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Macrocyclization of Folded Diamines in Cavitands

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Supporting Information

ABSTRACT: Synthetic access to water-soluble cavitands and capsules has moved recognition events from organic solvents into aqueous media. Here we report the binding and reactivity of long-chain α,ω-diamines (C_{11} to C_{18}) in cavitand hosts. The containers bind the diamines in folded conformations that bury the hydrocarbon chains and expose the amino groups to the aqueous medium. Their acylation with succinic anhydride results in improved yields of monofunctionalized products. The cavitand-bound amino acid products were cyclized to the corresponding macrocyclic dilactams in D_2O using water-soluble carbodiimide. Direct reaction of the folded diamines in the cavitand with activated diesters of succinic acid and glutaric acids resulted in 54−96% yields of the 17- to 25-membered dilactams. These cavitand-chaperoned reactions provided 3- to 10-fold improvements over the yields obtained in bulk solution and offer an alternative to high dilution methods. The cavitand induces unlikely conformations in flexible guests and channels their reactivity along otherwise improbable paths.

We recently prepared the cavitands **1** and **2** (Figure 1) and showed their binding of hydrophobic and amphiphilic guests in water (D_2O). Small guests such as octane and ibuprofen are taken up by **1a** as open-ended complexes,[1] while longer guests such as tetradecane and stilbene induce dimerization and are bound in closed capsules.[2] Capsule formation through hydrogen-bonding[3] can be prevented by octamethylation as in **1b**, in which long guests such as tridecanol, bola-amphiphiles and α,ω-dodecane diols are bound in unusual bent conformations.[1] We have taken advantage of guest folding—it brings the ends closer together—to template medium-ring lactamization reactions of ω-amino acids (Figure 1).[4] Other applications led to high yields of monofunctionalized products during the Staudinger reduction of diazides[5] and macrocyclization of di-isocyanates to ureas.[6] The ability of the cavitand to protect[7a] buried functions provides a general approach to desymmetrization reactions.[7b] The functionally identical cavitand **2** is available in gram-scale quantities[8] and shows better solubility in water; here we use it for the synthesis of large (17−25-membered) ring compounds. The application combines the protective action of the cavitand **2** that allows monofunctionalization with its template effects that coax folded, long-chain intermediates toward difficult cyclization reactions.

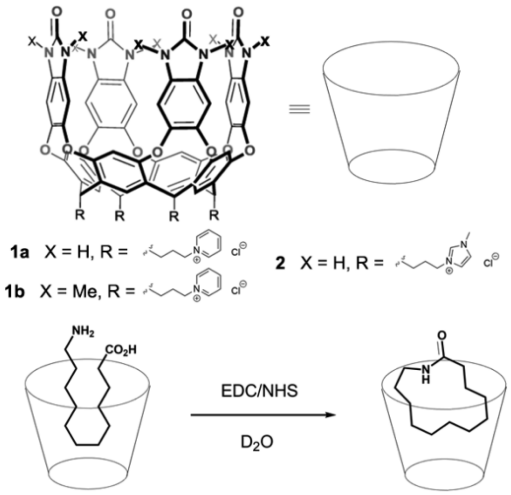

Figure 1. Top: Structures and the cartoon depiction of water-soluble deep cavitands. Bottom: Cyclization of folded amino acid complexes in cavitand **2** gives good yields of lactams using the water-soluble carbodiimide EDC.[4]

Sonication of diamines with **2** in D_2O gave 1:1 complexes that were characterized by NMR spectroscopy (Figure 2 and Supporting Information (SI)). The upfield shifts of nearly −4.0 ppm for the signals of the C_{12} diamine guest's central methylenes (Figure 2, spectrum a) place them deep in the cavitand, as is expected for binding in a symmetrical, folded manner. Five signals are upfield shifted, placing 10 CH_2 groups within the shielding manifold of the cavitand's aromatic panels. The guest assumes a U-shaped arrangement that buries its hydrophobic surfaces and solvates the cavitand's interior while exposing the amine groups to D_2O and reagents in the bulk solvent.

Addition of succinic anhydride and base (NaOH) to the diamine complexes gave clean monofunctionalization reactions. Acylation occurs at only one end of the diamine; it desymmetrizes the guest, and the spectra are accordingly more complex (Figure 2, spectrum c,d and SI). The anhydride was added in several portions, but even excess anhydride did not lead to reaction at the other amino end. Table 1 summarizes the results for several long-chain diamines.

