CONTAINER MOLECULES AS CATALYSTS IN ORGANIC CHEMISTRY

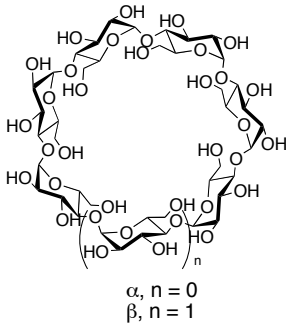
Reported by Ronald A. Smaldone February 21, 2005

INTRODUCTION

Since Linus Pauling first postulated that enzymes preferentially bind the transition state to catalyze reactions,[1] chemists have been inspired by the efficiency and selectivity of enzymatic catalysis. The molecular recognition properties of synthetic container molecules have generated interest since the first step of enzymatic catalysis is the recognition of a substrate through binding. In the case of synthetic container molecules, this binding places the substrate in close proximity to a reactive group on the host, or another bound substrate, thereby increasing the effective molarity[2] of the reaction rather than directly binding the transition state. Designing synthetic supramolecules with catalytic activity has proved a difficult endeavor;[3] however, it has yielded some important insights into enzyme catalysis. This report will highlight examples of strategies taken to develop container molecule-based catalysts using different structural motifs, including cyclodextrins, capsule and cavitand molecules, and coordination complexes and how, despite the incorporation of some of Nature's principles, they have yet to achieve the catalytic efficiency of enzymes.

CATALYTIC CYCLODEXTRINS

Cyclodextrins were discovered by Villiers in 1891,[4] and since that time their molecular recognition properties have been extensively studied.[5] To date, cyclodextrin has been used to catalyze a number of reactions; however, only a few key examples will be discussed in detail.[6,7] The use of cyclodextrin non-catalytically to influence product geometry or reaction pathway has also been extensively studied, but will not be covered.[8]



α, n = 0
β, n = 1

Figure 1. α (**1**) and β (**2**) cyclodextrin

The first reported example of cyclodextrin catalysis was the regioselective chlorination of anisole by hypochlorous acid.[9,10] In the absence of **1**, the chlorination of anisole results in a mixture of ortho and para isomers. Addition of □ however, increased the preference for chlorination of the para site. Kinetic studies determined that when the anisole was bound in the cavity of **1**, the ortho position was nearly inert to chlorination, but the rate of para chlorination was enhanced by 5.3 fold. A plausible explanation for the enhanced regioselectivity is that the anisole bound inside the cavity, blocks the ortho position,

leaving only the para site exposed (Figure 2). Additionally, the kinetic order of hypochlorous acid changed from second order to first order upon addition of α-cyclodextrin. It was proposed that the enhanced rate of chlorination at the para site as well as the change in dependence on hypochlorous acid arose through transfer of the chlorine atom of hypochlorous acid to a hydroxyl group on the cyclodextrin rim.[11] To reach the maximum observed para:ortho ratio of 96:4 however, nearly 19 equivalents of the catalyst were necessary.

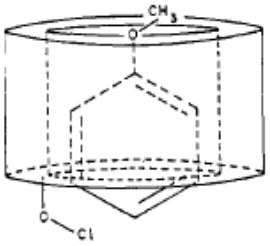


Figure 2. Proposed reactive complex for anisole chlorination

The scope of cyclodextrin catalysis was broadened through the addition of functional groups to the edge of the structure. The enzyme ribonuclease A employs the imidazole rings of two histidine amino acids to hydrolyze RNA through a bifunctional mechanism. A synthetic bifunctional mimic of this enzyme was created to catalyze the ring opening hydrolysis of a cyclic phosphate (Figure 3) by the addition of two imidazole groups onto the secondary face (smaller opening) of **2.**[12,13] It was originally hypothesized that the ideal placement of the imidazole groups would be at opposing ends of the cyclodextrin **5**. This modified cyclodextrin catalyzed the ring opening, but through a different mechanism than the natural enzyme (Scheme 1). With the imidazole groups in adjacent positions on cyclodextrin **6**, the proximity of the protonated imidazole to the oxyanion of the phosphate group allowed for the biomimetic mechanism to occur. The increased activity of **6** was confirmed through comparison of its pH-rate profile to that of **5**. The reaction rate of hydrolysis using **6** was only 230 times smaller than ribonuclease A;[14] however, **3** is a more reactive substrate than a typical RNA nucleotide. Breslow proposes that the reaction rate discrepancies could have arisen from the lack of other stabilizing forces on the enzyme mimic. For example, the ammonium group on lysine-141 of ribonuclease A is believed to stabilize the negative charge on the substrate throughout the reaction. The tight binding of **3** by β-cyclodextrin also is believed to have a detrimental effect on the rate by inhibiting the substrate's ability to adopt an ideal geometry for each step of the reaction.

