# Synthesis and Complexation Studies of Regioisomers and Conformational Isomers of *p-tert*-Butylcalix[4]arene Bearing Pyridine or Pyridine *N*-Oxide Pendant Groups at the Lower Rim

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Selected title compounds have been prepared in order to provide calix[4]arene ligands having different shapes of the calix[4]arene skeleton (cone, partial cone, 1,2-alternate, or 1,3-alternate) and spacial arrangements (*syn*-proximal, *syn*-distal, or *anti*-distal) of pendant pyridine or pyridine *N*-oxide binding groups. The structure of 1,2-alternate tetrakis[(2-pyridylmethyl)oxy]calix[4]arene **9**, obtained in low yield by direct alkylation of the parent *p-tert*-butylcalix[4]arene **1** with PicCl·HCl and $Cs_2CO_3$, has been elucidated by single crystal X-ray analysis. *N*-Oxide derivatives have been obtained in good yield by *m*-CPBA oxidation of the appropriate pyridinocalix[4]arene precursors in dry $Et_2O$ or THF. The $^1H$ and $^{13}C$ NMR spectral changes upon *N*-oxide formation are discussed. Extraction studies with alkali metal picrates from an aqueous solution into $CH_2Cl_2$ have shown that the ionophoric efficiency is low. The highest phase-transfer values are observed for cone tetrapyridinocalix[4]arene **7** (selectivity follows the order $Na^+ > K^+ > Rb^+ > Cs^+ > Li^+$), whereas the corresponding *N*-oxide **7a** has no activity. However, NMR complexation studies with $Na^+$ and $K^+$, while confirming a low complexation rate, indicate that in aprotic solvents tetra-*N*-oxide derivative **7a** is a good complexer having a faster kinetic than its pyridino precursor **7**.

## Introduction

Calixarenes are cavity-containing macrocyclic compounds, which are the focus of considerable interest in the field of host–guest and supramolecular chemistry as three-dimensional building blocks for the design of selective cation receptors and carriers.[1] Cation selectivity and ionophoric activity of calixarene-based receptors and carriers has been shown to depend on several factors, including the ring size of the calixarene skeleton, its conformation and conformation mobility, lipophilicity, the chemical nature (donor ability) and spatial arrangement of the binding functionalities, and the degree of preorganization of the receptor.[1b]

The coordination behavior of ligands derived from the smallest members of this family, *i.e.* calix[4]arenes, has been investigated in detail by several groups. The parent calix[4]arenes are conformationally flexible molecules, but upon lower rim functionalization with substituents larger than an Et group,[2] these macrocycles may adopt four extreme conformations, designated as cone, partial cone, 1,2-alternate, and 1,3-alternate, thus providing additional shapes for selective molecular recognition. The attachment of ester,[3] keto,[4] amide,[5] and thioamide[6] binding sites to the lower rim of calix[4]arenes has produced a series of new lipophilic cation receptors in a fixed cone conformation with remarkable complexing properties toward alkali metal cations with a peak selectivity for $Na^+$. However, even minor changes in the regioselective functionalization[7] or conformation[8] of the chemically modified calixarene can be associated with drastic changes in the complexation properties.

Functionalization of calix[4]arenes by the base-catalyzed O-alkylation with halomethyl *N*-heterocyclic reagents has been recently introduced in order to obtain "universal" ligands for both hard and soft metal ions, which in principle should exhibit some advantages over amide and ester structures, because of a high stability in a wide pH range.[9,10]

Following earlier work on the synthesis, structure, and properties of pyridino-containing calix[4]arenes,[10,11] we report now on the synthesis, structural characterization, and alkali metal cation complexation studies of some selected regioisomers and conformational isomers of

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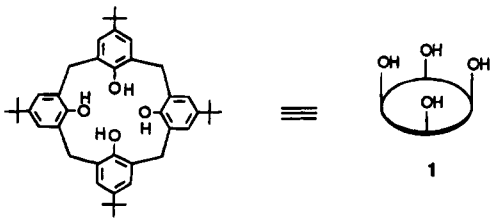
**Chart 1**



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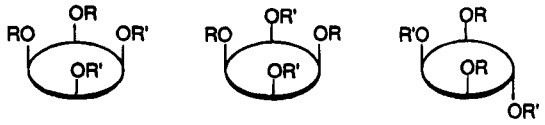
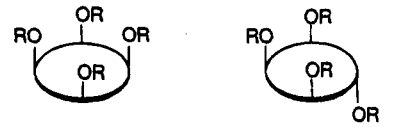


*syn*-proximal *syn*-distal *anti*-distal

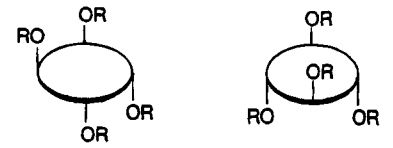
| | R | R' | | R | R' | | R | R' |
|---|---|---|---|---|---|---|---|---|
| **2** | H | $CH_2Py$ | **4** | H | $CH_2Py$ | **6** | Bn | $CH_2Py$ |
| **2a** | H | $CH_2Py(O)$ | **4a** | H | $CH_2Py(O)$ | **6a** | Bn | $CH_2Py(O)$ |
| **3** | Bn | $CH_2Py$ | **5** | Bn | $CH_2Py$ | | | |
| **3a** | Bn | $CH_2Py(O)$ | **5a** | Bn | $CH_2Py(O)$ | | | |



cone partial cone

**7** R = $CH_2Py$ **8** R = $CH_2Py$

**7a** R = $CH_2Py(O)$ **8a** R = $CH_2Py(O)$



1,2-alternate 1,3-alternate

**9** R = $CH_2Py$ **10** R = $CH_2Py$

**9a** R = $CH_2Py(O)$ **10a** R = $CH_2Py(O)$

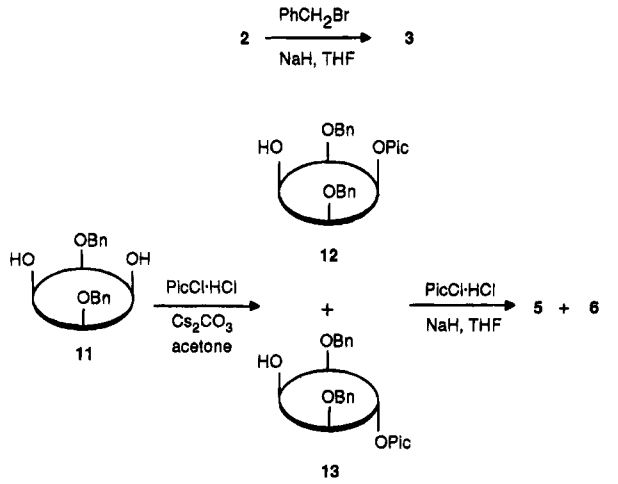
*p-tert*-butylcalix[4]arene bearing 2-pyridylmethyl or 2-pyridylmethyl *N*-oxide pendant groups at the lower rim. The first examples of calix[4]arenes containing pyridine *N*-oxide binding groups in a cone conformation, and their proclivity to form photoactive lanthanide complexes, have been described in a previous paper in this series.[11a]

The compounds chosen for this study are shown in Chart 1 and may contain two binding functionalities in a *syn*-distal, *syn*-proximal, or *anti*-distal relationship (compounds **2**–**6** and **2a**–**6a**), as well as four binding sites in a fixed cone, partial cone, 1,2-alternate, or 1,3-alternate conformation (compounds **7**–**10** and **7a**–**10a**).

## Results and Discussion

**Synthesis of Pyridinocalix[4]arene Precursors.** Most of the pyridinocalix[4]arenes used in this study have been prepared by direct O-alkylation of *p-tert*-butylcalix[4]arene **1** with 2-(chloromethyl)pyridine hydrochloride (PicCl·HCl), according to reported procedures.[11c]

**Scheme 1**



The synthetic routes to the new bis-benzylated dipyridinocalix[4]arenes are shown in Scheme 1. *bis*(*syn*-prox)Calix[4]arene **3** was obtained in high yield by subjecting *syn*-proximal bis[(2-pyridylmethyl)oxy]calix[4]arene **2** to an excess of benzyl bromide (4 equiv) in dry THF in the presence of NaH. A set of three pairs of doublets (1:2:1 ratio) for the bridging methylene protons and a pattern of three resonances around 31 ppm for the pertinent carbon atoms provide evidence that the cone conformation is maintained after the above chemical transformation.

Di-O-benzylated conformers **5** and **6** were obtained in 22 and 56% overall yield, respectively, through a two-step synthesis starting from the known *syn*-distal 1,3-di-O-benzylated calix[4]arene **11**.[12] Alkylation of **11** with PicCl·HCl and $Cs_2CO_3$ in refluxing acetone afforded tri-O-alkylated cone and partial cone conformers **12** and **13** in a roughly 1:3 ratio. An aliquot of the crude reaction mixture was subjected to careful chromatographic separation to give the pure components, which were fully characterized by microanalytical and spectral data. Further alkylation of the crude mixture (conformers **12** and **13**) with additional PicCl·HCl in dry THF in the presence of NaH afforded tetra-O-alkylated cone **5** and partial cone **6**, which could be easily separated by column chromatography.

