Chiral Softballs: Synthesis and Molecular Recognition Properties

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Abstract: Studies on the different congeners of the softball were undertaken to explore structural variants for enantioselective encapsulation. Two different spacer elements in the monomeric subunit render the dimeric softball chiral although the monomer itself is achiral. The dimers represent capsules with dissymmetric cavities with volumes ranging from 190 to 390 Å^3. The cavities are distorted spheres, and asymmetric guests, such as naturally occurring terpenes, generally prefer one enantiomer of the capsule to its mirror image. The selectivities are moderate (up to 4:1). The complexation studies show that the host capsules are flexible enough to arrange themselves comfortably around a guest but still maintain enough rigidity to be influenced by the occupancy of a chiral guest. The enantiomeric capsules can interconvert (racemize) by dissociation and recombination of their subunits.

Introduction

Enantioselection has always been a motive of molecular recognition. So many different chiral receptors have been examined that another version might be hard to justify: Cyclodextrins,[1] crown ethers,[2] cryptophanes,[3] cyclophanes,[4] carcerands,[5] baskets,[6] and even some structures that are not macrocyclic[7] have all been worked over. These structures often have high symmetries, and the cavities, when they do have cavities, are not particularly asymmetric. The enantioselectivity, particularly with neutral targets, leaves something to be desired,[8] and we have kept an inner eye on the problem. As our early work with cleft-like structures became more sophisticated and the concave receptors made contact with an ever-increasing fraction of the convex targets' surfaces, it appeared feasible to create a receptor that completely surrounds its target. This defines, of course, a molecule within a molecule, one of the emerging tools of modern physical organic chemistry. They provide chambers that stabilize reactive intermediates,[9] reveal new forms of stereoisomerism,[10] accelerate reactions,[11] and probe the intrinsic characteristic of the liquid state.[12] This research was undertaken to invent and evaluate molecule-within-molecule complexes that feature dissymmetric cavities.

Rigid structures are typically associated with selective recognition, so that carcerands and cryptophanes, held together by covalent bonds, would seem to have an advantage for enantioselectivity. These molecular hosts show high energetic barriers to guest exchange and often require forcing conditions to equilibrate; only modest selectivities have been seen. The use of weak intermolecular forces instead of covalent bonds for assembly of the receptor imparts reversibility to the guest-exchange process, a process that we call encapsulation.[13,14] We found that dissymmetric spaces were also accessible through assemblies held together by weak intermolecular forces. Guest enantioselectivity was possible even with the flexibility inherent in such systems. Moreover, stereochemical information was shown to flow from the host to the guest and vice versa.

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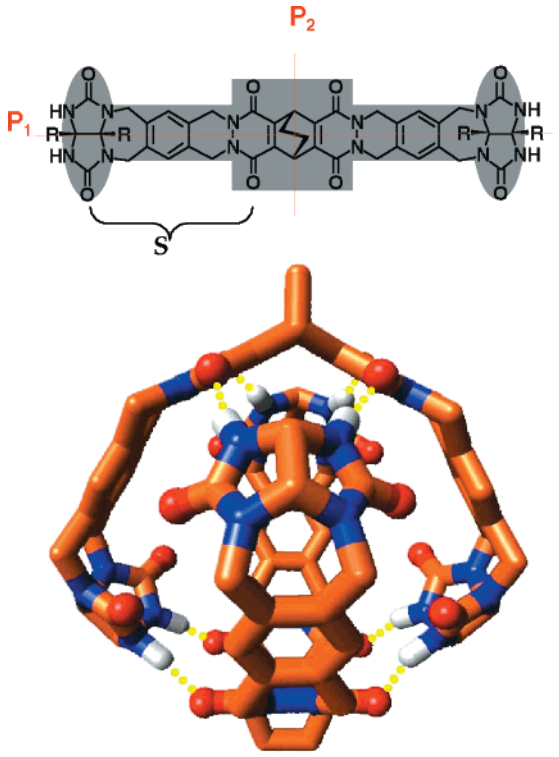

Figure 1. Original softball; (a) structural depiction of the monomer overlaid on a cartoon depiction showing the planes of symmetry in the monomer; (b) molecular model of the dimer (Some hydrogens and groups have been omitted for clarity; colors: red, oxygen; blue, nitrogen; orange, carbon).

The first examples of chiral capsules formed through self-assembly were used to study the dynamics of assembly and guest exchange in the "tennis ball."[15] In these, the capsule was desymmetrized by adding external stereogenic centers that did not alter the shape of the roughly spherical cavity. Calixarene dimers functionalized with chiral groups on their peripheries were the next stop on this journey.[16] These external groups controlled the clockwise or counterclockwise orientation of the ureas that hold the capsule together and created a chiral lining for the cavity. Such capsules showed modest enantioselective binding. We also prepared a chiral capsule by the self-assembly of four optically active subunits.[17] The tetrameric capsule showed a special affinity for small ketones and was able to discriminate between their enantiomers in solution.

Chiral Softballs

For access to a larger and inherently chiral cavity, we took the "softball" as our starting point. The original softball (Figure 1) assembles through self-complementary hydrogen-bonding between the subunits and it exists as a highly symmetrical, pseudospherical dimer in noncompetitive organic solvents.[18] It is formed from monomers possessing two planes of symmetry (P_1, P_2, in Figure 1) since both spacers (S) connected to the centerpiece are identical. The planes of symmetry are conserved in the dimeric assembly. When different spacers are used in the same subunit, the monomer still maintains one plane of symmetry and is achiral, but dimerization of the achiral monomer reduces the symmetry to a C_2 symmetry axis, and the capsule becomes chiral (Figure 2). The dimeric assembly exists as a racemic mixture of two enantiomeric capsules when the guests inside are symmetrical. The enantiomers can and do interconvert by dissociation and recombination of the subunits. As was the case in the tennis ball, this first generation of chiral softballs used two different glycolurils ($S \neq S'$, Figure 2). The capsule has a chiral surface but an achiral cavity for all practical purposes. The asymmetric information was too far from the guest for steric or electrostatic interactions, and only the magnetic interactions were influenced as demonstrated by ^{1}H NMR.[19] Accordingly, no enantioselectivity was observed in the encapsulation of chiral guests.

