

## Cage-Catalyzed Knoevenagel Condensation under Neutral Conditions in Water

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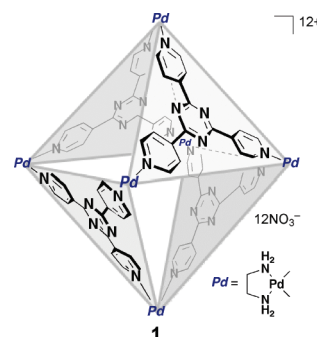
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## Supporting Information

**ABSTRACT:** A cationic coordination cage dramatically accelerates the Knoevenagel condensation of aromatic aldehydes in water under neutral conditions. The addition of a nucleophile to the aldehyde to generate anionic intermediates seems to be facilitated by the cationic environment of the cavity. The products are ejected from the cage as a result of the host–guest size discrepancy. As a result, the condensation is promoted by a catalytic amount of the cage.

Reversible dehydration condensation in water is in principle a difficult transformation because the large excess of water pushes the equilibrium in favor of the hydrated compounds.<sup>1</sup> To date, dehydration reactions in water have usually been achieved by employing the local hydrophobic environment of emulsion droplets<sup>2</sup> but have not yet been established in a homogeneous aqueous environment.<sup>3</sup> On the contrary, naturally elaborated enzymes easily accomplish the homogeneous dehydration in water even under neutral conditions at ambient temperature. Learning the mechanism of catalysis from enzymes is therefore an intriguing approach to shift conventional dehydration reactions in organic media into environmentally benign aqueous systems.<sup>1,4</sup>

There are several tricks in enzyme catalysis: (1) providing hydrophobic pockets, (2) strong substrate binding therein, (3) transition-state or intermediate stabilization, and (4) weak product binding.<sup>5</sup> Many previous synthetic hosts have fulfilled conditions (1) and (2), but rarely have (3) and (4) been met.<sup>6,7</sup> Regarding (3), enzymes stabilize the oxyanion intermediate resulting from the carbonyl addition of nucleophilic species by their positively charged surroundings.<sup>8</sup> We thus assumed that hydrophobic cationic cavities could fulfill conditions (1)–(3) and examined a dehydration condensation with 12+ charged  $M_6L_4$  cage **1**, which has shown remarkable molecular recognition abilities toward organic substrates.<sup>6c</sup> We found that cage **1** efficiently promotes the Knoevenagel condensation of various aromatic aldehydes in water.<sup>9</sup> The reaction conditions are very mild (neutral, room temperature), and more surprisingly, the reaction proceeds catalytically as condensed products are spontaneously released from the cage because of their poor fit to the cage, thus fulfilling condition (4). We also note that the present reaction provides a fine example of an electrostatic counterpart for Bergman and Raymond's cage-catalyzed reactions where cationic intermediates are stabilized by an anionic cage host.<sup>7</sup>



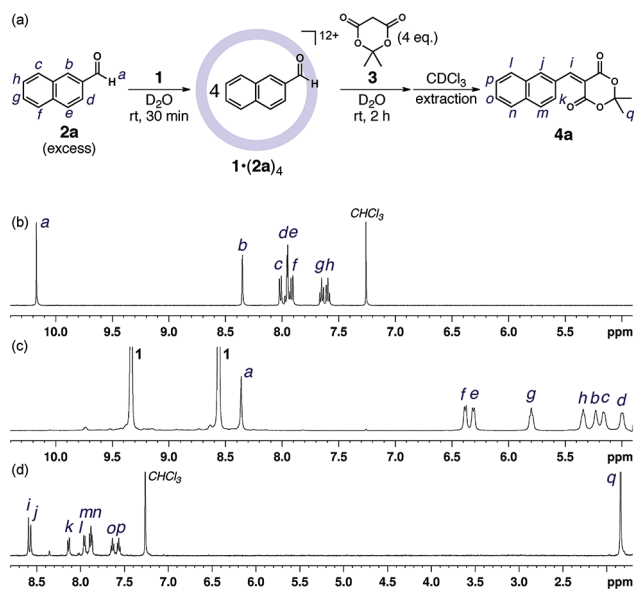
Cage **1** (5.0 mM in  $D_2O$ , 1.0 mL) was treated with 2-naphthaldehyde (**2a**, 8 equiv, suspended) for 30 min at room temperature (Figure 1a). After removal of the excess guest by filtration, the quantitative formation of the inclusion complex **1**·(**2a**)<sub>4</sub> was observed by <sup>1</sup>H NMR analysis (Figure 1b,c). The aromatic protons of **2a** were considerably upfield-shifted (e.g.,  $\Delta\delta = -3.12$  ppm for  $H_b$ ). Subsequently, Meldrum's acid (**3**, 4 equiv) was added to the solution. After 2 h at room temperature, the product was extracted with chloroform, and NMR spectroscopy showed the formation of condensation product **4a** in 92% yield (Figure 1d).

