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Organic Reactions Mediated by Cyclodextrins

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Contents

1. Introduction

Since their discovery, the cyclodextrins(CDs) have served as prototypes for novel host compounds and catalysts. The use of CDs as *microvessels* to perform chemical reactions has attracted the interest of chemists since the 1960s.[1] Bender et al. carried out detailed and systematic studies on the CD-induced hydrolysis of phenyl acetate and discovered a significant substrate specificity in the reaction rates.[2] Since then reactions catalyzed by CDs have been continuously reported. Such catalytic mechanisms have been precisely clarified by the use of analytical and physicochemical information.

The effects of CDs on the organic reactions are divided mainly into two types. The first is the effect on covalent bonds where the reaction proceeds according to the Michaelis–Menten type. CD and the reactant initially form a CD–reactant reaction intermediate involving a covalent bond which then leads to the product. These catalytic effects have been studied and reported as the enzyme model. Various advanced “enzyme models” and “artificial enzymes” have been envisioned through the chemical modification of CDs by using detailed molecular design. The development of techniques for the precise chemical modification of CDs[3] has undoubtedly made an essential contribution to progress in this field. The second effect does not involve a covalent bond. The hydrophobic cavity of the CD gives the reactant access to a new reaction environment, an “*extra reaction field*” in which the reactivity, such as rate or selectivity, changes. In these cases, the role of the CD is not always defined as catalyst. More correctly, the CD *mediates* the reactions. There are many excellent reviews available on CDs and their catalyzed reactions.[4] This review mainly concentrates on recent developments of organic reactions *mediated* by native or simply modified CDs and in the use of CDs as *the extra reaction field* rather than as enzyme models.

Keiko Takahashi was born in Morioka, northern Japan, in 1955. She studied chemistry and pharmacy in Tohoku University. Her master’s thesis (1981) was on the subject of photocontrol of molecular functions. She received the doctor’s degree in 1986 under the supervision of Professor Tetsuo Osa. Her doctoral work dealt with the control of reactions by host–guest complexation of cyclodextrins. In 1993, she was appointed as an associate professor, Department of Industrial Chemistry, Tokyo Institute of Polytechnics. Her research interests lie in the area of supramolecules with a particular focus on molecular recognition and control organic reactions using modified cyclodextrins which have flexible arms.

2. The Cyclodextrin Reaction Media

Most of our understanding of CD inclusion phenomena has been derived from studying an aqueous phase in an equilibrium state. In this state, the hydrophobic forces are assumed to be responsible for driving a guest into the CD’s hydrophobic interior, where a 1:1 host–guest complex usually forms and where is no interaction with other CD molecules. Before describing various organic reactions mediated by CDs, some explanation of inclusion phenomena is warranted.

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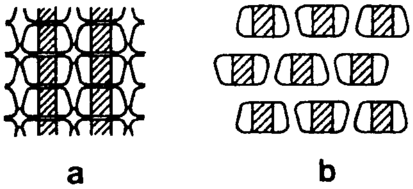


Figure 1. Examples of spatial organization of solid CD complex: (a) channel type and (b) cage type.[111]

1. *Existence of a Naked Reactant.* Organic reactions are dynamic processes. Therefore, the study of organic reactions mediated by CDs cannot ignore the guest molecule outside the CD cavity. When a large excess of CD is added to the reaction system, almost all the reactant is included in CD cavities. However, the probability of a naked reactant is not quite zero since it is controlled by the concentration of both reactant and CD.

2. *Complexation Mode.* The possibility of simultaneous formation of complexes with different stoichiometries has also to be considered.[5] Four types of CD, guest complexes with 1:1, 1:2, 2:1 and 2:2 stoichiometry, have been observed depending on the size and structural features of the guest with respect to the host cavity. The cooperative binding, a bimolecular process, has been observed[6] as well as a unimolecular process a 1:1 complex in either a "head-to-tail" or "head-to-head" state. Moreover, a study of the fluorescence decay of a number of anilinonaphthalene sulfonates in the presence of a β-CD supported the view that a 1:1 complex can be present in several slightly different conformations.[7] There are, in fact, various conformations and orientations of reactants as well as varying mobilities in a reactant−CD complex.

3. *Specific Interactions.* Depending on the solvent and the nature of host and guest, the complexation is based on a combination of several intermolecular interactions: steric fit, van der Waals interactions, dispersive forces, dipole−dipole interactions, charge-transfer interactions, electrostatic interactions, and hydrogen bonding. The choice of reaction media used in CD systems also depends on the above combination of interactions. The study of the organic reaction *mediated* by CDs means the study of weak interactions.

4. *Inclusion Phenomena in Solid States.* CDs can also include guest molecules in the solid state.[8] Such host−guest complexes are clearly be separated from the clathrates (lattice inclusion compounds), which occur only in the solid state, and from the crown ethers, which occur in solution. Inclusion complexes in the gas and liquid phases are not expected to be the same. In nonaqueous environments, the short-range London forces[9] or polar interactions[10,11] are responsible for host−guest complexation. Such complexes are ordered in a crystalline network. Two main structural types have been recognized: the channel- or cage-type molecular arrangement[12] (Figure 1). In the channel-type structure, the molecules are piled in a "head-to-head" or "head-to-tail" orientation. In the cage-type structure, the cavity of single CD molecule faces and is blocked by other CD molecules, resulting in isolated cages. The natural orientation of guest molecules in crystals and the tight molecular packing around them may be crucial to the course of the reaction. This is especially true for photochemistry of the system as shown later.

The CD cavity is less polar than the bulk aqueous medium. It is known that the permittivity in the CD cavity is almost the same as that of dioxane. There are specific interactions between the CD and the reactant. The microenvironment around the reactant in the CD cavity is different from that in the reaction media. Three distinct microenvironmental effects are expected: (1) *microsolvent effects*, (2) *the protection of unstable intermediates or products*, and (3) *the solubilization of the reactant*. In addition, conformational effects can also be expected: (4) *the control of reactant conformation*, (5) *control of the orientation between reactants*, and (6) *control of the size of molecule*. A combination of several of these effects are evident for organic reactions.

3. The Effect of CDs on Reactions

3.1. Organic Reactions in Solid CD Complexes

In this section, organic reactions involving a solid CD complex of reactant in the solid state and in suspension are described. Inclusion complexes can be precipitated from aqueous solutions of CD by using an excess of the guest reagent. The crystalline inclusion complexes are usually obtained by using a simple method: A substrate is added to a saturated aqueous solution of the CD, and after the solution is stirred for 2 h to 7 days, the resultant precipitate is filtered and the crystalline product obtained quantitatively. In this case, the particular environment effect involving the CD is known as the "cage" effect.

3.1.1. Reactions in Gas–Solid Systems

Asymmetric bromination of alkenes via a gas−solid reaction has already been achieved using a single chiral crystal lattice of 4,4′-dimethylchalcone.[13] Complete enantioselectivity has been also achieved in the asymmetric halogenation of methacrylic acid using solid α-CD complexes.[14] Other halogenation and hydro halogenation reactions of alkenes such as crotonic, methacrylic, *trans*-cinnamic[15] and maleic acids, ethyl *trans*-cinnamate,[16] styrene,[17] and *trans*-butenoic acid[18] have been carried out in a crystalline α- or β-CD complex. Representative results are summarized in Table 1. The advantage of using a CD complex, rather than other crystal lattices, is that a variety of substrates can be used without the problem of large single crystal formation or concern

Table 1. Selective Reactions in Gas−Solid CD Systems

substrate	CD	reagent	yield (%)	optical yield (%)	ref
crotonic acid	α	HBr	28.6	29	15
methacrylic acid	α	Cl_2	17.4	100	15
maleic acid	β	Cl_2	53.0	88	15
trans-cinnamic acid	β	Br_2	2.5	40	15
(in DMSO)	β	Br_2	4.4	6	15
ethyl *trans*-cinnamate	α	HBr	17	46 (*R*)	16
	β	HBr	21	31 (*S*)	16
styrene	α	Br_2	90	0	17
	α	Cl_2	38	14 (*S*)	17
	β	Cl_2	22	8 (*S*)	17
trans-2-butenoic acid	α	HBr	60	58.4 (*S*)	18
	α	HCl	23	64.4 (*S*)	18

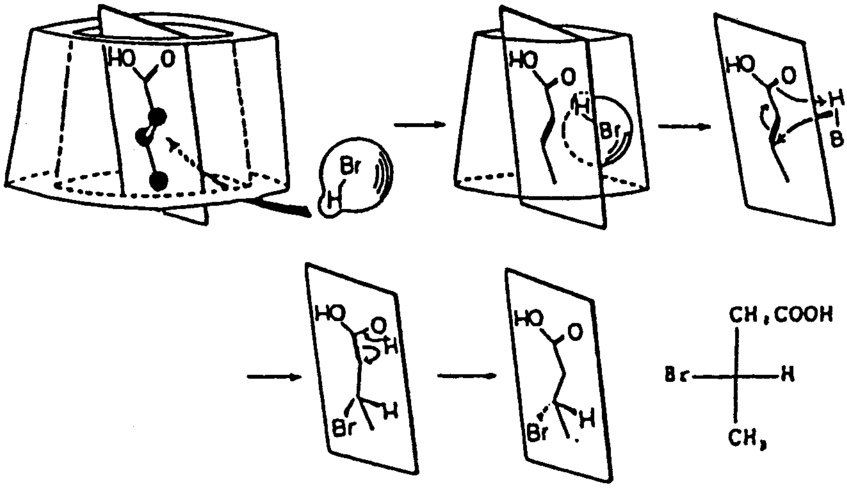


Figure 2. Reaction mechanism of asymmetric addition of hydrogen bromide to *trans*-2-butenoic acid in α-CD.[18]

about chirality. The CD crystalline complex was defined as a "microcrystal".[15] The crystal structures of the CD−guest complexes have been extensively studied by several groups and clarified at the molecular level.[12] A mechanism for asymmetric induction has been suggested on the basis of the X-ray crystal structure of the complex. As shown in Figure 2, asymmetric hydro halogenation should occur inside the cavity. In the crystalline complex of β-CD, the guest acid is anchored by the hydrogen bond between the primary hydroxyl group of the CD and the doubly bonded oxygen of the guest acid. The alkenic bond penetrates into the chiral environment in the middle of the cavity. The reagent molecules, consisting of a proton and a halide anion, apparently attack enantioselectively on the inclined plane of the carbon−carbon double bond from the side facing the wider opening site of the secondary hydroxyl site. When the reaction was repeated under homogeneous conditions in DMSO[15] solution, the ee dropped to 6% as a result of the release of microcrystals.

When a crystalline solid β-CD−coumarin complex was mixed with sodium borohydride in the solid state at 0 °C for 48 h, about 80% of the coumarin was reduced with *cis*-*o*-hydroxycinnamyl alcohol the major product (69%, Figure 3).[19] When the reaction was repeated in aqueous Na_2CO_3, the yield of *cis*-*o*-hydroxycinnamyl alcohol was decreased and both the structure 1,2- and 1,4-addition products were increased. The rigidity of the CD complex structure causes the regioselectivity.

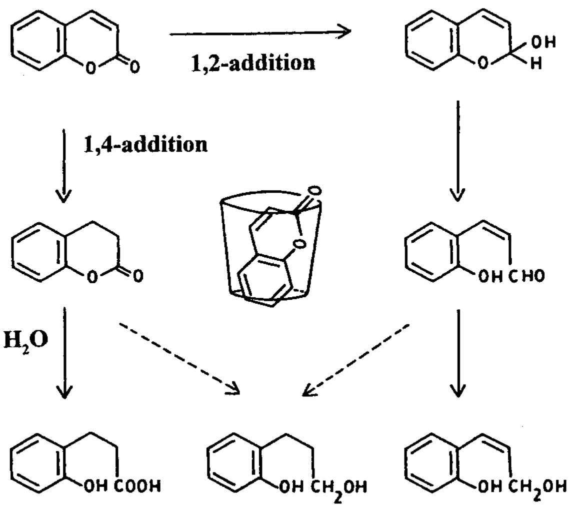


Figure 3. Reduction of coumarine with $NaBH_4$ and postulated conformation of β-CD−coumarin complex.[19]

3.1.2. Reactions in Liquid–Solid Systems

Using a microcrystal of a CD complex has also induced selective reaction in liquid-phase reactions in suspension. Asymmetric bromination of chalcone and benzylideneacetate in a crystalline β-CD complex was carried out in Br_2/CCl_4 solution in 60% ee.[20] The reduction of ketones using CD crystalline complex is quite a useful and simple route to chiral alcohols. Representative results are summarized in Table 2. Fornasier et al.[21] have achieved an ee of 32% using β-CD−ketone complexes suspended in a sodium borohydride ($NaBH_4$) aqueous alkaline solution. The highly asymmetric reduction of ketones has been achieved with crystalline CD complexes of achiral amine-boranes as reducing reagent (≤91% ee) by Sakuraba et al.[22] and with $NaBH_4$ in the presence of alkaline salts (≤84% ee)[23] by Kawajiri et al. (Figure 4). The explanation of the role of the alkaline salt can probably be ascribed to a salting-out effect. Hydrogen bonding between the carbonyl group of the substrate and β-CD secondary hydroxy groups may result in the enantiomeric face-selective attack of the hydride anion.

