Biomimetic Reactions Catalyzed by Cyclodextrins and Their Derivatives

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Introduction

Cyclodextrins are extremely attractive components of artificial enzymes and other biomimetic materials. They are readily available, they bind hydrophobic substrates into their cavities in water solution, and they have two rims of hydroxyl groups (Figure 1) that can either react with substrates themselves or be used to attach other catalytic and functional groups. Of course, they have disadvantages. For one, unless they are extensively modified their complexes with substrates can be rather flexible and, perhaps, with unpredictable preferred geometry. They are also unstable to strong acid. Thus for some purposes such synthetic cavity species as calixerenes[1] or synthetic macrocycles[2−4] may have advantages. However, one of the chief advantages of cyclodextrins is highly attractive—they are readily available, so it is possible to avoid the synthesis of a binding group and go directly to studies of what can be achieved with their use. Afterward, the lessons learned may be applied to other systems with advantage.

This review will cover all the literature on reactions in which cyclodextrins bind substrates and then either catalyze their reactions or mimic a step in an enzymatic catalytic sequence. However, it will not describe work in which cyclodextrins simply change the course of a reaction without playing an obvious catalytic role involving substrate binding. For example, there are systems in which the main function of the cyclodextrin seems to be to complex a metal ion and keep it in solution.[5−11] There are other studies in which binding into a cyclodextrin simply alters the selectivity of attack by an external reagent in some way[12−24] or causes solubilization to facilitate phase transfer catalysis.[12,25,26] Presumably such other areas are described elsewhere in this volume.

While much work on artificial enzymes using cyclodextrins has been done in the author's laboratory, and will be described, every effort is made to describe all the relevant work in the field. Several reviews of this subject already exist and should be consulted for further information.[2,27−70] The readily

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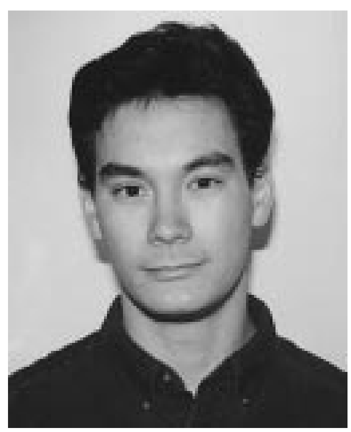

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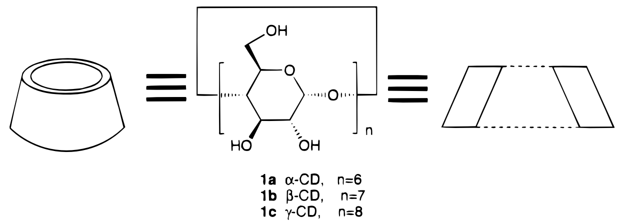

Figure 1. Various representations of the cyclodextrins.

available cyclodextrins (Figure 1), produced enzymatically, are cyclohexaamylose (α-cyclodextrin, **1a**), cycloheptaamylose (*β*-cyclodextrin, **1b**), and cyclooctaamylose (*γ*-cyclodextrin, **1c**). In this review they will be abbreviated as α-CD, *β*-CD, and *γ*-CD, respectively.

Simple Cyclodextrins

Interest in cyclodextrins as components of enzyme models was first stimulated with the publication of the book *Einschlussverbindungen* (Inclusion Compounds).[56] In early work, it was shown that cyclodextrin as its oxyanion **2** could react with some bound pyrophosphates[71,72] or carboxylic esters.[73,74] In later work, it was shown that esters bound into the cyclodextrin cavity could acylate the hydroxyl groups on the cyclodextrin rim with some geometric preferences (Figure 2).[75−78] For example, *m*-nitrophenyl acetate (**3**) transferred its acetyl group to a secondary side hydroxyl of *β*-CD about 100 times as rapidly as it hydrolyzed under the same conditions in the absence of *β*-CD.[76] This is of course not a catalytic reaction but is related to the first step of serine proteases in which an acyl group is transferred to a serine hydroxyl in the first enzymatic step. Some computer modeling of this process has been reported.[79]

The rate acceleration, interesting as it was, seemed small as a model of what one could expect in an enzyme−substrate complex. Molecular model building[80] indicated that the reaction of *m*-nitrophenyl acetate with a cyclodextrin hydroxyl had a problem: the well-bound substrate was pulled partly out of the cavity when it added the *β*-CD hydroxyl group to form the tetrahedral intermediate. Thus other substrates were examined where this would not occur, and the cavity was also modified.[81] Some very large accelerations of cyclodextrin acylations were seen. A series of *p*-nitrophenyl ferroceneacrylate esters (e.g. **4a**) bound well into the cavity, and acylated a *β*-CD hydroxyl group with as much as a 5 900 000-fold acceleration relative to substrate hydrolysis under the same conditions (Figure 3).[82] Molecular model

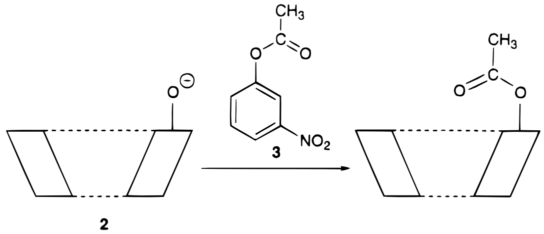

Figure 2. Substrate **3** binding into the cavity of the cyclodextrin. Anion **2** is then acetylated.[75−78]

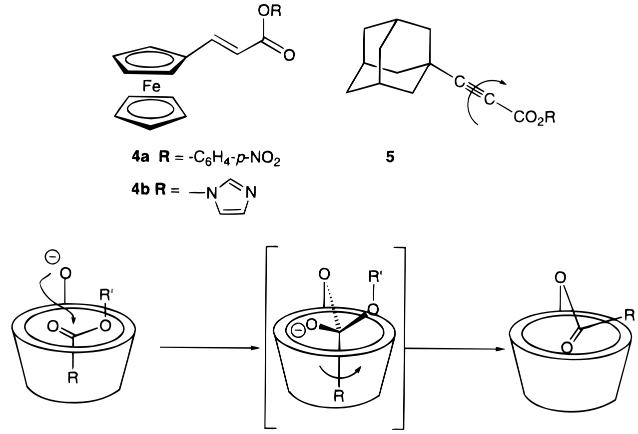

Figure 3. Substrate **4a** acylating *β*-CD with a very large acceleration. With the poorer leaving group in **4b** the rate acceleration is slower because of the preferred geometry of the product.[82] In substrate **5** the free rotation solves this geometric problem.[86]

building[80] and physical studies[83] indicated that the tetrahedral intermediate, and transition states that resemble it, are bound almost as deeply as was the substrate. This very large acceleration seems a better model for the effect of proximity, as in an enzyme−substrate complex.

The substrates examined were rather rigid,[84] which helps accelerate the reaction by holding the ester group precisely over the *β*-CD secondary side hydroxyl group. However, for **4b** with imidazole, a poorer leaving group than the *p*-nitrophenoxide ion in **4a**, the acceleration was smaller,[82] and when the phenyl esters carried less activating groups than *p*-nitro, the accelerations were also smaller.[85] This reflected a fundamental problem with rigid esters—the oxygen atom of the nucleophilic hydroxyl group must attack perpendicular to the ester group plane but end up as part of the new ester, in the ester plane (Figure 3).[86] The rotation needed to convert the tetrahedral intermediate to the acylated cyclodextrin was blocked by excessive rigidity. When a degree of freedom was introduced in substrate **5** that permitted this rotation, the problem was solved.[86] This calls attention to the need to consider not only the geometry of the substrate−cyclodextrin complex, and not only the geometric change on proceeding to the transition state or related intermediate, but also the geometric changes needed for the entire reaction. Otherwise a late step may become rate determining.

