Pergamon

Tetrahedron Letters 41 (2000) 9465–9470

TETRAHEDRON LETTERS

Hemicarcerands containing tosylamide bridges†

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Received 30 August 2000; revised 13 September 2000; accepted 18 September 2000

Abstract

Two new hemicarcerand hosts with tosylamide bridges are found to be relatively selective binders. The tosyl groups could not be removed without destroying the hosts. A crystal structure of the smaller host suggests that two of the four 28-membered ring portals are rigidly locked in an open position.

1. Introduction

Eight-fold shell closure reactions between bowl-shaped tetrol **1**[1] and tritosylated bridging compounds **2**[2] or **4**[3] gave hemicarcerands **3** and **5** (Scheme 1) in templated reactions in 72 and 32% yields, respectively. Hemicarcerands are hollow hosts whose interiors are occupied by guests to form hemicarceplexes, which are more or less stabilized in solution by steric inhibition of guests passing through the large rings that compose the shell of the host. The rates of entry and departure of dissolved guests into and out of host interiors usually show high temperature dependence, and provide measures of molecular recognition in complexation and decomplexation. Scheme 1 provides a drawing of a generalized hemicarceplex in which X are spanners, A are bridging groups, whose structure allows manipulation of the size and polar properties of the host, while R group changes help to control solubilities. This paper explores the synthesis, binding properties and a crystal structure of hemicarceplexes whose hosts contain four tosylamide bridging groups, both as unusual compounds in their own right, and as possible sources of hosts containing four amino groups.

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† This paper is dedicated to Professor Harry Wasserman on the occasion of his 80th birthday. His career demonstrates that productivity, high standards and joyfulness are not mutually exclusive characteristics in scientists.

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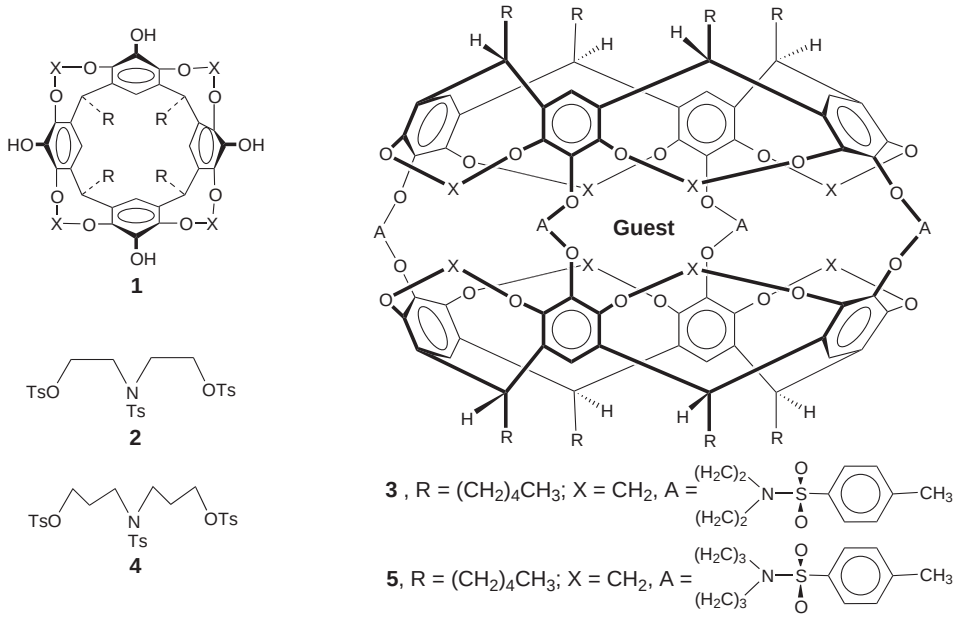
PII: S0040-4039(00)01612-9



Scheme 1. Cavitand bowl **1** reacts with bridging units **2** and **4** to produce hosts **3** and **5**, respectively

2. Synthesis

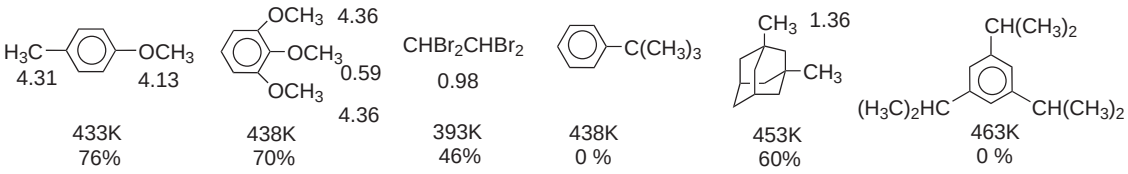
Host **3** was synthesized in 72% and host **5** in 32% yields,[‡] by the same general procedure.[§] The unusually high yield for **3** in a reaction involving the formation of eight bonds is probably due to templation by DMA, which is removed from the host during isolation, possibly reflecting the limited number of conformations available to **2**. High yield cyclizations involving **2** are known.[4] Various attempts to remove the remaining tosylate group from the bridges of hosts **3** and **5** failed. The reagent used previously in a similar deprotection reaction,[5] sodium anthracenide in tetrahydrofuran (THF), gave a mixture of products. Detosylation using sodium bis(2-methoxyethoxy)aluminum hydride[6] also produced mixtures. Intermediates such as $^{-}N[(CH_2)_2OAr]_2$ undergoing intramolecular S_N2 reactions with OAr as leaving group may explain the shell-cleaved products observed in these mixtures.

