Diastereoselective Noncovalent Synthesis of Hydrogen-Bonded Double-Rosette Assemblies

Leonard J. Prins, Ron Hulst, Peter Timmerman,* and David N. Reinhoudt*[a]

Abstract: Chiral centers present either in the dimelamine components of calix[4]arene **1** or in the cyanurate components CA quantitatively induce one handedness (*P* or *M*) in the corresponding hydrogen-bonded assemblies $\mathbf{1}_3\cdot(CA)_6$ ($de > 98\,\%$). The high degree of chiral induction results from the presence of six chiral centers in close proximity (C_α) to the core of the assembly. A much lower level of chiral induction is observed for assemblies with chiral centers that are more remote (C_β). All diastereomerically pure assemblies $\mathbf{1}_3\cdot(CA)_6$ exhibit very high CD activities ($|\Delta\varepsilon_{max}| \sim 100\,L\,mol^{-1}\,cm^{-1}$), in sharp contrast to the low CD activities ($|\Delta\varepsilon_{max}| \leq 8\,L\,mol^{-1}\,cm^{-1}$) shown by the free components. The assemblies display spontaneous resolution under thermodynamically controlled conditions (i.e., heteromeric assemblies containing both peripheral *R* and *S* centers are not observed. Remarkable assembly behavior is observed if both components **1** and CA are chiral. In general, formation of well-defined assemblies is only observed when both components contain unidirectional information for the induction of either *M* or *P* chirality.

Keywords: diastereoselectivity · hydrogen bonds · noncovalent interactions · self-assembly · supramolecular chirality

Introduction

Biological H-bonded structures express abundant supramolecular chirality; for example, the double helix of DNA,[1] the triple helix of collagen,[2] or the α-helical coiled coil of myosin.[3] The generation of chiral assemblies—consequently with chiral binding sites—means that chirality plays an important role in biological molecular recognition processes. Control over the supramolecular chirality of synthetic assemblies is of crucial importance for their application in the fields of molecular recognition, catalysis, and materials science.[4–6] Just like metal-coordinated assemblies,[7, 8] many synthetic H-bonded assemblies display supramolecular chirality as a result of the dissymmetric arrangement of their achiral components (Figure 1).[9–13] The general method for controlling supramolecular chirality is the introduction of chiral substituents into the components. In this way, the resulting assembly exists as a mixture of two diastereomers, the diastereomeric excess (*de*) of which is determined by the difference in ΔG°.

Initial efforts to induce diastereoselectivity in H-bonded capsules by chiral-guest encapsulation resulted only in moderate *de*'s of $\sim 35\,\%$.[10a] In the meantime, quantitative diastereoselection in capsules with a chiral exterior was achieved.[10b] In a similar fashion, diastereomeric rosette assemblies have been synthesized with a maximum *de* of 50 % through the use of chiral cyanurate components.[12] Recently, ^{1}H NMR studies by Davis and Gottarelli et al. have shown that the supramolecular chirality in guanosine octamers, templated by K^+, is quantitatively induced by the eight chiral sugar moieties.[13]

Meijer et al. demonstrated the strong induction of supramolecular helicity in H-bonded macromolecular stacks comprising chiral components.[14] Similar results were obtained with other H-bonded macromolecular assemblies.[15–17] Analysis of the diastereoselectivity of the assembly process is severely complicated by the fact that individual assemblies may comprise domains of opposite helicity separated by helix inversion points. For that reason, the induction of chirality in macromolecular assemblies is commonly analyzed by means of chiral amplification experiments.[18–20]

In a previous communication we showed that the supramolecular chirality of the hydrogen-bonded assemblies $\mathbf{1}_3\cdot(CA)_6$ can be quantitatively induced by chiral centers present in the components (Figure 2).[21] In this paper we give full details of these experiments, together with new results that reveal that the extent of chiral induction is strongly related to the distance between the chiral centers and the core of the assembly. Furthermore, the assembly behavior of chiral dimelamines **1** with chiral cyanurates CA is described, and reveals a remarkable sensitivity to conflicting chiral information present in both components.

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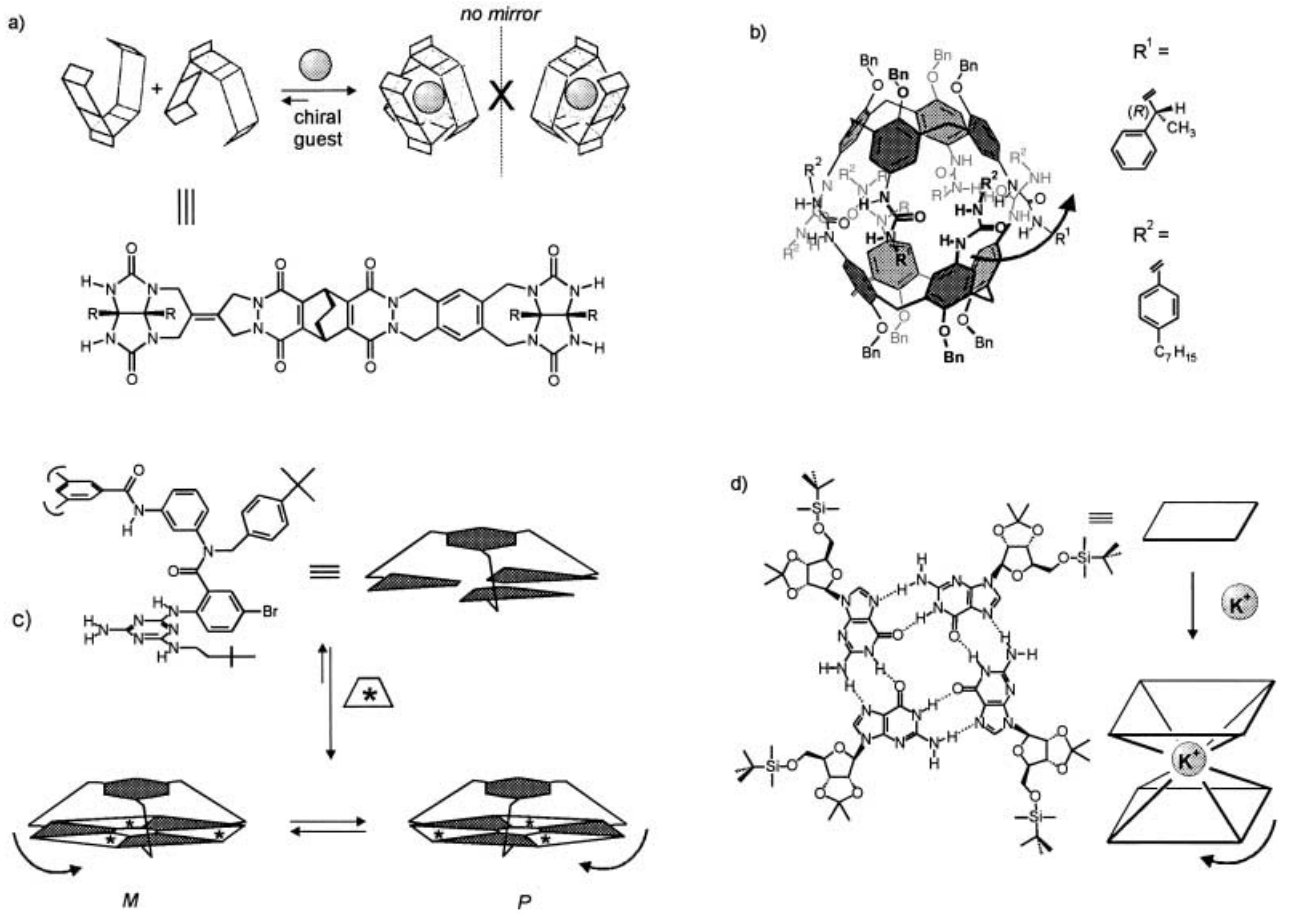

Figure 1. Examples of chiral H-bonded capsules: a) Supramolecular chirality in capsules, caused by a dissymmetric arrangement of the components.[10] b) Supramolecular chirality in a tetraurea calix[4]arene capsule consisting of differently substituted urea units.[11] c) Supramolecular chirality in rosette assemblies as a result of two possible orientations (*M* or *P*) of the melamine fragments.[12] d) Stacking of two G-quartets in a supramolecularly chiral head-to-tail arrangement templated by K^+.[13] The arrows indicate the handedness of the assemblies.

Results and Discussion

Calix[4]arene-based double-rosette assemblies: Earlier work in our group showed that assemblies $\mathbf{1}_3\cdot(CA)_6$ form spontaneously when calix[4]arene dimelamines **1** are mixed either with barbiturates or with cyanurates (CA) in a 1:2 ratio in apolar solvents such as chloroform, toluene, or benzene.[22–24] In principle, the assemblies can exist in three different isomeric forms: with D_3, C_{3h}, or C_s symmetry (Figure 2).[28] The X-ray crystal structure of assembly $\mathbf{1b}_3\cdot(DEB)_6$ clearly shows that this particular assembly fully adopts a D_3-symmetric structure (Figure 3), which is chiral.[24] This form of supramolecular chirality is the result of an antiparallel orientation of the two melamine fragments of **1b**, which can be either clockwise (*P*) or counterclockwise (*M*) (Scheme 1).[31] In order for $\mathbf{1b}_3\cdot(DEB)_6$ to form, all three calix[4]arene dimelamines in the assembly must have an identical orientation of the melamine fragments: that is, either all (*P*)-**1b** or all (*M*)-**1b**.

The *M* and *P* isomers of assembly $\mathbf{1b}_3\cdot(DEB)_6$ exist in an enantiomeric relationship and are therefore equal in free energy ($\Delta G^\circ_M = \Delta G^\circ_P$). Consequently, assembly $\mathbf{1b}_3\cdot(DEB)_6$ is present in solution as a racemic mixture of the *M* and *P* enantiomers. Upon addition of 10 equivalents of Pirkle's reagent, a well-known chiral shift reagent, to a 1.0 mM solution of $\mathbf{1b}_3\cdot(DEB)_6$, splitting of the calix[4]arene CH_2 bridge proton signals of **1b** was observed (Figure 4a, b). None of the other proton signals was affected; this indicates that Pirkle's reagent forms a weak complex with $\mathbf{1b}_3\cdot(DEB)_6$, presumably through coordination of the hydroxyl group to the nitrogen of the triazine ring of **1b** that is not involved in hydrogen bonding. The same experiment performed with an assembly with exclusively *P* chirality ($\mathbf{1c}_3\cdot(R\text{CYA})_6$, vide infra) did not result in splitting of the signals; this indicates that the splitting observed for assembly $\mathbf{1b}_3\cdot(DEB)_6$ is indeed related to the presence of both *M* and *P* enantiomers (Figure 4c, d).

The binding of Pirkle's reagent is too weak to cause a measurable energy difference between the *M* and *P* isomers of assemblies $\mathbf{1b}_3\cdot(DEB)_6$. In order to study whether chiral centers in the components can induce diastereoselection in assemblies $\mathbf{1}_3\cdot(CA)_6$, chiral analogues of both **1** and CA were synthesized. The chiral analogues of CA include both barbiturates and cyanurates.

Synthesis: Dimelamines **1a**–**c** and bis(chlorotriazine) **2** were synthesized by literature procedures.[24] Similarly, calix[4]-arene dimelamines **1d**–**1g** were synthesized by treatment of

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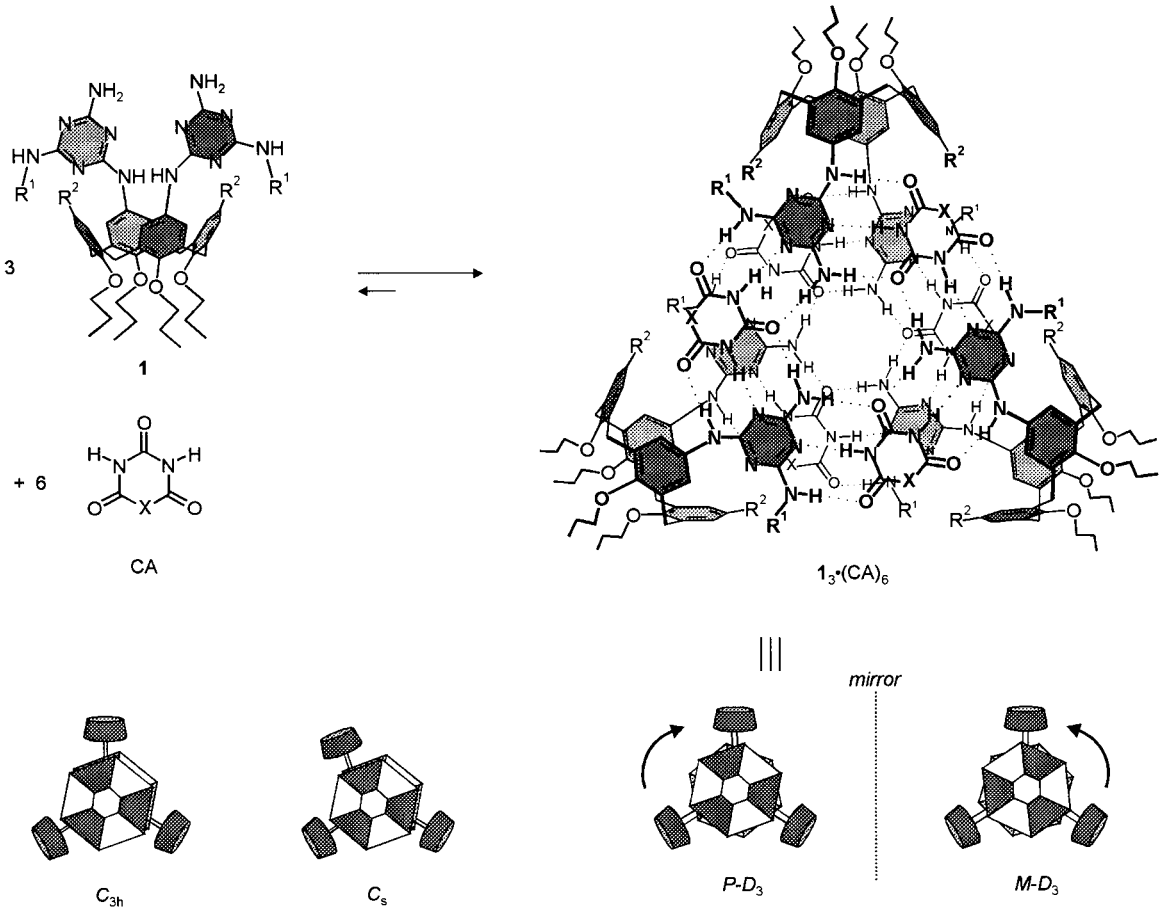