Without the cage, aldehyde **2a** (mostly suspended) gave only a trace amount of the condensation product (~2%) in an aqueous solution of **3**. Even under homogeneous conditions in MeOH, the condensation proceeded poorly (~8%). These results indicate that cage **1** is not merely a dissolving reagent but also promotes the condensation in water. The hydrophobic cavity of the cage is crucial for the reaction because the cage components, (en)Pd(NO<sub>3</sub>)<sub>2</sub> or 2,4,6-tripryridyl-1,3,5-triazine, did not promote the reaction.

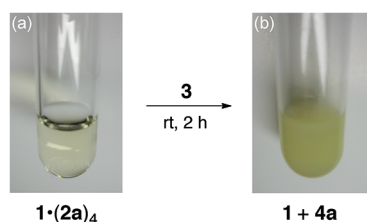
We noted that a clear, pale-yellow solution of inclusion complex **1**·(**2a**)<sub>4</sub> became turbid during the reaction with **3** as a result of the precipitation of **4a** as a yellow powder (Figure 2). NMR measurements corroborated that the condensation product **4a** was scarcely encapsulated within cage **1** (see Figure S10 in the Supporting Information). The poor fit of **4a** to cage **1** is probably due to **4a** having too large a volume to be fully encapsulated in the cage. The spontaneous release of the product from the cavity encouraged us to predict that catalytic turnover of the reaction would occur and thus to examine the reaction with a catalytic amount of cage **1**. Aldehyde **2a** (78 mg, 0.50 mmol) and compound **3** (72 mg, 0.50 mmol) were mixed

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**Figure 1.** Knoevenagel condensation of 2-naphthaldehyde (**2a**) with Meldrum's acid (**3**) in cage **1**. (a) Schematic representation of the formation of inclusion complex **1·(2a)<sub>4</sub>** and the subsequent Knoevenagel condensation with **3** leading to condensation product **4a**. (b–d) <sup>1</sup>H NMR spectra (500 MHz, 300 K) of (b) aldehyde **2a** (in CDCl<sub>3</sub>), (c) inclusion complex **1·(2a)<sub>4</sub>** (in D<sub>2</sub>O), and (d) condensation product **4a** obtained after extraction without purification (in CDCl<sub>3</sub>).



**Figure 2.** Photographs of the sample mixture in the Knoevenagel condensation of inclusion complex **1·(2a)<sub>4</sub>** with **3** (a) before and (b) after the addition of **3**.

in water (5.0 mL) in the presence of cage **1** (1 mol %), and the resulting solution was stirred at room temperature. After 6 h, condensation product **4a** was formed in 96% yield. Encapsulation of aldehyde **2a** by cage **1** is essential for the catalytic condensation because 1-adamantanol, a strong binder for the cage, completely inhibited the catalytic condensation.

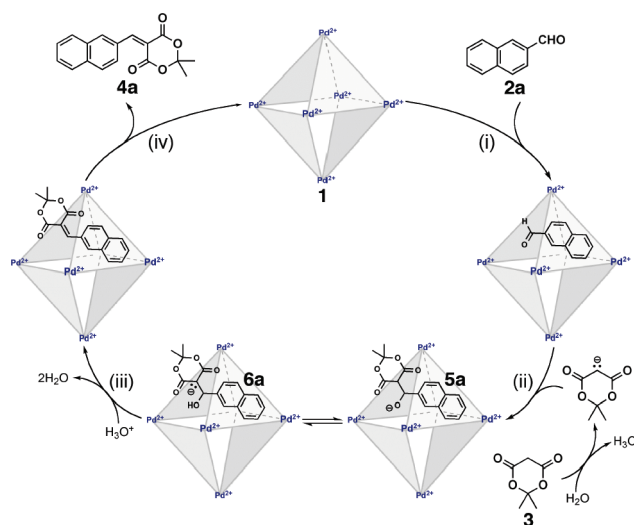
Despite the very mild conditions, even sterically hindered aldehydes underwent efficient condensation with the cage catalyst (Table 1). Because of steric congestion of the aromatic group, the Knoevenagel condensation of 9-anthraldehyde (**2b**) hardly occurred (<1%) in a control experiment without the cage (entry 2). In the presence of cage **1**, however, the condensation of **2b** with **3** was effectively promoted to give **4b** in 63% yield.<sup>10</sup> Similarly, 1-naphthaldehyde (**2c**) gave **4c** in 67% yield (entry 3). In contrast, benzaldehyde (**2d**), which is sterically nondemanding but only weakly bound to the cage, was not a suitable substrate, and the product yield (38%) was almost comparable to that in the control experiment (26%) (entry 4).<sup>11</sup> Because cationic cage **1** prefers electron-rich guests, methoxy- and amino-substituted naphthaldehydes **2e** and **2f** were good substrates, giving the corresponding adducts in yields of 96 and 82%, respectively (entries 5 and 6).

