Synthesis and Alkali Metal Ion Binding Properties of Two Rigid Sterochemical Isomers of Calix[6]arene Bis-crown-4

Michael T. Blanda,*,[†] Dustin B. Farmer,[†] Jennifer S. Brodbelt,[‡] and Brian J. Goolsby[‡]

Contribution from the Department of Chemistry, Southwest Texas State University, San Marcos, Texas 78666, and Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

Received June 1, 1999

Abstract: Cone and 1,2,3-alternate stereochemical isomers of 37,40-diallyloxy-(38,42),(39,41)-bis-crown-4 calix[6]arene, **3** and **4** were isolated in moderate yields by bridging the dialkylated calix[6]arene **2** with triethylene glycol di-*p*-tosylate. The alkali metal complex stoichiometries, association constants, and ion selectivities of **3** and **4** were studied by ^{1}H NMR titration experiments, liquid−liquid extraction, electrospray ionization mass spectroscopy, and X-ray crystallography. Good agreement between the gas-phase and solution-phase studies regarding these metal binding properties was observed. Both conformers formed 1:1 complexes with all alkali metal ions but were structurally preorganized such that each exhibited a strong preference for the larger cesium ion as evidenced by the "deep-cavity" cesium complex of host **4**, wherein π-metal interactions helped to stabilize the complex. The Cs^+/Na^+ selectivity factor for **4** was found to be 1500, while that of **3** was only 140.

Introduction

Calixcrowns are macromolecular hybrid structures composed of calix[*n*]arenes and crown ethers which have been demonstrated to be very effective complexing agents for alkali and other metal ions.[1] In particular, calix[4]arene crown-6 hosts have been extensively investigated in the sequestration and removal of radioactive Cs^{137} ions from aqueous waste mixtures.[2] Calixcrowns have been constructed from all four conformational isomers of calix[4]arenes (cone, partial cone, 1,2-, and 1,3-alternate) and structure−property correlations have been developed to a level where application of these molecules has become common. Since they contain a single crown ether strap, the mono-bridged calixcrowns all form 1:1 complexes. In addition to the calixcrowns which have only a single crown moiety, there are numerous examples of calix-bis-crowns which have been primarily composed of calix[4]arenes and two oxa- or azacrown units.[3] These ditopic, bis-bridged calixcrowns generally form 2:1 (guest to host) adducts when they are completely complexed. Since the introduction of a second bridging unit generally increases the rigidity of the calix[4]arene framework, we extended the concept to calix[6]arenes in the anticipation that either new conformers, or more rigid versions of known ones, would result. Even though calix[6]arenes are members of the "major" calixarene family, their conformational possibilities and thus metal complexation properties have not been studied in as much detail as the calix[4]arenes. Mono-bridged calix[6]arene crowns have appeared in the literature, wherein the A and D rings or A and C rings were bridged with pentaethylene[4a] and triethylene glycol[4b] units, respectively. Single aromatic bridging units have also been used to span the lower rim of calix[6]arenes and generally provide the cone conformation.[5] With the exception of one reported bis phosphate-bridged calix[6]arene,[6] no other types of bis-bridged calix[6]arenes have been documented. Utilization of the larger rigidified calix[6]arenes necessitates general methods of synthesizing and characterizing them. Once achieved, they have the potential to be the next generation of molecular sensor materials and may enjoy the popularity and application rivaling that of calix[4]arenes including recovery of cesium and uranium, ion-selective electrodes, field-effect transistors, phase-transfer catalysts, hydrolysis catalysts, and stabilizers for organic polymers.[7] Toward this end, we report herein the synthesis and alkali metal binding properties of two noninterchangeable isomers of calix[6]arene bis-crown-4 (see **3** and **4** in Figure 1). As evidenced by NMR

[†] Southwest Texas State University.

[‡] The University of Texas at Austin.

[1] (a) For reviews and references on calix[4]crowns, see: Asfari, Z.; Wenger, S.; and Vicens, J. *Supramol. Sci.* **1994**, *1*, 103−110. (b) Asfari, Z.; Wenger, S.; and Vicens, J. *Pure Appl. Chem.* **1995**, *67*, 1037−1043. (c) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767−2777. For references on 1,2-alternate calixcrowns, see: (d) Arduini, A.; Domiano, L.; Pochini, A.; Secchi, A.; Ungarro, R.; Ugozzoli, F.; Struck, O.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1997**, *53*, 3767−3776. (e) Pappalardo, S.; Petringa, A.; Parisi, M. F.; Ferguson, G. *Tetrahedron Lett.* **1996**, *37*, 3907−3910. For refernces on calix[8]crowns, see: (f) Geraci, C.; Chessari, G.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1997**, 921−922.

[2] (a) Asfari, Z.; Pulpoka, B.; Saadioui, M.; Wenger, S.; Nierlich, M.; Thuery, P.; Reynier, N.; Dozol, J.-F.; Vencens, *J. Mol. Recognit. Inclusion, Proc. 9th Int. Symp.* **1998**, 173−178. (b) Hill, C.; Dozol, J.-F.; Lamare, V.; Rouquette, H.; Eymard, S.; Tournois, B.; Vincens, J.; Asfari, Z.; Bressot, C. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 399−408.

[3] (a) Arnaud-Neu, F.; Asfari, Z.; Souley, B.; Vicens, J. *New J. Chem* **1996**, *20*, 453−463. (b) Aeungmaitrepirom, W.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1997**, *38*, 1907−1910. (c) Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1996**, *37*, 8747−8750.

