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Deepened chiral cavitands

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ABSTRACT

Deep cavitands bearing eight asymmetric centers on their upper rims are prepared from octamino resorcinarenes. The resorcinarenes are acylated with Fmoc D- and L-alanine or Fmoc glycine acid chlorides. The asymmetric centers create a chiral magnetic environment as shown by binding achiral ε-caprolactam. The chiral steric environment shows modest enantioselectivity (55% de) for chiral guests such as pinane diols bound inside the cavitand.

1. Introduction

One goal of molecular recognition is selective binding of stereoisomers by synthetic host structures.[1] Intuitively, the target molecule should be completely surrounded by a receptor that provides a complementary, congruent surface. Encapsulation meets some of these desired characteristics, particularly for reactive species.[2] In practice, the difficulty in functionalizing the concave surfaces of capsules makes this impractical. Some success has been seen with simpler cleft-like structures,[3] but naturally occurring aptamers that do succeed in selective binding provide a model of how it can be done: many asymmetric elements on a linear peptide or nucleic acid sequence can fold around the surfaces of the target.[4]

Deep cavitands are promising platforms in this regard. These synthetic receptors are built up from resorcinarenes and adopt a folded conformation around guests that properly fill the space.[5] The challenge is to position chiral elements on the cavitand that make effective contacts with the guest inside. The vase-like shape is stabilized by a seam of cooperative intramolecular hydrogen bonds present in the upper rim of the molecule[6] or even covalent bonds.[7] Their mono- and difunctionalization is not straightforward[8] but has led to a number of intriguing applications including sensor devices. We report here the synthesis and characterization of a new family of deep, chiral cavitands.

2. Results and discussion

Compounds **2a**–**c** were prepared by reduction of the known octanitro cavitand **1**[9] with tin chloride to the corresponding octamine. That was acylated with the Fmoc protected amino acid chlorides[10] derived from L-Ala, D-Ala, or Gly. The respective cavitands **2a**–**c** bearing eight Fmoc-amino acyl groups on structure's upper rim were obtained in 41–48% yield (Fig. 1).

In solution, compounds **2a** and **2b** fold into a 'vase-like' conformation in different nonprotic organic solvents: they exhibit methine proton resonances around 5.7 ppm, characteristic of the C_4 vase structure (Fig. 2a). In this conformation two cyclodiastereoisomers[11] with clockwise and counterclockwise orientations of the amide bonds are possible for each compound, depending on the arrangement adopted by the upper rim's hydrogen-bonded array. In either arrangement the two amide NH groups present in each wall of the cavitand are not equivalent since they are involved, alternatively, in *interannular* and *intraannular* hydrogen bonds that maintain the vase conformation. Yet, only one set of two amide NH resonances is observed in the downfield region of the ^{1}H NMR spectra of **2a** and **2b**[12] (at ~10.3 ppm and another at ~9.3 ppm) (Fig. 2a). Only one of the two possible cyclodiastereoisomers is present in solution at ambient temperatures.

In other words, the head-to-tail seam of intramolecular hydrogen bonds along the upper rim of structures **2a** and **2b** is unidirectional, fixed by the asymmetric centers of the alanines. Moreover, variable temperature experiments and 2D EXSY experiments confirm this structure, and rule out an interconversion process. Specifically, the internal dynamics of **2a** and **2b** were probed through 2D EXSY spectra in $CDCl_3$ using various mixing times (ranging from 0.3 to 1.0 s). No exchange of the amide N–H