Figure 2. Formation of assemblies $\mathbf{1}_3\cdot(CA)_6$ from calix[4]arene dimelamines **1** and barbiturates/cyanurates CA. Schematic representations of the possible isomers with D_3, C_{3h}, and C_s symmetry. Both the *M* and the *P* enantiomers of the D_3 symmetrical isomer are depicted.

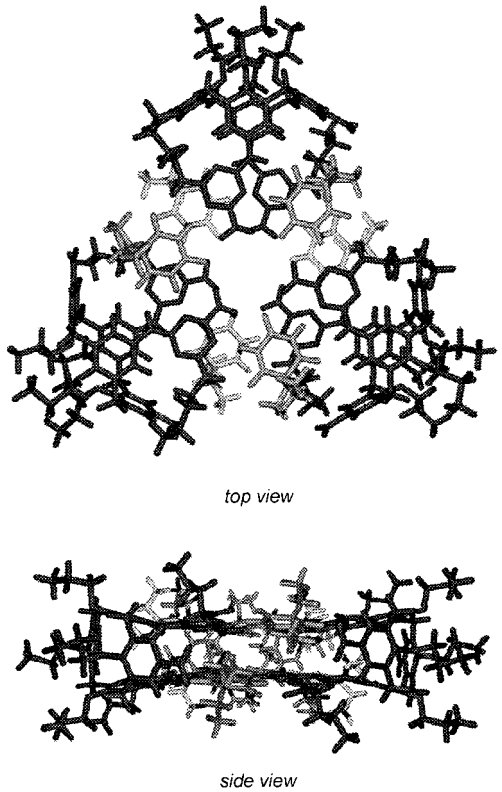

Figure 3. X-Ray crystal structure of $\mathbf{1b}_3\cdot(DEB)_6$.[24]

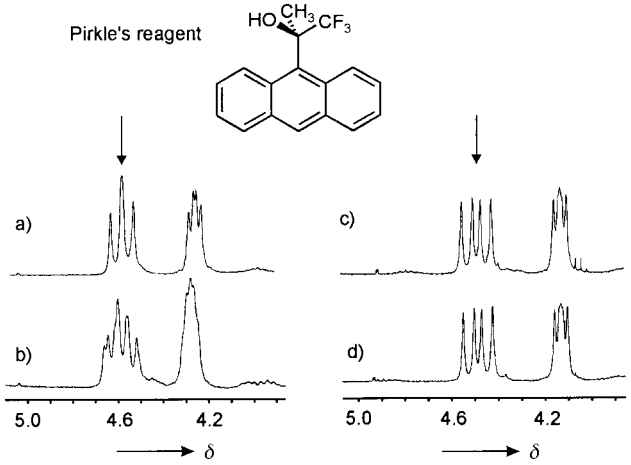

Figure 4. a and b) Addition of 10 equivalents of Pirkle's reagent to a 1.0 mM solution of racemic assembly $\mathbf{1b}_3\cdot(DEB)_6$ in [D_2]dichloromethane results in a splitting of the signals corresponding to the CH_2 bridge protons of **1b** (indicated with an arrow). c and d) No splitting was observed when the same experiment was performed with assembly $\mathbf{1c}_3\cdot(R\text{CYA})_6$, which is present exclusively as the *P* isomer.

bis(chlorotriazine) **2** with an excess of the corresponding amine (99% *ee*) in THF (Scheme 2), in yields varying between 65–85%.

The synthesis of cyanurates *R*CYA and *S*CYA started with condensation of the corresponding amines (*ee* > 99%) with an

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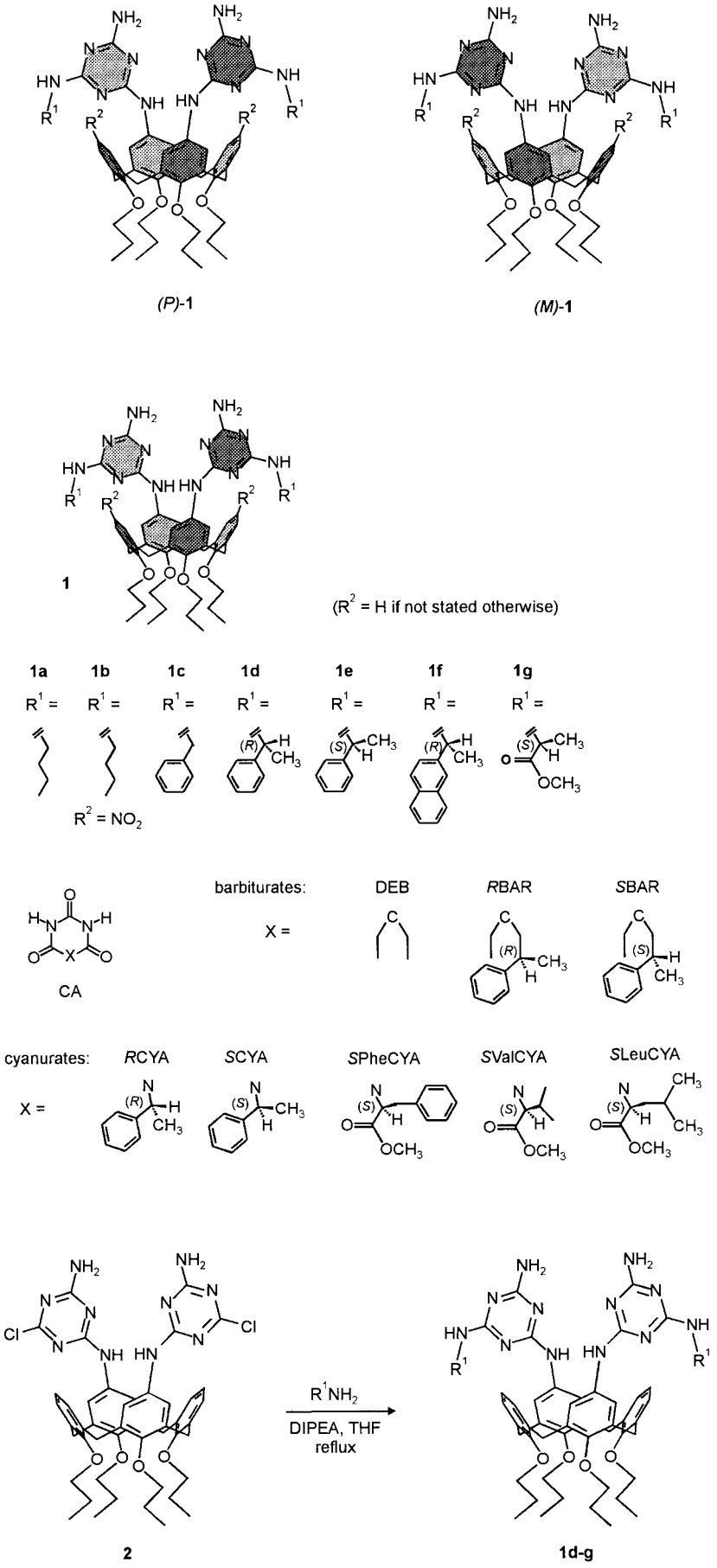
excess of nitrobiuret to give the nitrobiuret adducts (*R*)-**3** and (*S*)-**3** (Method A, Scheme 3).[32] Subsequent ring-closure with diethyl carbonate and sodium ethoxide gave *R*CYA and *S*CYA in overall yields of 74% and 82%, respectively. The cyanurates *S*PheCYA, *S*ValCYA, and *S*LeuCYA were prepared in one step by treatment of the corresponding methyl-ester-protected L-amino acids (*ee* > 99%) with *N*-chlorocarbonyl isocyanate, in yields varying between 50% and 65% (Method B, Scheme 3).[33]

The chiral barbiturates *R*BAR and *S*BAR were prepared in three steps starting with the bromination of (*R*)-2-phenylpropan-1-ol and (*S*)-2-phenylpropan-1-ol (*ee*'*s* > 99%), followed by alkylation with diethyl ethylmalonate to give (*R*)-**5** and (*S*)-**5**, respectively (Scheme 4). Ring closure of (*R*)-**5** and (*S*)-**5** with urea in the presence of sodium ethoxide gave *R*BAR and *S*BAR in overall yields of 14% and 16%, respectively.

Induction of supramolecular chirality through the use of chiral dimelamines: Mixing dimelamine **1d** (R^1 = (*R*)-1-phenylethyl) and DEB in a 1:2 ratio in either chloroform or toluene resulted in the quantitative formation of assembly $\mathbf{1d}_3 \cdot (DEB)_6$, as shown by ^{1}H NMR spectroscopy (Figure 5) and MALDI-TOF mass spectrometry. The 1:2 stoichiometry of the components **1d** and DEB was confirmed by integration of the CH_2 bridge-proton resonances of **1d** (*k*–*n*) and the NH-proton resonances of DEB (*a* and *b*). The ^{1}H NMR spectrum of assembly $\mathbf{1d}_3 \cdot (DEB)_6$ in [D_8]toluene is highly characteristic of double-rosette assemblies in general and will therefore be discussed in detail. Similar results were obtained in [D]chloroform.



Scheme 2. Synthesis of calix[4]arene dimelamines **1d**–**g**.

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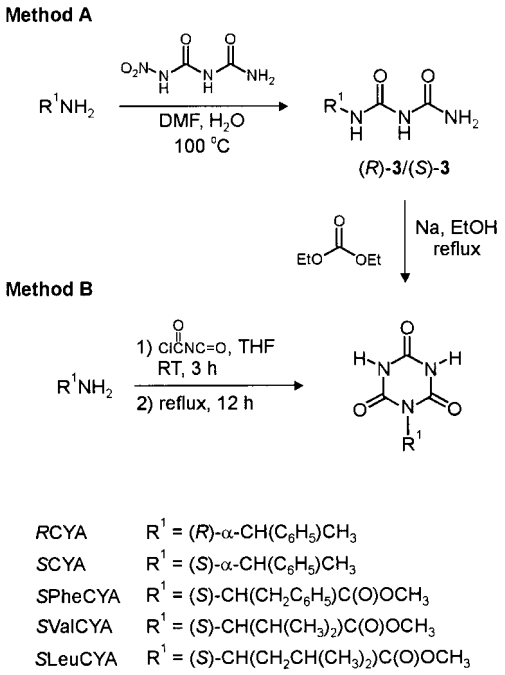


Scheme 3. Synthesis of cyanurates *R*CYA, *S*CYA, *S*PheCYA, *S*ValCYA, and *S*LeuCYA.

