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A Zinc(II)-Included Hemicryptophane: Facile Synthesis, Characterization, and Catalytic Activity

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A zinc(II)-included hemicryptophane, which has a zinc(II) center embedded in the cavity, was synthesized and characterized. The catalytic activity of the hemicryptophane was tested in the hydrolysis of methyl *para*-nitrophenyl carbonate (MPC). A direct comparison between the hemicryptophane and the model complex, which lacks a cavity, demonstrated that the cage structure enhanced the catalytic activity.

Much of the inspiration for the design of supramolecular catalysis arises from the observation and understanding of the enzyme catalysis.[1] Molecular capsules which provide precise internal spaces have been created as the active site of the artificial enzyme.[2] However, a few examples of molecular capsules that contain a transition metal complex within the internal space for recognition and catalysis have been reported.[3−5] In this study, we selected hemicryptophane, which has been reported by Dutasta,[4−6] to construct such an internal functionalized molecular capsule catalyst. Hemicryptophane is composed of a catalytic site and a suitable binding pocket for a particular substrate in the internal space. The catalytic site and the binding pocket are connected by the rigid spacer.

The synthetic pathway that led to the preparation of hemicryptophane **2** is outlined in Scheme 1. (*Rac*)-tri(benzaldehyde)-substituted CTV **1** was furnished by a known procedure.[6] A solution of CTV **1** and tris(2-aminoethyl)amine (tren) in a diluted acetonitrile and methanol mixture (3:7) was refluxed, and then sodium tetrahydroborate was added to the solution. Hemicryptophane **2** was obtained in 97% yield from **1**.

The single crystals of **2** were obtained by slow evaporation from an acetonitrile solution. The X-ray crystal structure of **2** is shown in Figure 1. The crystal structure of **2** exhibits the preorganized cavity by the CTV and the tren moieties. An acetonitrile molecule is encapsulated in the cavity and is

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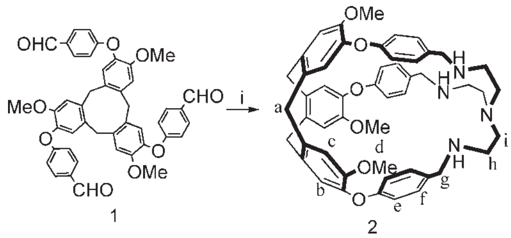
(8) Crystal data of **2**: $C_{57}H_{67}N_7O_8$, M_w = 978.20, monoclinic, space group $P2_1/c$; a = 15.8289(3) Å, b = 18.2279(3) Å, c = 17.9070(3) Å, α = 90.0000°, β = 92.8142(7) °, γ = 90.0000°, V = 5160.45(16) Å^3; Z = 4; μ = 0.085 mm^{-1}; R_1 = 0.0392, wR_2 = 0.1017; goodness-of-fit (GOF) on F^2 = 1.042. CCDC 771645. Crystal data of **3**: $C_{55}H_{66}N_4O_{13}Zn$, M_w = 1056.53, triclinic, space group $P\bar{1}$; a = 11.1164(5) Å, b = 15.0225(6) Å, c = 17.5824(8) Å, α = 64.3547(10) °, β = 78.9111(12) °, γ = 81.7640(12) °, V = 2591.55(20) Å^3; Z = 2; μ = 0.543 mm^{-1}; R_1 = 0.0681, wR_2 = 0.2441; goodness-of-fit (GOF) on F^2 = 1.128. CCDC 771644.

stabilized through CH−π interactions [$d(\mathrm{C\cdots C{=}C}) = 3.8$ Å] and by a hydrogen bond [$d(\mathrm{N}_{(4)}\cdots\mathrm{N}_{(5)}) = 3.296$ Å]. The NMR spectrum of **2** indicates that **2** is a C_3-symmetrical conformation in $CDCl_3$ solution (Figure 2).

Scheme 1. [a]



[a] (i) Tris(2-aminoethyl)amine, *p*-TsOH, then $NaBH_4$, 97%.

The addition of zinc acetate into the acetonitrile solution of **2** resulted in the formation of zinc(II)-included hemicryptophane **3** in 86% yield.

