Transfer of Chiral Information through Molecular Assembly

Ronald K. Castellano,[†,§] Colin Nuckolls,[†] and Julius Rebek, Jr.*[,†]

Contribution from The Skaggs Institute for Chemical Biology and the Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, and the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Abstract: Calix[4]arenes substituted with ureas on their upper, wider rims form dimers in solution held together by a seam of 16 hydrogen bonds. The resulting molecular capsules have interiors capable of accommodating small-molecule guests. By virtue of the assembly process, a head-to-tail arrangement of ureas is formed that can assume either a clockwise or counterclockwise orientation around the equator of the capsule. Amino acids on the urea functions have a dramatic effect on the dimerization behavior of the calixarenes. First, the chiral derivatives display a preference for associating with calixarenes substituted with arylureas rather than with themselves. This selectivity for heterodimerization is *exclusive* with amino acids that have β-branched side chains such as isoleucine and valine. Second, the point chirality of the amino acids is transferred upon assembly giving rise to a chiral capsule with only *one* direction to its head-to-tail arrangement of ureas. Circular dichroic spectroscopy is used to assign the absolute configuration of these capsules. The chirality of the capsule can be sensed by chiral guests where enantioselective binding is observed.

Calix[4]arenes functionalized with ureas on their wider rims have self-complementary recognition sites and assemble into dimeric structures (Figure 1).[1,2] A "tongue-in-groove" hydrogen bonding pattern is formed between two identical pieces producing a capsule that is S_8-symmetric and achiral (Figure 2a).[1] When the capsule is assembled from two different halves, a chiral, C_4-symmetric heterodimer results. The head-to-tail urea directionality of its hydrogen bonding seam defines enantiomers (Figure 2b).[3] Equal populations of both clockwise (CW) and counterclockwise (CCW) species exist as there are no energetic differences between them. Such is the case for molecules **1** and **2** (Figure 3), which preferentially form heterodimeric pairs in solution.[4] This exclusive recognition has been used to engineer discrete, multicomponent assemblies of nanometer dimension and informational polymers.[4b]

Stereocenters near the ureas serve to introduce a second chirality element, beyond the urea directionality, and diastereomeric complexes are generated. Just as with conventional diastereomers, the energies and populations of these assemblies are not expected to be equal. Herein, we report molecules that not only heterodimerize with exclusivity but also have a single-handed direction to their urea rotation. The resulting capsules are nonracemic and capable of discriminating between enantiomers of guest molecules. This work builds on the previous observation that calixarene tetraureas derived from L-norleucine, **3**,[4a] gave 50−90%[5] selectivity for forming heterodimers with **1**.[6] Within these heterodimers the urea rotation appeared to be solely in one direction—the peripheral chirality was transferred to the capsule lining.[7] Moreover, chiral guests were shown to

* Address correspondence to this author at The Scripps Research Institute.
† The Scripps Research Institute.
§ Massachusetts Institute of Technology.

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(3) Formally 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.

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(5) Heterodimerization propensity was found to be solvent-dependent.

(6) Statistically, 1:1 combination of homodimers AA and BB gives heterodimers AB and BA, equivalent species, as 50% of the mixture. See ref 2a for details.

(7) Remote chirality can direct molecular assembly. In hydrogen-bonded assemblies: (a) Prins, L. J.; Huskens, J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498−502. (b) Russell, K. C.; Lehn, J.-M.; Kyritsakas, N.; DeCian, A.; Fischer, J. *New J. Chem.* **1998**, 123−128. (c) Simanek, E. E.; Qiao, S.; Choi, I. S.; Whitesides, G. M. *J. Org. Chem.* **1997**, *62*, 2619−2621. In polymeric systems and liquid crystals: (d) Yashima, E.; Maeda, K.; Okamoto, Y. *Nature* **1999**, *399*, 449−451. (e) Langeveld-Voss, B. M. W.; Waterval, R. J. M.; Janssen, R. A. J.; Meijer, E. W. *Macromolecules* **1999**, *32*, 227−230. (f) Engelkamp, H.; Middelbeek, S.; Nolte, R. J. M. *Science* **1999**, *284*, 785−788. (g) Schlitzer, D. S.; Novak, B. M. *J. Am. Chem. Soc.* **1998**, *120*, 2196−2197. (h) Rowan, A. E.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 63−68 and references therein. (i) Sommerdijk, N. A. J. M.; Buynsters, P. J. J. A.; Akdemir, H.; Geurts, D. G.; Pistorius, A. M. A.; Feiters, M. C.; Nolte, R. J. M.; Zwanenburg, B. *Chem. Eur. J.* **1998**, *4*, 127−136. (j) Green, M. M.; Zanella, S.; Gu, H.; Sato, T.; Gottarelli, G.; Jha, S. K.; Spada, G. P.; Schoevaars, A. M.; Feringa, B.; Teramoto, A. *J. Am. Chem. Soc.* **1998**, *120*, 9810−9817. (k) Mayer, S.; Maxein, G.; Zentel, R. *Macromolecules* **1998**, *31*, 8522−8525. (l) Gu, H.; Nakamura, Y.; Sato, T.; Teramoto, A.; Green, M. M.; Jha, S. K.; Andreola, C.; Reidy, M. P. *Macromolecules* **1998**, *31*, 6362−6368. (m) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6345−6359. (n) Palmans, A. R. A.; Vekemans, J. A. J. M.; Havinga, E. E.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2648−2651. (o) Green, M. M.; Peterson, N. C.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S. *Science* **1995**, *268*, 1860−1866 and references therein. (p) Gulik-Krzywicki, T.; Fouquey, C.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 163−167. (q) Fouquey, C.; Lehn, J.-M.; Levelut, A.-M. *Adv. Mater.* **1990**, *2*, 254−257.

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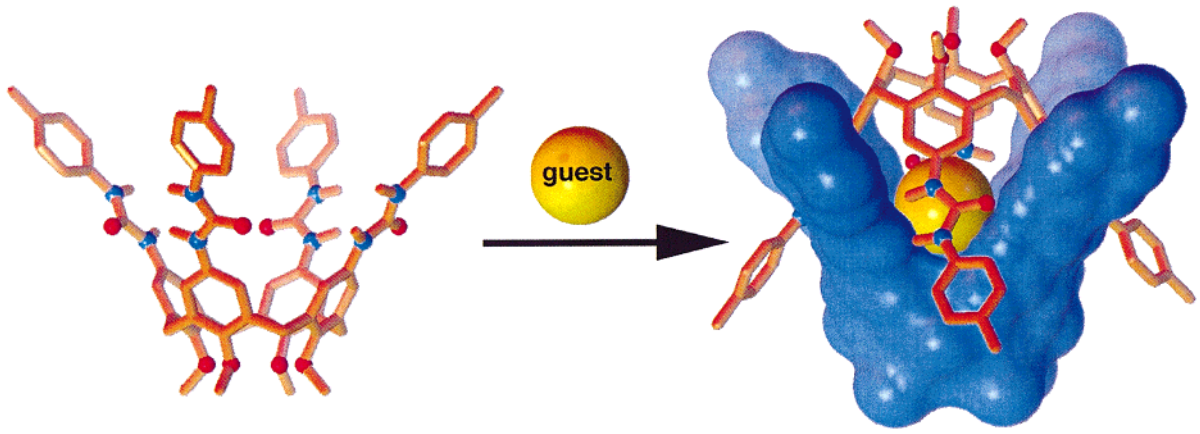

Figure 1. Calix[4]arenes with arylureas on their wider rims dimerize in solution in the presence of a small-molecule guest. The assembly features a head-to-tail arrangement of ureas which form up to 16 intermolecular hydrogen bonds.

