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Communication

Selective Macrocycle Formation in Cavitands

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ABSTRACT: The traditional end-to-end cyclization of long-chain linear precursors is difficult and often unpredictable because the unfavorable entropy of macrocyclic closure allows undesired intermolecular reactions to compete. Here, we apply cavitands to the selective intramolecular aldol/dehydration reaction of long-chain α,ω-dialdehydes in aqueous solution. Hydrophobic forces drive the dialdehydes into the cavitands in folded conformations and favor macrocyclization reactions over intermolecular reactions observed in bulk solution. The macrocyclic aldol reaction products are isolated in good yields (30−85%) over a wide range (11 to 17-membered rings). Unlike conventional templates that become guests inside their assembled hosts, cavitands reverse the roles and resemble the situation in biological catalysis—the templates are hosts for guests undergoing the assisted reaction processes.

The efficient synthesis of macrocycles is challenging because bringing together the two ends of a long-chain precursor is improbable. Success requires the rate of the intramolecular cyclization (I to II, Figure 1) to be faster than

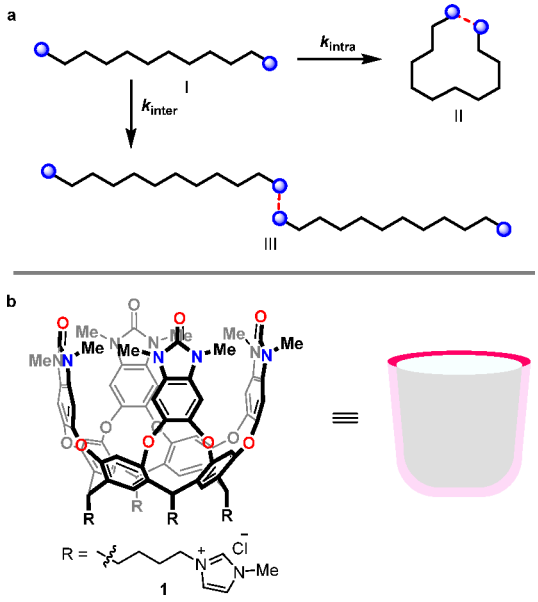

Figure 1. (a) Macrocyclization vs bimolecular reaction. (b) Chemical structure and the cartoon depiction of the water-soluble, deep cavitand **1**.

the competing intermolecular reaction (I to III, Figure 1), and the common tactic used to overcome the problem is to use high dilution conditions.[1] This can reduce intermolecular reaction rates remarkably but requires large volumes of solvent and slow addition of reactants (e.g., using syringe drives) with long reaction times and is often highly substrate dependent. Alternative macrocyclization methods involve template effects, controlling the conformation of the precursor by some chemical or bioprocess[2] to one favorable ring closure−preorganization.[3] Accordingly, several methods have been developed, comprising guest-mediated macrocyclization,[4−6] ring-closing metathesis,[7] foldamer-templated catalysis of cyclization,[8] and incorporation of curved components.[9]

Molecular container hosts can fundamentally change the chemical and physical properties of guests and are relevant to this issue.[10−18] In earlier work, we developed a series of water-soluble, deep cavitands[19−22] in which long-chain guests such as α,ω-dienes are bound in unique, bent conformations.[23] Earlier, folded alkyl chains were observed for guests bound by cucurbiturils,[24] especially when the guests bear polar temini.[25] Cavitands such as **1** bind guests in their hydrophobic interiors in a way that guest ends are near the open end of the container, exposed to water and reagents in solution. The cavitand is a template that "pushes" the guest termini closer together and offers alternatives to ring expansion methods.[26] Several reactions including monofunctionalization[27−29] and macrolactamization[23,30,31] were chaperoned by the cavitand, and here we describe its application to the intramolecular aldol condensation of long-chain, linear dialdehydes.