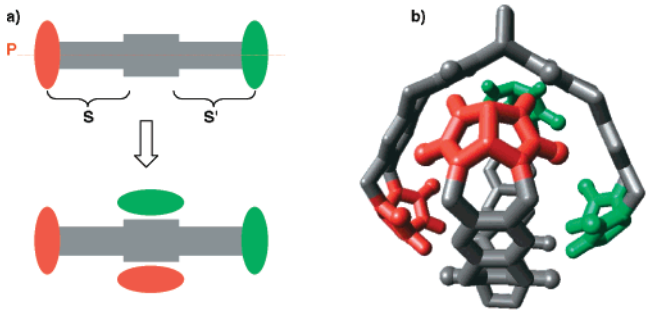

Figure 2. First generation of chiral softballs; (a) dimerization breaks up the plane of symmetry; (b) molecular model of the dimer; the red and green colors represent the two different glycolurils in the spacers S and S′ (Some hydrogens and other atoms have been omitted for clarity).

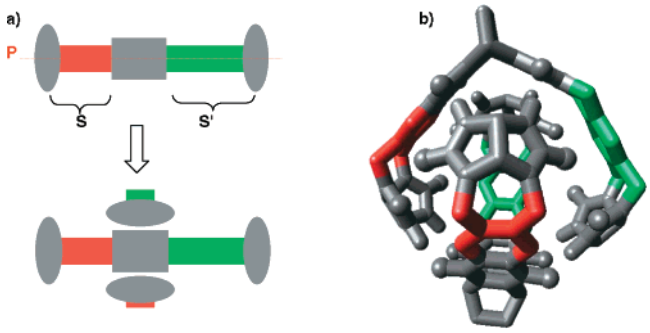

Figure 3. Second generation of chiral softballs; (a) dimerization breaks up the plane of symmetry; (b) molecular model of the dimer; the red and green colors represent the two different spacers S and S′ (Some hydrogens and other atoms have been omitted for clarity).

Changes in the spacers of the subunits were required to move the chirality into the cavity where the molecular recognition takes place. But would the changes compromise self-complementarity? Certain elements of self-recognition, such as the hydrogen-bond acceptors in the central bicyclic unit and their complementary donors on the terminal glycolurils, are required in any version of the softball. Fortunately, the dimer tolerates some diversity in the size of the spacers between the centerpiece and the ends, and these were systematically varied. Therefore, the dimeric capsules were formed having chiral surfaces and, more importantly, chiral cavities (Figure 3b). The pseudosphere inside becomes somewhat distorted, and the chirality of the host can be in direct contact with the guest in steric and electrostatic senses.

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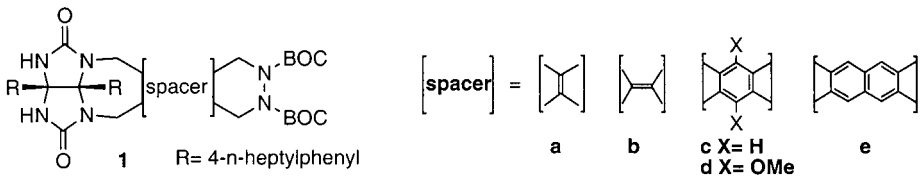
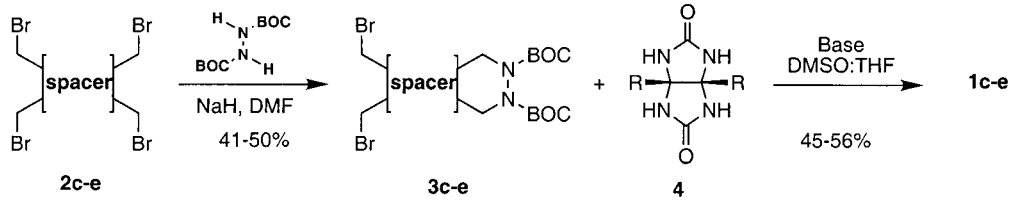
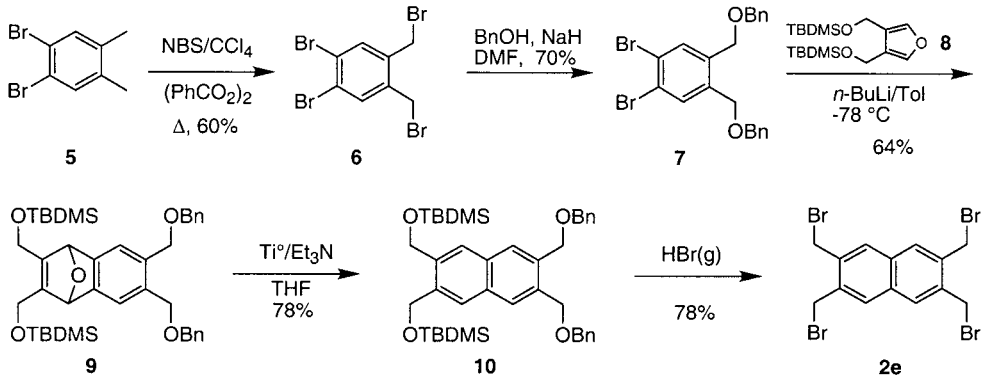


Figure 4. Different spacers used in the construction of the softballs.