Since this earliest work, a number of esters have been examined that bind into the cyclodextrin cavity and then react with a cyclodextrin hydroxyl group. These include derivatives of adamantane[87,88] and of various other hydrophobic species,[89−105] in some cases with enantioselectivity.[91−93,98,106−109] The structural selectivity of such hydrolyses has been used for the analysis of mixtures.[110] Particularly interesting are some cases (e.g. **6** in Figure 4) in which two cyclodextrins cooperate in the cleavage of an ester, with both the acyl and the alkyl group bound into a cyclodextrin.[94,97,111,112] Building on this, some cyclodextrin dimers such as **7** also cleave esters that can bind into both cyclodextrin cavities.[113]

Cleavages of bound esters have been performed using cyclodextrin polymers.[114−116] Some activated

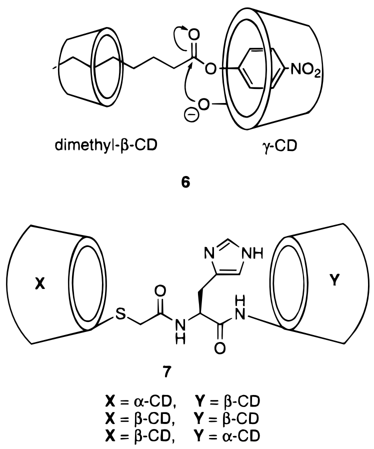

Figure 4. Ester cleavage when the substrate is bound into two cyclodextrin rings, either separate (**6**)[112] or as a dimer (**7**).[113]

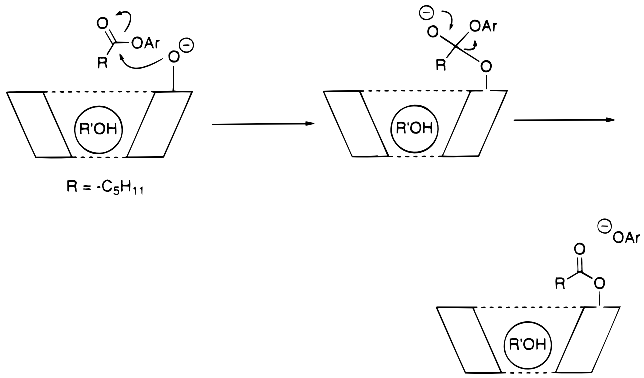

Figure 5. Geometric problem with substrates that acylate cyclodextrins but form products that are more poorly bound into the cyclodextrin cavity can be partially solved with additional binding species.[125−127]

amides have also been cleaved[117−119] as well as a carbonate ester.[120] Addition of an additional ligand can promote the formation of a ternary complex—substrate, ligand, cyclodextrin—sometimes with improved reaction rate.[99,121−124]

An interesting series of studies involved ester cleavage in the presence of a cyclodextrin and an additional species such as an alcohol that can bind into the cyclodextrin cavity (Figure 5).[125−127] The additional bound ligand weakens substrate binding but strengthens the binding of the transition state for the acylation reaction. Studies from the same laboratory examined the effect of dimethyl sulfoxide on the cleavage of esters by α-CD and β-CD[128] and the kinetics of ester cleavage by γ-CD and a modified β-CD.[23] Aspirin is cleaved by α-CD and β-CD.[129]

Cleavage of phosphate esters by nucleophilic attack of a cyclodextrin oxyanion, to form a phosphorylated cyclodextrin, has also been studied.[130] Simple β-CD accelerates the cleavage of bis(p-nitrophenyl) phosphate by almost 2 orders of magnitude,[131] and some fluorophosphate nerve gases acylate cyclodextrins rapidly.[132−134] Polymers containing cyclodextrins have also been examined for phosphate cleavages.[135]

Simple cyclodextrins can act as catalysts and not just reactants. The earliest example was the chlorination of anisole catalyzed by α-CD (Figure 6).[136−138] Mechanistic studies showed that the anisole binds

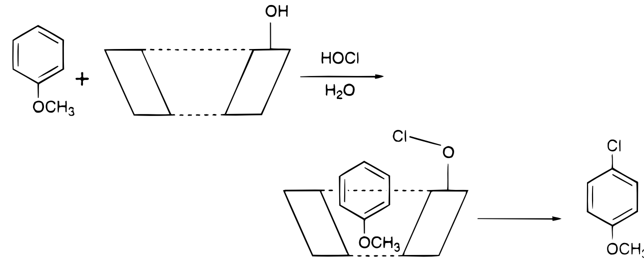

Figure 6. Anisole is selectively chlorinated in the para position when it binds into α-CD and the chlorine is delivered from a cyclodextrin hydroxyl group.[136−138]

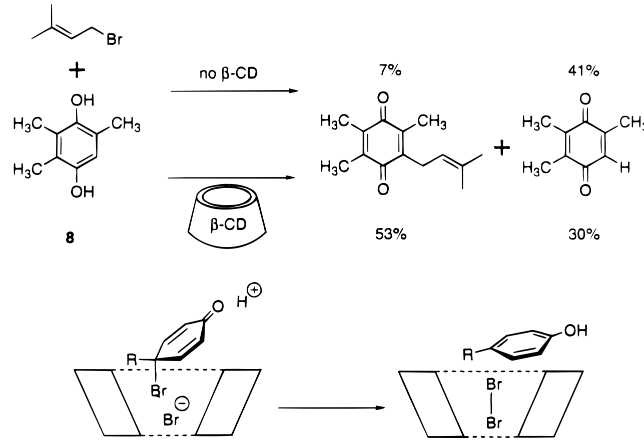

Figure 7. Cyclodextrin binding promotes the alkylation of substrate **8**[140] and the debromination of a bromocyclohexadienone.[148]

into the cavity and that the hypochlorous acid reagent transfers a chlorine atom to a cyclodextrin hydroxyl group, which is then relayed to the anisole. The result was that a chlorination that randomly attacks both the ortho and para positions of anisole without the cyclodextrin became completely specific for para chlorination in the complex and with an increased rate and changed kinetics, but the specificity was changed with other substrates that bind differently. It was also shown that binding in the cyclodextrin protected the substrate from reagents that could not be catalytically delivered by the cyclodextrin hydroxyl groups.

Interestingly, an enzyme that catalyzes the chlorination of anisole is not selective but forms both the o- and p-chloroanisole. The enzyme functions chiefly to convert chloride ion into HOCl.[139] This indicated that artificial enzymes could have advantages over natural enzymes that were not optimized for chemical processes of interest.

Some related reactions have been reported subsequently. For example, an interesting alkylation of a hydroquinone is promoted modestly by binding into a cyclodextrin (Figure 7).[140] Also, there are many examples in which the point of reaction of an external reagent is influenced when a substrate binds into a cyclodextrin cavity[12−24,141−144] but so far with no evidence that the cyclodextrin catalyzes the process as it does in the HOCl chlorinations. The bromination of anisole and some phenols shows at most a slight acceleration by α-CD and is often retarded because tribromide ion binds into the cyclodextrin cavity.[145,146] However, α-CD catalyzes the debromi-

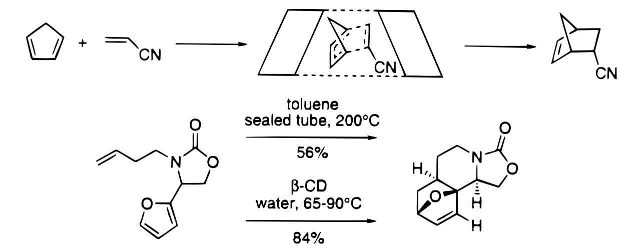

Figure 8. Bimolecular[150] or intramolecular[153] Diels–Alder reactions can be promoted by cyclodextrin binding.

