J|A|C|S COMMUNICATIONS

Published on Web 05/05/2010

Enzymelike Catalysis of the Nazarov Cyclization by Supramolecular Encapsulation

Courtney J. Hastings, Michael D. Pluth, Robert G. Bergman,* and Kenneth N. Raymond*

Department of Chemistry, University of California, Berkeley, California 94720-1460, and Division of Chemical Sciences, Lawrence Berkeley National Laboratory, Berkeley, California 94720-1460

Received March 29, 2010; E-mail: rbergman@berkeley.edu; raymond@socrates.berkeley.edu

A primary goal in the design and synthesis of molecular hosts is the selective recognition and binding of a variety of guests using noncovalent interactions.[1] Supramolecular catalysis, which is the application of such hosts toward catalysis,[2] has much in common with many enzymatic reactions,[2b,3] chiefly the use of both spatially appropriate binding pockets and precisely oriented functional groups to recognize and activate specific substrate molecules. Although there are now many examples that demonstrate how selective encapsulation in a host cavity can enhance the reactivity of a bound guest, all have failed to reach the degree of increased reactivity typical of enzymes.[4] We now report the use of a self-assembled coordination cage to catalyze the Nazarov cyclization, a carbon−carbon bond-forming reaction that proceeds under mild, aqueous conditions. The acceleration in this system is over a million-fold, representing the first example of supramolecular catalysis that achieves a level of rate enhancement comparable to that observed in several enzymes. We explain the unprecedented degree of rate increase as due to the combination of (a) preorganization of the encapsulated substrate molecule, (b) stabilization of the transition state of the cyclization by constrictive binding, and (c) an increase in the basicity of the complexed alcohol functionality.

Raymond and co-workers have designed the supramolecular host (**1**) having Ga_4L_6 stoichiometry (L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene; Figure 1) that exploits reversible metal−ligand interactions to spontaneously self-assemble.[5,6] In these assemblies, the biscatecholate ligands span the edges of a tetrahedron whose vertices are occupied by metal ions. Polyanion **1** is soluble in water and other polar solvents, while the host interior is paneled by the naphthalene rings of the ligand, creating a hydrophobic inner environment. A wide variety of cationic guests can be encapsulated in **1**, from quaternary ammonium and phosphonium cations to organometallic complexes. In aqueous solution, neutral molecules such as hydrocarbons are bound by **1** because of the hydrophobic effect.[7]

Our approach toward supramolecular catalysis using **1** exploits the preference of the polyanionic host for encapsulating monocationic guests. Encapsulation in **1** can perturb acid−base equilibria to favor the protonation of a wide range of amines and phosphines, even at strongly basic pH.[8] This behavior led to the development of proton-catalyzed hydrolysis reactions inside **1**, in which a protonated transition state is stabilized in the host interior.[9] The stabilization of even transient protonated species produces a several thousand-fold rate acceleration of orthoformate and acetal hydrolysis under basic conditions. However, even this substantial acceleration does not reach that typically seen in enzyme-catalyzed reactions.

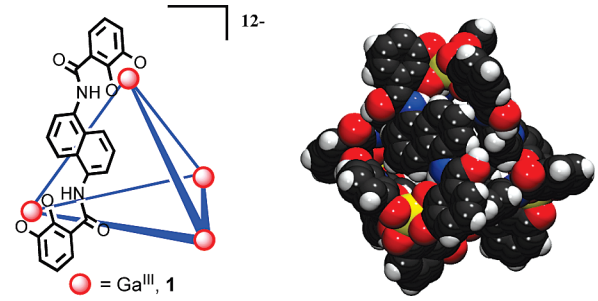


Figure 1. (left) Schematic view of **1** in which the bisbidentate ligands are represented by blue lines and the gallium atoms by red circles. (right) Space-filling model of **1**.

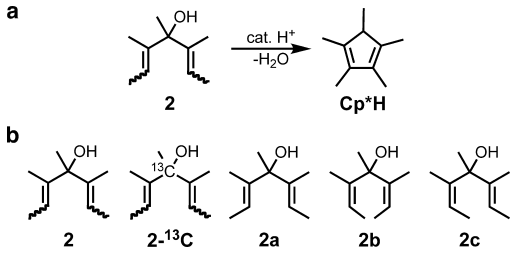
Having demonstrated the ability of **1** to perform acid-catalyzed hydrolysis reactions, we sought to apply this reactivity to more synthetically useful acid-catalyzed reaction types. Acid-catalyzed cyclizations are particularly interesting because **1** could accelerate such a reaction both by enhancing the basicity of the bound substrate and by preorganizing the substrate in a reactive conformation.[10] The Nazarov cyclization, an acid-catalyzed reaction in which a 1,4-dien-3-ol forms a cyclopentadiene (e.g., the example shown in Scheme 1a), is attractive from this perspective. This reaction proceeds via the intermediacy of a diallylic carbocation that undergoes conrotatory electrocyclic ring closure in accordance with the Woodward−Hoffmann rules.[11] This reaction is widely utilized in synthetic organic chemistry as well as in organometallic chemistry, where it has provided a route to substituted polymethylcyclopentadienyl ligands.[12]

