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Efficient Self-Sorting of a Racemic Tetra-Urea Calix[4]Pyrrole into a Single Heterodimeric Capsule

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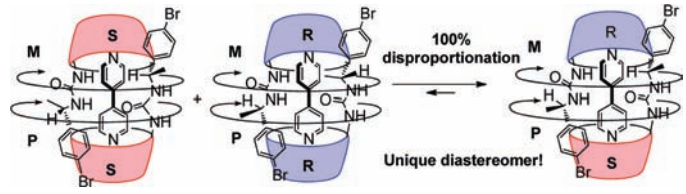
ABSTRACT



A racemic calix[4]pyrrole self-sorts into a single achiral heterodimeric capsule. This process is induced either by encapsulation of one ditopic or two monotopic *N*-oxide guests. The influence of the guest structure in the dynamics of the disproportionation process of the two homochiral capsules is reported. The unidirectional sense of rotation of the urea groups assigned to the heterodimeric capsule is explained as the outcome of an induction of chirality from the stereogenic centers.

Self-assembly of a racemic chiral monomer into dimeric aggregates, whether driven by metal coordination, donor−acceptor interaction, or hydrogen-bonding, can either be highly diastereoselective or give rise to a near-statistical mixture of isomeric structures. Highly diastereoselective processes are the expected outcome of either self-recognition (one enantiomer exclusively recognizes itself to form a homodimer)[1] or self-discrimination (one enantiomer recognizes its antipode yielding a heterodimer).[2] Examples of both types of processes have been reported and constitute exquisite cases of molecular self-sorting due to the structural similarity of the components.[3] Many chiral ligands used in asymmetric synthesis feature efficient self-sorting processes, which can often be inferred from nonlinear effects where low ee ligands yield products with higher ee's.[4] Within the area of self-assembly driven by hydrogen bonding Alajarín, Pastor et al. reported a highly diastereoselective self-discrimination process in the formation of dimeric capsules derived from racemic tris(m-ureidobenzyl)amines bearing a single stereogenic α-carbon atom.[5] In the same vein, Rebek et al. briefly described the formation of homo and heterodimeric capsules during the self-assembly of a racemic tetraurea-calix[4]arene derivative bearing an α-methylbenzyl stereogenic center on its distal urea nitrogen atoms.[6] The attachment of other types of stereogenic centers disrupted the formation of the homocapsule from the enantiomerically pure compounds and, to the best of our knowledge, no results were published on

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the self-assembly of racemic mixtures.[7] Recently, we showed that the α,α,α,α-stereoisomer of *meso*-tetraphenyl tetramethyl calix[4]pyrrole substituted with ureas at the *para* positions, **1a**, forms dimers in solution capable of encapsulating molecular guests such as 4,4′-dipyridyl *N*,*N*′-dioxide **2**.[8] Compared to their calix[4]arene capsules,[9] our calix[4]pyrrole analogues displayed (a) a sizable increase (∼ 62%) of the internal cavity, (b) the presence of four endohedral hydrogen bond donor sites that converge on the enlarged interior, and (c) some additional geometrical features and intermolecular forces that hold the capsular assembly together. We undertook the present work to evaluate the diasteroselectivity (i.e., self-sorting) of the self-assembly process of a racemic tetraurea-calix[4]pyrrole monomer into dimeric capsules.

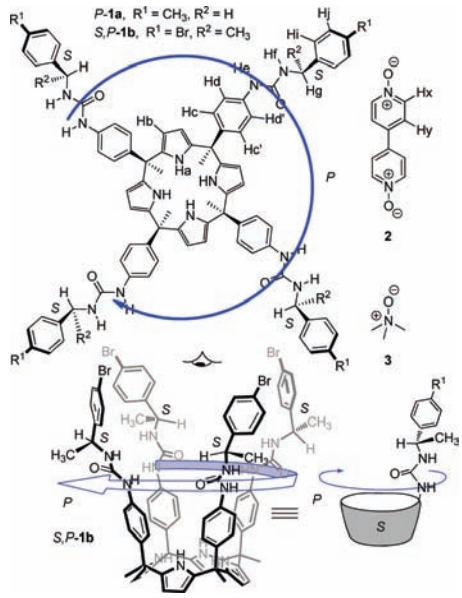

Figure 1. Molecular structures of the compounds used in this study and three-dimensional representation of the cone conformation for the cyclochiral diastereoisomer *S*,*P*-**1b**.