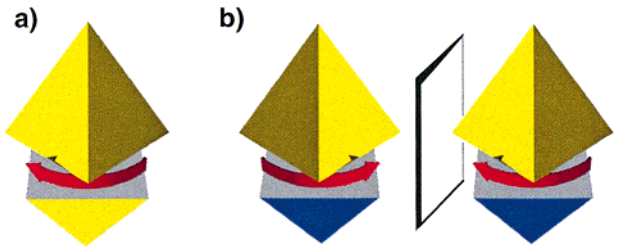

Figure 2. Pictorial representations of dimer symmetry. (a) Homodimeric calixarenes are *achiral* and S_8-symmetric. (b) Heterodimeric capsules are *chiral* and C_4-symmetric—the head-to-tail directionality of the ureas (red arrow) defines the chirality.

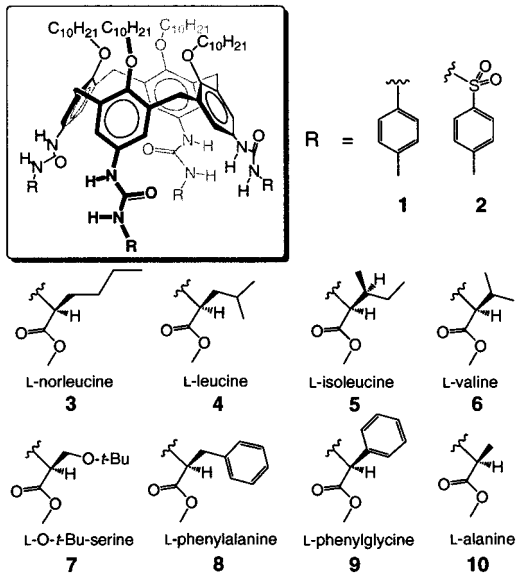

Figure 3. Of the calixarene tetraureas prepared, **5** and **6**, derived from β-branched amino acids, exclusively form heterodimers when combined with arylurea **1**.

be sensitive to the asymmetric microenvironment within the capsule, where their enantiomers were distinguishable by NMR.

Results and Discussion

Preparation of Calixarene Tetraureas and Self-Assembly. Optically active tetraureas **3**−**10** (Figure 3) were prepared through reaction of the known tetraamine[8] with the appropriate isocyanates derived from amino acid methyl esters.[9] The aliphatic substituents on these tetraurea calixarenes impart them with good solubility in many chlorinated and aromatic solvents. Also presumably due to the long alkyl chains, these compounds have not provided crystals of high enough quality for X-ray diffraction. However, a crystal structure of a calixarene tetraurea functionalized with esters on its lower rim has been been reported by Böhmer and co-workers.[2b]

The ^{1}H NMR spectra of **3**−**10** are sharp in DMF-d_7 and show four equivalent ureas in each case.[10] However, they are less well-behaved in solvents that typically promote assembly into discrete dimeric structures. For example, in $CDCl_3$, broad, uninterpretable NMR spectra result, indicative of nonspecific aggregation. The same is true in C_6D_6, with the exception of isoleucine-derived **5** and valine-derived **6**. Here the spectra are fairly sharp and reveal the symmetry that arises from homodimerization of two chiral monomers. While the chiral centers of each half of these homodimers are the same they must have their ureas rotated 180° with respect to one another to accommodate self-assembly. The top and bottom halves of the homodimer are no longer equivalent resulting in the same C_4 symmetry as observed for heterodimers from achiral components, such as in the union of **1** and **2**. This is shown in the energy-minimized molecular model[11] of dimer **6**·**6** (Figure 4). The ^{1}H NMR spectrum of these homodimeric assemblies (vide infra) shows a total of four urea −NH proton singlets and four calixarene aryl doublets (two from each half). Additionally, two distinct $-CH_3$ singlets appear for the methyl esters, separated by ~0.3 ppm.

Selective Heterodimerization. The preferential heterodimerization of **1** and **2** allows for the *predictable* formation of large assemblies.[4b] Combination of *chiral* calixarene tetraureas with **1** could, in theory, provide both exclusive *and* diastereoselective heterodimer formation, representing the next level of programmed information. Calixarenes **3**−**10** were combined both with arylurea **1** and sulfonylurea **2**, 1:1, in both $CDCl_3$ and C_6D_6, and the heterodimerization process was monitored in terms of the degree of assembly and diastereoselectivity. Remarkably,

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(9) Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364−7366.

(10) For calix[4]arenes functionalized with L-alanine units on their upper rims with similar symmetry, see: Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897−905.

(11) Modeling was performed using MacroModel 6.5 and the MMFF force-field: Mohamadi, F.; Richards, N. G. J.; Guidia, W. C.; Liskamp, R.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

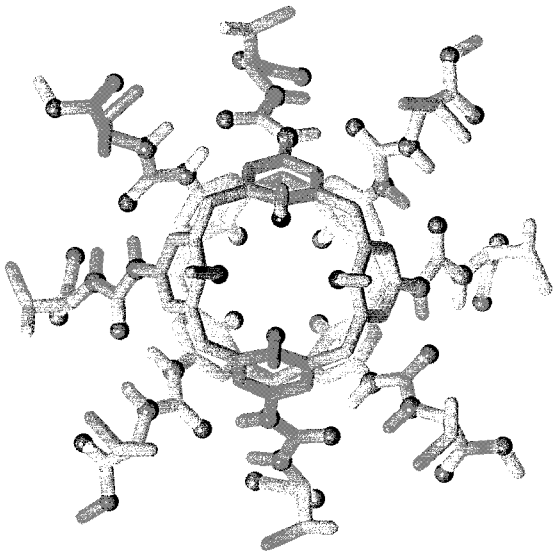

Figure 4. Homodimers of chiral tetraureas are C_4-symmetric. As shown for assembly **6·6**, the top and bottom halves of the capsule are different, related by a 180° torsion about the urea−calixarene bond. Alkyl chains have been omitted for clarity.