Conformational assignments for the new tri- and tetra-*O*-alkylated calix[4]arenes followed from analysis of their $^1H$ and $^{13}C$ NMR spectra. The cone structure **12** is firmly established by the presence of two AB quartets for the bridging methylene protons with a $\Delta\delta$ separation between *exo* and *endo* hydrogens of 1.11 ± 0.06 ppm[13] and by a set of two resonances for the pertinent carbon atoms

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(13) In the calix[*n*]arene series ($n$ = 4, 6, and 8), the $\Delta\delta$ values of the $ArCH_2Ar$ protons have been correlated to the relative orientation of adjacent aromatic rings ($\Delta\delta$ > 1 with cone conformation or *syn* orientation, $\Delta\delta$ *ca.* 0.5 with flattened cone or out orientation, $\Delta\delta$ *ca.* 0.0 ppm with 1,3-alternate or *anti* orientation): (a) Reference 1a, pp 110–111. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160. Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917.

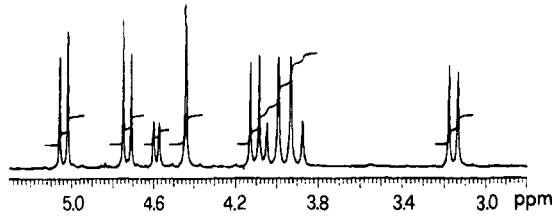


**Figure 1.** Methylene region in the $^1$H NMR spectrum (250 MHz, $CDCl_3$, 295 K) of partial cone tri-O-alkylated calix[4]-arene **13**.

at $\delta$ 30.58 and 31.46 ppm.[14] Accordingly, cone **5** displays an AB quartet for $ArCH_2Ar$ protons with a $\Delta\delta$ separation of 1.34 ppm and a single resonance for the pertinent carbons at $\delta$ 30.97 ppm.

On the other hand, partial cone structure **13** exhibits two AB quartets for $ArCH_2Ar$ protons with a $\Delta\delta$ separation of 0.95 and 0.12 ppm and two resonances for the pertinent carbon atoms at $\delta$ 32.33 (*syn* orientation of the flanking aryl moieties) and 39.32 ppm (*anti* orientation of the flanking aryl moieties). Similarly, tetrasubstituted **6** shows two AB systems for $ArCH_2Ar$ protons with $\Delta\delta$ separations of 1.04 and 0.06 ppm, respectively, and the expected two-resonance pattern for the relevant carbons at $\delta$ 31.43 and 39.15 ppm.

The methylene region in the $^1$H NMR spectrum of compound **13** is shown in Figure 1. Along with the expected pattern for $ArCH_2Ar$ and oxymethylenes, an additional doublet at $\delta$ 4.59 ppm ($J$ = 8.2 Hz) integrating for one proton is present, which correlates with 4-PyH in the COSY spectra (not shown), and is therefore assigned to the 3-positioned pyridyl proton of the substituent attached to the inverted phenol unit. A chemical shift comparison with the corresponding 3-PyH in the cone conformer **12** ($\delta$ 8.55) reveals a dramatic upfield shift for this proton ($\Delta\delta$ = 3.96 ppm), strongly suggesting that the inverted pyridyl unit is tightly accommodated inside the hydrophobic cavity generated by the remaining three aryl moieties, in a sort of self-inclusion complex. The ring nitrogen is oriented outward to the cavity, whereas the H3 is subjected to the ring current shielding effect from the two flanking aryl units. A similar trend is also observed for partial cone structure **6** (a doublet at 4.67 ($J$ = 7.7 Hz) assignable to 3-PyH), although in this case, a less efficient shielding effect is observed ($\Delta\delta$ = 3.10 ppm). Therefore, this self-inclusion phenomenon appears to be very common for partial cone structures derived from *p-tert*-butylcalix[4]arene, carrying planar appendages (pyridine, quinoline) at the inverted phenol unit.[11c,f]

Tetrakis[(2-pyridylmethyl)oxy]calix[4]arene conformers are prepared by treatment of the parent calix[4]arene **1** with a large excess of PicCl·HCl in dry DMF in the presence of a base.[11c] The conformational outcome of the reaction strongly depends upon the identity and strength of the base applied. The reaction with NaH is stereoselective and produces only the cone conformer **7**. By using weaker bases, such as alkali metal carbonates, mixtures of conformers are obtained. A scrutiny of the already reported reaction with $Cs_2CO_3$ has allowed us to isolate partial cone **8** (54%) and 1,3-alternate **10** (18%) conformers as the main products, along with a small amount of the hitherto unknown 1,2-alternate conformer **9** (2%).

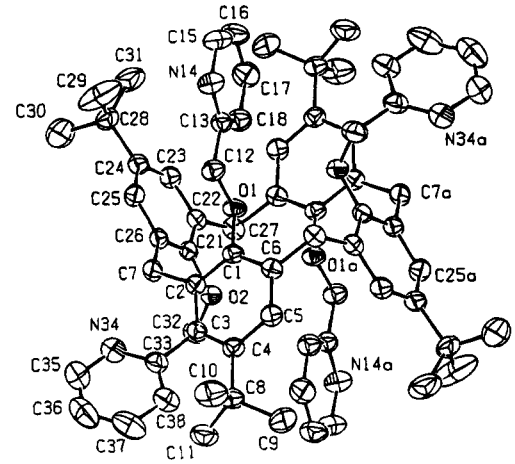


**Figure 2.** ORTEP plot of the structure of **9** with the crystallographic numbering scheme. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are drawn at the 50% probability level.

Structure **9** has been assigned by NMR spectroscopy and confirmed by a single-crystal X-ray analysis. The $^1$H NMR spectrum of **9** is characterized by a sharp singlet for *tert*-butyl groups, an AB quartet ($J$ = 12.4 Hz) and a singlet (1:1 ratio) for $ArCH_2Ar$ protons, an AB quartet ($J$ = 13.2 Hz) for diastereotopic oxymethylenes, an AB system ($J$ = 2.2 Hz) for aryl protons, and a four-spin system for pyridyl protons. The 1,2-alternate structure is further corroborated by two resonances for $ArCH_2Ar$ carbons at $\delta$ 29.88 and 39.21 ppm, confirming the presence of both *syn*- and *anti*-oriented diarylmethane subunits.

In the solid state, the molecule has crystallographic inversion symmetry and is clearly the 1,2-alternate conformer (Figure 2). The conformation adopted has pairs of opposite $O-CH_2-C_5H_4N$ moieties filling what would have been cavities in each side of the calix (Figure 3). The calix[4]arene conformation can be quantitatively described by the interplanar angles made by the aromatic rings with the central $(CH_2)_4$ moiety; the values are 56.6(1) and 109.8(1)°, respectively, for rings C1–C6 and C21–C26. An alternative way of describing calix[4]arene conformations in terms of torsion angles $\phi$ and $\chi$ has been proposed by Ugozzoli and Andreetti;[15] the values for the present compound are in Table 1, from which it can be seen that the sign sequence of the torsion angles is +−, ++, −+, −−, characteristic of a 1,2-alternate conformation. Molecular dimensions are entirely in accord with accepted values and have been deposited.

***N*-Oxide Derivatives. (a) Synthesis.** Regioisomers and conformational isomers of *p-tert*-butylcalix[4]arene containing pyridylmethyl 1-oxide pendant groups at the lower rim (compounds **2a**–**10a**, Chart 1) were synthesized in good yield by treating each pyridinyl precursor with an excess of *m*-chloroperoxybenzoic acid (*m*-CPBA) in dry $Et_2O$ (for dipyridinocalix[4]arenes) or THF (for tetrapyridinocalix[4]arenes). By using a limiting amount of *m*-CPBA, mixtures of products of partial oxidation are obtained. In particular, oxidation of *syn*-proximal bis-[(2-pyridylmethyl)oxy]calix[4]arene **2** with 2 equiv of *m*-CPBA afforded, in addition to bis-*N*-oxide **2a**, sizeable quantities of the inherently chiral mono-*N*-oxide derivative **14**.

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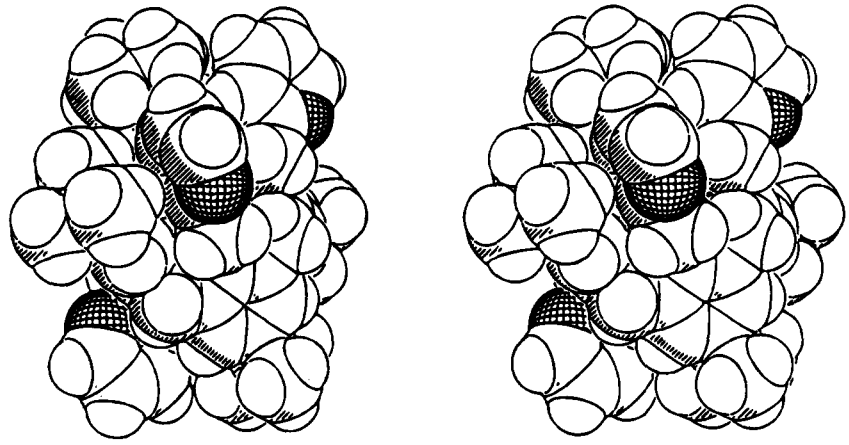
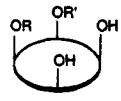


**Figure 3.** Stereoview of molecule **9** prepared with PLUTON with the atoms drawn as their van der Waals spheres.

**Table 1. Values of Torsion Angles $\phi$ and $\chi$ for 9 Defining the Calix[4]arene Conformation**[a]

| ring | $\phi$ | $\chi$ |
|---|---|---|
| C1–C6/C21′–C26′ | +86.2(2) | −72.8(2) |
| C21′–C26′/C1′–C6′ | +125.9(3) | +144.1(3) |
| C1′–C6′/C21–C27 | −86.2(2) | +72.8(2) |
| C21–C27/C1–C6 | −125.9(3) | −144.1(3) |

[a] Atoms marked with a prime are obtained from the atoms in the asymmetric unit by applying the symmetry transformation $-x, -y, -z$.