Brief sonication of dialdehydes such as dodecanedial **2a** (4 mM) with cavitand **1** (1 equiv) in D_2O produces 1:1 complexes. Two species are seen to be present (complex **A** and complex **B**) with characteristic ^{1}H NMR spectra shown in Figure 2 (see also the Supporting Information), and the assignments were obtained by 2D COSY experiments (Figure S1). Complex **A** is the complex of dialdehyde **2a** with the cavitand **1**, and the bound dialdehyde shows five time-averaged signals clustered around 0.2 to −1.3 ppm. The conformation of dialdehyde inside the cavitand **1** is not fixed but moves rapidly on the NMR chemical shift time scale. The motion is probably

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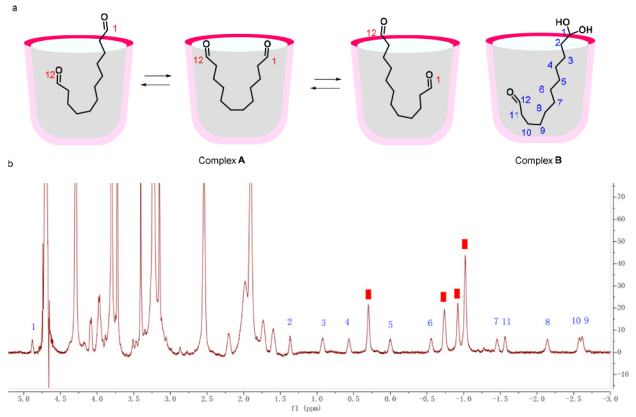

Figure 2. (a) Cartoons of complexes **A** and **B**. (b) Partial ^{1}H NMR spectrum of **2a**@cavitand **1**. The peaks labeled with red rectangles are from the dynamic complex **A**, and the peaks labeled with blue numbers are from the more static complex **B**.

"yo-yo like" between two J-shaped conformations. Complex **B** is the complex of dialdehyde monohydrate **2a** with the cavitand **1**, and the guest assumes a folded arrangement that is more static. Earlier studies indicate that a typical methylene group fixed at the bottom of the cavity appears at −2.7 ppm,[23,29,32] and complex **B** features such upfield signals. The ratio of complex **A** to **B** is about 0.6 to 0.4 based on ^{1}H NMR integration (Figure S2). This is unremarkable, as hydration equilibria for simple aliphatic aldehydes in water are typically near unity.[33,34] The dihydrate is also expected to be present, but it is soluble enough in water (D_2O) to remain in bulk solvent as shown by NMR signals between 1.5 to 2 ppm.

We used cavitand **1** as a chaperone to form a 12-membered ring, cyclododecene-1-aldehyde **3b**, from the corresponding C13 dialdehyde **2b** (Figure 3). The complex was prepared by

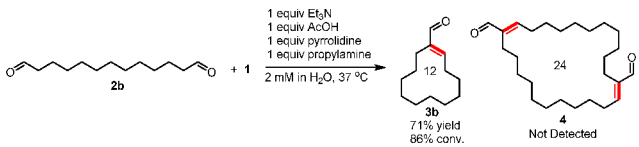

Figure 3. Selective intramolecular aldol condensation in the cavitand. Conversion based on the ratio of the substrates and products from ^{1}H NMR after extraction of the mixture. The yield of **3b** was 71% while **4** was not detected.

stirring the dialdehyde and cavitand **1** for 2 h (2.0 mM), followed by treatment with 1 equiv each of pyrrolidine, propylamine, acetic acid, and triethylamine at 37 °C, conditions based on precedents from Gellman's studies.[8] The reaction was monitored by ^{1}H NMR spectroscopy (in D_2O, see Supporting Information), and the desired product **3b** was obtained in 71% isolated yield after 20 h. The cyclodimer **4** was not detected. In contrast, when the reaction was performed in 4% H_2O, 96% isopropanol in the absence of cavitand **1**, and under the same conditions, the desired compound **3b** was not obtained. Instead, the cyclodimer **4** (20% yield) was isolated. The same reaction was performed in H_2O in the absence of cavitand **1** and under the same conditions, guaranteeing high dilution. The cyclic compound **3b** or **4** was not detected (83% conv); instead, oligomers were formed.

