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A Deep Cavitand Templates Lactam Formation in Water

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Supporting Information

ABSTRACT: Cyclization reactions are common processes in organic chemistry and show familiar patterns of reaction rates vs ring size. While the details vary with the nature of bond being made and the number of unsaturated atoms, small rings typically form quickly despite angle strain, medium size rings form very slowly due to internal strains, and large rings form slowly (when they form at all) because fewer and less probable conformations bring the ends of the substrate together. High dilution is commonly used to slow the competing bi- and higher molecular processes. Here we apply cavitands to the formation of medium size lactams from ω-amino acids in aqueous (D_2O) solution. The cavitands bind the amino acids in folded conformations that favor cyclization by bringing the ends closer together. Yields of a 12-membered lactam are improved 4.1-fold and 13-membered lactam 2.8-fold by the cavitand template. The results open possibilities for moving organic reactions into water even when the processes involve dehydration.

High dilution and template effects are tactics often used to enhance cyclization reactions. The templates frequently involve metal ions: Pedersen[1] discovered that K^+ templated the synthesis of 18-crown-6, while Sauvage used Cu^+ to enhance the synthesis of catenanes.[2] Pedersen's result was unexpected and subsequently became the foundation of host/guest chemistry. Sauvage's was carefully planned and gave the first mechanically linked devices.[3] Modern supramolecular chemistry has also applied template effects. Synthetic capsules in water were used as templates to facilitate five- or six-membered ring formation[4−8] or channel reaction pathways along otherwise unlikely paths.[9] The concave inner surfaces of capsules and cavitands bend guests into conformations that bring the termini close together, favorable for cyclization reactions.

Medium to large rings pose problems in addition to mere size: Transition structures for medium-sized rings create transannular and torsional strains along saturated alkyl chains and bringing the ends together for cyclization limits the otherwise free rotations of several single bonds. These enthalpic and entropic factors contribute to high activation energies and slow cyclization rates. Here we show that a water-soluble, deep cavitand is a template for 12- and 13-membered lactam synthesis. Hydrophobic effects bend the alkyl chains of the appropriate α,ω-amino acids into favorable shapes for cyclization and overcome the factors that otherwise thwart the reaction.

There are many reports of bent alkanes inside container molecules, but reactions performed on the folded states appear to be overlooked. The earliest folded alkyl was deduced by Turro[10] for a surfactant bound inside a γ-cyclodextrin. Bola-amphiphiles folded in cucurbiturils were observed by Kim,[11] both in solution and the solid state. More recently, Gibb has described folded and other shapes of alkanes in capsules by NMR methods.[12] We also reported a water-soluble, deep cavitand **1** (Figure 1) capable of

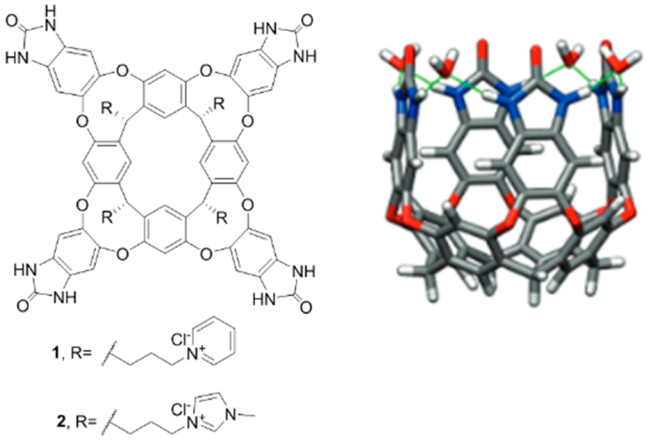

Figure 1. (Left) Structures of the water-soluble, deep cavitands **1** and **2**. (Right) Modeled structure of the cavitand form; the four bridging water molecules on the corners stabilize the vase conformation. The "feet" have been deleted.

sequestering hydrophobic guests in unusual conformations from aqueous solutions.[13−15] Bola-amphiphiles such as ω-amino acids fold to fit their hydrophobic parts into **1** and expose the polar termini to the solvent water (D_2O):[15] The close proximity of the functional ends suggest cyclization reactions. The pyridinium ions of **1** are effective in imparting water solubility at concentrations of typical NMR investigations (1 mM), but bound guests were partially released when reagents were introduced that altered the reaction medium. The substrates liberated to the solvent can react independently and compromise the efficiency of the cavitand as container for the intramolecular pathway. The pyridinium feet of **1** were replaced with

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methylimidazolium ions of the cavitand **2** (Figure 1) which conferred higher solubility and somewhat greater stability to the complexes.

