Reversible Molecular Capsules Composed of Two Cavitands Linked via an Assortment of Charged-Hydrogen Bonds and Covalent Bonds

Robert G. Chapman and John C. Sherman*

Contribution from the Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, BC, Canada V6T 1Z1

Received May 7, 1998

Abstract: Six new cavitand bowls are reported (**6**, **7**, **8**, **9**, **11**, and **12**), as are three bis-bowl compounds (**4**, **13**, and **14**). Eight new complexes (**4**·guest, **7C**·guest, **8C**·guest, **9C**·guest, **14**·guest, **15**·guest, **15C**·guest, and **16C**·guest) that reversibly encapsulate small molecules are reported. Two or more charged-hydrogen bonds (CHBs) or covalent linkages between the bowls are required to form stable complexes. Guest exchange rates vary from milliseconds to days. Thermodynamically, these complexes display an enthalpy−entropy compensation. The relative stability of complex **3**·pyrazine versus complex **3**·chloroform is 170 000 in nitrobenzene-d_5 at 298 K. Apparent stability constants in nitrobenzene-d_5 at 298 K yield 1.1×10^9 M^{-1} for complex **3**·pyrazine. The absolute stability constant for complex **4**·pyrazine in nitrobenzene-d_5 at 333 K is 3.5×10^6 M^{-1}.

Introduction

A variety of media, from liposomes to zeolites,[1] are capable of encapsulation of small molecules. A subset of these, often called capsules, have received great attention recently.[2] Capsules[2a] can be considered reversible assemblies or complexes where a nearly closed-off spheroid is formed that can encapsulate guest molecules in solution, while excluding solvent. To explore these systems with due rigor, a thorough understanding of their structure and thermodynamic stability is imperative. We have shown that capsule **3**·guest (see Scheme 1) is highly guest-selective,[3] which bodes well for a detailed study of the forces that drive such encapsulation. Whereas such capsules encapsulate guests reversibly, with a large range in guest exchange rates, compounds called carceplexes are related, but they entrap molecules permanently, with escape possible only by rupture of covalent bonds.[2b,4] We have recently described the template effects involved in the formation of carceplex **2**·guest (Scheme 1)[5] as well as the relevance of capsule **3**·guest to this template effect.[3] We have shown that the two "bowls" of capsule **3**·guest are linked by four charged-hydrogen bonds (CHBs) and that the capsule will not form in the absence of CHBs.[3] We report here a study of the number of CHBs and/or covalent linkages needed to form such capsules. We report the guest-selectivities for various capsules as well as the relative host affinities for a given guest. We begin with a determination of the absolute guest-affinity in these complexes (only relative stabilities for capsule **3**·guest have been reported previously), then we present the guest-selectivity for eight new complexes, the guest exchange rates, the relative host-selectivities, and the relative thermodynamic stabilities of the complexes. We close with a discussion of the relevance of this work to the mechanism of the reaction to form carceplex **2**·guest.

Results and Discussion

1. Absolute Guest-Affinity of the Complexes. 1.1. The Free "Species" of Tetrol 1 and DBU in $CDCl_3$. The studies reported previously on capsule **3**·guest were performed in $CDCl_3$, and revealed a free species in addition to the complexes; these species were in equilibrium in slow exchange on the ^1H NMR time scale.[3] To calculate an equilibrium constant for a complex, the concentration of the free species must be determined. To do so, one must know the molecularity of this species: Is it tetrol **1** (Scheme 1), a dimer of tetrol **1**, or an aggregate? What is the protonation state of the free species? Does it too carry a −4 charge as well as four DBU·H^+ counterions?[6]

1.1.1. Tetrol 1 Dimerizes in $CDCl_3$ in the Presence of DBU. Two titrations of tetrol **1b** in $CDCl_3$ with DBU were conducted by using the chemical shifts of the *para* H's (H_p,

(1) (a) Lasic, D. D.; Papahadjopoulos, D. *Science* **1995**, *267*, 1275−1276. (b) Zones, S. I.; Nakagawa, Y.; Yuen, L. T.; Harris, T. V. *J. Am. Chem. Soc.* **1996**, *118*, 7558−7567.

(2) (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1688 and references therein. (b) Chapman, R. G.; Sherman, J. C. *Tetrahedron* **1997**, *53*, 15911−15946 and references therein. (c) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712. (d) Rose, K. N.; Barbour, L. J.; Orr, G. W.; Atwood, J. L. *J. Chem. Soc., Chem. Commun.* **1998**, 407−408. (e) Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613−615. (f) Miklis, P.; Çagin, T.; Goddard, W. A. *J. Am. Chem. Soc.* **1997**, *119*, 7458−7462. (g) Lee, S. B.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501−8504. (h) Jeon, Y.-H.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790−9791. (i) Arduini, A.; Domiano, L.; Ogliosi, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 7866−7868. See also: (j) Vögtle, F. et al. *Liebigs Ann.* **1996**, 1697−1704.

(3) (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.

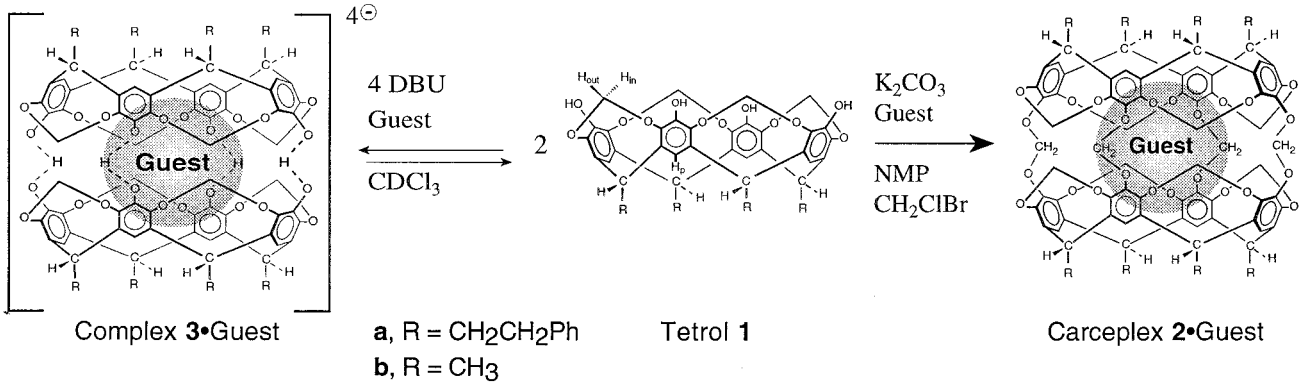
(4) Cram, D. J.; Cram, J. M. *Container Compounds and Their Guests*; The Royal Society of Chemistry: Cambridge, 1994.

(5) (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*, 4103−4110.

(6) Abbreviations: CHBs, charged-hydrogen bonds; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; DBU·H^+, protonated DBU.; $\Delta\delta$, the difference in chemical shifts in ppm, usually between free and entrapped guests; $\Delta\nu$, the difference in resonant frequency in Hz, usually between free and entrapped guests; K_{rel}, relative stability constant; K_s, stability constant; K_{app}, apparent stability constant; "**C**", as in **15C**·guest indicates a charged complex; CPK, Corey−Pauling−Koltun space filling models; NMP, *N*-methylpyrrolidinone.

S0002-7863(98)01596-0 CCC: $15.00
Published on Web 09/11/1998

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



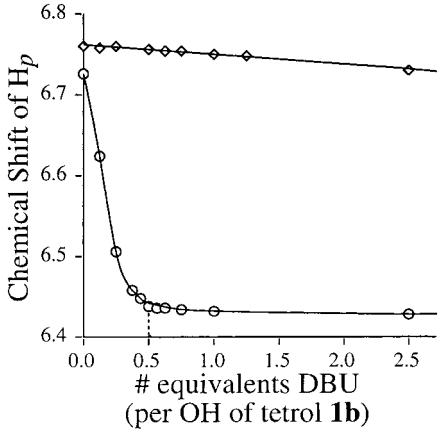


Figure 1. Titration of tetrol **1b** with DBU: diamonds, 0.047 mM tetrol **1b** at 323 K; circles, 2.63 mM tetrol **1b** at 263 K.

