Catalytic Deprotection of Acetals In Strongly Basic Solution Using 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 due to 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] Usually aqueous acids or organic solutions acidified with organic or inorganic acids have been used for reconversion of the acetal functionality to the corresponding carbonyl group; however, recently 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 TESOTf-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 solution.[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 strongly 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 *bis*-bidentate catecholamide ligands span the edges. The strong mechanical coupling of the ligands transfers the chirality from one metal center to the other, thereby requiring the ΔΔΔΔ or ΛΛΛΛ configurations of the assembly. While the 12- overall charge imparts water solubility, the naphthalene walls of the assembly provide a hydrophobic environment which is isolated from the bulk aqueous solution. This hydrophobic cavity has been utilized to kinetically stabilize a variety of water-sensitive guests such as tropylium,[11] iminium ions,[12] diazonium ions,[13] and reactive phosphonium species.[14] Furthermore, **1** has been used to encapsulate catalysts[15] for organic transformations as well as act as a catalyst for the 3-aza-Cope rearrangement of enammonium substrates[16] and the hydrolysis of acid-labile orthoformates.[17]

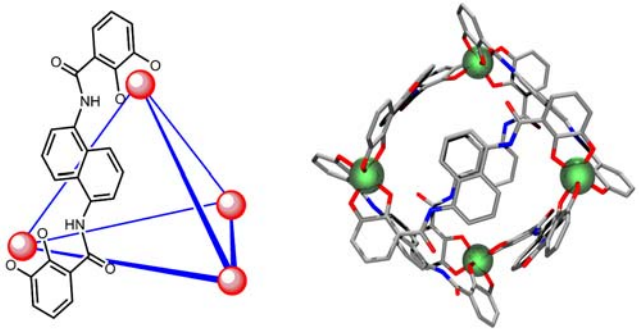
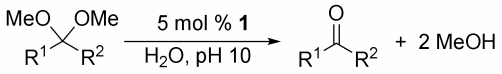


Figure 1 Left: A schematic representation of the host M_4L_6 assembly. Only one ligand is shown for clarity. Right: A model of the empty assembly; hydrogen atoms are omitted for clarity.

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 ability of **1** to favor encapsulation of monocationic guests, we anticipated that the rates of 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 (acetone and methanol). 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, confirming that **1** is active in the catalysis.

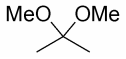
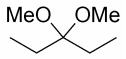
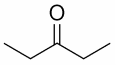
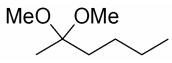
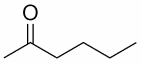
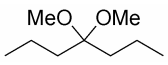
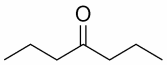
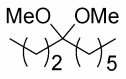
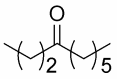
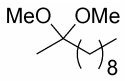
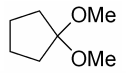
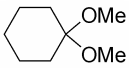
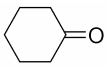
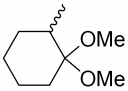
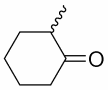
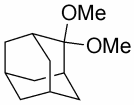
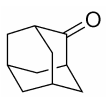
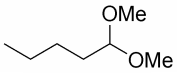
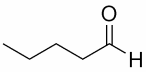
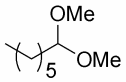
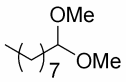
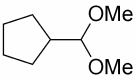
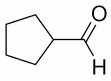
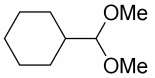
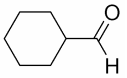


Scheme 1. Catalytic deprotection of acetals under basic conditions using **1** as a catalyst.

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. Dimethylsulfoxide was used as an internal integration standard. To examine the reaction scope, a variety of alkyl acetals and ketals were screened (Table 1). Smaller substrates, which are able to fit into the cavity of **1**, are readily hydrolyzed. However, larger substrates, such as 2,2-dimethoxyundecane (entry 6) or 1,1-dimethoxynonane (entry 7), remain unchanged, suggesting that they are too large to enter the interior cavity of **1**. The basic solution caused

aldehyde products to be converted to the corresponding aldehyde hydrates. Saturation of the reaction mixture with NaCl followed by extraction with CH_2Cl_2 allowed for the isolation of sufficiently hydrophobic ketone products (entries 5, 7, 8 and 9).

Table 1. Scope of acetal hydrolysis using 5 mol % **1** in H_2O buffered to pH 10 with 100 mM carbonate. The reactions were run at 50 °C for six hrs under N_2.

Entry	Substrate	Product[a]	Yield (%)[b]
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] Product aldehydes were subsequently hydrated to the aldehyde hydrate in the basic reaction medium
[b] NMR yields based on an internal standard (DMSO). Isolated yields are in parentheses.