[4] (a) Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591−598. (b) Chen, Y.; Li, J.; Xin, J.; Zhong, Z.; Gong, S.; Lu, X. *Synth. Comm.* **1999**, *29*, 705−711.

[5] (a) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572−6579. (b) Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862−4867. (c) Ross, H.; Lüning, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2555−2556. (d) Saiki, T.; Goto, K.; Tokitoh, N.; Okazaki, R. *J. Org. Chem.* **1996**, *61*, 2924−2925. (e) Li, J.; Chen, Y.; Lu, X. *Tetrahedron* **1999**, *55*, 10365−10374.

[6] Moran, J. K.; Roundhill, D. M. *Phosphorus, Sulfur, Silicon* **1992**, *71*, 7. (b) Aleksiuk, O.; Grynszpan, F.; Biali, S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 237.

10.1021/ja991810h CCC: $19.00

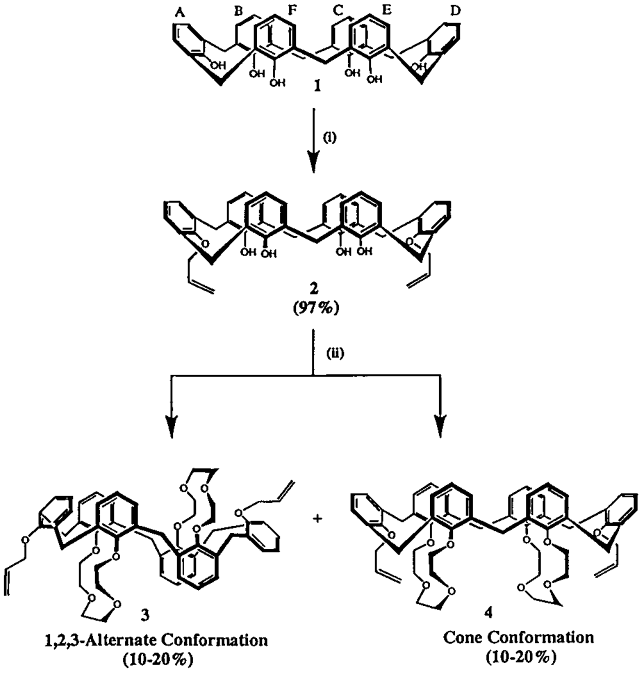

Figure 1. Synthesis of calix[6]arene-bis-crown-4 isomers **3** and **4**.

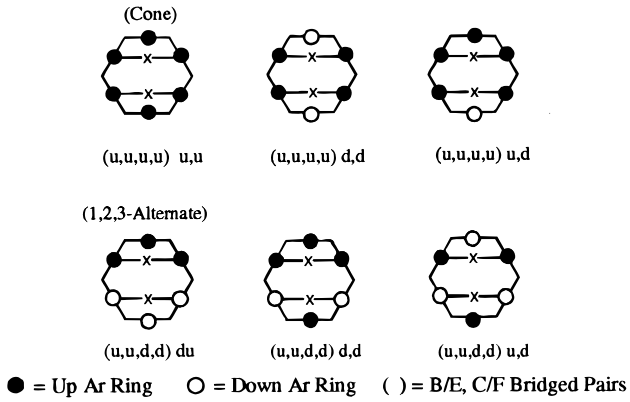

Figure 2. Possible stereochemical isomers resulting from bis-bridging.

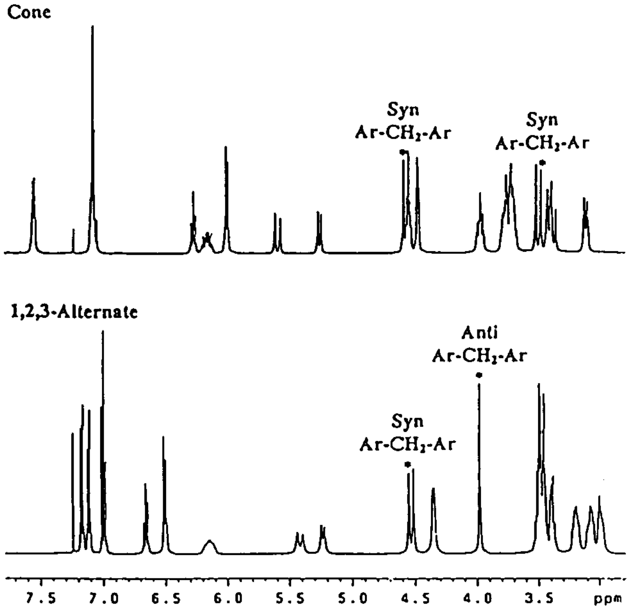

Figure 3. Room temperature ^{1}H NMR spectra of host **3** (bottom) and **4** (top) in $CDCl_3$.

spectroscopy and X-ray crystallography, one of the isomers assumes the 1,2,3-alternate conformation, while the other adopts the cone conformation.

Synthesis and Characterization. Both isomers of calix[6]-bis-crown-4 were isolated from the same bridging reaction involving 37,40-diallyloxycalix[6]arene, **2** (see Figure 1). This principle starting material was obtained by selectively alkylating the lower rims of the A and D rings of de-*tert*-butylcalix[6]-arene, **1**. Treatment of **1** with $K^+(CH_3)_3SiO^-$ in the presence of allyl bromide provided **2** in excellent yield (96%) and high purity.[8] Placement of the allyl groups on the lower rim of the A and D rings predisposed the remaining B, C, E, and F rings for bridging with bis electrophiles.