In the oxidation of aryl sulfides, optically active sulfoxides have been obtained by the combination of sodium hypochlorite and a CD complex of thioacetate (≤54% ee)[24] (Figure 5, Table 3) and of peracetic acid and alkyl sulfide in a crystalline CD complex (≤81% ee).[25] The product of the latter reaction, optically pure methyl 1-naphthyl sulfoxide has been utilized as a chiral auxiliary in nucleophilic addition to alkyl phenyl ketones with perfect stereoselectivity.[26] The enantiomeric excess observed for α,α-dichloromethyl sulfoxide obtained from resolution of this racemic mixture by β-CD is negligible (<1%). This fact suggests that asymmetric oxidations are not due to optical resolution but rather to kinetic selection during the reaction. No asymmetric induction was observed in the homogeneous oxidation of the β-CD−*n*-butyl phenyl sulfide complex dissolved in DMSO,[25] or in the halogenation of *trans*-cinnamic acid.[16] The oxidation of the solid CD complex was carried out in other solvents such as CCl_4, pentane, CH_2Cl_2, ac-

Table 2. Asymmetric Reductions with CDs under Heterogeneous Conditions

substrate	CD	reagent	media	yield (%)	optical yield (%)	ref
(*E*)$PhCH{=}CHCOCH_3$					32 (*S*)	21
m-$CH_3C_6H_4COCH_3$	β	$NaBH_4$	0.2 M Na_2CO_3	*a*	16 (*R*)	21
1-$(C_{10}H_7)CH{=}CHCOCH_3$					4 (*S*)	21
$FcCH{=}CHCOCH_3$					23 (*S*)	21
$C_6H_5COCF_3$	α	C_6H_5N	water	50	4 (*S*)	22
$C_6H_5COCF_3$	β	C_6H_5N	water	96	13 (*S*)	22
$C_6H_5COCF_3$	γ	C_6H_5N	water	93	8 (*R*)	22
$C_6H_5COCF_3$	β	$(CH_3)_3N$	water	27	2 (*R*)	22
$C_6H_5COCH_2Cl$	β	C_6H_5N	water	70	36 (*S*)	22
$C_6H_5COCH_2Cl$	β	$(CH_3)_3N$	water	50	2 (*R*)	22
$C_6H_5COCH_2Br$	β	C_6H_5N	water	67	20 (*R*)	22
$C_6H_5COCH_3$	β	C_6H_5N	water	8	91 (*S*)	22
$C_6H_5C_2H_4COCH_3$	β	C_6H_5N	water	26	89 (*R*)	22
$C_2H_5COCH_3$	β	C_6H_5N	water	22	47 (*S*)	22
$C_6H_5COCO_2CH_3$	β	C_6H_5N	water	63	7 (*R*)	22
acetylferrocene	β	$NaBH_4$	water	*b*	34.3 (*R*)	23
			LiCl/water	*b*	32.2 (*R*)	23
			NaCl/water	*b*	51.7 (*R*)	23
			KCl/water	*b*	40.7 (*R*)	23
benzoylferrocene	β	$NaBH_4$	water	*b*	49.2	23
			LiCl/water	*b*	43.0	23
			NaCl/water	*b*	82.0	23
			KCl/water	*b*	84.0	23

[a] Yield of 80–97%. [b] The chemical yield was not reported in the reference.

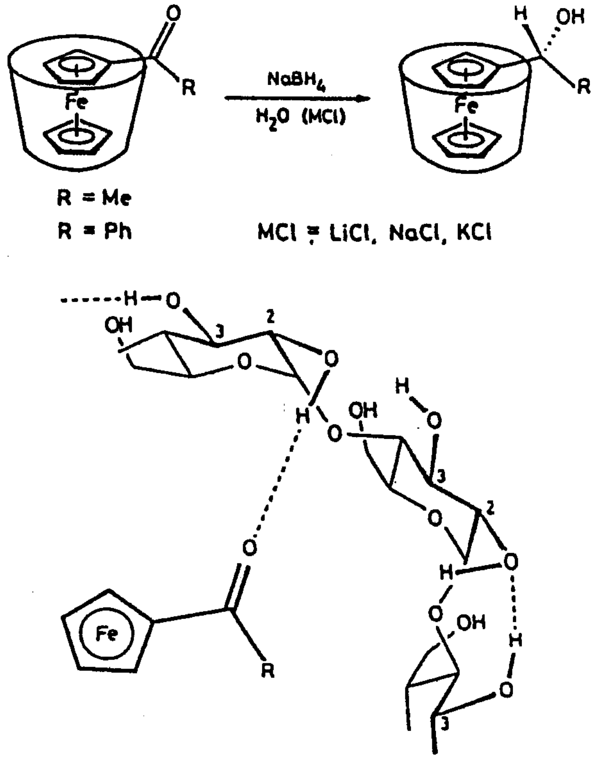
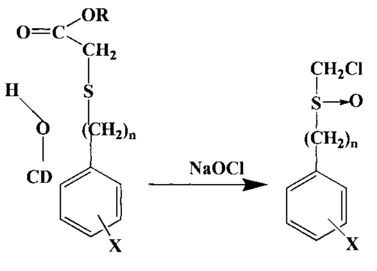


Figure 4. Asymmetric induction from ferrocenyl ketones with a CD complex and inclusion complex predicted by molecular model construction:[23] Me, CH_3; Ph, phenyl.

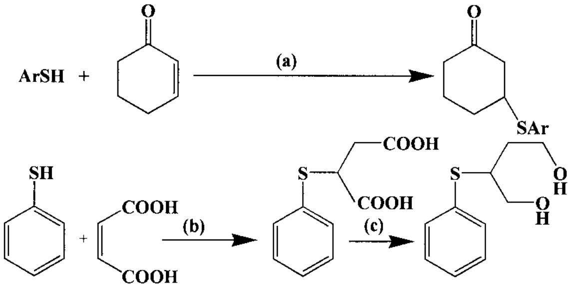


R=C_2H_5, $C(CH_3)_3$, n=0,1 X=H,*p*-CH_3,*p*-Cl

Figure 5. Asymmetric oxidation of arylsulfide in a crystalline CD complex.

etone, and methanol.[25] The highest optical yield was observed in water and in CCl_4 (45 and 40%, respectively), and the optical yield decreased in the order of solvents given above. This solvent effect seems to be correlated to the ratio of released guest molecule from the solid CD complex. These results show that the asymmetric oxidation of sulfide requires that the guest molecule be held rigidly in the chiral cavity of the CD complex in the solid state. Enantioselectivity depends on the size of the hydrophobic cavity. The oxidation of alkyl phenyl sulfides in the β-CD complexes resulted in higher chiral induction than that in the α-CD complexes. Conversely, an increase in chiral induction was observed in the oxidation of alkyl naphthyl sulfides with the γ-CD complex.[25] Fornasier et al. have reported on the effect of the precomplexation of reactant with CD on the enantioselectivity of the oxidation.[27] The CD–oxidant complexation is more effective than the CD–substrate complexation. A reversed configuration has been observed between the complexation with cyclohexanone and arylthiol in Michael additions (Table 4, Figure 6, ≤30% ee).[28]

Even under homogeneous conditions, without precomplexation treatment, the precipitation of CD was observed in a highly enantioselective reaction.[29] The rearrangement of allylic xanthates in water proceeds enantioselectively (Figure 7, Table 5).[30]



(a) suspended in water under N_2, at 0-25C, 7days with CD

(b)suspended in water under N_2, at 0-25C, 7days with CD

(c) $LiAlH_4$

Figure 6. Michael addition in a CD complex.

Table 3. Asymmetric Oxidations with CD under Heterogeneous Conditions[24−26]

substrate	CD	conditions	yield (%)	optical yield (%)
Ph-S-CH_2CO_2Et	*β*	NaOCl/water	*a*	3.7
Ph-S-$CH_2CO_2Bt^t$	*β*	NaOCl/water	*a*	53.8
p-MeC_6H_4-S-CH_2CO_2Et	*β*	NaOCl/water	*a*	5.4
p-MeC_6H_4-S-$CH_2CO_2Bt^t$	*β*	NaOCl/water	*a*	36.7
p-ClC_6H_4-S-CH_2CO_2Et	*β*	NaOCl/water	*a*	2.8
p-ClC_6H_4-S-$CH_2CO_2Bt^t$	*β*	NaOCl/water	*a*	21.6
$PhCH_2$-S-CH_2CO_2Et	*β*	NaOCl/water	*a*	6.7
$PhCH_2$-S-$CH_2CO_2Bt^t$	*β*	NaOCl/water	*a*	35.6
methyl phenyl sulfide	α	CH_3COOOH/water	96	4 *(S)*
	β	CH_3COOOH/water	98	15 *(S)*
ethyl phenyl sulfide	α	CH_3COOOH/water	97	10 *(S)*
	β	CH_3COOOH/water	95	26 *(S)*
phenyl propyl sulfide	α	CH_3COOOH/water	95	11
	β	CH_3COOOH/water	92	30
n-butyl phenyl sulfide	α	CH_3COOOH/water	98	6 *(R)*
	β	CH_3COOOH/water	94	45 *(R)*
	β	CH_3COOOH/CCl_4	*b*	40 *(R)*
	β	CH_3COOOH/pentane	*b*	30 *(R)*
	β	CH_3COOOH/CH_2Cl_2	*b*	14 *(R)*
	β	CH_3COOOH/acetone	*b*	5 *(R)*
	β	CH_3COOOH/CH_3OH	*b*	1 *(R)*
	β	CH_3COOOH/DMSO	*b*	0
isobutyl phenyl sulfide	α	CH_3COOOH/water	96	3 *(R)*
	β	CH_3COOOH/water	90	57 *(R)*
tert-butyl phenyl sulfide	α	CH_3COOOH/water	95	7 *(R)*
	β	CH_3COOOH/water	75	38 *(R)*
methyl 1-naphthyl sulfide	α	CH_3COOOH/water	92	1 *(S)*
	β	CH_3COOOH/water	95	81 *(S)*
	γ	CH_3COOOH/water	97	19 *(S)*
	DM*β*CD	CH_3COOOH/water	80	8 *(S)*
	TM*β*CD	CH_3COOOH/water	65	4 *(S)*
isobutyl 1-naphthyl sulfide	*β*	CH_3COOOH/water	40	31
	γ	CH_3COOOH/water	42	53
methyl 2-naphthyl sulfide	*β*	CH_3COOOH/water	98	49 *(R)*
	γ	CH_3COOOH/water	94	34 *(R)*
methyl 9-phenanthryl sulfide	*γ*	CH_3COOOH/water	87	37

[a] Yield of 8−10% [b] Yield of 80−90%.

Table 4. Dependence of Asymmetric Reaction on Precomplexation

guest in CD complex	CD	reagent	yield (%)	optical yield (% ee)
		Oxidation[27]		
both phenyl methyl sulfide and *m*-ClPBA[a]	*β* —-	45	12.4 (*S*)	
m-ClPBA	*β*	PMS	86	10.7 (*S*)
phenyl methyl sulfide	*β*	*m*-ClPBA	78	2.3 (*S*)
		Michael Addition[28]		
benzenethiol	α	2-cyclohexanone	67	1 (*S*)
	β	2-cyclohexanone	93	30 (*S*)
	γ	2-cyclohexanone	10	10 (*S*)
	β	2-cyclohexanone	39	4 (*S*)[b]
p-methylbenzenethiol	*β*	2-cyclohexanone	39	7 (*R*)
p-*tert*-butylbenzenethiol	*β*	2-cyclohexanone	35	5 (*R*)
benzylthiol	*β*	2-cyclohexanone	50	1 (*R*)
2-cyclohexanone	*β*	benzenethiol	84	4 (*R*)
	β	benzenethiol	66	0
	β	*p*-methylbenzenethiol	56	9 (*R*)[b]
	β	*p*-methylbenzenethiol	65	1 (*S*)
	β	*p*-*tert*-butylbenzenethiol	82	6 (*S*)
	β	benzylthiol	61	2 (*S*)

[a] *m*-Chloroperoxybenzoic acid. [b] Reaction carried out in triethylamine.

Table 5. Sigmatropic Rearrangement in a Water−Solid CD System[30]

reactant	CD	yield(%)	optical yield (% ee)
O-cinnamyl *S*-methyl dithiocarbonate	α	40	3.3
	β	80	45.9
	γ	87	12.0
O-cinnamyl *S*-ethyl dithiocarbonate	*β*	80	10.4
O-cinnamyl *S*-phenyl dithiocarbonate	*β*	67	10.7
O-crotyl *S*-methyl dithiocarbonate	*β*	54	2.4
O-crotyl *S*-phenyl dithiocarbonate	*β*	82	−
O-geranyl *S*-methyl dithiocarbonate	*β*	70	−

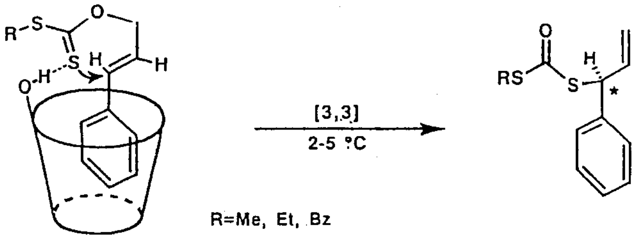


Figure 7. [3,3]-Sigmatropic rearrangement of an allylic xanthate in *β*-CD complex.[30]

3.1.3. Photochemical Reactions in Solid CD Complex Systems

The use of solid CD complexes in many photochemical reactions has been reported. Solid β- and γ-CD complexes also contribute to the stereochemical control of photodimerzation processes. By using solid CD complexes, excellent yields of photodimers of substituted coumarins were produced [31](Figure 8). The isomeric distribution of the photodimers was very different from that obtained only with the neat solid. As shown for the 4,6- and 4,7-dimethyl-substituted derivatives, which dimerize with high yields in the solid complex phase but not in the neat solid, the nature of the photodimers formed depended on the cavity size and was assumed to reflect the orientation of the coumarins in the cavity. The 7-monosubstituted derivatives do not dimerize in solid β-CD, but dimerize efficiently in media such as γ-CD complexes and neat solid. Suppression of the above reaction is explained by the formation of 1:1 complexes.

