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Review Article

Asymmetric Reactions with Cyclodextrins

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Abstract. Cyclodextrins have great potential for exploitation as a useful tool for asymmetric induction. Many kinds of asymmetric reaction have been achieved in the presence of cyclodextrin under various conditions such as the solid phase, heterogeneous suspension or homogeneous aqueous or organic solution. Complexation is essential for asymmetric induction. What is necessary to improve CDs for greater asymmetric induction?

Key words: Cyclodextrin, asymmetric reaction, microcrystal.

1. Introduction

There has been continuing interest in asymmetric synthesis and in the study of the discrimination between enantiomeric chiral species both because of the practical applications and the analogy with biological systems. In spite of the increasing availability of enzymes as chiral catalysts, nonenzymatic catalytic asymmetric synthesis is still a powerful tool in organic chemistry. Many asymmetric reactions have been successfully achieved using chiral reagents. Significant asymmetric induction has also been achieved using an achiral reagent in a chiral environment such as reaction under phase-transfer conditions, reaction in liquid crystals, micelles, organic or inorganic solid lattices and inclusion compounds.

Cyclodextrins (CDs), which are naturally occurring doughnut-shaped molecules composed of 6, 7 and 8-D-glucose units, are among the most extensively investigated biomimetic models of enzymes [1] (Figure 1). A fascinating property of CDs is their ability to incorporate other organic compounds into their cavity, both in the solid state and in solution. Such host-guest complexes must clearly be distinguished from clathrate (lattice inclusion compounds), which occur only in the solid state [2]. This property suggests that CDs are attractive inclusion compounds which can control the reaction in any phases as a micro-environment factor. In this review, we stress the ability of CD to induce asymmetric reactions rather than their use as enzyme models.

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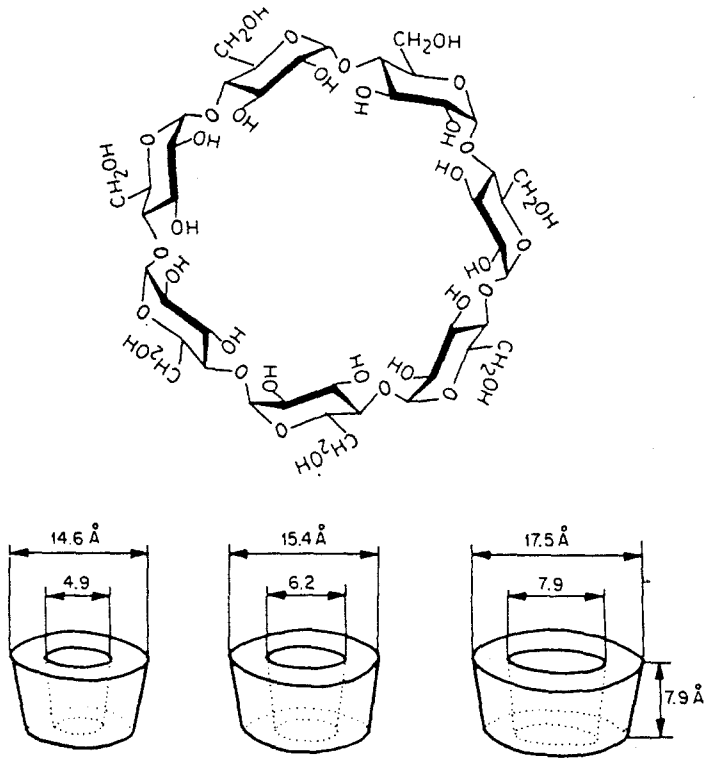

Fig. 1. Structure of β-cyclodextrin and the molecular dimensions of α-, β- and γ-cyclodextrins [1].

2. Molecular Recognition with Cyclodextrins

CDs, which consist of D-glucose with an α-1,4 linkage, can recognize an enantiomer and can influence the enantioselectivity and reaction rate, in particular in the cleavage of carboxylic acid esters [3]. The functionalization of the CD hydroxyl groups and the selection of the appropriate substrate geometry may result in over a million fold rate enhancement. The largest enantioselectivity factor reported in the literature [4] is greater than 60, the average value being much lower [5].

Although considerable success has been achieved with chemically modified CDs [6], the utilization of simple CDs as a tool for asymmetric synthesis has been less satisfactory.

Breslow *et al.* described the first example of coenzyme attached CD, in which a pyridoxamine residue was covalently linked to a primary carbon of β-CD; the modified CD should catalyze transamination as an artificial enzyme [7]. In the synthesis of phenylalanine from phenylpyruvic acid the L enantiomer was preferentially formed in a 3 to 1 ratio [8] (Figure 2). Tabushi *et al.* have reported that the other type of artificial vitamin B_6 enzyme, A-(modified B_6)-B-[ω-amino(ethylamino)]-

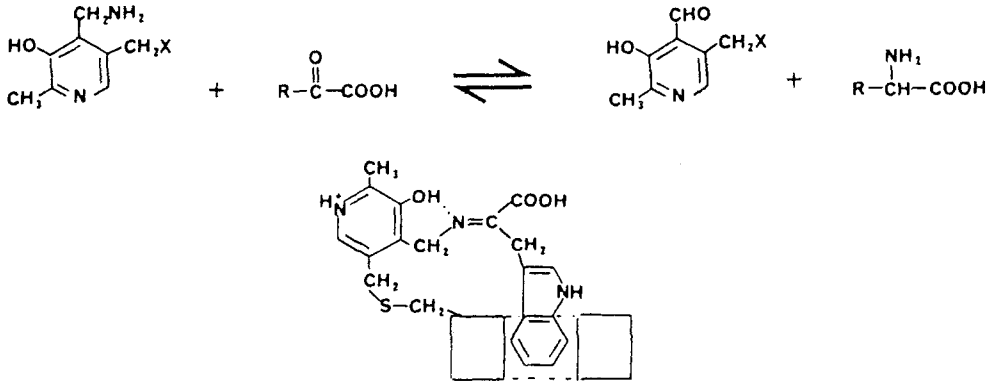

Fig. 2. Chiral induction in an amino acid formed *via* artificial B_6 catalysis [8].

$RCOCO_2H$	L/D
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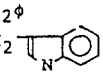
= CH_2 	95/5
= ϕ	98/2

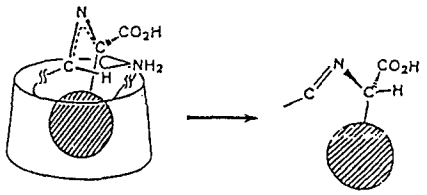


Fig. 3. Transamination by a pyridoxamine-β-cyclodextrin artificial enzyme [9].

β-CD, accelerates conversion from keto acids to L-amino acids in a 98/2, 98/2, 95/5 L/D ratio for phenylglycine, phenylalanine and tryptophan, respectively [9] (Figure 3). Recently, Weber *et al.* reported that the 2,6-permethylated β-CD-linked iron and manganese porphyrins catalyze the enantioselective oxygenation of a racemic mixture of (*S*)-α-pinene with molecular oxygen under irradiation with visible light [10] (Figure 4).

CDs are also powerful resolving agents for racemic mixtures [11]; their recognition ability has been recently examined by circular dichroism spectra, ^1H, ^{13}C or ^{19}F NMR spectroscopy and molecular dynamics simulation [12]. CDs have already been used as chiral mobile-phase additives or as chiral stationary phases in HPLC, GC, TLC [13] or capillary zone electrophoresis [14] for direct enantiomeric separation.

