Elucidation of "Twistomers" in Container Compounds

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Stereochemistry in supramolecular chemistry is an increasingly active area of research, as demonstrated by numerous stereochemically unique discoveries.[1] Encapsulating media provide particularly unusual environments and have been shown to create new types of stereoisomers, called carceromers, and to constrain molecular and conformational mobility of molecules within their confines.[2−4] Cram et al. concluded that the mobility of DMSO within carceplexes and hemicarceplexes is restricted by the shell, as suggested by the splitting of host and guest signals at low temperature in ^{1}H NMR spectra.[5−7] We report here, on the basis of a dynamic ^{1}H NMR study, that the splitting of guest signals in such experiments is actually due to a previously unexplored dynamic of such systems, namely, twisting of top and bottom bowls with respect to one another.

Known crystal structures relevant to the present study are of carceplex **1a**·dimethylacetamide,[5] carceplex **1b**·pyrazine,[8] complex **2**·pyrazine,[9] and hemicarceplex **3**·DMF.[6] All are chiral due to interbowl twists of 13−21°. In solution, the time scale by which these helical conformational stereoisomers (we will call them "twistomers") interconvert was unexplored. Twistomers of highly symmetric systems such as carceplexes **1**·guest (D_{4h}) or complexes **2**·guest (D_{4h}) that contain an achiral guest cannot be observed via ^{1}H NMR spectroscopy even if interconversion is slow because the resulting racemic twistomers remain highly symmetric (D_4).[10] However, introduction of a chiral guest reduces the symmetry of these systems and allows exploration of twistomers. Thus, at 223 K, the ^{1}H NMR spectrum (Figure 1) of carceplex **1b**·(*R*)-(−)-2-butanol yields two sets of host and guest signals.[11] This is consistent with freezing out of twistomers, which would yield two diastereomeric carceplexes (Figure 2).[12] The energy barrier for interconversion of these twistomers is 12.6 ± 0.1 kcal/mol based on the coalescence temperature of five host and guest signals.[13]

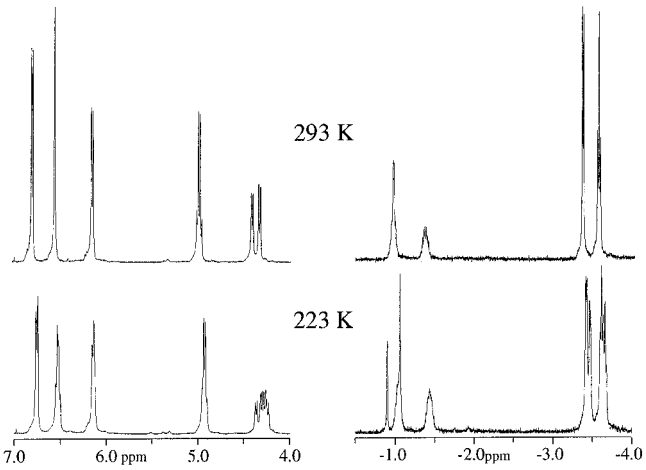

Figure 1. Variable temperature 400 MHz ^{1}H NMR spectra of carceplex **1b**·(*R*)-(−)-2-butanol in $CDCl_3$. Assignments (ppm) at 293 K: aryl protons 6.80, 6.78; interbowl OCH_2O 6.54; H_{out} 6.14; methine 4.99; H_{in} 4.43, 4.34; $CH_3CHO\underline{H}C\underline{H}_xH_yCH_3$ −0.97; $CH_3CHOHCH_x\underline{H}_yCH_3$ −1.37; $C\underline{H}_3CHOHCH_2CH_3$ −3.33; $CH_3CHOHCH_2C\underline{H}_3$ −3.54. Not shown: $CH_3C\underline{H}OHCH_2CH_3$ (0.82); and the pendent methyl group (1.69).

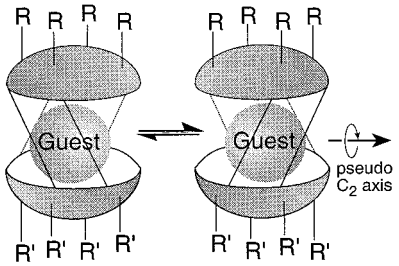

Figure 2. Schematic representation of the diastereomeric twistomers of carceplex **1b**·(*R*)-(−)-2-butanol (R = R′ = CH_3) and carceplex **1c**·DMSO (R = CH_2CH_2Ph, R′ = CH_3).