Selective benzoin acetate photolysis was achieved by using both β- and γ-CD complexes.[32] Efficient caging for radical pair recombination induced a remarkable preference for the formation of the photocyclization product.[33] In photoreactions of α-alkyldibenzyl ketones,[34] completely selective coupling was observed with the solid CD complex. In the photolysis of α,α-dimethyldeoxybenzoin, the formation of a significant amount of the photorearranged product, 4-isopropylbenzophenone, was obtained.[35] Intramolecular H-abstraction leading to enantioselective photoconversions was achieved in the photolysis of benzaldehyde with a solid β-CD complex (Figure 9).[36] The selective photoreactivity of the β-CD complex is rationalized by hypothesizing a 2:2 crystal arrangement resulting from the association of two 1:1 complexes in a "head-to-head" orientation. In the case of α-CD, the determined "head-to-tail" structure of the crystal clearly explains the lack of reactivity. In the case of γ-CD, the reaction occurs between a pair of benzaldehyde molecules contained in the CD cavity with a 1:2 stoichiometry. The photoreaction did not produce significant optical asymmetry in the products, owing to the larger reorientational mobility of the radical fragments as compared with that in

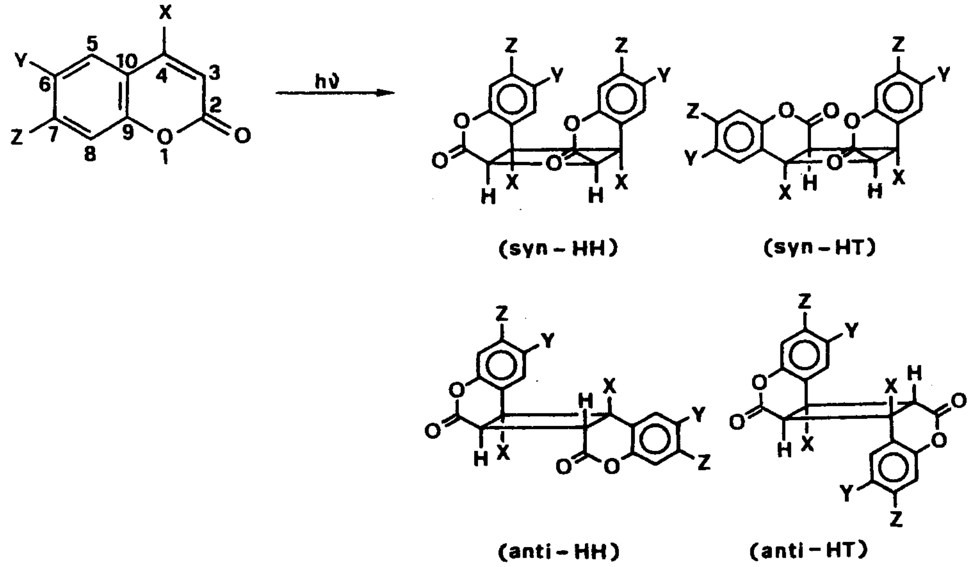


Figure 8. Four conformations of photodimerized coumarin.[31]

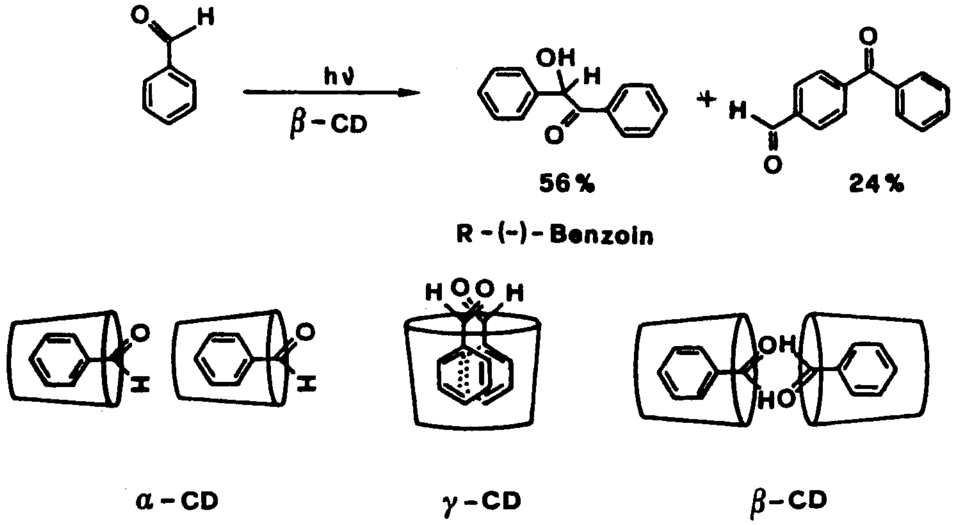


Figure 9. Enantioselective photoconversion of benzaldehyde and dependence of host–guest conformation on the cavity size of CD.[36]

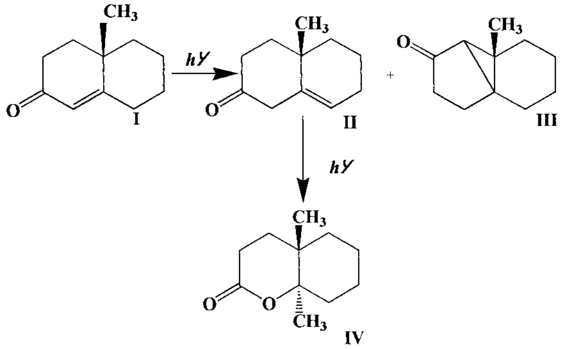


Figure 10. The formation of the products by photolysis of (R)-$\Delta^{1,9}$-10-methyl-2-octalone.

the β-CD complex dimer. The photorearrangement of benzenesulfoanilide in the solid β-CD phase was achieved with over 99% *ortho* selectivity, whereas the formation of the *ortho* product was not observed in homogeneous solutions such as benzene and methanol.[37] Similar effects were obtained in the photo-Claisen rearrangement of *m*-alkoxyallyl ethers[38] and the photolysis of benzyl phenyl esters[39] and the cyclic compound, (R)-Δ-10-methyl-2-octanone.[40] As shown in Figure 10, the product ratio is dependent on the solvent, with II favored in nonpolar media. In the α-CD solid complex, II is the major product (over 95% of the total product). In the photolysis of the complex dissolved in water, a new product, IV, was isolated, as a result of the addition of water.

3.2. Organic Reactions with Cyclodextrin in Solution

3.2.1. Hydrolysis

Most CD-mediated hydrolysis reactions proceed according to the Michaelis–Menten type. Initially, CD and the reactant form a tetrahedral CD–reactant reaction intermediate with a covalent bond. Then the secondary alkoxide ions of the CDs acting as nucleophiles attack the reactants. Such effects have been studied and reported for the enzyme model rather than *"extra reaction field effect"*. However, hydrolysis reactions have attracted great attention. Some representative artificial systems are described below.

Complexes of Ce^{IV} and α-, β-, or γ-CDs efficiently hydrolyze DNA at pH 8 and 50 °C.[41] The half-life of a phosphodiester linkage is around 5 h. Since the half-life without the CD–Ce^{IV} complexes is 200 million years, acceleration by the complexes is 10^{12} fold. The homogeneous complexes can be used as active sites for the artificial nucleases which selectively hydrolyze DNAs at the target sites.[42] Complexes of Ce^{IV} and γ-CDs also efficiently hydrolyzes the 3′,5′-cyclicmonophosphates of adenosine and guanosine (cyclic AMP and cyclic GMP) with half-lives of 7 and 16 s, respectively, in homogeneous solution at pH 7 and 30 °C.[43]

Peptide bonds in di- and tripeptides were also efficiently hydrolyzed by a γ-CD–Ce^{IV} complex at pH 7 and 60 °C.[44] Apparently 80% of peptide bonds were decomposed within 24 h. In this case, the main function of the γ-CD is to solubilize the Ce^{IV} ion, rather than to directly participate in the catalytic function. Without the presence of a CD, Ce^{IV} ions rapidly precipitate due to the formation of hydroxide gel in both hydrolysis reactions of DNA and peptide. It has been proposed that hydrogen bonds are formed between the hydroxyl groups of CDs and the coordinated water molecules around the Ce^{IV} ion.[44] The metal ion would be located at the top of the cavity.

Partially methylated β-CDs hydrolyze 2,4-dinitrophenyl sulfate esters, as for carboxylate, carbonate, and phosphate esters, catalytically at pH 6.8 and 25 °C. The dipolar environment provided by CDs may be important for fast hydrolysis.[45] CDs also accelerate the hydrolysis of amides derived from aromatic amines and strong acids such as trifluoroacetic acid[46] with a 2:1 cooperative binding. The hydrolysis of a series of 4-substituted *N*-methyltrifluoroacetanilides with and without α- and β-CD at $7.5 < \text{pH} < 10.6$ has been reported.[47] Both α- and β-CD catalyze the hydrolysis of *N*-methyl-4-nitrotrifluoroacetanilide, but inhibit the hydrolysis of the 4-chloroanilides which are less reactive. The CD cavity may provide an environment complementary to the transition state for expulsion of the anilide leaving group forming 1:1 CD–reactant complexes. This report suggests that the CD cannot provide general acid catalysis for breakdown of the tetrahedral intermediate, which is the key function of enzymes designed to hydrolyze amide bonds. The enolization of indan-2-one was catalyzed by β-CD in basic solution.[48] The enolization is also catalyzed by the secondary alkoxide ions of CDs as nucleophiles attack the reactants. In this reaction, the alkoxide ions of CDs act as general bases toward indan-2-one, facilitated by partial inclusion of the transition state in the CD cavity.

The CD-mediated hydrolysis of *p*-nitrophenyl ester afforded us many historical and famous reactions[2] as well as the new role of CD cavities, such as bimodal transition binding[5,6i,45] and "outside cavity complex" formation.[49] The tetrahedral intermediate does not accommodate the *p*-nitrophenyl acetate moiety in its CD cavity. When a small hydrophobic molecule such as cyclohexanol was added to the solution, it occupied the vacant hydrophobic space of the intermediate, exhibiting no retardation effect on the hydrolytic cleavage of *p*-nitrophenyl acetate. The effects of DMSO on the kinetics of cleavage of nitrophenyl alkanoates by α- and β-CD in a basic solution has been reported.[50] The cleavage of *m-tert*-butylphenyl acetate is more accelerated in 60% (v/v) aqueous DMSO than in water because the solvent change weakens the substrate binding more than the transition-state binding.

Acyl transfer might very well be the next important target to be achieved within a CD cavity. The reaction of α-amino acid anions with *p*-nitrophenyl acetate bound to β-CD was accelerated by up to 20–30-fold.[51] The effect of the CD was attributed to reaction within a weak ternary complex formed by hydrogen bonding of the carboxylate group of the amino acid anion to secondary hydroxyl groups on the rim of the CD. Recently, different results have been reported for acyl transfer. The binding of *p*-nitrophenyl esters to CDs to some extent affects their susceptibility to attack by simple nucleophiles.[52] The CD-mediated reactions of *p*-nitrophenyl alkanonoate esters with other nucleophiles, including simple alkylamines that strongly bind to CDs.

The catalytic activity of CDs in hydrolysis affords the resolution of structural isomers[53] and optical isomers.[54] The methods are based on the observation that rate constants for the CD-catalyzed hydrolysis of selected structural isomers are significantly different.

3.2.2. Substitution

Breslow and Campell were the first to show that selective aromatic substitution can take place within the α-CD system.[55] They found that treatment of anisol in water at room temperature with HOCl and an excess of an α-CD resulted in 96% chlorination at the para position of the anisol ring. This phenomenon opened the way for use of CDs as "mediators" for selective in organic reactions. The results indicate that not only does the CD block substitution at all but one aromatic ring position, but it also actively catalyzes substitution at the unblocked position. One or more secondary hydroxyl groups can be converted into a hydrochlorite to explain the increased rate of chlorination in the complex (Figure 11).

