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Catalyzing Methanolysis of Alkyl Halides in the Interior of an Amphiphilic Molecular Basket

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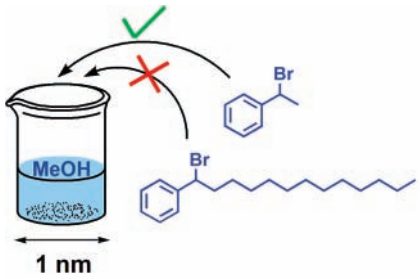
ABSTRACT



A molecular basket with four cholate units assembled on a cone-shaped calix[4]arene assumed reversed micelle-like conformation in 5% methanol/carbon tetrachloride. The inwardly facing hydroxyl groups on the cholates concentrated the polar solvent from the mostly nonpolar mixture. Methanolysis of alkyl halides benefited from the concentrated pocket of methanol if the substrate was capable of entering the basket. Substrates that were too large or too hydrophobic to fit within the basket showed no rate acceleration.

The behavior of molecules strongly depends on their environment. In the active site of an enzyme, the microenvironment around the substrate differs substantially from the bulk reaction mixture (i.e., water in most cases). Within this microenvironment, polarity suitable for the transition, functional groups useful for catalysis, and specific shapes important to selectivity can be engineered to promote enzymatic reactions. Not surprisingly, chemists have long been interested in generating "nanoreactors" to control chemical reactivity.[1,2] Nanoreactors prepared through either covalent construction or self-assembly have been reported.[3] For example, Rebek and co-workers functionalized resorcinarene-derived deep cavitands and used them to achieve molecular recognition and to enhance chemical reactivity.[3a] Recently, they reported a self-assembled capsule that dramatically shifted the ring/chain isomerization of a Schiff base.[3b] Using self-assembled coordination cages, Fujita and colleagues obtained unusual regioselectivity in a Diels−Alder reaction and developed efficient catalysts operable in aqueous solution.[3c] Although different types of reactions such as oxidation[3d,f] and nitrene rearrangement[3e] have been investigated in recent years, the nanoreactors involved invariably were rigid structures.[3] On the other hand, natural enzymes are formed by the folding of conformationally mobile peptide chains, and the controlled conformational changes of enzymes are critical to their function and regulation.

Using cholic acid as the building block, we recently synthesized a series of amphiphiles whose conformations are controlled by solvent polarity.[4] Molecular basket **1** has four

(1) 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*, 1445−1489 and references therein.

(2) Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 2068−2078 and references therein.

(3) For some recent examples, see: (a) Purse, B. W.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10777−10782. (b) Iwasawa, T.; Mann, E.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 9308−9309. (c) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251−254. (d) Yoshizawa, M.; Miyagi, S.; Kawano, M.; Ishiguro, K.; Fujita, M. *J. Am. Chem. Soc.* **2004**, *126*, 9172−9173. (e) Warmuth, R.; Makowiec, S. *J. Am. Chem. Soc.* **2007**, *129*, 1233−1241. (f) Natarajan, A.; Kaanumalle, L. S.; Jockusch, S.; Gibb, C. L. D.; Gibb, B. C.; Turro, N. J.; Ramamurthy, V. *J. Am. Chem. Soc.* **2007**, *129*, 4132−4133.

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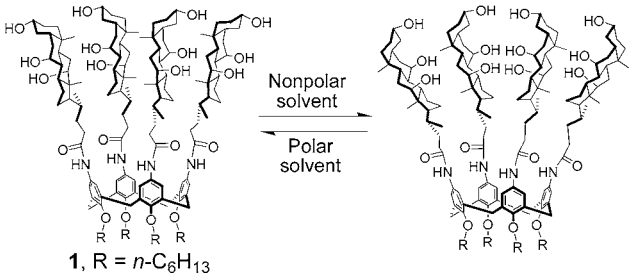
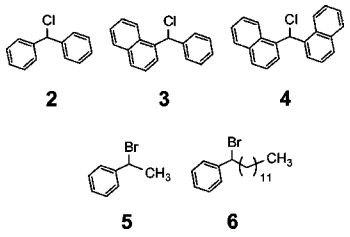
cholate units assembled on a cone-shaped calix[4]arene scaffold.[4a−c] When dissolved in a polar solvent such as methanol, the hydrophobic faces of the cholates turn inward to form a conformer that resembles a unimolecular micelle (**1**, left). In nonpolar solvents, the hydrophilic faces point inward instead, resulting in a reversed micelle-like conformer (**1**, right).[5]



The reversed micelle-like conformer typically is formed in a solvent mixture consisting of mostly a nonpolar solvent (e.g., CCl_4, chloroform, or THF) and a small amount of a polar solvent (e.g, methanol or DMSO).[4a−c] With the introverted hydroxyl groups, this conformer can concentrate the polar solvent from the bulk.[4c] Tiny pockets of the polar solvent are located in the interior of basket **1**, while the surrounding medium is largely a nonpolar solvent mixture. In other words, the highest concentration of the polar solvent is found in the interior of **1** in such a solvent mixture. As a result, a substrate reactive toward *the polar solvent* should be most reactive if it can enter the molecular basket. Performing reactions in such a confined environment has



an immediate consequence in selectivity.[6] Substrates that can easily access the pockets of the polar solvent will be helped by the basket, whereas reactants excluded by the basket will not.