**14** R = $CH_2Py$; R' = $CH_2Py(O)$

Compounds **3a** and **8a–10a** precipitated from the reaction mixture as adducts with *m*-chlorobenzoic acid (*m*-CBA), as indicated by microanalytical data and $^1H$ NMR spectral analysis. The free ligands could be obtained by stirring a $CHCl_3$ solution of each adduct with solid $K_2CO_3$ for 30 min, followed by filtration of the salt, removal of the solvent, and recrystallization. In the other cases, *N*-oxide calix[4]arenes were purified by column chromatography on neutral alumina, by eluting with a gradient of MeOH in AcOEt. The molecular weight of all new compounds was deduced by FAB (+) MS spectroscopy.

**(b) NMR Spectral Features.** The NMR spectral patterns of *N*-oxide derivatives **2a–10a** are reminiscent of those of their pyridino precursors **2–10**, the only remarkable difference being a significant to large shift of the proton and carbon resonances in the heteroaromatic portion of the molecule. This can be interpreted in terms of increased electron density at the C2, C4, and C6 carbons (upfield shift of relevant protons and carbons ($\Delta\delta_C$ = 9.2–10.3 ppm)) and decreased electron density at the C3 and C5 atoms (downfield shift of relevant protons and carbons ($\Delta\delta_C$ = 0–2.3 ppm)), in the light of the resonance effect of the *N*-oxide group. The changes in $^{13}C$ shifts found for pyridine *N*-oxide calix[4]arenes **2a–10a**, as compared to those for the unoxidized parent compounds, parallel those reported for model compounds 2-picoline and 2-picoline *N*-oxide.[16]

The $^1H$ NMR spectra of the adducts of *N*-oxide calix[4]arene derivatives (compounds **2a**, **9a**, and **10a**) with

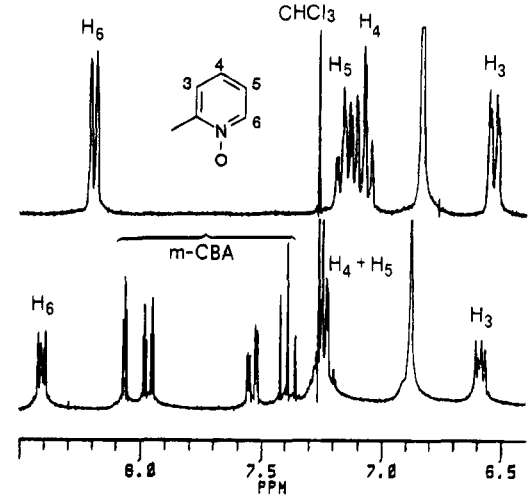



**Figure 4.** Aromatic region and chemical shift assignments in the $^1H$ NMR spectra (250 MHz, $CDCl_3$, 295 K) of 1,3-alternate tetrakis[[(1-oxopyrid-2-yl)methyl]oxy]calix[4]arene **10a** (top) and its adduct with *m*-CBA (bottom).

*m*-CBA can almost be superimposed onto those of the free ligands, except for the *N*-heterocyclic protons which undergo a downfield shift, suggestive of hydrogen-bonding formation between *N*-oxide functionalities and carboxy groups. The aromatic portion in the $^1H$ NMR spectra of **10a** and its adduct with *m*-CBA is shown in Figure 4.

Similar to the pertinent pyridinocalix[4]arene precursors, the very upfield resonance of H3 protons of the inverted pyridine *N*-oxide unit in partial cone structures **6a** and **8a** ($\delta$ 4.29 and 4.40 ppm, respectively) provides evidence that this group is also tightly accommodated into the hydrophobic calix cavity generated by the other three *syn*-oriented phenoxy residues.

The NMR spectra of the inherently chiral ($A^\alpha A^\alpha B^\alpha C^\alpha$ type[11f,17]) mono-*N*-oxide **14** deserve a brief comment. Because of the molecular asymmetry, the $^1H$ NMR spectra are very complex, and to cope with NMR analysis, we resorted to 2D COSY NMR experiments for attributions. The methylene and oxymethylene region, diagnostically important for conformational assignments, displays a 20-line pattern, which was analyzed in terms of six partly superimposed AB systems, as substantiated by appropriate cross-peak correlations in the COSY

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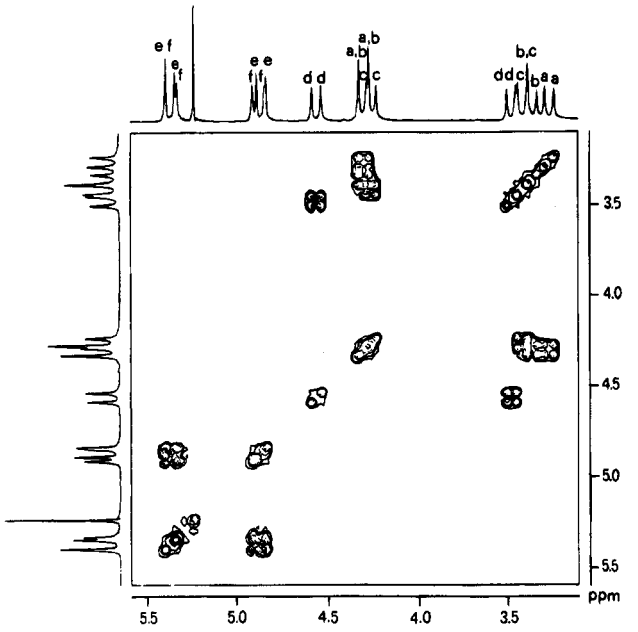



**Figure 5.** Methylene region of the COSY spectrum (250 MHz, $CDCl_3$, 295 K) of inherently chiral mono-*N*-oxide calix[4]arene **14**. Letters a–d refer to the four AB systems for the bridging methylenes and letters e and f to those of the two oxymethylene groups.

**Table 2. Percentage Extraction of Metal Picrates into $CH_2Cl_2$ by Pyridino and Pyridine *N*-Oxide Calix[4]arene Derivatives at 23 °C under Neutral Conditions**[a]

| ligand | $Li^+$ | $Na^+$ | $K^+$ | $Rb^+$ | $Cs^+$ |
|---|---|---|---|---|---|
| **2** | 0.9 | 0 | 0 | 0 | 0 |
| **3** | 0 | 0 (7.7)[b] | 0 | 0 | 0 |
| **4** | 0 | 0 | 0 | 0 | 0 |
| **5** | 3.8 | 6.6 (24.0)[b] | 4.7 | 4.4 | 4.0 |
| **6** | 1.6 | 2.1 (4.0)[b] | 2.5 | 2.3 | 2.2 |
| **7** | 3.8 | 6.3 (25.2)[b] | 4.8 | 4.4 | 4.2 |
| **8** | 1.6 | 2.6 | 2.4 | 2.7 | 1.4 |
| **9** | 0 | 0 | 0 | 0 | 0 |
| **10** | 0.6 | 0.8 | 1.6 | 1.6 | 0 |
| **2a** | 0 | 2.5 | 2.8 | 2.3 | 0 |
| **3a** | 0 | 1.1 | 0 | 0 | 0 |
| **4a** | 0 | 1.0 | 0 | 0 | 0 |
| **5a** | 1.9 | 2.9 | 2.7 | 2.1 | 2.0 |
| **6a** | 1.0 | 1.7 | 2.3 | 2.4 | 0 |
| **7a** | 0 | 0 (11.1)[b] | 0 | 0 | 0 |
| **8a** | 0 | 0 | 0 | 0 | 0 |
| **9a** | 0 | 0 | 0 | 0 | 0 |
| **10a** | 0 | 0 | 0 | 0 | 0 |

[a] Solutions of metal picrates in water and calixarene ligands in $CH_2Cl_2$ were $2.5 \times 10^{-4}$ M. [b] Ionic strength = 0.1 M ($NaClO_4$).

spectrum shown in Figure 5. The $^{13}C$ NMR spectrum shows 46 of the 48 expected resonances for carbon atoms, which were partly assigned by DEPT experiments (see the Experimental Section).

**Complexation Studies.** In order to assess the complexing ability of pyridino and pyridine *N*-oxide calix[4]arenes, two-phase alkali metal picrate extraction experiments[18] from water into $CH_2Cl_2$ under neutral conditions at 23 °C were conducted, with the results shown in Table 2.

The efficiency of our ionophores is low, as compared to that of classic calix[4]arenes bearing carbonyl functionalities at the lower rim,[1] and the highest phase-transfer values are observed for cone tetrapyridinocalix[4]arene **7**, where selectivity follows the order $Na^+ > K^+ > Rb^+ > Cs^+ > Li^+$. Extractability could be significantly increased by increasing the ionic strength of the aqueous solution by addition of 0.1 M perchlorate salt. Surprisingly, the ionophoric activity of *N*-oxide calixarenes is almost absent, probably due to strong hydrogen-bonding formation between N–O functionalities and water molecules at the water–$CH_2Cl_2$ interface.