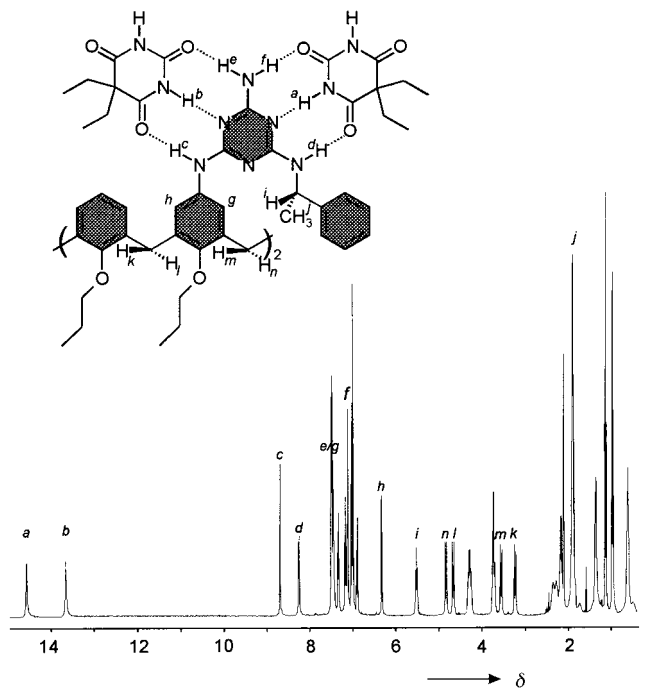
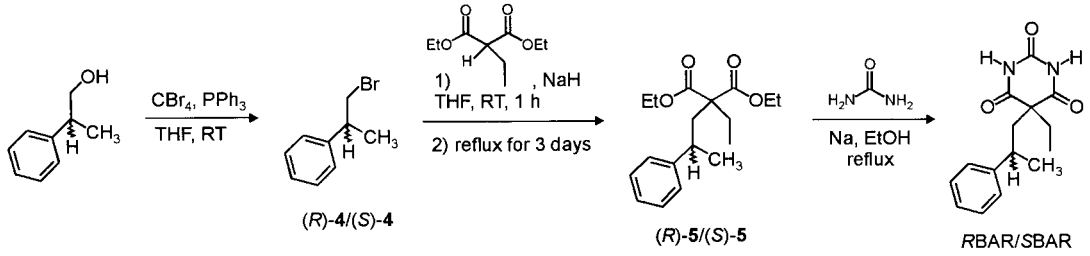


Figure 5. ^{1}H NMR spectrum of assembly $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ recorded in [D_8]toluene (5 mM, 400 MHz, 298 K), with assignment of the proton signals.

As a result of H-bonding, the NH_{DEB} protons (*a* and *b*) are strongly shifted downfield from their normal position ($\delta_{NH,free,DEB} = 8.40$). Two signals are observed at $\delta = 13.67$ and 14.59, due to the fact that the *a* and *b* protons reside in chemically different environments within the assembly. This is a result of the nonsymmetrical substitution of the melamine fragments of **1d**. Furthermore, it shows that the DEB components are in slow exchange on the ^{1}H NMR chemical shift timescale. Similarly, strong downfield shifts are observed for the NH and NH_2 protons of the melamine fragments of **1d** (*c*–*f*), which appear at $\delta = 8.71$, 8.26, 7.48, and 7.14, respectively. Two signals at $\delta = 6.35$ and 7.48 are observed for the aromatic protons *g* and *h* of the melamine-substituted phenyl rings of **1d**. On the basis of ^{1}H NMR studies by Ungaro et al., the signal at $\delta = 6.35$ (*h*) is indicative of a pinched cone conformation of **1d** with the two melamine-substituted phenyls in close proximity.[34] The fact that the other signal appears at $\delta = 7.48$ (*g*) is attributable to the formation of a weak hydrogen bond between this proton and the triazine ring nitrogen not involved in H-bonding.

^{1}H NMR spectroscopy also provides important information on the symmetry of assembly $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$. Assembly $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ can exist in three different isomeric forms: with D_3, C_{3h}, or C_s symmetry. Because **1d** is chiral, the D_3 isomer can be present in two diastereomeric forms, with either *M* or *P* chirality. The symmetry of the assembly is most clearly reflected by the number of signals observed for the NH_{DEB} protons.[28] Based on symmetry arguments, two, four, and twelve signals are predicted for the D_3, C_{3h}, and C_s isomers, respectively. The presence of only two signals at $\delta = 13.67$ and 14.59 implies that assembly $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ is exclusively present as one of the two possible diastereomers with D_3 symmetry: *M*-D_3 or *P*-D_3. The presence of both the *M* and the *P* diastereomers of the D_3 isomer would result in four signals for the NH_{DEB} protons. That the presence of two signals for the NH_{DEB} protons results from a fast exchange between the *M*-D_3 and *P*-D_3 isomers can be ruled out, since in that case only one signal would be expected for protons *g* and *h*, and only two doublets for the CH_2 protons *k*–*n* in **1b**. The complete absence of signals for the other diastereomer indicates that its concentration must be $\leq 10^{-4}$ M, based on the sensitivity threshold of ^{1}H NMR spectroscopy. Since the assembly concentration is 5×10^{-3} M, this means that the chiral substituents in **1d** induce a $de \geq 98\%$ in assembly $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$. This corresponds to a ΔG° (298 K) between the *M* and the *P* diastereomers of ≥ 11.4 kJ mol^{-1}.

The ^{1}H NMR spectra of assemblies $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1f}_3\cdot(\mathrm{DEB})_6$ in either [D]chloroform or [D_8]toluene only show one set of proton signals. This means that the (*R*)-1-naphthylethyl



Scheme 4. Synthesis of barbiturates *R*BAR and *S*BAR.

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substituent in **1f** and the L-alanine substituent in **1g** also quantitatively induce a single handedness in the corresponding assemblies.

Additional evidence for the formation of assembly $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ was obtained from MALDI-TOF mass spectrometry after Ag^+-labeling.[29, 30] The MALDI-TOF mass spectrum shows a strong signal at $m/z = 4358.3$ (calcd for $C_{234}H_{288}N_{48}O_{30}\cdot{}^{107}Ag^+$: 4360.2), corresponding to the monovalent Ag^+ complex. No other signals for partially formed assemblies were detected. Presumably, the Ag^+ cation is complexed between the phenyl ring of the appended (*R*)-1-phenylethyl substituent and the melamine-substituted phenyl rings of **1d**.

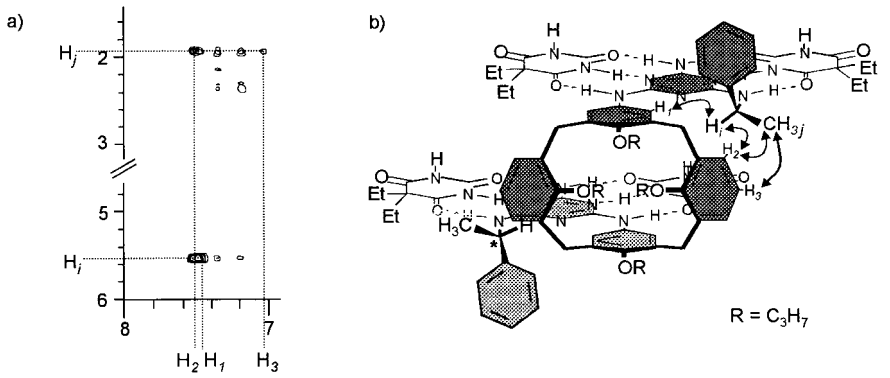

Figure 6. a) Part of the ROESY spectrum of $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ recorded in [D_8]toluene (1.0 mM, 400 MHz, 298 K), showing the most important connectivities. b) Three-dimensional representation of the orientation of the (*S*)-1-phenylethyl substituent, based on the observed connectivities.

The ^{1}H NMR and MALDI-TOF spectra of $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ are identical to the spectra of $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$. The only difference between these enantiomeric assemblies is reflected by their different optical activities (vide infra).

Determination of the absolute configuration of assembly $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$: Two-dimensional Rotating Frame Overhauser Effect Spectroscopy (ROESY) was used to correlate the *S* absolute configuration in the chiral substituents in **1e** to the induction of *P* chirality in assembly $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$. Connectivities were observed between protons H_i and H_1-H_2 and protons H_j and H_2-H_3 (Figure 6). These connectivities are only possible if assembly $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ adopts a *P* configuration. If the assembly were to adopt an *M* configuration, connectivities between protons H_i and H_3 and protons H_j and H_1 would be expected. No connectivities between the protons of the appended phenyl group and any of the protons H_{1-3} were observed; this indicates that the phenyl group is directed away from the assembly. In addition, the fact that five different signals were observed for the appended phenyl group shows that the chiral substituent adopts a very rigid conformation.

CD spectroscopy: It was found that assemblies $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ have very strong CDs ($|\Delta\varepsilon_{max}| \sim 100\ \mathrm{L\,mol^{-1}\,cm^{-1}}$). In sharp contrast, the individual components **1d** and **1e** are hardly CD active ($|\Delta\varepsilon_{max}| \leq 8\ \mathrm{L\,mol^{-1}\,cm^{-1}}$); this indicates that the observed CD is a direct result of assembly formation (Figure 7a). The strong

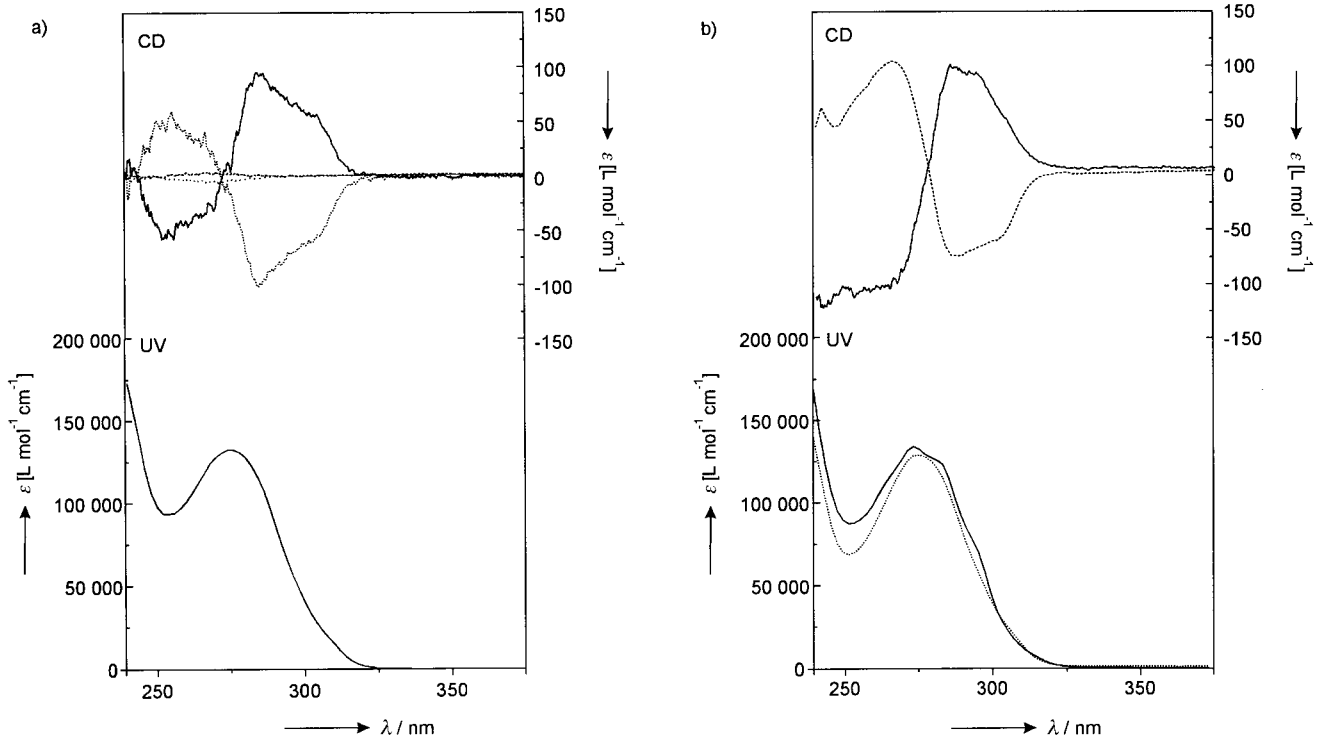

Figure 7. a) CD spectra of **1d** (– – –), **1e** (···), $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ (——), and $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ (••••), together with the UV spectrum of $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$. All spectra were recorded in dichloromethane (3.0 mM for **1d** and **1e**, 1.0 mM for $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$) at 298 K. b) CD and UV spectra of assemblies $\mathbf{1f}_3\cdot(\mathrm{DEB})_6$ (——) and $\mathbf{1g}_3\cdot(\mathrm{DEB})_6$ (••••). All spectra were recorded in chloroform (1.0 mM) at 298 K.

intensity of the Cotton effects, the bisignate nature of the CD curves, and the fact that the intercept with the *x*-axis coincides with the maximum in the UV spectra all indicate that the observed CD is mainly a result of exciton coupling between chromophores present in the core of the assemblies.[35] It is almost impossible to determine which chromophores are exciton-coupled, since all chromophores in the assemblies have overlapping UV absorptions.

