Chiral Capsules: Asymmetric Binding in Calixarene-Based Dimers

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Molecular capsules are formed when calix[4]arenes with appropriate functional groups dimerize.[1−4] The capsules are held together by a cyclic array of hydrogen bonds and we consider in this communication those systems featuring ureas attached to the larger rim of the calixarene subunits (Figure 1).[1,2,3a] These dimers reversibly encapsulate smaller molecules under slow exchange with respect to the NMR time scale. We report here on the uncommon asymmetric microenvironments[5,6] that are encountered by guests within these capsule hosts.

Homodimers **1·1** of calixarene derivatives (Figure 1) feature S_8 symmetry and are achiral. However, encapsulation of polycyclic compounds of suitable size and shape, i.e., (1*R*)-(+)-nopinone **2**, (1*R*)-(−)-myrtenal **3**, (1*R*)-(+)-camphor **4**, and tricyclene[7] **5** (Figure 2), results in complexes of reduced symmetry: the top and bottom halves of the dimer are no longer magnetically equivalent. For example, the ¹H NMR spectrum of the **1a·2·1a** complex in *p*-xylene-*d₁₀* (Figure 3B[8]), shows a doubling of the resonance patterns of the calixarene (Figure 3A). That (1*R*)-(+)-nopinone is inside the capsule is apparent from the large upfield shifts of the geminal methyl groups. Sym-
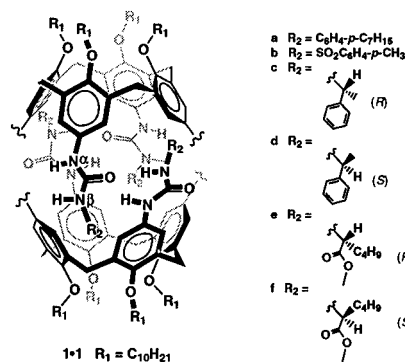
Figure 1. Schematic view of head-to-tail urea functions that hold the dimeric capsules together. Some ureas are omitted in the structure for clarity.
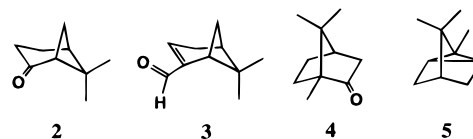
Figure 2. Structures of the guests used in encapsulation studies.

metrical guests, such as the tricyclic structure **5**, can complicate the ¹H NMR spectrum even further (Figure 3C). Evidently, more than one complex is formed since two sets of signals for encapsulated species are seen. The unequal populations point to preferential orientations and restricted internal rotation of the guest within the dimer,[9] a surprising feature for an assembly held together by only weak intermolecular forces. Additionally, a NOESY experiment with the **1a·2·1a** complex shows an NOE contact between the upfield methyl group of the guest (δ −2.2, Figure 3B) and only *one* of the two upfield urea −NH resonances of the dimer (N_αH, Figure 1). The $\Delta\delta$ between the methyl groups of the free and encapsulated guests is very different (e.g., for free nopinone in *p*-xylene-*d₁₀* $\Delta\delta = 0.40$,[10] for encapsulated nopinone $\Delta\delta = 1.5$)—this is consistent with the groups experiencing different local environments within the complex.[11] On the basis of these data, it is reasonable to assume that guests **2** and **3** (a structural analogue) preferentially align their long axis along the S_8 axis of the dimer, positioning one methyl group in the shielding zone[9a] of one hemisphere.

Preferred guest orientation is also evident through encapsulation studies within a heterodimer, i.e., a capsule of which the top and bottom halves are not chemically equivalent. Böhmer and co-workers have shown that the combination of two homodimeric species resulted in statistical disproportionation to the corresponding heterodimer.[2a] An unexpected disproportionation, far from statistical, occurs when aryl urea compound **1a** and sulfonyl urea compound **1b**[3a] are combined: the heterodimer is formed *exclusively*. While the reasons for the preference remain obscure,[12] they provide access to a capsule that has unique "northern" and "southern" hemispheres. In this capsule a directionality is defined by the head-to-tail circle of urea functions involved in hydrogen bonding at the equator: the arrangement can be either clockwise or counterclockwise

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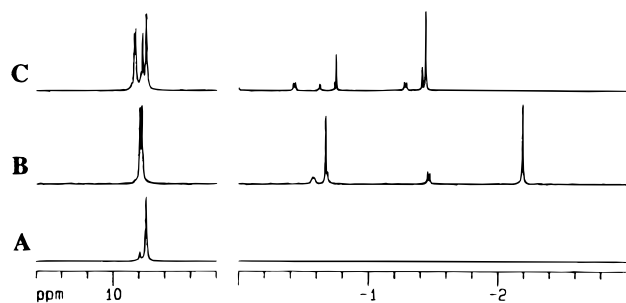
(4) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255−8258.

