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Synthesis and Conformational Studies of Lower Rim Cyanomethyl Substituted Calix[4]arenes

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The conformational inversion characteristics of calix[4]arenes carrying cyanomethyl groups on the lower rim have been investigated. Complete conversion from a 1,3-alternate to a partial cone conformation was observed for the 1,3-dicyanomethyl ether of calix[4]arene at room temperature, while at higher temperatures further inversion to a 1:1 mixture of partial cone and cone conformers occurred.

Keywords: Conformation inversion; Calix[4]arene; 1,3-Alternate; Partial cone; Cone

INTRODUCTION

It was first recognized by Cornforth [1] that calix[4]arenes can exist in four well-defined conformations, later named by Gutsche as cone [2,3], partial cone, 1,2-alternate, and 1,3-alternate. At room temperature, rapid interconversion among these conformers occurs by the "oxygen through the annulus" pathway [4,5]. However, if the hydrogen atoms of the OH groups are replaced by a sufficiently large group, the conformational interconversion is curtailed, and conformationally stable compounds can be isolated and characterized. In the case of calix[4]arenes Shinkai has shown that the necessary size appears to begin with the propyl group [6,7]. Even though CPK space filling models suggest otherwise, both the tetramethyl and tetraethyl ethers of calix[4]arenes are conformationally mobile at room temperature, although the latter was considerably less. Given this sequence of methyl < ethyl < propyl, it was of interest to determine where cyanomethyl falls in this progression of effective group size.

