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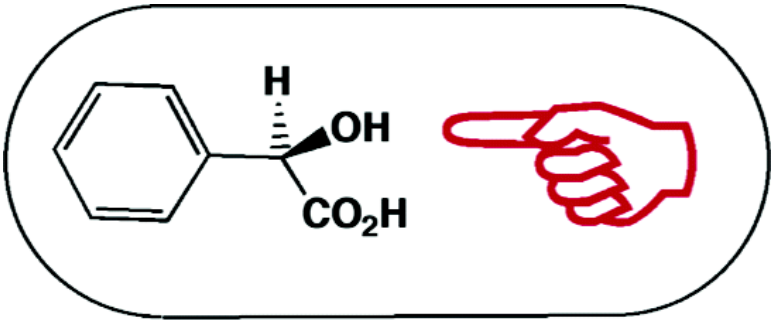


**Chiral objects and spaces in achiral cavities**

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# Asymmetric Environments in Encapsulation Complexes

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***Abstract:*** Symmetrical, self-assembled capsules capable of surrounding two guests offer a new approach to enantioselection through coencapsulation: when one guest is chiral, the space remaining is also chiral. This notion is explored within a cylindrical capsule. The dimensions of the capsule select appropriately sized combinations of guests, the shape of the capsule prevents tumbling of rigid molecules, and the chemical surface of the capsule orients polar functions within. Chiral carboxylic acids such as mandelic acid and α-Br-butyric acid are identified as promising compounds for this purpose, but diastereoselection is modest (<25% de).

## Introduction

The synthesis of capsules with asymmetric spaces can be accomplished with assemblies held together with covalent bonds,[1] and − through the principles of self-assembly − with hydrogen bonds,[2] salt bridges,[3] or metal/ligand interactions.[4,5] Enantioselection of guests within these hosts is, by the lofty standards of catalytic asymmetric synthesis, inadequate, and the syntheses are lengthy and problematic. An alternative, made possible by the availability of larger capsules, is reported here. It involves the encapsulation of two different *chiral* guests in an *achiral* host. While the selectivity presently is poor, the method may have wider applicability: the lifetimes and limited inner space of capsules are likely to amplify recognition phenomena.

## Background

Reversibly formed assemblies capable of encapsulating two different guests are recent inventions[6] but offer possibilities of new forms of stereoisomerism,[7] data storage,[8] and acceleration of bimolecular reactions.[9] With two chiral guests, diastereomeric complexes can be formed, a process that comprises classical resolution methods. Obviously, either guest alone in the capsule would leave a chiral space, but can that space distinguish between enantiomers of the second guest? Lest the readers cavil to this seemingly simplistic solution to asymmetric recognition, we remind them of another characteristic of the capsules: when only about one-half of the space in the capsule is filled, the two guests might easily avoid each other. Capsules are known to select guests that provide good fits; for the liquid phase, a good fit means filling only ∼55% of the cavity.[10] This fact does not inspire confidence, but the pessimism is offset by a single proof of principle: we found that an enantiomeric pair was preferentially encapsulated over two molecules of the same handedness.[11] This observation provided the departure for the present research. Also relevant is the notion of "peristatic" chirality, a concept that predates reversibly formed capsules.[12] The application here also has origins common with NMR shift reagents. The coencapsulation complexes are confined in space and time, and they have much longer contact times and more defined orientations than the complexes between typical shift reagents and their analytes.

