New Molecular Vessels: Synthesis and Chiroselective Recognition

Shoichi Saito, Colin Nuckolls, and Julius Rebek, Jr.*

Contribution from The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received June 21, 2000

Abstract: A new structural motif for synthetic receptors is reported. This new motif allows for the incorporation of a variety of nonracemic groups into the structure’s upper rim. These stereocenters effectively transfer their asymmetry to the flexible walls of the vessel and result in handed spaces with increased stability in protic media. Their synthesis and chiroselective recognition for their guest molecules are described.

Synthetic receptors such as 1 are maintained in their receptive states by a seam of hydrogen bonds.1 These molecular hosts show high barriers to the exchange of guests in solution,2 form complexes with ions in the gas phase,3 and yield molecule-within-molecule crystals in the solid state.4 We report here a new structural motif, 2, that allows for the incorporation of a variety of nonracemic groups into the structure’s upper rim. These stereocenters effectively transfer their asymmetry to the flexible walls of the vessel and result in handed spaces with increased stability in protic media.

The synthesis of these molecules 2a–g5 involves the straightforward condensation of each of the protected dichloroimides with Högberg’s resorcinarene6 followed by liberation of the alcohol function (Scheme 1). The solution-phase conformation of the structures can be monitored by NMR: when in the vase-like C2 conformation (shown in Figure 1), the methine protons appear at ca. 5.6 ppm; when the walls interconvert between the two pseudo-C2v, “kite” conformations7 (not shown) these same signals appear upfield of 4 ppm.8 Using this criterion, structures 2a–f exist in the vase shape in CDCl3—a solvent that does not effectively compete for hydrogen bonds—and the kite-like conformation in competitive media such as DMF.9

Two different arrangements of intramolecular hydrogen bonds (Figure 1) are predicted through molecular modeling.10 In both models, the walls collapse inward presumably to minimize the repulsive interactions between the oxygens of neighboring carbonyls and to bring the hydroxyls into proximity for hydrogen bonding. The hydrogen bond donors in Figure 1a bifurcate between the carbonyls of its own and neighboring phthalimide. Alternatively, the hydroxyls of each phthalimide cooperate as donor and acceptor as in Figure 1b to form a cyclic seam of hydrogen bonds. We cannot distinguish between the two motifs, (1) Rudkevich, D. M.; Rebek, J., Jr. Eur. J. Org. Chem. 1999, 1991–2005 and references therein.
(9) The methine chemical shift for 2a–f is 5.6 ± 0.1 ppm in CDCl3 and 4.0 ± 0.1 ppm in DMF-d7. In CDCl3 appropriately sized guest molecules could be added and their resonances appeared upfield of 0 ppm but did not appear in DMF-d7.
but in either case the symmetry, structure, and function of the lower portion of the cavitand would be conserved.

Structures 2a–f form kinetically stable complexes in solution with a variety of small, molecular guests. By kinetically stable we mean slow exchange of guests on the NMR time scale (600 MHz, ambient temperatures), an admittedly arbitrary criterion, but one that has advantageous consequences. Separate signals are seen for free and bound guests and the latter appear upfield of 0 ppm due to the anisotropy provided by the numerous aromatic rings that line the interior (Figure 2b,c). Some of the guests are shown in Figure 2a.

Not all alcohol substituents on the imides display this self-folding behavior; for example, 2g is incapable of binding small molecular guests. Its methine protons resonate much further upfield (4.8 ppm) than those of 2a–f, indicating it is not held in the vase-like, C₄ conformation.

As shown in Figure 3a, the inward folding of the walls in either of the structures introduces an element of dissymmetry that exists in equilibrium between its two C₄-symmetric cycloenantiomers. To be sure, the interconversion between the cycle of hydrogen bonds in Figure 1b involves the merest of proton motions and is expected to be very fast, but the rearrangement of the walls could be much slower. To bias the cycloenantiomerism we prepared molecules 2c–f bearing nonracemic groups in either of the two positions near the hydroxyls. The effect is seen in the bisignate CD spectrum shown in Figure 3b (in CHCl₃). Because the stereocenters in the molecule are not themselves chromophores, this asymmetric absorption could result from exciton coupling between the walls of the cavitand. The position of the zero point in the CD spectrum is close to

(11) The cavity size for 2b is ca. 140 Å³ when folded as in Figure 1a and ca. 150 Å³ as in Figure 1b. These volumes were determined by using the GRASP program (Nicholls, A.; Sharp, K. A.; Honig, B. Proteins 1991, 11, 281–96) and applying the method described in detail by Mecozzi and Rebek (Mecozzi, S.; Rebek, J. Jr. Chem. Eur. J. 1998, 4, 1016–22). Vessel 2a encapsulates adamantane, 1-adamantanol, and 1-adamantanol, but would not encapsulate amino- or amidoadamantanes; 2b–f prefers smaller bicyclic structures such as norbornene and cyclohexane derivatives.

(12) The affinities for all guests were low and an excess amount (ca. 50 equiv) was used in each case.

(13) Saturated carbons of guests inside these cavities appear between 0 and -3 ppm.