Similar reactions using electrogenerated Cl_2 in sodium chloride solution instead of HOCl have given substantially the same results.[56] In relation to the chlorination of phenol and its derivatives, other halogen atoms have been regioselectively introduced into a phenolic compound using CDs. When bromine is used as the halogenating reagent, the formation of an inclusion complex between the CD and molecular bromine must be considered. Significant effects can be anticipated for organic reactions showing sensitivity to solvent polarity. The CD cavity is less polar than the bulk aqueous medium. Furthermore, since the formation of complexes with the CD lowers the concentrations of the free reactants in solution, one might reasonably expect that bromination in aqueous solution would be strongly retarded or even inhibited by CDs. The bromination of anisol[57] and phenols[58] were fairly retarded in the presence of α-CD. Why? Tee et al. made detailed and systematic studies on α-CD-mediated bromination[59] and debromination[60] of a broad range of phenyl derivatives, and discovered that catalytic bromination ensues from a configuration in which the bromine is inside the α-CD cavity while the substrate is outside in a largely aqueous environment (Figure 12). In the reverse direction, catalyzed debromination occurs by attack of α-CD-bound bromide ion on the dienone, with acid catalysis. This catalysis results from the alternating solvation of the reactants but cannot be a simple microsolvent effect. Rather it is an "interfacial phenomenon", arising from the differential nature of the environment in which the catalyzed reaction takes place. Similar to bromination, iodation of phenol with $I_2{-}I$ was also affected by the presence of β-CDs. The result affected ortho/para selectivity.[61] The chlorination of acetanilide by chlorine gas in the presence of α-CD gave over 90% of the para-substituted product.[62]

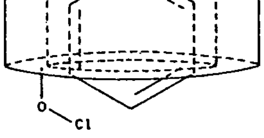


Figure 11. Schematic representation of an anisol molecule in the cavity of α-CD. Eighteen hydroxyl groups ring the rim of the cavity, one of which is written as its hypochlorite ester to indicate a mechanism by which the increased rate of chlorination in the complex may be explained.[55]

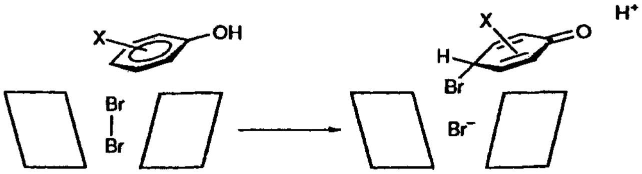


Figure 12. Electrophilic bromine attack mediated by CD.[59]

Other electrophilic substitution reactions have also been reported. Both α- and β-CDs facilitate the coupling between benzene diazonium cations and phenol with an up to 6-fold rate enhancement.[63] This may be due to the stabilizing effect of CDs of the reaction intermediate, namely a σ-complex with a positive charge on the phenyl ring originating from phenol. The σ-complex was spectrophotometrically detected using β-CD.[64]

The selective allylation, carboxylation, formylation, and dihalomethylation of the para position of phenol was successfully mediated by CD in alkaline aqueous solution. With α-CD, only *p*-hydroxybenzaldehyde was synthesized.[65] The key step for achieving selectivity is the formation of a ternary complex of CD, phenol, and $CHCl_3$. The chloroform molecule is transformed into dichlorocarbene by the action of hydroxide anion; this active intermediate then immediately attacks the closest proximal para position of the included phenol. The phenol hydroxy group is exposed to the bulk aqueous phase, and thus the para position must be buried within the CD cavity. The formylation of phenol with CCl_4 in NaOH aqueous solution, which is known as the Reimer−Tieman reaction, gives hydroxybenzaldehyde in very low yield. The reaction of phenols with CCl_4 and the addition of copper powder in an alkaline aqueous solution by the use of β-CD proceeded to give *p*-hydroxybenzoic acid in 59% yield with 99% para selectivity.[66] In a similar manner, the carboxylation of benzoic acid,[67−69] 4-biphenyl carboxylic acid,[70] 2-naphthalenecarboxylic acid,[71] and naphthalene[72] achieved the selective synthesis of terephthalic acid (100% selectivity), 4,4-biphenylcarboxylic acid (71% selectivity), and 2,6-naphthalenedicarboxylic acid with an 84% selectivity from 2-naphthalenecarboxylic acid, and 79% from naphthalene (Figure 13). The hydroxyl group of phenol has an activating effect on electrophilic substitution of the aromatic ring. On the contrary, the carboxyl group of benzoic acid has a deactivating effect. Consequently, the substitution

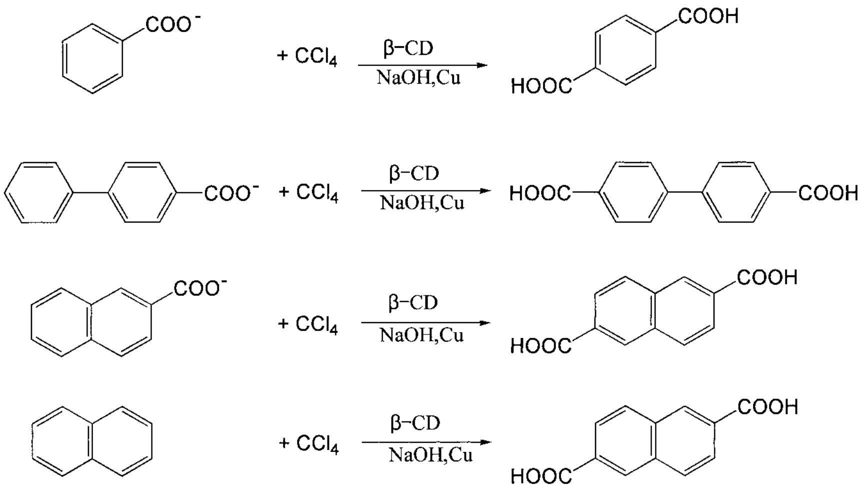


Figure 13. Stereoselective carboxylation mediated by β-CD cavity.

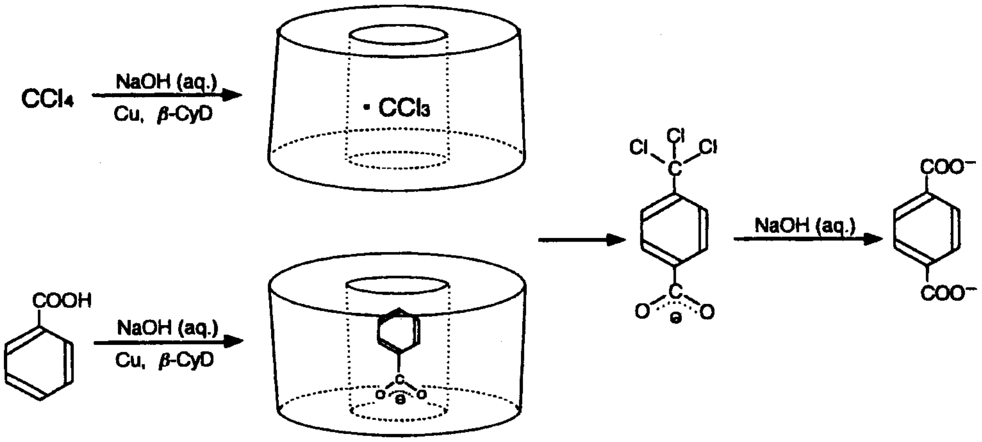


Figure 14. Selective substitution in an alkaline solution with Cu.[69]

of carboxyl derivatives should occur slightly preferentially at the meta position. It is interesting that CD-mediated carboxylation gives excellent yields with para selectivity. The essential factor in the carboxylation is that both substrates and carbon tetrachloride are included in β-CD cavities with a 1:1 stoichiometry in the reaction mixture. This was established by looking at ^{1}H chemical shifts. The carbon tetrachloride included in β-CD may react with metallic copper powder, or copper(I) chloride, to form the trichloromethyl radical as the active species rather than trichloromethyl ion. Copper is not a catalyst but a reactant. Each reactant included in CD comes together to react stereoselectively.[69] A representative mechanism is indicated in Figure 14.

The benzoate anion is axially incorporated into the cavity of the β-CD with orientation such that the carboxylate group is at the primary hydroxyl side of the β-CD. The high selectivity was attributed to the conformation of the β-CD–benzoate inclusion complex. Thus, β-CD mediated both the process by which the trichloromethyl radical is formed via a unimodal system and the carboxylation via a bimodal system. In α- and γ-CD cavities, trichloromethyl radical was hardly formed.

The effect of CDs on the *Z*/*E* selectivity in the Witting reaction with semistabilized ylides has been reported.[73] For the same Wittig reaction, an increase in the *Z* selectivity from 57% to 92% has been obtained with DMF as solvent, and an increase in the *E* selectivity from 67% to 80% has been obtained with ethanol as solvent. The binding of the substrate to CDs in a dipolar aprotic solvent such as DMF is weaker than that in water.[74] A correlation between the size of the CD cavity and the selectivity was observed; addition of a larger sized CD gave good selectivity, so that CD complexation seems to affect the reaction selectivity in DMF. The results are discussed in light of recent results on the mechanism for the Wittig reaction and are best rationalized in terms of the Vedejs four-center mechanism[73] (Figure 15).

3.2.3. Reduction

$NaBH_4$ is the most generally used reduction reagent in aqueous solution albeit with poor selectivity. The first study of CD-mediated asymmetric induction without precomplexation was the reduction of aryl trifluoromethyl ketones with $NaBH_4$ in an alkaline aqueous solution of sodium cholate micelle. Optically active carbinols in 0–10% ee were obtained in the presence of a 10-fold molar excess of β-CD over the substrate,[75] but in 10–46%ee with bovine serum albumin (BSA) in place of sodium cholate under the same conditions. The high selectivity may be due to the stability of the CD–substrate complexes and the orientation of the carbonyl group within the complex. Sodium dithionate which is also easily handled and

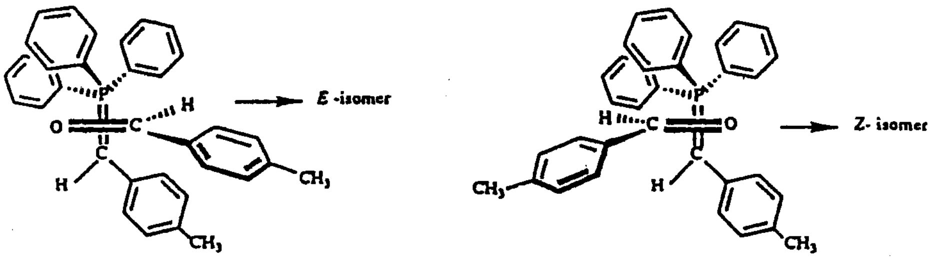


Figure 15. Hypothetical transition state in the Wittig reaction between 4-methyl benzaldehyde and (4′-methylbenzyl)-triphenylphosphonium bromide for the four-center mechanism; in the reaction, (*E*)- or (*Z*)-4,4′-dimethylstilbene are yielded.[73]

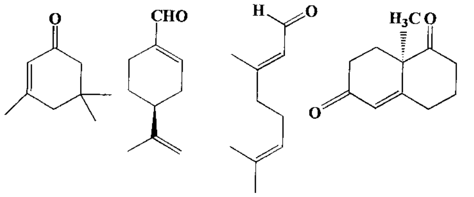


Figure 16. Substrates for reductions mediated by CD.

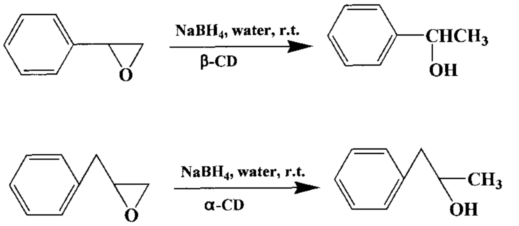


Figure 17. Ring-opening reaction of styrene oxide and 1,2-epoxy-3-phenylpropane with $NaBH_4$ mediated by β- and α-CD, respectively.

Table 6. Asymmetric Reduction in the Presence of Various Monosubstituted CDs in Aqueous Buffer Solution with $NaBH_4$[80]

substrate	cyclodextrin	optical yeild (ee %)
benzoylformic acid	α-CD	0
	β-CD	4 *(R)*
	γ-CD	2 *(S)*
	6-amino-6-deoxy-β-CD	18 *(R)*
	6-deoxy-6-(dimethylamino)-β-CD	26 *(R)*
	6-(benzylamino)-6-deoxy-β-CD	24 *(R)*
	6-deoxy-6-(phenethylamino)-β-CD	33 *(R)*
	6-deoxy-6-(phenylpropylamino)-β-CD	8 *(R)*
indol-3-pyruvic acid	β-CD	4 *(R)*
	6-amino-6-deoxy-β-CD	36 *(R)*
	6-deoxy-6-(dimethylamino)-β-CD	38 *(R)*
	6-(benzylamino)-6-deoxy-β-CD	36 *(R)*
	6-deoxy-6-(phenethylamino)-β-CD	39 *(R)*

a water soluble reducing reagent with β-CD has been used for the stereoselective reduction of (*R*)-(−)-carvone,[76] menthone[77] and the compounds which has carbon−carbon double bond of the α,β-carbonyl group[78] (Figure 16). Interestingly, a remarkabe effect by the CD on the menthone product was found in mixed-solvent systems. Aqueous DMF (1:1) increased the yield from 14.0% without CD to 76% with β-CD in water, the menthol/neomenthol ratio being 3.6/1.0. Under phase-transfer conditions, lipophilic CD, heptakis(2,6-di-*O*-methyl)-β-CD(DMCD), in water−benzene mixture gave 82.0% yield with a good stereoselectivity (the menthol/neomenthol ratio being 2.0/1.0). DMCD also affected the reaction of the compounds which has carbon−carbon double bond of the α,β-carbonyl group in water−toluene mixture (1:1). Both complexation and reduction seem to occur mainly in the organic phase, leading to a very high yield.

