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Factors influencing solvent adduct formation by calixarenes in the solid state

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Structural studies of seven very differently functionalised derivatives of calix[4]arene have been used to provide an analysis of the numerous factors which may influence solvent adduct formation by calixarenes. Evidence is presented that even where a solvent guest is included within the calixarene cavity, interactions solely within the cavity cannot be seen as the sole influences upon the guest position and orientation.

Introduction

Structural studies of calixarenes and of calix[4]arene derivatives in particular have proved useful in the characterisation of intermolecular association through labile and (presumably) weak interactions.[1] At room temperature, however, the information available may be diminished by spatial averaging of some atomic positions due to various molecular motions. Thus, the *cone* conformation of calix[4]arenes is frequently found to be of fourfold symmetry, even in the cases of adducts where a solvent guest of such a form as for this to be strictly impossible is found within the calixarene cavity. The combination of low-temperature structural studies and variable temperature solid-state nuclear magnetic resonance measurements has been used to show that a variety of motions within the lattices of crystalline calixarene adducts can occur and may be responsible for the unexpectedly high symmetry apparent in many room temperature structure determinations.[1b] A significant point made by others[2] is that this may give rise to erroneously glib interpretations of the forces at work in these adducts. Thus, there is a continuing need for precise structural characterisation to expose the full complexity of the interactions in calixarene derivatives. In the present work we present results for systems spanning a broad range of characteristics but reflecting the operation of many common factors.

Experimental

Synthesis

p-tert-Butylcalix[4]arene, **1**,[3] the tetrakis (hydroxyethyl) ether of **1**,**2**,[4] and the tetra-, **3**,[5] and hexa-hydro, **4**,[6] derivatives of calix[4]arene were obtained using published procedures. The 1,3-diethyl ether of **1**, a known compound, **5**,[7] was obtained unexpectedly as the product of an attempt to conduct the base hydrolysis of the bis-di(ethoxycarbonyl)methyl ether of **5**.[8]

1,3-bis(propargyl)-*p-tert*-butylcalix[4]arene 6. *p-tert*-butylcalix[4]arene (3.86 g; 5.90 mmol), potassium carbonate (1.97 g; 14.3 mmol) and propargyl bromide (2.40 g; 20.3 mmol) in acetone (100 mL) were heated together at reflux for 15 h. The reaction mixture was filtered, the filtrate evaporated to dryness and the residue triturated with methanol to give the product as a white solid (yield 3.45 g, 80%), mp 215–216 °C after recrystallisation from $CHCl_3$ by addition of methanol. ^{1}H- NMR (200 MHz, $CDCl_3$): δ 7.29 (s, 2H, ArO*H*), 7.16 (s, 4H, Ar*H*), 6.76 (s, 4H, Ar*H*), 6.52 (s, 2H, CC*H*), 4.78 (d, 4H, J = 3.1 Hz, OCH_2 C), 4.43 (d, 4H, J = 13.8 Hz, ArCH_2 Ar), 4.36 (d, 4H, J = 13.8 Hz, ArCH_2 Ar), 1.34 (s, 18H, C(CH_3)$_3$), 0.94 (s, 18H, C(CH_3)$_3$).

Tris(*p*-cymeneruthenium(II))-hexahydrocalix[4]arene sulfate-bisulfate 7. This was obtained from **4** by a procedure analogous to that known[9] for the tetrakis derivative of **1**. Thus, Ru_2-(cymene)$_2Cl_4$ (182 mg) was dissolved in a mixture of acetone (10 mL) water (10 mL) and CF_3CO_2H (1 mL). Ag_2SO_4 (180 mg) was added and the reaction mixture was stirred for 2 h before filtration and removal of the solvent under reduced pressure. CF_3CO_2H (10 mL) and the reduced calixarene **4** (75 mg) were added to the residue and this mixture was heated at reflux for 48 h. The resulting solution was then cooled to room temperature and concentrated to 1 mL under reduced pressure before adding acetone (10 mL). The insoluble material was filtered off and washed with acetone to give a pale yellow hygroscopic powder (110 mg). Pale yellow, X-ray quality crystals were grown by dissolving the pale yellow powder in water (5 mL) and then allowing the slow vapour diffusion of acetonitrile over 3 d. ^{1}H NMR (500 MHz, D_2O): δ 6.89 (d, J = 5.9Hz, 2H), 6.80 and 6.76 (AB system, J = 6.7 Hz, 4H), 6.61 (dd, J = 1.0 Hz, J = 5.9 Hz, 2H), 6.59 (d, J = 6.5 Hz, 2H), 6.56 (d, J = 6.5 Hz, 2H), 6.52 (d, J = 6.1 Hz, 2H), 6.46 (d, J = 6.5 Hz, 2H), 6.40 (dd, J = 5.8 Hz, J = 5.8 Hz, 1H), 6.39 (d, J = 5.9 Hz, 2H), 6.13 (dd, J = 5.8 Hz, J = 5.8 Hz, 2H), 4.15 (d, J = 12.7 Hz, 2H), 3.37 (dd, J = 13.1 Hz, J = 3.6 Hz, 2H), 3.24 (d, J = 12.7 Hz, 2H), 2.89 (heptet, J = 6.9 Hz, 1H), 2.79 (heptet, J = 6.9 Hz, 2H), 2.39 (s, 3H), 2.28 (s, 6H), 2.16 (dd, J = 10.5 Hz, J = 10.5 Hz, 1H), 1.98 (dd, J = 12.9 Hz, J = 4.1 Hz, 2H), 1.78 (m, 3H), 1.57 (m, 3H), 1.32 (d, J = 6.9 Hz, 6H), 1.25 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 12.7 Hz, 6H), 0.73 (m, 2H).

Tetrahydro-*p-tert*-butylcalix[4]arene oxime 8. **3** (1.53 g) and NH_2OH·HCl (5.0 g) were added to a mixture of methanol

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(60 mL) and pyridine (15 mL) and the mixture was heated at reflux for 8 h. The solvent was evaporated under reduced pressure and dichloromethane (50 mL) was added to the remaining residue. The extract formed was washed with 1 mol L^{-1} HCl (10 mL), water (2 × 20 mL) and dried ($MgSO_4$). The dichloromethane was removed under reduced pressure and the crude oxime was recrystallised from chloroform to yield colourless crystals (1.11 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, J = 7.3 Hz, J = 1.3 Hz, H(4,5), Ar), 7.19 (dd, J = 7.6 Hz, J = 1.3 Hz, H(3,4), Ar), 7.13 (bd, J = 7.5 Hz, H(3,3), Ar), 7.06 (bd, J = 7.5 Hz, H(3,5), Ar), 7.02 (dd, J = 7.4 Hz, J = 1.6 Hz, H(2,3), Ar), 6.98 (dd, J = 7.4 Hz, J = 1.6 Hz, H(2,5), Ar), 6.93 (dd, J = 7.3 Hz, J = 7.3 Hz,H(4,4), Ar), 6.82 (dd, J = 7.5 Hz, J = 7.5 Hz, H(3,4), Ar), 6.71 (dd, J = 7.4 Hz, J = 7.4 Hz, H(2,4), Ar), 4.24 (d, J = 15.6 Hz, H(4), ArCH_2), 4.00 (d, J = 14.2 Hz, H(3), ArCH_2), 3.94 (d, J = 15.6 Hz, H(4), ArCH_2), 3.60 (bdd, J = 12 Hz, J = 4.8 Hz,H(12), C=NOHCH_{eq}), 3.40 (d, J = 14.2 Hz, H(3), ArCH_2), 3.32 (dd, J = 12.8 Hz, J = 12.8 Hz, H(2), ArCH_2), 3.08 (dd, J = 14.4 Hz, J = 9.2 Hz, H(1), ArCH_2), 2.80 (ddd, J = 9.2 Hz, J = 13.1, J = 3Hz, H(1,6), C=NOHCH_{ax}), 2.25 (dd, J = 12.8 Hz, J = 1.6 Hz, H(2), ArCH_2), 2.16 (bdd, J = 13.1 Hz, J = 3 Hz, H_{eq}(1,5), CH_2), 1.91 (bd, J = 13.1 Hz, H_{eq}(1,3), CH_2), 1.81 (ddddd, J = 13.1 Hz, J = 13.1 Hz, J = 13.1 Hz, J = 3.0 Hz, J = 3.0 Hz, H_{ax}(1,4), CH_2), 1.68–1.63 (m, 2H_{ax}(1,3), H_{eq}(1,4)), 1.46 (dddd, J = 13.1 Hz, J = 13.1 Hz, J = 3.7 Hz, J = 3.7 Hz, H_{ax}(1,5)). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 165.41 (CNOH), 154.10 (Ar), 152.11(Ar), 149.91 (Ar), 132.00 (Ar), 130.26 (Ar), 129.36 (Ar), 129.30 (Ar), 128.36 (Ar), 128.25 (Ar), 128.16 (Ar), 128.11(Ar), 127.67 (Ar), 126.83 (Ar), 126.35 (Ar),126.17 (Ar), 121.07 (Ar), 121.05 (Ar), 119.76 (Ar), 42.65 (CH_{ax} C(1,6)), 37.71, 36.77 (ArCH_2), 36.34, 34.02 (CH_{eq} C(1,2)), 34.00, 33.94, 30.65 (ArCH_2), 21.27. (Atom numbers as in the structure diagram.)

