New Molecular Vessels: Synthesis and Chiroselective Recognition

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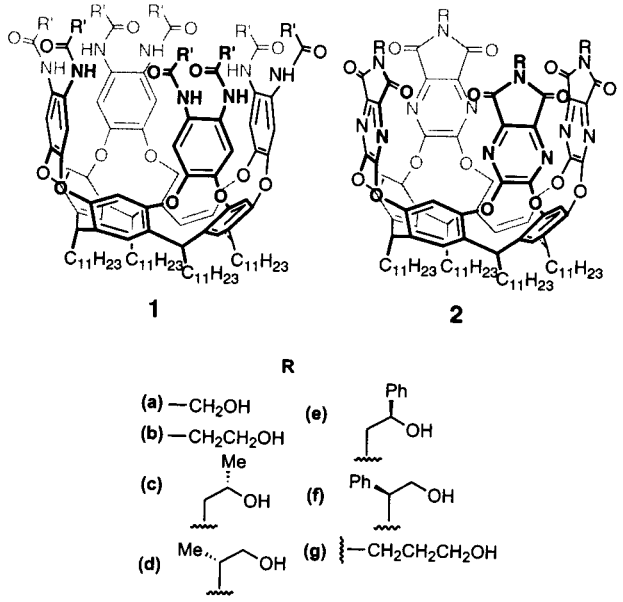
Received June 21, 2000

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**−**g**[5] involves the straightforward condensation of each of the protected dichloroimides with Högberg's resorcinarene[6] 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 C_4 conformation (shown in Figure 1), the methine protons appear at ca. 5.6 ppm; when the walls *interconvert* between the two pseudo-C_{2v}, "kite" conformations[7] (not shown) these same signals appear upfield of 4 ppm.[8] Using this criterion, structures **2a**−**f** exist in the vase shape in $CDCl_3$—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 bonds. 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.

(2) Kinetically stable host−guest complexes of a resorcinarene containing a hydrogen-bonding seam were first shown by Aoyama and co-workers: (a) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349−54. (b) Kobayashi, K.; Asakawa, Y.; Kikuchi, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1993**, *115*, 2648−54. More closely related molecules also show high barriers to guest exchange: (c) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 12216−25. (d) Ma, S.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2600−2602 and the work cited in ref 1 therein.

(3) For cavitands without a seam of hydrogen bonds, see: (a) Vincenti, M.; Dalcanale, E.; Soncini, P.; Guglielmetti, G. *J. Am. Chem. Soc.* **1990**, *112*, 445−7. (b) Vincenti, M.; Minero, C.; Pelizzetti, E.; Secchi, A.; Dalcanale, E. *Pure Appl. Chem.* **1995**, *67*, 1075−84. (c) Dickert, F. L.; Baumler, U. P. A.; Stathopulos, H. *Anal. Chem.* **1997**, *69*, 1000−5.

(4) For cavitands containing a seam of hydrogen bonds that crystallize as "molecule-within-vase" complexes, see: Shivanyuk, A.; Rissanen, K.; Konner, S. K., Rudkevich, D. M.; Rebek, J., Jr. *Helv. Chim. Acta* In press.

(5) The synthetic method generally follows the procedure developed by Cram and co-workers: Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826−8. Protocols and characterization for the syntheses of **2a**−**g** can be found in the Supporting Information.

(6) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046−8.

(7) A description of the dynamic folding process for similar molecules (derivatives of **1**) can be found in: Tucci, F.; Rudkevich, D.; Rebek, J., Jr. *Chem., Eur. J.* **2000**, *122*, 4573−82.

(8) The methine protons of flexible-walled cavitands resonate at 5.67 ppm in the C_{4v} (vase) conformation and at 3.92 ppm in the dynamic, C_{2v} (kite) conformation: (a) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707−14. (b) Cram, D. J.; Choi, H.-J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748−65. The methine protons for cavitands whose walls are covalently held upright but slightly open resonate at 4.96 ppm: Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229−37.

(9) The methine chemical shift for **2a**−**f** is 5.6 ± 0.1 ppm in $CDCl_3$ and 4.0 ± 0.1 ppm in DMF-d_7. In $CDCl_3$ appropriately sized guest molecules could be added and their resonances appeared upfield of 0 ppm but did not appear in DMF-d_7.

(10) Molecular modeling of assemblies was carried out using MacroModel 6.5 and the Amber* force field: Mohamadi, F.; Richards, N. G. J.; Guide, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−67.