Scheme 1. Synthesis of Spacers through the Unprotected Method



Scheme 2. Synthesis of Naphthalene Spacer



Results

Synthesis. The Spacers. The synthesis of the unsymmetrical monomers involves the attachment of structures sketched in Figure 4 (**1a**−**e**) to a constant centerpiece. Structures **1c**−**e** were prepared from unprotected glycolurils. First, alkylation of di-*tert*-butyl hydrazodicarboxylate with one of the tetrabromides **2c**−**e**, gave hydrazides **3c**−**e**.[20] Then, in a second alkylation, **3** was treated with the glycoluril **4** to give **1c**−**e** (Scheme 1).[21]

Although there are various synthetic routes to tetrabromomethylnaphthalene **2e**, they are not suitable for the preparation of multigram quantities.[22,3b] Instead, we developed the route depicted in Scheme 2. Treatment of 1,2-dibromo-4,5-dimethylbenzene **6**[23] with NBS and benzoyl peroxide gave the tetrabromide **6**. Nucleophilic substitution on **6** with benzylate transformed it into the dibenzyl ether **7**. Treatment of **7** with butyllithium in the presence of TBDMS-protected 3,4-hydroxymethyl furan **8**[24] gave the Diels−Alder adduct **9** in moderate yield. Reduction of **9** with Ti(0)[25] followed by treatment of **10** with HBr(g) afforded the tetrabromide **2e** in 61% combined yield.

The protected glycoluril strategy used *p*-methoxy benzyl groups (PMBs) in the synthesis of the two smallest spacers **1a**, **b** (Scheme 3). Di-PMB glycoluril **11**[26] was alkylated with tetra(bromomethyl)ethylene **12**[27] to give dibromide **13**. Deprotection using ceric ammonium nitrate (CAN) followed by alkylation of the di-BOC-protected hydrazine gave **1b** in 38% combined yield. For the isomeric **1a**, the 2,3-bis(iodomethyl)-1,3-butadiene **15**[28] was employed in the first alkylation. The resulting diene **16** was deprotected using CAN then treated with di-*tert*-butyl azodicarboxylate in a hetero-Diels−Alder reaction. This gave **1a** in 45% combined yield.

The Centerpiece. The centerpiece synthesis is depicted in Scheme 4. The first unsymmetrical monomers were prepared using the symmetric tetraester **24b**,[29,30] prepared in eight steps, with a 10% overall yield.[31] This approach, involving sequential acylation of two different spacers, gave a mixture that was

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(24) This compound was prepared in two steps from comercially available 3,4-dimethyl furan dicarboxylate, by reduction with $LiAlH_4$ followed by protection with TBDMSCl. For details, see: (a) Jenneskens, L. W.; Kostermans, G. B. M.; ten Brink, H. J.; de Wolf, W. H.; Bickelhaupt, F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2121. (b) Atasoy, B.; Ozen, R. *Tetrahedron* **1997**, *53*, 13867. (c) Anderson, W. K.; Dewey, R. H. *J. Med. Chem.* **1979**, *22*, 1270.

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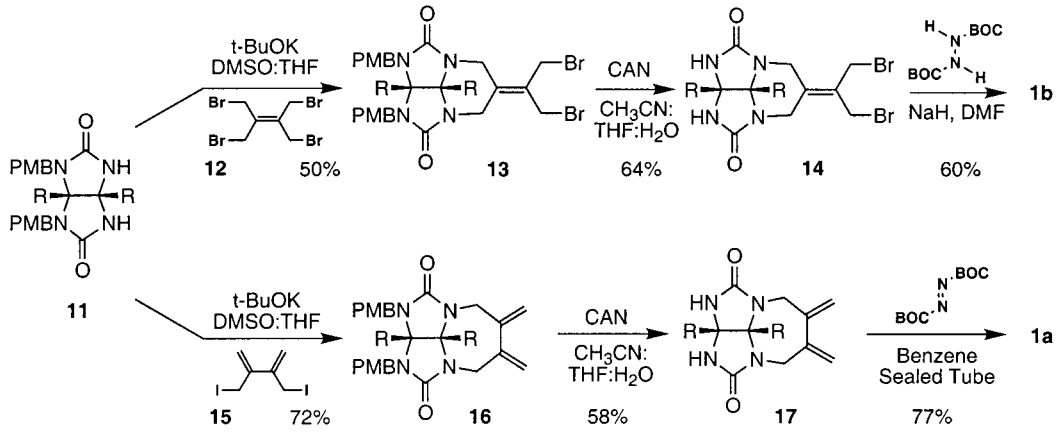
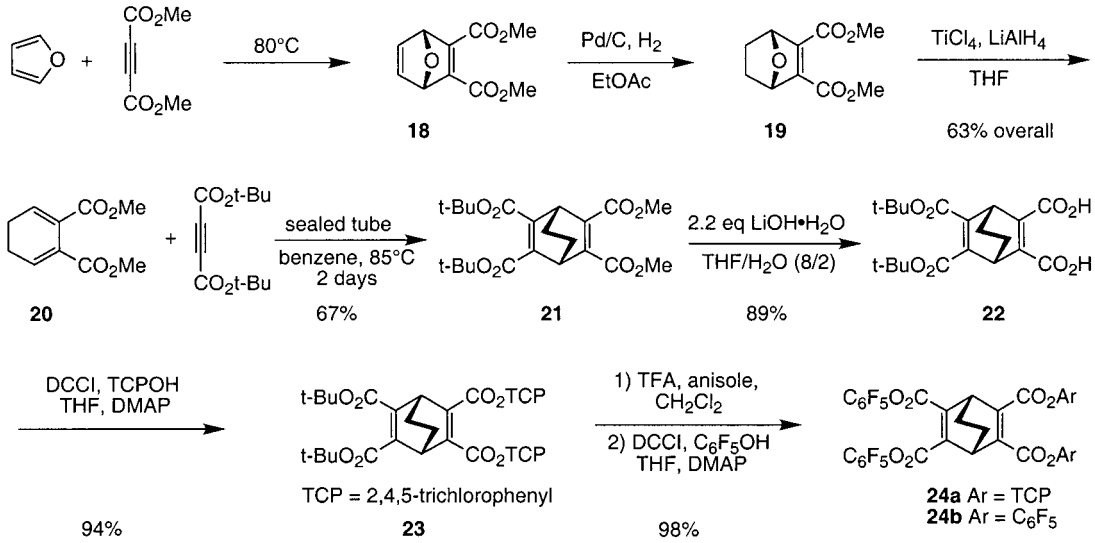
Scheme 3. Synthesis of Spacers through the Protected Method