Scheme 1) as a probe (Figure 1). At 263 K and 2.63 mM tetrol **1b** (conditions that would favor a dimer of tetrol **1b**), the maximum $\Delta\delta$[6] occurs when 0.5 equiv of DBU were added per hydroxyl group (Figure 1). Therefore, the "free" species at low temperature and high concentration is most likely a complex of two molecules of tetrol **1b** interconnected by four CHBs. At 0.047 mM tetrol **1b** and 323 K, DBU titration had no significant effect on the chemical shift of H_p (Figure 1). This titration indicates that at this temperature and concentration the "free" species is most likely monomeric tetrol **1b**.[7,8] Similar titrations were obtained in the presence of pyrazine as guest to give capsule **3**·pyrazine.[3]

1.1.2. The Free Species in $CDCl_3$ Is Capsule 3·Chloroform. The titration experiments described above give no information regarding the chemical species (or lack thereof) encapsulated within the dimer of tetrol **1b**. We thus looked for encapsulation of $CHCl_3$ in $CDCl_3$ by performing a P1331 solvent suppression experiment on a 50/50 v/v $CHCl_3/CDCl_3$ solution containing tetrol **1b** (5.0 mM) and DBU (10.5 mM).[9a] Upon cooling to 273 K, a new signal appeared at 4.6 ppm, which was assigned to encapsulated $CHCl_3$. This 2.64 ppm $\Delta\delta$ correlates with the 2.81 ppm $\Delta\delta$ observed for incarcerated $CHCl_3$ in carceplex **2a**·$CHCl_3$.[5b] Only one set of host signals was observed even down to 223 K; these signals most likely represent 100% capsule **3b**·chloroform, as one would not expect a difference in coalescence temperature for host and guest that is greater than 50 K ($\Delta\nu$ for the free and complexed host signals would have to be <2 Hz).[10] Unfortunately, the P1331 experiment does not provide accurate integration,[9a] but crude relative integration of the methine peak of tetrol **1b** indicates that the complex is at least 70% filled with chloroform (35% occupied with $CHCl_3$ and 35% occupied with $CDCl_3$).[11]

1.2. K_{rel} of 3b·Guest in $CDCl_3$. At 298 K and 3.7 mM tetrol **1b**, the equilibrium constant (K_{eq}) for any capsule **3**·guest in $CDCl_3$ is equal to the relative stability constant (K_{rel}) for **3**·guest:**3**·$CDCl_3$ (see eqs 1 and 2).

$$(\mathbf{3}\cdot CDCl_3)\cdot(DBU\cdot H^+)_4 + \text{guest} \rightleftharpoons (\mathbf{3}\cdot\text{guest})\cdot(DBU\cdot H^+)_4 + CDCl_3 \quad (1)$$

$$K_{eq} = K_{rel} = \{[(\mathbf{3}\cdot\text{guest})\cdot(DBU\cdot H^+)_4][CDCl_3]\}/\{[(\mathbf{3}\cdot CDCl_3)\cdot(DBU\cdot H^+)_4][\text{guest}]\} \quad (2)$$

For **3b**·pyrazine, this relative stability is 110 000 at 298 K.[12] To determine the absolute stability constant for capsule **3b**·$CDCl_3$ in $CDCl_3$ would require either (1) generation and characterization of a monomeric species, and determination of DBU/DBU·H^+ concentrations,[13] or (2) generation and characterization of an empty dimer. Since neither is practical, we turned to nitrobenzene-d_5 as a solvent.[11]

1.3. K_{app} in Nitrobenzene-d_5. We were unable to determine the nature of the free species of tetrol **1b** and DBU in

(7) The putative empty dimer could contain dissolved gases.

(8) The ^{1}H NMR spectra of a mixture of tetrol **1b**:DBU (1:2.1) at 298 K were recorded over a concentration range of 0.076 to 3.72 mM tetrol **1b**, resulting in chemical shifts of H_p ranging from 6.64 to 6.46 ppm, respectively. In contrast, the ^{1}H NMR spectra of tetrol **1b** alone recorded over a concentration range of 0.084 to 2.36 mM (at 298 K) showed no change in chemical shift of H_p (6.746 ppm). Thus, dimerization requires base. Only a single set of host signals was observed in all spectra, which strongly suggests that the dimer of tetrol **1b** and the monomer are in fast exchange on the ^{1}H NMR time scale at 263 K.

(9) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: New York, 1987; Vol. 6, (a) pp 172−176, (b) pp 188−190, p 215.

(10) Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*; Wiley: New York, 1990; pp 194−7.

(11) We confirmed that capsule **3b**·$CHCl_3$ is stable by characterizing it (see Supporting Information) in nitrobenzene-d_5, which cannot act as a guest due to its bulkiness, is stable toward DBU, and solubilizes all the components as well as the complex. (1,1,2,2-Tetrachloroethane-d_2 reacts with DBU and capsule **3b**·guest is not soluble in toluene-d_8.).

(12) The K_{rel} for **3b**·pyrazine: **3b**·$CDCl_3$ in $CDCl_3$ as solvent was determined at 298 K by using 3.7 mM tetrol **1b** and 1.9 mM pyrazine, by integration of host signals for **3b**·pyrazine and **3b**·$CDCl_3$, and subtraction of [**3b**·pyrazine] from $[\text{pyrazine}]_{initial}$ to yield $[\text{pyrazine}]_{free}$; $[CDCl_3]_{initial} \sim [CDCl_3]_{free} = 12.4$ M. This K_{rel} (110 000) agrees with the K_{rel} for **3b**·pyrazine: **3b**·$CHCl_3$ in nitrobenzene-d_5 at 298 K (170 000, ref 3b), which further supports the conclusion that the free species in $CDCl_3$ is capsule **3**·$CDCl_3$.

(13) DBU and DBU·H^+ are in fast exchange on the NMR time scale even at low temperature in $CDCl_3$. Therefore, the concentration of DBU and DBH·H^+ cannot be determined accurately. Moreover, the equation for the absolute stability constant for capsule **3**·$CDCl_3$ from neutral **1b** would include four deprotonations, which would yield a very large equilibrium constant that is dominated by four superimposed acid dissociation constants.

nitrobenzene-d_5, as ^{1}H NMR spectra of tetrol **1b** and DBU in nitrobenzene-d_5 are very broad due to aggregation.[14] Proper calculation of the absolute stability constant for capsule **3b**·guest in nitrobenzene required determination of the aggregation state of the free species, which is nontrivial. However, if we treat the free species in nitrobenzene-d_5 as an empty dimer, we can calculate an apparent stability constant: $K_{app} = [(\mathbf{3b}\cdot\text{guest})\cdot(\text{DBU}\cdot\text{H}^+)_4]/\{[(\mathbf{1}\cdot\mathbf{1})\cdot(\text{DBU}\cdot\text{H}^+)_4][\text{guest}]\}$, where $(\mathbf{1}\cdot\mathbf{1})(\text{DBU}\cdot\text{H}^+)_4$ is an empty dimer linked by four CHBs. The concentrations of capsule **3**·guest, the putative empty dimer, and free guest can be determined from integration of the ^{1}H NMR spectra. We had to find a very poor guest that binds weakly enough in nitrobenzene to avoid saturation of tetrol **1**. *N*-Methylpyrrolidinone (NMP) served well as such a guest. Thus, the K_{app} for complex **3b**·NMP in nitrobenzene-d_5 was determined to be 1100 and 280 M^{-1}, at 298 and 313 K, respectively. Since the relative stability constants for capsule **3b**·guest have been determined for several guests from pyrazine down to NMP in nitrobenzene-d_5,[3b] we can generate K_{app} for all these guests as well. For example, K_{app} for capsule **3**·pyrazine in nitrobenzene-d_5 at 298 K is 1.1×10^9 M^{-1}![15]

1.4. K_s of Bis-Bowl 4·Guest. A more direct approach to determine the absolute stability constant for a capsular complex is to develop a capsule that is neutral and monomeric when free. We accomplished this by covalently linking two bowls to create bis-bowl **4** (Figure 2),[16] which is not only neutral and monomeric in nitrobenzene-d_5, but also "empty."[17] NMP was again chosen as the guest because it exhibits weak binding, and it yields host ^{1}H NMR signals that are resolved from free bis-bowl **4**. Thus, integration of H_{in}'s (3.58 ppm for **4**, 3.74 ppm for **4**·NMP) from the ^{1}H NMR spectrum of bis-bowl **4** (1.36 mM) and NMP (3.26 mM) in nitrobenzene-d_5 at 333 K[17] led to K_s = [bis-bowl **4**·NMP]/[bis-bowl **4**][NMP] = 410 ± 40 M^{-1} and K_s = 390 M^{-1} for a degassed sample.[19]