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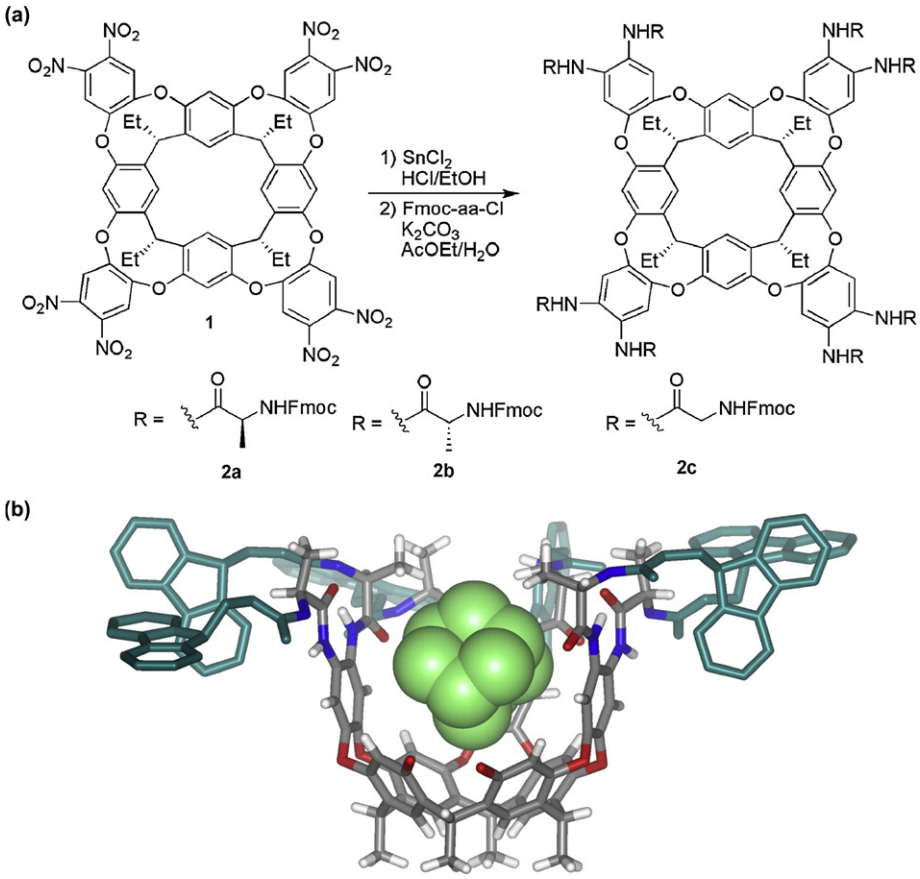

Figure 1. (a) Synthesis of cavitands **2a**–**c**; (b) energy minimized structure (Spartan; AM1 force field) of the folded complex of **2a** with adamantane. The front wall and some hydrogens are omitted for clarity.

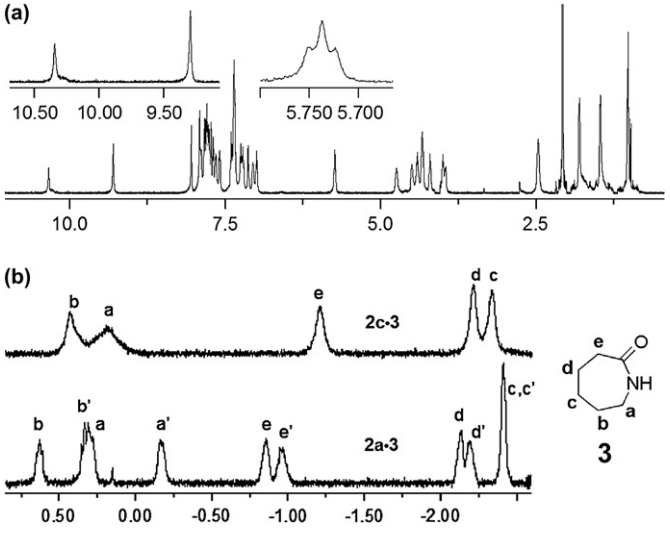

Figure 2. (a) ^{1}H NMR spectra (600 MHz, 300 K) of **2a** in acetone-d_6 with expansions of the amide *NH* and the methine fingerprint resonances; (b) upfield ^{1}H NMR spectra (600 MHz, 300 K) regions of **3** complexed with achiral **2c** (top) and chiral **2a** (bottom).

signals was observed. Variable temperature ^{1}H NMR experiments were carried out in $CDCl_3$ (260–340 K) and benzene-d_6 (280–350 K). Again, no exchange between the amide N–H signals was observed in this range of temperatures.