3. Asymmetric Reactions in a Chiral Environment

The role of ordered or constrained media in modifying the reactivity of a substrate is being increasingly recognized as an important control element in organic reactions [15]. Several examples of dramatic alternation in reaction states and selectivity

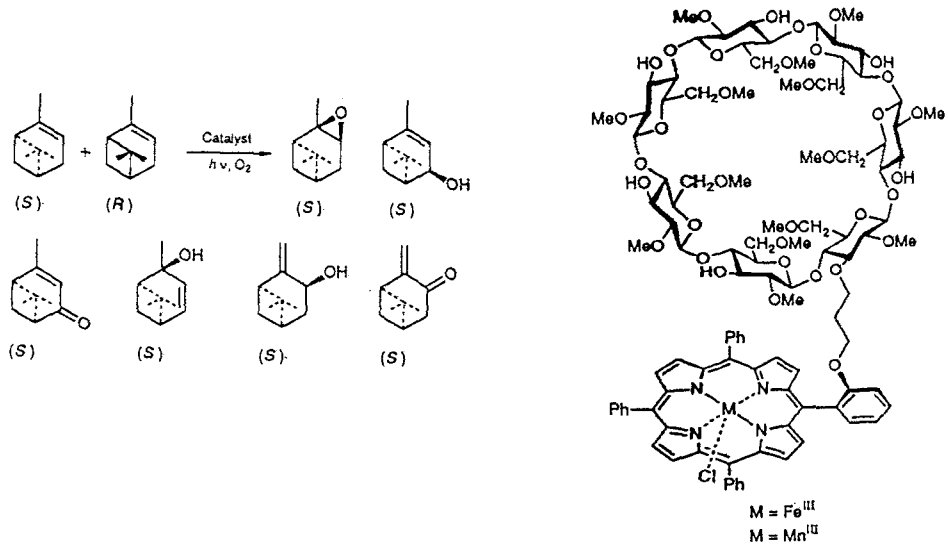


Fig. 4. Photocatalytic oxygenation of a racemic α-pinene mixture with β-CD linked iron and manganese porphyrins [10].

have been observed in chiral micelles [16], liquid crystals [17], organic or inorganic solid lattices [18], inclusion compounds [25–27] and proteins such as bovine serum albumin (BSA) [20–23]. Among the above 'environments', many reviews have been devoted to reaction in the solid state lattice [19], which are useful for synthetic purposes. Synthesis with high regio- and stereo-selectivity by means of processes occurring within a host lattice have been carried out. BSA, one of the carrier proteins in biosystems, can be regarded as a natural inclusion compound. The versatility of BSA as a chiral catalyst or chiral environment has been emphasized by the enantioselective hydroxylation of alkenes [20], in the Darzens condensation [21], the reduction of aromatic ketones ($\leq$ 78% ee) [22] and the oxidation of sulfides ($\leq$ 80% ee) [23] in the liquid phase. Interestingly, when these reactions were also studied with CDs, better enantioselectivity was observed with BSA compared with CD in all cases. Recently, the reduction of ketones with the combination of $NaBH_3CN$ and antibodies in high enantiomeric excess has been reported [24]. There are few reports on highly asymmetric inductions in organic inclusion compounds [25–27] except for CDs. Enantioselective intramolecular thiolysis with the combination of a synthetic macrocyclic molecular catalyst and primary ammonium ester salts has been reported. The largest enantioselectivity factor in the reaction rate [25] was 90. The only remarkable exceptions are represented by asymmetric reduction of ketones in a water-soluble chiral paracyclophane complex with sodium borohydride in acidic water ($\leq$ 10% ee) [26] and in a chiral crown ether crystalline complex with borane ammonia in toluene ($\leq$ 13% ee) [27].

TABLE I. Asymmetric reactions with CD under heterogeneous conditions.

Substrate	Cyclodextrin	Reagent	Reaction state	Yield[%]	Optical yield[%]	Ref.
Halogenation and hydrohalogenation						
crotonic acid	α	HBr	gas-solid	28.6	29	28
methacrylic acid	α	Cl_2	gas-solid	17.4	100	28
maleic acid	β	Cl_2	gas-solid	53.0	88	28
trans-cinnamic acid	β	Br_2	gas-solid	1.5	15	28
	β	Br_2	gas-solid	2.5	40	28
	β	Br_2	in DMSO	4.4	6	28
ethyl *trans*-cinnamate	α	HBr	gas-solid	17	46(R)	30
	β	HBr	gas-solid	21	31(S)	30
styrene	α	Br_2	gas-solid	90	0	31
	α	Cl_2	gas-solid	25	0	31
	α	Cl_2	gas-solid	38	14(S)	31
	β	Cl_2	gas-solid	47	0	31
	β	Cl_2	gas-solid	22	8(S)	31
trans-2-butenoic acid	α	HBr	gas-solid	60	58.4(S)	32
	α	HBr	gas-solid	28.6	29.0(S)	32
	α	HCl	gas-solid	23	64.4(S)	32
	α	HCl	gas-solid	41	32.2(S)	32
Reduction						
(E)PhCH=CHCOCH$_3$	β	$NaBH_4$	0.2MNa_2CO_3	[a]	32(S)	35
m-$CH_3C_6H_4COCH_3$	β	$NaBH_4$	0.2MNa_2CO_3	[a]	16(R)	35
1-($C_{10}H_7$)CH=CHCOCH$_3$	β	$NaBH_4$	0.2MNa_2CO_3	[a]	4(S)	35
FcCH=CHCOCH$_3$	β	$NaBH_4$	0.2MNa_2CO_3	[a]	23(S)	35
$C_6H_5COCF_3$	α	C_6H_5N	water	50	4(S)	36
$C_6H_5COCF_3$	β	C_6H_5N	water	96	13(S)	36
$C_6H_5COCF_3$	γ	C_6H_5N	water	93	8(R)	36
$C_6H_5COCF_3$	β	$(CH_3)_3N$	water	27	2(R)	36
$C_6H_5COCH_2Cl$	β	C_6H_5N	water	70	36(S)	36
$C_6H_5COCH_2Cl$	β	$(CH_3)_3N$	water	50	2(R)	36
$C_6H_5COCH_2Br$	β	C_6H_5N	water	67	20(R)	36
$C_6H_5COCH_3$	β	C_6H_5N	water	8	91(S)	36
$C_6H_5C_2H_4COCH_3$	β	C_6H_5N	water	26	89(R)	36
$C_2H_5COCH_3$	β	C_6H_5N	water	22	47(S)	36
$C_6H_5COCO_2CH_3$	β	C_6H_5N	water	63	7(R)	36
acetylferrocene	β	$NaBH_4$	water	[b]	34.3(R)	37
	β	$NaBH_4$	LiCl/water	[b]	32.2(R)	37
	β	$NaBH_4$	NaCl/water	[b]	51.7(R)	37
	β	$NaBH_4$	KCl/water	[b]	40.7(R)	37
benzoylferrocene	β	$NaBH_4$	water	[b]	49.2	37
	β	$NaBH_4$	LiCl/water	[b]	43.0	37
	β	$NaBH_4$	NaCl/water	[b]	82.0	37
	β	$NaBH_4$	KCl/water	[b]	84.0	37

TABLE I. Continued.

