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Catalysis by a Synthetic Receptor Sealed at One End and Functionalized at the Other

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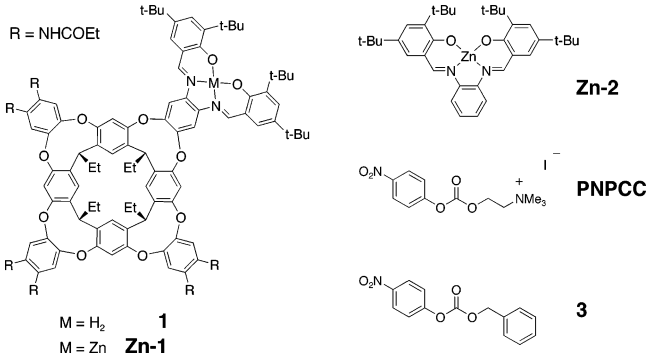
Cavitands derived from resorcinarenes are macrocyclic structures with one open end.[1] Deep cavitands act as hosts that can more or less completely surround their guests while displaying high selectivities.[2] Specifically, a trimethylammonium "knob" fits snugly within deeper cavitands, and guests bearing this feature are more predictably positioned within than in other macrocyclic receptors.[3] Calixarenes and cavitands bearing additional functionalities on their peripheries are able to catalyze methanolysis[4] or aminolysis[5] reactions of choline derivatives, respectively. We describe here a salen functionalized cavitand (**1**), its zinc(II) complex (**Zn-1**) and relate how the metal can accelerate reactions of choline derivatives.

The catalyst (**Zn-1**) is a resorcin-[4]-arene fused to a salen-type ligand,[6] and its synthesis was accomplished by the condensation of the appropriate salicylaldehyde with a diamino cavitand,[7] followed by metalation with $ZnEt_2$[8] (see Supporting Information). Both **1** and **Zn-1** are in the vaselike shape in CH_2Cl_2, as their methine protons appear between 5.5 and 6 ppm in the ^{1}H NMR spectra.[9] The seam of hydrogen bonds provided by the six secondary amides stabilizes this conformation, but the structure permits dynamic exchange: guests enter and depart slowly on the NMR time scale by the folding and unfolding of the cavitand.[10]

The guest (reactant) is *para*-nitrophenyl choline carbonate (PNPCC), and the (admittedly) easy reaction is its hydrolysis; PNPCC is used as a reactive acetylcholine derivative[4] because the *para*-nitrophenolate anion released does not compete with the ester for the metal. The Lewis acid zinc(II) was expected to activate the well-positioned carbonyl toward reactions with an external nucleophile. An energy-minimized structure of the PNPCC@**Zn-1** complex shows that cation−π interactions[11] and a C═O- - -Zn coordination bond occur simultaneously (Figure 1, left).



Kinetic studies of the PNPCC hydrolysis by water present in commercial[12] CH_2Cl_2 (0.01%, i.e., more than 100 equiv compared to the quantity of PNPCC) were performed as described by de Mendoza[4] (Table 1). The reactions were carried out in CH_2Cl_2 buffered with CF_3CO_2H/EtN(i-Pr)$_2$ at different concentrations of **Zn-1** and monitored by UV−vis spectroscopy (λ_{max} = 405 nm of the *para*-nitrophenolate). Key experimental kinetic curves are shown in Figure 1.[13] The reaction is found to be first-order in PNPCC, and the observed rate constants (k_{obsd}) are summarized in the Table.

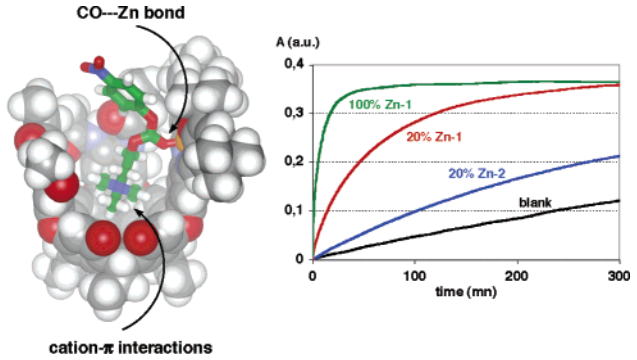
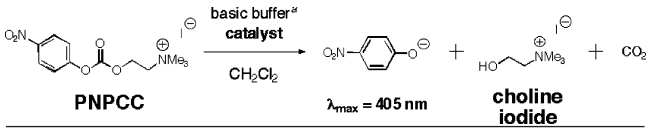


Figure 1. Left: energy-minimized structure (CaChe 4.9©) of the complex between **Zn-1** (CPK) and the PNPCC (stick); the front wall has been removed for viewing clarity. Right: experimental kinetic curves for entries 1 (black), 3 (red), 5 (green), and 6 (blue) of Table 1.