(18) Pedersen, C. J. *Fed. Proc.* **1968**, *27*, 1305.

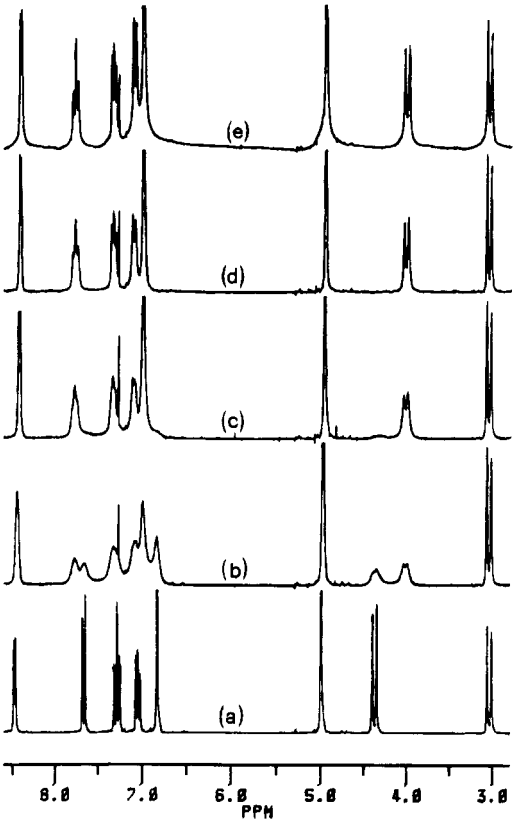



**Figure 6.** Complexation of $Na^+$ by cone tetrapyridinocalix[4]arene **7**. The 3.0–8.5 ppm region in the $^1H$ NMR spectrum (250 MHz, $CDCl_3$, 295 K) of the free ligand (a) and at different time intervals from the addition of solid NaSCN: (b) 10 min, (c) 1 d, (d) 4d, and (e) 8d.

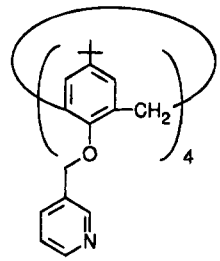
Complexation of alkali metal cations by pyridino and pyridine *N*-oxide calix[4]arenes in aprotic solvents can be easily detected by either $^1H$ or $^{13}C$ NMR measurements. The addition of NaSCN to **7** initially caused considerable broadening of most signals and splitting of the heteroaromatic and axial methylene protons, indicating that complexation with $Na^+$ was occurring (Figure 6b). $^1H$ NMR spectra were repeatedly scanned at various time intervals (1 to 8 d) (Figure 6c–e). After 1 d, th signals of the ligand had almost disappeared, whereas resonances of the $Na^+$ complex were still broadened (Figure 6c); the latter became sharp after 4 d (Figure 6d), and on the 8th day, a fine structure of heteroaromatic multiplets could be observed (Figure 6e), indicating that the equilibrium was reached.

Upon complex formation, the chemical shifts of most signals change, with the exception of *tert*-butyl and equatorial methylene protons. 3-Pyridyl and concomitantly axial methylene protons undergo a remarkable upfield shift ($\Delta\delta$ = 0.59 and 0.39 ppm, respectively), while 4- and 5-pyridyl protons move in opposite directions with a deshielding of 0.48 and 0.26 ppm, respectively.

These results may be interpreted in terms of the slow complexation rate of pyridinocalix[4]arene **7** with $Na^+$ (as

suggested by the 24 h reaction time required to reach a distribution equilibrium in extraction experiments). In the solid state (and likely in solution), the ligand adopts a distorted cone conformation (approaching a $C_{2v}$ symmetry), and in agreement with MM2 molecular mechanics calculations, the ring nitrogen atoms assume a *trans* configuration relative to the ethereal oxygens, as a result of electrostatic repulsion between the two heteroatoms.[11c] Thus, the low complexation rate of **7** has to be ascribed to the low preorganization of the nitrogen binding sites before complexation and to the energy required for *all-cis* reorganization of heteroatoms.[19]

We do believe that the $Na^+$ cation in the complex is encapsulated into the hydrophilic cavity generated by the ethereal oxygens and 2-pyridyl nitrogens, in a fashion similar to that described by Ungaro et al. for the $K^+$ complex with a calix[4]arene tetraester.[5a] This conclusion is corroborated by the fact that the structural isomer cone 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(3-pyridylmethyl)oxy]calix[4]arene (**15**), obtained in 70% yield by alkylation of **1** with an excess of PicCl·HCl and $K_2CO_3$ in dry DMF, is unable to form a complex with $Na^+$ because of the unfavorable geometry created by the 3-pyridinyl substituents, indirectly confirming that in **7** complexation of $Na^+$ is realized through a cooperative effect of oxygen and nitrogen donor atoms.




**15**

Complexation of **7** with KSCN is very similar to that observed for NaSCN, the most notable difference being a much lower complexation rate. A broadened spectrum of the $K^+$ complex could be obtained only after 8 d, so that one can estimate that the complexation rate of $K^+$ by **7** is about 8 times slower than that of $Na^+$.

Conversely, the complexation rate of alkali metal cations by pyridine *N*-oxide calix[4]arene **7a** in aprotic solvents is much faster, as one could expect from the replacement of soft donor sites by hard ones. The addition of solid NaSCN to a $CDCl_3$ solution of **7a** initially produced a splitting and broadening of heteroaromatic, oxymethylene, and $ArCH_2Ar$ protons (Figure 7b), but after about 14 h, the broad signals disappeared totally, and new sharp resonances arising from the $Na^+$ complex were obtained (Figure 7c).

Upon complexation, the 4-, 5-, and 6-pyridine *N*-oxide protons undergo a downfield shift with $\Delta\delta$ in the range 0.37−0.76 ppm, while the remaining 3-pyridinyl *N*-oxide protons shift 0.88 ppm upfield, relative to those of the uncomplexed ligand. The oxymethylene protons appear as a very broad signal at $\delta$ 5.39 ppm (deshielding of 0.17 ppm), while methylene protons are shifted at a higher magnetic field (with a shielding of 0.96 ppm for the axial protons and 0.35 ppm for the equatorial ones).

(19) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645.

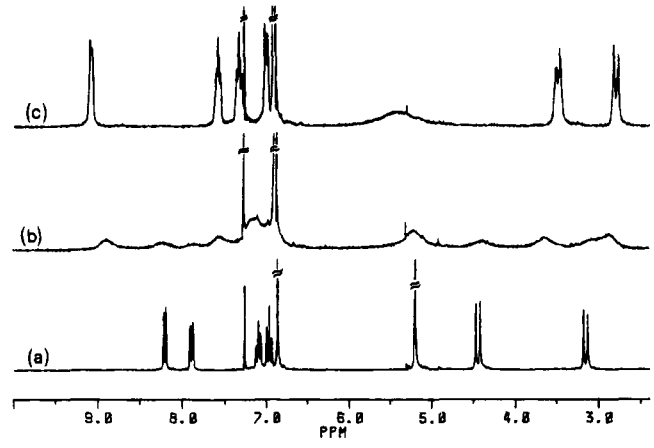



**Figure 7.** Complexation of $Na^+$ by cone tetrapyridine *N*-oxide calix[4]arene **7a**. The $^1H$ NMR spectrum (250 MHz, $CDCl_3$, 295 K) of the free ligand (a), immediately after the addition of solid NaSCN (b), and after 14 h (c).

The $^1H$ NMR spectra of the KSCN complex with **7a** are qualitatively similar to those of its $Na^+$ complex. However, broadening of the signals persisted for a longer time, and only on the 4th d of exposure to solid KSCN did the equilibrium appear to be reached.

The $^{13}C$ NMR spectra of $Na^+$ and $K^+$ complexes with **7a** have been measured in $CDCl_3$ solution. Upon complexation, the resonances of the carbons of the calix[4]arene skeleton are affected little, while significant downfield shifts (up to 2.83 ppm) are observed for oxymethylene and heteroaromatic carbons, the latter due to a reduced resonance effect of *N*-oxide groups involved in the complexation.

## Conclusions

Regioisomers and conformational isomers of *p-tert*-butylcalix[4]arene bearing 2-pyridylmethyl or 2-pyridylmethyl 1-oxide pendant units at the lower rim have been synthesized and characterized. Extraction studies with alkali metal picrates from an aqueous solution into $CH_2Cl_2$ have shown that the efficiency of these ligands is low, as compared to that of classic calix[4]arenes possessing carbonyl functionalities at the lower rim. The highest phase-transfer values are observed for cone tetrapyridinocalix[4]arene **7** (with a preference for $Na^+$), while its *N*-oxide derivative **7a** is almost inactive. In contrast, NMR complexation studies of cone structures **7** and **7a** with $Na^+$ and $K^+$, while confirming a low complexation rate, provide evidence that tetra-*N*-oxide derivative **7a** is a faster complexer than **7** in aprotic solvents.

