ORGANIC LETTERS

2004
Vol. 6, No. 2
241−243

Differential and Substrate-Selective Reactivity of Calix[4]arene Derivatives with Cyclenyl-Zn(II) Modifications at the Upper Rim

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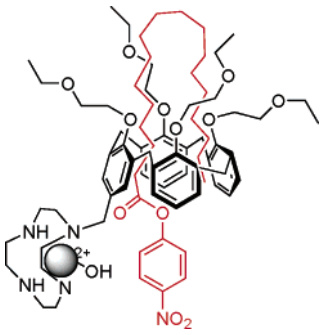
Received October 23, 2003

ABSTRACT



Novel "cone conformation" calix[4]arene derivatives, carrying either one or two cyclen (1,4,7,10-tetra-azacyclododecane) moieties at the upper rim, have been synthesized. The hydrolytic activities of the Zn(II) complexes of these calixarenes were studied. A surprising behavior was observed with *p*-nitrophenylstearate; whereas the bis-cyclenyl-2Zn(II) complex showed negligible hydrolytic activity over the background, the mononuclear complex showed a significant 400-fold rate increase at pH 8.5.

Although producing a functional model (mimic) for most of the enzymes remains extremely challenging, the active site of a metalloenzyme features a catalytically active metal center, the activity of which can be replicated in much simpler abiotic systems. In fact, even simple hydrated metal ions, if made persistent in aqueous solutions, can be reasonably active toward many substrates.[1] Thus, the reductionist approach where the enzyme is essentially treated as a "receptor" with a nearby reactive functional groups is more likely to succeed with the metalloenzymes. Hydrolytic metalloenzymes have been mimicked in a number of supramolecular systems. Most of the earlier work in enzyme mimics utilized cyclodextrins as the selective binding unit. Cyclodextrins have moderate affinities for aromatic substrates in aqueous solutions, and thus appropriate derivatives lead to satisfactory enzymes models.[2] Calixarenes and especially calix[4]arene have attracted attention, as the regioselective modification of calixarenes[3] is more straightforward and the conformational flexibility can be adjusted as desired with a unique potential for allosteric modulation. There are recent examples[4] of calixarene-based metalloenzyme mimics that hydrolyze activated phosphate substrates in mixed aqueous solvents.

As active metal center, one is not limited to nature's choices. High charge-to-size ratio cations such as Co(III),[5]

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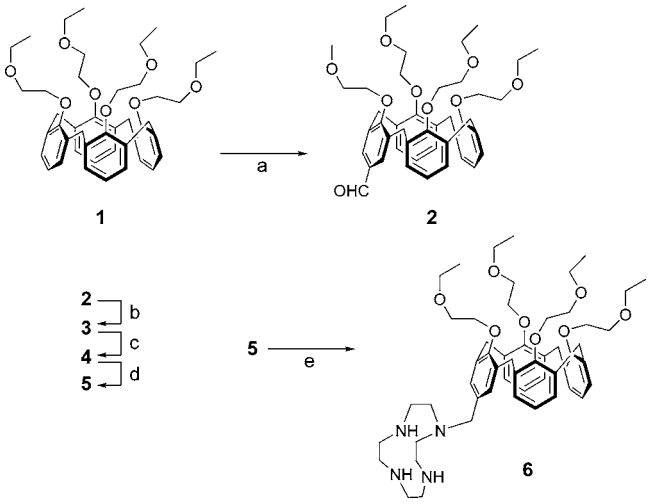
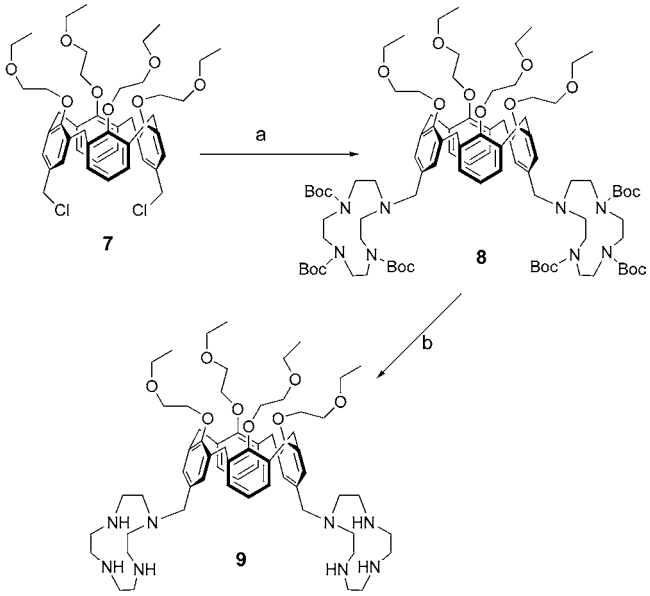
10.1021/ol0360694 CCC: $27.50
Published on Web 12/18/2003

Scheme 1. Synthesis of Monocyclen Derivative of Calix[4]arene[a]



[a] Reagents and conditions: (a) CH_3OCHCl_2, $SnCl_4$, $CHCl_3$, −10 °C, 1 h (50%); (b) $NaBH_4$, EtOH, rt, 3 h (72%); (c) $SOCl_2$, CH_2Cl_2, rt, 24 h (78%); (d) tri-*t*-Boc-cyclen, toluene, DIEA, Δ, 48 h (40%); (e) TFA/CH_2Cl_2, rt, 1 h (67%).

Scheme 2. Synthesis of Dicyclen Derivative[a]



[a] Reagents and conditions: (a) tri-*t*-Boc-cyclen, toluene, DIEA, Δ, 48 h (22%); (b) TFA/CH_2Cl_2, rt, 1 h (49%).

