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Can the Presence of Chemically Inert Species Modify the Face Selectivity in Asymmetric Induction by Cyclodextrins?

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Abstract. Reduction of β-cyclodextrin (β-CD) aromatic ketone (acetophenone and acetonaphthones) inclusion compounds were carried out in the presence of a large number of chemically inert species as potential co-guests. In several cases, it was observed that stoichiometric molar ratios of these compounds to ketone significantly modify the chiral induction yielding the inverted alcohol enantiomer and increasing the face selectivity. The results were found to depend strongly on the respective structure and shape of both the ketone and the additive, and on the molar ratio of β-CD:ketone:third compound. These observations suggest the formation of a three-component inclusion complex in which the geometry of binding of the substrate and its mobility are changed with respect to the binary system.

Key words: β-Cyclodextrin complex, reduction, chiral induction, three-component inclusion compound.

1. Introduction

Cyclodextrins (CDs) can act as a host by accommodating guest molecules in their hydrophobic cavity [1]. They have found applications in the food and drug industry for their ability to solubilize and stabilize included species [1–3]. In chemistry, the utility of CDs lies in their capability to separate structural, geometrical and optical isomers [4] and in their catalytic properties [5]. In the latter case, the inclusion of a guest in a constrained micro-environment of a defined shape gives rise to selective catalysts that mimic enzyme action [6]. A recent review [7] pointed out the great potential of CDs as useful tools for asymmetric induction in organic chemistry. However, stereoselectivities are generally lower than those obtained with more sophisticated chiral reagents. Several reasons for this lack of selectivity can be advanced. Among other things, we can assume that the modest enantioselectivities usually observed arise from the binding geometry for which the prochiral center is not located in the appropriate micro-environment and from the high mobility of

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the guest within the cavity of CDs. Support for these ideas is found in asymmetric reactions performed on crystalline inclusion complexes. Complete or nearly complete enantioselectivities were obtained for some compounds [8–10], indicating that restricted motion due to the solid state allows the reactive site to be maintained in a tighter asymmetric micro-environment.

Our work deals with another way to limit the degree of freedom of the included guest. The starting point was to suppose that tighter attachment can take place through the presence of a second molecule within the CD cavity, the co-guest, leading to a better efficiency for the chiral induction. Recent studies have provided strong evidence for the formation of ternary inclusion complexes involving two guests in the same cavity of CD. For example, the addition of third species, such as alcohols [11] or amines [12], to CD:polyaromatic hydrocarbon binary systems results in changes of their spectroscopic properties and in an increase of their apparent association constants. The authors concluded that the formation of three-component inclusion complexes occurs in which the co-guest occupies the residual spatial void remaining after binding of the molecule having the higher affinity for the CD cavity. Other authors have postulated the formation of ternary inclusion compounds to explain results obtained in bimolecular reactions carried out in the presence of CDs [13–15]. More recently, Tee *et al.* found that basic cleavage of *p*-nitrophenyl esters by β-CD is catalysed by alcohols, and some other additives [16]. In the latter example, the third component is believed to act as an inert spacer by the formation of ternary complexes which in some cases affords rate enhancements of esterolysis. These authors called it '*spectator catalysis*'.

Fornasier *et al.* reported poor to moderate asymmetric inductions for the reduction of aryl ketones by aqueous $NaBH_4$ in the presence of β-CD, depending on the molecular structure of the included molecule [17]. The present paper examines the effect of chemically inert species as potential co-guests on this reaction in order to determine whether the asymmetric induction by CD can be improved in the presence of additives.

2. Experimental

2.1. General

All the chemicals were used as purchased (Aldrich). β-CD was a gift from Ringdex Company. The following techniques were used for product analysis: NMR spectroscopy (Brüker A 2000), gas chromatography (Varian 3700), polarimetry (Perkin-Elmer 241MC).

2.2. Preparation of Three-Component Systems (molar ratio β-CD:ketone:third component 1:1:1)

Equimolar amounts (3×10^{-3} mol) of ketone and third compound were added to a suspension of β-CD (3.4 g; 3×10^{-3} mol) in 40 mL of 0.2 M aqueous Na_2CO_3.

TABLE I. Chiral induction in reduction by $NaBH_4$ of β-cyclodextrin/ketone complexes in the presence of different alcohols.