Scheme 4. Synthesis of the Unsymmetrical Activated Tetraester



difficult to purify. Subsequently, we devised a synthesis of the unsymmetrically substituted activated tetraester **24a**. This started from dimethyl acetylenedicarboxylate (DMAD) and furan, which undergo Diels−Alder cycloaddition. The product **18** was hydrogenated and then deoxygenated with Ti(0) to afford **20** in 63% overall yield.[32] Reaction of diester **20** with commercially available di-*tert*-butyl acetylenedicarboxylate afforded unsymmetrical tetraester **21** after 2 days in 67% yield (based on recovered **20**). Selective saponification of the methyl esters using lithium hydroxide provided diacid diester **22** in 89% yield. Steglich esterification with trichlorophenol gave **23** in 94% yield.[33] Acidic deprotection followed by a second Steglich esterification with pentafluorophenol provided unsymmetrical activated tetraester **24a** in excellent (34%) overall yield.

Deprotection of one of the spacers **1a**−**e** using HCl(g) followed by reaction with 1 equiv of **24a** gave the "half-monomer-diesters" (Scheme 5). The resulting diesters could be further reacted in "one pot" with a different previously deprotected spacer.[26,34] Alternatively, the intermediate could be isolated; this had the advantage of requiring only about half the amount of the second deprotected spacer. Preparation of dihydroxy monomer **31** required an additional step, the demethylation of **28** using $AlCl_3$ in methylene chloride (43% yield).

Characterization of the Dimers. In solvents that are not good guests, that is, chloroform-*d*, methylene chloride-d_2, and *p*-xylene-d_{10}, none of the monomers **26**−**31** gave well-defined dimeric assemblies as revealed by their broadened ^{1}H NMR spectra. In solvents that are good guests such as benzene-d_6 or toluene-d_8 the spectra showed sharp signals and the downfield N−H resonances characteristic of dimeric assemblies (Figure 5).

Encapsulation studies with chiral guests (Chart 1) showed the formation of diastereomeric complexes. Figure 6 shows the ^{1}H NMR spectrum of **g20@26•26**, which is representative of all of the other encapsulation complexes: each diastereomer shows four N−H peaks, and the signals for the guests inside are doubled. The choice of *p*-xylene-d_{10} in the encapsulation studies has to do with its size: one molecule of solvent is generally too small, and two are too big for the cavity. This prevents the formation of stable solvent-filled complexes. In the case of the smallest monomer **25**, one molecule of *p*-xylene-d_{10} is of the appropriate size (vol = 118 Å^3, packing coefficient

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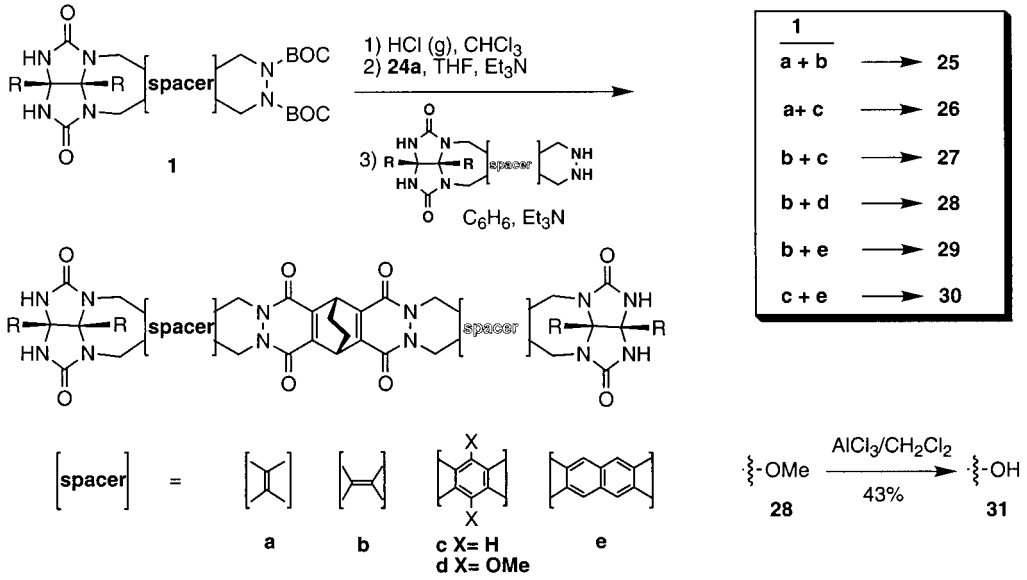
(34) The compounds **25**−**27** and **29**−**31** were obtained together with their corresponding geometrical isomers, which were separated by chromatographic methods. For more details, see: (b) Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 846. (c) Tokunaga, Y.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2656.

Scheme 5. Final Coupling in the Preparation of the Monomers



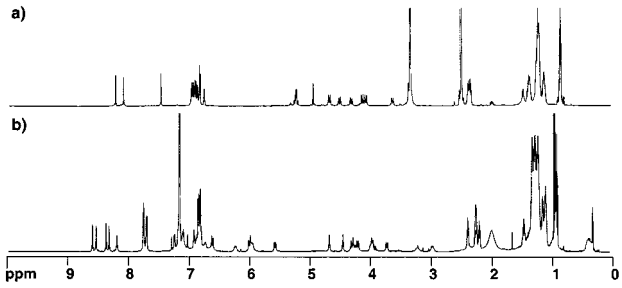


Figure 5. (a) Spectra of **26** in DMSO-d_6 (b) and in benzene-d_6 where it exists as a dimeric capsule.