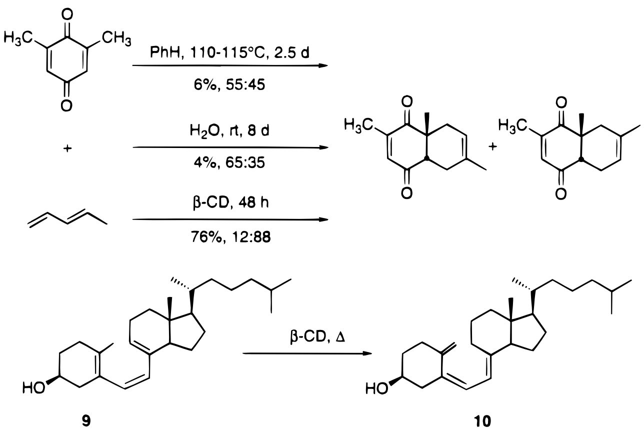

Figure 9. Cyclodextrin binding can promote the regioselectivity of a Diels–Alder reaction[161] and the thermal isomerization of **9** to **10**.[163]

nation of some bromocyclohexadienones (the proposed mechanism is shown in Figure 7), the reverse of one of the steps in the bromination of aromatic rings.[147,148] α-CD also modestly catalyzes the reaction of formic acid with bromine.[149]

The Diels–Alder reaction is an example of an important chemical process for which enzyme catalysts are not available. Models indicated that β-CD could bind cyclopentadiene into its cavity along with a slim dienophile such as acrylonitrile (Figure 8 shows this and an intramolecular case), and for this reason the addition reaction was accelerated by β-CD.[150–153] The process has been computer modeled.[154] By contrast, the smaller α-CD inhibited the reaction by binding only the cyclopentadiene, and β-CD was also an inhibitor for Diels–Alder reactions with larger components. Interestingly, this study showed that water itself also strongly promoted the Diels–Alder reactions, because of the hydrophobic effect. This observation has led to a major interest in water solvent effects on organic reactions.

An important feature of Diels–Alder reactions in cyclodextrins,[150] and for that matter in water solution itself,[155–160] is an increase in the selectivity for products produced from the most compact transition states. It has also been seen that the regioselectivity of a Diels–Alder reaction which has a choice of reaction positions can be enhanced when the reaction occurs inside a cyclodextrin cavity (Figure 9).[161] Related to this, some photocycloaddition reactions can take place in a cyclodextrin cavity, with altered selectivity.[162] Also, the thermal isomerization of previtamin D3 **9** to vitamin D3 **10** is catalyzed by complexation into β-CD.[163] The cis–trans thermal isomerizations of azobenzenes are inhibited by binding into β-CD,[164] as is an internal charge-transfer reaction that requires geometric twisting of the substrate.[165]

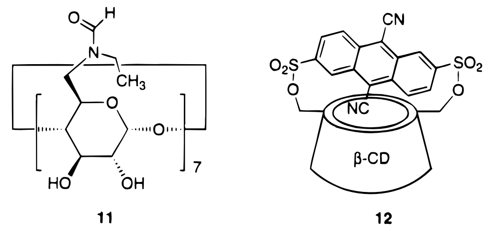

Figure 10. Flexible capping of the cyclodextrin cavity in **11**[81,166] and rigid capping in **12**.[167]

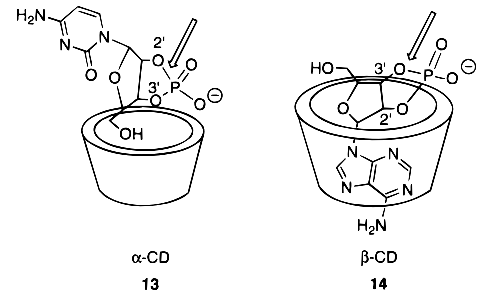

Figure 11. Cyclodextrin binding promotes the selective cleavage of cyclic phosphate groups in **13** and **14**.[172,176]

The cavity of a cyclodextrin can be modified, e.g. by capping it. Flexible capping in **11** has been described,[81,166] as well as capping by a rigid floor in **12** (Figure 10).[167–171] Somewhat better acylation rates by bound substrates relative to reactions with unmodified cyclodextrins were observed in a few cases.[81,166]

An interesting series of studies examined the hydrolysis of nucleoside 2′,3′-cyclic phosphates in the presence of cyclodextrins.[172–176] The hydrolysis was selective for cleavage of the bond at either the 2′ (cf. **13**) or the 3′ position (cf. **14**), depending on the cyclodextrin and substrate used (Figure 11). Polyribonucleotides are also cleaved.[176]

Enolizations are catalyzed,[177,178] as well as aldol condensations[179,180] and decarboxylations.[181] Some reports have appeared dealing with free radical reactions within cyclodextrin complexes.[182,183]

Cyclodextrins Carrying Catalytic or Reactive Groups

For the best enzyme models, one must combine the cyclodextrin binding ability with functional groups more effective than the hydroxyls of the simple cyclodextrins. Thus a decision has to be made whether to use the secondary or the primary face of the cyclodextrin for such attachment. Many substrates can bind with their reactive sections on either side of the cyclodextrin, so either face can be used to attach catalytic functions. For example, the first compound **15** referred to as an “artificial enzyme” in the literature was prepared by attaching a metal-binding group to the cyclodextrin secondary face (Figure 12).[184] The copper ion catalyzed the hydrolysis of substrates that could bind into the cyclodextrin

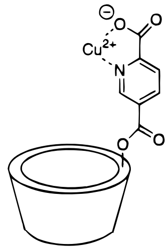

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Figure 12. The first compound, **15**, described as an artificial enzyme.[184]

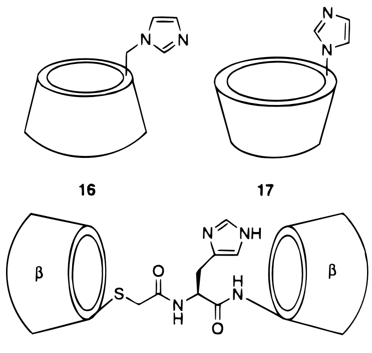

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Figure 13. Imidazole rings can be attached to the primary face of a cyclodextrin in **16**[195] or to the secondary face in **17**.[196,197]

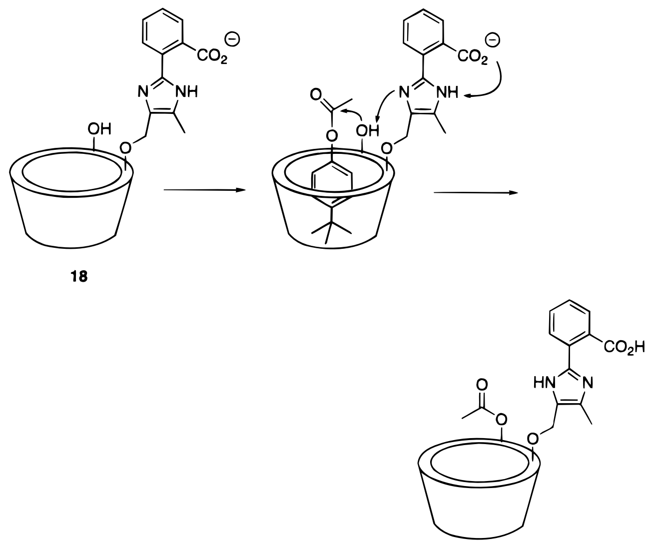
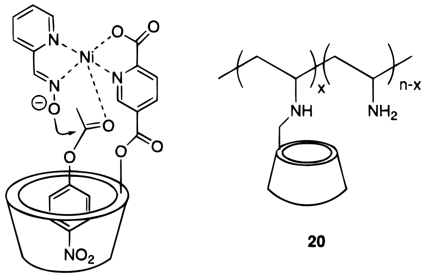


Figure 14. A compound, **18**, designed to mimic the catalytic triad in chymotrypsin.[199−203] Other work[204,205] showed that the indicated mechanism does not occur.



20

19

Figure 15. Metal complex **19** cleaving bound esters with catalytic turnover.[34] Functionalized CD-polymer−metal complexes **20** have also been shown to catalyze ester hydrolysis.[216]

cavity but that were not metal ligands and not normally hydrolyzed by copper complexes without the cyclodextrin binding component. In other work described later, it was shown that catalysts with a metal ion bound to the cyclodextrin primary face could also be effective.