Cavitand **2** showed solubility in water (D_2O) of up to 17 mM, and solutions for typical NMR investigations (1 mM) in D_2O were achieved with brief shaking at room temperature. In the absence of guests, both vase and kite conformations of **1** and **2** are present in D_2O solutions: the vases correspond to the minor species and show methine C−H signals at ∼5.7 and ∼5.6 ppm, respectively (see SI).[16,17] The kites show the (multiple) aryl C−H signals consistent with two-fold symmetry[18] and likely exist as dimeric velcraplexes that reduce solvent-exposed hydrophobic surfaces.[19,20] Appropriate guests that fit into, fill, and solvate the cavitand host's hydrophobic interior shift the equilibrium to the vase conformation. The ^{1}H NMR signals for bound guests appear hugely upfield-shifted (to nearly −5 ppm).[21,22] The capacity of **2** for organic guests in aqueous solutions[23−30] was explored using different bolamphiphiles (e.g., *α*,*ω*-amino acids, *α*,*ω*-diamines, *α*,*ω*-diacids, *α*,*ω*-diols) with C11 and C12 alkyl spacers (Figure 2 and SI). These spacers were selected for their availability and optimal affinity for the congener cavitand **1**.[15]

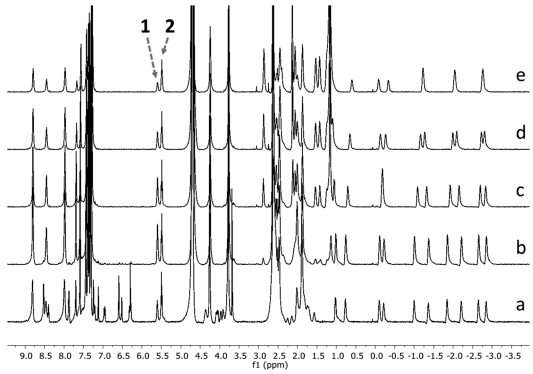


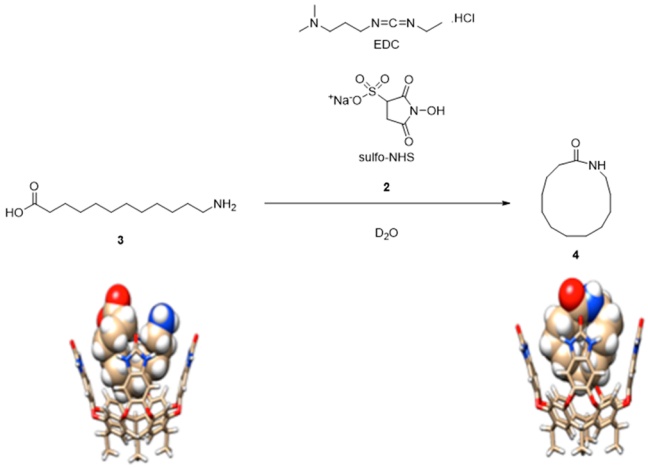
Figure 2. ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of the complexes of **1** (1.0 mM) and **2** (1.0 mM) with (a) substoichiometric amounts and (b) excess of *ω*-amino-dodecanoic acid **3**; the characteristic methine signals of the vase forms are indicated with arrows. Spectra after addition of NaOD (c) 1 equiv, (d) 2 equiv, (e) 4 equiv The NaOD was added as 1% (v/v) solution in D_2O.

Competitive binding experiments with **1** revealed that generally **2** shows higher affinity for these guests. The cavitands **1** and **2** were dissolved in D_2O (1 mM), and substoichiometric amounts of guest were sequentially added until the kite conformation was no longer observed. The ratio between the methine signals of **1** to **2** increases (up to ∼1) as the guests were added, indicating the higher affinity of **2** before saturation occurs and all of **1** also assumes the complexed vase conformation (Figure 2 and SI). Complexes of **2** also showed higher stability to strong base (NaOD), while both **1** and **2** were stable to strong acid (DCl) (Figure 2 and SI).

Both cavitands **1** and **2** feature the same hydrophilic urea rims and hydrophobic interior of the binding site, so equal binding affinities for different guests would be expected. Perhaps the better binding of **2** involves its improved solubility. The mechanism of binding by these deep cavitands requires the dissociation of the velcrand dimer, and a conformational change from the kite to vase forms at an energetic cost of ca. 10−12 kcal mol^{-1}.[19] The increased solubility of the monomeric forms of **2** could lower the conformational energy costs for binding.

