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Metal complexes of functionalized cyclodextrins as enzyme models and chiral receptors

Enrico Rizzarelli [a,b], Graziella Vecchio [a,*]

[a] *Dipartimento di Scienze Chimiche, Università di Catania, Catania, Italy*
[b] *Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico Farmaceutico, CNR, V.le A. Doria 8, 95125 Catania, Italy*

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Contents

Abstract

Cyclodextrins (CDs) are cyclic oligomers of α-1,4 linked D-glucopyranose. The main feature of CDs is an hydrophobic cavity which renders these molecules unusual. By appropriate functionalization new systems can be obtained and the features of these molecules can be increased and modulated. Among the various applications the building of molecular receptors and enzyme models by cyclodextrins is a particularly fascinating field. The present review will be a survey of the metal complexing properties of CDs and a report on some recent results of metal complexes formed by functionalized cyclodextrins. The metal ion can assist the host–guest interaction often increasing the properties of CDs to act as chiral receptors. Furthermore it can act as catalytic center in the mimicking of some

* Corresponding author. Fax: +39-09-5580138.
E-mail address: gvecchio@dipchi.unict.it (G. Vecchio)

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1. Introduction

Cyclodextrins (CDs) are cyclic oligomers of α-1,4 linked D-glucopyranose (Fig. 1). The most important members of this class consist of 6 (α-CD), 7 (β-CD), or 8 (γ-CD) glucose units, in addition to other types [1,2]. The main feature of CDs is an hydrophobic cavity, generally described as truncated cone shaped where OH groups are disposed outside. The primary 6-OHs are around the narrow rim and the secondary 2,3 OHs around the wider rim [1–3]. The presence of the hydrophobic cavity renders these molecules unusual [1–4] and the ability of these molecules to form inclusion complexes with a large range of guests, polar or apolar determines the well known applications of CDs, described extensively in the literature [2,4,5]. Furthermore because of the presence of chiral carbon atoms and of a chiral cavity, these molecules have been used as chiral receptors [3] with applications especially in chromatography.

Together with the ability to host and to recognize substrates, CDs are able to catalyze some chemical reactions. Catalysis by CDs can involve formation of covalent intermediates (covalent catalysis) or the CD cavity can simply provide an apolar and spacially restricted reaction medium for the included substrate (non-covalent catalysis) [1,3]. In catalyzing these reactions, CDs show similar kinetic features to enzymatic systems namely saturation, stereospecificity and enantioselectivity for the involvement of the cavity. The native CDs can work as covalent catalysts only at basic pHs, where the OH groups can be deprotonated and act as nucleophiles [1,3,6,7]. The functionalization of CDs besides improving

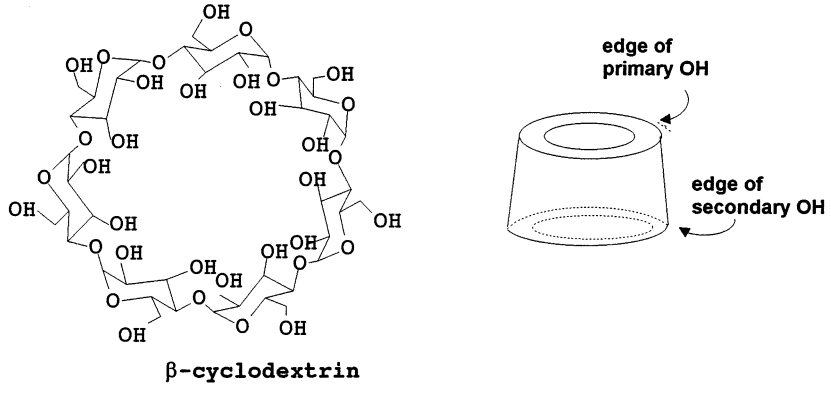


Fig. 1. Structural formula of β-cyclodextrins and schematical representation of the truncated cone shape of cyclodextrins.

their properties as artificial enzymes [1,8–13] and chiral selectors [14–23], renders these molecules capable of complexation with metal ions [1,3,10,24–28] with a huge increase in their applications.

Most of the 1000 papers published each year on CDs concern cyclodextrin inclusion complexes and only a few deal with cyclodextrin metal complex chemistry. The metal ion can assist the host–guest interactions often enhancing the properties of CDs as chiral receptors and enzyme models. Enzymes are molecular catalysts which recognize and then transform substrates that are very often chiral substrates. The substrate recognition process is the first important step in the enzymatic mechanism. As a consequence the molecular recognition properties of modified CDs assisted by metal ions, are preliminary to the investigation of the biomimetic catalytic process.

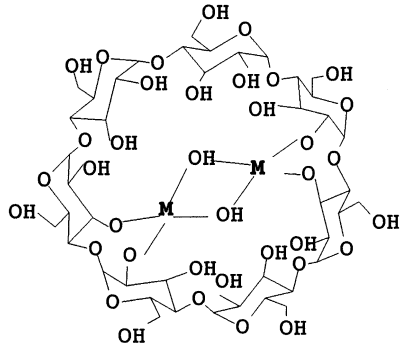
The present review surveys the metal complexing properties of both native and functionalized CDs and reports on recent results of metal complexes formed by functionalized cyclodextrins.

2. Metal complexes of unmodified cyclodextrins

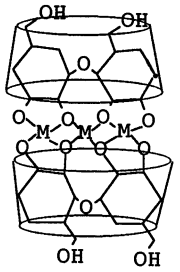
Using the Werner concept of a first and second coordination sphere, native CDs can act very simply as second sphere coordination ligands. The cavity can in fact include metal complexes forming adducts. An interesting review on this topic has been reported [29].

In the first coordination sphere, since CDs have only OH groups, they are able to complex metal ions at basic pH.

The first metal complexes of α- and β-CDs were reported by Matsui [30,31].



