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Templation effects on formation of a hemicarceplex

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We have shown previously that the reaction to form carceplex 3•guest has dramatic templation requirements where the best template molecule studied is one million times more effective at bridging the two bowl-shaped precursors than the poorest template. Here, we investigate the template requirements for the formation of hemicarceplex 4•guest which is similar to carceplex 3•guest in cavity size and shape. The two compounds differ in that 4•guest lacks one of the four inter-bowl methylene bridges and thus has a portal and reduced symmetry relative to carceplex 3•guest (C_{2v} vs D_{4h}). Thus, the template requirements for hemicarceplex 4•guest are more stringent because the two bowls can, in principle, misalign. We have found that despite these differences, the same template effect holds. We conclude that the same forces are at play in each reaction. These forces include 1) favorable van der Waals interactions between the template molecule and the forming cavity of the carceplex or hemicarceplex 2) unfavorable steric strain being imparted to the complex and 3) hydrogen bonds between the bowls. We also demonstrate the utility of matrix-assisted laser desorption ionization (MALDI) as a mild mass spectrometric technique for non-volatile organic compounds and complexes.

INTRODUCTION

Templation plays a role in the transformations that occur in a variety of reactions[1] and has widespread relevance to natural and non-natural systems such as the assembly of synthetic proteins,[2] the creation of molecularly imprinted polymers[3] and DNA replication. We are trying to elucidate the non-covalent forces that are often responsible for templation by exploring the template effect on the reactions to form carceplexes and hemicarceplexes. Carceplexes are closed surface compounds that contain permanently entrapped guest molecules within their shells such that guest escape can only occur by rupture of covalent bonds.[4] Hemicarceplexes are similar compounds, but they possess small portals through which guests can escape upon sufficient heating.[5] We recently reported a template effect that ranged one million-fold between good and poor template molecules in the formation of carceplex **3**•guest.[6] We interpreted the factor of one million to be a measure of the relative rate of the guest-determining-steps (GDS, the step beyond which guest exchange no longer occurs) when the reaction is run in the presence of the best versus the worst template molecules. We concluded that the better templates have more favorable van der Waals interactions with the cavity of the complex involved in the transition state of the GDS and impart the least strain to this complex.

In the case of carceplex **3**•guest, the reaction starts with tetrol **1**, whose symmetry precludes misalignment between two tetrol molecules, and ultimately yields carceplex **3**•guest (see **Fig. 1**) which has D_{4h} symmetry. To further probe the nature of the templation to form carceplex **3**•guest, we decided to investigate the template requirements for the formation of hemicarceplex **4**•guest, which has been synthesized by Cram.[5g] This compound has a cavity that is similar in size and shape to carceplex **3**•guest and is formed in an analogous reaction involving the formation of methylene bridges using CH_2BrCl[5g] (see **Fig. 1**). In contrast to carceplex **3**•guest, hemicarceplex **4**•guest contains a portal and has less symmetry than carceplex **3**•guest (C_{2v} vs D_{4h}). During the reaction to form hemicarceplex **4**•guest, two triol **2** molecules can, in principle, misalign leading to side products (see **Fig. 2**). We report here that despite the portal of hemicarceplex **4**•guest, its lower symmetry and the potential of two triols to misalign, the same forces that govern the templation of carceplex **3**•guest drive the formation of hemicarceplex **4**•guest.

RESULTS AND DISCUSSION

Of the 24 template molecules that were used in the carceplex competition experiments to generate template ra-

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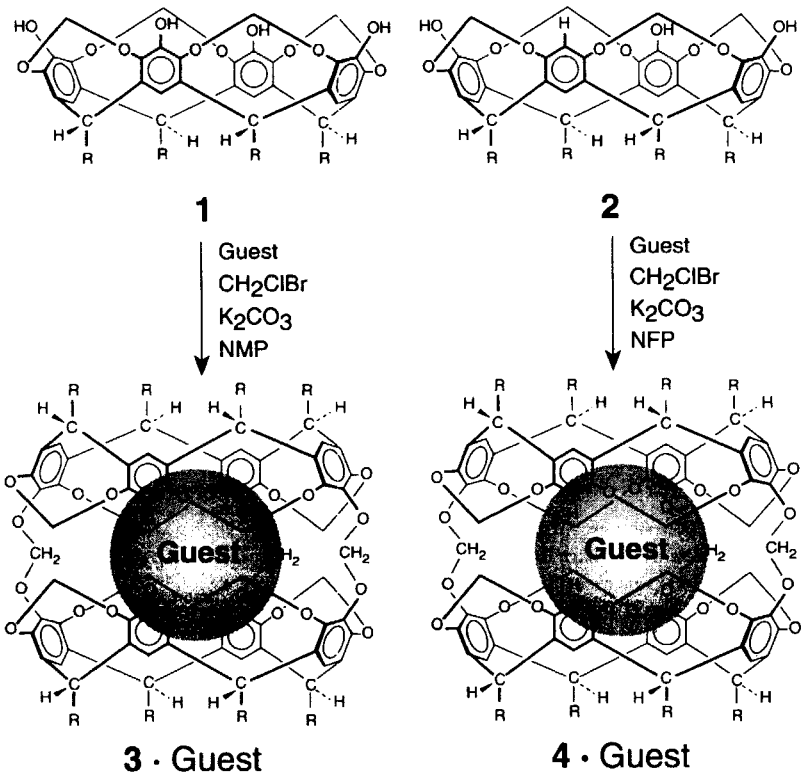


