VIP Supramolecular Catalysis

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Catalytic Deprotection of Acetals in Basic Solution with a Self-Assembled Supramolecular "Nanozyme"**

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Acetals are among the most commonly used protecting groups for aldehydes and ketones in organic synthesis because of their ease of installation and resistance to cleavage in neutral or basic solution.[1] The common methods for hydrolyzing acetals almost always involve the use of either Brønsted acid or Lewis acid catalysts.[2] A number of reports have documented a variety of strategies for acetal cleavage under mild conditions. These include the use of Lewis acids such as bismuth(III)[3] or cerium(IV),[4,5] functionalized silica gel, such as silica sulfuric acid[6] or silica-supported pyridinium *p*-toluenesulfonate,[7] or the use of silicon-based reagents such as triethylsilyltrifluoromethanesulfonyl-2,6-lutidine.[8] Despite these mild reagents, all of the above conditions require either added acid or overall acidic media. Markó and co-workers recently reported the first example of acetal deprotection under mildly basic conditions using catalytic cerium ammonium nitrate at pH 8 in a water/acetonitrile mixture.[5] Also recently, Rao and co-workers described a purely aqueous system at neutral pH for the deprotection of acetals using β-cyclodextrin as the catalyst.[9] Herein, we report the hydrolysis of acetals in basic aqueous solution using a self-assembled supramolecular host as the catalyst.

During the last decade, we have used metal–ligand interactions for the formation of well-defined supramolecular assemblies with the stoichiometry M_4L_6 (M = Ga^{III} (**1** refers to $K_{12}[Ga_4L_6]$), Al^{III}, In^{III}, Fe^{III}, Ti^{IV}, or Ge^{IV}, L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene; Figure 1).[10] The metal ions occupy the vertices of the tetrahedron and the bisbidentate catecholamide ligands span the edges. The rigid ligands transfer the chirality from one metal vertex to the other, thereby requiring the ΔΔΔΔ or ΛΛΛΛ configurations of the assembly. Whereas the −12 overall charge

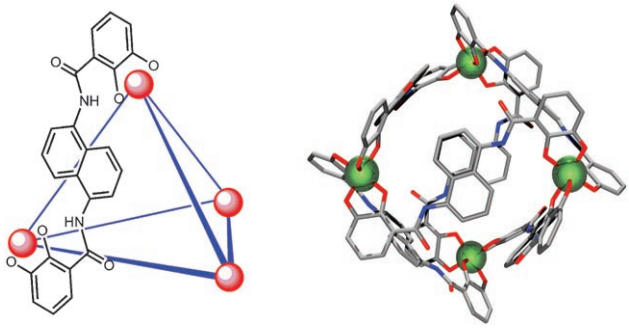
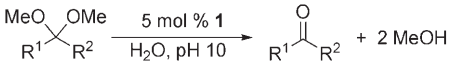


Figure 1. Left: A schematic representation of the host M_4L_6 assembly. Only one ligand is shown for clarity. Right: A model of the empty assembly; Ga green, O red, N blue, C gray; hydrogen atoms are omitted for clarity.

imparts water solubility, the naphthalene walls of the assembly provide a hydrophobic cavity which is isolated from the bulk aqueous solution. This hydrophobic cavity has been utilized to stabilize a variety of water-sensitive guests, such as tropylium,[11] iminium,[12] diazonium,[13] protonated amine,[14] and reactive phosphonium species.[15] Furthermore, **1** has been used to encapsulate catalysts[16] for organic transformations as well as act as a catalyst for the 3-aza-Cope rearrangement of enammonium substrates[17] and the hydrolysis of acid-labile orthoformates.[18]

Our recent work using **1** as a catalyst for orthoformate hydrolysis prompted our investigation of the ability of **1** to catalyze the deprotection of acetals (Scheme 1). With the



Scheme 1. Catalytic deprotection of acetals under basic conditions using **1** as a catalyst.

ability of **1** to favor encapsulation of monocationic guests, we anticipated that acetal hydrolysis could be accelerated by stabilization of any of the cationic protonated intermediates along the mechanistic pathway upon encapsulation in **1**. In contrast to the stability of 2,2-dimethoxypropane in H_2O at pH 10, addition of the acetal to a solution of **1** at this pH quickly yielded the products of hydrolysis. Addition of a strongly binding inhibitor for the interior cavity of **1**, such as NEt_4^+ ($\log K_a = 4.55$), inhibited the overall reaction, thus confirming that **1** is active in the catalysis.