2. Stability of Capsule 3·Guest in Polar Solvents. It is that extremely stable complexes can be formed as capsule **3**·guest or capsule **4**·guest. In fact, complexes **3**·DMSO and **3**·dioxane are stable in the polar solvent NMP.[20] The stability of supramolecular complexes that rely on hydrogen bonding is often measured by the percentage of DMSO they can withstand before the complex is destroyed.[21] Indeed, capsules **3**·DMSO and **3**·pyrazine are highly stable in neat DMSO.[22] In addition, the K_{rel} for capsule **3b**·pyrazine:capsule **3b**·DMSO-d_6 in DMSO-d_6 at 298 K is in moderate agreement with the K_{rel}'s determined[3b] in $CDCl_3$ and nitrobenzene-d_5 at 298 K (K_{rel} = 110, 92, and 17 in DMSO, $CDCl_3$, and nitrobenzene-d_5, respectively). In protic solvents such as CD_3OD, no evidence for formation of capsule **3b**·guest was observed. In fact, capsule **3b**·pyrazine in $CDCl_3$ can be eliminated by the addition of 10% CD_3OD as indicated by the disappearance of the signal for encapsulated pyrazine and an increase in intensity of the signal for free pyrazine in the ^{1}H NMR spectrum. It would be interesting to see if complexes such as **3b**·guest can form in water, where the hydrophobic effect may compensate for the weakened hydrated CHBs. Efforts are currently underway to produce water-soluble cavitands so we can explore such phenomenon.[23]

3. Preparation and Characterization of Other Bis-Bowl Complexes. 3.1. Host Preparations. Figure 2 provides drawings of all hosts. Tetraprotio bowl **5** was prepared by known methods.[24] Monol **6** (11%), A,B-diol **7** (1%), A,C-diol **8** (1.4%),[14] and triol **9** (21%)[25] were obtained as the byproducts of the reaction to produce tetrol **1b**. More reasonable quantities of A,B-diol **7** were obtained via a route developed by Reinhoudt, who used C_{11} feet.[26] Thus, tris-bridged tetrabromo cavitand **10**[27] was selectively debrominated to yield tris-bridged dibromo cavitand **11** (67%), which was bridged to give cavitand **12** (95%), whose bromines were then converted to hydroxyls via standard conditions to yield A,B-diol **7** (40%). Hexaprotio bis-bowl **13** was prepared by methylene bridging 2 equiv of monol **6** (81%). Likewise, tetraprotio bis-bowl **14** was obtained from 2 equiv of A,B-diol **7** (61%).[26b,28] Tetrahydroxy bis-bowl **15** and hexahydroxy bis-bowl **16** were prepared by partial bridging of tetrol **1b** in nitrobenzene as solvent as described previously.[5b] Tetramethoxy bis-bowl **4** was obtained by methylation of **15** (74%).[29]

3.2. Formation of Complexes. As stated earlier, tetrol **1** does not form a complex with pyrazine in the absence of base;[3] thus, four neutral hydrogen bonds are apparently not sufficient to form a complex under the given conditions.[30] One CHB is insufficient to form a complex in $CDCl_3$.[31] In contrast, A,B-

(14) The broadness of **1b** and DBU in nitrobenzene-d_5 is not due to binding of O_2 as observed in related species: Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717−27. The same reference reports the phenethyl-footed derivative of A,C-diol **8**.

(15) In nitrobenzene-d_5 at 298 K, K_{app} for capsule **3b**·NMP (1100 M^{-1}) multiplied by K_{rel} for **3b**·pyrazine: **3b**·NMP (980 000, ref 3b) = K_{app} for **3b**·pyrazine = 1.1×10^9 M^{-1}.

(16) Preparation of bis-bowl **4** and related species are given in Section 3.1.

(17) The ^{1}H NMR signals for the intrabowl methylene protons that line the interior of the bowls of bis-bowl **4** (1.15 mM) were slightly broad in nitrobenzene-d_5 at 333 K due to binding of O_2; this broadness was augmented by saturation with O_2 and eliminated by saturation with N_2 (see ref 14). The measurements were performed at 333 K because spectra of bis-bowl **4**·guest were better resolved, equilibrium to form complexes with guests was reached faster, and bis-bowl **4** had greater solubility.

(18) The ^{1}H NMR spectrum of complex **4**·NMP is complicated at 333 K due to the top/bottom asymmetry of the host, induced by the large NMP, which rotates slowly (on the ^{1}H NMR time scale) about the host's C_2 axes.

(19) Since K_{app} for **3b**·NMP is only 280 M^{-1} at 313 K (Section 1.3) and **3b**·guest generally has higher guest-affinity than **4**·guest (Section 3.4), we conclude that tetrol **1b** in the presence of DBU in nitrobenzene-d_5 exists as an aggregate of ∼5−20 molecules under the conditions reported, which results in a diminished apparent stability constant when the aggregate is treated as an empty dimer.

(20) For characterization of **3b**·guest in NMP, see Supporting Information.

(21) Branda, N.; Grotsfeld, R. M.; Valdés, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 85−88.

(22) For characterization of **3b**·DMSO and **3b**·pyrazine in DMSO-d_6, see Supporting Information.

(23) Mezo, A. R.; Sherman, J. C. *J. Org. Chem.* In press.

(24) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826−5828.

(25) The phenethyl-footed derivative of triol **9** has been reported: Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194−2204.

(26) (a) Timmerman, P.; van Mook, M. G. A.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1992**, *33*, 3377−3380. See also refs 14 and 28 for the phenethyl-footed derivative of **7**. (b) The C_{11}-footed derivative of bis-bowl **14** has been reported: Timmerman, P.; Boerrigter, H.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 167−191.

(27) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 2554−2560.

(28) For a phenethyl-footed derivative of bis-bowl **14**, see: Robbins, T. A.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1515−1516.

(29) Methylene linkage of A,C-diol **8** in DMF yields the corresponding bis-bowl·DMF, which is isolable and is thus a carceplex or a hemicarceplex (ref 14; see also Tanner, M. E. Ph.D. Thesis, University of California, Los Angeles, 1990; pp 126−128). In addition, triol **9** has been methylene-linked to give not only the corresponding tris-bridged hemicarceplex (ref 14) but also the corresponding bis-linked species where a free hydroxyl is present on each bowl, A,C to each other. This species was isolated containing DMSO and was stable in solution at 353 K for hours; thus, it too is a carceplex or a hemicarceplex (ref 14 and above thesis cited). Finally tetrol **1b** has been bis-linked in the A,C positions, leaving four hydroxyls; this compound holds DMSO in its cavity even after prolonged heating, and is thus a carceplex (ref 5b).

