Restricted Motion of Guests Confined in Carceplexes and Capsules

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Guest orientation within carceplexes and capsules was determined qualitatively from NMR data, and the molecular mobility of guests was determined via coalescence of ^{1}H NMR signals. Both are highly dependent on guest size and shape, as is interconversion of twistomers. Incarceration of 1,4-thioxane results in a large (1.8 kcal/mol) constraint on thioxane's conformational mobility (chair-to-chair interconversion). Similar conformational constraints (1.6 kcal/mol) were determined for 1,4-dioxane both when incarcerated in carceplex **1b** and when encapsulated reversibly in capsule **3b**. Encapsulation-induced conformational constraints of this magnitude are unprecedented, and are particularly striking for the noncovalently linked capsules.

Introduction

Chemistry in confined media is currently a highly active area of research.[1] Confined media comprise the solid state as well as discrete species in solution such as carceplexes and capsules. The molecular (as opposed to conformational) mobility of guests permanently entrapped in carceplexes has been reported by Cram and others.[2] Rebek has described the effect of reversible capsules on the conformational freedom of guests.[3] We have recently elucidated the twisting of cavitands with respect to each other in carceplexes and related capsules.[4] Here we report the conformational restrictions put on guests encapsulated in carceplexes and capsules. The effects are surprisingly large, and are most likely due to the rigidity of the cavitand subunits and the inflexibility of the intercavitand linkers.

We begin with a discussion of guest orientation within a carceplex or capsule based on ^{1}H NMR chemical shifts. We follow with the molecular mobility of encapsulated guests, and then present conformational restrictions of confined guests. Twisting of the cavitands is integral to each of these phenomena and is discussed in these sections.

Table 1. δ (ppm) Values of Guest Molecules in Carceplexes 1a·Guest at Ambient Temperature in $CDCl_3$

Guest		δ bound (ppm)	δ free (ppm)[a]	Δδ ppm[b]
pyrazine		4.07	8.58	4.51
pyrazine[c]		3.99	8.58	4.59
1,4-dioxane		-0.28	3.68	3.96
thioxane	H_a	-0.01	3.88	3.89
	$H_{a'}$	-0.17	3.88	4.05
	H_b	-1.55	2.60	4.15
	$H_{b'}$	-1.60	2.60	4.20
DMA	H_a	1.04	3.02	1.98
	H_b	-1.46	2.94	4.40
	H_c	-2.40	2.09	4.49
2-butanone	H_a	-0.05	2.41	2.46
	H_b	-2.36	2.10	4.46
	H_c	-3.43	1.01	4.44
ethylmethylsulfide	H_a	-0.10	2.46	2.56
	H_b	-2.29	2.05	4.34
	H_c	-3.23	1.21	4.44
pyridine	H_a	6.34	7.68	1.34
	H_b	4.02	8.62	4.60
	H_c	2.73	7.30	4.57
pyridazine	H_a	4.64	9.22	4.58
	H_b	4.39	7.49	3.10
NMP	H_a	1.46	3.25	1.79
	H_b	-1.79	2.70	4.49
	H_c	-1.79	2.22	4.01
	H_d	-2.13	1.89	4.02

[a] δ of free guest determined in $CDCl_3$ at ambient temperature. [b] $\Delta\delta = \delta_{free} - \delta_{entrapped}$. [c] Carceplex **1b**·pyrazine.

Results

Guest Orientation. Comparison of the crystal structures of carceplexes **1a**·DMA[5] and **1b**·pyrazine[2c] with the ^{1}H NMR $\Delta\delta$ (δ of free guest − δ of encapsulated guest) of the guest protons (Table 1) demonstrates that larger $\Delta\delta$ values imply closer proximity of these moieties to the arenes lining the top and bottom of the hosts' cavities.

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(1) (a) Rebek, J., Jr. *Acc. Chem. Res.* **1998**, *32*, 278−286. (b) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203−209.

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(3) (a) O'Leary, B. M.; Grotzfeld, R. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 11701−11702. (b) Hilmersson, G.; Rebek, J., Jr. *Magn. Reson. Chem.* **1998**, *36*, 663−669. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. See also: Kirchhoff, P. D.; Dutasta, J.-P.; Collet, A.; McCammon, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 381−390.

(4) In a variety of bisbowl systems, the two cavitands are twisted with respect to one another. We have called the two enantiomeric forms twistomers: Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 1962−1963.

