# A Versatile Six-Component Molecular Capsule Based on Benign Synthons – Selective Confinement of a Heterogeneous Molecular Aggregate

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Solvent interactions in the formation of novel H-bonded capsules, comprised of four substituted terpyridines and two *C*-methylcalix[4]resorcinarenes (both synthons synthesized using "green" methodology), are shown to determine the size and shape of the guest cavity. Two representative host-guest complexes showing centred and off-centred apexes with respect to the calixarenes are described in detail, showing the inclusion of four guest molecules in the solid state.

## Introduction

Supramolecular host-guest complexes constructed from cone shaped polyaromatic macrocycles such as calixarenes and related cavitands including calix[4]resorcinarenes have been widely studied.[1–3] A recent aspect of this chemistry is the confinement of molecules within supramolecular capsules (nano-cages), which are formed by the head-to-head (upper rim-to-upper rim) approach of two cavitands,[1–8] or, in one case, from the assembly of six calix[4]resorcinarenes (and eight water molecules) into a snub cube, also with the cavities of the host molecules directed inwards.[9] Some capsules are hetero-multicomponent, comprised of cavitands interacting with other organic supramolecular synthons.[4–9]

Molecular capsules find applications in clean chemical synthesis,[10,11] drug delivery, materials and separation sciences,[12] and they are structurally related to compartments in biological systems such as those in viruses.[10,13] The interior of molecular capsules can be regarded as a new phase of matter,[14] and despite the synthesis of large cavities capable of binding several guest molecules, for example in the foregoing snub cube capsule,[10] a detailed understanding of the interplay and orientation of the guest molecules relative to each other and the principle axes of the capsule is restricted to two molecules.[6] Herein we report the synthesis and structural elucidation of hetero-multicomponent capsules based on two calix[4]resorcinarene and four terpyridine molecules. Also reported are the syntheses of the supramolecular synthons using benign procedures effectively embracing the principles of green chemistry as part of a new paradigm in the drive towards sustainable technologies in supramolecular chemistry and beyond.[15] The capsules have large internal volumes occupied by four guest molecules, either four disordered toluenes or, selectively, two toluenes and two diethyl ethers ordered within the crystal lattice. We note that four large *o*-carborane molecules can be confined in a cationic pyridyl-palladium capsule, although without their position and orientation within the capsule being established,[16] and N-pyridine-metal complexes in general can form a diverse range of capsules.[17–26] A large bowl-shaped pyridyl-palladium complex can assemble into "capsule-like" structures with four ordered benzene molecules or six ordered *cis*-stilbenes, although the two bowls are not associated through coordination or H-bonding interactions.[27] The largest coordination capsule reported is a $Cu_{12}L_8$ cage containing 5–6 disordered DMF guest molecules.[28] We also note that the self-assembly of six hydroxyresorcinarenes into an octahedron sphere is reported to have an internal volume of 1520 Å$^3$ containing ten acetonitrile guest molecules in the solid state.[29]

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## Results and Discussion

Capsules **1** and **2** were formed by the addition of *C*-methylcalix[4]resorcinarene and 4′-(4-octyloxyphenyl)-4,2′:6′,4′′-terpyridine to warm solutions of 1:1 toluene/ethanol and 1:1 toluene/diethyl ether, respectively (Scheme 1). Upon slow evaporation, both reaction media afforded yellow gels, which on standing for about two weeks resulted in small, fragile, dark-yellow crystals (ca. 10% yield). $^1$H NMR studies of the crystals in $CDCl_3$ and [$D_6$]acetone confirmed the ratios of constituents to be 3:2:1 (toluene/terpyridine/calix[4]resorcinarene) for capsule **1** (and verified the absence of ethanol) and 2:2:2:1 (diethyl ether/toluene/terpyridine/calix[4]resorcinarene) for capsule **2**. There was no evidence for the existence of the assembled capsule on the chemical shift NMR time scale (300 K). The terpyridine was conveniently prepared in high yield involving sequential solvent-free aldol and Michael addition reactions, as recently developed for related terpyridines,[30] for which con-