Two families of isomers can potentially be produced: those with the pairs of bridged rings *syn* to each other (u, u, u, u) and those with *anti*-oriented bridged pairs (u, u, d, d).[9] Within each family, the number of different conformers is a function of the bridging pattern (i.e., B−C, E−F vs B−E, C−F) and the relative orientations of the A and D rings with respect to the bridge-pairs. Considering all of these structural variations, there are a total of six possible conformational isomers (Figure 2).

When **2** was treated with triethylene glycol-di-*p*-tosylate and sodium hydride in THF/DMF (90/10), approximately equal amounts of **3** and **4** were isolated (see Figure 1). The total amount of these bis-crowns was consistently 20−30% of the reaction mixture, and the two isomers were separated and purified by means of column chromatography. There were other minor fractions present; however, they were not isolated. When the reaction conditions were changed to Cs_2CO_3 as the base in acetonitrile, the reaction mixture became more complex, and the yields of **3** and **4** were dramatically reduced.

Structural Analysis of 1,2,3-Alternate Stereoisomer (3). The 1,2,3-alternate conformation of **3** in solution could be readily determined from one- and two-dimensional NMR spectroscopy (^{1}H, ^{13}C, ^{1}H/^{1}H COSY, ^{1}H/^{13}C HETCOR) taken in $CDCl_3$ at room temperature. In the ^{1}H spectrum, the most diagnostic conformational indicator was the signal pattern observed for the two types of $ArCH_2Ar$ protons (see Figure 3).

The methylene protons between *syn*-oriented aromatic rings appeared as an AB quartet and had a $\Delta\delta$ (1.05 ppm) similar to that observed for the endo- and exo- protons of cone calix[4]-arenes.[9] The $ArCH_2Ar$ hydrogens between *anti*-oriented rings appeared as a singlet with half the intensity of the AB quartet. Corroborating evidence for the two types of $ArCH_2Ar$ methylene carbons was obtained from the ^{13}C spectrum in which there were two signals observed at 31.55 and 31.13 ppm (intensity 1:2,

---

(7) (a) Agrawal, Y. K.; Kunji, S.; Menon, S. K. *Rev. Anal. Chem.* **1998**, *17*, 69−139. (b) Arnaud-Neu, F.; Schwing-Weill, M.-J. *Synth. Met.* **1997**, *90*, 157−164. (c) Schierbaum, K. D. *Sens. Actuators, B* **1994**, *18−19*, 71. (d) Perrin, R.; Lamartine, R.; Perrin, M. *Pure Appl. Chem.* **1993**, *65*, 1549−1559. (e) Perrin, R.; Harris, S. J. *Top. Inclusion Chem.* **1991**, Vol. 3, 235−259.

(8) Nam, K. C.; Park, K. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 153−155.

(9) In using the modified up/down designation for calixarene conformations, one aryl ring is arbitrarily assigned as being up (u) relative to the mean plane defined by the $ArCH_2Ar$ carbons. The other aryl rings in the cyclic array are then designated by proceeding around the ring. Departures from true up/down orientations are handled by additional "o" or "i" notation. For example, rings that project outward may be described as uo or do for "up out" and "down out". (a) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. *Calixarenes Revisited*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1998.

$\Delta\delta = 0.42$ ppm at RT). It is interesting that the 1,2,3-alternate conformation of **3** seems to violate the ^{13}C rule for determining conformations in calix[6]arenes.[10] It has been suggested that a $\Delta\delta$ smaller than 1 ppm means the ArCH$_2$Ar carbons are either all *syn* or *anti*.[10] The chemical shift of the methylene carbons between the *anti*-oriented rings are shielded to higher fields than expected (approximately 6 ppm) while the signal for the *syn*-oriented methylenes has a "normal" chemical shift.

The presence of just 10 signals for all of the aromatic carbons in the ^{13}C NMR spectrum of **3** is a consequence of its symmetry (σ_h, C_2, and i). The same symmetry elements also operate on the crown ether moieties; thus, only three signals were observed for the 12 methylene carbons of the crown-4 units. Surprisingly, the COSY and HETCOR spectra indicated that the methylene hydrogens of the crown units are diastereotopic with the $\Delta\delta$ between pairs of signals ranging from 0.086 to 0.260 ppm.

The 1,2,3-alternate conformation of **3** was ultimately confirmed using X-ray crystallography.[11] A CPK molecular model of **3** shows that the two crown moieties are on opposite sides of the molecule and that the B−F and C−E rings are bridged. A 30-membered ring containing eight oxygen atoms is created by the two polyether straps and atoms of the four bridged calixarene rings. The four phenolic oxygen atoms of the bridged calixarene rings are nearly coplanar with the remaining oxygen atoms in the polyether straps situated above and below the plane. Accordingly, the conformation can be described using the following stereochemical notation (u, uo, do, d, do, uo) relative to the A ring.[9]

