Template Effects in the Formation of a Tetramethylene-Bridged Hemicarceplex

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Abstract: We report a study of the template effect in the formation of tetramethylene-bridged hemicarceplex **7**·guest. Two tetrol cavitands were bridged with 1,4-dibromobutane in the presence of suitable template (guest) molecules in *N*-formylpiperidine as solvent. Selectivity was observed when competing templates were present during the reaction: the relative templating abilities (template ratios) of 30 different guest molecules range by 3600-fold, and manifest a significant preference for para-disubstituted benzenes. Twenty-one of the 30 hemicarceplexes used in this templation study are new. The trend in guest selectivity is markedly different from previous studies in which smaller cavities (e.g., carceplex **2**·guest) are formed. In such studies, capsule **3**·guest was a good transition state model, whereas this is not the case in the present work.

Introduction

Templation plays a key role in many biological processes and in supramolecular chemistry[1] in the formation of crown ethers,[2] catenanes and rotaxanes,[3] molecularly imprinted polymers,[4] zeolites,[5] molecular capsules,[6,7] and carceplexes and hemicarceplexes.[8] A cornerstone of supramolecular chemistry is the quest for the elucidation of the interactions that drive such molecular recognition processes. Carceplexes and hemicarceplexes provide simple, sensitive probes for such investigations. Carceplexes are globe-shaped container molecules capable of permanently entrapping smaller molecules as guests, which cannot escape without breaking covalent bonds.[8a] Hemicarceplexes can be isolated with guests intact, but they contain large portals through which guest egress is possible given the appropriate conditions.[8a] Templating agents appear to be required for the formation of carceplexes,[1,8,9] as none have ever been isolated empty. Likewise, most hemicarceplexes have been isolated with attendant guest.[8a−d] Yet, the details of the templated processes for the formation of carceplexes[10] and hemicarceplexes[11] have only been reported for a few systems.

We have reported a 10^6-fold range in guest dependence for a kinetic template effect in the formation of carceplex **2**·guest (Scheme 1).[10] Template ratios reflect the relative ability of each guest to enhance the rate of the guest-determining step (GDS, the step in the reaction sequence during which the guest becomes permanently entrapped). Such template ratios were determined via competition experiments, where two guests are present

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(1) Chapman, R. G.; Sherman, J. C *Tetrahedron* **1997**, *53*, 47, 15911−15945. Makeiff, D. A.; Sherman, J. C. *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1999; pp 105−131.

(2) Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017−7036. Busch, D. J.; Vance, A. L.; Kolchinski, A. G. *Comprehensive Supramolecular Chemistry*; Lehn, J.-M., Atwood, J. L., MacNicol, D. D., Vögtle, F., Eds.; Permagon: New York, 1996; Vol. 9, p 2 and references therein.

(3) Schill, G. *Catenanes, Rotaxanes, and Knots*; Acedemic Press; New York, 1971. Vögtle, F.; Dünnwald, T.; Schmidt, T. *Acc. Chem. Res.* **1996**, *29*, 451−460. Raymo, F. M.; Stoddart J. F. *Chem. Rev.* **1999**, *99*, 1643−1663. Sauvage, J.-P. *Acc. Chem. Res.* **1998**, *31*, 611−619. Hamilton, D. G.; Feeder, N.; Prodi, L.; Teat, S. J.; Clegg, W.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1998**, *120*, 1096−1097. Capobianchi, S. Doddi, G.; Ercolani, G.; Mencarelli, P. *J. Org. Chem.* **1998**, *63*, 8088−8089. Fujita, M. *Acc. Chem. Res.* **1999**, *32*, 53−61. Hübner, G. M.; Gläser, J.; Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3, 383−386.

(4) Wulff, G. *Template Induced Control of Stereochemistry for the Synthesis of Polymers*; Wulff, G., Ed.; Kluwer Academic Publishers: Netherlands, 1995; Vol. 473, pp 13−19. Spivak, D. Gilmore, M. A.; Shea, K. J. *J. Am. Chem. Soc.* **1997**, *119*, 4388−4393. Wulff, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1812−1832. Uezu, K.; Nakamura, H.; Kanno, J.-i.; Sugo, T.; Goto, M.; Nakashio, F. *Macromolecules* **1997**, *30*, 3888−3891. Yoshida, M.; Uezu, K.; Goto, M.; Furusaki, S. *Macromolecules* **1999**, *32*, 1237−1243. Kanekiyo, Y.; Ono, Y.; Inoue, K. Sano, M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 557−561.