As a proof of principle, 10 equiv of 3,4,5-trimethylhepta-2,5-dien-4-ol **2** (obtained as a mixture of the three possible olefin stereoisomers; Scheme 1b) was added to a solution of **1** in H_2O (buffered at pH 11.0) and heated to 50 °C. Under these reaction conditions, a set of peaks corresponding to host−guest complexes of **2** was observed by ^{1}H NMR spectroscopy. After 12 h, the organic products were extracted into CH_2Cl_2, whereupon GC−MS analysis showed the complete consumption of the starting material and the quantitative formation of the Nazarov product, Cp*H. A control reaction run using 1.1 equiv of a strongly binding guest (NEt_4^+) to block the host interior halted product formation through a mechanism analogous to enzyme inhibition.[13]

Having obtained these preliminary results, we sought to quantify the rate enhancement of the catalyzed reaction over the background reaction. Because of the low solubility of substrate **2** in water, further studies were carried out in D_2O with 50% added DMSO-d_6. The three possible stereoisomers of **2** (Scheme 1b) were independently synthesized for these experiments. Under these

10.1021/ja102633e

Scheme 1. (a) General Scheme for the Acid-Catalyzed Nazarov Reaction of Pentadienols To Form Cyclopentadienes; (b) Pentadienol Reactants for the Nazarov Cyclization Used in This Study

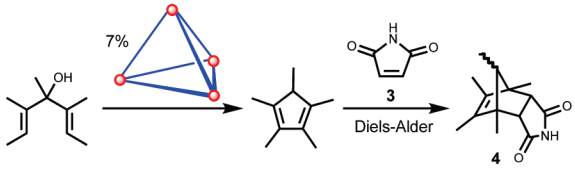


conditions, the disappearance of each of the three stereoisomers of **2** catalyzed by 7 mol % **1** was monitored by ^{1}H NMR spectroscopy. The product of these reactions, Cp*H, is not soluble under these conditions and was not observed during the course of the reaction, but it could be extracted into an organic solvent after the reaction was complete. Again, no reaction was observed when a strongly binding guest was added to exclude the substrate from the interior of **1**.

For all three stereoisomers of **2**, the initial reactions were rapid, but deviation from pseudo-first-order kinetic behavior was observed as the reaction progressed. In each case, k_{obs} for the disappearance of starting material (calculated from the slope of a plot of ln[**2**] vs time) was constant at the beginning of the reaction and then decreased as the reaction proceeded. This effect was especially severe for the reaction of substrate **2a**, which nearly halted after 25% conversion. This decrease in reaction rate is consistent with product inhibition, a common occurrence in both synthetic and enzymatic catalysis when the host does not bind the reactant substantially more strongly than it binds the product.[14] Competition experiments involving Cp*H and the stereoisomers of **2** showed that Cp*H is a competitive guest. Adding a full equivalent of Cp*H to the **1**-catalyzed reaction shut down the Nazarov cyclization. These experiments clearly implicated product inhibition as the cause of the decrease in k_{obs} observed as the reaction progressed.[15]

A solution to this problem was developed by chemically converting the product Cp*H into a poor guest, a strategy that has been utilized in other examples of supramolecular catalysis.[10] The addition of maleimide (**3**) to the **1**-catalyzed Nazarov cyclization completely alleviated product inhibition by converting Cp*H into the Diels−Alder adduct **4**, which is soluble under the reaction conditions (Scheme 2). In the reaction using maleimide as a trapping agent, the rate of Diels−Alder adduct formation was equal to rate of starting material consumption, implying that no Cp*H built up in solution. The concentration-versus-time plots for reactions with added maleimide subsequently showed no deviation from pseudo-first-order behavior, indicating that product inhibition was eliminated. Competitive binding experiments involving Cp*H and **4** showed that **4** is a weaker-binding guest, which explains why it did not noticeably retard the reaction rate.