Crystallisation

A crystal of **A**, **1**·1¼CH_3CN, was obtained by chance selection from a mass of crystals obtained by recrystallisation of **1** from acetonitrile. Crystals of two (α and β) forms of **B**, **5**·Me_2CO, were obtained from ambient temperature vapour diffusion of water into acetone solutions of **5**. Crystals of **C**, **2**·½$C_6H_5CH_3$, were obtained by slow evaporation of a toluene solution of **2**. Crystals of unsolvated **D** (= **6**) were obtained by slow cooling of its solution in hot $CHCl_3$ and crystals of **E**, **8**·$CHCl_3$, were obtained similarly. Crystals of **F**, **4**·{Ru(p-cymene)}$_3$·$(SO_4)_2$·$(HSO_4)_2$·7H_2O·CH_3CN, were obtained as described above.

Structure determinations

Full spheres of CCD area-detector diffractometer data were measured (Bruker AXS instrument, ω-scans, $2\theta_{max}$ = 58°; monochromatic Mo K_α radiation, λ = 0.7107$_3$ Å; *T ca.* 153 K for all except **B**α and **F** (298 K)) yielding $N_{t(otal)}$ reflections, merging to N unique after 'empirical'/multiscan absorption correction (proprietary software; R_{int} quoted), N_o with $F > 4\sigma(F)$ considered 'observed' and used in the large block least squares refinement, refining anisotropic displacement parameter forms for the non-hydrogen atoms; individual diversities in procedure are recorded below as 'variata'. Conventional residuals R, R_w on $|F|$ are recorded, (reflection weights: $(\sigma^2(F) + 0.0004\,F^2)^{-1}$), neutral atom complex scattering factors being employed within the Xtal 3.7 program system.[10] Pertinent results are given below and in the figures, the latter showing 50% (153 K) or 20 % (298 K) probability amplitude displacement envelopes for the non-hydrogen atoms, hydrogen atoms, where shown, having arbitrary radii of 0.1 Å. CCDC reference numbers 215809–215815. See http://www.rsc.org/suppdata/ob/b3/b308214h/ for crystallographic data in .cif or other electronic format.

Crystal/refinement data

A = 1·1¼MeCN ≡ $C_{44}H_{56}O_4$·1¼C_2H_3N

M = 700.2. Orthorhombic, space group $Pna2_1$ (C_{2v}^9, No. 33), a = 26.365(1), b = 12.614(1), c = 12.585(3) Å, V = 4186 Å^3, D_c (Z = 4) = 1.11$_1$ g cm^{-3}. μ_{Mo} = 0.7 cm^{-1}; specimen: 0.25 × 0.12 × 0.06 mm; 'T'$_{min/max}$ = 0.63. N_t = 40712, N = 3854 (R_{int} = 0.11), N_o = 3310; R = 0.073, R_w = 0.078. $|\Delta\rho_{max}|$ = 0.33(3) e Å^{-3}.

Variata. $2\theta_{max}$ was 50°. Solvent residue site occupancies were (i) (within the calyx) constrained at unity after trial refinement, (ii) (interstitial) 0.25(1), by refinement. Extensive rotational disorder of the *tert*-butyl groups was found, component occupancies of (a) 14*n* set at 0.5/0.5 after trial refinement, (b) 24*n*, 34*n*, 44*n* major and minor components refining to 0.69(2), 0.73(2), 0.75(1) and complements, respectively. (x, y, z, U_{iso})$_H$ were constrained at estimates. The structure having no significant anomalous scatterer, 'Friedel' data were merged in the refinement.

B = 5·Me_2CO ≡ $C_{48}H_{64}O_4$·C_3H_6O, M = 763.1.

α-form. Triclinic, space group $P\bar{1}$ (C_i^1, No. 2), a = 12.594(1), b = 18.060(2), c = 22.178(2) Å, α = 97.231(2), β = 97.264(2), γ = 104.726(1)°, V = 4773 Å^3, D_c (Z = 4) = 1.06$_0$ g cm^{-3}, μ_{Mo} = 0.7 cm^{-1}; specimen: 0.78 × 0.55 × 0.44 mm (no correction). N_t = 41719, N = 22411 (R_{int} = 0.074), N_o = 11558; R = 0.073, R_w = 0.088. $|\Delta\rho_{max}|$ = 0.65(5) e Å^{-3}.

Variata. The temperature for this, the initial, determination was 298 K. The material was isomorphous with the previously determined ethanol solvate[7] and was refined in a similar setting, rotational disorder being resolved for one of the *tert*-butyl groups of molecule 1 as in the ethanol solvate, and in one of those of molecule 2 as well, both being refined with the two components of each set at equal occupancy after trial refinement. Hydrogen atoms of the phenolic groups were located but not refined, others being constrained at estimates. The acetone was modelled on the basis of refinement behaviour with the carbonyl group projecting into the cavity; this assignment was less unambiguous than desired, and at a later period, with the advent of a low-temperature facility, a redetermination was undertaken, on a freshly crystallized specimen, at *ca.* 153 K, yielding, instead, a second, β-form.

β-form. Triclinic, space group $P\bar{1}$, a = 12.439(3), b = 13.780(3), c = 14.061(3) Å, α = 78.082(4), β = 88.428(4), γ = 76.002(4)°, V = 2287 Å^3, D_c (Z = 2) = 1.10$_8$ g cm^{-3}, μ_{Mo} = 0.7 cm^{-1}; specimen: 0.25 × 0.15 × 0.08 mm (no correction). N_t = 25047, N = 11118 (R_{int} = 0.061), N_o = 5999; R = 0.075, R_w = 0.081. $|\Delta\rho_{max}|$ = 1.0(1) e Å^{-3}.

Variata. Hydrogen atoms were located throughout but not refined, consistent, in the case of the solvent molecule, with direction of one of the methyl groups into the calyx.

C = 2·½$PhCH_3$ ≡ $C_{52}H_{72}O_8$·½C_7H_8

M = 871.2. Triclinic, space group $P\bar{1}$, a = 21.163(2), b = 21.401(2), c = 25.508(2) Å, α = 107.194(1), β = 108.912(1), γ = 90.083(2)°. V = 10380 Å^3, D_c (Z = 8) = 1.11$_5$ g cm^{-3}, μ_{Mo} = 0.7 cm^{-1}, specimen: 0.65 × 0.45 × 0.10 mm, 'T'$_{min/max}$ = 0.81. N_t = 100479, N = 45822 (R_{int} = 0.032), N_o = 21601; R = 0.11, R_w = 0.12. $|\Delta\rho_{max}|$ = 1.79(4) e Å^{-3}.

Variata. Crystals grew as micaceously twinned plates, a single specimen being achieved by cleavage; at room temperature, using a single counter instrument, data were weak and limited in extent with a correspondingly unsatisfactory refinement. At low temperature with CCD data, more auspicious behaviour was obtained. *tert*-Butyl group 34 was modelled as rotationally

disordered over two sets of sites, occupancies refining to x = 0.699(8) and complement. Solvent residues were modelled in terms of toluene, disordered over two sets of sites, occupancies constrained at 0.6, 0.4 after trial refinement, ring geometries constrained as rigid bodies. $(x, y, z, U_{iso})_H$ were constrained at estimated values throughout, phenolic hydrogens (not located) excepted.