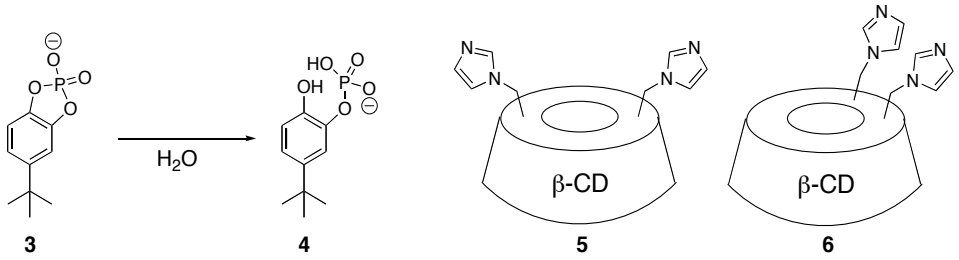
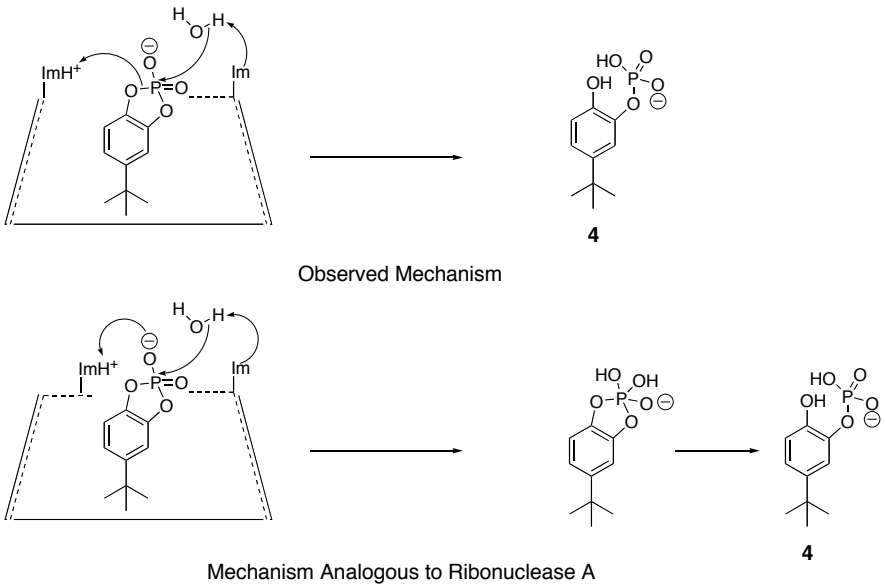


Figure 3. Desired ring opening hydrolyisis reaction and cartoon representation of modified cyclodextrin based ribonuclease mimic

Scheme 1



The cytochrome P450 superfamily of enzymes perform selective hydroxylations of substrates through the use of an iron heme porphyrin. Recently, Breslow and co-workers designed and synthesized oxidation catalyst **7** which incorporated four β-cyclodextrin rings with a manganese porphyrin to mimic the action of cytochrome P450,[15,16] and was capable of up to 650 turnovers (Figure 4).[17] The cyclodextrin rings were able to bind to hydrophobic groups on the substrate and position it over the manganese active site to allow for selective oxidation to occur. This enzyme mimic oxidized several different substrates, by either hydroxylation or epoxidation, with a stoichiometric oxidant. Of the reported examples, the most impressive was the site-selective hydroxylation of a steroid derivative. The steroid androstane-3,17-diol **8** bearing hydrophobic *tert*-butylphenyl groups, was oxidized both regio and enantioselectively by catalyst **7** at the 6-position to give **9** using stoichiometric amounts of iodosobenzene (Scheme 2). No other oxidation products were observed despite the presence of more reactive sites on the steroid.

