Design, Synthesis, and Comparison of Crystal, Solution, and Calculated Structures within a New Family of Cavitands

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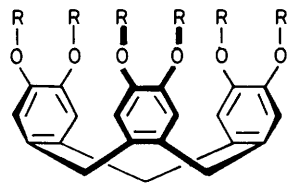
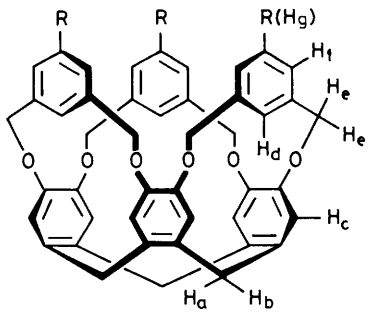
A new family of cavitands based on [1.1.1]orthocyclophane has been designed and synthesized, one member of which provided crystal, solution, and calculated structures that are almost identical.

Structural recognition in complexation depends on stereoelectronically complementary binding sites in hosts and guests.[1] Extensive studies have demonstrated the importance of preorganization of each complexing partner to their free energies of association.[2] To act co-operatively, binding sites must converge from the concave surface of a host to meet divergent binding sites of guests. Very few of the over six million organic compounds that have been synthesized possess enforced concave surfaces of molecular dimensions, and thus qualify as cavitands.[3]

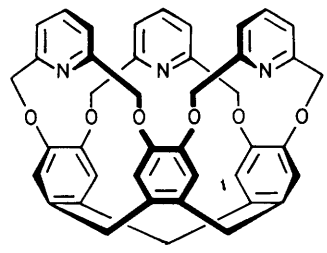
This paper reports six members of a new family of cavitands that are easy to synthesize and modify. They are prepared from cyclotriveratrylene[4] (**1**), and provide a simple approach to a variety of highly structured and potentially useful hosts. Demethylation of (**1**) gives (**2**), ordinary derivatives of which shell-invert rapidly on the human time scale at 60—90 °C.[5] To block this process and increase the expanse of the concave surface of (**2**), compounds (**3**)—(**8**) were designed with the help of Corey–Pauling–Koltun (CPK) molecular models. In models, three five- or six-atom bridges were found to span the three pairs of the closer transannularly located oxygens. If three or more of these atoms are part of a rigid aromatic or heterocyclic ring system, reactions used to construct the bridges should be free of competing ring closures linking the



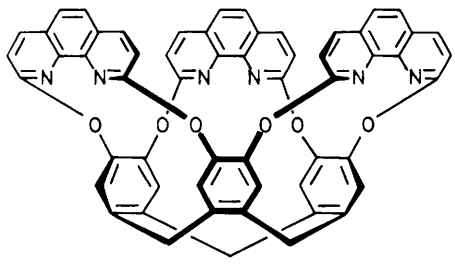
(**1**) R = Me
(**2**) R = H



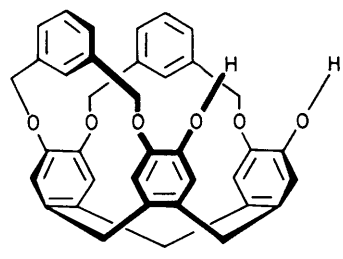
(**3**) R = H
(**4**) R = Me_3C
(**5**) R = Br



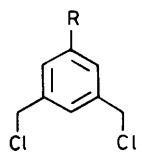
(**6**)



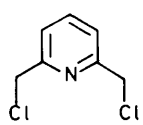
(**7**)



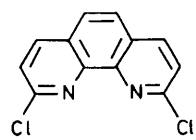
(**8**)



(**9**) R = H
(**10**) R = Me_3C
(**11**) R = Br



(**12**)



(**13**)

two oxygens of the same catechol unit. This expectation was realized in the syntheses of (**3**)—(**8**).

