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Synthesis, Binding Properties and Crystal Structure of a Hemicarcerand Containing Four Pentamethylenedioxy Groups Spanning Two Bowls

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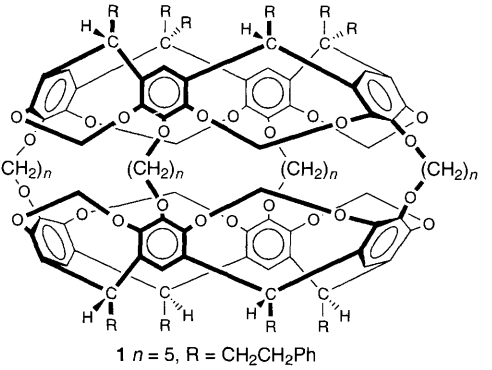
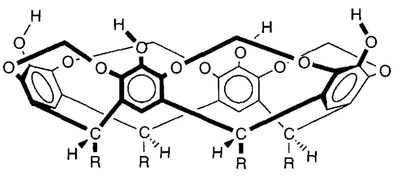
Hemicarcerand **1**, whose synthesis from two tetrol bowls and four pentamethylene ditosylate molecules was templated by veratrole, was found to bind in solution (one-to-one) eighteen different guests; the crystal structure of 1⊙4MeCN is centrosymmetric; hemicarcerand **2**, containing four hexamethylenedioxy groups, is also discussed.

We report here the structural recognition properties in binding organic molecules as guests incarcerated in the interior of hemicarcerands **1**[†,‡] and **2**.[†,‡] The analogue of **1**, host **4**,[1] was found to incarcerate the largest number of guest compounds through constrictive binding of any hemicarcerands we have yet examined. The portals of **4** through which guests must pass during complexation or decomplexation are 26-membered rings, whereas those of **1** are 28-membered, and those of **2** and **3**[2] are 30-membered. Important questions about constraints offered to passage of guests through portals of varying size and shape have never before been subject to a systematic study, of which this report is part.

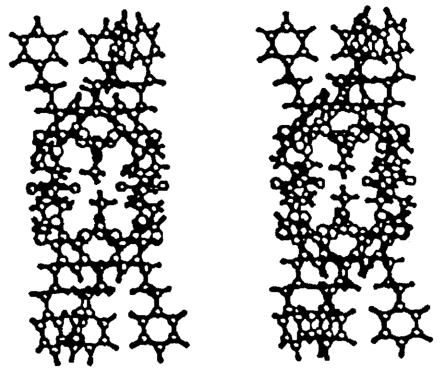
A crystal structure of **1**⊙4MeCN was determined.[‡,§] The complex possesses a point of inversion, the symmetry element most common to carcerands, hemicarcerands and their complexes.[3] Stereoview A shows that two of the MeCN molecules are completely within the cavity with their nitrogen atoms occupying the two polar regions, and their methyl groups the equatorial region. The methyl hydrogen atoms have been included in their calculated positions. The nitrogen atoms were identified by the short 1.27(4) Å distance to the attached carbon, which contrasts with the carbon-to-methyl distance of 1.42(4) Å. These two guests are aligned roughly parallel to their respective proximate ArO groups. This arrangement allows the dipoles of the MeCN guests to compensate for the dipoles of their proximate 1,2,3-oxygen-substituted aryl groups. In stereoview B the observer is looking down the roughly colinear axes of the two portal-occupying MeCN guests. The long interatomic distances of 1.61 and 1.76 Å in these guests in the crystal indicate some disorder along their linear axes, and prevent identification of N and Me. In stereoview C, the two sets of four ArO oxygens are connected by lines, and only the guests and the bridges of the host are included. This view as well as view A shows that the two polar regions are little rotated with respect to one another (2°), but that the nearly planar (±0.04 Å) and parallel (5.59 Å apart) oxygen planes have slipped from having a common (normal) polar axis by 3.02 Å. The latter feature is also visible in B. In C, the four guest atoms nearest the cavity centre are coplanar, but the plane follows the tilt of the cavity, visible in B.