Scheme 2. Conversion of Cp*H into a Noncompetitive Guest (**4**) To Alleviate Product Inhibition



The catalysis under these conditions was quite efficient, and turnover numbers of up to 160 were achieved. The observed rate constants for the catalyzed cyclization of *Z*,*Z* substrate **2b** and *E*,*Z* substrate **2c** were an order of magnitude larger than that for the cyclization of *E*,*E* substrate **2a** (Table 1). We find it remarkable that the reactivities of these three substrates are so different when they differ only in stereochemistry at positions remote from the forming carbocation. Since guest exchange is fast relative to the reaction rate, the rate constants for the reaction of host-bound substrate, k_{cat}, were calculated from the Michaelis−Menten equation using experimentally determined K_M values. Substrate **2a** was too weakly bound under the mixed-solvent conditions for the K_M value to be measured, so its k_{cat} value is not reported.

In order to quantify the rate acceleration attributable to catalysis, the background reaction rate for each substrate was measured in the absence of **1**. The uncatalyzed reaction are extremely slow under these reaction conditions and strongly depend on the substrate stereochemistry, with methyl groups in the *Z* configuration giving the slowest reaction. This suggests that the reacting molecule must adopt a U-shaped conformation prior to or at the transition state of the rate-determining step in order to react. This compact conformation necessary for reaction is sterically disfavored by *Z* methyl groups in comparison with the linear conformation of the same molecule (Scheme 3).

Scheme 3. Linear and U-Shaped Conformations of Substrate **2b**

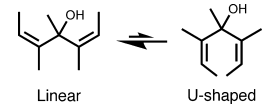


Table 1. Kinetic Data for Nazarov Substrates at 45 °C with Maleimide Added as a Trapping Agent

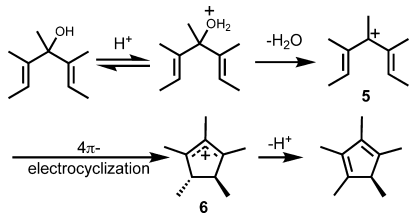
substrate	k_{obs} (s^{-1})	K_M (mM)	k_{cat} (s^{-1})	k_{uncat} (s^{-1})	rate acceleration (k_{cat}/k_{uncat})
2a	$5.1(1) \times 10^{-5}$	–	–	$4.0(3) \times 10^{-8}$	–
2b	$4.2(1) \times 10^{-4}$	42(1)	$1.6(1) \times 10^{-2}$	$7.7(8) \times 10^{-9}$	2 100 000
2c	$1.08(2) \times 10^{-3}$	91(1)	$5.7(1) \times 10^{-2}$	$3.3(1) \times 10^{-8}$	1 700 000

The rate accelerations of the catalyzed reaction over the uncatalyzed reaction are on the order of 10^6, which are the largest measured for supramolecular catalysis by orders of magnitude.[16] This very high level of catalytic activity is reminiscent of enzymatic catalysis. The observed rate acceleration is too large to be explained only by an increase in the basicity of the bound substrate. In previous studies, we observed a maximum of 4 orders of magnitude in the equilibrium shift of protonated amines and a thousand-fold rate acceleration in the hydrolysis of orthoformates.[8,9a] We propose that the additional rate enhancement in this system is due to constrictive binding in the pocket of **1**, which favors both the U-shaped conformation of the substrate and the compact transition state of the electrocyclization. Constrictive binding is responsible for rate enhancements of nearly 3 orders of magnitude in the **1**-catalyzed aza-Cope rearrangement of enammonium cations, where encapsulation preorganizes the substrate into a reactive conformation.[10] We conclude that the million-fold rate enhancement in this system is due to the combination of an increase in the basicity of the alcohol functionality upon encapsulation, preorganization of the bound substrate, and stabilization of the transition state of the electrocyclic reaction. We suggest that combining the effects

of constrictive binding with functional-group activation may represent a general strategy for achieving enhanced reactivity in supramolecular catalysis.