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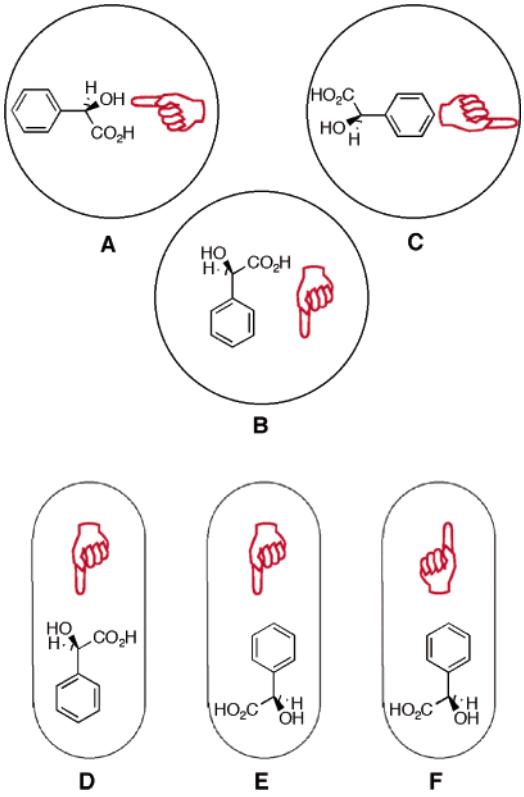


***Figure 1.*** Top: Orientations of (*R*)-mandelic acid in a spherical capsule; the arrangement in (A) is more likely to result in selective interactions with another chiral guest (hand) than that in (B) or (C). Bottom: Restricted tumbling of guests in a cylindrical capsule provides a chiral environment more likely to be effective in (D) rather than in (E) or (F).

Consider a capsule that features (as most do) a roughly spherical cavity; it allows a chiral guest such as (*R*)-mandelic acid to tumble freely (Figure 1).

The remaining space is an ensemble of shapes, not all of which are expected to recognize and discriminate stereochemical features of another guest, for example, the right hand of the figure: the arrangement (A) leaves a more effective chiral space than (B) or (C). The tumbling of the same compound might be slowed in a capsule of cylindrical shape and appropriate size, resulting in only two possibilities, (D) and (E). Of these, the orientation that places the asymmetric element near the middle of the capsule, closer to the other guest as in (D), is expected to be more effective in distinguishing enantiomers than the one in which it is at the end (E). In summary, the asymmetric recognition depends on a capsule that (1) binds more than one molecule, (2) preferentially binds two different molecules, and (3) positions them in an orientation that brings their asymmetric elements near one another. Few systems offer these features.

The dimeric capsule $\mathbf{1}_2$ (Figure 2) offers a roughly cylindrical shape that can be filled with one long (dicyclohexylcarbodiimide), two medium ($\gamma$-picoline), and three small (isopropyl chloride) guests. Two *p*-xylenes are too large to be accommodated, and one does not fill enough space. Cyclopropane alone is likewise not encapsulated. Given a mixture of cyclopropane and *p*-xylene, $\mathbf{1}_2$ encapsulates one of each.[13] *The dimensions of the capsule can be used to fit appropriately sized combinations.* The NMR spectrum of this arrangement shows different signals for the methyl groups of the encapsulated

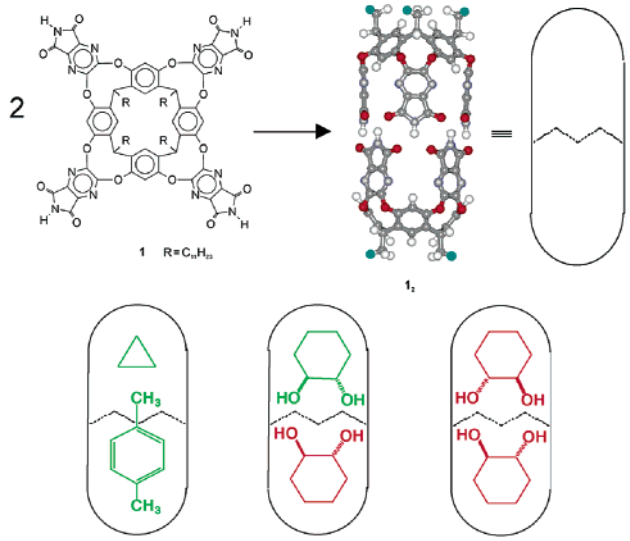


***Figure 2.*** Top: Line drawing of the subunit and the ball-and-stick representation of capsule $\mathbf{1}_2$. Long, peripheral pendant chains have been removed and are indicated by green balls. Cartoon representation used elsewhere is on the right. Bottom: Coencapsulation complexes. Size matching (left) allows the encapsulation of the small cyclopropane when the large *p*-xylene is available; the capsule does not accommodate one or two *p*-xylenes alone. The pairing of enantiomers (center) of cyclohexane diol is slightly favored over the encapsulation of two identical molecules (right).