Table 1. Percentage of Heterodimer Formed upon Combination of Arylurea **1** and Amino Acid Derivatives **3**−**10**[a]

Mixture	Amino Acid Residue	$CDCl_3$	C_6D_6
1+3		50%[b]	90%
1+4		50%[b]	90%
1+5		90%[b]	100%
1+6		>90%[b]	100%
1+7	O-*t*-Bu	25%	75%[b]
1+8		<10%	73%
1+9		43%[c]	90%[d]
1+10	CH_3	<10%[e]	50%[f]

[a] Unless otherwise specified the percentages shown reflect formation of one of two possible heterodimers. Percentages vary ±5%. [b] <5% non-specific aggregation. [c] 6.4:1 ratio of heterodimers. [d] 1.9:1 ratio of heterodimers. [e] Broad spectrum. [f] 3.4:1 ratio of heterodimers.

in the cases explored here *no* heterodimerization could be observed between the amino acid derived ureas and **2**.[12] This is in contrast to heterodimerization of **3**−**10** with **1**, the results of which are summarized in Table 1. In all cases heterodimerization occurs and three observations are noteworthy. First, for all but two mixtures, only *one* of two possible diastereomeric heterodimers, CW−S or CCW−S,[13] is formed. Second, the heterodimerization of isoleucine-derived **5** and valine-derived **6**, when either is combined with **1**, is *exclusive* in C_6D_6. Finally,

(12) Compounds **3**−**10** do, however, show at best statistical heterodimerization with the enantiomers of **5** and **6**, derived from D-isoleucine and D-valine, respectively.

(13) CW and CCW refer to the head-to-tail urea directionality when viewed from the narrow rim of the arylurea **1** in the heterodimer. R or S refers to the absolute stereochemistry of the amino acid side chains.

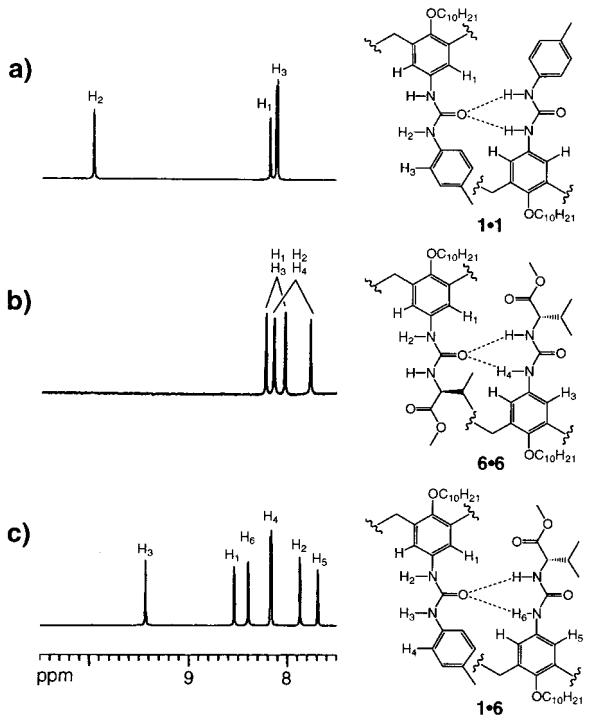

Figure 5. Downfield region of the ^{1}H NMR spectrum (C_6D_6, ~1 mM, 600 MHz) from (a) the **1·1** homodimer, (b) the **6·6** homodimer, and (c) the exclusively formed **1·6** heterodimer.

for all cases changing solvents from chloroform to benzene causes an increase in the heterodimerization propensity.

The origins of these selectivities can be probed by examining the two best cases, **1·5** and **1·6**. Evidence for exclusive and stereoselective heterodimerization comes from NMR and circular dichroism (CD) experiments. Figure 5c shows a portion of the proton spectrum that arises upon combination of calixarenes derivatized with valine ureas, **6**, and arylureas, **1**, at ~1 mM in C_6D_6. Clearly none of the downfield resonances in the spectrum originate from either the arylurea homodimer (Figure 5a) or the valine urea homodimer (Figure 5b). Moreover, only one resonance for the methyl ester can be observed upfield (not shown). Figure 6 shows energy-minimized[11] structures of the two possible complexes of **1·6**, CW−S (a) and CCW−S (b). Although an assignment cannot be made as to which diastereomeric complex is formed, the relative positioning of the chiral substituents is quite different in each case. For the **1·10** mixture, for example, two heterodimers are easily discernible by ^{1}H NMR, as shown in the partial spectrum in Figure 7.

The nature of the interaction governing this remarkable selectivity can be probed through ROESY spectroscopy of dimer **1·6** in C_6D_6. The most revealing contacts are those between the amino acid substituent of **6** with **1**, some of which are predicted by the modeling shown in Figure 6. NOEs appear for the α proton of the chiral urea, H_5 (4.6 ppm), with the entire hydrogen bonding face of **1**, including the tolyl group (Figure 8). Additionally, the geminal methyl groups of the valine urea interact with the tolyl group, and modeling confirms that they are within 3−4 Å, adequate distances for favorable interactions between them.[14] NOE contacts are also observed between the downfield urea −NH of **1**, H_9 (9.4 ppm), and *one* aryl proton of **6**, H_2 (7.7 ppm). Likewise, the tolyl group of **1** is within

(14) Possibly observed here, CH/π interactions can significantly influence molecular conformation: Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047−10056 and references therein.