Is the microenvironment of the cavity affected by this unidirectional orientation of the hydrogen bond seam? In organic nonprotic solvents, compounds **2a**–**c** form kinetically stable complexes with molecular guest that present the right size and shape to fill the cavity and separate signals are observed for the free and bound guests. Some of the signals for the bound species present the characteristic chemical shifts of inclusion in anisotropic shielded environments and are observed upfield of 0 ppm. These atoms are deep in the cavity, far from the asymmetric elements. The asymmetric nature of the cavity of **2a** and **2b** was examined by binding experiments with achiral guests. In the ^{1}H NMR spectra of the nonchiral (control) cavitand **2c** in the presence of ε-caprolactam (**3**) all the equivalent protons of the bound guest were isochronous (Fig. 2b). On the other hand, the signals of **3** bound to cavitand **2a** were non-equivalent owing to the location of **3** in a *chiral magnetic environment* (Fig. 2b). Similar behavior was observed with other achiral guests such as norbornene or quinuclidine.

Additional influence of the asymmetric environment in these cavitands came from binding experiments of **2a** and **2b** with a chiral guest such as (+)-nopinone (**4**) (Fig. 3a). On addition of excess of **4** (ca. 15 equiv) to a 1:1 mixture solution of **2a** and **2b** in acetone-d_6, two sets of signals in the upfield region of the ^{1}H NMR spectra appeared, which were attributed to the corresponding diastereomeric caviplexes **2a**·**4** and **2b**·**4**. The identity of each complex was determined by recording independent ^{1}H NMR spectra of **2a**·**4** and **2b**·**4**. We also observed a degree of discrimination between enantiomeric guests by cavitand **2a**. In the upfield region of the ^{1}H NMR spectra of **2a** in the presence of a racemic mixture of pinanediol (**5**), two sets of signals corresponding to both possible diastereomeric caviplexes **2a**·(−)-**5** and **2a**·(+)-**5** were observed. The ratio of ca. 3.5:1 reflects the relative association constants and corresponds to ca. 55% de (Fig. 3b).

The asymmetric characteristics of cavitands **2a** and **2b** were examined by CD spectroscopy. A chloroform solution (C=100 μM) of compound **2a** displayed bisignated curves with a double Cotton

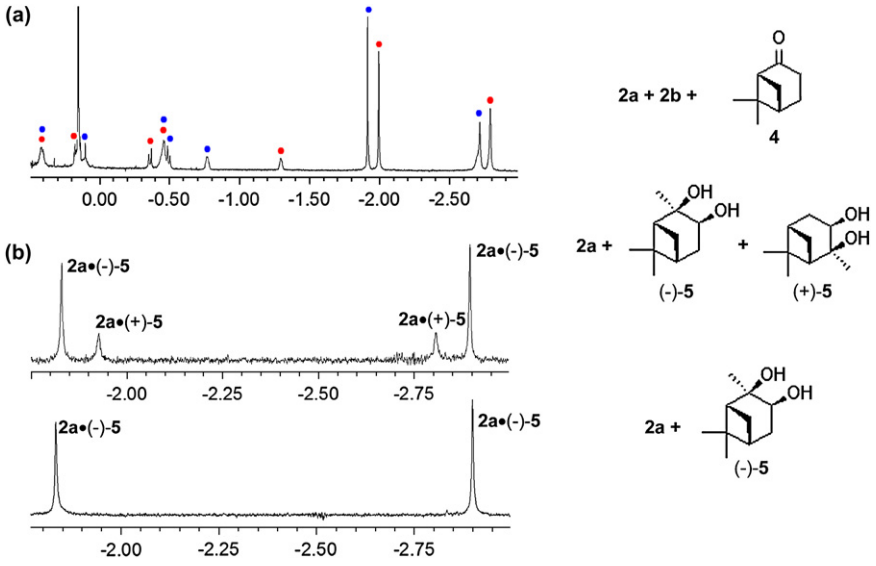

Figure 3. (a) Upfield region of ^{1}H NMR spectra (600 MHz, 300 K) in acetone-d_6 of (+)-nopinone (**4**) in presence of a 1:1 mixture of **2a** and **2b**; (b) upfield ^{1}H NMR spectra (600 MHz, 300 K) regions of **2a** in presence of a 1:1 mixture of (+)-**5** and (−)-**5** (top) and (−)-**5** (bottom).