Figure 1 Reactions schemes for carceplex **3**•guest and hemicarceplex **4**•guest. NMP, *N*-methyl-2-pyrrolidinone; NFP, *N*-formylpiperidine.

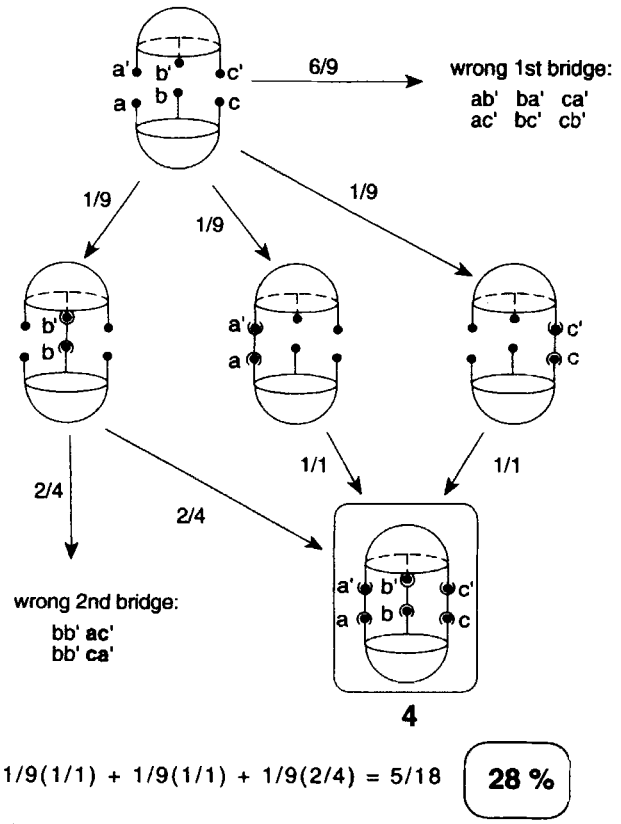


Figure 2 Schematic representation for statistical yield in the formation of hemicarceplex **4**•guest from triol **2**.

tios,[6] we chose nine (see **Fig. 3**) that spanned from one to one million in template abilities and used them in a similar series of competition reactions using triol **2** to form hemicarceplex **4**•guest (see **Fig. 1**). We chose *N*-formylpiperidine (NFP) as the solvent for the present study because NFP is not a suitable template and thus simplifies the competition reactions (*N*-methyl-2-pyrrolidinone, NMP, which was used as the solvent in the carceplex work, is a poor, but suitable template). These competition reactions entailed mixing two guests in solvent with triol **2**, CH_2BrCl and K_2CO_3 and stirring the reaction mixture for several days as indicated in **Table 1**. Following reaction work up, ^1H NMR spectra of the mixture of hemicarceplexes were obtained and the ratio of hemicarceplexes was determined by integration of the encapsulated guest signals (errors are estimated to be ± 10%). To minimize the errors in integration, the reactions were run starting with an unequal amount of two guests so that the resulting mixture of hemicarceplexes were close to 1:1. Control reactions were run to be sure that no guest exchange occurred in the hemicarceplexes subsequent to their formation. If such exchange took place, our ratios would be complicated by an equilibrium effect of complexation of guests to the empty hemicarcerand **4** rather than cleanly reflecting the ratio of the rates of the GDS. The controls entailed taking each of our hemicarceplexes and mixing them in NFP for one