Structural Analysis of Cone Stereoisomer (4). The cone conformation of isomer **4** was most clearly demonstrated by presence of two AB quartets for the ArCH$_2$Ar protons (2:1 ratio) in the ^{1}H NMR spectrum (see Figure 3). The $\Delta\delta$ between the AB pairs was 1.08 and 1.18 ppm, respectively and the coupling constants ($J = 16.4$ Hz) were similar to those observed for calix[4]arenes locked into the cone conformation.[9] Even though all of the ArCH$_2$Ar carbons are situated between *syn*-oriented aromatic rings, there are two different types: those flanked only by the bridged rings and those flanked by the bridged rings and the allyl-functionalized rings (30.88 and 27.09 ppm, respectively). The $\Delta\delta$ of 3.79 ppm is again contrary to the general rule that, when the $\Delta\delta$ is greater than 3 ppm, both *syn* and *anti* orientations are present in the calix[6]arene.[10] In this case it is the *syn*-oriented methylene carbons between the bridged ring pairs that is shifted to higher than normal fields by approximately 3 ppm. Similar to the 1,2,3-alternate conformer, the molecule has a high degree of symmetry as evidenced by the relative simplicity of the ^{13}C spectrum in which only 10 aromatic signals and three for the crown units were observed. A comparison of the chemical shifts of the para and meta hydrogens of the A and D rings in **3** (6.66 and 6.51 ppm) and **4** (6.29 and 6.03 ppm) suggests that in **4**, on average, the rings are canted inward and shielded by the B, C, E, and F rings. Just as in isomer **3**, the methylene hydrogens of the crown moieties are diastereotopic, but the $\Delta\delta$ values between diastereotopic hydrogens are larger (0.89 ppm).

Metal Binding Studies of 3 and 4. ^{1}H NMR experiments. ^{1}H NMR spectroscopy was used to investigate the conformational changes of the hosts and stoichiometries of the complexes formed between the bis-crown-4 hosts and alkali metal picrate salts at room temperature in CDCl$_3$. The rate of exchange between free and complexed host was rapid on the 400 MHz NMR time scale at room temperature for **3** binding Li$^+$, Na$^+$, K$^+$, and Rb$^+$ ions while **4** was in rapid exchange with its Li$^+$, Na$^+$, and K$^+$ complexes. With two crown ether straps on opposite sides of the molecule it was speculated that **3** might form 2:1 (guest to host) complexes. This question was answered using the method of continuous variations (Job plot) to probe the binding of the relatively small sodium cation.[12] We chose the sodium cation for this study on the basis of the fact that a calixcrown-4 compound reported by Shinkai exhibited unusually high sodium selectivity.[13] Under fast exchange conditions, the changes in the chemical shifts of the crown methylene carbons in the ^{13}C NMR spectrum of **3** were used to monitor the complexation process. The curve for sodium binding maximized at a mole fraction of host equal to 0.5 which meant that the concentration of the complex was highest when the stoichiometry was 1:1 (see Figure 4). Even though the crown-4 units are on opposite sides of the molecule, they appear to coordinate metal ions cooperatively instead of independently in the formation of a 1:1 complex. Alternatively, the initially bound cation may be in rapid exchange between the two crown binding sites. This could have the effect of excluding a second cation due to electrostatic repulsion. In either case, it is the relative position of the two crown straps within the superstructure of the host that dictates the stoichiometry and cation selectivity, not the size of the crown ether strap.

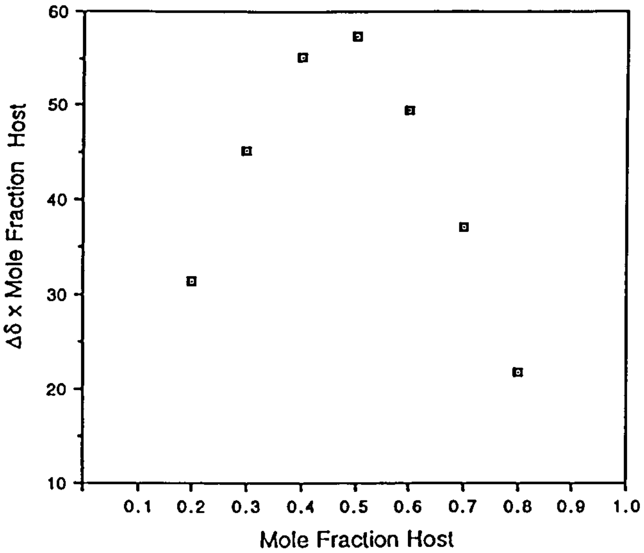

Figure 4. Job plot for determination of **3**−Na$^+$ complex stoichiometry in CDCl$_3$/CD$_3$OD.

The exchange rate for complexation was slow on the NMR time scale when host **3** bound cesium and when host **4** bound cesium and rubidium. Titration experiments confirmed that both hosts formed only 1:1 complexes with these ions as well. For example when 1 equiv of cesium picrate was added to **4**, the complex was the only detectable species. Even though association constants were not calculated from the NMR experiments, qualitatively, fast exchange can be related to weaker binding interactions between hosts and guests, while slow exchange generally indicates stronger binding.[14] Therefore, both hosts **3** and **4** appear to show a higher binding affinity for the larger cesium and rubidium ions over the smaller alkali metals. Unlike

---

[10] Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3871−3879.

[11] The X-ray crystal structure for the 1,2,3-alternate conformer **3** was solved, but the *R* value was only 13%. Even though this is not ideal, it is still sufficient to determine the conformation.

[12] Connors, K. A. *Binding Constants*; Wiley & Sons: New York, 1987; pp 24−28.

[13] Matsumoto, H.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 77−80.

[14] Feeney, J.; Batchelor, J. G.; Albrand, J. P.; Roberts, G. K. *J. Magn. Reson.* **1979**, *33*, 519−529.