The CD curves of (*M*)-$\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and (*P*)-$\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ are perfect mirror images; this reflects their enantiomeric relationship. The sign of the CD curve is therefore a good measure of the supramolecular chirality of the assembly: assemblies with *M* chirality give positive CD curves, whereas assemblies with *P* chirality give negative CD curves. This seems to contradict theoretical studies by Harada and Nakanishi, who found that in cases of exciton coupling a positive CD curve originates from a *P* configuration of the chromophores.[36] However, it should be emphasized that the assignment of *M* and *P* chirality to assemblies $\mathbf{1}_3\cdot(\mathrm{CA})_6$ is arbitrarily based on the relative orientation of the melamine fragments in **1**, and not on the relative orientation of the exciton-coupled chromophores. Recently published assembly studies with a chromogenic barbiturate clearly show consistency between the assignment of *M* and *P* chirality to the assembly and the observed CD of the chromophores.[37]

The CD spectra of assemblies $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$–$\mathbf{1g}_3\cdot(\mathrm{DEB})_6$ all have very similar shapes and amplitudes (Figure 7b). Apparently, peripheral chromophores (benzyl, carbonyl, naphthyl) only affect the intensity of the Cotton effect at wavelengths lower than 275 nm. For higher wavelengths, the CD spectra of assemblies $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$–$\mathbf{1g}_3\cdot(\mathrm{DEB})_6$ are virtually identical. From the sign of the CD curves it can be concluded that the (*R*)-1-naphthylethyl substituents in **1f** induce *M* chirality and the L-alanine substituents in **1g** induce *P* chirality.

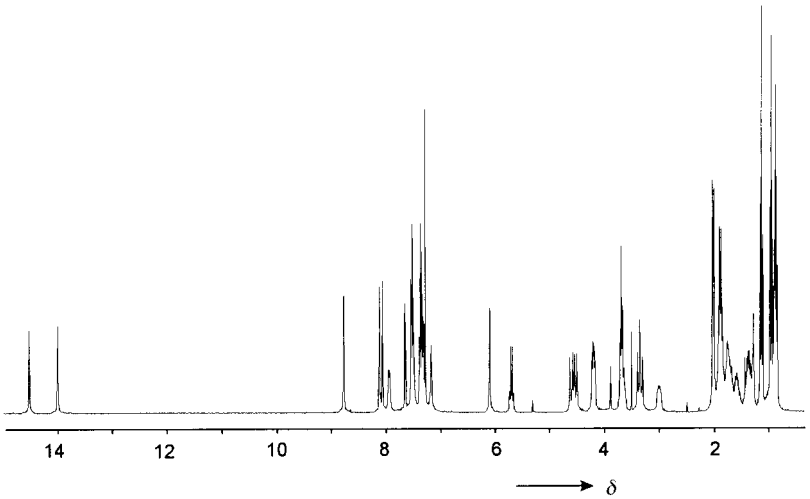

Figure 8. ^{1}H NMR spectrum of assembly $\mathbf{1b}_3\cdot(\mathrm{RCYA})_6$ in [D]chloroform (1.0 mM) at 298 K.

Just like assemblies $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$–$\mathbf{1g}_3\cdot(\mathrm{DEB})_6$, assembly $\mathbf{1b}_3\cdot(\mathit{R}\mathrm{CYA})_6$ is strongly CD active (Figure 9). The negative CD curve shows that *R*CYA induces *P* chirality. It is interesting to note that the same chiral group [(*R*)-1-phenylethyl] induces *P* chirality when present in the cyanurate component and *M* chirality when present in the dimelamine

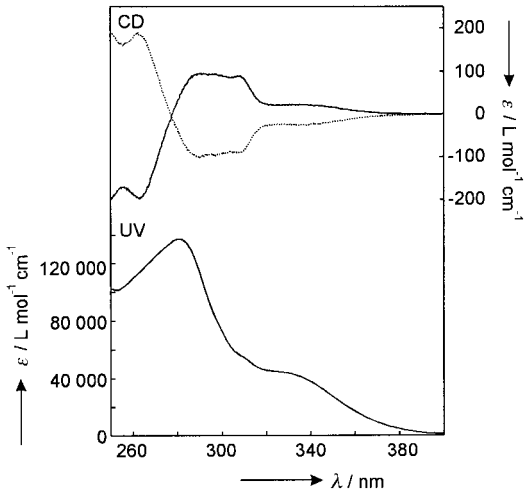

Figure 9. CD and UV spectra of assemblies $\mathbf{1b}_3\cdot(\mathit{R}\mathrm{CYA})_6$ (••••) and $\mathbf{1b}_3\cdot(\mathit{S}\mathrm{CYA})_6$ (——) in dichloromethane (1.0 mM) at 298 K.

Induction of supramolecular chirality through the use of chiral cyanurates: Assembly $\mathbf{1b}_3\cdot(\mathit{R}\mathrm{CYA})_6$ forms quantitatively upon mixing **1b** and *R*CYA in a 1:2 ratio in [D]chloroform, as shown by the presence of the characteristic signals for double-rosette assemblies in the ^{1}H NMR spectrum (Figure 8). As in the cases of assemblies $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$–$\mathbf{1g}_3\cdot(\mathrm{DEB})_6$, which incorporate chiral dimelamines, only one set of signals is observed; this means that *R*CYA quantitatively induces the chirality of $\mathbf{1b}_3\cdot(\mathit{R}\mathrm{CYA})_6$. Additional evidence for the quantitative induction was obtained from the addition of 10 equivalents of Pirkle's reagent to a 1.0 mM solution of $\mathbf{1c}_3\cdot(\mathit{R}\mathrm{CYA})_6$ in [D_2]dichloromethane. In contrast to racemic assembly $\mathbf{1c}_3\cdot(\mathrm{DEB})_6$, no splitting of the signals was observed (Figure 4c and d).

component ($\mathbf{1d}_3\cdot(\mathrm{DEB})_6$). This makes perfect sense if the location of the chiral centers with respect to the calix[4]arene is considered (Figure 2). When present in the cyanurate component, the chiral center is located on the left-hand side of the calix[4]arene (*P* isomer), whereas it is located on the right-hand side when present in the dimelamine component.

The CD spectrum of assembly $\mathbf{1b}_3\cdot(\mathit{R}\mathrm{CYA})_6$ shows a Cotton effect at 335 nm ($\Delta\varepsilon_{335} = -25\ \mathrm{L\,mol^{-1}\,cm^{-1}}$) originating from the NO_2-substituted phenyl groups of the calix[4]arenes. This unambiguously shows that the chiral centers present in *R*CYA create a chiral environment for the NO_2-substituted phenyl groups of **1b**. The enantiomeric assembly (*M*)-$\mathbf{1b}_3\cdot(\mathit{S}\mathrm{CYA})_6$ forms when *S*CYA is used; this is clearly reflected in the identical ^{1}H NMR spectrum and the mirror-

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image CD curve. Similar results ($de \geq 98\,\%$) were obtained for combinations of *R*CYA (and *S*CYA) with achiral dimelamines **1a** and **1c**.

In addition, it was found that the amino-acid-derivatized cyanurates *S*PheCYA, *S*ValCYA, and *S*LeuCYA all quantitatively induce chirality in assemblies formed with any one of the achiral dimelamines **1a**, **1b**, or **1c** ($de > 98\,\%$). The ^{1}H NMR spectra, recorded variously in [D]chloroform, [D_8]toluene, or [D_6]benzene, all show the exclusive presence of one diastereomer. The CD curves all have shapes and intensities similar to those of assemblies $(\mathbf{1d-g})_3\cdot(DEB)_6$ ($\Delta\varepsilon_{max} \sim 100\,L\,mol^{-1}\,cm^{-1}$). The negative sign of the CD curves shows that all L-amino-acid-based cyanurates induce *P* chirality in the corresponding assemblies.

Induction of supramolecular chirality through the use of chiral barbiturates: All chiral dimelamines and cyanurates so far studied quantitatively induce supramolecular chirality in assemblies $\mathbf{1}_3\cdot(CA)_6$. A common characteristic of all these components is that the chiral centers are located at the closest possible proximity (at C_α) to the core of the assemblies. In order to determine the inducing effect of chiral centers more remote from the core, the assembly behavior of chiral barbiturates *R*BAR and *S*BAR, with chiral centers at C_β, was studied.

Assembly of **1b** with either *R*BAR or *S*BAR results in the quantitative formation of assemblies $\mathbf{1b}_3\cdot(RBAR)_6$ and $\mathbf{1b}_3\cdot(SBAR)_6$, as shown by ^{1}H NMR spectroscopy. In contrast to previously studied assemblies incorporating chiral components, the ^{1}H NMR spectrum of assembly $\mathbf{1b}_3\cdot(RBAR)_6$ in [D]chloroform contains *two* sharp sets of signals for all protons (the $\delta = 13-15$ region is depicted in Figure 10a). The unequal intensities of the signals show that two different isomers of assembly $\mathbf{1b}_3\cdot(RBAR)_6$ are present. Based on symmetry arguments, the number of signals can only be explained by the presence of both the *M* and *P* diastereomers of $\mathbf{1b}_3\cdot(RBAR)_6$, with a uniform orientation of the *R*BAR components.[38] Corey–Pauling–Kultun models indeed suggest that the NO_2 groups in **1b** only allow one orientation of the *R*BAR units in assembly $\mathbf{1b}_3\cdot(RBAR)_6$, with the chiral substituent pointing away from the assembly. The concentrations of both diastereomers were determined by integration of the NH_{DEB} signals, which gave a *de* of 17% ($\Delta G^\circ(298\,K) = 0.9\,kJ\,mol^{-1}$). From the positive CD curve measured for assembly $\mathbf{1b}_3\cdot(RBAR)_6$, it was concluded that the *M* diastereomer has the higher thermodynamic stability ($-\Delta G^\circ_P < -\Delta G^\circ_M$) (Figure 10d).

Remarkably, the *de* is strongly solvent-dependent (Figure 10b and c). In [D_8]toluene, a much higher *de* of 88% ($\Delta G^\circ_{M/P}(298\,K) = 6.9\,kJ\,mol^{-1}$) was observed. In [$D_6$]benzene, signals corresponding to the unfavorable *P* diastereomer were hardly detectable; this means that *R*BAR nearly quantitatively induces *M* chirality in assembly $\mathbf{1b}_3\cdot(RBAR)_6$ ($de = 96\,\%$; $\Delta G^\circ_{M/P}(298\,K) = 9.6\,kJ\,mol^{-1}$). The reason for the large difference between chloroform and toluene/benzene is not known, but could be due to the increased strength of H-bonds in apolar solvents such as toluene and benzene. This reduces the flexibility of the assembly, thus enhancing the steric effects at its periphery.

Different results were obtained for assemblies $\mathbf{1a}_3\cdot(RBAR)_6$ and $\mathbf{1c}_3\cdot(RBAR)_6$, which lack the NO_2 substituents of **1b**. The ^{1}H NMR spectra of $\mathbf{1a}_3\cdot(RBAR)_6$ and $\mathbf{1c}_3\cdot(RBAR)_6$ show a large number of signals (>10) in the $\delta = 13-15$ region, which prevents determination of the *de*. Apparently, in the absence of the NO_2 substituents, two different orientations for *R*BAR are possible; this results in a large number of different isomers of assemblies $\mathbf{1a}_3\cdot(RBAR)_6$ and $\mathbf{1c}_3\cdot(RBAR)_6$.

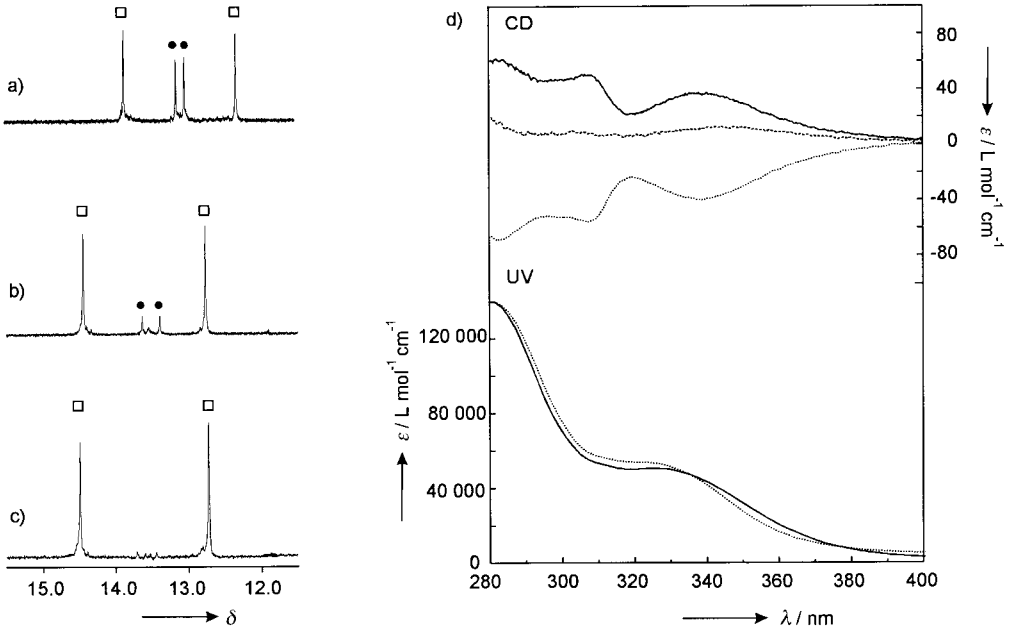
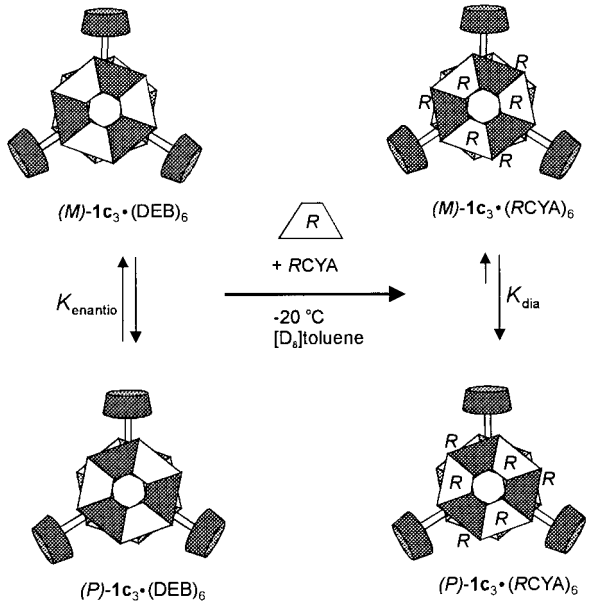


Figure 10. Part of the ^{1}H NMR spectrum of assembly $\mathbf{1b}_3\cdot(RBAR)_6$ in: a) [D]chloroform, b) [D_8]toluene, and c) [D_6]benzene. All spectra were recorded at 1.0 mM concentrations at 298 K. □ = *M* diastereoisomer, ● = *P* diastereoisomer, d) CD spectra of assembly $\mathbf{1b}_3\cdot(RBAR)_6$ in chloroform (- - - -) and benzene (——), and assembly $\mathbf{1b}_3\cdot(SBAR)_6$ in benzene (••••), together with UV spectra of assembly $\mathbf{1b}_3\cdot(RBAR)_6$ in chloroform (- - - -) and benzene (——). All spectra were recorded at 1.0 mM concentrations at 298 K.

