PERKIN 2

Synthesis, X-ray structure and alkali-metal binding properties of a new hexahomotriazacalix[3]arene

Philip D. Hampton,* Weidong Tong, Si Wu and Eileen N. Duesler

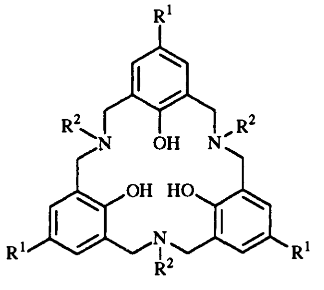
Department of Chemistry, University of New Mexico, Albuquerque, New Mexico, 87131, USA

Hexahomotriazacalix[3]arene† 1 has been synthesized by the reaction of 2,6-bis(chloromethyl)-4-methylphenol 6 with glycine methyl ester hydrochloride under high-dilution conditions. The crystal structure of 1 indicates that the macrocycle adopts a cone shape in the solid state with all three ester groups on the same side and within the cone of the macrocycle. In contrast with the calixarenes, macrocycle 1 exhibits only a modest degree of cupping. ^1H NMR spectra indicate that the cone and partial cone isomers of 1 are rapidly interconverting in the NMR timescale at room temperature. Macrocycle 1 exhibits no significant extraction of alkali metal picrates from aqueous solution.

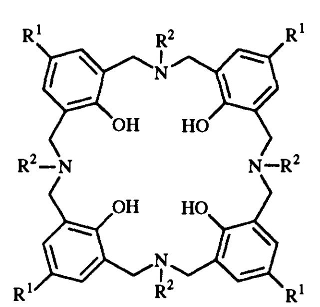
Calixarenes and related macrocycles have received considerable attention for their host–guest chemistry and for their coordination chemistry with metals.[1–4] They possess a number of conformations that have been exploited as binding pockets for host molecules. Structural modification of the calixarenes is, however, limited since only the phenolic oxygens (the 'lower rim') and the aryl ring *para*-substituents (the 'upper rim') can be modified. In contrast to the calixarenes, the hexahomotriazacalix[3]arene macrocycles **1** and **2a–d**‡ and the octahomotetraazacalix[4]arene **3**‡ possess R^2 groups on the nitrogens in the macrocycle ring which provide an additional site for structural modification. Our interest in examining the host–guest properties of the hexahomotriazacalix[3]arene macrocycles has led us to develop a new synthetic route to these macrocycles.

Takemura and co-workers[4] first reported the synthesis of hexahomotriazacalix[3]arenes **2a–d** by the thermal condensation of a 2,6-bis(hydroxymethyl)phenol **5** ($R = CH_3$, Bu^t) with a primary amine at high temperatures. Macrocycle **2a** was observed to extract alkali and alkaline earth metals, and exhibited a pH dependent extraction of uranyl ion (UO_2^{2+}).[4a] Robson and co-workers[5] have reported the synthesis of octahomotetraazacalix[4]arene **4**.‡

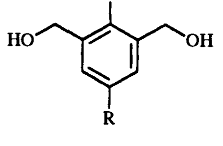
In this paper, we describe the synthesis and crystal structure of hexahomotriazacalix[3]arene **1** which possesses methoxycarbonylmethyl substituents on the nitrogen atoms in the macrocycle ring. Macrocycle **1** is the first structurally characterized hexahomotriazacalix[3]arene.



1 $R^1 = CH_3$, $R^2 = CH_2CO_2CH_3$
2a $R^1 = CH_3$, $R^2 = CH_2Ph$
2b $R^1 = Bu^t$, $R^2 = CH_2Ph$
2c $R^1 = CH_3$, $R^2 = CH_2$-2-pyridyl
2d $R^1 = CH_3$, $R^2 = (S)CH(CH_3)Ph$



3 $R^1 = CH_3$, $R^2 = CH_2CO_2CH_3$
4 $R^1 = CH_3$, $R^2 = H$



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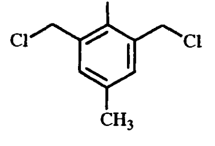