## Experimental Section

**General Comments.** Melting points were determined on a Kofler or Electrothermal melting point apparatus and are uncorrected. Chemical shifts ($\delta$) refer to $CDCl_3$ solutions from internal $Me_4Si$. Multiplicities in $^{13}C$ NMR spectra were obtained by DEPT experiments. For FAB (+) MS, 3-nitrobenzyl alcohol was used as a matrix. All chemicals were reagent grade and were used without further purification. Anhydrous DMF, $Et_2O$, and THF were purchased from Fluka. $R_f$ values were measured using silica gel TLC plates (absorbant thickness, 250 $\mu$m) containing a fluorescence indicator. Most pyridinocalix[4]arene precursors were available from previous work.[11c]

**5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(2-pyridylmethyl)oxy]-27,28-bis(benzyloxy)calix[4]arene, Cone Conformer (3).** A stirred mixture of **2** (0.25 g, 0.3 mmol), benzyl bromide (0.2 g, 1.2 mmol), and NaH (30 mg, 1.2 mmol) in anhydrous THF (10 mL) was refluxed for 2 h. The reaction was quenched by addition of a few drops of water, and the solvent evaporated. The residue was partitioned between water and $CH_2Cl_2$. The organic layer was separated from the water layer and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent followed by recrystallization gave **3** (0.25 g, 83%) as colorless needles: mp 233–236 °C ($CH_2Cl_2$–MeOH); $^1$H NMR $\delta$ 1.08 (s, 36 H), 2.88, 2.95, 3.05 (d, $J$ = 12.6 Hz, 1:2:1 ratio, 4 H), 4.23, 4.27, 4.39 (d, $J$ = 12.6 Hz, 1:2:1 ratio, 4 H), 4.83, 4.87 (ABq, $J$ = 11.6 Hz, 4 H), 4.97 (s, 4 H), 6.76–6.80 (m, 8 H), 7.05–7.29 (m, 14 H), 7.81 (d, $J$ = 7.8 Hz, 2 H), and 8.51 (d, $J$ = 4.8 Hz, 2 H); $^{13}$C NMR $\delta$ 30.83, 30.94, 31.25 (t), 31.40 (q), 33.80 (s), 76.83, 77.72 (t), 122.13, 123.11, 124.99, 125.08, 125.20, 125.30 (d), 127.52, 127.83, 129.52 (d), 133.52, 133.56, 133.85, 133.89 (s), 136.28 (d), 137.97, 144.60, 144.77 (s), 148.42 (d), 152.38, 152.75, and 158.40 (s); FAB (+) MS $m/z$ (relative intensity) 1011 (100, MH$^+$). Anal. Calcd for $C_{70}H_{78}N_2O_4$: C, 83.10; H, 7.77; N, 2.77. Found: C, 83.33; H, 7.88; N, 2.64.

**Alkylation of 5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)calix[4]arene (11) with PicCl·HCl.** A stirred mixture of **11** (3.74 g, 4.5 mmol), PicCl·HCl (2.96 g, 18 mmol), and $Cs_2CO_3$ (11.7 g, 36 mmol) in acetone (200 mL) was refluxed for 20 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated to dryness to give an oily residue (5.7 g). An aliquot (200 mg) was chromatographed (column, $SiO_2$) by eluting with a gradient of AcOEt in cyclohexane to give tri-O-alkylated conformers **12** and **13** in a roughly 3:1 ratio.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)-26-[(2-pyridylmethyl)oxy]-28-hydroxycalix[4]arene, cone conformer (12):** 28 mg; mp 215–217 °C (acetone); $R_f$ = 0.42 (cyclohexane–AcOEt, 4:1); $^1$H NMR $\delta$ 0.83, 1.31, 1.35 (s, 2:1:1 ratio, 36 H), 3.07, 4.24 (ABq, $J$ = 12.5 Hz, 4 H), 3.10, 4.16 (ABq, $J$ = 13.5 Hz, 4 H), 4.50, 4.53 (ABq, $J$ = 11.1 Hz, 4 H), 4.93 (s, 2 H), 6.51 (d, $J$ = 2.3 Hz, 2 H), 6.57 (s, 1 H), 6.64 (d, $J$ = 2.4 Hz, 2 H), 7.0–7.2 (m, 15 H), 7.41 (td, $J$ = 7.7, 1.7 Hz, 1 H), 8.43 (d, $J$ = 4.9 Hz, 1 H), and 8.55 (d, $J$ = 7.7 Hz, 1 H); $^{13}$C NMR $\delta$ 30.58, 31.46 (t), 31.01, 31.68, 31.74 (q), 33.70, 33.79, 34.15 (s), 78.04 (t), 121.94, 124.56, 124.92, 125.00, 125.65, 127.88, 128.11, 129.13 (d), 128.09, 132.06, 132.53, 135.55 (s), 136.21 (d), 136.69, 141.00, 145.49, 146.05 (s), 147.04 (d), 150.59, 150.76, 153.08, and 158.12 (s); FAB (+) MS $m/z$ (relative intensity) 920 (100, MH$^+$). Anal. Calcd for $C_{64}H_{73}NO_4$: C, 83.53; H, 8.00; N, 1.52. Found: C, 83.67; H, 8.17; N, 1.58.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)-26-[(2-pyridylmethyl)oxy]-28-hydroxycalix[4]arene, partial cone conformer (13):** 85 mg; mp 200–203 °C (MeOH); $R_f$ = 0.56 (cyclohexane–AcOEt, 4:1); $^1$H NMR $\delta$ 0.70, 1.13, 1.35 (s, 2:1:1 ratio, 36 H), 3.16, 4.11 (ABq, $J$ = 12.7 Hz, 4 H), 3.91, 4.01 (ABq, $J$ = 17.0 Hz, 4 H), 4.44 (s, 2 H), 4.59 (d, $J$ = 8.2 Hz, 1 H), 4.73, 5.04 (ABq, $J$ = 11.8 Hz, 4 H), 6.07 (td, $J$ = 7.8, 1.7 Hz, 1 H), 6.61 (d, $J$ = 2.3 Hz, 2 H), 6.62 (m, 1 H), 6.81 (d, $J$ = 2.4 Hz, 2 H), 7.08 (d, $J$ = 3.2 Hz, 4 H), 7.21 (m, 10 H), 7.99 (s, 1 H), and 8.09 (d, $J$ = 4.9 Hz, 1 H); $^{13}$C NMR $\delta$ 30.83, 31.33, 31.81 (q), 32.33 (t), 33.46, 33.92, 33.94 (s), 39.32 (t), 68.91, 75.18 (t), 120.05, 120.72, 124.43, 124.77, 125.63, 126.00, 127.41, 127.60, 128.27 (d), 128.69, 132.27, 132.81 (s), 136.25 (d), 137.49, 141.13, 145.82, 146.01 (s), 146.73 (d), 150.57, 152.12, 152.42, and 157.34 (s); FAB (+) MS $m/z$ (relative intensity) 920 (100, MH$^+$). Anal. Calcd for $C_{64}H_{73}NO_4$: C, 83.53; H, 8.00; N, 1.52. Found: C, 83.27; H, 8.11; N, 1.45.

The above residue was dissolved in anhydrous THF (30 mL) and treated with NaH (0.24 g, 10 mmol) and additional PicCl·HCl (0.49 g). The resulting mixture was refluxed under stirring for 2 h. It was then cooled in an ice bath, treated with MeOH (1 mL) to destroy excess NaH, and diluted with water (15 mL). The mixture was extracted with $CH_2Cl_2$, washed with water, and dried ($Na_2SO_4$). The solvent was removed in vacuo, and the residue was chromatographed (column, $SiO_2$) using a gradient of AcOEt in cyclohexane as an eluent to give tetra-O-alkylated conformers **5** and **6**.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)-26,28-bis[(2-pyridylmethyl)oxy]calix[4]arene, cone conformer (5):** 22% overall yield; mp 219–221 °C ($CH_2Cl_2$–MeOH); $R_f$ = 0.21 (cyclohexane–AcOEt, 4:1); $^1$H NMR $\delta$ 1.02, 1.14 (s, 18 H each), 2.96, 4.30 (ABq, $J$ = 12.6 Hz, 8 H), 4.81, 5.03 (s, 4 H each), 6.72, 6.85 (s, 4 H each), 7.05 (m, 2 H), 7.10–7.24 (m, 12 H), 7.77 (d, $J$ = 7.7 Hz, 2 H), and 8.51 (d, $J$ = 4.9 Hz, 2 H); $^{13}$C NMR $\delta$ 30.97 (t), 31.35, 31.49 (q), 33.79, 33.87 (s), 77.02, 77.84 (t), 122.11, 123.45, 125.03, 125.29, 127.48, 127.94, 129.10 (d), 133.47, 133.89 (s), 136.21 (d), 137.97, 144.59, 144.79 (s), 148.33 (d), 152.12, 153.21, and 158.46 (s); FAB (+) MS $m/z$ (relative intensity) 1011 (100, MH$^+$). Anal. Calcd for $C_{70}H_{78}N_2O_4$: C, 83.10; H, 7.77; N, 2.77. Found: C, 82.94; H, 7.90; N, 2.72.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)-26,28-bis[(2-pyridylmethyl)oxy]calix[4]arene, partial cone conformer (6):** 56% overall yield; mp 208–210 °C ($CH_2Cl_2$–MeOH); $R_f$ = 0.43 (cyclohexane–AcOEt, 4:1); $^1$H NMR $\delta$ 0.68, 1.37, 1.47 (s, 2:1:1 ratio, 36 H), 2.90, 3.94 (ABq, $J$ = 12.2 Hz, 4 H), 3.62, 3.66 (ABq, $J$ = 16.5 Hz, 4 H), 4.28, 4.31 (ABq, $J$ = 11.4 Hz, 4 H), 4.35 (s, 2 H), 4.67 (d, $J$ = 7.7 Hz, 1 H), 4.79 (s, 2 H), 6.33 (td, $J$ = 7.7, 1.8 Hz, 1 H), 6.50 (d, $J$ = 2.4 Hz, 2 H), 6.69 (m, 5 H), 6.75 (d, $J$ = 2.4 Hz, 2 H), 7.07–7.21 (m, 11 H), 7.33 (td, $J$ = 7.7, 1.8 Hz, 1 H), 7.59 (d, $J$ = 7.8 Hz, 1 H), 8.16 (d, $J$ = 4.9 Hz, 1 H), and 8.45 (d, $J$ = 4.9 Hz, 1 H); $^{13}$C NMR $\delta$ 31.43, 39.15 (t), 30.84, 31.70, 31.87 (q), 33.38, 34.26 (s), 69.46, 75.13, 75.38 (t), 120.51, 120.79, 121.17, 124.58, 125.06, 125.19, 126.25, 127.71, 127.82, 129.56 (d), 132.55, 133.28, 133.91, 135.65 (s), 136.08, 136.26 (d), 137.31, 144.77, 144.83, 145.66 (s), 146.99, 147.04 (d), 152.35, 152.78, 153.00, 157.75, and 158.52 (s); FAB (+) MS $m/z$ (relative intensity) 1011 (100, MH$^+$). Anal. Calcd for $C_{70}H_{78}N_2O_4$: C, 83.10; H, 7.77; N, 2.77. Found: C, 83.34; H, 7.66; N, 2.61.