Less symmetric hosts do not require a prochiral guest for twistomers to be observed.[14] Thus, upon cooling, the ^{1}H NMR spectrum of A,B-bis-bridged complex **4**·pyrazine increases in complexity, which is attributable to the reduction of symmetry from C_{2v} to C_2, due to freezing out of the twistomers. For example, at 298 K a broad signal at 2.83 ppm (representing four of the H_{in} protons) splits into two broad doublets at 223 K (δ = 3.20 and 2.06 ppm).[15] The $\Delta G^{\ddagger}$ for interconversion of these twistomers is 11.5 ± 0.1 kcal/mol based on the coalescence temperatures of five separate host protons.[13] Similarly, the variable temperature ^{1}H NMR spectra of A,B-bis-bridged complex **5**·pyrazine and A,B-bis-bridged complex **6**·pyrazine gave $\Delta G^{\ddagger}$ values for twistomer

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(10) The variable temperature ^{1}H NMR of carceplex **1a**·pyrazine did not show any sign of asymmetry over the temperature range of 223−323 K.

(11) Over the temperature range studied (223−323 K), carceplex **1b**·(*R*)-(−)-2-butanol exhibits top and bottom asymmetry because 2-butanol rotates slowly about the C_2 axes of the host. The rotation of oblong-shaped guest molecules such as 2-butanol, DMA, and methyl acetate about the C_2-axes is generally slow on the ^{1}H NMR time scale at ambient temperature.

(12) These two diastereomeric carceplexes are only marginally different in stability, as determined by the relative integration (1.0:1.2) of the guest signals in the ^{1}H NMR spectrum at 223 K. For chiral recognition in related systems, see: Tokunaga, Y.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 66−69. Canceill, J.; Cesario, M.; Collet, A.; Guilhem, J.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1985**, 361−363. Rivera, J. M.; Martin, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1021−1023. Castellano, R. K.; Kim, B. H.; Rebek, J. J. *J. Am. Chem. Soc.* **1997**, *119*, 12671−12672.

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(14) Cram et al. recently demonstrated that the methyls of DMSO remain split, diastereotopic, in a chiral hemicarceplex from −80 to −180 °C: Park, B. S.; Knobler, C. B.; Eid, C. N.; Warmuth, R.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1998**, 55−56.

(15) The large range in chemical shifts of the H_{in} protons (1.14 ppm for those mentioned in the text and a 3.4 ppm range for all eight H_{in} protons) suggests that there is a preferred orientation of pyrazine about the long axis of this host.

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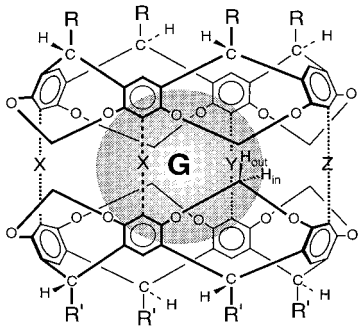

1a•guest: X = Y = Z = OCH_2O; R = R' = CH_2CH_2Ph
1b•guest: X = Y = Z = OCH_2O; R = R' = CH_3
1c•guest: X = Y = Z = OCH_2O; R = CH_2CH_2Ph, R' = CH_3
2•guest: X = Y = Z = OHO^-; R = R' = CH_3
3•guest: X = Y = OCH_2O, Z = H, H; R = R' = CH_2CH_2Ph
4•guest: X = OCH_2O, Y = Z = H, H; R = R' = CH_3
5•guest: X = OCH_2O, Y = Z = OH, OH; R = R' = CH_3
6•guest: X = OCH_2O, Y = Z = OCH_3, OCH_3; R = R' = CH_3

interconversion of 11.8 ± 0.2 and 12.1 ± 0.1 kcal/mol, respectively.[13]