D = 6 ≡ $C_{50}H_{60}O_4$

M = 725.0. Monoclinic, space group $P2_1/n$, (C_{2h}^5, No. 14; variant), a = 12.307(1), b = 31.192(3), c = 12.430(1) Å, β = 112.518(1)°, V = 4408 Å^3, D_c (Z = 4) = 1.09$_2$ g cm^{-3}, μ_{Mo} = 0.7 cm^{-1}, specimen: 0.40 × 0.25 × 0.10 mm, 'T'$_{min/max}$ = 0.88. N_t = 43877, N = 9830 (R_{int} = 0.035), N_o = 7111; R = 0.046, R_w = 0.052. $|\Delta\rho_{max}|$ = 0.29(3) e Å^{-3}.

Variata. $(x, y, z, U_{iso})_H$ were refined throughout.

E = 8·$CHCl_3$ ≡ $C_{28}H_{29}NO_4$·$CHCl_3$

M 562.9. Triclinic, space group $P\bar{1}$, a = 11.187(2), b = 12.038(2), c = 12.244(2) Å, α = 61.561(2), β = 69.877(2), γ = 74.679(2)°, V = 1351 Å^3, D_c (Z = 2) = 1.38$_3$ g cm^{-3}, μ_{Mo} = 3.8 cm^{-1}, specimen: 0.45 × 0.32 × 0.15 mm, 'T'$_{min/max}$ = 0.83. N_t = 15258, N = 6575 (R_{int} = 0.021), N_o = 5077. R = 0.042, R_w = 0.047. $|\Delta\rho_{max}|$ = 0.91(3) e Å^{-3}.

Variata. $(x, y, z, U_{iso})_H$ were refined throughout.

F = Hexahydrocalix[4]arene-tris{(*p*-cymene)ruthenium(II)} bis(hydrogensulfate) bis(sulfate) heptahydrate acetonitrile solvate 4·{Ru(p-cymene)}$_3$·$(SO_4)_2$·$(HSO_4)_2$·7H_2O·CH_3CN ≡ $C_{60}H_{91}NO_{27}Ru_3S_4$

M = 1689.8. Orthorhombic, space group $Pnma$ (D_{2h}^{16}, No. 62), a = 19.111(2), b = 19.764(2), c = 18.122(2) Å, V = 6845 Å^3, D_c (Z = 4) = 1.64$_0$ g cm^{-3}, μ_{Mo} = 8.6 cm^{-1}, specimen: 0.60 × 0.18 × 0.10 mm, 'T' $_{min/max}$ = 0.67. N_t = 20602, N = 9053 (R_{int} = 0.034), N_o = 5481; R = 0.053, R_w = 0.055, $|\Delta\rho_{max}|$ = 1.07(6) e Å^{-3}.

Variata. The packing of the lattice components appears to be dominated by the cations, the remaining components filling the interstices, with less than desirable definition in consequence of considerable disorder, most obvious in the isopropyl substituent of cation ring 1 and sulfate moiety 2, the latter modelled as rotationally disordered about S(2)–O(21) over two sets of sites of equal occupancy after trial refinement. Substantial difference map residues were modelled as water molecule oxygen atoms, O(4,5) half-weighted. Hydrogen atoms associated with the anion, solvent and phenolic components of the cation were not located, the imputed stoichiometry (above) resting on charge-balance considerations.

Results and discussion

Structural studies of solvated "parent" (phenolic) calix[4]arenes have been essential in developing an understanding of many important calixarene properties such as the definition and stabilisation of conformations and the inclusion of various guests within cavities defined by particular conformations.[11] Thus, the preference for the *cone* conformation of *p-tert*-butylcalix[4]arene is conventionally ascribed to the importance of extended hydrogen-bonding possible when all four phenolic hydroxyl groups project to the same side of the mean macrocyclic plane,[12] and the inclusion of molecules such as acetonitrile in a 'methyl-in' direction by this calixarene is attributed to favourable CH_3-π interactions possible for this configuration.[1a] Perhaps unsurprisingly given the seemingly slight difference in composition between *p-tert*-butylcalix[4]arene·CH_3CN and *p-tert*-butylcalix[4]arene·1.25CH_3CN, the presently-determined structure of the latter, **A**, shows close similarities to that known for the former[13] (tetragonal, space group $P4/n$, a = 12.7194(4), c = 12.7668(3) Å, V = 2065 Å^3, T 123 K; the molecule disposed about a crystallographic *4*-axis with the solvent lying on that axis) and could thus be seen as providing further justification for these conclusions. However, there are aspects of both structures deserving of further attention.

One of the basic difficulties in the crystallography of acetonitrile adducts of calixarenes is to establish the orientation of the acetonitrile with respect to its host. Most crudely put, in the case of inclusion by a *cone* calix[4]arene, is it 'methyl in' or 'methyl out'? The former is usually assumed to be the most likely, since it appears to be firmly established for the solution state on the basis of inclusion-induced shifts in ^{1}H NMR spectra.[1a] The present refinement model of structure **A** (Fig. 1) is based upon the 'methyl in' configuration, as found for **1**·CH_3CN, and this may be explicable in terms of inclusion being due to CH_3-π interactions,[1a,11,14] though it may be noted that it is also consistent with favourable relative orientation of the CH_3CN and calixarene dipoles, indicating that other dispersive interactions may play a role. In this regard, it may be significant that the 'additional' (0.25) lattice CH_3CN in **A** is oriented such that its dipole is parallel to that of the included molecule. However, this orientation is also such that the N atom

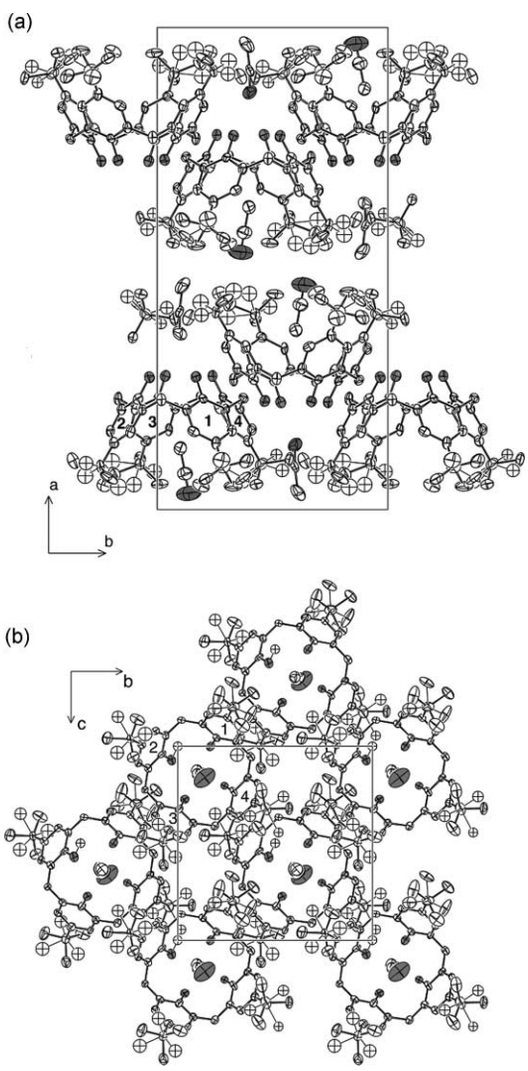

Fig. 1 (a) The array of **1**·1.25CH_3CN, **A**, projected down the orthorhombic c axis; the contents of the cell are organised in two layers, partitioned at x = 0, ½. In this and all following crystallographic figures, the non-carbon atom ellipsoids are identified by their grey shading. (b) The layer containing the asymmetric unit, between x = 0, ½, is shown, projected down a, for comparison with (a).

Table 1 Tetra-*tert*-butylcalix[4]arene solvate comparators

(a) Interplanar dihedral angles. The O_4 'plane' is taken as datum, θ_n° being the dihedral angle between it and the C_6 phenyl plane *n*.

