Binding Properties and Crystal Structure of a Hemicarcerand Containing Four Diethylene Glycol Units Connecting Two Bowls

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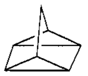
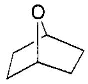
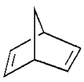
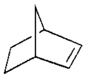
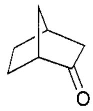
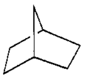
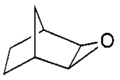
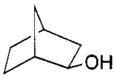
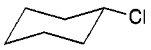
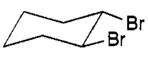
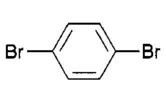
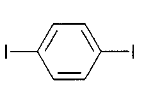
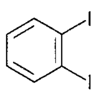
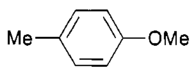
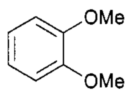
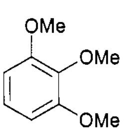
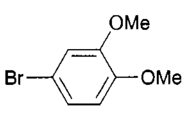
A hemicarcerand composed of two bowls attached at their rims with four $O(CH_2CH_2O)_2$ units, when heated with 22 guests containing 6–12 rigidly-arranged non-hydrogen atoms, formed 22 isolable, characterized hemicarceplexes, but failed to form isolable complexes with 34 other potential guests of the same molecular size range.

Host **1**† was synthesized‡,[1] in 40–47% yields from tetrol **2**[2] and 8 moles of $(TsOCH_2CH_2)_2O$, and was free of guest (C + H analysis, MS FAB and ^1H NMR spectra). When **1** was heated to 100–190 °C with very large excesses of potential guests, neat or in Ph_2O, complexes were formed, isolated and characterized. Table 1 shows the structures of 22 guests that formed isolable complexes, the completeness of their characterizations, the temperatures of their formations, their yields, their stabilities, and the 500 MHz ^1H NMR signal upfield shift ranges of the guest's protons due to complexation. The signal of the inward-facing protons of the host's 8 OCH_2O groups at δ 4.26 (broad doublet at 25 °C in $CDCl_3$) sharpened in the complexes and moved upfield by as much as 0.09 ppm (2-norbornanone as guest), or downfield by as much as 0.25 ppm ($HOCH_2CHBrCHBrCH_2OH$).

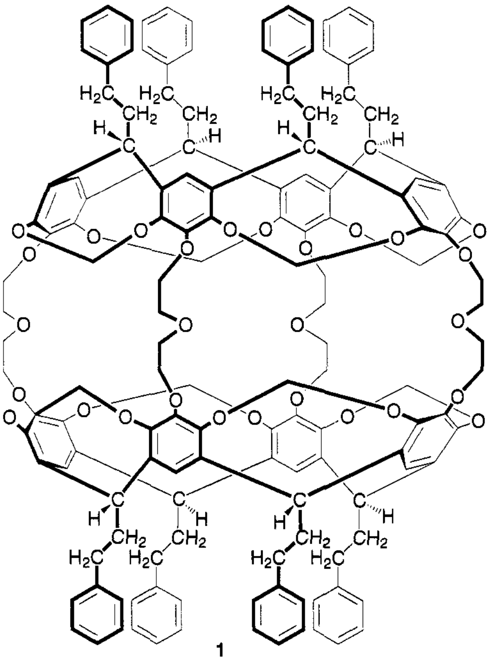
Potential guests that failed under similar conditions to provide isolable complexes of **1** follow: $C(CH_2OH)_4$; $C(CH_2Cl)_4$; Me_3CI; $(MeOCH_2)_3CH$; ribose; deoxyribose; *exo*-norbornylchloride; *exo*-3-chloronorbornanone; camphor; 2-oxo[1.2.3]bicyclooctane; 1,4-diaza[2.2.2]bicyclooctane; [2.2.2]bicyclooctane; adamantane; 1,3,5-$(HO)_3C_6H_3$; 1,2-$Me_2C_6H_4$; 2-MeC_6H_4OMe; 3-MeC_6H_4OMe; 1,2-$Et_2C_6H_4$; 1,4-$Et_2C_6H_4$; 1,4-$(MeO)_2C_6H_4$; 2,3-$(HO)_2C_6H_3Me$; 1,2-$(EtO)_2C_6H_4$; 4-IC_6H_4OMe; 1,3-$(MeO)_2C_6H_4$; 1,2,4-$Cl_3C_6H_3$; 1,2,4-$Br_3C_6H_3$; C_6H_5I; C_6H_5OMe; C_6H_5Me; 1,4-$Me_2C_6H_4$; $C_6H_5NH_2$; MeCHClCHClMe; $MeCOCH_2COMe$; and Me_2NCOMe.

