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Cavitands as Chaperones for Monofunctional and Ring-Forming Reactions in Water

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Supporting Information

ABSTRACT: Cyclic processes involving medium-sized rings show low rates because internal strains—torsions and transannular interactions—are created during the reactions. High dilution is often used to slow the competing bi- and higher-molecular processes but cannot accelerate the desired cyclization reaction. Here we apply cavitands to the formation of medium- to large-sized rings through conversion of long-chain diisocyanates to cyclic ureas. The reactions take place in aqueous (D_2O) solution, where hydrophobic forces drive the starting materials into the cavitands in folded conformations. The guest assumes the shape to fill the space properly, which brings the reacting ends closer together than they are in bulk solvent. Complexation overcomes some of the internal strains involved in precyclization shapes of the guest molecules and accelerates the cyclization. The results augur well for applications of water-soluble cavitands to related processes such as remote functionalization reactions.

We recently reported the synthesis and characterization of the deep cavitand **1** (Figure 1) and its ability to bind

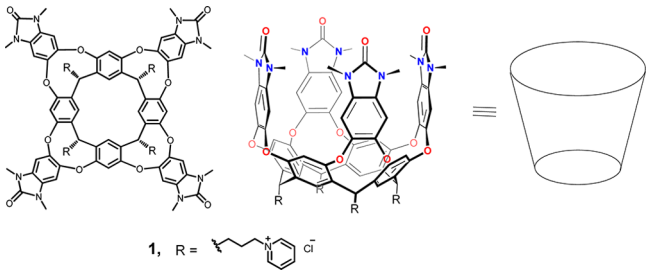
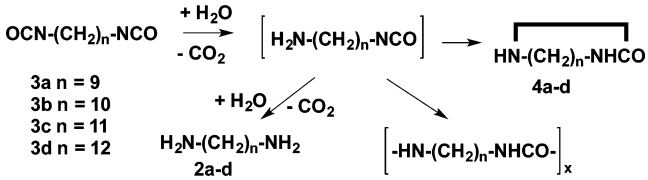


Figure 1. Structure, shape, and cartoon of the deep, water-soluble cavitand **1**.

hydrophobic compounds in water.[1] Bola-amphiphiles[2] are bound by these cavitands in folded conformations: the hydrophobic regions of the guest are bound within the container's aromatic walls, while the polar ends are exposed at the rim and directed into the aqueous medium. The complexation brings the termini closer together, and its functional groups are exposed to reagents in the bulk solution in an otherwise improbable conformation. Here we describe applications to macrocyclic urea synthesis. Cyclic ureas of five-, six-, and seven-membered rings are easy to prepare and are often synthesized by the reaction of the appropriate diamines with phosgene, urea, or some other activated form of carbon dioxide.[3] Large-ring cyclic ureas are more demanding and are prepared by controlled reactions of α,ω-diisocyanates with water under high dilution in water/acetone solvent mixtures (Scheme 1).[4] We used this method for comparison with the process chaperoned by the deep, water-soluble cavitand in D_2O.

Scheme 1. Reactions of Diisocyanates in Aqueous Solution



The substrates, α,ω-diisocyanates C9 (**3a**), C10 (**3b**), and C11 (**3c**), were easily synthesized from diamines C9−C11 (**2a−c**) using triphosgene and saturated $NaHCO_3$ solution; the diisocyanate C12 (**3d**) is commercially available. Cyclic urea standards C9−C11 (**4a−d**) were synthesized through high dilution (syringe pump) conditions in water/acetone (see pS3 in the Supporting Information). Brief shaking of diisocyanates **3a−d** (2 mM) with **1** (2 mM) in D_2O gave stoichiometric complexes, and their NMR spectra are shown in Figures 2a and 3a. The diisocyanate guests show signals clustered around 0 to −1 ppm (i.e., $\Delta\delta$ of about −1 to −2 ppm), and their simple pattern speaks for overall symmetrical structures. However, earlier studies with this cavitand indicated that methylenes fixed near the bottom of the cavity experience larger upfield shifts (i.e., $\Delta\delta$ of about −4 ppm) and show resonances at −2.7 ppm. Methylenes near the rim show little or no upfield shift.[5] Accordingly, the methylene chains of these diisocyanates are not fixed in the cavitand. Instead, the spectrum indicates a yoyo-like motion that rapidly interconverts the two J-shaped conformations on the NMR time scale (Figure 4). In the two resting states, a given methylene resides sometimes in and sometimes out of the cavitand. The average anisotropy experienced by the nonterminal methylenes is about −2 ppm,

