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Rigidification of the Cone Conformation of *p-tert*-Butylcalix[4]arene with Carbamate Groups on the Lower Rim

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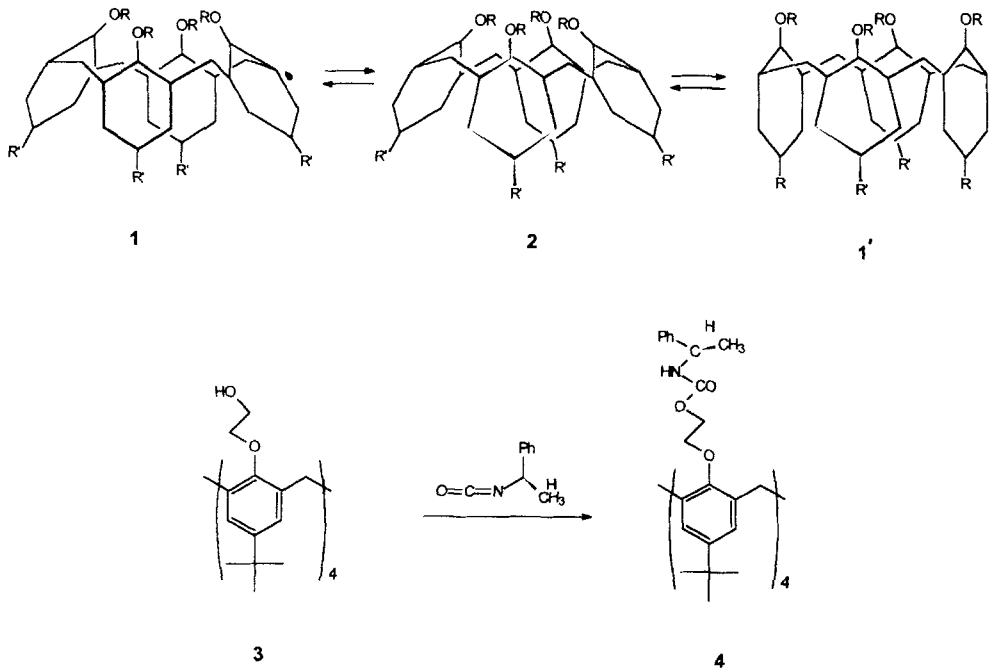
The conformation of a *p-tert*-butylcalix[4]arene with four (*R*)-1(1-phenyl-ethyl)carbamic acid ethoxyester residues on the lower rim has been investigated by X-ray diffraction and ^{1}H NMR analysis. The molecule adopts a pinched cone conformation in the solid state with intramolecular hydrogen bonding between the carbonyl groups and the nitrogen atoms of proximal carbamate podands. The NMR evidence indicates that this conformation persists in solution at room temperature. At temperatures >80°C the NMR spectrum is that of a time-averaged C_{4v} symmetrical cone conformation.

Keywords: Calix[4]arene carbonate, pinched cone conformation, intramolecular H-bonding

INTRODUCTION

Although interconversion between the four extreme conformations of calix[4]arenes, viz. cone, partial cone, 1,2-alternate and 1,3-alternate, can be blocked by derivatization of the hydroxyl groups on the lower rim with groups larger than ethyl [1], these derivatives do retain some degree of movement within the molecular skeleton. This is well exemplified by several calix[4]arene derivatives in the cone conformation for which both solution and solid state structures are available [2]. X-Ray crystal structures of many calix[4]arenes reveal a pronounced tendency to adopt a C_{2v} symmetrical structure **1** in which the cone conformation is pinched in such a way that the two opposite aromatic rings are almost parallel while the other two are almost normal to each other. In contrast, ^{1}H NMR studies of these molecules in solution reveal time-averaged C_{4v} symmetrical cone conformations **2** resulting from a rapid interconversion (on the NMR timescale) between two identical C_{2v} symmetrical pinched cone conformations **1** and **1'** (Scheme 1) [2]. Molecular mechanics calculations suggest that structures with C_{2v} symmetry should be more stable than the more symmetrical C_{4v} structures [3]. Since the shape and relative stability of the pinched cone conformation may influence the ability of calix[4]arene derivatives to function as receptors for guest species, it is useful to have ways of immobilising it in solution at ordinary temperatures. Several groups have shown that this can be achieved by



SCHEME 1

adding upper rim substituents capable of intramolecular hydrogen bonding. Regen [4] and Arduini [5] and their respective collaborators found that the presence of carboxylic acid groups on the upper rim increased the barrier to interconversion to the extent that the pinched cone conformation could be observed in solution at room temperature. Reinhoudt's group [6] have used thiourea or acetamido groups, also on the upper rim, to achieve the same effect. As far as we are aware there have been no comparable attempts to use non-covalent bonding on the lower rim to stabilize the pinched cone conformation. Here we present an example of such stabilization.