In a direct study of the question of facial selectivity, catalysts were prepared with a phosphate group attached to either the primary or the secondary face of β-CD, and it was found that both were effective.[185] Thus for many purposes either cyclodextrin face is suitable for catalytic group attachment,[186−188] but there are also examples of substrates that preferentially bind into the secondary face of β-CD, which is somewhat more open.[189−192] With such substrates, the facial placement of the catalytic group will matter.[193,194]

Attachment of a simple catalytic group to a cyclodextrin can afford interesting enzyme mimics. For example, an imidazole ring has been attached to a primary (in **16**)[195] or secondary (in **17**) [196,197] face and into the linker of a cyclodextrin dimer **7** (Figure 13).[198] In **18**, an imidazole carries a benzoate group in a position to imitate the function of the aspartate ion in the catalytic triad characteristic of serine proteases such as chymotrypsin (Figure 14).[199−203]

It was claimed that compound **18** acted to hydrolyze a bound substrate using the imidazole as a base with the carboxylate hydrogen bonded to it, as in the enzymes for which it was a putative mimic. However, the data reported did not support this claim but instead made it clear that the additional functional groups played no useful role. For instance, the reaction rate was said to be first order in hydroxide ion at pH's above neutrality, not consistent with catalysis by the attached imidazole group. The reaction was simply the normal reaction of unsubstituted cyclodextrin with the bound substrate and actually at a slower rate than for cyclodextrin without the added functionality. Independent work in two other laboratories showed that the imidazole and carboxylate in **18** play no catalytic role but instead impede the reaction.[204,205] Thus there is as yet no true mimic of the serine protease enzymes.[117,124,206,207]

Cyclodextrins carrying nucleophilic groups for more effective ester cleavage, albeit not with catalysis, have been widely studied.[93,193,194,200,208−215] A quite effective true hydrolytic catalyst (**19**) was constructed using a nickel oximate ligand bound to a cyclodextrin carrying another metal binding group (Figure 15).[34] The oxime oxyanion is acylated, and the product then hydrolyzes to regenerate the catalyst. Also, a polymer with β-CD linked to poly(ethylenimine) can bind metal ions to the nitrogen atoms and catalyze the hydrolysis of bound esters.[216] A poly(vinylamine) **20** linked to cyclodextrins acts as a nucleophile toward *p*-nitrophenyl acetate.[217]

Glyoxalase enzymes use thiols to isomerize α-keto aldehydes to hydroxy acids. A mimic **21** carrying an aminoethanethiol group on the primary face of β-CD binds 2-naphthylglyoxal and catalyzes its rearrangement with a modest advantage over an analogue without the cyclodextrin (Figure 16).[218] In a system

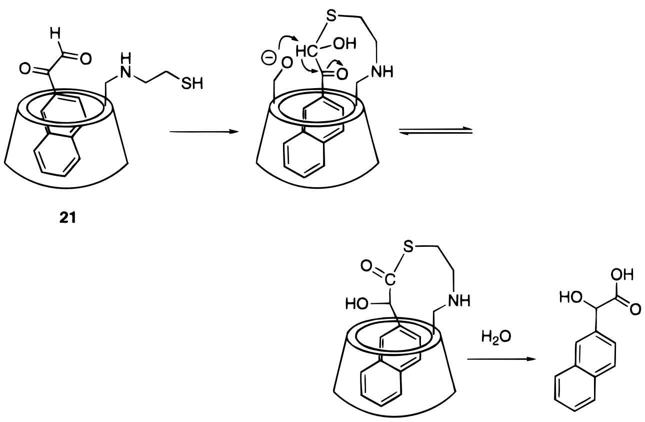


Figure 16. A mimic of glyoxalase enzymes.[218]

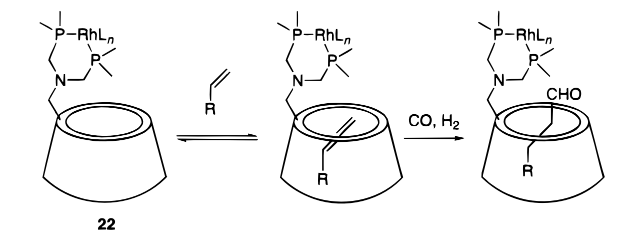


Figure 17. Rhodium complex **22** catalyzing the reductive carbonylation of a bound olefin.[219]

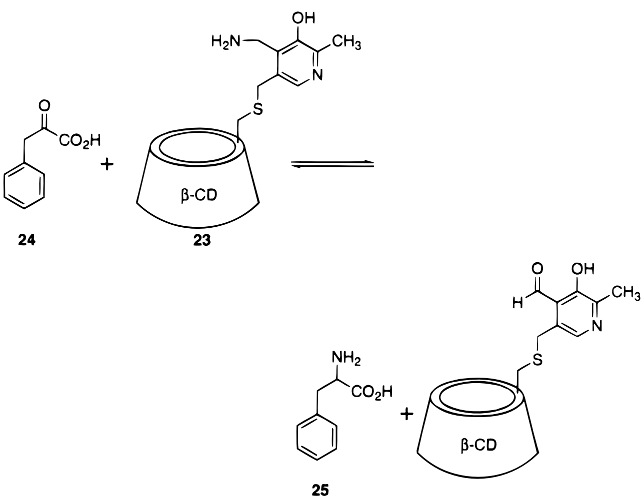


Figure 18. The first artificial enzyme, **23**, that combined a coenzyme with a cyclodextrin binding group.[224] It selectively converts **24** to **25**.

22 that imitates the style of an enzymatic reaction, if not its details, a bis(phosphine) has been attached to the primary face of β-CD and used to bind rhodium and catalyze reactions of bound substrates (Figure 17).[219] Other systems with metal ligands attached to cyclodextrins have also been described.[220−223]

Enzymes frequently use coenzymes to perform catalytic functions not possible with normal amino acid side chains of the enzyme itself. Thus it is of interest to attach coenzymes to cyclodextrins, as mimics of the enzyme−coenzyme combination. The first example was a catalyst **23** in which pyridoxamine was linked to the primary face of β-CD through a sulfur atom.[224] Catalyst **23** was able to transform α-keto acids (**24**) to α-amino acids (**25**), as pyridoxamine itself does, but with selectivity (Figure 18). That is, phenylpyruvic acid was transaminated ca.

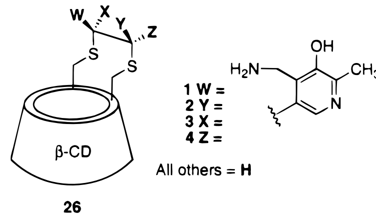


Figure 19. Four catalysts **26**(**1**−**4**) that mimic **23**, but with extra selectivity.[225]

100 times as rapidly as was pyruvic acid by **23**, while simple pyridoxamine shows no such selectivity. Compound **23** is selective because of binding of the phenyl group into the β-CD cavity. With the better binding (*p*-*tert*-butylphenyl)pyruvic acid, the selectivity relative to pyruvic acid exceeds 15 000.[225]

Another enzyme mimic was prepared with the pyridoxamine attached to the secondary face of β-CD.[226] Its properties were similar to those of the primary derivative. As another comparison, an artificial macrocyclic bonding species was used in place of the cyclodextrin.[227]

To fix pyridoxamine to the cyclodextrin with even better defined geometry, a set of four compounds **26-(1−4)** was made by reacting a pyridoxaminedithiol with β-CD-6A,6B-diiodide (Figure 19). As molecular models suggested, one pair of isomers **26(1)** and **26-(2)** with the pyridoxamine held over the β-CD cavity had a preference for p-substituted phenylpyruvic acids, while the other pair held the pyridoxamine to the side and preferred m-substituted phenylpyruvic acid substrates.[225]

Enzymes that synthesize amino acids by transamination do so with stereoselectivity. Thus in transamination by an artificial enzyme there has been much interest in learning how to direct the proton addition to a particular face of the developing amino acid. The earliest example **23** of such an enzyme mimic[224] afforded amino acids with some selectivity, because of the chirality of the cyclodextrin unit. However, more selectivity is expected if the proton is delivered by a chirally mounted basic group, as in the enzyme.

