Titolo rivista/libro: Progress in Biological Chirality

Titolo articolo/sezione: Chiral Spaces in Encapsulation Complexes

Autore/i: Scarso

ISSN:

DOI:

Anno: 2004

Volume:

Fascicolo:

Editore:

Pag. iniziale: 261

Pag. finale: 270

Progress in Biological Chirality
G. Pályi, C. Zucchi and L. Caglioti (Editors)

Chapter 22

Chiral Spaces in Encapsulation Complexes

Alessandro Scarso, Alexander Shivanyuk, Osamu Hayashida and Julius Rebek, Jr.*
The Skaggs Institute for Chemical Biology and The Department of Chemistry, The Scripps Research Institute, MB-26, 10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
jrebek@scripps.edu

Encapsulation complexes are assemblies in which small molecule guests are completely surrounded by large molecule hosts [1, 2, 3, 4]. The hosts are made up of subunits held together by intermolecular forces: hydrogen bonds, van der Waal's forces and metal-ligand contacts. The assemblies are formed reversibly and are dynamic; they come together and dissipate on time scales ranging from milliseconds to days, long enough for their study by NMR methods. When multiple hosts can assemble from a given set of subunits, template effects can be expected and they have recently been reported [5, 6, 7, 8, 9].

The synthesis of capsules with asymmetric spaces has also been accomplished, but enantioselection of guests within these hosts is inadequate, whether the capsules are held together with covalent bonds [10], hydrogen bonds [11] or metal/ligand interactions [12, 13]. Moreover, the syntheses are lengthy and problematic and in this chapter we report alternatives. The first involves creation of capsules from achiral precursors and imprinting them chiral guests. The second involves the space left in a large achiral host when a small chiral guest is encapsulated. While the enantioselectivity is still low, the methods may have wider applicability.

We consider the capsule **1a•1a** (Figure 1a [5]), formed when two self-complementary subunits **1a** dimerize in organic solvents. A seam of eight hydrogen bonds holds the subunits together. The dimer has only C_2 axes and exists as a pair of enantiomers even though each subunit features a plane of symmetry. The cavity of the capsule is chiral and asymmetric guests generally prefer one enantiomer of the capsule to its mirror image. The enantiomeric capsules racemize by complete dissociation and recombination of their subunits – a slow process – but guest exchange does not require this dissociation. Rather, guests get in and out of these capsules through flaps opened by the breaking of hydrogen bonds – a faster process [14, 15, 16].

A related structure **1b** with additional hydrogen bonding possibilities was prepared [17]. It has a slower rate of racemization when it dimerizes into capsules **1b•1b.** Parts of the NMR spectrum of **1b•1b** alone and with added chiral guest, (+)-pinanediol **(+)2** are shown in Figure 2 (Figure 1b). The broad signals of **1b•1b** in *p*-xylene-d_{10} are characteristic of unspecific aggregation. On the addition of 3 equivalents **(+)2** a sharp spectrum is obtained in which the

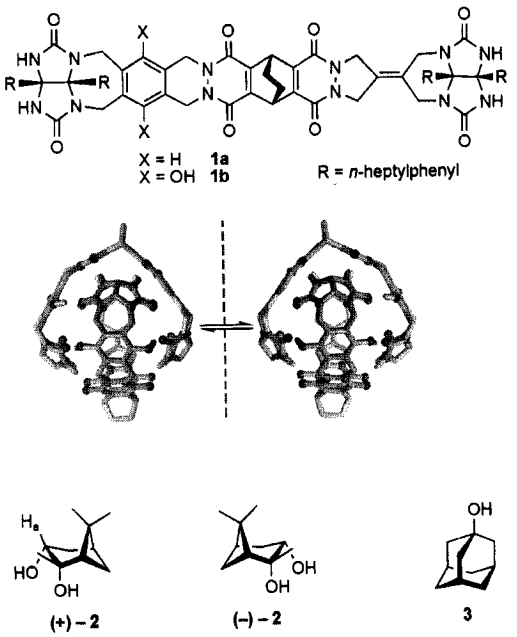

Figure 1. (Top) Line drawing of the monomers 1. (Middle) Energy-minimized [18] model of the dimeric assembly **1b•1b**. Some hydrogens and the *n*-heptylphenyl groups of the dimer are omitted for clarity. (Bottom) Guests used in the study