Since our previous report on tetraurea-calix[4]pyrrole dimeric capsules,[8] we have been able to grow single crystals of the achiral **2**⊂**1a**$_2$ self-assembly that were suitable for X-ray diffraction analysis. The solid-state structure of the assembly is reported in this letter and depicted in Figure 2. The distances and angles for the hydrogen bonds in the urea belt are similar to those reported for the dimer of tetraurea calix[4]arene (Supporting Information).[9b] Due to the benzylic tetrahedral carbons in **1a**, the aryl unit bends slightly to accommodate two intermolecular edge-to-face (CH···π) interactions with the protons of the aromatic ring of the neighboring calixpyrrole core. At least sixteen intermolecular CH···π interactions between the aromatic CHs of the *meso*-phenyls and the aryl rings of the benzyl substituents were observed in the structure of **2**⊂**1a**$_2$. These types of interactions, absent in the dimer of the corresponding phenyl substituted tetraurea calix[4]arene, likely play an important role for controlling the conformation adopted by the monomer and the thermodynamic and kinetic stability of the capsule.

The design of our chiral tetraurea calix[4]pyrrole monomer, that is all *S*-**1b** = *S*-**1b** is based on the substitution of one of the hydrogen atoms at the four benzylic carbons of **1a** for a methyl group to create four stereogenic centers with the same absolute configuration.

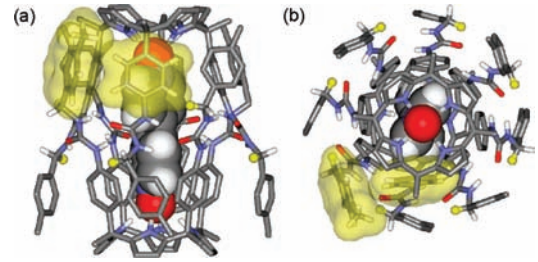

Figure 2. X-ray structure of **2**⊂**1a**$_2$, (a) side and (b) top view. Selected CH-π interactions are indicated using surface representation. Encapsulated **2** is shown as a CPK model. Pseudo-*cis* hydrogen atoms are highlighted in yellow (see text).

The dimerization of two enantiomerically pure calixpyrrole monomers would yield a homocapsule, that is, *S*,*S*-**1b**$_2$. Due to the head-to-tail orientation of the urea carbonyls the *S*,*S*-**1b**$_2$ homocapsule must be formed by two cyclochiral diastereoisomeric halves designated as *S*,*P*-**1b** and *S*,*M*-**1b**.[10] An important difference between the two cyclodiastereomers concerns the relative spatial arrangement of the urea carbonyl and the benzylic methyl group (see below). It is only possible to assemble a unique capsule from pairing enantiomerically pure tetraureas *S*-**1b** (i.e., *S*,*M*•*S*,*P* is identical to *S*,*P*•*S*,*M*). In the self-assembly of racemic tetraurea **1b**, however, multiple dimeric capsules may be possible. The number of possibilities is simplified if the requirement for complementarity between the senses of rotation of the urea groups upon capsule formation is taken into consideration. In this case, only three possible diastereomeric capsules should arise from the self-assembly of racemic **1b**; two achiral centrosymmetric (*meso*) capsules A and B (*S*,*M*•*R*,*P*; *R*,*M*•*S*,*P*; S_8) and one chiral capsules produced as a racemic mixture of C* and *ent*-C* (*SM*•*SP*, *RP*•*RM*; C_4) (Figure 3).