Reductive ring opening of epoxides with $NaBH_4$ has also been influenced by the addition of CDs. Styrene oxide smoothly underwent a ring-opening reaction with $NaBH_4$ and 2 mol equiv of a β-CD[79] to give 1-phenylethanol with high selectivity of up to 90%. 2-Phenylethanol, however, was preferentially formed in the absence of a β-CD (Figure 17). The kinetic resolution of the racemic epoxide was observed. Kinetic studies suggest that the resolution is based on the different reaction rates between the two enantiomers included in the CD cavity. Chiral recognition in the complex formation was excluded as the reason for the enrichment of the *S* form. It is considered that the reaction rate of the $NaBH_4$ reduction for the β-CD−*R* form is faster than that for the β-CD−*S* form, this rate difference giving preferentially the *S* form. Similar phenomena have been reported in an oxidation in crystalline complexes.[25] The reaction of other epoxides, such as 1,2-epoxyindan and 1,2-epoxy-3-phenylpropane were affected by the presence of an α-CD to proceed smoothly with high regioselectivities. The α-CD includes these styrene derivative in a 2:1 stoichiometry.

Whether in an aqueous or an organic solvent, it is possible that the reagent or substrate can still form a host−guest complex through specific interaction with the CD. Adequate modification of the β-CD attaching to a new interaction point or adequate change of the hydrophobic cavity can be expected to result in an appreciable ee in an asymmetric reaction (Table 6). Higher enantioselectivity in the reduction of benzoylformic acid (BFA) using $NaBH_4$ has been reported using 6-amino-6-deoxy-β-CD (ACD) as the host in place of β-CD in neutral aqueous buffer solution.[80] The phenyl group can be used as a cavity size control factor and the sp^3 carbons between the parent CD cavity and the phenyl group can be used as a flexible arm.[81] As shown in Figure 18, the enantioselectivity was related to the orientation of the substrate in the presence of a "self-guest group": In the case of BFA, when the substrate is held between the hydrophobic cavity and the bulky hydrophobic substituent of the modified CD, a higher ee is obtained. When BFA cannot participate in the self-inclusion, then lower ee's are observed. Although in the case of an oval-shaped substrate, such as indol-3-pyruvic acid (IPA), which cannot participate in self-inclusion, but can form an outside complex with the CD derivatives near the rim of CD, high enantioselectivities were then observed with almost all of the amino-CD derivatives, irrespective of the position of

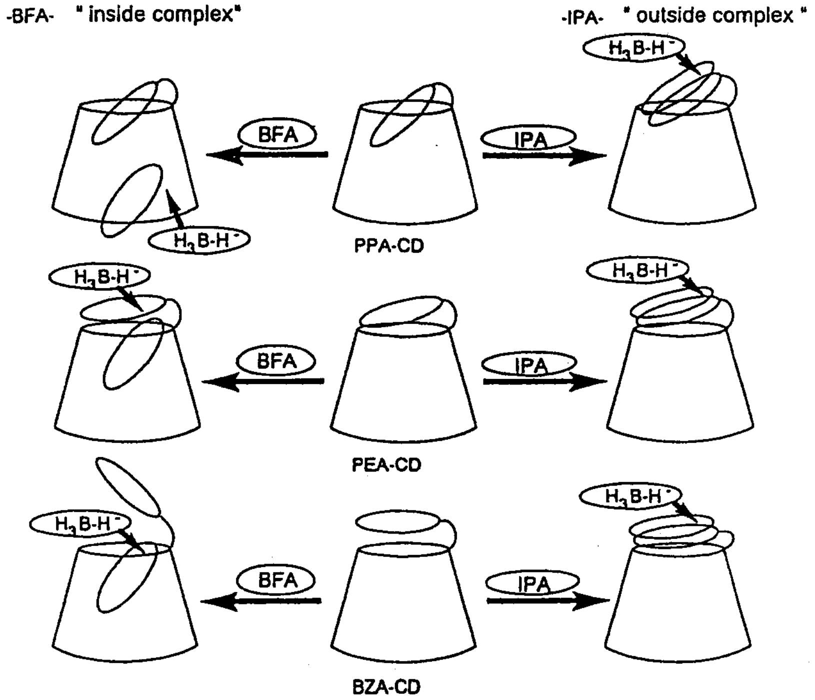


Figure 18. Suggested orientation of substituent-modified CD complex.[4c,82]

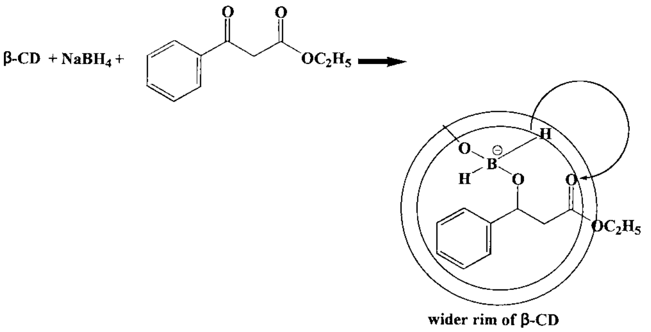


Figure 19. Effect of CD in reduction with $NaBH_4$.

the substituent.[82] These results suggest that the rim of CD cavity also may lead to substantial improvements in organic reactions.

Recently, Doussot et al. have reported that regio- and stereoselectivity in the reduction of substituted epoxides and aromatic ketones with $NaBH_4$ in the presence of CDs depended mainly on interactions with the wider rim, the secondary hydroxy side, of the CD. This result means that an alkoxyborohydride intermediate is formed in the first step of the reaction[83] (Figure 19).

CD also can mediate electrochemical reduction reactions. In the presence of β-CD or mono-6-deoxy-6-[*N*-(2-aminoethyl)]amino-β-CD (β-CDen), BFA was reduced electrocatalytically with methyl viologen (MV^{2+}), the two-electron reduction product of which behaves as the active reductant, with excellent yields (99%) and enentioselectivity, 14% ee (*S*) and 19% (*S*), respectively.[84] A mechanism was not proposed. However, it has been reported that β-CD included methyl viologen[85] in a 1:1 stoichiometry as well as MV bound more strongly than either MV^+ or MV^{2+} to β-CD.

The electrochemical reduction of acetophenone and ethyl cinnamate was also studied with β-CD.[86] CDs in electrochemical reduction has been used as inhibitors to prevent the formation of byproducts by protecting the reaction site of the accommodated substrate.

3.2.4. Oxidation

As shown in Table 7, the asymmetric oxidation of sulfides has also been reported.[87] The most successful enantioselectivity (33% ee) was obtained using a specially designed substrate (*m*-*tert*-butylphenylethyl sulfide) by (*m*-chlorophenyl)perbenzoic acid (*m*-ClPBA) with excess β-CD in aqueous solution at 4 °C. No appreciable ee's ($<$1%) could be observed in the resulting sulfoxides using other oxidants such as H_2O_2, NaOCl, or $NaIO_4$ in aqueous solution and in homogeneous DMF solutions.[27] Some reactions with appreciable ee's in organic solvents have been reported. An optically purity of 30% for *n*-butyl phenyl sulfoxide was obtained in a pyridine solution with H_2O_2 as the oxidant.[29] Interestingly, heterogeneous oxidation using a solid CD complex of the same series of substrates in water containing CH_3CO_3H produced the sulfoxide with the opposite configuration. The homogeneous reactions produced (*R*)-ethyl, (*S*)-*n*-butyl, and (*S*)-isobutyl phenyl sulfoxides in optical yields of 9.8%, 30.0%, and 1.7%, respectively, whereas the heterogeneous reactions gave the corresponding sulfoxides with the opposite configurations in higher optical yields: *S* 26, *R* 42, and *R* 57% ee, respectively (Figure 20). In these experiments, although the oxidation was carried out without any precomplex treatment, the precipitation of β-CD was observed during the reaction which had a high enantioselectivity. This fact indicated that the CD−substrate complex was formed even in pyridine solution. The configurational differences of the CD−complex structure in either water or pyridine seem to reflect the optical yields.

Table 7. Asymmetric Oxidation of Sulfides Mediated by CD[29,87]

substrate	CD	reagent	media	yield (%)	optical yield (%)
ethyl tolyl sulfide	α	H_2O_2	water	*a*	0.4
	α	*m*-ClPBA[b]	water	*a*	7.5
	β	H_2O_2	pyridine	32	2.0
ethyl 4-*tert*-butylphenyl sulfide	β	H_2O_2	water	*a*	0.4
ethyl 4-*tert*-butylphenyl sulfide	β	H_2O_2	water	*a*	6.7
	α	H_2O_2	water	*a*	4.6
	γ	H_2O_2	water	*a*	4.1
	β	*m*-ClPBA[b]	water	*a*	20.7
	β	*m*-ClPBA[b]	water	*a*	33.7
	β	*t*-BuOOH	water	*a*	19.7
	β	$PhI(OAc)_2$	water	*a*	25.9
methyl *n*-propyl sulfide	β	H_2O_2	pyridine	50	0.90 *(R)*
methyl *n*-butyl sulfide	β	H_2O_2	pyridine	50	0.25 *(S)*
benzyl methyl sulfide	β	H_2O_2	pyridine	50	2.80 *(S)*
benzyl ethyl sulfide	β	H_2O_2	pyridine	68	1.10 *(S)*
benzyl-*n*-propylsulfide	β	H_2O_2	pyridine	58	0
benzyl isopropyl sulfide	β	H_2O_2	pyridine	58	2.10 *(S)*
phenyl methyl sulfide	β	H_2O_2	pyridine	38	0.03 *(S)*
phenyl ethyl sulfide	β	H_2O_2	pyridine	69	9.80 *(R)*
phenyl *n*-butyl sulfide	β	H_2O_2	pyridine	12	30.00 *(S)*
phenyl isobutyl sulfide	β	H_2O_2	pyridine	60	0.40 *(R)*
tolyl methyl sulfide	β	H_2O_2	pyridine	12	1.70 *(S)*
tolyl ethyl sulfide	β	H_2O_2	pyridine	32	2.00 *(S)*
tolyl *n*-butyl sulfide	β	H_2O_2	pyridine	61	3.10 *(R)*
	β	H_2O_2	pyridine	109	8.90 *(S)*

[a] Yield 60−70%. [b] *m*-Chloroperoxybenzoic acid.

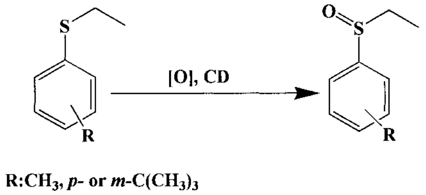


Figure 20. Asymmetric oxidation of sulfide.

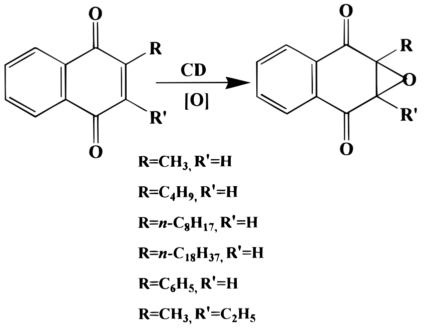


Figure 21. Asymmetric epoxidation of vitamin K derivatives with CD.

The addition of an oxygen atom to an alkenic double bond gives an epoxide. Colonna et al. have reported the asymmetric epoxidation (Weitz−Scheffer epoxidation) of vitamin K_3 analogues in aqueous alkaline buffer solution or in DMF−solid Na_2CO_3 in the presence of both α- and β-CD[88] (Figure 21, Table 8). The epoxidation of 2-methyl-1,4-naphthoquinone (vitamin K_3) with *tert*-butyl hydroperoxide and β-CD in pH 9 buffer solution and in DMF−solid Na_2CO_3 gave a product with optical yields of 22 and 24%, respectively. The reaction with α-CD, on the other hand, gave the corresponding product without enantioselectivity. The highest ee was observed using an α-CD in the epoxidation of 2-*n*-octyl- or 2-*n*-octadecyl-1,4,-naphthoquinone, both of which are large molecules for the cavity size of an α-CD, in DMF−solid Na_2CO_3 (39 and 48% ee, respectively). These are the highest enantioselectivities reported so far in dipolar aprotic solvents. It is possible that the oxidant can still give an inclusion complex through interactions with the polar groups of the CD in DMF, so that the stereoselectivity of the reaction can be attained through the asymmetric environment provided by the oxidant. Although the mechanism of epoxidation is clearly different in the two solvents, DMF and the aqueous buffer, it is difficult to account for the higher enantioselectivities observed in DMF with respect to the aqueous medium.