Employing methods described in the literature, a calix[4]arene carrying two OCH_2CN and two OCH_2CO_2Et groups on the lower rim (**3**) was synthesized and found to assume a 1,3-alternate conformation. Surprisingly, however, a transformation of this compound from a 1,3-alternate conformer to a partial cone conformer occurred at room temperature [8]. To investigate this phenomenon in greater detail, a variety of tetrasubstituted calix[4]arenes were synthesized and their conformational properties studied, including compounds **3**–**8**.

RESULTS AND DISCUSSION

Synthesis and Characterization of Tetrasubstituted Calix[4]arenes

The tetrasubstituted calix[4]arenes **3**–**8** were obtained by treating calix[4]arenes **1** and **2** with the appropriate alkylating agents, as shown in Scheme 1. Treatment of **1** with Cs_2CO_3 and (a) ethyl chloroacetate produced a mixture of the 1,3-alternate (**3**) and cone (**4**) conformers, (b) chloroacetonitrile produced a mixture of partial cone (**5**) and cone (**6**) conformers, and (c) propyl or butyl bromide produced only the 1,3-alternate conformers (**7a** and **7b**). Treatment of **2** with chloroacetonitrile in the presence of Cs_2CO_3, on the other hand, produced only the partial cone conformer (**8**), suggesting that the conformational rigidity of **2** over **1** could determine the product conformation.

The δ 3.6–4.2 region of the ^{1}H NMR spectrum (Fig. 1a) of **3** shows a quartet arising from

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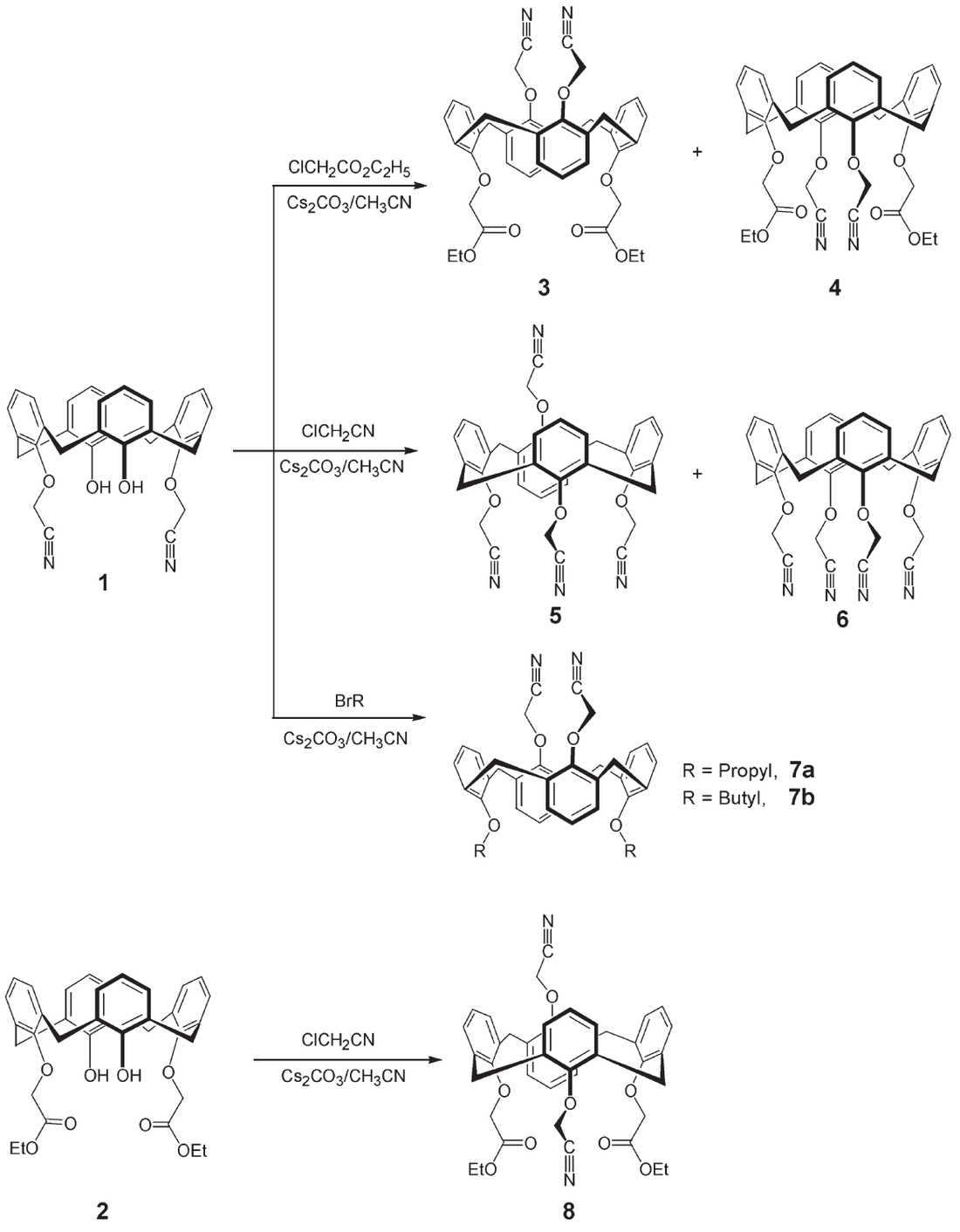