RESULTS AND DISCUSSION

During the course of work designed to produce calixarenes with pendant chiral groups on the lower rim capable of chiral recognition with possible application in enantiomer separation *via* chromatography, we prepared the tetracarbamate **4**. This compound was readily obtained from tetraalcohol **3** [7] by treatment with (*R*)-1(1-phenylethyl) isocyanate. The ^{1}H NMR spectrum of **3** displayed a complex series of signals, quite unlike the simple pattern of a C_{4v} symmetrical cone conformation observed for **3**. In particular there appeared three broad singlets for the t-butyl groups and a series of multiplets for the aromatic protons and the protons of the carbamate groups. To exclude the possibility that conformational inversion to a non-cone form had occurred during the preparation of **4**, the four carbamate groups were removed reductively by treatment with lithium aluminium hydride whereupon tetraalcohol **3** was recovered conformationally unchanged. This result suggested that the tetracarbamate possessed additional features which stabilised the pinched cone conformations.

X-Ray diffraction was used to probe the solid-state structure of **4**, in particular the special disposition of the four carbamate podands. The

unit cell contains two independent calix[4]arene molecules A and B (Fig. 1). The conformation of the calixarene core for molecules A and B of **4** are defined by the angles made with the plane of the four methylene carbon atoms: for molecule A, 95.1(3)°, 137.2(4)°, 95.5(3)°, and 136.0(2)°; and for molecule B, 93.1(3)°, 143.7(4)°, 95.3(3)°, and 136.7(2)°. The two opposite rings C1–C6 and C23–C28 are almost parallel with an interplanar angle of 0.8(2)° and 2.3(2)° for A and B, respectively. The other two rings C12 – C17 and C34 – C39 are approximately normal to one another with interplanal angles of 86.8(3)° (A) and 79.4(3)° (B). This is a typical pinched cone conformation. The conformations adopoted by the pendant carbamate moieties are a consequence of both intramolecular and intermolecular hydrogen bonding. Individual molecules are linked *via* two intermolecular N—H—O hydrogen bonds into infinite chains consisting of alternating A and B molecules, parallel to the b axis. The chains are further stabilized by weak edge-to-face C— H – π interactions between neighbouring A and B molecules. Intramolecularly, there are two hydrogen bonds N—H—O between each pair of proximal podands, and it is these interactions which help stabilize the pinched conformation revealed in solution by the ^{1}H NMR spectrum (Tab. I). This conformation is, however, not completely fixed. The effect of temperature on the NMR spectrum indicated that even at room temperature there is still some conformational motion probably resulting from a slow exchange process involving two equivalent pinched cone conformations. At −20°C this process is completely frozen out while at temperatures >80°C the exchange rate is such that only the time averaged characteristic C_{4v} arrangement is observed. From the coalescence temperature $T_c = 42$°C of the *t*-butyl singlets (at 500 MHz in $CDCl_2$-$CDCl_2$) an energy barrier of 14.4 kcal mol^{-1} can be calculated for tetracarbamate **4**, representing the interconversion of two equivalent pinched cone conformations with the C_{4v} symmetrical cone as the transition state.