In aqueous alkaline solution, the unprotonated 2- and 3-OH can coordinate copper(II) ions [30,31]. On the basis of spectroscopic, potentiometric and conductometric experiments a binuclear hydroxy bridge structure was proposed. Each copper(II) ion is bound to the CD through a 2-OH and a 3-OH of an adjacent ring. Other similar metal complexes with Mn(II) have been described [32]. More recently complexes where copper(II) [33] or lead(II) [34] ions complex with the OHs on the lower rim of two CDs, forming a multinuclear sandwich-type complex, have been described.

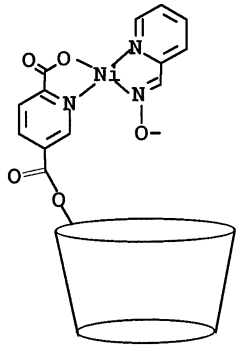


In the case of copper(II) four metal ions are complexed by two β-CD and the structure is stabilized by Li(I) ions. In the case of lead(II), 16 atoms are complexed by two γ-CD. These complexes can be formed only at basic pH with few applications. The deceleration effect of the copper(II) complexes Cu_2α-CD and Cu_2β-CD towards the hydrolysis of *o*-, *p*-, *m*-nitrophenylacetate and other carboxylic or phosphoric esters have been studied [35]. This effect which depends on the dimension of the cavity (α- or β-CD) is stereoselective in dependence on the disposition of phenyl ring (*o*-, *m*-, or *p*-) and the structure of the acid (acetate or phosphate). It can be explained by considering the conformational changes of the cavity induced by the complexation. The role of the metal ion on the activity and on the selectivity of this system has been reported [35].

3. Metal complexes of functionalized cyclodextrins

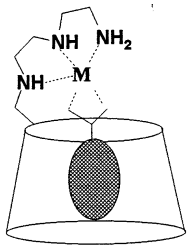
Functionalization is an excellent way to improve the complexing ability of CDs and thus a great number of metal complexes of functionalized CDs have been characterized [36–49]. Some of these complexes have been mainly investigated as enzyme models.

The 'Breslow enzyme' was the first example of a metalloenzyme model by a 3-functionalized CD.



The CD cavity acts as the binding site for the substrate and the functionalizing unit is able to complex a metal ion (nickel(II) or copper(II)). The metal ion acts as a bridge between the binding site and the catalytic site which is an oximate molecule [26].

In 1977 Tabushi reported another important advantage of the functionalization with moieties, i.e. the ability to complex metal ions [24] describing the metal complex of 6-deoxy-6-diethylentriamine-β-CD with zinc(II) as host. The zinc(II) complex binds some carboxylate anions with higher constants and larger selectivity than the 6-deoxy-6-diethylentriamine-β-CD or the β-CD alone [24]. The metal ion is a very important recognition element which can cooperate with the molecular recognition of the cavity.



This metal complex is thus a double recognition system, which provides a step toward multirecognition systems such as biological systems.

These two examples can be considered the first examples of the main field of application of cyclodextrin metal complexes.

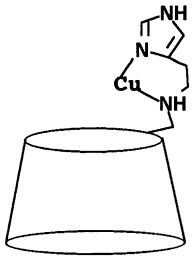
3.1. Chiral selectors

The simple functionalization often increases the enantioselectivity of CDs, because appropriate functional groups capable of interaction with some families of guests can be added [14,15,18].

The first example of a chiral selector by appropriate functionalization of β-cyclodextrin was reported by Tabushi [14]. Two functionalized cyclodextrin regioisomers 6A-1-pyrrolidyl,6B-(*o*-carboxyphenyl)thio-6A,6B-dideoxy-β-CD and 6A-(o-carboxyphenyl)thio,6B-1-pyrrolidyl,6A,6B-dideoxy-β-CD were reported to be chiral selectors of tryptophan [14]. The charge interactions of zwitterionic amino acids with the functional groups of the CD cooperate in the interaction of the indole with the cavity. The effect of this interaction is very similar for both isomers and in both cases the thermodynamic enantioselectivity is small, $\Delta\Delta G$ being 0.7 kJ mol^{-1}. Other functionalized cyclodextrins have been investigated as chiral selectors of amino acids [19,21].

To increase the chiral recognition ability of functionalized CDs, metal complexes of derivatized CDs have been investigated [18,50–62]. Some of these new multisite recognition systems act as chiral abiotic receptors, showing thermodynamic stereoselectivity assessed not only by different $\Delta G°$ values but also by different values of enthalpy and entropy changes in the formation of ternary complexes of amino acids. The diastereoisomeric mixed complexes were characterized by means of spectroscopic (CD, EPR and fluorescence) studies and the enantioselectivity shown has been related to bonding details.

In particular, the copper(II) complex of 6-deoxy-6-histamine-β-cyclodextrin (CDhm) represents the first example of a metal complexes in this new class of chiral selectors capable of resolving a racemic mixture of amino acids [50–52].



The chromatographic enantioselectivity has been tested using $[Cu(CDhm)]^{2+}$ as a chiral additive to the eluent in ligand exchange chromatography (LEC). In the case of tryptophan a good chromatographic separation factor was found ($\alpha_{L/D} = 1.23$) and the difference in the $\Delta\Delta G°$ (2.0 kJ mol^{-1}), indicates a significant increase in the molecular recognition ability assisted by the metal ion in comparison with the multisite model of Tabushi [14]

The thermodynamic data of the mixed complexes formed by $[Cu(CDhm)]^{2+}$ with amino acids deserve some further comments. In fact, on the basis of enthalpy and entropy changes, a tentative structure of the diastereoisomers has been hypothesized, rationalizing the different stability constant values. In complexes with aliphatic amino acids and with histidine the thermodynamic enantioselectivity is absent or insignificant, while in the case of amino acids containing an aromatic residue, the ternary complexes of the D-enantiomer are significantly more stable than those of the L-enantiomer [51]. The determination of $\Delta H°$ and $\Delta S°$ values related to the formation of copper(II) ternary complexes, suggest a solvophobic interaction between the indole residue and the cavity with the D-isomer interacting more than the L-isomer. In fact, the differences in $\Delta G°$ values are due to a more exothermic enthalpy value associated with the formation of a complex with the D-isomer. Assuming a preferred *cis* disposition of amino groups on the coordination plane like in the case of analogous mixed complexes of histamine with some amino acids [53], the CPK models suggest an interaction between the aromatic ring and the cavity only in the case of the D-enantiomer of amino acids, while in the complexes with the L-enantiomer the aromatic residue sticks out of the cavity (Fig. 2). The entropy changes, less favourable in the case of the D-isomer could result from the loss of the rotational freedom of the side chain. This effect predominates over the desolvation effect.