*p*-xylene. Because the two guests are too large to slip past each other within the capsule, the separate methyl signals result from restricted tumbling of the *p*-xylene guest. Toluene, in contrast, tumbles rapidly on the NMR time scale when inside the capsule.[14] *The shape of the capsule can be used to fix rigid molecules.* The seam of imides that hold the capsule together through hydrogen bonding also influences the positions of the guests: polar functions are attracted to the center of the capsule where they can interact with their complements. *The lining of the capsule can be used to orient polar molecules.* These inherent characteristics of the capsule and the reduced dimensions of the space involved can be depended on, whatever the application.

## Results and Discussion

Addition of (*R*)-styrene oxide **2a** (Figure 3) to a solution of $\mathbf{1}_2$ in mesitylene-$d_{12}$ gives an NMR spectrum showing broad uninterpretable signals. Like *p*-xylene, one molecule of **2a** fills too little space, while two fill too much, and only undefined aggregates are present in the solution. Addition of isopropyl chloride results in quantitative formation of the coencapsulation complex. The $^1$H NMR spectrum shows doubling of the signals for the host corresponding to two nonequivalent halves of the capsule, and two doublets ($-2.54$ and $-2.59$ ppm) for the diastereotopic methyl protons of the coencapsulated isopropyl chloride (Figure 4a). The large upfield shifts place its methyls near the end of the capsule.

The asymmetric magnetic environment imposed on the smaller guest by the chiral epoxide positions the oxirane near the center of the capsule. In the absence of the host capsule, these two compounds, alone or together, show the same NMR spectra. As a further control, the coencapsulation of phenylcy-

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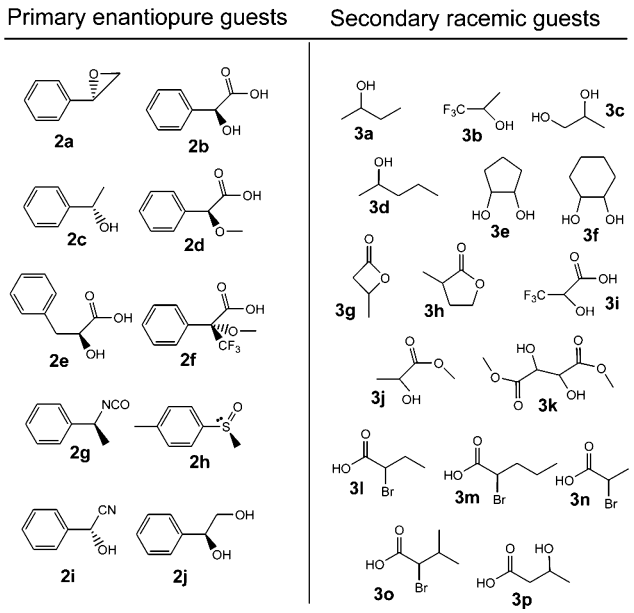


***Figure 3.*** Primary enantiopure guests (left) and secondary racemic guests (right) used in the coencapsulation studies.