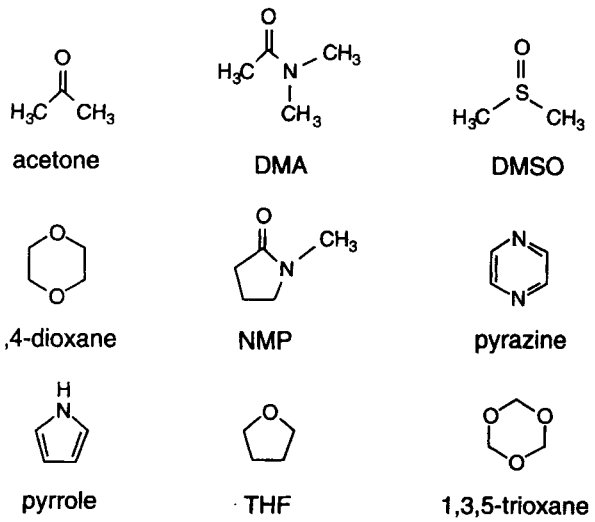


Figure 3 Guests used in competition experiments. DMA, dimethylacetamide; DMSO, dimethylsulfoxide; NMP, *N*-methyl-2-pyrrolidinone; THF, tetrahydrofuran.

day at ambient temperature and two days at 60°C in the presence of K_2CO_3, CH_2BrCl, KCl, KBr and 100 equivalents of each of the remaining eight guests. No guest exchange greater than 5% (which is within our error of ±10%) was observed for any of these controls. We also performed crosschecks to be sure that our tabulation of template ratios reflects the relative rates of the same step (i.e., is the GDS in each competition the same?). For example, a crosscheck between pyrazine and acetone gave a ratio of 340 which agrees with 270, the value from **Table 1**; a crosscheck between acetone and NMP gave a ratio of 520 which agrees with 620 from **Table 1**. Taken together, 340 times 520 is 170,000 which agrees with 170,000 from **Table 1**.

The results for the hemicarceplex experiments are shown in **Table 1** along with the carceplex results[6] for comparison. The results show that the yields and template ratios for each template molecule are similar for the carceplex and hemicarceplex systems. The greatest disparity is the template ability of NMP which is about ten times better at templation in the hemicarceplex reaction. The correlation of the template ratios for the carceplex and hemicarceplex reactions is made more apparent by the log plot shown in **Figure 4**. The correlation factor R for the line in **Figure 4** is 0.97 and becomes 0.99 if NMP is omitted from the plot. The slope of the line is 0.92 and becomes 1.02 without NMP. This plot indicates that the template molecules have a similar effect on the relative rates of the GDS of the reactions. Thus, the interactions necessary to stabilize the transition states in the GDS are similar and are largely independent of the low symmetry of triol **2**, hemicarceplex **4**•guest and the transition states formed. Likewise, the presence of a portal in the product does not have a major impact on the template effect. These results support our earlier conclusions[6] that the template effect is principally a function of favorable van der Waals interactions of the template molecules with the interior of the shell formed in the transition state that is involved in the GDS, with minimum strain being imparted into the complex formed with the best template. Poor templates either have poor van der Waals contacts with the cavity, impart strain into the system or both. The slight difference in NMP's template ability for carceplex and hemicarceplex formation may be due to the portal of **4** which may relieve some of the strain imparted by the large NMP molecule.

The potential of two triol **2** molecules to misalign does not reduce the efficiency of the formation of hemicarceplex **4**•guest to any great extent. A statistical analysis of the reaction pathways to form hemicarceplex **4**•guest is shown in **Fig. 2**. Cram discussed a slightly different statistical analysis of this reaction, but came up with essentially the same conclusions.[5g] The statistical yield of

Table 1 Yields and template ratios for hemicarceplex **4**•guest and carceplex **3**•guest

Guest	*% Yield of 4•Guest*[a]	*% Yield of 3•Guest*[b]	*Template Ratio for 4•Guest*	*Template Ratio for 3•Guest*[b]
pyrazine	56	87	170 000[c]	1 000 000
1,4-dioxane	57	68	52 000[c]	290 000
DMSO	51	63	6 200[c]	70 000
THF	39	50	1100[c]	12 000
acetone	40	51	620[c]	6 700
pyrrole	48	73	360[d]	1 000
1,3,5-trioxane	16	24	10[d]	100
DMA	14	15	2[d]	20
NMP	11[e]	5	1[d]	1

[a] Yield of pure hemicarceplex **4**•guest in the presence of only one template molecule (5 mole % guest, 2 days at 25°C, 2 days at 60°C).
[b] From reference 6. Reactions were run in NMP as solvent.
[c] 1 mole % guests, 2 days at 60°C.
[d] 5 mole % guests, 1 day at 25°C, 2 days at 60°C.
[e] Reaction was run in neat NMP as solvent.