The hydrolysis reactions were screened by mild heating (50 °C) of 5 mol % of **1** with respect to the acetal substrate at pH 10 in H_2O in a sealed NMR tube using dimethylsulfoxide

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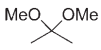
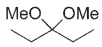
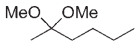
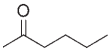
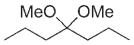
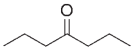
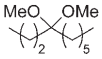
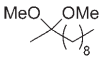
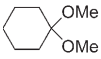
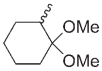
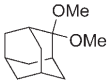
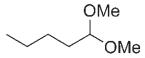
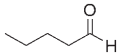
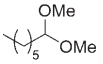
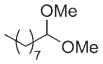
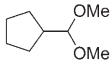
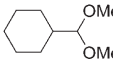
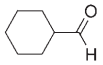
as an internal integration standard. To examine the reaction scope, a variety of alkyl acetals and ketals were screened (Table 1).[19] Smaller substrates, which are able to fit into the cavity of **1**, are readily hydrolyzed. However, substrates that are too large to enter **1**, such as 2,2-dimethoxyundecane (Table 1, entry 6) or 1,1-dimethoxynonane (Table 1, entry 13), remain unchanged. The basic solution caused aldehyde products to be converted into the corresponding aldehyde hydrates. Saturation of the reaction mixture with NaCl and subsequent extraction with CH_2Cl_2 allowed the isolation of sufficiently hydrophobic ketone products (Table 1, entries 5, 7, 8, and 9).

Table 1: Scope of acetal hydrolysis using **1** as catalyst.[a]

Entry	Substrate	Product[b]	Yield [%][c]
1			>95
2			>95
3			>95
4			>95
5			>95 (92)
6			<5
7			>95 (88)
8			>95 (86)
9			>95 (79)
10			87
11			>95
12			>95
13			<5
14			>95
15			>95

[a] Reaction conditions: 5 mol% **1** in H_2O, pH 10, 100 mM, 50°C for 6 h under N_2. [b] Product aldehydes were subsequently hydrated to the aldehyde hydrate in the basic reaction medium. [c] NMR yields based on an internal standard (DMSO). Yields of isolated product are in parentheses.

Monitoring the reaction by ^{1}H NMR spectroscopy also suggests that **1** is the active catalyst. Small acetals, such as 2,2-dimethoxypropane, are not observed inside **1**, but the substrate ^{1}H NMR resonances appear broad, which suggests fast guest exchange on the NMR timescale. However, for bulky substrates, such as 2,2-dimethoxyadamantane (Table 1, entry 10), a 1:1 host–guest complex is observed, thus indicating slow guest ingress and egress on the NMR timescale (Figure 2).

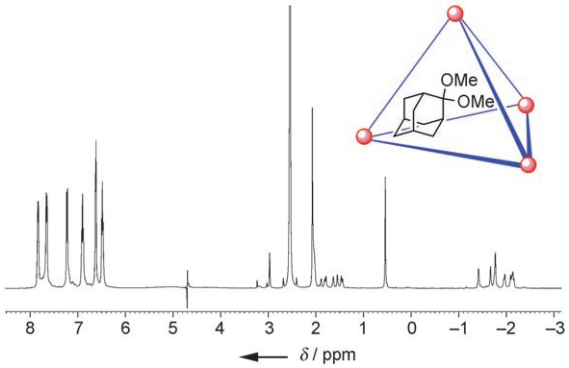


Figure 2. ^{1}H NMR spectrum of [2,2-dimethoxyadamantane⊂**1**]$^{12-}$ in H_2O (25°C, 5.6 mM, 500 MHz).