Species	θ_1	θ_2	θ_3	θ_4
1·$C_6H_5NO_2$ (*P*4/*n*)[a]	55.9(1)	—	—	—
1·CH_3CN (*P*4/*n*)[b]	56.95(4)	—	—	—
1·$C_6H_5NO_2$ (*Pna*2$_1$)[a]	53.5(1)	55.0(1)	59.1(1)	49.7(1)
1·CH_3CN (*Pna*2$_1$)[a]	58.0(2)	57.8(2)	58.4(2)	57.8(2)
5·CH_3CH_2OH ($P\bar{1}$) (mol. 1)[d]	60.4(2)	58.1(2)	57.7(2)	64.3(1)
(mol. 2)	57.1(2)	62.7(1)	51.8(1)	62.5(1)
5·$(CH_3)_2CO$ (298 K)($P\bar{1}$;α) (mol. 1)[a]	59.3(1)	58.5(1)	59.0(1)	61.9(1)
(mol. 2)	55.3(1)	63.2(1)	50.3(1)	62.5(1)
(153 K)($P\bar{1}$;β)	44.3(1)	65.0(1)	59.7(1)	69.0(1)
2·½C_7H_8 (mol. 1)[c]	40.7(1)	89.6(1)	54.8(1)	88.0(1)
(mol. 2)	40.3(1)	88.8(1)	55.0(1)	86.4(1)
(mol. 3)	36.9(1)	89.6(1)	58.9(1)	89.2(1)
(mol. 4)	37.9(1)	87.9(1)	58.4(1)	85.1(1)
6[c]	47.41(5)	86.82(5)	35.10(5)	80.31(5)

(b) 'Phenolic' O ··· O distances/Å; r_{mn} is O(m) ··· O(n) of the molecule.

Species	r_{12}	r_{23}	r_{34}	r_{41}
1·$C_6H_5NO_2$ (*P*4/*n*)[a]	2.670(6)	—	—	—
1·CH_3CN (*P*4/*n*)[b]	2.692(2)	—	—	—
1·$C_6H_5NO_2$ (*Pna*2$_1$)[a]	2.684(3)	2.660(4)	2.684(3)	2.623(3)
1·CH_3CN (*Pna*2$_1$)[a]	2.698(6)	2.695(8)	2.726(6)	2.720(6)
5·CH_3CH_2OH ($P\bar{1}$) (mol. 1)[d]	2.696(5)	2.966(3)	2.704(5)	3.034(6)
(mol. 2)	2.706(3)	2.952(5)	2.689(3)	2.984(5)
5·$(CH_3)_2CO$ (298 K)($P\bar{1}$;α) (mol. 1)[a]	2.699(3)	2.978(3)	2.723(3)	3.020(4)
(mol. 2)	2.763(3)	2.872(3)	2.731(3)	2.897(3)
(153 K) ($P\bar{1}$;β)	2.646(3)	3.046(4)	2.738(3)	2.939(4)
2·½C_7H_8 (mol. 1)[c]	3.269(7)	3.315(7)	3.329(7)	3.149(6)
(mol. 2)	3.329(7)	3.299(6)	3.349(7)	3.107(6)
(mol. 3)	3.143(7)	3.498(6)	3.319(6)	3.340(6)
(mol. 4)	3.265(7)	3.478(7)	3.356(6)	3.266(6)
6[c]	2.832(3)	2.953(2)	2.819(2)	3.132(2)

[a] Ref. 15. [b] Ref. 13. [c] This work. [d] Ref. 7.

ascribed to the lattice molecule lies within hydrogen-bonding distance (N ··· O 3.02(3)–3.08(3) Å) of four surrounding calixarene phenolic oxygens. The saturated end of this molecule (positive end of the dipole) lies at 3.68(4) Å from the N of the included molecule (negative end of this dipole) but within similar distances of *tert*-butyl methyl carbon atoms, distances which are also comparable with the separation between the N of the included molecule and C atoms of *tert*-butyl methyl groups of both its host and adjacent calixarenes in the lattice. Thus, the bilayer structure of the lattice (Fig. 1(b)), which is very similar to that in **1**·CH_3CN, can be seen as involving numerous dispersive interactions and it becomes very difficult, from this view, to conclude that inclusion must be primarily attributed to CH_3-π interactions. The same dilemma in discerning the specific forces at work has been recognised in consideration of the structures of a closely analogous pair of *p-tert*-butylcalix[4]arene solvates formed with nitrobenzene.[15] The 'α'-form of **1**·$C_6H_5NO_2$ is orthorhombic, space group set as *Pc*2$_1$*n*, with cell dimensions and a cell array closely similar to the tetragonal, 'β'-form (actually a mixed nitrobenzene–propanol solvate; space group *P*4/*n*) but with an axis doubled: α-form – a = 12.4355(4), b = 12.9346(5), c = 26.756(1) Å, V = 4304 Å^3; β-form – a = 12.95(1), c = 12.57(1) Å, V = 2106 Å^3 (both 150 K). Presumably the evidence of these solvates for both crystal and solvent systems is indicative that the energy difference between the two forms is delicately poised, the acetonitrile content indicative of susceptibility to minor variations in crystallization conditions. Conformational indicators for these systems are aggregated in Table 1; the two tetragonal solvates with symmetrical cones (quasi-4*mm*) are very similar, as is the present orthorhombic MeCN solvate, the orthorhombic nitrobenzene solvate more quirky in respect of features such as C_6/O_4 interplanar dihedral descriptors.

The 'apolar end in' orientation of an included guest exemplified in **1**·1¼CH_3CN may be regarded as typical of inclusion complexes of **1**[1a] but it appears not to be found in **1**·dmso,[16] another *P*4/*n* structure, in which the orientation of the dimethylsulfoxide guest has been treated as disordered with respect to the orientation of the $S(CH_3)_2$ moiety about the effective C_4 axis of the formula unit but with the oxygen atom furthest inserted into the calixarene cavity. In this rather beautiful opposed-columnar structure, factors reinforcing fourfold symmetry of the calixarene may be intermolecular stacking interactions of the aromatic rings, indicated by approaches of 3.41(1) Å between C(2) atoms, and intermolecular bridging-methylene–aromatic interactions indicated by an approach of the methylene C to within 3.46 Å of the centroid of an aromatic ring. Such calixarene–calixarene interactions have been noted in many other systems[1a,17,18] and indeed they can be found within the structure of **1**·1¼CH_3CN, further reinforcing the notion that it may be misleading to consider the forces determining the form of the 'molecular unit' in a crystalline solid solely in terms of the structure of that molecular unit.

As with CH_3CN, the difficulties in unambiguously assigning the orientation of a small guest such as acetone in a large molecule such as the 1,3-diethyl ether of *p-tert*-butylcalix[4]arene, **5**, from crystallographic data alone, can be considerable. An initial study of the acetone monosolvate, **5**·Me_2CO = **B**α, (Fig. 2(a,b)) found it to be isomorphous with the known ethanol solvate but, at room temperature, the assignment of the components of the acetone moiety not being secured to our satisfaction, a low temperature study was undertaken on a fresh recrystallisation,