Alcohol	Binding constant alcohol:β-CD from Ref. 19	Acetophenone		1-acetonaphthone		2-acetonaphthone	
		ee %	yield %	ee %	yield %	ee %	yield %
None	–	5 *S*(–)	70	44 *R*(+)	61	22 *S*(–)	61
Isopropanol	3.8	3 *S*(–)	69	7 *R*(+)	59	16 *S*(–)	59
1-butanol	16.6	3 *S*(–)	77	6 *R*(+)	68	11 *S*(–)	78
1-pentanol	63.1	0	37	12 *R*(+)	48	19 *S*(–)	61

(molar ratio β-CD:ketone:alcohol = 1:1:1)

The mixture was stirred overnight at room temperature. The slurry obtained was allowed to react without isolation of inclusion compounds.

For other stoichiometries, the amount of ketone was kept constant and the corresponding molar ratios of β-CD and of third component were varied to the desired value.

2.3. General Procedure for the $NaBH_4$ Reduction

$NaBH_4$ (6×10^{-3} mol) was added to the freshly prepared suspension of three-component systems. The slurry was then stirred at room temperature and the reaction monitored by TLC (CH_2Cl_2). When the reduction of ketones was completed, the mixture was neutralized with 6M HCl and extracted with diethyl ether (5×10 mL). The combined ether extracts were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the resulting alcohol was purified by TLC (CH_2Cl_2). The enantiomeric excess (ee) value was determined from the integral ratios of signals obtained by gas chromatographic analysis on a chiral capillary column (column CYDEX-B, Scientific Glass Engineering). Polarimetric measurements gave the absolute configuration of the alcohol obtained [18]. Values of ee were expressed as the mean of triplicate experiments.

3. Results and Discussion

The reduction of ketones was carried out under heterogeneous conditions without isolation of inclusion complexes [19]. The third species was added to the aqueous suspension of β-CD at the same time as the ketone. We first investigated the effect of alcohols on the enantioselectivity in the β-CD-mediated reduction of acetophenone and acetonaphthones by aqueous $NaBH_4$ in a molar ratio β-CD:ketone:alcohol of 1:1:1. The data obtained, summarized in Table I, show a marked decrease of the enantioface selectivity when reductions were performed in the presence of different simple alcohols. Even larger effects were observed for higher alcohol concentrations.

TABLE II. Chiral induction in reduction by $NaBH_4$ of β-cyclodextrin/ketone complexes in the presence of different tertiary amines and amides.

Third species	Molar ratio[a]	Acetophenone		1-acetonaphthone		2-acetonaphthone	
		ee %	yield %	ee %	yield %	ee %	yield %
Amine							
trimethylamine	1:1:1	< 1	60	< 1	74	16 *S*(–)	71
	2:1:1	4 *S*(–)	60	50 *R*(+)	32	26 *S*(–)	58
triethylamine	1:1:1	15 *R*(+)	40	0	38	5 *S*(–)	34
	2:1:1	43 *R*(+)	50	44 *R*(+)	44	23 *S*(–)	26
tributylamine	1:1:1	3 *S*(–)	38	22 *R*(+)	58	11 *S*(–)	38
	2:1:1	9 *S*(–)	50	39 *R*(+)	24	11 *S*(–)	27
diethylethanol-amine	1:1:1	5 *S*(–)	42	–	–	–	–
	2:1:1	18 *S*(–)	55	34 *R*(+)	30	29 *S*(–)	44
pyridine	1:1:1	3 *S*(–)	56	2 *R*(+)	42	8 *S*(–)	70
2-picoline	1:1:1	3 *S*(–)	58	17 *R*(+)	70	16 *S*(–)	77
3-picoline	1:1:1	0	77	14 *R*(+)	77	14 *S*(–)	80
4-picoline	1:1:1	2 *S*(–)	53	9 *R*(+)	72	4 *S*(–)	72
2,6-dimethyl-pyridine	1:1:1	2 *S*(–)	60	9 *R*(+)	74	4 S(–)	81
N-methyl-imidazol	1:1:1	5 *S*(–)	44	5 *R*(+)	65	8 *S*(–)	55
Amide							
N-methyl-pyrrolidone	1:1:1	4 *S*(–)	62	25 *R*(+)	58	12 *S*(–)	55
N, *N*′dimethyl-formamide	1:1:1	4 *S*(–)	53	25 *R*(+)	62	8 *S*(–)	45
N, *N*′dimethyl-acetamide	1:1:1	5 *S*(–)	41	11 *R*(+)	50	9 *S*(–)	68
None	1:1:0	5 *S*(–)	70	44 *R*(+)	61	22 *S*(–)	61
	2:1:0	6 *S*(–)	58	53 *R*(+)	58	24 *S*(–)	61