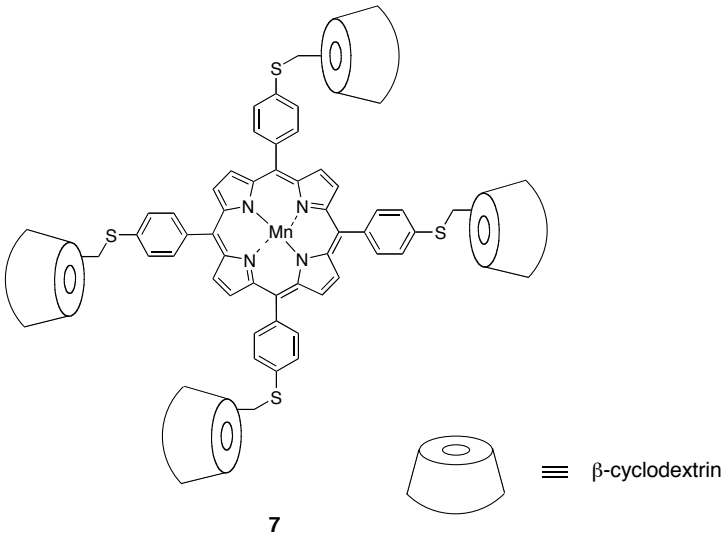


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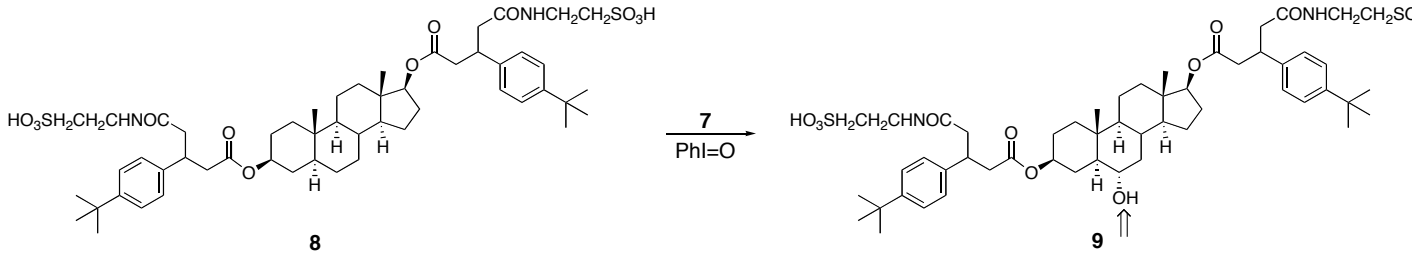
Figure 4. Cytochrome P450 mimic

Scheme 2



8 **9**

CAPSULE AND CAVITAND MOLECULES

Cavitands have also been used as catalysts. Resorcinarene-based cavitand molecules are bowl-shaped structures that have been modified with functional groups around their edges to catalyze various reactions including alkylation, aminolysis and hydrolysis (Figure 5).[18,19,20] Another approach to catalysis involves the use of structures with a well-defined cavity capable of encapsulating guest molecules. Rebek and co-workers have devised a dimeric capsule (**10**) they refer to as a "molecular softball" that self-assembles in organic solvents and is capable of binding organic molecules within its hydrophobic interior (Figure 6). It also has been shown to catalyze a Diels-Alder reaction.[21, 22]