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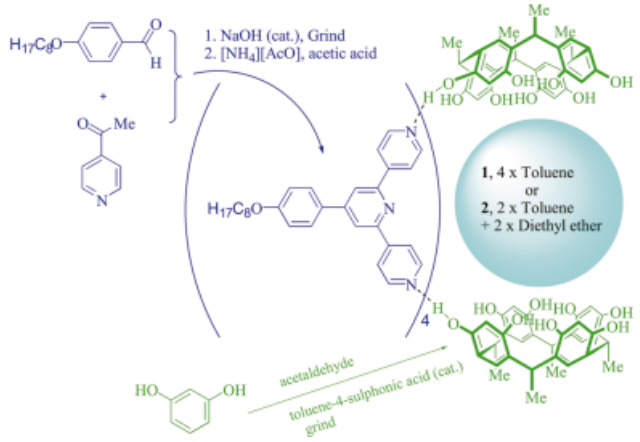
ventional methods are low yielding and generate considerable waste.[31,32] The calix[4]resorcinarene was also readily prepared in high yield as the cavitand $C_{4v}$ isomer under solvent-free conditions,[33] which dispenses with the need for using large volumes of acid and solvent.[34]

The solid state structures of **1** and **2** were determined by X-ray crystallography. Despite the weak, poor quality data obtained, the presence of encapsulated solvent molecules was clearly established, albeit with toluene molecules modelled at lower occupancies than indicated by NMR analysis. For capsule **1**, (Figure 1) the guest toluene molecules were poorly defined. However, four toluene positions within the capsule (two of which are crystallographically independent) could be identified. Capsule **2** is of higher complexity with a heterogeneous mixture of guest diethyl ether and toluene molecules. In this case the positions of the guests are well defined (Figure 2), and the structure represents an unusual example of multiply ordered guest molecules within a capsule.




Scheme 1

There is a structural relationship between the capsules and their enclosed constituents. In capsule **1** the calix[4]resorcinarenes are symmetrically aligned head-to-head, whereas in capsule **2** the two calix[4]resorcinarenes are "skewed" relative to each other. The relative size and shape of **1** and **2** are represented in Figure 3, along with estimated internal dimensions (based on atomic positions observed in the solid state).

Both capsules are held together by a total of eight N···HO hydrogen bonds, although the H atoms were not located in the structure determination (corresponding N···O distances 2.677−2.713 Å). The *C*-methylcalix[4]resorcinarenes are distorted from the usual $C_{4v}$ symmetry, whereby the two opposite phenyl rings which contain the phenolic protons hydrogen bonded to the terpyridines are signific-