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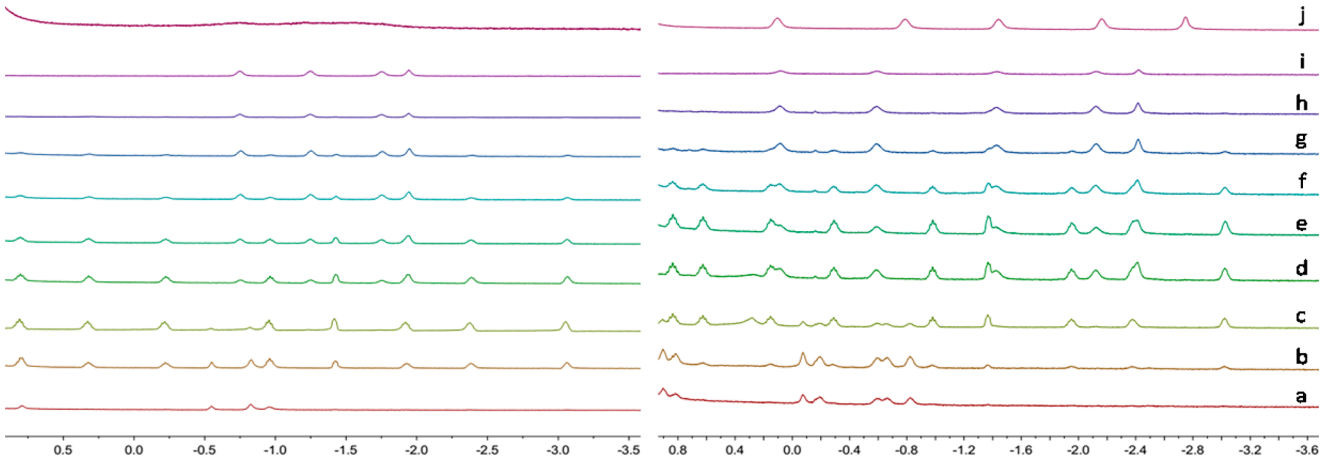

Figure 2. (a–h) Partial ^{1}H NMR (400 MHz, D_2O, 298 K) spectra of diisocyanates C10 **3b** (left) and C12 **3d** (right) with cavitand **1** recorded at sequential sonication times of (a) 1 min, (b) 10 min, (c) 30 min, (d) 4 h, (e) 7 h, (f) 14 h, (g) 16 h, and (h) 19 h. (i, j) Spectra of (i) authentic cyclic urea **4b** (left) and **4d** (right) with **1** and (j) authentic diamine **2b** (left) and **2d** (right) with **1**.

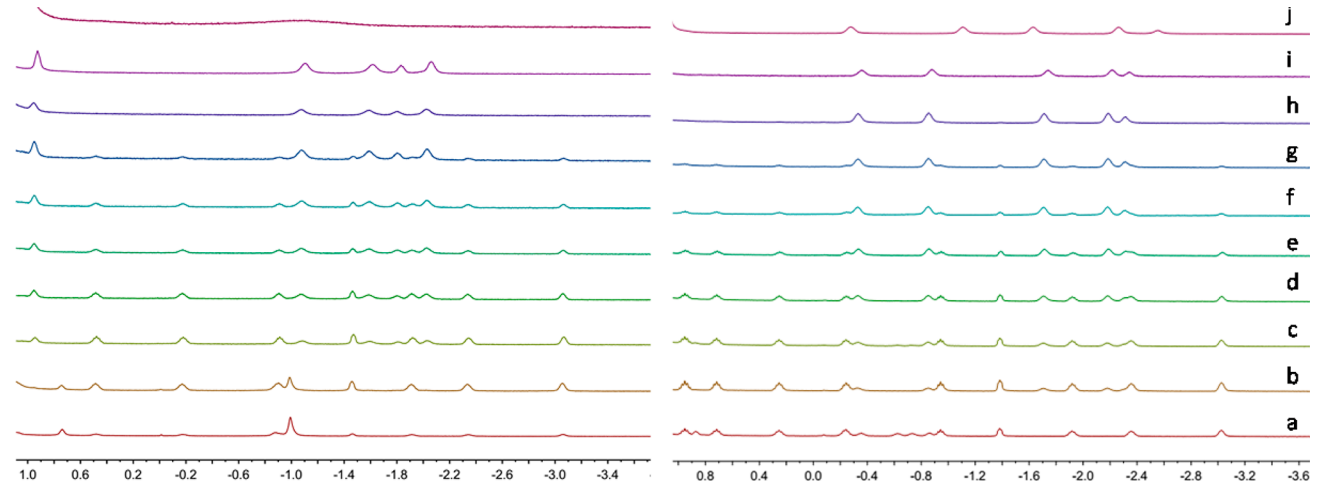

Figure 3. (a–h) Partial ^{1}H NMR (400 MHz, D_2O, 298 K) spectra of diisocyanates C9 **3a** (left) and C11 **3c** (right) with cavitand **1** recorded at sequential sonication times of (a) 5 min, (b) 1 h, (c) 3 h, (d) 4 h, (e) 8 h, (f) 10 h, (g) 14 h, and (h) 18 h. (i, j) Spectra of (i) authentic cyclic urea **4a** (left) and **4c** (right) with **1** and (j) authentic diamine **2a** (left) and **2c** (right) with **1**.