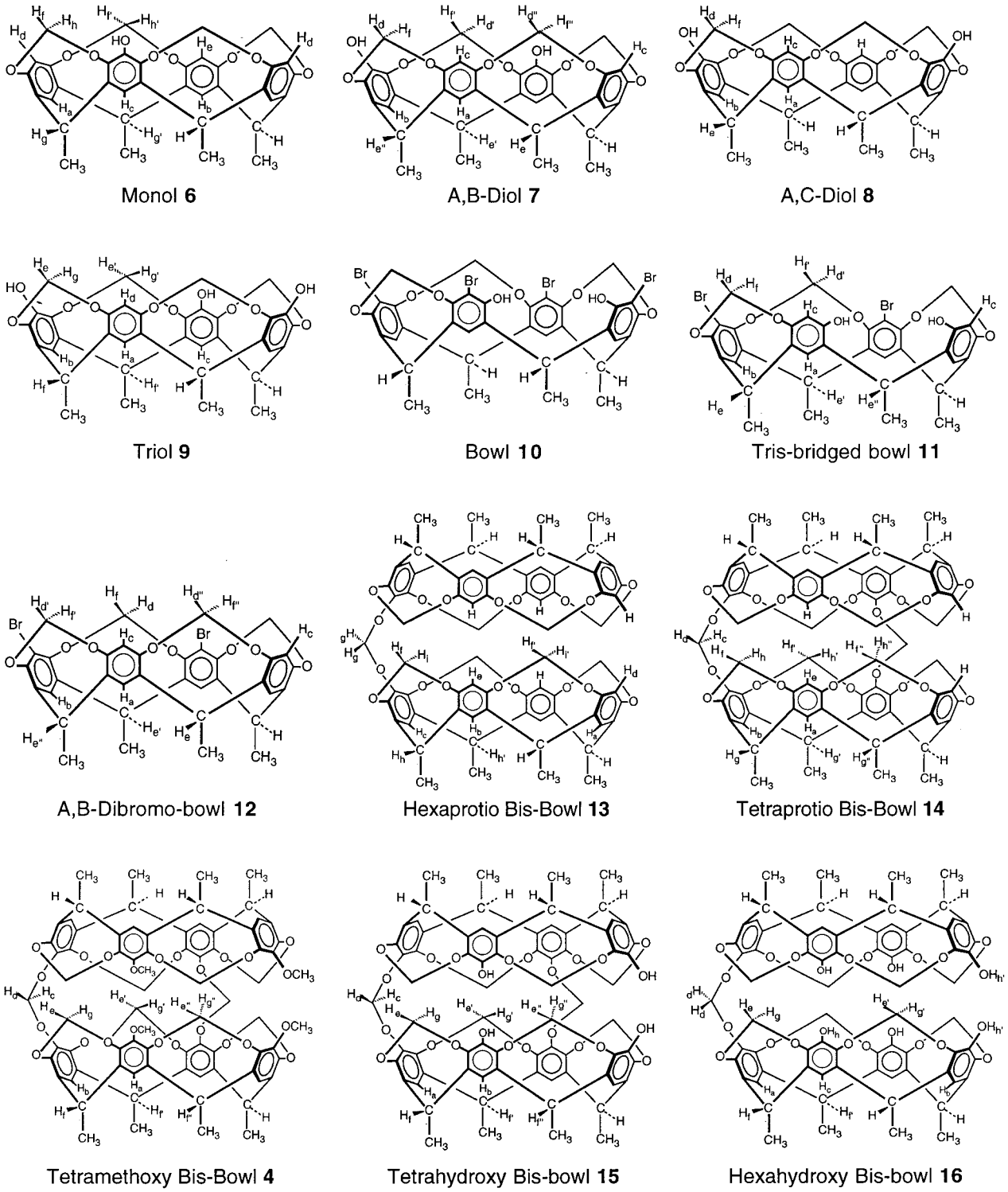


Figure 2. Drawings of hosts. Bowl **5** is the same as tetrol **1b**, except the four hydroxyls are replaced by hydrogens.

diol **7**, A,C-diol **8**, and triol **9**[32] all form complexes.[33] Thus, two CHBs are necessary and sufficient to link two bowls and encapsulate guests.[34] From here on, all charged complexes except **3**·guest will be denoted by a "**C**";[6] thus **7C**·guest is the charged complex formed from two molecules of diol **7** + guest, where the two bowls are linked by CHBs as shown for **3**·guest in Scheme 1 (structures and ^{1}H NMR data for all new complexes are given in the Supporting Information).

Mono-bridged hexaprotio bis-bowl **13** does not form a complex under standard conditions.[30] In contrast, A,B-bis-bridged bis-bowl tetraprotio **14** does form a complex.[35] Thus, one covalent link between two bowls is not sufficient to form a capsule, but two links are. Likewise A,B-bis-bridged tet-

(30) As a control, we subjected tetraprotio bowl **5** to complexation conditions and saw no evidence for a complex: the ^{1}H NMR spectrum of tetraprotio bowl **5** (12 mM) and pyrazine (12 mM) in $CDCl_3$ at ambient temperature showed no new peaks nor any change in chemical shifts of host or guest.

(31) The ^{1}H NMR spectrum of monol **6** (9.5 mM), DBU (5.7 mM), and pyrazine (4.8 mM) in $CDCl_3$ showed no evidence of complexation, even down to 223 K. For evidence of complex **6C** (see ref 6 for **6C** nomenclature) in nitrobenzene-d_5, see Supporting Information.

(32) For the bowl alignment and the orientation and mobility of pyrazine in triol-complex **9C**·guest (see ref 6 for **9C** nomenclature), see Supporting Information.

rahydroxy bis-bowl **15** forms a complex both in the absence (**15**·guest) and in the presence (**15C**·guest) of DBU, and bis-bowl **4** forms a complex (vide supra). Most noteworthy is that **14**·guest, **15**·guest, and **4**·guest *represent the first bis-bowl complexes that are neutral*. Bis-bowl **16** forms a complex in the presence of DBU (**16C**·guest), but not under neutral conditions. Thus, to form a complex with reasonable stability under standard conditions, two bowls must be linked by a combination of two or more CHBs or OCH_2O linkages.

3.3. Guest Exchange Rates. The rate of guest exchange in the complexes presented here varies significantly. Exchange rates are (1) generally slower as the number of CHBs or covalent linkages is increased, (2) generally slower in nitrobenzene-d_5 than in $CDCl_3$, (3) naturally faster at higher temperatures, and (4) highly dependent on the guest, as decomplexation is the slow step, and the thermodynamically more stable complexes (see Section 3.4) generally decomplex more slowly. Some quantitative as well as qualitative examples to illustrate these trends are given below. Half-lives or decomplexaion rates were determined as reported earlier for **3b**·guest[3b] and as explained in the experimental section; qualitative rates were determined by observation of slow, intermediate, or fast exchange on the ^{1}H NMR time scale, or by determining equilibration times as described in Section 3.4.

3.3.1. Host Dependence on Exchange Rates. At 298 K in $CDCl_3$, diol complexes **7C**·pyrazine and **8C**·pyrazine exchange pyrazine at ~1000 s^{-1}; triol complex **9C**·pyrazine exchanges in seconds; tetrol complex **3b**·pyrazine, tetraprotio complex **14**·pyrazine, and hexahydroxy complex **16C**·pyrazine exchange in minutes; the half-life for tetrahydroxy complex **15**·pyrazine is 4 h. At 333 K in nitrobenzene-d_5, complex **4**·MeOAc exchanges in a few minutes, while **15C**·MeOAc has a half-life of ~1 d. At ambient temperature in $CDCl_3$, egress of $CHCl_3$ from tetrahydroxy **15**·$CHCl_3$ is less than a few minutes, while in the corresponding charged complex, **15C**·$CHCl_3$, some of this guest remains intact after 4 days! Interestingly, excess base increases the rate of proton exchange, but decreases the rate of guest exchange, presumably by diminishing the concentration of neutral phenolics and thus diminishing the ease with which the two bowls can part.

3.3.2. Guests. Whereas diol complexes **7C**·guest and **8C**·guest exchange their guests in seconds to minutes in $CDCl_3$ at 253 K when guests are pyrazine, dioxane, or pyridine, exchange is ~1000 s^{-1} with DMSO, acetone, or benzene as guests. Whereas the half-life for decomplexation in tetrahydroxy **15**·pyrazine is 4 h at 298 K in $CDCl_3$, loss of $CHCl_3$ from **15**·$CHCl_3$ occurs in seconds to minutes under the same conditions. The half-life for **3b**·guest at 253 K in $CDCl_3$ is 21 h for pyrazine, 4.2 h for dioxane, and 1 h for DMSO.

3.3.3. Solvent. Complex **3b**·pyrazine exchanges in minutes in $CDCl_3$ at 298 K, but has a half-life of 1.5 h in nitrobenzene-d_5 at 298 K.

3.3.4. Temperature. The half-life for **3b**·pyrazine in $CDCl_3$ is 1−2 min at 298 K, 59 min at 273 K, and 21 h at 253 K.

3.4. Guest-Selectivities. We have shown previously that complex **3b**·guest manifests very high guest selectivity, where for example, **3b**·pyrazine is 980 000 times more stable than **3b**·NMP in nitrobenzene-d_5 at 313 K.[3b] Here we explore the guest-selectivity for the new complexes As discussed in Section 3.3, the complexes have vastly different exchange rates, depending on the host, the guest, the solvent, and of course the temperature. Thus, all the hosts could not be compared under identical conditions, but several sets of data could be generated and comparisons can be made.