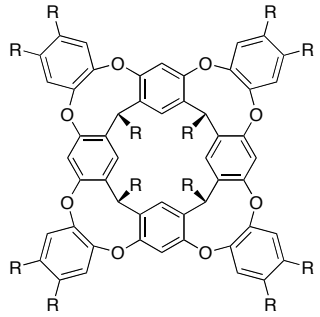
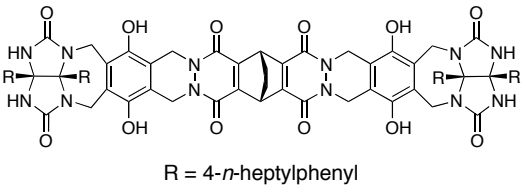
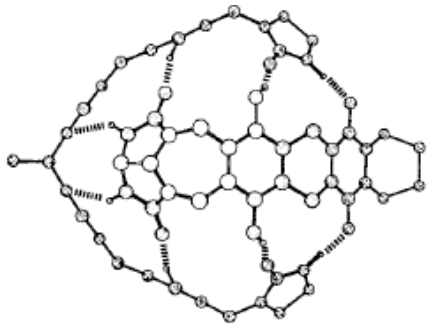


Figure 5. Resorcinarene-based cavitand. R-groups are varied depending on the desired function.



10a



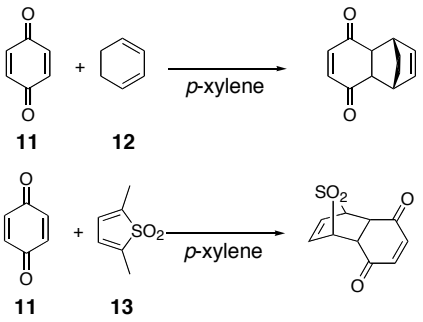
10b

Figure 6. Molecular "softball" in both monomeric (**10a**) and dimeric (**10b**) forms

Rebek and co-workers achieved both rate enhancement as well as turnover using dimeric capsule **10b** as a catalyst in a Diels-Alder reaction. The cycloaddition between *p*-benzoquinone **11** and cyclohexadiene **12** was chosen as a model reaction due to its uncatalyzed half-life of 460 days at room

temperature (4 mM concentration) because it would show very little background (Scheme 3). Cavitand **10b**, accelerated the reaction by 170 fold; however, the product inhibited turnover since it strongly binds to **10b**. Rebek and co-workers addressed this problem, by replacing **12** with 2,5-dimethylthiophene dioxide (**13**) as the diene component (Scheme 3). It was initially thought upon heating, the reaction would evolve SO_2, changing the product geometry enough to decrease its binding affinity and allow turnover to occur.[23] Turnover was observed using this set of substrates; however the Diels-Alder adduct did not extrude SO_2. In this case, the encapsulation of two molecules of dieneophile **11** inside capsule **10** was a sufficient driving force to expel one molecule of Diels-Alder adduct despite the unfavorable decrease in entropy. Although the rate enhancement of the Diels-Alder reaction was significantly diminished using **13** (10 fold) when compared to **12** (170 fold), the goal of catalytic turnover was achieved. The lack of functionality on the interior of the cavity prevents the catalyst from influencing the relative orientation of the diene and the dieneophile to one another. Thus the proper geometry necessary for the Diels-Alder reaction to occur must be found through random motion of the reactants.

Scheme 3



Houk and co-workers performed a detailed, kinetic analysis of Rebek's softball-catalyzed Diels-Alder reaction.[24] This analysis determined that the poor catalytic activity of the softball, as well as that of some other synthetic non-covalent catalysts, could be attributed to the catalyst's preferential binding of the substrates as opposed to the transition state of the reaction, evidenced by the poor catalytic turnover observed in the reaction. This is antithetical to enzyme catalysis and will likely be a focal point for improvement in future synthetic catalysts.

Resorcinarene-based molecular cavitands have also been employed as the binding component of a catalytic functional group. The selective hydrolysis and aminolysis of *p*-nitrophenyl choline carbonate (PNPCC) was achieved through both edge functionalization and cation-π interaction[25] of the trimethlyammonium moiety of the substrate. Through the addition of a zinc (II) salen complex onto the cavitand (**14**), the hydrolysis of PNPCC was observed with both rate acceleration and catalytic turnover. Using 20 mol % of **14**, the hydrolysis was accelerated by 12 fold. The reaction catalyzed by **14** also occurred five times faster than a reaction using the corresponding control zinc salen complex that did not contain the cavitand. Use of a stoichiometric amount of the cavitand resulted in a modest rate enhancement of 53 fold.

