# Templation in the Formation of Carceplexes

Robert G. Chapman and John C. Sherman*

*Department of Chemistry, University of British Columbia, Vancouver, BC, Canada V6T 1Z1*

*Received February 26, 1998*

The formation of carceplexes and hemicarceplexes involves an assembly process whereby a molecular template is entrapped between two bowl-shaped molecules. The process can be highly selective such that a million-fold range in template recognition has been realized. The relative template abilities, or template ratios, for 34 molecules in forming carceplex **2**·guest is described. Species with one, two, and three bridges linking the two "bowls" are reported and were used to delineate the guest-determining step of the reaction. The effect of base and solvent on the reaction are also described, and a discussion of the reaction mechanism is presented.

## Introduction

Molecular recognition is integral to myriad functions, from biological processes to molecular devices.[1] An understanding of the noncovalent interactions that govern the recognition process is paramount to the elucidation of newly discovered natural systems and to the design and modification of de novo systems. An ideal model to study such noncovalent interactions is one that is easily and fully characterizable and shows high selectivity in its recognition. One of the most striking examples of such guest selectivity by a designed host system is where guest molecules function as templates in the formation of carceplexes, which are closed surface compounds that incarcerate smaller molecules or ions.[2a] The creation of carceplexes and their relations, hemicarceplexes, has proliferated recently, yet the mechanism of their formation is still poorly understood.[2] The formation of such species is of wide interest, as the assembly process that is responsible involves not only sophisticated molecular recognition but also molecular encapsulation and an unusually sensitive templation process.[3]

In the formation of carceplex **2**·guest, two bowl-shaped molecules (tetrol **1**) wrap around a guest/template molecule and the two "bowls" get sewn together by the irreversible formation of four $OCH_2O$ bridges (Scheme 1).[4] In this process, seven molecules come together and eight new covalent bonds form. Yet, the reaction is highly efficient, with yields as high as 87%.[5] The reaction appears to work only if a suitable template molecule is present, and the abilities of template molecules to form this carceplex were found to vary by $10^6$-fold. This remarkable selectivity was underscored by the determination of a 75% yield of carceplex **2a**·pyrazine (the best template) in the presence of only a stoichiometric amount of pyrazine in *N*-methylpyrrolidinone (NMP, the poorest template)[6] as solvent (i.e., $10^4$-fold excess NMP).[5] What drives this reaction?

In a preliminary report, the extremely large gap in template abilities between pyrazine and NMP was filled in by 22 other guests-as-templates that had intermediary template abilities.[5] The templating ability of one guest or template molecule versus another were called *template ratios*. The template ratios were determined by competition experiments whereby two guests are present during carceplex formation and the product ratios carceplex **2**·guest 1:carceplex **2**·guest 2, were determined from integration of $^1$H NMR spectra to generate a template ratio; thus, template ratios and product ratios are synonomous in our system.[5] What is the significance of template ratios? Since the formation of the $OCH_2O$ bridges between the two bowls is irreversible, there must be a key bridge that locks the guests within the capsule irreversibly, with respect to the time scale of the experiment. This particular bridge formation would be considered the guest-determining step (GDS),[6] the step beyond which the guest no longer exchanges under the reaction conditions. Regarding the guest/template molecules, what comes before or after the GDS is irrelevant to their ultimate fate. That is, the ratio of template molecules entrapped in the carceplex is determined solely by their competition at the GDS. Thus, just as a product ratio represents the relative rate of a product-determining step,[6] a template ratio reflects the relative rate of reaction of the GDS for two different guest molecules. More generally, for a series of molecules the template ratios reflect the relative rates of the GDS for that series of guest molecules. This step is $10^6$ times faster in the presence of pyrazine than in the presence of NMP.

(1) *Comprehensive Supramolecular Chemistry*; Lehn, J.-M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: New York, 1996.

(2) (a) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 2575−2576. (b) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*, from the series Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1994. (c) Sherman, J. C. *Tetrahedron* **1995**, *51*, 3395−3422. (d) Sherman, J. C. In *Large Ring Compounds*; Semlyen, J. A., Ed.; John Wiley & Sons, Ltd.: London, 1996; pp 507−524. (e) Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 3229−3244. (f) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590−5604. (g) van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reindoudt, D. N. *Chem. Eur. J.* **1997**, *3*, 639−654.

(3) Chapman, R. G.; Sherman, J. C. *Tetrahedron* **1997**, *53*, 15911−15946, and references therein.

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

(5) Chapman, R. G.; Chopra, N.; Cochien, E. D.; Sherman, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 369−370.

(6) Abbreviations: NMP, *N*-methylpyrrolidinone; GDS, guest-determining step (the GDS is also the product-determining step; we use GDS because our focus is on the guest or template effect in the assembly process); DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMA, dimethylacetamide; CPK, Corey−Pauling−Koltun space filling models; $\Delta\delta$d, the difference in chemical shifts, usually between free and entrapped guests; MALDI, matrix-assisted laser desorption ionization.

S0022-3263(98)00358-2 CCC: $15.00 
Published on Web 05/15/1998

**Scheme 1. Formation of Carceplex 2·Guest and Complex 3·Guest from Tetrol 1**

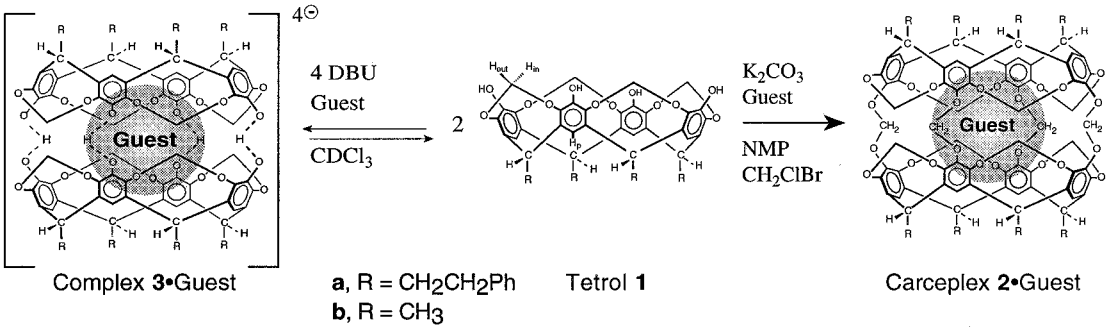
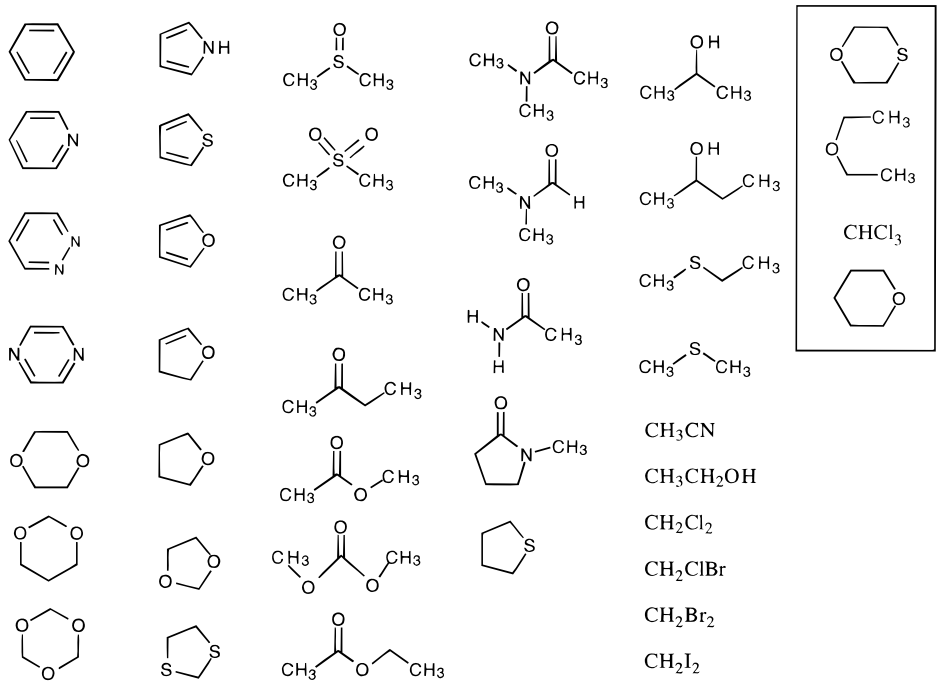