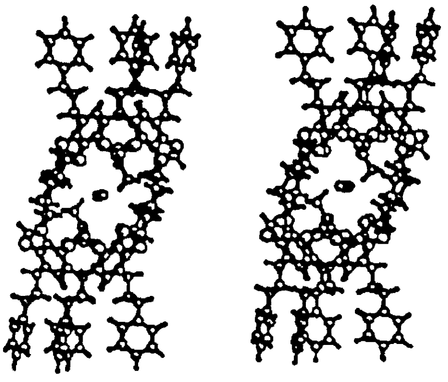
1 $n = 5$, R = CH_2CH_2Ph
2 $n = 6$, R = CH_2CH_2Ph
3 $n = 6$, R = $(CH_2)_4Me$
4 $n = 4$, R = CH_2CH_2Ph



5 R = CH_2CH_2Ph



1⊙4MeCN, stereoview A of crystal structure



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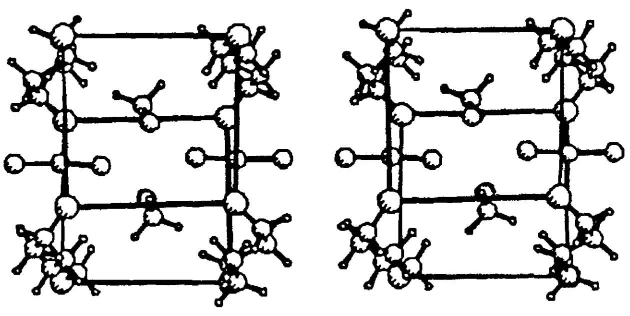

1⊙4MeCN, stereoview C of crystal structure

Host **1** and guests **6–23** formed[‡] one-to-one complexes when heated neat or in Ph_2O at 160 °C or above, which were stable enough for isolation and full characterization.[†] Deviations from the standard preparations[‡] are noted (parenthetically) close to the structures. As with the complexes of host **4**, the inner-facing protons of the eight intrahemispheric OCH_2O bridges of the host were the most sensitive to guest presence, moving from δ 4.40 for uncomplexed **1** upfield by as much as 0.29 ppm in the ^1H NMR spectrum ($CDCl_3$, 500 MHz) of **1⊙6**, **1⊙7**, **1⊙8** and **1⊙21** to downfield only in that of **1⊙21** (0.14) and of **1⊙22** (0.04). The two sets of doublets for this proton for **1⊙21** indicate that the guest cannot rotate around its equatorial axis rapidly on the ^1H NMR time scale at 25 °C. The $\Delta\delta$ (upfield) for guest protons due to complexation ranged from 0.31 ppm for the 5-Ar-*H* of **1⊙12** to the 4.10 ppm value for 1-OMe and 3-OMe protons of the same complex, while $\Delta\delta$ for the 2-OMe proton signal was 0.54 ppm. Corey–Pauling–Koltun (CPK) models of **1⊙12** indicate the 1-OMe and 3-OMe protons occupy the aryl-composed polar regions of the host, while the 2-OMe protons are proximate to an $O(CH_2)_5O$ bridge. As observed with other hosts, as the $O(CH_2)_nO$ bridging groups become longer with respect to the lengths of the guests, the guest $\Delta\delta$ values decrease, so that for most of these complexes of **1** the values are 1–2 ppm.

Attempts to isolate complexes of **1** using the above procedure failed when the potential guests were as follows: coumarin; quadricyclane; norbornadiene; *endo*-2-norbornanol; bicyclo[3.2.1]oct-2-ene; 1,3-$(MeO)_2C_6H_4$; 1,4-$(MeO)_2C_6H_4$; 1,4-$Et_2C_6H_4$; 4-MeC_6H_4Et; 4-IC_6H_4OMe; 1,3,5-$Br_3C_6H_3$; 2,4,6-$Br_3C_6H_2OH$; 2,4,6-$Br_3C_6H_2NH_2$; 2,4,6-$I_3C_6H_2OH$; aspirin; [2.2]paracyclophane; ferrocene; *N*-formylmorpholine and $Br_2CHCHBr_2$ (110 °C, higher temperatures give decomposition). Comparisons between these non-guests and **6–23** show that **1** possesses both gross and subtle structural recognition properties in selecting guests with which it forms complexes stable enough for isolation. Generally, complexes of **4** were much more kinetically stable in solution than those of **1**.