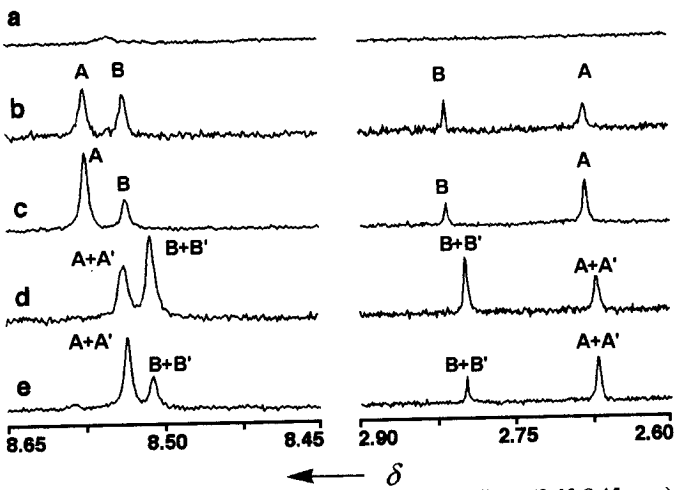

Figure 2. Selected NH resonances of ^{1}H-NMR spectra showing of the dimer (8.65-8.45 ppm) and Ha peaks for the guest in the enantiomeric capsules (2.90-2.60 ppm). The labels A and A' are the thermodynamically more stable complexes of (+)**2** and (-)**2**, respectively, while B and B' are the less stable complexes. a) **1b•1b** alone in *p*-xylene-d_{10} (0.825 mM); b) 4 min and c) 120 h after addition of 3 eq of (+)**2**; d) 17 min and e) 191 h after addition of 30 eq of (–)**2** other than those of the acids

two diastereomeric complexes are observed in approximately equal amounts (Figure 2b).

After a few days, the system reaches its thermodynamic equilibrium at a 50% diastereomeric excess of the favored isomer (Figure 2c). The half-life for equilibration ~20 hours) is the lifetime of the assembly.

When 30 equivalents of the enantiomer **(-)2** was added to the equilibrated mixture, the ratio of the two diastereomers partially inverts. This indicates a situation - unique to reversibly formed assemblies - in which a temporary excess of the less stable diastereomeric complex exists (Figure 2d). This occurs because the guest exchange process is much faster than dissociation of the two halves of the capsule. The rate of guest exchange ($t_{1/2}$ ~ 1 min) is in line with that observed in similar systems [16]. The new guest **(-)2** is now present in the capsule that formed preferentially around **(+)2**. Eventually the mixture of diastereomers returns to equilibrium. The half-life is ~ 10 hours and the original 50% d.e. is achieved (Figure 2e). The rate is twice as fast as that measured for the initial equilibration, and is likely due to the high concentration of the polar, hydrogen-bonding **2** in the exchange mixture [19].

Additional competition experiments established the situation scheme shown in Figure 3.

The memory, or "ghost" persists through multiple guest exchanges. For example, a solution of **1b•1b** templated with **(+)-2**. The solvent and the excess guest was removed, leaving only **1b•(+)2•1b.** The complex was redissolved in benzene and excess 1-adamantanol, **3**, was added. This displaced the guest **(+)2** into the solution. The solvent was removed and extraction gave a solution free of **(+)-2**. However, we were unable to detect any optical activity by polarimetry of this solution. When this solution was treated with excess **(-)2**, the NMR spectrum again showed a 2:1 excess of the less stable diastereomeric complex. Accordingly, that the chiral memory was maintained even in the absence of chiral guests.

The memory of the capsule reflects the relative rates of guest and monomer exchange. The

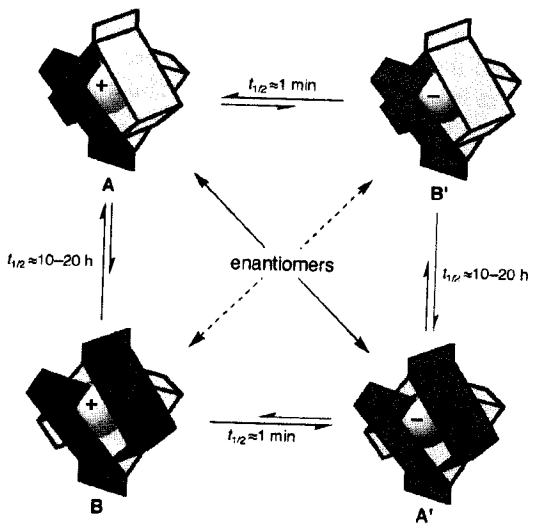

Figure 3. Cartoon representations of the exchange equilibria. Guest exchanges are the horizontal equilibria and monomer exchanges are the vertical equilibria. The cartoons not intended to imply the assign a stereochemistry to the assemblies