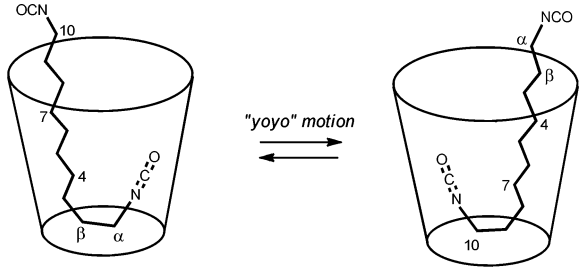

Figure 4. Cartoons of the complex of diisocyanate C10 **3b** with **1**. The ends exchange positions rapidly on the NMR time scale, and averaged signals result.

and their signals at around −0.7 ppm are consistent with this "yoyo" motion.

As can be seen in the traces in Figures 2 and 3, the ^{1}H NMR signals of the complexed diisocyanates decrease in intensity and then disappear after a few minutes of sonication and are replaced by a new set of peaks in the upfield region. These signals range from +1.2 to −3.0 ppm; 8 and 10 separate signals are distinguished for the initial products from **3a–d**, respectively. These signals indicate unsymmetrical complexes in which the guests are static: one end of the guest stays inside the cavitand and experiences large magnetic shielding, while the other remains outside. The upfield shifts ($\Delta\delta$) are summarized in Figure 5 for the intermediate and the authentic urea product **4b**. The methylenes of the alkyl chain achieve upfield shifts with

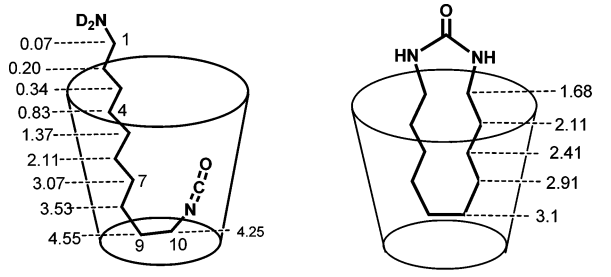

Figure 5. (left) Cartoon of the aminodecane isocyanate complex, which relates the upfield shifts ($-\Delta\delta$ in ppm) to the depth of the CH_2 groups in the cavitand. The upfield shifts shown were calculated from spectra of free aminoisocyanate in water by sonication in D_2O for 17 h. (right) Cartoon of urea product **4b** in the cavitand; the values of $\Delta\delta$ (in ppm) shown were calculated from spectra of free ureas in water.

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$-\Delta\delta$ of up to 4.5 ppm. This value reflects how deep a $-CH_2-$**CH_2**$-CH_2-$ can penetrate this cavitand. The exposed end has reacted with water to form a carbamate, which loses CO_2 to give the monoamine monoisocyanate of the NMR spectrum.[6] The chemical shifts of the NMR signals were assigned on the basis of correlation spectroscopy (COSY) (Figure 5 and Figures S15–S23 in the Supporting Information) and reflect the depth of a given nucleus in the cavity.

The signals of the aminoisocyanate intermediates disappear with continued sonication as the signals of the cyclic urea guests grow in, as can be seen in the stacked spectra in Figures 2 and 3. The aminoisocyanate is the necessary reaction intermediate for cyclic urea formation through an intramolecular reaction in the cavitand (Figure 5). The nucleophilicity of the nearby amino group is decades greater than that of the solvent D_2O.[7] Intermolecular reactions leading to di- and oligourea products are inhibited, as the isocyanate ends of the aminoisocyanate intermediates are fixed deep and kept dry in the cavitand. Reference spectra of authentic diamines in the cavitand (top traces in Figures 2 and 3) indicate that no diamine signals appear during the cavitand-chaperoned reactions.

Unbiased control reactions in these systems are challenging because the diisocyanates are practically insoluble in water. Accordingly, cosolvents (D_2O and 10% acetone-d_6) were used to compare the efficiency of the cavitand-chaperoned cyclizations with that of the cyclizations in bulk solvent. We prepared samples spiked with dimethyl sulfone (0.6 mM) as a water-soluble internal standard. For instance, compound **3b** in D_2O/acetone-d_6 (10/1 v/v) was sonicated for 19 h, after which the solvent was removed and excess cavitand **1** (6 mM) in D_2O was added to completely sequester the cyclic urea. Under these conditions, mostly oligomeric products were formed, even though the low solubility of the diisocyanate in this solvent system ensured high-dilution conditions. Small amounts of macrocyclic ureas were nonetheless detected (see Figures S24–S27). The yields of 12- to 15-membered cyclic ureas were improved 4–6 fold by **1** (Table 1), as calculated by NMR integration using the standard (see pp S19–S24 in the Supporting Information). However, in the absence of cavitand **1**, sonication of diisocyanates **3a–d** in D_2O alone for 19 h led to no cyclic urea signals after addition of **1**; only diisocyanate and monoaminoisocyanate signals were seen in the cavitand (Figures S28–S31).