[a] Molar ratio β-CD:ketone:third species

The results seem to provide evidence for the competitive binding of alcohols to β-CD, since the complexation is essential for asymmetric induction. The association constants found in the literature [20], however, indicate very low affinities for β-CD among the alcohols studied. It is unlikely that the equilibrium of aromatic ketone binding to β-CD is significantly shifted by stoichiometric amounts of small alcohols. In addition, it has to be noted that the enantioselectivity for acetonaphthones is higher in the presence of 1-pentanol than in the presence of the other two alcohols, in spite of its larger binding constant to β-CD. These results cannot be due to a solvent effect because the alcohols were added in a stoichoimetric molar

fraction with respect to the other reactants. We therefore propose that the process responsible for the changes of asymmetric induction could be the formation of three-component inclusion systems.

On the basis of this approach, we examined the effect of a large number of other chemically inert compounds, such as tertiary amines and amides (Table II).

The data obtained were disappointing, since most of the chiral inductions were very low. The addition of a third species to the reaction medium generally resulted in a large decrease of ee values. It was previously reported that an augmentation of the chiral induction in the oxidation of aryl sulfides was obtained with molar ratios of β-CD:substrate higher than 1:1 [21, 22]. We observed the same trend for binary systems. Besides, the effect due to the presence of a third compound is minimized by increasing the molar ratio of β-CD:ketone.

The only striking result observed was for the reduction of acetophenone in the presence of triethylamine. Values of ee increased three times for a β-CD:ketone: amine molar ratio of 1:1:1 and more than seven times for a ratio of 2:1:1. Moreover, the prevailing enantiomer was $R(+)$ 2-phenyl ethanol, the absolute configuration of which is opposite to that observed in the reduction of the binary acetophenone:β-CD system. Clearly, in this particular case, there is a process involving triethylamine which gives rise to a dramatic enhancement of the chiral induction and to an inverted face selectivity. From the inspection of CPK space-filling models, it appears that the β-CD cavity loosely binds acetophenone. The building of a ternary complex shows that there is not enough room for the complete inclusion of both acetophenone and triethylamine molecules inside the β-CD cavity. If, as we propose, a three-component complex forms, triethylamine is most probably only partially included, considering the predictible relative affinity of both guests to β-CD. Thus, a better space filling is achieved in the complex formation. This molecular arrangement imposes a considerable restriction on the rotational motion of acetophenone by steric hindrance, which must definitely affect the face selectivity.

In contrast, as previously outlined [17,22], naphthalene derivatives fit better into the β-CD cavity accounting for higher chiral inductions observed for binary β-CD–acetonaphthone systems. Obviously, if a three-component complex occurs, the molecular arrangement has less chance to be in the appropriate geometry for the enantioface attack by hydride anion. This conclusion is consistent with the effect of a third species on the enantioselectivity of acetonaphthone reduction and with the fact that high molar ratios of β-CD partially restore the chiral induction.

Unfortunately, we cannot find a simple dependence of the enantioselectivity on the chemical structure of co-guests and on their ability to bind to β-CD. For example, trimethylamine (molar ratio 1:1:1) prevented the asymmetric reduction of acetophenone and 1-acetonaphthone, but not that of 2-acetonaphthone, whereas tributylamine, having a much higher binding affinity for β-CD owing to its longer alkyl chains, shows no such strong inhibition. On the other hand, it was expected that hydrogen bonding might act as an additional binding to anchor strongly the substrate in an appropriate geometry to undergo asymmetric reduction. Surpris-

ingly, the attachment of one hydroxyl group on the triethylamine structure, that is diethyl ethanolamine, annihilates the chiral induction obtained with unsubstituted triethylamine in the reduction of acetophenone. However, increases in selectivity (without inversion of configuration) were observed with that compound in the cases of acetophenone and 2-acetonaphthone when β-CD was used in a two-fold excess.