Substrate	Cyclodextrin	Reagent	Reaction state	Yield[%]	Optical yield[%]	Ref.
Oxidation						
Ph-S-CH_2CO_2Et	β	NaOCl	water	[c]	3.7	38
Ph-S-$CH_2CO_2Bu^t$	β	NaOCl	water	[c]	53.8	38
p-MeC_6H_4-S-CH_2CO_2Et	β	NaOCl	water	[c]	5.4	38
p-MeC_6H_4-S-$CH_2CO_2Bu^t$	β	NaOCl	water	[c]	36.7	38
p-ClC_6H_4-S-CH_2CO_2Et	β	NaOCl	water	[c]	2.8	38
p-ClC_6H_4-S-$CH_2CO_2Bu^t$	β	NaOCl	water	[c]	21.6	38
$PhCH_2$-S-CH_2CO_2Et	β	NaOCl	water	[c]	6.7	38
$PhCH_2$-S-$CH_2CO_2Bu^t$	β	NaOCl	water	[c]	35.6	38
methylphenylsulfide	α	CH_3COOOH	water	96	4(S)	39
	β	CH_3COOOH	water	98	15(S)	39
ethylphenylsulfide	α	CH_3COOOH	water	97	10(S)	39
	β	CH_3COOOH	water	95	26(S)	39
phenylpropylsulfide	α	CH_3COOOH	water	95	11	39
	β	CH_3COOOH	water	92	30	39
n-butylphenylsulfide	α	CH_3COOOH	water	98	6(R)	39
	β	CH_3COOOH	water	94	45(R)	39
	β	CH_3COOOH	CCl_4	[d]	40(R)	39
	β	CH_3COOOH	pentane	[d]	30(R)	39
	β	CH_3COOOH	CH_2Cl_2	[d]	14(R)	39
	β	CH_3COOOH	acetone	[d]	5(R)	39
	β	CH_3COOOH	methanol	[d]	1(R)	39
	β	CH_3COOOH	DMSO	[d]	0	39
i-butylphenylsulfide	α	CH_3COOOH	water	96	3(R)	39
	β	CH_3COOOH	water	90	57(R)	39
t-butylphenylsulfide	α	CH_3COOOH	water	95	7(R)	39
	β	CH_3COOOH	water	75	38(R)	39
methyl-1-nalhthylsulfide	α	CH_3COOOH	water	92	1(S)	39
	β	CH_3COOOH	water	95	81(S)	39
	γ	CH_3COOOH	water	97	19(S)	39
	DMβCD	CH_3COOOH	water	80	8(S)	39
	TMβCD	CH_3COOOH	water	65	4(S)	39
i-butyl-1-naphthylsulfide	β	CH_3COOOH	water	40	31	39
	γ	CH_3COOOH	water	42	53	39
methyl-2-naphthylsulfide	β	CH_3COOOH	water	98	49(R)	39
	γ	CH_3COOOH	water	94	34(R)	39
methyl-9-phenanthrylsulfide	γ	CH_3COOOH	water	87	37	39

[a] 80–97%.

[b] Chemical yield not reported in the reference.

[c] 8–10%.

[d] 80–90%.

TABLE II. Asymmetric sigmatropic rearrangement with CD in suspension.

Substrate	CD	Solvent for suspension	Yield (%)	Optical yield(% ee)	Ref.
O-cinnamyl S-methyl dithiocarbonate	α	water	40	3.3	40
	β	water	80	45.9	40
	γ	water	87	12.0	40
O-cinnamyl S-ethyl dithiocarbonate	β	water	80	10.4	40
O-cinnamyl S-phenyl dithiocarbonate	β	water	67	10.7	40
O-crotyl S-methyl dithiocarbonate	β	water	54	2.4	40
O-crotyl S-phenyl dithiocarbonate	β	water	82	–	40
O-geranyl S-methyl dithiocarbonate	β	water	70	–	40

4. Asymmetric Reactions in Crystalline CD Complexes

In this section, asymmetric reactions with a crystalline CD complex of a substrate or reagent in the solid-state and in suspension are described. Representative results are summarized in Tables I, II and III. The crystalline inclusion complexes were usually obtained by a simple method; a substrate was added to a saturated aqueous solution of CD, and after stirring for 2 h–7 days, the resultant precipitate was filtered and the crystalline 1 : 1 or 2 : 1 complex was obtained quantitatively. The advantage of solid crystalline complexation is (a) full complexation of the substrate and (b) the possibility of a highly concentrated reaction. Moreover, in the solid-phase, the crystalline environment or the other interactions do not intervene through its overall asymmetry; only parts of the host molecules play an important role directly like reactions in other crystalline solid-phases.

Complete enantioselectivity has been achieved in the asymmetric halogenation of methacrylic acid using α-CD complexes in the solid state [28]. Other halogenation and hydrohalogenation reactions of olefines such as crotonic, methacrylic, *trans*-cinnamic [29] and maleic acids, ethyl *trans*-cinnamate [30], styrene [31] and *trans*-butenoic acid [32] have been carried out in a crystalline α- or β-CD complex (Table I). Asymmetric bromination of olefines *via* a gas-solid reaction has already been achieved using a single chiral crystal lattice of 4,4′-dimethylchalcone [33]. The advantage of a CD complex is that a variety of substrates can be used without the problem of large single crystal formation or concern about their chirality. Sakuraba *et al.* defined the CD crystalline complex as a 'microcrystal'. The crystal structures of the CD-guest complexes have been extensively studied by several groups [34] and clarified at the molecular level. A mechanism for the chiral induction has been suggested on the basis of the X-ray crystal structure of the complex. As shown in Figure 5, asymmetric hydrogenation should occur on the inside of 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 olefinic bond penetrates into the chiral envi-

TABLE III. Asymmetric reaction of guest in CD complexes.

Guest in CD complex	CD	Reagent	Solvent	Yield (%)	Optical yield(% ee)	Ref.
Oxidation						
phenyl methylsulfide and *m*-ClPBA	β	–	water	45	12.4(S)	43
m-ClPBA	β	phenyl methylsulfide	water	86	10.7(S)	43
phenyl methylsulfide	β	*m*-ClPBA	water	78	2.3(S)	43
Michael addition						
benzenethiol	α	2-cyclohexanone	water	67	1(S)	41
	β	2-cyclohexanone	water	93	30(S)	41
	γ	2-cyclohexanone	water	10	10(S)	41
	β	2-cyclohexanone	Et_3N	50	4(S)	41
p-methylbenzenethiol	β	2-cyclohexanone	water	39	7(R)	41
p-tert-butylbenzenethiol	β	2-cyclohexanone	water	35	5(R)	41
benzylthiol	β	2-cyclohexanone	water	50	1(R)	41
2-cyclohexanone	β	benzenethiol	water	84	4(R)	41
	β	benzenethiol	water	66	0	41
	β	*p*-methylbenzenethiol	Et_3N	56	9(R)	41
	β	*p*-methylbenzenethiol	water	65	1(S)	41
	β	*p-tert*-butylbenzenethiol	water	82	6(S)	41
	β	benzylthiol	water	61	2(S)	41

ronment in the middle of the cavity. The reagent molecules, consisting of a proton and a halide anion, apparently attack enantioselectivity 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 solution, the ee dropped to 6% because of the release of microcrystals.