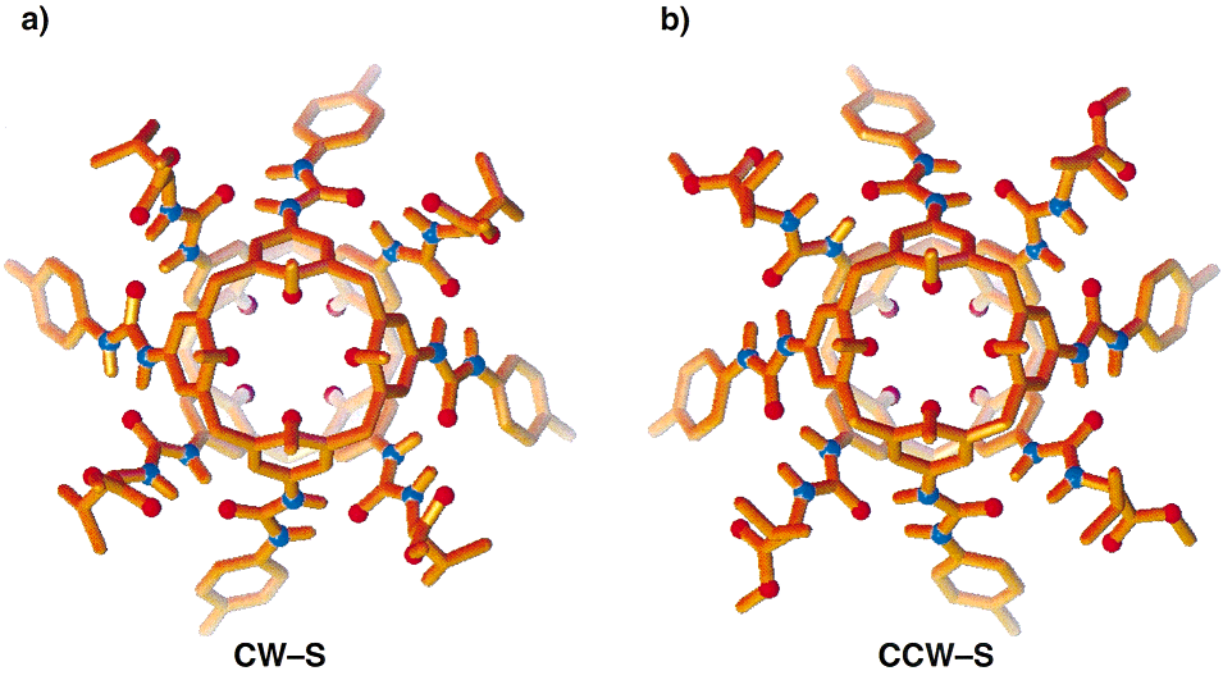

Figure 6. Energy-minimized structures[11] depicting the two possible diastereomers that result from hetereodimerization of **1** and **6**. Clockwise (CW) and counterclockwise (CCW) refer to the urea directionality as viewed from the narrow rim of the arylurea, and S refers to the absolute stereochemistry of the chiral side chains. Alkyl chains have been omitted for clarity.

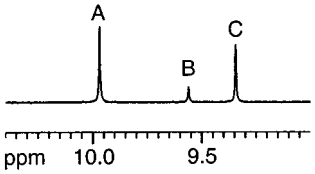

Figure 7. Downfield −NH region of the ^{1}H NMR spectrum (C_6D_6, ~1 mM, 600 MHz) that results from equimolar amounts of **1** and **10**. Resonance A arises from the **1·1** homodimer, and resonances B and C represent the two diastereomers of **1·10**.

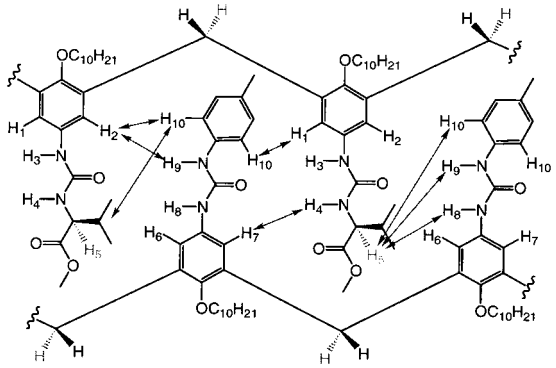

Figure 8. Arrows indicate important NOE contacts from a ROESY spectrum (600 MHz) of the **1·6** heterodimer (C_6D_6, ~1 mM).

communication distance of both aryl protons of **6**, H_1 (6.4 ppm) and H_2, as it is positioned between them. Finally, the upfield urea −NH of **6** (H_4, 7.2 ppm), which is appropriately split into a doublet in the spectrum, is within close proximity to *one* of the aryl protons of **1**, H_7 (8.5 ppm). These contacts speak to a fixed orientation of the ureas in the heterodimer and identify the chiral elements of the amino acid ureas as important contributors to the observed selectivity.

Not surprisingly, the weak interactions from which the selectivity originates are sensitive to subtle changes in structure and medium—the systems discussed here are highly cooperative. On the basis of the results shown in Table 1 and the ROESY data, β-branched amino acid derivatives **5** and **6** experience favorable contacts in the heterodimeric state to form exclusively one diastereomeric assembly. When β-branching is removed in norleucine urea **3** and leucine urea **4**, the selectivity falls from exclusive heterodimerization to 90% in C_6D_6. This decrease in heterodimerization preference appears to correspond with loss of contact between the β-branch substituents and the arylureas of **1**. Phenylalanine **8** and *tert*-butylated serine **7** provide even less regioselectivity as the alkyl chains of **5** and **6** are now replaced by substituted methylenes. There is a lack of substituents to offer significant contacts with the arylurea upon assembly. In all cases diastereoselectivity is maintained.

Phenylglycine-derived calixarene **9** and alanine-derived **10** give mixed results. Both of these compounds suffer from poor diastereoselectivity. Alanine does not have any substitution that would favor more than statistical heterodimerization and the side chains of **9** may be too rigid to adopt a comfortable conformation in the heterodimer. At this point, the interactions that determine the stereoselectivity in these assemblies remain largely unclear, but their sensitivity to both solvent and temperature[15] suggest that they are weak and highly cooperative.

The discrepancy between $CDCl_3$ and C_6D_6 in promoting heterodimer formation speaks to the fragility of these systems and the weak forces that hold them together. Modeling[11] indicates that the volume of the heterodimeric cavity is smaller (~20 Å^3) than that of the homodimer, and so certainly, the size and fit of the solvent/guest in each of these cavities plays a role in determining which capsule emerges. It also appears that polarity differences between the two solvents result in significant selectivity differences—more polar solvents apparently begin to disrupt the sensitive noncovalent interactions between the arylurea **1** and the chiral side chains of amino acids.

(15) Variable-temperature ^{1}H NMR studies were performed on assembly **1·10** in C_6D_6. Upon heating from 295 to 345 K the heterodimer concentration decreases by 20%, and assembly is driven to the homodimeric states, in agreement with entropic arguments, while the selectivity remains essentially unchanged. See the Supporting Information for details.

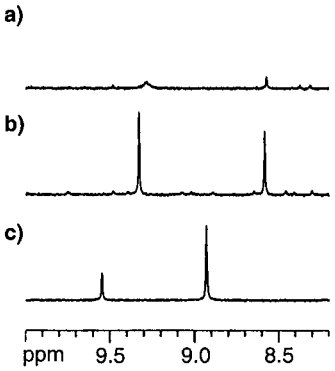

Figure 9. ^{1}H NMR (~1 mM, 600 MHz) shows an increasing heterodimerization propensity as the solvent is changed from (a) CD_2Cl_2 ($\epsilon = 8.9$) to (b) $CDCl_3$ ($\epsilon = 4.7$) to (c) CCl_4 ($\epsilon = 2.2$) for an equimolar mixture of **1** and **4**. The furthest downfield −NH peak arises from the **1·1** homodimer, and the upfield −NH peak represents one diastereomer of the **1·4** heterodimer.