Monitoring the reaction by ^{1}H NMR also suggests that **1** is the active catalyst. For smaller acetals, such as 2,2-dimethoxypropane, no encapsulated guest is observed although the substrate resonances broaden. This is most likely because the substrates are exchanging quickly on the NMR time scale. However, for larger acetals, broad resonances are observed upfield, suggesting a rapidly exchanging guest. For very bulky substrates, such as 2,2-dimethoxyadamantane (entry 10), the substrate is observed to be cleanly encapsulated in a 1:1 host-guest complex indicating slow guest ingress and egress on the NMR time scale (Figure 2).

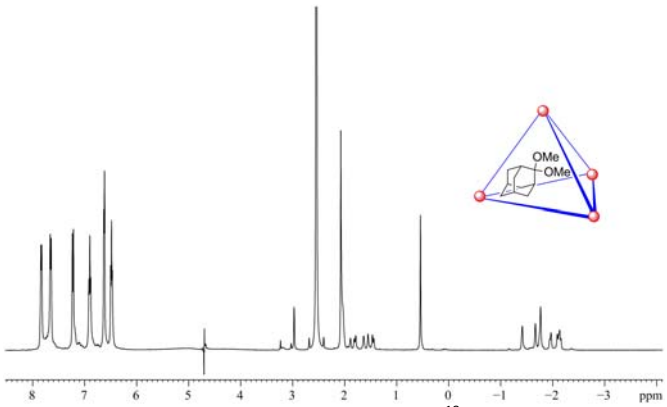


Figure 2 ^{1}H NMR spectrum [2,2-dimethoxyadamantane ⊂ **1**]$^{12-}$ in H_2O (25 °C, 5.6 mM, 500 MHz).

By monitoring the ^{1}H NMR spectrum of 2,2-dimethoxyadamantane during the course of the reaction, new peaks corresponding to the encapsulated product, 2-adamantanone, were observed. With the observation that both the substrate and product were encapsulated, we sought to determine the binding affinities of both molecules within **1** in order to help 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 substrate in the system; this insured a uniform activity of the substrate throughout the experiments. The total amount of substrate in solution can be defined as in equation 1, where S_t is the total substrate concentration, s_0 is the 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.[18]

$$S_t = s_o + \frac{K_a s_0 \mathbf{1}_t}{1 + K_a s_0} \qquad (1)$$

Using this equation (with the collected data), the binding constants, K_a, for the substrates 2,2-dimethoxyadamantane (the starting material for entry **10** in Table 1) and its hydrolysis product 2-adamantanone were determined (Figure 3). Monitoring the encapsulation of both substrates over a concentration range from 2.8 mM to 40 mM **1**, in a 25:1 H_2O:D_2O solution buffered to pH 10 with 100 mM carbonate yielded binding constants of 3100 M^{-1} and 700 M^{-1} for 2,2-dimethoxyadamantane and 2-adamantanone, respectively. The solubilities of 2,2-dimethoxyadamantane and 2-adamantanone in H_2O were thus found to be 10.5(3) mM and 1.3(3) mM respectively. Lastly, the slope of the plot is less than one, confirming the formation of a 1:1 host:guest complex. As expected, the hydrolysis product is bound less tightly by **1** and is much less soluble in water than the substrate, which allows for the observed catalytic turnover.

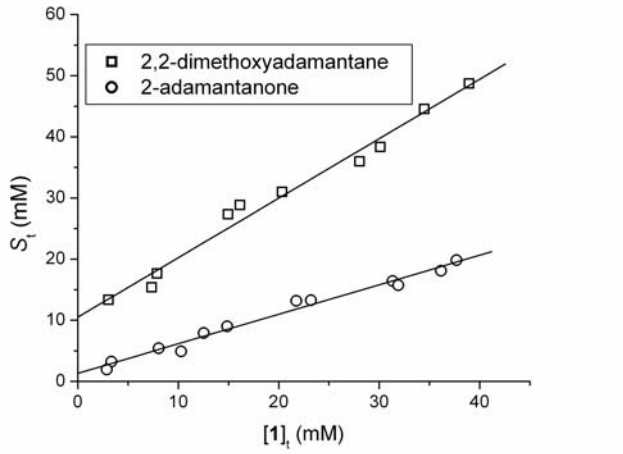


Figure 3 Binding constant determination from equation 1 for 2,2-dimethoxyadamantane and 2-adamantanone in **1** in a 25:1 H_2O:D_2O solution buffered to pH 10 with 100 mM carbonate, measured at 298K.

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 for this reaction.