We evaluated the aldol reaction with the various dialdehyde compounds in Figure 4 and monitored by ^{1}H NMR in D_2O

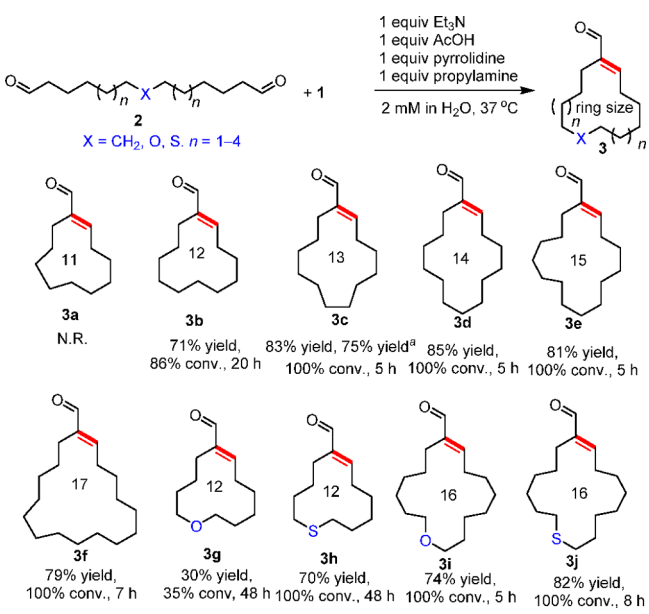

Figure 4. Scope of selective intramolecular aldol condensations in cavitand **1**. Yields are isolated, and conversions are based on the ratio of the substrates and products from ^{1}H NMR after extraction of the reaction solution. [a] Reaction was conducted with 50 mg of **2c**.

(Figures S4–S13). Reactions of dialdehydes with different chain lengths proceeded smoothly (**2b**–**2f**), giving the desired products in good yields. Dialdehydes bearing heteroatoms also afford the desired macrocycles in moderate to good yields (**2g**–**2j**). When the reaction was conducted with 50 mg of **2c**, the yield (75%) of **3c** decreased slightly.

The chain length affects the rate of reaction. The reaction rates forming 12-membered macrocycles were slow (**2b**, **2g**, **2h**), and dodecanedial (**2a**) did not react. These medium-sized rings show large transannular strains, and perhaps the two aldehydes are too deep in the cavity to interact with the acid and base catalysts in bulk solution. Stoichiometric amounts of cavitand **1** are required for the macrocyclization, but the cavitand can be recovered and reused with no effect on the reaction outcomes. Since direct competition experiments showed macrocycle **3c** to be a better guest than dialdehyde **2c**, classic product inhibition is expected (Figures S14–S16). Allyl deuterated product (55% D incorporation) was observed when **2c** was treated in D_2O under standard conditions. After further experimentation, higher deuteration (>95%) was achieved by increasing the amount pyrrolidine from 1 to 3 equiv (Figure 5).[35]

In summary, intramolecular aldol condensation of dialdehydes for macrocyclization can be achieved in a cavitand

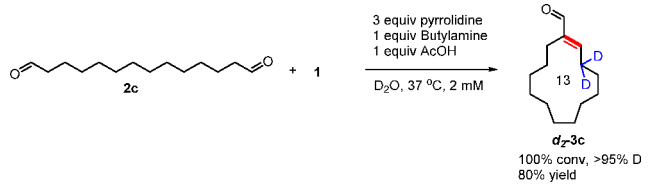

Figure 5. Formation of deuterated product.

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J. Am. Chem. Soc. 2021, 143, 2190–2193

chaperone. The cavitand **1** can fold the dialdehydes to bring the termini closer together and poised for the aldol reaction. Linear dialdehydes, including heteroatomic dialdehydes, reacted smoothly and afforded 11- to17-membered macrocycles in good yields and good selectivity while shorter dialdehydes were unreactive and protected from reagents in solution. Typically, templates are convex structures such as ions that "pull" components of the compound undergoing reaction inward to bring the relevant functions together. The container molecules use concave surfaces as templates to accomplish this by "pushing" on the substrate and remain hosts throughout the process. The applications shown here are stoichiometric in the cavitand, and efforts to develop catalytic cycles are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12302.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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