To test the hypothesis, we studied the methanolysis of several alkyl halides (**2**−**6**), which differ in size/hydrophobicity and in their reactivity toward methanol. Diphenylmethyl chloride (**2**) was studied initially because its methanolysis only leads to one product (the methyl ether). Under our experimental conditions (5−15% methanol in CCl_4), it probably solvolyzes through an ion-pair mechanism.[7] In addition to the simplicity of the reaction outcome, the singlet methine peaks from the starting material and the product have very different chemical shifts (at ca. δ 6.0 and 5.2 ppm, respectively), greatly facilitating the kinetic measurements by ^{1}H NMR spectroscopy.

The reaction was studied in three solvent mixtures—5, 10, and 15% CD_3OD/CCl_4. Figure 1a shows the yields of the methyl ether product as a function of time. The data fit well to the first-order kinetics (Figure 1b), from which the rate constants were obtained. As indicated by Figure 1b, the reaction was well behaved, showing linearity even at 90% conversion.

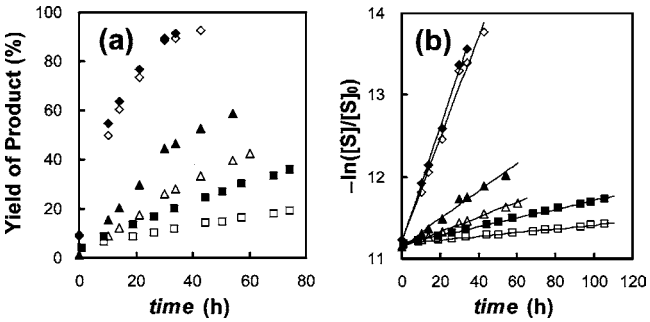


Figure 1. Methanolysis of diphenylmethyl chloride (**2**) with 20 mol % compound **1** in 5% (■), 10% (▲), and 15% (◆) CD_3OD/CCl_4 at 20 °C. The open data points (□, △, ◇) are for the control experiments with no compound **1** present in the corresponding solvent mixtures. [S] is the concentration of the substrate at different times.

Table 1 summarizes the kinetic data. The rate constant was 2.30×10^{-3} h^{-1} for the methanolysis of substrate **2** in 5% CD_3OD/CCl_4 (Table 1, entry 1). In the presence of 20 mol % of basket **1**, the rate constant more than doubled to 5.31×10^{-3} h^{-1}. Although the rate acceleration (k_{cat}/k_{uncat} = 2.3) was modest, it clearly indicates that the basket compound is beneficial to the reaction.

With an increase of methanol in the reaction mixture, the reversed micelle-like conformer of compound **1** becomes less stable.[4a−c] In addition, preferential solvation (i.e., the "polar solvent-concentrating effect") is less significant when there is more polar solvent in the bulk mixture.[4c] Therefore, catalysis is expected to be less efficient. This prediction was confirmed. The rate acceleration became less significant (k_{cat}/k_{uncat} = 1.2, entry 2) in 10% methanol and almost disappeared

(4) (a) Ryu, E.-H.; Zhao, Y. *Org. Lett.* **2004**, *6*, 3187−3189. (b) Zhao, Y.; Ryu, E.-H. *J. Org. Chem.* **2005**, *70*, 7585−7591. (c) Ryu, E.-H.; Yan, J.; Zhong, Z.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 7205−7213. (d) Zhao, Y.; Zhong, Z. *J. Am. Chem. Soc.* **2005**, *127*, 17894−17901. (e) Zhao, Y.; Zhong, Z.; Ryu, E.-H. *J. Am. Chem. Soc.* **2007**, *129*, 218−225.

(5) For some recent examples of interconvertible unimolecular micelles and reversed micelles, see: (a) Basu, S.; Vutukuri, D. R.; Shyamroy, S.; Sandanaraj, B. S.; Thayumanavan, S. *J. Am. Chem. Soc.* **2004**, *126*, 9890−9891. (b) Vutukuri, D. R.; Basu, S.; Thayumanavan, S. *J. Am. Chem. Soc.* **2004**, *126*, 15636−15637. (c) Ghosh, S.; Maitra, U. *Org. Lett.* **2006**, *8*, 399−402.