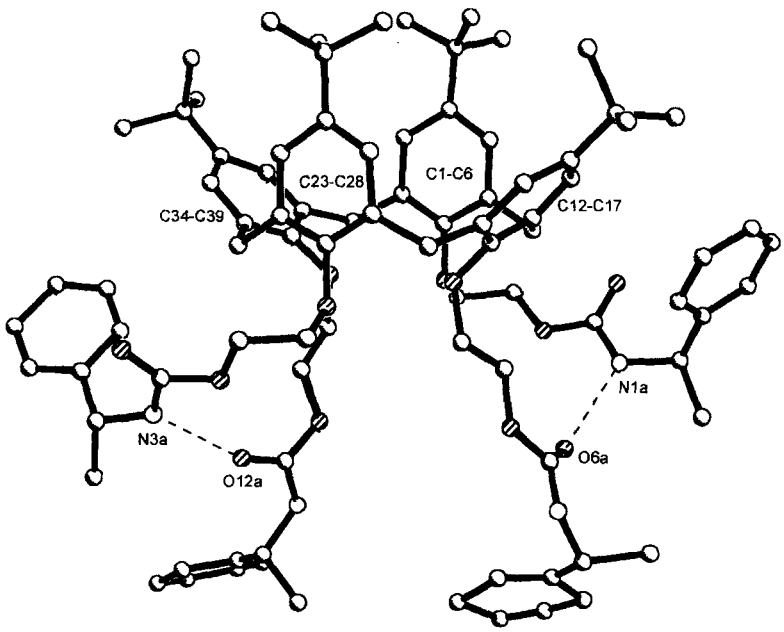


FIGURE 1 X-ray view of Compound **4**.

TABLE I Geometry of the hydrogen bonds in **4**

D–H — A	r(H — A) Å	r(X — A) Å	angle(D–H — A)°
N1A-H1A-O6A	2.022 (9)	2.882 (9)	165.2 (3)
N2A-H2A1-O9B'	2.157 (11)	2.839 (11)	133.9 (4)
N3A-H3A1-O12A	2.020 (11)	2.872 (11)	162.9 (3)
N4A-H4A1-O3B''	2.067 (10)	2.906 (10)	159.0 (4)
N1B-H1B1-O6B	2.105 (10)	2.962 (10)	164.2 (3)
N2B-H2B1-O9A'''	2.097 (9)	2.878 (9)	147.4 (3)
N3B-H3B1-O12B	2.005 (12)	2.881 (12)	172.8 (4)
N4B-H4B1-O3A''''	2.017 (9)	2.807 (9)	148.6 (3)

Symmetry codes are: $'=x, y+1, z+1$, $''=x, y, z+1$, $'''=x, y-1, z-1$, $''''=x, y, z-1$.

EXPERIMENTAL

X-Ray Crystallography

Crystal data were collected using a Siemens SMART system with graphite monochromated Mo-Kα radiation at *ca.* 160 K in a dinitrogen stream. Lorentz and polarization corrections were applied. The structure was solved by direct methods and the non-hydrogen atoms, except the methyl and amide benzyl groups, were refined with anisotropic thermal parameters. Hydrogen-atoms were added at idealised positions and a riding model with fixed thermal parameters, ($U_{iso} = 1.2\ U_{eq}$ for the atom to which they are bonded, 1.5 U_{eq} for methyl hydrogen atoms), was used for subsequent refinements. The absolute configuration is determined by the known configuration of the pendant amide groups. The function minimised was $\Sigma[\omega(|F_o|^2 - |F_c|^2)]$ with reflections weights $\omega^{-1} = [\sigma^2|F_o|^2 + (g_1P)^2 + (g_2P)]$ where $P = [\max |F_o|^2 + 2|F_c|^2]/3$. The SHELXTL PC [8] and SHELXL-93 [9] packages were used for data reduction, and structure solution and refinement.

Crystal Data for **4** $C_{88}H_{108}N_4O_{12}$: M = 1413.78, triclinic, space group P1, a = 15.8439 (14) Å, b = 16.328 (2) Å, c = 18.006 (2) Å, $\alpha = 91.190$ (2)°, $\beta = 115.817$ (2)°, $\gamma = 93.034$ (2)°, $U = 4182.4$ (7) $Å^{-3}$, Z = 2, $D_c = 1.123$ Mg m^{-3}, F(000) = 1520, $\mu = 0.074$ mm^{-1}. Crystal dimensions = 0.57 × 0.28 × 0.22 mm. A total of 20909 reflections were measured ($R_{int} = 0.035$) for $4 < 2\Theta < 45$ and 16396 independent reflections were used in the refinement. The final parameters were wR2 = 0.2362 and R1 = 0.0874 [$1 > 2\sigma 1$], S = 1.142, 1500 parameters, weighting scheme $g_1 = 0.12$, $g_2 = 0.0$ $(\Delta/\sigma)_{max} < 0.001$ $(\Delta\rho)_{max,\ min} = 0.563, -0.332$ e^{-3}.

Additional material available from the Cambridge Crystallographic Data Centre comprises tables of all bond lengths and angles, thermal parameters and structure factors.