**Table 1. Suitable Template Molecules. The Boxed Molecules Formed Carceplex 2a·Guest but Were Characterized as Mixtures**




Alternatively, the transition state for the GDS is 8.3 kcal/mol lower in the presence of pyrazine than in the presence of NMP at 300 K.[7]

But what drives the reaction? To answer this question directly, one must examine the transition state for the GDS. As this is not readily available, a complex formed between two bowls and a guest molecule, complex **3**·guest, was explored.[8] It was determined that the guest selectivity of this complex correlated with the template ratios. Thus, complex **3**·guest represents a good transition state model for the GDS in the formation of carceplex **2**·guest.[8] This paper reports the determination of the GDS, the characterization of four new intermediates containing 1−3 interbowl bridges, and the effect of base and solvent on the reaction. In addition, the template ratios for 10 new guests are reported. Finally, a discussion of the reaction mechanism is provided.

(7) The 8.3 kcal/mol difference in activation energy was calculated using the following equation: $\Delta\Delta G^{\ddagger} = -RT \ln(k_{pyrazine}/k_{NMP})$, where $T = 300$ K, $k_{NMP}$ is the rate constant for formation of carceplex **2a**·NMP, and $k_{pyrazine}$ is the rate constant for formation of carceplex **2a**·pyrazine; $k_{pyrazine}/k_{NMP} = 10^6$.

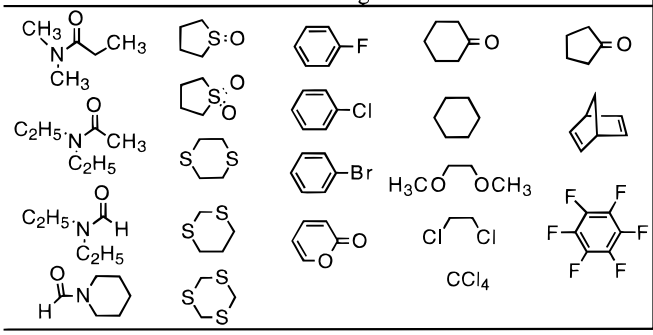
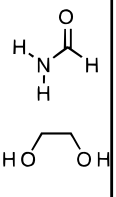
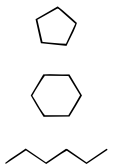
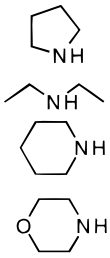
(8) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082.

## Results and Discussion

**1. Determination of Template Ratios.** The first step in investigating the assembly process to form carceplex **2**·guest is to screen for successful template molecules. The choice of reaction solvent is critical, for a polar solvent facilitates the bridging reactions and one ideally wants a noncompetitive template molecule as solvent. The relatively large dipolar aprotic solvent NMP was chosen as the bulk solvent for screening potential template molecules for such reasons. Thus, 70 potential template molecules were screened by incorporating them as cosolvents (~5 mol % based on NMP) into the reaction mixtures, and the reactions were run over 2 days at 60 °C. Of these 70 template molecules, 40 molecules were found to be suitable templates for the formation of carceplex **2a**·guest (Table 1) while 30 molecules were unsuitable templates (Table 2). Guests that did not lead to formation of carceplex **2a**·guest were classified (Table 2) in terms of their size, basicity, or polarity, as these properties are the most likely causes for their unsuitability as templates.[9]

The diverse range of incorporated guest molecules (Table 1) prompted us to investigate their templating abilities further. Thus, competition experiments were

**Table 2. Unsuitable Guests**

| Too Large | Too Polar | Too Apolar | Too Basic |
|---|---|---|---|
|  |  |  |  |

performed on 34 of the successful template molecules to generate template ratios (Table 3).[5,9−11] Each of the template ratios were referenced to the poorest template (NMP) which was arbitrarily given a value of 1.

**2. Interpretation of Template Ratios.** The data from Table 2 and Table 3 demonstrate some definite trends, most notably in guest size. For instance, the largest suitable template, NMP, is the only template to have as many as seven non-hydrogen atoms. For the unsuitable templates, the majority are simply too large for the interior of the carceplex. It is fairly remarkable just how selective the carceplex is toward the size of its guest molecule. For example, benzene is a reasonably good template molecule, but fluorobenzene is unsuitable; carceplex formation is apparently sensitive to the substitution of a hydrogen (van der Waals radius = 1.2 Å)[12] for a fluorine (van der Waals radius = 1.47 Å),[12] although this differentiation could also be electronic in nature. Furthermore, 1,4-dioxane is 21 times better than the slightly larger 1,4-thioxane; moreover, 1,4-dithiane (both oxygens replaced by sulfur) is an altogether unsuitable