SCHEME 1 Synthesis of tetrasubstituted calix[4]arenes.

the OC***H***$_2$CH$_3$ group, a singlet arising from the C***H***$_2$CN group, a singlet arising from the OC***H***$_2$CO group, and a pair of resonances arising from the calixarene bridge CH_2 groups, characteristic of a 1,3-alternate conformation. The latter are, indeed, a pair of doublets at δ 4.09 and 3.86 was revealed by a COSY spectrum of **3**. The δ 6.8–7.2 region shows two doublets and a pair of triplets for the 12 aromatic protons. Further confirmation of the 1,3-alternate structure is provided by the ^{13}C NMR spectrum (Fig. 2a), which shows a single peak at δ 37.28, characteristic of calixarenes in which the aryl rings are *anti* to one another [9]. Similarly, the ^{1}H and ^{13}C NMR spectra of **7a**, **7b**,

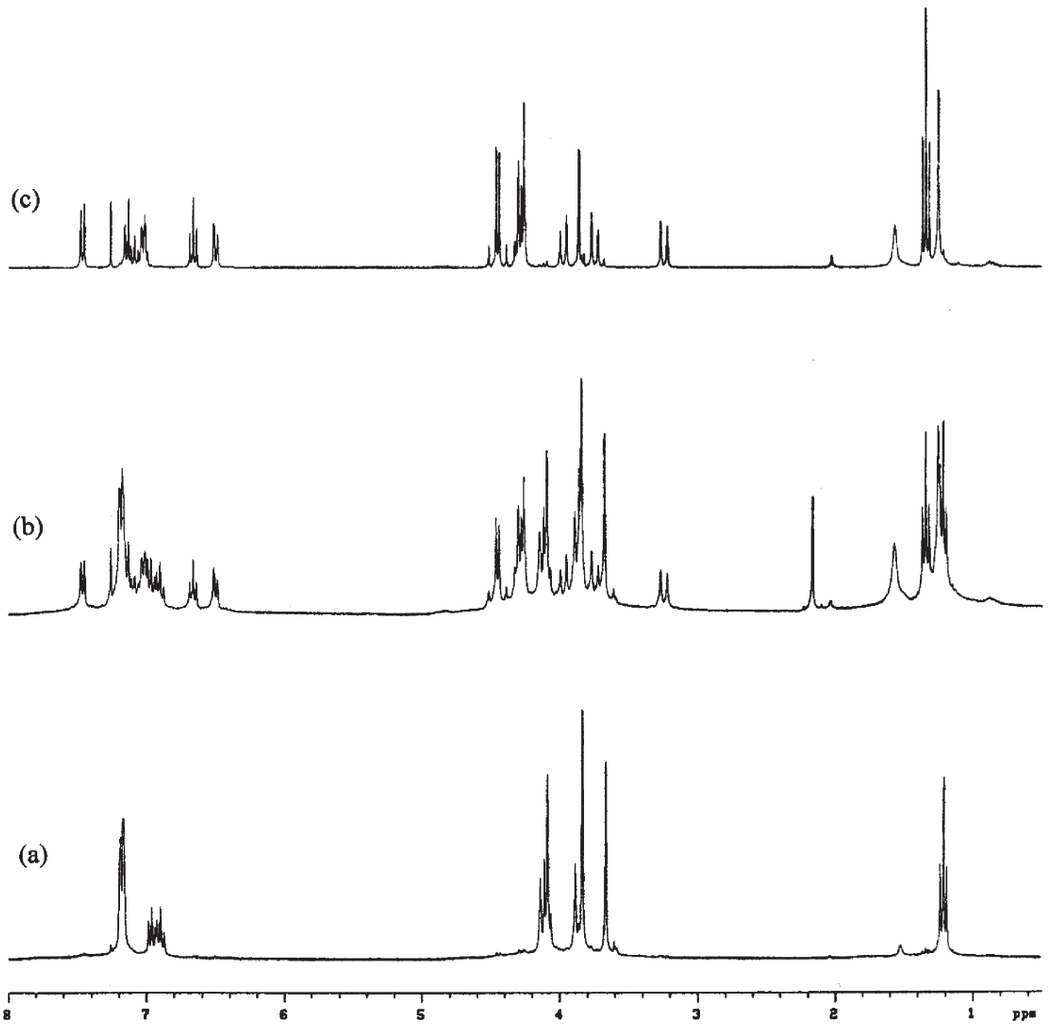
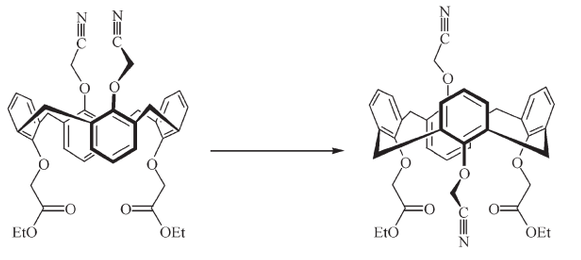