CDs are often used for the retardation or inhibition of oxygenation in the food industries because CDs accommodate a variety of substrates in the protection of the guest from other reagents. Interestingly, the oxidation of inorganic compounds by oxygen has also been reported.[89] The oxidation of iodine to I_3^- by oxygen dissolved in water containing $HClO_4$ was accelerated by using an α-CD. The oxidation rate of iodide is first order in the concentrations of α-CD and $HClO_4$, whereas it is second order in the KI concentration. These results are consistent with the formation of a ternary inclusion complex of α-CD, hydrogen iodide, and oxygen. α-CD is the most effective because a small hydrogen iodide molecule is likely to be most favorably bound to the small cavity of α-CD.

Davies et al. made detailed and systematic studies on the reaction between para-substituted aryl alkyl sulfides and substituted perbenzoic acids and alkyl percarboxylic acids with α-CD, and suggested a mechanism.[6i−k] The principal pathway is the reaction of the 2:1 CD−peracid complex with the unbound sulfide, although the extent of transition state stabilization by the second CD molecule is only about the same as its stabilization of the peracid in the ground state (Figure 22).[90] A similar reaction is the

Table 8. Weiz–Scheffer Epoxidation Mediated by CDs[88]

substrate	CD	reagent	media	yield (%)	optical yield (%)
2-methyl-1,4-naphthoquinone	β	*t*-BuOOH		33	22
	α	*t*-BuOOH		100	0
	β	H_2O_2	buffer solution	100	2
	β	NaOCl	(pH 9)	98	1
	β	HPP[a]		47	0
	β	MCPBA		100	2
	β	*t*-BuOOH	DMF/Na_2CO_3	96	24
	α	*t*-BuOOH	DMF/Na_2CO_3	99	0
	β	*t*-BuOOH	DMF/$NaHCO_3$	0	–
	β	*t*-BuOOH	DMF/NaOH	53	14
	β	*t*-BuOOH	DMSO/Na_2CO_3	65	14
	β	*t*-BuOOH	DMSO/$NaHCO_3$	80	7
	β	*t*-BuOOH	DMSO/NaOH	66	
2-*n*-octyl-1,4-naphthoquinone	β	*t*-BuOOH	DMF/Na_2CO_3	90	41
	α	*t*-BuOOH	DMF/Na_2CO_3	61	48
	β	HPP[a]	DMF/Na_2CO_3	87	19
	β	MCPBA	DMF/Na_2CO_3	0	0
2-*n*-butyl-1,4-naphthoquinone	β	*t*-BuOOH	DMF/Na_2CO_3	76	30
	α	*t*-BuOOH	DMF/Na_2CO_3	79	39
2-*n*-octadecyl-1,4-naphthoquinone	β	*t*-BuOOH	DMF/Na_2CO_3	47	27

[a] 2-Hydroperoxy-2-phenylpropane.

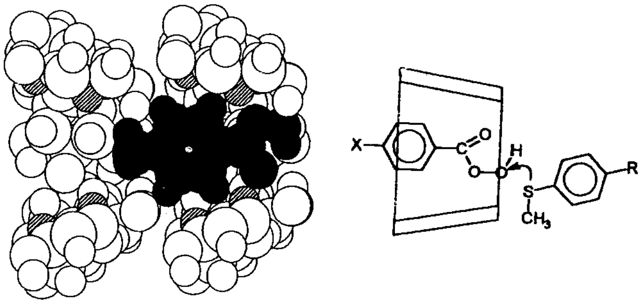


Figure 22. (Right) A 2:1 complex of α-CD with 4-methylperbenzoic acid (H-5 and H-3 protons shown cross-hached)[6k] and (left) the mechanism of the oxidation of alkyl sulfide by peracid.[90]

α-CD-mediated reaction between iodide and substituted perbenzoic acids by both unimodal and bimodal CD systems.

The oxidation of formic acid to CO_2 in an aqueous solution has also been mediated by an α-CD with bromine.[91]

Similar to reduction, electrochemical oxidation with CD have been reported. The $[FeCp(CpCH_2N(CH_3)_3)]^+$ cation which was included in α-, β-, and γ-CDs decreased the rate constant for oxidation by bispyridine-2,6-dicarboxylatecobalate(III), while the rate constant of ascorbic acid oxidations by $[FeCp(CpCH_2N(CH_3)_3)]^{2+}$ increased when the oxidant was included.[92] The deceleration and acceleration of electron-transfer reactions upon CD inclusion of the reduced and oxidized ferrocenes, respectively, are primarily the result of an increase in the reduction potential of the $[FeCp(CpCH_2N(CH_3)_3)]^{+/2+}$couple. This couple is also included in the hydrophilic calixarene derivative and the redox potential of the inclusion complex decreased. These results suggest the acceleration in the rate of oxidation of the $[FeCp(CpCH_2N(CH_3)_3)]^+$ cation in the calixarene cavity.[93]

3.2.5. Addition

Intermolecular Diels–Alder reactions in aqueous solution were affected by the addition of CDs. This observation was first noted in 1980 by Breslow.[94] The origin of this acceleration was attributed to a hydrophobic effect. When a furan molecule was heated in an aqueous solution at 89 °C for 6 h, epimeric mixtures (the ratio: 0.5) of Diels–Alder adducts were formed in a 20% yield. The same reaction with an equivalent of a β-CD enhanced the yield to 91% with an epimeric ratio of 0.67[95] (Figure 23). The authors suggested that in order for an intramolecular reaction to occur, both the diene and dienophile had to be simultaneously included within the β-CD cavity. They did not exclude, however, the possibility that complexing the dithiane portion of the molecule would also result in juxtapositioning the two reactive ends of the molecule. With an α-CD, no improvement in reaction yield was observed. The role played by β-CD in intramolecular cyclization reactions of organic molecules in an aqueous solution reinforces the importance of hydrophobic interactions in the cavity. The addition of a less polar cosolvent could also be used to influence the stereoselectivity in Diels–Alder reactions.[95]

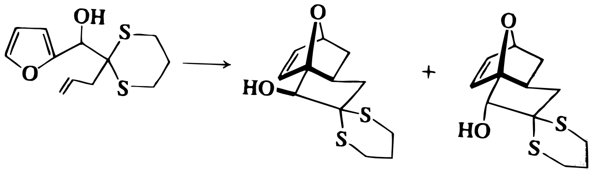


Figure 23. Intramolecular Diels–Alder reaction.

Intermolecular Diels–Alder reactions between cyclopentadiene and diethyl fumarate exhibited a saturation kinetics with respect to β-CD concentration.[96] The saturation kinetics disappeared when the dienophile was changed from diethyl fumarate to ethyl acrylate. In this case, only cyclopentadiene could be trapped in the β-CD cavity. The reaction of cyclopentadiene with ethyl fumarate in the presence of the highest possible concentration of β-CD (0.015 M in water) showed on 21% ee enantioselectivity[97] (Figure 24). The β-CD assists Diels–Alder reactions in the solid phase[98] as well as in high polar organic solvents. There seems to be no simple correlation

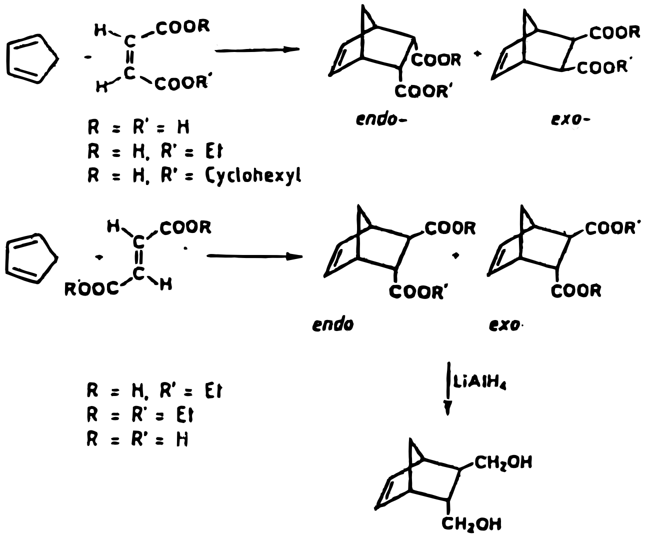


Figure 24. Diels–Alder reaction mediated by CD.[97]

$$\mathrm{FcCHO} \xrightarrow{\mathrm{ZnEt_2,TMCD}} \mathrm{FcCHOHCH_2CH_3 + FcCHOCH_2CH_3 + FcCH_2OH}$$

Fc=ferrocenylcarboxyaldehyde

Figure 25. Enantioselective addition of the diethylzinc to aldehydes mediated by alkylated CDs.

between the effect of CD and the substituent parameters of dienophiles when cyclopentadiene was used as diene.[99] The thermodynamics of the Diels–Alder reaction of glycoorganic dienes in aqueous solution with either β-CD or glucose has also been reported.[100] The observed rate enhancement is larger in glucose or saccharose solutions than in pure water. Interestingly, the reaction in concentrated solutions of glucose or other simple carbohydrates is even faster than in a saturated solution of β-CD. The origin of this acceleration is discussed in terms of water–sugar interactions.

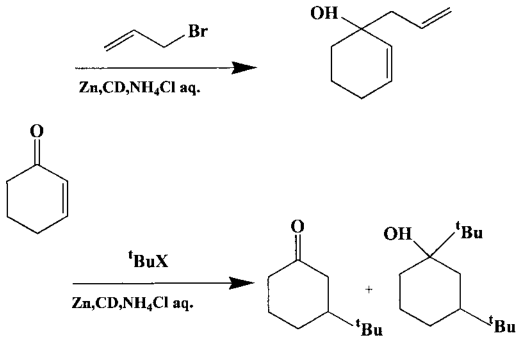


Figure 26. Allylation and *tert*-butylation of 2-cyclohexanone in a 5:1 water–THF media with CD.

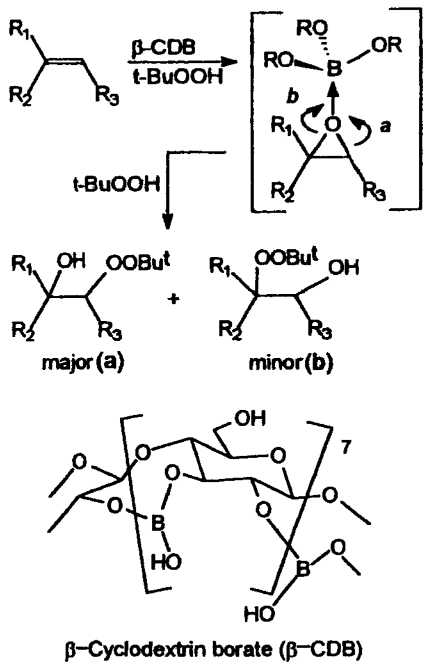


Figure 27. The mechanism of oxygenation with *t*-BuOOH (top) and β-CD borate (bottom).[103]

The enantioselective addition of diethylzinc to aldehydes and allylation and *tert*-butylation promoted by alkylated CDs have been reported.[101] Dialkylzincs act as very effective alkyl donors to aldehydes in aprotic organic solvents. Treatment of ferrocenylcarboxyaldehyde (Fc-CHO) in degassed hexane–toluene (1:1) at room temperature with diethylzinc and heptkis(2,3,6-*O*,*O*′, *O*″-trimethyl)-β-CD (TMCD) gave the chiral secondary alcohol, $\mathrm{FcCHOHCH_2CH_3}$, in 20% ee (Figure 25). Similar reactions using heptkis(2,6-*O*,*O*′-dimethyl-3-*O*-butyl)-β-CD (DMBCD) instead of TMCD have given substantially the same results. When β-CD or DMCD was used only the aldehyde was recovered. The synthesis of other aromatic aldehydes under similar conditions gave very small enantioselectivity (up to 6%). Although the role of CD was not clear, the formation of a ternary complex from the CD, aldehyde, and diethylzinc was expected. β-CD, DMCD, and TMCD also promoted remarkably good yields in the allylation and *tert*-butylation of 2-cyclohexanone using Zn dust and alkyl halides in a 5:1 water–THF solution. In particular, the reaction with *tert*-butyl bromide and TMCD raised the asymmetric induction (50% ee)[102] (Figure 26).

Hydroxy-substituted dialkyl perepoxides have been of interest as radical sources and they are usually prepared from the respective epoxides and an alkyl hydroperoxide using acidic or basic catalysts. β-CD borate catalyzes the sensitive oxygenation of aryl substituted alkenes in a single step in the presence of *t*-BuOOH in good yield (63–86%).[103] As shown in Figure 27, the mechanism of the reaction suggested that the epoxide was initially formed in the oxygenation and was then opened to give the dioxy alcohol.

A template-detected synthesis of (±)-allosamizoline and its 3,4-epimers has been reported.[104] In this reaction, enhancing the steric shielding of the β face of the cyclopentene by complexing the benzyl group with a β-CD reverses the ratio of the two diols (62% yield based upon 24% recovery of starting material) to 1:2 in favor of the isomer corresponding to the originally assigned structure of allosamizoline (Figure 28).