(5) Xu, T.; Munson, E. J.; Haw, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 1962−1972. Zones, S. I.; Nakagawa, Y.; Yuen, L. T.; Harris, T. V. *J. Am. Chem. Soc.* **1996**, *118*, 7558−7567. Pitchumani, K.; Warrier, M. Cui, C.; Weiss, R. G.; Ramamurthy, V. *Tetrahedron. Lett.* **1996**, *37*, 6251−6254. Lewis, D. K.; Willock, D. J.; Catlow, C. R. A.; Thomas, J. M.; Hutchings, G. J. *Nature* **1996**, *382*, 604−606. Tung, C.-H.; Wu, L.-Z.; Yuan, Z.-Y.; Su, N. *J. Am. Chem. Soc.* **1998**, *120*, 11594−11602. Ekambaram, S.; Sevov, S. C. *Angew. Chem., Int. Ed.* **1999**, *38* (3), 372−375.

(6) Rebek, J., Jr. *Chem. Soc. Rev.* **1996**, 255−264. Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. Higler, I.; Verboom, W.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 2689−2702. de Mendoza, J. *Chem. Eur. J.* **1998**, *4*, 8, 1373−1376. MacGillivray, L.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018−1033. Whang, D.; Heo, J.; Park, J. H.; Kim, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1, 78−80. Fox, O. D.; Dalley, K.; Harrison, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 7111−7112. Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286.

(7) (a) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082. (b) Chapman, R. G.; Olovsson, G.; Trotter, J.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6252−6260. (c) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 9818−9826.

(8) (a) Maverick, E.; Cram, D. J. *Chapter 12: Carcerands and Hemicarcerands: Hosts that Imprison Molecular Guests*; Vögtle, F., Vol. Ed.; in the series *Comprehensive Supramolecular Chemistry*; Lehn, J. -M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Ed.; Permagon: New York, 1996; Vol. 2, pp 367−418. (b) Cram, D. J.; Cram, J. M. *Container Compounds and Their Guests*; The Royal Society of Chemistry: Cambridge, 1994; Vol. 4. (c) Sherman, J. C. In *Large Ring Molecules*; Semlyen, J. A., Ed.; J. Wiley & Sons: West Sussex, England, 1996; pp 507−524. (d) Sherman, J. C. *Tetrahedron* **1995**, *51*, 3395−3422. (e) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967. (f) Chopra, N.; Sherman, J. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 16, 1727−1729. (g) Chopra, N.; Sherman, J. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1955−1957. (h) van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *3*, 44, 639−654. (i) Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 6, 613−615.

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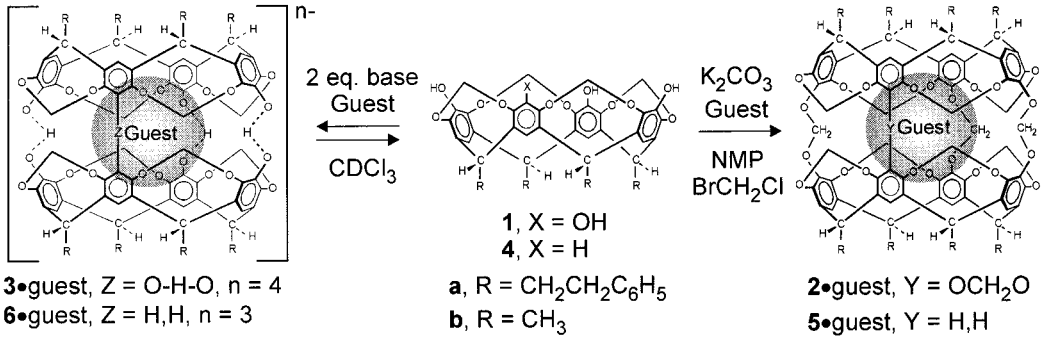
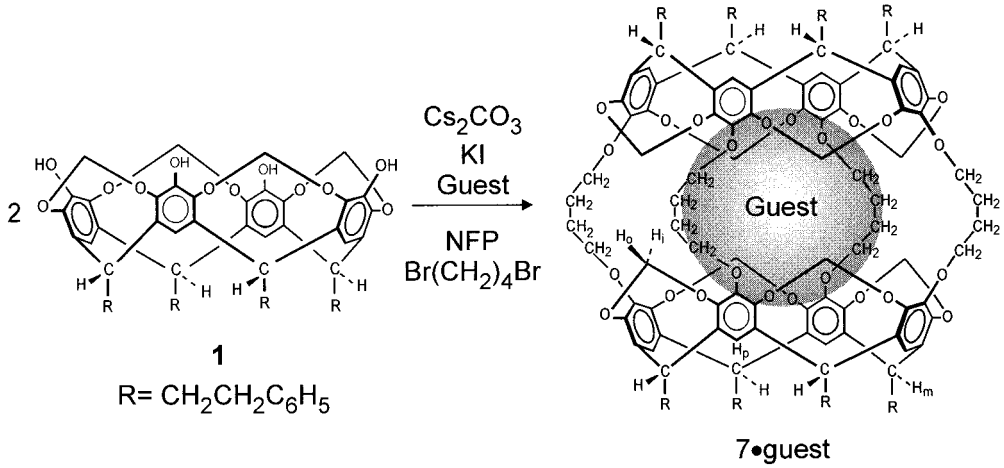
Scheme 1



