Study of Templation and Molecular Encapsulation Using Highly Stable and Guest-Selective Self-Assembling Structures

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The phenomenon of self-assembly is common to both the biological and physical sciences, from the formation of cell membranes to the formation of monolayers, and thus is of widespread interest. Our investigations into self-assembly have led to the demonstration of a template effect that ranges 10^6-fold in the formation of carceplex **2a**•guest (Scheme 1).[1] We report here a self-assembling structure (**3**) that entails the encapsulation of a guest (template) molecule by two molecules of tetrol **1**, which is the starting material for carceplex **2**•guest. We have determined the relative stabilities of complexes **3b**•guest, with six different guest molecules, and discuss the correlation of the guest selectivities with the *template ratios*[1] obtained in the formation of carceplex **2b**•guest. We think these complexes will provide an unusual opportunity to study noncovalent interactions in general, as subtle variations in guests are manifested by large changes in the energies of binding.

During the one-pot synthesis of carceplex **2a**•guest, eight covalent (C−O) bonds are formed and seven molecules are brought together, including the guest (Scheme 1).[2] The reaction requires a suitable guest/template molecule as illustrated by the range in yields from 0% in the presence of no suitable templates to 87% in the presence of the best template molecule, pyrazine.[1] Template ratios[1] were determined for 24 guest/template molecules and indicate the relative rates of the guest-determining step (the step beyond which no guest exchange occurs) in the formation of carceplex **2a**•guest. One approach to understanding the driving forces for this dramatic template effect is to explore the potential for association of the starting tetrol "bowls" with the template molecules; such a complex could serve as a model for the transition state of the guest-determining step.

The ^{1}H NMR spectrum (Figure 1) of a mixture of tetrol **1b**,[3] pyrazine, and the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in $CDCl_3$ indicates the formation of a complex,[4] which was characterized as follows. Complex **3b**•pyrazine undergoes slow exchange on the ^{1}H NMR time scale at ambient temperature as is evident by the two sets of host and guest signals.[4] Integration of the complexed host and guest signals yields a ratio of two "bowls" to one pyrazine. This ratio is supported by electrospray mass spectra, which gave **3b**•pyrazine as the most intense signal.[5]

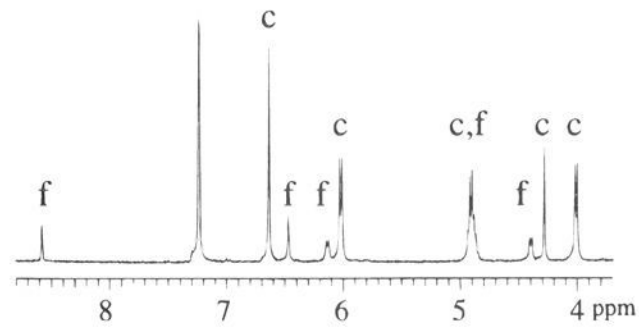

Figure 1. ^{1}H NMR spectrum of tetrol **1b** (3.7 mM), DBU (7.8 mM), and pyrazine (1.9 mM) in $CDCl_3$ at 25 °C. Peaks labeled "f" are signals for the "free" species (see note 4); peaks labeled "c" are signals for complex **3b**•pyrazine. Assignments are δ (ppm) 8.6, free pyrazine; 7.24, $CHCl_3$; 6.6, H_p of **3b**•pyrazine; 6.5, H_p of "free"; 6.1, H_{out} of "free"; 6.0, H_{out} of **3b**•pyrazine; 4.9, methine; 4.5, H_{in} of "free"; 4.3, encapsulated pyrazine; 4.0, H_{in} of **3b**•pyrazine. The methyls are at 1.7 ppm (not shown). See Scheme 1 for the assignments of H_p, H_{in}, and H_{out}.