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Table 2. Range in ^{1}H NMR $\Delta\delta$ (ppm) Values of Host Signals for Carceplexes 1a·Guest in $CDCl_3$ at Ambient Temperature

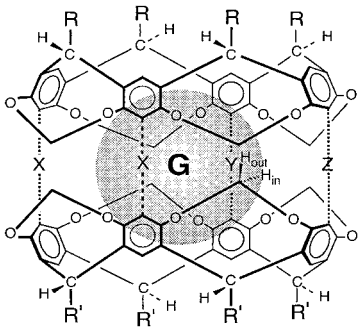
guest	H_p[a] (ppm)	H_b[b] (ppm)	H_{out}[c] (ppm)	H_{in}[c] (ppm)
all aromatic guests	6.93−6.84	6.52−6.47	6.12−6.02	4.26−4.10
all nonaromatic guests[d]	6.78−6.63	6.61−6.54	6.24−6.08	4.86−4.26

[a] H_p, H *para* to interbowl acetal. [b] H_b, CH_2 of interbowl acetal. [c] H_{in}, H_{out}, see structure block. [d] Excludes the ^{1}H NMR signals for carceplex **1a**·NMP, which was anomalous: H_p (6.74, 6.71), H_b (6.32), H_{out} (6.03), and H_{in} (4.68).

Data for nine representative guests are given in Table 1 (30 more are provided in the Supporting Information). Generally, $\Delta\delta$ values over 4 ppm indicate a close proximity to the arenes, while $\Delta\delta$ values of less than 2 ppm indicate positioning near the host's equator.

As has been observed by Cram in hemicarceplexes,[6] host protons that line the cavity are sensitive to the encapsulated guest. Table 2 summarizes the range of δ for host protons in the presence of 7 aromatic guests and 33 nonaromatic guests in carceplex **1a**·guest. The sensitivity of host protons is indeed high for protons lining the cavity, and low for peripheral protons: Whereas H_{in} varies by 0.76 ppm, the pendent group protons and the methine protons of the host vary by <0.06 ppm.

Comparison of carceplexes **1a** and **1b** reveals the effect of the pendent group (CH_3 versus CH_2CH_2Ph) on guests. For six guests (pyrazine, pyridine, 1,4-dioxane, DMSO, acetone, and benzene), the guest $\Delta\delta$ (δ of **1a** − δ of **1b**) values for respective pairs of carceplexes vary from 0.04 to 0.08 ppm. This is a significant effect for so remote a group and indeed has facilitated the determination of energy barriers to molecular mobility within the carceplex.[2c,7,8]



1a•guest: X = Y = Z = OCH_2O; R = R' = CH_2CH_2Ph
1b•guest: X = Y = Z = OCH_2O; R = R' = CH_3
1c•guest: X = Y = Z = OCH_2O; R = CH_2CH_2Ph, R' = CH_3
2•guest: X = OCH_2O, Y = Z = H, H; R = R' = CH_3
3a•guest: X = Y = Z = OHO^-; R = CH_2CH_2Ph, R' = CH_3
3b•guest: X = Y = Z = OHO^-; R = R' = CH_3
4•guest: X = Y = OHO^-; Z = H, H, R = CH_2CH_2Ph, R' = CH_3

Some insight can also be gained regarding the guest orientation with respect to the C_4 (or pseudo-C_4) axis of the host. For example, bisbowl **2**·guest[8] manifests three nonequivalent H_{in} protons. The range in δ (ppm) for these protons with different guests (Table 3) is 2.48 (pyrazine), 2.24 (pyridine), 1.15 (benzene), and 0.07 (dioxane). The shielding/deshielding regions of the aromatic guests clearly have a dramatic effect as a result of the highly rigid host and the highly anisotropic environment of the host's cavity. These data suggest that the aromatic guests are oriented in the cavity as depicted in Figure 1. We can speculate that guests such as 1,4-dioxane have orientations similar to those of the aromatic guests on the basis of their similarity in shape, although such guests do not create an anisotropic environment to the same extent as the aromatic guests. The observation of a single set of ^{1}H NMR signals for these guests suggests that they move rapidly about the host's C_4 axis on the ^{1}H NMR time scale.