(PC) = 0.61)[35] and competes very effectively with any added guests. Accordingly, **25** behaved like the other monomers in aromatic solvents, but no encapsulation complexes were observed using *p*-xylene-d_{10} containing a variety of guests of the appropriate size and shape. Encapsulation attempts in chloroform-*d* and methylene chloride-d_2 were also unsuccessful.

The diastereomeric excesses (de's) for complexes **g20@27•27** and **g20@31•31** were measured at various temperatures, and these results are plotted in Figure 7. The following equations can be extracted: for **g20@27•27**, de $= -0.10T + 31$; for **g20@31•31**, de $= -0.54T + 63$. Assuming that both complexes have a linear behavior at all temperatures, **g20@31•31** should reach de = 100% at −68 °C whereas **g20@27•27** reaches the maximum de of 58% only at −273 °C.

Discussion

When the guests themselves are chiral, the assemblies are diastereomeric, and the populations of the two diastereomers will be determined by whatever molecular recognition exists between the space inside the host and the shape and functionality of the guest.The guest structures and their respective volumes are given in Chart 1. Table 1 gives the de's observed and the packing coefficients (PCs) calculated from the guest volumes and the cavity sizes of the various capsules. The latter figures are given in Table 2.

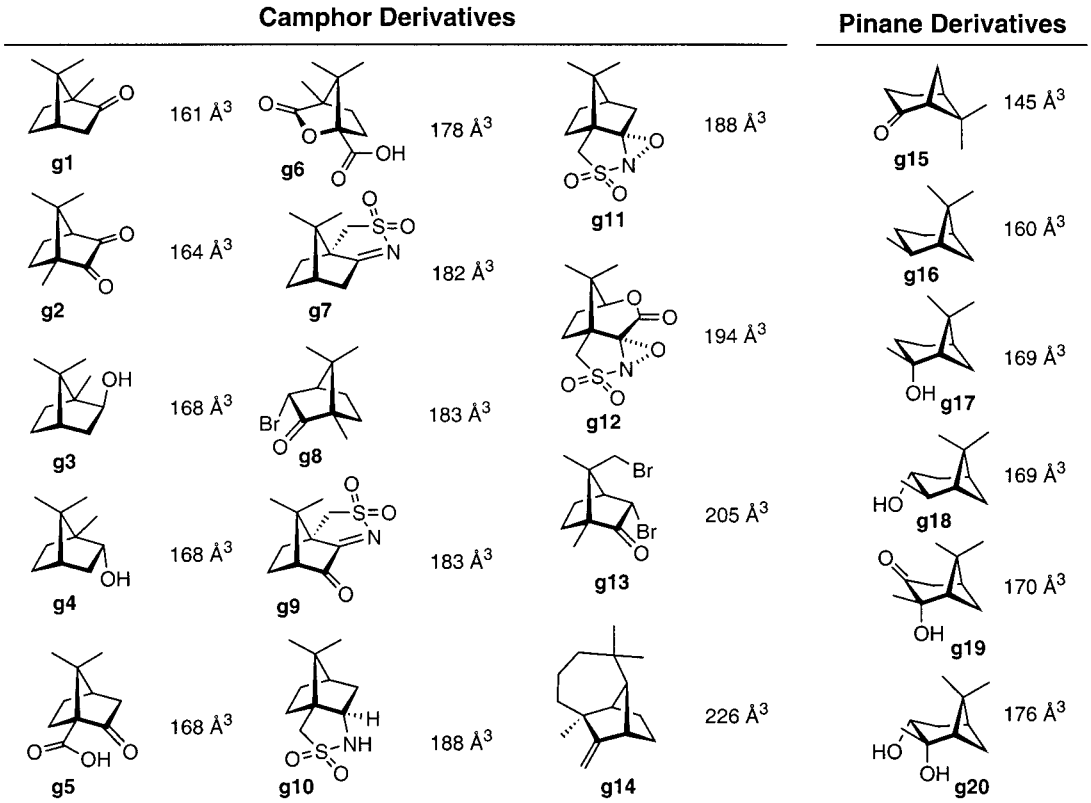
Encapsulation studies for molecules **26**−**27** and **29**−**31** with the chiral guests were intended to yield information regarding the factors governing the diastereoselectivities. Nevertheless, making meaningful comparisons between the selectivities displayed by different capsules is risky business: a change of spacer alters not only the size and shape of the cavity, but also the electronic properties of the lining of the host in contact with the guest (Figure 8a). At the same time, alterations in guest size necessarily come with other functional and stereochemical changes. Only comparisons between minimally perturbed systems are in order, and we limit ourselves to those. For example, comparisons between **26** and **27** are relatively safe: the changes are mainly in the size and shape of the cavities, while the electronics should be very similar. With capsules **26•26** and **27•27** and using pinane derivatives, we see a trend of increasing selectivities as the PC increases, with a maximum selectivity being attained with the largest guest of the series **g20**. Selectivities are also higher with the smaller **26•26** where more contacts between the guest and the inner surface are expected. Pinane **g16** gives an induction of 16%, and an addition of a hydroxyl group at the tertiary carbon (**g17**) *increases* the selectivity by 4%. A hydroxyl group on the neighboring secondary carbon (**g18**) *decreases* the selectivity by 6% instead. Assuming these figures are outside the experimental error, they exemplify the exquisite selectivity that these systems have to offer.

With camphor derivatives of a approximately constant size, the PC range is narrower than with the pinane derivatives described above. Oxidation of the methylene group alpha to the carbonyl (**g2**) in camphor **g1** decreases the selectivity by 5%, but oxidation of the bridgehead methyl to a carboxyl group (**g5**) abolishes all of the selectivity. If the carbonyl group in camphor **g1** is reduced, the selectivity drops regardless of the stereochemistry of the resulting alcohol (**g3**, **g4**).