These results coupled with Corey–Pauling–Koltun (CPK) molecular model examinations suggest there are three classes of guests. Those of the first class, which formed isolable

Table 1 Guests complexed by Host **1**, complexation temperature, isolated yield, stability and upfield proton shift ranges (ppm) in ^1H NMR spectra

 **3**;† 100 °C; 60%; $t_{1/2}$, 20 min in $CDCl_3$ at 60 °C; Δδ 1.55–1.96	 **4**;† 150 °C; >90%; $t_{1/2}$, 10 h in $CDCl_3$ at 60 °C; Δδ 1.38–2.77	 **5**;† 100 °C; >90%; $t_{1/2}$, 30 min in $CDCl_3$ at 60 °C; Δδ 1.51–2.19	 **6**;† 100 °C; >80%; $t_{1/2}$, 11 h in $CDCl_3$ at 60 °C; Δδ 1.39–2.25	 **7**;† 100 °C; >70%; decomplexed 10% in $CDCl_3$ in 3d; Δδ 1.48–1.92
 **8**;† 190 °C; >50%; stable in $C_6D_5NO_2$ at 100 °C; Δδ 1.48–1.92	 **9**;† 150 °C; 60%; stable in $CDCl_3$ at 25 °C; Δδ 1.39–2.03	 **10**;† 190 °C; >60%; stable in $CDCl_3$ at 25 °C; Δδ 0.86–1.92	$CHCl_2CHCl_2$ **11**;† 100 °C; >90%; $t_{1/2}$, 1.1 h in *o*- $(CD_3)_2C_6D_4$ at 130 °C; Δδ 1.10	(±)MeCHBrCHBrMe **12**;§ 150 °C; >90%; $t_{1/2}$, 7.0 h in *o*- $(CD_3)_2C_6D_4$ at 130 °C; Δδ 0.60–1.25
(±)$HOCH_2CHBr$- $CHBrCH_2OH$ **13**;§ 150 °C; > 90%; unstable in $CDCl_3$ at 25 °C; Δδ 0.89–1.25	 **14**;§ 150 °C; > 90%; unstable in $CDCl_3$ at 25 °C; Δδ 0.9–1.16	 **15**;† 150 °C; > 90%; unstable in $CDCl_3$ at 25 °C; Δδ 1.03–1.74	 **16**;§ 150 °C; > 90%; unstable in $CDCl_3$ at 25 °C; Δδ 0.9–1.7	 **17**;† 150 °C; > 90%; stable in $CDCl_3$ at 25 °C; Δδ 0.60–1.25
 **18**;§ 150 °C; >90%; unstable in $CDCl_3$ at 25 °C; Δδ 0.73	 **19**;§ 150 °C; >90%; unstable in $CDCl_3$ at 25 °C; Δδ 0.73	 **20**;† 150 °C; >90%; unstable in $CDCl_3$ at 25 °C; Δδ 1.43–1.50	 **21**;§ 150 °C; >90%; unstable in $CDCl_3$ at 25 °C; Δδ 4.00 OMe; 3.87, ArMe	 **22**;§ 150 °C; >90%; unstable in $CDCl_3$ at 25 °C; Δδ 1.35–2.14
	 **23**;† 150 °C; > 90%; stable in $CDCl_3$ at 25 °C; Δδ 0.57–4.18	 **24**;† 150 °C; > 90%; stable in $CDCl_3$ at 25 °C; Δδ 0.73–3.77		

complexes, are listed in Table 1. Models (CPK) of these guests could be forced with varying difficulty into the cavity of a model of **1** without breaking (non-worn) bonds of the models. However, models of those complexes that were unstable over time at 25 °C in $CDCl_3$ such as the cyclohexyl mono-halides and *para*-disubstituted benzenes offered little steric barrier to assembly or disassembly. The second class of guests includes those which did not form isolable complexes up to 150–190 °C because their activation free energies for complexation were too high. Model examination suggests molecules such as $C(CH_2OH)_4$, adamantane, [2.2.2]bicyclooctane or camphor are in this class. What was not predicted by models was our inability to get complexes such as those of 1,2-$Me_2C_6H_4$, 4-IC_6H_4OMe and 2-MeC_6H_4OMe. We suggest that binding affinities and constrictive binding[1] must add to one another before stable complexes are formed. The third class of guests are those that form complexes very rapidly, but also decomplex easily and do not survive the isolation (precipitation and preparative TLC). Guests such as C_6H_5I, C_6H_5OMe, C_6H_5Me, 1,4-$Me_2C_6H_4$, $MeCOCH_2COMe$ and Me_2NCOMe are examples.



