Sodium Binding Effects on Conformational Exchange in a Diquinone Calix[4]arene

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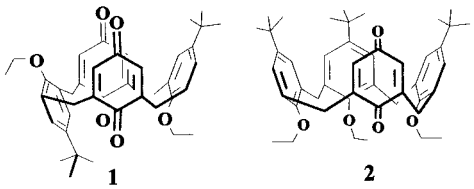
Abstract: NMR studies show that a 2,4-diethoxycalix[4]arene-1,3-diquinone undergoes an unusually slow conformational change, from a predominantly anti-aryl conformation to that of a syn-aryl conformation, in the presence of Na^+ ion. Dramatic changes are observed throughout the entire NMR spectral region. *A novel finding is that the timescale of this conversion is unusually long, taking many hours at room temperature to complete*. The kinetics of this conformational change over the range of 5−55 °C were measured in a binary solvent system. The rate constants are on the order of 10^{-5}−10^{-4} s^{-1} in the presence or absence of Na^+. These results suggest a cation effect on the equilibrium position of the anti and syn complexes rather than on the rate of interconversion. The kinetics of interconversion in the presence and absence of the salt are the same. The rate determining step corresponds to rotation of an aryl moiety through the annulus of the calixarene. Additionally, we note that the initially dominant anti-aryl conformer appears to be a kinetic product of the oxidation step of the synthesis with $Tl(CF_3CO_2)_3$. Variable-temperature NMR studies in the absence of salt show a stable ∼4:1 ratio of anti to syn conformer, while the compound, as initially prepared in solution, exhibits a ratio of >50:1.

Introduction

In the past decade, calixarenes and the related calixresorcarenes have received considerable attention as potential building blocks for sensing systems.[1] Binding efficiency in these systems typically relies on preorganizing the host calixarene to bind a neutral, cationic, or anionic guest. Much attention in the field has centered on the study of the conformers of the ionophoric calix[4]arenes.[1a] The four conformations of the calix[4]arenes, cone, partial cone (paco), 1,3-alternate (1,3-alt), and 1,2-alternate (1,2-alt), are especially important determinants of the binding efficiency and selectivity of ion-binding calixarenes.[2] Recent studies of calixcrowns, calixarenes in which two opposing aryl units are connected by a polyether chain, exemplify the search for systems with carefully controlled conformations and high cation binding efficiency and selectivity.[2a,3] These systems have been designed to provide a preorganized cation binding cavity with a well defined binding domain. In tetramethyl ether calix[4]arene systems Reinhoudt,[4] Shinkai,[5] Detellier,[6] and others have shown that a conformationally mobile calixarene can readily adapt to an orientation that optimizes binding. The polarity of the solvent has also been noted to have an effect on the conformation of calix[4]-arenes.[5b] Thus, a system that is not preorganized for optimum binding can be organized by the presence of the templating guest in an appropriate solvent.

Over the past several years, we have studied a number of calixquinones, calixarenes in which one or more aromatic units have been oxidized to 1,4-benzoquinone moieties.[7] Examples are provided by diquinone **1** and monoquinone **2**. These



1 **2**

compounds have been studied by electrochemical, ESR, and NMR methods, both as the free calixarenes and as the alkali metal ion complexes. In this paper we present NMR results for **1** that demonstrate a slow sodium-induced conversion from an anti-aryl oriented conformer (shown above as structure **1**) to a syn-aryl conformation, which is more favorable for ion binding. As mentioned above, work by Shinkai,[5] Detellier,[6] and others has shown that calix[4]arene conformational changes can result upon complexation of metal ions. Ungaro et al. have shown by high-temperature (90 °C) NMR that the syn-aryl

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(2) For example: (a) Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979. (b) Takeshita, M.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088.

(3) (a) 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. (b) Dijkstra, P. J.; Brunink, J. A.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567. (c) Yamamoto, J.; Shinkai, S. *Chem. Lett.* **1994**, 1115. (d) Asfari, Z.; Wenger, S.; Vicens, J. *J. Inclusion Phenom.* **1994**, *19*, 137.

(4) Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385.

(5) (a) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955. (b) Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron* **1993**, *49*, 9937 and references therein. (c) Shinkai, S.; Araki, K.; Kubota, M.; Arimura, T.; Matsuda, T. *J. Org. Chem.* **1991**, *56*, 295.

(6) Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1995**, *117*, 8536.

(7) Gómez-Kaifer, M.; Reddy, P. A.; Gutsche, C. D.; Echegoyen, L. *J. Am. Chem. Soc.* **1994**, *116*, 3580.

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conformer of **1** can be generated in significant amounts.[8] *The change observed here is unique in that it occurs over an unusually long period of time, on the order of many hours or days, at significantly lower temperatures*. We have studied the kinetics of this conformational exchange in the presence and absence of Na^+ by ^{1}H-NMR spectroscopy over the temperature range of 5−55 °C in a binary solvent system. The results suggest that the presence of sodium ion favors a syn-cone-Na^+ complex, and does not affect the rate of interconversion between the conformers.

The X-ray structure of **1** shows that the preferred solid state conformer is that of a partial cone ("paco"), with the aryl units in an anti orientation (anti-paco)[8] as shown above for structure **1**. In solution the quinone units are expected to be conformationally mobile, undergoing continuous, rapid rotation through the annulus of the calixarene, while the aryl units maintain their anti orientation. The **1**-*syn* conformer may be formed by heating samples of the anti conformer of **1** or by addition of alkali metal ions, as discussed below.

Experimental Section

Chemicals and Solutions. The synthesis of the calixquinones has been published elsewhere.[9] NMR spectra of the calixarene were obtained in a binary solvent system consisting of 70/30 (v/v) CD_3CN (Aldrich, 99.5% D)/$CDCl_3$ (MSD Isotopes, 99.8% D). Sodium ion was added as the trifluoromethanesulfonate (triflate) salt (Aldrich, 98%), which was dried under vacuum (heated to 100 °C) for 24 h prior to use. For the ^{1}H- and ^{13}C-NMR experiments, the salt was added as a solid, directly into the NMR tube containing a 9 mM solution of **1,** while for the ^{23}Na-NMR experiments, the solid calixarene was added to 15 mM solutions of the sodium salt. Other relevant concentrations are mentioned in the text or the figure captions. Cryptand[2.2.1] (Aldrich) was added to the NMR samples by means of a small capillary tube, placed directly in the NMR tube, below the level of the detection region.

NMR Measurements. Samples for all experiments were run in 5 mm OD (Aldrich) tubes. ^{1}H-NMR spectra were obtained with a Varian VXR-400 spectrometer equipped with the manufacturer's variable-temperature unit, which is accurate to within ∼1 °C, at an operating frequency of 399.94 MHz. Spectra were processed without line broadening, typically with a zero-fill to 132K data points to enhance digital resolution. The typical acquisition time was 2.5 s, with a recycle delay of 2 s.