Table 3. ^{1}H NMR Assignments for Bisbowl 2·Guest at 298 K in $CDCl_3$

guest	proton[a]	δ	proton	δ
pyrazine	$H_{out(a)}$ or $H_{out(b)}$	6.14	$H_{in(a)}$ or $H_{in(b)}$	5.33
	$H_{out(a)}$ or $H_{out(b)}$	5.91	$H_{in(a)}$ or $H_{in(b)}$	4.92
	$H_{out(c)}$	5.57	$H_{in(c)}$	2.85
pyridine	$H_{out(a)}$ or $H_{out(b)}$	6.16	$H_{in(a)}$ or $H_{in(b)}$	5.26
	$H_{out(a)}$ or $H_{out(b)}$	5.92	$H_{in(a)}$ or $H_{in(b)}$	4.52
	$H_{out(c)}$	5.52	$H_{in(c)}$	3.02
benzene	$H_{out(a)}$ or $H_{out(b)}$	6.27	$H_{in(a)}$ or $H_{in(b)}$	4.66
	$H_{out(a)}$ or $H_{out(b)}$	5.90	$H_{in(a)}$ or $H_{in(b)}$	4.44
	$H_{out(c)}$	5.79	$H_{in(c)}$	3.51
1,4-dioxane	$H_{out(a)}$ or $H_{out(b)}$	6.17	$H_{in(a)}$ or $H_{in(b)}$	4.40
	$H_{out(a)}$ or $H_{out(b)}$	5.97	$H_{in(a)}$ or $H_{in(b)}$	4.33
	$H_{out(c)}$	5.80	$H_{in(c)}$	4.33

[a] See Figure 1 for designation of protons.

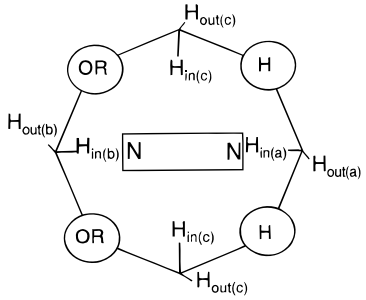


Figure 1. Schematic representaion of the favored orientation of pyrazine within bis-bowl **2**·guest. The perspective is looking down the host's C_4 axis; pyrazine's C_2 axis containing the nitrogens is along the equator of the host and is perpendicular to the host's C_4 axis.

Molecular Mobility of Guests. Guests such as DMA have energy barriers to rotation about the hosts' C_2 axes that are too high to measure by the conventional method of coalescence of ^{1}H NMR signals.[5] Others such as DMF have corresponding barriers that are too low to be readily determined.[5] Still others such as pyrazine have measurable barriers: $\Delta G^{\ddagger} = 19$ kcal/mol for carceplex **1c**,[2c] 18 kcal/mol for capsule **3a**·guest,[7] and 17 kcal/mol for capsule **4**·guest.[8,9] Thus, the highly rigid hosts preclude the mobility of large oblong guests about the hosts' C_2 axes, allow free mobility of small guests, and clamp down tightly on even slightly oblong guests (i.e., pyrazine). Molecular mobilities of 1,4-dioxane and 1,4-thioxane are presented below.

(5) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194−2204.
(6) Yoon, J.; Sheu, C.; Houk, K. N.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1996**, *61*, 9323−9329.
(7) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082.
(8) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 9819−9826.
(9) Reinhoudt has reported carceromers, where asymmetric carceplexes have slightly different (thermodynamically) orientational preferences with respect to the pseudo-C_2 axes of the host. See ref 2b.