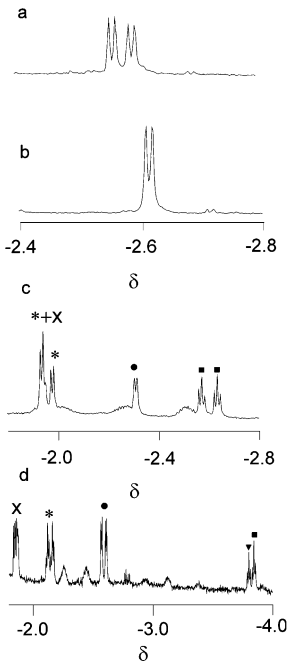


***Figure 4.*** Upfield region of the $^1$H NMR spectra (600 MHz, 300 K) of encapsulation complexes of $\mathbf{1_2}$ (1 mmol) in mesitylene-$d_{12}$ (0.5 mL) and 25 $\mu$L of each liquid guest. (a) (*R*)-Styrene oxide with *i*-PrCl; (b) phenylcyclopropane with *i*-PrCl; (c) (*R*)-styrene oxide with (±)-2-BuCl: ■, * the 4- and 1-methyl groups, respectively, of 2-BuCl encapsulated with (*R*)-styrene oxide; the signals marked × and ● are the 4- and 1-methyl groups, respectively, of the capsule containing two 2-BuCl guests;[15] (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; × 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. Mandelic acid is insoluble in the solvent alone but dissolves on the addition of butanol.

clopropane with isopropyl chloride showed a stoichiometric complex with only one doublet at −2.61 ppm (Figure 4b). Some screening of coguests with the epoxide revealed that the combinations of racemic 2-butyl chloride, 2-butanol, or 2-pentanol with the epoxide gave capsules including one molecule

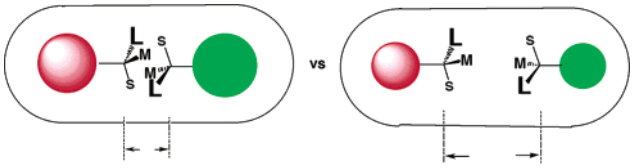


***Figure 5.*** Interdigitation of large, medium, and small groups on the left is forced by a high packing coefficient and is expected to be more effective in enantioselection than the more remote arrangement of asymmetric centers on the right. The interdigitated arrangement minimizes steric clashes when asymmetric centers of opposite chirality interact.[16]

of each guest. Two sets of signals in a 1:1 ratio correspond to the methyl protons of the encapsulated halide (Figure 4c), and their chemical shifts indicate that the ethyl group of the halide in the coencapsulation complex is near the end of the capsule. No diastereoselection is observed, even though the asymmetric features of both guests are near the capsule's center. Evidently, space exists between the two guests. Their complementarity of shape is not enough to result in preferential arrangements that produce selectivity; in other words, their interface lacks steric detail. Only the feeblest of intermolecular forces are available to bring the guests into contact with each other, and, accordingly, they stay apart (Figure 5).

The use of racemic 2-butanol **3a** or 2-pentanol **3d** with (*R*)-styrene oxide gave similar results − no diastereoselectivity was observed. With these alcohols, two more diastereomeric complexes are also present, due to the encapsulation of two molecules of 2-butanol or 2-pentanol (i.e., $R + S$, $R + R$, and $S + S$ couples). Again, no stereoselection is detected, and yet the asymmetric centers are both near the middle of the capsule, and intermolecular hydrogen bonding between the two alcohols is expected.[17]

Somewhat better results were obtained with (*S*)-mandelic acid **2b**. The acid is scarcely soluble in the solution of $\mathbf{1_2}$ in mesitylene-$d_{12}$ but dissolves upon addition of racemic 2-butanol. The $^1$H NMR spectrum shows the formation of two diastereomeric capsules (Figure 2d), the ratio of which varied with temperature: 1.1 at 303 K and 1.3 at 283 K. The identity of the diastereomeric complexes was established by coencapsulation of **2b** with (*R*)-2-butanol. This enantiomer is the preferred guest for the complex with (*S*)-mandelic acid.