In a study of such transamination with a chirally mounted base, but not involving cyclodextrins, it was found that optically active amino acids could be produced with up to 98% selectivity.[228] However, less success has attended attempts to extend this to artificial enzymes based on cyclodextrins. A compound **27** carrying both a pyridoxamine and an ethylenediamine unit attached to β-CD on neighboring primary methylene groups was prepared and studied for its ability to form amino acids from keto acids with chiral selectivity (Figure 20). Although quite good selectivities were reported,[229] it has proven difficult to duplicate these findings. In some alternate approaches, optical induction has indeed been produced with related catalysts (**28**) but so far not in high 90% selectivities.[230]

Pyridoxal phosphate is the coenzyme for many processes involving amino acids, including the conversion of serine and indole to tryptophan. A compound **29** has been synthesized coupling pyridoxal to β-CD on its primary side. This artificial enzyme

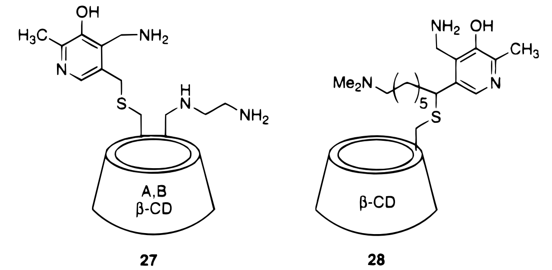


Figure 20. Two transaminase mimics, **27** and **28**, that produce amino acids with some optical selectivity.[229,230]

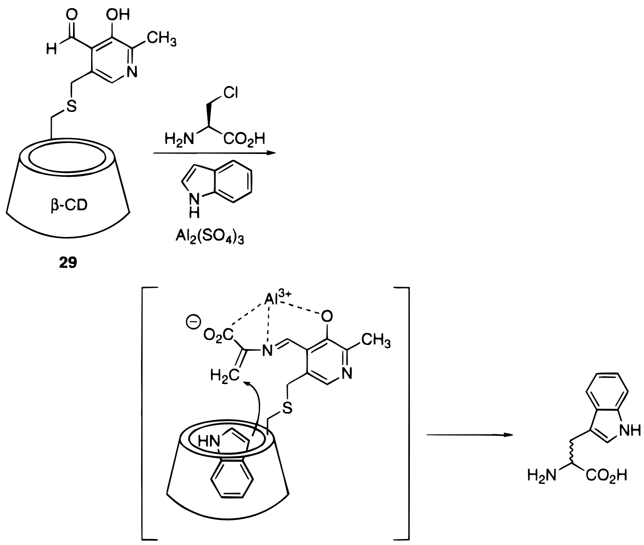


Figure 21. Catalyst **29** mimics tryptophan synthase.[231]

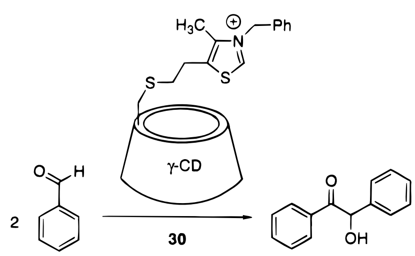


Figure 22. Compound **30** catalyzes the benzoin condensation by binding two benzaldehydes into the γ-CD cavity and coupling them with a thiazolium catalytic group.[240,241]

mimicked tryptophan synthase, by coupling a dehydroalanine intermediate formed on the pyridoxal unit to an indole held in the cyclodextrin ring (Figure 21).[231]

Thiamine pyrophosphate is the coenzyme for many important biochemical reactions that formally require the intermediacy of an acyl anion. This involves the addition of the thiazolium C-2 anion to the carbonyl group of the substrate,[232−239] which acts much as cyanide ion does in the benzoin condensation. Consistent with this, thiazolium salts will catalyze the benzoin condensation (Figure 22). Since γ-cyclodextrin has a cavity large enough to bind two phenyl rings simultaneously, an artificial enzyme **30** was synthesized with a thiazolium ring linked to γ-cyclodextrin.[240,241] It was the most effective catalyst known for benzoin condensation, apparently because it could bind two benzaldehydes and then link them with catalysis by the thiazolium group.

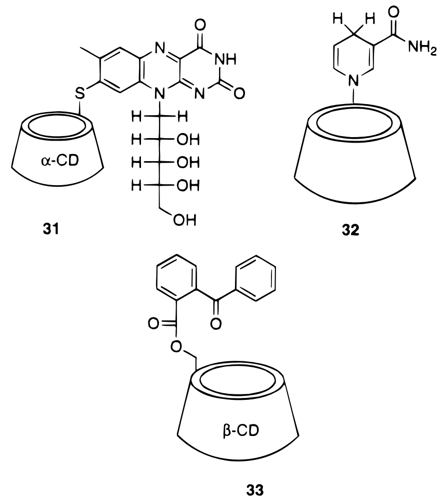


Figure 23. Cyclodextrins carrying coenzyme groups such as flavin (**31**)[242−244] and nicotinamide (**32**)[245−247] catalyze enzymelike reactions. The benzophenone group in **33** can transfer electrons to a bound substrate.[248]

Flavins are coenzymes for electron-transfer reactions. Several research groups have attached a flavin to a cyclodextrin (e.g. **31**), so as to promote electron transfers involving bound substrates (Figure 23). In one study,[242] a flavin was attached to α-CD and was found to show preferential electron transfers to nicotinamide derivatives that can bind into the cyclodextrin cavity. In another study, a flavin was attached to either the primary or the secondary rim of β-CD, and the oxidation of bound thiols was investigated.[243,244]

Nicotinamide is the functional component of some coenzymes that perform oxidation−reduction reactions, often involving hydride transfers. Dihydronicotinamide has been covalently linked to the primary carbon of both α-CD and β-CD, and the properties of the compounds **32** have been compared.[245−247] They reduce bound substrates with increased rates compared with reactions of unlinked dihydronicotinamide and substrate. When an electrophoric benzophenone is linked to β-CD, compound **33** promotes the electrochemical reduction of a bound substrate.[248] Apparently an electron is first added to the benzophenone system and from it into the bound substrate to induce reaction.

Coenzyme B-12 catalyzes some remarkable rearrangements, acting along with appropriate enzymes. Two studies have been done so far to try to make an enzyme mimic using cyclodextrin and vitamin B-12. In the first study,[249] B-12 was directly linked to a primary methylene group of β-CD by a carbon−cobalt bond in **34**. When the B-12 dissociated from the cyclodextrin, a cyclodextrin radical **35** was produced. This mimics the formation of a deoxyadenosyl radical in the enzymatic process, when the B-12 unit dissociates from the ribose linked to its cobalt atom. The cyclodextrinyl radical was able to abstract a phenyl selenide group from a substrate bound into the β-CD cavity in **35**, just as deoxyadenosine can abstract a hydrogen atom from a substrate bound to its enzyme (Figure 24). This is a necessary step in developing a mimic for the enzymes that use coenzyme B-12, but

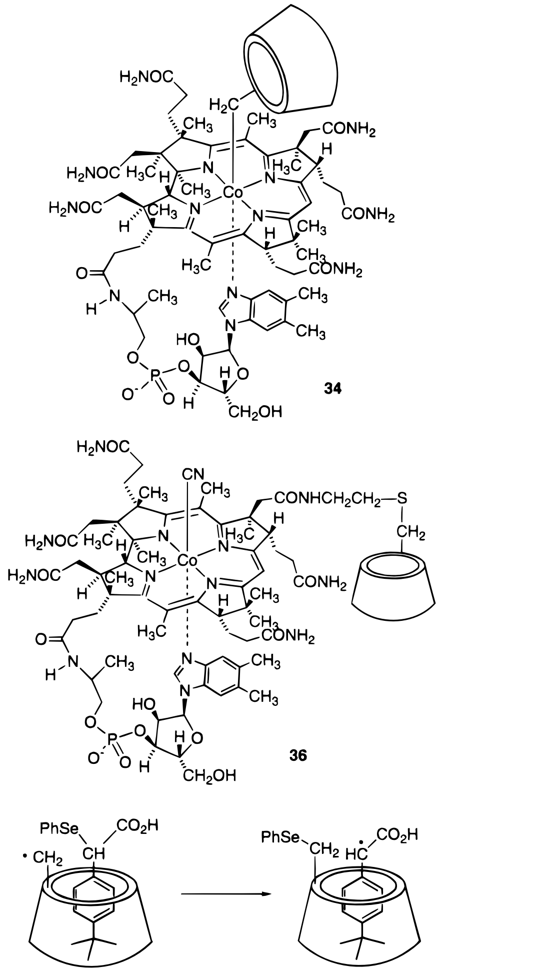


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Figure 24. Cyclodextrin **34** carrying vitamin B-12 mimics. In **35**, formed from **34**, the ability of coenzyme B-12 to perform group transfers.[249] In **36** the cyclodextrin adds some selectivity to such reactions.[250]

there is still much to do before a complete mimic is made.