Treatment of dry hexol (**2**) with dichlorides (**9**)—(**13**) in dry $HCONMe_2$ or Me_2SO in the presence of Cs_2CO_3 (Kellogg's macroring closure)[6] gave corresponding cavitands (**3**)—(**7**),† in which three new 14- or 15-membered rings were introduced into the systems. In a preliminary and incomplete reaction between (**2**) and 1,3-$C_6H_4(CH_2Br)_2$ (Cs_2CO_3–$HCONMe_2$), a 2% yield of (**3**) and a 15% of (**8**) were obtained, suggesting that the first two macroring closures occurred faster than the third. Thus cavitands with mixed bridges can undoubtedly be assembled. The crystal structure of (**3**)·CH_2Cl_2 was determined,‡ a stereodrawing of which is given in Figure 1, in which the viewer looks *into the cavity* from its open face. The host possesses a mirror plane destroyed by the CH_2Cl_2 guest, whose atoms are distributed on either side of the mirror plane with equal probability to give, in effect, enantiomeric structures, only one of which is shown in Figure 1. One Cl and the CH_2 group of the guest are deep in the cavity, and the other Cl extends upward, oriented so that the CH_2–Cl group contacts one of the upward-tilted aryl groups of the host. The top of that Cl atom extends slightly higher than the cavity both in (**3**)·CH_2Cl_2 (Figure 1) and in a CPK model of it.

Molecular model (CPK) examination of (**3**) indicated that while the [1.1.1]orthocyclophane and six attached oxygens of the cavitand are essentially rigid, the 1,3-xylyl bridges are conformationally very mobile. The three phenyls can orient upward (Pu) from the cavity bottom (see phenyls at 4 and 8 o'clock in Figure 1) or outward (Po) from the cavity top (see phenyl at 12 o'clock in Figure 1). The methylene hydrogens of the 1,3-xylyl bridges can orient upward (Mu) from the cavity bottom (see CH_2 groups at 11 and 1 o'clock in Figure 1), or outward (Mo) from the cavity middle (see CH_2 groups at 3, 5, 7, and 9 o'clock in Figure 1). Furthermore, MoPuMo and

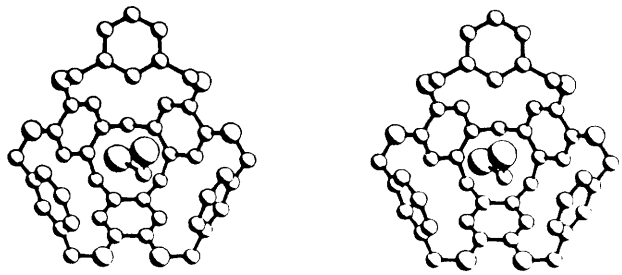


Figure 1. Crystal structure of (**3**)·CH_2Cl_2.

MuPoMu arrangements appear much less strained than MuPuMu, and somewhat less strained than MoPoMo arrangements. Notice that Figure 1 shows two MoPuMo conformations and one MuPoMu conformation, signified by the notation $(MoPuMo)_2(MuPoMu)$. In models of the four conformations with C_{3v} symmetry, $(MoPuMo)_3$ and $(MuPoMu)_3$ seem more stable than either $(MoPoMo)_3$ or $(MuPuMu)_3$. Likewise, conformations with C_3 symmetry, $(MuPuMo)_3$ or $(MuPoMo)_3$, appear more stable than either $(MoPoMo)_3$ or $(MuPuMu)_3$. Any combination of CH_2 and phenyl orientations seems unstrained as long as PuMuMuPu, PuMuMuPo, MoPoMo, or MuPuMu sequences are avoided. The cavity volumes decrease in the order $(MuPuMo)_3 > (MoPuMo)_3 > (MuPoMu)_3$.