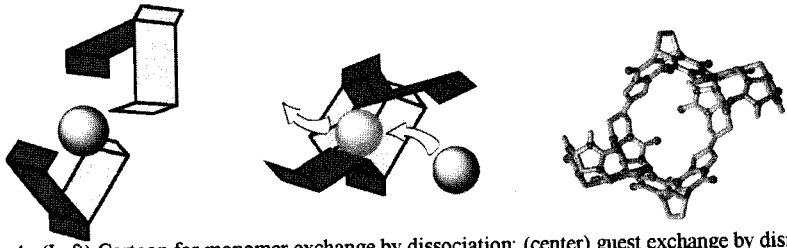

Figure 4. (Left) Cartoon for monomer exchange by dissociation; (center) guest exchange by disrupting hydrogen bonds; (right) energy-minimized structure of the intermediate showing the openings for guest exchange

exchange of subunits **1b** requires the complete dissociation of the capsule (Figure 4a), while guest exchange proceeds through openings that only disrupt a part of the seam of hydrogen bonds that hold the capsule together (Figure 4b). The inversion of the pyridazinyl ring of **1b** creates openings in the dimer that are large enough to allow passage of incoming and outgoing guests (Figure 4c [15]). Many thousands of molecules enter and depart the capsule during its lifetime, but each guest will experience the imprinted asymmetric microenvironment of the capsule.

Examples of nonracemic chiral encapsulation complexes are rare [20, 21, 22] and the imprinting [23, 24] described here provides another route to such systems. It is likely that similar behaviors will also emerge from capsule held together by metal-ligand interactions [8].

The second system showing chiral spaces requires the encapsulation of two different guests. Consider placing a chiral object in an achiral space, a glove in a box for example (Figure 5). Since the glove is chiral the space remaining in the box becomes chiral. Now if a second chiral object enters the box, some selection is expected, especially if the two objects interact. That space should distinguish between enantiomers of the second guest. Relevant here for the molecular scale is the notion of "peristatic" chirality [25].

Reversibly formed capsules capable of surrounding two guest molecules – coencapsulation - are recent inventions [26] that can show of new forms of stereoisomerism [27], suggest possibilities for data storage [28] and permit encapsulated bimolecular reactions [29]. The guests of a coencapsulation complex are confined in space and time; they have much longer contact times and more defined orientations than the diffusion complexes in bulk solution. Diastereomeric complexes can be formed with two chiral guests, and either guest alone in the capsule would leave a chiral remaining space, but capsules are not formed if they are not properly filled. Instead, capsules are known to select guests that provide good fits. A good fit for the liquid phase means filling ~55% of the cavity [30]. We explored the concept with the