Obviously, the third component is not directly involved in the reduction mechanism since compounds of similar chemical structure gave rise to different effects on enantioselectivity. The results reported in Table II show that the ability of potential co-guest molecules to positively or negatively affect the enantioselectivity strongly depends on the structure of both the ketone and the third species. This agrees with our working hypothesis suggesting the participation of one molecule of a third compound to the process of chiral induction through the formation of a ternary inclusion complex. Only a few molecular arrangements with respect to a given ketone substrate are favorable to the asymmetric attack of hydride ions, so that the size, the shape, and the hydrophobic character are of prime importance in controlling the enantioselectivity. All these parameters should be considered in order to achieve predictive chiral induction by CDs with a process involving co-guests.

Finally, we investigated the effect of various concentrations of third species on the chiral induction at a fixed molar ratio β-CD:ketone of 2:1. We chose three combinations of ketone:third compound and examined the more interesting aspects of enantioselectivity enhancement and chiral inversion. The selected systems were acetophenone:triethylamine, 1-acetonaphthone:*N*-methylpyrrolidone, and 2-acetonaphthone:1-pentanol. The ee values obtained for different molar ratios are shown in Figures 1–3.

Curves 1 and 3 corresponding to the dependence of the asymmetric reduction of acetophenone and 2-acetonaphthone on the concentration of triethylamine and 1-pentanol, respectively, have a similar profile. Chiral induction first increases, the best ee value being achieved with a molar ratio ketone:third compound of 1:2. Beyond this ratio, increasing the concentration of the third species resulted for each case in a strong decrease of enantioselectivity. Note that the enantiomer predominantly formed in the reduction of 2-acetonaphthone has the configuration of that observed upon addition of 1-pentanol in contrast to the case of acetophenone and triethylamine.

On the other hand, the combination composed of β-CD, 1-acetonaphthone, and *N*-methylpyrrolidone appears to have a completely opposite behavior (Figure 2). The chiral induction first strongly decreases upon addition of *N*-methylpyrrolidone and then increases moderately after a minimum value reached at a molar ratio of about 1:2. Interestingly, the preferential chirality induced by two and more molar equivalents of *N*-methylpyrrolidone was the inverse of that obtained for lower ratios.

Again, these results can be reasonably explained by our hypothesis on the formation of three-component inclusion compounds. The maximum effect observed

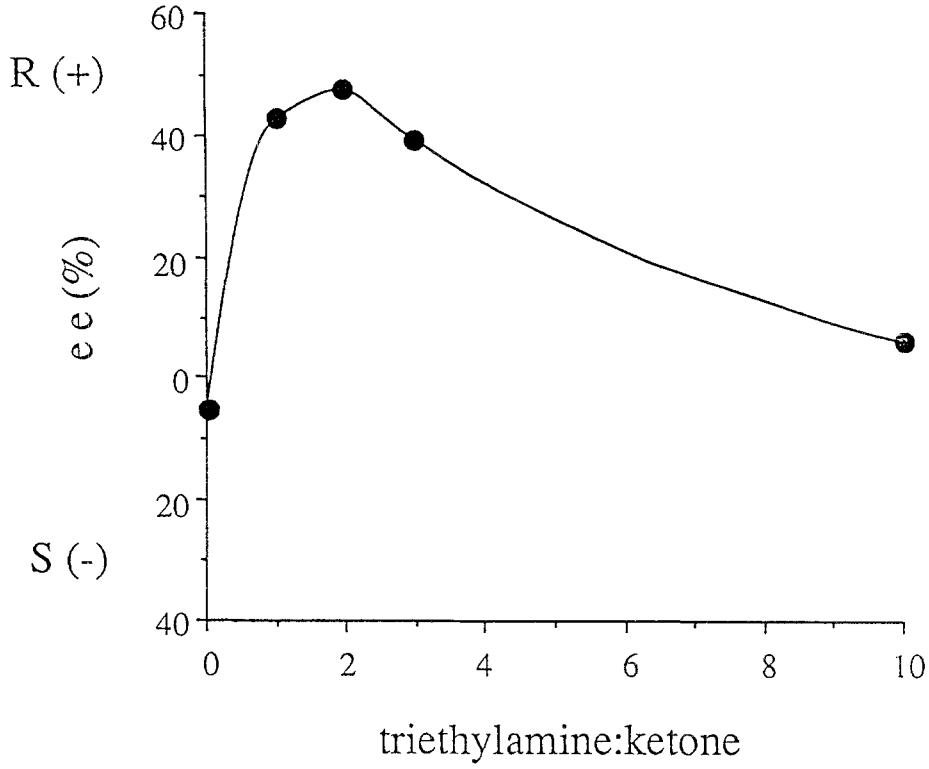

Fig. 1. Variation of the β-CD chiral induction in the reduction of acetophenone as a function of the molar ratio triethylamine:ketone (fixed molar ratio β-CD:ketone of 2:1).