The assembly studies with *R*BAR and *S*BAR clearly show that the location of the chiral centers with respect to the assembly core is critical for chiral induction. The smaller inducing effect of chiral barbiturates *R*BAR and *S*BAR in comparison with those of chiral cyanurates and dimelamines is attributed to the increased distance between the chiral centers and the core of the assembly.

Observation of error correction in H-bonded assemblies: All assembly studies described so far were performed under thermodynamically controlled conditions: the assemblies were at thermodynamic equilibrium when the measurements (^{1}H NMR or CD) were performed. In order to learn more about the chiral induction process, experiments were performed under conditions in which the thermodynamic equilibrium was reached slowly.

Assembly $\mathbf{1c}_3\cdot(\mathrm{DEB})_6$ is, by definition, present as a racemic mixture of the *M* and *P* enantiomers (Scheme 5). Upon addition of 1.2 equivalents of *R*CYA (relative to DEB) to a 1.0 mM solution of $\mathbf{1c}_3\cdot(\mathrm{DEB})_6$ at $-20\,^\circ$C, the barbiturates are replaced by cyanurates, because of their higher affinity for the melamine units.[7, 39, 40] As a result, a 50:50 mixture of the *M* and *P* diastereomers of $\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$ is formed, as judged from the presence of two main sets of signals for the NH protons in the resulting ^{1}H NMR spectrum of assembly $\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$ (Figure 11a). The additional small signals most probably arise from heteromeric assemblies containing both DEB and *R*CYA. Previously reported kinetic studies have revealed that under these conditions ($-20\,^\circ$C, [D$_8$]toluene) the interconversion between the *M* and *P* enantiomers is very slow.[41] As a result, both the *M* and *P* diastereomers of $\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$ are initially formed in equal amounts as the kinetic products of the exchange reaction.



Scheme 5. The addition of 1.2 equivalents of *R*CYA (relative to DEB) to a 1.0 mM solution of assembly $\mathbf{1c}_3\cdot(\mathrm{DEB})_6$ in [D$_8$]toluene at 253 K results in the formation of diastereomeric assemblies (*M*)-$\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$ and (*P*)-$\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$.

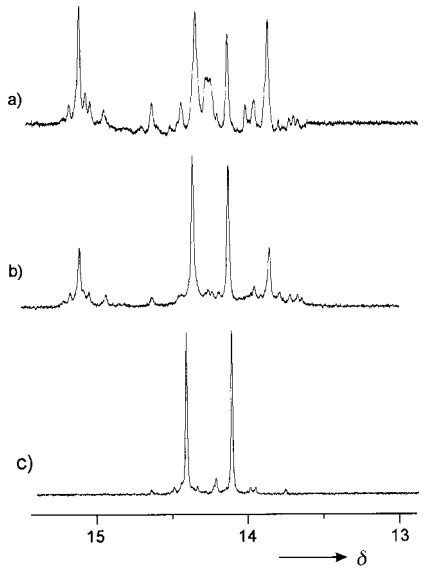


Figure 11. Part of the ^{1}H NMR spectrum of assembly $\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$ in [D$_8$]toluene: a) immediately after the addition of *R*CYA at 253 K, b) at 273 K ($\sim$10 minutes), and c) at 298 K ($\sim$20 minutes).

However, with increasing temperature, the two signals at $\delta =$ 15.10 and 13.86 slowly disappear (Figure 11b) and ultimately only one set of signals remains, at $\delta = 14.52$ and 14.21 (Figure 11c).[42] These signals correspond to the *P* diastereomer of $\mathbf{1c}_3\cdot(R\mathrm{CYA})_6$, which has the highest thermodynamic stability. These results clearly illustrate the error-correction process that occurs in dynamic assemblies, and which is one of the most attractive properties of noncovalent synthesis.

Spontaneous resolution under dynamic conditions: The exclusive formation of assemblies (*M*)-$\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and (*P*)-$\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ shows the strong preference of dimelamines **1d** and **1e** to become incorporated into assemblies with *M* or *P* chirality, respectively. In order to study the possibility of whether **1d** or **1e** can also adopt the unfavorable *P* or *M* configurations, mixtures of assemblies (*M*)-$\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and (*P*)-$\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ were studied.[21] The exchange of achiral components **1a** and **1b** in a mixture of racemic homomeric assemblies $\mathbf{1a}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1b}_3\cdot(\mathrm{DEB})_6$ causes the formation of heteromeric assemblies $\mathbf{1a}_n\mathbf{1b}_{3-n}\cdot(\mathrm{DEB})_6$ ($n = 1,2$). Previously, ^{1}H NMR studies showed that, for these assemblies, the distribution is nearly statistical (homomer/heteromer = 1:3).[43] Mixtures of diastereomerically pure assemblies (*M*)-$\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and (*P*)-$\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ display completely different behavior. The ^{1}H NMR spectrum of a 1:1 mixture of these assemblies in [D$_8$]toluene is identical to that of the separate assemblies (Figure 12a–c). No additional signals were observed; this indicates that the heteromeric assemblies $\mathbf{1d}_n\mathbf{1e}_{3-n}\cdot(\mathrm{DEB})_6$ ($n = 1,2$) were not formed to a significant extent. Titration experiments of (*M*)-$\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ with (*P*)-$\mathbf{1e}_3\cdot(\mathrm{DEB})_6$, monitored by CD spectroscopy, show similar results (i.e., a strictly linear decrease in the CD intensity (Figure 12d)). Other systems commonly show a different dependence of the CD intensity on the *R*:*S* ratio.[44, 45] In those

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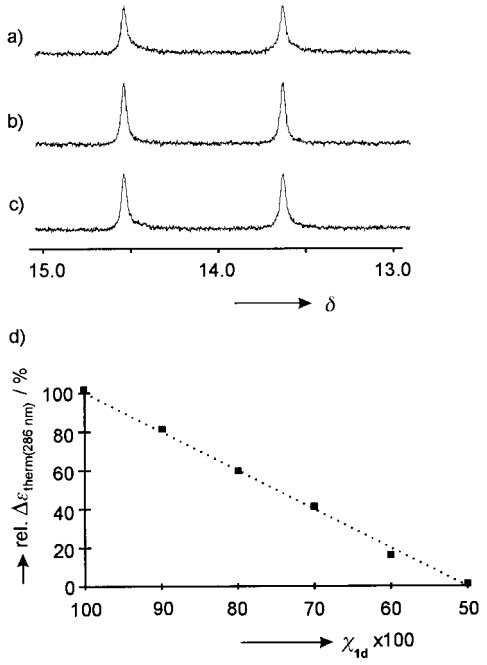

Figure 12. Sections of the ^{1}H NMR spectra of: a) $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$, b) $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$, and c) a 1:1 mixture of $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$. All spectra were recorded in [D_8]toluene (1.0 mM) at 298 K. d) Plot of the CD intensity at 286 nm (■) versus the mole fraction of **1d** in a mixture of assemblies $\mathbf{1d}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1e}_3\cdot(\mathrm{DEB})_6$. The dashed line represents the expected curve if no heteromeric assemblies $\mathbf{1d}_n\mathbf{1e}_{3-n}\cdot(\mathrm{DEB})_6$ ($n=1,2$) are formed. All CD spectra were recorded in toluene (1.0 mM) at 298 K.

cases, the supramolecular chirality of the assemblies is determined by the excess of *R* over *S* components or vice versa, a principle commonly referred to as the "majority rule".[44] For the assemblies discussed here, this would imply that assembly $\mathbf{1d}_2\mathbf{1e}\cdot(\mathrm{DEB})_6$ should have a preference for *M* chirality, since it incorporates two *R* components **1d** and one *S* component **1e**. Analogously, assembly $\mathbf{1d1e}_2\cdot(\mathrm{DEB})_6$ should have a preference for *P* chirality. The presence of these heteromeric assemblies would result in a nonlinear decrease in the CD intensity for increasing amounts of (*P*)-$\mathbf{1e}_3\cdot(\mathrm{DEB})_6$ up to 50%. The observed linear decrease thus implies that components **1d** and **1e** do not participate in the heteromeric assemblies $\mathbf{1d}_n\mathbf{1e}_{3-n}\cdot(\mathrm{DEB})_6$ ($n=1,2$); this emphasizes their strong preference either for *M* or for *P* helicity.

The self-resolution displayed in solution by these H-bonded assemblies had previously only been observed for H-bonded assemblies in the solid[17] and liquid-crystalline[46] states. Very recently, Davis et al. reported a similar enantiomeric self-sorting in a racemic mixture of D- and L-isoguanosines.[47, 48]

Assemblies incorporating both chiral dimelamines and chiral cyanurates: All studies discussed so far have demonstrated the quantitative inducing effect of both chiral cyanurates and dimelamines on the supramolecular chirality of the corresponding assemblies. This raises the question of what happens if both components **1** and CA are chiral and have opposite preferences for *M* or *P* chirality. Therefore, the assembly behavior of both **1d** and its enantiomer **1e** with chiral cyanurate *S*CYA was studied. ^{1}H NMR spectra recorded in [D_2]dichloromethane reveal the formation of both assemblies $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ and $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$ (Figure 13a and b). Both spectra show sharp signals, indicating well-defined assemblies. Integral comparison of the CH_2 bridge protons of dimelamines **1d** and **1e** with the NH_{SCYA} protons shows that both assemblies $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ and $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$ form nearly quantitatively ($\geq$98 and 95%, respectively). The difference between the ^{1}H NMR spectra reveals the diastereomeric relationship between assemblies $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ and $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$. CD spectroscopy shows a strong optical activity for assembly $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ with characteristic shape and intensity (Figure 13c). The positive sign shows that assembly $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ displays *M* chirality. This is consistent with previous studies that revealed that both **1d** and *S*CYA induce *M* chirality. On the other hand, assembly $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$ is hardly CD active (Figure 13c).[49] This shows that the conflicting chiral components **1e** and *S*CYA either strongly affect the orientation of the chromophores responsible for the CD activity or coincidentally cause identical but opposite CD activity. The absence of the characteristic CD curve prevents the assignment of either *M* or *P* chirality to assembly $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$.

The difference in assembly behavior of any of the chiral cyanurates *S*PheCYA, *S*ValCYA, or *S*LeuCYA with dimel-

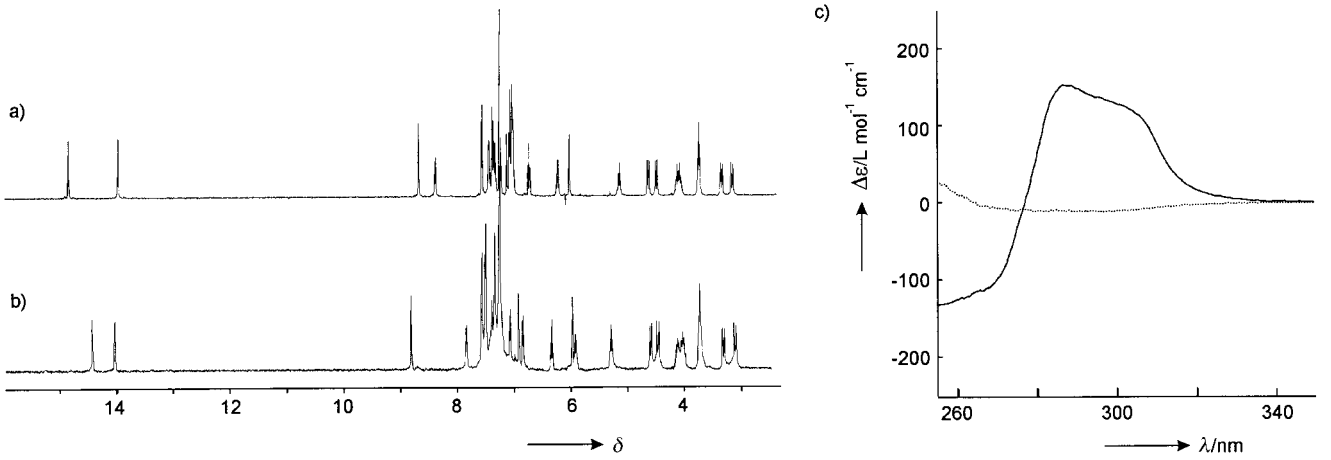

Figure 13. ^{1}H NMR spectra of: a) assembly $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ and b) $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$ in [D_2]dichloromethane (1.0 mM) at 298 K. c) CD spectra of $\mathbf{1d}_3\cdot(S\mathrm{CYA})_6$ (——) and $\mathbf{1e}_3\cdot(S\mathrm{CYA})_6$ (••••) in dichloromethane (1.0 mM) at 298 K.