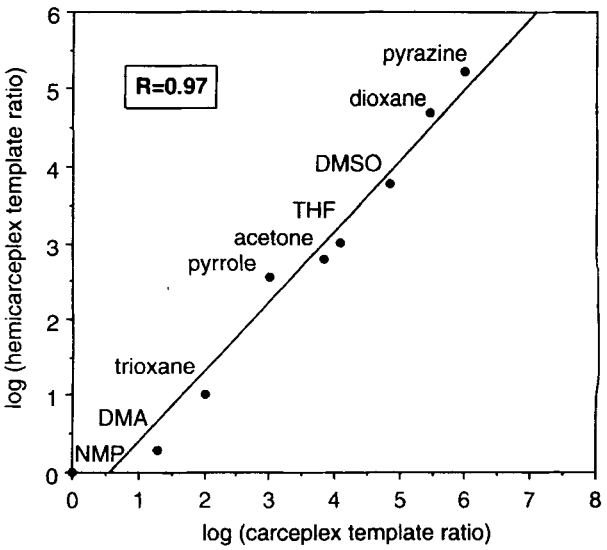


Figure 4 Correlation between hemicarceplex and carceplex template ratios.

28% is surpassed by most of our templates and was surpassed by Cram using dimethylsulfoxide or dimethylacetamide as solvents and template molecules. The template molecules are clearly important in bringing the two triols together, but proper alignment of the triol molecules must also occur. It seems likely that hydrogen bonds can form between the phenolic hydroxyls of opposing triols.[5g] The most stable arrangement would be for two triols to align all six phenols so that three hydrogen bonds can form. Such an association prior to bridging could account for the better than statistical yields observed. Indeed, we have recently seen evidence for a ternary complex between two molecules of triol **2** and the template molecule pyrazine, which will be reported elsewhere.[7]

The hemicarceplexes described in this paper were all fully characterized by the usual methods as described in the Experimental Section. These hemicarceplexes. as well as the analogous ones made by Cram,[5g] yield significantly more intense peaks for the empty hemicarcerand **4** than for the intact hemicarceplex **4**•guest in the mass spectrum when samples were subjected to fast atom bombardment (FAB), laser desorption or desorption chemical ionization (DCI) mass spectrometries. In the FAB experiments, the most intense peak for the intact hemicarceplex (**4**•guest + H^+) was obtained when dimethylacetamide was the guest and yielded a peak that was 18% of the peak corresponding to the empty hemicarcerand (**4** + H^+).[5g] In the laser desorption experiments, the peak for (**4**•α-pyrone + Na^+) was 75% of the peak for (**4**+ Na^+).[8] In general, it is very difficult to obtain peaks of the intact hemicarceplexes since the energy needed to volatilize and ionize these molecules is sufficient to promote the guest's escape from the complex. We have investigated the application of matrix-assisted laser desorption ionization (MALDI) to these hemicarceplexes since this technique has been shown to be a mild technique that causes minimum fragmentation in biomolecules[9] and synthetic polymers.[10] **Table 2** lists the relative peak intensity for the empty hemcarcerand and intact hemicarceplex peaks by MALDI [(M + Na^+) and (M•guest + Na^+), respectively] and by DCI [(M + H^+) and (M•guest + H^+), respectively] for six of the hemicarceplexes reported in this paper. It is evident from **Table 2** that MALDI is the mass spectrometry method of choice for these compounds and may be useful in general for non-volatile, neutral molecules that have a tendency to fragment. MALDI may prove fruitful for both strained compounds and for non-covalent complexes.

Table 2 Peak intensities of hemicarceplexes **4**•guest and empty hemicarcerands **4** by MALDI and DCI

Guest	*Relative Peak Intensity (%)*			
	MALDI[a]		*DCI*[b]	
	Empty 4	*4•Guest*	*Empty 4*	*4•Guest*
pyrazine	15	100	100	3
1,4-dioxane	29	100	100	2
DMSO	27	100	100	0
THF	72	100	100	2
acetone	54	100	100	0
NMP	48	100	100	0

[a] Peaks correspond to Na^+ adducts. The matrix was 2,5-dihydroxybenzoic acid. Laser power was between 3:60 and 3:97.
[b] Peaks correspond to H^+ adducts. The carrier gas was CH_4.