The photocycloaddition of 5-susbstituted adamantan-2-ones with fumaronitrile exhibited a limited face selectivity in aqueous solution with β-CD. The reac-

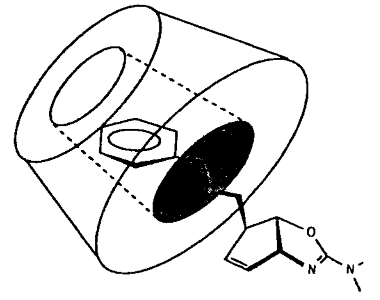


Figure 28. Steric shielding effect of CD complex on the alkylation.[104]

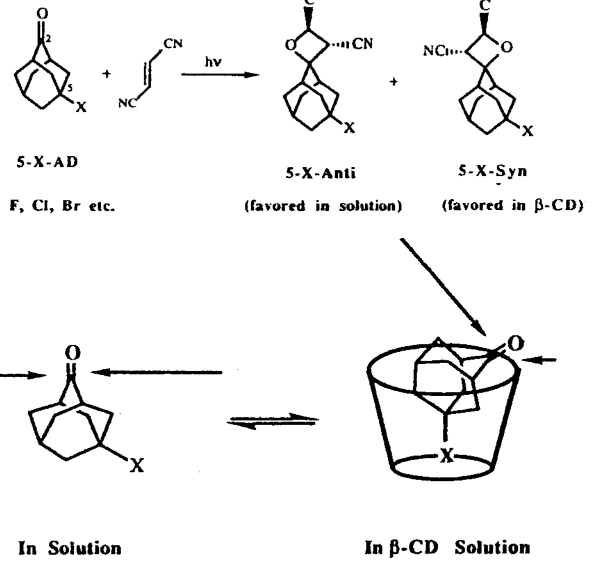


Figure 29. Face selectivity of photocycloaddition with CD.[106]

tion gave the syn adduct preferentially. The anti–syn ratio was largely dependent on the substituents at the 5-position in adamantan-2-one.[105] When 5-(trimethylsilyl)adamantan-2-one was used, excellent face selectivity (98:2) was achieved[106] only in the presence of a β-CD. No preferential selectivity was observed in the addition of either α- and γ-CD. The effect of CDs on the face selectivity was interpreted by assuming that the π-face syn to the bulky 5-substituent of the inclusion complex was partially blocked by the torus of the β-CD (Figure 29).

The inclusion complexation and the photodimerization of anthracene-2-sulfonate in the presence of a set of CDs carrying amino groups at the primary face (hexakis-, heptakis-, and octakis(6-amino-2,3-di-*O*-methyl-6-deoxy)CDs; α-, β-, and γ-PACDs) has been reported.[107] In neutral and alkaline media only β-PACD gives the 2:2 inclusion complex. In sufficiently acidic media stronger inclusion occurs with the help of acid–base ion pairing in all PACDs. The relative rates for the PACD-promoted photodimerization are closely related to the complexation mode.

3.2.6. Transfer, Elimination, Isomerization, and the Other Reactions

The rate of deprotonation of several β-keto esters in alkaline aqueous solution was increased by using α- and β-CDs. From the kinetic studies, it was suggested that the binding of the β-keto esters in the CD cavities, adjacent to a basic oxyanion site, enhances the reactivity of the CD anions toward these weak carbon acids by an order of magnitude of at least 2–4 (Figure 30).[108]

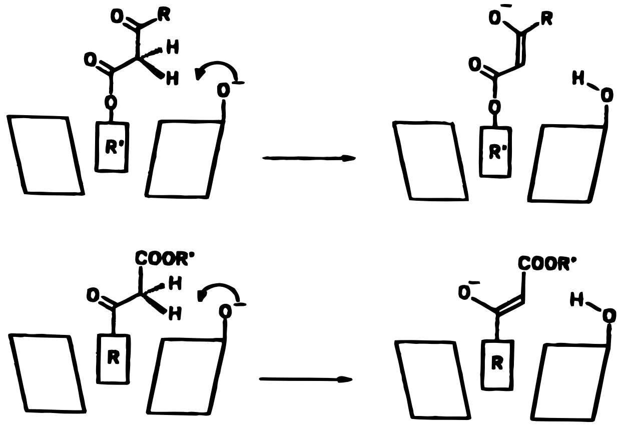


Figure 30. The effect of CD on the deprotonation.[108]

Pyrolysis of *O*-furfuryl *S*-alkyl dithiocarbamate (xanthates) gave furfuryl alkyl sulfides together with *S*-alkyl dithocarbamates. This reaction was affected by the polarity of the solvent. The addition of 2 mol equiv β-CD promoted a change in the ratio of the sulfides (Figure 31). This is because the furan ring of the guest molecules is entirely included within the cavity and the C=S group makes a hydrogen bond with the hydrogen groups of the CD. These phenomena shed light on the mechanism for the conversion reaction of furfuryl xanthates to furfuryl alkyl sulfides.[109]

In the thermal isomerization between provitamin D_3 and vitamin D_3 in an aqueous solution, the forward and reverse rate constants were increased by β-CD complexation by more than 40 and 600 times, respectively, compared with those in hexane. The reaction in aqueous solution is the fastest reported rate for this isomerization[110] (Figure 32). The effect was attributed to the thermodynamically unfavorable *cZc* conformers of provitamin D_3 which were stabilized by β-CD, and thus the rate of this isomerization was increased. This conformation-controlled process may play an important role in the modulation of the provitamin $D_3 \rightleftharpoons$ vitamin D_3 endocrine system in vivo such as occur in the sea urchin.

3.2.7. Photochemical Reactions

Photophysical and photochemical deactivation pathways in CD inclusion complexes were reviewed by Bortolus and Monti[111] and included 371 references. CDs affect various kinds of photophysical processes, such as excimer and exciplex emission, twisted intramolecular charge transfer (TICT) emission, proton transfer, and phosphorescence. Fluorescence and absorbance of 10-hydroxybenzo[*h*]quinoline (10HBQ) was enhanced in both β- and γ-CD cavities as well as in micellar media such as hexadecyltrimethylammonium (CTAB), sodium dodecyl sulfate (SDS), or polyoxyethylene lauryl ether. 10HBQ was included in both CDs with a 1:1 stoichiometry. This hydro-

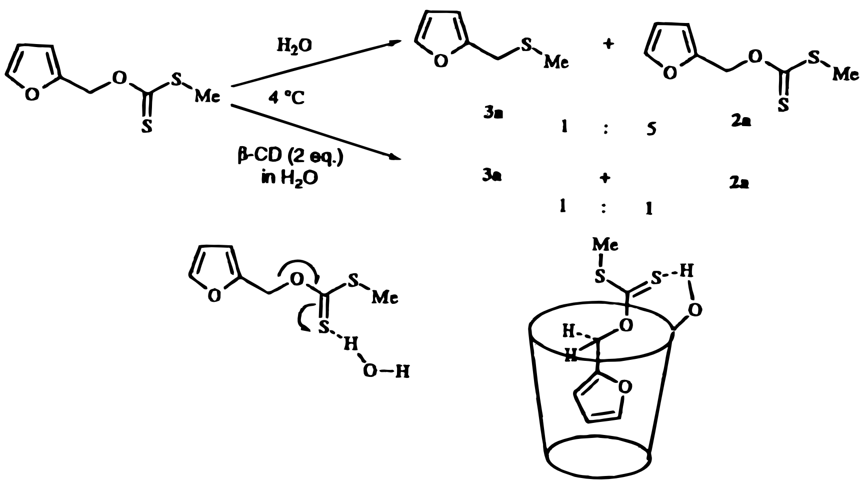


Figure 31. The effect of CD as polarity controller on the pyrolysis of xanthate.[109]

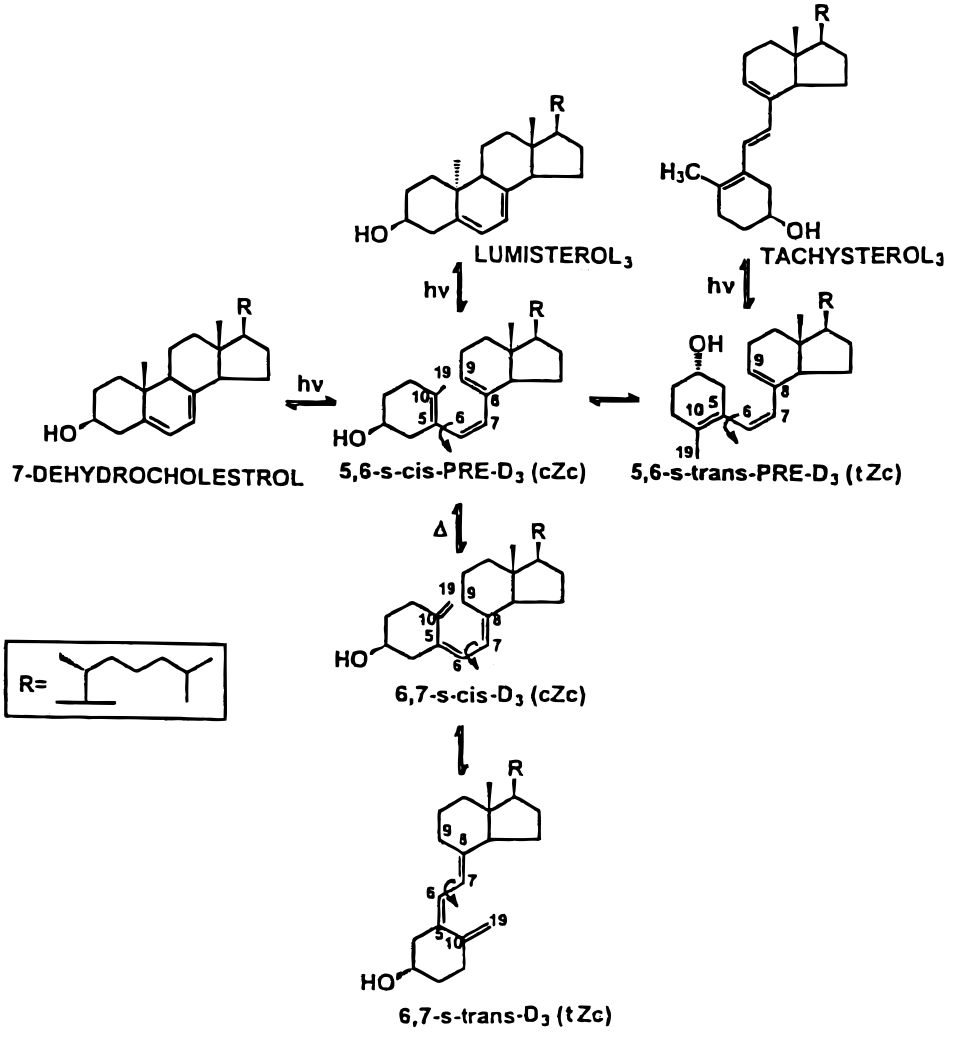


Figure 32. Scheme for conformation-controlled photolysis of 7-dehydrocholesterol and thermal isomerization between provitamin D_3 and vitamin D_3.[110]

phobic environment seemed to reduce the rate of the radiationless transition of the excited tautomer state.[112]

The first application of CD as a tool in photochemical reactions is the photo-Fries rearrangement of phenyl esters in solution[113] (Figure 33). The overall quantum yield of the reaction and the product distribution was highly dependent on the ability and polarity of the solvent. Recently, not only unimolecular but also bimolecular processes in aqueous solution and in the solid phase have been reported. The variation of photochemical parameters, enhancement of photoconversion rates, regio-, stereo-, and asymmetric inductions on the product distribution, and protection from undesired photoprocesses have all been reported.[111] The effect of the CDs was

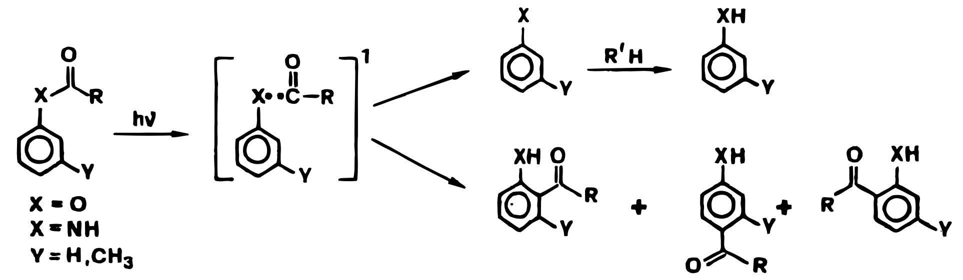


Figure 33. Historical photoreaction, Fries reaction, mediated by CD.[113]

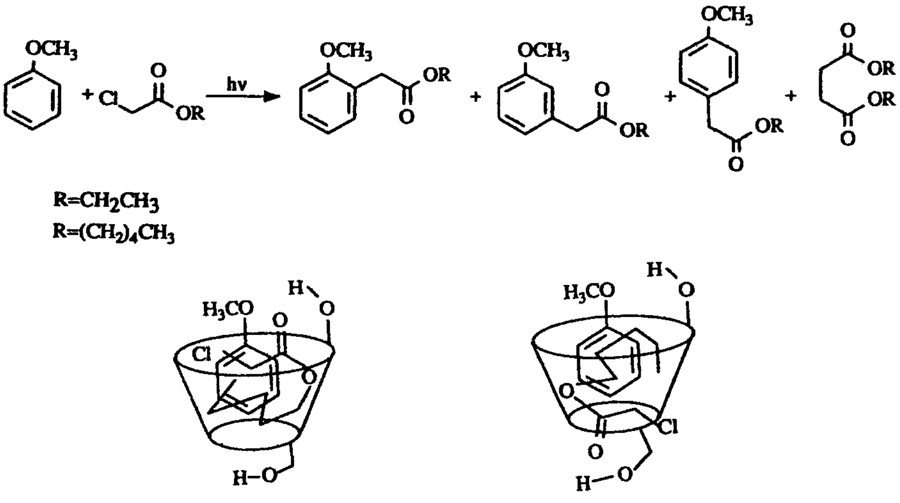


Figure 34. Intermolecular photoalkoxycarbonylmethylation of anisole.[116]

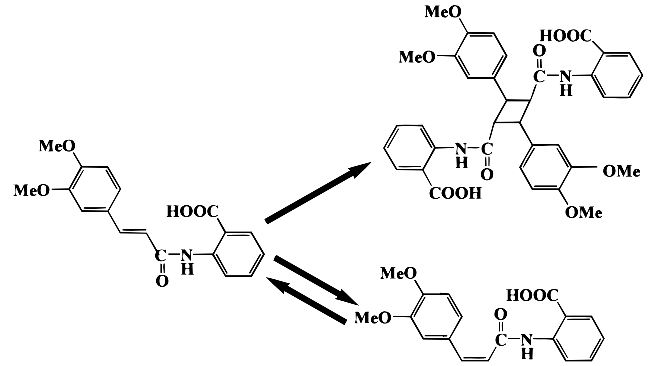


Figure 35. The photoisomerization of *N*-(3,4-dimethoxycinnamoyl)anthranilic acid.[117]

attributed to (1) microenvironmental effects on the deactivation processes of the excited state, (2) the complexation mode of the ground state, and (3) physical and chemical constraints imposed on the evolution of the intermediates. Some studies particularly in solid-phase reactions were discussed in section 3.1.3.