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(10) Throughout the text of this paper, cyclochiral refers to conformationally cyclochiral compounds. The designation is defined in the following sequence: the stereogenic center (*S*) and the cyclochirality (*P* or *M*). The (*P*/*M*) notation defines the cyclochiral conformation viewed from a position above the cavity. The two cyclodiastereomers *S*,*P* and *S*,*M* can be expected to have different energies. Szumna, A. *Org. Biomol. Chem.* **2007**, *5*, 1358–1368, and references cited therein.

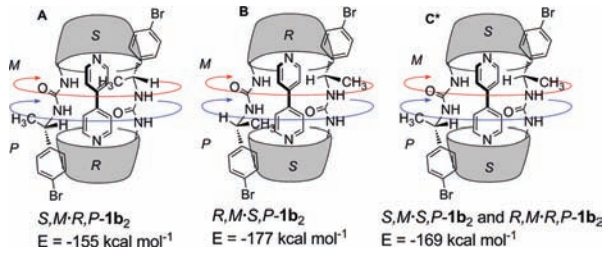

Figure 3. Schematic representation of the three expected diastereomeric capsules resulting from the self-assembly of racemic **1b** induced by encapsulation of **2**.

Optically active tetraurea calix[4]pyrroles *R*-**1b** and *S*-**1b** were obtained in good yields (65 and 62%, respectively) from the reaction of the known tetraamine calix[4]pyrrole[8] with commercially available (*R*)- and (*S*)-1-bromo-4-(1-isocyanatoethyl)benzene. The tetraureas are scarcely soluble in chlorinated solvents and insoluble in aromatic ones. The ^{1}H NMR spectra of *R*-**1b** or *S*-**1b** in $CHCl_3$-*d* give broad signals indicative of nonspecific aggregation. In contrast, DMSO-d_6 solutions of these compounds gave sharp ^{1}H NMR spectra consistent with a time-averaged C_4 symmetry.

We initially tested the self-assembly of each enantiomerically pure chiral tetraurea **1b** in separate experiments using CH_2Cl_2-d_2 by adding one equivalent of 4,4′-dipyridyl *N*,*N*′-dioxide **2** as the template. Despite the low solubility of *S*-**1b** in CH_2Cl_2-d_2, a clean solution was obtained after shaking the mixture for just a few minutes. The ^{1}H NMR spectrum of the solution shows fairly sharp signals consistent with the symmetry of the homodimer. The absolute configuration of the carbon stereogenic centers is the same in both monomers but, as mentioned above, they must be conformationally cyclochiral enantiomers with their ureas rotated 180° to accommodate the capsule assembly. Thus, the two monomers paired in the (*S*,*P*•*S*,*M*)-**1b**$_2$ capsule are no longer equivalent yielding an overall C_4 symmetry. As seen in Figure 4a, two signals for the pyrrole NHs, labeled a, were distinguishable in the downfield region and two different protons for the north and south benzylic methyne were also observed (δ = 4.95 and 4.85 ppm, labeled g). Four different proton signals, labeled x and y, were also detected for encapsulated **2**. Surprisingly, we did not observe separate signals for the aromatic protons *ortho* to the urea (d, d′) in the *meso* phenyl substituents (this observation had constituted the first indication of capsule formation in the calix[4]arene series).[9a] The asymmetry should be derived from the unidirectional sense of orientation of the urea groups and their slow interconversion on the ^{1}H NMR time scale. Naturally, the observation of this asymmetry in (*S*,*M*•*S*,*P*)-**1b**$_2$ would require slow rotation on the ^{1}H NMR time scale of the C_{meso}-phenyl bond. Therefore, we conclude that, although the change in direction of the urea belt in **2**⊂(*S*,*M*•*SP*)-**1b**$_2$ is slow on the ^{1}H NMR time scale, the rotation of the C_{meso}-phenyl bond is fast.