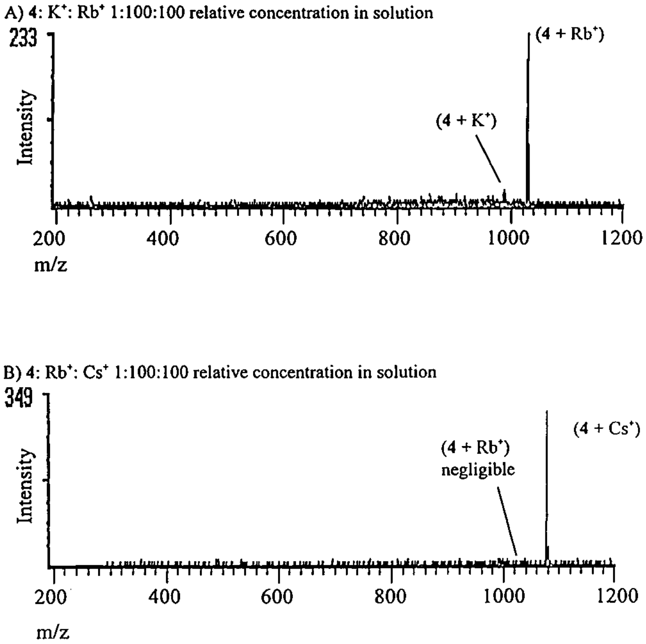

Figure 5. Electrospray ionization mass spectra for competition studies of host **4** with K^+ vs Rb^+ (top) and Cs^+ vs Rb^+ (bottom).

calix[4]-bis-crowns which form 2:1 complexes,[1−3] the two crown units in hosts **3** and **4** exhibit cooperative binding in the formation of only 1:1 complexes. The cooperative nature of the two crown-4 units actually reverses the binding selectivity of the crown-4 units and demonstrates the principle of host preorganization. If they operate independently, then there is high sodium selectivity,[13] but when they act in concert, the hosts have very high selectivity for larger cations.

Gas-Phase Binding Studies. Electrospray ionization mass spectroscopy was also used to evaluate the alkali metal binding selectivities and complex stoichiometries of **3** and **4**. In the electrospray ionization method, complexes are formed in an appropriate solution and transported into the gas phase via a process in which they remain charged and are solvated. The ions that are observed in the resulting mass spectra reflect the types and distributions of complexes initially present in solution. The electrospray ionization mass spectrometric method has been developed recently to estimate binding selectivities of host and binding constants of host−guest complexes based on measurement of the ion intensities of relevant complexes observed after spraying solutions containing well-defined compositions of host and guest species.[15] For the present study, solutions were prepared by mixing aliquots of chloroform containing the host at 5×10^{-5} M and equal volumes of methanol solutions containing alkali metal salts at 5×10^{-3} M. These mixtures, having a final host:alkali metal 1:alkali metal 2 ratio of 1:100:100, were analyzed by an electrospray ionization quadrupole ion trap mass spectrometer. Examples of the mass spectra are shown in Figure 5 for host **4** with K^+ and Rb^+, and Rb^+ and Cs^+. These types of mixtures produce clean and intense spectra that contained only 1:1 host:alkali metal complexes without interferences from solvated complexes. Even at guest-to-host ratios of 100:1, the formation of 2:1 host:metal complexes are not observed, confirming that complexation of two metal ions by a single host does not occur. As shown in Figure 5, host **4** has a significant preference for complexation of Rb^+ over K^+ (Figure 5A) and an even greater affinity for Cs^+ over Rb^+ (Figure 5B). The results are similar for host **3** (data not shown), but careful measurement of the intensities of the complexes reveals that host **4** demonstrates a higher degree of selectivity than that of **3**.

Table 1: Association Constants for Complexes of Alkali Metals with Hosts **3** and **4** in $CHCl_3$ Derived from Metal Picrate Extraction Studies[a]

	1,2,3-alternate (**3**) $K_{ass} \times 10^{-5}$ M^{-1}	cone (**4**) $K_{ass} \times 10^{-5}$ M^{-1}
Cs	390	8000
Rb	16	810
K	3	21
Na	1	5
Li	4	8

[a] The precision of the method is described in ref 16.

The selectivity can be expressed as a ratio of the intensity (I) of one alkali metal complex to that of another, such as $I_{(\text{host } 4\ +\ K^+)}/I_{(\text{host } 4\ +\ Na^+)}$. For example, the K^+/Na^+ selectivity for host **3** is 11:1, whereas it is 20:1 for host **4**. Likewise, the Rb^+/K^+ selectivity for host **3** is 5:1, whereas it is 13:1 for host **4**. The Cs^+/Rb^+ selectivities were so large that they exceeded the dynamic range of the ion trap mass spectrometer (i.e., the intensities of the Rb^+ complexes were indiscernible from the baseline), thus preventing assignment of a finite ratio. To obtain a more quantitative estimation of the Cs^+/Rb^+ selectivity, solutions containing 1:10:10 and 1:1:1 ratios of host-to-Rb^+-to-Cs^+ were sprayed in order to influence the equilibrium established in solution, but even at these reduced rations the (host + Cs^+) complexes dominated the spectra. This great preference for Cs^+ complexation over a wide range of solution compositions suggest that the binding constants for the host:Cs^+ complexes are at least 2 orders of magnitude greater than those for the host:Rb^+ complexes in the chloroform/methanol solutions.

In addition to the overall greater selectivity of host **4** relative to host **3**, the intensities of the complexes containing host **4** were typically two times greater than those of host **3**. This result suggests that the binding constant of host **4** is greater than that of host **3**, in agreement with the results presented later in Table 1. Direct comparison of the binding affinities of host **3** and **4** by electrospray ionization mass spectrometric measurements of solutions containing both hosts with a single alkali metal could not be undertaken because these two hosts possess the same molecular weight, thus prohibiting distinction of their complexes.