FIGURE 1 ^{1}H NMR spectrum of **3** in $CDCl_3$ (a) within 1 h (1,3-alternate conformation), (b) after 2 days (a mixture of 1,3-alternate and partial cone conformations), (c) after 10 days (partial cone conformation).

and **9** were compatible with a 1,3-alternate conformation.

Conformational Studies



The ^{1}H NMR spectrum of **3** in $CDCl_3$, initially showing a pattern characteristic of a 1,3-alternate conformation, changed over the course of 2 days at room temperature to show a pattern indicating the presence of some of the partial cone conformer (Fig. 1b). After 10 days the transformation of 1,3-alternate to partial cone conformer was complete (Fig. 1c), producing **8**, which was also obtained from **2**, as described above. The partial cone structure was inferred from the ^{1}H NMR spectrum of **8** that shows a much more complex pattern of resonances than that of **3** in both the aromatic region and the methylene region. The appearance of only one triplet at δ 1.21 arising from the CO_2Et groups indicates that the aryl residue bearing these moieties must be *syn* to one another and that the aryl residues bearing the CN groups must, therefore, be *anti* to one another. The presence of resonances at δ 36.1 and 31.4 from the ^{13}C NMR spectrum is also compatible with a partial cone conformation (Fig. 2b) [9].

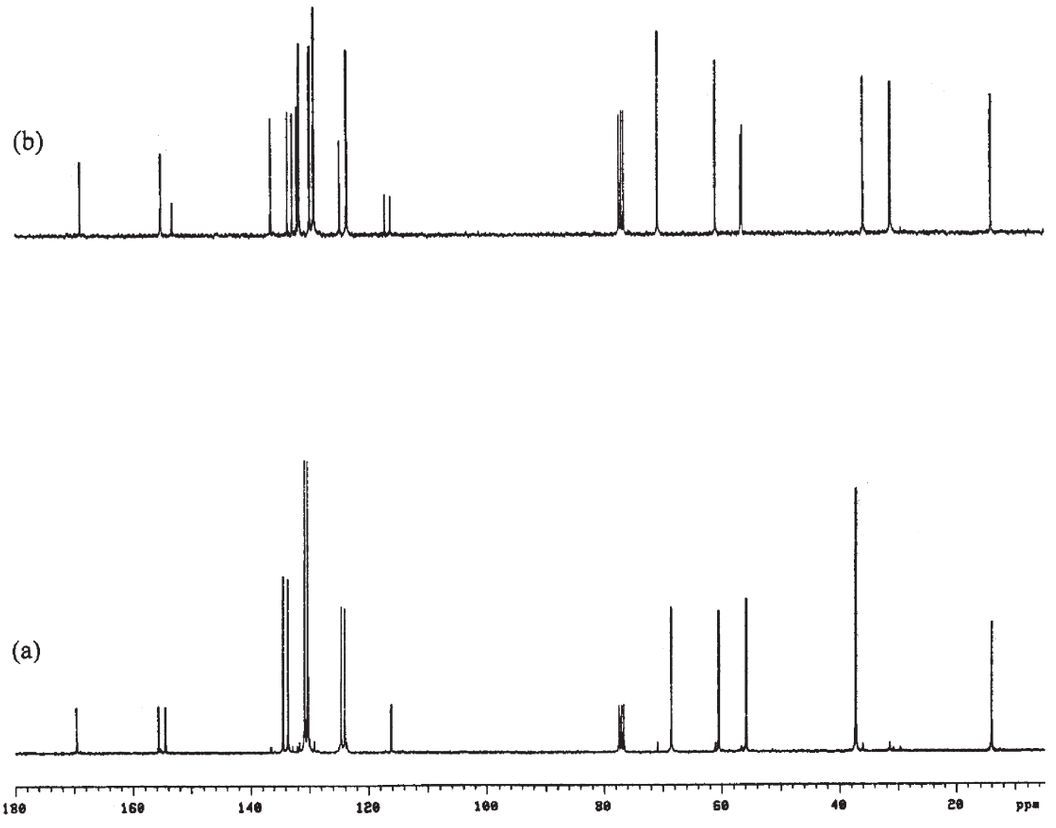
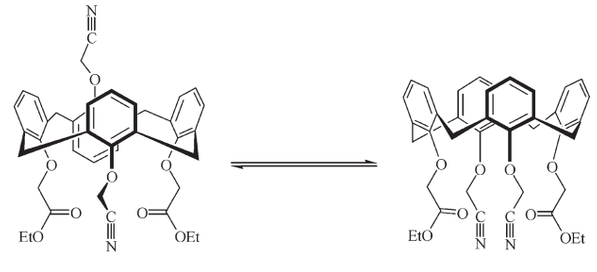


FIGURE 2 ^{13}C NMR spectrum of **3** in $CDCl_3$ (a) within 1 h (1,3-alternate conformation), (b) after 10 days (partial cone conformation).

The ^{13}C NMR spectra of **3**, as initially formed and after standing for 10 days, are also compatible with 1,3-alternate and partial cone conformations, respectively. To accelerate the conformational interconversion, the temperature was raised. As anticipated, the necessary time was decreased in the manner shown in Table I. When **3** was heated to its melting point (mp 131°C) the conversion occurred immediately, and the solid partial cone conformer **8** (mp 161°C) was obtained.

The conversion of the 1,3-alternate to the partial cone conformer of **3**, involving the reorientation of an aryl residue carrying a OCH_2CN moiety via a "through the annulus pathway", suggested the possibility of further conformational inversion to the cone conformer. This does, in fact, occur but only at much higher temperature. When **8** was heated for a day at 170°C, a 1:1 mixture[†] of partial cone (**8**) and cone (**4**) conformers was formed, as indicated by the ^1H NMR spectrum shown in Fig. 3. The assignment of the cone structure to **4** is based on the appearance of a pair of doublets at δ 4.50 and 3.29 for the bridge methylene protons and two singlets at δ 5.29 and 4.48 for the methylene groups of OCH_2CN and OCH_2CO_2Et, respectively. The ^{13}C NMR spectrum of **4** shows a single peak at δ 31.2 for the bridge methylene groups, in accordance with a cone conformation. Extended heating of **4** failed to change the product ratio, which remained at 1:1 even after 7 days, suggesting that an equilibrium between the two conformers is established. On this premise, it was surmised that the same equilibrium mixture should be produced starting with a pure sample of the cone conformer **3** as, indeed, was the case. When heated at 217°C the equilibration time was shortened to 3 h.



[†]Mixture ratio was calculated based on the integration of ^1H NMR spectrum.