Scheme 2



during the formation of the carceplex. The beauty of such systems is that two different templates can promote the same reaction, but the products are tagged with different entrapped guests. Thus, we can readily measure how much product is generated by each template. These measurements are precise and via a series of competitions, they can cover a limitless range in templating abilities. In the case of carceplex **2**·guest, the GDS is 10^6 times faster in the presence of the best guest than in the presence of the poorest measured guest.[10]

We have also reported the formation of a reversible, charged hydrogen bonded capsule (**3**·guest, Scheme 1) whose relative thermodynamic stabilities mirror the kinetic template ratios of carceplex **2**·guest.[7] Thus, capsule **3**·guest is a good transition state model for the GDS in the formation of carceplex **2**·guest.[7a] In addition, singly and doubly covalently bridged intermediates reversibly encapsulate guests with the same relative guest affinity as **3**·guest.[7c,10] Thus, templation is in effect from the beginning (formation of **3**·guest) and continues on through the GDS, which was determined to be the formation of the second covalent bridge.[10b] Consistent with these results was the finding that triol **4** forms a reversible capsule (**6**·guest) with like guest selectivity to **3**·guest[7c] and that the template effect in forming the corresponding tris-bridged hemicarceplex **5**·guest, proceeds with like guest selectivity to carceplex **2**·guest.[11a] Clearly these systems all have cavities of similar size, shape, and electrostatics.

Cram has reported the synthesis of hemicarceplex **7**·guest (Scheme 2) from the same precursor (tetrol **1**) used to make carceplex **2**·guest.[12] Cram called **7**·guest the most versatile hemicarceplex of the lot.[12] Perhaps the most fascinating illustration of its utility is the generation of benzyne within the interior of **7**.[13,14] Clearly, capsule **3**·guest can form during the reaction to give **7**·guest. The question we pose is: is capsule **3**·guest a good transition-state model for the formation of **7**·guest? If the GDS occurs early (first or second bridges), this should be the case. If late (third or fourth bridge), the cavity size and shape of the transition state may deviate significantly from that of **3**·guest; this would also demonstrate that **3**·guest is not necessarily a good transition state model for all compounds for which tetrol **1** is a precursor.

We report here on the template effect in the formation of tetramethylene-bridged hemicarceplex **7**·guest from shell-closure reactions involving tetrol **1**, base, and linker, in the presence of suitable guest molecules. In total, 84 different templates were investigated, and 30 template ratios were determined.

Results

Reaction Conditions/Synthesis. To screen guests, choice of solvent is crucial, as it may act as a template, and thus competitively exclude poorer guests. Table 1 summarizes

(9) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194−2204.

(10) (a) Chapman, R. G.; Chopra, N.; Cochien, E. D.; Sherman, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 369−370. (b) Chapman, R. G.; Sherman, J. C. *J. Org. Chem.* **1998**, *63*, 12, 4103−4110.

(11) (a) Chopra, N.; Sherman, J. C. *Supramol. Chem.* **1995**, *5*, 31−37. (b) Byun, Y.-S.; Robbins, T. A.; Knobler, C.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1947−1948. (c) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590−5604.

(12) (a) Robbins, T. A.; Knobler, C. B.; Bellow, D. R.; Cram, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 111−112. (b) Yoon, J.; Sheu, C.; Houk, K. N.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1996**, *61*, 9323−9339.

(13) Warmuth, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 12, 1347−1350. Warmuth, R. *J. Chem. Soc., Chem. Commun.* **1998**, 59−60.

(14) Several other interesting investigations into the chemistry of hemicarceplex **7**·guest have been reported. Robbins, T. A.; Cram, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 12199. Kurdistani, S. K.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 5, 1659−1660. Place, D.; Brown, J.; Deshayes, K. *Tetrahedron Lett.* **1998**, *39*, 5915−5918.

Table 1. Formation of Hemicarceplex 7·Guest in Various Solvents[i]

entry[a]	solvent	guest(s)[b]	t, days	% yield 7·guest
1[c]	DMF	DMA[d]	2	4.7
2[c]	DMA		2	30
3[c]	NMP	DMA[d]	2	16
4[c]	NFP	DMA[d]	2	13
5[c]	1-acetyl-3-methyl-piperidine	DMA[d]	2	4.5
6[c]	tetramethylene sulfone	NMP, 2-butanol[d]	2	0
7[c]	DMPU	NMP, 2-butanol[d]	2	0
8[c]	nitrobenzene	DMA, NMP[d]	2	0
9[c]	ethyl acetate	ethyl acetate[e]	2	0
10[c]	cyclohexane	DMA, NMP[e]	2	<1
11[c]	cyclohexane	DMA, NMP[e]	4	<1
12[c]	acetonitrile	DMA, NMP[e]	2	0
13[c]	acetone	NMP, 2-butanol[e]	2	0
14[c]	2-butanone	NMP, 2-butanol[e]	2	2.5
15[c]	2-butanone	NMP, 2-butanol[e]	4	2.4
16[c]	THF	NMP, 2-butanol[e]	2	0
17[f,g]	DMA	-	4	30
18[h,g]	DMSO	-	7	18