10.1021/ja002220i CCC: $19.00
Published on Web 09/23/2000

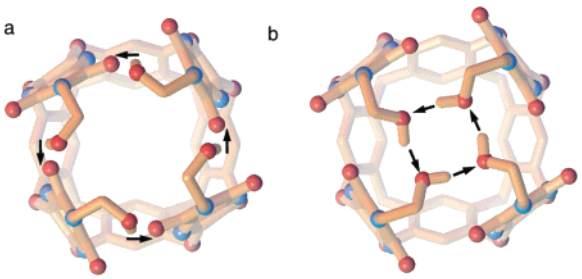
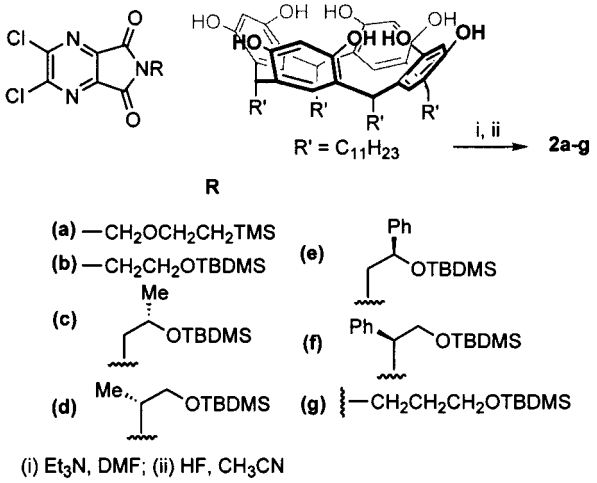


Figure 1. Two different arrangements of intramolecular hydrogen bonds in the vase-like conformation of **2a**.

Scheme 1. Synthesis of **2a**−**g**



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.[11,12] 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).[13] 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.[14] Its methine protons resonate much further upfield (4.8 ppm) than those of **2a**−**f**, indicating it is not held in the vase-like, C_4 conformation.[15]

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 C_4-symmetric cyclo-

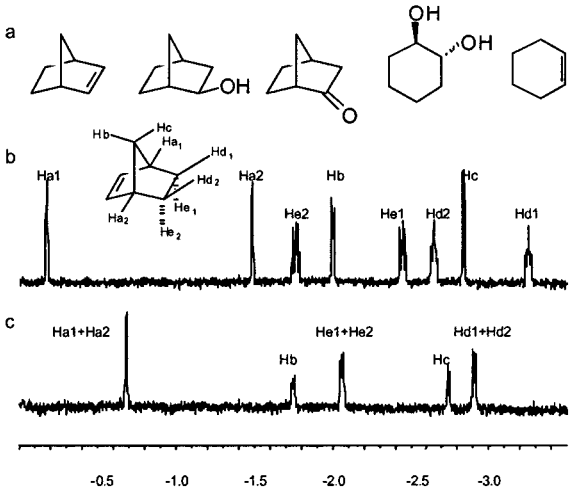


Figure 2. (a) Representative sample of the guests that were encapsulated in **2c**−**f**. (b) Upfield ^{1}H NMR resonances for norbornene in optically active **2c**. (c) Upfield ^{1}H NMR resonances for norbornene in **2b**.

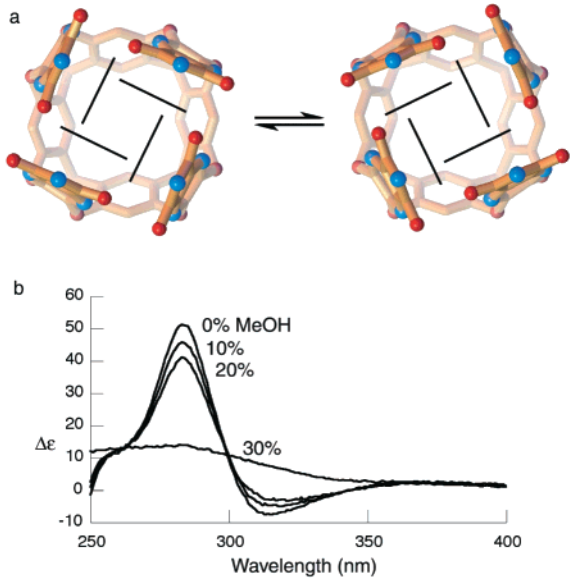


Figure 3. (a) Depiction of the equilibrium between the two enantiomeric, folded forms of the vase-like conformation. (b) Circular dichroism spectra for **2d** in $CHCl_3$. The intensity of the CD spectra decreases as methanol is added to the solution.

enantiomers.[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,[17] 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 $CHCl_3$).[18] 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 Å → Å^3 when folded as in Figure 1a and ca. 150 Å → Å^3 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) For examples and definitions of cycloenantiomers see: (a) Prelog, V.; Gerlach, H. *Helv. Chim. Acta* **1964**, *47*, 2288−2294. (b) Yamamoto, C.; Okamoto, Y.; Schmidt, T.; Jäger, R.; Vögtle, F. *J. Am. Chem. Soc.* **1997**, *119*, 10547−10548 and references therein.

