (20 mL) was stirred at 60−70 °C for 30 min. Afterward, solid PicCl·HCl (0.39 g, 2.4 mmol) was added portionwise. The mixture was kept at 60−70 °C for 24 h. The solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (neutral Al_2O_3, *n*-hexane−AcOEt, 2:1) to give the desired inherently chiral partial cone conformer **5** (70% yield), followed by cone conformer **4** (13% yield).

3,4-Bis[(2-pyridylmethyl)oxy]-(1,2)-*p*-*tert*-butylcalix[4]-crown-5, partial cone conformer (5): mp 268−271 °C (MeOH); ^{1}H NMR δ 0.79, 0.83, 1.09, 1.33 (s, 9 H each), 3.16, 4.20 (AX, J = 12.2 Hz, 2 H), 3.17, 4.62 (AX, J = 12.2 Hz, 2 H), 3.29−4.11 (m, 20 H), 4.53 (s, 2 H), 4.74, 4.99 (ABq, J = 13.4 Hz, 2 H), 5.47 (br t, J = 4.5 Hz, 1 H), 6.62 (br s, 2 H), 6.86 (m, 4 H), 6.96 (d, J = 2.3 Hz, 1 H), 7.14 (m, 3 H), 7.19 (m, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.80 (td, J = 7.7, 1.7 Hz, 1 H), 8.30 (m, 1 H), 8.53 (dt, J = 4.9, 0.8 Hz, 1 H); ^{13}C NMR δ 30.7, 30.9, 38.4, 38.8 (t), 31.07, 31.12, 31.4, 31.6 (q), 33.5, 34.1 (s), 69.2, 70.3 (×2), 70.6, 71.0, 71.4 (×2), 72.2, 72.9, 74.4 (t), 120.6, 121.1, 121.9, 122.7 (d), 124.7, 124.9, 125.1, 125.3 (×3), 126.2, 126.5 (d), 132.0, 132.2, 132.7, 132.8, 133.8, 134.16, 134.23, 135.8 (s), 136.5, 137.1 (d), 144.5, 144.7, 144.8, 145.2 (s), 147.7, 148.1 (d), 152.4, 153.0, 153.2, 153.4 (s), 157.8, and 158.4 (s); MS, *m/z* 1011 (10, MNa^+), 989 (100, MH^+). Anal. Calcd for $C_{64}H_{80}N_2O_7$: C, 77.70; H, 8.15; N, 2.83. Found: C, 77.98; H, 8.28; N, 3.04.

Structural Analysis for 1. Details of the X-ray experimental conditions, cell data, data collection, and refinement for molecule **1** are summarized in Table S1 (Supporting Information). Molecule **1** crystallized in the monoclinic system, space group $P2_1/n$, determined uniquely from the systematic absences. The crystal diffracted very poorly, and only 31% of the data were "observed" at the 2σ level in the data collection. The structure was solved using SHELXS86[32] and NRCVAX94.[33] All the methyl carbons of the four ^{t}Bu groups were disordered over two orientations, and the C5−O6−C7 portion of the polyether chain was ill-defined. The positioning of the N atoms in the pyridyl rings was made after location of the relevant ring H atoms using the COFOUR option in NRCVAX94. For the SHELXL93[34] refinement, all aromatic rings were constrained to be planar hexagons and the various bond lengths were constrained to lie within chemically sensible values by use of various AFIX and DFIX options in SHELXL93. As the extent of the data did not justify full anisotropic refinement, the analysis was concluded at the end of isotropic full-matrix refinement when the conformation of the molecule had been determined unequivocally. The occupancies of the ^{t}Bu groups refined to the following values: A, 0.52/0.48(4); B, 0.80/0.20(2); C, 0.58/0.42(2); D, 0.72/0.28(2). The ORTEP diagrams were prepared using ORTEPII[35] as implemented in PLATON.[36] Examination of the structure with PLATON showed that there were no solvent accessible voids in the crystal lattice.