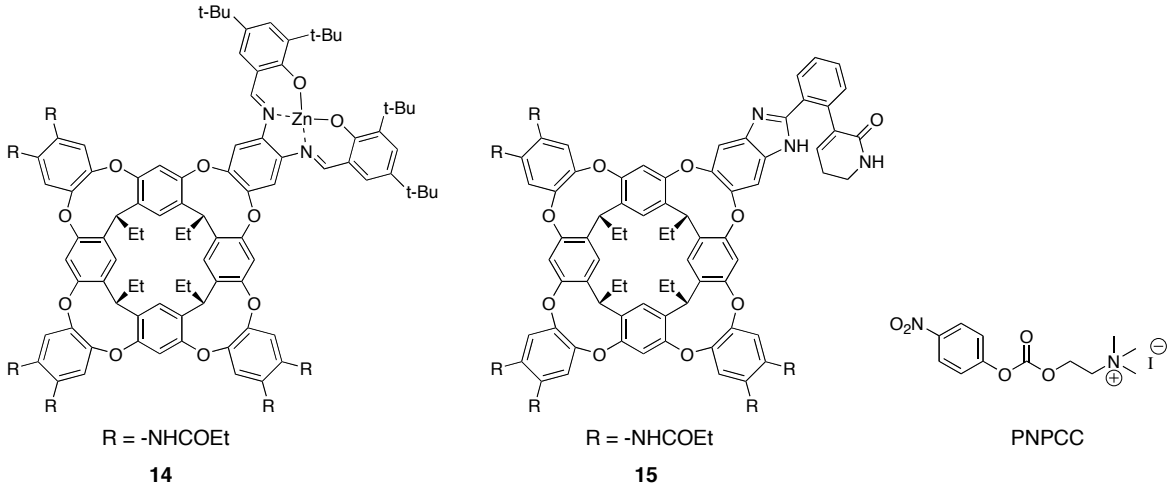


Figure 7. Resorcinarene-based cavitand catalysts and acetylcholine derivative PNPCC

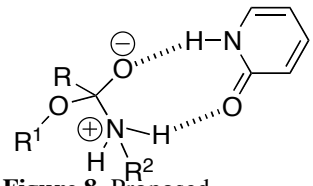


Figure 8. Proposed stabilization of tetrahedral intermediate of aminolysis by 2-pyridone moiety

When a 2-pyridone group was attached to the edge of the cavitand **15**, the aminolysis rate of PNPCC was accelerated by presumably binding to the tetrahedral intermediate.[26] The 2-pyridone group is capable of forming one hydrogen bond with the carbonate reactant, and two with the tetrahedral intermediate (Figure 8). This is relevant to catalysis since it resembles the action of natural enzymes in that forward progress of the reaction is encouraged. As with **14**, rate enhancement was observed with a catalytic amount of **15**. The activity however, was extremely modest. The aminolysis of PNPCC with propylamine was only accelerated two fold compared to the background reaction when 10 mol % of catalyst was used. The poor catalyst could be attributed to a weakly hydrogen bonded complex in the proposed tetrahedral intermediate. This hypothesis is supported by the observation that the use of 2- pyridone in excess as a control only resulted in a 10% enhancement in the rate, indicating that it is a poor catalyst itself.

METAL COORDINATION CAGE CAPSULES

Self-assembled coordination cages, more specifically the M_4L_6 type, are another class of supramolecular catalysts.[27] These molecules are shaped like a polygonal tetrahedron, and are hollow on the inside. Each edge of the tetrahedron is a bis-bidentate ligand, held in place by a coordinating metal.