Metal Picrate Extraction Studies of 3 and 4. The alkali metal binding properties of both isomers were investigated using the metal picrate extraction method wherein aqueous solutions of the picrate salts are shaken with chloroform solutions of the hosts.[16] The amount of picrate ion extracted into the organic phase was then determined from its absorption in the UV spectrum (380 nm) and from subtraction of the original aqueous phase. The percent extraction of metal picrate salts by **3** and **4** demonstrated that both conformers display a high selectivity for the larger rubidium and cesium ions. For example, the cone conformer **4** extracted 51% of the cesium picrate from a 9.2×10^{-4} M aqueous solution into the chloroform solution of the host at a 1:1 (host-to-guest) ratio, but extracted only 3% of the

---

(15) (a) Blair, S. M.; Kempen, E. C.; Brodbelt, J. S. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1049−1059. (b) Blair. S. M.; Brodbelt, J. S.; Reddy, G. M.; Marchand, A. P. *J. Mass Spectrom.* **1998**, *33*, 721−728. (c) Kempen, E. C.; Brodbelt, J. S.; Bartsch, R. A.; Jang, Y.; Kim, J. S. *Anal. Chem.* **1999**, *71*, 5493−5500. (d) Goolsby, B. J.; Brodbelt, J. S.; Adou, E.; Blanda, M. T. *J. Mass. Spectrom.* **1999**, *193*, 197−204.

(16) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928−4941.

Rb^+ salt and almost none of the smaller Li^+, Na^+, and K^+ salts. The extraction constants (K_e) were determined according to eq 1 and the association constants were calculated from the relationship of $K_{ass} = K_e/K_d$, where K_d is the distribution constant of the individual metal picrate salts in chloroform.[16]

$$K_e = [M^+\cdot Host\cdot Pic^-]_{org}/[M^+]_{aq}\,[Pic\text{-}]_{aq}[Host]_{org} \qquad (1)$$

The results of extraction studies conducted on bis-crowns **3** and **4** are summarized in Table 1. The K_e and K_{ass} values reinforced the premise derived from the NMR results that both hosts have high affinities for Cs^+ and Rb^+ over K^+, Na^+, Li^+. The cone isomer **4** binds cesium approximately 10 times better than rubidium, but about 400 times better than potassium and 1500 times better than sodium or lithium.

The 1,2,3-alternate conformer exhibited the same selectivity trend, but the selectivity ratios are not quite as high. For example, **3** bound cesium roughly 25 times tighter than it does rubidium and only 144 times better than the smaller cations. The Cs^+/Na^+ selectivity factor of 1500 observed with host **4** is somewhat lower than those observed in some cesium-selective calix[4]arene crown-6 hosts,[1c] but higher than that of a bis-crown host derived from calix[8]arene.[1f]

Another general trend is that the cone isomer **4** binds cesium and rubidium ions about an order of magnitude better than **3**, but both bind the smaller cations equally well. These results can most certainly be attributed to the orientations of the oxygen atoms imposed on them by the bridging units. The cone conformer has a large bowl shape which is lined with eight convergent oxygen atoms, while the oxygen atoms in the 1,2,3-alternate isomer are in a 30-membered macrocyclic structure and held far apart. In comparison to other cesium-selective calixcrown-6 compounds, the K_{ass} of the bis-crown cone isomer **4** is similar and toward the higher end, while **3** is toward the lower.[1−3] It is noteworthy that there is very good qualitative agreement between the solution- and gas-phase binding studies concerning the complex stoichiometries, binding affinities, and ion selectivities. Quantitatively, the two methods agree well on the Cs^+/K^+, Na^+, or Li^+ ratios; however, the Cs^+/Rb^+ ratios differ by about an order of magnitude.

X-ray Crystal Structure of Cone-Cesium Complex. The X-ray crystal structure of cone−cesium complex (see Figure 6) verified that the calix[6]arene framework is indeed in the cone conformation (ui, uo, uo, ui, uo, uo) and that the two crown units cooperatively bind the cesium ion. The para carbons (C5, C11, C23, and C29) of the B, C, E and F rings define a rectangular plane with average dimensions of 11.45 × 5.54 Å. In the solid state the A and D rings come within 3.885 Å of each other (C17−C35).

The coordination sphere around the metal looks asymmetric in that there are apparently no ligands above the metal. However, the A and D rings of the calixarene are canted over the top of the cavity, and their centroids come within 3.78 Å of the cesium cation. This is slightly farther than the π-metal distances reported in some calix[4]crowns derived from the 1,3-alternate conformation,[17] but it is not unreasonable to conclude that long-range interactions between the cation and the A and D rings are present in the solid state. One explanation for their proximity is that they are held in position by interactions with the cesium ion.

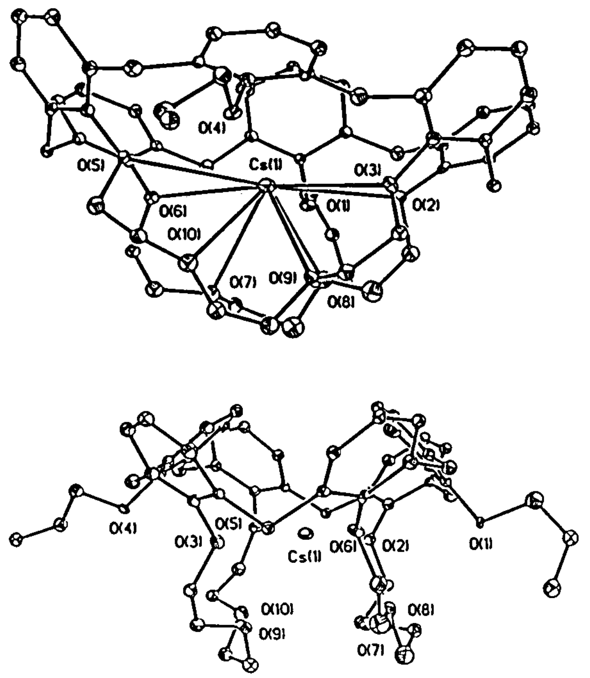

Figure 6. X-ray crystal structure of **4**−Cs^+ complex. Hydrogen atoms, solvent molecules, and $B(Ph)_4$ anion have been omitted for clarity.