Application of molecular mechanical calculations to the enthalpic stability of sample conformations provided the following results§ (kcal mol^{-1}; cal = 4.184 J): $(MoPuMo)_3$, 70.4; same host·CH_2Cl_2, 59.2; $(MuPoMu)_3$, 76.3; $(MoPoMo)_3$, 95.5; $(MuPuMo)_3$, 72.9; same host·CH_2Cl_2, 67.8; $(MuPoMo)_3$, 78.8; $(MoPuMo)_2(MoPoMo)$, 81.2; $(MoPuMo)_2(MuPoMu)$, 73.1; same host·CH_2Cl_2, 59.4. The calculations are performed using a dielectric constant ε of 1.5 for the hosts with no solvent and of 9 (ε for dichloromethane) for the hosts with dichloromethane inside the cavity. Notice that the host involved with the last two values is the one found in the crystal structure in Figure 1. The values suggest that this host with a CH_2Cl_2 inside is 13.7 kcal mol^{-1} more stable than the free host. The drawing in Figure 2(a) corresponds to the *host structure* calculated for $(MoPuMo)_2(MuPoMu)$·CH_2Cl_2 viewed from the side of the two Pu aryls. The drawing in Figure 2(b) corresponds to the *host structure* of the crystal structure of (**3**)·CH_2Cl_2 similarly viewed. The agreement between Figure 2(a) and (b) is both visible and dramatic. Thus the techniques of molecular design, synthesis, crystal structure determination, and molecular mechanics merge to provide coherence to inclusion complex (**3**)·CH_2Cl_2.

The ^1H n.m.r. spectra (200 MHz) of (**3**)—(**7**) in CD_2Cl_2 all indicate nonequivalence of the H_a and H_b chemical shifts in compatibility with the blocking of the [1.1.1]orthocyclophane ring inversion by the bridges. The multiplicity of each proton was compatible with either the compounds having C_{3v} symmetry, or with their conformations equilibrating rapidly to

† New compounds (**3**)—(**8**) all gave expected 200 MHz ^1H n.m.r. spectra, M^+ mass spectral ions, elemental analyses within 0.30% (usually as solvates), m.p. >360 °C (usually), and the following yields in the ring closures: (**3**)·CH_2Cl_2 (42%); (**4**)·$1.5H_2O$ (5%), m.p. 153 °C; (**5**)·$(CH_2)_4O$ (38%); (**6**) (25%); (**7**)·CH_2Cl_2 (17%); (**8**)·$HCONMe_2$ (15%). Conditions for the critical macroring closure are exemplified in the synthesis of (**5**). A solution of very dry (**2**) (0.792 g) and (**11**) (1.81 g) in very pure, dry, and degassed Me_2SO (50 ml) was added by syringe pump over 28 h to a fine suspension of Cs_2CO_3 (11.9 g) in pure Me_2SO (150 ml) stirred under Ar at 75 °C. After stirring at 75 °C for an additional 24 h, the mixture was evaporated *in vacuo*. The residue was shaken with H_2O and $CHCl_3$, and the organic layer was dried ($MgSO_4$) and evaporated to give a residue which was submitted to chromatography (medium pressure) on silica gel with $CHCl_3$–MeOH as the mobile phase to give 608 mg of (**5**)·$CHCl_3$ (38%), m.p. >360 °C. This material was freed of $CHCl_3$ by evaporating repeatedly dry $(CH_2)_4O$ [100 ml; $(CH_2)_4O$ = tetrahydrofuran] from solutions of (**5**)·$CHCl_3$ (700 mg) in dry $(CH_2)_4O$ to give 670 mg (38%) of (**5**)·$(CH_2)_4O$, mass spectrum (70 eV) *m/z* 909, M^+ (100%); m.p. >360 °C; ^1H n.m.r. (CD_2Cl_2, 200 MHz) δ 1.82 [m, 4H, $(CH_2)_4O$], 3.24 (d, 3H, *J* 14 Hz, $ArCH_2Ar$), 3.69 [m, 4H, $(CH_2)_4O$], 4.44 (d, 3H, *J* 14 Hz, $ArCH_2Ar$), 4.99 (d, 6H, *J* 14 Hz, $ArCH_2O$), 5.09 (d, 6H, *J* 14 Hz, $ArCH_2O$), 6.52 [s, 6H, ArH of $(ArCH_2)_3$], 7.31 (s, 3H, BrArH), and 7.49 (s, 6H, BrArH).