**Table 3. Carceplex 2a·Guest Yields and Competition Experiments**

| | guest | yield, %[a] | template ratio[b] | condns[b] |
|---|---|---|---|---|
| 1 | pyrazine | 87 | 1000000 | A |
| 2 | methyl acetate | 75 | 470000 | A |
| 3 | 1,4-dioxane | 68 | 290000 | A |
| 4 | dimethyl sulfide | 52 | 180000 | A |
| 5 | ethyl methyl sulfide | 67 | 130000 | A |
| 6 | dimethyl carbonate | 52 | 73000 | A |
| 7 | DMSO | 63 | 70000 | A |
| 8 | 1,3-dioxolane | 64 | 38000 | A |
| 9 | 2-butanone | 75 | 37000 | A |
| 10 | pyridine | 46 | 34000 | A |
| 12 | dimethyl sulphone | 60 | 19000 | A |
| 12 | 1,4-thioxane | 55[c] | 14000 | A |
| 13 | 2,3-dihydrofuran | 38 | 13000 | A |
| 14 | furan | 54 | 12000 | A |
| 15 | tetrahydrofuran | 50 | 12000 | A |
| 16 | pyridazine | 30 | 8600 | A |
| 17 | acetone | 51 | 6700 | A |
| 18 | thiophene | 23 | 5800 | A |
| 19 | 1,3-dithiolane | 43 | 4400 | A |
| 20 | (±)-2-butanol | 47 | 2800 | A |
| 21 | benzene | 43 | 2400 | A |
| 22 | 2-propanol | 74 | 1500 | A |
| 23 | pyrrole | 73 | 1000 | B |
| 24 | tetrahydrothiophene | 34 | 410 | B |
| 25 | 1,3-dioxane | 45 | 200 | B |
| 26 | acetamide | 26 | 160 | B |
| 27 | trioxane | 24 | 100 | B |
| 28 | acetonitrile | 35 | 73 | B |
| 29 | ethanol | 38 | 61 | B |
| 30 | ethyl acetate | 17 | 45 | B |
| 31 | diethyl ether | 14[d] | 21 | B |
| 32 | dimethylacetamide | 15 | 20 | B |
| 33 | dimethylformamide | 4 | 7 | B |
| 34 | NMP | 5[e] | 1 | B |

[a] Yield refers to the reaction run with only one guest. [b] Conditions A: 1 mol % guests, 2 days, 60 °C. Conditions B: 5 mol % guests, 1 day ambient temperature, 2 days, 60 °C. [c] Characterized as a mixture of carceplex **2a**·1,4-thioxane (86%) and carceplex **2a**·1,4-dioxane (14%). [d] Characterized as a mixture of carceplex **2a**·diethyl ether (96%) and carceplex **2a**·bromochloromethane (4%). [e] Reaction run in neat NMP.

(9) In the presence of pyrazine and the four secondary amines, carceplex **2**·pyrazine formed, confirming that the amines are poor templates and were not merely degrading $CH_2BrCl$. The cause of their unsuitability is unknown and may be due to their solvation by NMP, not necessarily their basicity. There are also several carceplexes not included in Table 1 that were characterized only by $^1H$ NMR spectroscopy that deserve mention. Imidazole, 1,2,4-triazole, and cyclopentadiene all gave carceplexes **2a**·guest in < 5% yields. Also, methanol gave a mixture of carceplexes **2a**·guest in < 5% yield; $^1H$ NMR spectra of this material indicated that the majority was carceplex **2a**·NMP and carceplex **2a**·$CH_2BrCl$, but there were also signals at −0.58 and −0.62 ppm that could not be assigned and may be due to entrapped methanol. None of these guests were included in the competition experiments.

(10) A number of the carceplexes were initially isolated as mixtures with carceplex **2a**·NMP. Such mixtures were obtained using the following guests: acetamide, trioxane, acetonitrile, ethanol, ethyl acetate, dimethylacetamide, and dimethylformamide. These mixtures, however, were readily separated via silica gel chromatography to give carceplex **2a**·NMP and the respective carceplex **2a**·guest. There were also a number of guest molecules that led to an inseparable mixture of carceplexes: $CHCl_3$, diethyl ether, and tetrahydropyran furnished an inseparable mixture of carceplexes **2a**·guest and **2a**·$CH_2BrCl$. Generally, a guest molecule is a very poor template when the small amount of $CH_2BrCl$ present in the reaction (1 mmol of $CH_2BrCl$ compared to 50 mmol of guest) effectively competes with it. The carceplex **2a**·$CH_2BrCl$ impurity in principle can be avoided by use of a larger bridging material. Although both dibromomethane and diiodomethane are suitable for the bridging reaction, their template ability surpasses that of the poor guests; therefore, they were not suitable for this purpose. Methylene ditosylate is a bridging material that is too large to fit in the interior of a carceplex. Indeed, this bridging material was successfully used in the formation of carceplex **2a**·pyrazine and could, in principle, be used to create pure carceplexes using poorer templates. Nevertheless, carceplexes **2a**·$CHCl_3$, **2a**·tetrahydropyran, and **2a**·diethyl ether were characterized as mixtures by $^1H$ NMR and matrix-assisted laser desorption ionization mass spectrometry. Of these guests, only diethyl ether was included in our competition experiments because it only yielded a small impurity (<4%) of carceplex **2a**·$CH_2BrCl$. The dihalomethanes were omitted from the competition experiments since they act as bridging reagents. The reactions carried out with 1,4-thioxane as guest resulted in an inseparable mixture of carceplexes **2a**·1,4-thioxane and **2a**·1,4-dioxane in a 7:1 ratio (1,4-thioxane contains ~1% impurity of 1,4-dioxane). The superior templating ability of 1,4-dioxane over 1,4-thioxane results in a 14% yield of carceplex **2a**·1,4-dioxane in the presence of a vast excess of 1,4-thioxane.

(11) The experimental procedure and a sample calculation for the generation of template ratios is given in the Supporting Information.

(12) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York, 1990; p 120.

template. The formation of carceplexes is very sensitive to the addition of a single methylene. For example, methyl acetate is $10^4$ times better than ethyl acetate, and 1,3-dioxolane is 190 times better than 1,3-dioxane. The addition of an oxygen can also create differences in template abilities. For example, dimethyl sulfide is 2.5 times better than DMSO which is itself 3.7 times better than dimethyl sulfone. Substantial differences in template abilities exist between pyrazine, pyridine, and benzene, which only differ by the substitution of a nitrogen(s) for a C−H(s). Pyrazine is 29 times better as a template than pyridine which is itself 14 times better than benzene; the introduction of an extra hydrogen apparently causes significant steric strain in the transition state of the GDS, although, again, electronic effects may also be important.

Polarity of the template molecules becomes important only at the extremes. Although the polarity of the suitable templates spans a diverse range from DMSO ($\epsilon_r = 46$)[13] to benzene ($\epsilon_r = 2$),[13] both highly polar molecules such as water and highly apolar molecules such as cyclopentane are unsuitable templates. High symmetry tends to increase the templating power of guests as is evident with 1,4-dioxane which is 1400 times better than 1,3-dioxane. Similarly, pyrazine (1,4-diazabenzene) is 120 times better than pyridazine (1,2-diazabenzene). Cyclic guests are much better than acyclic guests. For example, 1,4-dioxane is the third best template while dimethoxyethane is an unsuitable template. Furthermore, THF is 570 times better than diethyl ether.