(14) All of the guests that were shown to be effective for 2a–f (and a host of other structures) were tested for 2g and none shown were encapsulated.

(15) Presumably the longer chain imparts too many degrees of freedom in the linker for the cyclic structures to form.

(16) To be sure, the interconversion between the cycle of hydrogen bonds in Figure 1b involves the merest of proton motions and is expected to be very fast, but the rearrangement of the walls could be much slower. To bias the cycloenantiomerism we prepared molecules 2c–f bearing nonracemic groups in either of the two positions near the hydroxyls. The effect is seen in the bisignate CD spectrum shown in Figure 3b (in CHCl₃). Because the stereocenters in the molecule are not themselves chromophores, this asymmetric absorption could result from exciton coupling between the walls of the cavitand. The position of the zero point in the CD spectrum is close to
the UV/vis maximum for the phthalimide chromophore implying that these portions of the wall are oriented as shown in Figure 3a. So, while being held in proximity by the hydrogen bond seam, the stereogenic groups effectively transfer their chirality to the cavitaand walls, thus biasing the equilibrium between the two enantiomeric, folded forms (Figure 3a).

Molecules 2d–f also show similar circular dichroisms, and these spectra are diminished to nearly no signal by adding solvents such as MeOH that effectively compete for the hydrogen bonds (shown in Figure 3b). Similar 1H NMR experiments correlated the MeOH-induced disappearance of the CD signals with guest release. Increasing the steric bulk around the hydrogen-bonding seam helps the structures resist MeOH denaturation. For example, molecule 2d requires 30% methanol (v/v in CHCl3) to show guest release in the NMR and loss of CD activity while 2e requires 60% methanol (v/v in CHCl3) to see similar effects.

Additional support for a fixed stereogenic cavity in the hosts (2e–f) comes from the binding of norbornene, an achiral guest. In any of these the 1H NMR resonances for the guest can be reassuringly seen upfield of 0 ppm (shown in Figure 2b for 2e). All of the bound norbornene’s resonances are non-equivalent, and a 1H–1H COSY spectrum shows that all of the protons are correlated with each other: all of these resonances come from a desymmetrization of norbornene in chiral environment.21 In contrast, norbornene inside cavitaand 2b does not show desymmetrization (Figure 2c). Molecule 2b must rapidly flutter between its two, cycloenantiomeric forms on the NMR time scale producing an average signal characteristic of norbornene in an achiral environment.

The vessels discriminate between enantiomeric guests. The 1H NMR spectra from host–guest complexes between non-racemic or racemic trans-1,2-cyclohexanediol in 2c and 2d are shown in Figure 4. For 2c there is approximately an equal amount of each enantiomer of cyclohexanediol (Figure 4a,b) while the isomeric 2d shows a 33% de (Figure 4c,d). Apparently, when the stereocenter is closer to the phthalimides the stereogenic environment inside the capsule becomes more pronounced (twisted). This is in agreement with the CD experiments that show a larger induced signal for 2d as compared to that of 2c. Increasing the steric bulk further by using a phenyl instead a methyl further increases the diastereoselectivity to ca. 60% de for 2e and 2f. These are large values considering the complex and sizes. It is now possible to monofunctionalize the lower alkyl groups of the resorcinarene,23 and applications in affinity chromatography appear likely. We will report on these developments in due course.

Acknowledgment. We are grateful to the Salk Research Foundation and the National Institutes of Health. S.S. thanks Sankyo Co., Ltd. for fellowship support. C.N. thanks the National Institutes of Health for a postdoctoral fellowship (1999–2001). We thank Professor Dmitry Rudkevich and Dr. Stephen Craig for insightful discussions. We additionally thank Professor Reza Ghadiri for the use of his CD spectrometer, Dr. Laura Pasternack for help with the NMR experiments, Fraser Hof for molecular graphics design, and Mrs. Ellen Choi for invaluable experimental assistance.

Supporting Information Available: Experimental procedures for 2a–g along with the COSY spectrum for norbornene in 2c (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002220I


(19) The UV/vis maximum for the synthetic precursor to these molecules (the dichlorophthalimide) occurs at ca. 290 nm.


(21) This COSY spectrum can be found in the Supporting Information.

Figure 4. The 1H NMR spectra in m-xylene-d10 for host–guest complexes between (a) racemic trans-1,2-cyclohexanediol and 2c, (b) optically active trans-1,2-cyclohexanediol and 2c, (c) racemic trans-1,2-cyclohexanediol and 2d, and (d) optically active trans-1,2-cyclohexanediol and 2d. The diastereomeric excesses were determined by integration of the resonances in these spectra.

Finally, subtle variations in the structure of the spacer can result in drastically different binding properties. For example, adamantane is a welcome guest in 1 or 2a but is excluded from 2b–f, while norbornene or trans-1,2-cyclohexanediol can be bound by 2b–f but show no interest in occupying 2a.

The rapid and efficient synthetic access to the vessels could produce a variety of final structures with differing cavity shapes and sizes. It is now possible to monofunctionalize the lower alkyl groups of the resorcinarene,23 and applications in affinity chromatography appear likely. We will report on these developments in due course.