The hydroxyl groups in **31** were expected to increase the enantioselectivity of a given guest relative to **27**. Our rationale was that increasing the number of hydrogen-bonds from eight to twelve would generate a more rigid (i.e., pre-organized) and stable capsule. The hydroquinone spacer forms an additional four hydrogen bonds when compared to the other capsules. In benzene-d_6 **31** shows sharp ^{1}H NMR signals, and the downfield N−H and O−H resonances are characteristic of dimeric assemblies. There are six signals between δ 8.30 ppm and δ 9.11 ppm, which correspond to the four N−H and two hydroxyl

(35) Packing coefficient or PC is defined as the ratio of the volume of the guest molecule divided by the volume of the empty cavity of the capsule.

Chart 1. Chiral Guests Used in Encapsulation Studies and Their Volumes[41]



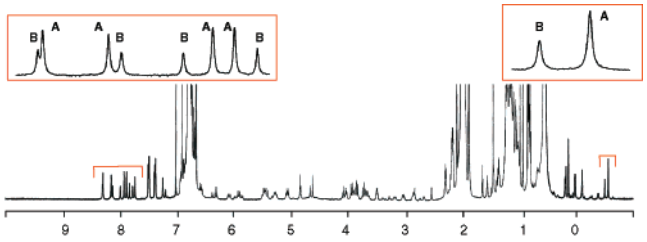


Figure 6. ^{1}H NMR spectrum at 600 MHz in *p*-xylene-d_{10} of **g20@26•26**. The insets show the expanded regions corresponding to the NH groups of the host (left) and one of the methyl groups of the guest inside the cavity (right).

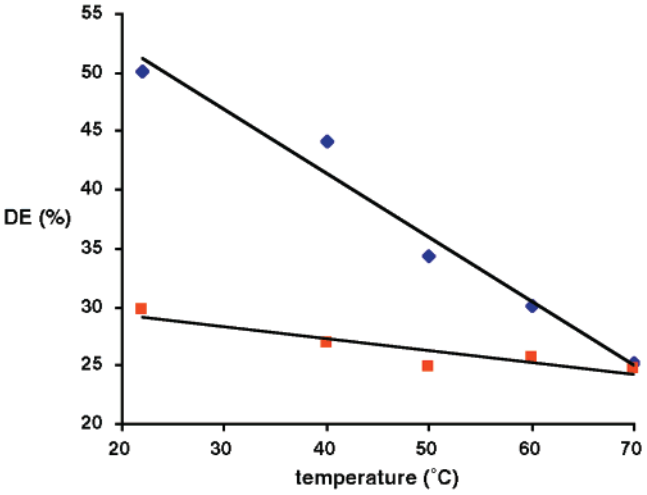


Figure 7. Diastereomeric excess in **g20@27•27** (square) and **g20@31•31** (diamond) as a function of temperature.

groups making hydrogen bonds. The capsules also had an increased kinetic stability: Initially the diastereomeric complexes were in a 1:1 ratio, but reached equilibrium only after a few days.[36] Contrary to our expectations, the selectivities were decreased relative to **27**, at approximately half of its values. The exceptions were **g15** and **g20**. These examples serve to

Table 1. Diastereomeric Excesses for Chiral Softballs as a Function of Different Guests at 295 K[a]

guest	PC	de (%)	guest	PC	de (%)
		g@26·26			
g1 c	0.70	17	**g16** p	0.69	16
g2 c	0.71	12	**g17** p	0.73	20
g3 c	0.73	8	**g18** p	0.73	10
g4 c	0.73	8	**g19** p	0.74	29
g5 c	0.73	0	**g20** p	0.76	35
g15 p	0.63	0			
		g@27·27			
g1 c	0.67	12	**g19** p	0.71	19
g2 c	0.68	6	**g20** p	0.73	32
g15 p	0.60	0			
		g@31·31			
g1 c	0.66	6	**g19** p	0.70	7
g2 c	0.67	3	**g20** p	0.72	50
g15 p	0.59	7			
		g@29·29			
g1 c	0.54	-	**g12** c	0.65	44
g7 c	0.61	34	**g14** c	0.75	-
g8 c	0.61	-	**g15** p	0.48	-
g9 c	0.61	56	**g19** p	0.57	-
g10 c	0.63	0	**g20** p	0.59	-
g11 c	0.63	60			
		g@30·30			
g6 c	0.46	*b*	**g11** c	0.49	0
g7 c	0.47	6	**g12** c	0.50	-
g8 c	0.47	-	**g13** c	0.53	-
g9 c	0.47	-	**g14** c	0.58	36
g10 c	0.49	44	**g20** p	0.45	-

[a] p = pinane derivatives; c = camphor derivatives. The de values have an estimated ± 2% error. PC = vol guest/vol cavity [b] Insoluble in *p*-xylene-d_{10}.