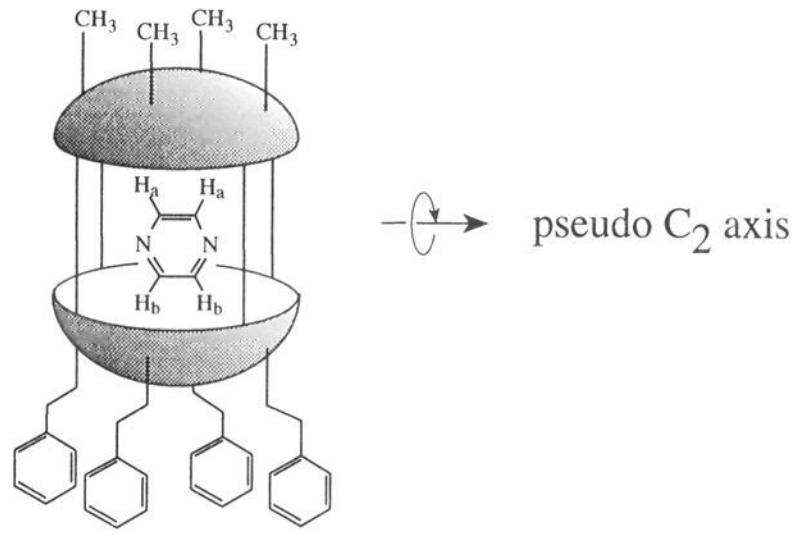

Figure 2. Schematic representation of asymmetric complex **3c**•pyrazine. Pyrazine is oriented with the nitrogens at the "equator" of the complex, as protons H_a and H_b are nonequivalent. The vertical lines connecting the two bowls represent charged hydrogen bonds.

The chemical shift for complexed pyrazine is shifted upfield 4.3 ppm from its uncomplexed position in $CDCl_3$, which is similar to the 4.6 ppm upfield shift observed for entrapped pyrazine in carceplex **2b**•pyrazine.[1,3] Furthermore, in asymmetric complex **3c**•pyrazine,[6] the pyrazine protons consist of two meta-split doublets (for H_a and H_b, Figure 2), as was observed in the corresponding asymmetric carceplex, **2c**•pyrazine.[3] Thus, pyrazine is oriented in the cavity of asymmetric complex **3c**•pyrazine as shown in Figure 2. Moreover, coalescence of the two pyrazine signals gave an energy barrier for rotation of pyrazine about the pseudo-C_2 axes of the complex. The barrier was 18 kcal/mol, which is similar to the 19 kcal/mol barrier determined for the corresponding rotation in asymmetric carceplex **2c**•pyrazine.[3] Thus, the magnetic environment formed around pyrazine in asymmetric complex **3c**•pyrazine, as well as the orientation and mobility of the encapsulated pyrazine, strongly resembles that found in asymmetric carceplex **2c**•pyrazine.

To probe the noncovalent interactions between the two bowls, a $CDCl_3$ solution of tetrol **1b** and pyrazine was titrated with DBU. The resulting ^{1}H NMR spectra showed that the fraction

(1) Chapman, R. G.; Chopra, N.; Cochien, E. D.; Sherman, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 369−370. Template ratios were determined by measurement of the carceplex **2a**•guest product ratios from competition reactions in the presence of two or more guests. The template ratios for carceplex **2b**•guest reported in Table 1 were determined as described in the above reference, but at ambient temperature, using tetrol **1b**. The guests reported in Table 1 span only about halfway down the table of template ratios that was reported in the above reference.

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

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

(4) Upon addition of $^1/_2$ equiv of trifluoroacetic acid per hydroxyl to complex **3b**•pyrazine, tetrol **1b** and free pyrazine were regenerated, demonstrating that formation of the complex is reversible and can be switched by adjustment of pH. The "free" species consists of a combination of complex **3b**•$CDCl_3$ and tetrol **1b**, which are in fast exchange on the ^{1}H NMR time scale at 298 K. Complex **3b**•$CHCl_3$ was characterized by suppression of the $CHCl_3$ signal in the ^{1}H NMR spectrum of tetrol **1b** and DBU in 1:1 $CHCl_3/CDCl_3$ at 273 K.

(5) A tetra-[$(n$-Bu$)_4$N$^+$] salt of complex **3b**•pyrazine was prepared by dissolving tetrol **1b** with 2.1 equiv of aqueous $(n$-Bu$)_4$N$^+$HO$^-$ and 6 equiv of pyrazine in 9:1 $CHCl_3/CH_3OH$. The solvent was removed *in vacuo* and dried for 2 days at 0.01 Torr at ambient temperature to yield a solid that had a 2:4.1:1 **1b**:$(n$-Bu$)_4$N$^+$:pyrazine ratio. This complex exchanges guest over a period of hours in CD_3CN, DMSO-d_6, and acetone-d_6, while the DBUH$^+$ salts of complex **3b**•pyrazine in $CDCl_3$ exchange over a period of minutes. Electrospray mass spectra of a 10^{-4} M CH_3CN solution of the tetra-[$(n$-Bu$)_4$N$^+$] salt of complex **3b**•pyrazine gave **3b**•pyrazine (a combination of the singly, doubly, and triply negatively charged species) as the most intense signal.

(6) A mixture of tetrols **1a** and **1b**, pyrazine, and DBU in $CDCl_3$ yields a mixture of the three complexes **3a**•pyrazine, **3b**•pyrazine, and the asymmetric **3c**•pyrazine. For a discussion of the orientation and rotational energy barrier of pyrazine in carceplex **2c**•pyrazine, see ref 3.