With the addition of the two polyether chains at the lower rim, the whole structure has a deep bowl shape with the eight oxygens of the two parallel crown-4 units directed toward the center. The four phenolic oxygens of the bridged rings (O2, O3, O5, and O6) are almost coplanar as evidenced by the −12° dihedral angle between the planes defined by O3−O2−O6 and O5−O6−O2. The lengths of the plane are defined by the O2−O6 and O3−O5 distances (7.14 and 7.73 Å, respectively) and the widths are defined by the O2−O3 and O5−O6 distances (3.52 Å and 3.36 Å, respectively). The four remaining oxygens in the ether chains are below the plane, while the oxygen atoms of the A and D rings are directed away from the cavity.

The Cs−O bond lengths to the phenolic oxygens vary from 3.407 to 3.611 Å with the average being 3.523 Å. The four bond angles between the cesium ion and the bridged oxygens are 119.34° (O3−Cs−O5), 124.41° (O2−Cs−O6), 57.23° (O2−Cs−O3), and 59.75° (O5−Cs−O6) and add up to just slightly more than 360° (angle summation = 360.73°). The cesium cation is coordinated to all eight oxygen atoms and lies essentially in the center of the phenolic oxygen plane. As seen in Figure 6, the cesium ion is coordinated on its bottom side to the four ether oxygens atoms (O7, O8, O9, and O10) in the two crown straps. The average distance to the cesium ion of 3.189 Å is shorter than that to the phenolic oxygens with the individual distances ranging from 3.093 to 3.299 Å. The cesium ion could possibly enter the cavity through the calix opening or through an opening between the crown units. A molecular model of **4** suggests that the A and D rings are more flexible than the crown moieties which would tend to favor the through-the-calix pathway for complexation.

Conclusions

Cone and 1,2,3-alternate conformational isomers of 37,40-diallylcalix[6]arene bis-crown 4, **3** and **4**, were isolated in moderate yields by bridging the dialkylated calix[6]arene **2** with triethylene glycol di-*p*-tosylate. Alkali metal binding properties

---

(17) (a) Asfari, Z.; Naumann, C.; Vicens, J.: Nierlich, M.; Thuery, P.; Bressor, C.; Lamare, V.; Dozol, J.-F. *New J. Chem.* **1996**, *20*, 1183−1194. (b) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.; Egberink, J.; de Jong, F.; Reinhoudt, D. *J. Am. Chem. Soc.* **1995**, *117*, 2767−2777. (c) Ungaro, R.; Casnati, A.; Ugozzoli, F.; Pochini, A.; Dozol, J.; Hill, C.; Rouquette, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1506−1508. (d) Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979−6985.

of both isomers were studied in chloroform by ^{1}H NMR titration experiments, liquid−liquid extraction, electrospray-ionization mass spectroscopy, and X-ray crystallography. Both conformers formed 1:1 complexes with all alkali metal ions. The 1:1 complex stoichiometries observed with **4** are most likely a consequence of cooperative binding of one metal ion by the two crown moieties. Alternatively, one metal ion guest may be in rapid exchange between the two opposing crown straps in the 1,2,3-alternate isomer **3**. Even though **3** could potentially accommodate an additional metal ion, it is prohibited via electrostatic repulsion by the initially complexed cation. Both **3** and **4** displayed a strong preference for the larger cesium ion over the smaller alkali metal ions, with **4** being more selective than **3**. The Cs^+/Na^+ selectivity factor of 1500 observed with host **4** is somewhat lower than those observed in some cesium-selective calix[4]arene crown-6 hosts,[1a−c] but higher than that of a bis-crown host derived from calix[8]arene.[1f] The crystal structure of the Cs^+ complex of **4** indicated that the cesium ion was coordinated to all eight oxygen atoms of the parallel crown-4 rings to form a "deep-cavity" complex. There was also evidence of π-metal interactions with two aromatic rings canted over the cavity of the calixarene framework. This type of p-metal interaction has been previously observed in calix[4]arenes but not in calix[6]- or calix[8]arenes.

Experimental Section

All chemical reactions were performed under inert nitrogen or argon atmospheres. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. All other solvents and reagents were used as received. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ and were referenced to the residual $CHCl_3$ or to $CDCl_3$. Melting points were obtained in unsealed capillary tubes and are uncorrected. Metal picrates were prepared according to known procedures.[18] Solutions of the salts were prepared with deionized water. The parent compound, 5,11,17,-23,29,35-hexa-*tert*-butylcalix[6]arene was prepared according to known procedures and the de-*tert*-butylated compound, **1,** was obtained by treatment of the parent compound with $AlCl_3$ and phenol.[19]

37,40-Diallyloxy-(38−42),(39−41)-bis-crown-4-calix[6]arenes 3 and 4. The diallyl compound **2**[4] (2.0 g, 2.8 mmol) was dissolved in 100 mL of THF−DMF (10:1). To this was added 0.68 g (17 mmol) of NaH, and the mixture was stirred for 30 min at room temperature. Triethylene glycol di-*p*-tosylate (3.2 g, 6.8 mmol) dissolved in 50 mL of THF was added via syringe, and the reaction was heated to reflux for 12 h. The solvent was removed under reduced pressure, and the residue was redissolved in $CHCl_3$ and washed with 2 × 100 mL of 1 N HCl and 100 mL of brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated. Separation of **3** and **4** was effected by column chromatography on silica gel (90% $CHCl_3$−10% EtOAc).