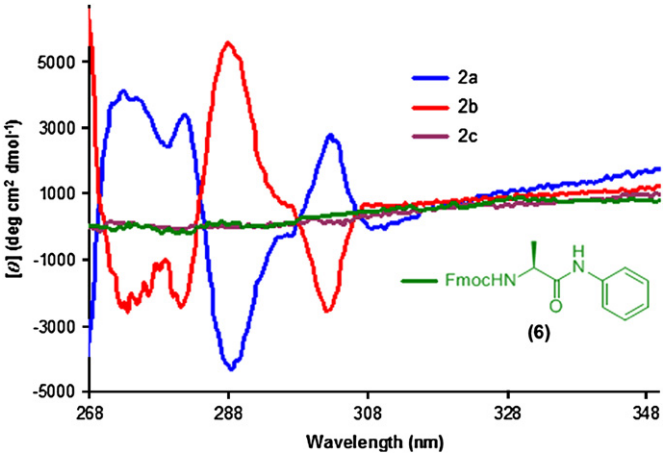

Figure 4. CD spectra of **2a**, **2b**, **2c**, and **6** in chloroform.

effect,[13] showing positive CD bands around 273, 281, and 300 nm and a negative band at 290 nm (Fig. 4). Cavitand **2b** presented an identical but totally inverted CD spectrum, confirming the enantiomeric relationship between both molecules. The coincidence of the inflection points (ca. 300 and 280 nm) with the absorption wavelength ranges of resorcinarenes and the Fmoc group, besides the large intensity of the split CD curve is consistent with a typical exciton coupling mechanism of multichromophoric chiral molecules.[14] The shorter wavelength CD bands at 275 and 280 nm are attributable to the transmission of asymmetry from the chiral groups present in the upper rim to resorcinarene's cavitand skeleton. The achiral **2c** and the chiral wall mimic model compound Fmoc-Ala-NHPh (**6**) did not show any detectable CD bands (Fig. 4). The CD results support a highly ordered asymmetric structure in cavitands **2a** and **2b** that is consistent with the unidirectional hydrogen-bonded arrangement structure.

The reasons for the preference of one cyclodiastereoisomer over the other in compounds **2a**–**2b** are not obvious, but steric factors probably play a key role. The energy minimized structure of the complex between cavitand **2a** and adamantane (Fig. 1b) shows that the hydrogen bond network of the upper rim adopts a counterclockwise orientation, with the Fmoc groups positioned outward in the bulk solvent in order to minimize steric clashes. Furthermore, in this conformation, the NH groups present in the carbamates can participate in the hydrogen bond seam, increasing the stability of the folded structure. Cross peaks detected in ROESY experiments of **2a** are consistent with this structure.

3. Conclusions

These preliminary results indicate that it is possible to control the chirality in the microenvironments present in these molecular containers. The directionality of the hydrogen bond array is controlled by the presence of appropriately positioned asymmetric centers. The asymmetry is both electronic and steric: the array of head-to-tail amides provides an anisotropic electronic environment whereas the asymmetric centers further up cavitand's rim provide spaces that are chiral. The result is a hydrophobic pocket with a chiral opening, which resembles the environment present in protein interiors. Placing asymmetric elements deep into synthetic concave surfaces remains a challenge for the future. In the meantime the number of rim functionalized cavitands for use in recognition and catalysis continues to grow.[8d,15]

The synthesis of cavitands with chiral elements that further intrude into the cavity and impart solubility in protic solvents[16] is currently ongoing and will be reported in due course.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DRX-600 spectrometer. Proton (^{1}H) chemical shifts, reported in parts per million (ppm), were indirectly referenced to external tetramethylsilane employing resonances due to trace monoprotio-solvent as an internal reference. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc., and used without further purification. 2D EXSY (2D NOESY) experiments were acquired with spectrum width of 18 ppm, relaxation delay (d_1) between each scan of 2.5 s and mixing times ranging from 0.3 to 1.0 s.

CD spectra were recorded on an AVIV model 202 CD spectrometer, at 25 °C, using 0.2 cm path-length cell. Mean residue ellipticity was calculated after the solvent baseline was subtracted from sample spectra.

4.2. Materials

Compounds **3**, **4**, (+)-**5**, and (−)-**5** were purchased from Aldrich Chemical Company and were used as received. Cavitand **1**,[9] Fmoc-Ala-Cl,[10] Fmoc-D-Ala-Cl,[10] Fmoc-Gly-Cl,[10] and compound **6**[17] were synthesized according to the literature.