Asymmetric induction using a 'microcrystal of a CD complex' has also been applied to liquid-phase reactions in suspension: e.g. reduction of ketones [35–37], oxidation of aryl sulfides [38, 39], rearrangement of allylic xanthates ($\leq$ 46% ee) [40] (Figure 6) and Michael addition ($\leq$ 30% ee) [41] (Figure 7, Table III). The reduction of ketones with a CD crystalline complex is quite a useful and simple way of obtaining a chiral alcohol of high optical purity. 36% ee has been achieved with β-CD-ketone complexes suspended in a sodium borohydride ($NaBH_4$) aqueous alkaline solution by Fornasier *et al.* [35]. Highly enantioselective reduction of ketones has been achieved with crystalline CD complexes of achiral amine-boranes as reducing reagent ($\leq$ 91% ee) [36] by Sakuraba *et al.* and with $NaBH_4$ in the presence of alkaline salts ($\leq$ 84% ee) [37] by Kawajiri *et al.* (Figure 8). These strong asymmetric inductions may be attributed to the steric requirement in the inclusion

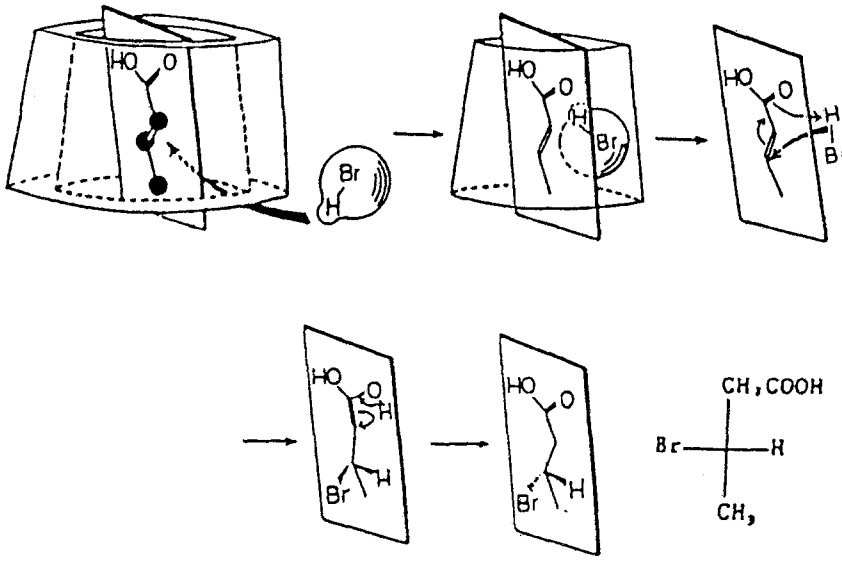


Fig. 5. Reaction mechanism of asymmetric addition of hydrogen bromide to *trans*-2-butenoic acid in α-cyclodextrin [32].

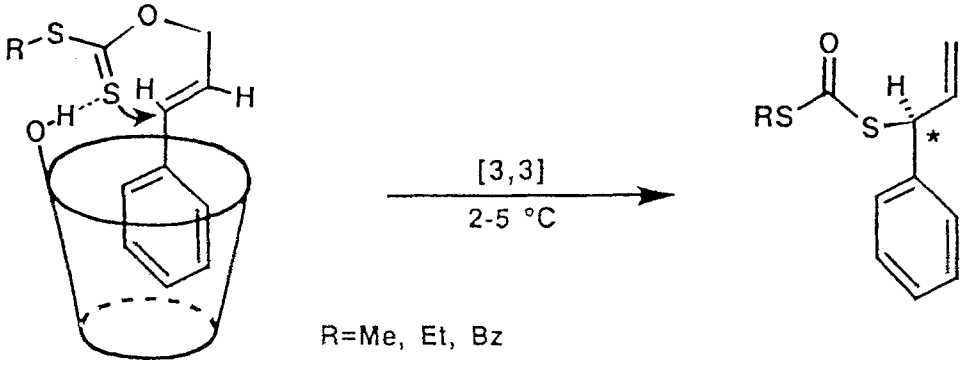


Fig. 6. [3,3]-Sigmatropic rearrangement of an allylic xanthate in β-CD complexes [40].

complex formation with a combination of several factors, such as hydrophobic binding and hydrogen bonds. The augmentation by alkaline salt can probably be ascribed to a salting-out effect. In the oxidation of aryl sulfides, optically active sulfoxides have been obtained by the combination of sodium hypochlorite and a CD complex of thioacetate ($\leq$ 53% ee) [38] (Figure 9) and of peracetic acid and alkyl sulfide in a crystalline CD complex ($\leq$ 81% ee) [39]. The product of the latter reaction, optically pure methyl 1-naphthyl sulfoxide has been utilized as a chiral auxiliary in the nucleophilic addition to alkyl phenyl ketones with perfect stereoselectivity [42]. The enantiomeric excess observed for α, α-dichloromethyl sulfoxide

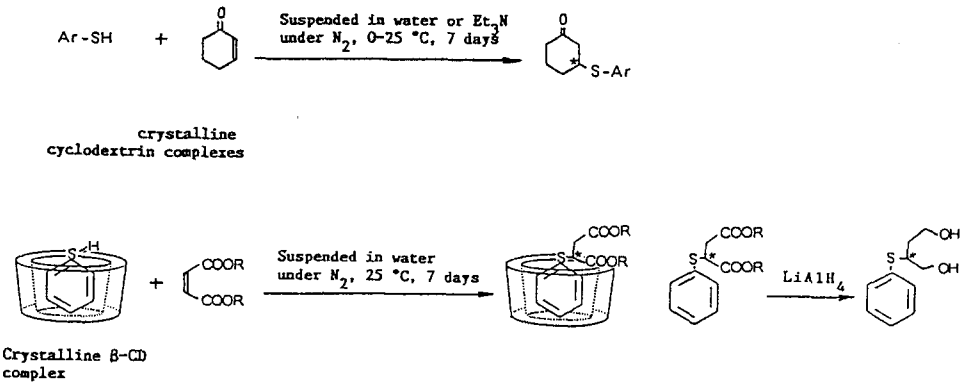


Fig. 7. Michael addition in a CD complex [42].

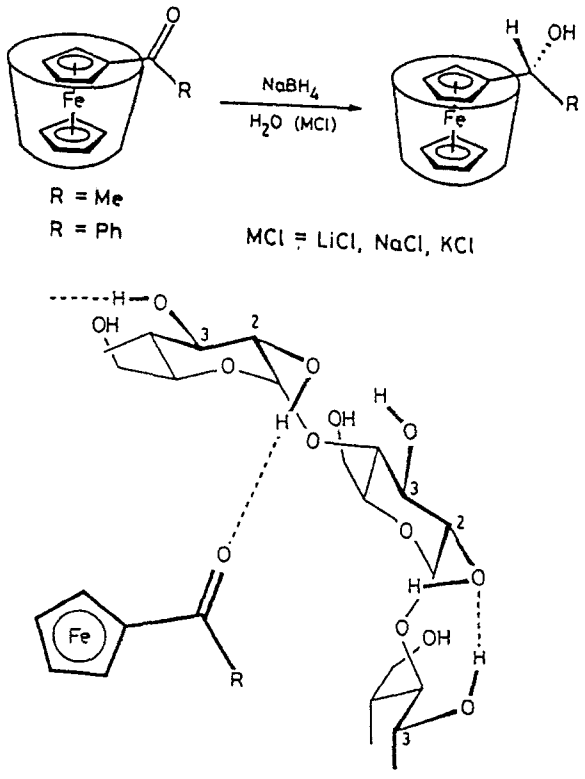
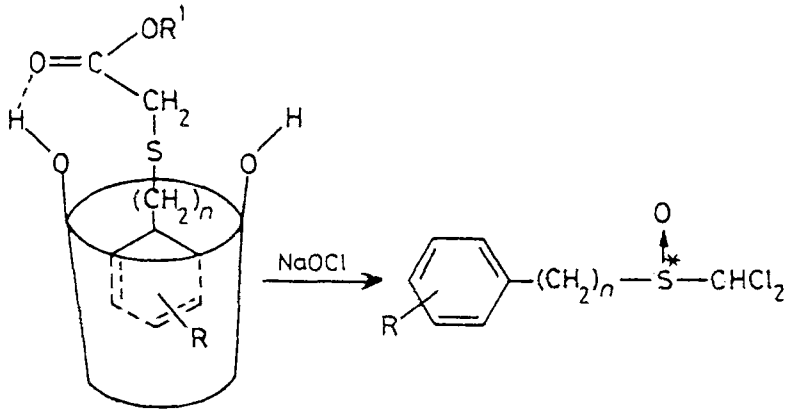


Fig. 8. Asymmetric induction from ferrocenyl ketones with a CD complex and inclusion complex predicted by molecular model construction [37].