Another general trend that can be gleaned from Table 3 is that the yields usually increase with increasing template abilities of the guest molecules. For example, the best guest (pyrazine) has the highest yield and the poorest guests (NMP and DMF) have the lowest yields. Yet, there are many exceptions to this trend. Therefore, the yield alone is not strictly indicative of the template ability of the guest molecules for formation of carceplex **2a**·guest as has been explained earlier.[5]

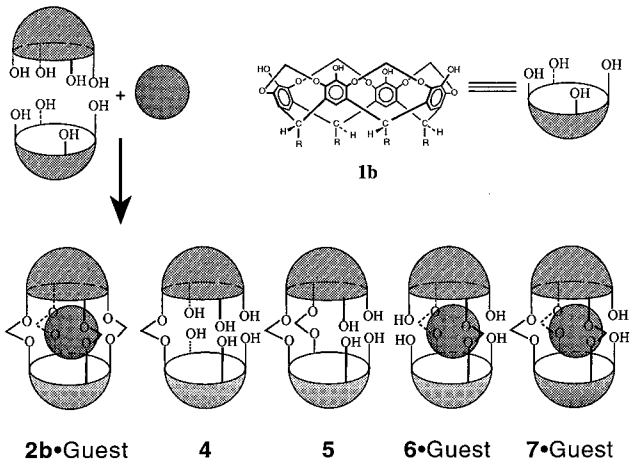
There was no correlation found between our template ratios (Table 3) and solvent parameters such as acceptor number, dielectric constant,[13] dipole moment,[13] $E_T$,[13] or Hildebrand's $\delta$.[14] Graphs of ln(template ratios) versus these five solvent parameters result in correlations of $r^2 < 0.14$. Therefore, the polarity of the template does not appear to be a dominant factor in the template abilities of the guest molecules. Additionally, there were no apparent similarities between template ratios and the theoretical MM2 calculated energies for carceplex **2a**·guest.[5] More sophisticated theoretical studies of carceplex **2**·guest and complex **3**·guest have been performed and yield a reproduction of the general trend observed experimentally.[15]

**3. The Guest-Determining Step (GDS).** To delineate the driving forces for formation of carceplex **2**·guest and the ensuing template effect, one should ideally look at the transition state of the GDS and compare different templates at that point. Which step is the GDS? The search for the GDS is described below; it entailed a closer analysis of the carceplex reaction in general.

**Table 4. Disappearance of Tetrol 1a at 25 °C**

| time (h) | % tetrol remaining guest = pyrazine | % tetrol remaining guest = NMP |
|---|---|---|
| 6 | 13 | 83 |
| 12 | 0 | 80 |
| 48 | 0 | 10 |

**Scheme 2. Schematic Representation of Carceplex Intermediates (R = $CH_3$)**




**(a) Isolation of Reaction Intermediates.** Is the selectivity observed for the formation of carceplex **2**·guest the result of the formation of the first interbowl (O−$CH_2$−O) bridge? To address this question, we looked at the rate of formation of the first bridge by following the disappearance of the starting material (tetrol **1a**) using both our best guest (pyrazine) and our poorest guest (NMP) under identical reaction conditions. We found that the disappearance of tetrol is much faster in the presence of 1 mol % pyrazine in NMP than in neat NMP (Table 4). This indicates that, relative to NMP, pyrazine accelerates the formation of the first bridge in the carceplex reaction. However, these findings do not provide information about the actual GDS. We therefore focused our attention on the isolation of reaction intermediates (Scheme 2), with the intention of performing competition reactions starting from each intermediate. We expected that the corresponding template ratios might not agree with the template ratios in Table 3 (i.e., starting from tetrol **1a**). If this were the case, we would conclude that that particular intermediate is already past the GDS on the carceplex reaction pathway.

Initially, we attempted to isolate the intermediates by performing the reaction under normal conditions except that the reaction was stopped prematurely. Unfortunately, unreacted tetrol **1a** and the final product, carceplex **2a**·guest, predominated. No intermediates were isolated. This is noteworthy, as it shows that the reaction is highly cooperative. To isolate carceplex reaction intermediates and in a general search for clues to what drives this reaction, we performed the carceplex reaction in various solvents using various bases.

**(b) Effect of Base on the Formation of Carceplex 2·Guest.** What base strength is suitable for the formation of carceplex **2**·guest? Do metal cations play a significant role in the formation of carceplexes by forming salt bridges between two tetrol molecules prior to covalent bond formation? To answer these questions, a series

(13) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988, see Chapter 2 and the Appendix.

(14) Hildebrand, J. H.; Prausnitz, J. M.; Scott, R. L. *Regular and Related Solutions*; Van Nostrand Reinhold Co.: New York, 1970; pp 27, 213−215.

(15) Nakamura, K.; Sheu, C.; Keating, A. E.; Houk, K. N.; Sherman, J. C.; Chapman, R. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 4321−4322.

**Table 5. Effect of Base on Formation of Carceplex 2a·Guest**

| base | equiv of base | p$K_a$[a] | % yield of **2a**·pyrazine |
|---|---|---|---|
| pyrazine | 60 | 0.65 | 0, **1a** recovered |
| NaOAc | 30 | 5 | 0, **1a** recovered |
| pyridine | 30 | 5.25 | 0, **1a** recovered |
| $NaHCO_3$ | 30 | 6.35 | 78 |
| morpholine | 30 | 8.21 | 0, **1a** recovered |
| triethylamine | 30 | 10 | 0, **1a** recovered |
| $K_2CO_3$ | 30 | 10 | 80 |
| DBU | 60 | 12 | 60 |
| $LiC_5H_5$ | 30 | 15 | 5 |
| KOH | 200 | 15.7 | 80 |
| *t*-BuOK | 30 | 19 | 60 |
| NaH | 30 | 40 | 0, **1a** recovered |

[a] p$K_a$ of conjugate acid in $H_2O$.