CONCLUSIONS

We have shown that the same forces that govern the templation of carceplex **3**•guest drive the formation of hemicarceplex **4**•guest, despite the presence of a portal in hemicarceplex **4**•guest, its lower symmetry and its potential to misalign. The driving forces for templation are an optimum of favorable van der Waals interactions of the template molecules with the walls of the cavity formed in the transition state of the GDS, with minimum strain being imparted into the complex. The template molecule also plays a role in bringing the bowls together and hydrogen bonds may help align the bowls prior to the GDS. Finally, MALDI is the definitive mass spectrometric technique for carceplexes and hemicarceplexes and may be generally useful as a mild mass spectrometric technique for non-volatile organic compounds and complexes.

EXPERIMENTAL

General

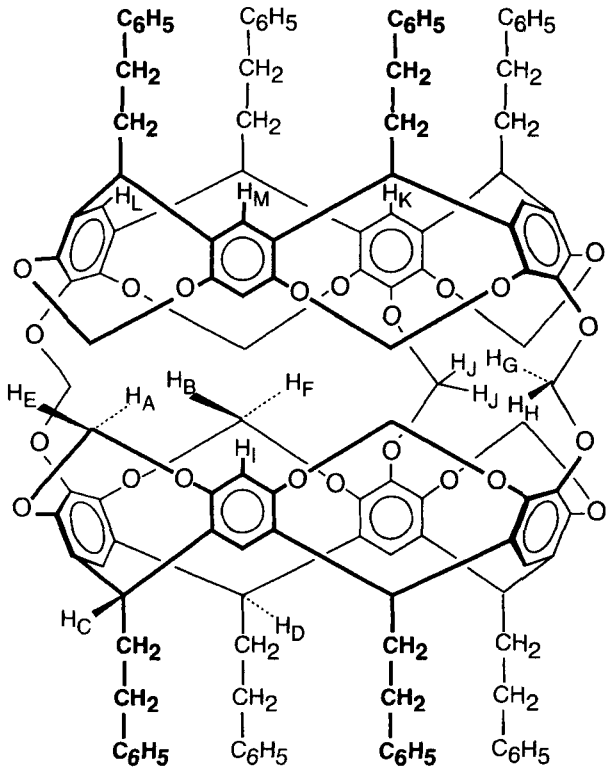
N-Formylpiperidine (Aldrich) was stirred over BaO for 24 hours, distilled under reduced pressure, and stored under N_2 over 4Å molecular sieves prior to use. Pyrrole was distilled under reduced pressure and stored in the dark under N_2 over 4Å molecular sieves prior to use. All other reagents (Aldrich) were used without further purification. Proton NMR spectra were run on a Bruker WH-400 spectrometer in $CDCl_3$ using the residual ^1H signal as a reference. Mass spectra were recorded on a Kratos Concept II HQ (DCI) and a VG Tofspec in linear mode (MALDI). Melting points (uncorrected) were measured on a Mel-Temp II apparatus. Silica gel (BDH, 230–400) was used for column chromatography. Silica thin-layer chromatography was performed on Aldrich glass-backed plates (silica gel 60, F_{254}, 0.25 mm). MALDI mass spectrometry samples were prepared by mixing 2 μL of a 300 μM sample in 50:50 (v/v) THF:$CHCl_3$ solvent with 2μL of 50 mM 2,5-dihydroxybenzoic acid matrix in THF. This mixture (2μL) was applied to a MALDI target disc and allowed to dry in air for 10 minutes before the target discs were inserted into the spectrome-

ter. Laser power was between 3:60 and 3:97. Our mass accuracies are all within 0.15% of theory, which is typical for MALDI.[11] Calculated molecular masses are averaged and not exact, due to the limited resolution of MALDI.