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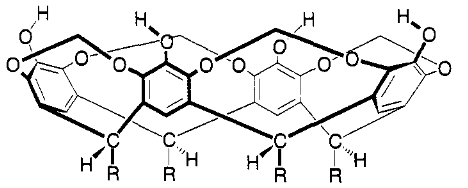
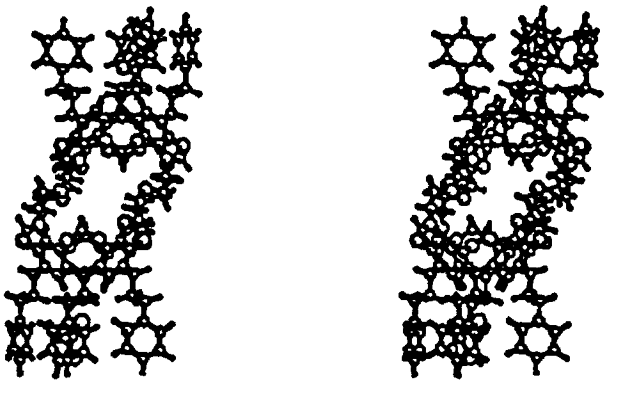


2 R = CH_2CH_2Ph



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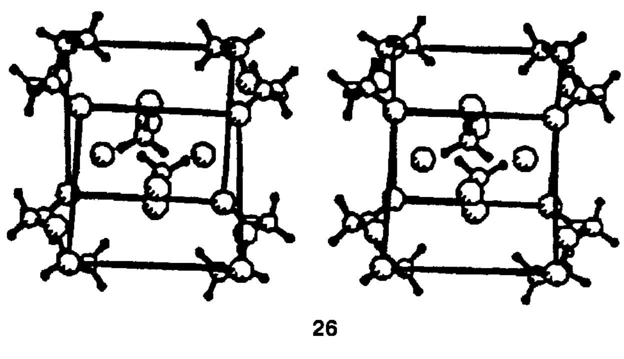

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As was observed for the analogue of **1** in which four 1,2-$(OCH_2)_2C_6H_4$ connecting groups replace the four $O(CH_2CH_2O)_2$ groups of **1**,[1] the decomplexation rates (^1H NMR determined) of **1**⊙**G** varied widely with solvent. For example, the $t_{1/2}$ values of **1**⊙**5** and **1**⊙**6** in $CDCl_3$ at 60 °C were 0.5 and 11 h respectively, whereas in $C_6D_5NO_2$ at 100 °C, $t_{1/2}$ for **1**⊙**5** was 1.7 h, and there was no decomplexation for **1**⊙**6** over several days. In another example, complex **1**⊙**11** in $CDCl_3$ at 25 °C had a $t_{1/2}$ of *ca.* 20 h, while in 1,2-$(CD_3)_2C_6D_4$ at 130 °C, $t_{1/2}$ = 7 h. This high dependence of rate on solvent reflects the differences between solvation free energies of the transition states for complexation–decomplexation, and of the fully complexed and non-complexed states. The rate constants for both complexation and decomplexation were determined in 1,2-$(CD_3)_2C_6D_4$ for **1**⊙**11** at 100 °C and 130 °C, from which the equilibrium constants for complexation were calculated to be 50 and 12 $dm^3\ mol^{-1}$, respectively. Thus for this system, $\Delta G^{\theta}_{100\,°C} = -2.9\ kcal\ mol^{-1}$ (1 cal = 4.184 J), somewhat less negative than the values obtained for the *o*-xylyl-bridge system mentioned above.[1]

Complex **1**⊙**17** dissolved in 1,2-$(CD_3)_2C_6D_4$ exhibited two different chemical shifts in the 500 MHz ^1H NMR spectrum for the 8 inward-turned OCH_2O protons at 22 °C, which coalesced at T_c = 138 °C, with $\Delta G^{\ddagger}_{138\,°C} = 27\ kcal\ mol^{-1}$. This phenomenon is due to restricted rotation of the *trans*-1,2-dibromocyclohexane guest relative to the host at the lower temperatures. Non-like-ended guests in other like-ended hosts have provided similar behavior.[3]