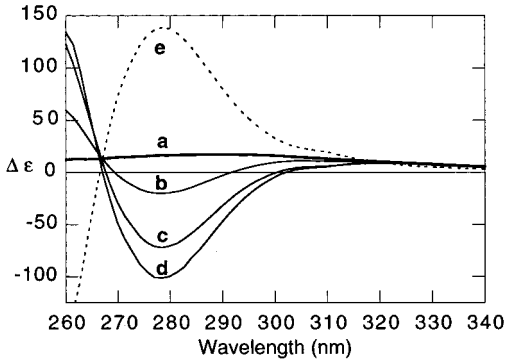

Figure 10. CD spectra of **5** in $CHCl_3$ ($c = 1.2 \times 10^{-4}$ M, $l = 1$ mm) as an increasing amount of **1** is added: (a) 0 equiv of **1**, (b) 0.2 equiv of **1**, (c) 0.5 equiv of **1**, and (d) 1 equiv of **1**. (e) CD spectrum of the enantiomer of **5** (D-isoleucine ureas) with an equimolar amount of **1** ($CHCl_3$, $c = 1.2 \times 10^{-4}$ M, $l = 1$ mm).

This is supported experimentally by mixing equimolar amounts of **1** and **4** in three solvents of decreasing dielectric constant (Figure 9a−c). In CD_2Cl_2 ($\epsilon = 8.9$,[16] Figure 9a), a solvent known to discourage dimerization of calixarene tetraureas,[2] the spectrum is broad, and no significant assembly is detected. In $CDCl_3$ ($\epsilon = 4.7$, Figure 9b), the resonances are sharp, although assembly is only ~40% selective for heterodimerization and not completely stereoselective. Finally, in CCl_4 ($\epsilon = 2.2$, Figure 9c), preferential and stereoselective heterodimerization is observed, 90 and 100%, respectively, similar to that found in C_6D_6 ($\epsilon = 2.3$, Table 1).

Unlike the previously observed heterodimerization between **1** and **2** based around the acidity of the sulfonylureas, the pK_a of the amino acid-derived ureas is only one factor in this heterodimerization process. Compounds **3**−**10** are similarly functionalized[17] and have similar acidities, but their heterodimerization percentages vary greatly. Morever, arylureas and alkylureas (e.g. octylurea) form heterodimers in near statistical ratios.[2a] The side chains of the amino acids are providing vital contacts in the dimeric assembly and are responsible for instructing the molecules to rotate their ureas unidirectionally.

Absolute Stereochemistry. CD spectroscopy is used to determine the single-handedness of the **1·5** heterodimeric assembly.[3b,7,18] Chiral compound **5** alone in chloroform (Figure 10a) shows a weak CD maximum ($\Delta\epsilon < 10$) at the same wavelength as its UV maximum, 260 nm. There is no chirality transferred from the amino acid side chain to the calixarene chromophore, thus a weak CD signal is observed. Titration of *achiral* **1** into the solution of **5** induces a large, bisignate CD response ($\Delta\epsilon \sim -100$ at the endpoint). The signal continues to increase as **1** is added to **5** (Figure 10b−d) until the latter is saturated, at about 1 equiv of **1**.

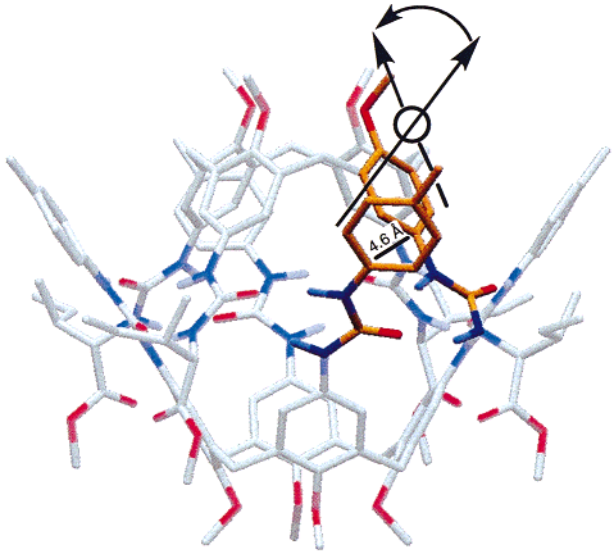

Figure 11. An energy-minimized structure[11] showing the absolute configuration of the heterodimer **1·5** whose dipoles (arrows) give rise to the exciton-coupled CD spectrum.

Molecular modeling suggests that this CD response arises from coupling between the dipoles of **1**'s tolyl groups and the calixarene rings of **5**, as depicted in Figure 11. In only one of the two diastereomers is this arrangement possible. When the heterodimer is viewed from the side, the dipole axis of the tolyl group is rotated to the right relative to the dipole axis of the aromatic ring of the amino acid-derived calixarene—a left-handed twist. In other words, when the assembly is viewed from the arylurea pole, the ureas rotate clockwise giving rise to the absolute stereochemistry shown in Figure 6a (CW−S). That these signals arise from the dimerization of the desired assemblies is further confirmed through titration of the **1·5** solution with methanol, a hydrogen bond disrupter. The results are self-evident as shown in Figure 12a−d. The CD signal diminishes until, ultimately, at ~4% methanol (v/v) in chloroform, essentially no CD activity is observed as the species are monomeric.[19] The enantiomeric assembly of **1·5**, derived from D-valine and prepared analogously, offers a CD curve of opposite sign and roughly equal intensity (Figure 10e).

(16) Leonard, J.; Lygo, B.; Proctor, G. *Advanced Practical Organic Chemistry*, 2nd ed.; Chapman & Hall: New York, 1995; p 277.

(17) The chemical shift of the proximal −NH of **3**−**10** in DMF-d_7 varies from 8.56 ppm for **7** to 8.23 ppm for **10**. The distal −NH shifts from 6.90 ppm in **9** to 6.24 ppm in **8**.

(18) Essentially identical results were obtained for assembly **1·6** (Supporting Information). For CD in related molecular recognition studies 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) Harada, N.; Nakanishi, K.; *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(19) The sensitivity of these highly cooperative assemblies to solvents that compete for hydrogen bonds, e.g. methanol, DMSO, and DMF, has been reported. See refs 2 and 4 for details.