[a] Reagents were added to solutions under stirring of Cs_2CO_3 with heating. [b] Guest concentration was 1 mol % of the solvent. [c] KI was added. 1,4-Dibromobutane linker was added directly to the reaction mixture. [d] Reactions were at 80 °C. [e] Reactions were at reflux. [f] 1,4-Butanediol ditosylate linker was added slowly over a period of 48 h at 60 °C, after which the reaction was stirred at 60−70 °C for an additional 48 h (ref 12a). [g] See ref 13a. [h] Similar to footnote f, except 1,4-butanedioldditosylate was added over 120 h (ref 12a). [i] Abbreviations: DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide, NMP = *N*-methylpyrrolidinone, NFP = *N*-formylpiperidine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinonone, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide.

reaction conditions and product yields using a variety of solvents. Guests were added in these experiments because ideal solvents would not act as templates, and no product would be observed in the absence of a suitable template. Cram has reported the synthesis of **7**·*N*,*N*-dimethylacetamide (**7**·DMA) in 30% yield,[12a] which we reproduced under slightly modified conditions (entry 2, Table 1). Unfortunately, DMA turned out to be too good a template to serve as a suitable solvent. From the solvent data shown in Table 1, *N*-formylpiperidine (NFP) gives a reasonable yield (13%) of **7**·guest where the guest is not NFP (i.e., NFP is a poor template); thus NFP was the solvent of choice. 1,4-dibromobutane was chosen as the linker over Cram's 1,4-butanediol ditosylate because of commercial availability. Yields of hemicarceplex **7**·guest (i.e., **7**·guest the reported in Table 2) in NFP were generally 5−10% (see Experimental Section).

Conditions used (Scheme 2) for screening potential guest molecules were as follows: addition of tetrol **1**, Cs_2CO_3 (19 equiv per tetrol **1**), KI (0.8 equiv per linker), and guest in NFP at 80 °C. The mixture was stirred for at least 10 min at this temperature before adding 1,4-dibromobutane (10 equiv per tetrol **1**). Reactions were allowed to proceed for 48 h at 80 °C prior to workup.

Guest Screening. Eighty-four guests were screened using 1−50 mol % guest, in NFP. Guests were chosen that appeared complementary to the interior of **7** on the basis of Corey−Pauling−Koltun (CPK) models, or that have been reported by Cram as **7**·guest.[15] Of the total 84 guests screened, 37 were found to behave as unsuitable guests (Chart 1). These molecules are qualitatively categorized as being potentially too large in some dimension, too reactive, too small, too basic, or too apolar to act as suitable templates in the formation of hemicarceplex **7**·guest.

(15) Cram has reported the preparation of **7**·guest by a nontemplated procedure involving guest exchange from **7**·DMA. See ref 12a.

Table 2. Template Ratios[c]

guest	template ratio for **7**·guest	template ratio for **2**·guest[a]
p-xylene	3600	
4-bromotoluene	2800	
p-dibromobenzene	2100	
4-chlorotoluene	2000	
anisole	1900	
1-bromo-4-chlorobenzene	1700	
p-dichlorobenzene	840	
1-bromo-4-iodobenzene	730	
1-chloro-4-iodobenzene	620	
4-methylanisole	580	
3-pentanol	490	
iodobenzene	460	
4-chloroanisole	450	
thioanisole	440	
bromobenzene	240	
2-butanol[b]	200	2 800
toluene	140	
2-pentanol[b]	140	
benzene	110	2 400
chlorobenzene	110	
2,4-pentanediol[b]	100	
3-hexanol[b]	99	
cyclohexane	58	
fluorobenzene	39	
NMP	28	1
DMA	26	20
DMSO	17	180 000
DMI	16	
isopropyl acetate	10	
NFP	1	