Experimental Section

General procedure for reaction screening: In a N_2 filled glove box, 10 mg (2.8 μmol) $K_{12}Ga_4L_6$ was added to 500 μL of H_2O 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 isolated yields: Into a 3 mL vial in the glove box, 20 mg (5.6 μmol) $K_{12}Ga_4L_6$ was added to 1.0 mL of H_2O buffered to pH = 10 with K_2CO_3, 20 equiv. of the desired substrate, and a stir bar were added. The vial was removed from the glove box and heated at 50 °C for six hours in an oil bath at which point the solution was cooled to room temperature and saturated with NaCl. The resulting solution was extracted with CH_2Cl_2 (3 x 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 solution 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 up to a volume of 600 μL with buffered solution. Spectra were recorded with 8 scans using the Watergate solvent suppression pulse sequence with a delay time of 10 seconds between each scan.

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[1] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley and Sons, New York, **1978**.

[2] a.) M. Nakamura, H. Isobe, E. Nakamura, *Chem. Rev.* **2003**, *103*, 1295; b.) P. Deslongchamps, Y. L. Dory, S. Li, *Can. J. Chem.* **1994**, *72*, 2021; c.) V. V. Pchelintsev, A. Y. Sokolov, G. E. Zaikov, *Polymer Degradation and Stability* **1988**, *21*, 285; d.) A. J. Kirby, *Acc. Chem. Res.* **1984**, *17*, 305; e.) J. P. Knowles, A. Whiting, *Eur. J. Org. Chem.* **2007**, *20*, 3365.

[3] a.) K. J. Eash, M. S. Pulia, L. C. Wieland, R. S. Mohan, *J. Org. Chem.* **2000**, *65*, 8399; b.) G. Sabitha, R. S. Babu, E. V. Reddy, J. S. Yadav, *Chem. Lett.* **2000**, *9*, 1074; c.) N. Komatsu, A. Taniguchi, S. Wada, H. Suzuki, *Adv. Synth. Catal.* **2001**, *343*, 473; d.) M. D. Carrigan, D. Sarapa, R. C. Smith, L. C. Wieland, R. S. Mohan, *J. Org. Chem.* **2002**, *67*, 1027.

[4] a.) A. Ates, A. Gautier, B. Leroy, J.-M. Plancher, Y. Quesnel, J.-C. Vanherck, I. E. Marko, *Tetrahedron* **2003**, *59*, 8989; b.) R. Dalpozzo, A. De Nino, L. Maiuolo, A. Procopio, A. Tagarelli, G. Sindona, G. Bartoli, *J. Org. Chem.* **2002**, *67*, 9093.

[5] I. E. Marko, A. Ates, A. Gautier, B. Leroy, J.-M. Plancher, Y. Quesnel, J.-C. Vanherck, *Angew. Chem. Int. Ed.* **1999**, *38*, 3207.

[6] B. F. Mirjalili, M. A. Zolfigol, A. Bamoniri, *Molecules* **2002**, *7*, 751.

[7] Y. He, M. Johansson, O. Sterner, *Synth. Commun.* **2004**, *34*, 4153.

[8] H. Fujioka, T. Okitsu, Y. Sawama, N. Murata, R. Li, Y. Kita, *J. Am. Chem. Soc.* **2006**, *128*, 5930.

[9] N. S. Krishnaveni, K. Surendra, M. A. Reddy, Y. V. D. Nageswar, K. R. Rao, *J. Org. Chem.* **2003**, *68*, 2018.

[10] a.) D. L. Caulder, C. Bruckner, R. E. Powers, S. Konig, T. N. Parac, J. A. Leary, K. N. Raymond, *J. Am. Chem. Soc.* **2001**, *123*, 8923; b.) D. L. Caulder, R. E. Powers, T. N. Parac, K. N. Raymond, *Angew. Chem. Int. Ed.* **1998**, *37*, 1840; c.) D. L. Caulder, K. N. Raymond, *J. Chem. Soc, Dalton Trans.* **1999**, *8*, 1185; d.) D. L. Caulder, K. N. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975.

[11] J. L. Brumaghim, M. Michels, D. Pagliero, K. N. Raymond, *Eur. J. Org. Chem.* **2004**, *24*, 5115.

[12] V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 14464.

[13] J. L. Brumaghim, M. Michels, K. N. Raymond, *Eur. J. Org. Chem.* **2004**, *22*, 4552.

[14] M. Ziegler, J. L. Brumaghim, K. N. Raymond, *Angew. Chem. Int. Ed.* **2000**, *39*, 4119.

[15] D. H. Leung, R. G. Bergman, K. N. Raymond, **2007**, *129*, 2746.

[16] a.) D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem. Int. Ed.* **2004**, *43*, 6748; b.) D. Fiedler, H. van Halbeek, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 10240.

[17] M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85.

[18] K. A. Conners, *Binding Constants, The Measurement of Molecular Complex Stability*, John Wiley & Sons, New York, **1987**.

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