(6) Phase separation of solvents can be also realized by reversed micelles formed by the aggregation of conventional surfactants—e.g., a pool of water is typically used to stabilize reversed micelles formed by surfactants. Even though reversed micelles have been studied extensively as reaction media for reactions, their interior tend to be much larger (depending on the amount of water added) than small organic molecules. For catalysis in micelles and reversed micelles, see: Fendler, J. H.; Fendler, E. J. *Catalysis in Micelles and Macromolecular Systems*; Academic Press: London, 1975.

(7) (a) Bunton, C. A.; Mhala, M. M.; Moffatt, J. R. *J. Org. Chem.* **1984**, *49*, 3639−3641. (b) Schade, C.; Mayr, H. *Tetrahedron* **1988**, *44*, 5761−5770.

Table 1. Rate Constants of Methanolysis of Alkyl Halides at 20 °C

entry	substrate	catalyst	CD_3OD (%)[a]	k (h^{-1})	k_{cat}/k_{uncat}
1	**2**	**1**[b]	5	5.31×10^{-3}	2.3
	2	none	5	2.30×10^{-3}	
2	**2**	**1**[b]	10	1.30×10^{-2}	1.2
	2	none	10	1.09×10^{-2}	
3	**2**	**1**[b]	15	4.29×10^{-2}	1.1
	2	none	15	3.99×10^{-2}	
4	**3**	**1**[b]	5	1.70×10^{-2}	1.8
	3	none	5	0.92×10^{-2}	
5	**4**	**1**[b]	5	6.96×10^{-2}	1.1
	4	none	5	6.26×10^{-2}	
6	**5**	**1**[b]	5	1.26×10^{-3}	4.1
	5	**7**[c]	5	3.09×10^{-4}	1.0
	5	none	5	3.22×10^{-4}	
7	**6**	**1**[b]	5	–[d]	–
	6	none	5	–[d]	
8	**5**	none	30	7.42×10^{-3}	3.1[e]
	6	none	30	2.42×10^{-3}	
9	**5**	none	50	2.31×10^{-2}	2.9[e]
	6	none	50	7.97×10^{-3}	

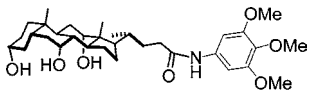
[a] The volume percentage of CD_3OD in CCl_4. [b] The catalyst was used at 20 mol % with respect to the substrate. [c] The catalyst was used at 80 mol % with respect to the substrate. [d] Only 1−2% of the substrate methanolyzed during 130 h. [e] The ratio shown is k(**5**)/k(**6**).

in 15% methanol ($k_{cat}/k_{uncat} = 1.1$, entry 3, also see Figure 1). Note that as the percentage of methanol went from 15 to 5%, the uncatalyzed reactions became slower as well (entries 3−3). The result is reasonable because a decrease in methanol not only reduces the concentration of the nucleophile, but also makes the overall solvent less polar, unfavorable to a reaction with a charge-separated transition state.

To demonstrate the hypothesized selectivity, we studied the methanolysis of the mononaphthyl chloride **3** and the dinaphthyl chloride **4** in 5% CD_3OD/CCl_4. According to our previous work, the interior of basket **1** is large enough to accommodate phenyl β-D-glucopyranoside,[4b] a guest similar in size to chloride **2**. Therefore, the idea was that, as the two phenyl groups were replaced by the naphthyl one after another, the substrate would become too large eventually to fit within the basket, and would not benefit from the methanol within basket **1**. Moreover, the naphthyl groups increase the substrate's hydrophobicity, which also discourages the substrate from entering the polar solvent-filled molecular basket. The data in Table 1 does support such a notion. With one of the phenyls replaced by a naphthyl group, the rate acceleration in substrate **3** decreased to $k_{cat}/k_{uncat} = 1.8$ (entry 4) from 2.3 in **1** (entry 1). When both phenyl groups were replaced, almost no acceleration ($k_{cat}/k_{uncat} = 1.1$, entry 5) was observed in substrate **4**.

However, we also noticed that, as the phenyl groups were replaced by naphthyl, the uncatalyzed reaction became faster. The rate constant was 0.92×10^{-2} h^{-1} for **3** (entry 4) and 6.26×10^{-2} h^{-1} for **4** (entry 5), as compared to 2.30×10^{-3} h^{-1} for **2** (entry 1). Because a faster reactant does not need as much help from a catalyst as a slower reactant, it is possible that the diminishing rate acceleration for **4** might not result from its exclusion from the basket but, instead, could be simply a result of its faster, uncatalyzed reaction.

