

A Functionalized, Deep Cavitaand Catalyzes the Aminolysis of a Choline Derivative

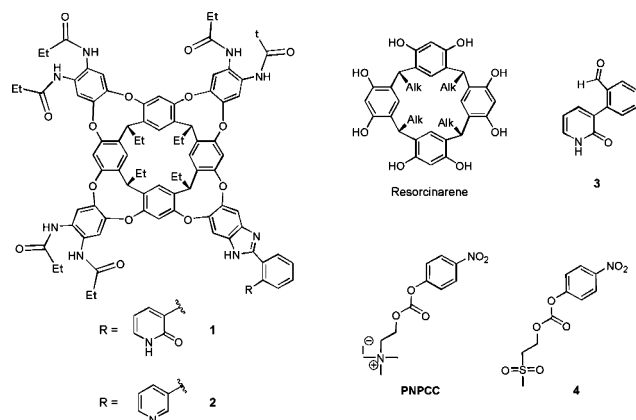
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Cavitands are bowl-shaped structures widely used in studies of molecular recognition.¹ Most are derived from condensation of resorcinol with aldehydes through Högberg's² efficient synthesis. The cyclic tetramers (resorcinarenes) have a history as hosts,³ but their greater potential as modules for more elaborate structures—carcerands,⁴ velcraands,⁵ and deeper cavitands⁶—was recognized by Cram⁷ and Dalcanele.⁸ We found a way to stabilize the vase-like conformation⁹ and, subsequently, a means to monofunctionalize its rim.¹⁰ The result is a host structure that more or less surrounds a guest and presents it with a well-positioned functional group. The principles of molecular recognition-based catalysis are well known and have been applied in the context of crown ethers,¹¹ cyclodextrins,¹² cyclophanes,¹³ and other synthetic receptors,¹⁴ but the combination of inwardly directed functional group and cavitand receptor is unique. Here we explore its consequences in catalysis.

Acetylcholine and other guests bearing a trimethylammonium knob bind strongly to deep cavitands in organic solvents.¹⁵ This recognition was used to position reactive centers on a guest near functional groups known to catalyze aminolysis reactions attached to the host. Specifically, pyridone is a known bifunctional catalyst for the breakdown of tetrahedral intermediates.¹⁶ The aminolysis of active esters in aprotic organic solvents proceeds through the rapid, reversible formation of a tetrahedral intermediate followed by its rate-determining breakdown to products.¹⁷ The mechanism of the catalysis by pyridone is depicted in Scheme 1. The tetrahedral intermediate of the reaction can form two H-bonds to the pyridone of **1**, while the ester reactant and amide product can form only one. Accordingly, the higher-energy species along the reaction coordinate are more complementary to **1**, a prerequisite for minimizing product inhibition and encouraging turnover.



The cavitand **1** was synthesized through condensation of the known hexaamide diamino cavitand¹⁸ with the aldehyde **3** in 47% isolated yield. A calculated structure of **1** (Maestro, Amber force field) with the tetrahedral intermediate does allow the desired

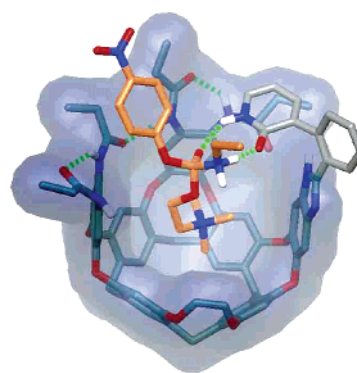
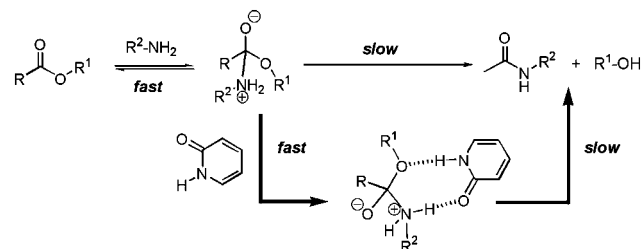


Figure 1. Energy-minimized structure of the cavitand **1** with the tetrahedral intermediate formed from PNPCC and propylamine. One of the four walls and some atoms have been omitted for clarity.