We applied the cavitand **2** to cyclize the inexpensive *ω*-amino-dodecanoic acid **3** (Scheme 1). The NMR traces of the

Scheme 1. (Top) Cyclization of 3 to 4 with EDC and Sulfo-NHS in the Presence of 2 and (Bottom) Models of the Complexes of 2 with Folded 3 (Left) and 4 (Right)



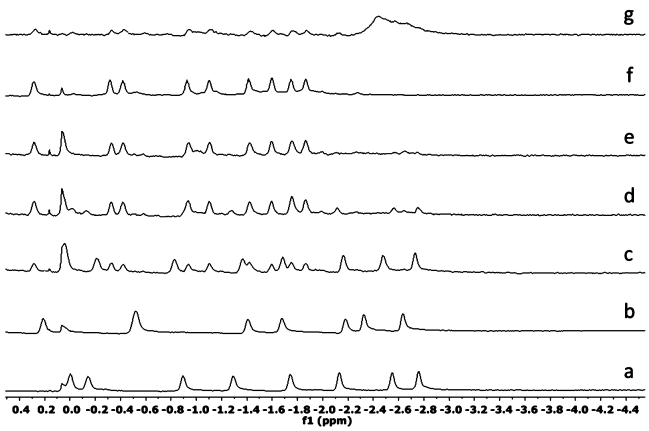


Figure 3. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of the lactamization of **3** (1 mM) with **2** (excess) and sulfo-NHS (1 mM) using sequential additions of 2 equiv EDC. (a) **3** (1 mM) with **2** (excess); (b) sample (a), sulfo-NHS (1 mM), and EDC (2 equiv); (c) sample (a) and EDC (6 equiv); (d) sample (a) and EDC (12 equiv); (e) sample (a) and EDC (18 equiv); (f) the target product, **4** (1 mM) with **2** (excess). (g) Solution control experiment: **3** (1 mM), sulfo-NHS (1 mM), and EDC (18 equiv) were allowed to react; after complete consumption of EDC, cavitand **2** (excess) was added to sequester the lactam product.

complexed substrate are shown in Figure 3, where 9 of the 11 methylenes are seen within the shielding manifold of the cavitand and shifted upfield. The amino acid lies in a U-shaped arrangement inside the cavitand, with its polar functions exposed to the solvent water and relatively close together.

The water-soluble dehydrating agent (1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide, EDC) was used with the additive sulfo-*N*-hydroxy-succinimide (sulfo-NHS) (Scheme 1). Sulfo-NHS enhances the water solubility of its esters and was expected to keep the active ester of the *ω*-amino-dodecanoate exposed to the reaction medium and near the amino end. The stacked spectra (Figure 3) show the lactam signals grow in with

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time and added EDC. The pH (pD) of the solution gradually rose from 5.4 to 6.8 during the course of the reaction (see SI).

In the absence of cavitand under these conditions, mostly oligomeric products were formed, even though the low solubility of the amino acid in D_2O ensured high-dilution conditions. The small amount of lactam formed was detected by adding **2** after the reaction (Figure 3g). The yield of 13-membered laurolactam (**4**) was improved 2.8-fold in the presence of **2** (see SI). The effect of the cavitand was more dramatic when ω-amino-undecanoic acid **5** was employed as substrate (Figure 4). In the absence of cavitand the amount of lactam formed was negligible, and addition of **2** provided 4.1-fold improved yield, as measured by NMR integration (see SI).