To probe the mechanism of this reaction, we sought to identify the encapsulated species observed during the reaction, which must be the resting state of the catalyst. The ^{13}C-labeled compound **2-^{13}C**, prepared as a mixture of three stereoisomers, was used for this purpose. If the encapsulated species is either the dienyl cation **5** or the cyclized allyl cation **6** (Scheme 4), there should be a dramatic shift in the ^{13}C NMR resonance of the labeled carbon.[17] When **2-^{13}C** was encapsulated in **1**, the enriched ^{13}C resonances were shifted upfield by only a few parts per million relative to those of the unencapsulated alcohol. This is consistent with encapsulation of the neutral alcohol **2-^{13}C**. The hydrophobic binding of neutral alkanes and arenes in **1** has been reported, and it is likely that the encapsulation of **2** is similar. The observation of the **1**-bound substrate as the catalyst resting state is consistent with our proposed mechanism, in which reversible protonation of the host-bound substrate is followed by loss of water and rate-determining electrocyclization. Future work will be directed toward deducing the full rate law of this reaction.

Scheme 4. Mechanism of the Nazarov Cyclization, Showing Possible Intermediates That Are Encapsulated in **1** as the Catalyst Resting State



In conclusion, we have demonstrated the efficient catalysis of the Nazarov cyclization of 1,4-pentadien-3-ols by a self-assembled host in water and mixed water/DMSO. The rate of the catalyzed reaction is up to 2 100 000 times larger than that of the uncatalyzed reaction, representing the first instance of supramolecular catalysis that achieves rate enhancements comparable in size to those seen in enzymatic systems. The origin of this dramatic effect is attributed to the preorganization of the reactant and stabilization of the transition state by constrictive binding as well as an increase in basicity of the alcohol group of the bound reactant. Preliminary mechanistic studies are consistent with this explanation.

Acknowledgment. We gratefully acknowledge financial support from the Director of the Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy under Contract DE-AC02-05CH11231 and through fellowships from the NSF (to M.D.P.) and Chevron (to C.J.H.). The authors thank Lee Bishop, Casey Brown, Jeff Mugridge, and Dr. Carmelo Sgarlatta for helpful discussions.

Supporting Information Available: Experimental details, kinetic data, and characterization of host−guest complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009. (b) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488. (c) Oshovsky, G. V.; Reinhoudt, I. D. N.; Verboom, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2366. (d) Schmuck, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5830. (e) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*, 1st ed.; Wiley: Chichester, U.K., 2000.

(2) (a) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997. (b) Kirby, A. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 708. (c) Vriezema, D. M.; Aragonès, M. C.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445. (d) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418.

(3) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.

(4) Radzicka, A.; Wolfenden, R. A. *Science* **1995**, *267*, 90.

(5) Caulder, D. L.; Raymond, K. N. *Acc. Chem. Res.* **1999**, *32*, 975.

(6) Work by other groups on metal−ligand polyhedra is described in the following articles and the references therein: (a) Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38*, 369. (b) Northrop, B. H.; Zheng, Y.; Chi, K.; Stang, P. J. *Acc. Chem. Res.* **2009**, *42*, 1554. (c) Saalfrank, R. W.; Maid, H.; Scheurer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8794.

(7) Biros, S. M.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12094.

(8) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 11459.

(9) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2009**, *42*, 1650, and references therein.

(10) Fiedler, D.; van Halbeek, H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 10240.

(11) Campbell, P. H.; Chiu, N. W. K.; Deugau, K.; Miller, I. J.; Sorensen, T. S. *J. Am. Chem. Soc.* **1969**, *91*, 6404.

(12) (a) Threlkel, R. S.; Bercaw, J. E.; Seidler, P. F.; Stryker, J. M.; Bergman, R. G. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 505−508. (b) King, R. B.; Bisnette, M. B. *J. Organomet. Chem.* **1967**, *8*, 287.

(13) Hastings, C. J.; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10977.

(14) (a) Kang, J. M.; Hilmersson, G.; Santamaria, J.; Rebek, J. *J. Am. Chem. Soc.* **1998**, *120*, 3650. (b) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129*, 7000. (c) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347.

(15) Although product inhibition occurs in these experiments, we observed quantitative yields in our preliminary experiments in the absence of cosolvent. This is most likely due to the long reaction time of that experiment and the low concentration in D_2O of Cp*H relative to **2** resulting from the greater solubility of **2** in water.

(16) (a) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302. (b) Marinescu, L. G.; Bols, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4590. Very large rate accelerations were observed in the stoichiometric acylation of cyclodextrins: (c) Trainor, G. L.; Breslow, R. *J. Am. Chem. Soc.* **1981**, *103*, 154. Million-fold rate enhancements were observed using an enzyme-mimicking polymer catalyst: (d) Skouta, R.; Wei, S.; Breslow, R. *J. Am. Chem. Soc.* **2009**, *131*, 15604.

(17) Sorensen, T. S. *J. Am. Chem. Soc.* **1967**, *89*, 3782.

JA102633E