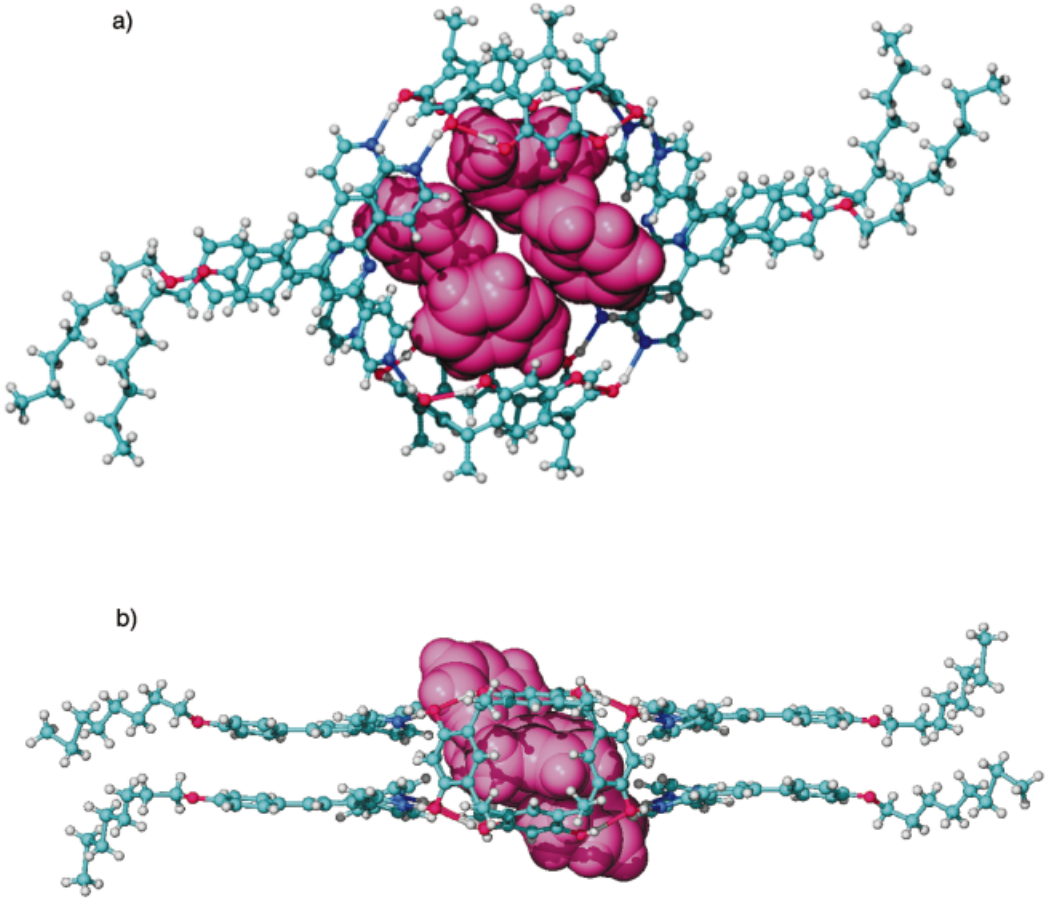



Figure 1. (a) and (b) Molecular structure of capsule **1**

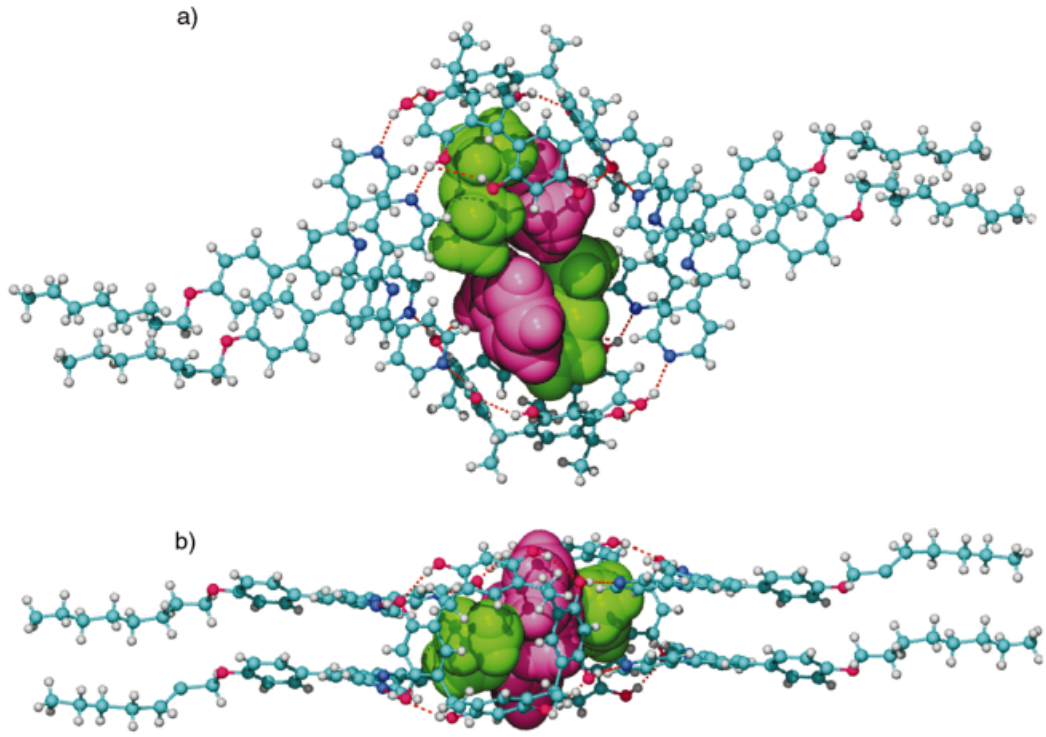



Figure 2. (a) and (b) Molecular structure of capsule **2**

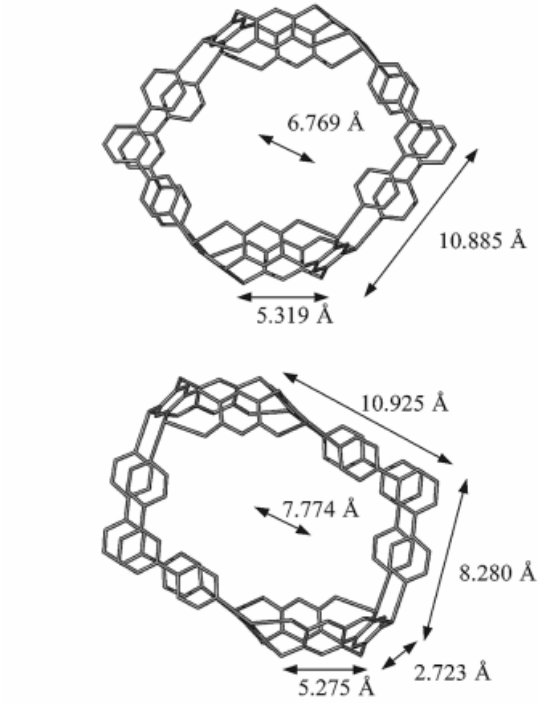



Figure 3. Cavity geometries of capsules **1** and **2**

antly more obtuse relative to each other (**1**: 144.39°; **2**: 135.62°) than the other opposing pair of phenyl rings (**1**: 106.62°; **2**: 114.30°). There are two pairs of π-stacked terpyridines [the central pyridine rings are separated by 3.687 Å (**1**) and 3.812 Å (**2**)] which have distance complementarity for H-bonding of each pair to the OH groups of one phenyl ring. This is found in H-bonded complexes of N-heterocycles with calix[4]resorcinarenes.[6,35−38] It is noteworthy that the π-stacking of two olefin-substituted pyridines in association with H-bonding to resorcinol (cf. **1** and **2**) has been used to direct photochemical [2+2] reactions.[39]

In **2**, two toluene and two diethyl ether molecules are independently orientated within the constraints of the capsule, in the absence of intermolecular associations with neighbouring guests, and pervade the cavities (Figure 1 and 2). The methyl groups of the diethyl ether reside in the base of the calix[4]resorcinarenes and the cleft between the terpyridine units. The skewed nature of the capsule indicates that the host complex prefers to self-assemble selectively around two diethyl ether molecules and two toluene molecules rather than the four positions of toluene guests observed in capsule **1**. Indeed, there was no evidence of capsule **1** in any of the crystals grown from toluene/diethyl ether media. Capsule **2** accommodates the four solvent molecules more efficiently, with less penetration beyond the confines of the capsule (Figure 1 and 2), and this is consistent with the larger size of the capsule (Figure 3) and that the molar volume of toluene (93.8 $Å^3$) is larger than that of diethyl ether (82.3 $Å^3$).[40]

## Conclusion

These results demonstrate that the availability of the new terpyridine ligand and the well-known calix[4]resorcinarene,

both using a benign approach, allows access to a new type of supramolecular capsule, and in so doing minimises the amount of overall waste. Guest recognition properties, including selectivity, and the flexibility in size and shape of the hosts, depending on complementarity of inter-guest, host−guest and interactions between the synthons making up the capsule, are significant in relation to mimicking biological molecular encapsulation,[9] and lead into the realms of using capsules in separation science.