1,2,3-Alternate isomer 3: 0.4 g (15%), rf = 0.7, mp = 235−240 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.15 (d of d, J = 7.2 Hz, 4H) 7.13−7.11 (d of d, J = 7.6 Hz, 4H) 6.99 (t, J = 7.6 Hz, 4H) 6.66 (t, J = 8.0 Hz, 2H) 6.51 (d, J = 7.6 Hz, 4H) 6.19−6.13 (m, 2H) 5.41 (d, J = 16.0 Hz, 2H) 5.23 (d, J = 10.4 Hz, 2H) 4.55 (d, J = 15.2 Hz, 4H) 4.36 (d, J = 5.6 Hz, 4H) 3.99 (s, 4H) 3.54−3.38 (m, 16H) 3.24 (m, 4H) 3.11 (m, 4H) 3.03 (m, 4H). 13C NMR (100 MHz, $CDCl_3$) δ 156.47, 154.33, 134.70, 134.39, 133.97, 133.48, 130.17, 129.66, 126.66, 123.69, 123.37, 117.52, 74.43, 72.57, 70.78, 69.98, 31.61, 31.28. Anal. Calcd for $C_{60}H_{64}O_{10}$: C 76.25, H 6.83. Found: C 76.49, H 6.92.

Cone isomer 4: 0.3 g (11%), rf = 0.6, mp = 230−232 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (d of d, J = 6.8 Hz, 4H) 7.12−7.06 (d of t, J = 8H) 6.29 (t, J = 7.6 Hz, 2H) 6.17 (m, 2H) 6.03 (d, J = 7.6 Hz, 4H) 5.65−5.61 (d of d, J = 17.2 Hz, 2H) 5.30−5.27 (d of d, J = 10.4 Hz, 2H) 4.61 (d, J = 16.4 Hz, 4H) 4.59 (d, J = 13.2 Hz, 2H) 4.51 (d, J = 3.6 Hz, 4H) 4.02 (d, J = 9.0 Hz, 4H) 3.85−3.72 (m, 12H) 3.54 (d, J = 13.6 Hz, 4H) 3.46−3.43 (m, 6H) 3.13 (d, J = 10.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.63, 154.21, 135.09, 134.29, 134.20, 133.25, 130.63, 129.46, 125.99, 123.76, 122.94, 116.29, 73.54, 72.52, 71.43, 70.66, 30.88, 27.09. Anal. Calcd for $C_{60}H_{64}O_{10}$: C 76.25, H 6.83. Found: C 76.66, H 6.87.

NMR Experiments. In the titration experiments, solutions of the hosts and metal picrate salts were prepared in 1 mL volumetric flasks. The solid compounds were placed directly into the flask, and $CDCl_3$ was added to the mark. The solutions were stirred for several hours to ensure that all components were dissolved. The solutions were then transferred to NMR tubes, and their spectra were recorded at room temperature. In the Job plot analysis, solutions of host:guest ratios ranging from 80:20 to 20:80 were prepared in 1 mL volumetric flasks. Aliquots of a 1 M NaSCN solution in CD_3OD were added to the flask containing the hosts dissolved in $CDCl_3$. The total solvent composition was then adjusted to be 90% $CDCl_3$ and 10% CD_3OD. Spectra of the hosts in the absence of added guest were obtained in the various $CDCl_3$/CD_3OD solutions so that shifts due to changes in the solvent composition could be quantified.

Extraction Experiments. Extractions were done according to the procedure described by Arduini where equal volumes (2 mL) of chloroform containing host and an aqueous solution of metal picrates were thoroughly shaken in 8 mL glass vials.[19] Aliquots were taken from each phase, and the picrate concentration in the organic phase was determined from the decrease in the aqueous phase ($\epsilon_{354\ \mathrm{nm}}$ = 14 500 cm^{-1} M^{-1}) and reconfirmed by the increase in the chloroform layer ($\epsilon_{380\ \mathrm{nm}}$ = 18 000 cm^{-1} M^{-1}). The concentrations of hosts **3** and **4** were fixed at 1.0×10^{-3} M. The picrate concentrations of the original aqueous phases were 9.4, 9.1, 8.1, 9.6, and 9.4 × 10^{-4} M for Li^+, Na^+, K^+, Rb^+, and Cs^+, respectively.

Host 4/Cs+ complex. Approximately 100 mg of **4** was dissolved in 2 mL of $CHCl_3$. To this was added 2 mol equiv of cesium tetraphenyl borate dissolved in 0.5 mL of CH_3OH. The solution was mixed well and allowed to stand at room temperature for several day. The clear crystals were then transferred to a clean vial.

Acknowledgment. We thank the Robert A. Welch Foundation for financial support (Grant No. AI-1240). We also thank Professor Carl Carrano and Dr. Norman Dean (SWT) for the X-ray crystallographic structural determination and helpful discussions. Financial support for the X-ray facilities was obtained from NSF Grant No. USE-9151286.

Supporting Information Available: Tables of crystal data and structure refinement (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991810H

---

[18] Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreeti, G. D.; Ugozzoli, F.; *Tetrahedron* **1986**, *42*, 2089−2100.

[19] Gutsche, C. D.; Lin, L. *Tetrahedron* **1986**, *42*, 1633−1640.