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amines **1d** and **1e** is even more pronounced. Assembly of **1e** with any one of these cyanurates in [D]chloroform or [D_8]toluene results in the clean formation of assemblies $\mathbf{1e}_3\cdot(S\text{PheCYA})_6$, $\mathbf{1e}_3\cdot(S\text{ValCYA})_6$, or $\mathbf{1e}_3\cdot(S\text{LeuCYA})_6$, as concluded from the ^{1}H NMR spectra (Figure 14a). The sharp signals indicate the formation of well-defined, highly symmetrical assemblies. Furthermore, all assemblies exhibit the bisignate CD curve characteristic for assemblies with *P* chirality. The maximum CD intensity for assembly $\mathbf{1e}_3\cdot(S\text{PheCYA})_6$ ($\Delta\varepsilon_{max} = -124\ \text{L mol}^{-1}\text{cm}^{-1}$) is slightly higher than commonly observed ($\Delta\varepsilon_{max} \sim 100\ \text{L mol}^{-1}\text{cm}^{-1}$); this might be caused by the increased number of chromophores (Figure 14c). Earlier it was shown that **1e** and any one of these *S* cyanurates all induce *P* chirality in the corresponding assemblies. Therefore, no conflicting chiral information that would prevent assembly formation is present in the components of $\mathbf{1e}_3\cdot(S\text{PheCYA})_6$, $\mathbf{1e}_3\cdot(S\text{ValCYA})_6$, and $\mathbf{1e}_3\cdot(S\text{LeuCYA})_6$.

The assembly behavior of **1d** with *S*PheCYA, *S*ValCYA, or *S*LeuCYA is completely different. A chirality conflict arises, because **1d** has a preference for *M* chirality. As a result, $\mathbf{1d}_3\cdot(S\text{PheCYA})_6$, $\mathbf{1d}_3\cdot(S\text{ValCYA})_6$, and $\mathbf{1d}_3\cdot(S\text{LeuCYA})_6$ do not form. Only broad signals were observed in the ^{1}H NMR spectra of these mixtures in both [D]chloroform and [D_8]toluene; this indicates the formation of undefined assemblies (Figure 14b). H-Bonding must take place, as downfield signals are observed in the $\delta = 13-15$ region. In addition, the CD curves have a completely different shape from the CD curves commonly observed for well-defined double-rosette assemblies (Figure 14c). Compared to cyanurate *R*CYA, the amino-acid-derivatized cyanurates *S*PheCYA, *S*ValCYA, and *S*LeuCYA apparently either have less flexibility to adapt to the unfavorable *M* chirality induced by chiral dimelamines **1d** or simply do not fit.

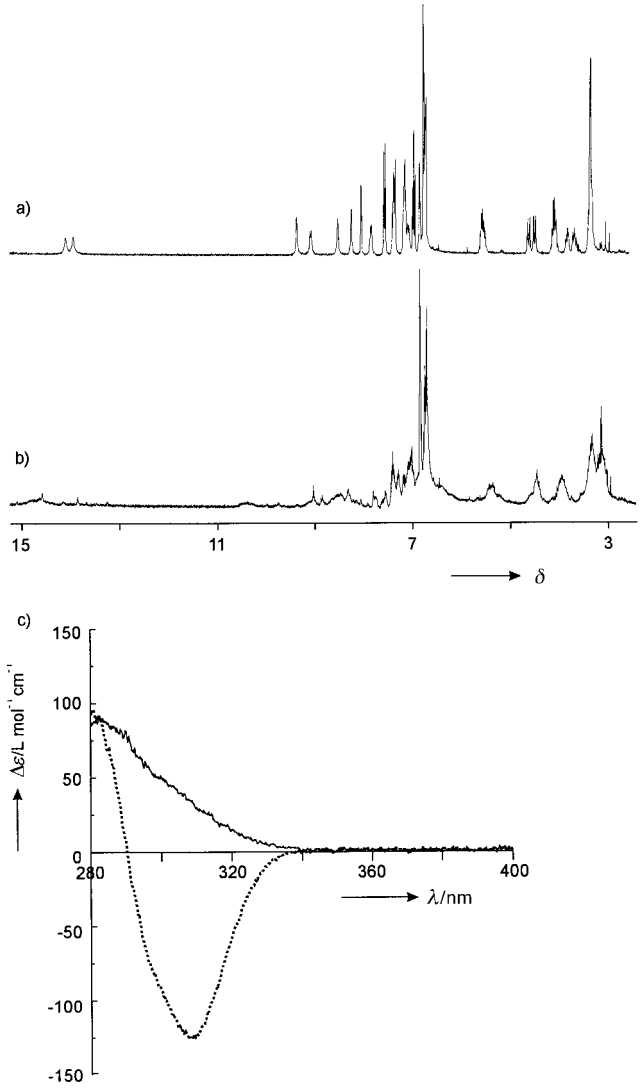

Figure 14. ^{1}H NMR spectra of: a) assembly $\mathbf{1e}_3\cdot(S\text{PheCYA})_6$, and b) assembly $\mathbf{1d}_3\cdot(S\text{PheCYA})_6$ in [D_8]toluene (1.0 mM) at 298 K. c) CD spectra of assemblies $\mathbf{1e}_3\cdot(S\text{PheCYA})_6$ (••••) and $\mathbf{1d}_3\cdot(S\text{PheCYA})_6$ (——) in toluene (1.0 mM) at 298 K.

Conclusion

The supramolecular chirality of assemblies $\mathbf{1}_3\cdot(\text{CA})_6$ can be controlled quantitatively ($de \geq 98\,\%$) by the incorporation of chiral centers into either the calix[4]arene dimelamine or the cyanurate components. The high degree of induction is a result of the presence of a total of six chiral centers in close proximity to the core of the assemblies. The studies with chiral barbiturates show that the chiral induction is much less when the chiral centers are present at the C_β-position. Furthermore, these studies showed that the extent of chiral induction is highly solvent dependent. A quantitative induction of chirality ($de = 96\,\%$) was only observed in benzene. All assemblies are strongly CD active, in contrast to the individual components, which hardly show any CD activity. This makes CD spectroscopy a suitable tool with which to study assembly formation with dilution or titration studies. The assemblies display spontaneous resolution under thermodynamically controlled conditions, that is, no heteromeric assemblies containing both *M*- and *P*-inducing components are observed. This strong preference becomes even more evident when the assembly behavior of chiral dimelamines and chiral cyanurates is considered. Generally, well-defined assemblies only form when the complementary components contain unidirectional information.

Application of the results described in this paper, for example in nanotechnology[52a] and for selective guest recognition, are currently under investigation. Interesting results in both areas have recently come forward and will be described shortly.[52b, 53]

Experimental Section

THF was freshly distilled from Na/benzophenone, EtOAc and hexane (referring here to the petroleum ether fraction with b.p. 60–80 °C) from K_2CO_3, and CH_2Cl_2 from $CaCl_2$. All chemicals were of reagent grade and used without further purification. NMR spectra were recorded either on a Bruker AC250 (250 MHz) or on a Varian Unity 300 (^{1}H NMR 300 MHz) spectrometer at room temperature. Residual solvent protons were used as internal standard, and chemical shifts are given relative to tetramethylsilane (TMS). CD spectra were recorded on a JASCO J-715 spectropolarimeter at room temperature. UV/Vis spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer at room temperature. FAB-MS spectra were recorded with a Finnigan MAT90 spectrom-

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eter, with *m*-nitrobenzyl alcohol (NBA) as a matrix. EI mass spectra were recorded on a Finnigan MAT 90 spectrometer with an ionizing voltage of 70 eV. MALDI-TOF measurements were performed on a PerSeptive Biosystems Voyager-DE-RP MALDI-TOF mass spectrometer equipped with delayed extraction.[50] A UV nitrogen laser ($\lambda = 337$ nm) that produced 3 ns pulses was used, and the mass spectra were obtained both in the linear and in the reflectron modes. Mass assignments were performed with nonmanipulated spectra (no smoothing or centering, etc.). Elemental analyses were performed with a Carlo Erba EA1106. The presence of solvents in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Flash column chromatography was performed with silica gel (SiO_2, 0.040–0.063 mm, 230–240 mesh, Merck).

Calix[4]arene dimelamines **1a**–**1c** and bis(chlorotriazine) **2** were synthesized according to literature procedures.[24] Barbiturate DEB was obtained from Fluka.

General procedure for the synthesis of calix[4]arene dimelamines 1: A solution of bis(chlorotriazine) **2**, diisopropylethylamine (12 equiv.), and the corresponding amine (36 equiv.) in THF (25–50 mL) was heated under reflux for 12 h. The mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (2 × 25 mL) and brine (25 mL), and dried over Na_2SO_4. Evaporation of the solvent gave **1** as a crude product, which was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 90:9.5:0.5).

5,17-*N*,*N*′-Bis[4-amino-6-(*R*)-1-phenylethylamino-1,3,5-triazin-2-yl]diamino-25,26,27,28-tetrapropoxycalix[4]arene (1d): Compound **1d** was obtained as a white solid (65%). ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.5$ (brs, 2H; NH), 7.4–7.2 (m, 12H; ArH, NH), 6.2–6.1 (m, 14H; ArH, NH_2), 5.26 (brs, 2H; C*H*CH$_3$), 4.32, 3.02 (ABq, ^2J(H,H) = 12.8 Hz, 8H; ArCH_2Ar), 3.89, 3.63 (2t, ^3J(H,H) = 8.3 Hz, 8H; OCH$_2$), 2.1–1.8 (m, 8H; OCH$_2$CH_2), 1.42 (d, ^3J(H,H) = 6.1 Hz, 6H; CHCH_3), 1.09, 0.89 (t, ^3J(H,H) = 7.4 Hz, 12H; OCH$_2$CH$_2$CH_3); MS (FAB): *m/z*: 1049.6 ([M^++H], calcd: 1049.6); elemental analysis calcd (%) for $C_{62}H_{72}N_{12}O_4 \cdot 0.2\,CH_3OH$: C 70.76, H 6.95, N 15.92; found C 70.56, H 6.83, N 15.85.

5,17-*N*,*N*′-Bis[4-amino-6-(*S*)-1-phenylethylamino-1,3,5-triazin-2-yl]diamino-25,26,27,28-tetrapropoxycalix[4]arene (1e): Compound **1e** was obtained as a white solid (67%). The ^{1}H NMR and FAB-MS spectrum of **1e** were identical to those of compound **1d**; elemental analysis calcd (%) for $C_{62}H_{72}N_{12}O_4 \cdot 0.2\,CH_3OH$: C 70.76, H 6.95, N 15.92; found C 70.43, H 6.75, N 15.62.

5,17-*N*,*N*′-Bis[4-amino-6-(*R*)-1-naphthylethylamino-1,3,5-triazin-2-yl]diamino-25,26,27,28-tetrapropoxycalix[4]arene (1f): Compound **1f** was obtained as a white solid (75%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta =$ 8.6 (brs, 2H; NH), 8.3 (brs, 2H; NH), 7.9–7.2 (m, 18H; ArH), 6.3–6.2 (m, 10H; ArH, NH_2), 6.1 (brs, 2H; CHCH$_3$), 4.32, 3.03 (ABq, ^2J(H,H) = 12.8 Hz, 8H; ArCH_2Ar), 3.80, 3.63 (2t, ^3J(H,H) = 8.3 Hz, 8H; OCH$_2$), 1.9–1.8 (m, 8H; OCH$_2$CH_2), 1.62 (d, ^3J(H,H) = 6.1 Hz, 6H; CHCH_3), 1.15, 0.91 (t, ^3J(H,H) = 7.4 Hz, 12H; OCH$_2$CH$_2$CH_3); MS (FAB): *m/z*: 1149.6 ([M^++H], calcd: 1149.6); elemental analysis calcd (%) for $C_{70}H_{76}N_{12}O_4 \cdot 0.2\,CH_3OH$: C 72.97, H 6.69, N 14.55; found C 72.77, H 6.61, N 14.89.