## Experimental Section

**General:** All chemicals were used as supplied, unless noted otherwise. NMR spectra were recorded on a Bruker DPX300 spectrometer. Mass spectra were recorded using Chemical Ionisation or Electrospray Ionisation techniques on a Bruker BioApex 47e FTMS (4.7 Tesla) fitted with an Analytica electrospray source spectrometer. The infrared spectra were recorded on a Perkin−Elmer 1610 FTIR in the range 4000−400 $cm^{-1}$ as KBr discs. X-ray data were recorded on an Enraf−Nonius KappaCCD diffractometer at 123 K. All elemental analyses were performed by Chemical and Micro Analytical Services, Australia.

***C*-Methylcalix[4]resorcinarene:** *C*-Methylcalix[4]resorcinarene was readily prepared by the slow addition of acetaldehyde (221 mg, 5.15 mmol) to a stirred aggregate of solid resorcinol (567 mg, 5.15 mmol) and *p*-toluenesulfonic acid (50 mg, 0.02 mmol). The solid product was ground with a pestle and mortar (ca. 5 min.) at −78 °C, and the sticky yellow reaction mixture was left to solidify at room temperature (ca. 2 h). The crude product was then washed with water (ca. 5 mL) and recrystallised from methanol. Yield: 580 mg (82.8%, 4.26 mmol). $C_{32}H_{32}O_8$ (544.59): calcd. C 70.57, H 5.92; found C 70.25, H 6.05. − MS (ESI+) for $C_{32}H_{32}O_8Na$ ($[M + Na]^+$): calcd: 567.58; found 567.4. − $^1H$ NMR (300 MHz, [D$_6$]acetone, 300.0 K): δ =1.75 (d, $^3J$ = 7.42 Hz, 12 H, $CH_3$), 4.51 (q, $^3J$ = 7.42 Hz, 4 H, CH), 6.20 (s, 4 H, Ar *ortho* OH), 7.63 (s, 4 H, Ar *meta* OH), 8.43 (s, 8 H, OH). − $^{13}C$ NMR (75 MHz, [D$_6$]-acetone, 300.0 K): δ = 20.2, 103.3, 103.4, 124.9, 125.9, 152.0.