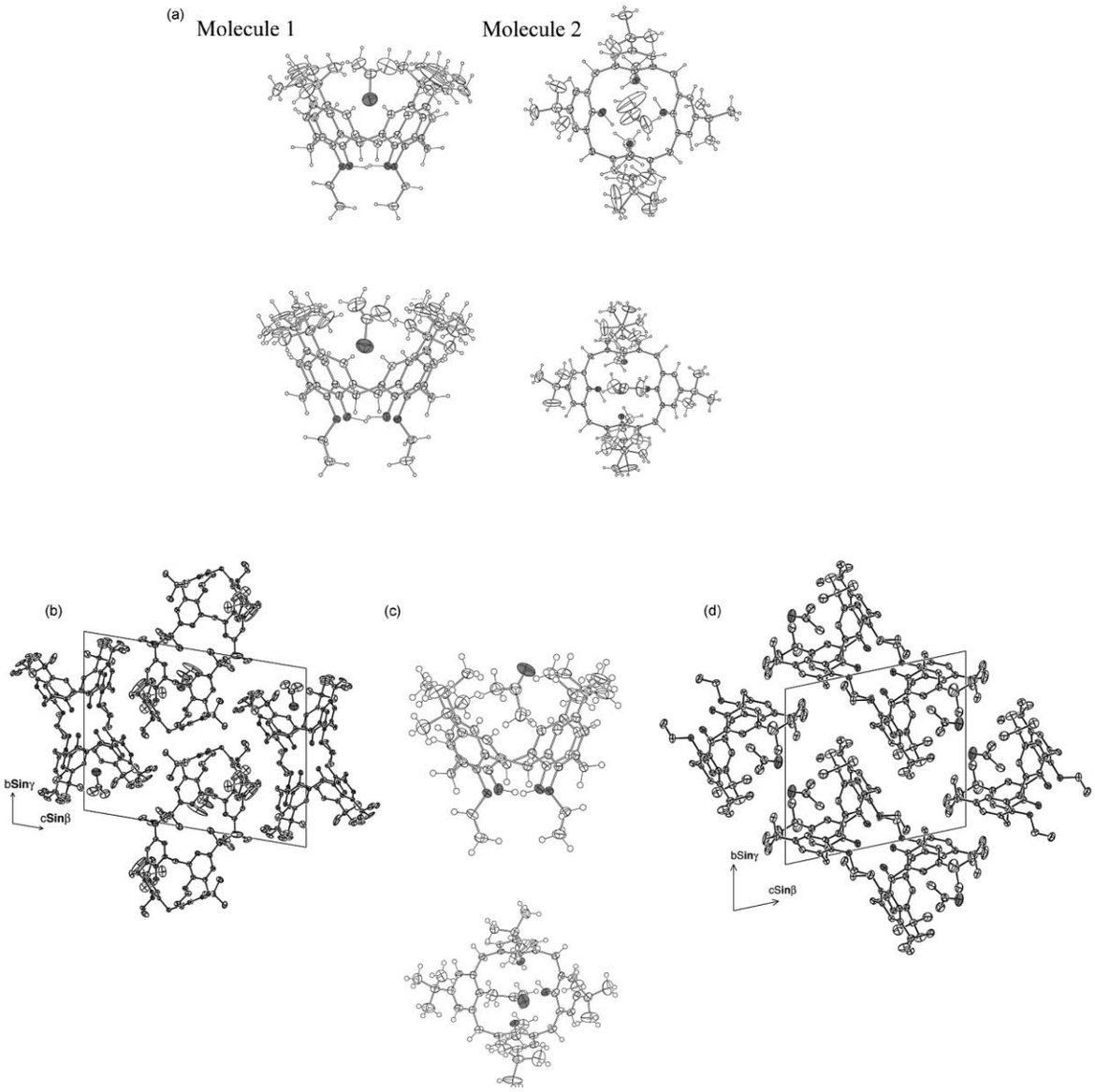

Fig. 2 (a) Projections of the two molecules of the α-form of **5**, (i) normal to and (ii) down the calyx axes. (b) Unit cell contents of the α-acetone solvate, **B**, projected down *a*. (c) A single molecule of the β-form, projected (i) normal to and (ii) down, the calyx axis. (d) Unit cell contents of the β-form projected down *a*.

a new (**B**β) polymorph, also an (included) acetone monosolvate, being obtained (Fig. 2(c,d)). For **B**β, one rather than two (**5**·Me_2CO) formula units, devoid of crystallographic symmetry, comprise the asymmetric unit of the structure. The latter form is devoid of disorder associated with certain *tert*-butyl substituents in the α-phase, and is more definitive regarding the solvent disposition *vis-à-vis* the calyx, which is seemingly 'methyl in' rather than 'carbonyl in' (though of course it is possible that the average orientation of the guest may be temperature dependent). This corresponds to an antiparallel arrangement of calixarene and guest dipoles, which is also the orientation of nearest-neighbour acetone (guest) dipoles, so that diffuse dipolar interactions may be a major determinant of the overall structure. Note that in the ethanol solvate, full resolution of the disorder in the orientation of the guest was not possible but the molecule does not appear to be aligned in a manner which could be simply described as either 'hydroxyl in' or 'methyl in'. The α and β forms of **5**·Me_2CO have considerable similarity in crystal packing (*e.g.* Figs. 2(b,d)), though one of the subtle differences is that in the β-form, the methyl carbon atom of an ethyl group makes a close approach to an aromatic ring of an adjacent calixarene molecule (C ··· centroid 3.49_4 Å), whereas in the α-form it is the methylene carbon which is close (C ··· centroid 3.55_7 Å). Again, 'bilayer' arrays can be discerned which allow a multitude of approaches of *tert*-butyl methyl groups to one another and to both the outwardly projecting methyl group and O atom of the acetone molecules. The phenyl ring dispositions *vis-à-vis* the O_4 plane in the two molecules of the ethanol solvate are diverse, the C_6/O_4 interplanar dihedral angles ranging between 51.8(1)–64.3(1)°, with a similar range closely parallel in the α-acetone solvate (50.3(1)–63.2(1)°); in the β polymorph, the range is much larger (44.3(1)–69.0(1)°; (Table 1(a)), the unsubstituted rings being rather 'flatter' than the substituted. These variations are accompanied by divergences in the phenolic O ··· O distances (Table 1(b)), the asymmetry correlating with the directionality of the inferred hydrogen bonds (H(111) ··· O(121), H(131) ··· O(141), 1.7 (both); H(211) ··· O(221), H(231) ··· O(241) 1.8 (both) (α-form, all est.); H(11) ··· O(21) 1.8, H(31) ··· O(41) 1.9 Å (β-form) (est.)).

Although it is well known that toluene can be included within a calix[4]arene cavity,[1,19] the toluene of solvation in **C**, **2**·½$C_6H_5CH_3$, is not found to be so. As might have been anticipated, there is an extended hydrogen-bond array in the solid involving the hydroxyethyl substituents and this may be a major factor explaining the distorted *cone* conformations found, this