Energy minimized structures for these coencapsulation complexes are shown in Figure 6. The only significant contacts between guests were in the mandelic acid/butanol case. Here, the acid and alcohol can be expected to make contact as hydrogen bond donor and acceptor, respectively. This arrangement brings the asymmetric centers closer than they would be if no contact existed between the two guests, but they are still at some distance from each other.

The testing of 2-butanol, 1,2-propanediol, *trans*-1,2-cyclopentanediol, 1-phenylethanol, mandelonitrile, and many others (Figure 3) gave, in most cases, broad NMR signals for the encapsulated guests. Likewise, experiments using esters such as enantiopure dimethyl-tartrate with 2-butanol showed no

(15) Under these conditions, 2-chlorobutane, 2-butanol, and 2-pentanol all form encapsulation complexes with two 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.

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(17) For (±)-2-pentanol, $CH_3$ triplet $\delta = -2.55$ and $-2.58$, $\Delta\delta = -3.40$ and $-3.43$; $CH_3$ doublet $\delta = -1.74$ and $-1.87$, $\Delta\delta = -2.79$ and $-2.82$.

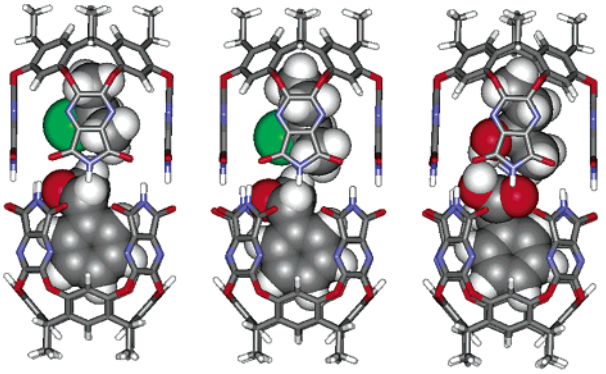

***Figure 6.*** Energy optimized structures ($MM^+$ force field[18]) of the coencapsulation complexes. (*R*)-Styrene oxide **2a** and isopropyl chloride (left); (*R*)-styrene **2a** and (*R*)-2-Cl-butane (middle); (*S*)-mandelic acid **2b** and (*R*)-2-butanol (right).

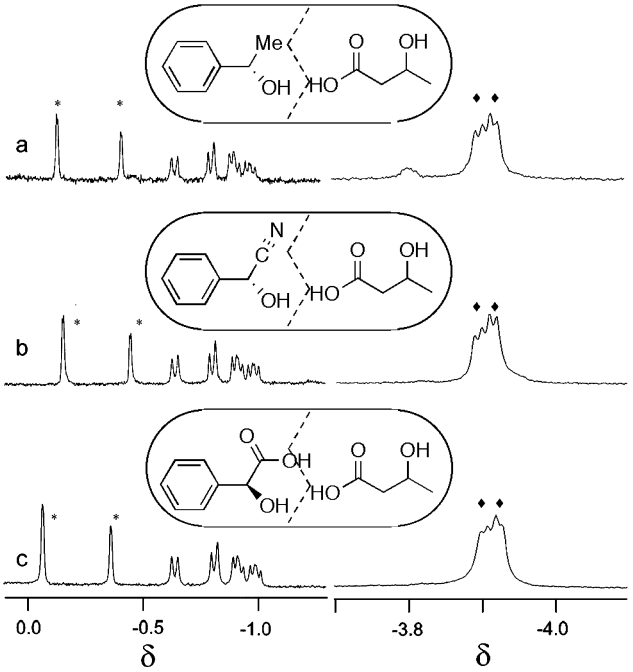


***Figure 7.*** Upfield region of the $^1$H NMR spectra (600 MHz) of encapsulation complexes of $\mathbf{1}_2$ (1 mmol) and 25 $\mu$L of each liquid guest and 10 mg for each solid guest in mesitylene-$d_{12}$ at 273 K. (a) (*S*)-1-Phenylethanol **2c** and (±)-3-hydroxybutyric acid **3p**; (b) (*R*)-mandelonitrile **2i** and **3p**; (c) (*S*)-mandelic acid **2b** and **3p** (* and ◆ are the hydroxy and methyl groups, respectively).

selectivity. The peaks were not resolved even at temperatures below 273 K. Only with (*S*)-1-phenylethanol **2c** and (±)-2-butanol was there some measurable stereoselectivity (ca. 1.1), but the spectrum was still broad, and the integration was performed on the NH of the two diastereomeric capsules.