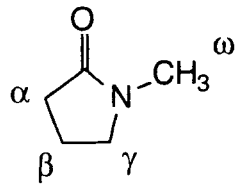
13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•$C_4H_4N_2$. Procedure "A" : To 50 mL of *N*-formylpiperidine (NFP) were added 107 mg (0.106 mmol) of triol 2, 33.5 μL (0.515 mmol) of CH_2BrCl, 1.0 g (7.23 mmol) of K_2CO_3, and 18.1 mg (2.25 mmol) of pyrazine. The reaction was stirred under N_2 for 2 days at ambient temperature and then for 2 days at 60°C. The solvent was removed *in vacuo* and $CHCl_3$ (100 mL) was added to the crude mixture. The $CHCl_3$ was washed with 2M HCl (3×40 mL), then with saturated $NaHCO_3$ (100 mL) and finally with brine (100 mL). The $CHCl_3$ solution was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$ and eluted through a pad of silica gel with $CHCl_3$. The solvent was removed *in vacuo* and the residue was recrystallized from $CHCl_3$-EtOAc to give 63 mg of 4•$C_4H_4N_2$ (56%). mp>300°C. ^{1}H NMR ($CDCl_3$) δ 2.52 (m, 16H, $CH_2CH_2C_6H_5$), 2.66 (m, 16 H, $CH_2CH_2C_6H_5$), 4.09 (s, 4H, $C_4H_4N_2$), 4.19 (br s, 8H, H_A, H_B), 4.86 (t, 4H, H_C or H_D, J=7.8 Hz), 4.92 (t, 4H, H_C or H_D, J=7.8 Hz), 5.82 (d, 4H, H_E or H_F, J=7.0 Hz), 6.04 (d, 4H, H_E or H_F, J=7.4 Hz), 6.26 (d, 2H, H_G or H_H, J=6.3 Hz), 6.44 (d, 2H, H_G or H_H, J=6.4 Hz), 6.55 (s, 2H, H_I or H_J), 6.58 (s, 2H, H_I or H_J), 6.90 (s, 2H, H_K), 6.92 (s, 4H, H_L), 7.10–7.30 (br m, H_M, $CH_2CH_2C_6H_5$, $CHCl_3$); MS (MALDI) m/e 2144 (M•pyrazine + Na^+, 100%); Calcd for $C_{135}H_{116}O_{22}N_2$: 2141. Anal. Calcd for $C_{135}H_{116}N_2O_{22}$: C, 76.54; H, 5.52; N, 1.32. Found: C, 76.23; H, 5.52; N, 1.26.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•$C_4H_8O_2$. Procedure "A" was employed using 99 mg (0.099 mmol) of triol 2 and 383 μL (4.49 mmol) dioxane in 50 mL of NFP yielding 56 mg of 4•$C_4H_8O_2$ (53%). mp>300°C. ^{1}H NMR ($CDCl_3$) δ−0.21 (br s, 8H, $C_4H_8O_2$), 2.45 (m, 16H, $CH_2CH_2C_6H_5$), 2.62 (m, 16H, $CH_2CH_2C_6H_5$), 4.44 (d, 8H, H_A, H_B, J=7.3 Hz), 4.80 (t, 4H, H_C or H_D, J=7.9 Hz), 4.89 (t, 4H, H_C or H_D, J=7.9 Hz), 5.96 (br s, 4H, H_E or H_F), 6.20 (d, 4H, H_E or H_F, J=6.5 Hz), 6.50 (d, 2H, H_G or H_H, J=6.2 Hz), 6.50 (s, 2H, H_I), 6.54 (s, 2H, H_J), 6.68 (s, 2H, H_K), 6.70 (d, 2H, H_G or H_H, J=6.4 Hz), 6.76 (s, 4H, H_L), 7.08 (s, 2H, H_M), 7.10–7.30 (br m, $CH_2CH_2C_6H_5$, $CHCl_3$); MS (MALDI) m/e 2147 (M•dioxane + Na^+, 100%); Calcd for $C_{135}H_{120}O_{24}$: 2149. Anal. Calcd for $C_{135}H_{120}O_{24}$: C, 76.25; H, 5.69. Found: C, 75.96; H, 5.60.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•$(CH_3)_2CO$. Procedure "B" was employed. This procedure is similar to "A", but with the gradual addition of CH_2ClBr, so as to avoid its entrap-