R = H, *p*-Me, or p-Cl; n = 0 or 1; X = Et or Bu^t.

Fig. 9. Asymmetric oxidation with β-CD [38].

obtained from this resolution of a racemic mixture by β-CD is negligible (< 1%). This fact suggests that the asymmetric oxidations are not due to optical resolution but are due to kinetic selection in the reaction. No chiral induction was observed in the homogeneous oxidation of the β-CD-*n*-butyl phenyl sulfide complex dissolved in DMSO, or in the halogenation of *trans*-cinnamic acid. The oxidation of the solid CD complex was carried out in other solvents such as CCl_4, pentane, CH_2Cl_2, acetone and methanol. 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 the released guest molecule from the solid CD complex. These results show that the enantioselective oxidation of sulfide requires the guest molecule to be held rigidly in the chiral cavity of the CD complex in the solid state. The enantioselectivity depended on the size of the hydrophobic cavity; the oxidation of alkyl phenyl sulfoxides 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 sulfoxides with the γ-CD complex [39]. However, the binding constants, $K(M^{-1})$, were not correlated with the chiral induction for the oxidation with the crystalline CD complexes [39]. Fornasier *et al.* have reported the effect of the pre-complexation of reactant with CD on the enantioselectivity of the oxidation [43]. The CD-oxidant complexation is more effective than CD-substrate complexation. Moreover, a reversed configuration has been observed between the complexation with cyclohexanone and arylthiol in Michael addition [41] (Table III). Even under homogeneous conditions, without pre-complexation treatment, the precipitation of CD was observed in a highly enantioselective reaction [44]. Although it is certain

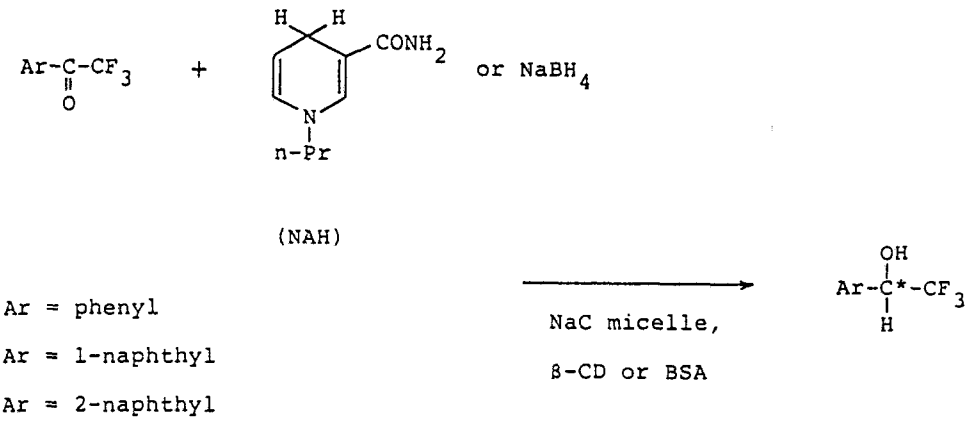


Fig. 10. Asymmetric reduction in NaC micelle solution in the presence of CD or BSA [45].

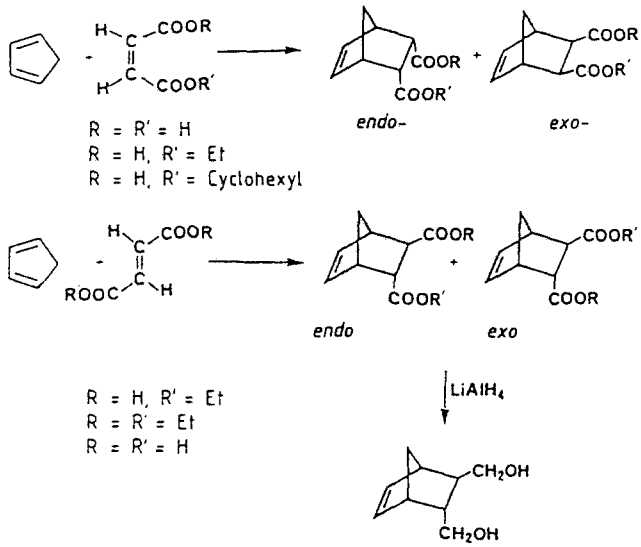


Fig. 11. Diels-Alder reaction in homogeneous solution in the presence of CD [46].

that crystalline complex formation is important for the asymmetric reaction, other parameters in the system apart from the binding constant should be considered, in order to elucidate the mechanism.

5. Asymmetric Reaction with Cyclodextrin without Crystalline Formation

The requirements for an efficient asymmetric synthesis in solution are quite different from those in the crystalline phase. The crystalline environment does not

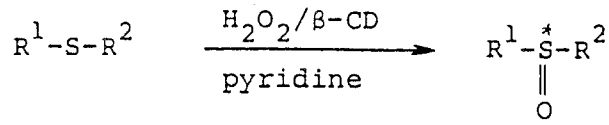
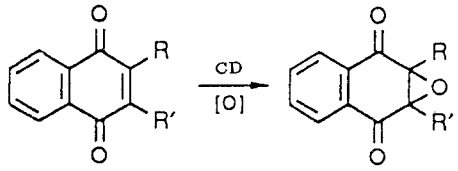


Fig. 12. Asymmetric oxidation of sulfides in pyridine [44].



R = CH_3, R' = H
R = C_4H_9, R' = H
R = n-C_8H_{17}, R' = H
R = n-$C_{18}H_{37}$, R' = H
R = C_6H_5, R' = H
R = CH_3, R' = C_2H_5
R = CH_3, R' = phytyl

Fig. 13. Asymmetric epoxidation of vitamin K derivatives in the presence of CD [49].

intervene through its overall asymmetry; only parts of the host molecules play an important role directly. As already discussed in Section 4, a considerable amount of success in asymmetric induction has been obtained with crystalline CD complexes. Although CDs have been shown to bind hydrophobic molecules into their cavities in aqueous solution, the observed stereoselectivities under homogeneous conditions, even in aqueous solution, are generally poorer than with CD crystalline complexation, the ee being $\leq 50\%$ (Table IV). However, investigation in solution

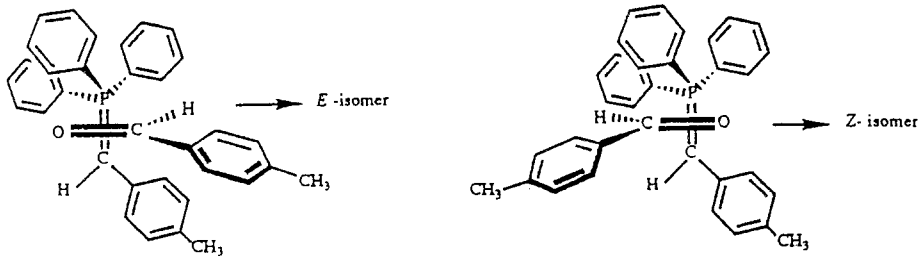
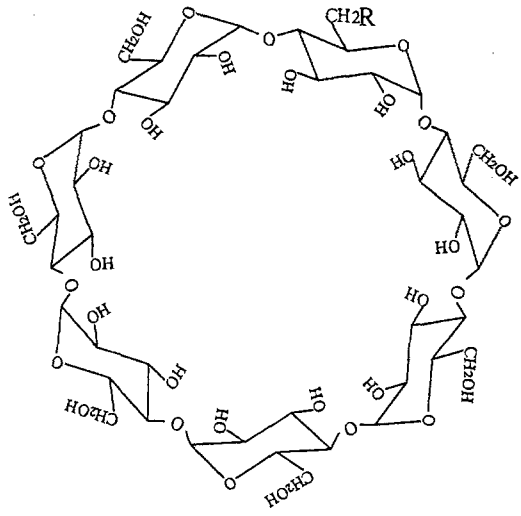


Fig. 14. Hypothetical transition state in the Wittig reaction for the four-center mechanism [50].