**4′-(4-Octyloxyphenyl)-4,2′: 6′,4′′-terpyridine:** This compound was synthesized by aggregating 4-acetylpyridine (2.00 g, 16.5 mmol), freshly distilled 4-octyloxybenzaldehyde (1.93 g, 8.26 mmol) and sodium hydroxide pellets (1.00 g, 25.0 mmol) in a pestle and mortar until a pale yellow powder was formed (ca. 15 min.). [Diketone: MS (ESI+) for $C_{31}H_{36}N_2O_3Na$ ($[M + Na]^+$): calcd: 481.58; found 481. − FT-IR (KBr): $\nu_{(C=O)}$ = 1685 $cm^{-1}$]. The powder was then added to a stirred solution of ammonium acetate (5.00 g, excess) in glacial acetic acid (300 mL). The reaction was heated at reflux (2 h), affording a dark green solution. The reaction mixture was neutralized with saturated potassium carbonate, and the white product was precipitated out of solution by the addition of distilled water (50 mL), collected and recrystallized from methanol. Yield: 3.11 g (86.1%, 7.12 mmol). $C_{29}H_{31}N_3O$ (437.58): calcd. C 79.60, H 7.14, N 9.60; found C 79.55, H 7.28, N 9.38. − MS (EI+) for $C_{29}H_{31}N_3O$ ($[M]^+$): calcd: 437.58; found 438. − $^1H$ NMR (300 MHz, $CDCl_3$, 300.0 K): δ = 0.89 (t, $^3J$ = 6.8 Hz, 3 H, $CH_3$), 1.40 (m, 8 H, alkyl chain), 1.83 (m, 2 H, $OCH_2CH_2$), 4.04 (t, $^3J$ = 6.3 Hz, 2 H, $OCH_2$), 7.05 (AA′XX′, 2 H, phenyl *ortho* to $OC_8H_{17}$ chain), 7.68 (AA′XX′, 2 H, phenyl *meta* to $OC_8H_{17}$ chain), 7.99 (s, 2 H, central pyridine), 8.05 (AA′XX′, 4 H, pyridine *meta* to N, *ortho* to central pyridine), 8.77 (AA′XX′, 4 H, pyridine *ortho* to N). − $^{13}C$ NMR (75 MHz, $CDCl_3$, 300.0 K): δ = 15.2, 23.8, 27.2, 27.8, 30.3, 30.6, 32.9, 69.4, 116.4, 119.4, 122.4, 129.4, 130.8, 147.4, 151.5, 151.8, 156.2, 161.7.

**Capsule (1), (terpyridyl)$_4$(calix[4]resorcinarene)$_2$(toluene)$_4$:** Crystallized from a solution of *C*-methylcalix[4]resorcinarene (50 mg, 9.18 × $10^{-2}$ mmol) and 4′-(4-octyloxyphenyl)-4,2′:6′,4′′-terpyridine (80 mg, 18.4 × $10^{-2}$ mmol) in toluene (1.0 mL) and ethanol (1.0 mL) by slow evaporation techniques (ca. 10% yield).

**Capsule (2), (terpyridyl)$_4$(calix[4]resorcinarene)$_2$(diethyl ether)$_2$(toluene)$_2$:** Crystallized from a solution of *C*-methylcalix[4]resorcinarene (50 mg, 9.23 × $10^{-2}$ mmol) and 4′-(4-octyloxyphenyl)-4,2′:6′,4′′-terpyridine (80 mg, 18.3 × $10^{-2}$ mmol) in toluene (1.0 mL) and diethyl ether (1.0 mL) by slow evaporation techniques (ca. 10% yield).

**X-ray Crystallographic Study:** Data were measured on an Enraf−Nonius KappaCCD diffractometer with Mo-$K_\alpha$ radiation (λ = 0.71073 Å) at 123(1) K. The structures were solved by direct methods and refined by full-matrix least-squares on $F^2$ with SHELX software.[41]

**Capsule (1) (terpyridyl)$_2$(calix[4]resorcinarene)(toluene)$_2$:** $C_{104}H_{120}N_6O_{10}$, $M_r$ = 1614.06, dark yellow prism (dimensions 0.15 × 0.06 × 0.05 mm), triclinic, space group $P\bar{1}$, $a$ = 15.6340(3), $b$ = 16.5422(4), $c$ = 20.3818(6) Å, α = 78.385(1), β = 79.429(2), γ = 63.911(1) °, $V$ = 4610.1(2) Å$^3$, $Z$ = 2, $\rho_{calcd.}$ = 1.163 g $cm^{-3}$, $F$(000) = 1732, μ = 0.074 $mm^{-1}$ (no correction), 68334 data measured, of which 12028 were independent [$R$(int) = 0.1503], $2\theta_{max}$ = 45°, 925 parameters, $R_1$ = 0.1260 [for 5235 data with $I > 2\sigma(I)$], $wR2$ = 0.3714 (for all data). Solvent molecules and alkyl chains were refined isotropically, all other non-hydrogen atoms were refined anisotropically. Residual electron density within the molecular cavity of the capsule was diffuse and modelled as toluene solvent molecules, as indicated by NMR analysis. Two such toluene molecules were modelled each at 50% occupancy with rigid body constraints for the phenyl group and common displacement parameters for carbon positions. The hydrogen atoms were included at geometrically calculated positions.