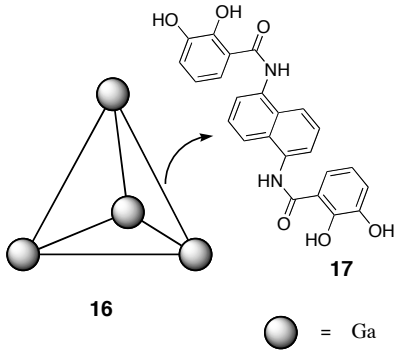
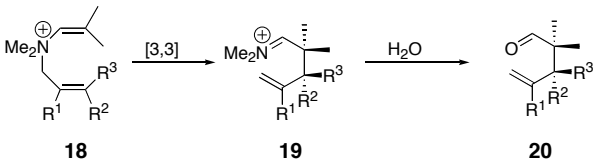


Figure 9. Illustration of coordination cage catalyst

Raymond and Bergman recently developed an M_4L_6 complex **16** that catalyzes a [3,3] aza-Cope rearrangement (Scheme 4).[28,29] The complex uses bis-bidentate ligand

17 and gallium (III) to form a cage with an overall -12 charge (Figure 9). This negative charge allows for the binding of cationic guests into the cavity. Encapsulation of cationic substrate **18** inside cage **16** elicited a range of rate enhancements from 5-854 fold. It was observed that increasing the size of R^2 results in the greatest acceleration. The authors hypothesized that increasing the size at this position forces the molecule into the reactive conformation when encapsulated by **16**. Since **16** does not make any covalent bonds with the substrate, the rate acceleration comes solely from the pre-organization of **18** into its six-membered reactive conformation. This conclusion was confirmed by the measurement of the $\Delta H^{\neq}$ and $\Delta S^{\neq}$. For **18** when R^2 = Et, the unencapsulated reaction had activation parameters of $\Delta H^{\neq}$ = 23.1 kcal/mol and $\Delta S^{\neq}$ = -8 e.u. In the presence of **16** however, the values change to $\Delta H^{\neq}$ = 23.0 kcal/mol and $\Delta S^{\neq}$ = +2 e.u., representing a significant change in entropy of activation.

Scheme 4



18 **19** **20**

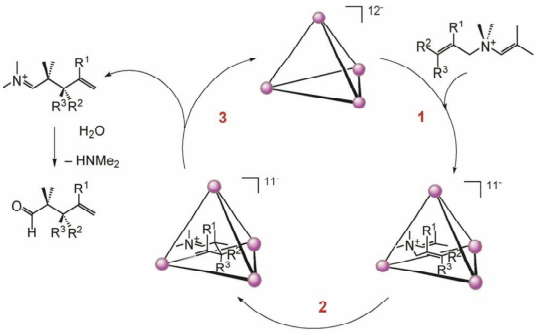


Figure 10. Proposed catalytic cycle for rearrangement

Catalytic turnover was also possible with catalyst **16**. After rearrangement, the iminium guest **19** can exit the cavity and be hydrolyzed to the corresponding aldehyde **20**. Once the uncharged aldehyde forms, it is no longer a suitable guest for **16**, preventing product inhibition from occurring. The proposed catalytic cycle is illustrated in Figure 10.

DESIGN STRATEGIES FOR FUTURE RESEARCH

Several hypotheses on the limitations of these catalysts have been proposed. Container molecules are often designed with structural rigidity in mind; however, some flexibility may be necessary to accommodate the motion of reactants throughout the course of a reaction.[3] The molecular recognition properties of containers must also be expanded to include the transition state geometry of a reaction.[24] Preferential binding of substrate ground states leave catalysts susceptible to product inhibition as well as poor catalytic activity. In addition to transition state binding, it has been proposed that strong direction of substrates into a favorable orientation for reaction could be the result of such dramatic activity in enzymes.[30] The investigation of container molecules as templates of substrate orientation may be an avenue for future study.

CONCLUSION

Catalysis of organic reactions by container molecules has steadily progressed since the first reported examples nearly 40 years ago. However, the ultimate goal of matching the activity and selectivity of enzymes has not yet been reached. These catalysts are plagued by a wide range of problems including product inhibition, poor catalytic activity, and inability to distinguish the transition state of a reaction from the ground state. The results presented show that although there have been advances in the versatility of container molecule based catalysts, these molecules fall dramatically short of the power exhibited in enzymatic catalysis.

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