Rate information was obtained by following the integrated resonance of the aromatic protons in the anti and syn conformers. The kinetic data for **1** at 5 °C (*vide infra*) were obtained from a sample that was stored in a refrigerator at 5 °C for 60 days. The spectra of this sample were run at room temperature, as the kinetics made observation at 5 °C, *in situ* for the duration of the monitoring process, unnecessary. The kinetics of conversion at room temperature were deemed to be sufficiently slow that little interconversion occurred in the short time required to acquire the spectra. All other spectra were obtained with the sample in the spectrometer, at the prescribed temperature, for the duration of the monitoring period.

Binding constant determinations were performed by heating a sample of **1** for 12 h at 50 °C (in the NMR spectrometer) to generate the maximum attainable amount of the **1**-*syn* conformer. Additions of the solid salt were then made, and the spectra were acquired for 1 to 4 h after each addition to be assured that equilibration was complete. The chemical shift resonances for both the syn aromatic and quinone protons were employed for the analysis. Estimates of binding constants based on NMR chemical shifts were made by employing MINSQ software and a simple BASIC program, which permits iterative estimates of the binding constant based on chemical shifts. Values obtained for K were then used to generate a curve of chemical shift points for comparison. Equilibrium constants for the anti to syn conversion were estimated based on the integration of the peaks in the aromatic region of the ^{1}H-NMR spectra at various temperatures.

For ^{23}Na spectra, typically 2500 transients were acquired with 4K data points, zero-filled to 32K data points, and processed with a line broadening of 1 Hz. Spectra were referenced to saturated NaCl in 85/15 (v/v) Barnstead H_2O/D_2O (Aldrich) and were obtained at an operating frequency of 105.8 MHz. All spectra were obtained while spinning in a locked mode. T_1 and T_2 times were determined by the inversion recovery and (Carr−Purcell−Meiboom−Gill) spin echo pulse sequences, respectively, provided by Varian. Data were obtained from a minimum of ten arrayed delay times for each experiment. Results obtained for T_2 were also compared to the values obtained by line width determinations and found to be reasonably similar.

Monte Carlo Simulations. Interconversion of the conformers was studied by Monte Carlo (MC) simulation, using OPLS[10] on an IRIS Indigo workstation with Macromodel Version 3.5X. Computations were done in the gas phase, based on a starting geometry that sought to reproduce the known X-ray structure as closely as possible. As explained below, the focus of our interest was limited to the conversion from the anti-partial cone to the syn conformers. Energy limits were set at no more than 12 kcal/mol above the starting energy, with a maximum of 1000 stored structures. The simulations were run to completion, and the global minima within the scope of the search were examined.

Results and Discussion

Conformers of 1. The various conformers that can be present in solution are presented in Scheme 1. The predominant conformation of **1** in solution was initially unclear, having been first thought to be in a rigid cone conformation.[12] Subsequent studies showed this calixarene to be in a conformation in which the aryl units are oriented anti to one another.[8] Ungaro and co-workers found that the ^{1}H-NMR spectrum of **1** changed little over the temperature range of −40 to +80 °C in $CDCl_3$. The appearance of a second conformer was noted after prolonged heating at 90 °C in DMSO-d_6 and was assigned to a species with a syn orientation of the aryl units. We have good evidence from 1D-NOE studies (*vide infra*) that the predominant conformation present in solution at room temperature is indeed the anti-aryl conformer, **1**-*anti*. Results also suggest that the second species is in the syn orientation, **1**-*syn*.

In solution, the quinone moieties can rotate rapidly, in and out of the annulus of the calixarene, thereby moving from the anti-partial cone to an *anti*-1,2-alternate or inverted (with respect to initial orientation) anti-partial cone conformation. Thus, the relative conformation of **1** is determined solely by the orientation of the aryl units, since the quinone units rotate continuously at room temperature. It is therefore more accurate to refer to the conformers observed by NMR as *anti* and *syn*, since at room temperature and in the absence of a bound species the quinones are expected to rotate freely. Under these conditions the anti oriented conformers dominate the NMR spectrum. The rapid rotation of the quinone moieties provides a simplification of the NMR spectrum, but also makes detection of the rarely observed 1,2-alt[4] impossible at room temperature.

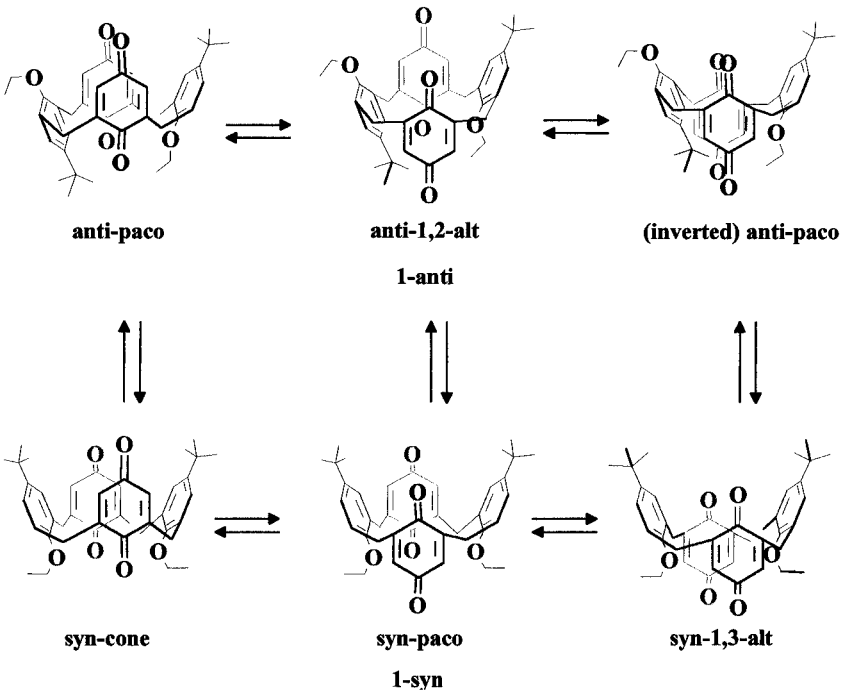
^{1}H-NMR in the Absence of Na^+. Figure 1 shows the initial room temperature ^{1}H spectrum of **1**. The aromatic region of the spectrum shows two singlet peaks, at 7.22 and 6.26 ppm, corresponding to aryl and quinone protons, respectively. The methylene region displays an AB quartet with doublets (J = 13.6 Hz) centered on 3.78 and 3.32 ppm, corresponding to the expected pattern for the diastereotopic protons on the methylene bridges. The quartet at 3.40 ppm corresponds to the methylene

(8) Casnati, A.; Comelli, E.; Fabbi, M.; Bocchi, V.; Mori, G.; Uggozoli, F.; Manotti Lafredi, A. M.; Pochini, A.; Ungaro, R. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 384. We should note that two *slightly* different conformations ("half-independent molecules") of the anti-paco structure exist in the solid state, as the authors note.