[‡] These new compounds gave C and H elementary analyses within 0.36% of theory, M^+ m/z signals of intensity 100 in their FAB MS spectra and ^1H NMR spectra consistent with their structures.

[§] Host **3** was synthesized as follows: a mixture of 0.68 mmol of **1**, 2.2 mmol of **2** and 7.3 mmol of Cs_2CO_3 in 450 mL of *N*,*N*′-dimethylacetamide (DMA) was heated at 343 K for 24 h under argon. A 1.4 mmol portion of **2** was added and the stirred suspension was heated at 343 K (24 h) and then 360 K (20 h). The mixture was cooled to 298 K, evaporated under vacuum and the residue partitioned between $CHCl_3$ and 10% aqueous NaCl. The $CHCl_3$ layer was dried ($MgSO_4$), concentrated and flash chromatographed on silica gel (150 g). Elution of the column with $CHCl_3$–ethyl ether (49:1 and 19:1) gave 0.65 g (72%) of **3**: mp >570 K. In the synthesis of **5**, a mixture of 0.68 mmol of **1**, 2.13 g of **4** (1.3 and 0.83 g portions) and 7.3 mmol of Cs_2CO_3 in 450 mL of DMA gave 300 mg (32%) of **5**, mp >570 K, after silica gel flash chromatography.

3. Complexation

The results of complexation studies of **3** with typical guests **6**–**9** and of **5** with guests **10** and **11** are shown in Scheme 2. Hemicarceplexes **3**⊙**6** and **3**⊙**8** are unstable over time in solution; indeed **3**⊙**6** decomplexes with $t_{1/2} \sim 1$ h at room temperature.¶ Host **5** forms a stable complex with guest **10** but not with **11**. The guests' structures are provided in Scheme 2 with the complexation temperatures, yields, and the $\Delta\delta$ values ($\Delta\delta = \delta_{\text{uncomplexed}} - \delta_{\text{complexed}}$) for the indicated guest protons.



Scheme 2. Complexation of hosts **3** (guests **6**–**9**) and **5** (guests **10** and **11**). Temperatures, yields of complex, and $\Delta\delta$ values for indicated guest protons are shown

4. Crystal structure

The X-ray crystal structure of **3**⊙**6**·$7CH_3OC_6H_4CH_3$ at 156 K provides the most precise atomic positions yet available in our series of related hemicarcerands.‖ One molecule of host crystallizes with one molecule of **6** as guest, about a center of symmetry which requires the guest to be disordered. Seven additional molecules of **6** are arranged interstitially in the unit cell. Fig. 1 shows a stereoview of host and guest from the side, and a top view of the central cavity, as defined by the eight O atoms that tether the bridges (A in Scheme 1). In the top view the O atoms are joined by solid lines to emphasize the dimensions and shape of the cavity, which is an average of 6.5 Å long on a side and 4.8 Å deep. The bridges, including H atoms, and the guest in one of its two orientations, are also shown.

¶ Complexations of **3** and **5** were carried out in 100-fold or greater (w/w) excesses of potential guests, neat, at 433–463 K for 3–4 days under argon. The mixtures were cooled to ~330 K and poured into 100 mL of MeOH. The precipitated products **3**⊙**6**, **3**⊙**7**, **3**⊙**8** and **5**⊙**10** were dried at 10^{-5} Torr (298 K) for 18 h and weighed. The ^{1}H NMR spectra were taken in $CDCl_3$ on a Bruker ARX 400 Mhz spectrometer. The half-life for decomplexation of **3**⊙**6** was determined by integration of the guest aryl CH_3 for free and complexed **6**. Two different chemical shifts were observed for aryl H in the polar caps of the host ($\delta = 6.79$, 4H, and $\delta = 6.83$, 4H).