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Results and discussion

Synthesis of Hexahomotriazacalix[3]arene 1

The synthesis of macrocycle **1** was accomplished by reacting 2,6-bis(chloromethyl)-4-methylphenol **6** with glycine methyl ester hydrochloride in dimethylformamide (DMF) under high-dilution conditions (0.025 mol dm^{-3} of reagents) in the presence of potassium carbonate [reaction (1)]. The crude product was chromatographed on silica gel to yield a mixture of **1** and **3** in 43% yield. Recrystallization of the mixture from 6:1 cyclohexane–benzene yielded pure macrocycle **1** in 19% yield. Macrocycle **1** was characterized by elemental analysis, FTIR, ^1H and ^{13}C NMR, mass spectroscopy and a single crystal X-ray study.

$$\mathbf{6} + CH_3O_2CCH_2NH_3{}^+Cl^- \xrightarrow[\text{DMF, 60 °C}]{K_2CO_3} \mathbf{1} + \mathbf{3} \quad (1)$$

The ^1H NMR spectrum of isolated macrocycle **1** consists of singlets assigned to the aromatic, methyl and ring ($ArCH_2$) and

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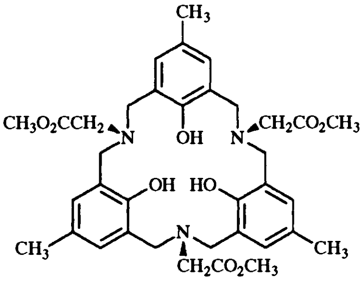
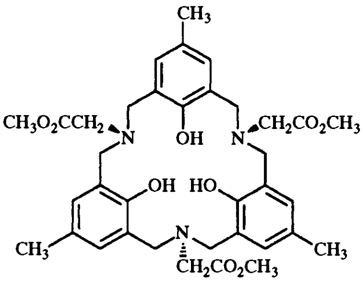
† IUPAC name is $1^2,5^2,9^2$-trihydroxy-3,7,11-bis(methoxycarbonylmethyl)-$1^5,5^5,9^5$-trimethyl-3,7,11-triaza-1,5,9(1,3)-tribenzenacyclododecaphane.

‡ The IUPAC general name for **1** and **2** is $1^2,5^2,9^2$-trihydroxy-3,7,11-triaza-1,5,9(1,3)-tribenzenacyclododecaphane and for **3** and **4** is $1^2,5^2,9^2,13^2$-tetrahydroxy-3,7,11,15-tetraaza-1,5,9,13(1,3)-tetrabenzenacyclohexadecaphane.



Cone Isomer



Partial Cone Isomer

substituent ($CH_2CO_2CH_3$) methylene protons. This spectrum matches the major component in the spectrum of mixtures of **1** and **3**. Based on the integration of the methylene singlets for macrocycles **1** and **3**, the ratio of the macrocycles **1**:**3** in the crude product is 6:1. The theoretical yield of **1** is *ca.* 37%, which is significantly higher than the isolated yield of 19%. The ^1H NMR spectrum and elemental analysis indicate the presence of one molecule of cyclohexane per two molecules of **1**.

Each of the macrocycle signals observed is a singlet which requires that the cone and partial cone isomers of compound **1** must be rapidly interconverting in the NMR timescale. The isomerization of **1** at room temperature is not surprising, since nitrogen inversion is known to have a low activation barrier.[6]

X-Ray structure analysis of hexahomotriazacalix[3]arene 1

X-Ray quality crystals of macrocycle **1** could be isolated by slow evaporation of a cyclohexane solution of a mixture of **1** and **3**. Details of the X-ray analysis are given in the Experimental section. An ORTEP diagram is provided in Fig. 1 and a side-view is provided in Fig. 2. Selected bond lengths and angles are listed in Table 1.

The unit cell contains two molecules of **1** which possess crystallographic $3m$ symmetry and one molecule of a disordered cyclohexane molecule which is centred at the origin and has $\bar{3}m$ symmetry. The cyclohexane molecule was observed to be planar with 120° bond angles and short C–C bonds (1.426 Å); this structure is due to the superposition of two cyclohexane rings rotated 60° with respect to one another. There is also disorder in the orientation of the hydrogen bonding in the centre of the macrocycle.