(9) Reddy, P. A.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *Isr. J. Chem.* **1992**, *32*, 89.

(10) Jorgensen, W. L.; Gao, J. *J. Phys. Chem.* **1986**, *90*, 2174.

Scheme 1



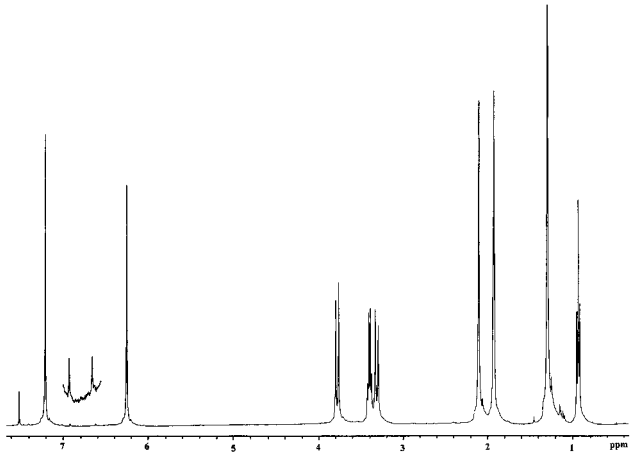


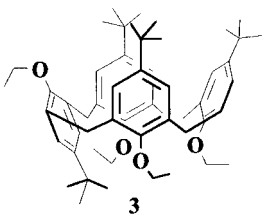
Figure 1. Room temperature ^{1}H-NMR spectrum of a 9 mM solution of **1** in 70% CD_3CN/30% $CDCl_3$, in the absence of Na^+. The inset expansion shows the small peaks attributable to the cone conformer at this temperature. Solvent peaks appear at 7.52 ($CHCl_3$ from $CDCl_3$, shifted due to binary solvent composition), 2.10 (H_2O, also shifted), and 1.93 ppm (CD_2HCN).

groups on the ethoxy tails. At higher field, resonances for the *tert*-butyl and methyl groups are noted at 1.30 and 0.94 ppm, respectively. The chemical shifts are given in Table 1. The conformation assigned to this spectrum is that of **1**-*anti*.

Visible in the aromatic region of the room temperature spectrum of pure **1** are two small peaks, at 6.93 and 6.62 ppm, as shown in the expansion inset in the aromatic region of Figure 1. These peaks, which have been assigned to the **1**-*syn* conformer,[8] increase in intensity (relative to the aromatic resonances assigned to the anti conformer) upon heating the sample above room temperature.[11] At room temperature, the ratio of anti to syn conformers appears to be in excess of 50:1 and is stable over time. The assignment of the small peaks (i.e., which of these small peaks corresponds to the syn-aryl protons and which to the syn-quinone protons) is difficult to assess from this spectrum, and is discussed in detail below.

Conformational Interconversion. Expanding on the work of Reinhoudt et al.,[4] recent studies by Blixt and Detellier have elegantly demonstrated that the path for conversion from one conformer to another in a simple methoxy-tailed calix[4]arene involves a central partial cone intermediate, which is the most stable conformation for this calixarene.[13] A similar pattern should be observed here. Assuming a dominant anti-paco conformer, the remaining conformers of **1** are expected to form from this partial cone. Although rotation of the aryl unit permits formation of the *syn* cone, paco, and 1,3-alt conformers, it should be emphasized that it is only the orientation of the quinone units that determines the relative conformations of the calixarene, as shown above.

Conformational interconversion from the anti-paco to the *anti*-1,2-alternate is easy to envision, requiring rotation of a quinone ring. The anti to syn conversion process is more difficult to rationalize as it requires rotation of an aromatic unit, with its bulky ethoxy tail, through the annulus of the calixarene (refer to Scheme 1), a feat which seems impossible with simple CPK models. Reinhoudt[4a] and Shinkai[5a] have reported that the interconversion of an tetra(ethyl ether) derivative of calix[4]-arene, **3,** can occur at temperatures above 100 °C. Room



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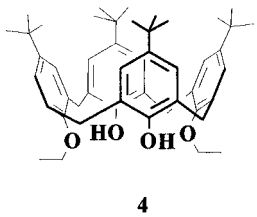

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temperature NMR spectra of this calixarene show that the

(11) While similar results were obtained for this system in DMSO by Ungaro and co-workers (ref 8 above), we have found that in our binary solvent, and in pure CD_3CN, interconversion between the syn and anti conformers occurs at much lower temperatures. It is noticeable even at 35 °C. In contrast, Ungaro and co-workers report that the spectrum of **1** in DMSO is unchanged over the temperature range from −40 to 80 °C.

(12) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

(13) Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1994**, *116*, 11957.

Table 1. Chemical Shift Positions Observed for the Conformers and Na^+ Complex of **1**

species	chemical shift, ppm		
	aromatic region	methylene region[a]	alkyl region
anti	7.22 (ArH)	3.80, 3.32 (ABq, $ArCH_2Q$)	1.30 (*t*-Bu)
	6.26 (QH)	3.40 ($-OCH_2-$)	0.94 ($-CH_3$)
syn	6.93 (ArH)	3.75, 3.38 (ABq, $ArCH_2Q$)	1.14 (*t*-Bu)
	6.62 (QH)	3.68 ($-OCH_2-$)	1.18 ($-CH_3$)
syn-cone-Na^+ Complex	6.79 (AH)[b]	4.04, 3.16 (ABq, $ArCH_2Q$)	0.99 (*t*-Bu)
(1:1)	6.81 (QH)[b]	3.85 ($-OCH_2-$)	1.47 ($-CH_3$)

[a] For ABq $J = 13$ Hz. [b] The position of these resonances depends on the amount of Na^+ present in solution. See text.

solution conformation is that of a fixed partial cone. Heating or refluxing in $CHCl_2CHCl_2$ ($T \geq 132$ °C) results in the generation of the remaining conformers, especially the elusive 1,2-alt conformer.[4,5a] In contrast, compound **4**, which is structurally very similar to diquinone **1**, was found to be in a stable cone conformation, and it was unaffected by temperature changes over the range −20 to +60 °C.[5a]

Due to the obvious differences between calixarenes **3** and **4** and diquinone **1**, we pursued computational studies to verify that rotation of the aryl units also occurred in these systems. Results obtained with Macromodel 3.5X confirm that rotation of the aryl units can indeed occur in diquinone **1**. A gas-phase Monte Carlo (MC) conformational search, with the starting geometry of the minimized **1**-*anti*-partial cone (built according to the X-ray structure), found both the cone and the 1,3-alternate, with the aromatic units in syn orientation, as stable conformers. Interestingly, the 1,2-alternate (which does not require rotation of an aryl unit) was not observed, nor was the syn-paco conformer. Formation of the syn-cone and 1,3-alt conformers from the anti-partial cone was achieved by rotation of the ethoxy tailed (lower rim) end of the aryl unit through the annulus of the calixarene. The energies of the anti-paco and the syn-cone conformers are roughly similar, with the gas-phase energy of the syn-1,3-alternate representing the gas-phase global minimum in the search performed. We should reiterate that the focus of our interest in the computational study was narrow and limited exclusively to the confirmation that the rotation of an ethoxy-arene moiety from the anti to the syn conformation can occur, permitting formation of the remaining conformers. A full exploration of the conformational space was beyond the scope of our resources, but the approach we employed clearly demonstrated that the rotation can occur.