‡ *Crystal data* for compound (**3**)·CH_2Cl_2, small, colourless platelets from CH_2Cl_2–cyclohexane, orthorhombic, space group *Pcmn* (standard setting *Pnma*), $a = 12.676(1)$, $b = 16.347(1)$, $c = 19.024(1)$ Å, $U = 3942$ Å^3, $Z = 4$ (eight half molecules related by mirror at $y = 1/4$, disordered CH_2Cl_2). The crystal was examined on a modified Picker FACS-1 diffractometer, Mo-K_α radiation, at 128 K. The structure was determined by direct methods. Refinement of 151 parameters [2002 reflections with $I > 3\sigma(I)$] led to $R = 0.107$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ The calculations used Allinger's MM2 program with the 1977 parameters (U. Burkert and N. L. Allinger, 'Molecular Mechanics,' American Chemical Society, Washington, D.C., 1982) augmented with aromatic ring parameters of Beckhaus (H.-D. Beckhaus, *Chem. Ber.*, 1983, **116**, 86), and C_{Ar}–C_{Ar}–O–C(sp^3) torsional parameters defined to reproduce *ab initio* molecular orbital calculations on the barrier to rotation of anisole. The C_{Ar}–C_{Ar}–C(sp^3)–O torsional constants were set equal to the allyl alcohol torsional parameters derived by Spellmeyer (D. C. Spellmeyer and K. N. Houk, in preparation).

provide a C_{3v} time-averaged conformation. Molecular models indicate that (7) possesses enforced C_{3v} symmetry, whereas the others undoubtedly average to give the appearance of this symmetry. The temperature dependence of the spectra of (3) and (4) in CD_2Cl_2 from 180 to 300 K and of (3) in $(CD_3)_2SO$ from 300 to 400 K were determined [(4) was insoluble in $(CD_3)_2SO$]. At 180 K the peaks started to broaden, but the multiplicities did not change. Thus the different conformations equilibrate very rapidly on the ^1H n.m.r. time scale.¶

A molecular model of the $(MoPuMo)_3$ conformation for (4) can hardly be constructed because of repulsions between the three converging Me_3C groups. However, those for $(MoPuMo)_2(MuPoMu)$ with either CH_2Cl_2 or Me_2SO enclosed in the cavity appear unstrained. The ^1H n.m.r. temperature and solvent dependence data, coupled with the molecular mechanical calculations and model examination, suggest that (3) and (4) have the following solution structures. At 180 K, (3)·CD_2Cl_2 exists as $(MoPuMo)_3\cdot CD_2Cl_2$, which goes toward $(MoPuMo)_2(MuPoMu)\cdot CH_2Cl_2$ at 300 K. At 300 K, (3)·$(CD_3)_2SO$ exists largely as $(MoPuMo)_3\cdot(CD_3)_2SO$ or $(MoPuMo)_2(MuPoMu)\cdot(CD_3)_2SO$, and as the temperature is raised to 400 K, these go towards $(MoPuMo)(MuPoMu)_2\cdot(CD_3)_2SO$. At 180 K, (4)·$CD_2Cl_2$ exists as $(MoPuMo)_2(MuPoMu)\cdot CD_2Cl_2$, which at 300 K becomes richer in $(MoPuMo)(MuPoMu)_2\cdot CD_2Cl_2$. The effects of temperature and solvent changes on the gross structures of these partially conformationally mobile caviplexes indicate further that entropy and solvation play important roles in determining the structures of complexes.[7]