**Table 6. Solvents for the Carceplex Reaction Using DBU as the Base**

| solvent | guest | time (days) | % yield of **2a**·guest |
|---|---|---|---|
| acetone[a,b] | acetone | 2 | 10[c] |
| acetone[a,d] | acetone | 8 | 65[c] |
| THF[a,b] | THF | 2 | 0[c] |
| THF[a,d] | THF | 8 | 20[c] |
| benzene[a,d] | benzene | 10 | 30[c] |
| $CHCl_3$[a,d] | pyrazine | 10 | 0[e] |
| toluene[d,f] | pyrazine | 5 | 25 |
| cyclohexane[d,f] | MeOAc | 6 | 60 |
| xylenes[d,f] | pyrazine | 8 | 0 |
| $CHCl_2CHCl_2$[d,f] | pyrazine | 2 | 0 |
| nitrobenzene[d,f] | pyrazine | 2 | 70 |

[a] Reaction mixture was refluxed. [b] Twelve equivalents of $CH_2BrCl$ were added at the start. [c] A trace of intermediates was formed. [d] Ten equivalents of $CH_2BrCl$ were added per day. [e] Tetrol **1a** was recovered. [f] Reaction mixture was stirred at 60 °C.

of standardized reactions were run in the presence of various bases in NMP using pyrazine as the template molecule and bromochloromethane as the bridging reagent. The results are summarized in Table 5 and indicate that weak bases such as pyrazine, NaOAc, and pyridine are too weak to lead to carceplex formation, whereas exceedingly strong bases such as NaH are also unsuitable. The suitable bases range in p$K_a$ from 6 to 19 (p$K_a$ values of conjugate acids in $H_2O$). Although the amine bases triethylamine and morpholine fall in the correct p$K_a$ range, they are not suitable for formation of carceplex **2**·guest. This may be the result of triethylamine and morpholine being too weakly basic in NMP, the solvent used for the reaction.

The successful formation of carceplex **2a**·pyrazine with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base indicates that metal salt bridges are not necessary for carceplex formation. Moreover, this discovery is particularly noteworthy because it greatly expands the number of potential solvent systems that can be explored for carceplex formation due to the greater solubility of DBU over $M_2CO_3$ (M = K or Cs) in apolar organic solvents.

**(c) Effect of Solvent on the Formation of Carceplex 2·Guest.** Although the above experiments indicate that the formation of carceplex **2**·guest is sensitive to the base employed, they did not provide any evidence about carceplex reaction intermediates. We therefore explored a variety of solvents systems for running the carceplex reaction using DBU as the base (Table 6). Generally, the reaction to form carceplexes proceeds slower in these low-polarity solvents than in NMP. Nonetheless, when acetone, THF, and benzene were used as bulk solvents, trace amounts of carceplex reaction intermediates were detected. It is interesting to note that the highly apolar solvent cyclohexane led to carceplex formation.

Of the solvents employed, nitrobenzene proved to be the most successful because it produced carceplexes in good yields and was itself not a competitive guest. When tetrol **1b** (pendent group = methyl),[16] 2.1 equiv of DBU, $CH_2I_2$, and 5 mol % DMSO as guest were stirred at 60 °C in nitrobenzene for 2 h, a mixture of carceplex intermediates resulted (Scheme 2). This reaction yielded 27% monobridged **4**, 16% A,B-bis-bridged **5**, and 18% recovered tetrol **1b**. Other reaction products included A,C-bis-bridged **6**·DMSO, tris-bridged **7**·DMSO, and carceplex **2b**·DMSO. Intermediates **6** and **7** were formed as mixtures with a small percentage of $CH_2I_2$ as guest and therefore could not be fully characterized. It was, however, possible to isolate the A,C-bis-bridged **6**·DMSO and tris-bridged **7**·DMSO species from the reaction of tetrol **1b** with $CH_2BrCl$ and potassium carbonate in DMSO (at ambient temperature for 18 h), in 4.6% and 22% yields, respectively; in addition, 7.6% of carceplex **2b**·DMSO was isolated under these conditions.

**(d) Determination of the GDS.** Intermediates A,C-bis-bridged **6**·DMSO and tris-bridged **7**·DMSO each contain a tightly encapsulated molecule of DMSO which remained encapsulated after workup. The stability of A,C-bis-bridged **6**·DMSO and tris-bridged **7**·DMSO was tested by recording their $^1$H NMR spectra in deuterated nitrobenzene as a function of time and temperature. No noticeable changes in their $^1$H NMR spectra were observed, even at temperatures as high as 120 °C for 48 h! Therefore, the activation energy for egress of DMSO from the holes in **6**·DMSO and **7**·DMSO is large; thus, these compounds can be regarded as carceplexes. Nevertheless, we further examined **6**·DMSO and **7**·DMSO to be sure that they are past the GDS on the carceplex reaction pathway. We thus performed competition experiments with **6**·DMSO and **7**·DMSO in the presence of pyrazine, a superior template molecule, to furnish the corresponding carceplex **2b**·guest. In both cases, these reactions resulted in the isolation of only carceplex **2b**·DMSO, which shows that no guest exchange occurs with these intermediates; they are past the GDS on the carceplex reaction pathway.

A,B-Bis-bridged **5** and monobridged **4** were isolated with no detectable encapsulated guest. Examination of these two intermediates by CPK models[6] indicates that they have significant openings that allow for easy guest escape. Does the guest-determining step for carceplex formation occur after the formation of these intermediates? We performed competition experiments using these two intermediates and tetrol **1b** at ambient temperature using six of the templates from Table 3 (results from Table 3 were obtained at 60 °C using tetrol **1a**). The results of these competition studies are presented in Table 7. The template ratios between tetrol **1b** and monobridged **4** correlate well (a log−log plot of the template ratios gave $r^2 = 1.0$) while the template ratios

(16) The preparation of carceplex **2b**·guest (i.e., R = $CH_3$) was realized partway through this work (see ref 17). The advantages of the methyl "feet" over the phenethyl feet are manifold, including the following: (1) The $^1$H NMR spectra are simpler with methyl feet and create a larger open window to observe entrapped guest. (2) Although solubility was feared to be a problem, carceplex **2b**·guest is actually more soluble in chloroform than carceplex **2a**·guest. (3) Crystals grown from methyl-footed carceplexes are far more stable, and their X-ray crystal structures are easier to solve.

**Table 7. Template Ratios Starting from 1b, 4, and 5**

| guest | from tetrol **1b** | from monobridged **4** | from A,B-bis-bridged **5** |
|---|---|---|---|
| pyrazine | 860.0 | 1130.0 | 40.0 |
| 1,4-dioxane | 177.0 | 245.0 | 5.4 |
| DMSO | 18.8 | 21.0 | 17.0 |
| pyridine | 13.5 | 17.0 | 19.0 |
| acetone | 1.8 | 2.0 | 3.0 |
| benzene | 1.0 | 1.0 | 1.0 |

for tetrol **1b** and A,B-bis-bridged **5** show a poor correlation (a log−log plot of the template ratios yields $r^2 = 0.7$).