(5) Although considerable attention has been focused on the synthesis of chiral monomeric calix[4]arenes, this work has yet to be extended to the generation of chiral capsules. For inherently chiral calix[4]arenes see: (a) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997−4006. (b) Ferguson, G.; Gallagher, J. F.; Giunta, L.; Neri, P.; Pappalardo, S.; Parisi, M. *J. Org. Chem.* **1994**, *59*, 42−53. (c) Pappalardo, S.; Ferguson, G.; Neri, P.; Rocco, C. *J. Org. Chem.* **1995**, *60*, 4576−4584. (d) Fu, D.-K.; Xu, B.; Swager, T. M. *J. Org. Chem.* **1996**, *61*, 802−804. (e) Ikeda, A.; Yoshimura, M.; Lhoták, P.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1945−1950. (f) Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019−2030 and references therein. (g) Otsuka, H.; Shinkai, S. *Supramol. Sci.* **1997**, *3*, 189−205 and references therein.

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(7) Tricyclene = 1,7,7-trimethyltricyclo[2.2.1.0²,⁶]heptane.

(8) Although only representative portions of the spectra are shown in Figure 3, resonance doubling occurs throughout the spectra and is most pronounced in the NH, ArH, and bridge CH₂ regions.

(9) This type of phenomenon is analogous to the "carceroisomerism" previously observed in carceplexes: (a) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194−2204. (b) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2345−2348. (c) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082.

(10) This difference is slightly larger in CDCl₃ ($\Delta\delta = 0.48$).

(11) Preliminary support for this trend has been obtained through a variable temperature ¹H NMR experiment performed on a solution of **1a·2·1a** in *p*-xylene-*d₁₀*. Over the temperature range 295−395 K the two peaks from N_βH coalesce, whereas $\Delta\delta$ between remaining split signals gradually decreases, e.g., $\Delta\delta$ between the methyl groups of the encapsulated guest decreases by 0.4 ppm.

Figure 3. (A) Calix[4]arene dimer **1a·1a** in *p*-xylene-d_{10}. (B) The addition of (1*R*)-(+)-nopinone to **1a·1a** gives two downfield $N_\beta H$ signals (Figure 1) and one set of upfield signals for the encapsulated guest. (C) Addition of tricyclic guest **5** (Figure 2) to **1a·1a** shows several $N_\beta H$ resonances and two different encapsulated species. Note that some of the capsules still contain *p*-xylene-d_{10}.
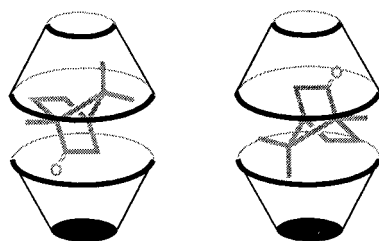
Figure 4. Schematic depictions of the proposed orientations of (1*R*)-(+)-camphor in the aryl−sulfonyl (**1a·1b**) heterodimer.

as viewed from either hemisphere. In short, the heterodimers exist as a pair of enantiomers.[21] Encapsulation of **3** in the **1a·1b** system gives rise to diastereomeric complexes and two encapsulated species are observed by ^{1}H NMR (see Supporting Information). The difference in chemical shifts between the two sets of three methyl singlets suggests that they are in quite different magnetic environments, most likely the guest has two preferred orientations within the dimer cavity[13] as proposed in Figure 4. Further evidence for such orientational preferences and restricted motion was obtained through the encapsulation of **2** in the **1a·1b** heterodimer. The spectra in this case are time dependent, and equilibrium between two major encapsulated guest species is reached only after a few days at room temperature.[14]

Encapsulation of asymmetric guests within symmetrical cavities or cavities with chiral linings was next expanded to optically active capsules. These compounds were accessible through reaction of the tetraamine precursor[15] of **1** with the commercially available isocyanates of α-methylbenzylamine (to give **1c** and **1d**) or those derived from amino acids (to give **1e** and **1f**).[16] The latter showed better solubility in aromatic solvents and featured sharp ^{1}H NMR spectra of the monomeric state in DMF-d_7, but did not appear to dimerize in CDCl$_3$ or aromatic solvents.[17] A mixture of either **1e** or **1f** with **1a** did show ^{1}H NMR evidence of the respective heterodimers (**1a·1e**

(12) Preference for heterodimerization in this case can be partially rationalized in that the increased acidity of the sulfonyl urea complements the relative basicity of the aryl urea. Interestingly, such heterodimer preference is exclusive to aryl ureas—alkyl ureas show less than 10% heterodimer formation by ^{1}H NMR.