Difunctional compounds with symmetrical, independently acting sites in bulk solution can give a maximum yield of 36.8%

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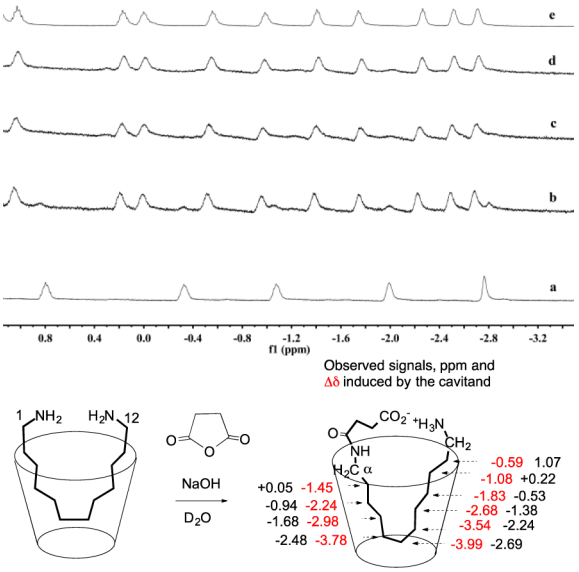

Figure 2. Top: Upfield portions of the NMR spectra of cavitand **2** complexes (400 MHz, 299.5 K, D_2O). (a) C_{12} diamine (1 mM)/cavitand (excess) in D_2O; (b) after adding 1 equiv of NaOH (70 mM in D_2O) with 1 equiv of succinic anhydride solution (87 mM in CD_3OD) and shaking for 4 min by hand, followed by another 1 equiv of NaOH and 1 equiv of succinic anhydride and shaking for another 4 min; (c) after adding another 1 equiv of base and anhydride to (b) and shaking for 4 min; (d) sample (c) after 30 min; (e) the authentic amino acid product with excess cavitand in D_2O. Bottom: The reaction involved; the observed ^1H NMR signals (from COSY spectra) are shown in black, and the calculated upfield shifts ($\Delta\delta$) are in red.

Table 1. Amino Acid Syntheses from Diamines and Succinic Anhydride[a]

	yields (%)		
diamine	with cavitand	without cavitand	improvement factor
C_{11}	64	26	2.4
C_{12}	71	27	2.6
C_{14}	61	34	1.8
C_{16}	64	34	1.9

[a]See SI for the reaction details.

monofunctionalized products and comparable amounts of unreacted and difunctionalized material.[7b] The absence of diacylated product in the cavitand-chaperoned reaction speaks for some form of communication between the folded ends of the guest; they no longer act independently.

Shorter diamines have appreciable solubilities in water that give background reactions in the bulk solvent which raise uncertainties in the product origins. Control reactions (without cavitand **2**) were performed as homogeneous solutions in CD_3OD, and the yields (Table 1) reflect the statistical nature of the process: The cavitands, on average, roughly double the yields of the desired monofunctional products. Perfect controls (in D_2O) are precluded by insolubility.

The chemical shifts observed for the amino acid from the C_{12} diamine and succinic anhydride (shown in the cartoon of Figure 2) are assigned on the basis of COSY spectra (see SI). The propinquity of acid and base termini as shown in the cartoon is merely a reasonable assumption. The terminal groups are poised for macrocyclization, since the cavitand forces a U-turn in the conformation and brings the ends together. The water-soluble dehydrating agent EDC was added to the folded amino acids from the C_{11} and C_{12} diamine along with a soluble NHS additive. The corresponding macrocyclic dilactams were obtained in 66% (from the C_{11} amino acid) and 64% (from the C_{12} amino acid) yields. The yields are 2.0- and 1.4-fold improvements, respectively, compared with the results without the cavitand in CD_3OD/D_2O (v/v, 4/1) (see SI).

Direct macrocyclization reactions of the complexed diamines were even more successful (Table 2). Addition of the di-NHS

Table 2. Direct Macrocyclic Dilactam Syntheses Using Succinyl Spacers[a]

	yields (%)		
diamine	with cavitand	without cavitand	improvement factor
C_{11}	87	11	7.9
C_{12}	84	13	6.5
C_{14}	90	9	10.0
C_{16}	68	12	5.7
C_{18}	54	10	5.4

[a]See SI for the reaction details.