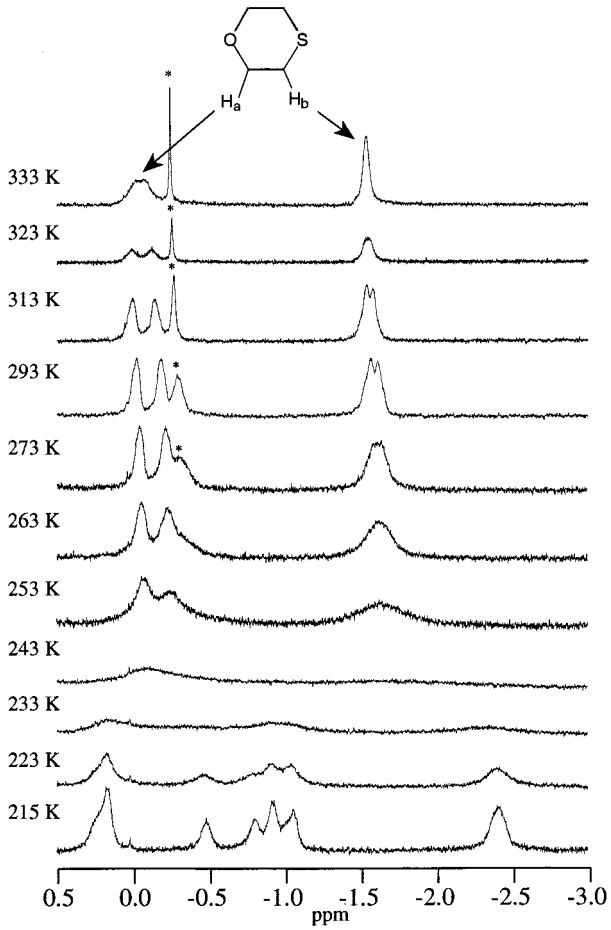


Figure 2. Variable temperature 400 MHz ^{1}H NMR spectra of carceplex **1a**·1,4-thioxane in $CDCl_3$. The asterisk indicates a carceplex **1a**·1,4-dioxane impurity in the sample.

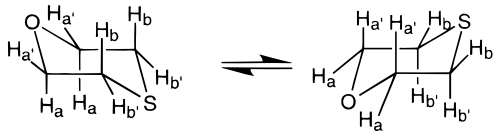


Figure 3. Chair conformations of 1,4-thioxane.

Conformational Constraints due to Confinement. In carceplex **1a**·1,4-thioxane,[10,11] at 333 K in $CDCl_3$, the guest $\Delta\delta$ (δ of free guest $-$ δ of entrapped guest) are about 3.95 ppm (OCH_2) and 4.14 ppm (SCH_2; see Figure 2), which are consistent with the guest's protons residing near the arenes of the host and the guest's heteroatoms residing near the equator. As the sample is cooled to 293 K, the guest signals each split into two resonances. These new $\Delta\delta$ values are moderate, which is consistent with freezing out of twistomers.[4,12] Further cooling to 215 K yields a complex spectrum, with a great range in $\Delta\delta$ for both the OCH_2 and SCH_2 protons, which suggests that the two chair conformations (Figure 3) have been frozen out[12] and the axial and equatorial protons reside in markedly different regions of the host. Examination of CPK models suggests that the equatorial protons extend deepest into the arenes of the host. At 215 K, all eight protons are nonequivalent, although two coincide.[12]

The value of $\Delta G^{\ddagger}$ for interconversion of twistomers in **1a**·1,4-thioxane is 16.3 ± 0.3 and 16.5 ± 0.3 kcal/mol on the basis of coalescence of the OCH_2 (T_c = 333 K) and SCH_2 (T_c = 323 K) protons, respectively (Figure 3). For carceplexes **1a**·DMSO[5] and **1b**·2-butanol,[4] this value is 13.6 ± 0.1 and 12.6 ± 0.1 kcal/mol, respectively. Thus, thioxane dramatically exacerbates the difficulty in hurdling the twistomer barrier.

The value of $\Delta G^{\ddagger}$ for interconversion of chair conformations (ring-flipping) of thioxane in carceplex **1a**·1,4-thioxane is 10.8 ± 0.4 kcal/mol. The value of $\Delta G^{\ddagger}$ for ring-flipping of 1,4-thioxane in solution is about 9.0 kcal/mol in vinyl chloride[13] or $CFCl_3$.[14] Thus, the constraint caused by incarceration is 1.8 kcal/mol! This is a remarkably large effect for such systems.

The variable temperature NMR spectra for carceplex **1b**·1,4-dioxane and capsule **3b**·1,4-dioxane are shown in Figure 4. On the basis of the same $\Delta\delta$ arguments made for 1,4-thioxane,[12] we calculate the value of $\Delta G^{\ddagger}$ for ring-flipping to be 11.3 ± 0.3 kcal/mol for each (both T_c = 253 K), and for twistomer interconversion it is 11.8 ± 0.3 kcal/mol for the carceplex and 11.7 ± 0.3 kcal/mol for the capsule (for both the carceplex and the capsule, T_c = 243 K for guest protons and 233 K for H_{in} of the host; vide infra). The similar energies for the carceplex and capsules suggest that their cavity size and rigidity are very similar. The similar energies for twisting and ring-flipping are coincidental. The energy barrier for ring-flipping 1,4-dioxane free in 10% TMS/37% CH_2Cl_2, 37% CH_2CHCl, and 16% dioxane is 9.70 kcal/mol.[15] Thus, both the carceplex and the capsule provide a restrictive environment that puts a 1.6 kcal/mol constraint on ring-flipping of 1,4-dioxane. It is interesting to note that whereas the solution determination of dioxane's ring-

(10) The **1a**·1,4-thioxane sample was contaminated with a small amount of **1a**·dioxane, due to a small impurity of dioxane in the thioxane and the much higher preference for dioxane over thioxane: see ref 11.