Carboxylic acids generally gave spectra that were readily interpretable. The methyl ether of mandelic acid **2d** showed reduced selectivity for the alcohols, while acids of similar size like phenyl-lactic **2e** or MTPA **2f** (methoxy-trifluoromethyl-phenylacetic acid) were not coencapsulated with 2-butanol (one of the smaller secondary chiral guests). Two molecules of **3p** are encapsulated in $\mathbf{1}_2$, but no selectivity is observed. This guest gave modest selectivities in complexes with aromatics at 273 K: (*S*)-mandelic acid **2b** showed ~1.5 ratio (18% de); (*R*)-mandelonitrile **2i** and (*R*)-1-phenylethanol **2c** each showed ~1.6 ratios (21% de) (Figure 7).

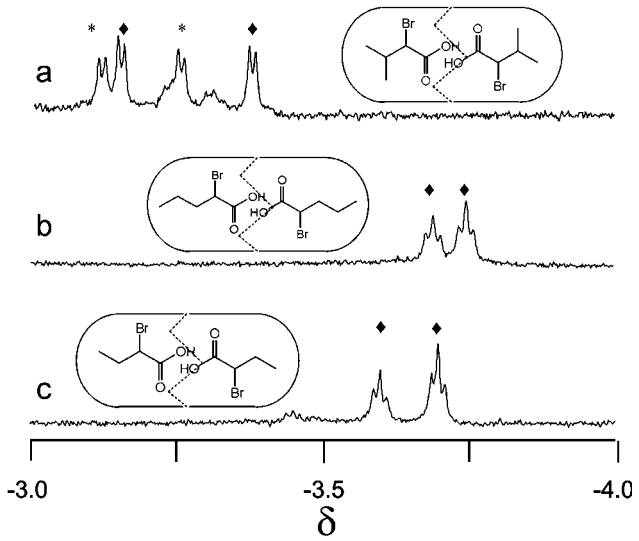


***Figure 8.*** Upfield region of the $^1$H NMR spectra (600 MHz) of encapsulation complexes of $\mathbf{1}_2$ (1 mmol) and 25 $\mu$L of each liquid guest and 10 mg for each solid guest in mesitylene-$d_{12}$ at 298 K. (a) (±)-2-Bromo-3-methylbutyric acid **3o** (* and ◆ are the methyl groups); (b) (±)-2-bromovaleric acid **3m** (◆ are the methyl groups); (c) (±)-2-bromobutyric acid **3e** (◆ are the methyl groups).

***Table 1.*** Diastereoselectivity Ratios for the Encapsulation of Two Molecules of α-Bromo Acids in $\mathbf{1}_2$

| guest | diast. ratio (298 K) |
|---|---|
| (±)-2-bromo-3-methylbutyric acid **3o** | 1.5 |
| (±)-2-bromovaleric acid **3m** | 1.3 |
| (±)-2-bromobutyric acid **3e** | 1.6 |