In the second study,[250] a β-CD group was attached to a propionic acid side chain of vitamin B-12 in **36**. It was found that this species could catalyze some rearrangements related to those of the enzyme and with a preference for substrates that bind into the β-CD cavity.

Enzymes often use acid and base catalysts derived from their amino acid side chains, and it is common for them to use more than one such group in simultaneous bifunctional or multifunctional catalysis. Thus it is of interest to imitate this feature in artificial enzymes. For example, the enzyme ribonuclease A uses two imidazole groups, of histidines 12 and 119, as its principal catalytic groups in the hydrolysis of RNA. To mimic this enzyme, two imidazole rings were attached to the primary face of β-CD, by displacement on β-CD diiodides.[251−254]

By the use of appropriate bridging groups it is possible to make disulfonate esters of β-CD on neighboring glucose units (AB), on units one further apart (AC), or on units separated by two glucose residues (AD) (Figure 25).[225,255] These were converted to the related diiodides, and reaction with

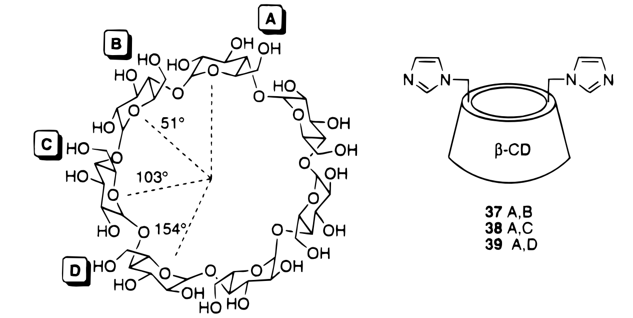


Figure 25. The AB (**37**), AC (**38**), and AD (**39**) isomers of a cyclodextrin carrying two imidazoles on the primary carbons.[225,255]

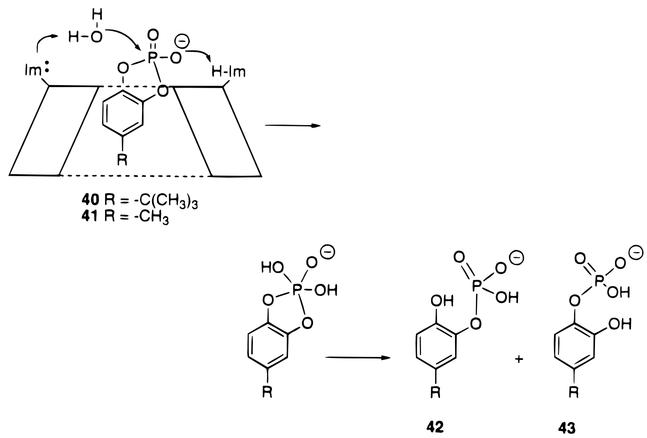
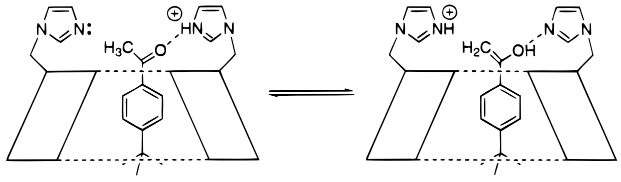


Figure 26. Cyclodextrin bis(imidazoles) catalyzing the hydrolysis of substrates **40** and **41**.[256] Loosely fitting complexes form both **42** and **43**, but a tight complex is selective for **42**.[258]

imidazole afforded catalysts **37**−**39**. All three of these enzyme mimics were able to catalyze the hydrolysis of a cyclic phosphate **40** that could bind well into the β-CD cavity, and all three showed a bell-shaped pH vs rate profile with a rate maximum near pH 6.2 (Figure 26). This is almost identical to the pH vs rate profile for the enzyme ribonuclease itself and indicates that one imidazole functions in its protonated form while the other is unprotonated. Isotope effect studies showed that the two catalytic groups were operating simultaneously.[256]

In the classical mechanism for the enzyme, the hydrolysis of the cyclic phosphate intermediate in RNA cleavage involves water delivery to the phosphorus atom by the unprotonated imidazole while the leaving group is protonated by the imidazolium ion. If the enzyme mimics used a similar mechanism, the AD isomer **39** would be the most active, since it has the best geometry for this mechanism. However, it was found that the best catalyst for the hydrolysis of the cyclic phosphate **40** was the AB isomer **37**. This indicated that the function of the imidazolium ion was to protonate the phosphate anionic oxygen, which it can reach better than in the other catalyst isomers. It has been argued that the enzyme itself uses a similar mechanism,[257] but there is no general agreement yet on this idea.

A study was made on the importance of a tight fit of substrate into the binding cavity for such enzyme model systems.[258] The substrates were either the *tert*-butyl derivative **40** or an analogue **41** with a



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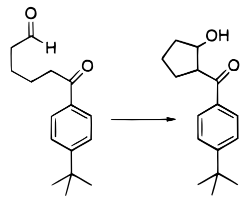

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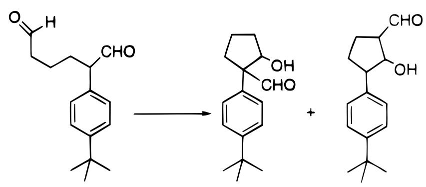

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Figure 27. Cyclodextrin bis(imidazoles) catalyzing the enolization of **44**[259] and the aldol condensation of **45** and **46**.[261,262]

methyl group instead. The catalysts were all AB diimidazoles, but using α, *β*, or *γ*-cyclodextrins. The strongest binding was seen with the *tert*-butylated substrate **40** into the *β*-CD derivative **37**, and this combination also gave the fastest rate of hydrolysis. It was also the most selective. The other catalyst–substrate combinations afforded mixtures of products **42** and **43**, but with the **37**, **40** combination only product **42** could be detected. To achieve optimum catalysis, it is important that there be no significant flexibility in the catalyst–substrate complex (except that needed to permit the reaction to occur).

With the availability of a set of cyclodextrin catalysts carrying two imidazoles in different geometries, it is possible to investigate other reactions that are catalyzed by simultaneous acid–base proton transfers. One process examined was the enolization of a bound ketone, *p*-*tert*-butylacetophenone (**44**), which binds well into *β*-CD (Figure 27).[259,260] The reaction showed a bell-shaped pH vs rate curve, indicating that both the imidazole and the imidazolium ion played a catalytic role. It was found that the best isomer for the enolization, monitored by deuterium exchange, was the AD isomer. This indicated what the preferred geometry is for proton abstraction from carbon, an important matter not easily determined without the geometric information furnished by these bifunctional catalysts. The same catalyst set has also been examined, and found effective, in two intramolecular aldol condensations involving keto aldehyde **45** and dialdehyde **46**.[261,262]

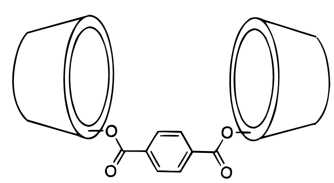
Synthetic approaches to cyclodextrins carrying two or three imidazoles on the C-3 secondary side positions have recently been reported[263,264] as well as a compound with cyclic L-His–L-His linked to the primary carbon of *β*-CD.[265] It will be interesting to see their catalytic abilities.