NMR Results in the Presence of Na^+. Preliminary ^{1}H-NMR binding studies of several of the calixquinones were mentioned briefly in previous work.[7] While all of the calixquinones were found to bind Na^+ ions, ^{1}H-NMR evidence for binding to Na^+ was reported only for **2** at that time. No mixture of conformers of any of the calixquinones was noted, although the spectra were examined immediately after the samples had been prepared. In an effort to characterize the Na^+ binding constants of the remaining systems, complementing the electrochemical binding studies, we pursued further examination of these systems by ^{1}H and ^{23}Na NMR titration experiments. A binary solvent system of $CD_3CN/CDCl_3$ (2.3:1) was employed in order to obtain desirable concentrations of both calixquinone and sodium salt. At this time, serendipitously, we noted that the ^{23}Na-NMR spectrum of Na^+ in the presence of **1** changed slowly over time. Figure 2a shows the ^{23}Na spectrum for the free Na^+ while Figure 2b shows the spectrum observed for Na^+ in the presence of the calixarene **1**. Initially, there is a small change in the chemical shift position and slight broadening (from 15 to 19 Hz) of the ^{23}Na resonance. After several hours, both the line broadening and chemical shift change are more noticeable, and after days, they are quite dramatic (see Figure 2, inset plot). For a sample stored at 5 °C, the broadening increased from 19 Hz to more than 160 Hz (Figure 2c) over the course of 50 days. Preliminary measurements of the ^{23}Na longitudinal (T_1) and transverse (T_2) relaxation times for these samples yielded, within error, values that are similar and in the millisecond range. This suggests that the observed line broadening is *not* due to chemical exchange, since T_{2ex} contributions to T_2 would be expected to decrease this relaxation component versus T_1, which is unaffected by exchange processes.[14] Since a single line is observed by ^{23}Na NMR, the total line width is the sum of the line width contributed by Na^+ and any Na^+ complexes. Thus, the increase in line width over time appears to be attributable to the slow formation of a complex with an asymmetric distribution of charge around the Na^+ ion. Based on further evidence discussed below, we feel that this complex is likely to be that of **1**-*syn*-

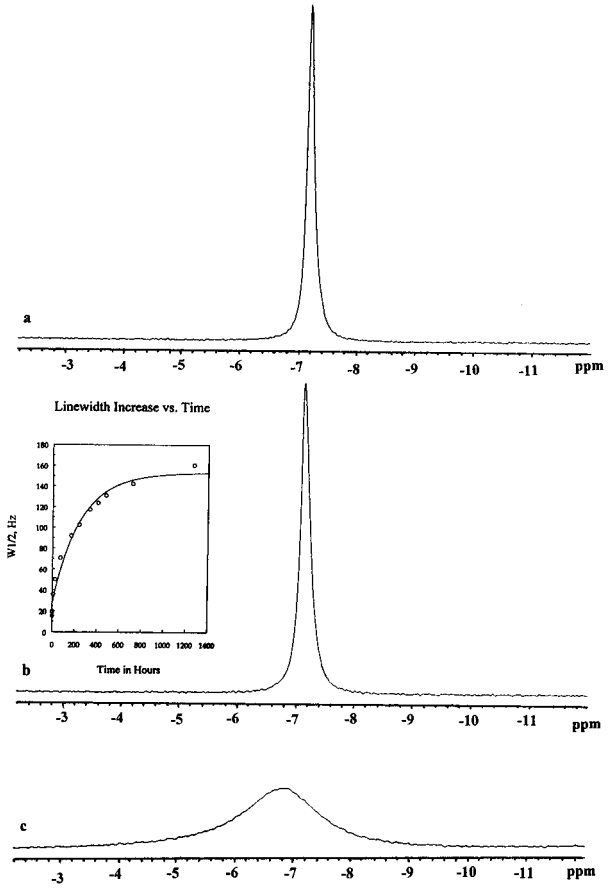


Figure 2. ^{23}Na-NMR spectra of a solution containing (a) 15 mM sodium trifluoromethanesulfonate in 70% CD_3CN/30% $CDCl_3$, (b) the same solution in the presence of 9 mM of calixarene **1**, immediately after addition (the inset plot shows the change in line width of the ^{23}Na resonance over the course of 53 days), and (c) the same solution after storage for 53 days at 5 °C.

(14) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982.

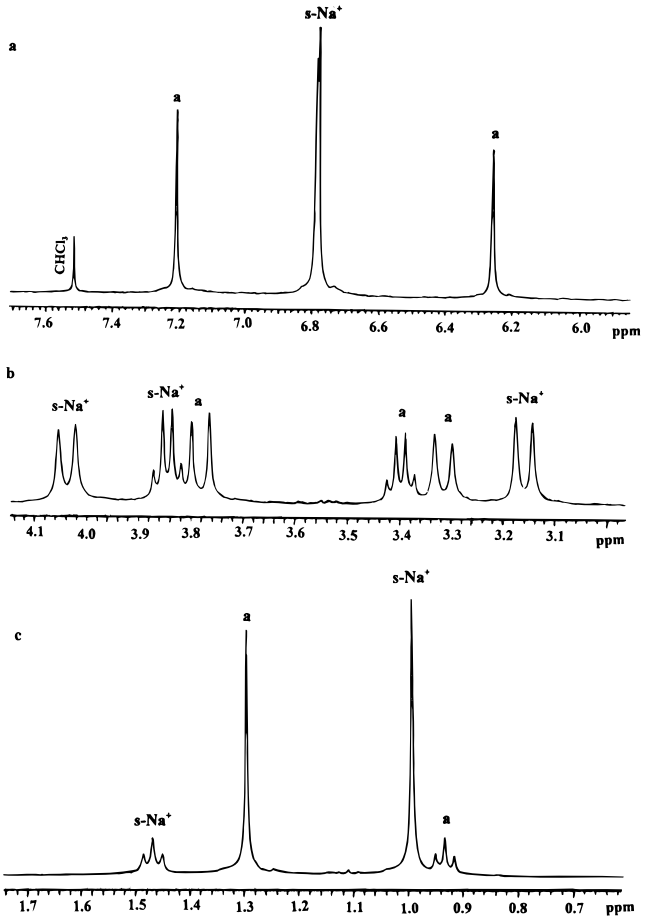


Figure 3. Room temperature ^{1}H-NMR spectrum of a 9 mM solution of **1** in 70% CD_3CN/30% $CDCl_3$, in the presence of 15 mM Na^+ after 17 days at 5 °C (sufficient time to generate an approximate 1:1 ratio of the conformers at this temperature): (a) the aromatic region (the peak at 7.52 ppm is due to $CHCl_3$); (b) the methylene region; and (c) the alkyl region. The a and s denote **1**-*anti* and **1**-*syn* conformer peaks.