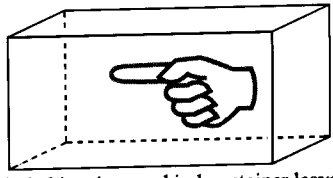

Figure 5. A chiral object in an achiral container leaves a chiral space

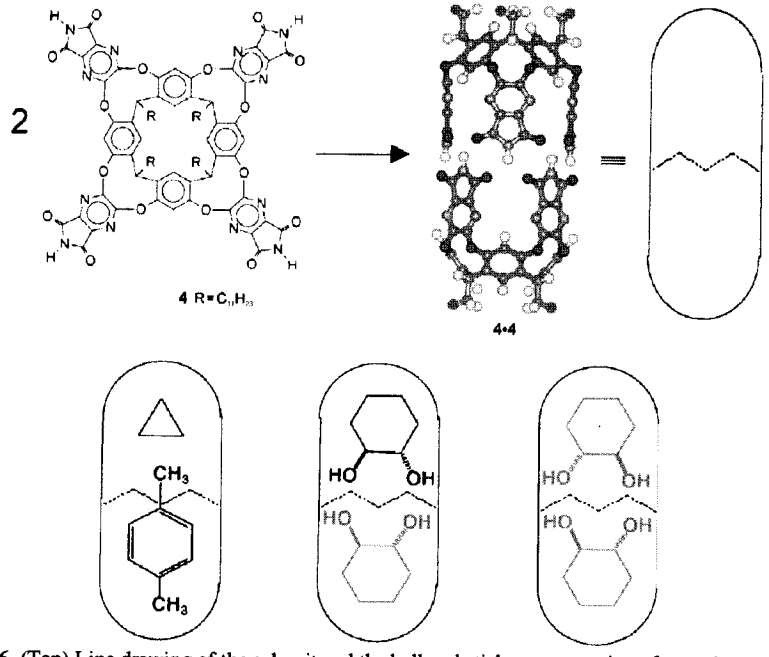

Figure 6. (Top) Line drawing of the subunit and the ball and stick representation of capsule **4•4**. Long, peripheral pendant chains have been removed. Cartoon representation used elsewhere in this work is shown on the left. Bottom: Coencapsulation complexes. Size matching (left) Coencapsulation of the small cyclopropane occurs when the large p-xylene is available. The enantiomers of cyclohexane diol (center) are slightly favored over two identical molecules (right)

cylindrical capsule of Figure 6.

Earlier we found that an enantiomeric pair of cyclohexane diols fills the space in a capsule slightly better than two molecules of the same handedness (Figure 6) [31]. This observation may be related to the preference in nature for centrosymmetric crystals or, alternatively stated, the higher melting points of racemates vs enantiopure compounds. This generality is far from absolute, as we shall relate below. The capsule is too short to accommodate two p-xylenes and cyclopropane alone is not encapsulated. But a mixture of cyclopropane and p-xylene, **4•4** results in the coencapsulation complex [32]. The NMR spectrum of this arrangement shows different signals for the methyl groups of the encapsulated xylene. The separate methyl signals result from two restricted motions of the p-xylene guest: tumbling is slow on the NMR timescale and the two guests are too large to slip past each other while within the capsule. Shorter aromatics tumble rapidly on the NMR timescale inside the capsule [33]. The dimensions of the capsule select appropriately sized combinations and its shape can be used to fix rigid molecules. Polar functions are attracted to the seam of hydrogen bonds that holds the capsule together. These inherent characteristics of the capsule were useful for the enantioselection.

A combination of (R)-styrene oxide **5** and isopropyl chloride in a solution of **4•4** in mesitylene-d_{12} gives an NMR spectrum showing the coencapsulation complex that features