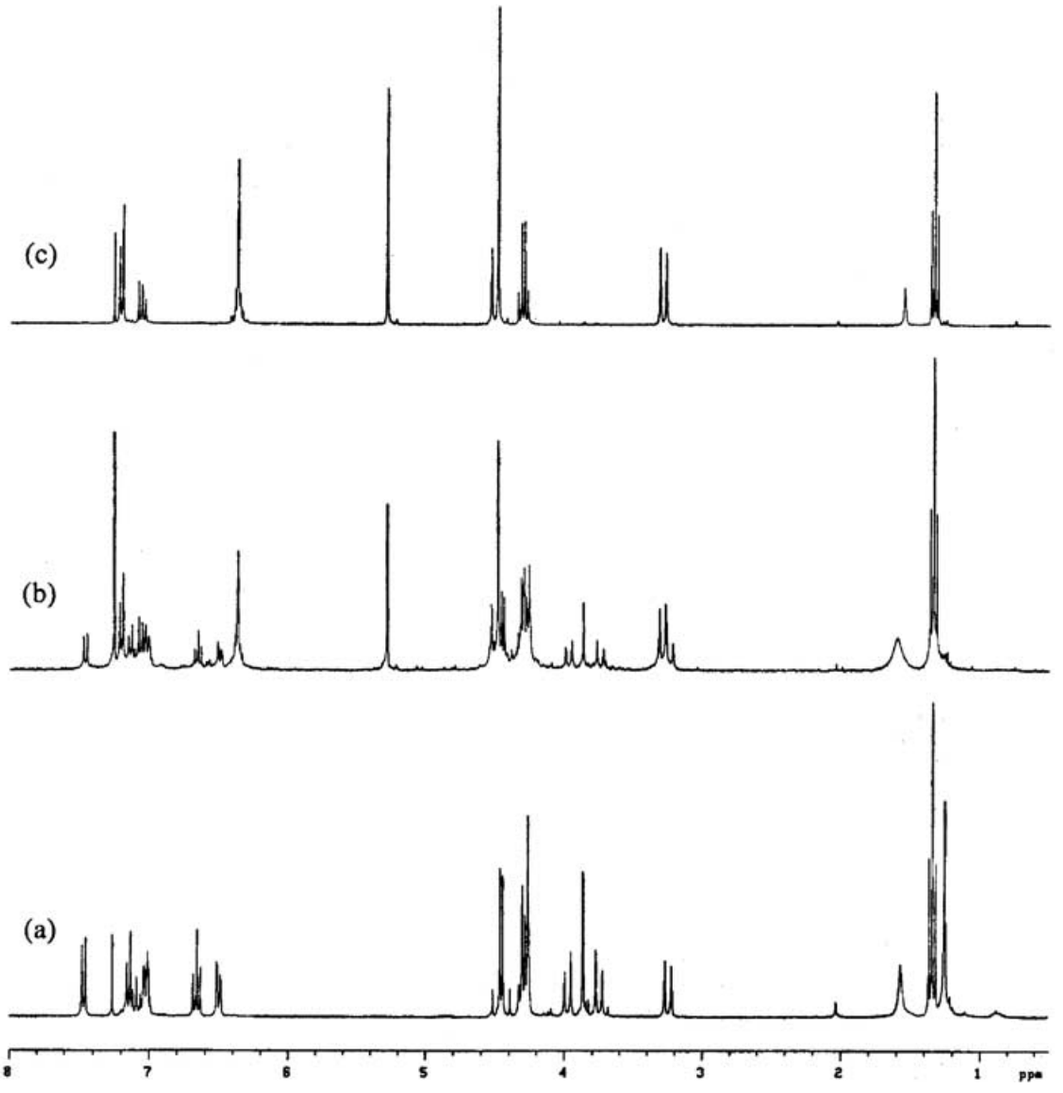


FIGURE 3 ^{1}H NMR spectrum of (a) **8** (partial cone conformation) (b) **8** after 1 day at 170°C (a mixture of partial cone and cone conformations) (c) **4** (pure cone conformer obtained from separate reaction) in $CDCl_3$.

TABLE I Conformational conversion of tetrasubstituted calix[4]-arenes at various temperatures

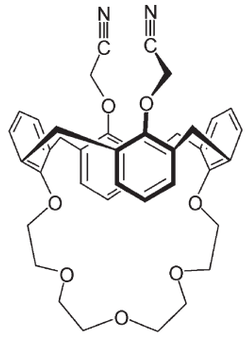
Starting compounds	Temperature	Time	Conversion compounds
3	Room temperature*	0	**3** only
		2 days	**3**:**8** = 1:1.5
		7 days	**3**:**8** = 1:7
		10 days	**8** only
	Melting (131°C)	–	**8** only
8	170°C†	1 day	**8**:**4** = 1:1
		7 days	**8**:**4** = 1:1
	217°C‡	30 min	**8**:**4** = 1:1
		3 h	**8**:**4** = 1:1
4	170°C	1 day	**8**:**4** = 1:1.2
		3 days	**8**:**4** = 1:1
	217°C	3 h	**8**:**4** = 1:1
5	217°C	1 h	**5**:**6** = 3:2
6	217°C	1 h	**5**:**6** = 3:2

*In $CDCl_3$ solution. †Samples in capillary are sealed and heated in boiling 2-aminoethanol. ‡Samples in capillary are sealed and heated in boiling *N*,*N*-diethylaniline.

Similar conformational behavior was observed for the tetra-*O*-cyanomethyl derivatives **5** and **6**. Thus, when **5** was heated in boiling *N*,*N*-diethylaniline for 1 h, a 3:2 ratio of partial cone conformer **5** and cone conformer **6** was observed, and the same ratio was attained starting with **6**. In contrast to Shinkai's observation [7] that a 1,2-alternate conformer is formed when the sterically-related tetraethyl ether of *p*-*tert*-butylcalix[4]calixarene is heated, none of this conformer was observed in the present case.