The X-ray structure indicates that **1** adopts a 'cone' conformation in the solid-state (Fig. 2) where the three methoxycarbonylmethyl groups are contained within the 'cone' of the macrocycle. The cone size of **1**, which is defined as the diameter of a circle inscribed through the three nitrogen atoms, is found to be 6.2 Å. The cupping of the macrocycle can be defined by the dihedral angle between the mean planes of the aromatic rings and the molecular three-fold axis. The large dihedral angle (153.2°) indicates that hexahomotriazacalix[3]arene **1** possesses a relatively shallow cup compared with the calixarenes: *p-tert*-butylcalix[4]arene (123°), *p*-(1,1,3,3-tetramethylbutyl)calix[4]arene (average 123°) and *p-tert*-butylcalix[5]arene (average 132°).[7] The extent of cupping of **1** is comparable to that of *p-tert*-butylhexahomotrioxacalix[3]arene **7a**[8] (average 143°) and *p*-isopropylhexahomotrioxacalix[3]arene **7b**[9] (average 147°).

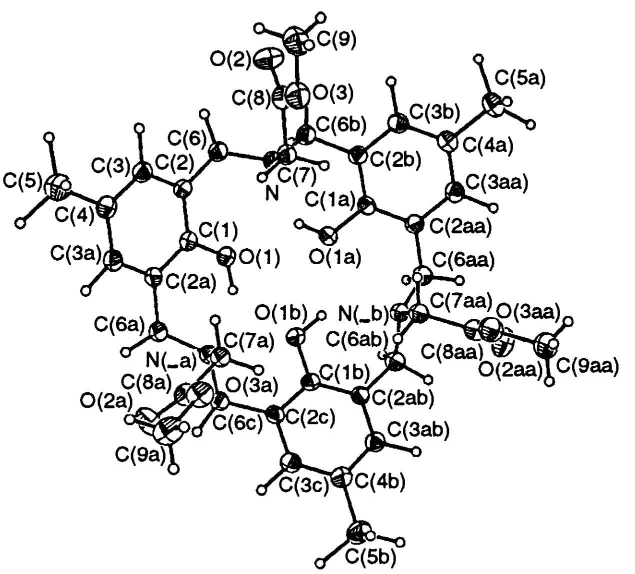


Fig. 1 ORTEP drawing of hexahomotriazacalix[3]arene **1**. Ellipsoids are drawn at the 20% probability level.

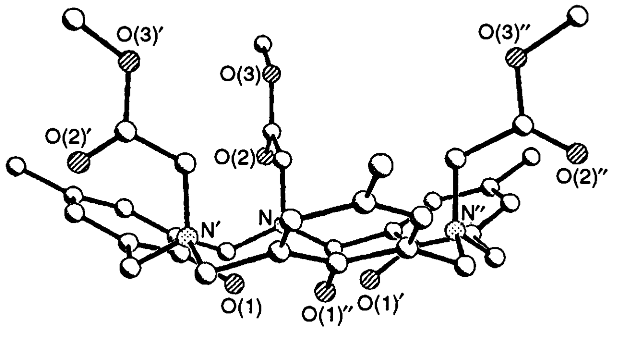


Fig. 2 Ball and stick drawing (side-view) of hexahomotriazacalix[3]arene **1**. Hydrogen atoms are omitted for clarity.

The small O(1)–O(1A) (2.900 Å) and O(1)–N (2.912 Å) separations are consistent with hydrogen bonding between a phenolic OH group, a nitrogen atom and the adjacent phenolic oxygen. The O(1)–O(1A) separations in **1** are larger than those in *p-tert*-butylcalix[4]arene (2.670 Å), *p*-(1,1,3,3-tetramethylbutyl)calix[4]arene (average 2.66 Å) and *p-tert*-butylcalix[5]arene (average 2.84 Å).[7] Macrocycle **1** has O(1)–O(1A) separations which are comparable to the hexahomotrioxacalix[3]arenes **7a**[8] (average 3.03 Å) and **7b**[9] (average 2.90 Å). The large O(1)–O(1A) separations in **1**, **7a** and **7b** could be due to weakening of the O(1)–H ··· O(1A) hydrogen bond owing to hydrogen bonding with the amine or ether linkages.