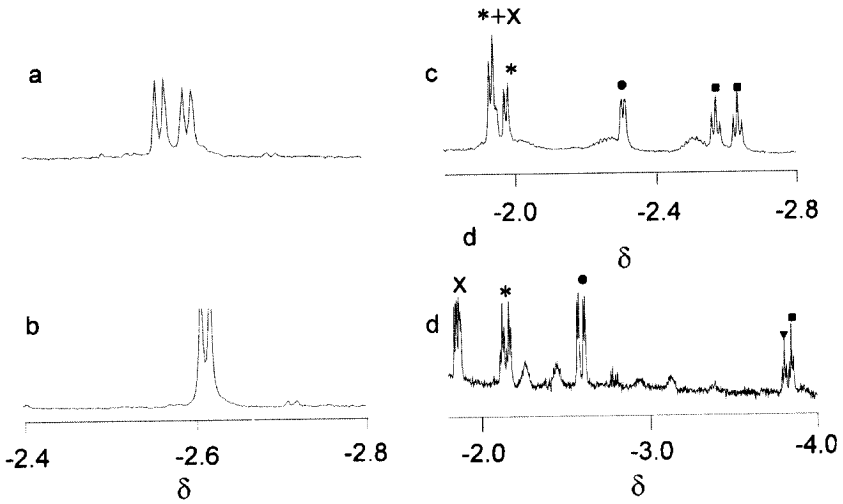

Figure 7. Upfield region of the ^{1}H-NMR spectra (600 MHz, 300 K) of coencapsulation complexes of **4•4** in mesitylene-d_{12} and various liquid guests. a) (R) - styrene oxide with i-PrCl; b) phenylcyclopropane with i-PrCl; c) (R) - styrene oxide with (±) 2-BuCl: ■, * the 4- and 1- methyl groups, respectively, of 2-BuCl encapsulated with (R) - styrene oxide; the signals marked x and • are the 4- and 1-methyl groups, respectively, of the capsule containing two 2-BuCl guests [34]; d) (S)-mandelic acid with (±)- 2-BuOH: ■ is the 4-methyl group of (R) 2-BuOH and ▼ is the 4-methyl group of (S) 2-BuOH coencapsulated with the acid; x represents the 1-methyl groups of both diastereomeric complexes; the signals marked * and • are the 1 and 4 methyl groups, respectively, of the capsule containing two 2-BuOH guests

diastereotopic methyl groups of the smaller guest (Fig. 7). The large upfield shifts place its methyls near the end of the capsule while the observed magnetic anisotropy place the epoxide function near the capsule's center.

In contrast, the coencapsulation of phenylcyclopropane and isopropyl chloride showed a complex with only one doublet at –2.61 ppm (Fig. 7b). The chiral epoxide with coguests racemic 2-butyl chloride, 2- butanol or 2-pentanol gave capsules including one molecule of each guest. Two sets of signals in 1:1 ratio correspond to the methyl protons of the encapsulated halide (Fig. 7c), and the chemical shifts indicate that the ethyl group of the halide is near the end of the capsule. No diastereoselection was observed, even though the asymmetric features of both guests are near the capsule's center, because no attractive forces are in play between the two guests. Their interface lacks steric contacts and they stay as far apart as possible (Figure 8) [35].

We had expected that racemic 2-butanol or 2-pentanol with (R)-styrene oxide would provide hydrogen bonds between the coguests but no diastereoselectivity was observed. With these alcohols, other diastereomeric complexes are also present. These arise from the encapsulation of two molecules of 2-butanol or 2-pentanol (i.e. R+S, R+R and S+S couples). Even so, no stereoselection is detected, yet the asymmetric centers are near the middle of the capsule and intermolecular hydrogen bonding between the two alcohols should exist.

We obtained some better results with the superior donor (S)-mandelic acid **6**. The ^{1}H-NMR spectrum showed the formation of two diastereomeric capsules (Figure 7d), and their ratios

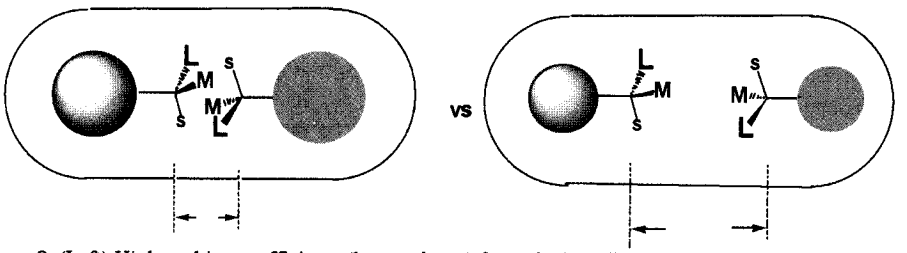

Figure 8. (Left) High packing coefficients (large spheres) force the interdigitation of large, medium and small groups. (Right) Smaller coguests result in a more remote arrangement of asymmetric centers and lower enantioselection

varied with temperature: 1.1 at 303 K and 1.3 at 283 K. Coencapsulation of **6** with (R)-2-butanol established the identity of the diastereomeric complexes. This enantiomer was the better guest for the coecapsulation with (S)-mandelic acid.

The contacts between mandelic acid and butanol guests were found in the energy minimized structures shown in Fig. 9. This arrangement brings the asymmetric centers closer but they are still at too far away from one another.