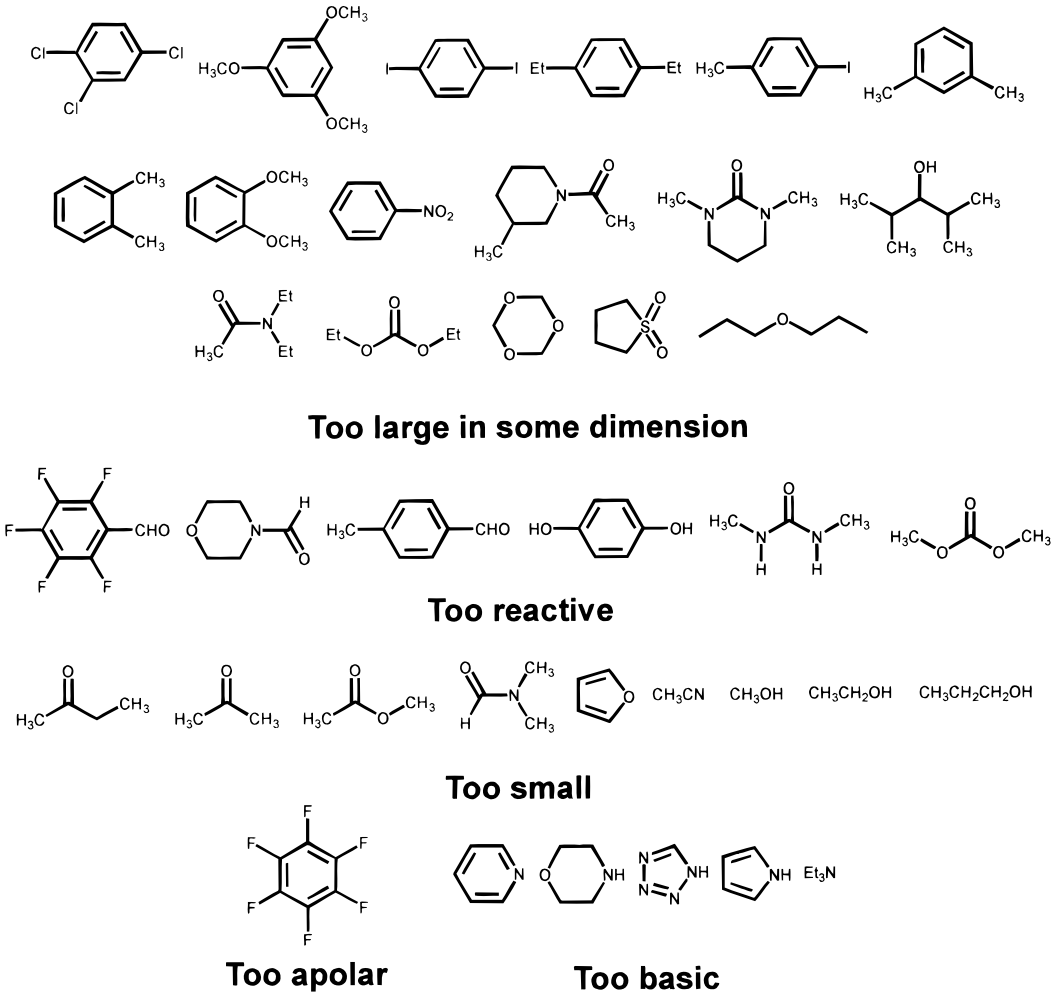
[a] From ref 10. [b] Racemic mixtures were used. [c] Abbreviations: DMI = 1,3-dimethyl-2-imidazolidinone. See Table 1 for other abbreviations.

^{1}H NMR spectroscopic and/or MALDI mass spectrometric data on the product mixtures isolated from 17 screening reactions (using the guests 2-propanol, *n*-propyl acetate, ethyl acetate, cyclohexanone, tetramethylene sulfoxide, THF, 1,4-thioxane, 1,4-dithiane, 1,4-dioxane, thiophene, pyrazine, 4-fluorotoluene, *p*-difluorobenzene, 1-chloro-4-iodobenzene, 1-bromo-4-fluorobenzene, 1-chloro-4-fluorobenzene, or 4-bromoanisole) suggested that these guests are suitable templates. Unfortunately, none of these hemicarceplexes could be obtained pure.[16] Therefore, the templation study was limited to the 30 remaining guests (Table 2).

Determination of Template Ratios. Competition Experiments. Template ratios (Table 2), were determined by head-to-head competition reactions between pairs of adjacent guests in NFP, where product ratios for each pair were multiplied from the bottom to the top of the table. Product ratios were determined by integration of each set of guest signals in the ^{1}H NMR spectra. Guests (templates) were added at concentrations that yield a relative integration of approximately 1:1, and the template ratios were adjusted accordingly. Cross-check competition experiments between the nonadjacent guests in Table 2 confirmed the accuracy of the method (see Supporting Information for more details).[17] For example, competition of the best

(16) All hemicarceplexes obtained from shell closure reactions in NFP were isolated as mixtures containing **7**·guest and **7**·NFP. In most cases, the hemicarceplex **7**·guest products could not be separated by chromatography on normal phase silica gel due to similar retention factors. Hemicarceplex products present in the reaction mixtures were identified by ^{1}H NMR spectroscopy and MALDI mass spectrometry. Pure samples of each new host−guest complex were prepared via guest exchange from **7**·DMA (similar to Cram's method, ref 12a). See Supporting Information for further details.

Chart 1. Unsuitable Guests for the Templated Formation of Hemicarceplex 7·Guest.



guest *p*-xylene directly against NFP gave a template ratio of 3600,[18] which is identical to the value listed in Table 2.