Amino- and polyaminocyclodextrins have significant catalytic properties. Cyclodextrin amines can catalyze or inhibit catechol autoxidation,[266] can act as catalysts for decarboxylation,[267] can catalyze deuterium exchange[268] or perform aldol condensations,[269,270] or can add metal binding and catalysis [271] or electrostatic binding[272,273] to the normal cyclodextrin properties.

Cyclodextrin Dimers and Tetramers

Cyclodextrins bind typical substrates in water with binding constants of ca. 10^4 M^{-1} or less. (A recent exception is lithocholic acid, whose binding constant to *β*-CD exceeds 10^6 M^{-1}.[190]) Thus it was of interest to make artificial enzymes that use two or more cyclodextrins to bind substrates well. It would be expected that a substrate that binds to both cyclodextrin cavities could have a binding constant exceeding 10^8 M^{-1}. Simple additivity of the binding free energies would lead to 10^8 M^{-1}, while the entropy advantage of the chelate effect should lead to an even larger binding constant than that.

The earliest study seems to be that of a cyclodextrin dimer **47** linked on the secondary face by a terephthalate group (Figure 28).[274] Several other dimers have been constructed in which two cyclodextrins are joined by various linkers.[214,275–284] In a systematic study, dimers made up of *β*-CD linked in various ways (**48**–**50**) were examined with substrates such as **51** that could put two good binding groups into the cyclodextrin cavities.[285] With such relatively rigid substrates carrying two *tert*-butylphenyl groups, binding constants exceeding 10^9 M^{-1} were observed.



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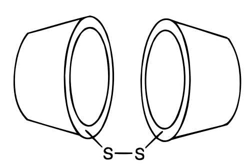

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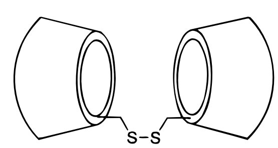

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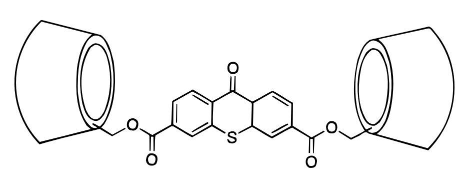

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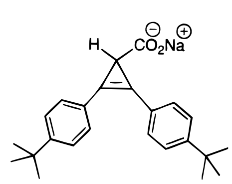


51

with **50**, $K_a = 7.0 \times 10^8$ M^{-1}

Figure 28. Cyclodextrin dimers **47**–**50** and a substrate **51** that is strongly bound by such dimers.[274,285]

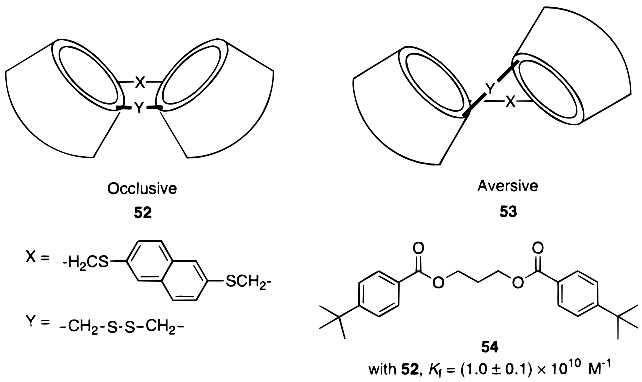


Figure 29. Occlusive isomer **52** of a doubly linked cyclodextrin dimer can bind appropriate substrates with very high affinities and shape selectivities.[286]

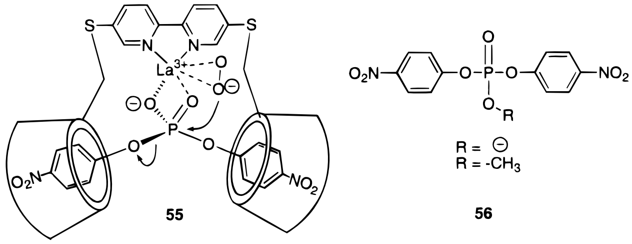


Figure 30. A cyclodextrin dimer **55** that can bind both ends of a substrate and hold it onto a catalytic metal ion is very effective at ester hydrolysis with turnover.[291−293]

The substrates were rigid, but the β-CD dimers had a single linker between them, so binding involved a loss of flexibility. Thus dimers **52** and **53** were made with two links attached to neighboring primary hydroxyls in β-CD (Figure 29).[286] With a flexible substrate **54** that could fit well, the binding constant to **52** was 10^{10} M^{-1}, and with a rigid substrate of the correct shape it exceeded 10^{11} M^{-1}, comparable to the binding constants of very strong antibodies. However, **53** did not show strong binding.

Heterodimers have also been made linking two different cyclodextrins[287,288] and even cyclodextrin tetramers.[289,290]

If a cyclodextrin dimer has a catalytic group in the linker, one might observe strong catalysis in complexes where a substrate functional group is held directly above the catalytic linker group. This has been observed. For example, the β-CD dimer **55** with a linker containing a bipyridyl group can form complexes with metal ions (Figure 30). These are very effective at hydrolyzing ester substrates (e.g. **56**) with two hydrophobic ends that can bind into the cyclodextrin cavities of the catalyst.[291−293] A cyclodextrin dimer carrying an imidazole unit attached to the linker has already been mentioned.[198]

One of the biggest challenges in the field of artificial enzymes is to imitate the ability of enzymes to perform selective reactions at particular points in a bound substrate. Enzymes can override the intrinsic reactivity of a substrate by such geometric control. For example, in the biosynthesis of cholesterol there are steps in which unactivated methyl groups are enzymatically oxidized in the presence of untouched olefinic groups. Although some substrates had been functionalized using such principles, the catalysts

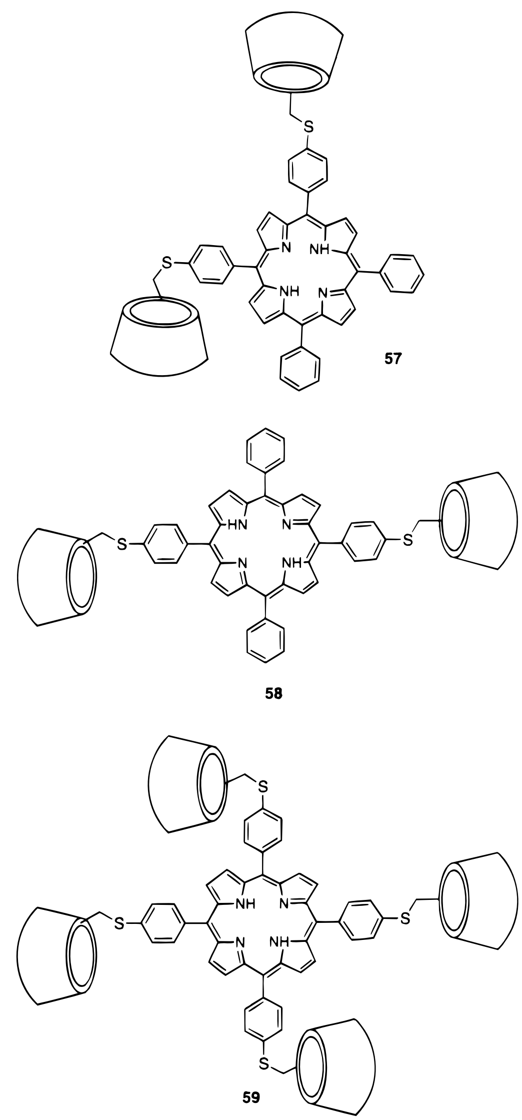


Figure 31. Porphyrins carrying attached cyclodextrin rings to bind substrates.[290]

were covalently attached to the substrates, so catalytic turnover was not achieved.[28,294−303]

To make a selective oxidation catalyst capable of turnover, metalloporphyrins were synthesized carrying two or four β-CD groups (Figure 31).[290] It was found that the Mn(III) complex of **59**, the porphyrin bearing four β-CD rings, could selectively catalyze the oxidation of olefinic substrates such as **60** that bind into two cyclodextrin rings to stretch the substrate across the porphyrin ring, with the substrate double bond directly above the porphyrin metal atom. This was also true when only two β-CD rings were present on opposite sides of the porphyrin, in **58**, but not when they were on adjacent positions in **57**. Reasonable catalytic turnover was observed.