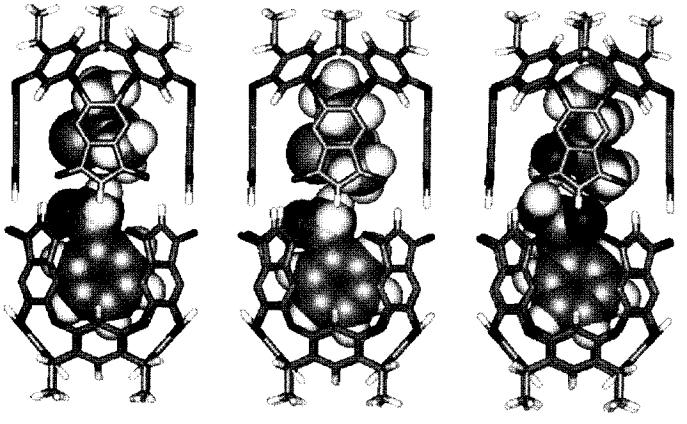

Figure 9. Structures (obtained from the MM^+ force field calculations [36]) of the coencapsulation complexes. (R)-styrene oxide with i-PrCl (left); (R)-styrene and (R)-2-Cl-butane (middle); (S)-mandelic acid and (R)-2-butanol (right)

Table 1.

Guest	Enant. Ratio (298 K)
(±)-2-bromo-3-methylbutyric acid	1.5
(±)-2-bromovaleric acid	1.3
(±)-2-bromobutyric acid	1.6

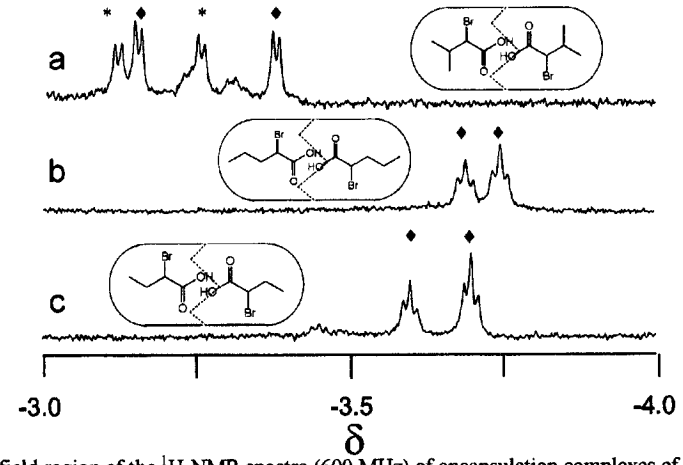

Figure 10. Upfield region of the ^{1}H-NMR spectra (600 MHz) of encapsulation complexes of I_2 and guests in mesitylene-d_{12} at 298 K. a) (±)-2-bromo-3-methylbutyric acid (* and ♦ are 4 and 3-methyl groups of 2-bromo-3-methylbutyric acid); b) (±)-2-bromovaleric acid (♦ are 4-methyl groups of 2-bromovaleric acid); c) (±)-2-bromobutyric acid (♦ are 4-methyl groups of 2-bromo-butyric acid)

Carboxylic acids gave clearly interpretable spectra, but the two molecules of 3-hydroxybutyric acid **7** were encapsulated without diastereoselectivity. This guest gave modest selectivities in complexes with aromatics at 273K: (S)-mandelic acid showed 18% de, while (R)-mandelonitrile **8** and (R)-1-phenylethanol **9** each showed 21% de. The isomeric 2-OH butyric acid, with the asymmetric center nearer the coguest, poorly resolved spectra. Instead, we found that small α–bromo acids were good guests. Two molecules are encapsulated and with modest selectivity (Table 1 and Figure 10).

Little differences in the length or in the shape of the acids cause differences in stereoselection. We assume that interguest hydrogen bonding occurs and that leaves the stereocenters at some distance. Figure 11 shows the results of Molecular Modeling MM+ and emphasizes that the acids' centers are, on average, further apart than the alcohols'.

The acid appears important for good interactions between guests and two acids are also effective. This is unexpected as the hydrogen bonded dimers place their asymmetric centers no closer than 6.7 Å (Fig 11). The diastereoselectivities are poor: with partners that have weak