Slow diffusion of diethyl ether in an acetonitrile solution of **3** resulted in crystals suitable for X-ray crystal structure analysis. The X-ray crystal structure of **3** is shown in Figure 3. The zinc(II) center is coordinated to the N_4 core of the tren cap and to the acetate anion. The zinc(II)-included hemicryptophane **3** has three 23-membered entrances into the cavity. The acetate anion is embedded in the cavity. The Zn−N average distance for the trigonal base of the pyramid is 2.217 Å, and the tertiary N atom capping the system is more

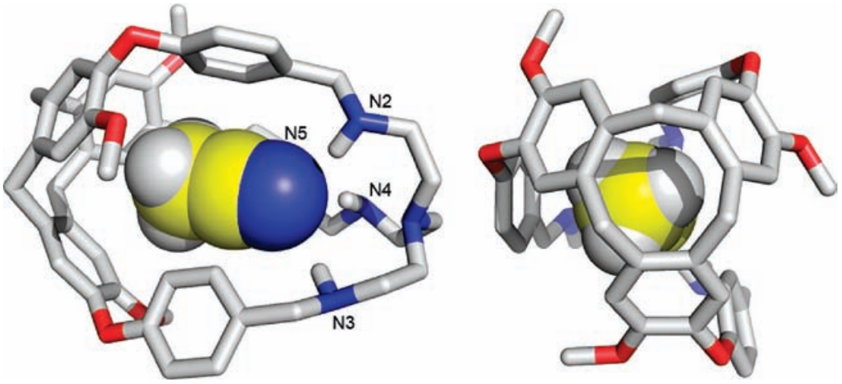


Figure 1. Crystal structures of $\mathbf{2}\cdot CH_3CN$ (left, side view; right, top view). The location of the hydrogen atoms of the amino groups and the acetonitrile molecule was calculated. Other hydrogen atoms and solvents of crystallization were omitted for clarity. Selected bond lengths (Å): N(2)−N(5), 3.455(2); N(3)−N(5), 3.787; N(4)−N(5), 3.296(2).

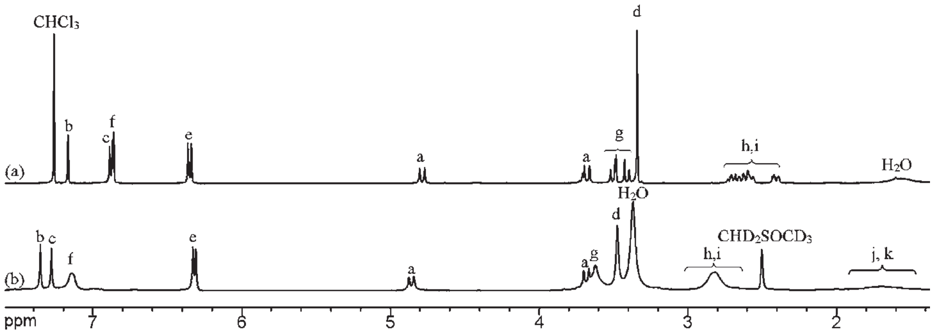


Figure 2. ^1H NMR spectra (400 MHz, 295 K). (a) **2** in $CDCl_3$. (b) **3** in DMSO-d_6.