The chemical shift of the phenolic proton (10.07 ppm) in the ^1H NMR spectrum of **1** and the slow exchange of these protons with water in the NMR timescale also provide evidence for hydrogen bonding in **1**. The position of the O–H stretch for **1** (3266 cm^{-1}) is in contrast to the 2800 cm^{-1} stretch reported for macrocycles **2a** and **2b** by Takemura and co-workers.[4] The weaker hydrogen bonding in macrocycle **1** may be due to the presence of the electron-withdrawing methoxycarbonylmethyl groups.

Dependence of yields and selectivity on reaction conditions

Table 2 lists **1**:**3** ratios for crude mixtures of macrocycles **1** and **3**, and the isolated yields of macrocycle **1** for a range of reaction conditions. The yield and the selectivity of the reaction both decreased when the reaction temperature was increased from 60–90 °C. At 120 °C only a low yield of the crude mixture of **1** and **3** could be isolated. When sodium carbonate was used as the base, the yields and the selectivity were lower than with potassium carbonate. Trace amounts of macrocycles **1** and **3**

Table 1 Selected bond lengths (Å) and bond angles (deg) for hexahomotriazacalix[3]arene **1**

Bond lengths (Å)[a]

O(1)–C(1)	1.366(6)	C(1)–C(2A)	1.395(5)
C(1)–C(2B)	1.395(5)	C(2)–C(3)	1.385(5)
C(2)–C(6)	1.503(7)	C(2)–C(1A)	1.395(4)
C(3)–C(4A)	1.386(6)	C(4)–C(5)	1.522(9)
C(4)–C(3A)	1.386(6)	C(4)–C(3B)	1.386(4)
C(6)–N	1.466(4)	N–C(7)	1.447(6)
N–C(6A)	1.466(4)	C(7)–C(8)	1.514(8)
C(8)–O(2)	1.199(8)	C(8)–O(3)	1.336(7)
O(3)–C(9)	1.441(8)	C(10)–C(10A)	1.426(13)
C(10)–C(10B)	1.426(13)		

Bond angles (degrees)[a]

O(1)–C(1)–C(2A)	119.5(2)	O(1)–C(1)–C(2B)	119.5(2)
C(2A)–C(1)–C(2B)	120.8(4)	C(3)–C(2)–C(6)	121.5(3)
C(3)–C(2)–C(1A)	118.6(4)	C(6)–C(2)–C(1A)	119.8(3)
C(2)–C(3)–C(4A)	121.7(4)	C(5)–C(4)–C(3A)	120.7(3)
C(5)–C(4)–C(3B)	120.7(3)	C(3A)–C(4)–C(3B)	118.5(5)
C(2)–C(6)–N	111.8(3)	C(6)–N–C(7)	114.7(2)
C(6)–N–C(6A)	113.8(4)	C(7)–N–C(6A)	114.7(2)
N–C(7)–C(8)	116.1(4)	C(7)–C(8)–O(2)	126.6(5)
C(7)–C(8)–O(3)	110.3(5)	O(2)–C(8)–O(3)	123.1(6)
C(8)–O(3)–C(9)	117.5(5)	C(10A)–C(10)–C(10B)	120.0(6)

Atoms	Generated from	Symmetry operation
C(1A), C(4A)	C(1), C(4)	$x, -1 + y, z$
C(2A), C(3A)	C(2), C(3)	$x, 1 + y, z$
C(2B), C(3B)	C(2), C(3)	$1 - x + y, 1 + y, z$
C(6A)	C(6)	$x, x - y, z$
C(10A)	C(10)	$y, y - x, -z$
C(10B)	C(10)	$x - y, x, -z$

[a] Generation of symmetry equivalent atoms found in lower part of table.

were detected with lithium carbonate as the base, but it was not possible to obtain yields and selectivity for this reaction.