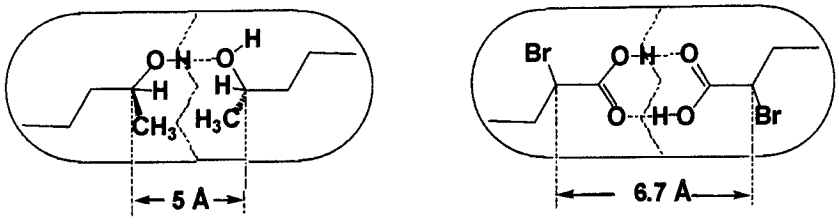

Figure 11. Asymmetric centers of hydrogen bonded alcohols can be closer to each other than those of the acids

attractions or with alcohols there is no selectivity; only with carboxylic acids can some (up to 25% de) be observed. The volume of the capsule translates into ~4 M concentration of each guest inside and the lifetime of the complex is on the order of 1 second. The guests are isolated in space and in time and a chiral guest has ample opportunity to provide an effective asymmetric magnetic environment for its partner. Perhaps the two-point connections and the stronger hydrogen bonds of the dimeric acids increase the lifetimes of complexes. As a final observation, 2-bromo-3-methyl butyric acid (commercially available in optically active and racemic forms) gave the best stereoselection with itself, rather than its mirror image. Are these attractions between dipoles? Steric and magnetic environments appear insufficient for diastereoselection; multiple attractive contacts between guests should be more effective and provide the challenge.

Acknowledgements

We are grateful to the Skaggs Foundation and the National Institutes of Health (GM 50174) for financial support.

References

[1] M.M. Conn and J. Rebek Jr., *Chem. Rev.* 97 (1997) 1647-1668.
[2] T. Kusukawa and M. Fujita, *J. Am. Chem. Soc.* 121 (1999) 1397-1398.
[3] T.N. Parac, D.L. Caulder and K.N. Raymond, *J. Am. Chem. Soc.* 120 (1998) 8003-8004.
[4] R.G. Chapman and J.C. Sherman, *J. Am. Chem. Soc.* 120 (1998) 9818-9826.
[5] J.M. Rivera, T. Martin, J. Rebek Jr., *Science* 279 (1998) 1021-1023.
[6] (a) M. Scherer, D.L. Caulder, D.W. Johnson and K.N. Raymond, *Angew. Chem.* 111 (1999) 1690-1694. (b) M. Scherer, D.L. Caulder, D. W. Johnson and K.N. Raymond, *Angew. Chem., Int. Ed.* 38 (1999) 1588-1592.
[7] F. Ibukuro, T. Kusukawa and M. Fujita, *J. Am. Chem. Soc.* 120 (1998) 8561-8562.
[8] S. Hiraoka and M. Fujita, *J. Am. Chem. Soc.* 121 (1999) 10239-10240.
[9] H. Hof, C. Nuckolls and J. Rebek Jr., *J. Am. Chem. Soc.* 122 (2000) 4251-4252.
[10] (a) J. Canceill, L. Lacombe and A. Collet, *J. Am. Chem. Soc.* 107 (1985) 6993-6996. (b) J. Yoon and D.J. Cram, *J. Am. Chem. Soc.* 119 (1997) 11796-11806. (c) J.K. Judice and D.J. Cram, *J. Am. Chem. Soc.* 113 (1991) 2790-2791.
[11] (a) J.M. Rivera, T. Martin and J. Rebek Jr., *J. Am Chem. Soc.* 123 (2001) 5213-5220. (b) J. Tokunaga and J. Rebek Jr., *J. Am Chem. Soc.* 120 (1998) 66-69. (c) F. Hof, S.L. Craig, C. Nuckolls and J. Rebek Jr., *Angew. Chem., Int. Ed.* 41 (2002) 1488-1508. (d) R.K. Castellano, B.H. Kim and J. Rebek Jr., *J. Am. Chem. Soc.* 119 (1997) 12671-12672.
[12] (a) M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kusukawa and K. Biradha, *Chem. Comm.* (2001) 509-518. (b) S. Hirakoa and M. Fujita, *J. Am. Chem. Soc.* 121 (1999) 10239-10240. (c) T. Kusukawa and M. Fujita, *J. Am. Chem. Soc.* 124 (2002) 13576-13582.
[13] D.L. Caulder and K.N. Raymond, *Acc. Chem. Res.* 32 (1999) 975-892.
[14] T. Szabo, G. Hilmersson and J. Rebek Jr., *J. Am. Chem. Soc.* 120 (1998) 6193-6194.
[15] X. Wang and K.N. Houk, *Org. Lett.* 1 (1999) 591-594.
[16] J. Santamaria, T. Martin, G. Hilmersson, S.L. Craig and J. Rebek Jr., *Proc. Natl. Acad. Sci. USA* 96 (1999) 8344-8347.
[17] J.M. Rivera, S.L. Craig, T. Martin and J. Rebek Jr., *Angew. Chem., Int. Ed.* 39 (2000) 2130-2132.
[18] F. Mohamadi, N.G.J. Richards, W.C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W.C. Still, *J. Comp. Chem.* 11 (1990) 440-467.
[19] Even low concentrations of hydrogen-bonding molecules can have dramatic effects on the rates of assembly processes. R.K. Castellano, S.L. Craig, C. Nuckolls and J. Rebek Jr., *J. Am. Chem. Soc.* 122 (2000) 7876-7822.