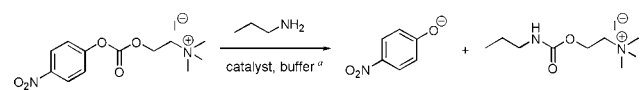
Scheme 1. Pyridone-Catalyzed Aminolysis of Esters

H-bonds necessary for the catalytic action and shows some rotational freedom of the pyridone with respect to the rim of the cavitand. This provides some flexibility to reach the optimum stabilization of the intermediate and, in turn, to facilitate its breakdown to products (Figure 1).

The modeling also shows the rotation of the pyridone into and out of the cavity to be restricted by steric clashes with the neighboring amides. ¹H NOE experiments at 213 K show clear chemical exchange between the two atropisomers of **2**:¹⁹ the required *introverted* and the unreactive *extraverted* conformations.²⁰ Integration of the cross-peaks gives an energetic barrier of 12.7 kcal/mol⁻¹ for the in/out interconversion, a barrier that allows rapid interconversion at room temperature.

For the substrate, we used the same *p*-nitrophenyl choline carbonate (PNPCC) that has been used as an analogue of acetylcholine.²¹ Its aminolysis can be conveniently monitored using UV detection of the released *p*-nitrophenolate. Initial runs showed that **1** is a potent catalyst for this reaction (Table 1).

In contrast, model pyridine cavitand **2**, 2-pyridone itself, or a mixture of both (entries 3, 4, and 5, respectively) proved ineffective in catalyzing the reaction. The absence of catalysis in the presence of the free catalytic motif—2-pyridone (entries 4 and 5)—was somewhat puzzling. Yet, 2-pyridone is a known catalyst for the aminolysis of *esters*, not carbonates. In fact, the tetrahedral

Table 1. Aminolysis of PNPCC in the Presence of Catalysts


entry	catalyst	mole %	v_0 ($\mu\text{M}\cdot\text{min}^{-1}$) ^b	$v_0 \text{ cat.}/v_0 \text{ uncat.}$
1	—	—	1.6	1
2	1	10	3.5	2.2
3	2	10	1.6	1
4	2-pyridone	10	1.6	1
5	2 + 2-pyridone	10	1.6	1
6	1	17	6.0	3.7
7	1	87	16.5	10.3
8	1	193	25.0	15.6
9	2-pyridone	193	1.8	1.1

^a Conditions: 40 μM PNPCC, 40 μM propylamine, 20 mM Hünig's base, 0.5 mM TFA in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$, 99/1, room temperature. ^b In the absence of propylamine (bufferolysis) $v_0 = 0.4 \mu\text{M}\cdot\text{min}^{-1}$.

intermediate formed after the attack of the amine onto the carbonate is less likely to form and more reactive than the one obtained from corresponding esters.^{17b} Consequently, the intermediate may either undergo the uncatalyzed reaction or revert to the starting amine and PNPCC before the pyridone can form the catalytically active complex (Scheme 1), unless the pyridone is in close vicinity of the intermediate as in **1**. These results suggest a synergy between the recognition of the ammonium of PNPCC in the cavity of **1** and the catalytic activity brought to bear by the pyridone located on the rim of **1**.

The quantity of catalyst has a marked effect on the initial rates of the reaction (entries 2 and 6–9).²² The reaction is accelerated up to ca. 16 times in the presence of 2 equiv of catalyst (entry 8), compared with the modest (10%) acceleration observed in the presence of 2 equiv of pyridone under the same conditions (entry 9).²³ Given the very low binding constant of PNPCC to **1** in $\text{CD}_2\text{Cl}_2/\text{CD}_3\text{CN}$ ($K_a = 17 \text{ M}^{-1}$),²⁴ this translates into rate acceleration of ca. 6000 (0.17 equiv of **1**) when comparing the reaction in the bulk and the reaction inside **1**. The weak binding affinity of PNPCC to **1** was anticipated—and desired—to provide catalytic turnover, and turnover does clearly take place. In fact, after 50% conversion, the aminolysis rate of PNPCC in the presence of 10 mol % of **1** remains higher than the *initial* rate of the reaction in the absence of catalyst.