‖ A suspension of 2.5 mg of host **3** in 4 mL of 4-methylanisole was refluxed for 20 m, cooled to 298 K and the flask stoppered. Formation of crystals occurred over several weeks. *Crystal data*: $C_{212}H_{260}N_4O_{40}S_4$, triclinic, space group $P\bar{1}$, $a = 13.038(5)$, $b = 18.544(7)$, $c = 22.716(9)$ Å, $\alpha = 113.665(8)$, $\beta = 91.147(9)$, $\gamma = 104.578(8)°$, $V = 4822.7(32)$ Å^3, $Z = 1$, $T = 156$ K, Mo Kα radiation, $\theta_{\max} = 24°$, solved by direct methods, refined by full-matrix least-squares on F^2 with 15 109 unique reflections to $R(F) = 0.070$ for 6710 reflections with $F > 4\sigma(F)$, GOF = 1.17. Sulfur atoms were refined anisotropically, all other non-H atoms refined isotropically, H atoms located geometrically and refined riding with distance and angle constraints and U_{iso} based on that of the attached C.

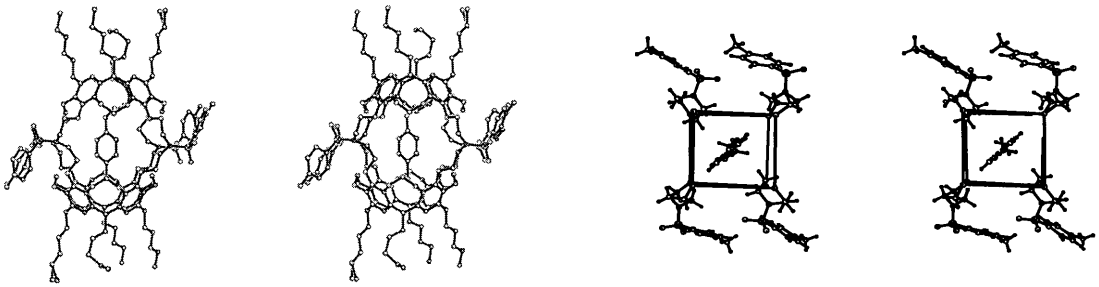
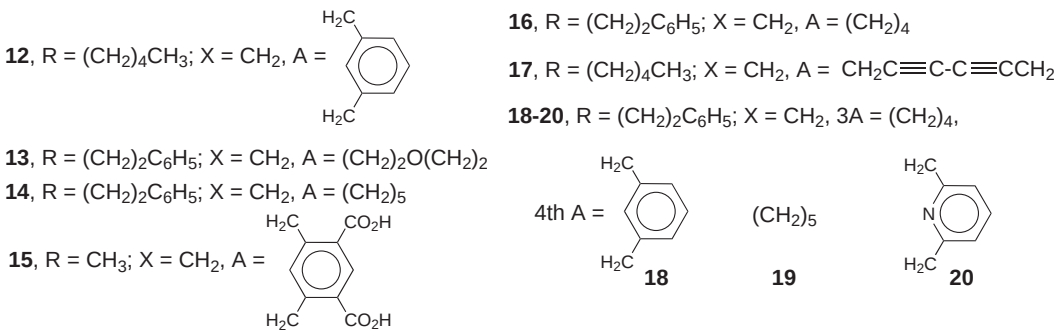


Figure 1. Left: side stereoview of the crystal structure of **3**⊙**6**. The guest is disordered over two positions related by the center of symmetry; only one position is shown. In addition, the terminal methyl group of a *n*-pentyl 'foot' is disordered (see top right, lower left of host for centrosymmetrically related groups); both methyl C atoms, each at 50% occupancy, are shown. Hydrogen atoms and solvent molecules are omitted for clarity. Right: top stereoview of the bridges, cavity and guest. The eight O atoms that join the bridges to the bowls are connected by solid lines. The conformations of the bridges produce two open portals (left and right). The two stereoviews together show the orientation of the guest in the cavity

5. Discussion

Hemicarcerand **3** is the fifth member of a series containing four 28-membered ring portals. Each host is synthesized from two cavitands (X = CH_2) bridged between the aryl O with five contiguous atoms (groups A in Scheme 1). The bridging groups in the first three hemicarcerands are *m*-xylyl[7] **12**, diethyleneoxy[8] **13** and pentamethylene[9] **14**, as shown in Scheme 3. The fourth host, **15**, with methyl 'feet', R, and two carboxylic acid moieties on each bridge, is water soluble.[10] As a host, **3** may also be compared to **16**, a flexible hemicarcerand with tetramethylene bridges.[11] Host **5** with 32-membered ring portals may be similar in size to **17**,[1] whose A group incorporates six bridging C atoms and thus has rather rigid, 30-membered ring portals.