[20] R.K. Castellano, B.H. Kim and J. Rebek Jr., *J. Am. Chem. Soc.* 119 (1997) 12671-12672.
[21] R.K. Castellano, C. Nuckolls and J. Rebek, Jr., *J. Am. Chem. Soc.* 121 (1999) 11156-11163.
[22] C. Nuckolls, F. Hof, T. Martin and J. Rebek Jr., *J. Am. Chem. Soc.* 121 (1999) 10281-10285.
[23] For examples of imprinting in covalent materials, see: (a) K.J. Shea, *Trends Polym. Sci.* 2 (1994) 166-173. (b) G. Wulff, *Angew. Chem.* 107 (1995) 1958-1979; G. Wulff, *Angew. Chem., Int. Ed. Engl.* 34 (1995) 1812-1832. (c) K. Mosbach and O. Ramstroem, *Biotechnology* 14 (1996) 163-170. (d) H. Shi, W.-B. Tsai, M.D. Garrison, S. Ferrari and B.D. Ratner, *Nature* 398 (1999) 593-597. (e) K. Polborn and K. Severin, *Chem. Commun.* 24 (1999) 2481-2482. (f) K. Dabulis and A.M. Klibanov, *Biotechnol. Bioeng.* 39 (1992) 176-185.
[24] For examples of memory effects in noncovalent materials, see: (a) Y. Furusho, T. Kimura, Y. Mizuno and T. Aida, *J. Am. Chem. Soc.* 119 (1997) 5267-5268. (b) E. Yashima, K. Maeda and Y. Okamoto, *Nature* 399 (1999) 449-451.
[25] E. Graf, R. Graff, M.W. Hosseini, C. Huguenard and F. Taulelle, *Chem. Commun.* (1997) 1458-1460.
[26] (a) T. Heinz, D. Rudkevich and J. Rebek Jr., *Nature*, 394 (1998) 764-766. (b) M.K. Ebbing, M.-J. Villa, J.-M. Malpuesta, P. Prados and J. de Mendoza, *Proc. Natl. Acad. Sci. USA* 99 (2002) 4962-4966. (c) A. Shivanyuk and J. Rebek Jr., *Chem. Commun.* (2001) 2424-2425.
[27] A. Shivanyuk and J. Rebek Jr., *J. Am. Chem. Soc.* 124 (2002) 12074-12075.
[28] A. Shivanyuk and J. Rebek Jr., *Angew. Chem., Int. Ed.* 42 (2003) 684-686.
[29] J. Chen and J. Rebek Jr., *Org. Lett.* 4 (2002) 327-329.
[30] S. Mecozzi and J. Rebek Jr., *Chem.-A Eur. J.* 4 (1998) 1016-1022.
[31] T. Heinz, D.M. Rudkevich and J. Rebek Jr., *Angew. Chem., Int. Ed.* 38 (1999) 1136-1139.
[32] A. Shivanyuk, A. Scarso and J. Rebek Jr., *Chem. Comm.* (2003) 1230-1231.
[33] S.K. Körner, F.C. Tucci, D.M. Rudkevich, T. Heinz and J. Rebek Jr., *Chem. Eur. J.* 6 (2000) 187-195.
[34] Under these conditions, 2-Cl-butane, 2-butanol and 2-pentanol all form encapsulation complexes with 2 guests inside. The complexes are diastereomeric: one meso-form including two guests of opposite handedness and those with two molecules of R or S 2-butanol. The diastereomeric capsules are formed in equal amounts.
[35] J. Rebek Jr., B. Askew, M. Doa and P. Ballester, *J. Am. Chem. Soc.* 109 (1987) 4119-4120.
[36] Hyperchem TM. Release 7. Hypercube Inc. 2002.