Combining the results for the monobridged **4** and A,B-bis-bridged **5** with those of the A,C-bis-bridged **6**·DMSO and the tris-bridged **7**·DMSO, we conclude that the formation of the second $OCH_2O$ bridge in the carceplex reaction (either A,B-bis or A,C-bis) is the GDS. After formation of this second $OCH_2O$ bridge, the guest is irreversibly entrapped under the reaction conditions, and subsequent bridging leads to the corresponding product (carceplex **2**·guest). Therefore, the formation of the second bridge is $10^6$ times faster in the presence of pyrazine than in the presence of NMP. We suggest that the poor correlation ($r^2 = 0.7$) for the template ratios determined for the formation of carceplex **2b**·guest from A,B-bis-bridged **5** versus tetrol **1b** is a result of guest exchange being slower than formation of the third $OCH_2O$ bridge (thus, the normal template ratios are skewed by the guest's in-rate). Indeed, in experiments to be reported shortly,[18] charged complexes corresponding to A,B-bis-bridged **5**·guest were found to exchange guests over a period of days, which is far slower than bridge formation. Interestingly, neutral complexes corresponding to A,B-bis-bridged **5**·guest exchange their guests over a period of minutes; thus, neutral A,B-bis-bridged **5** is isolated without guest.

**5. Preassociation of Bowls Prior to Bridge Formation.** Investigation into the template requirements for the formation of carceplex **2**·guest led to a similar investigation into the template requirements for the formation of a hemicarceplex where one of the four ($ArOCH_2OAr$) linkages is replaced by (ArH, HAr), thus leaving a hole in the side of the capsule.[19] The reaction to form this hemicarceplex is statistically more demanding than the reaction to form carceplex **2**·guest because there is the potential for misalignment during formation of the first bridge between two starting triol molecules.[20] Template ratios were determined, and a good correlation was found with the template ratios measured for the formation of carceplex **2a**·guest ($r = 0.97$).[19] Therefore, the driving forces are similar for the two processes. The favorable interactions between the template and the forming host compounds overwhelm any disparity that might be caused by the lower symmetry of the hemicarceplex. Also, much greater than statistical yields were observed, which suggests that hydrogen bonding may play an integral role in aligning the bowls prior to covalent bond formation. Indeed, in complex **3**·guest, two molecules of tetrol **1** are linked via charged hydrogen bonds. The guest selectivities of complex **3**·guest correlate with the template ratios reported here, and thus, the complex is a good transition state model for the GDS in the formation of carceplex **2**·guest.[8]

## Conclusions

The mechanism for formation of carceplex **2**·guest as we understand it to date is as follows: Complex **3**·guest forms, followed by formation of the first bridge, with guests still in fast exchange. The formation of the second bridge, either A,B or A,C, is then the GDS. The host species formed during the transition state of this step is highly rigid and binds strongly with high selectivity to guests such as pyrazine. The most stable complexes (i.e., those containing the best template molecule) form the second bridge the fastest, thereby entrapping more of that guest under the reaction conditions. Subsequent bridging leads to product.

The carceplex reaction discussed here is an excellent model for the study of noncovalent interactions between molecules because small changes in guest size, shape, and/or electronic properties results in vast differences in incarceration propensities. For example, the substitution of a nitrogen of pyrazine with a methine group to give pyridine disrupts the complementarity of pyrazine with the forming cavity as illustrated by the 29-fold decrease in the template ratio. Substitution of both nitrogens of pyrazine for two methines to give benzene results in a 420-fold decrease in the template effect.

Pyrazine's favorable noncovalent interactions with the forming carceplex lowers the Gibbs free energy of activation for this step by 8.3 kcal/mol relative to NMP at 300 K. The ability of the forming carceplex to recognize subtle changes in guest properties ultimately led to a million-fold difference in template ratios between the poorest template (NMP) and the best template (pyrazine). The formation of the second $OCH_2O$ interbowl bridge was found to be the step responsible for the selectivity (GDS) observed in the formation of carceplex **2**·guest. Poorer guests/templates such as NMP may provide fewer favorable noncovalent interactions and more unfavorable interactions in the transition state of the GDS, thus leading to slower formation of the second bridge. Guests such as pyrazine provide many favorable noncovalent interactions that stabilize the transition state for formation of the second $OCH_2O$ bridge.

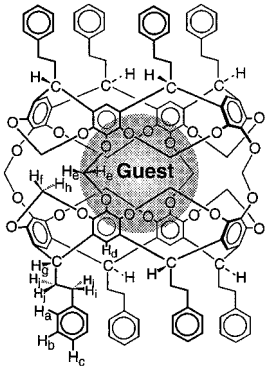
Better guests generally afford higher yields of carceplex **2**·guest. Poorer guests most likely allow more polymerization to occur from the monobridged species. In addition, some guests may cause low yields because they can react with the bridging material (e.g., dimethyl sulfide, pyridine, thiophene). Some guests may lower yields by distortion of the host after the GDS and, thus, inhibit final bridging (e.g., benzene, DMA, NMP). These tendencies may lower the yields somewhat, but they will have only a small effect on the template ratios.[5]

This study of 34 carceplexes has provided valuable insight into the nature of noncovalent interactions. Current studies include a detailed analysis of complex **3**·guest and related species as well as investigations into the template effect in systems that contain larger cavities and those that cannot form complex **3**·guest. Hopefully, the information gained from these studies will enable us to create more complex assemblies such as very large carceplexes and polymeric capsules.

(17) Fraser, J. R.; Borecka, B.; Trotter, J.; Sherman, J. C. *J. Org. Chem.* **1995**, *60*, 1207−13.
(18) Chapman, R. G.; J.; Sherman, J. C. Unpublished results.
(19) Chopra, N.; Sherman, J. C. *Supramol. Chem.* **1995**, *5*, 31−7.
(20) A derivative of compound **7** where the pendent groups are phenethyls has been reported: Kurdistani, S. K.; Robbins, T. A.; Cram. D. J. *J. Chem. Soc., Chem Commun.* **1995**, 1259−1260.

## Experimental Section

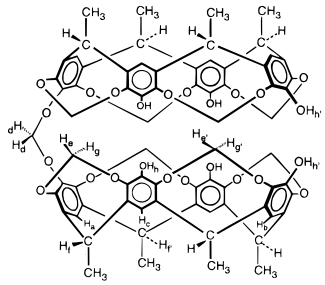
**General Experimental.** See also ref 17. Nitrobenzene and NMP were stirred over BaO for 24 h, distilled under reduced pressure, and stored under $N_2$ over 4 Å molecular sieves prior to use. All other commercially available reagents were used as purchased without further purification unless stated otherwise. Desorption chemical ionization (DCI) and liquid secondary ion mass spectrometry (LSIMS) mass spectra were recorded on a Kratos Concept II HQ, and matrix assisted laser desorption ionization (MALDI) mass spectra were recorded on a VG Tofspec in reflectron mode with 3,5-dihydroxybenzoic acid used as the matrix. Melting points were measured on a Mel-Temp II apparatus. $^1$H NMR spectra were recorded on a Bruker WH-400 spectrometer in $CDCl_3$ at ambient temperature using the residual $^1$H as a reference (7.24 ppm) unless noted otherwise. For characterization of carceplexes **2a**·DMF, **2a**·DMA, and **2a**·DMSO, see ref 4. For characterization of carceplex **2b**·pyrazine, see ref 17.