Discussion

Guest Orientation and Mobility. Table 3 (see Supporting Information) lists the ^{1}H NMR chemical shift data for the bound and free guests in each of the 30 different hemicarceplexes.[19] Protons buried deep within the aryl-lined hemispheres show large $\Delta\delta$ values, while protons near the equatorial region show smaller $\Delta\delta$ values. For example, $\Delta\delta$ values for methyl protons of *p*-xylene, 1,4-bromotoluene, 1,4-chlorotoluene, 1,4-methylanisole, or 1,4-chloroanisole are large (4.14−4.43), while those for the ortho and meta aryl protons are small (0.77−1.22): para-disubstituted benzene guests are generally orientated within the host situating the para substituents deep within the northern and southern hemispheres, while the aryl hydrogens are located near the equator. This is consistent with previous ^{1}H NMR and X-ray crystallographic data.[12] In addition, two sets of host signals are also observed for hemicarceplexes **7**·guest with para-disubstituted benzene guests containing different substituents, which demonstrates that such guests have restricted rotation about the C_2 axes of the host on the ^{1}H NMR time scale. These orientations and mobilities of guests (see Supporting Information for more details) demonstrate their complementarity to the cavity of **7**·guest.

General Trends in Templating Abilities. The best templates in the formation of **7**·guest are clearly para-disubstituted benzenes (Table 2). Guest size appears to be an important factor: substituent size follows SCH_3 > OCH_3 > I > Br ≈ CH_3 > Cl > F > H. For para-disubstituted benzenes, two substituents the size of Br or CH_3 appear optimal. Larger or smaller substituents reduce the template ratios. For monosubstituted benzenes, the ideal substituent size is OCH_3; again, larger or smaller substituents reduce the template ratios. Somewhat anomalous is fluorobenzene, which is a weaker template than benzene, even though F is a bit larger than H. The strong electronegativity of F appears to be important here;[20]

(17) Since hemicarcerand **7** contains large portals through which smaller guest molecules can pass, to be sure that the template ratios in Table 2 are due to a kinetic template effect, guest exchange after host formation must be checked. Thus, control experiments were performed for each hemicarceplex **7**·guest, which involved separately subjecting each to standard reaction conditions in the presence of two or more potentially competitive guests (at concentrations of 1 mol % of the solvent). Competing guests were chosen such that one guest was a slightly better template and the other a slightly worse template than the guest in **7**·guest. Guest exchange was investigated by ^{1}H NMR spectroscopy. In the 30 control experiments performed, guest exchange was only observed for hemicarceplex **7**·NFP in the presence of *p*-xylene and 2-butanol, where <14% of **7**·2-butanol formed.

(18) The low selectivity observed for the guests in Table 3 in the formation of **7**·guest compared to that found for **2**·guest (60 °C) prompted us to investigate the effect of temperature on selectivity. Reported competition experiments in the formation of **2**·guest were conducted at 60 °C (see ref 11). *p*-Xylene was competed against NFP in separate reactions at various temperatures ranging from ambient to 80 °C. No significant changes in selectivity were observed.

(19) ^{1}H NMR assignments for the host signals of new hemicarceplexes (see Experimental Section) were based on analogy to previously reported hemicarceplexes (**7**·guest, see refs 12−14).

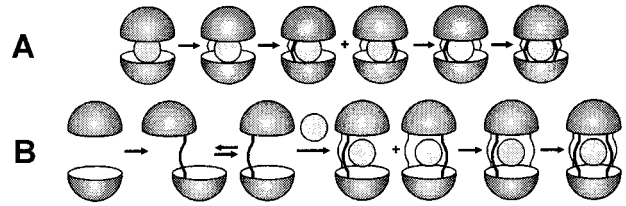


Figure 1. Template effect is at play throughout the reaction in the formation of carceplex **2**·guest (A). Polymerization is minimized due to preorganization imparted by the template/guest in all stages. Template effect in the formation of hemicarceplex **7**·guest only occurs during the formation of either the third or fourth bridge (B). Precursors (e.g., monobridged intermediate) could readily polymerize since no preorganization is imparted by the template/guest.

this is corroborated by the observation that hexafluorobenzene is not a suitable template.

Selectivity for aliphatic alcohols increases on the order of 3-hexanol < 2,4-pentanediol < 2-pentanol < 2-butanol < 3-pentanol. Size and shape appear to be the most important factors governing their templating abilities. For example, insertion of an additional methylene unit between C1 and C2 (to give 3-pentanol), and C2 and C3 (to give 2-pentanol) in 2-butanol results in an increase and a decrease in templating ability, respectively. The more symmetric 3-pentanol is able to form more optimal vdW contacts with the host where the two terminal methyls are placed deeply within the polar hemispheres of the host. Stabilization may be possible through CH-π interactions between the guest methyl protons and the host's arenes. Relegating the polar hydroxy group to the acetal-containing equator of the host may also be significant. Inserting an oxygen atom at the 4-carbon of 2-pentanol (to give 2,4-pentandiol), results in only a slight decrease in templating ability. Extending the carbon chain length of 3-pentanol from five to six carbons (to give 3-hexanol) significantly reduces templating power 5-fold. Additional methyl groups introduced at C2 and C4 of 3-pentanol (to give 2,4-dimethyl-3-pentanol), results in a complete shutdown of observed templating ability.