5,17-*N*,*N*′-Bis[4-amino-6-(*N*-l-alaninemethylester)-1,3,5-triazin-2-yl]diamino-25,26,27,28-tetrapropoxycalix[4]arene (1g): Compound **1g** was obtained as a white solid (43%). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.5$ (brs, 2H; NH), 7.4–7.3 (m, 4H; ArH), 7.0 (brs, 2H; NH), 6.2–6.1 (m, 10H; ArH, NH_2), 4.5 (brs, 2H; C*H*CH$_3$), 4.30, 3.08 (ABq; ^2J(H,H) = 12.8 Hz, 8H; ArCH_2Ar), 3.88, 3.70 (2t, ^3J(H,H) = 8.3 Hz, 8H; OCH$_2$), 3.61 (s, 6H; OCH$_3$), 1.9–1.8 (m, 8H; OCH$_2$CH_2), 1.33 (d, ^3J(H,H) = 7.0 Hz, 6H; CHCH_3), 1.06, 0.87 (t, ^3J(H,H) = 7.4 Hz, 12H; OCH$_2$CH$_2$CH_3); MS (FAB): *m/z*: 1013.4 ([M^++H], calcd: 1013.5); elemental analysis calcd (%) for $C_{54}H_{68}N_{12}O_8 \cdot 0.2\,CH_3OH$: C 63.86, H 6.80, N 16.49; found C 63.74, H 6.73, N 16.40.

***N*-[(*R*)-1-Phenylethyl]imidocarbonic acid ((*R*)-3)**: Nitrobiuret[32] (2.3 g, 15.5 mmol) was added to a solution of (*R*)-1-phenylethylamine (1.88 g, 15.5 mmol) in DMF (25 mL) and H_2O (5 mL). The mixture was heated at 95 °C for 1 h, after which a second portion of nitrobiuret (1.88 g, 15.5 mmol) was added. Heating was continued for 1 hour, after which a final portion of nitrobiuret (1.88 g, 15.5 mmol) was added. After having been heated for another hour, the mixture was cooled to room temperature, and H_2O (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were washed with 1N HCl (2 × 25 mL) and brine (25 mL), and dried over $MgSO_4$. After evaporation of the solvents, compound (*R*)-**3** was obtained as a colorless oil (3.0 g, 93%). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.51$ (s, 1H; C(=O)NHC(=O)), 7.91 (d; ^3J(H,N) = 7.3 Hz, 1H; C*HN*HC(=O)), 7.33–7.20 (m, 5H; Ar*H*), 6.73 (s, 2H; NH_2), 4.80 (dq, ^3J(H,H) = 7.3 Hz, 1H; C*H*), 1.35 (d, ^3J(H,H) = 7.3 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 155.4$, 153.5, 144.3, 128.4, 126.8, 125.6, 48.4, 22.8; MS (EI): *m/z*: 207.1 ([M^++H], calcd: 208.1).

***N*-[(*S*)-1-Phenylethyl]imidocarbonic acid ((*S*)-3)**: Compound (*S*)-**3** was obtained as a colorless oil (97%) by the same procedure as used for (*R*)-**3**. The ^{1}H and ^{13}C NMR and the MS spectra of (*S*)-**3** were identical to those of compound (*R*)-**3**.

***N*-[(*R*)-1-Phenylethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (*R*CYA)**: Compound (*R*)-**3** (1.0 g, 4.8 mmol) and diethyl carbonate (1.20 g, 10.2 mmol) were added to a solution of Na (0.34 g, 14.8 mmol) in EtOH (20 mL), and the mixture was heated under reflux overnight. After the mixture had cooled to room temperature, toluene (25 mL) was added, and the resulting precipitate was filtered off and redissolved in H_2O (25 mL). The solution was acidified with 6N HCl to pH ~ 1–2, after which the resulting precipitate was collected, washed with H_2O (2 × 25 mL), and dried under high vacuum. *R*CYA was obtained as a white solid (80%). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): $\delta = 11.4$ (s, 2H; NH), 7.30–7.20 (m, 5H; ArH), 5.80 (q, ^3J(H,H) = 7.3 Hz, 1H; C*H*), 1.72 (d, ^3J(H,H) = 7.3 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 149.5$, 148.6, 140.2, 128.0, 126.7, 126.2, 49. 9, 16.2; MS (FAB): *m/z*: 234.1 ([M^++H], calcd: 234.1); elemental analysis calcd (%) for $C_{11}H_{11}N_3O_3 \cdot 0.3\,H_2O$: C 55.37, H 4.90, N 17.61; found C 55.27, H 4.94, N 17.33.

***N*-[(*S*)-1-Phenylethyl]-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (*S*CYA)**: Compound *S*CYA was obtained as a white solid (85%) by the same procedure as used for *R*CYA. The ^{1}H and ^{13}C NMR and FAB-MS spectra of *S*CYA were identical to those of compound *R*CYA; elemental analysis calcd (%) for $C_{11}H_{11}N_3O_3$: C 56.65, H 4.75, N 18.02; found C 56.55, H 4.73, N 17.86.

General procedure for the synthesis of cyanurates *S*PheCYA, *S*ValCYA, and *S*LeuCYA (Method B):[33] This reaction must be performed under flame-dried conditions and under a continuous flow of argon. Before leaving the system, the argon was passed through water in order to trap any phosgene formed. The HCl salt of the corresponding methyl-ester-protected amino acid was suspended in THF, and *N*-chlorocarbonyl isocyanate (2 equiv.) was added slowly. After being stirred at room temperature for 2 hours, the mixture was heated under reflux for 2 days. After evaporation of the solvent, the residue was redissolved in CH_2Cl_2 (50 mL), washed with H_2O (2 × 25 mL), dried over Na_2SO_4, and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 90:9.5:0.5). Occasionally, the products were recrystallized from MeOH.

***N*-(l-Phenylalanine methyl ester)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (*S*PheCYA)**: Compound *S*PheCYA was obtained as a white solid (62%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 11.61$ (s, 2H; NH), 7.28–7.15 (m, 5H; ArH), 5.46 (dd, ^3J(H,H) = 5.7 Hz, ^3J(H,H) = 10.2 Hz, 1H; C*H*), 3.39 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 5.7 Hz, 1H; C*H*HC*H*H), 3.65 (s, 3H; OCH_3), 3.17 (dd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 10.2 Hz, 1H; C*H*HC*H*H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 164.1$, 143.6, 142.4, 131.5, 124.5, 124.2, 122.7, 51.1, 48.5, 29.8; MS (FAB): *m/z*: 292.1 ([M^++H], calcd: 292.1); elemental analysis calcd (%) for $C_{13}H_{13}N_3O_5$: C 53.61, H 4.50, N 14.43; found C 53.62, H 4.56, N 14.42.

***N*-(l-Valine methyl ester)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (*S*ValCYA)**: Compound *S*ValCYA was obtained as a white solid (50%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 11.73$ (s, 2H; NH), 4.72 (d, ^3J(H,H) = 9.3 Hz, 1H; C*H*), 3.59 (s, 3H; OCH$_3$), 2.51–2.40 (m, 1H; C*H*CH), 1.10 (d, ^3J(H,H) = 6.6 Hz, 3H; CCH$_3$), 0.77 (d, ^3J(H,H) = 6.9 Hz, 3H; CCH$_3$); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 164.8$, 145.5, 144.1, 54.1, 48.0, 23.3, 17.4, 14.6; MS (FAB): *m/z*: 244.1 ([M^++H], calcd: 244.1); elemental analysis calcd (%) for $C_9H_{13}N_3O_5$: C 44.45, H 5.39, N 17.28; found C 44.55, H 5.50, N 17.25.

***N*-(l-Leucine methyl ester)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (*S*LeuCYA)**: Compound *S*LeuCYA was obtained as a white solid in 66% yield. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 11.67$ (s, 2H; NH), 5.13 (dd, ^3J(H,H) = 5.7 Hz, ^3J(H,H) = 8.7 Hz, 1H; C*H*), 3.60 (s, 3H; OCH$_3$), 1.87 (m, 2H; CH$_2$), 1.53 (m, 1H; C*H*(CH$_3$)$_2$), 0.87 (d, ^3J(H,H) = 6.6 Hz, 3H; CHCH_3), 0.85 (d, ^3J(H,H) = 6.6 Hz, 3H; CHCH_3); ^{13}C NMR (75 MHz,

[D_6]DMSO, 25 °C): δ = 165.7, 145.3, 144.3, 48.3, 47.7, 33.1, 20.3, 18.9, 17.5; MS (FAB): *m/z*: 258.1 ([M^++H], calcd: 258.1); elemental analysis calcd (%) for $C_{10}H_{15}N_3O_5$: C 46.69, H 5.88, N 16.33; found C 46.82, H 5.91, N 16.07.

(*R*)-2-Phenyl-1-bromopropane ((*R*)-4):[51] Triphenylphosphine (12.0 g, 45.9 mmol) was added to a mixture of (*R*)-2-phenylpropan-1-ol (5.0 g, 36.7 mmol) and CBr_4 (15.2 g, 45.9 mmol) in the minimum amount of THF (25 mL) required to dissolve the reagents. After being stirred at room temperature for 2 hours, the reaction mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$. Evaporation of the solvent gave (*R*)-**4** as a crude product, which, after filtration, was purified by column chromatography (SiO_2, CH_2Cl_2/hexane 80:20). Compound (*R*)-**4** was obtained as a colorless oil (7.10 g, 97 %). ^{1}H NMR (300 MHz, [D]chloroform, 25 °C): δ = 7.43 – 7.27 (m, 5H; ArH), 3.65 (dd, ^2J(H,H) = 9.9 Hz, ^3J(H,H) = 8.1 Hz, 1H; C*H*HBr), 3.54 (dd, ^2J(H,H) = 9.9 Hz, ^3J(H,H) = 6.3 Hz, 1H; CH*H*Br), 3.34 – 3.10 (m, 1H; CH), 1.49 (d, ^3J(H,H) = 7.2 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, [D]chloroform, 25 °C): δ = 143.23, 128.12, 126.57, 126.51, 41.74, 39.49, 19.50; MS (EI): *m/z*: 200.0 ([M^++H], calcd: 199.0).

(*S*)-2-Phenyl-1-bromopropane ((*S*)-4): Compound (*S*)-**4** was obtained as a white solid (95 %) by following the same procedure as used for (*R*)-**4**. The ^{1}H and ^{13}C NMR and EI-MS spectra of (*S*)-**4** were identical to those of compound (*R*)-**4**.

Diethyl 2-[(*R*)-2-phenylpropyl]-2-ethylmalonate ((*R*)-5): After trituration with hexane, NaH (55 % dispersion in mineral oil, 0.32 g, 7.2 mmol) was suspended in THF (100 mL), and diethyl ethylmalonate (2.3 g, 12.2 mmol) was added dropwise at 0 °C. After the mixture had been stirred for 1 hr at room temperature, (*R*)-**4** (1.2 g, 6.0 mmol) was added, and the mixture was stirred for a further 30 minutes at room temperature and subsequently heated under reflux for 3 days. After evaporation of the solvent, the residue was redissolved in CH_2Cl_2 (100 mL), washed with H_2O (2 × 25 mL) and brine (25 mL), and dried over Na_2SO_4. The solvent was evaporated, and residual diethyl ethylmalonate was removed under high vacuum (p = 0.1 Torr at T = 80 °C). Compound (*R*)-**5** was obtained as a colorless oil (0.73 g, 40 %) after column chromatography (SiO_2, CH_2Cl_2). ^{1}H NMR (300 MHz, [D]chloroform, 25 °C): δ = 7.30 – 7.14 (m, 5H; ArH), 4.13 (dq, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 7.2 Hz, 1H; OC*H*HCH$_3$), 4.12 (dq, ^2J(H,H) = 9.6 Hz, ^3J(H,H) = 7.2 Hz, 1H; OCH*H*CH$_3$), 3.87 (dq, ^2J(H,H) = 10.5 Hz, ^3J(H,H) = 7.2 Hz, 1H; OC*H*HCH$_3$), 3.65 (dq, ^2J(H,H) = 10.5 Hz, ^3J(H,H) = 7.2 Hz, 1H; OCH*H*CH$_3$), 2.81 – 2.69 (m, 1H; C*H*), 2.40 (dd, ^2J(H,H) = 14.4 Hz, ^3J(H,H) = 9.0 Hz, 1H; C*CH*HC), 2.25 (dd, ^2J(H,H) = 14.4 Hz, ^3J(H,H) = 4.8 Hz, 1H; C*CH*HC), 1.97 (dq, ^2J(H,H) = 14.4 Hz, ^3J(H,H) = 7.2 Hz, 1H; CC*H*HCH$_3$), 1.94 (dq, ^2J(H,H) = 14.4 Hz, ^3J(H,H) = 7.2 Hz, 1H; CC*H*HCH$_3$), 1.26 (d, ^3J(H,H) = 7.2 Hz, 3H; C*CH$_3$), 1.23 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH$_2$C*H*$_3$), 1.10 (t, ^3J(H,H) = 7.2 Hz, 3H; OCH$_2$C*H*$_3$), 0.78 (t, ^3J(H,H) = 7.2 Hz, 3H; CCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, [D]chloroform, 25 °C): δ = 171.35, 170.71, 146.23, 127.62, 126.77, 125.56, 60.42, 60.17, 56.85, 38.39, 35.22, 24.57, 24.33, 13.49, 13.25, 7.91; MS (FAB, glycerine matrix): *m/z* 307.2 ([M^++H], calcd: 307.2).