Scheme 1



Scheme 2

ment during the synthesis. To 50 mL of NFP was added 99 mg (0.099 mmol) of triol 2, 25 μL (0.46 mmol) of CH_2ClBr, 1.5 g (10.8 mmol) of K_2CO_3 and 1.0 mL (13.6 mmol) of acetone as guest. An additional 25 μL of CH_2ClBr were added daily, giving a total of 75μL (1.38 mmol). Purification gave 30 mg of 4•$(CH_3)_2CO$ (29%). mp>300°C. ^1H NMR ($CDCl_3$) δ -1.60 (s, 6H, $(CH_3)_2CO$), 2.45 (m, 16H, $CH_2CH_2C_6H_5$), 2.63 (m, 16H, $CH_2CH_2C_6H_5$), 4.30 (m, 8H, H_A, H_B), 4.80 (t, 4H, H_C or H_D, J=7.9 Hz), 4.89 (t, 4H, H_C or H_D, J=7.9 Hz), 5.94 (d, 4H, H_E or H_F, J-7.1 Hz), 6.21 (d, 4H, H_E or H_F, J=7.5 Hz), 6.43 (br s, 2H, H_G or H_H), 6.58 (s, 2H, H_I), 6.60 (s, 2H, H_J), 6.61 (d, 2H, H_G or H_H, J=6.4 Hz), 6.72 (s, 2H, H_K), 6.79 (s, 4H, H_L), 7.08 (s, 2H, H_M), 7.10–7.30 (br m, $CH_2CH_2C_6H_5$, $CHCl_3$); MS (MALDI) m/e 2118 (M•acetone + Na^+, 100%); Calcd for $C_{134}H_{118}O_{23}$: 2119. Anal. Calcd for $C_{134}H_{118}O_{23}$: C, 76.77; H, 5.67. Found: C, 76.39; H, 5.68.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•C_4H_4NH. Procedure "B" was employed using 102 mg (0.102 mmol) of triol **2** and 1.0 mL (14.4 mmol) distilled pyrrole in 50 mL NFP. Purification yielded 42 mg of 4•C_4H_4NH (48%). mp>300°C. ^1H NMR ($CDCl_3$) δ 2.51 (br, 16H, $CH_2CH_2C_6H_5$), 2.65 (br, 16H, $CH_2CH_2C_6H_5$), 3.04 (m, 2H, H_α or H_β of C_4H_4NH), 3.37 (m, 2H, H_α or H_β of C_4H_4NH), 4.12 (d, 4H, H_A or H_B, J=6.8 Hz), 4.17 (s, 1H, N–H of C_4H_4NH), 4.21 (d, 4H, H_A or H_B, J=7.4 Hz), 4.82 (t, 4H, H_C or H_D, J=7.8 Hz), 4.90 (t, 4H, H_C or H_D, J=7.9 Hz), 5.88 (d, 4H, H_E or H_F, J=6.9 Hz), 6.10 (d, 4H, H_E or H_F, J=7.3 Hz), 6.40 (s, 2H, H_I), 6.46 (d, 2H, H_G or H_H, J=6.4 Hz), 6.50 (s, 2H, H_J), 6.59 (d, 2H, H_G or H_H, J=6.4 Hz), 6.83 (s, 2H, H_K), 6.91 (s, 4H, H_L), 7.10–7.30 (br m, H_M, $CH_2CH_2C_6H_5$, $CHCl_3$); MS (MALDI) m/e 2127 (M•pyrrole + Na^+, 100%); Calcd for $C_{135}H_{117}O_{22}N$: 2128. Anal. Calcd for $C_{135}H_{117}NO_{22}$: C, 77.02; H, 5.60; N, 0.67. Found: C, 76.83; H, 5.66; N, 0.67.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•$C_3H_6O_3$. Procedure "B" was used with 104 mg (0.104 mmol) of triol **2** and 2.0 g (22.2 mmol) of trioxane yielding 18 mg of 4•$C_3H_6O_3$ (16%). mp>300°C. ^1H NMR ($CDCl_3$) δ 1.90 (s, 6H, $C_3H_6O_3$), 2.46 (m, 16H, $CH_2CH_2C_6H_5$), 2.63 (m, 16H, $CH_2CH_2C_6H_5$), 4.36 (d, 4H, H_A or H_B, J=7.1 Hz), 4.46 (d, 4H, H_A or H_B, J=6.7 Hz), 4.80 (t, 4H, H_C or H_D, J=7.9 Hz), 4.89 (t, 4H, H_C or H_D, J=7.9 Hz), 5.97 (d, 4H, H_E or H_F, J=7.1 Hz), 6.18 (d, 4H, H_E or H_F, J=7.5 Hz), 6.46 (br s, 4H, H_G or H_H, H_I), 6.56 (s, 2H, H_J), 6.65 (d, 2H, H_G or H_H, J=6.4 Hz), 6.72 (s, 2H, H_K), 6.78 (s, 4H, H_L), 7.08 (s, 2H, H_M), 7.10–7.30 (m, $CH_2CH_2C_6H_5$, $CHCl_3$); MS (MALDI) m/e 2151 (M•trioxane + Na^+, 100%); Calcd for $C_{134}H_{118}O_{25}$: 2151. Anal. Calcd for $C_{134}H_{118}O_{25}$: C, 75.62; H, 5.59. Found: C, 75.36; H, 5.74.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•C_4H_9NO. Procedure "C" was employed, where the reaction was run in neat guest as solvent with 207 mg (0.207 mmol) of triol 2 and 50 mL of NMP. Addition of 60 μL of a 5M stock solution of CH_2ClBr (in NMP) was made daily for a total of 240 μL (1.2 mmol). Purification-yielded 24 mg of 4•C_4H_9NO (11%). Asymmetry is induced in the host due to restricted rotation of the bulky NMP guest. The northern and southern hemispheres are no longer equivalent, and doubling of most of the host signals is observed. mp>300°C. ^1H NMR ($CDCl_3$) δ -1.95 (m, 2H, H_β), -1.73 (s, 2H, $H\omega$), -1.66 (m, 2H, H_α or H_γ), 1.32 (m, 2H, H_α or H_γ), 2.47 (m, 16H, $CH_2CH_2C_6H_5$), 2.65 (m, 16H, $CH_2CH_2C_6H_5$), 4.45–4.62 (m, 8H, H_A, H_B), 4.84 (t, 4H, H_C or H_D, J=7.7 Hz), 4.91 (t, 4H, H_C or H_D, J=7.7 Hz), 5.70 (d, 2H, H_E or H_F, J=6.9 Hz), 5.77 (d, 2H, H_E or H_F, J=7.4 Hz), 6.07 (d, 2H, H_G or H_H, J=5.2 Hz), 6.13 (m, 4H, H_E or H_F), 6.41 (br s, 2H, H_G or H_H), 6.55 (s, 2H, H_J), 6.71 (s, 1H, H_I or H_K), 6.76 (s, 1H, H_I or H_K), 6.77 (s, 1H, H_I or H_K), 6.79 (s, 2H, H_L), 6.81 (s, 3H, H_I, H_K or H_L), 6.94 (s, 1H, H_M), 7.06 (s, 1H, H_M), 7.10–7.30 (m, $CH_2CH_2C_6H_5$, $CHCl_3$); MS (MALDI) m/e 2160 (M•NMP + Na^+, 100%); Calcd for $C_{136}H_{121}NO_{23}$: 2160. Anal. Calcd for $C_{136}H_{121}O_{23}N$: C, 76.42; H, 5.71; N, 0.66. Found: C, 76.10; H, 5.59; N, 0.60.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•$(CH_3)_2SO$. Procedure "A" was employed using 104 mg (0.103 mmol) of triol **2** and 319 μL