Metal picrate extraction studies

The ability of macrocycle **1** to extract metal picrates from water was investigated by stirring a solution of the macrocycle in methylene chloride separately with aqueous solutions of lithium, sodium, potassium, rubidium and caesium picrate. The percent extraction was less than 0.2% after 24 h. A similar weak extraction of alkali metals was reported by Takemura and co-workers for **2a**.[4]

Conclusion

The new hexahomotriazacalix[3]arene **1** exhibits a cup shape in the solid state with all three of its ester functional groups surrounding the cavity of the macrocycle. Although the macrocycle possesses a well defined pocket for inclusion chemistry, it does not extract alkali metal picrates. The failure of **1** to bind alkali metals may be due to strong hydrogen bonding in the core of the macrocycle which makes both the phenolic oxygens and the nitrogen atoms poor donors to metals. Modification of the *N*-substituents and the phenolic oxygens is currently being investigated to generate new hosts for the inclusion of metals and organic molecules.

Experimental

General procedures

All solvents and reagents were obtained from commercial sources and used without further purification. Melting points are uncorrected. All compounds were single component by TLC. NMR spectra were recorded on a Bruker AC-250. EI mass spectra were obtained on a Finnegan 4600 mass spectrometer. Chemical shifts were referenced to either tetramethylsilane or protonated solvent impurities. Attached proton test experiments were carried out on ^{13}C NMR spectra so that negative peaks [APT(−)] and positive peaks [APT(+)] correspond to carbon atoms possessing an odd and even number of hydrogens, respectively. Coupling constants (*J*) are reported in Hz.

Table 2 Yields of hexahomotriazacalix[3]arene **1** and reaction selectivity (**1**:**3**) and their dependence on reaction conditions

[**6**]/mol dm^{-3}	T/°C	Base	**1**:**3**	Yield (%)[a]
0.025	60	K_2CO_3	6	19
0.025	90	K_2CO_3	3	14
0.1	60	K_2CO_3	3	14
0.025	60	Na_2CO_3	2	12

[a] Yield of isolated macrocycle **1**.

Literature procedures were used for the synthesis of 2,6-bis(hydroxymethyl)-4-methylphenol **5** (R = CH_3) and 2,6-bis(chloromethyl)-4-methylphenol **6**.[5,10] Metal picrates were synthesized by reaction of picric acid with a stoichiometric amount of the corresponding metal hydroxide in methanol.

Synthesis of hexahomotriazacalix[3]arene 1

A mixture of 3.0 g of finely ground potassium carbonate (7.2 mmol), 0.60 g of glycine methyl ester hydrochloride (4.9 mmol) and 200 cm^3 DMF was stirred in a 250 cm^3 three-necked round-bottom flask at 60 °C under nitrogen for 1 h. To this flask a solution of 1.0 g of 2,6-bis(chloromethyl)-4-methylphenol (4.9 mmol) in 15 cm^3 DMF was added over 1 h. After 6 h, the reaction was cooled to room temperature and filtered. DMF was removed on a rotary evaporator and the residue was dried *in vacuo*. Purification by column chromatography (20:1 $CHCl_3$–ethanol) resulted in a 43% yield of a crude mixture of macrocycles **1** and **3**. The crude product was recrystallized from 6:1 cyclohexane–benzene to yield macrocycle **1** (216 mg, 19% yield) as a colourless, crystalline solid, mp 105–109 °C [Found: C, 66.5; H, 7.1; N, 5.8. $C_{36}H_{45}N_3O_9\cdot(C_6H_{12})_{0.5}$ requires C, 66.36; H, 7.28; N, 5.95%]; ν_{max}(KBr)/cm^{-1} 3266 (OH), 3015, 2951, 2926, 2853 (CH), 1742 (C=O), 1485, 1439 (C=C), 1200, 1155 (C–O) and 982; δ_H(250 MHz; [$^2H_6$] acetone) 2.19 (9 H, s, ArCH$_3$), 3.06 (6 H, s, CH_2CO_2), 3.54 (9 H, s, OCH_3), 4.02 (12 H, s, ArCH$_2$), 6.85 (6 H, s, aryl protons) and 10.07 (3 H, s, OH); δ_C(62.9 MHz; [$^2H_6$] acetone; proton decoupled) 20.4 [3 C, APT(−), ArCH$_3$], 47.7 [3 C, APT(+), ester CH_2], 51.2 [3 C, APT(−), OCH_3], 56.6 [6 C, APT(+), ArCH$_2$], 124.3 [6 C, APT(+), 2,6-aryl], 128.1 [3 C, APT(+), 4-aryl], 131.3 [6 C, APT(−), 3,5-aryl], 155.8 [3 C, APT(+), 1-aryl] and 171.1 [3 C, APT(+), carbonyl]; *m/z* 663 (M^+, 0.3%).