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

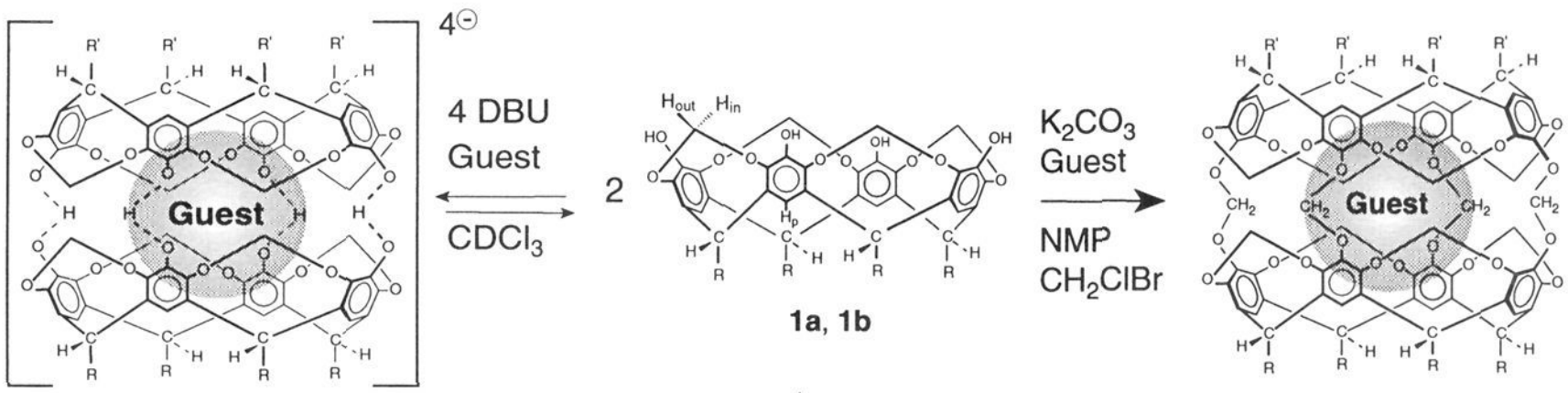

Table 1. Relative Stabilities of Complexes **3b**·Guest and Template Ratios for Carceplex **2b**·Guest

guest	K_{rel}	template ratio (TR)[a]	ln(K_{rel})	ln(TR)
pyrazine	580	860	6.4	6.8
dioxane	71	180	4.3	5.2
DMSO	14	19	2.6	2.9
pyridine	9.5	14	2.2	2.6
acetone-d_6	0.90	2	−0.1	0.6
benzene-d_6	1.0	1	0.0	0.0

[a] TR determined at 298 K using tetrol **1b** (see note 1).

of complex **3b**·pyrazine[7] increased until $^1/_2$ equiv of DBU per hydroxyl of tetrol **1b** had been added, indicating that half of the phenolic hydroxyls are deprotonated in complex **3b**·pyrazine.[4] Furthermore, the ^{1}H NMR spectrum of the tetra-[$(n$-Bu)$_4$N$^+$] salt of complex **3b**·pyrazine[5] contains a singlet at 15.6 ppm in acetone-d_6 at 200 K, which integrates to four protons per complex **3b**·pyrazine.[8] We conclude that four strong charged hydrogen bonds[9] are formed between the two bowls as depicted in Scheme 1.

The relative stabilities, K_{rel}, of complexes **3b**·guest were determined via competition experiments, by integrating host signals in the ^{1}H NMR spectra of mixtures of tetrol **1b**, DBU, guest 1, and guest 2 in $CDCl_3$.[10] The results, recorded in Table 1, show that complex **3b**·guest is highly guest-selective, as discussed below.

Is complex **3b**·guest a good transition state model for the guest-determining step in the formation of carceplex **2b**·guest? A plot of the ln(template ratio for carceplex **2b**·guest) versus ln(K_{rel} for complex **3b**·guest) for the six guests from Table 1 yields a correlation of $r^2 = 0.99$. This correlation indicates that the nature of the guest has a similar effect on the relative free energies of complexation for complexes **3b**·guest and on the relative activation energies for the guest-determining step in formation of carceplex **2b**·guest (all at ambient temperature). This agreement implies that the interactions that govern the formation of carceplex **2b**·guest are similar to those that drive the formation of the complexes, and thus, these complexes provide simple and useful transition state models for the guest-determining step in the formation of carceplex **2b**·guest.