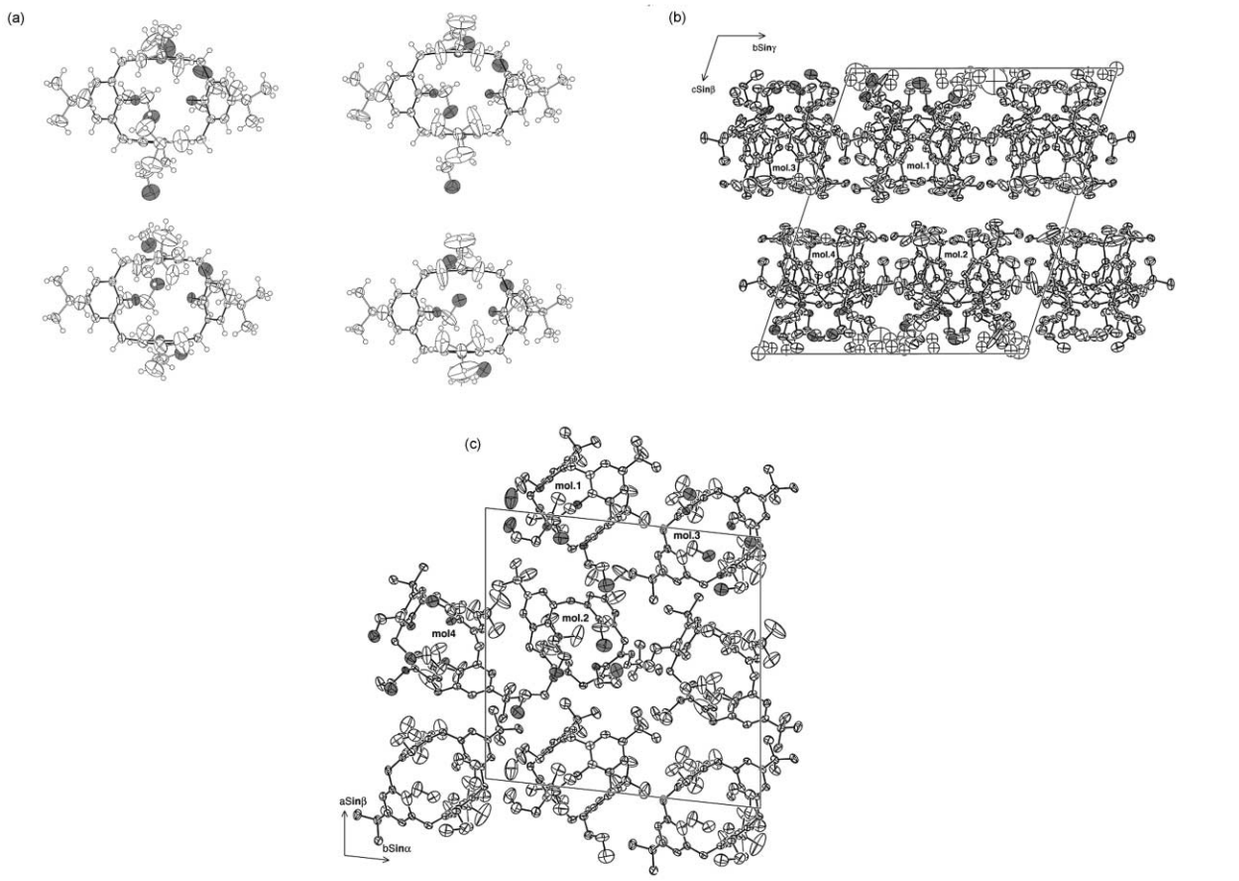

Fig. 3 (a) Individual projections of molecules 1–4 of **2** (making up the single sheet of Fig. 3(b)) down the axis of the calyx in each case. Note that there are two types and that the two examples of each type within the sheets (of Fig. 3(b)) are enantiomers, *viz.* molecules 1,2 (type 1) and molecules 3,4 (type 2). (b) Unit cell contents of **2**·1/2PhCH$_3$, **C**, projected down *a*, showing the (cleavage) plane at $z = ½$, with the sheet of the four molecules depicted in (a), and its image, hydrogen-bonded across $z = 0$, making up a 'sandwich' containing the solvent molecules about that plane. (c) The single sheet of molecules of **2**, between $z = 0$ and $z = ½$, viewed down *c* (molecules 2,4 are inversion relatives of those in the asymmetric unit). Note that all within the same sheet have the same polarity of their calices.

in turn possibly explaining why the calixarene cavities appear unoccupied. The toluene is in fact found to be associated with the hydroxyethyl entities, the essential details of the very complicated solid state structure of **C** being as follows:

(i) The non-hydrogen component of the substrate, four independent molecules in the asymmetric unit, (Fig. 3(a)), is well-defined, disorder being evident in one of the *tert*-butyl substituents (# 34), modelled as rotationally disordered over two sets of sites, occupancies refining to 0.699(8) and complement. Difference map residues were modelled in terms of two molecules of toluene of solvation, also disordered, two sets of sites with occupancies 0.6 and complement, constrained thus in population, comprising the adopted model. Despite the use of low temperature, displacement parameters in this component of the model are pervasively high, with the concomitant limited precision of the determination overall not permitting refinement of hydrogen atoms, a deficiency particularly pertinent to the hydroxylic hydrogen atoms which could not be located definitively.

(ii) The structure is comprised of infinite sandwiches of molecules, the outer layers inversion related about the *ab* plane, about which the 'filling' of disordered solvent is disposed, and across which, intermolecular hydrogen bonds arising from the confronting hydroxylic groupings may be postulated. The presence of toluene in this region of the structure does not appear to be a consequence of any aromatic–aromatic interactions involving the calixarene phenyl rings and, interestingly, both methylene and oxygen atoms of the hydroxyethyl chains come within comparable distances (~3.8 Å) of the toluene ring C atoms, indicating once again that numerous weak attractions may underlie the solvate formation. Successive sandwiches, sheathed at their peripheries by the *tert*-butyl substituents, confront each other about the $z = ½$ plane (Fig. 3(b)); one of the component sheets of the sandwich is shown in Fig. 3(c). Insofar as conformations within the individual molecules are concerned, taking the [O(*n*11)]$_4$ arrays as defining *ad hoc* datum 'planes', we find that in all molecules, ring 1 as defined is 'flatter' than the others, with ring 3 somewhat less flattened, and rings 2 and 4 'upright'; dihedral angles of the C$_6$ planes of rings 1–4 to their associated O$_4$ plane are 40.7(1), 89.6(1), 54.8(1), 88.0(1)° (mol. 1); 40.3(1), 88.8(1), 55.0(1), 86.4(1) (mol. 2); 36.9(1), 89.6(1), 58.9(1), 89.2(1) (mol. 3); 37.9(1), 87.9(1), 58.4(1), 85.1(1)° (mol. 4). Insofar as the hydrogen-bonding of the hydroxyl groups is concerned, O(*nm*1) ··· O(*nm*11) are typically *ca* 2.9–3.0 Å; the torsion angle O–C–C–O is typically *ca* ± 70° for all groupings except those associated with rings 12 and 22 where they are *ca* 180°, so that some internal O–H ··· O interaction may be feasible, albeit unlikely, in all but these latter two cases. Similar or shorter distances are found between groups of the other molecules of the asymmetric unit on the image of the array across the $z = 0$ plane, offering more certain scope for such interactions for all groups.

(iii) Within a given sheet, Fig. 3(c), containing one each of molecules 1–4, all molecular axes through the calices have the same polarity, the hydroxyl face of the sheet and its image directed towards the $z = 0$ face of the cell, entrapping the solvent molecules as the centre of a sandwich about that plane, Fig. 3(b), while the *tert*-butyl groups comprise the 'outer' face of the sheet (and sandwich) confronting those of the next sandwich about $z = ½$. The four independent molecules of the asymmetric unit are set with the same chirality, entailing partitioning between the two sheets. The molecules fall into two

distinct types, one type represented by the pair of molecules 1, 2, the most conspicuous characteristic of which is that the hydroxyl of ring 2 is everted from the calix, while in the pair 3, 4 it lies closer to its projection. In all molecules, the hydroxyl of ring 3 lies beneath bridging carbon 4 (C(*n*4)) in projection, presumably hydrogen bonding intramolecularly to the hydroxyl of ring 4 in molecules 1, 2 (O(*n*313) ··· O(*n*413) 2.89(2), 2.74(1) Å), while the hydroxyl of plane 1 is directed toward the ether oxygen of plane 2 in type 1 (O(*n*113) ··· O(*n*21) 2.771(8), 2.738(9) (*n* = 1,2) and of plane 4 in type 2 (O(*n*113) ··· O(*n*41) 2.766(7), 2.814(9) Å (*n* = 3,4), also the hydroxyl in the latter (··· O(*n*413) 2.685(9), 2.699(9) Å). Hydrogen bonding contacts across the $z = 0$ plane may reasonably be postulated for all hydroxyls of all planes of molecules 1,2; all except those of plane 1 for molecules 3,4, are intermolecular (see above); O(1313) ··· O(3313) 2.721(9) and O(2313) ··· O(4313) 2.735(10) Å within the sheet; and O(1113) ··· O(3213)($2 - x$, $\bar{y}$, $\bar{z}$) 2.83(1), O(1213) ··· O(4413)(x, y, $z - 1$) 2.702(9), O(1413) ··· O(3313)($2 - x$, $\bar{y}$, $\bar{z}$) 3.00(1), O(2113) ··· O(4213)($1 - x$, $1 - y$, $2 - z$) 2.764(8), O(2413) ··· O(4313)-($1 - x$, $1 - y$, $2 - z$) 2.86(1) Å between. It is of interest to note that in the structure of the simple tetrapropyl ether the cone reverts to the symmetrical form, with O_4/C_6 interplanar dihedral angles closely ranged between 63.44(7) and 66.44(7)°.

Although the assumption that chloroform is too large a molecule to be included within a *cone* calix[4]arene cavity has been used as the basis of its use as a solvent for the study of inclusion equilibria,[1a] there are various reasons to expect that it may interact with aromatic molecules and with phenolic calixarenes in particular (see below), so that the observation that **D** deposited from chloroform as an unsolvated species was of especial interest. The structure determination, devoid of the problems accompanying disorder and solvation found for **E**, is nicely precise, enabling refinement of all hydrogen atoms, and a single molecule, devoid of crystallographic symmetry, comprises the asymmetric unit of the structure. The distorted *cone* conformation of the molecule is almost a simple reflection of the 1,3-dialkylation pattern, the dihedral angles of the C_6 aromatic planes to the O_4 'plane' being 86.82(5), 35.10(5), 80.31(5) and 47.41(5)° respectively. Intramolecular hydrogen bonds between the residual phenolic hydrogen atoms and the ethereal oxygen atoms reinforce this near-twofold molecular symmetry; H(11) ··· O(41), H(31) ··· O(21) are 1.92(3), 1.99(3) Å. The *cone* axis is oriented approximately parallel to *b* and the molecules lie in columns, parallel to the *ac* diagonal (Fig. 4). The orientations of the propargyl groups of a given molecule are not identical but, for both, the methylene carbon atoms are involved in close approaches (3.49_5, 3.62_9 Å) to the centroid of an aromatic ring of an adjacent calixarene. These interactions extend throughout a bilayer sheet and may explain why the oxygenated calixarene rims are facing, since there are no approaches indicative of intermolecular hydrogen bonds, which might otherwise explain this orientation. The acetylenic carbon atoms are involved in approaches ~3.8 Å to many other atoms (aliphatic and aromatic) and there are no obvious major reasons for their specific array. Facing *tert*-butylated rims of the calixarenes form the other aspect of the bilayer system but again without any particularly close approaches and certainly none which could be considered to correspond to occupancy of the calixarene cavity by a methyl group from an adjacent molecule (such as appears to give rise to 'hermaphrodite pair' formation in closely related systems[18b]). No structural oddities appear to be associated with the lack of inclusion, a result which is consistent with the belief that inclusion results from rather weak and possibly generalised interactions.