4.3. Preparation of cavitands 2a–c

Octanitro cavitand **1** (2.50 g, 2.0 mmol) and tin(II) chloride (17.54 g, 46.5 mmol) were combined in ethanol (180 mL) and 37% HCl (50 mL). After being heated at 65 °C overnight, the reaction was cooled and most of the ethanol was removed using a rotary evaporator. Water (50 mL) was added, and the resulting precipitate was filtered, washed with water, and dried under high vacuum to give the octamine product as the hydrochloride salt (1.45 g, 70%), which was used without further purification. To a suspension of the octamine hydrochloride (0.4 mmol) in ethyl acetate (10 mL) and a solution of potassium carbonate (6 g in 30 mL water) was added. The mixture was stirred vigorously and a solution of the appropriate Fmoc-aa-Cl (6.0 mmol in 20 mL ethyl acetate) was slowly added. The reaction mixture was stirred overnight at room temperature. The organic layer was collected, washed with 1 N HCl and brine, and then dried over Na_2SO_4. Evaporation of the solvent provided the crude product, which was purified by column chromatography (hexane/AcOEt mixtures) to afford the desired products **2a**–**c** as pale yellow solids.

Compound **2a** was obtained in 46% yield employing Fmoc-Ala-Cl, mp 135–137 °C. ^{1}H NMR (600 MHz, acetone-d_6) δ 10.34 (s, 4H), 9.30 (s, 4H), 8.04 (br s, 4H), 7.90–7.88 (m, 8H), 7.84–7.50 (m, 20H), 7.30 (m, 4H), 7.68 (m, 4H), 7.65 (m, 4H), 7.58 (m, 4H), 7.40–7.28 (m, 20H), 7.25 (m, 4H), 7.21 (m, 4H), 7.13 (m, 4H), 7.05 (m, 4H), 7.00 (m, 4H), 7.74 (t, J=7.9 Hz, 4H), 4.74 (m, 4H), 4.92 (m, 4H), 4.40 (m, 4H), 4.33 (m, 8H), 4.20 (m, 4H), 4.00 (m, 4H), 3.96 (m, 4H), 2.46 (m, 8H), 1.80 (m, 12H), 1.47 (m, 12H), 1.01 (m, 12). ^{13}C NMR (150 MHz, acetone-d_6) δ 173.5, 173.2, 170.4, 157.9, 156.1, 155.3, 151.0, 149.9, 144.6, 144.4, 144.2, 141.6, 141.5, 141.4, 141.3, 136.4, 136.1, 130.5, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.3, 126.5, 126.0, 125.8, 125.5, 125.2, 122.7, 121.2, 121.1, 120.3, 120.2, 120.1, 120.0, 116.8, 67.5, 67.3, 60.0, 53.1, 51.3, 47.4, 47.3, 36.1, 25.4, 20.4, 18.6, 17.9, 14.0, 12.5. HRMS (ESI, M+2H$^+$/2): calcd for $C_{204}H_{176}N_{16}O_{32}$: 1681.6392. Found: 1681.6385.

Compound **2b** was obtained in a 41% yield employing Fmoc-D-Ala-Cl. The spectroscopic data were identical with those described for compound **2a**.

Compound **2c**: following the procedure described above, compound **2c** was obtained in a 48% yield employing Fmoc-Gly-Cl, mp 115–117 °C. ^{1}H NMR (600 MHz, acetone-d_6) δ 9.63 (br s, 8H), 7.98–6.94 (m, 80H), 5.81 (m, 4H), 5.72 (br s, 8H), 4.40–3.84 (m, 40H), 2.47 (m, 8H), 1.02 (m, 12H). ^{13}C NMR (150 MHz, acetone-d_6) δ 169.7, 157.3, 155.2, 150.0, 144.3, 141.4, 136.3, 127.8, 127.6, 127.3, 125.7, 125.5, 120.1, 116.5, 67.5, 47.3, 44.6, 36.2, 25.7, 12.5. HRMS (ESI, M+2H$^+$/2): calcd for $C_{196}H_{160}N_{16}O_{32}$: 1625.5692. Found: 1625.5978.

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