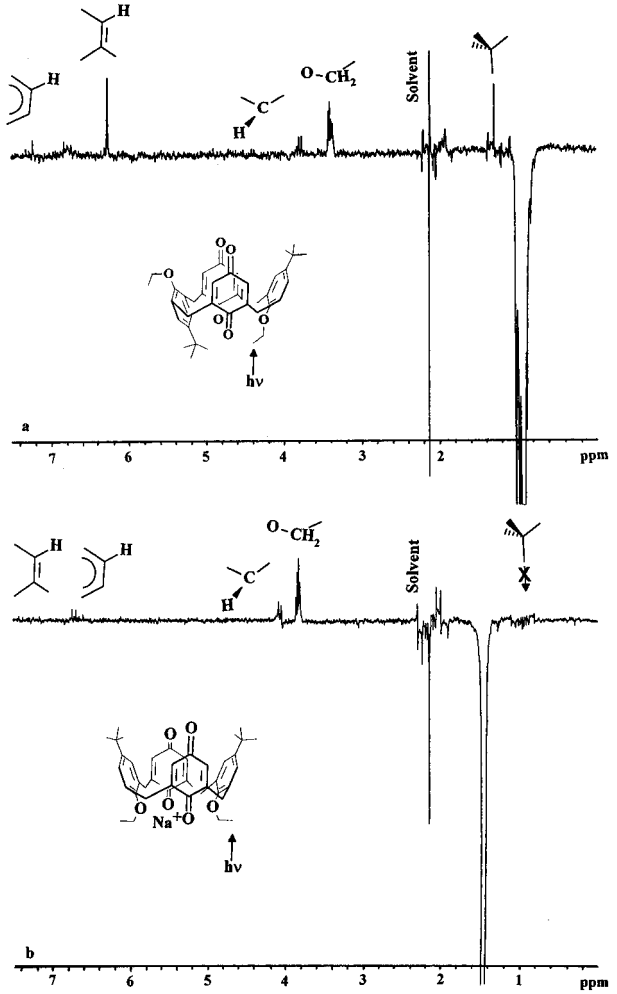


Figure 4. Difference NOE spectra of a 7 mM solution of **1** in 70% CD_3CN/30% $CDCl_3$. Saturated resonances appear in negative phase: (a) saturation of the **1**-*anti* methyl resonance at 0.94 ppm, and (b) in the presence of Na^+, saturation of the **1**-*syn* methyl resonance at 1.47 ppm.[15]

Na^+. We plan to further explore the ^{23}Na-NMR spectra of this system in later work.

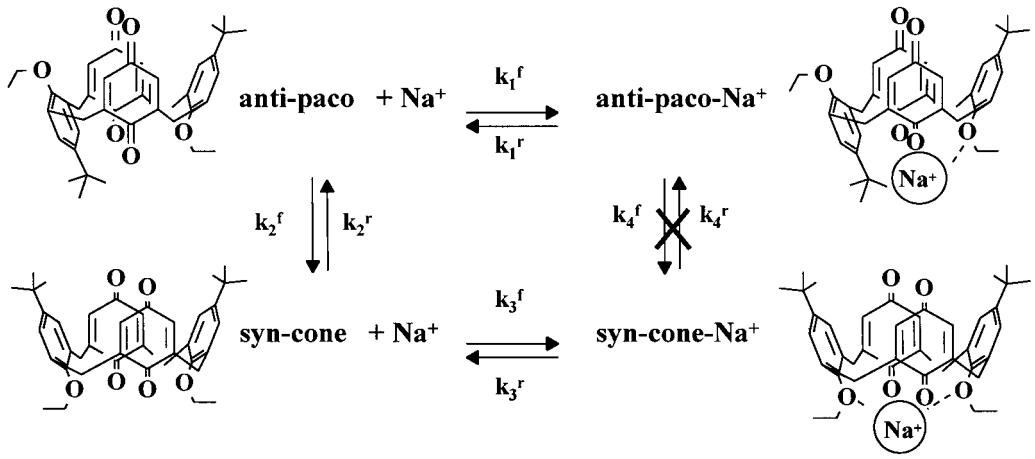
The ^{1}H- and ^{13}C-NMR spectra of **1** were also found to be dramatically affected throughout the entire region of the spectrum. Figure 3a shows the result observed in the aromatic region of the ^{1}H-NMR spectrum of **1** after several days in the presence of excess Na^+. In the presence of an excess of Na^+, the aromatic peaks assigned to the syn conformer change chemical shift position and grow continuously in intensity. While the chemical shifts of the aromatic resonances attributed to the syn conformer are sensitive to the presence of Na^+ ions in solution, additional peaks corresponding to the syn-Na^+ complex are also observed throughout the full spectral region, see Figure 3, spectra b and c. (In this figure a and s are used to differentiate the **1**-*anti* and **1**-*syn* conformer resonances, respectively.) The chemical shift positions attributed to the Na^+ complex are also noted in Table 1. The resonances attributed to the partial cone conformer are unaffected with respect to chemical shift.

Assuming that the observed spectral changes correspond to an anti → syn conversion process resulting from Na^+ complexation, these results are remarkable in that *they are observed at temperatures as low as 5* °C. This temperature is far below those reported for interconversion of the ethyl ether derivatives studied by Reinhoudt[4] and Shinkai[5a] and still substantially below the temperatures employed by Ungaro and co-workers for pure solutions of **1**.[8] Indeed, the results of Reinhoudt, Shinkai, and Ungaro suggest that ethyl ether derivatives should be *inflexible* at room temperature.