Using the area of the exchange peaks of the pyrrole NHs in an EXSY experiment, we calculated an energy barrier of $\Delta G^{\ddagger}$ = 18.1 kcal/mol for the change in direction of the urea

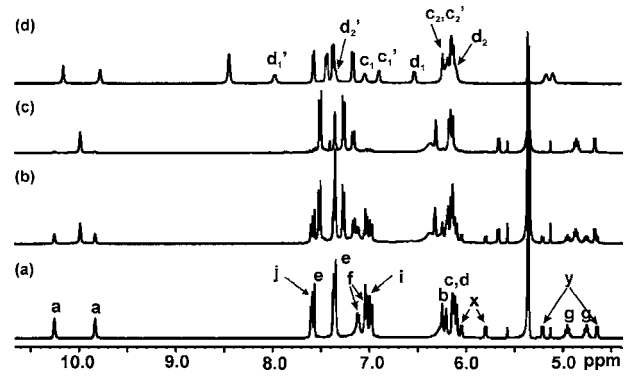

Figure 4. ^{1}H-NMR spectra of (a) homocapsule **2**⊂*R*-**1b**$_2$ in CH_2Cl_2-d_2, (b) mixture of capsules resulting from racemic **1b** in CH_2Cl_2-d_2, (c) an identically prepared mixture after two days in CH_2Cl_2-d_2:THF-d_8 10:1, and (d) homocapsule $\mathbf{3}_2$⊂*R*-**1b**$_2$ in CH_2Cl_2-d_2. The two sets of signals for the diastereotopic protons c,c′ and d,d′ from the two diasterotopic *meso*-phenyl groups (1,2) are indicated.

belt. The complementary relationship that exists between the sense of rotation of the ureas in the two calixpyrrole monomers in **2**⊂(*S*,*M*•*SP*)-**1b**$_2$ forces a different spatial orientation of their H and −CH_3 benzylic substituents in each cyclodiastereoconformer. A pseudo-*cis* arrangement of the H atom and the urea carbonyl is adopted in the *P* cyclodiastereoisomer while in the *M* cyclodiastereoisomer it is the −CH_3 group that is located in pseudo-*cis* with respect to the carbonyl. This subtle conformational difference was evaluated using molecular mechanics calculations and augurs well for a self-discriminating process during the assembly of racemic **1b** (Figure 3 and FigS.14, Supporting Information). Next, we experimentally probed the extent of diastereoselectivity of the self-assembly of racemic tetraurea **1b** using the same conditions described above for the enantiomerically pure compound. The ^{1}H NMR spectrum of the resulting solution shows the signals previously assigned to the protons of the homodimer, now assembled as a racemic mixture of enantiomers, and the presence of a new set of proton signals (Figure 4b). The number of new proton signals corresponds to the exclusive formation of one of the two possible heterodimers with S_8 centrosymmetry (meso assembly with equivalent halves). Molecular modeling studies assigned a lower energy to the (*S*,*P*•*R*,*M*)-**1b**$_2$ heterodimeric capsule in which both monomers can adopt a conformation that positions the benzylic hydrogens in a pseudo-*cis* orientation with respect to the urea carbonyls. Consequently, we tentatively assign this structure to that of the heterodimeric capsule. The integration of the proton signals corresponding to the two capsules afforded a 2:1 hetero:homo ratio that did not change significantly with time. This value is far from the 1:1 statistical ratio indicating a moderate level of self-discrimation. In striking contrast to this result, when preformed homocapsules ((*S*,*M*•*S*,*P*)-**1b**$_2$ and (*R*,*M*•*R*,*P*)-**1b**$_2$) are mixed in equimolar amounts, the ^{1}H NMR analysis of the mixture revealed the exclusive presence of the homomeric assembly as a racemate (Figure 4b). Heating the solution for one week at 313 K in a sealed NMR tube resulted in the