The propyl and butyl esters **7a** and **7b** behave in a fashion similar to that of **3**, undergoing conformational interconversion to the corresponding partial cone conformers via a "through the annulus" reorientation of the aryl moieties residues carrying the OCH_2CN moieties. And also, in similar fashion, the calixcrown-5 compound **9**, initially isolated

as the 1,3-alternate conformer, undergoes conformational interconversion to the partial cone conformer at room temperature, although more slowly than **3**.



9

In conclusion, calix[4]arenes comprising aryl carrying OCH_2CN undergo conformational interconversions involving the "through the annulus pathway" of these units, as demonstrated by 1,3-alternate to partial cone interconversions and partial cone to cone interconversions. The conformational stability of these calix[4]arenes appears to increase in the order: $1,2\text{-alternate} \ll 1,3\text{-alternate} < \text{partial cone} = \text{cone}$.

MATERIAL AND METHODS

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. The melting points of all compounds were recorded on a Mel-Temp apparatus without calibration. Infrared (IR) spectra were determined on a FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a 300 and 500 MHz spectrometer. Thin layer chromatography (TLC) analyses were carried out on silica gel plates.

25,27-Bis[(cyanomethyl)oxy]-26,28-dihydroxycalix[4]-arene (**1**). The compound was prepared by the procedure reported previously [10].

25,27-Bis[(ethoxycarbonylmethyl)oxy]-26,28-dihydroxycalix[4]arene (**2**). The compound was prepared by the procedure reported previously [10].

25,27-Bis[(ethoxycarbonylmethyl)oxy]-26,28-bis[(cyanomethyl)oxy]calix[4]arene (**3** and **4**). To a solution of **1** (0.2 g, 0.4 mmol) and Cs_2CO_3 (0.5 g, 1.5 mmol) in 30 ml CH_3CN, ethyl chloroacetate (0.1 ml, 1.16 mmol) was added and the reaction mixture stirred for 12 h at room temperature. The solvents were removed and the residue was taken up in $CHCl_3$ (100 ml) and washed with 0.1 N HCl (100 ml) followed by water. Evaporation of $CHCl_3$ gave the crude products which were separated by column chromatography (eluent, $CHCl_3$:*n*-hexane:ethyl acetate = 6:3:1) to yield the 1,3-alternate product **3** (0.09 g, 34%) and cone conformer **4** (0.1 g, 37%). **3** mp 130–131°C; ^{1}H NMR ($CDCl_3$) δ 7.18 (two d, 8H, ArH, $J = 7.2$ Hz), 6.96 (t, 2H, ArH, $J = 7.8$ Hz), 6.90 (t, 2H, ArH, $J = 7.5$ Hz), 4.10 (q, 4H, $-OCH_2CH_3$, $J = 7.5$ Hz), 4.09 and 3.86 (a pair of d, 8H, $ArCH_2Ar$, $J = 14.8$ Hz), 3.84, and 3.67 (two s, 8H, $-OCH_2CN$ and $-OCH_2CO_2-$), 1.21 (t, 6H, $-CH_3$, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.4 ($-CO_2-$), 155.6, 154.4, 134.4, 133.6, 130.8, 130.2, 124.6, and 124.0 (Ar), 116.2 (–CN), 68.6, 60.5, and 55.8 ($-OCH_2-$), 37.3 ($ArCH_2Ar$), 14.0 ($-CH_3$); FAB MS *m/z* 675.2 (M^+, Calcd 674.7). Anal. Calcd for $C_{40}H_{38}N_2O_8$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.80; H, 5.63; N, 4.12. **4** mp 164–165°C; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 4H, ArH, $J = 7.5$ Hz), 7.05 (t, 2H, ArH, $J = 7.2$ Hz), 6.37 (s, 6H, ArH), 5.29 and 4.48 (two s, 8H, $-OCH_2-$), 4.50 and 3.29 (a pair of d, 8H, $ArCH_2Ar$, $J = 13.5$ Hz), 4.30 (q, 4H, $-OCH_2CH_3$, $J = 7.1$ Hz), 1.33 (t, 6H, $-CH_3$, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.2 ($-CO_2-$), 155.1, 153.7, 136.5, 132.4, 129.4, 128.2, 124.9 and 123.6 (Ar), 117.4 (–CN), 71.6, 61.1, and 58.8 ($-OCH_2-$), 31.2 ($ArCH_2Ar$), 14.2 ($-CH_3$); FAB MS *m/z* 675.2 (M^+, Calcd 674.7). Anal. Calcd for $C_{40}H_{38}N_2O_8$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.74; H, 5.68; N, 4.07.