Stereoview **25** shows the crystal structure of **1** in which its 2 CH_2Cl_2 and 2 H_2O molecules are omitted.¶ Stereoview **26** is a drawing in which only the four bridging $O(CH_2CH_2O)_2$ groups of the host are included, and the two sets of four bridgehead phenyl oxygens in each hemisphere are connected to form two near squares occupying two parallel planes 4.64 Å apart. These squares are not rotated with respect to each other, but are displaced from having a common perpendicular axis by 2.67 Å. Two molecules of CH_2Cl_2 and two of H_2O are arranged centrosymmetrically in the cavity, with one Cl atom of each guest penetrating into a polar cavity 0.89 Å beyond the O_4 square, and with the two H_2O molecules located in the equatorial region, probably hydrogen-bonded to terminal oxygens of two different bridges. The portals of **1** are 28-membered rings, large enough to explain why only guests with large cross-sections in all three dimensions are trapped inside by quenching the hot mixtures of host and guest. The portals are also large enough to explain why the rates of entry and departure of linear or singly-branched potential guests are high enough to make ^1H NMR detection of their complexes in solution possible only at low temperature. This is the first crystal structure of a hemicarceplex that contains two different kinds of guests at the same time.

This survey of the binding properties of **1** toward compounds containing 6-11 heavy atoms and varying numbers of hydrogens demonstrates a high degree of structural recognition by host of guest which undoubtedly varies with solvent. The results coupled with those obtained earlier with other hemicarcerands suggest that hosts immobilized by bonding to solid supports should show large separation factors among many guests in affinity chromatography, potentially useful in separation and diagnostic science. The authors thank the U.S. Public Health Service for the supporting Research Grant, GM-12640.

Received, 24th April 1995; Com. 5/02615F

Footnotes

† These compounds gave C and H elementary analyses within 0.3% of theory, M^+ *m/z* signals of substantial intensity in their FAB MS and ^1H NMR spectra consistent with their structures.

‡ This procedure, patterned after a similar one in reference 1, involved Me_2NCOMe-Cs_2CO_3-20 h, 70 °C, then 8 h, 100 °C, high dilution. Use of Rb_2CO_3 or K_2CO_3 in place of Cs_2CO_3 had little effect on the yield. The solvent was evaporated under vacuum, the residue was dissolved in $CHCl_3$, the mixture was filtered through celite, and the 30 mL of filtrate was poured into 300 mL of MeOH. The precipitated product was chromatographed (silica gel, 5% Me_2CO-$CHCl_3$) to give **1**.† Complexations of **1** (10–20 mg) by guest (100–200 equiv.) either neat or with 0.2 to 1.0 mL of Ph_2O were carried out for 3 d at 100, 150–160 or 180–190 °C and the solutions poured into 50 mL of MeOH (hexane was the precipitant with Cl, Br and I-cyclohexane guests). The precipitate formed was separated from free host by preparative TLC, silica gel- Me_2CO in $CHCl_3$ (5% *v*/*v*).

§ M^+ *m/z* signals of substantial intensity were observed in their FAB MS, and ^1H NMR spectra were consistent with their structures.

¶ *Crystal data* for $1 \odot (2CH_2Cl_2,2H_2O) \cdot 8CH_2Cl_2$ (crystallized from MeOH–CH_2Cl_2 and determined at 25 °C), triclinic space group $P\bar{1}$, a = 14.921(2), b = 15.154(3), c = 17.194(3) Å, α = 99.702(4), β = 96.327(4), γ = 95.039(4)°, V = 3787 $Å^3$, Z = 1, 8325 unique reflections, 2379 > $2\sigma(I)$, and was refined to R = 0.156 (*SHELX76*[4]). Measurement was discontinued after 2θ = 95° (Cu-K_α radiation) in the present study because no more data could be 'observed'. Therefore, no atoms were refined with anisotropy, and H atoms are in calculated positions, C–H = 1.08 Å. The two bowls are related by an inversion centre in the middle of the cavity (see **25** and **26**).

The 'square' formed by the PhO oxygen atoms (**26**) is planar to within 0.03 Å and the O···O sides of the square range in length from 6.35(3) to 6.92(3) Å. The angles at the corners of the squares range from 87.4(3) to 93.2(4)°.

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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