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(2-pyridylmethyl)oxy]calix[4]arene, 1,2-Alternate Conformer (9).** A stirred mixture of **1** (0.74 g, 1 mmol), PicCl·HCl (3.28 g, 20 mmol), and $Cs_2CO_3$ (13 g, 40 mmol) in dry DMF (20 mL) was heated at 70 °C for 36 h. Usual workup followed by careful chromatography (column, $SiO_2$, a gradient of AcOEt in cyclohexane as an eluent) gave the known[11c] tetra-O-alkylated 1,3-alternate **10** (18–20%) and partial cone **8** (50–54%), along with the hitherto unreported 1,2-alternate stereoisomer **9** (2–3%): mp 275–277 °C dec (AcOEt); $R_f$ = 0.33 (cyclohexane–AcOEt, 1:1); FAB (+) MS $m/z$ (relative intensity) 1013 (100, MH$^+$). For NMR spectral data, see ref 11g. Anal. Calcd for $C_{68}H_{76}N_4O_4$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.47; H, 7.39; N, 5.67.

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(3-pyridylmethyl)oxy]calix[4]arene, Cone Conformer (15).** A stirred slurry of **1** (0.74 g, 1 mmol), 3-(chloromethyl)pyridine hydrochloride (3.28 g, 20 mmol), and $K_2CO_3$ (5.5 g, 40 mmol) in dry DMF (20 mL) was heated at 60 °C for 20 h under $N_2$. After cooling, the reaction mixture was poured into water (100 mL) and extracted with $CHCl_3$. The organic solution was dried over anhydrous $Na_2SO_4$ and evaporated. The residue was extracted with hot hexane (2 × 20 mL) to remove the excess of alkylating agent. The insoluble material was then subjected to column chromatography (neutral alumina, eluent 0–2% MeOH in AcOEt) to give **15** in 70% yield: mp 256–258 °C (AcOEt); $^1$H NMR $\delta$ 1.05 (s, 36 H), 2.80, 3.95 (ABq, $J$ = 12.6 Hz, 8 H), 4.84 (s, 8 H), 6.72 (s, 8 H), 7.13 (dd, $J$ = 7.8, 4.8 Hz, 4 H), 7.49 (m, 4 H), 8.55 (dd, $J$ = 4.8, 1.4 Hz, 4 H), and 8.57 (d, $J$ = 1.8 Hz, 4 H); $^{13}$C NMR $\delta$ 30.66 (t), 31.02 (q), 33.58 (s), 73.71 (t), 122.53, 124.92 (d), 132.63, 133.61 (s), 136.39 (d), 145.35 (s), 148.78, 150.63 (d), and 151.28 (s); FAB (+) MS $m/z$ (relative intensity) 1013 (MH$^+$). Anal. Calcd for $C_{68}H_{76}N_4O_4$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.88; H, 7.74; N, 5.45.

**General Procedures for the *m*-CPBA Oxidation of Pyridinocalix[4]arenes. Method A. Bis-*N*-Oxides.** To a chilled solution of the appropriate bis[(2-pyridylmethyl)oxy]-calix[4]arene (0.3 mmol) in dry $Et_2O$ (30 mL) was added dropwise a solution of *m*-CPBA (4 equiv) in $Et_2O$ (10 mL). The reaction mixture was stirred at rt for 24 h, and the solvent evaporated. The residue was dissolved in $CHCl_3$ (30 mL) and treated with anhydrous $K_2CO_3$ (2–3 g). The mixture was stirred for 0.5 h at rt and filtered. The solvent was removed in vacuo to leave the crude bis-*N*-oxide. It was further purified

by chromatography (column, neutral $Al_2O_3$), eluting with a gradient of MeOH (0–2%) in AcOEt.

**Method B. Tetra-*N*-Oxides.** To a chilled solution of tetrakis[(2-pyridylmethyl)oxy]calix[4]arene (0.3 g, 0.3 mmol) in anhydrous THF (20 mL) was added dropwise a solution of *m*-CPBA (8 equiv) in THF (10 mL). The reaction mixture was stirred for 3 h. With the exception of the cone conformer, from the reaction mixture was formed a precipitate, which was shown ($^1$H NMR, elemental analysis) to be a *m*-CBA–tetra-*N*-oxide adduct. Usual workup followed by chromatography (column, neutral $Al_2O_3$, a gradient of MeOH (0–10%) in AcOEt) gave the corresponding tetra-*N*-oxide.

***syn-prox*-5,11,17,23-Tetra-*tert*-butyl-25,26-bis[(1-oxopyrid-2-yl)methyl]oxy]-27,28-dihydroxycalix[4]arene (2a):** 59% yield; mp 157–159 °C ($Et_2O$); $^1$H NMR $\delta$ 1.17, 1.20 (s, 18 H each), 3.39, 4.26 (ABq, $J$ = 13.6 Hz, 4 H), 3.47, 4.18 (ABq, $J$ = 13.8 Hz, 2 H), 3.48, 4.52 (ABq, $J$ = 12.6 Hz, 2 H), 4.99, 5.22 (ABq, $J$ = 15.2 Hz, 4 H), 6.9–7.2 (m, 12 H), 7.92 (bd, $J$ = 6.3 Hz, 2 H), 8.21 (dd, $J$ = 6.1, 1.3 Hz, 2 H), and 8.74 (bs, 2 H); $^{13}$C NMR $\delta$ 30.37, 32.45, 32.77 (t), 31.16, 31.40 (q), 33.79, 34.07 (s), 71.10 (t), 124.54, 125.30, 125.40, 126.11, 126.19 (d), 127.30, 127.56, 132.84, 133.88 (s), 138.90 (d), 142.59, 147.41, 147.90, 148.85, and 150.99 (s); FAB (+) MS $m/z$ (relative intensity) 863 (100, MH$^+$). Anal. Calcd for $C_{56}H_{66}N_2O_6$: C, 77.92; H, 7.71; N, 3.25. Found: C, 78.11; H, 7.65; N, 3.40.

By carrying the oxidation with a defect of *m*-CPBA (2 equiv), sizeable quantities (30–35%) of the chiral mono-*N*-oxide **14** could also be isolated.

***syn-prox*-5,11,17,23-Tetra-*tert*-butyl-25-[(2-pyridylmethyl)oxy]-26-[[(1-oxopyrid-2-yl)methyl]oxy]-27,28-dihydroxycalix[4]arene (14):** mp 141–144 °C ($Et_2O$); $^1$H NMR $\delta$ 1.08, 1.20, 1.21, 1.22 (s, 9 H each), 3.26, 4.30 (ABq, $J$ = 13.0 Hz, 2 H), 3.36, 4.31 (ABq, $J$ = 13.2 Hz, 2 H), 3.41, 4.26 (ABq, $J$ = 13.4 Hz, 2 H), 3.47, 4.56 (ABq, $J$ = 12.7 Hz, 2 H), 4.86, 5.37 (ABq, $J$ = 12.6 Hz, 2 H), 4.87, 5.36 (ABq, $J$ = 16.3 Hz, 2 H), 6.88–7.24 (overlapped, 11 H), 7.32 (d, $J$ = 7.8 Hz, 1 H), 7.55 (dt, $J$ = 7.7, 1.7 Hz, 1 H), 8.20 (dd, $J$ = 6.3, 0.9 Hz, 1 H), 8.25 (bd, $J$ = 8.5 Hz, 1 H), 8.63 (dd, $J$ = 4.9, 0.8 Hz, 1 H), 8.83, and 9.87 (bs, 1 H each); $^{13}$C NMR $\delta$ 30.96 (t), 31.16, 31.33, 31.44, 31.56 (q), 32.33, 32.71, 33.18 (t), 33.80, 33.86, 33.98, 34.16 (s), 71.03, 77.94 (t), 122.12, 122.98, 123.73, 124.89, 125.14, 125.26, 125.47, 125.70, 125.81, 126.23, 126.35, 126.80 (d), 126.89, 126.99, 127.77, 129.20, 132.86, 132.97, 133.02, 134.56 (s), 136.79, 138.60 (d), 141.84, 142.57, 146.53, 147.35, 148.28 (s), 149.13 (d), 150.08, 151.53, 151.88, and 156.53 (s); FAB (+) MS $m/z$ (relative intensity) 847 (100, MH$^+$). Anal. Calcd for $C_{56}H_{66}N_2O_5$: C, 79.40; H, 7.85; N, 3.31. Found: C, 79.68; H, 7.72; N, 3.44.