In this reaction the metalloporphyrin accepts an oxygen atom from a simple reagent, such as iodosobenzene, and then transfers that oxygen to the bound substrate (Figure 32). After the product dissociates, a second substrate binds and the process repeats. This is fundamentally the same description as for enzymes of the class cytochrome P-450, which catalyze selective olefin oxidation as well.

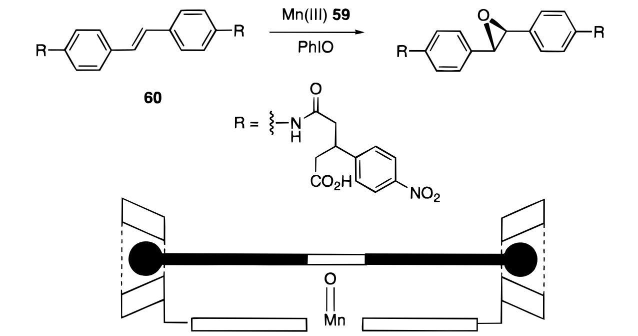


Figure 32. Metalloporphyrins derived from **58** and **59** catalyzing selective epoxidations of bound olefins.[290]

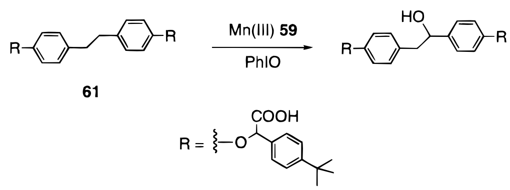
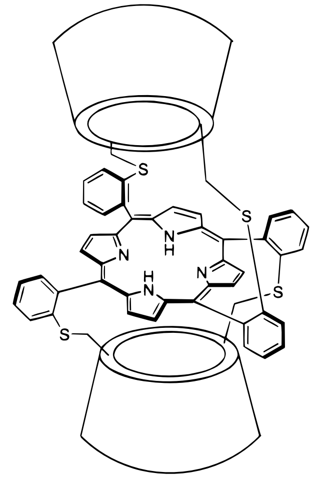


Figure 33. A metalloporphyrin derived from **59** catalyzing the hydroxylation of a benzylic carbon of **61** with 650 turnovers.[304−306]

Cytochrome P-450 enzymes also hydroxylate saturated carbon atoms, and it is of greater practical importance to imitate this process. Thus the same catalyst based on **59**, carrying a Mn(III), was examined with saturated substrates that could bind into two β-CD rings and stretch across the metalloporphyrin ring. It was found that the dihydrostilbene **61** was catalytically hydroxylated and with catalytic turnover of 650 (Figure 33).[304−306] More interesting was the result with a steroid substrate.

Androstanediol (**62**) was converted to the diester **63**—which has *tert*-butylphenyl binding groups, and water solubilizing functionality—and submitted to the action of iodosobenzene with catalysis by the Mn(III) complex of **59**. It was found that the process was completely selective for hydroxylation at a single carbon atom of the steroid, within the limits of detection (Figure 34). Carbon 6 of the steroid was hydroxylated with regio- and stereospecificity and with 3−5 turnovers before the catalyst was itself destroyed by oxidation.[304] Clearly such a catalytic system has great potential for performing useful oxidations, once the catalyst is made more stable and the geometry of the catalyst−substrate complex is adjusted so as to direct oxidations at will to otherwise inaccessible sites on the substrate.



64

Figure 35. Cyclodextrins locked onto the face of a metalloporphyrin, as the iron complex of **64**, catalyzing the epoxidation of cyclohexene.[307−310]

Binding of the two ends of the substrate is critical for these results. In both the olefin and the steroid oxidations, no product was formed under these conditions with substrates that did not carry the *tert*-butylphenyl binding groups. Furthermore, a steroid carrying only one such group was oxidized but without single-site selectivity.

A dimer **64** has also been prepared in which two cyclodextrins are held on an iron tetraarylporphyrin, one on each face (Figure 35).[307−310] It bound cyclohexene into the cyclodextrin cavity and catalyzed its oxidation more effectively than did a simple iron porphyrin lacking the cyclodextrin binding groups.

One of the most interesting examples of a cyclodextrin acting to mimic an enzyme is the observation that it facilitates the folding of a protein.[311] This mimics the role of chaperones, proteins that help guide the folding of other proteins.

Noncatalytic Biomimesis

A number of systems have been constructed to imitate biological functions other than enzymatic catalysis. For example, when a chromophoric material is bound into a cyclodextrin, it can undergo

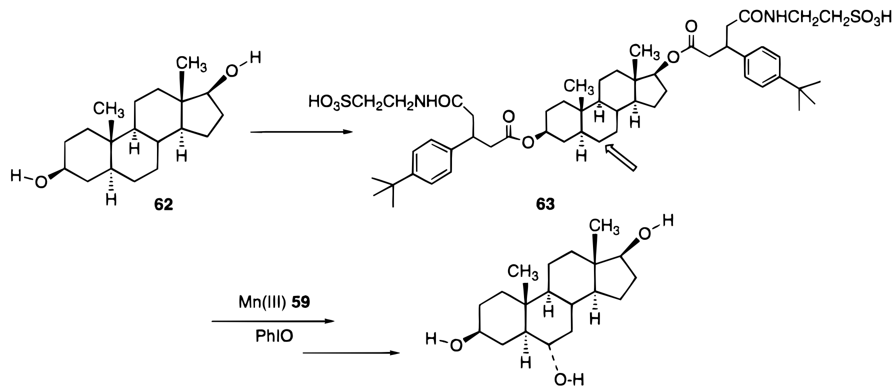


Figure 34. Steroid **62** is converted to diester **63**, which is selectively hydroxylated at a single unactivated carbon atom because of geometric control in the catalyst−substrate complex.[304]

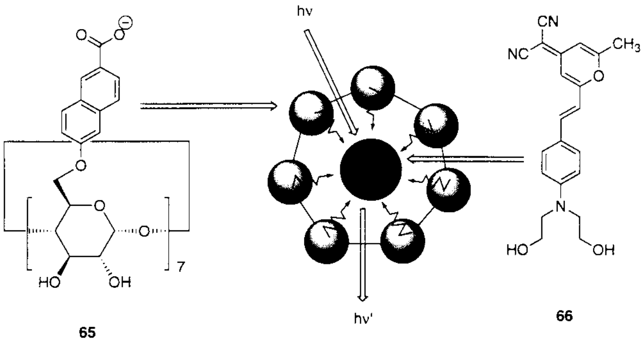


Figure 36. Naphthalene units in **65** acting as antennae to funnel light energy into the bound merocyanine dye 66.[312−314]

energy transfer with other chromophores covalently attached to the cyclodextrin. A striking example is the report that attachment of seven naphthalene units to the primary hydroxyl groups of β-CD in **65** permits them to act as antennae for energy transfer into a bound merocyanine dye (Figure 36).[312−314] This imitates one of the important features of the photosynthetic center. A cyclodextrin carrying naphthalene units has also been used as the base for other antenna studies, part of a series going back to 1981.[315,316]

Furthermore, the selective binding of molecules by cyclodextrin derivatives can be thought of as mimicking the binding of antigens by antibodies. There is a large and growing literature devoted to such molecular recognition, sometimes with extremely large binding constants.[286] While this is an important area, covering it exhaustively would expand this review beyond sensible limits.

Conclusions

It is clear that many interesting catalysts can be constructed, based on cyclodextrins, that perform biomimetic chemistry and other processes of interest. Since the cyclodextrin is used to bind a substrate, such species can be considered to be artificial enzymes. These catalysts generally show substrate specificity, for molecules that can bind into the cyclodextrin cavity. They often show specificity in the products formed, including stereospecificity. Thus they have many of the properties of enzymes. In the future, we can expect ever more effective catalysts based on the principles that have been elucidated by the work described in this review.

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