Diastereoselection of chiral acids in a cylindrical capsule†

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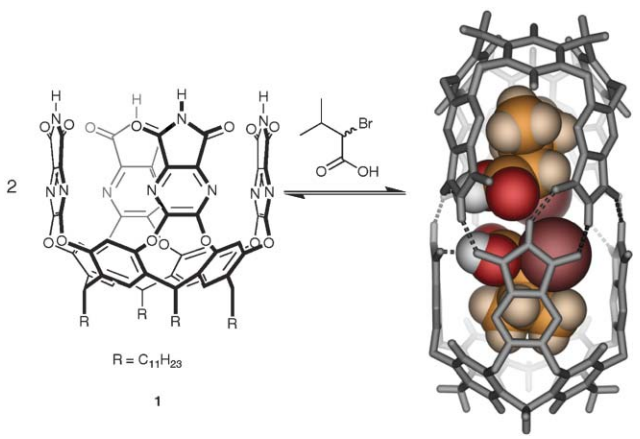
The cylindrical dimeric capsule binds two chiral carboxylic acids with modest selectivity for homochiral or heterochiral pairs.

Reversibly formed capsules, held together by non-covalent forces, selectively isolate molecules from bulk solvent.[1] The contact time of coencapsulated molecules is long (seconds) compared to diffusion-limited encounters observed (10^{-10} s) and the guests are held at close range. The dimeric capsule $\mathbf{1_2}$ has the additional ability to orient the molecules held inside its cylindrical cavity (Scheme 1).[2] One, two, or three guests are accommodated by the capsule interior—a space of about 440 Å^3. These factors contribute to intermolecular interactions and arrangements that cannot otherwise be seen.[3] More conventional forms of isomerism also exist: coencapsulation of two molecules of *trans*-1,2-cyclohexanediol shows selectivity in favor of the racemic pair[4] (one diol and its enantiomer are preferred over two identical molecules) while (*R*)-mandelic acid, coencapsulated with other guests such as chiral alcohols, shows modest enantioselectivity.[5] Coencapsulation of two different carboxylic acids has been reported in a related capsule featuring ureas.[6] We report here some unexpected coencapsulation preferences of chiral carboxylic acids with seemingly remote asymmetric centers.

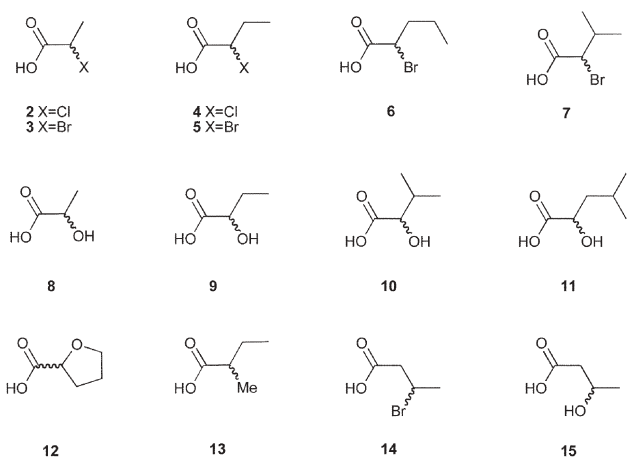


Scheme 1 Dimerization of **1** forms a cylindrical capsule with two molecules of (*R*)-2-bromo-3-methylbutyric acid (**7**). The structure was minimized with the OPLS force field in Macromodel software. The acids prefer hydrogen bonding to the capsule rather than each other, an arrangement that brings their asymmetric centers near one another.

A variety of commercially available chiral acids are readily encapsulated using mesitylene-d_{12}, the best NMR solvent that is not itself a guest for the capsule (Scheme 2). The α-haloacids **2–4** show no diastereoselectivity, and give multiple capsule species in solution. Acids **5** and **6** are only available in racemic form. They show preferences but the diastereomeric pair cannot be identified. Only **7** is available in both racemic and enantiopure forms. We find that the preferred pair consists of two molecules of the *same* chirality, as shown in Scheme 1.

Some likely α-hydroxyacids were also examined (Table 1). DL-Lactic acid (**8**) is a poor guest and shows no selectivity, nor does racemic 2-hydroxybutyric acid (**9**). Hydroxy acid **10** prefers encapsulation as a racemate, in contrast to the corresponding bromide **7**. The proton of the acid's asymmetric carbon appears as two partially overlapping singlets in the upfield NMR with a 1.2 : 1 ratio favoring the heterochiral pair (Fig. 1). All of the other protons overlap perfectly, and temperature (275–325 K) had no significant effect on this ratio. The slightly longer hydroxyisocaproic acid **11** prefers the same chirality, and guest **12**, wherein the oxygen is held in the ring of a tetrahydrofuran, prefers the racemate. Significant diastereoselectivity is also observed for 2-methylbutyric acid (**13**), which prefers the homochiral pair (Fig. 1). This compound is roughly isosteric with haloacid **5**, for which the stereo-preference is unknown.

These results indicate interaction between the asymmetric centers. In a conventional hydrogen bonded acid dimer the α-carbons are some 7 Å apart. Further separation of the asymmetric centers, as in the β-butyric acids (8.9 Å), reduces this



Scheme 2 Selection of chiral acid guests.