NOE Studies of 1 and Its Na^+ Complex. As mentioned above, based on difference NOE spectra of the free calixarene, we confirmed that the initial conformation of the calixarene was anti-aryl. Positive NOE effects are noted on the *tert*-butyl, methylene, quinone, and aryl resonances upon irradiation of the methyl group on the ethoxy tail, as shown in Figure 4a. These results demonstrate the proximity of the methyl group to the quinone and aromatic ring hydrogens, as well as an aryl *tert*-butyl group, a finding consistent with an anti orientation, and probably that of a partial cone. (Although the quinones rotate at room temperature, two of the four possible orientations for the quinones, considering one moiety labeled, result in paco structures. The relative rarity of the 1,2-alt conformer,[4] since

(15) In spectrum a) saturation of the **1**-*anti* methyl resonance at 0.94 ppm yields positive NOEs on the *tert*-butyl resonance, the neighboring methylene on the tail (3.40 ppm), the sidearm methylene resonance at 3.80 ppm, the quinone protons at 6.26 ppm, and the aromatic resonance at 7.22 ppm (weak). In contrast, in spectrum b, saturation of the **1**-*syn* methyl resonance at 1.47 ppm (solution contains Na^+) yields a similar pattern of NOEs, including positive effects on the neighboring methylene on the tail (3.68 ppm) and on the sidearm methylene resonance at 4.04 ppm; however, the NOE enhancement observed in the aromatic region is very weak, though an effect is noted for both the aryl and quinone protons. No enhancement was seen on the *tert*-butyl resonance (0.99 ppm), although the baseline in this region possibly suggests some very weak effect. In the NOE spectra of the free **1**-*syn* conformer (not shown here), irradiation of the methyl resonance did not result in enhancement of the corresponding *tert*-butyl resonance.

Scheme 2



it is typically considered thermodynamically unfavored, makes this interpretation plausible. Shinkai has suggested this conformer may be more stable at higher temperatures.[5a]) NOE enhancements generated by saturating the *tert*-butyl resonance are noted on the aromatic and quinone resonances, as well, further supporting this point. (Examination of the enhancement of the methyl resonance is difficult in this instance due to the intensity of the neighboring saturated *tert*-butyl resonance, which greatly distorts the baseline in the alkyl region of the spectrum.) The shift in the position of the aromatic peaks attributed to the syn conformer, upon addition of Na^+, suggests formation of a syn-cone-Na^+ complex. Figure 4b shows the NOE difference spectrum of the calixarene-Na^+ complex. The absence of a positive NOE between the methyl and the *tert*-butyl resonances clearly suggests the conformation of this complex is no longer anti, while the NOEs observed would be consistent with those expected for the cone conformer.

The Kinetics of Na^+ Binding and the Relation to Conformational Exchange. The binding scheme suggested by the NMR spectra is depicted in Scheme 2. On the basis of our NOE results, we chose to depict the anti conformer as a partial cone and the syn conformer as a cone. Although the rates for k_2^f and k_2^r can be obtained, the k_1, k_3, and k_4 rates are not accessible from the NMR data. Examination of the NMR spectra in the presence of Na^+ shows that no anti-paco-Na^+ complex peaks are evident. Since no anti-paco complex is observed we assume that while the rate of formation and decomplexation is very fast, the equilibrium constant for this process is low, and thus the concentration of the free **1**-*anti* dominates.[16] We do, however, have sound evidence that the Na^+ complex of **1**-*anti* forms, based on previously published electrochemical data.[7] Assuming that the **1**-*anti* complex, like the **1**-*syn* complex, would yield an averaged chemical shift, the small amount of **1**-*anti*-Na^+ that might be formed in such a process would not be sufficient to significantly affect the chemical shift position or cause broadening of the aromatic and quinone peaks. This scenario means that Na^+ binding for the anti complex cannot be probed by ^{1}H NMR. Thus, the rate that can be measured by the disappearance of the free **1**-*anti* conformer by NMR is an overall rate that combines two steps (arguably, as discussed below, k_2^f and k_3^f) to the **1**-*syn*-Na^+ complex. (It must be emphasized that this is a qualitative rather than a true first-order or pseudo-first-order rate. Sufficiently high concentrations of the salt, to permit pseudo-first-order conditions, cannot be attained due to the insolubility of **1** in polar solvents.) Values of this overall rate, obtained at various temperatures, are presented in Table 2, while a plot of these data is presented in Figure 5.

Table 2. Kinetics Data for Decrease in *anti*-Paco-**1**

	k,[a] s^{-1}	estimated error
1 (no Na^+)		
45 °C	1.2×10^{-4} (1)	$\pm 9 \times 10^{-5}$
50 °C	2.0×10^{-4} (2)	$\pm 1 \times 10^{-4}$
55 °C	2.6×10^{-4} (1)	$\pm 2 \times 10^{-4}$
65 °C[b]	6.4×10^{-4} (2)	$\pm 5 \times 10^{-4}$
1−Na^+ complex		
5 °C	1.8×10^{-6} (1)	$\pm 8 \times 10^{-7}$
25 °C	1.44×10^{-5} (1)	$\pm 5.5 \times 10^{-6}$
35 °C	3.02×10^{-5} (2)	$\pm 1.5 \times 10^{-5}$
45 °C	8.10×10^{-5} (1)	$\pm 2.5 \times 10^{-5}$
55 °C	1.02×10^{-4} (1)	$\pm 4.8 \times 10^{-5}$

[a] Numbers in parentheses reflect number of experiments conducted to obtain the value. [b] Value obtained in pure CD_3CN.

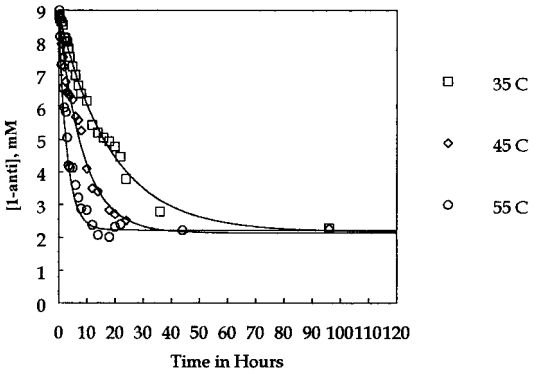


Figure 5. Plot of the ^{1}H-NMR kinetics data for the decrease in the concentration of the **1**-*anti* conformer at 35, 45, and 55 °C.

The rate of conversion from free syn to syn-cone complex (k_3 processes) appears to be fast on the NMR time scale at room temperature, yielding averaged chemical shift resonances for the peaks in the aromatic region. By first heating a solution of **1** to generate the free syn, one can use the aryl and quinone cone resonances to assess binding of Na^+ to **1**-*syn*. A plot of the binding data is shown in Figure 6. The ratio of **1** to Na^+ in the complex was found to be 1:1, and the Na^+ binding constant with the cone conformer was estimated to be 856 M^{-1} (±12 M^{-1}) at 25 °C. Low-temperature NMR studies at less than stoichiometric concentrations of salt have permitted resolution of the free and bound syn resonances. As shown in Figure 7a,

(16) Recent studies of this system, and of a series of diquinone calix[4]arenes, by ^{23}Na NMR have suggested that the binding constant for the anti conformer of **1** is <50 M^{-1}. The high salt concentrations required to observe a substantial amount of the anti complex (unachievable in this solvent mixture), along with the continuous conversion of anti to syn in the presence of the salt, make accurate determination of the anti conformer's binding constant difficult.