The CD spectra confirm this hypothesis: complexes with the D-isomer show a larger $|\Delta\varepsilon|$ than those with the L-isomer, thus suggesting a larger interaction of the aromatic chain with the cavity in the case of D-isomer. The $[Cu(CDhm)]^{2+}$ has been used as the eluent in HPLC using LEC, and the chromatographic enantioselectivity is in keeping with the thermodynamic enantioselectivity: the D-enantiomers of amino acids—thermodynamically more stable—were eluted first then the L-enantiomers. The best resolution was observed in the case of aromatic amino acids.

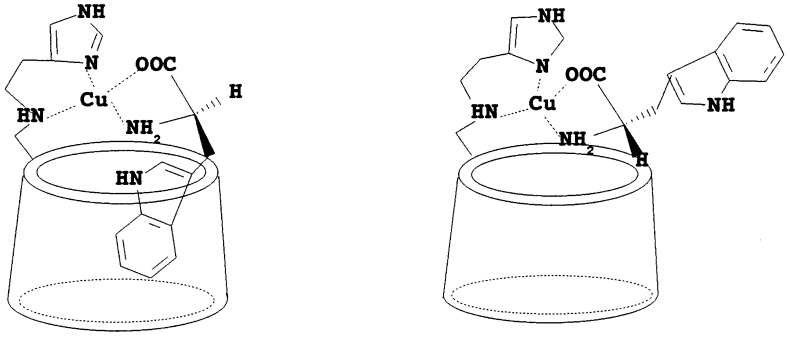
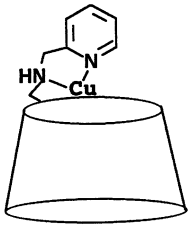


Fig. 2. Schematic of copper(II) ternary complexes of CDhm and $TrpO^-$ (L-$TrpO^-$ on the right and D-TrpO on the left).

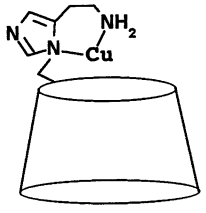
The fluorescence spectroscopy investigation in the case of ternary complexes with $TrpO^-$ confirms the inclusion of the indole in the case of the D-isomer.

The geometric disposition of the amino groups would appear to be important also in the explanation of the behaviour of copper(II) ternary complexes of 6-deoxy-6-(2-aminomethylpyridine)-β-cyclodextrin (CDampy) [54].



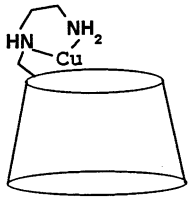
This ligand is similar to CDhm, but with a shorter chain binds the aromatic ring to the cavity. The ternary complex with D-TrpO is more stable than that of L-$TrpO^-$, as in the case of CDhm. The ternary complexes of D-AlaO or L-AlaO show the same stability. Also in this system the preferential *cis* disposition of the amine groups on the co-ordination plane of the metal ion determines the orientation of the indole residue of the D-isomer towards the cyclodextrin cavity. The CD spectra and the chromatographic behaviour are consistent with the thermodynamic results.

The 6-deoxy-6-[4-(2-aminoethyl)imidazolyl]-β-cyclodextrin **2** (CDmh) [55,56] was synthesized to verify the '*cis*-effect' described in the case of the CDhm and CDampy copper(II) complexes.



The histamine is bound to the cavity though the imidazole nitrogen and an inversion of behaviour in comparison to the CDhm could be hypothesized if the '*cis*-effect' is involved in determining the chiral recognition mechanism. Concerning the mixed copper(II) complexes of CDmh with amino acids, while no differences in stability have been found in the case of alanine, the complex with the D-isomer of tryptophan is less stable than the complex with the L-isomer. In fact, the indole ring can interact with the cavity only in the case of L-tryptophan. In keeping with the observed trend, the CD spectra show the inversion of behaviour with respect to the case of CDhm. A large Cotton effect is observed in the case of L-amino acids which can interact more strongly with the cavity. The chromatographic enantioselectivity is consistent with the thermodynamic enantioselectivity: the L-isomer of Trp is eluted faster than the D-isomer. The rigidity of the side chain moiety bound to the cavity through imidazole probably determines the good enantioselectivity shown for this complex towards tryptophan and reduces the range of aromatic acids which can be recognized. In fact only the L/D-Trp is resolved.

The 6-deoxy-6(2-aminoethylamino)-β-cyclodextrin copper(II) complexes do not show appreciable thermodynamic enantioselectivity [57]:

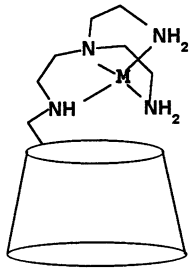


this behaviour is in agreement with the recognition model described for other systems. The two coordinating nitrogen atoms of CD are two aliphatic amino groups and no significant differences can be supposed between a *cis* or a *trans* disposition of the amino groups on the coordination plane. The small differences which are too small to be evident in the thermodynamic parameters, are evident in LEC where only the L/D-TrpO$^-$ is resolved: the D-isomer is eluted first, and then the L-isomer, suggesting a slight preference for a *cis* disposition of NH_2 groups in comparison with the NH group.