During the course of the reaction of 2,2-dimethoxyadamantane, new peaks appeared in the ^{1}H NMR spectrum corresponding to the encapsulated product 2-adamantanone. With the observation that both the acetal and product were encapsulated, we sought to determine the binding affinities of both molecules within **1** to help to explain the catalytic turnover. The total substrate, both free in solution and encapsulated, was monitored as a function of the concentration of **1**. The concentration of free substrate in solution was kept constant by always maintaining the presence of solid or liquid acetal in the system, which ensured a uniform activity of starting material throughout the experiments. The total amount of acetal in solution can be defined as in Equation (1), in which S_t is its total concentration, s_0 is the

$$S_t = s_0 + \frac{K_a s_0 [\mathbf{1}]_t}{1 + K_a s_0} \quad (1)$$

constant concentration of free substrate in solution, $[\mathbf{1}]_t$ is the total concentration of **1**, and K_a is the association constant for the host–guest complex.[20]

By using this equation, the association constants were determined for 2,2-dimethoxyadamantane (entry 10 in Table 1) and its hydrolysis product 2-adamantanone (Figure 3). By monitoring the encapsulation of both organic compounds over a concentration range from 2.8 to 40 mM **1**, association constants of 3100 M^{-1} (2,2-dimethoxyadamantane) and 700 M^{-1} (2-adamantanone) were determined. As expected, the hydrolysis product is bound less tightly by **1** and is much less soluble in water than the starting material, which allows the observed catalytic turnover.

In conclusion, this work demonstrates the ability of a self-assembled supramolecular assembly to catalyze the hydrolysis of acetals and ketals in basic solution. Current work is underway to establish the mechanism of hydrolysis in **1** and to quantify the magnitude of the rate accelerations.

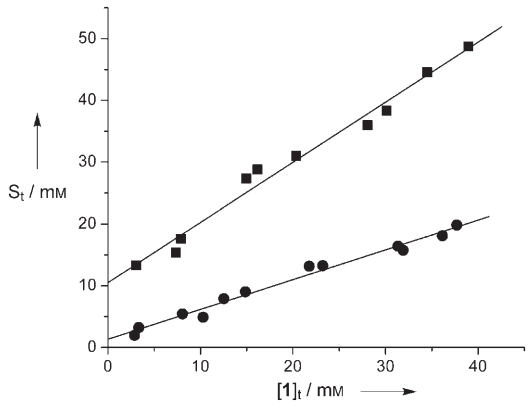


Figure 3. Binding constant determination from Equation (1) for 2,2-dimethoxyadamantane (■) and 2-adamantanone (●) in **1** in 25:1 H_2O/D_2O, pH 10, 100 mM K_2CO_3, measured at 298 K.

Experimental Section

General procedure for reaction screening: In a N_2-filled glove box, $K_{12}[Ga_4L_6]$ (10 mg, 2.8 μmol) was added to H_2O (500 μL) buffered to pH 10 with K_2CO_3. DMSO was added as an internal standard. The NMR tube was removed from the glove box and 10 equiv of the acetal or ketal was added by syringe. A capillary containing D_2O was also added to facilitate locking. The NMR tube was flame-sealed and heated in an oil bath at the indicated temperature. The product conversions were determined by two methods for each substrate: 1) monitoring methanol production and 2) adding 300–400 μL of CD_3CN to solubilize the product. Details for preparation of the substrates are included in the Supporting Information.

General procedure for yields of isolated product: $K_{12}[Ga_4L_6]$ (20 mg, 5.6 μmol), H_2O (1.0 mL) buffered to pH 10 with K_2CO_3, 20 equiv of the desired substrate, and a stir bar were added into a 3-mL vial in the glove box. The vial was removed from the glove box and heated at 50 °C for 6 hours in an oil bath after which the solution was cooled to room temperature and saturated with NaCl. The resulting solution was extracted with CH_2Cl_2 (3 × 2 mL). The extract was dried over $MgSO_4$ and residual solvent removed to afford the product ketone or aldehyde.

General procedure for binding constant determination: All solutions were prepared using a 25:1 H_2O/D_2O mixture buffered to pH 10 with 100 mM K_2CO_3. In a N_2-filled glove box, stock solutions of $K_{12}[Ga_4L_6]$ and DMSO (internal standard) were combined in the desired ratios and brought to a volume of 600 μL with buffered solution. Spectra were recorded with 8 scans by using the Watergate solvent suppression pulse sequence with a delay time of 10 seconds.

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