***bis*(*syn-prox*)-5,11,17,23-Tetra-*tert*-butyl-25,26-bis[[(1-oxopyrid-2-yl)methyl]oxy]-27,28-bis(benzyloxy)calix[4]arene (3a):** 77% yield; mp 234–236 °C ($Et_2O$); $^1$H NMR $\delta$ 1.08, 1.10 (s, 18 H each), 3.00, 3.02, 3.19 (d, $J$ = 12.6 Hz, 1:2:1 ratio, 4 H), 4.21, 4.36, 4.41 (d, $J$ = 12.6 Hz, 2:1:1 ratio, 4 H), 4.80, 4.91 (ABq, $J$ = 11.5 Hz, 4 H), 4.94, 5.01 (ABq, $J$ = 16.8 Hz, 4 H), 6.77 (t, $J$ = 7.7 Hz, 2 H), 6.81 (s, 4 H), 6.86, 6.88 (ABq, $J$ = 2.3 Hz, 4 H), 7.06–7.26 (m, 12 H), 8.16 (dd, $J$ = 7.8, 1.3 Hz, 2 H), and 8.22 (d, $J$ = 6.3 Hz, 2 H); $^{13}$C NMR $\delta$ 29.59, 30.26, 30.93 (t), 31.30, 31.35 (q), 33.79, 33.85 (s), 70.95, 77.31 (t), 123.75, 124.71, 125.13, 125.28, 125.37, 125.55, 125.66, 127.87, 129.61 (d), 133.35, 133.47, 133.67, 133.83, 137.36 (s), 138.42 (d), 145.00, 145.69, 149.21, 151.82, and 152.10 (s); FAB (+) MS $m/z$ (relative intensity) 1043 (100, MH$^+$). Anal. Calcd for $C_{70}H_{78}N_2O_6$: C, 80.58; H, 7.53; N, 2.68. Found: C, 80,26; H, 7.75; N, 2.60.

***syn-dist*-5,11,17,23-Tetra-*tert*-butyl-25,27-bis[[(1-oxopyrid-2-yl)methyl]oxy]-26,28-dihydroxycalix[4]arene (4a):** 66% yield, mp 156–158 °C (MeOH); $^1$H NMR $\delta$ 0.93, 1.30 (s, 18 H each), 3.37, 4.20 (ABq, $J$ = 13.2 Hz, 8 H), 5.33 (s, 4 H), 6.79, 7.10 (s, 4 H each), 6.91 (s, 2 H), 7.23–7.34 (m, 4 H), 8.31 (dd, $J$ = 5.8, 1.6 Hz, 2 H), and 8.52 (dd, $J$ = 7.3, 2.7 Hz, 2 H); $^{13}$C NMR $\delta$ 30.84, 31.61 (q), 31.48 (t), 33.83, 33.90 (s), 71.69 (t), 123.67, 124.14, 125.17, 125.76 (d), 126.22, 127.53, 131.98 (s), 139.11 (d), 142.20, 147.82, 148.72, 149.24, and 150.24 (s); FAB (+) MS $m/z$ (relative intensity) 863 (100, MH$^+$). Anal. Calcd for $C_{56}H_{66}N_2O_6$: C, 77.92; H, 7.71; N, 3.25. Found: C, 78.04; H, 7.87; N, 3.32.

***bis*(*syn-dist*)-5,11,17,23-Tetra-*tert*-butyl-25,27-bis[[(1-oxopyrid-2-yl)methyl]oxy]-26,28-bis(benzyloxy)calix[4]arene (5a):** 80% yield; mp 236–238 °C ($CH_3CN$); $^1$H NMR $\delta$ 0.94, 1.26 (s, 18 H each), 3.08, 4.39 (ABq, $J$ = 12.7 Hz, 8 H), 4.72 (s, 4 H), 5.32 (s, 4 H), 6.32 (dt, $J$ = 7.8, 1.0 Hz, 2 H), 6.67, 7.05 (s, 4 H each), 6.87 (m, 2 H), 7.16 (m, 10 H), 8.13 (dd, $J$ = 6.4, 0.8 Hz, 2 H), and 8.34 (dd, $J$ = 7.9, 1.8 Hz, 2 H); $^{13}$C NMR $\delta$ 30.74 (t), 31.12, 31.48 (q), 33.73, 33.94 (s), 71.25, 77.85 (t), 123.39, 124.98, 125.24, 125.46, 125.82, 127.89, 128.19, 128.99 (d), 132.64, 134.24, 136.98 (s), 137.97 (d), 145.14, 145.75, 149.37, 151.09, and 153.90 (s); FAB (+) MS, $m/z$ (relative intensity) 1043 (100, MH$^+$). Anal. Calcd for $C_{70}H_{78}N_2O_6$: C, 80.58; H, 7.53; N, 2.68. Found: C, 80.79; H, 7.65; N, 2.73.

***anti-dist*-5,11,17,23-Tetra-*tert*-butyl-25,27-bis[[(1-oxopyrid-2-yl)methyl]oxy]-26,28-bis(benzyloxy)calix[4]arene (6a):** 77% yield; mp 240–243 °C ($CH_3CN$); $^1$H NMR $\delta$ 0.71, 1.39, 1.53 (s, 2:1:1 ratio, 36 H), 3.04, 4.00 (ABq, $J$ = 12.3 Hz, 4 H), 3.63, 3.67 (ABq, $J$ = 17.1 Hz, 4 H), 4.20 (s, 4 H), 4.29 (d, $J$ = 6.6 Hz, 1 H), 4.37 (s, 2 H), 4.92 (s, 2 H), 5.68 (t, $J$ = 7.6 Hz, 1 H), 6.54, 6.76 (ABq, $J$ = 2.3 Hz, 4 H), 6.68 (m, 5 H), 6.98 (m, 1 H), 7.09–7.23 (m, 11 H), 7.51 (d, $J$ = 6.7 Hz, 1 H), 7.82 (d, $J$ = 6.1 Hz, 1 H), and 8.07 (d, $J$ = 5.8 Hz, 1 H); $^{13}$C NMR $\delta$ 30.65 (q), 31.36 (t), 31.51, 31.70 (q), 33.30, 34.18, 34.21 (s), 38.90 (t), 63.50, 68.68, 75.65 (t), 122.12, 122.53, 123.54, 124.16, 124.93, 125.35, 125.51, 125.80, 125.88, 127.77, 127.85, 128.13, 129.28 (d), 132.57, 132.70, 134.00, 135.71, 136.44 (s), 136.66, 136.72 (d), 144.99, 145.42, 146.49, 147.90, 148.20, 151.97, 152.17, and 152.73 (s); FAB (+) MS $m/z$ (relative intensity) 1043 (100, MH$^+$). Anal. Calcd for $C_{70}H_{78}N_2O_6$: C, 80.58; H, 7.53; N, 2.68. Found: C, 80.46; H, 7.80; N, 2.54.

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[[(1-oxopyrid-2-yl)methyl]oxy]calix[4]arene, cone conformer (7a):** 48% yield; mp 243–245 °C ($CH_3CN$) (lit.[11a] mp not reported); $^{13}$C NMR $\delta$ 30.38 (t), 31.27 (q), 33.86 (s), 71.06 (t), 124.28, 125.53 (d), 133.35 (s), 138.79 (d), 145.80 (s), 148.58 (s), and 152.15 (s).

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[[(1-oxopyrid-2-yl)methyl]oxy]calix[4]arene, partial cone conformer (8a):** 71% yield; mp 163–165 °C ($CCl_4$); $^1$H NMR $\delta$ 0.75, 1.26, 1.38 (s, 2:1:1 ratio, 36 H), 3.22, 4.43 (ABq, $J$ = 12.2 Hz, 4 H), 3.90, 4.09 (ABq, $J$ = 17.3 Hz, 4 H), 4.37 (d, $J$ = 8.2 Hz, 1 H), 4.48 (s, 2 H), 4.95 (s, 4 H), 5.04 (s, 2 H), 5.91 (t, $J$ = 7.8 Hz, 1 H), 6.62, 6.87 (ABq, $J$ = 2.3 Hz, 4 H), 6.69–6.83 (m, 3 H), 7.03–7.08 (m, 4 H), 7.17, 7.26 (s, 2 H each), 7.20 (m, 3 H), 7.89, and 8.12 (m, 2 H each); $^{13}$C NMR $\delta$ 30.79, 31.55 (q), 31.11 (t), 33.53, 34.15, 34.33 (s), 38.95, 63.87, 68.57, 70.01 (t), 122.34, 123.20, 123.53, 124.34, 125.09, 125.31, 125.45, 125.58, 125.99, 126.24, 126.53, 126.67 (d), 131.76, 133.14, 133.37, 135.22 (s), 137.24, 138.14, 138.84 (d), 145.87, 146.44, 148.15, 148.25, 148.36, 152.28, and 152.70 (s); FAB (+) MS $m/z$ (relative intensity) 1077 (100, MH$^+$). Anal. Calcd for $C_{68}H_{76}N_4O_8$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.53; H, 7.28; N, 5.11.