***Table 2.*** Diastereoselectivity Ratios for the Encapsulation of Racemic α-Bromo Acids with Enantiopure Aromatic Guests in $\mathbf{1}_2$

| guest 1 | guest 2 | diast. ratio (298 K) |
|---|---|---|
| | (±)-2-Br-butyric acid **3e** | 1.2 |
| (*S*)-mandelic acid **2b** | (±)-2-Br-valeric acid **3m** | 1.0 |
| | (±)-3-Me-2-Br-butyric acid **3o** | 1.2 |
| | (±)-2-Br-butyric acid **3e** | 1.3 |
| (*S*)-1-phenylethanol **2c** | (±)-2-Br-valeric acid **3m** | 1.4 |
| | (±)-3-Me-2-Br-butyric acid **3o** | 1.5 |
| | (±)-2-Br-butyric acid **3e** | 1.1 |
| (*R*)-mandelonitrile **2i** | (±)-2-Br-valeric acid **3m** | *a* |
| | (±)-3-Me-2-Br-butyric acid **3o** | 1.0 |

[a] Could not be determined due to overlap of the signals.

The isomeric 2-OH butyric acid, with the asymmetric center nearer the coguest, is commercially available only as sodium salt; it gave poorly resolved spectra even when the acidified form was generated in situ. Instead, we used small α-bromo acids and found them to be good guests. Two molecules are encapsulated with modest selectivity (Table 1) (Figure 8).

Small differences in the length or in the shape of the acids cause differences in stereoselection, even if the stereocenters are not very close. Simple modeling shows the centers are more than 6 Å from each other. These halo-acids are easily coencapsulated with enantiopure aromatic alcohols or acids (Table 2). They all show clear spectra and diastereoselectivities up to 1.5 (de = 20%).

## Summary and Outlook

The capsule isolates the guests in space and in time: the volume of the capsule translates into ~4 M concentration of each guest inside, and the lifetime of the complex is on the

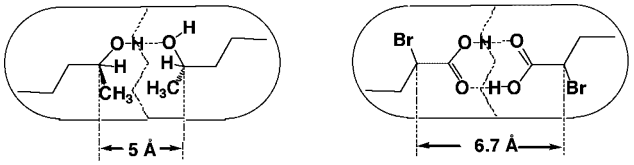


***Figure 9.*** Asymmetric centers of hydrogen bonded alcohols on the left can be closer to each other than those of the acids on the right.

order of 1 s. Accordingly, a chiral guest has ample opportunity to provide an effective asymmetric magnetic environment for its partner. Yet, the diastereoselectivities are poor: with partners that have little affinity for each other or with alcohols that have hydrogen bonds to hold the guests together, there is no selectivity; only with carboxylic acids can de (up to 25%) be observed. The acid appears important for good interactions between guests, and two acids are also effective. This is puzzling as the hydrogen bonded dimers, typical of carboxylic acids in solution, place their asymmetric centers at some distance (Figure 9). The asymmetric centers of the alcohols can, on average, be closer. Perhaps, the stronger hydrogen bonds, the two-point connections, and increased lifetimes of complexes provided by the acids are more important than distance. At any rate, α-bromoacids give the best stereoselection in mixed complexes with (*S*)-1-phenylethanol **2c**. For the moment, we conclude that for diastereoselection, multipoint attractive contacts between guests in the inner space could be more effective; evidently, asymmetric, steric, and magnetic environments are not enough. Achieving appropriate intermolecular contacts between guests is the challenge.

## Experimental Section

**General.** $^1$H NMR spectra were recorded on a Bruker DRX-600 (600 MHz) spectrometer at different temperatures. Guests were purchased from Aldrich and used without further purification. Compound **1** was prepared following literature procedures.[19]

**Encapsulation Studies.** $^1$H NMR experiments were carried out using a 600 MHz spectrometer. Mesitylene-$d_{12}$ was used as purchased from Cambridge Isotope Laboratories, Inc. In encapsulation experiments, the concentration of $\mathbf{1}_2$ was 1 mM, and liquid guests were added in excess. Typically, between 10 and 25 $\mu$L of the pure liquid was added, and the NMR tube was simply shaken until a clear solution was obtained. For solid guests, the amount added was between 10 and 20 mg, and the tube was sonicated for 15 min to accelerate the dissolution/encapsulation process. The integration of NMR peaks was performed using the program WinNMR.

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