The relative stabilities of one complex versus another were determined by integration of ^{1}H NMR samples prepared containing the host, base (if needed), and two guests in quantities and ratios that would yield a roughly 1:1 ratio of complexes. K_{rel}'s were then generated for a series of guests as follows: if K_{rel} for A:B is 3 and for B:C is 7, then K_{rel}'s generated for A:B:C would be 21:7:1. The procedure has been described for complex **3b**·guest[3b] and is given in the Supporting Information for the complexes reported here. It is imperative that the samples reach equilibrium, which was usually determined simply by re-recording the ^{1}H NMR spectra over time until no further changes in the spectra were observed. Table 1 records the K_{rel}'s. Data for complex **3b**·guest[3b] are included for comparisons.

Not surprisingly, the temperature dependence of the guest-selectivity is lower selectivity at higher temperatures. The solvent dependence of the guest-selectivities is fairly modest and has been discussed in detail for complex **3b**·guest.[3b] The most obvious conclusion one can make from Table 1 is that the same general guest-selectivity holds, regardless of the host system, the solvent, or the temperature. For example, pyrazine is the best guest in all systems. Nevertheless, there are some variations that are worthy of discussion. From Table 1, it appears that the A,B-linked complexes (**7C**·guest, **14**·guest, **15**·guest, and **4**·guest) all have a relatively high affinity for pyridine; this may be due to the complementarity of pyridine's dipole with that of these hosts. Another notable feature is that DMSO is relatively poor in the neutral complexes (**14**·guest, **15**·guest, and **4**·guest), although it is also relatively poor in capsule **16C**·guest, which may be anomalous. Perhaps DMSO can participate in hydrogen bonding in the charged complexes. Capsule **4**·guest manifests lower guest-selectivity than **3b**·guest. Alternatively, **4** appears have about a 10−15-fold higher affinity for benzene than **3b**·guest. This is likely to be due to the methoxyls, which may force the bowls apart somewhat and create a slightly larger cavity than that for **3b**·guest; the larger cavity would be more complementary to the large benzene.

3.5. Relative Stabilities of Complexes·Methyl Acetate. The K_{rel}'s discussed thus far have been limited to the guest-selectivities for each host. We now compare the relative affinities of the hosts for the same guest, methyl acetate. We chose methyl acetate for the following reasons: (1) it forms a very stable complex with all hosts, (2) the signals for encapsulated methyl acetate appear in an open window in the ^{1}H NMR spectra, and (3) the ^{1}H NMR signals for encapsulated methyl acetate vary considerably among the series of complexes studied; this facilitates integration of a pair of encapsulated guest signals.

Competition experiments were run similar to those described in Section 3.4, except that here two complexes were competing for a limited amount of methyl acetate. For example, a mixture

(33) As explained in Section 3.3, some complexes required lower temperatures to manifest slow exchange on the ^{1}H NMR time scale (ca. 0.01 s), while some required higher temperatures to reach equilibrium in a reasonable amount of time (i.e., hours).

(34) The ESIMS of complex **3b**·pyazine gave rise to, among other signals, a doubly charged species (i.e., two bowls linked by only two CHBs), but no such species was observed in solution (see ref 5b). We reasoned that such a species is kinetically stable (and observable in the gas phase), but not thermodynamically stable in solution since the tetra-charged species is far more stable. The formation of **7C**·guest and **8C**·guest in solution confirms that such doubly charged bis-bowl species are in fact stable, in these cases, both kinetically and thermodynamically.

(35) The ^{1}H NMR spectrum of tetraprotio bis-bowl **14** is extremely broad in $CDCl_3$ at ambient temperature due to the dynamics of the host; the spectrum is resolved at 223 K. Addition of pyrazine to this sample gave **14**·pyrazine, which confirms that the structure of the host is indeed the "C" isomer and not the "Z" isomer.

Table 1. Relative Stability Constants (K_{rel}'s) for Various Complexes

	in $CDCl_3$ at 253 K		
guest	**8C**·G	**7C**·G	**3b**·G
pyrazine	630	71	220
dioxane-d_8	85	3.0	14
pyridine-d_5	1.0	1.0	1.0
	in $CDCl_3$ at 273 K		
guest	**9C**·G	**16C**·G	**3b**·G
pyrazine	4400	2400	4100
dioxane	290	200	260
pyridine-d_5	28	19	21
DMSO-d_6	13	3.8	12
benzene-d_6	1.7	1.8	2.0
acetone-d_6	1.0	1.0	1.0
	in $CDCl_3$ at 298 K		
guest	**14**·G	**15**·G	**3b**·G
pyrazine	3200	3000	1400
dioxane	96	170	86
pyridine-d_5	17	46	11
DMSO-d_6	2.7		15
benzene-d_6	1.1	2.6	1.1
acetone-d_6	1.0	1.0	1.0
	in nitrobenzene-d_5 at 333 K		
guest	**4**·G	**3b**·G	
pyrazine	8500	110,000	
MeOAc	3700	48,000	
pyridine	4200	1200	
1,4-dioxane	2800	20,000	
DMSO	390	13,000	
acetone	42	300	
benzene	110	110[a]	
1,3-dioxane	36		
DMA	62		
$CHCl_3$	1.5		
NMP	1.0		
CH_2I_2	4200		
CH_2Br_2	190		
CH_2ClBr	39		
CH_2Cl_2	7.1		
morpholine	810		

[a] Benzene arbitrarily set at 110 for comparison.

Table 2. K_{rel}'s of Various Complexes·Methyl Acetate in Nitrobenzene-d_5 (MA = Methyl Acetate)

complex·MA	K_{rel}[a]
A,B-bis-bridged **15C**·MA	19[b]
3b·MA	18
triol **9C**·MA	6.7
tetra-OMe **4**·MA	5.9
(tetrol **1b**)·MA·(triol **9**)	5.6
mono-bridged **16C**·MA	4.1
A,B-bis-bridged **15**·MA	3.9
A,C-diol **8C**·MA	1.0
A,B-diol **7C**·MA	1.0

[a] K_{rel}'s determined at 298 K. [b] Relative stability constant of A,B-bis-bridged **15C**·methyl acetate to complex **3b**·methyl acetate was determined at 333 K.

of tetrol **1b**, triol **9**, DBU, and methyl acetate in nitrobenzene-d_5 at 298 K gave guest signals in the upfield region of the ^{1}H NMR that correspond to complex **3b**·methyl acetate and triol complex **9C**·methyl acetate as well as signals that were assigned to the asymmetric charged complex (tetrol **1b**)· methyl acetate·(triol **9**). The resulting K_{rel}'s are listed in Table 2.

The most striking feature of Table 2 is that the hosts have a surprisingly small range in stabilities. In addition, one trend is clear: the number of CHBs is important to the overall stability of the methyl acetate complexes: **3b**·methyl acetate > triol **9C**·methyl acetate > A,C-diol **8C**·methyl acetate = A,B-diol **7C**·methyl acetate. Also, the addition of CHBs to **15**·methyl acetate to give **15C**·methyl acetate creates a stronger complex. Interestingly, the three complexes that have three CHBs (asymmetric (tetrol **1b**)·methyl acetate·(triol **9**), triol **9C**·methyl acetate, and monobridged **16C**·methyl acetate) all have very similar stabilities. These results suggest that the presence of the CHBs in these complexes is a major component of their overall stabilities.

Table 3. Thermodynamic Data for K_{rel}'s of Various Complexes·Methyl Acetate in Nitrobenzene-d_5 (MA = Methyl Acetate)[a]

	3b·MA	**9C**·MA	**15**·MA	**4**·MA	**16C**·MA
$\Delta\Delta H°$, kcal/mol	1.8	−1.0	2.7	3.7	0.0
$\Delta\Delta S°$, eu[b]	8.8	−2.3	9.8	12.3	0.0
$T\Delta\Delta S°$, kcal/mol[c]	2.6	−0.7	3.0	3.7	0.0
$\Delta\Delta G°$, kcal/mol[c]	−0.9	−0.3	−0.2	0.0	0.0

[a] Errors are estimated to be ±30% mainly due to integration of the ^{1}H NMR spectra. [b] eu = entropy units. [c] Temperature = 300 K.