Table 2. Volume Values for the Cavities of Various Chiral Softballs[41]

capsule	cavity vol (Å^3)
25•25	190
26•26	230
27•27	270
31•31	270
29•29	300
30•30	390

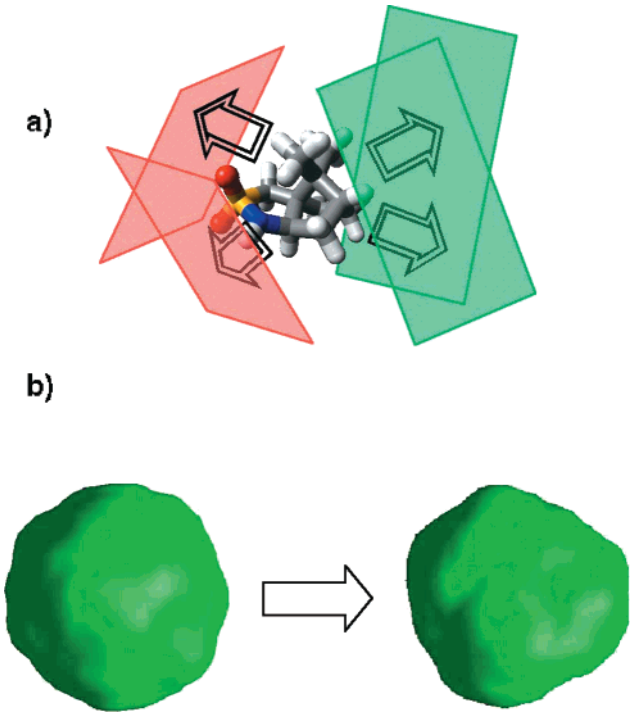


Figure 8. Factors responsible for the diastereoselectivities: (a) *electrostatic*: represented by the arrows between the guest and the interior surface of the cavity including π-surfaces and atoms at the interface of the two monomers; (b) *steric*: distortion of the pseudo-spherical cavity of the original softball (left) generates a dissymmetric space in the chiral softball (**26•26**) (right).

illustrate how subtle factors, perhaps related to electron-rich walls, can alter the recognition processes in ways that remain unpredictable.

With the bigger capsules **29•29** and **30•30**, guests with PCs smaller than 0.58 were not encapsulated (with a few exceptions). Brominated derivatives (**g8** and **g13**) regardless of their PC values were not encapsulated. This may be due to some subtle halogen$-\pi$ repulsion or simply an unforeseen shape mismatch. Some of the trends observed for the smaller capsules (**26•26** and **27•27**) also hold for these bigger systems. Longifolene (**g14**), which has an optimal PC within **30•30**, gives an induction of 34%, whereas the same guest in **29•29** is not encapsulated due to its large PC value (0.75). Camphor sulfonyl derivatives (**g7** and **g9**−**g12**) were good guests for **29•29**, presumably because of the good values for their PCs (0.60−0.65). The selectivities with these guests were also good with the exception of **g10**, which had none. Apparently, the presence of the N−H group causes loss in selectivity: **g7** in which the N−H group is oxidized as an imine shows 34% de. In the bigger capsule **30•30,** the **g10** gives an induction of 44%, despite the fact of having a relatively low PC (0.49). On the other hand **g7** gives only 6% de which is about one-sixth the value the same guest has in **29•29**. The reasons for these results are unclear, and molecular modeling has offered little help. The interactions

Table 3. Thermodynamic Data for Selected Complexes[a]

guest	K'_A (M^{-1})	$-\Delta G°_A$ (kcal mol^{-1})	K'_B (M^{-1})	$-\Delta G°_B$ (kcal mol^{-1})
		g@26•26		
g1	420	3.5	300	3.3
g2	310	3.4	250	3.2
g15	290	3.3	270	3.3
g19	300	3.4	170	3.0
g20	390	3.5	190	3.1
		g@27•27		
g1	1100	4.1	870	4.0
g2	960	4.0	850	4.0
g15	630	3.8	620	3.8
g19	1200	4.1	800	3.9
g20	810	3.9	420	3.5

[a] Abbreviations: K′, apparent association constants; $-\Delta G°$, free energies of formation in *p*-xylene-d_{10} at 295 K.

between the guest and a phenyl ring or a double bond of the host should be different, but the electronic environments in the cavities are of greater effect than expected.

Table 3 summarizes some thermodynamic parameters for selected guests in **26•26** and **27•27**. The more rigid (i.e., preorganized)[37] capsule **27•27** shows binding constants consistently higher than **26•26**, an average 0.6 kcal mol^{-1} for the predominant diastereomers (A) and 0.7 kcal mol^{-1} for the subordinate diastereomers (B). In other words, the degree of selectivity has no clear correlation with the magnitude of the binding constant. For example, **g20** has a binding constant for **27•27** which is 0.2 kcal mol^{-1} lower than **g1,** but the selectivity is almost three times higher. The relative stabilities of the diastereomeric complexes are independent of the absolute value of the binding constant. [38]

Factors Controlling Enantioselectivities. Like most chemical phenomena, electrostatics and sterics are the key factors controlling the selectivities in the chiral softballs (Figure 8). The predominant surface feature of the cavities is the number of π bonds, and that of the guests is the CH groups. Accordingly, CH/π interactions should be a determinant for enantioselectivity. The enthalpic contribution of a single CH/π interaction is small, but these interactions usually occur simultaneously in multiple groups.[39] The presence of guest functional groups capable of hydrogen-bonding to the host are important for affinity as well as for selectivity. In particular, guests that offer a specific array of hydrogen-bonding sites to interact with the seam of hydrogen bonds that hold the host together are preferred. For example, a molecular dynamics simulation[40,41] of **g20@26•26** shows the formation of a hydrogen bond network between the two hydroxyl groups of the guest and the carbonyls of the host. The hydrogen bonds between the host and the encapsulated guest are formed in a reversible way: due to the dynamics of the complex, they constantly slide along the interior surface by use of different donor/acceptor groups on the host. The encapsulation of a specific guest is therefore dependent on the nature of the intermolecular forces engaged in the binding process.

In the steric factors category, the PCs and the shape of the host are important as well for affinity and for selectivity. We have shown previously that molecules with the right shape are bound more strongly when their volumes are around 55% of the cavity volume.[40] These cavities are globular in nature; therefore, it is expected that guests with a spherical shape are

(36) For a detailed account on this behavior see: Rivera, J. M.; Craig, S. L.; Martín, T.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 2130.