The mobility of DMSO within the interior of various bis−bowl hosts has been extensively studied.[5,7] Cram and Sherman suggested that, for example, the energy barrier for rotation of DMSO about the C_2 axes of carceplex **1a**•DMSO was 12.7 ± 0.2 and 13.6 ± 0.2 kcal/mol as determined from the coalescence temperatures of the H_{in} and guest signals, respectively.[5] We now suggest that the difference in these numbers is not due to experimental error and that, in fact, these energy barriers represent two separate and independent processes, namely, rotation of DMSO about the host's C_2 axes (12.7 kcal/mol) and freezing of twistomers (13.6 kcal/mol). When only the twistomers are frozen, the symmetry of carceplex **1a**•DMSO is reduced from D_{4h} to D_4, and the enantiotopic methyl groups of DMSO become diastereotopic and thus split into two singlets.[14,16] When the rotation of DMSO about the C_2 axes of the carceplex becomes slow, the symmetry is further reduced to C_4, which renders the H_{in} on the top and bottom bowls nonequivalent. To further substantiate this twistomer interpretation, we synthesized carceplex **1c**•DMSO (Figure 2) so that diastereomeric carceplexes would be formed when both twistomers and guest rotation are frozen out. A single guest peak is observed for DMSO in the ^{1}H NMR spectrum at 293 K, and there are two doublets for the host H_{in} protons because the top and bottom bowls differ in their attached pendent group. At 223 K, there are four singlets for DMSO and four doublets for the host H_{in} protons, which is consistent with the formation of diastereomeric twistomers due to slowing of *both* twistomer interconversion and of DMSO rotation about the pseudo-C_2 axes.[17]

(16) Similarly, the enantiotopic methyl groups of DMSO have been shown to be nonequivalent (diastereotopic) in both a chiral solvent and in the presence of a chiral shift reagent. Kainosho, M.; Ajisaka, K.; Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1972**, *94*, 5924−5926. Goering, H. L.; Eikenberry, J. N.; Koermer, G. S.; Lattimer, C. J. *J. Am. Chem. Soc.* **1974**, *96*, 1493−1501.

Cram et al. used the activation energies determined from the coalescence temperature of the DMSO signals of various DMSO carceplexes as an indication of the internal size of the hosts' cavities, reasoning that larger cavities would allow DMSO to rotate more freely inside.[7] But it is more than likely that they were actually measuring $\Delta G^‡$ for twistomer interconversions, not $\Delta G^‡$ for rotation of DMSO about the hosts' C_2's.[18] Thus, some of their interpretations may be worth revisiting. Below, we briefly discuss a related issue in our system.

We determined the twistomer $\Delta G^‡$ values for charged-hydrogen bonded complex **2**•DMSO in $CDCl_3$ to be 13.4 ± 0.2 kcal/mol based on the coalescence of the guest signal, and the $\Delta G^‡$ for rotation of DMSO about the C_2 axes of the host to be 12.6 ± 0.2 kcal/mol, based on the coalescence of H_{in}. The similarity of these values to those for carceplex **1a**•DMSO[5] suggests that OHO^- versus OCH_2O bridges are not significant to either process. In contrast, our data above suggests that there does seem to be a dependence of twistomer $\Delta G^‡$ on guest (cf. 12.6 kcal/mol for **1b**•(*R*)-(−)-2-butanol and 13.6 kcal/mol for **1a**•DMSO), which is likely due to host−guest interactions and the extent of conjugation of the aryl ethers with their respective aromatic rings of the bowls: smaller, better guests (e.g., DMSO is a better template for the formation of carceplexes **1a**•guest than 2-butanol)[19] should provide stronger host−guest interactions and more conjugation in the ground state and, thus lead to higher $\Delta G^‡$'s. A related study on the role of twistomers in guest mobility within these container compounds will be reported on shortly.

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Supporting Information Available: Preparation of carceplex **1b**•(*R*)-(−)-2-butanol and carceplex **1c**•DMSO, table of $\Delta G^‡$'s, figures of variable temperature ^{1}H NMR spectra of carceplex **1c**•DMSO and A,B-bis-bridged complex **4**•pyrazine (PDF). This material is free of charge via the Internet at http://pubs.acs.org.

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(17) Unfortunately, resolution of the two processes was not possible using the DMSO signals: the $\Delta G^‡$'s are in the range of 12.8−13.1 kcal/mol. Nevertheless, the coalescence of H_{in} yields $\Delta G^‡$ = 12.8 kcal/mol, which represents the lowest energy transition, which we suggest is the C_2 rotation of DMSO.

(18) Freezing the rotation of DMSO about the hosts' C_2's likely does occur as we have shown in our systems, but with a slightly lower $\Delta G^‡$ than the interconversion of the twistomers. If so, use of H_{in} as a handle gives the $\Delta G^‡$ for the C_2 rotation, while use of the DMSO methyls (which Cram et al. used) gives only twistomer information. Incidentally, Cram and Sherman did suggest (ref 5) that "the rotation of the northern and the southern hemispheres of carceplex **2a**•DMA, as determined by its crystal structure, probably extends to carceplex **2a**•DMSO as well. If so, the transition occurring at 255 K may reflect a freezing out of equilibrations between the directions of rotations of the northern relative to the southern hemispheres, which may occur once the guests' motions are constrained."

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