Metal picrate binding studies

Aqueous solutions of lithium, sodium, potassium, rubidium or caesium picrates (5.0 cm^3, 5.0 mmol dm^{-3}) were stirred with solutions of **1** in CH_2Cl_2 (5.0 cm^3, 0.50 mmol dm^{-3}) at room temperature for 24 h. The absorbances of the CH_2Cl_2 layers at 378 nm (ε 1.8 × 10^4 dm^3 mol^{-1} cm^{-1} in CH_2Cl_2)[11] were all less than 0.20 absorbance units which corresponds to a maximum concentration of 11 µmol dm^{-3} picrate; thus, less than 0.2% of the metal picrates were extracted into the organic phase.

X-Ray structure analysis

X-Ray quality crystals of **1** were grown by slow evaporation of a cyclohexane solution of a mixture of **1** and **3** at room temperature.

Crystal data

$C_{39}H_{51}N_3O_9$, $M = 705.8$. Trigonal, $a = 15.950$ (1) Å, $c = 8.828$ (1) Å, $\alpha = \beta = 90.00°$, $\gamma = 120°$, $V = 1945.0$ (3) Å^3 (cell determination used 46 reflections in the 2θ range from 10.0–25.4 deg, $\lambda = 0.710\,73$ Å), space group $P\bar{3}m1$, $Z = 2$, $D_x = 1.205$ mg m^{-3}, $F(000) = 756$. Clear, colourless hexagonal prisms. Crystal dimensions 0.36 × 0.36 × 0.53 mm, μ(Mo-Kα) = 0.086 mm^{-1}.

Data collection and processing

Siemens R3m/V diffractometer, ω scan mode at 293 K with ω scan width = 1.0 deg, ω scan speed 6.0–40 deg min^{-1}, graphite-monochromated Mo-Kα radiation; 6986 reflections measured ($2.0 \leqslant 2\theta \leqslant 50°$, $0 \leqslant h \leqslant 16$, $-18 \leqslant k \leqslant 16$, $-10 \leqslant l \leqslant 10$), 1292 unique ($R_{int} = 0.027$), giving 813 with $F > 2.5\sigma(F)$. Observed standard intensity ratios showed a 7% decline during the course of data collection; the observed range was 1.01–0.92. Intensities were scaled on standard intensity ratios. No corrections for absorption or extinction were made.

Structure analysis and refinement

Direct methods using Siemens SHELXTL PLUS (PC Version).[12] Full-matrix, least-squares refinement on $\Sigma w(F_o - F_c)^2$. Scattering factors were taken from the literature.[13] Hydrogen atoms were calculated and allowed to ride on the carbon atom to which they were bonded with fixed isotropic U values set to 1.25 U (equiv.) of the parent atom. Number of parameters refined = 93, data-to-parameter ratio = 8.7:1. Final R indices for observed data: $R = 0.062$, $R_w = 0.071$, goodness-of-fit = 1.02. Weighting scheme $w = 1/[\sigma^2(F) + 0.0050F^2]$. Crystal data has been deposited at the Cambridge Crystallographic Data Centre.§

Acknowledgements

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society and to Sandia National Laboratories for partial support of this research. We acknowledge Dr Ruby Ju for performing elemental analyses. We thank Dr Todd Alam for assistance in obtaining and interpreting APT and INEPT spectra for macrocycle **1**. The NSF Chemical Instrumentation Program is acknowledged for providing a low field NMR spectrometer.

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§ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/2.

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Paper 5/07135F
Received 27*th October* 1995
Accepted 17*th January* 1996