Diethyl 2-[(*S*)-2-phenylpropyl]-2-ethylmalonate ((*S*)-5): Compound (*S*)-**5** was obtained as a colorless oil (38 %) by the same procedure as used for (*R*)-**5**. The ^{1}H and ^{13}C NMR and FAB-MS spectra of (*S*)-**5** were identical to those of compound (*R*)-**5**.

5-[(*R*)-2-Phenylpropyl]-5′-ethylbarbiturate (*R*BAR): A solution of (*R*)-**5** (0.53 g, 1.7 mmol) in EtOH (5 mL) was added dropwise to a solution of Na (0.17g, 7.3 mmol) in EtOH (20 mL) at room temperature. The mixture was heated under reflux for 2 days, after which the solvent was evaporated. The residue was redissolved in water (50 mL), acidified to pH ~ 2 – 3 with 6 N HCl, and extracted with CH_2Cl_2 (4 × 25 mL). After being dried over Na_2SO_4, the combined organic fractions were evaporated to dryness. Compound *R*BAR was obtained as a white solid (0.18 g, 38 %) after column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 90:9.5:0.5). ^{1}H NMR (300 MHz, [D_8]THF, 25 °C): δ = 10.40 (s, 1H; NH), 9.93 (s, 1H; NH), 7.19 – 7.06 (m, 5H; ArH), 2.81 – 2.69 (m, 1H; C*H), 2.41 (dd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 9.6 Hz, 1H; C*CH*HC), 2.13 (dd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 5.4 Hz, 1H; C*CH*HC), 1.85 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2CH$_3$), 1.16 (d, ^3J(H,H) = 6.9 Hz, 3H; C*CH$_3$), 0.74 (t, ^3J(H,H) = 7.2 Hz, 3H; CH$_2$CH_3); ^{13}C NMR (75 MHz, [D_8]THF, 25 °C): δ = 172.2, 171.5, 148.5, 144.3, 127.4, 126.9, 125.7, 54.3, 45.1, 36.9, 33.9, 22.3, 7.6; MS (FAB): *m/z*: 275.2 ([M^++H], calcd: 275.1); elemental analysis calcd (%) for $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61, N 10.21; found C 65.89, H 6.73, N 9.76.

5-[(*S*)-2-Phenylpropyl]-5′-ethylbarbiturate (*S*BAR): *S*BAR was obtained as a white solid (43 %) by the same procedure as used for *R*BAR. The ^{1}H and ^{13}C NMR and FAB-MS spectra of *S*BAR were identical to those of compound *R*BAR; elemental analysis calcd (%) for $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61, N 10.21; found C 65.52, H 6.30, N 9.66 (± 0.23).

General procedure for the formation of assemblies $1_3 \cdot (CA)_6$: Two methods were randomly used for the formation of H-bonded assemblies $1_3 \cdot (CA)_6$.

Method 1: After both components **1** and CA had been dissolved in a 1:2 ratio in THF, the solvent was evaporated, and the resulting assembly was dried under high vacuum.

Method 2: Components **1** and CA were both suspended, in a 1:2 ratio, in the desired organic solvent. After 30 minutes' sonication, a clear solution of the assembly was obtained.

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[1] J. D. Watson, F. H. C. Crick, *Nature* **1953**, *171*, 737 – 738.
[2] K. Okuyama, S. Arnott, M. Takanyanagi, M. Kakudo, *J. Mol. Biol.* **1981**, *152*, 427 – 443.
[3] H. M. Warrick, J. A. Spudich, *Annu. Rev. Cell. Biol.* **1987**, *3*, 379 – 422.
[4] G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen, D. M. Gordon, *Acc. Chem. Res.* **1995**, *28*, 37 – 44.
[5] D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242 – 1286; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154 – 1194.
[6] L. J. Prins, D. N. Reinhoudt, P. Timmerman, *Angew. Chem.* **2001**, *113*, 2446 – 2492; *Angew. Chem. Int. Ed.* **2001**, *40*, 2383 – 2426.
[7] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005 – 2062.
[8] F. R. Keene, *Chem. Soc. Rev.* **1998**, *27*, 185 – 193.
[9] J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**.
[10] a) J. Rivera, T. Martín, J. Rebek Jr., *Science* **1998**, *279*, 1021 – 1023; b) R. K. Castellano, C. Nuckolls, J. Rebek Jr., *J. Am. Chem. Soc.* **1999**, *121*, 11156 – 11163.
[11] R. K. Castellano, B. H. Kim, J. Rebek Jr., *J. Am. Chem. Soc.* **1997**, *119*, 12671 – 12672.
[12] E. E. Simanek, S. Qiao, I. S. Choi, G. M. Whitesides, *J. Org. Chem.* **1997**, *62*, 2619 – 2621.
[13] A. L. Marlow, E. Mezzina, G. P. Spada, S. Masiero, J. T. Davis, G. Gottarelli, *J. Org. Chem.* **1999**, *64*, 5116 – 5123.
[14] L. Brunsveld, M. Zhang, M. Glasbeek, J. A. J. M. Vekemans, E. W. Meijer, *J. Am. Chem. Soc.* **2000**, *122*, 6175.
[15] M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee, N. Khazanovich, *Nature* **1993**, *366*, 324 – 327.
[16] N. Kimizuka, T. Kawasaki, K. Hirata, T. Kunitake, *J. Am. Chem. Soc.* **1995**, *117*, 6360 – 6361.
[17] K. C. Russell, J.-M. Lehn, N. Kyritsakas, A. DeCian, J. Fischer, *New J. Chem.* **1998**, *22*, 123 – 128.
[18] M. M. Green, M. P. Rediy, R. J. Johnson, G. Darling, D. J. O'Leary, G. Willson, *J. Am. Chem. Soc.* **1989**, *111*, 6452 – 6454.
[19] L. Brunsveld, B. G. G. Lohmeijer, J. A. J. M. Vekemans, E. W. Meijer, *Chem. Commun.* **2000**, 2305 – 2306.
[20] L. Brunsveld, A. P. H. J. Schenning, M. A. C. Broeren, H. M. Janssen, J. A. J. M. Vekemans, E. W. Meijer, *Chem. Lett.* **2000**, 292 – 293.
[21] L. J. Prins, J. Huskens, F. De Jong, P. Timmerman, D. N. Reinhoudt, *Nature* **1999**, *398*, 498 – 502.
[22] R. H. Vreekamp, PhD Thesis, University of Twente (The Netherlands), **1995**, Chapter 6.
[23] R. H. Vreekamp, J. P. M. Van Duynhoven, M. Hubert, W. Verboom, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1306 – 1309; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1215 – 1218.

  0947-6539/02/0810-2300 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 10

[24] P. Timmerman, R. H. Vreekamp, R. Hulst, W. Verboom, D. N. Reinhoudt, K. Rissanen, K. A. Udachin, J. Ripmeester, *Chem. Eur. J.* **1997**, *3*, 1823 – 1832.
[25] C. T. Seto, G. M. Whitesides, *J. Am. Chem. Soc.* **1990**, *112*, 6409 – 6411.
[26] J.-M. Lehn, M. Mascal, A. DeCian, J. Fischer, *J. Chem. Soc. Chem. Commun.* **1990**, 479 – 480.
[27] J.-L. Weidmann, K. A. Jolliffe, L. J. Prins, P. Timmerman, D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **2000**, *10*, 2077 – 2089.
[28] L. J. Prins, K. A. Jolliffe, R. Hulst, P. Timmerman, D. N. Reinhoudt, *J. Am. Chem. Soc.* **2000**, *122*, 3617 – 3627.
[29] K. A. Jolliffe, M. Crego Calama, R. Fokkens, N. M. M. Nibbering, P. Timmerman, D. N. Reinhoudt, *Angew. Chem.* **1998**, *110*, 1294 – 1297; *Angew. Chem. Int. Ed.* **1998**, *37*, 1247 – 1251.
[30] P. Timmerman, K. A. Jolliffe, M. Crego Calama, J.-L. Weidmann, L. J. Prins, F. Cardullo, B. H. M. Snellink-Ruel, R. Fokkens, N. M. M. Nibbering, S. Shinkai, D. N. Reinhoudt, *Chem. Eur. J.* **2000**, *6*, 4104 – 4115.
[31] V. Prelog, G. Helmchen, *Angew. Chem.* **1982**, *94*, 614 – 631; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567 – 594.
[32] C. T. Seto, J. P. Mathias, G. M. Whitesides, *J. Am. Chem. Soc.* **1993**, *115*, 1321 – 1329.
[33] N. Kimizuka, T. Kawasaki, K. Hirata, T. Kunitake, *J. Am. Chem. Soc.* **1998**, *120*, 4094 – 4104.
[34] A. Arduini, S. Fanni, G. Manfredi, A. Pochini, R. Ungaro, A.-R. Sicuri, F. Ugozzoli, *J. Org. Chem.* **1995**, *60*, 1448 – 1453.
[35] For a comprehensive explanation of CD spectroscopy, see: E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.
[36] N. Harada, K. Nakanishi, *Acc. Chem. Res.* **1972**, *5*, 257 – 263.
[37] L. J. Prins, C. Thalacker, F. Würthner, P. Timmerman, D. N. Reinhoudt, *Proc. Natl. Acad. Sci. USA*, **2001**, *98*, 10042 – 10045.
[38] In principle, a C_{3h}-symmetrical assembly with a uniform orientation of the *R*BAR units could also give rise to four NH_{BAR} proton signals (see ref. [28]). However, the formation of this isomer is sterically impossible when *R*BAR units are used. In addition to this, the signals would all need to have equal intensities.
[39] H. S. Shieh, D. Voet, *Acta Crystallogr. Sect. B: Struct. Sci.* **1976**, *32*, 2354 – 2360 .
[40] M. Mascal, P. S. Fallon, A. S. Batsanov, B. R. Heywood, S. Champ, M. Colclough, *J. Chem. Soc. Chem. Commun.* **1995**, 805 – 806.
[41] L. J. Prins, F. De Jong, P. Timmerman, D. N. Reinhoudt, *Nature* **2000**, *408*, 181 – 184.
[42] In addition to this, it should be mentioned that the small signals disappear in time; this indeed suggests that they belong to heteromeric assemblies incorporating both DEB and *R*CYA units.
[43] M. Crego Calama, R. Fokkens, N. M. M. Nibbering, P. Timmerman, D. N. Reinhoudt, *Chem. Commun.* **1998**, 1021 – 1022.
[44] M. M. Green, N. C. Peterson, T. Sato, A. Teramoto, R. Cook, S. Lifson, *Science* **1995**, *268*, 1860 – 1866.
[45] E. Yashima, T. Matsushima, Y. Okamoto, *J. Am. Chem. Soc.* **1997**, *119*, 6345 – 6359.
[46] T. Gulik-Krzywicki, C. Fouquey, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 163 – 167.
[47] X. Shi, J. C. Fettinger, M. Cai, J. T. Davis, *Angew. Chem.* **2000**, *112*, 3254 – 3257; *Angew. Chem. Int. Ed.* **2000**, *39*, 3124 – 3127.
[48] X. D. Shi, J. C. Fettinger, J. T. Davis, *J. Am. Chem. Soc.* **2001**, *123*, 6738 – 6739.
[49] A close examination of the ^{1}H NMR spectrum of assembly $\mathbf{1e}_3\cdot(S\text{CYA})_6$ shows a slightly lower signal-to-noise ratio than seen in the spectrum of assembly $\mathbf{1e}_3\cdot(R\text{CYA})_6$. Moreover, the calix[4]arene CH_2 bridge signals at $\delta = 4.6 – 4.4$ and $3.3 – 3.1$ have unequal intensities. This might be due to the slightly lower stability of assembly $\mathbf{1e}_3\cdot(S\text{CYA})_6$.
[50] M. L. Vestal, P. Juhasz, S. A. Martin, *Rapid Commun. Mass Spectrom.* **1995**, *9*, 1044 – 1050.
[51] C. J. Hawker, J. M. J. Frechet, *J. Am. Chem. Soc.* **1990**, *112*, 7638 – 7647.
[52] a) H.-A. Klok, K. A. Jolliffe, C. L. Schauer, L. J. Prins, J. P. Spatz, M. Möller, P. Timmerman, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1999**, *121*, 7154 – 7155; b) H. Schönherr, V. Paraschiv, S. Zapotoczny, M. Crego-Calama, P. Timmerman, C. W. Frank, G. J. Vancso, D. N. Reinhoudt, *Proc. Natl. Acad. Sci. USA* **2002**, in press.
[53] T. Ishi-i, M. Crego-Calama, P. Timmerman, D. N. Reinhoudt, *Angew. Chem.* **2002**, in press.

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