(4.50 mmol) DMSO in 50 mL of NFP yielding 44.4 mg of **4**•$(CH_3)_2SO$ (40%). This compound had the same ^1H NMR spectrum as reported in the literature.[5g] MS (MALDI) m/e 2136 (M•DMSO + Na^+, 100%); Calcd for $C_{133}H_{118}O_{23}S$: 2139.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•C_4H_8O. Procedure "A" was also employed using 104 mg (0.103 mmol) of triol **2** and 366 μL (4.50 mmol) THF in 50 mL NFP yielding 32 mg of 4•C_4H_8O (29%). This compound had the same ^1H NMR spectrum as reported in the literature.[5g] MS (MALDI) m/e 2132 (M•THF + Na^+, 100%); Calcd for $C_{135}H_{120}O_{23}$: 2133.

13,59-(Epoxymethanoxy)-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H*,19*H*,21*H*,29*H*,47*H*,49*H*-bis[1,3]benzodioxocino[9,8-d:9',8'-*d*'']][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5-*j*:10,9-*j*':14,15-*j*'':20,19-*j*''']tetrakis[1,3]benzodioxocin, 1,19,21,29,47,49,57,62-octakis(2-phenylethyl)-, Stereoisomer, 4•$(CH_3)_2NCOCH_3$. Procedure "B" was used with 103 mg (0.103 mmol) of triol **2** and 2.2 mL (24 mmol) DMA in 50 mL of NFP yielding 15 mg of 4•$(CH_3)_2NCOCH_3$ (14%). This compound had the same ^1H NMR spectrum as reported in the literature.[5g]

Competition Experiments To 20 mL of *N*-formylpiperidine were added 20 mg (0.020 mmol) of triol **2**, 0.6 g (4.34 mmol) of K_2CO_3, 12 μL (0.185 mmol) of CH_2ClBr, and guest 1 (G1) and guest 2 (G2). The relative ratios of G1:G2 added were chosen so as to obtain a nearly 1:1 ratio in the NMR spectrum. The reactions were run according to the conditions described in **Table 1**. After purification of the products the product ratio for the mixture was calculated from the ^1H NMR spectra by integration of the guest peaks. The error in the integration was estimated to be ± 10%.

Control Experiments To 20 mL of *N*-formylpiperidine was added 10–15 mg of hemicarceplex **4**•guest, 0.6 g of K_2CO_3 (4.34 mmol), 12μL CH_2ClBr (0.185 mmol), excess KCl and KBr and 9.0 mmol each of all the other guests in **Table 1**. The mixture was stirred for one day at room temperature and two days at 60°C. After purification, examination of the ^1H NMR spectra showed that no more than 5% guest exchange was observed in any case. This is within our error of ± 10% for the ^1H NMR integration.

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