for the molar ratio β-CD:ketone:third component of 2:1:2 is likely due to the completion of the inclusion equilibrium because of the presence of two CD cavities. Two probable effects can be assumed due to the binding of a third component: a positive cooperative effect yielding a reinforcement of the face selectivity as in the case of 2-acetonaphthone and 1-pentanol (Figure 3), and the antagonistic effect giving the inverse enantiomer for some systems. For the latter, the resulting selectivity reflects the fit of the substrate to an asymmetric micro-environment in the three-component compound. Thus, the face selectivity can be increased as in the case of acetophenone and triethylamine (Figure 1) or decreased as in the case of 1-acetonaphthone and *N*-methylpyrrolidone (Figure 2) with respect to binary β-CD:ketone systems. This conclusion is consistent with the results reported in Table II, showing different behaviors of a given ketone depending on the geometry and shape of third components and, conversely, of a given third component on the structure of substrates.

The inhibition of chiral induction generally observed for higher concentations of third compounds must be related to a combination of an increased bulk solvent hydrophobicity and a competitive binding of the substrate and the additive for

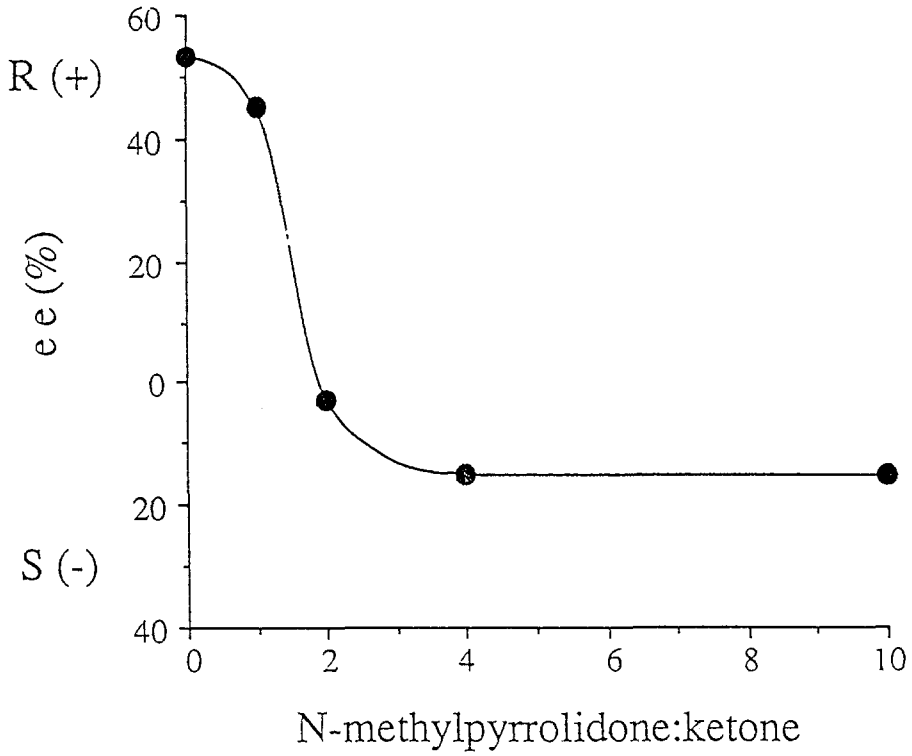

Fig. 2. Variation of the β-CD chiral induction in the reduction of 1-acetonaphthone as a function of the molar ratio *N*-methylpyrrolidone:ketone (fixed molar ratio β-CD:ketone of 2:1).

the β-CD cavity. Presumably, this expected behavior may be correlated with the apparent constants of complex formation.