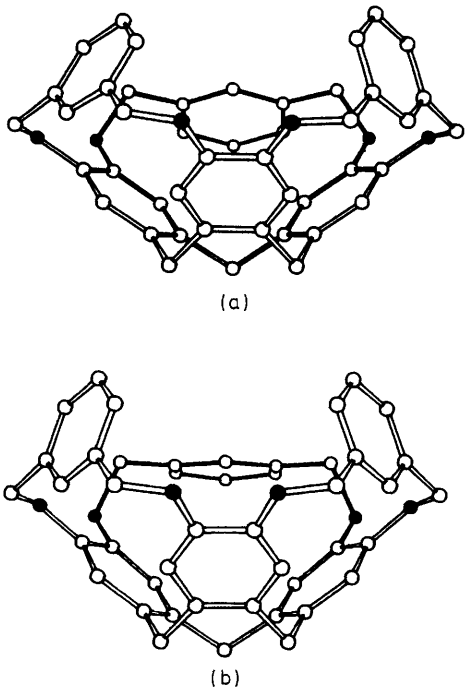


Figure 2. Comparison between (a) calculated structure and (b) crystal structure of the host in $(MoPuMo)_2(MuPoMu)\cdot CH_2Cl_2$.

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¶ Facts and tentative conclusions about the dependencies of conformations on temperature and solvent are as follows. (i) Resonances due to H_a, H_b, and H_c changed at most by ~0.12 p.p.m. as temperature, solvent, and host were changed. The carbons to which H_a and H_b are attached are rigidly held in place, and that of H_c moves relatively little in possible conformational changes to produce an almost invariant averaged signal for its protons. (ii) Resonances in (3) due to H_c moved upfield by ~0.35 p.p.m. as the temperature was increased from 180 to 400 K, corrected for a 0.25 movement downfield when $(CD_3)_2SO$ was substituted for CD_2Cl_2 at 300 K. Molecular models suggest that MuPoMu conformations are more shielding of H_c than MoPuMo conformations. Thus raising the temperature favours Po at the expense of Pu conformations, but changing the solvent from CD_2Cl_2 to $(CD_3)_2SO$ favours Pu conformations at the expense of Po. The latter conclusion correlates with the fact that $(MoPuMo)_3$ has a larger cavity [than $(MuPoMu)_3$] and $(CD_3)_2SO$ has larger special requirements than CH_2Cl_2 in models. (iii) Signals for H_f and H_g in (3) moved by only 0.1 p.p.m. downfield with heating and very little with solvent change. Those for H_f and for $C(CH_3)$ in (4) moved downfield by ~0.22 p.p.m. on warming in CD_2Cl_2 from 180 to 300 K. Since Pu appears more shielding of H_f than Po, this movement supports the conclusions of (ii). (iv) The signal for H_d was the most sensitive to solvent and temperature changes. At 180 K, δ values for (3) and (4) were almost identical, but when heated to 300 K, this signal of (3) moved 0.1 p.p.m. upfield while that of (4) moved 0.3 p.p.m. upfield. In changing solvents from CD_2Cl_2 to $(CD_3)_2SO$, H_d for (3) moved 0.5 p.p.m. downfield, but in going from 300 to 400 K in this solvent, it moved 0.35 p.p.m. upfield. Models of (3) and (4) suggest H_d is highly deshielded in Pu conformations [δ ~8 for (3) in $(CD_3)_2SO$ at 300 K] but distant from a magnetic environment in Po conformations. These facts likewise support the conclusions reached under (ii).

References

1 E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 2564.
2 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1039; D. J. Cram, K. D. Stewart, I. Goldberg, and K. N. Trueblood, *J. Am. Chem. Soc.*, 1985, **107**, 2574.
3 R. C. Helgeson, M. Lauer, and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1982, 101; D. J. Cram, *Science*, 1983, **219**, 1177.
4 G. M. Robinson, *J. Chem. Soc.*, 1915, 267; A. S. Linsey, *ibid.*, 1965, 1685.
5 A. Lüttringhaus and K. C. Peters, *Angew Chem., Int. Ed. Engl.*, 1966, **5**, 593; A. Collet and J. Gabard, *J. Org. Chem.*, 1980, **45**, 5400; A. Collet and G. Gottarelli, *J. Am. Chem. Soc.*, 1981, **103**, 206.
6 D. Piepers and R. M. Kellogg, *J. Chem. Soc.*, 1978, 383.
7 J. R. Moran, S. Karbach, and D. J. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 5826.