Ce(IV),[6] and Zr(IV)[7] have been demonstrated to have remarkable hydrolytic efficiencies. However, neutral pH instability and product inhibition seem to be major problems in these cases, if true enzymelike catalytic behavior is sought. Thus, our choice has been substitution-labile Zn(II) cation as the metal center with its flexible coordination geometry. The ligand we have focused on is 1,4,7,10-tetra-azacyclododecane (cyclen). Earlier work established its utility as a strong chelator of Zn(II), with the fifth coordination position almost invariably being water in aqueous solutions.[8] Moreover, the Zn(II)-cyclen motif has been utilized successfully in a number of model systems.[9] Thus, we set out to synthesize zinc(II) complexes of calixarene derivatives **6** and **9** in order to test cooperative action of two Zn(II) centers. The synthesis of the target molecules are shown in Schemes 1 and 2.

Calix[4]arene **7** was synthesized as described by Arduini[10] et al. Compound **4** was also synthesized in analogy to the same procedure. Tris-(*t*-boc)-protected cyclen[11] was then reacted with the chloromethyl compounds in NMP, and the products were purified by silica gel column chromatography. In the final steps of both syntheses, protecting groups were removed by DCM/TFA treatment at room temperature. Both compounds were isolated and characterized in analytically pure forms (see Supporting Information).

The cone conformation of calixarenes was ensured by ethoxyethyl substitution at the lower rim at an earlier stage in the synthesis, and that conformation is carried to the final product. The metal complexes of the ligands were prepared in situ by mixing with Zn(II) in the form of the perchlorate. Hydrolysis reactions were carried out in a solvent system comprising buffer-DMSO mixtures. A series of reactions at different pH values (buffer component) with different substrates (Figure 1) were carried out. The pH range of 7.0−8.5 studied; at higher pH values some precipitation of zinc(II) was apparent. Modest rate accelerations were obtained

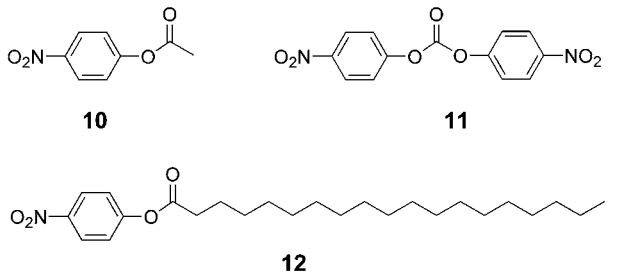


Figure 1. Activated ester substrates used this work.

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Table 1. Rate Accelerations (k_{cat}/k_{uncat}) Obtained Using Different Substrates at pH 8.5 under Pseudo-First-Order Conditions[a]

catalyst	*p*-NPA (**10**)	bis-*p*-NPC (**11**)	*p*-NPS (**12**)
6-Zn^{2+}	8.0	9.1	400
9-$2Zn^{2+}$	2.5	9.6	3.8

[a] The rates of the reactions were determined spectrophotometrically, by following the change in absorbance at 400 nm (*p*-nitrophenolate ion). The hydrolysis reactions for substrates **10** and **11** were carried out at 25 °C in a solvent mixture of 50% buffer/50% DMSO. The mixed solvent system contained 0.48 mM catalyst, 38 mM TRIS buffer, 38 μM substrate, and 0.48 mM Zn^{2+} for reactions catalyzed by **6** or 0.96 mM Zn^{2+} for reactions catalyzed by **9**. The rate constants for the uncatalyzed reactions (k_{uncat}) were determined in buffer/DMSO solutions of the substrates and are as follows: *p*-NPA (**10**), 1.0×10^{-5} s^{-1}; bis-*p*-NPC (**11**), 1.2×10^{-3} s^{-1}; *p*-NPS (**12**), 8.0×10^{-6} s^{-1}.

with bis-*p*-nitrophenyl carbonate and *p*-nitrophenylacetate as substrates and with no significant difference among the binuclear and mononuclear complexes (Table 1). With *p*-nitrophenylstearate, the binuclear complex did not show any better performance, but the mononuclear complex at pH 8.5 resulted in a 400-fold rate increase over that of the uncatalyzed reaction at the same pH.

Although the results seem to be surprising and counter-intuitive (negative-cooperativity between the metal centers?) at first, they can be better interpreted when one focuses on one of the fundamental requirements for efficient catalysis: productive binding. It appears that cyclen, especially the cyclenyl-Zinc(II) complex, is a nonflexible bulky substituent. It seems to block the entry of the aromatic groups into the calixarene cavity. This steric blocking is more effective in the zinc complex of the binucleating ligand **9**. This explains the low rate acceleration factors observed for the two substrates, **10** and **11**. A similar situation takes place with stearate and **9**-$2Zn^{2+}$. In these reactions, catalysis is likely to take place without substrate insertion into the calixarene cavity, at the periphery near the lower rim. However, only in the mononucleating ligand-Zn^{2+} complex can the long alkyl chain of **12** squeeze into the calixarene cavity to form a productive complex. Michaelis−Menten analysis of the pseudo-first-order hydrolysis data yields a K_m value of 0.028 mM for this substrate. This value is in the expected range for strong calixarene-binding substrates in similar solvent systems.[4b] The difference in binding affinities is reflected in the pseudo-first-order rate constants. Our results, while demonstrating the limits of calixarene functionalization for effective catalysis, also illustrate the versatility of the calixarene framework for catalyzing the reactions of structurally diverse substrates.

Acknowledgment. We thank METU-BAP and Turkish Academy of Sciences (TUBA) for grants supporting this research.

Supporting Information Available: Experimental procedures and characterization of compounds **2**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0360694

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