In contrast to **D**, the oxime of partially reduced (H_4) calix-[4]arene, **E**, crystallises from chloroform as a monosolvate, **E** = **8**·$CHCl_3$. Although the ketone from which **E** is derived has a *cone* conformation in the solid state,[5] given the fairly substantial modifications to the calixarene skeleton involved in **E**, it is perhaps unsurprising to find (Fig. 5(a)) that the molecule adopts the (relatively rare) *1,2-alternate* conformation in its crystalline form, so that it cannot be considered to offer a cavity suitable for small-molecule inclusion; interplanar dihedral angles between the aromatic rings are 2/3,4 73.21(8), 44.35(8); 3/4 81.18(8)°. This change in conformation from that of the parent ketone is concomitant with inversion of configuration at one of the ring carbon atoms adjacent to the carbonyl/oxime group, since the methylene substituents are *equatorial–equatorial* in the ketone but *equatorial–axial* in the present oxime (with retention of the chair conformation of the partially reduced ring). Assuming the *axial* orientation to be unfavourable, it may be that this is compensated for by the extensive hydrogen-bonding in **E**, and this appears to partly involve the chloroform solvate molecule. Thus, the chloroform molecule hydrogen-bonds to the oxime oxygen atom *via* a somewhat indirect approach (O(11) ··· H,C(0) 2.60(2), 3.170(3) Å), the nitrogen associated with the latter being hydrogen-bonded to OH(41) (N(11) ··· H,O(41) 1.76(3), 2.644(2) Å). OH(21) is hydrogen-bonded to O(31) (O(31) ··· H,O(21) 1.94(3), 2.758(3) Å). O(41) is also hydrogen-bonded intermolecularly to HO(11) ($\bar{x}$, $\bar{y}$ $1 - z$) (1.90(2), 2.741(2) Å), while O(31), perhaps curiously, is devoid of further associations. Parallel arrays of aromatic rings of the partially reduced calixarene suggest intermolecular stacking to be of some importance, though overlap is not extensive, with the closest atomic approach being 3.294(3) Å of two *meta* carbon atoms and others considerably more distant. The $CHCl_3$ molecule contributes to the extended lattice structure by bridging the calixarene it is linked to by a hydrogen bond to another through Cl ··· π interactions,[20] one Cl ··· aromatic ring centroid separation being 3.49_2 Å. Clearly, the structure of **D** is such that interactions of this nature with $CHCl_3$ may well occur in solution but presumably they are not sufficiently strong to resist replacement by others in the solid state. Interestingly, NMR studies in $CDCl_3$ indicate the persistence of the *1,2-alternate* structure in solution. The ^{1}H NMR assignment of axial (δ 2.80), H(1,6) and equatorial (δ 3.60), H(1,2) methine protons on the reduced ring was straightforward and unambiguous based on the coupling with H(1) and H(2) protons and the difference in coupling constants expected for axial and equatorial protons. From this, assignment for most of the other protons in the NMR spectrum was relatively straightforward using the results of NOESY and COSY 2-D experiments. NOEs observed (Fig. 5(b)) between H(4,5) and one of the C(4) methylene protons and between H(3,3) and the other methylene proton attached to C(4) are consistent with the *1,2-alternate* conformation.

An elegant method of not only enhancing the water solubility of calixarenes but also of assisting the inclusion of anions is the attachment of [Ru(II)cymene]$^{2+}$ units (externally) to the aromatic rings.[9] While the synthesis of the corresponding derivative, **F**, of the major isomer of hexahydrocalix[4]arene proceeds satisfactorily, determination of the crystal structure of the sulfate(bisulfate) shows that inclusion involves neither the anions nor an acetonitrile of solvation but, seemingly, one water molecule (Fig. 6(a)). One half of the formula unit makes up the asymmetric unit of the structure, the cation lying on a crystallographic mirror plane. Unfortunately, the nature of the structure obtained for the presently studied crystal is not such that all hydrogen atoms can be readily located and, in particular, there is considerable uncertainty in regard to acidic proton locations. Thus, it is possible that the (presumptive) oxygen atom within the cavity of this *cone*-form calixarene derivative may be associated with only one proton (hydroxide inclusion) or indeed no protons at all (oxide inclusion). The electric field induced by the proximity to three dipositive centres might well in effect enhance the acidity of a water molecule sufficiently for either situation to arise, though it is then difficult to see why this would not be even more favoured in the previously studied cases of true calix[4]arene derivatives where the total charge on the