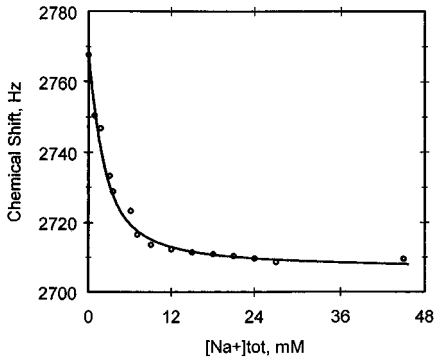


Figure 6. Plot of the ^{1}H-NMR binding constant data for the **1**-*syn*-Na^+ complex based on chemical shift positions of the aryl protons.

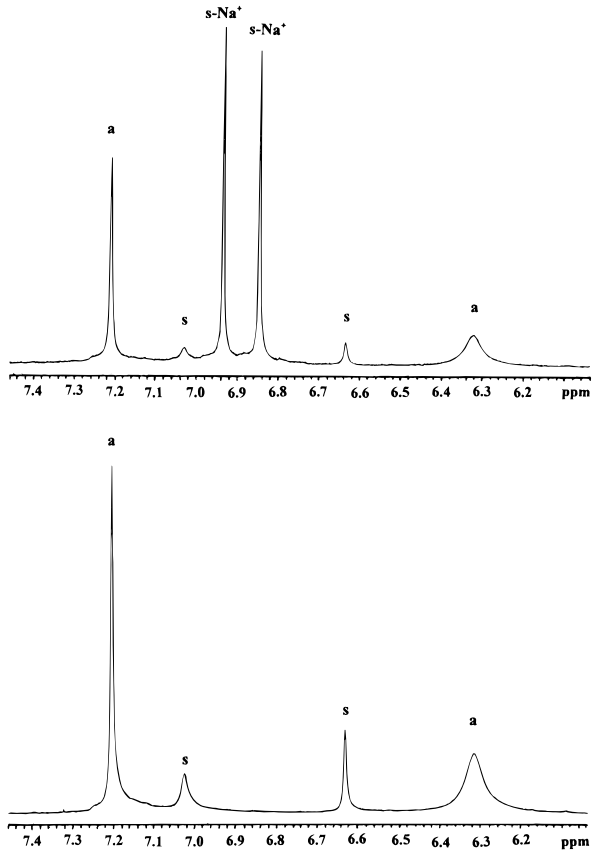


Figure 7. Aromatic region ^{1}H-NMR spectra at −60 °C of (a) 9 mM **1**/7 mM Na^+ showing resolved free **1**-*syn* and **1**-*syn*-Na^+ complex peaks and (b) 9 mM **1** in the absence of Na^+. Lack of broadening for the cone complex peaks in spectrum a suggests reduced mobility of the quinone moieties.

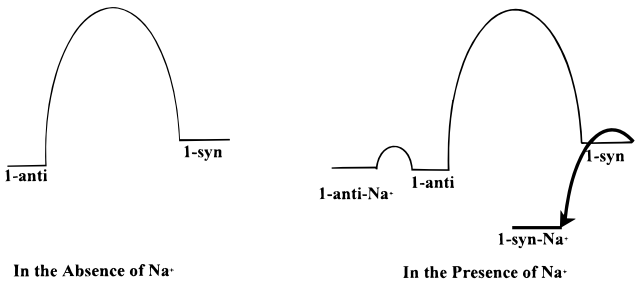
the aromatic region of the ^{1}H-NMR spectrum at −60 °C (at less than stoichiometric concentrations of Na^+) demonstrates the presence of both the free syn and the syn-cone-Na^+ complex. Figure 7b shows the spectrum of a diquinone solution (containing no Na^+) that had been heated for 12 h at 50 °C to generate the cone conformer and then subsequently cooled to −60 °C, for comparison. The chemical shift positions of the free syn conformer's aromatic peaks are virtually identical with those observed for the free syn positions observed in Figure 7a.

On the basis of the observations of the low-temperature spectrum shown in Figure 7b, we can also suggest assignments of the syn aromatic peaks in the absence of Na^+. Broadening of the *anti*-paco-quinone peak at 6.30 ppm (shifted slightly downfield, in comparison to the peak position observed at room temperature) is observed at low temperature, a finding that seems reasonable given the rapid rotation of the quinones at room temperature. Slowing down this process is likely to result in "freezing out" several variations in the quinone orientation, and suggests that some 1,2-alt may exist in solution. The subsequent observation that the syn peak at 7.03 ppm also broadens at low temperature would tend to suggest that this peak corresponds to the *syn*-quinone protons. Presumably, ring current effects of the two neighboring aryl units have resulted in the downfield shift of this conformer's quinone protons. The aryl protons, which show little if any broadening in the anti-paco conformation (7.22 ppm), would then likely correspond to the syn peak at 6.63 ppm, which also displays little broadening. Similar patterns of up- and downfield shifts are observed for other peaks in the spectra, most notably the methyl and *tert*-butyl resonances (see Table 1)

As mentioned above, conversion to the syn conformer also occurs in the absence of Na^+ ions, corresponding to the k_2^f step in Scheme 2, at elevated temperatures. The conversion to syn is incomplete in the range of temperatures surveyed, yielding an ∼4:1 ratio of anti to syn. These rates are also presented in Table 2. Since conversion is not complete and the time to reach a conformational equilibrium at each temperature was on the whole relatively brief, the error in these values is substantially higher. We were surprised to find that upon cooling, the ratio of the anti to syn conformers remained the same (4:1), even weeks after the sample solution had been heated, suggesting a metastable ratio of conformers. Subsequent results obtained from decomplexation studies (*vide infra*) suggest that, in fact, the initial solution ratio of anti to syn conformers (50:1) is the metastable state. Studies of the conversion in the absence of salt could potentially yield information about the energy of activation for the rotation of the aryl unit required to form the cone conformer. Due to the magnitude of error in the rates presented for this process, and the limited range of temperature available in the solvent mixture utilized for these experiments, we feel that the energy of activation cannot be estimated accurately.

From comparison of the rates in the presence and the absence of the Na^+ ions we see that the order of magnitude for the processes, within error, is the same. This suggests that *the presence of Na^+ does not increase the rate of conversion from the anti to the syn conformer*. The fact that virtually all of the **1**-*anti* conformer is converted to the **1**-*syn* complex in the presence of the ion even at low temperatures (in contrast to the conversion to only a 4:1 anti:syn ratio in the absence of the ion, and only at higher temperatures) does, however, clearly suggest that *the position of the equilibrium is shifted to favor the **1**-syn conformer (or rather its complex) in the presence of this ion.* The energies of activation for the processes leading to syn formation (either k_2^f or k_4^f) are the same. To understand this point one must consider that *in the presence or absence of the salt, the rotation of the aryl unit through the annulus of the calixarene is equally costly in energetic terms, but that once the rotation occurs, the syn-cone conformer is greatly stabilized in the presence of the Na^+ ion*. The energy scheme for these processes is shown in Scheme 3. Furthermore, the slow rate of conversion from syn to anti occurs on a time scale incompatible with the lifetime of the Na^+ complex. The ion is complexed and dissociated many times over the course of the time it takes for an aryl ring to rotate. While only small amounts of the **1**-*syn* conformer are observed to form at room temperature in the absence of Na^+, the rapid formation of the complex upon addition of the salt continually removes free **1**-*syn* and the equilibrium requirements decrease the free **1**-*anti* concentration. Thus, the path for the two-step process observed by NMR is via k_2 and k_3 rather than via k_1 and k_4.