Conclusions

Most obvious from Table 2 is that there is no correlation between template ratios for hemicarceplex **7**·guest and carceplex **2**·guest, which demonstrates that capsule **3**·guest is not a good transition-state model for the GDS in the formation of hemicarceplex **7**·guest. From these data and by examination of CPK models, it appears that the cavity size in the GDS is much larger than that of capsule **3**·guest, which indicates a late transition state that likely involves the formation of the third or fourth bridge (Figure 1B). Prior to this, guest exchange is likely to be fast (i.e., during formation of the first and second bridges). Therefore, although capsule **3**·guest can form in the presence of suitable guests during the reaction to produce carceplex **2**·guest, hemicarceplex **5**·guest, and hemicarceplex **7**·guest, it is only relevant in the formation of **2**·guest (Figure 1A) and **5**·guest.

The range in template ratios is smaller here than for carceplex **2**·guest, or hemicarceplex **5**·guest. This may be simply due to the solvent used in the reaction, which is a proven competitor in the formation of **7**·guest, and thus may cut off potential templates that have modest templating abilities. Unfortunately, we were unable to find a suitable solvent that is a poorer template than NFP.

The low hemicarceplex yields obtained can be attributed to the lack of preorganization between opposing bowls leading up to the GDS. A capsule such as **3**·guest is likely to be disrupted once a tetramethylene linkage is made (Figure 1B). Guests would not be expected to bind strongly at this point.[7c] Thus, the bowls can rotate freely, and upon alkylation, are free to react either intermolecularly or intramolecularly. The template effect does not take effect until after the fate of the product has been sealed by the formation of the second bridge (Figure 1B). By this time the detriment to the yield has already ensued.

This study has provided further insight into the nature of the noncovalent interactions involved in the templated formation of host−guest systems. We hope that this information will help lead to the design and creation of much larger assemblies which may eventually reach the complexity of those found in nature.

Experimental Section

General. All reagents were purchased form Aldrich Chemical Co., Inc., and were used without further purification unless stated otherwise. NFP, DMA, and DMSO were distilled and stored over 4 Å molecular sieves under an N_2 atmosphere. All reactions were carried out under a positive pressure of N_2, unless stated otherwise. ^{1}H NMR spectra were acquired using a Bruker WH-400 spectrometer in $CDCl_3$ at ambient temperature using the residual ^{1}H signal as the reference. Mass spectra were recorded on a Kratos Concept II HQ (DCI) and a VG Tofspec in reflectron mode (MALDI). Refer to structure **7**·guest (Scheme 2) for host proton labels, and Table 2 for guest proton labels. The characterization of **7**·NFP is provided below. The other **7**·guest characterizations are given in the Supporting Information.

General Templating Procedure for the Synthesis of 7·Guest. Procedure A. Tetrol **1** (50.0 mg, 0.049 mmol), Cs_2CO_3 (300.0 mg, 0.921 mmol, 19 equiv), and KI (60.0 mg, 0.361 mmol, 0.7 equiv per molecule of linker) were added to 20.0 mL of neat guest. The reaction was stirred at 80 °C for 10 min, and then 1,4-dibromobutane (60 μL, 0.502 mmol, 10 equiv) was added. The reaction was stirred further at 80 °C for 48 h, the solvent was removed in vacuo, and the yellow-brown residue was resuspended in 2 M HCl (20 mL) and extracted with $CHCl_3$ (3 × 10 mL). The $CHCl_3$ extracts were combined and dried over Mg_2SO_4, filtered, and the solvent was removed in vacuo. The resulting crude yellow-brown oil was then passed through silica gel (230−400 mesh) by eluting with either $CHCl_3$, CH_2Cl_2, or 6:1 CH_2Cl_2:hexanes. Precipitation of the product from $CHCl_3$ by addition of hexanes gave a white solid, which was dried in vacuo (0.01 mmHg) between 70 and 90 °C for 24 h.