**Capsule (2) (terpyridyl)$_2$(calix[4]resorcinarene)(diethyl ether)$_2$-(toluene)$_{1.5}$:** $C_{108.5}H_{128}N_6O_{12}$, $M_r$ = 1708.17, dark yellow prism (dimensions 0.20 × 0.10 × 0.07 mm), triclinic, space group $P\bar{1}$, $a$ = 15.5488(6), $b$ = 17.9043(7), $c$ = 20.5013(11) Å, α = 68.282(2), β = 74.704(2), γ = 68.709(3)°, $V$ = 4884.8(4) Å$^3$, $Z$ = 2, $\rho_{calcd.}$ = 1.161 g $cm^{-3}$, $F$(000) = 1834, μ = 0.075 $mm^{-1}$(no correction), 76698 data measured, of which 12634 were independent [$R$(int) = 0.205], $2\theta_{max}$ = 45°, 968 parameters, $R_1$ = 0.1604 [for 4404 data with $I > 2\sigma(I)$], $wR_2$ = 0.3749 (all data). The crystal was small and weakly diffracting (≈35% observed data), which did not allow for an anisotropic refinement of all atomic positions, hence the solvent molecules, one aromatic carbon and the alkyl chains were refined isotropically. Restraints were applied to some anisotropic displacement parameters of other carbon atoms. One solvent toluene molecule was refined at 50% occupancy and with a rigid group model for the phenyl group. Hydrogen atoms were included at geometrically calculated positions.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-156550 (capsule **1**) and CCDC-156551 (capsule **2**). Copies of the data can be obtained free of charge on application to

CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].