3.6. Relative Thermodynamic Stabilities of Various Complexes·Methyl Acetate. The small differences in selectivity for the complexes reported in Table 2 were somewhat surprising considering the structural differences between them, the differences in molecularity, and the number of counterions produced. Thus we conducted a thermodynamic analysis of these complexes: the temperature dependence of the relative stability constants for this series of complexes of methyl acetate was determined and the resulting $\Delta\Delta H°$, $\Delta\Delta S°$, and $\Delta\Delta G°$ were generated via van't Hoff plots (as described previously for **3b**·guest)[3b] and are given in Table 3.[36]

The trend in enthalpic favorability is **9C** > **16C** > **3b** > **15** > **4**. Charged complexes appear to be more enthalpically favored. This may be due to better π-donation to the carbonyl of methyl acetate. The hole in **9C** may allow hydrogen bonding from the carbonyl of methyl acetate to a DBU·H$^+$ counterion. The 1.8 kcal/mol difference between **16C** and **3b** may be the result of a snugger fit by **16C**, as OCH_2O linkages are shorter than O$^-$HO linkages.[3b,37]

The trend in entropic favorability is **4** > **15** > **3b** > **16C** > **9C**; this is the exact reverse of the enthalpy trend, which demonstrates an entropy−enthalpy compensation. The bis-bridged complexes (**4** and **15**) are favorable, likely because of their high degree of preorganization. The triol complex (**9C**) has many ways for the two bowls to align; all but one must be excluded, which costs in entropy. Complex **16C** is the only one that can potentially form oligomers; these must be excluded, again costing in entropy. This complex is also the only one that, upon complexation, has restricted rotation about an OCH_2O link. Another issue is the DBU·H$^+$ counterions. They may coordinate in a variety of up−down configurations, regarding the top and bottom bowls. Complex **3b** has the greatest number of variations here, and it manifests the largest favorable entropy of the complexes that have DBU·H$^+$ counterions. Finally, the two bowls of **3b** can come together four different ways, and all four form the complex. These entropic costs and benefits are no doubt present in different combinations for each complex and demonstrate the complexity of noncovalent interactions even in rigid, well-defined, highly sensitive systems.

4.0. Relevance of Complexes to Carceplex 2·Guest. The reaction to form carceplex **2**·guest from tetrol **1** proceeds through mono-bridged intermediate **16** and the guest-determining step (GDS) is formation of the second bridge (either A,B or A,C).[5b]

(36) The temperature dependence of K_{rel} for **7C**·methyl acetate and **8C**·methyl acetate were not studied because of intermediate exchange rates at temperatures greater than 298 K; likewise, very slow exchange in **15C**·methyl acetate precluded the same investigation.

(37) Fraser, J. R.; Borecka, B.; Trotter, J.; Sherman, J. C. *J. Org. Chem.* **1995**, *60*, 1207−1213.

We used complex **3**·guest as a model for the transition state of the GDS because the template ratios (i.e., guest-dependence) determined for carceplex **2**·guest correlated with the K_{rel}'s for complex **3**·guest.[3] The present results suggest that in fact any of the complexes reported here could serve as such transition state models since their K_{rel}'s manifest similar guest-selectivities; i.e., once the bowls are suitably preorganized by an assortment of CHBs and covalent links, a fairly uniform (in terms of size, shape, and electronics) cavity is formed, which is most complementary to pyrazine. As the reaction to form carceplex **2**·guest proceeds, bridge formation is quick and cooperative, as the intermediates are difficult to isolate, particularly the mono- and bis-bridged species.[5b] This is consistent with these species binding guests tightly, as reported in the present work, and thus, preorganizing the bowls for subsequent bridging. Indeed, high correlation of the template ratios to the K_{rel}'s, both in direction and in magnitude, suggests that the bulk of the template effect is due to binding; the actual rate constants cannot vary much with guest.

The GDS was concluded to be formation of the second bridge because template ratios starting from bis-bowl **15** did not agree with those starting from tetrol **1** or bis-bowl **16** (template ratios starting from **1** and **16** agreed with each other).[5b] But K_{rel}'s for bis-bowl **15** correlate with all the rest. Is there a dilemma? No. The K_{rel}'s were determined by letting the complexes come to equilibrium, but the template ratios were determined under uniform reaction conditions, which apparently do not allow equilibrium to be reached for bis-bowl **15** (really **15C** since base is present during the carceplex reaction), although equilibration can be reached with **16** or **1** (to give **16C**·guest or **3b**·guest, respectively).

One final note relating to carceplex **2**·guest: unreported experiments in our labs suggested that the template ratios for the bridging reagents decreased as follows: CH_2I_2 > CH_2Br_2 > CH_2BrCl > CH_2Cl_2. These went unreported because data for the template ratios were complicated by the role of these molecules as bridging agents. Nevertheless, this trend is reproduced by complex **4**·guest (Table 1), which does not react with these molecules. Again, the complexes and the formation of carceplex **2**·guest are highly guest-selective, where CH_2I_2 is 590 times better than CH_2Cl_2, even at 333 K.

Conclusions

Complex **3**·guest is a highly stable and highly guest-selective assembly that entails the encapsulation of guest molecules by two molecules of tetrol **1** in the presence of base. In chloroform as solvent, tetrol **1** exists as complex **3**·chloroform in the presence of base under standard conditions. The relative stability of **3**·pyrazine versus **3**·chloroform is 170 000 in nitrobenzene-d_5 at 298 K and 110 000 in $CDCl_3$ at 298 K. The free species in nitrobenzene-d_5 is an aggregate at the concentrations and temperatures studied. Treatment of this aggregate as an empty dimer of tetrol **1** yields an apparent stability constant in nitrobenzene-d_5 at 298 K of 1100 M^{-1} for complex **3**·NMP and 1.1×10^9 for **3**·pyrazine. Since the free species in nitrobenzene-d_5 is actually an aggregate, these numbers are *underestimated*.[19] The absolute stability constant for complex **4**·NMP in nitrobenzene-d_5 at 333 K is 410 M^{-1} and for **4**·pyrazine it is 3.5×10^6 M^{-1}, under the same conditions. Complex **3**·guest is stable enough to form in highly polar solvents such as NMP and DMSO.

Studies of eight new complexes demonstrate that two or more CHBs or covalent linkages between the bowls are required to form stable complexes. Guest exchange rates vary from milliseconds to days, thus bridging the gap between standard complexes (exchange rates up to minutes) and hemicarceplexes (exchange rates at least days). The exchange rates depend on temperature, host, solvent, and guest. The guest selectivities for all complexes are similar, and thus any one can be used as a transition state model for the GDS in the formation of carceplex **2**·guest. The hosts have very similar affinity for methyl acetate, but charged complexes are generally more enthalpically favored, while more preorganized hosts manifest entropic advantage. Thus, an enthalpy−entropy compensation appears to be at play.

These studies of an assortment of encapsulating species show that once two bowls are sufficiently preorganized by OCH_2O or O^-HO interbowl linkages, a cavity is formed that is complementary to guests such as pyrazine. The molecularity, nature of the interbowl linkages, and number of counterions do not have a dramatic effect on guest selectivity or on overall binding power, though enthalpy and entropy of binding may differ. The strength of these studies lies in the high selectivity, where tiny changes in the guest, for example, are met with large consequences for the energetics of the system. Such sensitivity is the result of the rigidity and well-defined nature of the hosts studied.

Current studies underway in our lab include the creation of water-soluble capsules, larger capsules, and higher-order capsules.

Experimental Section

General Procedures. Many procedures have been described previously.[37] $CDCl_3$, acetone-d_6, and DMSO-d_6 NMR solvents were stored over crushed 4 Å molecular sieves. ^{1}H NMR spectra were recorded on a Bruker WH-400 spectrometer in $CDCl_3$ (residual $CHCl_3$ used as a reference, $\delta = 7.24$ ppm) or in nitrobenzene-d_5 (residual protios used as references, $\delta = 8.11$, 7.67, and 7.50 ppm) unless noted otherwise. At temperatures other than ambient temperature, the ^{1}H NMR samples were equilibrated in the spectrometer for 20 min prior to data acquisition, unless noted otherwise. ^{2}H NMR spectra were recorded on a Varian XL-300 spectrometer. LSIMS and DCI mass spectrometry were performed on a Kratos Concept II HQ spectrometer.