Table 1. Yield Enhancements by Cavitand 1[a]

	yield (%)		
diisocyanate	with **1**	without **1**[b]	enhancement
3a	83	17	4.9
3b	81	15	5.4
3c	81	15	5.4
3d	88	13	6.7

[a]Yields were calculated on the basis of ^{1}H NMR integration using dimethyl sulfone as an internal standard. The concentration of substrate (**3a–d**) was 1.6 mM, and excess cavitand (6 mM) was used. [b]In water/acetone.

How does cavitand **1** facilitate this reaction? First, the cavitand dissolves the substrate, and one terminal isocyanate is surrounded by the aqueous solution. Without the cavitand, the reaction likely takes place at the interface of the solid organic and the aqueous phase, where the rate is limited by mass transport. Second, the bound reaction intermediate is folded. The isocyanate end is protected from intermolecular reactions, including hydrolysis to give the diamine. The amine terminus is the nearest nucleophile and is always closer than it would be in its uncomplexed counterpart.

In addition to the cavitand's action as a supramolecular solubilizing and protecting group,[8] it is also a template. The forces that bury hydrophobic surfaces and the shape of the space on offer push the reactions along congruent pathways; this is a general feature of reactions in container molecules.[9] Specifically, **1** can fold the intermediate aminoisocyanates, which are not readily observed in bulk solution, and enable the reaction that forms the cyclic ureas. With bola-amphiphiles in **1**, the polar end groups remain exposed to reagents in the aqueous medium and to each other. We have recently applied this feature to cyclization reactions of amino acids to form lactams,[10] and applications in other reluctant macrocyclization processes will be reported in the sequel.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04278.

Experimental procedures, NMR spectra, and details of yield calculations (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Zhang, K.-d.; Ajami, D.; Gavette, J. V.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2014**, *136*, 5264–5266.

(2) Gavette, J. V.; Zhang, K.-d.; Ajami, D.; Rebek, J., Jr. *Org. Biomol. Chem.* **2014**, *12*, 6561–6563.

(3) For examples, see: (a) Michels, J. G. *J. Org. Chem.* **1960**, *25*, 2246–2247. (b) Settppani, J. A.; Brown, R. T.; Bořkovee, A. B. *J. Heterocycl. Chem.* **1973**, *10*, 639–642.

(4) Ozaki, S.; Mukaiyama, T.; Uno, K. *J. Am. Chem. Soc.* **1957**, *79*, 4358–4360.

(5) Ajami, D.; Rebek, J., Jr. *Acc. Chem. Res.* **2013**, *46*, 990–999.

(6) Krol, P. *Prog. Mater. Sci.* **2007**, *52*, 915. Ionescu, M. *Chemistry and Technology of Polyols for Polyurethanes*; Rapra Technology, Ltd.: Shawbury, U.K., 2005.

(7) Delebecq, E.; Pascault, J.-P.; Boutevin, B.; Ganachaud, F. *Chem. Rev.* **2013**, *113*, 80–118.

(8) Elacqua, E.; Kaushik, P.; Groeneman, R. H.; Sumrak, J. C.; Bučar, D.-K.; MacGillivray, L. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 1037–1041.

(9) (a) Hastings, C. J.; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10977–10983. (b) Hastings, C. J.; Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 6938–6940. (c) Fiedler, D.; van Halbeek, H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 10240–10252. (d) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748–6751. (e) Kaanumalle, L. S.; Gibb, C. L.; Gibb, B. C.; Ramamurthy, V. *J. Am. Chem. Soc.* **2004**, *126*, 14366–14367. (f) Sundaresan, A. K.; Ramamurthy, V. *Org. Lett.* **2007**, *9*, 3575–3578.

DOI: 10.1021/jacs.6b04278
J. Am. Chem. Soc. 2016, 138, 7512–7515

(g) Jagadesan, P.; Mondal, B.; Parthasarathy, A.; Rao, V. J.; Ramamurthy, V. *Org. Lett.* **2013**, *15*, 1326−1329. (h) Sundaresan, A. K.; Ramamurthy, V. *Photochem. Photobiol. Sci.* **2008**, *7*, 1555−1564.
(10) Mosca, S.; Yu, Y.; Gavette, J. V.; Zhang, K.-D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2015**, *137*, 14582−14585.

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