After the characterization of these complexes in aqueous solution and the hypothesis of a *cis*-effect operating in the recognition mechanism, the solid state structure of [Cu(CDhm)(L-TrpO)]$^+$ was reported [58]. In this complex the L-TrpO$^-$ side chain is outside of the cavity and the two amino groups are in a *cis* disposition. This structure seems to be stabilized by a d–π interaction between the metal ion and the indole ring and by a π–π interaction between the two aromatic rings. On the basis of these results, some consideration can be given to the small enantioselectivity found in aqueous solution: the weak interactions found in the solid state might also survive in aqueous solution thus reducing the differences of enthalpy change between two diastereoisomeric ternary complexes. Furthermore, a *cis*/*trans* equilibrium more or less shifted towards the *cis* form is proposed in aqueous solution instead of a solid *cis* disposition (Fig. 3).

The nickel(II), zinc(II), copper(II), cobalt(II) complexes of 6-deoxy-6-(3-aminopropylamino)-β-cyclodextrin (CDpn) have been investigated as chiral selectors by potentiometry [59,62]. On the basis of stability constants and a comparison of thermodynamic stability of binary and ternary complexes, the authors suggest a recognition mechanism of the L/D-TrpO$^-$ for which the side chain of amino acid is included in the cavity in both diastereoisomer complexes [59,60]. Furthermore, the largest enantioselectivity has been found when the metal ion was nickel(II). When zinc(II) was used no enantioselectivity was found. In the case of cobalt(II) and copper(II) complexes, enantioselectivity is found though it is lower than in the case of nickel(II) complexes. Phenylalanine was also enantioselectively bound to metal complexes of CDpn: a good enantioselectivity was found in the case of the nickel(II) complex while a very low enatioselectivity was found in the case of cobalt(II) and copper(II) complexes [61]. No enantioselectivity was observed for Zn(II) complex [61].

Metal complexes of 6-(2-(bis(2-aminoethyl)amino)ethylamino)-6-deoxy-β-cyclodextrin (CDtren) with Ni(II), Cu(II) and Zn(II) have been investigated by potentiometry [62] but no significant enantioselective effect was found for TrpO$^-$.



Binary complexes are too strong in these cases and the authors suggest that only a weaker complexing ability of the ligand allows the metal ion to exert an enantioselective binding of amino acids.

Table 1 summarizes the thermodynamic enantioselectivity found in metal complexes of monofunctionalized cyclodextrins described above. The $\Delta \log K$ is the

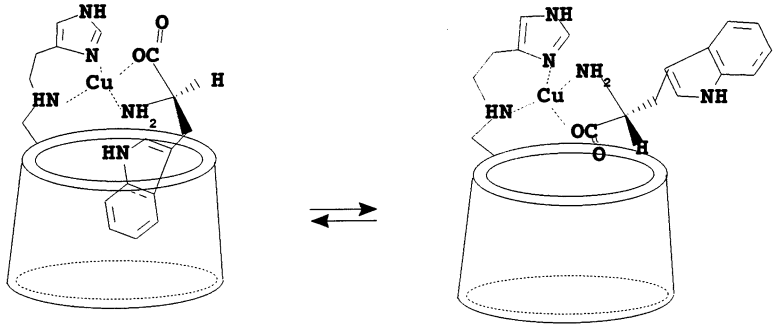


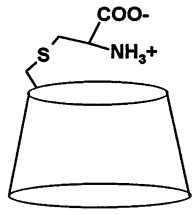
Fig. 3. *Cis–trans* equilibrium in copper(II) ternary complexes of CDhm.

Table 1
$\Delta \log K$ values of ternary complexes of monofunctionalized CDs with amino acids

Metal complex	AaO–	$\Delta \log K$	Ref.
$[Cu(CDhm)]^{2+}$	TrpO	0.35	[52]
$[Cu(CDhm)]^{2+}$	PheO	0.17	[52]
$[Cu(CDhm)]^{2+}$	TyrO	0.40	[52]
$[Cu(CDampy)]^{2+}$	TrpO	0.13	[54]
$[Cu(CDmh)]^{2+}$	TrpO	0.85	[56]
$[Cu(CDpn)]^{2+}$	TrpO	0.24	[60]
$[Cu(CDpn)]^{2+}$	PheO	0.30	[61]
$[Ni(CDpn)]^{2+}$	PheO	0.10	[61]
$[Ni(CDpn)]^{2+}$	TrpO	1.0	[60]
$[Co(CDpn)]^{2+}$	TrpO	0.28	[60]
$[Co(CDpn)]^{2+}$	PheO	0.09	[61]

difference between the formation constants of the two diastereoisomeric ternary complexes.

Some complexes of copper(II) cyclodextrin complexes functionalized with amino acids were investigated, to verify if the presence of a new chiral center on the coordination plane could increase the chiral recognition ability [63]. The 6-deoxy-6-*S*-(L)-cysteine-β-cyclodextrin and 6-deoxy-6-*S*-(D)-cysteine-β-cyclodextrin were used as ligands and the ability of their copper(II) complexes in the recognition of amino acids was tested by CD and LEC.



Only the of D-cysteine derivative was able to resolve $TrpO^-$ on LEC. In these cases the presence of a chiral center does not represent an advantage in chiral recognition ability. Probably the functionalizing moiety, bound to the cavity through a non-coordinating atom (the S atom), is not rigid enough to determine the efficient cooperation of the cavity and of the metal ion(II) in the recognition of the amino acid.