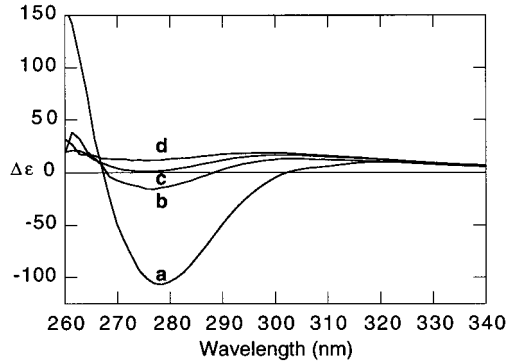

Figure 12. CD spectra of the **1·5** heterodimer: (a) spectrum from Figure 10d, (b) 0.8% (by volume) methanol added, (c) 1.5% methanol added, and (d) 3.0% methanol added.

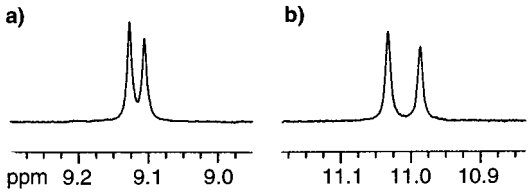

Figure 13. ^{1}H NMR spectra (~1 mM, *p*-xylene-d_{10}, 600 MHz) of the downfield −NH resonances show a 1.3:1 diastereomeric excess for binding racemic norcamphor (in excess) in (a) the **1·5** heterodimer and (b) the **1·2** heterodimer.

Asymmetric Microenvironments. Chiral guests within these heterodimeric assemblies can sense the hydrogen bond directionality that defines the capsule's handedness, and selectivity in their binding is observed.[20,21] Because chiral heterodimers have a defined urea direction, a mixture of enantiomeric guests produces two diastereomeric capsules. For example, when norcamphor is added to the **1·5** mixture, two diastereomeric assemblies are formed, CW-S-**R**[22] and CW-S-**S** (Figure 13a). The ratio of the two diastereomeric capsules is 1.3 to 1—the guest enantiomers are sensitive to the asymmetric environment of the capsule, and one is modestly discriminated.[23]

The **1·2** capsule is racemic with respect to its lining and a bound chiral guest gives diastereomeric assemblies, CW-**R** and CCW-**R**. Likewise, addition of a racemic guest forms four capsules—CW-**R** and CCW-**S**, as one enantiomeric pair, and CW-**S** and CCW-**R**, as the other. Addition of norcamphor, a racemic chiral guest, to a solution of **1·2** in *p*-xylene-d_{10} appropriately shows these two sets of assemblies (Figure 13b). The downfield sulfonylurea −NH singlets represent the two capsules, and integration confirms that they are not formed equally—there is again a 1.3-fold excess of one pair. Approximately the same diastereomeric excess is obtained for the nonracemic capsules. That both the racemic and nonracemic capsules discriminate equally between the norcamphor enantiomers is reassuring. Both capsules have different top and bottom halves and similar urea seams when viewed from the inside.

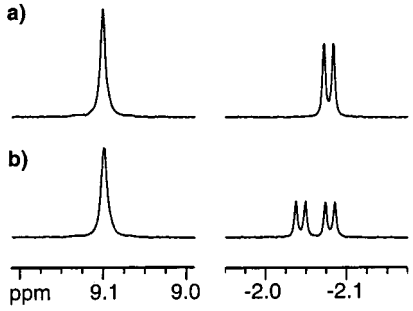

Figure 14. ^{1}H NMR spectra (~1 mM, *p*-xylene-d_{10}, 600 MHz) of the downfield host −NH (left) and upfield guest methyl (right) resonances when **1·5** encapsulates (a) (*R*)-(+)-3-methylcyclopentanone (in excess) and (b) (±)-3- methylcyclopentanone (in excess).

When (*R*)-(+)-3-methylcyclopentanone is added to a solution of **1·2** in *p*-xylene-d_{10}, two assemblies are formed, CW-**R** and CCW-**R**, as a 1.3:1 mixture of diastereomers (spectrum not shown).[24] Addition of the same guest to a solution of **1·5** in *p*-xylene-d_{10} shows *one* assembly by ^{1}H NMR, CW-S-**R** (Figure 14a). The methyl doublet of the guest is clearly visible upfield in the spectrum at −2.08 ppm. When the racemic guest is added to **1·5**, two assemblies are formed, CW-S-**R** and CW-S-**S**, and both enantiomers of the guest are detectable upfield in a 1:1 ratio, the methyl group of the **S** enantiomer appearing at −2.05 ppm (Figure 14b). The nearly identical chemical shifts of the two methyl groups suggest that both guest enantiomers experience similar environments within the capsule. ROESY spectroscopy supports this showing contacts between the CH_3 protons of the guest and the aryl −CH protons of **1**.[25] Just as with polycyclic guests in homodimer **1·1** and heterodimer **1·2**,[4a] the methyl group is most likely buried deeply in one hemisphere of the **1·5** assembly. It is unclear in this case why enantioselective binding is not observed, but it again speaks of the subtle interactions from which it arises.

Summary and Outlook. Species involved in molecular recognition are shuttled to a thermodynamic resting-state through a concert of weak, noncovalent interactions. Although selectivity in these processes can be understood at the level of hydrogen bonding and van der Waals contacts, a priori design, prediction of how individual interactions contribute to the final assembly, is challenging. The compounds explored here illustrate the consequences, both chemical and stereochemical, of a well-positioned, yet remote, chiral center on assembly. The asymmetry is transferred from one unit to the next around a capsule hydrogen bonding seam, until ultimately a stable assembly is formed. The transfer continues inward and affects the binding of chiral guests, where enantiomers are, albeit modestly, discriminated.

The discovery of a second exclusive heterodimeric assembly represents another step toward DNA-inspired, informational assemblies based on hydrogen-bonded calixarenes. Soon we hope to explore the transfer of peripheral chiral information beyond the scale of these dimeric assemblies in the context of their polymeric congeners.[4b,26]

(20) For hydrogen bonding-based asymmetric binding by synthetic receptors, see: (a) Dowden, J.; Edwards, P. D.; Flack, S. S.; Kilburn, J. D. *Chem. Eur. J.* **1999**, *5*, 79−89. (b) Lustenberger, P.; Martinborough, E.; Denti, T. M.; Diederich, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 747−761. (c) Pieters, R. J.; Cuntze, J.; Bonnet, M.; Diederich, F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1891−1900 and references therein. (d) Pieters, R. J.; Diederich, F. *Chem. Commun.* **1996**, 2255−2256. (e) Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554−8555. (f) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184−5186. (g) Jeong, K. S.; Muehldorf, A. V.; Rebek, J., Jr. *J. Am. Chem. Soc.*, **1990**,*112*, 6144−6145. (h) Reference 18c.