The overall stability of complexes **3b**·guest is reflected by the large range in the relative stabilities, particularly when one considers that complex **3b**·pyrazine predominates over complex **3b**·$CDCl_3$ in the presence of over 10,000-fold excess $CDCl_3$ at millimolar concentrations of tetrol **1b** (Figure 1).[4,10] Furthermore, observation of signals due to **3b**·DMSO[11] as well as **3b**·pyrazine in DMSO-d_6 as solvent is remarkable, since DMSO is a strong hydrogen bond acceptor and is notorious for precluding the formation of complexes that rely on hydrogen bonds for their formation.[12a]

In conclusion, we have discovered a complex that combines self-assembly and molecular encapsulation[12] and is reversible and strongly guest-selective. The complex serves as a simple transition state model for the guest-determining step in the formation of carceplex **2b**·guest and demonstrates that the driving forces in this reaction are charged hydrogen bonds between the bowls, and van der Waals and electrostatic interactions between the guests and the walls of the cavity formed by the two bowls. We believe that the large changes in binding energy brought about by small perturbations in the guests (cf. pyrazine and pyridine) make complex **3b**·guest a useful system to study noncovalent interactions; thus, we are probing these complexes further by theoretical as well as experimental means. We are also expanding on the prototypical complex, **3b**·guest, by creating both larger assemblies, with potential as drug delivery devices, and higher order complexes (tail-to-tail and side-to-side covalently linked bowls), which may provide new materials such as linear rods or two-dimensional bilayers.

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(7) The fraction complex represents the fraction of bowls that are involved in complex **3b**·pyrazine and was determined by integration of the corresponding free (I_f) and complexed (I_c) host signals (typically using H_{in}; see Scheme 1) in the ^{1}H NMR spectrum: fraction complex = $I_c/(I_c + I_f)$.

(8) Although the bases DBU and (n-Bu)$_4$N$^+$HO$^-$ yield complex **3b**·pyrazine in $CDCl_3$, Et_3N does not.

(9) For NMR and other data on strong hydrogen bonds, see: (a) Frey, P. A.; Whitt, S. A.; Tobin, J. B. *Science* **1994**, *264*, 1927−1930. (b) Perrin, C. L. *Science* **1994**, *266*, 1665−1668. (c) Brzezinski, B.; Szafran, M. *Org. Magn. Reson.* **1981**, *15*, 78−72. (d) Gunnarsson, G.; Wennerström, H.; Egan, W.; Forsén, S. *Chem. Phys. Lett.* **1976**, *38*, 96−99.

(10) Ratios of guest 1 and guest 2 in competition experiments were chosen that produce ca. 1:1 (**3b**·guest 1):(**3b**·guest 2) ratios, so that the integration is most accurate. For example, 2.63 mM tetrol **1b**, 5.52 mM DBU, 1.31 mM pyrazine, and 10.5 mM 1,4-dioxane gave a 1:1 **3b**·pyrazine:**3b**·dioxane ratio, which translates to a relative stability for **3b**·pyrazine/**3b**·dioxane of 8.0:1. These two complexes comprise over 90% of the bowl species in this solution; the remainder is the "free" species (see note 4).

(11) Complex **3b**·DMSO (dimethyl sulfoxide) was shown to form in DMSO as solvent by obtaining a ^{1}H NMR spectrum of tetrol **1b** and DBU in a 1:1 mixture of DMSO and DMSO-d_6 and suppressing the solvent peak at 2.49 ppm, which revealed complexed DMSO at −1.2 ppm at 298 K. Although complex **3b**·pyrazine is stable in DMSO-d_6, its formation was not observed in protic solvents such as methanol.

(12) For other assemblies that involve encapsulation, see: (a) Branda, N.; Grotsfeld, R. M; Valdés, C.; Rebek, J. *J. Am. Chem. Soc.* **1995**, *117*, 85−88. (b) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255−8258. (c) Bonar-Law; R. P.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1995**, *117*, 259−271. (d) Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10302−10306. (e) Yoshida, Z.; Takekuma, H.; Takekuma, S.; Matsubara, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1597−1599. (f) Harada, A.; Li, J.; Kamachi, M. *Nature* **1994**, *370*, 126−128. (g) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353−9354. (h) Inoue, Y.; Liu, Y.; Tong, L. H.; Shen, B. J.; Jin, D. S. *J. Am. Chem. Soc.* **1993**, *115*, 10637−10644. (i) Dick, D. L.; Rao, T. V. S.; Sukumaran, D.; Lawrence, D. S. *J. Am. Chem. Soc.* **1992**, *114*, 2664−2669. (j) Eftink, M. R.; Andy, M. L.; Bystrom, K.; Perlmutter, H. D.; Kristol, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 6765−6772.