**Table 1.** Cage-Catalyzed Knoevenagel Condensation of Aldehydes **2** with Meldrum's Acid (**3**).<sup>a</sup>

Entry	<b>2</b>	Yield of <b>4</b> (%) <sup>b</sup>	
		in <b>1</b>	without <b>1</b>
1		96	4
2		63 <sup>c</sup>	< 1 <sup>c</sup>
3		67 <sup>d</sup>	15 <sup>d</sup>
4		38	26
5		96	6
6		82	11

<sup>a</sup>Reaction conditions: aldehyde **2** (0.50 mmol), Meldrum's acid **3** (0.50 mmol), and cage **1** (1 mol %) in H<sub>2</sub>O (5.0 mL) at room temperature (rt) for 6 h unless otherwise noted. <sup>b</sup><sup>1</sup>H NMR yields. <sup>c</sup>96 h. <sup>d</sup>24 h.

The proposed mechanism for the catalytic Knoevenagel condensation within cage **1** is shown in Figure 3. First,

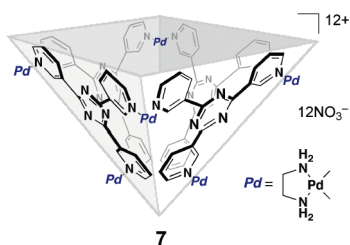


**Figure 3.** Proposed mechanism for the catalytic Knoevenagel condensation of aldehyde **2a** with **3** in the presence of cage **1**. For simplicity, the encapsulation number of guest molecules is not considered in this catalytic cycle.

aldehyde **2** is accommodated in cage **1** to form the inclusion complex **1·(2)<sub>n</sub>** (typically,  $n = 4$ ) [step (i)]. Meldrum's acid **3**, which is water-soluble and not a suitable guest for cage **1**, exists in equilibrium with its enolate form because of its low pK<sub>a</sub> value (4.83).<sup>12,13</sup> The enolate of **3** attacks encapsulated aldehyde **2** to

generate oxyanion intermediate **5** [step (ii)]. Presumably, this step is facilitated by cage **1** because the cationic charge of the cage can stabilize the anionic intermediate.<sup>14</sup> The loss of water via intermediate **6** should readily occur within the hydrophobic cavity to give dehydrated product **4** [step (iii)]. The product **4** is too large for the cavity and is spontaneously released from the cage [step (iv)] to be replaced with a new incoming molecule of **2**.

Oxyanion intermediate **5** [step (ii)] is effectively stabilized by the Pd<sup>2+</sup> centers located at every portal of the cage. If it is assumed that the nucleophilic addition of **3** occurs around a portal, the anionic intermediate **5** is most effectively stabilized by the three Pd<sup>2+</sup> centers sitting at the vertices of the roughly triangular shaped portal (see the proposed geometry of **5** in Figure 3). A control experiment was performed with bowl-shaped cage **7** that has a 12+ net charge and the same formula as cage **1** but does not have the closely arranged Pd<sup>2+</sup> centers around its open cavity. Although efficient host–guest complexation was observed with cage **7** [to form the inclusion complex 7·(2a)<sub>3</sub>], even with a stoichiometric amount of **7**, the Knoevenagel condensation product **4a** was obtained in only 17% yield under the same conditions (H<sub>2</sub>O, room temperature, 2 h).



In summary, we have successfully demonstrated dehydration condensation under neutral conditions in water catalyzed by synthetic cationic host **1**. Following the efficient binding of the substrate in the hydrophobic cavity, the condensation reaction seems to be facilitated by the stabilization of the anionic intermediate in the cationic environment of the cage, reminiscent of the tricks of enzyme catalysis. Further development of catalytic reactions by using cage **1** as a synthetic mimic of enzymes is currently under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and physical properties. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Unlike naphthaldehyde **2a**, two molecules of anthraldehyde **2b** are encapsulated within cage **1**.

- (11) Since droplets of benzaldehyde **2d** dissolve compound **3**, the condensation may take place in dispersed **2d**.

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- (13) Interactions between the outside of cage **1** and compound **3** are also negligible because the pH value of **3** in water did not change after the addition of cage **1**.

- (14) Knoevenagel condensation is accelerated by rare-earth-exchanged NaY zeolites, where electrostatic interactions between the embedded cations and the encapsulated substrates play an important role. See: Reddy, T. I.; Varma, R. S. *Tetrahedron Lett.* **1997**, 38, 1721.