^{1}H NMR spectra were recorded with General Electric QE 300 (^{1}H 300 MHz) and General Electric omega 500 (^{1}H 500 MHz) instruments with Me_4 Si as internal standard. Spectrometric mass measurements were carried out in a V.G. Organic Autospec mass spectrometer. Analytical TLC was performed on silica gel plates (SiO_2, Merck, 60 F_{254}), while silica gel 60 (SiO_2, Merck, flash chromatography) was used for preparative column chromatography. Microanalysis were carried out by the Microanalysis Service of the School of Chemistry.

Synthesis of Tetracarbamate 4

To a stirred solution of tetraalcohol **3** (1.25 g, 1.52 mmol) in dry toluene (10 ml) was added (*R*)-(+)-α-methylbenzylisocyanate (1.3 ml, 9.85 mmol) and the resulting mixture was refluxed under nitrogen for 48 h. Upon removal of the solvent under reduced pressure the crude product was purified by column chromatography (flash silica, hexane-ethyl acetate 65:35) to afford **4** as a white solid (1.27 g, 60%). m.p. 90 –

92°C. $[\alpha]_D^{20} = 45.2°$(c = 7.6 in $CHCl_3$). IR ν_{max} (KBr/cm^{-1}) 1702 (C=O), 3317 (N-H). MS (ES) *m/z* 1414.0 (M^++H, 100%). ^{1}H NMR 500 MHz (r.t): δ ($CDCl_3$) 7.38 – 6.42 (bm, ArH, 28H), 4.80 (m, CH, 4H), 4.53 (bs, OCH_2CH_2, 8H), 4.26 (bd, $ArCH_2Ar$, 4H, J = 12.3 Hz), 4.04 (bs, OCH_2CH_2, 8H), 3.09 (bd, $ArCH_2Ar$, 4H, J = 12.3 Hz), 1.47, 1.31, 1.06, 0.85 (set of bs, t-Bu + CH_3, 48H). ^{1}H NMR 500 MHz (343 K): δ ($CDCl_2$-$CDCl_2$) 7.26 – 7.16 (m, ArH, 20H), 6.77 (s, ArH, 8H), 5.94 (bs, NH, 4H), 4.76 (t, CH, 4H, J = 6.6 Hz), 4.49 (m, OCH_2, 8H), 4.33 (d, $ArCH_aAr$, 4H, J = 15 Hz), 4.10 (m, CH_2O, 8H), 3,11 (d, $ArCH_bAr$, 4H, J = 15 Hz), 1.43 (d, CH_3, 12H, J = 6.5 Hz), 1.08 (s, t-but, 36H). [reference $CHCl_2CHCl_2$ at δ = 5.95]. Anal. Calcd. for: $C_{88}H_{108}O_{12}N_4$: C, 74.7%, H, 7.7%, N, 4.0%. Found: C, 75.1%, H, 7.7%, N, 4.0%.

Reduction of 4 to 3

Tetracarbamate **4** (0.5 g, 0.35 mmol) was dissolved in dry THF (20 ml). To this solution an excess of $LiAlH_4$ (100 mg, 2.63 mmol) was added. The reaction mixture was stirred under nitrogen at r.t. for 20 h. Upon cooling the reaction mixture to 0°C, saturated ammonium chloride (aq.) solution was added dropwise until the hydrogen evolution subsided. Concentrated hydrochloric acid (1 ml) was added and the grey granular precipitate which formed was filtered off and washed with dichloromethane and THF. The organic filtrate was washed with brine (25 ml), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to leave the product as an off-white solid. Upon recrystallization from ethanol, tetraalcohol **3** was isolated as fine colourless crystalline needles (207 mg, 72%). m.p. = 328 – 330°C. (lit[7] >300°C). MS(ES) *m/z* 825.7 (M^+ + H, 100%), 847.7 (M^+ + Na, 35%). ^{1}H NMR 500 MHz: δ($CDCl_3$) 6.85 (s, ArH, 8H), 5.10 (bs, OH, 4H), 4.36 (d, $ArCH_2Ar$, 4H, J = 13.3Hz), 3.99 (m, OCH_2CH_2, 16H), 3.23 (d, $ArCH_2Ar$, 4H, J = 13.3 Hz), 1.09 (s, t-Bu, 36H). Anal. Calcd. for: $C_{52}H_{72}O_8$: C, 75.7%, H, 8.8%. Found: C, 75.3%, H, 9.1%.

Acknowledgments

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