Scheme 3. Hosts **12**–**20** (R, X and A are illustrated in Scheme 1)

In Table 1, the changes in chemical shifts for protons of guests **6** and **7** in hosts **3**, **12**, **13**, **14**, and **16**, and of guest **10** in hosts **5** and **17**, are compared. Previous complexation studies using a number of other hemicarcerands, for example six hosts with varying X groups and *m*-xylyl

Table 1
Guest $\Delta\delta$ values: changes in chemical shifts of guest protons relative to $(CH_3)_4Si$ in ^1H NMR spectra ($CDCl_3$ at 298 K). Hosts **3** and **5** compared with hosts of similar size[a]

Free guest **6**,	**3**⊙**6**[a]		**13**⊙**6**[8]	**16**⊙**6**[11]	**18**⊙**6**[13]	**19**⊙**6**[13]	Free guest **10**,	**5**⊙**10**[a]		**17**⊙**10**[1]
δ	δ	Δδ	Δδ	Δδ	Δδ	Δδ	δ	δ	Δδ	Δδ
OCH_3: 3.78	−0.35	4.13	4.00	4.13	4.04	4.06	CH_3: 0.78	−0.58	1.36	1.12
$ArCH_3$: 2.29	−2.02	4.31	3.87	4.40	4.25	4.27				
Free guest **7**,	**3**⊙**7**[a]		**12**⊙**7**[12]	**13**⊙**7**[8]	**14**⊙**7**[9]	**18**⊙**7**[13]				
δ	δ	Δδ	Δδ	Δδ	Δδ	Δδ				
1,3-OCH_3: 3.85	−0.51	4.36	3.96	4.18	4.10	4.26				
2-OCH_3: 3.86	3.27	0.59	0.56	0.57	0.54	0.81				

[a] This work. Other reference numbers given as superscripts after complex designation.

bridges,[12] or seven hosts with three tetramethylene bridges and a different fourth bridge,[13] provide similar $\Delta\delta$ values for the same guests. Of these hosts, **18** and **19** (Scheme 3), whose two largest portals are 27-membered rings, are included in the comparison in Table 1.

The largest $\Delta\delta$ values are consistently associated with those protons surrounded by the hosts' polar caps, the aryl-lined bowls. The present work confirms these findings, both by complexation behavior and by the relatively precise crystal study.

However, hosts **3** and **5** are quite selective binders. For example, **3** and **12** both bind **8**, **3** binds **6** but not **9**, yet **12** binds **9** but not **6**.[12] Though **3**⊙**6** and **3**⊙**8** can be isolated and characterized, neither is stable in solution. As for **5**, it binds **10** but not **11**, while **17** binds both.[1] It is also noteworthy that the ^1H NMR spectrum for **3**⊙**6** gives two signals for aryl H in the polar caps, indicating that **6** cannot rotate freely about the equatorial axis of the host. In this respect **3**, though its cavity is larger, is similar to **16**.[11]

In Fig. 1, the orientation of the guest in the crystal structure is seen to be consistent with the large $\Delta\delta$ values for the two sets of methyl protons. The top view of the host cavity and bridges shows that two of the 28-membered ring portals are open, and two are closed. The open portals and the like orientations of the tosyl groups, suggesting rigidity, are consistent with the narrow range of guests complexed by **3** and the short half-life for decomplexation of **3**⊙**6** in solution.

Previous crystal structures with guest **6** include **19**⊙**6**,[13] (two 26-membered ring and two 27-membered ring portals, Scheme 3) and **21**⊙**6**, **22**⊙**6** and **23**⊙**6**.[12] The last three are like **12** but with varying X groups, **21** with CH_2 in one bowl and CH_2CH_2 in the other, **22** with $X = CH_2CH_2$ in both bowls, and **23** with CH_2CH_2 in one bowl and $CH_2CH_2CH_2$ in the other. In Table 2 the cavity depths for the five crystal structures are listed in order of increasing host portal 'size'.

The two deepest cavities in the crystal studies are those of **3**⊙**6** and **21**⊙**6**, both stable in the crystal. Yet **3**⊙**6** is unstable, and **21**⊙**6** could not be characterized by ^1H NMR spectra[12] in solution.

Table 2
Cavity depths (distance between two planes of four bridging O atoms, Å) in crystal structures of hemicarceplexes with 4-methylanisole **6** as guest. Complexes listed in order of increasing maximum number of atoms in host portal rings[a]

19⊙**6**[13] 27-membered	**3**⊙**6**[a] 28-membered	**21**⊙**6**[12] 29-membered	**22**⊙**6**[12] 30-membered	**23**⊙**6**[12] 31-membered
4.10	4.82	4.70	4.65	4.49

[a] This work. Other reference numbers given as superscripts after complex designation.

6. Supplementary material

The Crystallographic Information File for **3**⊙**6**·7$CH_3OC_6H_4CH_3$ has been deposited with the Cambridge Crystallographic Data Centre (CCDC 150221).

Acknowledgements

This work was supported by a grant from the National Institutes of Health (GM-12640).

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