Therefore, in order to better understand the reason for the selectivity, we have to use substrates that are different in size/hydrophobicity but similar in reactivity. Essentially, we have to change the size/hydrophobicity of the substrate without changing the stability of the corresponding carbocation significantly.[8] Substrates **5** and **6** turned out to fulfill this criterion. In the presence of 20 mol % basket **1**, the smaller bromide **5** gave a rate constant of 1.26×10^{-3} h^{-1} in 5% methanol (entry 6). Compared to the uncatalyzed reaction, the basket-catalyzed reaction was 4.1 times faster. This rate acceleration was even higher that what was observed in **2**. Hence, a smaller, slower substrate does seem to benefit more from the basket. Importantly, the basket conformation of **1** was needed for the observed catalysis, because the monocholate derivative **7**, at 80 mol % (the same concentration of cholate as 20 mol % of **1**), did not help bromide **5** at all (entry 6).



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Bromide **6** was slower in solvolysis than **5**, consistent with the reported effect of alkyl on this type of reaction.[9] Only 1−2% of **6** reacted with methanol over 130 h, in the *presence or absence* of basket **1** (entry 7). Thus, little, if any, rate acceleration was obtained for this larger/more hydrophobic bromide, in contrast to what occurred in **5**. When the amount of methanol was increased to 30 and 50% in the reaction mixture, the reaction rate became measurable for **6**. The data indicate that the inherent reactivity of **6** is 3 times lower than that of **5** (entries 8 and 9). Assuming the inherent reactivity stays the same and bromide **6** is helped by the basket to the same extent as **5**, the rate constant for **6** in the *presence* of **1** would be 4×10^{-4} h^{-1}. The real rate constant must be slower than this because the uncatalyzed reaction of **5** ($k \approx 3 \times 10^{-4}$ h^{-1}, entry 6) was measurable, whereas the reaction of **6** was not (entry 7). Thus, the larger/more hydrophobic substrate indeed was not catalyzed by **1**.

Last, we placed bromides **5** and **6** in the same reaction mixture and carried out competitive methanolysis. In the presence of **1**, 17% of bromide **5** was converted to the product after 140 h, whereas a negligible amount of bromide **6** was converted (Figure 2a). In the absence of basket **1**, as shown by Figure 2b, neither showed much reactivity. Hence, the results once again indicate that the reaction of the smaller/

(8) It is difficult to design experiments to determine whether the size or the hydrophobicity of the substrate is more important under these conditions. Attaching hydrophobic groups to the substrate, as in this study, increases both its size and hydrophobicity. Attaching hydrophilic groups (to increase the size and decrease the hydrophobicity) is problematic. Hydrophilic groups typically have heteroatoms that may interfere with the solvolysis, e.g., through neighboring group participation. Also, the hydrophilic groups themselves are likely to alter the local solvent composition around the substrate and change the rate of methanolysis.

(9) Orlović, M.; Kronja, O.; Humski, K.; Borčić, S.; Pollar, E. *J. Org. Chem.* **1986**, *51*, 3253−3256.

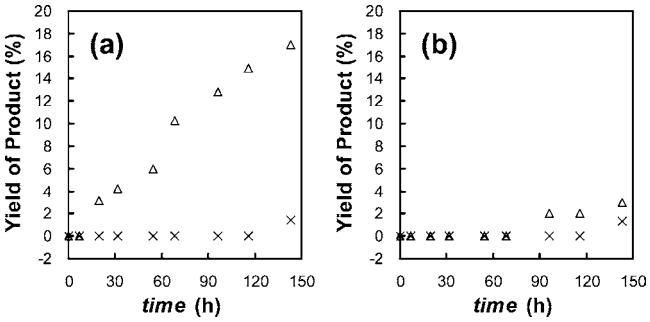

Figure 2. Competitive methanolysis of compounds **5** (△) and **6** (×) with (a) 20 mol % compound **1** and (b) without compound **1** in 5% CD_3OD/CCl_4.

less hydrophobic substrate is catalyzed by the basket, whereas the larger/more hydrophobic one is not.

In summary, basket **1** concentrates polar solvent within its interior from a largely nonpolar solvent mixture. Reactants capable of entering the basket can be selectively converted to products in the presence of reactants that do not fit due to size or hydrophobicity. Because the conformation of **1** is responsive to solvent polarity, this catalysis can be tuned up or down, depending on the solvent composition. The rate acceleration obtained was small but was significant, considering the unfavorable conditions under which the catalysis must occur—i.e., a hydrophobic substrate has to enter a hydrophilic cavity. More efficient catalysis is expected if the catalyst can be equipped with catalytic functionalities[10] and if the substrate can have a higher affinity for the catalyst.

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Supporting Information Available: Synthetic procedures, procedures for the kinetic measurements, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Recently, we reported a porphyrin catalyst with cholate groups around the catalytic center, see: Zhou, Y.; Ryu, E.-H.; Zhao, Y.; Woo, L. K. *Organometallics* **2007**, *26*, 358−364.