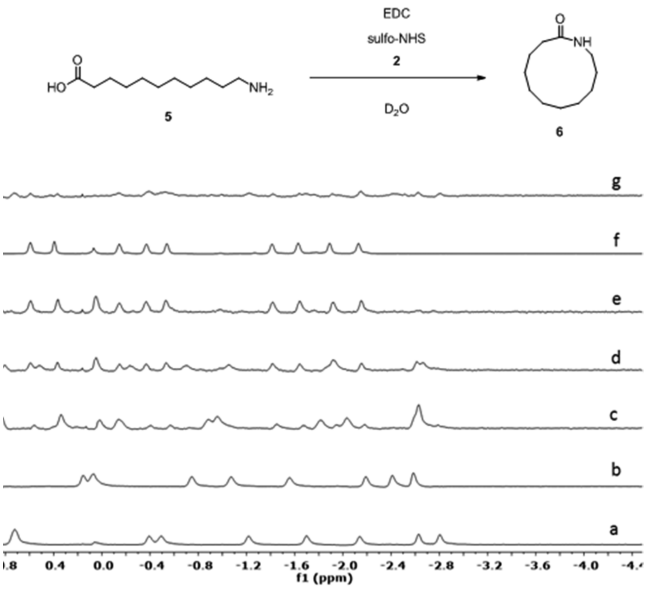

Figure 4. Partial ^{1}H NMR spectra (600 MHz, D_2O, 298 K) of the lactamization of **5** with **2** and sulfo-NHS (1 mM) using sequential additions of 2 equiv EDC. (a) **5** (1 mM) with **2** (excess); (b) sample (a), sulfo-NHS (1 mM), and EDC (2 equiv); (c) sample (a) and EDC (4 equiv); (d) sample (a) and EDC (8 equiv); (e) sample (a) and EDC (12 equiv); (f) the target product, **6** (1 mM) with **2** (excess). (g) Solution control experiment: **5** (1 mM), sulfo-NHS (1 mM), and EDC (12 equiv) were allowed to react; after complete consumption of EDC, cavitand **2** (excess) was added to sequester the lactam product.

We also prepared the *p*-NO_2-phenyl ester of **5** (C11PNP). Earlier reported attempts at cyclization of **5** under high dilution had failed to give reasonable yields of ω-amino-undecanoic acid lactam (**6**).[31] The amino ester was expected to adopt a U-shape in the cavitand, appropriate for cyclization. Indeed, C11PNP as the hydrochloride formed a stable complex with **2** (Figure 5). However, neutralization of the complex with NaOD (3 equiv) gave neither the free amine of the PNP ester nor lactam **6**. Instead, the complexed amino acid **5** was formed. Apparently, the *p*-NO_2-phenyl group becomes exposed to D_2O and suffers hydrolysis.

Outlook. One of the lessons emerging from the study of synthetic container compounds is that molecules in dilute solutions do not behave as they do in confined spaces; spaces like enzyme or receptor active sites. The keys to how enzymes work[32] comprise creating specialized microenvironments that alter the reactivity of catalytic groups, shielding the groups from contact with bulk solvent, and distorting the substrates to adopt high-energy conformations with increased reactivity. Synthetic

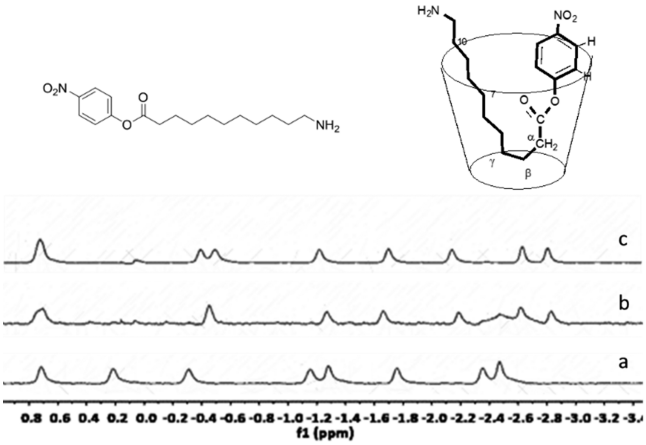

Figure 5. (Top) Structure of C11PNP (left) and cartoon of the complex with **2** (right). The relative positions of the C atoms in the cavitand correspond to their NMR signals and the NICS calculations[21] (see SI). (Bottom) ^{1}H NMR spectra (600 MHz, D_2O, 298 K) of the attempted lactamization of C11PNP. (a) C11PNP hydrochloride salt (1 mM) with **2** (excess); (b) sample (a) after addition of NaOD (3 equiv); (c) authentic amino acid **5** (1 mM) with 2 (excess).

receptors are seen to have parallel features. Species unknown in solution emerge in the protected space of container molecules: reactive intermediates such as activated acids,[33] hemiaminals, and other tetrahedral intermediates have been stabilized,[34] and contortions of alkyl groups into helices[35] are common.

Admittedly, the lactamization described here is stoichiometric in the cavitand and classical product inhibition places limits on its application. The efficient extraction of the (neutral) lactam products from their cavitand complexes with organic solvents bodes well for a future catalytic version of this reaction in a two-phase system. But the present study reveals a more pressing need: How to effect dehydration reactions in water? Nature's reagent, ATP, is ineffective in the absence of enzymes, but chemists have few alternatives such as EDC, used here in spectacular excess. One of the main themes of "green" chemistry is the wholesale movement of chemical reactions out of organic solvents and into water.[36] Complex formation between cavitands and these guests requires water, and subsequent reactions cannot require "dry" conditions. Can additives be found that modify the water's reactivity? The successful application of hexafluoroisopropanol, particularly in remote functionalization reactions,[37] offers promise in this regard.

■ ASSOCIATED CONTENT

Supporting Information

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Additional information and figures (PDF)

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Notes

The authors declare no competing financial interests.

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