ACD	$-NH_2$
DMCD	$-N(CH_3)_2$
BZACD	$-NHCH_2C_6H_5$
PEACD	$-NH(CH_2)_2C_5H_5$
PPACD	$-NH(CH_2)_3C_6H_5$
D-MBZACD	$-NHCH(CH_3)C_6H_5$
L-MBZACD	$-NHCH(CH_3)C_6H_5$
R-NEACD	$-NHCH(CH_3)C_{10}H_7$
S-NEACD	$-NHCH(CH_3)C_{10}H_7$

Fig. 15. Monoarylic amino-cyclodextrin derivatives.

can give information on the factors, e.g. the multiple interactions among substrate, reagent, CD and solvent, that control the enantioselectivity.

The first study of asymmetric induction with CD as a chiral environment was reduction of aryl trifluoromethyl ketones with $NaBH_4$ in an alkaline aqueous solution of sodium cholate micelle. Carbinols in 0–10% ee were obtained in the presence of a ten-fold molar excess of β-CD over the substrate but in 10–46% ee with BSA under the same conditions [45] (Figure 10). Diels-Alder reaction of cyclopentadiene with ethyl fumarate in the presence of the highest possible concentration of β-CD (0.015 M in water) shows 21% ee enantioselectivity [46] (Figure 11). The enantiomeric excess is limited by incomplete complexation; under the same conditions, the enantioselectivity for the addition of fumaric acid is below 1%. Asymmetric oxidation of sulfides has also been reported. The most successful enantioselectivity (33% ee) was obtained using a specially designed substrate (*m-tert*-butylphenylethyl sulfide) and oxidation by (*m*-chlorophenyl)benzoic acid(*m*-ClPBA) with excess β-CD in aqueous solution at 4 °C [47]. No appreciable ee's ($< 1\%$) could be observed in the resulting sulfoxides by using other ether oxidants such as H_2O_2, NaOCl, $NaIO_4$ in aqueous solution and in homogeneous solutions in DMF [43]. Actually, the weaker binding of the substrate to CDs in a dipolar aprotic solvent like DMF, with respect to water [48], correlates with the lower stereoselectivities. Some reactions in organic solvents have been reported with appreciable ee's. 30% opically pure *n*-butyl phenyl sulfoxide was obtained in a pyridine solution with H_2O_2 as the oxidant [44]. Interestingly, the heterogeneous oxidation with a solid CD complex of the same substrates in water containing CH_3CO_3H produced the sulfoxide with the opposite configuration; the homogeneous reactions produced

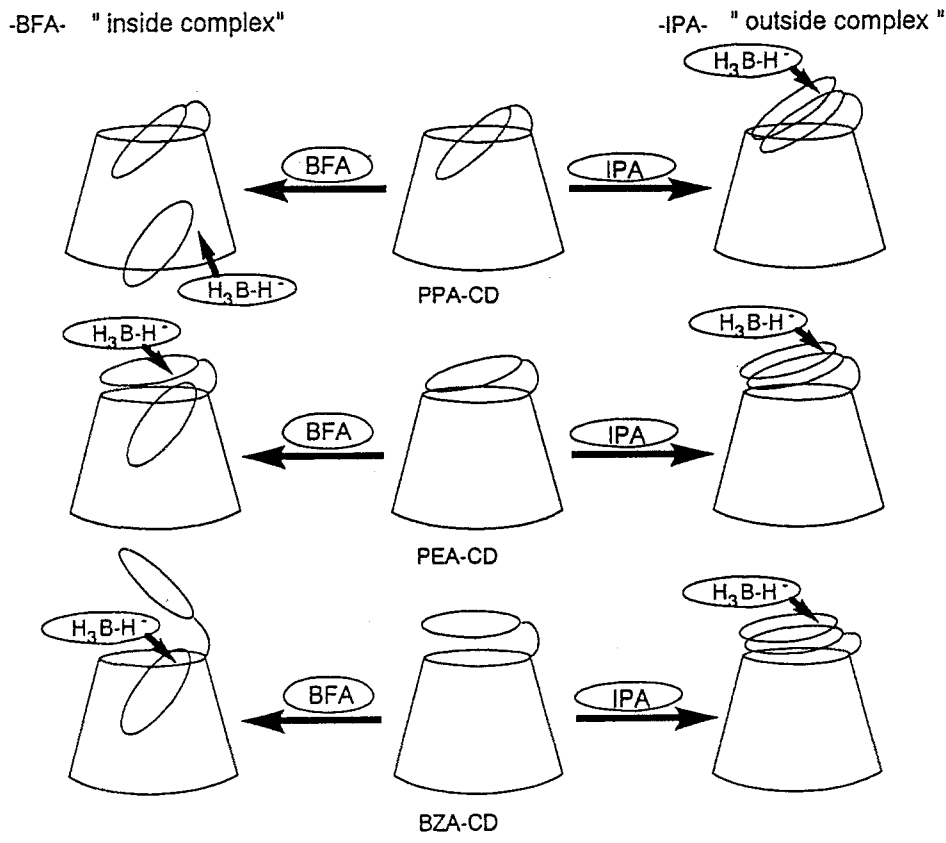
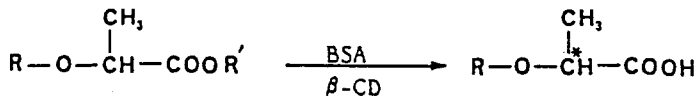
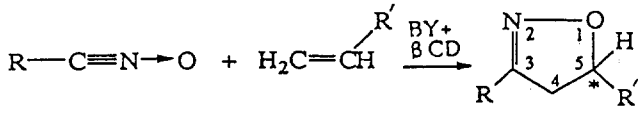


Fig. 16. Suggested orientation of substrate-modified CD complex by 2D NMR measurement.

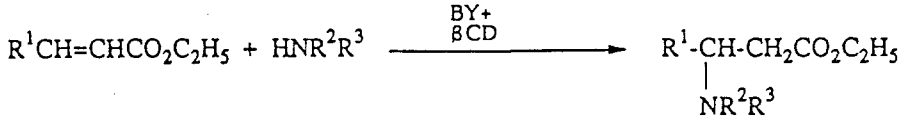
(*R*)-ethyl, (*S*)-*n*-butyl and (*S*)-isobutyl phenyl sulfoxides in optical yields of 9.8, 30.0 and 1.7%, respectively, whereas the heterogeneous reactions gave the corresponding sulfoxides with the opposite configurations in higher optical yields: *S* 26, *R* 42 and *R* 57% ee [40] (Figure 12), respectively. In this experiment, the oxidation was carried out without any pre-complex treatment, the precipitation of β-CD was observed during the reaction with high enantioselectivity. This fact indicated that the CD-substrate complex was formed even in pyridine solution. The differences in CD-complex structure in water and pyridine seem to reflect the optical yields and configuration. Colonna *et al.* have reported the asymmetric epoxidation (Weitz-Schiffer epoxidation) of vitamin K_3 analogues in aqueous alkaline buffer solution or in DMF/solid Na_2CO_3 in the presence of α- and β-CD [49] (Figure 13). The epoxidation of 2-methyl-1,4-naphthoquinone (Vitamin K_3) with *tert*-butyl hydroperoxide and β-CD in pH buffer solution and in DMF/solid Na_2CO_3 gave the product with optical yields of 22 and 24% respectively; whereas the reaction with α-CD gave the corresponding product without enantioselectiv-