Copper(II) complexes of difunctionalized CDs were investigated as chiral selectors using 6A,6X-diamino-6A,6X-dideoxy-β-cyclodextrin ($AXCDNH_2$, X = B, C, D) as ligands [64] (Fig. 4). The binary copper(II) complexes of three regioisomers have the same coordination features and the copper(II) is bound to the two nitrogen atoms in $AXCDNH_2$. These difunctionalized ligands have no chain on the CD rim and the guest can interact strongly with the cavity, furthermore allowing for a comparison among them to be possible. The chromatographic resolution by LEC of L/D-TrpO, -PheO, -TyrO was found only when the copper(II) complexes of

AB regioisomer were used. CPK models suggest that the complexation with the metal ion partially closes the entrance of the CD cavity and in the case of complexes with $ACCDNH_2$ and $ADCDNH_2$ the complexation of the amino acid and the interaction with the cavity cannot occur simultaneously. In the case of AB, in contrast to the monofunctionalized CD, the best resolution was observed in the case of Tyr and Phe with an aromatic ring smaller than indole. The CD spectra of the copper(II) ternary complexes of $ABCDNH_2$ with the L-and D-enantiomers are not enantiomeric: a larger Cotton effect was found in the case of complexes with the D-enantiomer. When the competitive guest 1-adamantanol is added to the $ABCDNH_2$ ternary complexes, the spectra changed confirming the involvement of the cavity in the recognition process. In these difunctionalized systems, the *cis*-effect cannot operate and the chiral recognition results from the interaction of amino acid side chain with the cavity. When this interaction cannot occur as in the case of AC- and AD-isomer no enantioselectivity was observed.

Another example of the molecular recognition by functionalized CD nickel(II) complexes was reported [65].

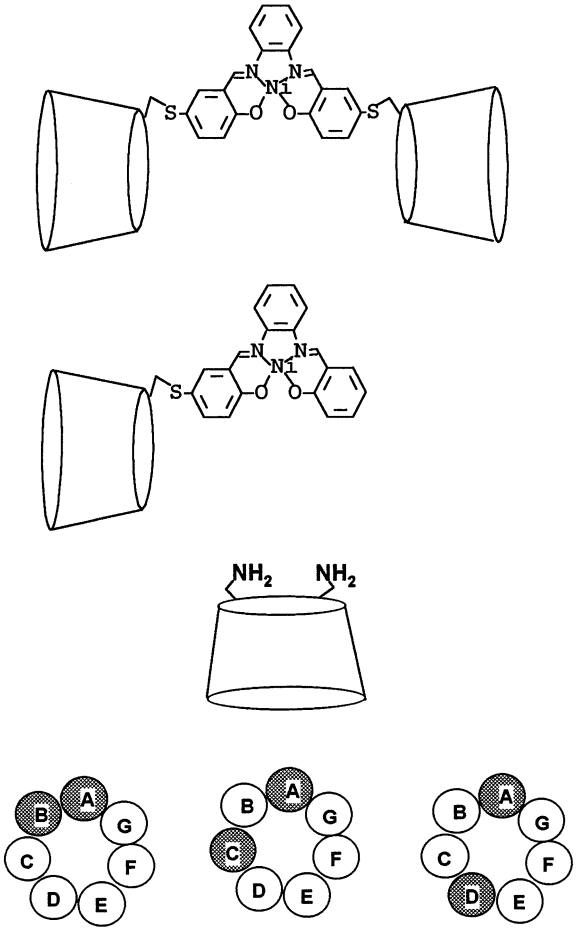


Fig. 4. Regioisomers of 6A,6X-diamino-6A,6X-dideoxy-β-CD (X = B, C or D).

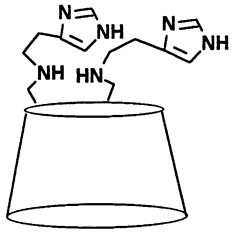
In these systems the metal ion does not assist the process. The nickel(II) complexes were used with some tripeptides bound to an hydrophilic poly(ethyleneglycol)polystyrene. Complexes with one or two CD cavities are able both to bind the tripeptides and the resulting complexes are absorbed to the gel. When a competitive guest is absorbed, desorption of the complex occurs. Sequences containing either L-Phe-D-Pro or D-Phe-L-Phe are selected, while tripeptides containing the diastereoisomeric homochiral dipeptides L-Phe-L-Pro or D-Phe-D-Pro are not selected.

3.2. Enzyme models

Enzyme models are often built using the two site approximation which is a very helpful simplification of an enzyme molecule [66]. The unfunctionalized CD cavity, because of its properties can be proposed as the binding site, but the OH groups as potential catalytic groups cannot efficiently mimic the catalytic sites of natural enzymes. Through chemical synthesis, appropriate functional groups which are similar to those involved in the catalysis mechanism of natural enzymes, can be bound to the CDs, thus mimicking the natural enzyme. Cyclodextrins with appropriate functional groups, which are able to complex metal ions with the same coordination features of natural systems, act as apoenzymes and their metal complexes can be studied as metallo–enzyme models. Various classes of these artificial enzymes will be presented.

3.3. Carbonic anhydrase models

Carbonic anhydrase was mimicked by Tabushi using the zinc(II) complex of a CD difunctionalized with two histamines in A,C position [67].

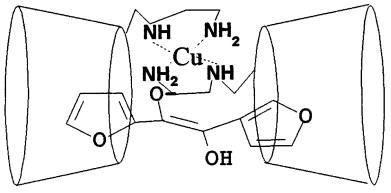


An imidazole buffer was added to the Zn(II) CD complex solutions obtaining coordination of the zinc(II) with the three imidazole nitrogen atoms (two from histamines and one from the imidazole of the buffer). An acceleration rate of CO_2 hydratation was observed ($K_{cat} = 10^3$). The coordination of the three imidazole rings with zinc(II) may be responsible for the catalytic effect of this system even if the secondary amino group of the histamine chains seem to promote the catalytic activity [67]. On this basis, as typically observed in similar metal complexes [68], the coordination of amino groups with zinc(II) should be considered. In the absence of zinc(II) or of Im buffer, no appreciable acceleration was observed. An analogous zinc(II) complex with *N*-methylhistamine, shows lower

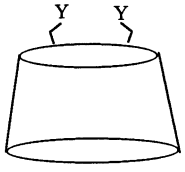
catalytic activity and thus the hydrophobic cavity is a factor which enhances the CO_2 hydration activity.