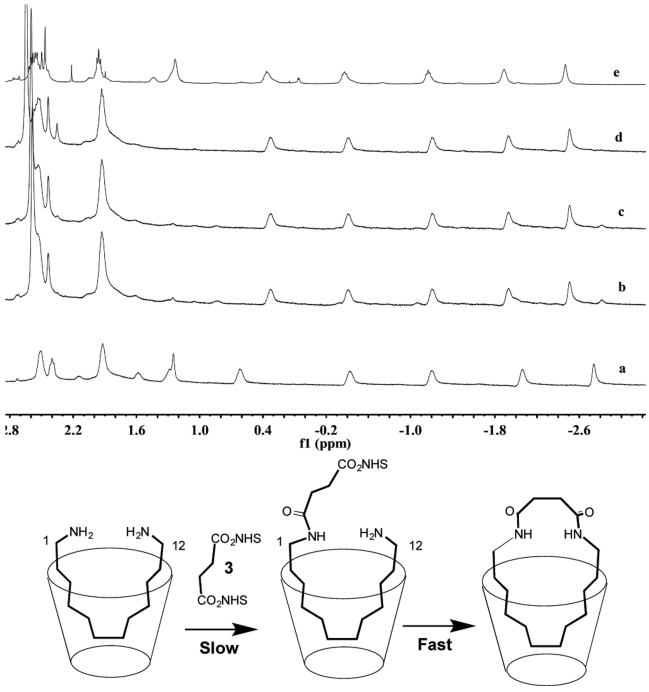

Figure 3. Top: Upfield portions of the NMR spectra of cavitand **2** complexes (400 MHz, 299.5 K, D_2O). (a) C_{12} diamine (1 mM)/cavitand (excess) in D_2O, after addition of 3 equiv of NaOH (70 mM in D_2O); (b) after adding excess di-NHS ester of succinic acid to (a) and shaking for 2 min by hand; (c) sample (b) after 12 min; (d) sample (b) after 100 min; (e) the authentic dilactam product with excess cavitand in D_2O. Bottom: The proposed reaction sequence; only the symmetrical diamine and dilactam are observed in the NMR.

ester **3** of succinic acid (Figure 3) and NaOH with brief shaking by hand showed the appearance of new compounds within minutes, and the diamine completely disappeared within 2 h (Figure 3). The signal patterns show that the products are also symmetrical and at nearly the same depths in the cavity as the diamines. Apparently, the unsymmetrical intermediate amino ester does not build up enough to be detected by NMR but

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cyclizes rapidly. Extraction into $CDCl_3$ gave the compound characterized as 1,6-diazacyclooctadecane-2,5-dione by ^1H NMR and HRMS (see SI). The product macrodilactams were identified with independently synthesized samples.

The direct macrocyclization reactions were extended to the di-NHS esters of glutaric acid. Again, rapid and clean cyclizations occurred to give the dilactam products (Table 3).

Table 3. Direct Macrocyclic Dilactam Syntheses Using Glutaryl Spacers[a]

	yields (%)		
diamine	with cavitand	without cavitand	improvement factor
C_{11}	93	22	4.2
C_{12}	96	30	3.2
C_{14}	94	22	4.3
C_{16}	95	24	4.0
C_{18}	72	21	3.4

[a]See SI for the reaction details.

Control reactions performed without **2** were done in DMSO solvent at the same 1 mM concentration of reagents. The reactions in this homogeneous solution gave low yields of macrocyclic products (Tables 2 and 3). The enhanced selectivity of the macrocyclization reaction in the cavitand varies from 3- to 10-fold.

Cavitand-mediated reactions differ from the classical template effects of supramolecular chemistry.[9] In the present case, the cavitand's walls push the guest into an otherwise unlikely conformation in a small space.[10] But unlike the cases in other container compounds,[11] the reactions here take place in the bulk solvent. The cavitand provides a vehicle for suitable guests to move their reactions from organic solvents into aqueous media.[12] Forcing flexible chain structures into improbable conformations offers advantages, as shown in recent catalytic applications.[13] While the cavitand here acts in stoichiometric quantities, it can be recovered and reused after extraction of the neutral products (see SI), several of which were previously unknown compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06950.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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