[1] C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, **1998.**
[2] D. M. Rudkevich, J. Rebek, Jr., *Eur. J. Org. Chem.* **1999**, 1991−2005.
[3] J. Rebek, Jr., *Chem. Commun.* **2000**, 637−643.
[4] T. Hienz, M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764−766.
[5] K. Kobayashi, T. Shirasaka, K. Yamaguchi, S. Sakamoto, E. Horn, N. Furukawa, *Chem. Commun.* **2000**, 41−42.
[6] L. R. MacGillivray, P. R. Diamente, J. L. Reid, J. A. Ripmeester, *Chem. Commun.* **2000**, 359−360.
[7] G. Ferguson, C. Glidewell, A. J. Lough, G. D. McManus, P. R. Meehan, *J. Mater. Chem.* **1998**, *8*, 2339−2345
[8] A. Lützen, A. R. Renslo, C. A. Schalley, B. M. O'Leary, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 7455−7456
[9] L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469−472.
[10] H. Ito, T. Kusukawa, M. Fujita, *Chem. Lett.* **2000**, 598−599.
[11] M. Yoshizawa, T. Kusukawa, M. Fujita, K. Yamaguchi, *J. Am. Chem. Soc.* **2000**, *122*, 6311−6312.
[12] See, for example, L. R. MacGillivray, J. L. Atwood, *Angew. Chem.* **1999**, *111*, 1080−1085; *Angew. Chem. Int. Ed.* **1999**, *38*, 1018−1033.
[13] T. Douglas, M. Young, *Nature* **1998**, *393*, 152−155.
[14] J. C. Sherman, D. J. Cram., *J. Am. Chem. Soc.* **1989**, *111*, 4527−4527.
[15] P. T. Anastas, J. C. Warner, *Green Chemistry, Theory and Practice*, Oxford University Press, **1998**.
[16] T. Kusukawa, M. Fujita, *Angew. Chem.* **1998**, *110*, 3327−3329, *Angew. Chem. Int. Ed.* **1998**, *37*, 3142−3144.
[17] N. Takeda, K. Umemoto, K. Yamaguchi, M. Fujita, *Nature* **1999**, *398*, 794−796.
[18] S. Hiraoka, Y. Kubota, M. Fujita, *Chem. Commun.* **2000**, 1509−1510.
[19] S. Hiraoka and M. Fujita, *J. Am. Chem. Soc.* **1999**, *121*, 10239−10240.
[20] K. Umemoto, K. Yamamguchi, M. Fujita, *J. Am. Chem. Soc.* **2000**, *122*, 7150−7151.
[21] B. Olenyuk, J. A. Whiteford, A. Fetchkotter, P. J. Stang, *Nature* **1999**, *398*, 796−799.
[22] B. Olenyuk, M. D. Levin, J. A. Whiteford, J. E. Shield, P. J. Stang, *J. Am. Chem. Soc.* **1999**, *121*, 10434−10435.
[23] M. D. Levin, P. J. Stang, *J. Am. Chem. Soc.* **2000**, *122*, 7428−7429.
[24] D. L. Caulder, K. N. Raymond, *J. Chem. Soc., Dalton Trans.* **1999**, 1185−1200.
[25] O. D. Fox, M. G. B. Drew, E. J. S. Wilkinson, P. D. Beer, *Chem. Commun.* **2000**, 391−392.
[26] D. L. Caulder, K. N. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975, and references therein.
[27] S.-Yan Yu, T. Kusukawa, K. Biradha, M. Fujita, *J. Am. Chem. Soc.* **2000**, *122*, 2665−2666.
[28] B. F. Abrahams, S. J. Egan, R. Robson, *J. Am. Chem. Soc.* **1999**, *121*, 3535−3536.
[29] T. Gerkensmeier, W. Iwanek, C. Agena, R. Fröhlich, S. Kotila, C. Näther, J. Mattay, *Eur. J. Org. Chem.* **1999**, 2257−2262.
[30] G. W. V. Cave, C. L. Raston, *Chem. Commun.* **2000**, 2199−2000.
[31] M. G. B. Drew, P. B. Iveson, M. J. Hudson, J. O. Liljenzin, L. Spjuth, P. Y. Cordier, A. Enarsson, C. Hill, C. Madic, *J. Chem. Soc., Dalton Trans.* **2000**, 821−830.
[32] G. W. V. Cave, F. P. Fanizzi, R. J. Deeth, W. Errington, J. P. Rourke, *Organometallics* **2000**, *19*, 1355−1364.
[33] G. W. V. Cave, B. A. Roberts, C. L. Raston, J. L. Scott, unpublished result.
[34] L. M. Tunstad, J. A. Tucker, E. Dalcanale, J. Weiser, J. A. Bryant, J. C. Sherman, R. C. Helgeson, C. B. Knobler, D. J. Cram, *J. Org. Chem.* **1989**, *54*, 1305−1312.
[35] L. R. MacGillivray, J. L. Atwood, *Chem. Commun.* **1999**, 181−182.
[36] L. R. MacGillivray, H. A. Spinney, J. L. Reid, J. A. Ripmeester, *Chem. Commun.* **2000**, 517−518.
[37] L. R. MacGillivray, J. L. Reid, J. A. Ripmeester, *Cryst Eng Commun* **1999**, 1−4.
[38] L. R. MacGillivray, J. L. Atwood, *J. Am. Chem. Soc.* **1997**, *119*, 6931−6932.
[39] L. R. MacGillivray, J. L. Reid, J. A. Ripmeester, *J. Am. Chem. Soc.* **2000**, *122*, 7817−7818.
[40] Calculated using X-seed, a graphical interface to the SHELX program suite, L. J. Barbour, **1999**, University of Missouri, USA.
[41] G. M. Sheldrick, University of Göttingen, Göttingen (Germany), **1998.**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