(37) **27•27** is more rigid due to the fact that one spacer is composed of five- and six-membered rings compared to the corresponding spacer in **26•26** which is composed of six- and seven-membered rings, respectively.

bound more strongly than linear or planar molecules. Selectivities increase as we maximize the contacts between the host and the guest (Figure 8a). Intuitively, the greatest selectivity is expected for guests of the right size that share the C_2 symmetry of the hosts, because they should be able to make extensive surface contacts with the lining of the cavity. At the same time, contacts reduce the translation and rotation of the guest within the host and incur an entropic penalty. For the moment, it appears that the host capsules are flexible enough to arrange comfortably around a guest but still maintain enough rigidity to be formed preferentially in the presence of a chiral guest.[41,42]

Variable-temperature (VT) experiments in which de values were measured at 10 °C intervals from 20 to 70 °C, showed that **31•31** is more susceptible to temperature changes (i.e., higher absolute value for the slope). These results are consistent with an enthalpically driven process and may reflect the four additional hydrogen bonds of **31•31** versus **27•27**. This feature in **31•31** also causes the system to reach host/guest equilibrium slowly ($t_{1/2} \approx 20$ h at 22 °C). In contrast, the other chiral softballs reach equilibria within minutes.

Conclusions

The premise—that completely surrounding a molecule is the ultimate in molecular and enantioselective recognition—is far from established here. The diastereomeric excesses evinced by these capsules are unimpressive by the standards of modern organic synthesis, under which <95% de is considered unacceptable (or worse, unpublishable). But by the standards of host−guest chemistry the accomplishments of this study (de's up to 60%) are good. Can these positions be reconciled? Probably. One *rapprochement* uses distances: The irreversible, product-determining transition states in covalent syntheses involve intermolecular distances on the order of 2 Å or less; the corresponding distances for the events of molecular recognition using weak intermolecular forces are at least 2.5 Å (that is why they are weak). The energetic gradient for steric effects along this change in distance is likely to be large. But the reader may well ask about the exquisite selectivity of enzymes and antibodies: they, too, use intermolecular forces. They do, indeed, but enjoy the benefits of evolution; the cycles of the genetic algorithm. These capsules are not evolved, although recent experiments with other encapsulation complexes show that diversity and selection can be made to work with them.[43] All that is needed is amplification and mutation—no mean feat as they have molecular replication as a requirement. For the moment, the present studies have shown that the stereochemistry of the host capsules can respond to guest shape. The principles of molecular recognition govern which cavities are assembled in the presence of the guest species,but the specific interactions that define the details remain unknown.

Supporting Information Available: Experimental procedures and characterization for all new compounds reported in this paper (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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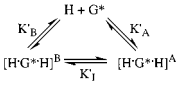
(38) All measurements were obtained by ^{1}H NMR experiments using the integrals for the peaks of the guest inside and outside the capsules. There is an estimated 10% error in these measurements. The equilibrium may be described as follows:



The following assumptions were made: (i) the amount of dimer (unfilled or filled with solvent) present before addition of the guest is negligible, (ii) after addition of the guest, all of the host material not assembled into the capsule is in the aggregate state, and (iii) the association of the guest with itself is negligible.

$$K'_{\mathrm{A}} = \frac{[\mathrm{H{\cdot}G^*{\cdot}H}]^{\mathrm{A}}}{[\mathrm{H}][\mathrm{G}^*]} = \frac{aV}{[h - 2(a+b)][g - (a+b)]} \quad (1)$$

$$K'_{\mathrm{B}} = \frac{[\mathrm{H{\cdot}G^*{\cdot}H}]^{\mathrm{B}}}{[\mathrm{H}][\mathrm{G}^*]} = \frac{aV}{[h - 2(a+b)][g - (a+b)]} \quad (2)$$

$$K'_{\mathrm{I}} = \frac{[\mathrm{H{\cdot}G^*{\cdot}H}]^{\mathrm{A}}}{[\mathrm{H{\cdot}G^*{\cdot}H}]^{\mathrm{B}}} = \frac{K'_{\mathrm{A}}}{K'_{\mathrm{B}}} \quad (3)$$

$$\Delta(\Delta G^\circ) = -RT \ln K'_{\mathrm{I}} \quad (4)$$

$$a = g\,(I_{\mathrm{gA}}/I_{\mathrm{gT}}) \quad (5)$$

$$b = g\,(I_{\mathrm{gB}}/I_{\mathrm{gT}}) \quad (6)$$

$$I_{\mathrm{gT}} = I_{\mathrm{gO}} + I_{\mathrm{gA}} + I_{\mathrm{gB}} \quad (7)$$

Where K'_{A} and K'_{B} are the apparent association constants for the predominant and the subordinate complexes respectively and K'_{I} is the apparent isomerization constant between the two complexes. In these equations H is the host, G* is the chiral guest, $[\mathrm{H{\cdot}G^*{\cdot}H}]^{\mathrm{A}}$ and $[\mathrm{H{\cdot}G^*{\cdot}H}]^{\mathrm{B}}$ are the concentrations of the predominant and the subordinate complexes respectively, I_{gO} is the integral for the signal of the guest outside the capsule, I_{gA} is the integral for the signal of the guest in complex A, I_{gB} is the integral for the signal of the guest in complex B, h is the initial amount of monomer (in mmol), g is the amount (in mmol) of guest added to the solution, a is the amount of guest (in mmol) in complex A, b is the amount of guest (in mmol) in complex B, and V is the total volume (in mL).

(39) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.

(40) Mecozzi, J. Rebek, Jr., *Chem. Eur. J.* **1998**, *4*, 1016.

(41) Molecular modeling of assemblies and guests 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. Cavity volumes of minimized structures were calculated with the GRASP program: Nicholls, A.; Sharp, K. A.; Honig, B. *Proteins* **1991**, *11*, 281.

(42) For a recent account on the identification of which chiral cavity is responsible for the recognition of a given guest through the synthesis of a kinetically stable optically pure capsule see: Rivera, J. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 7811.

(43) Hof, F.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4251.