R = substituted aryl; R^1 = alkyl



R = 2,4,6-Trimethylphenyl,
2,4,6-Trimethoxyphenyl
& 2,6-Dichlorophenyl
R' = 2-Pyridyl & 4-Pyridyl



R^1 = a: C_6H_5;b:4-$H_3CC_6H_4$;c:4-$H_3COC_6H_4$

HNR^2R^3 = a:$H_2NCH_2C_6H_5$;b:$H_2NCH_2CH_2C_6H_5$;c:HN

Fig. 17. Biocatalytic asymmetric reaction in the presence of CD [55, 56].

ity. The highest ee was observed with α-CD in the epoxidation of 2-*n*-octyl or 2-*n*-octadecyl-1,4-naphthoquinone, which are large molecules for the α-CD cavity size, 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 or be immobilized by interaction with the polar groups of the CD in DMF, so that the stereoselectivity of the reaction can be obtained by the asymmetric environment provided by the oxidant. Although the mechanism of epoxidation is clearly different in the two solvents, DMF and aqueous buffer, it is difficult to account for the higher enantioselectivities observed in DMF with respect to the aqueous medium. Recently, the effect of CDs on the Z/E-selectivity of the Wittig reaction with semistabilized ylides has been reported

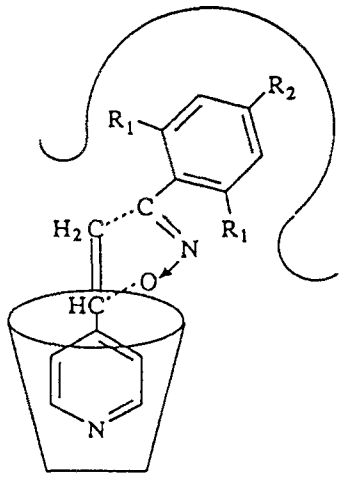


Fig. 18. Biocatalytic asymmetric cycloaddition using β-cyclodextrin [56a].

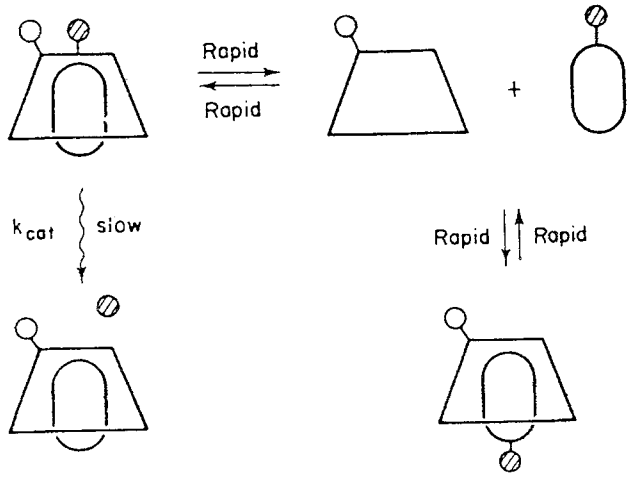


Fig. 19. Host-guest orientation determined by Bolzmann distribution [1].

[50]. 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 for the same Wittig reaction. A correlation between the size of the CD cavity and the selectivity was observed, the larger the CD the better is the selectivity, so that CD complexation or immobilization seems to affect the reaction selectivity in DMF. The results are discussed in the light of recent results on the mechanism for the Wittig reaction and are best rationalized in terms of the Vedejs four-center mechanism (Figure 14).

Whether in aqueous solvent or in organic solvent, it is possible that the reagent or substrate can still form an inclusion complex or be immobilized by interaction with CD. Adequate modification of the CD to attach a new interaction point or change the hydrophobic cavity can be expected to result in an appreciable ee in an asymmetric reaction (Table V, Figure 15).

Higher enantioselectivity in the reduction of benzoylformic acid (BFA) using $NaBH_4$ has been reported with 6-amino-6-deoxy-β-CD (ACD) rather than with β-CD as the host in neutral aqueous buffer solution [51]. The dependence of the ee on ionic strength and pH suggests that an electrostatic interaction between the amino residue on the rim of the CD ring and the carboxyl moiety of BFA should play an important role in enantioselectivity.

In our laboratory, several mono aromatic substituted CDs have been prepared. The phenyl group can be used as the cavity size control factor or as a 'self-guest molecule' and the sp^3 carbons between the parent CD cavity and the phenyl group can be used as the flexible arm [52]. Some of these CDs included their phenyl group in the hydrophobic cavity forming 'an intramolecular complex'. The 'intramolecular complex' was sometimes released by adding the guest molecules, which can be determined easily by NMR measurement. As shown in Figure 16 and Table V, the enantioselectivity was related to the shape of the hydrophobic cavity: (1) In the case of BFA, when the substrate was held between the hydrophobic cavity and the bulky hydrophobic substituent of the modified CD, a higher % ee was obtained. Because BFA could not release the intramolecular complex, a lower % ee could be observed with modified CDs which form intramolecular complexes. (2) In the case of a bigger substrate, indole-3-pyruvic acid (IPA), which forms an outside complex with CD derivatives, high enantioselectivities were observed with almost all of the amino-CD derivatives irrespective of the position of the substituent [53]. The enantioselectivity also depended on the kind of counter ion of the amino group [54]. It has not been clarified whether the phenomenon is mainly induced by a steric effect or an electrostatic effect. These results suggest that optimal modification of CD may lead to substantial improvements in asymmetric induction.

6. Biocatalytic Asymmetric Synthesis in the Presence of Cyclodextrin

The steric effect of CD has been reported in biocatalytic synthetic systems. In the system of a combination of natural and artificial enzymes, the prochiral guest molecule was included and rigidly fixed in the CD cavity, which should lead to preferential attack by the reagent from only one of the enantiotopic faces of the guest molecules and thus result in higher enantioselectivity (Figure 17).

BSA, one of the carrier proteins (see Section 3), catalyzed the hydrolysis of racemic aryloxypropionic esters and affords appreciable enantioselectivity (50–81% ee). The addition of β-CD in this reaction with BSA not only enhanced the enantioselectivity (80–99% ee) but also accelerated the rate of hydrolysis [55].

TABLE IV. Asymmetric reaction in the presence of CD without crystalline complex formation.