Scheme 3



The reversibility of these processes was addressed by addition, at room temperature, of Cryptand[2.2.1] to the Na^+ complex. Addition of the cryptand results in clear decomplexation, see Figure 8. Here we can see the slow decrease in the cone complex peaks after addition of [2.2.1]. However, the final ratio of conformers in the decomplexed calixarene sample was coincident with that noted upon heating and then cooling a sample of the free calixarene, 4:1 paco:cone. This further supports our conclusion that the original solution ratio of anti to syn conformer (>50:1) is metastable. Thus, formation (or isolation) of the diethoxy, di-*tert*-butyl calixarenediquinone in the anti orientation is a kinetically driven process, and the final 80% anti/20% syn ratio obtained after heating the free calixarene sample, or by removing the Na^+ from the calixarene, is the thermodynamic product ratio. (Work by Casnati et al. on a series of related diquinone calixarenes has yielded a similar product ratio of 4:1 paco:cone for a system lacking the *tert*-butyl groups.)[8]

We have also examined the binding effects of the other alkali metal ions, Li^+, K^+, Rb^+, and Cs^+, on **1**. Of these ions only K^+ was found to have an effect on the conformation of the calixarene, although to a lesser degree and with less dramatic chemical shift changes than those noted for the Na^+ complex. Additions of Li^+, Rb^+, and Cs^+ were found to have little effect on the ^1H spectrum, even in the sensitive aromatic region.

Conclusions

The slow conversion of **1** to the cone conformer in the presence of Na^+ appears to result from the favorable equilibrium position of the syn-cone-Na^+ complex. In both the presence and absence of Na^+, the interconversion of anti-paco to syn-cone requires the rotation of a single aryl unit. Thus, it is not surprising that the rate constants for the conformational process are the same. The unusual time scale of this process, as well as its occurrence at relatively low temperatures, does bear examination. The slow conformational exchange provides insight about the control of the preorganization of a calixarene based on hindered mobility.

Post-synthetically, the appropriate guest, solvent, and temperature conditions can readily exert sufficient influence on this moderately hindered host (**1**) to effect slow conformational conversion. Sterically hindered calixarenes typically have been designed with the thought of fixing a desired conformation. In this instance, the presence of a guest substantially alters the stability of a conformation that appears to be thermodynamically less favored in the absence of the guest. Furthermore, this conversion occurs within a temperature range in which the conformation of the calixarene was assumed to be fixed. Such a process might go undetected if the calixarene's conformation is not followed for a reasonably long period of time. We feel this finding may be of relevance to the development of calixarenes in sensor applications.

We are currently pursuing studies of the electrochemistry of the two conformers of **1**. Previous voltammetric studies of **1** were performed under conditions that would only permit examination of the behavior of the anti conformer.[7] The enhanced Na^+ binding suggested here for the syn conformation is thus of interest.

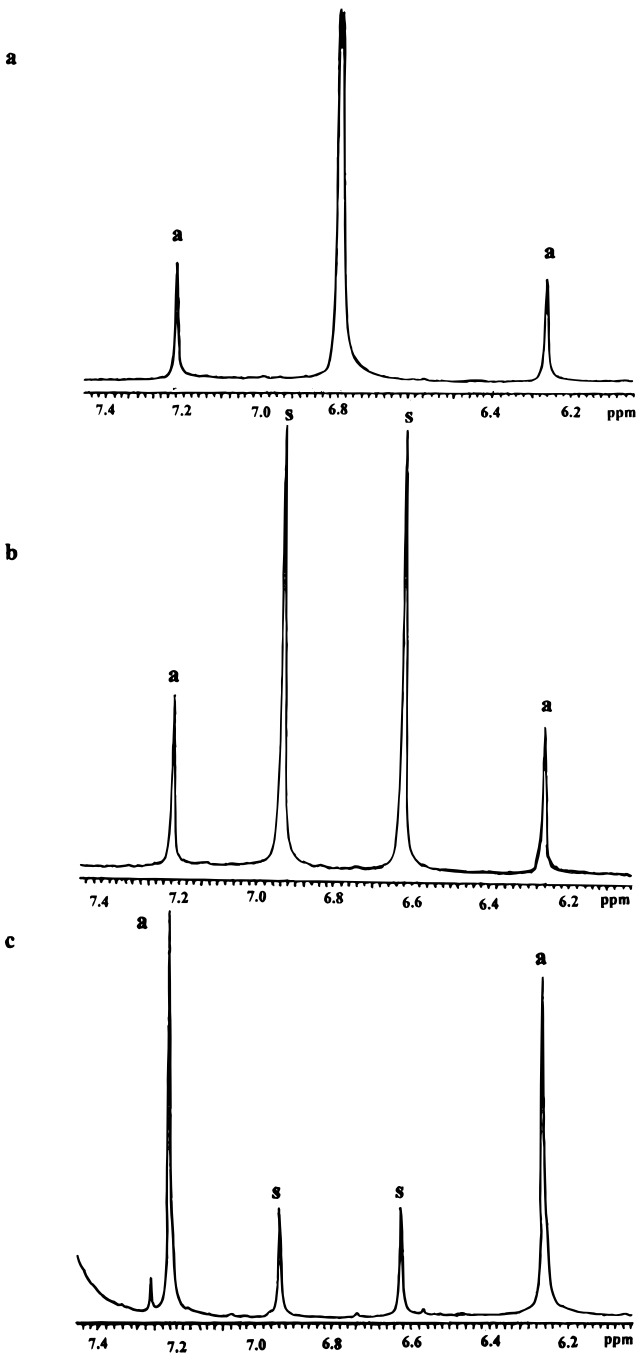


Figure 8. Aromatic region ^1H-NMR spectra at 25 °C of (a) 9 mM **1**/15 mM Na^+ showing the **1**-*syn*-Na^+ complex peaks at 6.80 ppm, (b) the same sample immediately after addition of 20 mM Cryptand[2.2.1], and (c) the same sample after 1 week, showing the stable ratio of 4:1 anti−syn. (Addition of the hygroscopic [2.2.1] increases the amount of protonated solvent.)

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