3.4. Artificial redox enzymes

One of the first examples of an artificial oxidase, where the metal ion acts as a redox center, is the copper(II) complex of 6-deoxy-6-(2-aminoethylamino)-β-CD [69]. This complex is able to oxidize furoin 20 times faster than either the uncatalyzed reaction or CD alone. The rate determining step is the enolization process which is stabilized by the copper(II) ion. The metal complex described to be active, is the species with two CDen molecules and one copper(II) ion. This dimer of cyclodextrin, obtained by complexation with copper(II) ion, includes furoin and the metal complex interacts with the substrate before its oxidation.



Copper(II) complexes of functionalized CDs with amines have also been proposed as superoxide dismutase (SOD) models and the O_2^- scavenger activity was determined by the classical indirect assay [70,71]. Furthermore, the protective action of these complexes towards the photosensitization process in the presence of membranes such as red blood cell membranes was determined. All cyclodextrin complexes show a larger activity than the analogous complexes without the cyclodextrin. When the equatorial field of the ligand is strong as in the case of 6-deoxy-6-diethylentriamine-β-cyclodextrin, low scavenger ability was determined probably since the axial binding of the O_2^- is disfavoured [70]. When cyclodextrins 6-difunctionalized with the histamine (AXCDhm, X = B, C, D) were used as ligands, the copper(II) complexes showed considerable superoxide dismutase mimicking activity [71].



Y = histamine (AXCDhm)

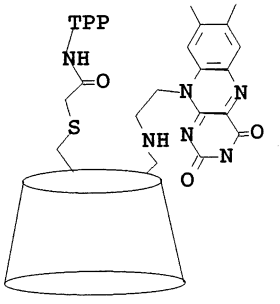
Y = 2-aminomethylpyridine (AXCDampy)

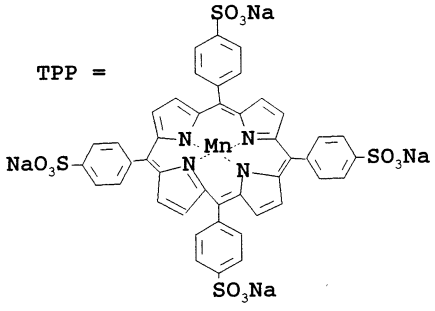
(X = B, C o D)

The activity depends on the regioisomer, that is on the position of the two histamine moieties. The complex of AB regioisomer shows a larger activity with respect to other isomers. On the basis of EPR spectra and AOM ligand field calculations, it was shown that the copper(II) complex with the AB isomer has a coordination polyhedron which is distorted towards a tetrahedral arrangement of

histamines, more than the other two isomers. The proximity of the two histamines in the AB isomer renders the coordination site flexible, and thus able to fit the stereochemical requirement of tetrahedral coordination of the copper(I), intermediate species in the catalytic mechanism. Copper(II) complexes of β-CD 6-difunctionalized with 2-aminoethylpyridine (AXCDampy, X = B, C, D) were also investigated as SOD models. These complexes are very effective scavengers of O_2^- [72]. As in the case of the histamine derivatives the complex with the AB-isomer is more active and shows a distortion of the coordination geometry similar to the AB histamine derivative. Comparison among the regioisomers is a useful way to modulate and investigate the role that the stability, coordination geometry, and equatorial field strength have on the catalytic process factors.

A molecular system mimicking the P-450/P-450 reductase system [73] for fast electron transfer from RNAH (coenzyme of the system) to porphyrin Mn(II) was also synthesized using an α-CD 6-difunctionalized in A,B position. A Mn(II) porphyrin on the A ring and a flavine at the B position were bound to the CD.

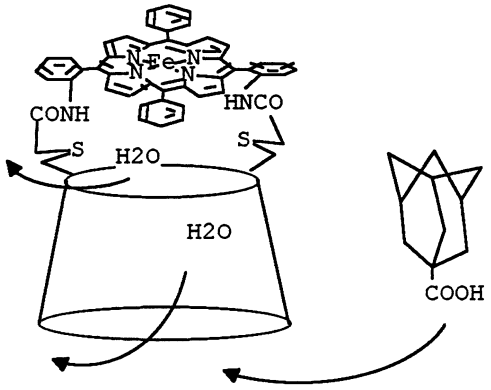




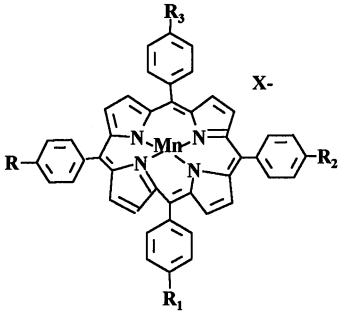
This system shows fast electron transfer from RNAH to the porphyrin with an acceleration 5.5 times higher with respect to an analogous system without a cyclodextrin cavity [73].

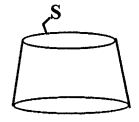
A very interesting enzyme P-450 model system was synthesized by Tabushi [73].

The P-450 active site was mimicked by functionalizing a β-CD capped in A,D positions. 'Spin control' (from low to high spin) of Fe(II) porphyrinato–cyclodextrin by adamantane carboxylate has been observed. The mechanism suggested for this spin control supposes that water molecules are replaced by adamantane carboxylate within the CD cavity.



Manganese(III) porphyrin complexes attached to two or four β-cyclodextrin molecules were investigated as catalysts for the epoxidation of some stilbene derivatives [74].