Syntheses of 1b, 7, 8, and 9. Tetrol **1b** was prepared as described previously.[37] Side products were obtained starting from 3.10 g (3.41 mmol) of the corresponding tetrabromo precursor: After removal of the THF reaction solvent, the resulting yellow solid was suspended in water, filtered, and washed. The filtrate was acidified with 10% aqueous HCl and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The two solids were refluxed in $CHCl_3$ (500 mL) and DMSO (2.4 mL, 34 mmol) was added. The suspension was cooled to 0 °C and filtered after 1 h. The resulting white solid (95% tetrol **1b** and 5% triol **9**) was dissolved in THF (200 mL) and dry loaded[37] onto a silica gel gravity column and eluted with ethyl acetate:hexanes (4:1), affording tetrol **1b** which was dried at 110 °C (0.1 mmHg) for 24 h (1.0 g, 45%). The $CHCl_3$ filtrate was also dry loaded onto a silica gel gravity column which was eluted with ethyl acetate:hexanes (1:1), affording the following byproducts, which were recrystallized from ethyl acetate/hexanes and dried at 110 °C (0.1 mmHg) for 24 h: monol **6** (230 mg, 11%), A,B-diol **7** (20 mg, 1%), A,C-diol **8** (30 mg, 1.4%), and triol **9** (417 mg, 21%). For all four compounds, mp >250 °C. An alternative route to diol **7** (**10** → **11** → **12** → **7**) follows.

Monol 6. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (s, 3H, H_a and H_b), 6.76 (s, 1H, H_c), 6.47 (s, 2H, H_d), 6.46 (s, 1H, H_e), 5.84 (d, $J = 6.9$ Hz, 2H, H_f or $H_{f'}$), 5.74 (d, $J = 7.1$ Hz, 2H, H_f or $H_{f'}$), 5.29 (s, 1H, OH), 4.94 (m, 4H, H_g and $H_{g'}$), 4.44 (d, $J = 6.9$ Hz, 2H, H_h or $H_{h'}$), 4.43 (d, $J = 7.0$ Hz, 2H, H_h or $H_{h'}$), 1.74 (m, 12H, CH_3); MS (LSIMS$^+$, Thioglycerol) *m*/*z* 608 (M^+; 100). Anal. Calcd for $C_{36}H_{32}O_9$: C, 71.04; H, 5.30. Found: C, 70.79; H, 5.23.

A,B-Diol 7. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 2H, H_a), 6.76 (s, 2H, H_b), 6.47 (s, 2H, H_c), 5.94 (d, J = 6.8 Hz, 1H, $H_{d'}$ or $H_{d''}$), 5.84 (d, J = 7.0 Hz, 2H, H_d), 5.74 (d, J = 7.1 Hz, 1H, $H_{d'}$ or $H_{d''}$), 5.37 (s, 2H, OH), 4.93 (m, 4H, H_e, $H_{e'}$, and $H_{e''}$), 4.44 (m, 4H, H_f, $H_{f'}$ and $H_{f''}$), 1.73 (m, 12H, CH_3); MS (LSIMS$^+$, Thioglycerol) *m*/*z* 624 (M^+; 100). Anal. Calcd for $C_{36}H_{32}O_{10}\cdot{}^1/_2H_2O$: C, 68.24; H, 5.25. Found: C, 68.11; H, 5.36.

A,C-diol 8. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (s, 2H, H_a), 6.75 (s, 2H, H_b), 6.49 (s, 2H, H_c), 5.84 (d, J = 7.0 Hz, 4H, H_d), 5.27 (s, 2H, OH), 4.93 (q, J = 7.4 Hz, 4H, H_e), 4.44 (d, J = 7.0 Hz, 4H, H_f), 1.73 (d, J = 7.4 Hz, 12H, CH_3); MS (LSIMS$^+$, Thioglycerol) *m*/*z* 624 (M^+; 100). Anal. Calcd for $C_{36}H_{32}O_{10}\cdot{}^1/_2$ H_2O: C, 68.24; H, 5.25. Found: C, 68.61; H, 5.26.

Triol 9. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 1H, H_a), 6.75 (s, 3H, H_b and H_c), 6.49 (s, 1H, H_d), 5.95 (d, J = 7.1 Hz, 2H, H_e or $H_{e'}$), 5.85 (d, J = 7.2 Hz, 2H, H_e or $H_{e'}$), 5.29 (s, 3H, OH), 4.92 (m, 4H, H_f and $H_{f'}$), 4.44 (d, J = 7.1 Hz, 2H, H_g or $H_{g'}$), 4.43 (d, J = 7.2 Hz, 2H, H_g or $H_{g'}$), 1.72 (m, 12H, CH_3); MS (LSIMS$^+$, Thioglycerol) *m*/*z* 640 (M^+; 100). Anal. Calcd for $C_{73}H_{64}O_{24}\cdot{}^1/_2H_2O$: C, 66.56; H, 5.12. Found: C, 66.71; H, 4.99.

A,B-Dibromo-Tris-Bridged Bowl 11. A solution of tetrabromo-tris-bridged bowl **10** (2.0 g, 2.23 mmol) in dry THF (300 mL) was cooled to −78 °C and *n*-butyllithium (4.2 mL of a 1.5 M solution in hexanes, 6.3 mmol) was added. After 1 min, the reaction mixture was quenched with excess H_2O and the solution was allowed to warm to ambient temperature over 1 h. The solvent was removed in vacuo and the resulting solid was dissolved in CH_2Cl_2 (200 mL) and washed with 2 M HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL) and dried over $MgSO_4$. The crude product was purified by silica gel gravity column (eluted with CH_2Cl_2), affording bowl **11** as a white solid, which was recrystallized from CH_2Cl_2/hexane and dried at 110 °C (0.1 mmHg) for 24 h (1.1 g, 67%): mp >250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (s, 2H, H_a or H_b), 7.18 (s, 2H, H_a or H_b), 7.07 (s, 2H, OH), 6.48 (s, 2H, H_c), 5.86 (d, J = 7.2 Hz, 2H, H_d), 5.70 (d, J = 7.2 Hz, 1H, $H_{d'}$), 5.00 (q, J = 7.4 Hz, 2H, H_e), 4.90 (q, J = 7.4 Hz, 1H, $H_{e'}$ or $H_{e''}$), 4.64 (q, J = 7.2 Hz, 1H, $H_{e'}$ or $H_{e''}$), 4.42 (d, J = 7.2 Hz, 2H, H_f), 4.35 (d, J = 7.2 Hz, 1H, $H_{f'}$), 1.77 (d, J = 7.4, Hz 6H, CH_3), 1.76 (d, J = 7.2 Hz, 3H, CH_3), 1.71 (d, J = 7.4 Hz, 3H, CH_3); MS (LSIMS$^+$, NOBA) *m*/*z* 738 (M^+; 100). Anal. Calcd for $C_{35}H_{30}O_8Br_2$: C, 56.93; H, 4.09. Found: C, 57.00; H, 4.14.

A,B-Dibromo-Bowl 12. A mixture of A,B-dibromo-tris-bridged bowl **11** (400 mg, 0.542 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and CH_2BrCl (1.4 mL, 22 mmol) in NMP (30 mL) was stirred at 60 °C for 2 d. 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 × 50 mL), and the combined organic solutions 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 purified by dry loading onto a silica gel gravity column (20 g) and eluted with $CHCl_3$, affording bowl **12** as a white solid that was recrystallized from CH_2Cl_2/hexane and dried at 110 °C (0.1 mmHg) for 24 h (404 mg, 95%): mp >250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (s, 2H, H_a or H_b), 7.18 (s, 2H, H_a or H_b), 6.49 (s, 2H, H_c), 5.94 (d, J = 7.3 Hz, 1H, H_d or $H_{d''}$), 5.84 (d, J = 7.2 Hz, 2H, $H_{d'}$), 5.74 (d, J = 7.2 Hz, 1H, H_d or $H_{d''}$), 5.00 (m, 4H, H_e, $H_{e'}$ and $H_{e''}$), 4.45 (d, J = 7.2 Hz, 1H, H_f or $H_{f''}$), 4.40 (d, J = 7.2 Hz, 2H, $H_{f'}$), 4.37 (d, J = 7.3 Hz, 1H, H_f or $H_{f''}$), 1.74 (m, 12H, CH_3); MS (LSIMS$^+$, NOBA) *m*/*z* 750 (M^+; 100). Anal. Calcd for $C_{36}H_{30}O_8Br_2$: C, 57.62; H, 4.03. Found: C, 57.96; H, 3.94.