appearance of weak proton signals corresponding to the heterodimer (*S,M*•*R,P*)-**1b**$_2$. Taken together, these results indicate that the three-particle aggregates formed are highly stable kinetically compared to their calix[4]arene analogues.[11] The extent of self-sorting in the assembly of the capsules observed under heterogeneous conditions is most likely given by kinetic control.[12] In order to investigate the extent of diastereoselectivity under thermodynamic control, we thought to reduce the thermodynamic and kinetic stabilities of the capsules by adding a competitive hydrogen bonding solvent. The addition of 10% THF-d_8 to an equimolar 1 mM solution mixture of preformed homodimeric capsules in CH_2Cl_2-d_2 induced their complete disproportionation into the heteromeric aggregates within 48 h at rt (Figure 4c). In short, the self-assembly of racemic calixpyrrole **1b** induced by **2** occurs with high diastereoselectivity, under thermodynamic control, and selects a single heteromeric capsule by means of a self-discriminating event. The operative mechanism at work here involves an induction of chirality from the remote stereogenic carbon centers to the energetically more favorable cyclodiastereomer. The urea directionalities of the conformationally more stable cyclochiral diastereoisomers (*R,M*-**1b** and *S,P*-**1b**) are present in the (*S,P*•*R,M*)-**1b**$_2$ heterocapsule.

The use of trimethylamine *N*-oxide **3**, a monotopic templating guest, affords a similar result. In this case, however, the disproportionation of the mixture of homocapsules is achieved after a few minutes and does not require the addition of a competitive solvent. We calculated an energy barrier of $\Delta G^{\ddagger} = 16.0$ kcal/mol for the change in direction of the urea belt in **3**$_2\subset$(*S,M*•*S,P*)-**1b**$_2$; this is 2 kcal mol^{-1} less than for the corresponding three-particle aggregate formed with **2**, and hints to a decrease in kinetic and thermodynamic stability. We were able to observe separate signals for the aromatic protons of the meso phenyl substituent (protons d and d′, Figure 4d). The three-dimensional structure of **3** compared to **2** slows down perhaps even stops the C_{meso}-phenyl bond rotation. Finally, the combination of chiral tetraurea *R*-**1b** with achiral **1a** provided both exclusive and diastereoselective formation of the heterodimer **3**$_2\subset$**1a**•**1b**. Next, we used CD spectroscopy to assign the directional sense of rotation of the ureas in this assembly.[7] The CD spectrum of **3**$_2\subset$**1a**•**1b** is bisignate and shows a strong positive first Cotton effect. This CD response probably arises mainly from the coupling of the electric transition dipoles of the Br-benzyl groups with those of the *meso*-phenyl substituents involved in the CH-π interactions.[13] In accordance with the exciton chirality rule, the positive chirality observed for the first Cotton effect should be produced by a clockwise coupling of the electric transition dipoles involved.[14] We used the X-ray structure of **2**$\subset$**1a**$_2$ to perform a homology construct of the two possible diastereomeric dimers **3**$_2\subset$(*M*•*R,P*)-**1a**•**1b** and **3**$_2\subset$(*P*•*R,M*)-**1a**•**1b** (SI). The transition electric dipoles of the two chromophores intersect at a positive torsion angle only for the **3**$_2\subset$(*P*•*R,M*)-**1a**•**1b** capsule (SI). This result corroborates our previous hypothesis of chiral induction from the carbon stereogenic center to a preferred cyclo diastereomer, *R* inducing *M*.

In summary, we have demonstrated the self-assembly of enantiomerically pure tetraurea calixpyrroles into homochiral dimeric capsules induced by encapsulation of **2**. When the assembly is tested using a racemic urea, a close to statistical mixture is obtained as the result of a kinetically controlled process. The capsules obtained by templation with **2** become kinetically less stable in the presence of small amounts of a competitive hydrogen bonding solvent (THF). Under these conditions, the self-assembly is controlled thermodynamically and occurs in a highly diastereoselective manner, producing a single heterodimeric capsule as the result of a self-discrimination event. The self-assembly induced by the monotopic *N*-oxide **3** is controlled thermodynamically even in the absence of THF, and is both exclusive and diastereoselective. The absolute configuration of the (*S,M*•*R,P*)-**1b**$_2$ capsule resulting from the self-discrimination event has been assigned using simple molecular modeling calculations and experimental CD measurements on a related model system.

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Supporting Information Available: Additional NMR spectra, detailed experimental procedures, molecular structures derived form the modeling studies and X-ray crystallographic data of **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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