$R_1 = R_2 = R_3 = R$ ($CDpor_4$)

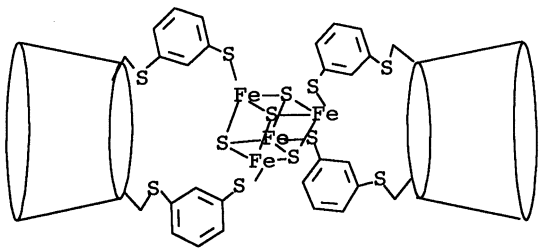
$R_2 = R$ and $R_3 = R_1 = H$ ($CDpor_2$)

$R_1 = R$ and $R_2 = R_3 = H$ ($CDpor_2'$)

The selectivity of these systems towards the substrate in the epoxidation reaction depends on the position of the cyclodextrins on the porphyrin ring, in keeping with the importance of an appropriate binding geometry for the substrate. In fact, the CDpor2 isomer is more selective in substrate recognition than the CDpor2′. The complex with four cyclodextrin cavities (CDpor4) shows good selectivity and a very good catalytic turnover.

This manganese CDpor4 complex was also investigated as a catalyst for the hydroxylation of steroids. Regioselective hydroxylation was reported depending on the geometry of the substrate [75].

Ferredoxin has also been mimicked [76]. The cluster F_4S_4 was bound to two β-cyclodextrin units difunctionalized through 1,3 dithiophenol.



The cluster is more stable towards hydrolysis than the same cluster without CD. In fact, the primary OH groups of CD can intramoleculary attack the iron atoms of the Fe_4S_4 cluster thus protecting the cluster from hydrolysis. The $E°$ value is -0.55 V, in the range of natural ferredoxins.

Furthermore an enantioselective P-450 cytochrome mimic has been described [77]. The heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin (DMCD), was functionalized with a metallo–porphyrin through a propyl spacer group and was able to resolve pirene enantiomers. The iron or manganese porphyrin obtained could catalyze the oxidation of a racemic mixture of α-pirene in the presence of oxygen and light ($\lambda > 350$ nm). Different product composition and enantiomeric ratios, with the *S*-isomer in excess, are observed depending on the catalyst and the solvent. The iron porphyrin is more enantioselective than the manganese porphyrin and a polar solvent increases the enantioselectivity of the reaction, probably modifying the interaction of the substrate with the cavity.

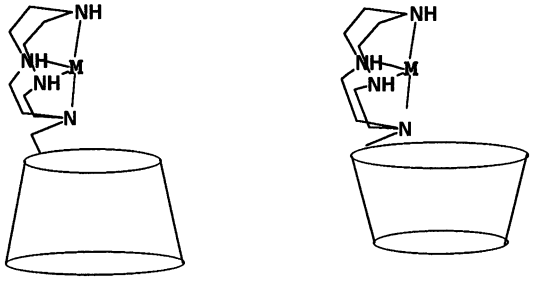
3.5. Artificial hydrolasis

Metal ions typically act as catalysts in the hydrolysis of coordinating substrates [78,79].

Metal complexes of functionalized CDs can also act as catalysts for non-coordinating substrates, with the cavity acting as a binding site. The first example of hydrolasis by CD metal complexes was the previously mentioned 'Breslow enzyme' [26]. In this system, the metal ion (nickel(II) or copper(II)) acts as a bridge between the catalytic moiety (pyridinecarboxaldoxime, PCA) and the binding site which is the cyclodextrin cavity. The cavity can bind *p*-nitrophenylacetate which is hydrolysed at pH 5.17 by means of the PCA unit which can be acetylated and then hydrolyzed by metal ion catalysis. The ternary complex with nickel(II) is about 4 times more active in the catalysis than the same amount of the binary complex PCA–Ni. The ternary complex of copper(II) hydrolyzes the *p*-nitrophenylester of glycine 6 times faster than the binary complex PCA–copper(II). These hydrolyses are inhibited by cyclohexanol, which can be included in the cavity and are not significantly catalysed when large substrates are used which cannot be included in the cavity thus suggesting the involvement of the cavity.

In other more recently described systems, the metal ion complexed CD acts as a catalytic center on the substrate.

Some β-CDs 6- or 3-functionalized cobalt(III) complexes with cyclen (CDcyclen(6) and CDcyclen(3)) were proposed as artificial hydrolases [80].



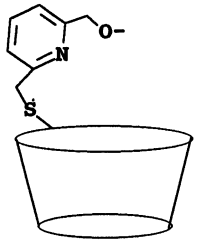
The 6-functionalized CD cobalt(III) complex shows a 900-fold enhancement for the metal promoted hydrolysis of *p*-nitrophenyl (PNP) acetate. The involvement of the CD cavity was ascertained by adding cyclohexanol which competitively inhibits the reaction. On the contrary, the cobalt(III) complex of 3-functionalized is a very poor catalyst for hydrolysis of PNP acetate. At pH 7, the hydrolysis occurs only 3.6 times faster than the uncatalyzed reaction. Noteworthy is the comparison with the parent complex, the simple $Co(cyclen)^{3+}$ which is not able to catalyze the hydrolysis of PNP acetate.

The authors [80] consider the differences in reactivity of the two isomers to be due to the complexation of an hydroxymethyl group adjacent to the functionalized ring which can occur only in the 6-derivative.

Furthermore they postulate that hindered rotation of the cyclen cobalt(III) complex group bound on the 3 position makes its interaction with PNP acetate less favourable. The properties of 3- and 6-functionalized cyclodextrins are typically very different. The secondary face rim is larger, and chiral centers are faced on it. In the 3-functionalized derivatives two chiral centers (C-2 and C-3) change their configurations after a nucleophilic substitution reaction and the functionalized unit becomes an altrose unit and a distorted cavity is formed.

The hydrolysis ability of other metal complexes of CDcyclen(6) have been reported [81,82]. The nickel(II) complex is able to hydrolyze *p*-nitrophenylphosphate (PNAP) at pH 7 about 16 times faster compared to the uncatalyzed reaction. When a zinc(II) complex (14-fold) or copper(II) complex (12-fold) were used a lower catalytic effect was reported [81]. A minor effect was reported for the CDcyclen metal complexes in the hydrolysis of PNP carbonate: they displayed a low acceleration factor (about 6-fold) as compared to the uncatalyzed reaction. The hydrolysis of *p*-nitrophenyltrifluoroacetanilide was largely promoted by the copper(II) complex (43-fold), while the nickel(II) and zinc(II) complexes show an acceleration factor of about 3-fold.