7·NFP. Procedure A was followed in neat NFP to give 3.2 mg (3%) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 24H, C_6H_5), 7.15 (m, 16H, C_6H_5), 6.84 (s, 8H, H_p), 5.76 (d, 8H, J = 6.8 Hz, H_o), 4.81 (t, 8H, J = 7.9 Hz, H_m), 4.47 (s, 1H, H_f) 4.17 (d, 8H, J = 6.8 Hz, H_i), 3.93 (br s, 16H, OCH_2CH_2), 2.67 (m, 16H, $CH_2CH_2C_6H_5$), 2.48 (m, 16H, $CH_2CH_2C_6H_5$), 2.09 (m, 2H, H_d or H_e), 2.04 (m, 2H, H_d or H_e), 1.92 (br s, 16H, OCH_2CH_2), 0.18 (m, 2H, H_b or H_c), −0.03 (m, 2H, H_b or H_c), −1.22 (m, 2H, H_a); MS (MALDI) *m*/*z* (rel intensity) 2387 ($(M\cdot C_6H_{11}NO + Na^+)^+$; 100), calcd for $C_{150}H_{147}NO_{25}\cdot Na^+$ = 2387.

Procedure A was also used to prepare **7**·NMP, **7**·DMA, and **7**·DMSO.

(20) It is noteworthy that preliminary template ratios (in parentheses) were determined for *p*-difluorobenzene (5), 1-chloro-4-fluorobenzene (42), 1-bromo-4-fluorobenzene (77), and 4-fluorotoluene (97). These template ratios are smaller than those for their respective protio analogues (fluorobenzene, chlorobenzene, bromobenzene, and toluene, respectively). These guests were not included in this study because pure samples could not be obtained.

Procedure B. Same as procedure A, except that NFP (20 mL) was used as the solvent, and the guest was added at a concentration of 1 mol % of the solvent. Procedure B was used to prepare **7**·1-bromo-4-chlorobenzene, **7**·1-bromo-4-iodobenzene, **7**·1-chloro-4-iodobenzene, **7**·iodobenzene, **7**·bromobenzene, **7**·benzene, and **7**·3-hexanol.

Procedure C. Same as procedure B, except that 2 mol % guest was used. Procedure C was used to prepare **7**·*p*-xylene, **7**·*p*-dibromobenzene, and **7**·*p*-dichlorobenzene

Procedure D. Same as procedure B, except that 5 mol % guest was used. Procedure D was used to prepare **7**·4-bromotoluene, **7**·4-chlorotoluene, **7**·anisole, **7**·*para*-methylanisole, **7**·3-pentanol, **7**·2-butanol, **7**·toluene, **7**·2-pentanol, **7**·chlorobenzene, **7**·2,4-pentanediol, **7**·cyclohexane, and **7**·isopropyl acetate.

Procedure E. Same as procedure B, except that 10 mol % guest was used. Procedure E was used to prepare **7**·4-chloroanisole, **7**·thioanisole, and **7**·fluorobenzene,

Procedure F. Same as procedure B, except that a 1:1 ratio of guest:solvent was used. Procedure F was used to prepare **7**·1,3-dimethyl-2-imidazolidinone.

Competition Experiments. Tetrol **1** (50.0 mg, 0.049 mmol), KI (60.0 mg, 0.361 mmol, 7.4 equiv), and Cs_2CO_3 (300 mg, 0.921 mmol, 19 equiv) were mixed in 20 mL of *N*-formylpiperidine, followed by the addition of guest 1 (G1) and guest 2 (G2) at 80 °C with stirring. The relative ratios of G1:G2 added to the reaction mixture were chosen so as to obtain close to a 1:1 ratio of hemicarceplexes to optimize integration in the ^{1}H NMR spectra. The reactions were allowed to stir for at least 10 min before adding 1,4-dibromobutane (60.0 μL, 0.493 mmol). After further stirring at 80 °C for 48 h, the solvent was removed in vacuo. The product mixture was then resuspended in $CHCl_3$ and triturated before filtering through a pad of Celite. The filtrate was evaporated, and the residue was "dry-loaded" onto a pad of silica gel and eluted with CH_2Cl_2. Solvent was remove in vacuo, and a solid was precipitated from $CHCl_3$ by addition of hexanes. The hemicarceplex product mixture was then dried at 0.01 mmHg at 70 °C for 24 h. Product ratios were calculated from the ^{1}H NMR spectra by integration of each set of guest signals. The error in the integration is estimated to be ±10%.[10]

Control Experiments. Hemicarceplex **7**·guest 1 (**7**·G1, 1 5 mg), KI (12 mg, 0.072 mmol), and Cs_2CO_3 (90 mg, 0.275 mmol) were dissolved in of *N*-formylpiperidine (4 mL). Guest 2 and guest 3 (G2 and G3 respectively, 1 mol % each) were added under N_2 and stirred at 80 °C before adding of 1,4-dibromobutane (12 μL, 0.099 mmol). Competing guests were chosen so that the template ratios for G3 < G1 < G2. The mixture was allowed to stir for 2 days at 80 °C before removing the solvent in vacuo. Purification of the crude product mixture was identical to the procedure used for the competition reactions.

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Supporting Information Available: Characterization of 29 hemicarceplexes (**7**·guest), procedures for determining template ratios and control experiments, and tables of guest ^{1}H NMR chemical shifts, conditions for the formation of **7**·guest, competition experiments, and crosscheck experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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