(11) Chapman, R. G.; Sherman, J. C. *J. Org. Chem.* **1998**, *63*, 4103−4110.

(12) Freezing out of ring-flipping eliminates two C_2 rotations for dioxane and one for thioxane, thus rendering nonequivalent the corresponding guest protons previously related via these C_2 rotations. Geminal protons also become nonequivalent due to loss of a plane of symmetry, as they become axial and equatorial. Freezing out the interconversion of twistomers eliminates all planes of symmetry, thereby rendering guest protons previously related via any plane of symmetry nonequivalent. Freezing of guest rotation about the host's C_2 axes that are perpendicular to the principal C_4 axis of the host renders host protons previously related by a C_2 rotation nonequivalent if there are no planes of symmetry and if the guest is not symmetric about these C_2 axes via a C_2 rotation. Thus, freezing the C_2 rotation of DMSO breaks the top/bottom symmetry of the host (eliminates symmetry via C_2 rotation), once twistomers are frozen (eliminates planes of symmetry; see ref 4). The chair conformations of thioxane and dioxane are similar to that of DMSO in that they do not have a C_2 axis of symmetry perpendicular to the principal C_4 axis of the host; therefore, when chair conformations, twistomers, and guest rotation about the C_2 axes are frozen, the top and bottom bowls become nonequivalent. In these situations, the symmetry of the system is the result of the symmetry of the components in combination with their respective molecular mobilities: When ring-flipping, twistomer interconversion, and rotation about the hosts' C_2 axes perpendicular to the principal C_4 axis are all frozen, thioxane has C_1 symmetry in the carceplex and dioxane has C_2 symmetry in the capsule or the carceplex, but as these guests rotate rapidly about the C_4 axis of the host, the symmetry of these systems is C_4.

(13) Jensen, F. R.; Neese, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 4922−4925. These authors report a $\Delta G^{\ddagger}$ value of 8.7 kcal/mol for interconversion between the chair and the twist-chair of thioxane. By halving the rate constant, one obtains a $\Delta G^{\ddagger}$ value of 9.0 kcal/mol for chair-to-chair interconversion.

(14) Barnes, J. C.; Hunter, G.; Lown, M. W. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1354−1356. The authors report a $\Delta G^{\ddagger}$ value of 11 kcal/mol, but must have miscalculated, as their data are consistent with 9.0 kcal/mol, which agrees with ref 13.

(15) Vergamini, P. J.; Vahrenkamp, H.; Dahl, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 6329−6330.

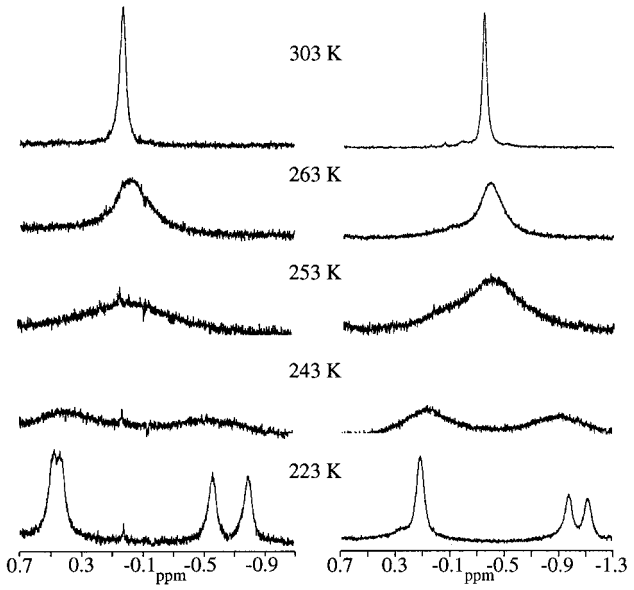


Figure 4. Guest region of variable temperature 400 MHz ^{1}H NMR spectra of carceplex **1b**·1,4-dioxane (right) and capsule **3b**·1,4-dioxane (left) in $CDCl_3$.

flipping energy barrier required a highly complicated experiment[15] due to the coincidence of axial and equatorial protons, the anisotropy created by our hosts renders this determination fairly straightforward.