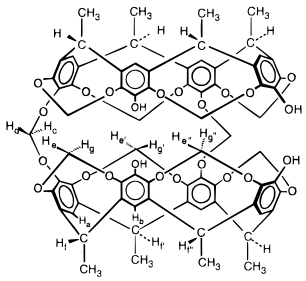

Carceplex **2a**•Guest

**2a·Pyrazine.** A mixture of tetrol **1a** (102 mg, 0.10 mmol), pyrazine (420 mg, 5.3 mmol), $K_2CO_3$ (1.4 g, 10 mmol), and $CH_2BrCl$ (65 mL, 1.0 mmol) in NMP (50 mL) was stirred at 60 °C for 24 h. An additional 1.0 mmol of $CH_2BrCl$ was added, and the reaction was stirred for an additional 24 h at 60 °C. The reaction mixture was concentrated in vacuo, water (50 mL) was added, and the slurry was acidified with 2 M HCl. The slurry was extracted with $CHCl_3$ (3 × 60 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$. Silica gel (0.5 g) was added to the $CHCl_3$ solution, and the solvent was removed in vacuo. The silica gel-absorbed sample was dry loaded onto a silica gel gravity column (20 g) and eluted with $CHCl_3$/hexanes (3:1), affording **2a**·pyrazine as a white solid which was recrystallized from $CHCl_3$/EtOAc and dried at 110 °C (0.1 mmHg) for 24 h (97 mg, 87%): mp >250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.13−7.24 (m, 40H, $H_a$, $H_b$, and $H_c$), 6.93 (s, 8H, $H_d$), 6.47 (s, 8H, $H_e$), 6.02 (d, $J$ = 7.5 Hz, 8H, $H_f$), 4.90 (t, $J$ = 7.9 Hz, 8H, $H_g$), 4.26 (d, $J$ = 7.5 Hz, 8H, $H_h$), 4.07 (s, 4H, $C_4H_4N_2$), 2.66 (m, 16H, $H_i$), 2.51 (m, 16H, $H_j$); MS (DCI, isobutane) $m/z$ (rel intensity) 2070 ((M − $CH_2$ + 2H)$^+$; 100), 2082 ($M^+$; 80), 2162 ((M·$C_4H_4N_2$)$^+$; 90), 2204 ((M·$C_4H_4N_2$ + $CH(CH_3)_2$)$^+$; 25). Anal. Calcd for $C_{136}H_{116}O_{24}N_2$: C, 75.54; H, 5.41; N, 1.30. Found: C, 75.41; H, 5.35; N, 1.23.

**2a·(±)-2-Butanol.** A mixture of tetrol **1a** (102 mg, 0.10 mmol), (±)-2-butanol (2.5 mL, 27 mmol), $K_2CO_3$ (1.4 g, 10 mmol), and $CH_2BrCl$ (65 mL, 1.0 mmol) in NMP (50 mL) was stirred at room temperature for 24 h. An additional 1.0 mmol of $CH_2BrCl$ was added, and the reaction was stirred at 60 °C for an additional 48 h. The reaction mixture was concentrated in vacuo, water (50 mL) was added, and the slurry was acidified with 2 M HCl. The slurry was extracted with $CHCl_3$ (3 × 60 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$. Silica gel (0.5 g) was added to the $CHCl_3$ solution, and the solvent was removed in vacuo. The silica gel-absorbed sample was dry loaded onto a silica gel gravity column (20 g) and eluted with $CHCl_3$/hexanes (3:1), affording **2a**·(±)-2-butanol as a white solid which was recrystallized from $CHCl_3$/EtOAc and dried at 110 °C (0.1 mmHg) for 24 h (51 mg, 47%): mp >250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.12−7.24 (m, 40H, $H_a$, $H_b$, $H_c$, $H_{a'}$, $H_{b'}$, and $H_{c'}$), 6.73 (s, 4H, $H_d$ or $H_{d'}$), 6.71 (s, 4H, $H_d$ or $H_{d'}$), 6.58 (s, 8H, $H_e$), 6.16 (d, $J$ = 7.3 Hz, 8H, $H_f$ and $H_{f'}$), 4.89 (t, $J$ = 7.9 Hz, 8H, $H_g$ and $H_{g'}$), 4.46 (d, $J$ = 7.3 Hz, 4H, $H_h$ or $H_{h'}$), 4.37 (d, $J$ = 7.3 Hz, 4H, $H_h$ or $H_{h'}$), 2.65 (m, 16H, $H_i$ and $H_{i'}$), 2.44 (m, 16H, $H_j$ and $H_{j'}$), 0.91 (br, 1H, $CH_3CHOHCH_2CH_3$), −0.93 (br, 2H, $CH_3CHOHCH_xH_yCH_3$), −1.32 (br, 1H, $CH_3CHOHCH_xH_yCH_3$), −3.27 (d, $J$ = 6.0 Hz, 3H, $CH_3CHOHCH_2CH_3$), −3.47 (t, $J$ = 7.3 Hz, 3H, $CH_3CHOHCH_2CH_3$); MS (MALDI) $m/z$ (rel intensity) 2180 ((M·$CH_3CHOHCH_2CH_3$ + $Na^+$)$^+$; 100) calcd for $C_{136}H_{122}O_{25}$·$Na^+$ = 2179. Anal. Calcd for $C_{136}H_{122}O_{25}$: C, 75.75; H, 5.70. Found: C, 75.35; H, 5.70.