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[[(1-oxopyrid-2-yl)methyl]oxy]calix[4]arene, 1,2-alternate conformer (9a):** 82% yield; mp 247–249 °C ($CH_3CN$–$CH_2Cl_2$); $^1$H NMR $\delta$ 1.13 (s, 36 H), 3.34, 4.33 (ABq, $J$ = 12.4 Hz, 4 H), 4.08 (s, 4 H), 4.69 (s, 8 H), 6.24 (dd, $J$ = 7.9, 1.5 Hz, 4 H), 6.59 (td, $J$ = 7.8, 0.7 Hz, 4 H), 6.86 (td, $J$ = 7.7, 1.9 Hz, 4 H), 7.04, 7.28 (ABq, $J$ = 2.3 Hz, 8 H), and 7.89 (d, $J$ = 6.1 Hz, 4 H); $^{13}$C NMR $\delta$ 29.92 (t), 31.29 (q), 34.04 (s), 39.07 (t), 67.96 (t), 123.15, 124.43, 124.95, 125.75, 126.29 (d), 132.19, 133.66 (s), 137.99 (d), 145.98, 148.12, and 153.25 (s); FAB (+) MS $m/z$ (relative intensity) 1077 (100, MH$^+$). Anal. Calcd for $C_{68}H_{76}N_4O_8$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.04; H, 7.26; N, 5.15.

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[[(1-oxopyrid-2-yl)methyl]oxy]calix[4]arene, 1,3-alternate conformer (10a):** 83% yield; mp 240–241 °C ($CH_3CN$–$CH_2Cl_2$); $^1$H NMR $\delta$ 0.85 (s, 36 H), 3.74 (s, 8 H), 4.88 (s, 8 H), 6.53 (dd, $J$ = 7.7, 2.1 Hz, 4 H), 6.83 (s, 8 H), 7.08 (dt, $J$ = 7.7, 1.4 Hz, 4 H), 7.16 (ddd, $J$ = 7.7, 6.3, 2.2 Hz, 4 H), and 8.19 (dd, $J$ = 6.3, 1.3 Hz, 4 H); $^{13}$C NMR $\delta$ 31.07 (q), 33.69 (s), 38.55, 66.08 (t), 123.96, 124.93, 125.95 (d), 126.00, 133.03 (s), 138.43 (d), 145.65, 148.49, and 153.52 (s); FAB (+) MS $m/z$ (relative intensity) 1077 (100, MH$^+$). Anal. Calcd for $C_{68}H_{76}N_4O_8$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.67; H, 7.30; N, 5.33.

**Extraction Experiments.** Metal picrates ($2.5 \times 10^{-4}$ M) were dissolved in doubly distilled and deionized water. Solutions of the calix[4]arene derivatives ($2.5 \times 10^{-4}$ M) were prepared in $CH_2Cl_2$. Equal volumes (5 mL) of the two solutions were magnetically stirred in a stoppered flask in a thermostated water bath at 23 °C for 24 h. More extended times (up to 8 d) did not appreciably change the extraction values. The two phases were separated, and the percentage extraction was determined by measuring the absorbance of the aqueous phase at the maximum absorption of the picrate anion (356 nm). The adsorbance $A$, i.e. of an experiment containing a calix[4]arene derivative in $CH_2Cl_2$, and the adsorbance $A_0$, i.e. of a blank experiment without a calix[4]arene derivative in $CH_2Cl_2$, were determined spectrophotometrically. The percentage cation extracted was calculated as the ratio $100 \times (A_0 - A)/A_0$.

**Preparation of Alkali Metal Complexes with Tetrasubstituted Calix[4]arene Cone Conformers.** To a solution of pyridine *N*-oxide calix[4]arene **7a** (0.1 mmol) in dry $CHCl_3$ (20 mL) was added solid alkali metal ($Na^+$ or $K^+$) thiocyanate or picrate salt (4 equiv). The mixture was stirred at rt for 24 h. After filtration, the solvent was evaporated to give the corresponding 1:1 complex in a nearly quantitative yield. Analytical samples were obtained by recrystallization from AcOEt–$CH_2Cl_2$ mixtures.

Complexes of **7** with NaSCN and KSCN were obtained by slow evaporation of the solvent from samples of $^1$H NMR complexation experiments.

**7·NaSCN complex:** $^1$H NMR $\delta$ 1.11 (s, 36 H), 3.04, 4.00 (ABq, $J$ = 12.4 Hz, 8 H), 4.94 (s, 8 H), 6.98 (s, 8 H), 7.08 (d, $J$ = 7.7 Hz, 4 H), 7.31 (dd, $J$ = 7.0, 5.3 Hz, 4 H), 7.75 (dt, $J$ = 7.6, 1.4 Hz, 4 H), and 8.40 (dd, $J$ = 4.1, 0.7 Hz, 4 H).

**7·KSCN complex:** $^1$H NMR $\delta$ 1.10 (s, 36 H), 3.03 (d, $J$ = 12.6 Hz, 4 H), 4.03 (bd, $J$ = 11.7 Hz, 4 H), 4.89 (s, 8 H), 6.92 (s, 8 H), 7.25 (bm, 8 H), 7.65 (bs, 4 H), and 8.32 (d, $J$ = 4.1 Hz, 4 H).

**7a·NaSCN complex:** mp 191–193 °C; $^1$H NMR $\delta$ 1.06 (s, 36 H), 2.80, 3.49 (ABq, $J$ = 12.3 Hz, 8 H), 5.39 (bs, 8 H), 6.89 (s, 8 H), 7.02 (d, $J$ = 7.2 Hz, 4 H), 7.38, 7.60 (t, $J$ = 6.9 Hz, 4 H each), and 9.02 (d, $J$ = 4.9 Hz, 4 H); $^{13}$C NMR $\delta$ 29.95 (t), 31.01 (q), 33.90 (s), 73.30 (t), 125.50, 127.90, 128.27, 128.36 (d), 133.71 (s), 140.89 (d), 145.89, 147.45, and 150.32 (s); FAB (+) MS $m/z$ (relative intensity) 1099 (100, $MNa^+$). Anal. Calcd for $C_{69}H_{76}N_5NaO_8S$: C, 71.54; H, 6.61; N, 6.04. Found: C, 71.23; H, 6.92; N, 5.88.

**7a·KSCN complex:** mp 194–196 °C; $^1$H NMR $\delta$ 1.07 (s, 36 H), 2.64, 3.26 (ABq, $J$ = 12.1 Hz, 8 H), 5.37 (bs, 8 H), 6.86 (d, $J$ = 7.3 Hz, 4 H), 6.94 (s, 8 H), 7.27 (t, $J$ = 7.5 Hz, 4 H), 7.50 (t, $J$ = 6.3 Hz, 4 H), and 8.94 (d, $J$ = 6.1 Hz, 4 H); $^{13}$C NMR $\delta$ 29.41 (t), 31.21 (q), 33.93 (s), 72.34 (t), 125.31, 127.06, 127.78 (d), 133.91 (s), 140.28 (d), 146.69, 146.85, and 150.86 (s); FAB (+) MS $m/z$ (relative intensity) 1115 (100, $MK^+$). Anal. Calcd for $C_{69}H_{76}N_5KO_8S$: C, 70.56; H, 6.52; N, 5.96. Found: C, 70.31; H, 6.75; N, 5.83.

**7a·$Na^+$ picrate complex:** mp 198–199 °C dec; $^1$H NMR $\delta$ 1.06 (s, 36 H), 2.89, 3.77 (ABq, $J$ = 12.1 Hz, 8 H), 5.32 (bs, 8 H), 6.89 (s, 8 H), 7.08 (bd, $J$ = 6.4 Hz, 4 H), 7.18 (t, $J$ = 7.6 Hz, 4 H), 7.36 (bt, $J$ = 6.8 Hz, 4 H), 8.67 (s, 2 H), and 8.69 (bd, $J$ = 6.2 Hz, 4 H); $^{13}$C NMR $\delta$ 29.41 (t), 31.11 (q), 34.02 (s), 73.11 (t), 125.67 (d), 126.31 (s), 126.58, 127.30, 127.69, 128.03 (d), 133.76 (s), 140.67 (d), 141.44, 146.01, 147.75, 150.23, and 162.36 (s); FAB (+) MS $m/z$ (relative intensity) 1099 (100, $MNa^+$). Anal. Calcd for $C_{74}H_{76}N_7NaO_{15}$: C, 67.00; H, 5.77; N, 7.39. Found: C, 66.75; H, 5.89; N, 7.15.

**Structural Analysis.** Details of the X-ray experimental conditions, cell data, data collection, refinement procedures, atomic coordinates, and molecular dimensions have been deposited with the Cambridge Crystallographic Data Centre.[20] The full list of crystallographic data is also available from one of the authors (G.F.) as a Crystallographic Information File (CIF). The ORTEP diagram (Figure 2) was prepared using ORTEPII[21] as implemented in PLATON.[22] Figure 3 was prepared with PLUTON.[23] Examination of the structures with PLATON showed that there were no solvent accessible voids in the crystal lattice.

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**Supplementary Material Available:** $^1$H and $^{13}$C NMR assignments for all new compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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