Extraction Experiments. Picrate extraction from water into CH_2Cl_2 was done by following Pedersen's procedure:[38] 5 mL of a 2.5 × 10^{-4} M solution of alkali-metal picrate in H_2O and 5 mL of a 2.5 × 10^{-4} M solution of calixarene in CH_2Cl_2 (Carlo Erba, ACS for analysis) were mechanically shaken in a stoppered glass tube for 2 min, then magnetically stirred in

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a thermostated bath at 20 ± 0.1 °C for 30 min, and finally left for a complete phase separation for another 30 min. The percentage extraction (% *E*) was calculated from the absorbance *A* of the aqueous phase measured at 355 nm using the following expression: % E = $100(A_0 - A)/A_0$, A_0 being the absorbance of the aqueous phase of a blank experiment carried out without calixarene.

Complexation Studies. The apparent stability constants β, corresponding to the equilibria $M^+ + L \rightleftharpoons ML^+$, were determined in MeOH (Carlo Erba, for analysis, water ≤ 0.01%) at 25 °C by UV absorption spectrophotometry as previously described.[39] All the spectra were recorded between 250 and 300 nm with a Shimadzu UV-2101 spectrophotometer, using quartz cells (Hellma) with optical path lengths of 0.5, 1, or 2 cm. The ligand concentration ranged between ca. 2.0×10^{-4} and 4.0×10^{-5} M. The following metal chlorides were used without further purification: LiCl (Fluka, MicroSelect), NaCl (SDS, analytical grade); KCl (Merck, pro analysis), RbCl (Merck, Suprapur), and CsCl (Merck, puriss). In all solutions the ionic strength was maintained at 0.01 M with Et_4NCl (Fluka, extra pure) recrystallized twice from water and dried under vacuum for 24 h before use.

The acid−base properties of the ligands were preliminarily investigated by determination of the protonation constants in MeOH at 25.0 ± 0.1 °C by pH-metric titrations under argon atmosphere as described earlier.[40] Initial volumes of 5 mL of ligand 1.0×10^{-3} M containing a slight excess (ca. 2.2 equiv) of HCl were titrated with Et_4NOH solution (ca. 0.040 M). The standard external reference solution of the combined glass electrode used was replaced by a 0.1 M solution of Et_4NCl. The electrode was calibrated before use with a solution of 10^{-2} M HCl in 0.09 M Et_4NCl, and the parameters *a* and *b* in the relation $-\log [H^+]_{real} = -\log [H]_{read} + a + b[H^+]$[41] were found to be 0.05 and −10.87, respectively, by measuring the pH of a 0.001 M solution of HCl in 0.099 M Et_4NCl. Complexation of K^+ by ligands **1** and **2** was also followed by competitive potentiometric measurements with H^+. Due to the limited quantity of ligands, the titrations were performed on solutions which were previously used to determine protonation constants after addition of KCl (1 equiv) and HCl (ca. 4.4 equiv).

The interpretation of the two kinds of experimental data was performed by the program Sirko.[42] For the treatment of pH-metric data, log $K_s = -16.70$[43] was settled as constant during the refinements.

Calorimetric Studies. The enthalpies of complexation (ΔH_c) were measured in MeOH at 25 °C by using an isoperibol titration calorimeter (Tronac 450, Orem, Utah) and following the general procedure as described elsewhere.[44] A solution of alkali-metal salt was titrated into a ligand solution (4×10^{-4} M ≤ C_L ≤ 6×10^{-4} M) until obtaining final metal-to-ligand ratios from 1 up to 2.5 depending on the stability constants. Program Sirko[42] was also employed to refine the enthalpy terms, the stability constants being settled as constants to their values found by spectrophotometry. If one knows β, ΔG_c can be calculated from $\Delta G_c = -RT \ln \beta$, and the values of the corresponding entropies of complexation (ΔS_c) were thus derived using the expression $\Delta G_c = \Delta H_c - T\Delta S_c$.

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Supporting Information Available: Text providing ^1H NMR spectral data ($CDCl_3$−CD_3OD, 1:1, v/v) for ligands **1**−**6** and their NaSCN and KSCN complexes and a table listing X-ray experimental details for compound **1** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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