25,26,27,28-Tetrakis[(cyanomethyl)oxy]calix[4]arene (**5** and **6**). Following the procedure described for **3**, **1** (0.5 g, 1.0 mmol), Cs_2CO_3 (1.0 g, 3.0 mmol), and chloroacetonitrile (0.2 ml, 3.2 mmol) was treated for 5 h. After removing the solvent, the residue was purified by column chromatography (eluent, $CHCl_3$:*n*-hexane:ethyl acetate = 6:3:1) to yield cone product **5** (0.21 g, 36%)and partial cone product **6** (0.18 g, 31%). **5** mp 230°C; ^{1}H NMR ($CDCl_3$) δ 6.79 (m, 12H, ArH), 4.86 (s, 8H, $-OCH_2-$), 4.40 and 3.42 (pair of d, 8H, $ArCH_2Ar$, $J = 13.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 154.2, 134.0, 129.2 and 125.1 (Ar), 116.5 (–CN), 59.4 ($-OCH_2-$), 31.4 ($ArCH_2Ar$); FAB MS *m/z* 580.8 (M^+, Calcd 580.6). Anal. Calcd for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65. Found: C, 73.96; H, 4.81; N, 9.08. **6** mp 195°C; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 2H, ArH, $J = 7.4$ Hz), 7.15 (m, 3H, ArH), 7.05 (m, 3H, ArH), 6.74 (t, 2H, ArH, $J = 7.5$ Hz), 6.55 (d, 2H, ArH, $J = 7.6$ Hz), 4.72 and 4.56 (pair of d, 4H, $-OCH_2-$, $J = 15.8$ Hz), 4.15 (s, 2H, $-OCH_2-$), 3.40 (s, 2H, $-OCH_2-$), 4.15, 3.93, 3.83, and 3.35 (two pair of d, 8H, $ArCH_2Ar$, $J = 14.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 157.4, 156.1, 155.5, 137.7, 135.7, 135.1, 134.0, 133.4, 132.4, 131.9, 131.6, 127.6, 127.1, and 126.2 (Ar), 119.2, 118.0, and 117.8 (–CN), 60.7, 58.8, and 58.7 ($-OCH_2-$), 38.5, and 33.7 ($ArCH_2Ar$); FAB MS *m/z* 580.9 (M^+, Calcd 580.6). Anal. Calcd for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.23; H, 4.66; N, 9.21.

25,27-Bis[(cyanomethyl)oxy]-26,28-dipropoxycalix[4]-arene (**7a**). Following the procedure described for **3**, **1** (0.2 g, 0.4 mmol), Cs_2CO_3 (0.5 g, 1.5 mmol)

and propyl bromide (0.75 ml, 10 mmol) was treated for 24 h. After removing the solvent, the residue was purified by column chromatography (eluent, $CHCl_3$:*n*-hexane:ethyl acetate = 6:3:1) to yield the 1,3-alternate product **7a** (0.10 g, 37%) from column chromatography (eluent, $CHCl_3$:*n*-hexane = 3:1). mp 148–149°C; ^{1}H NMR ($CDCl_3$) δ 7.18 and 7.06 (two d, 8H, ArH, $J = 7.5$ Hz), 6.98 and 6.87 (2 t, 4H, ArH, $J = 7.5$ Hz), 3.90 and 3.83 (pair of d, due to the small $\Delta\nu$ two large inner peaks and small outer peaks were observed, 8H, $ArCH_2Ar$, $J = 15.2$ Hz), 3.49 (t, 4H, $-OCH_2-$, $J = 7.5$ Hz), 3.36 (s, 4H, $-OCH_2-$) 1.34 (m, 4H, $-CH_2-$), 0.74 (t, 12H, $-CH_3$, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.1 ($-CO_2-$), 156.0, 154.2, 133.4, 132.6, 129.2, 129.1, 121.5 and 121.3 (Ar), 72.4, 67.8 and 59.4 ($-OCH_2-$), 35.9 ($ArCH_2Ar$), 21.9, 13.1 and 9.1 ($-CH_2-$ and CH_3).^{13}C NMR ($CDCl_3$) 157, 154, 134.3, 134.2, 130.7, 130.1, and 124 (Ar), 116.5 (–CN–), 72.7 and 55.7 ($-OCH_2-$), 37.8 (ArCH2Ar), 22.7 ($-CH_2-$), 10 ($-CH_3$); FAB MS m/z 586.2 (M^+, Calcd 586.7). Anal. Calcd for $C_{38}H_{38}N_2O_4$: C, 77.79; H, 6.53; N, 4.77. Found: C, 76.91; H, 6.53; N, 4.61.