Table 1. Kinetic Data of the Hydrolysis of the PNPCC



entry	catalyst (mole %)	k_{obsd} (10^{-3} mn^{-1})	$t_{50\%}$ (mn)	k_{obsd}/k_{uncat}
1	− (0)	1.6	>300	1
2	**Zn-1** (10)	10.3	85	6.4
3	**Zn-1** (20)	19.1	38	11.9
4	**Zn-1** (50)	43.7	9	27.3
5	**Zn-1** (100)	84.7	4	52.9
6	**Zn-2** (20)	3.6	230	2.3
7	**1** (20)	1.6	>300	1
8	**Zn-1** (20)[b]	3.9	173	2.4

[a] Conditions: 40 μM PNPCC, 20 mM Hünig's base, 0.5 mM TFA in CH_2Cl_2, room temperature. [b] Same conditions as in footnote a + 65 μM acetylcholine chloride.

Carbonate hydrolysis without catalyst is slow under these conditions, and only ca. 30% of the PNPCC is decomposed after 5 h (Table 1, entry 1). The reaction rate is significantly increased by the presence of **Zn-1** (entries 2−5), and the acceleration is more than 50-fold when 1 equiv of the cavitand is present (entry 5). Control experiments were used to estimate the catalytic efficiency of **Zn-1**.[13] When the compound **Zn-2** (salen wall without cavitand) is used as catalyst (0.2 equiv, entry 6), the zinc(II) cation plays its Lewis acid role and the reaction rate is increased, but is still five times slower than the reaction catalyzed with **Zn-1** (entry 3). No acceleration is observed with the metal-free salen cavitand **1** (entry 7). Acetylcholine acts as a competitive inhibitor (entry 8), owing to its structural similarity to PNPCC: the same distance exists between the carbonyl and the trimethylammonium moieties in both. With carbonate **3** as the substrate, hydrolysis using cavitand **Zn-1**

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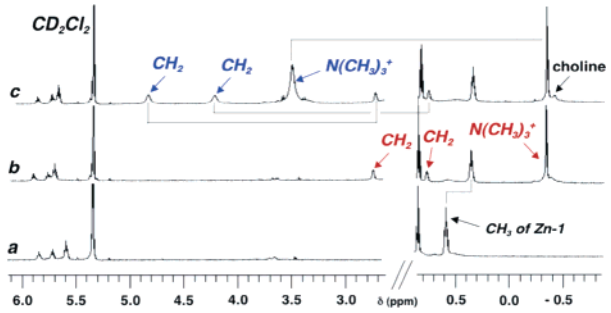

Figure 2. ^{1}H NMR study of the inclusion complex PNPCC@**Zn-1** (600 MHz, CD_2Cl_2, 300 K). (a) Guest-free cavitand **Zn-1**. (b) Inclusion complex PNPCC@**Zn-1** with 1 equiv of PNPCC. (c) Same as (b) with 2.4 equiv of PNPCC (encapsulated PNPCC signals in red and free PNPCC signals in blue).

as a catalyst is actually *slower* than the reaction performed with **Zn-2**. The cavitand **Zn-1** has no affinity for **3** and only the outer face of the salen ligand seems to be accessible to the substrate. Accordingly, the reaction of **3** with **Zn-2** is approximately twice as fast as that of **3** with **Zn-1**. (See Supporting Information.)

The reaction is slow enough without buffer at millimolar concentrations that the formation of the PNPCC@**Zn-1** complex can be observed by ^{1}H NMR spectroscopy (Figure 2).[13] The PNPCC signals are shifted upfield, and separate sets of signals for the free and bound host appear. When more than 1 equivalent of PNPCC is present, the free guest signals are observed (Figure 2c). When 1 equiv of PNPCC is used, no free guest can be detected (Figure 2b), indicating a high affinity of acetylcholine derivatives for the host **Zn-1**.[14] In Figure 2c, it is also possible to observe the formation of the choline@**Zn-1** complex, due to the hydrolysis of the PNPCC. Nevertheless, the choline produced in the course of the reaction seems to be a weak inhibitor, and at the micromolar concentrations used in the kinetic experiments guest dissociation is facile.[15]

The present system resembles another case in which a reaction inside a cyclophane with one closed end and a well-positioned functional group at the other offers unusual reactivity. Catalysis based on molecular recognition with functionalized crown ethers,[16] cyclodextrins,[17] cyclophanes,[18] and other open ended[19] or open sided[20] synthetic receptors is well-known. Rarely do these cases fix the reactive site of the substrate, and even more rarely do they properly position the catalyst's functional group. When both are present, these features appear optimal for catalysis. The exclusion of bulk solvent can also play a role. We intend to test these notions on more difficult reactions with these functionalized cavitands.

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Supporting Information Available: Experimental details, full synthetic procedures, characterization of new compounds, kinetic, and NMR data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Fischer Scientific's CH_2Cl_2 UN1593 HPLC-GC/MS grade.
(13) See Supporting Information for kinetic curves, ln[PNPCC] vs time plots, control experiments, and the ^{1}H NMR study.
(14) It is not possible to detect free acetylcholine or free choline by ^{1}H NMR when 1 equiv of guest is used. The binding of choline derivatives in related deep cavitands show K_a's of $>10^4$ M^{-1}.
(15) No exchange rate constants are available with the PNPCC due to the hydrolysis of this guest by the cavitand **Zn-1** on the time needed for 2D NOESY acquisition.
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