(21) For asymmetric binding in molecular assemblies, see: (a) Nuckolls, C.; Hot, F.; Martín, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 10281−10285. (b) Rivera, J. M.; Martín, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1021−1023. (c) Costante-Crassous, J.; Marrone, T. J.; Briggs, J. M.; McCammon, J. A.; Collet, A. *J. Am. Chem. Soc.* **1997**, *119*, 3818−3823. (d) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993−6996.

(22) The second, bold-faced **R** or **S** represents the stereochemistry of the guest.

(23) Similar selectivity is also observed in the binding of β-butyrolactone. This guest is not bound in the **1·2** heterodimer.

(24) Although encapsulated, 3-methylcyclopentanone is a relatively poor guest for assembly **1·2**.

(25) See the Supporting Information for details.

Experimental Section

General. ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra were recorded on a Bruker DRX-600 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000PC FT-IR spectrometer. Matrix-assisted laser desorption/ionization (MALDI) FTMS experiments were performed on an IonSpec FTMS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp. Circular dichroism (CD) spectra were recorded on an AVIV 62DS CD spectrometer. Dichloromethane (CH_2Cl_2) was passed through columns of activated aluminum oxide as described by Grubbs and co-workers prior to use.[27] Amino acid isocyanates were purchased from TCI America or prepared as indicated. All reagents were purchased from either Aldrich or Fluka and used as received. The syntheses of **1**,[28] **2**,[4a] and **3**[4a] have been described previously.

D-Isoleucine Methyl Ester Isocyanate.[9] To a flame-dried 100 mL round-bottomed flask was added the amino acid methyl ester amine hydrochloride (1.5 g, 8.2 mmol), CH_2Cl_2 (30 mL), and pyridine (2.7 mL, 33 mmol). The solution was cooled to 0 °C for 15 min prior to the addition of phosgene (1.93 M in toluene, 5.5 mL, 11 mmol). The solution gradually turned yellow, and gas evolution was observed. After ca. half of the phosgene was added a white precipitate formed and the mixture became viscous. Stirring was continued at 0 °C for 2 h. The suspension was transferred to a separatory funnel and washed with cold 0.5 M HCl (50 mL), cold water (50 mL), and cold brine (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a yellow oil under high vacuum. The crude product was purified by Kügelrohr distillation (75 °C, 0.05−0.1 mmHg). The isocyanate was isolated as a clear, colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.96 (d, 1H, J = 3.9 Hz), 3.81 (s, 3H), 1.97 (m, 1H), 1.35 (m, 1H), 1.25 (m, 1H), 1.00 (d, 3H, J = 6.9 Hz), 0.90 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 171.49, 126.80, 62.75, 52.97, 38.53, 24.22, 16.38, 11.47. $[\alpha]_D^{25}$ +10.2° (*c* 1.5, THF). IR (thin film) 2967, 2254, 1745, 1215 cm^{-1}.

D-Valine Methyl Ester Isocyanate. The compound was prepared as described for isoleucine. The crude product was purified by Kügelrohr distillation (75 °C, 0.05−0.1 mmHg). The isocyanate was isolated as a clear, colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.94 (d, 1H, J = 3.8 Hz), 3.81 (s, 3H), 2.23 (m, 1H), 1.02 (d, 3H, J = 6.8 Hz), 0.89 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 171.43, 126.89, 63.23, 53.02, 31.83, 19.68, 16.54. $[\alpha]_D^{25}$ +24.9°(*c* 1.3, THF). IR (thin film) 2968, 2258, 1744, 1215 cm^{-1}.

General Procedure for the Reaction of the Tetraamine[8] with Chiral Isocyanates. To a solution of the tetraamine in CH_2Cl_2 was added 5 equiv of the isocyanate. The solution was stirred at room temperature for 2−4 h prior to evaporation of the solvent and purification via either recrystallization from MeOH, precipitation from CH_2Cl_2 with MeOH, or precipitation from THF with MeOH. The tetraureas were generally isolated as white to off-white powders in 40−60% yield.

L-Leucine (4): ^{1}H NMR (DMF-d_7) δ 8.26 (s, 4H), 6.85 (s, 8H), 6.30 (d, 4H, J = 8.1 Hz), 4.40 (d, 4H, J = 12.7 Hz), 4.36 (m, 4H), 3.87 (t, 8H, J = 7.4 Hz), 3.70 (s, 12H), 3.08 (d, 4H, J = 12.9 Hz), 2.00−1.96 (m, 8H), 1.75−1.70 (m, 4H), 1.55 (m, 4H), 1.46−1.31 (m, 60H), 0.96−0.89 (m, 36H). ^{13}C NMR (DMF-d_7) δ 174.62, 155.59, 151.62, 134.93, 134.70, 118.74, 75.51, 51.81, 51.49, 41.52, 32.24, 31.37, 30.62, 30.45, 30.38, 30.16, 26.83, 24.97, 22.89, 22.76, 21.61, 14.01. IR (thin film) 3368, 2952, 2923, 2853, 1739, 1657, 1602, 1556, 1468, 1214 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{100}H_{160}N_8O_{16}$Na 1752.1850, found 1752.1863.

L-Isoleucine (5): ^{1}H NMR (DMF-d_7) δ 8.33 (s, 4H), 6.92 (d, 4H, J = 2.5 Hz), 6.82 (d, 4H, J = 2.4 Hz), 6.36 (d, 4H, J = 8.6 Hz), 4.40 (d, 4H, J = 12.6 Hz), 4.29 (dd, 4H, J = 8.5 Hz, 5.3 Hz), 3.87 (t, 8H, J = 7.5 Hz), 3.71 (s, 12H), 3.09 (d, 4H, J = 12.8 Hz), 2.03−1.98 (m, 8H), 1.84−1.80 (m, 4H), 1.47−1.31 (m, 60H), 1.22−1.18 (m, 4H), 0.92−0.87 (m, 36H). ^{13}C NMR (DMF-d_7) δ 173.44, 155.65, 151.52, 134.92, 134.88, 134.76, 118.68, 118.50, 75.57, 57.32, 51.60, 37.88, 32.24, 31.35, 30.62, 30.46, 30.38, 30.16, 26.83, 25.39, 22.89, 15.64, 14.01, 11.45. IR (thin film) 3370, 2952, 2923, 2853, 1739, 1660, 1602, 1556, 1468, 1214 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{100}H_{160}N_8O_{16}$Na 1752.1850, found 1752.1869.

D-Isoleucine: The identical spectral data was obtained as for L-isoleucine. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{100}H_{160}N_8O_{16}$Na 1752.1850, found 1752.1819.