25,27-Bis[(cyanomethyl)oxy]-26,28-dibutoxycalix[4]-arene (**7b**). Following the procedure described for **3**, **1** (0.2 g, 0.4 mmol), Cs_2CO_3 (0.5 g, 1.5 mmol) and butyl bromide (1 ml, 10 mmol) was treated for 24 h. After removing the solvent, the residue was purified by column chromatography (eluent, $CHCl_3$:*n*-hexane: ethyl acetate = 6:3:1) to yield the 1,3-alternate product **7b** (0.10 g, 37%) from column chromatography (eluent, $CHCl_3$:*n*-hexane = 3:1). mp 139–140°C; ^{1}H NMR ($CDCl_3$) δ 7.18 and 7.06 (two d, 8H, ArH, $J = 7.5$ Hz), 6.97 and 6.88 (two t, 4H, ArH, $J = 7.2$ Hz), 3.91 and 3.83 (pair of d, due to the small $\Delta\nu$ two large inner peaks and two small outer peaks were observed, 8H, $ArCH_2Ar$, $J = 15.9$ Hz), 3.54 (t, 4H, $-OCH_2-$, $J = 9.6$ Hz), 3.36 (s, 4H, $-OCH_2-$) 1.29 and 1.17 (two m, 8H, $-CH_2CH_2-$), 0.87 (t, 12H, $-CH_3$, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.1 ($-CO_2-$), 156.0, 154.2, 133.4, 132.6, 129.2, 129.1, 121.5 and 121.3 (Ar), 72.4, 67.8 and 59.4 ($-OCH_2-$), 35.9 ($ArCH_2Ar$), 21.9, 13.1 and 9.1 ($-CH_2-$ and CH_3). ^{13}C NMR ($CDCl_3$) 157.06, 154, 134.31, 134.21, 130.64, 130.08, and 124.03, 124 (Ar), 116.46 (–CN–), 70.97 and 55.74 ($-OCH_2-$), 37.86 (ArCH2Ar), 31.63 and 18.95 ($-CH_2-$), 14.13 ($-CH_3$); FAB MS m/z 615.0 (M^+, Calcd 614.8). Anal. Calcd for $C_{40}H_{42}N_2O_4$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.84; H, 6.70; N, 4.55.

25,27-Bis[(ethoxycarbonylmethyl)oxy]-26,28-bis[(cyanomethyl)oxy]calix[4]arene (**8**). Following the procedure described for **3**, **2** (0.24 g, 0.4 mmol), Cs_2CO_3 (0.5 g, 1.5 mmol) and an excess of bromoacetonitrile (or chloroacetonitrile) in 30 ml CH_3CN was treated for 72 h. After removing the solvent, the residue was purified by column chromatography (eluent, $CHCl_3$:*n*-hexane:ethyl acetate = 6:3:1) to yield the partial cone product **8** (0.15 g, 56%). **8** mp 160–161°C; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 2H, ArH, $J = 7.5$ Hz), 7.14 (d, 2H, ArH, $J = 7.5$ Hz), 7.03 (m, 4H, ArH), 6.66 (t, 2H, ArH, $J = 7.5$ Hz), 6.49 (d, 2H, ArH, $J = 7.5$ Hz), 4.45 (a pair of d, 4H, $-OCH_2-$, $J = 15.4$ Hz), 4.29 (m, 6H, $-OCH_2-$), 4.29, 3.97, 3.75 and 3.24 (two pairs of d, 8H, $ArCH_2Ar$, $J = 14.1$ Hz), 1.34 (t, 6H, $-CH_3$, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 168.9 ($-CO_2-$), 155.3, 155.1, 153.3, 136.5, 133.6, 132.8, 132.0, 131.7, 129.9, 129.2, 129.1, 124.9, 123.7 and 123.6 (Ar), 117.2 and 116.2 (–CN), 70.9, 61.1, 56.8 and 56.5 ($-OCH_2-$), 36.1 and 31.4 ($ArCH_2Ar$), 14.2 ($-CH_3$); FAB MS m/z 675.1 (M^+, Calcd 674.7). Anal. Calcd for $C_{40}H_{38}N_2O_8$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.68; H, 5.65; N, 4.11.

25,27-Bis[(cyanomethyl)oxy]calix[4]arene-crown-5 (**9**). Following the procedure described for **3**, **1** (0.20 g, 0.4 mmol), Cs_2CO_3 (0.5 g, 1.5 mmol) and tetraethylene glycol ditosylate (0.2 g, 0.4 mmol) treated for 20 h. After removing the solvent, the residue was purified by column chromatography (eluent, $CHCl_3$:*n*-hexane:ethyl acetate = 6:3:1) to yield the 1,3-alternate calix[4]crown **9** (0.16 g, 61%). mp >329°C dec.; ^{1}H NMR ($CDCl_3$) δ 7.21 and 7.16 (two d, 8H, ArH, $J = 7.5$ Hz), 7.00 (m, 4H, ArH), 3.97 and 3.90 (pair of d, 8H, $ArCH_2Ar$, $J = 16.2$ Hz), 3.53 (m, 16H, $-OCH_2-$) 3.20 (t, 4H, $-OCH_2-$, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 156.1, 154.1, 134.3, 134.2, 130.2, 129.9, 124.5 and 124.4 (Ar), 116.3 (–CN), 72.3, 70.6, 69.7, 69.1 and 55.6 ($-OCH_2-$), 37.8 ($ArCH_2Ar$); FAB MS m/z 661.0 (M^+, Calcd 660.8). Anal. Calcd for $C_{40}H_{40}N_2O_7$: C, 72.71; H, 6.10; N, 4.24. Found: C, 71.74; H, 6.06; N, 4.17.

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