(17) By analogy the cycle of hydrogen bonds at the lower rim of a calix[4]arene displays fast exchange between cycloenantiomers: (a) Saenger, W.; Betzel, C.; Hingerty, B.; Brown, G. M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 883−4. (b) Saenger, W.; Betzel, C.; Hingerty, B.; Brown, G. M. *Nature* **1982**, *296*, 581−3. (c) Saenger, W. *Nature* **1979**, *279*, 343−5.

the UV/vis maximum for the phthalimide chromophore[19] 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 cavitand 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).[20] Similar ^{1}H 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 $CHCl_3$) to show guest release in the NMR and loss of CD activity while **2e** requires 60% methanol (v/v in $CHCl_3$) to see similar effects.

Additional support for a fixed stereogenic cavity in the hosts (**2c**−**f**) comes from the binding of norbornene, an achiral guest. In any of these vessels the ^{1}H NMR resonances for the guest can be reassuringly seen upfield of 0 ppm (shown in Figure 2b for **2c**). All of the bound norbornene's resonances are nonequivalent, and a ^{1}H−^{1}H 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 cavitand **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 ^{1}H NMR spectra from host−guest complexes between nonracemic 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 is held together by the relatively weak and plastic hydrogen bonds.[22]

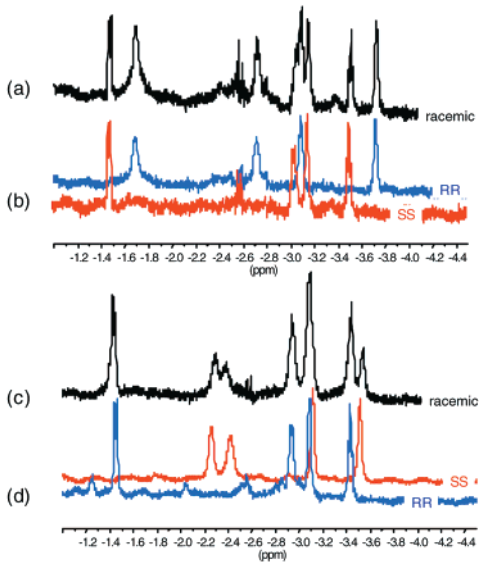


Figure 4. The ^{1}H NMR spectra in *m*-xylene-d_{10} for host−guest complexes between (a) racemic *trans*-1,2-cyclohexanediol and **2c**, (b) optically active *trans*-1,2-cyclohexanediol and **2c**, (c) racemic *trans*-1,2-cyclohexanediol and **2d**, and (d) optically active *trans*-1,2-cyclohexanediol 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.

Acknowledgment. We are grateful to the Skaggs 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.

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(18) This bisignate peak is unchanged when norbornene is added to the CD sample. For examples of CD used in similar context see: (a) Huang, X.; Rickman, B. H.; Borhan, B.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 6185−6186. (b) Furusho, Y.; Kimura, T.; Mizuno, Y.; Aida, T. *J. Am. Chem. Soc.* **1997**, *119*, 5267−5268. (c) Murakami, Y.; Hayashida, O.; Nagai, Y. *J. Am. Chem. Soc.* **1994**, *116*, 2611−2612. (d) Kikuchi, Y.; Kobayashi, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1351−1358. (e) Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10302−10306. (f) Zahn, S.; Canary, J. W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 305−307. (g) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

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

(20) Similar to the exciton coupling seen upon capsule formation: Castellano, R. K.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 11156−11163.

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

(22) Enantiomeric discrimination in structures held together by hydrogen bonds has been demonstrated for a variety of examples: (a) Rivera, J. M.; Martin, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1021−23. (b) Nuckolls, C.; Hof, F.; Martin, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 10281−5. (c) Reference 20.

(23) Saito, S.; Rudkevich, D. M.; Rebek, J., Jr. *Org. Lett.* **1999**, *1*, 1241−1244.