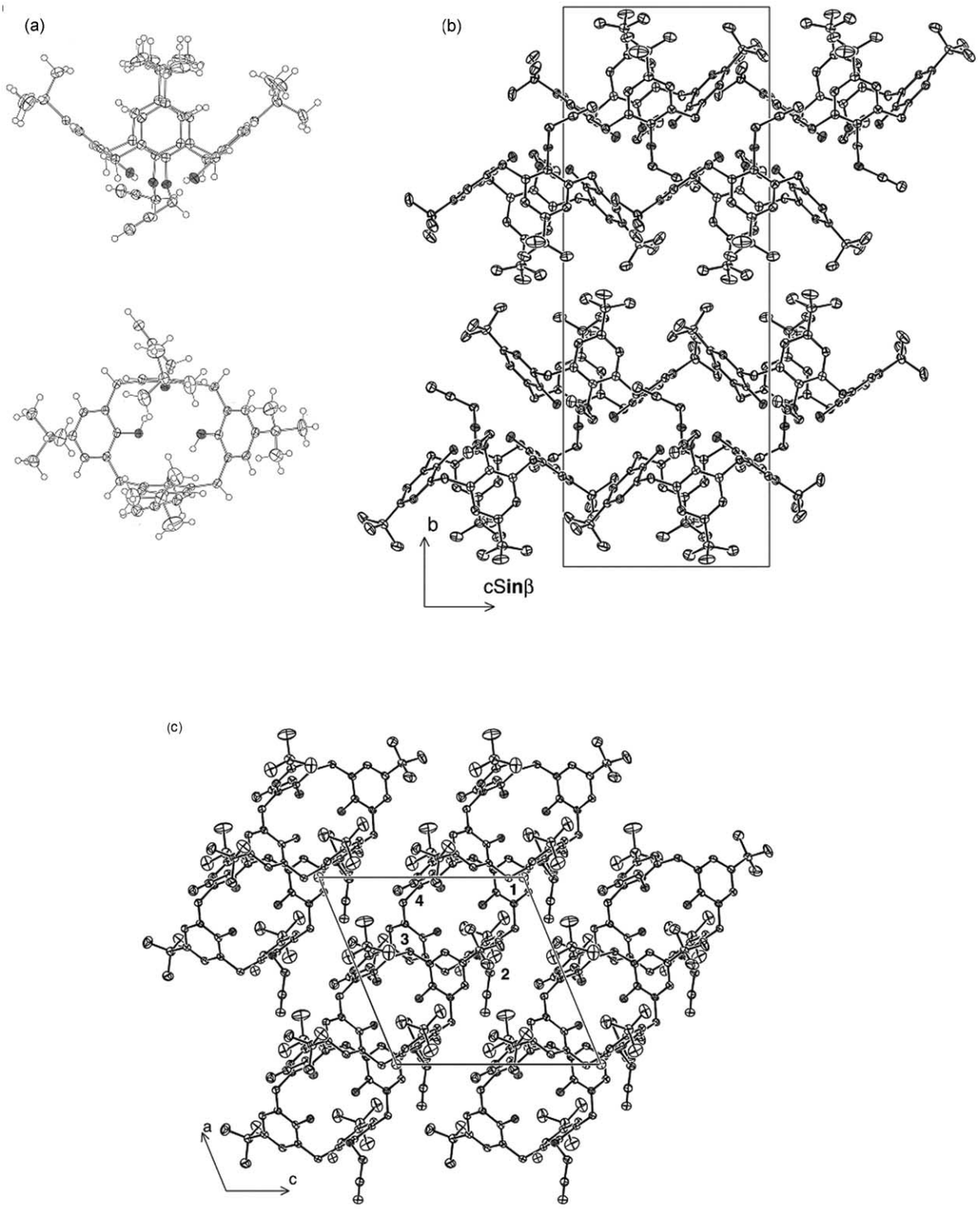

Fig. 4 (a) A single molecule of **6**, **D**, projected (i) normal to and (ii) down its cone axis. (b) Unit cell contents of **6** projected down *a*, showing the partitioning at $y = 0, ½$. (c) The half of the unit cell contents between $y = 0, ½$ projected down *b*, showing the columnar disposition of the molecules.

macrocycle may reach formally 8+. In addition, there are two residues assigned as symmetry-equivalent oxygen fragments (presumed to be of a water molecule or its conjugates) within hydrogen bonding distance of the included oxygen (O(02) ··· O(04),O(04) (x, ½ − y, ½ + z) 2.80(2) Å), suggesting at least some degree of proton association with the included atom. Inclusion of water by calixarenes has been only rarely characterised and then only for charged, water-soluble calixarenes, with OH-π interactions suggested as the cause of inclusion.[21] In the present case, the situation remains obscure even if it is assumed that the included species is truly water, since a p-bound arene unit could be considered susceptible to nucleophilic addition, *viz.*, it may be the oxygen atom which is directly involved in bonding to the arene units of the cavity. Regardless of this issue, it is once again the case that a great variety of attractive interactions may hold the complete lattice assembly together, with hydrogen bonding being particularly extensive. Interestingly, the acetonitrile of solvation appears to play a double bridging role, the nitrogen atom being equidistant (3.43(1) Å) from cymene ring carbon atoms of different complex units, while the methyl carbon also appears to be symmetrically sandwiched between separate (bi)sulfate oxygen atoms (C ··· O 3.46(1) Å). Interplanar dihedral angles between the aromatic rings of the present calyx are (1/2), (2/2′) 74.0(2),

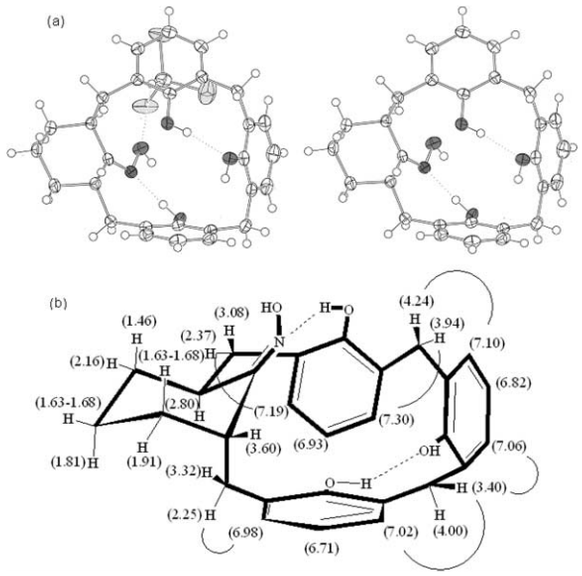

Fig. 5 (a) A single molecule of **8**, with and without the $CHCl_3$ molecule. (b) A representation of the molecule **8** in the *1,2-alternate* conformation,showing assigned ^{1}H chemical shifts and indicating protons involved in significant NOE interactions.

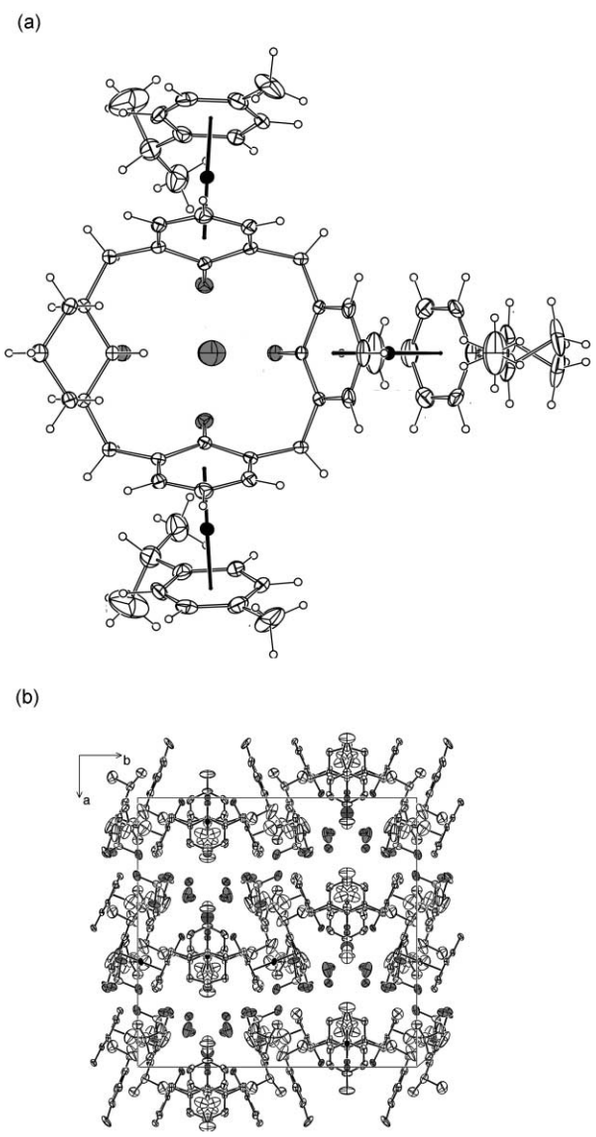

Fig. 6 (a) A single cation of **4**·{Ru(*p*-cymene)}$_3$, projected through the cone, with included water molecule; the crystallographic mirror plane lies horizontal in the page and normal to it. (b) Unit cell contents of **F** projected down *c*.

52.4(2)° (*cf.* the oxime above). O(1) ··· O(2), O(2) ··· O(31) are 2.635(6), 2.876(8) Å. Ru–C_6 (calyx)(centroid), (cymene)-(centroid) distances are: 1.73_7, 1.71_0 (Ru(1); 1.74_4, 1.71_3 Å (Ru(2)). The two sulfates lie in proximity, with O(12) ··· O(21) (the non-disordered oxygen of sulfate 2) ($1 - x$, $1 - y$, $1 - z$) being 2.54(1) Å, a possible location for a hydrogen atom, and O(11) being close to a water molecule oxygen O(11) ··· O(01) ($1 - x$, $1 - y$, $1 - z$) 2.86(1) Å, while O(13) is in the proximity of water molecule fragments (O(13) ··· O(04,05) 2.53(1), 2.84(1) Å). Parallel aromatic plane dispositions appear to be a significant determinant of crystal packing (Fig. 6(b)).

Conclusions

The arrays discussed presently fall within a very extensive context of calixarene structural chemistry and the interpretations offered could equally well be applied to such existing literature (as to some extent they have been [1]). Analyses of complete crystal lattice interactions are difficult and possibly controversial but potentially there is much to be gained in going beyond consideration of 'the molecule'. If inclusion in the solid state is a reflection not just of direct 'host–guest' interactions but also of the full range of associations involved in the formation of a crystal, then logically it might be concluded that this should be true in solution, so that a step beyond the simple argument that to observe inclusion in solution, a solvent too large for the cavity must be used, is to say that the appropriate choice of solvent may also influence the orientation of any included guest and the strength of host–guest binding (through, for example, 'external' influence on the 'internal' π-donor strength of a cavity). Solvent effects, so important in many aspects of calixarene synthesis,[11] may well yield to a detailed interpretation!

Acknowledgements

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