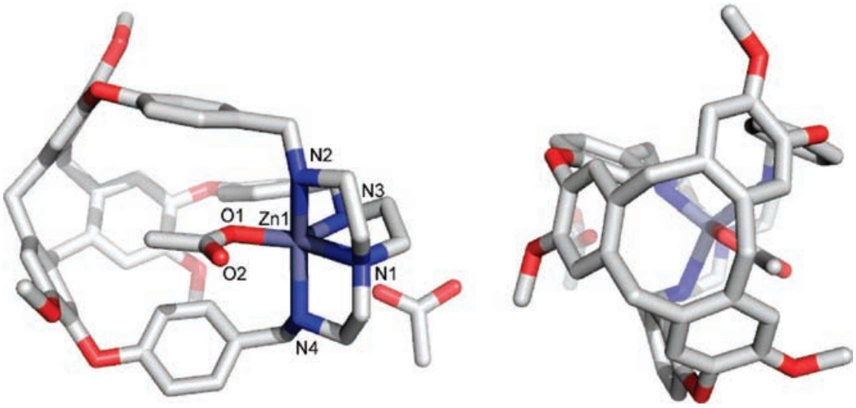


Figure 3. Crystal structures of **3** (left, side view; right, top view). All hydrogen atoms and solvents of crystallization were omitted for clarity. Selected bond lengths (Å) and angles (deg): Zn(1)−N(1), 2.150(4); Zn(1)−N(2), 2.292(3); Zn(1)−N(3), 2.102(3); Zn(1)−N(4), 2.258(3); Zn(1)−O(1), 1.957(3); N(1)−Zn(1)−N(2), 79.21(15); N(1)−Zn(1)−N(3), 87.13(16); N(1)−Zn(1)−N(4), 80.35(15).

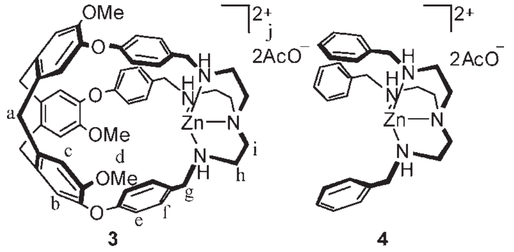
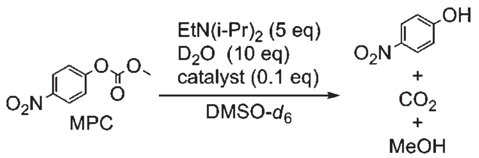


Figure 4. Structures of a zinc(II)-included hemicryptophane **3** and zinc(II) tris[2-(benzylamino)ethyl]amine complex **4**.

Scheme 2. Hydrolysis of MPC



loosely bound to the metal ion [$d(\mathrm{Zn}_{(1)}-\mathrm{N}_{(1)}= 2.150$ Å] than the acetate anion [$d(\mathrm{Zn}_{(1)}-\mathrm{O}_{(1)}) = 1.957$ Å]. The zinc(II)-included hemicryptophane **3** was characterized in solution as well (Figure 4). The profile is remarkably simple in DMSO solution, attesting to a C_3-symmetrical conformation. The peaks of two acetate anions are indistinguishable in the ^{1}H NMR spectrum at 295 K. This result indicates that zinc(II)-included hemicryptophane **3** contains the zinc(II) ion in the cavity in solution as well as in the solid state.

Kinetic studies of the MPC hydrolysis were performed (Scheme 2). The reactions were carried out in DMSO-d_6 with an excess amount of EtN(i-Pr)$_2$ and D_2O and 10 mol % of the zinc(II) catalyst and were monitored by ^{1}H NMR at 295K. The reaction was found to be first-order in MPC, and the observed rate constants (k_{obs}) are summarized in Table 1. Carbonate hydrolysis without a catalyst and with potassium acetate were slow under these conditions (entries 1 and 2). The reaction rates were slightly increased by the presence of zinc(II) acetate or zinc(II) tris[2-(benzylamino)ethyl]amine complex **4** (entries 3 and 4). It is noteworthy that the reaction rate of **3** was higher than that of **4**. This result indicates that the cage structure of a CTV moiety definitely enhanced the catalytic activity. The host−guest complex of **3** and MPC was not detected by NMR spectroscopy at 295 K, probably because the methyl carbonate moiety in MPC is smaller than the entrance of the cavity.

Table 1. Kinetic Data of the Hydrolysis of **MPC**[a]

entry	catalyst	$k_{obs}(10^{-3}\ h^{-1})$	k_{obs}/k_{uncat}
1	none	0.3	1
2	AcOK	0.5	1.7
3	Zn(OAc)$_2$	13	43
4	**4**	16	53
5	**3**	35	117

[a] Conditions: 85 μM MPC, 5.0 equiv of EtN(i-Pr)$_2$, 10 equiv of D_2O, and 0.1 equiv of catalyst in DMSO-d_6 at 295 K.

We have demonstrated facile synthesis and characterization of a hemicryptophane **2** having rigid phenyl spacers and its zinc complex **3**. Kinetic studies of the MPC hydrolysis were performed. A direct comparison between the zinc(II)-included hemicryptophane **3** and the model complex **4**, which lacks a cavity, demonstrated that the cage structure enhanced the catalytic activity.

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Supporting Information Available: Synthetic details, X-ray crystal data, and kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.