Substrate	Cyclodextrin	Reagent	Reaction state	Yield [%]	Optical yield[%]	Ref.
Reduction						
$C_6H_5COCF_3$	β	NAH	buffer/NaC micelle	[a]	3.7(R)	45
1-$C_{10}H_7COCF_3$	β	NAH	buffer/NaC micelle	[a]	1.1(R)	45
2-$C_{10}H_7COCF_3$	β	NAH	buffer/NaC micelle	[a]	5.8(R)	45
$C_6H_5COCF_3$	β	$NaBH_4$	buffer/NaC micelle	[a]	0	45
1-$C_{10}H_7COCF_3$	β	$NaBH_4$	buffer/NaC micelle	[a]	2.6(S)	45
2-$C_{10}H_7COCF_3$	β	$NaBH_4$	buffer/NaC micelle	[a]	10.0(S)	45
Diels-Alder reaction						
cyclopentadiene	β	ethyl fumalate	water	[b]	21.0	46
	β	fumalic acid	water	[b]	< 1	46
Oxidation						
ethyl tolylsulfide	α	H_2O_2	water	[c]	0.4	47
	α	m-ClPBA	water	[c]	-7.5	47
	β	H_2O_2	pyridine	32	2.00	44
ethyl-4-*tert*-butylphenyl sulfide	β	H_2O_2	water	[c]	0.4	47
ethyl-3-*tert*-butylphenylsulfide	β	H_2O_2	water	[c]	6.7	47
	α	H_2O_2	water	[c]	4.6	47
	γ	H_2O_2	water	[c]	-4.1	47
	β	m-ClPBA	water	[c]	20.7	47
	β	m-ClPBA	water	[c]	33.7	47
	β	t-BuOOH	water	[c]	19.7	47
	β	$PhI(OAc)_2$	water	[c]	-25.9	47
methyl-n-propylsulfide	β	H_2O_2	pyridine	50	0.90(R)	44
methyl-n-butylsulfide	β	H_2O_2	pyridine	50	0.25(S)	44
benzylmethylsulfide	β	H_2O_2	pyridine	50	2.80(S)	44
benzylethylsulfide	β	H_2O_2	pyridine	68	1.10(S)	44
benzyl-n-propylsulfide	β	H_2O_2	pyridine	58	0	44
benzyl-i-propylsulfide	β	H_2O_2	pyridine	58	2.10(S)	44
phenylmethylsulfide	β	H_2O_2	pyridine	38	0.03(S)	44
phenylethylsulfide	β	H_2O_2	pyridine	69	9.80(R)	44
phenyl-n-butylsulfide	β	H_2O_2	pyridine	12	30.00(S)	44
phenyl-i-butylsulfide	β	H_2O_2	pyridine	60	0.40(R)	44
tolylmethylsulfide	β	H_2O_2	pyridine	12	1.70(S)	44
tolylethylsulfide	β	H_2O_2	pyridine	32	2.00(S)	44
tolyl-n-butylsulfide	β	H_2O_2	pyridine	61	3.10(R)	44
	β	H_2O_2	pyridine	109	8.90(S)	44
2-methyl-1,4-naphthoquinone	β	t-BuOOH		33	22	49
	α	t-BuOOH		100	0	49
	β	H_2O_2	buffer solution (pH 9)	100	2	49
	β	NaOCl		98	1	49

TABLE IV. Continued.

Substrate	Cyclo-dextrin	Reagent	Reaction state	Yield [%]	Optical yield[%]	Ref.
	β	$PhC(CH_3)_2OOH$		47	0	49
	β	MCPBA		100	2	49
	β	t-BuOOH	DMF/Na_2CO_3	96	24	49
	α	t-BuOOH	DMF/Na_2CO_3	99	0	49
	β	t-BuOOH	$DMF/NaHCO_3$	0	–	49
	β	t-BuOOH	DMF/NaOH	53	14	49
	β	t-BuOOH	$DMSO/Na_2CO_3$	65	14	49
	β	t-BuOOH	$DMSO/NaHCO_3$	80	7	49
	β	t-BuOOH	DMSO/NaOH	66	9	49
2-n-octyl-1,4-naphthoquinone	β	t-BuOOH	DMF/Na_2CO_3	90	41	49
	α	t-BuOOH	DMF/Na_2CO_3	61	48	49
	β	$PhC(CH_3)_2OOH$	DMF/Na_2CO_3	87	19	49
	β	MCPBA	DMF/Na_2CO_3	0	0	49
2-n-butyl-1,4-naphthoquinone	β	t-BuOOH	DMF/Na_2CO_3	76	30	49
	α	t-BuOOH	DMF/Na_2CO_3	79	39	49
2-n-octadecyl-1,4-naphthoquinone	β	t-BuOOH	DMF/Na_2CO_3	47	27	49

[a] 20–60%.
[b] Chemical yield not reported in the reference.
[c] 60–70%.

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 the chiral recognition during cycloaddition can be improved by using cyclodextrin as an additional binding cavity [56] (Figure 18). In these reactions, the chemical yields were slightly affected and the enantioselectivity was enhanced (with an ee up to 70%).

7. Conclusion

CDs have great potential for exploitation as a useful tool for asymmetric induction because of the following advantages:

(1) Simplicity of the method: by adding CD or crystalline pre-complexed CD, high optical yields are obtained even in heterogeneous solution.

(2) Applicability to various reactions: In the presence of CD, various asymmetric inductions such as reduction of keto-acid and norbornenones, halogenation, hydrohalogenation, oxidation of sulfides, epoxidation, sigmatropic rearrangement, Michael addition, Diels-Alder reaction and Wittig reaction have been achieved in high optical yields using the combination of an achiral reagent and a prochiral substrate.

TABLE V. Asymmetric reduction in the presence of various monosubstituted CDs in aqueous buffer solution with $NaBH_4$.

Substrate	Cyclodextrin[a]	Optical yield(% ee)	Ref.
benzoformic acid	α	0	51
	β	4(R)	51
	γ	2(S)	51
	ACD	18(R)	53
	DMACD	26(R)	53
	BzACD	24(R)	53
	PEACD	33(R)	53
	PPACD	8(R)	53
indole-3-pyruvic acid	β	4(R)	53
	ACD	36(R)	53
	DMACD	38(R)	53
	BzACD	36(R)	53
	PEACD	39(R)	53
	PPACD	25(R)	53

[a] See Fig. 15; ACD: 6-amino-6-deoxy-β-cyclodextrin; DMACD: 6-deoxy-dimethylamino-β-cyclodextrin; BzACD: 6-benzylamino-6-deoxy-β-cyclodextrin; PEACD: 6-deoxy-6-phenethylamino-β-cyclodextrin; PPACD: 6-deoxy-6-phenylpropylamino-β-cyclodextrin.

(3) Availability under various conditions: The asymmetric induction with CD reported previously has been carried out in a gas-solid phase, heterogeneous suspension of water or organic solvent or homogeneous solution of buffer or organic solvent. A high optical yield has been achieved with a 'microcrystal CD complex' in the solid-state or heterogeneous suspension. On the other hand, it is interesting that appreciable optical yields have been achieved in organic solvents such as pyridine and DMF. It has been known that the main driving force of formation of an inclusion complex between a CD cavity and a guest molecule was hydrophobic interaction and the weaker binding of the substrate to CDs in a dipolar aprotic solvent with respect to water. The results in organic solvent suggest that other interactions such as a hydrogen bond and electrostatic interaction must be considered and the reaction may also proceed enantioselectively with CDs except in water.

In order to develop the asymmetric induction with a CD tool, it is necessary to clarify the reaction mechanism in detail. Complexation or immobilization certainly induced the asymmetry. First, we must know the molecular form of the complex with CD, prochiral substrate, achiral reagent or both molecules. Indeed, different ee values or reversed configuration has been observed depending on the size of the CD ring or the reaction solvent even when using the same combination of reactants

with the guest molecule. Second, it is most important and difficult to elucidate the respective enantiorecognition, the complex orientation in the reaction transition-state must be made clear at the molecular level. To estimate the availability of complex formation or explain the molecular recognition ability of CD, association constants have been mainly used. However, association constants alone are not enough to eplain the asymmetric induction. Other parameters including mobility should be considered. As shown in Figure 19, host-guest orientation is determined by the Bolzmann distribution [57]. From NMR measurements or fluorescence spectroscopy, the transient binding mode of the CD complex [58], and the mobility or conformational mobility can be deduced [59, 60]. These kinds of information would support the elucidation of the mechanism of asymmetric induction. On the other hand, the result of a reaction with a CD has the possibility of clarifying the transition-state as indicated in Section 5. Recently, it has been reported that the enantioselectivity of natural enzymes can be regulated by the solvent [61]. The investigation of asymmetric induction with a CD would provide information on the mechanism of natural enzyme selectivity.

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