A,B-Diol 7. A solution of A,B-dibromo-bowl **12** (500 mg, 0.666 mmol) in dry THF (50 mL) was cooled to −78 °C and *n*-butyllithium (2.08 mL of a 1.5 M solution in hexanes, 3.33 mmol) was added. After 1 min, $B(OMe)_3$ (0.454 mL, 4.00 mmol) was added and the solution was allowed to warm to ambient temperature over 2 h. The reaction mixture was cooled again to −78 °C, 1.5 M NaOH−15% H_2O_2 (24 mL) was added, and the reaction mixture was again allowed to warm to ambient temperature over 2 h. $Na_2S_2O_5$ (15 g, 79 mmol) was carefully added to quench the excess H_2O_2 followed by H_2O (100 mL), and removal of the THF in vacuo, furnishing a yellow solid that was filtered and washed with water. This material was then dissolved in $CHCl_3$ and dry loaded onto a silica gel gravity column that was eluted with ethyl acetate:hexanes (1:1), affording A,B-diol **7** as a white solid, which was recrystallized from CH_2Cl_2/hexane and dried at 110 °C (0.1 mmHg) for 24 h (165 mg, 40%). This material was identical (by ^{1}H NMR) to that obtained as a byproduct in the synthesis of tetrol **1b**.

Tetraprotio Bis-Bowl 14. A mixture of A,B-diol **7** (0.106 g, 0.168 mmol,), K_2CO_3 (1.0 g, 7.23 mmol), methyl acetate, (2.5 mL, 31.4 mmol), and CH_2BrCl (0.11 mL, 1.7 mmol) in NMP (50 mL) were stirred at room temperature for 24 h. An additional 1.7 mmol of CH_2BrCl was added and the reaction was stirred for an additional 48 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 × 40 mL), and the combined organic solutions 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 removed in vacuo. The silica gel absorbed sample was purified by dry loading onto a silica gel gravity column (20 g) and eluted with $(CH_2Cl)_2$:CCl_4 (3:1) affording bis-bowl **14** as a white solid that was recrystallized from CH_2Cl_2/hexane and dried at 110 °C (0.1 mmHg) for 24 h (65 mg, 61%): mp >250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz at 223K) δ 7.15 (s, 4H, H_a), 6.80 (s, 4H, H_b), 6.61 (d, J = 6.1 Hz, 2H, H_c or H_d), 6.40 (d, J = 6.1 Hz, 2H, H_c or H_d), 6.36 (s, 4H, H_e), 6.13 (d, J = 7.6 Hz, 2H, $H_{f'}$ or $H_{f''}$), 5.97 (br, 4H, H_f), 5.79 (d, J = 6.6 Hz, 2H, $H_{f'}$ or $H_{f''}$), 5.00 (q, J = 7.4 Hz, 2H, $H_{g'}$ or $H_{g''}$), 4.88 (q, J = 7.3, Hz 2H, $H_{g'}$ or $H_{g''}$), 4.81 (q, J = 7.1 Hz, 4H, H_g), 4.54 (d, J = 7.6 Hz, 2H, $H_{h'}$ or $H_{h''}$), 4.22 (m, 6H, H_h and ($H_{h'}$ or $H_{h''}$)), 1.73 (m, 12H, CH_3), 1.65 (d, J = 7.1, 12H, CH_3). MS (DCI, ammonia) *m*/*z* (rel intensity) 1291 ($(M + NH_4)^+$; 100). Anal. Calcd for $C_{74}H_{64}O_{20}\cdot H_2O$: C, 68.83; H, 5.15. Found: C, 68.92; H, 5.10.

Hexaprotio Bis-Bowl 13. A mixture of monol **6** (0.078 g, 0.128 mmol,), K_2CO_3 (1.5 g, 11 mmol), and CH_2I_2 (0.26 mL, 3.2 mmol) in NMP (50 mL) was stirred at 60 °C for 24 h. An additional 3.2 mmol of CH_2I_2 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 CH_2Cl_2 (3 × 40 mL), and the combined organic solutions 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 CH_2Cl_2 solution and the solvent removed in vacuo. The silica gel absorbed sample was purified by dry loading onto a silica gel gravity column (15 g) and eluted with ethyl acetate/hexanes (1:1) affording bis-bowl **13** as a white solid that was recrystallized from ethyl acetate/CH_2Cl_2/hexane and dried at 210 °C (0.1 mmHg) for 24 h (64 mg, 81%): mp >250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 2H, H_a), 7.20 (s, 4H, H_b), 6.99 (s, 2H, H_c), 6.47 (s, 2H, H_d), 6.44 (s, 4H, H_e), 5.72 (d, J = 7.0 Hz, 4H, H_f or $H_{f'}$), 5.50 (d, J = 7.3 Hz, 4H, H_f or $H_{f'}$), 5.39 (s, 2H, H_g), 4.91 (m, 8H, H_h and $H_{h'}$), 4.43 (d, J = 7.3 Hz, 4H, H_i or $H_{i'}$), 4.32 (d, J = 7.0 Hz, 4H, H_i or $H_{i'}$), 1.74 (m, 24H, CH_3); MS (LSIMS$^+$, NOBA) *m*/*z* (rel intensity) 1228 (M^+; 100). Anal. Calcd for $C_{73}H_{64}O_{18}\cdot H_2O$: C, 70.30; H, 5.33. Found: C, 70.60; H, 5.17.

Tetra-OMe Bis-Bowl 4. A mixture of A,B-bis-bowl **15** (0.053 g, 0.040 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and $SO_2(OCH_3)_2$ (0.15 mL, 1.6 mmol) in acetone (40 mL) was refluxed for 16 h. Diethylamine (1.0 mL, 10 mmol) was added and the reaction mixture was stirred for 1 h to quench any residual $SO(OCH_3)_2$. The reaction mixture was concentrated in vacuo, water (20 mL) was added, and the slurry was acidified with 2 M HCl. The slurry was extracted with $CHCl_3$ (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL) and dried over anhydrous $MgSO_4$. The $CHCl_3$ solution was concentrated in vacuo and purified by chromatography on a silica gel gravity column (20 g), and eluted with $CHCl_3$/hexanes/ethyl acetate (60:20:1), affording bis-bowl **4** as a white solid that was recrystallized from CH_2Cl_2/hexane and dried at 210 °C (0.1 mmHg) for 48 h (41 mg, 74%): mp >250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.89 (s, 4H, H_a or H_b), 6.79 (s, 4H, H_a or H_b), 6.69 (d, J = 6.1 Hz, 2H, H_c or H_d), 6.39 (br, 2H, H_c or H_d), 6.16 (d, J = 7.4 Hz, 2H, $H_{e'}$ or $H_{e''}$), 6.03 (d, J = 7.5 Hz, 4H, H_e), 5.77 (d, J = 7.5 Hz, 2H, $H_{e'}$ or $H_{e''}$), 5.05 (q, J = 7.4 Hz, 2H, $H_{f'}$ or $H_{f''}$), 4.97 (q, J = 7.4 Hz, 2H, $H_{f'}$ or $H_{f''}$), 4.87 (q, J = 7.4 Hz, 4H, H_f), 4.59 (br, 2H,

$H_{g'}$ or $H_{g''}$), 4.26 (d, J = 7.5 Hz, 2H, $H_{g'}$ or $H_{g''}$), 4.26 (d, J = 7.5 Hz, 4H, H_g), 3.84 (s, 12H, OCH_3), 1.72 (d, J = 7.4 Hz, 12H, CH_3), 1.64 (d, J = 7.4 Hz, 12H, CH_3); MS (LSIMS$^+$, Thioglycerol) m/z (rel intensity) 1393 (M^+; 100). Anal. Calcd for $C_{78}H_{72}O_{24}\cdot H_2O$: C, 66.38; H, 5.28. Found: C, 66.39; H, 5.17.

Acknowledgment. We thank NSERC of Canada for funding. 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 funding.

Supporting Information Available: Procedures for determination of K_{rel}'s for all new data, tables of ^{1}H NMR data for all new complexes, characterization of **3b**·$CHCl_3$ in nitrobenzene-d_5, characterization of **3b**·guest in NMP, characterization of **3b**·DMSO and **3b**·pyrazine in DMSO-d_6, characterization of **6C**·pyrazine in nitrobenzene-d_5, and bowl alignment and guest mobility and orientation in **9C**·pyrazine (16 pages print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981596H