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† Electronic supplementary information (ESI) available: description of computational methods and calculated structures of global minima. See http://www.rsc.org/suppdata/cc/b5/b503313f/index.sht

Table 1 Encapsulation of chiral guests in $\mathbf{1_2}$ by ^{1}H NMR

Guest	Size (Å^3)[a]	Preferred dimer[b]	d.r.
2	83	no selectivity	1 : 1
3	100	no selectivity	1 : 1
4	92	no selectivity	1 : 1
5	108	ND	1.6 : 1[5]
6	116	ND	1.3 : 1[5]
7	119	homochiral	1.5 : 1[5]
8	75	no selectivity	1 : 1
9	90	no selectivity	1 : 1
10	103	heterochiral	1.2 : 1
11	120	homochiral	1.2 : 1
12	99	heterochiral	1.3 : 1
13	99	homochiral	1.3 : 1
14	109	ND	1.15 : 1
15	89	no selectivity	1 : 1[7]

[a] Each guest was optimized with HyperChem (AM1 semi-empirical method) and the volume of its van der Waals surface was determined using WebLabViewer Pro. [b] ND = not determined.

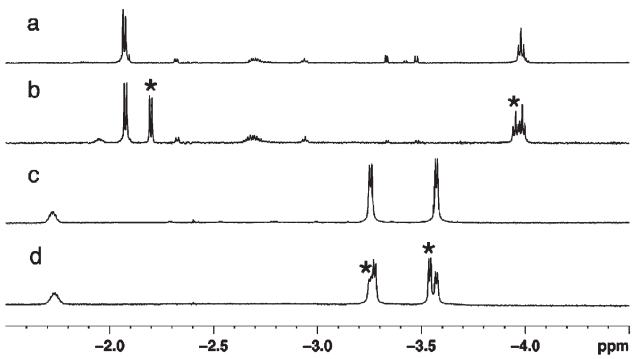

Fig. 1 Upfield ^{1}H NMR spectra of capsule $\mathbf{1_2}$ (600 MHz, 300 K, mesitylene-d_{12}) with representative guests: (a) (*S*)-2-methylbutyric acid, (b) racemic 2-methylbutyric acid (**13**), (c) (*S*)-2-hydroxy-3-methylbutyric acid, and (d) racemic 2-hydroxy-3-methylbutyric acid (**10**). Asterisks (*) indicate peaks for racemate dimers.

selectivity. For example, 3-bromobutyric acid (**14**) shows modest selectivity (*ca.* 1.15 : 1, *cf.* **5**), and 3-hydroxybutyric acid (**15**) shows none (*cf.* **9**). If the acids prefer hydrogen bonds to the seam of imides inside the capsule (rather than each other) their asymmetric centers are nearer one another (Scheme 1).

Monte Carlo conformational searches were performed with the OPLS force field[7] using Macromodel in Maestro (Table 2).[8] In each case, many lower energy conformers, with similar geometries,

Table 2 Comparison of calculated and experimental results of α-bromoacids

	From MCMM		From NMR	
Guest	Preferred dimer	Energy (kJ/mol)	Preferred dimer	Energy (kJ/mol)
3	Hetero	0.3	None	0
5	Hetero	5.2	ND[a]	1.2
6	Homo	4.3	ND	0.6
7	Homo	4.5	Homo	1.0

[a] ND = not determined.

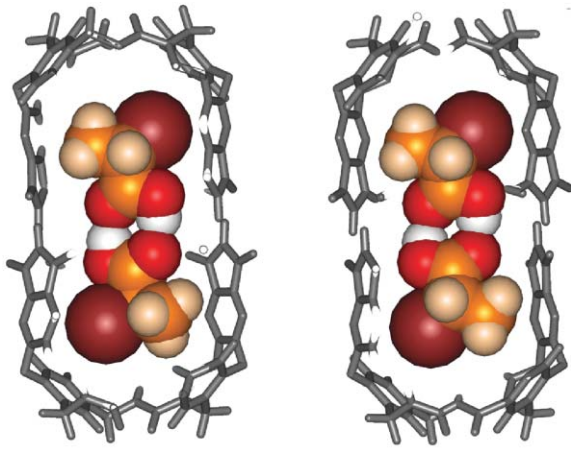

Fig. 2 Minimized structure for $\mathbf{1_2}$ containing *R*/*S*-**3** (left) and *S*/*S*-**3** (right). The front and back of the capsule have been removed to emphasize the available volume.

form a cluster of local minima with energies close to that of the global minimum. For the larger encapsulated acids, these local minima are in a small energy range and have very similar geometries. The lowest-energy conformation for each simulation was depicted in the text or ESI to show the structural features and to compute relative energies as well. Acid **3** shows no selectivity and there is no apparent energy difference *in silico*. This guest pair is able to rotate freely and to slide along the length of the capsule (Fig. 2). Guests **6** and **8** both prefer encapsulation of the homochiral pair. For these bigger guests, the low-energy structures show preferential hydrogen-bonding of the acid guest to the imide carbonyl of the host rather than to its co-guest (Scheme 1). Acid **5** is a more complicated case: low energy structures show either guest–guest or guest–host hydrogen bonds. The OPLS force field predicts preference for the racemic dimer.

The observed diastereoselectivities indicate small energetic differences ($\leqslant$1 kJ/mol) between the two possible isomers, but the achiral capsule does select a particular diastereomeric pair across a variety of carboxylic acid guests. Chiral resolution is best known in the solid state, where selectivity is controlled by crystallization of the less soluble pair.[9] The solubility difference is related to the overall thermodynamics—the balance of attractive and repulsive intermolecular forces. Inside the capsule, the interactions are strictly pairwise and in a confined space. A variety of factors may determine the observed selectivity, but it appears that the capsule's predilection for particular pairs is primarily based on the shapes of the diastereomeric complexes and their goodness of fit within the cavity.

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