For carceplex **1b**·1,4-dioxane, H_{in} coalesces at 233 K ($\Delta\nu = 40.0$ Hz). This requires freezing of twistomers, ring-flipping, and molecular motion of the guest about the host's C_2 axes.[12] The value of $\Delta G^{\ddagger}$ for this process is 11.4 $\pm$ 0.3 kcal/mol. This value should agree with the lowest energy process of the three, and in fact it agrees well with 11.3 kcal/mol for ring-flipping given above. It is impossible to say what the $\Delta G^{\ddagger}$ value is for guest rotation about the host's C_2 axes, other than that it is $\geq$11.4 kcal/mol. For capsule **3b**·1,4-dioxane and carceplex **1a**·1,4-thioxane, H_{in} broadens at low temperature, but was not observed to freeze out in either case. Most likely, rotation of the guest about the hosts' C_2 axes in these cases also has $\Delta G^{\ddagger}$ values greater than $\sim$11 kcal/mol, but T_c and $\Delta\nu$ could not be determined.

Discussion

Both the carceplex and capsules appear to be remarkably sensitive to guest size and shape in a variety of ways. We have reported extensively on the extreme selectivity of these hosts to guest recognition, both thermodynamic (binding in capsules)[7,16] and kinetic (template ratios in carceplexes).[11] It has also been shown here and elsewhere that molecular rotation about the hosts' C_2 axes varies from too fast to too slow to be measured by NMR.[2c,5,7−9] The high guest selectivity and sensitivity to guest motion are largely a result of the rigidity of the systems, which make them unforgiving to minute perturbations from ideal complementarity.

We now see that twistomer interconversion can range by as much as 3.9 kcal/mol, depending on the guest, with carceplex **1a**·1,4-thioxane manifesting the largest twistomer energy barrier by far. Why? The host's cavity appears to be larger in the transition state than in the ground state, according to unraveling of CPK models. As thioxane is a relatively large guest, steric factors would thus be expected to lower the transition state, not raise it. Thioxane is also a poorer guest[11] with respect to DMSO and dioxane, guests that have far lower twistomer energy barriers. Thus, simple lowering of the ground state is not a plausible explanation. It is noteworthy that carceplex **1a**·1,4-thioxane has a highly downfield shifted H_{in} relative to those of other carceplexes: whereas 35 of 40 carceplexes have $\delta \leq 4.60$ ppm for H_{in}, it is 4.80 ppm for thioxane. It appears that there is an interaction between the sulfur and H_{in} (several other sulfur-containing guests have a similarly shifted H_{in}; see the Supporting Information). Such an interaction may well be lost on passing from the ground state to the transition state.

Incarceration of 1,4-dioxane and 1,4-thioxane results in large constraints on the guests' conformational mobilities (i.e., ring-flipping). For 1,4-dioxane, the same constraint was observed when encapsulated reversibly in capsule **3b**. Rebek et al. have reported a 0.30 kcal/mol constraint on ring-flipping of cyclohexane when bound in a reversible capsule.[3] These authors suggest that this modest increase in activation energy is due to a lowering of the ground state via stabilizing host−guest interactions, rather than steric crowding in the transition state due to the constraints of confinement. They point out further that such steric constraints may be present in carceplexes, but are not likely to be manifested by reversible capsules, as capsules are more flexible. Theirs is a difficult argument because the overall effect they observe is rather small. The effects we observe are indeed quite large (1.8 and 1.6 kcal/mol for thioxane and dioxane, respectively). As we observe similar increases in the energy barriers for ring-flipping in carceplex **1b**·1,4-dioxane and reversible capsule **3b**·1,4-dioxane (both 1.6 kcal/mol higher than that of free guest in solution), it appears that the constraints imposed by the carceplex transcend capsules. In our system, the rigidity of the linkage in carceplexes and capsules must be similar. Although these ring-flipping constraints could indeed be due to ground-state effects, it seems at least equally plausible that they are due to a simple steric constraint in the transition state. What is clear is that the effects are pronounced, and this is a result of the rigidity of the system.

We have demonstrated via guest recognition, twistomer interconversion, guests' molecular rotation, and guests' conformational mobility that suitable rigidity in carceplexes and capsules leads to high sensitivity to small perturbations. Such sensitivity yields a useful system for studying a variety of phenomena, notably here novel supramolecular stereochemistry.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WH-400.

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Supporting Information Available: Table of δ values of guests for **1a**·guest and table of δ values of selected signals for carceplex **1a**·guest. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991433R

(16) Chapman, R. G.; Olovsson, G.; Trotter, J.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6252−6260.