As suggested by the energy-minimized structure (Figure 1), bulky primary amines such as tritylamine should experience substantial steric hindrance in this reaction within (and outside) the cavitand. Indeed, even though the uncatalyzed reaction with tritylamine is 2.5 times slower, no catalysis is observed in the presence of 10 mol % of **1**. Similarly, no catalysis is observed using the carbonate **4** as substrate. This result is expected since the sulfone function of **4** has no affinity for the cavity of **1**. Accordingly, we conclude that the ammonium of PNPCC—and of its subsequent tetrahedral intermediate—must be recognized by the pocket of **1** to experience catalysis in the aminolysis reaction. The pyridone is poised to aid the collapse of the tetrahedral intermediate formed from PNPCC.

In conclusion, the combination of a well-defined binding pocket and well-positioned functional groups creates a unique environment with catalytic properties and gives high substrate specificity in this and alkylation reactions.²⁵

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Supporting Information Available: Kinetics of PNPCC aminolysis; synthetic procedures and descriptions of compounds **1**, **2**, **3**, and PNPCC; ¹H NOE spectrum of **2** at 213 K. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Cram, D. J. *Science* **1983**, *219*, 1177–1183.
- (2) (a) Högborg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050. (b) Högborg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498–4500.
- (3) (a) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349–1354. (b) Kobayashi, K.; Asakawa, Y.; Kikuchi, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1993**, *115*, 2648–2654.
- (4) Reviews: (a) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931–967. (b) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663–2704.
- (5) (a) Moran, J. R.; Ericson, J. L.; Dalcanele, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707–5714. (b) Cram, D. J.; Choi, H.-J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748–7765.
- (6) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991.
- (7) (a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826. (b) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229.
- (8) (a) Dalcanele, E.; Soncini, P.; Bacchilega, G.; Ugozzoli, F. *J. Chem. Soc., Chem. Commun.* **1989**, 500–502. (b) Soncini, P.; Bonsignore, S.; Dalcanele, E.; Ugozzoli, F. *J. Org. Chem.* **1992**, *57*, 4608–4612.
- (9) (a) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 9911–9912. (b) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991–2005.
- (10) Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281–3283.
- (11) (a) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625–628. (b) Lehn, J.-M.; Ball, P. *The New Chemistry*; Cambridge University Press: 2000; Chapter 12, pp 300–351.
- (12) (a) Breslow, R.; Schmuck, C. *J. Am. Chem. Soc.* **1996**, *118*, 6601–6605. (b) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057–5067.
- (13) (a) Mattei, P.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 1555–1588. (b) Habicher, T.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1999**, *82*, 1066–1095.
- (14) (a) Tecilla, P.; Chang, S. K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9586–9590. (b) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50–52. (c) Chen, J.; Korner, S.; Craig, S. L.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **2002**, *415*, 385–386.
- (15) Atwood, J. L.; Szumna, A. *Chem. Commun.* **2003**, 940–941; Hof, F.; Trembleau, L.; Ullrich, E. C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 3150–3153.
- (16) Swain, C. G.; Brown, J. F., Jr. *J. Am. Chem. Soc.* **1952**, *71*, 2538–2543.
- (17) (a) Su, C.-W.; Watson, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 1854–1857. (b) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **2001**, *66*, 6000–6003.
- (18) Renslo, A. R.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4573–4582.
- (19) This experiment was carried out on **2** and not **1** as the appearance of two different species at cold temperature with **1** could result from the dimerization of the pyridone and not from the two atropisomers.
- (20) See Supporting Information.
- (21) Cuevas, F.; Di Stefano, S.; Magrans, J. O.; Prados, P.; Mandolini, L.; de Mendoza, J. *Chemistry* **2000**, *6*, 3228–3234.
- (22) The (un)catalyzed aminolysis of PNPCC is fast even in the presence of only one equivalent of propylamine relative to the carbonate. This precludes the use of pseudo-first-order conditions necessary to determine the rate constant of the reaction.
- (23) The pyridone is known to readily self-dimerize in aprotic solvents. Yet, under the very dilute conditions used in our study, the dimerization alone cannot account for the lower catalytic activity of the pyridone over **1**. For instance, it was found that 37% of the pyridone exists as a dimer in chloroform for an initial concentration of 2 mM (as compared to 0.04 mM in our case), see: Beak, P.; Covington, J. B.; Smith, S. G.; White, J. M.; Zeigler, J. M. *J. Org. Chem.* **1980**, *45*, 1354–1362.
- (24) The very low solubility of PNPCC in a mixture of CDCl_3 and CD_3CN precludes the accurate determination of the binding constant.
- (25) Purse, B. W.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 14682–14683.

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