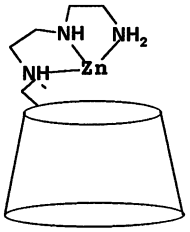
The 3-functionalized β-CD copper(II) complex with 2-hydroxymethylpyridine used to catalyze the hydrolysis of PNP of picolinic acid (PNPP), PNP of quinaldic acid (PNPQ) and its phenyl derivative (PNPQPh) at pH 6.3 [83].



These substrates are effective ligands for metal ions and can be included in the cavity thus a competition or a cooperation in the binding of substrate between the CD cavity and the metal ion is possible. The metal complex accelerates the cleavage of the three esters (the ligand alone does not). Nevertheless the catalytic activity of the CD metal complex in the hydrolysis of PNPP and PNPQ is lower than the analogous complex of 2-hydroxymethyl-6-*S*-ethylthiomethylpyridine, while in the

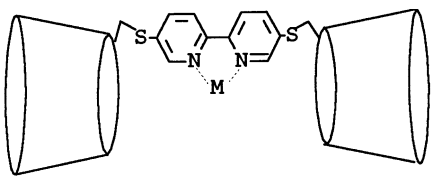
case of PNPQPh the two metal complexes show approximatively the same activity. The presence of the cavity in these hydrolyses is not advantagous for the reactions. Probably the geometry of the inclusion complex is not appropriate to allow a proximity of the catalytic center and ester group of the substrate. Comparison of kinetic data obtained with the cyclodextrin complex and the analogous system without CD suggest no cooperation but competition between the hydrophobic and metal ion recognition sites. In the case of PNPQPh the presence of a large aromatic side chain which fits in the cavity could orient the ester group in the proximity of the catalytic center. This hypothesis is confirmed by comparison of the results obtained when CD alone is used as catalyst at basic pH.

The 6-deoxy-6-diethylentriamine-β-cyclodextrin (CDdien) zinc(II) complex was investigated as a model of ribonuclease [84].



This complex is quite effective for the cleavage of ribonucleoside 2′,3′-cyclic phosphate and ribonucleotide dimers. The cleavage of 2′,3′-cyclic monophosphates of adenosine, guanosine, cytosine and uridine was carried out at pH 9.5 and its rate depends on the nucleoside. In the case of purine bases, adenosine and guanosine, the acceleration is 28- and 23-fold compared to the uncatalyzed reaction, while in the case of pyrimidine bases, cytosine and uridine, an acceleration of 3.5- and 9.6-fold was observed. The ligand alone is not able to catalyze the hydrolysis and the diethylentriamine zinc(II) complex shows a very slow catalytic effect. The presence of the cavity does not enhance the regioselectivity in the product formation and 3′-monophosphate and 2′-monophosphate are obtained as in the analogous system without cyclodextrin. The cleavage of ribonucleotide dimers was also accelerated by the zinc(II) complex: AdA and ApC, CpA and UpA were hydrolyzed at pH 11 3.4, 4.0, 1.4 and 1.3-fold faster than the uncatalyzed reaction. The CDdien copper(II) and the magnesium(II) complexes show a very small acceleration in cleavage of ApA.

The binding of substrate by multiple interactions is a useful way to achieve a catalyst–substrate complex stable and preorganized in the reactive geometry [85]. Breslow has described a CD dimer which has a double binding site for the substrate [86–88]. The two cyclodextrins are linked by a metal binding group.



Metal complexes of the cyclodextrin dimer have been investigated as catalysts in the hydrolysis of esters. The metal ion can assists the recognition of the substrate cooperating with the cavity binding and a metal hydroxide species acts as nucleophile, as observed in many metalloenzymes. The binding ability of this system was investigated in the case of the zinc(II) complex and it is better than that of the ligand alone. The binding constant with dialkylphosphoric esters, used as analogues of the transition state for ester and amide hydrolysis, are higher when compared to the binding constant of some carboxylic esters (the substrate, the ground state). This result suggests that these systems could be very efficient enzyme models. In the hydrolysis of *p*-nitrophenyl-3-indolepropionate, the copper(II) complex of this CD dimer, shows a very high rate enhancement (18 300-fold) compared to that observed in the absence of copper(II) (60-fold) at pH 7. The cooperation of the two cavities as binding sites results in the very high rate constants observed: the substrate is bound by two cavities and the resulting geometry of inclusion complexes is appropriate to have an effective catalysis [86]. The CD cavity shows a very large affinity towards the adamantane group and the hydrolysis of the nitrophenyl ester of 1-adamantylpropionic acid is 225 000-times faster than the uncatalyzed hydrolysis. Other substrates have been tested, but their lesser solubilities need the use of organic solvents which disfavour the inclusion complex formation. The zinc(II) and nickel(II) complexes are less effective than copper(II) complexes. The hydrolysis of PNP-3-indole propionate and of PNP-1-adamanthylpropiolicate catalyzed by the CD dimer metal complexes have been carried out in the presence of *E*-2-pyridincarbaldehyde oxime [87]. This molecule cooperates efficiently in the hydrolysis of these esters, particularly when the metal ion used was zinc(II).

The CD dimer lanthanum(III) metal complex has also been described as a catalyst for BNPP hydrolysis in the presence of H_2O_2 [87]. The presence of the CD dimer increases the rate constant in the case of anionic substrates such as bis(*p*-nitrophenyl)phosphate. The formation of a quadrimolecular complex was proposed at low lanthanum(III) concentration where the two cavities and the lanthanum ion cooperate in the recognition of substrate and the H_2O_2 is bound to the metal ion in proximity of the ester group [87].

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