L-Valine (6): ^{1}H NMR (DMF-d_7) δ 8.34 (s, 4H), 6.93 (d, 4H, J = 2.4 Hz), 6.82 (d, 4H, J = 2.4 Hz), 6.35 (d, 4H, J = 8.6 Hz), 4.40 (d, 4H, J = 12.6 Hz), 4.22 (dd, 4H, J = 8.5 Hz, 5.2 Hz), 3.87 (t, 8H, J = 7.4 Hz), 3.73 (s, 12H), 3.09 (d, 4H, J = 12.8 Hz), 2.10−2.05 (m, 4H), 2.02−1.98 (m, 8H), 1.47−1.31 (m, 56H), 0.94 (d, 24H, J = 6.9 Hz), 0.92−0.89 (m, 12H). ^{13}C NMR (DMF-d_7) δ 173.50, 155.74, 151.51, 134.92, 134.88, 134.78, 118.66, 118.48, 75.58, 58.21, 51.65, 32.24, 31.35, 31.05, 30.63, 30.46, 30.38, 30.16, 26.83, 22.89, 19.06, 17.74, 14.01. IR (thin film) 3371, 2951, 2924, 2853, 1741, 1660, 1602, 1557, 1468, 1215 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{96}H_{152}N_8O_{16}$Na 1696.1224, found 1696.1149.

D-Valine: The identical NMR data was obtained as for L-valine. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{96}H_{152}N_8O_{16}$Na 1696.1224, found 1696.1171.

L−*O*-*t*-Bu-serine (7): ^{1}H NMR (DMF-d_7) δ 8.56 (s, 4H), 7.04 (d, 4H, J = 2.4 Hz), 6.82 (d, 4H, J = 2.4 Hz), 6.34 (d, 4H, J = 8.7 Hz), 4.49 (dt, 4H, J = 8.6 Hz, 3.4 Hz), 4.41 (d, 4H, J = 12.5 Hz), 3.87 (t, 8H, J = 7.5 Hz), 3.80 (dd, 4H, J = 9.1 Hz, 3.4 Hz), 3.69 (s, 12H), 3.59 (dd, 4H, J = 9.1 Hz, 3.6 Hz), 3.09 (d, 4H, J = 12.7 Hz), 2.04−2.00 (m, 8H), 1.47−1.32 (m, 56H), 1.14 (s, 36H), 0.92−0.87 (m, 12H). ^{13}C NMR (DMF-d_7) δ 172.33, 155.47, 151.44, 134.87, 118.74, 118.54, 75.62, 73.23, 62.87, 53.74, 51.81, 32.24, 31.36, 30.64, 30.47, 30.37, 30.16, 27.07, 26.81, 22.89, 14.01. IR (thin film) 3357, 2923, 2853, 1741, 1654, 1602, 1558, 1467, 1212 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{104}H_{168}N_8O_{20}$Na 1872.2273, found 1872.2282.

L-Phenylalanine (8): ^{1}H NMR (DMF-d_7) δ 8.37 (s, 4H), 7.34 (m, 8H), 7.28−7.25 (m, 12H), 6.87 (d, 4H, J = 2.2 Hz), 6.79 (d, 4H, J = 2.2 Hz), 6.24 (d, 4H, J = 8.0 Hz), 4.61 (m, 4H), 4.37 (d, 4H, J = 12.6 Hz), 3.84 (t, 8H, J = 7.4 Hz), 3.67 (s, 12H), 3.11−3.02 (m, 12H), 2.00−1.96 (m, 8H), 1.45−1.31 (m, 56H), 0.91−0.89 (m, 12H). ^{13}C NMR (DMF-d_7) δ 173.36, 155.31, 151.54, 137.58, 134.87, 134.63, 129.67, 128.70, 127.03, 118.75, 118.65, 75.53, 54.53, 51.81, 38.25, 32.23, 31.32, 30.60, 30.44, 30.36, 30.15, 26.80, 22.88, 14.00. IR (thin film) 3368, 2923, 2853, 1740, 1654, 1603, 1556, 1467 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{112}H_{152}N_8O_{16}$Na 1888.1224, found 1888.1308.

L-Phenylglycine (9): ^{1}H NMR (DMF-d_7) δ 8.43 (s, 4H), 7.43 (m, 8H), 7.40−7.34 (m, 12H), 6.94 (d, 4H, J = 2.4 Hz), 6.90 (d, 4H, J = 7.3 Hz), 6.77 (d, 4H, J = 2.5 Hz), 5.41 (d, 4H, J = 7.4 Hz), 4.40 (d, 4H, J = 12.6 Hz), 3.86 (t, 8H, J = 7.5 Hz), 3.69 (s, 12H), 3.09 (d, 4H, J = 12.8 Hz), 2.00−1.96 (m, 8H), 1.45−1.31 (m, 56H), 0.91−0.89 (m, 12H). ^{13}C NMR (DMF-d_7) δ 172.38, 155.06, 151.64, 138.20, 134.95, 134.91, 134.60, 129.16, 128.53, 127.58, 118.76, 118.59, 75.55, 57.39, 52.30, 32.24, 31.33, 30.62, 30.45, 30.38, 30.16, 26.82, 22.89, 14.01. IR (thin film) 3369, 2950, 2923, 2853, 1743, 1659, 1602, 1556, 1470, 1216 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{108}H_{144}N_8O_{16}$Na 1832.0597, found 1832.0546.

L-Alanine (10). ^{1}H NMR (DMF-d_7) δ 8.23 (s, 4H), 6.94 (d, 4H, J = 2.4 Hz), 6.72 (d, 4H, J = 2.4 Hz), 6.34 (d, 4H, J = 7.5 Hz), 4.40 (d, 4H, J = 12.8 Hz), 4.31 (m, 4H), 3.86 (t, 8H, J = 7.4 Hz), 3.70 (s, 12H), 3.07 (d, 4H, J = 13.0 Hz), 1.99−1.95 (m, 8H), 1.48−1.31 (m, 56H), 1.33 (d, 12H, J = 7.2 Hz), 0.92−0.89 (m, 12H). ^{13}C NMR (DMF-d_7) δ 174.61, 155.37, 151.66, 134.99, 134.94, 134.68, 118.92, 118.67, 75.46, 51.87, 48.72, 32.24, 31.36, 30.64, 30.57, 30.45, 30.16, 26.85, 22.89, 18.09, 14.01. IR (thin film) 3369, 2923, 2853, 1740, 1658, 1600, 1556, 1467, 1216 cm^{-1}. HRMS (MALDI-FTMS; M + Na$^+$) calcd for $C_{88}H_{136}N_8O_{16}$Na 1583.9972, found 1583.9936.

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Supporting Information Available: ROESY data for the **1·6** assembly in C_6D_6 and the **1·5** assembly in *p*-xylene-d_{10} with (*R*)-(+)-3-methylcyclopentanone (PDF). VT ^{1}H NMR results from **1·4** and CD data on assembly **1·6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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