The nucleophilic photosubstitution of 3-nitroanisole in alkaline solution (pH 12) gave 3-nirophenolate through hydroxylation of the methoxy substituent.[114] The result of the addition of a β-CD resulted in a drastic rate reduction for the reaction. This result agrees with the premise that total shielding of the reactant lead to the inaccessibility of the reactive intermediate to hydroxide attack.

Competition between photosubstitution and photoreduction was observed in aqueous media for the reaction of 3- and 4-nitroanisoles and 4-nitroveratole with amines. Although in the solid state, nitroaromatic derivatives, phenylalanine, and β-CDs form a ternary complex with a ratio of 1:1:2, no photosubstitution product was formed and a total selectivity for the corresponding nitroso derivatives were observed. In the ternary complex formation, nitroaromatic derivatives and phenylalanine form 1:1 host−guest complex and the two 1:1 complexes form bimolar complex together. A small catalytic effect was also found in solution. The results suggest that the crystal arrangement of each host−guest complex was favorable in both redox photochemistry and in solution, i.e., each host−guest complex was separated.[115]

Photolysis of anisole and pentyl chloroacetate in isotropic media leads to alkylation products (in the ortho-, and para-positions) and dipentyl succinate in a 4:1 ratio (Figure 34). The reaction mechanism involves energy transfer from the excited anisole to the acetate ester, leading to cleavage of the C−Cl bond. The reactants form a ternary complex. A cage effect and geometric control are attributed to the observed selective product distribution in both α- and β-CD complexes in aqueous media.[116]

Photoisomerizations normally require large molecular distortions which are greatly influenced by the limitations on molecular mobility imposed through steric hindrance by the CD. This is seen in the photoisomerization of *N*-(3,4-dimethoxycinnamoyl)-anthranilic acid in the precesence of α-, β-, and γ-CDs with 1:1, 1:2, and 2:1 stoichiometry, respectively, in aqueous solution (Figure 35).[117] Inclusion of *trans*-4,4′-diacetamidostilbene in β-CD was reported to promote the formation of the cis photocyclization product only in DMSO. The CD cavity in effect

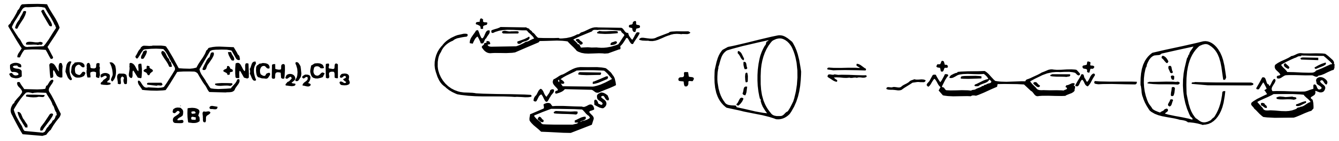


Figure 36. (Left) Viologen derivatives and (right) the mechanism of rotaxane-type complexes between α-CD and viologen derivatives.[122]

blocks the cis to trans photoreaction.[118] (*E*)-Cyclooctene is a chiral molecule. Photoisomerization of a (*Z*)-cyclooctene solid complex with *β*-CD proceeded nonenantioselectively. When the reaction was repeated in methanol−water solution with monobenzoic acid attached CD, the (*R*)-(−)-*E* form was formed in 6.2% ee.[119]

Intramolecular photocharge- or proton-transfer reactions are also affected by the effects of the CD cavity. *β*-CD includes *p*-(dimethylamino)chalcon in a 1:1 or 2:1 (host−guest*)* stoichiometry. The red shift in fluorescence emission spectra was associated with the formation of a 1:1 complex, while the blue shift was attributed to a 2:1 complex. The effect of *β*-CD on the intramolecular charge-transfer process was attributed the blocking the route to the nonfluorescent state P* one of the three excited states (E*, P*, A*, or TCIT), and the formation of *β*-CD-*p*-(dimethylamino)chalcon complex.[120] Intramolecular charge-transfer reactions of a pretwisted 2-biphenylcarboxylic acid (2BPAC) in α- or *β*-CD solutions were inhibited by a restraint on further twisting of the biphenyl group of the photoexcited 2BPAC in the CD cavity. The restraint on further conformational change is due to the reduced intramolecular hydrogen bonding of 2BPAC compared to in water, as well as to the reduced polarity of the CD cavity.[121]

Artificial photosynthesis models, where many donor−acceptor pairs based on viologen units as the acceptor and linked by methylene chains to porphyrin, phenothiazine, carbazole, and anthracene as donors, have been reported (Figure 36).[122] These systems are characterized by an intramolecular CT band in the spectral range 400−500 nm and by a conformational flexibility which allows the charge separation. However, as shown in Figure 36, on the addition of an α-CD, stable rotaxane-type complexes are formed in which encasement of the spacer forces the donor and the acceptor groups apart so that the CT band disappears. The activation parameters for complex formation indicated that the rate-determining step might be the penetration of the viologen unit which must be dehydrated before being included in the cavity. A dependence on the cavity size of CD was observed in this reaction system. Excellent yields of long-lived photogenerated radical pairs were detected in complexes of the phenothiazine−viologen−α-CD system with a relatively long chain spacer. With *β*-CD, lower yields were obtained. With *γ*-CD, the extended geometry is either unstable or impossible to achieve and the flexible free state did not allow observation of the radical pair. In the case of short-chain spacers, the same phenomena were observed as for *γ*-CD.[123]

Radiation-induced reactions in the presence of CDs has also been reported. *β*- and *γ*-CDs significantly reduced the rate constants of one-electron reductions of biphenyl sulfonates, but α-CD barely affected the reduction.[124] Addition of α- *β*-, or *γ*-CD retarded the decomposition and dechlorination of *o*-, *m*- and *p*-chlorophenols by the irradiation of *γ*-rays in deoxygenated water at room temperature. The observed effect was highly dependent on the cavity size of the CDs and as well as on the molecular shape of chlorophenols. But, the total yield of the main product, phenol, was greatly enhanced.[125] The effect was found to increase with the cavity dimensions. The CDs included the reaction intermediate radicals, which may enhance the possibility of encounterment between the intermediate radicals and the CD molecules in the hydrogen atom abstraction. Enhancement of the phenol yield results.

3.2.8. Biocatalytic and Catalytic Reactions

The steric effects of CDs in biocatalytic synthetic systems have been reported. In systems combining natural and artificial enzymes, if a prochiral guest molecule was included and rigidly fixed in the CD cavity, preferential attack by the reagent from only one of the enantiotopic faces of the guest molecule is enforced and this results in higher enantioselectivity. BSA, one of the carrier proteins, catalyzed the hydrolysis of racemic aryloxypropionic esters and afforded an appreciable enantioselectivity (50−81% ee). The addition of *β*-CD to this reaction with BSA, not only enhanced the enantioselectivity (80−99% ee), but also accelerated the rate of hydrolysis.[126] Rao et al. have demonstrated that baker's yeast can be used as a chiral catalyst in the asymmetric cycloaddition reaction of nitrileoxides or amines to the C≡C bond and that chiral recognition during cycloaddition can be improved by using CDs as an additional binding cavity.[127] In these reactions, the chemical yields were slightly affected and the enantioselectivity was enhanced (with an ee up to 70%). The *β*-galactosidases were activated by dimethyl-*β*- or α-CD, thus, enhancing the reaction rate of the hydrolysis of ganglioside G_{M1} acid.[128] The activation correlates with inclusion complex formation without an enzyme protein interaction, although the detailed mechanism of activation remains obscure. The utilization of such CDs is effective in the assay systems of glycosphingolipid hydrases.

Tagaki et al. indicated that CDs affected the catalytic activity in some reactions involving the inclusion of the catalyst; *γ*-CD completely inhibited the catalytic activity of dipotassium glycyrrhizinate in the hydrolysis of nonionic ester surfactant[129] (Figure 37), and *β*-CD showed a marked enhancement in the catalytic activity of 3-*endo*-(dimethylamino)methyl-1,7,7-trimethylnorbornan-2-*endo*-amine which catalyzes decarboxylation.[130] Methicilline−*β*-

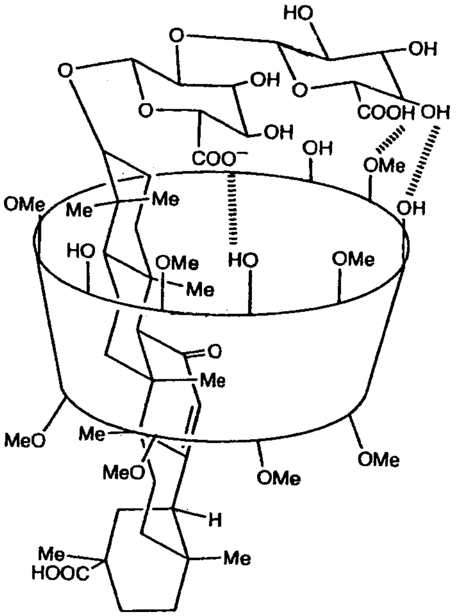


Figure 37. A conceptual structure of the GK2-heptakis-(2,6-*O*-dimethyl)-β-CD inclusion complex. For simplicity only arbitrarily selected hydrogen bondings are shown.[129]

CD derivatives act as effective inhibitors of β-lactamase.[131] In this case, CD acts as not inclusion group, but rather as a water-soluble group.

4. Concluding Remarks

Many intra- and intermolecular organic, photochemical, radiochemical, electrochemical, and biological reactions, have been carried out with uni- or bimolar CD cavities under various conditions, such as the solid phase, the heterogeneous suspension of water, or in organic solvents or in homogeneous solutions of buffers or organic solvents. The reactions were carried out either inside or outside the CD cavity. The main effect of the CD is to appreciably improve selectivity. A high selectivity has been achieved in the solid complex. On the other hand, it is interesting that appreciable selectivity has been achieved in organic solvents such as pyridine, DMF, THF, toluene, and CCl_4. It was known that the main driving force for formation of an inclusion complex between a CD cavity and a guest molecule is hydrophobic interaction and the weaker binding of the substrate to CDs in a dipolar aprotic solvent compared with water. The results in organic solvents and in the solid state suggest that other interactions, such as dipole−dipole interactions, charge-transfer interactions, electrostatic interactions and hydrogen bonding, and water−sugar interactions, must also be considered and that these reactions except that in water may also proceed with CDs.

To develop a CD-mediated reaction, it is necessary to clarify the reaction mechanism in detail. Complexation certainly induces selectivity. Although it is difficult to elucidate the role of the CD, the complex orientation in the reaction transition state must be made clear at the molecular level. Association constants alone are not enough for estimating the availability of complex formation or to explain the effects. Other parameters including mobility should be considered. Recently, it has been shown that the transient binding mode of the CD complex, and the mobility or conformational mobility can be deduced. Moreover, the transition-state pseudoequilibriun approach (K_{TS}), developed by Kurz for enzymology[132] and adapted for CD-mediated reactions by Tee,[48,50,133] is ideal for the analysis of multiple pathway reaction systems. This kind of information should support the elucidation of CD-mediated reaction. The early stages in CD chemistry presented a wide range of chemists with a very impressive concept, that of a host−guest complex which has been described as a ball in a bottomless pail.

We have shown that the ball or guest is not always particularly deeply embedded into the pail cavity. Other interactions play sufficiently significant roles that they recognize the ball and thus mediate the reaction. The so-called "rims" of the pail must also be considered.

The organic reactions mediated by CDs indicated here are mostly nonnatural systems, however, future investigation of CDs could provide a new world of a CD as a supramolecule and thus reveal important information on weak interactions in the mechanisms of natural biosystems.

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