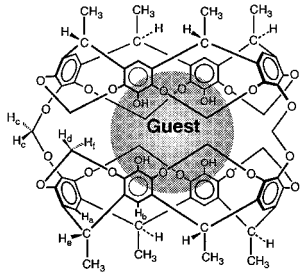
**4**



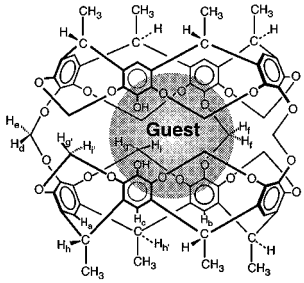
**5**

**Monobridged 4 and A,B-Bis-Bridged 5.** A mixture of tetrol **1b** (656 mg, 1.0 mmol), DBU (0.314 mL, 2.1 mmol), DMSO (5.0 mL, 70 mmol), and $CH_2I_2$ (0.80 mL, 10.0 mmol) in nitrobenzene (100 mL) was stirred at 60 °C for 2 h. The reaction mixture was concentrated in vacuo, water (50 mL) was added, and the slurry was acidified with 2 M HCl. The slurry was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$. Silica gel (5 g) was added to the organic solution, and the solvent was removed in vacuo. The silica gel-absorbed sample was dry loaded onto a silica gel gravity column (400 g) and eluted with MeOH/$CHCl_3$ (1:9). Reverse phase TLC with acetone/$H_2O$ (4:1) as eluent was used to follow the progress of the column chromatography. The products were recrystallized from benzene/ether/acetone/hexane and dried at 110 °C (0.1 mmHg) for 24 h affording **1b** (120 mg, 18.3%, recovered starting material), **5** (180 mg, 27.2%), and **4** (105 mg, 15.7%) as white solids. Compound **4** was characterized as follows: mp >250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.98 (s, 2H, $H_a$), 6.73 (s, 2H, $H_b$), 6.72 (s, 4H, $H_c$), 5.94 (d, $J$ = 6.8 Hz, 4H, $H_e$ or $H_{e'}$), 5.65 (d, $J$ = 7.0 Hz, 4H, $H_e$ or $H_{e'}$), 5.41 (s, 2H, $H_d$), 5.33 (br, 6H, $H_h$ and $H_{h'}$), 4.91 (m, 8H, $H_f$ and $H_{f'}$), 4.45 (d, $J$ = 6.8 Hz, 4H, $H_g$ or $H_{g'}$), 4.33 (d, $J$ = 7.0 Hz, 4H, $H_g$ or $H_{g'}$), 1.70 (m, 24H, $CH_3$); MS (DCI, ammonia) $m/z$ (rel intensity) 1342 ((M + $NH_4$)$^+$; 100). Anal. Calcd for $C_{73}H_{64}O_{24}$·$H_2O$: C, 65.27; H, 4.95. Found: C, 65.28; H, 5.08. Compound **5** was characterized as follows: mp >250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.82 (s, 4H, $H_a$), 6.72 (s, 4H, $H_b$), 6.62 (d, $J$ = 6.2 Hz, 2H, $H_c$ or $H_d$), 6.41 (br, 2H, $H_c$ or $H_d$), 6.19 (d, $J$ = 7.4 Hz, 2H, $H_{e'}$ or $H_{e''}$), 6.09 (d, $J$ = 7.1 Hz, 4H, $H_e$), 5.91 (d, $J$ = 6.8 Hz, 2H, $H_{e'}$ or $H_{e''}$), 5.42 (s, 4H, OH), 5.05 (q, $J$ = 7.4 Hz, 2H, $H_{f'}$ or $H_{f''}$), 4.89 (m, 6H, $H_f$ and ($H_{f'}$ or $H_{f''}$)), 4.61 (br, 2H, $H_{g'}$ or $H_{g''}$), 4.59 (m, 6H, $H_g$ and ($H_{g'}$ or $H_{g''}$)), 1.72 (d, $J$ = 7.4 Hz, 6H, $CH_3$), 1.69 (d, $J$ = 7.4 Hz, 6H, $CH_3$), 1.66 (d, $J$ = 7.4 Hz, 12H, $CH_3$); MS (DCI, ammonia) $m/z$ (rel intensity) 1354 ((M + $NH_4$)$^+$; 100). Anal. Calcd for $C_{74}H_{64}O_{24}$·$2H_2O$: C, 64.72; H, 4.99. Found: C, 64.75; H, 4.68.

**6·DMSO and 7·DMSO.** A mixture of tetrol **1b** (1.0 g, 1.52 mmol), $K_2CO_3$ (6.0 g, 43.4 mmol), and $CH_2BrCl$ (1.0 mL, 15.4 mmol) in DMSO (125 mL) was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, water (50 mL) was added, and the slurry was acidified with 2 M HCl. The slurry was extracted with $CHCl_3$/EtOAc 2:1 (3 ×




**6**•DMSO




**7**•DMSO

150 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$. Silica gel (5 g) was added to the organic solution, and the solvent was removed in vacuo. The silica gel-absorbed sample was dry loaded onto a silica gel gravity column (400 g) and eluted with 3% MeOH in $CHCl_3$. The products were recrystallized from ether/acetone/hexane and dried at 110 °C (0.1 mmHg) for 24 h affording **6**·DMSO (50 mg, 4.6%), **7**·DMSO (240 mg, 22.1%), and **2b**·DMSO (83 mg, 7.6%) as white solids. **6**·DMSO was characterized as follows: mp >250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.91 (s, 4H, $H_a$), 6.69 (s, 4H, $H_b$), 6.56 (s, 4H, $H_c$), 6.04 (d, $J$ = 7.2 Hz, 8H, $H_d$), 5.74 (s, 4H, OH), 4.93 (q, $J$ = 7.3 Hz, 8H, $H_e$), 4.31 (br, 8H, $H_f$), 1.69 (d, $J$ = 7.3 Hz, 24H, $CH_3$), −1.15 (s, 6H, $(CH_3)_2SO$); MS (MALDI) $m/z$ (rel intensity) 1438 (($M\cdot(CH_3)_2SO + Na^+)^+$; 100), calcd for $C_{76}H_{70}O_{25}S\cdot Na^+$ = 1438. Anal. Calcd for $C_{76}H_{70}O_{25}S\cdot 1.5H_2O$: C, 63.28; H, 5.10. Found: C, 63.25; H, 4.94. **7**·DMSO was characterized as follows:[20] mp >250 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.91 (s, 4H, $H_a$), 6.88 (s, 2H, $H_b$), 6.68 (s, 2H, $H_c$), 6.64 (d, $J$ = 6.4 Hz, 2H, $H_d$ or $H_e$), 6.52 (s, 2H, $H_f$), 6.45 (br, 2H, $H_d$ or $H_e$), 6.20 (d, $J$ = 7.6 Hz, 4H, $H_g$ or $H_{g'}$), 5.97 (d, $J$ = 7.2 Hz, 4H, $H_g$ or $H_{g'}$), 5.70 (s, 2H, OH), 5.00 (q, $J$ = 7.5 Hz, 4H, $H_h$ or $H_{h'}$), 4.92 (q, $J$ = 7.5 Hz, 4H, $H_h$ or $H_{h'}$), 4.63 (br, 4H, $H_i$ or $H_{i'}$), 4.19 (br, 4H, $H_i$ or $H_{i'}$), 1.71 (d, $J$ = 7.5 Hz, 12H, $CH_3$), 1.68 (d, $J$ = 7.5 Hz, 12H, $CH_3$), −1.22 (s, 6H, $(CH_3)_2SO$); MS (MALDI) $m/z$ (rel intensity) 1451 (($M\cdot(CH_3)_2SO + Na^+)^+$; 100), calcd for $C_{77}H_{70}O_{25}S\cdot Na^+$ = 1450. Anal. Calcd for $C_{77}H_{70}O_{25}S\cdot 1H_2O$: C, 63.98; H, 5.02. Found: C, 64.16; H, 4.92.

**Acknowledgment.** We thank NSERC of Canada for financial support. R.G.C. thanks NSERC and UBC for graduate fellowships. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

**Supporting Information Available:** Preparation and characterization of 40 carceplexes (**2a**·guest and **2b**·guest) and procedures for determining template ratios (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9803582