4. Conclusion

The results reported above clearly reveal that a stoichiometric amount of an inert compound, having a weaker affinity for the CD cavity than that of substrate, can completely modify the chiral induction by CDs. It is the first report describing such an effect on enantioselectivity. This stresses the role that organic compounds can play when added to the reaction medium.

Our findings fully agree with the conclusions of Tee *et al.* in their work on the effect of additives on the cleavage of *m*-nitrophenyl esters [16]. As already mentioned, they found in some cases rate enhancement of the cleavage depending on the structure of additives. This effect was explained by the formation of a ternary inclusion complex in the transition state. These authors have compared this catalysis to a paradigm for primitive allosteric effects because the binding and the reactivity of a substrate with a catalyst can be improved by the concomittant

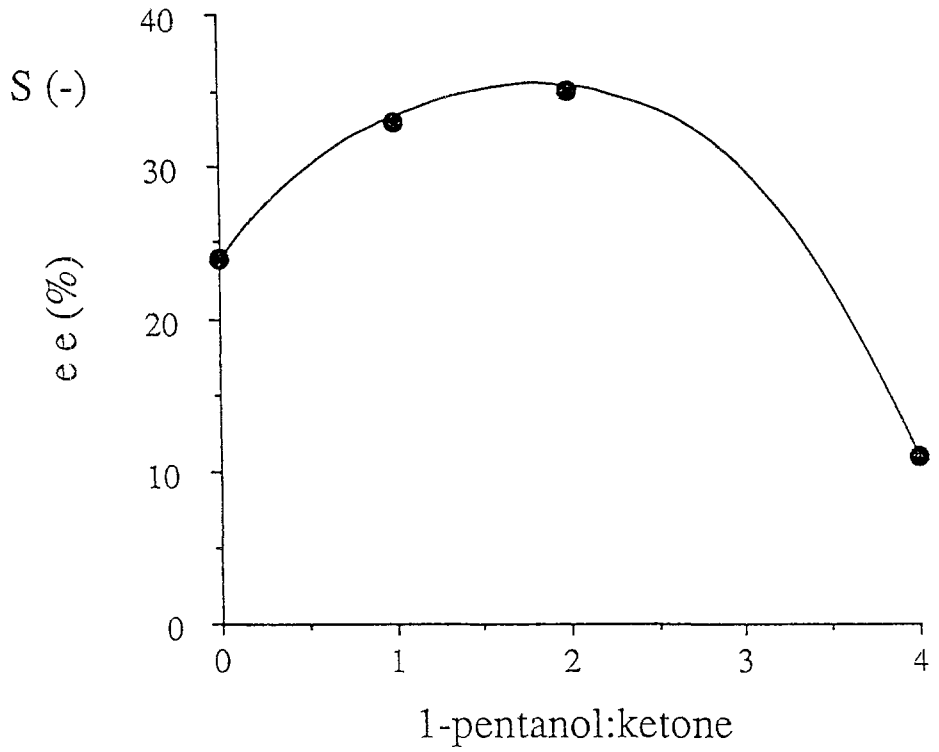

Fig. 3. Variation of the β-CD chiral induction in the reduction of 2-acetonaphthone as a function of the molar ratio pentanol:ketone (fixed molar ratio β-CD:ketone of 2:1).

binding of a third chemically inert species, as happens in a more complex way with enzymes. Although the mechanism of esterolysis by CDs is clearly different (covalent catalysis), we assume that a similar supposition can be made in our case.

Since only stoichoimetric amounts of this third species give rise to significant effects, we conclude that the formation of three-component inclusion compounds takes place. Under these conditions, the binding of the co-guest occurs in such a way as to modify the position and the mobility of the substrate within the constrained cavity by simple steric effects. An empirical screening of potential co-guests allowed us to find dramatic improvements of selectivity for reduction of aromatic ketones in the presence of β-CD. This suggests that an appropriate shape and structure of the co-guests, determined by molecular modelling, might optimize the fit of a substrate so that complete enantioselectivities of both enantiomers would be achieved. Although we have examined only three systems, we assume that the change of selectivity upon the addition of a third chemically inert compound is a general process in CD-mediated reactions. New developments in chiral induction by CDs could be expected in the future using this approach.

Further studies are now being undertaken to determine more precisely the structure responsible for the chiral induction in these three-component systems.

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