The addition of veratrole in the shell-closure reaction raised the yield of **1** from *ca.* 20 to 51%, probably due to a templating effect.[4] A similar addition in the synthesis of **2** raised the yield from 18 to 27%. The larger host, **2**, formed **2⊙G** complexes that survived isolation only with 2-adamantanone,[†] 12-crown-4 and 15-crown-5, the latter two complexes being characterised only by ^1H NMR and FAB-MS spectra. Attempts to form isolable complexes of **2** failed with the following guests: norbornene; norbornanone; bicyclo[2.2.2]oct-2-ene; norbornane; bicyclo[3.2.1]oct-2-ene; camphor; adamantane; 1-adamantylamine; 1-adamantylcarboxylic acid; 1,3-dimethyladamantane; 1-adamantanol; 2-adamantanol; 1,2,3-$(MeO)_3C_6H_3$; *p,p'*-biphenol; 4-PhC_6H_4OH; 4-PhC_6H_4OAc; tributyl phosphate; triphenyltriazine; triphenylphosphine; tripiperidinophosphine oxide; ferrocene; 18-crown-6 and [2.2]paracyclophane. As the interhemisphere-connecting chains get longer, they become more adaptable to guest entry and departure. Many of these possible guests undoubtedly complexed **2**, but the guest departure rates in solution were too high to allow isolation of the complexes.


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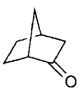
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(180 °C)
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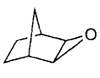
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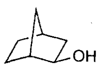
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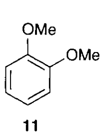
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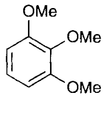
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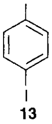
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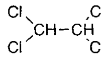
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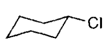
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(neat, 1 h heating)
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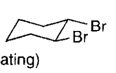
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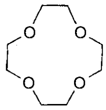
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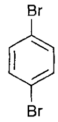
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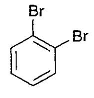
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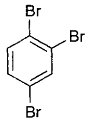
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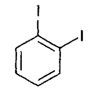
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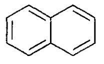
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Footnotes

[†] These new compounds gave C and H elementary analyses within 0.35% of theory, M^+ *m/z* signals of substantial intensity in their FAB MS and ^1H NMR spectra consistent with their structures.

[‡] Hemicarcerand **1** was synthesised from tetrol **5** and $TsO(CH_2)_5OTs$ as follows: **5** (1 mmol) with 4 mmol of $TsO(CH_2)_5OTs$ in *N*-methylpyrrolidinone–11% *v/v* veratrole, medium dilution, argon, stirred at 25 °C for 8 h, an additional 4 mmol of $TsO(CH_2)_5OTs$ added, 25 °C for 8 h, 65 °C for 24 h, 100 °C for 8 h. The cooled solution was evaporated (vacuum), the residue mixed with $CHCl_3$, filtered from salts, the solvent was evaporated and the product was precipitated with MeOH to give 10% **1**⊙1,2-$(MeO)_2C_6H_4$–90% **1**(^1H NMR). This material was heated at 150 °C for 14 h in Ph_2O to give after silica gel chromatography (2% EtOAc–$CHCl_3$), **1** (42–51%). In the absence of veratrole, the yield was *ca.* 20%. Host **2**[†] was similarly prepared in 20% yield except $TsO(CH_2)_6OTs$ in Me_2CONMe or in Me_2SO was used, and no complexed product was detected. A synthesis of **3**, an analogue of **2**, has been reported (ref. 2).

Complexations of **1** and **2** (10–20 mg) were carried out in the presence of 100- to 200-fold excesses of potential guests neat (0.2 to 1.0 mL of Ph_2O was added when needed for homogeneity) at 150–160 °C (unless otherwise indicated) for 2–4 d under argon. The cooled melt was drowned with MeOH, and the precipitate was purified by preparative silica-gel chromatography.

[§] The crystal structure of **1**⊙4MeCN (crystallised from $CHCl_3$–$PhNO_2$–MeOH–MeCN–pentane, determined at 25 °C) belongs to the triclinic space group $P\bar{1}$, a = 18.207(4), b = 21.478(4), c = 11.911(2) Å, α = 101.56(2), β = 102.57(2), γ = 105.16(2)°, V = 4221(2) Å^3, Z = 19,650 unique reflections, 4307 > $3\sigma(I)$, $2\theta_{max}$ = 105°, and was refined to R = 0.15 (SHELX76[5]). No atoms were refined with anisotropy. All H were placed in calculated positions. The phenyl rings of the $(CH_2)_2Ph$ 'feet' were refined as rigid groups, angles 120°, C–H = 1.08 Å. Refinement was carried out in 2 blocks, 298 hemicarcerand parameters and 116 solvent parameters. Solvent molecules in addition to the guests (per host molecule) are as follows: 4 MeCN (H atoms included for 2 of these), 10 water oxygen molecules (H atoms not included), and 4 unidentified solvent fragments.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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