(13) Molecular modeling favors the orientation shown in Figure 4 where one methyl group of (1*R*)-(+)-camphor is directed toward the pole of one hemisphere of the heterodimer, positioning the carbonyl group for interactions with the urea functions along the equator. Modeling was performed with use of MacroModel 5.5 and MM2* minimization: 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.

(14) The two major encapsulated species reflect the two different orientations of the guest along the north−south axis of the heterodimer (as in **1a·4·1b**). See the Supporting Information for details.

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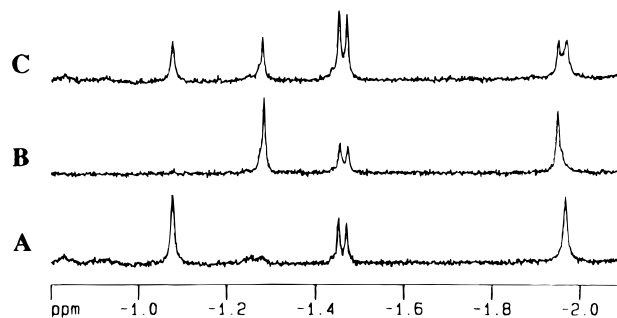
Figure 5. Chiral guest encapsulation by an optically active calix[4]-arene heterodimer. (A) Heterodimer **1a·1e** with (1*R*)-(+)-nopinone **2**. (B) Heterodimer **1a·1f** with **2**. (C) Heterodimer **1a·1f** with both (+)- and (−)-nopinone shows resonances for both enantiomers of the guest. The doublet at δ −1.45 is from nopinone within the **1a·1a** homodimer.

and **1a·1f**) in both CDCl$_3$ and C$_6$D$_6$; unfortunately, these solvents—good guests themselves—are not conducive to encapsulation studies. However, in *p*-xylene-d_{10} modest formation of heterodimeric **1a·1e** was observed in the presence of **2**. Only one set of upfield methyl singlets appear for the encapsulated guest (Figure 5A), suggesting that the guest has a preferred orientation along the north−south axis of the capsule **1a·1e**.[18] Observation of **2** in heterodimer **1a·1f** was accomplished in the same manner. This provided the *diastereomeric* complex and showed different chemical shifts for both the host and guest (Figure 5B). It is likely that the capsules **1a·1e** and **1a·1f** feature opposite senses of urea directionality and the chirality thus presented by the lining is responsible for the differences in chemical shifts. The *enantiomeric* complexes were also available in this system: (−)-nopinone was prepared[19] and encapsulated in both the **1a·1e** and **1a·1f** heterodimers. As expected, the **1a·(+)-nopinone·1e** system is equivalent to the **1a·(−)-nopinone·1f** complex by ^{1}H NMR (spectra not shown). Finally, addition of both nopinone enantiomers to **1a·1f** shows two diastereomeric complexes (Figure 5C).

In summary, the calix[4]arene dimers discussed provide a set of increasingly asymmetric environments: from S_8 to racemic to optically active. Of course, the peripheral asymmetric centers of **1e**, for example, are not well-positioned to provide steric information to guests inside, even though the sense of urea direction in such capsules appears to give an optically active lining.[20] A chiral *cavity shape* is the ultimate goal here, as a more effective resolving agent would be hard to imagine. Our current efforts are directed along these lines.

Supporting Information Available: Experimental details (compounds **1a−1f**, appropriate isocyanates, and (−)-nopinone), NOESY data, and representative ^{1}H NMR spectra (8 pages). See any current masthead page for ordering information and Internet access instructions.

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(17) Derivatives **1c** and **1d** are soluble in CDCl$_3$ and C$_6$D$_6$ (sparingly) where they are observed to both homo- and heterodimerize (**1c·1d**) by ^{1}H NMR. These derivatives are, however, insoluble in *p*-xylene-d_{10}. Derivatives **1e** and **1f** are soluble in all solvents but do not appear to either homo- or heterodimerize (**1e·1f**) by ^{1}H NMR.

(18) This is in contrast to nopinone's behavior when encapsulated in the aryl−sulfonyl heterodimer (**1a·1b**), where two orientations are observed.

(19) (−)-Nopinone was prepared via catalytic oxidative cleavage of (+)-β-pinene. See: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(20) Optically active guest selectivity has been demonstrated in covalently bonded hemicarceplexes with chiral spacers: Judice, J. K.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2790−2791.

(21) Defined as cycloenantiomerism, see: Prelog, V.; Gerlach, H. *Helv. Chim. Acta* **1964**, *47*, 2288−2294.