# Chiral Discrimination by Modified Cyclodextrins

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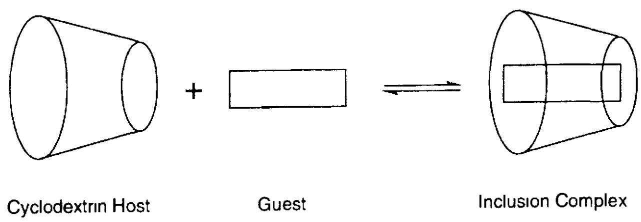
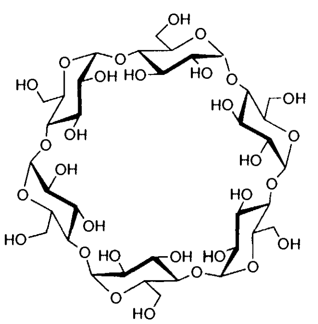
## 1 Introduction

The naturally occurring $\alpha$, $\beta$ and $\gamma$ cyclodextrins **1—3** are cyclic oligosaccharides, consisting of six, seven and eight $\alpha$ 1,4 linked D glucopyranose units, respectively. Interest in these compounds stems from the fact that they act as host molecules to form inclusion complexes with a wide variety of guests (Scheme 1).[1] The cyclodextrins each exist as a single enantiomer, with the consequence that when they act as host molecules, interaction with a racemic guest may lead to the formation of diastereoisomeric complexes of differing thermodynamic stability. This chiral discrimination by unmodified cyclodextrins has been intensively studied and extensively exploited, most notably through the work of Armstrong *et al.*,[2] in the development of cyclodextrin based chromatographic systems.

The extent of chiral discrimination displayed by the naturally occurring cyclodextrins is typically quite modest, however, with efficient resolution of racemates only resulting from repeated interactions with a cyclodextrin, as is the case with cyclodextrin based chromatography. The low enantioselectivity may be attributed to the inherent symmetry of the cyclodextrins, with each having an axis of symmetry. In addition, inclusion complex formation often occurs principally as a result of interaction of the hydrophobic annulus of the cyclodextrin with an achiral hydrophobic portion of




**Scheme 1** Inclusion complex association constant $K$ = [inclusion complex]/([cyclodextrin host][guest])



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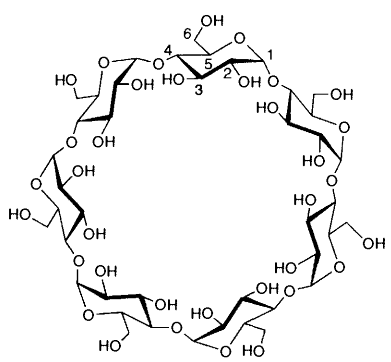

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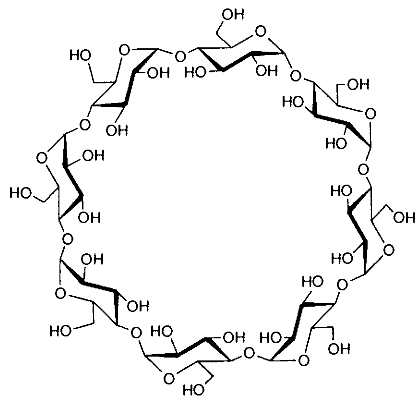

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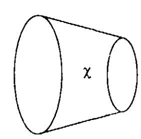
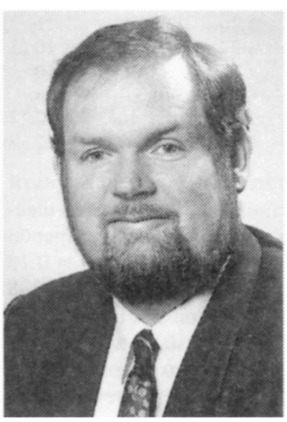


1 χ = α
2 χ = β
3 χ = γ

A truncated cone is often used to represent the torus of a cyclodextrin. A substituent drawn at the narrow end of the cone indicates that it replaces one of the C 6 hydroxy groups in the cyclodextrin, while a substituent drawn at the wide end of the cone indicates that it replaces either a C 2 or a C 3 hydroxy group.



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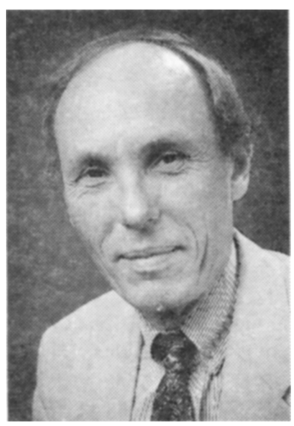


*Stephen Lincoln is head of the department of chemistry at the University of Adelaide where he holds a personal chair. He was born in Suffolk and graduated BSc (Tech) with first class honours from UMIST in 1962. He then decided to see the world and graduated with a PhD from the University of Adelaide in 1966. He went on to a post-doctoral position at Washington State University, returning to Adelaide as a lecturer in 1968. He was awarded a DSc by the University of Manchester in 1984. His research interests include inorganic and bioinorganic mechanisms and molecular recognition chemistry.*

a guest, and there is little interaction between the chiral centres of the cyclodextrin and those of the guest It follows that increased chiral discrimination can be expected with modified cyclodextrins where, through the modification, the degree of asymmetry of the cyclodextrin has been increased and there is the possibility of greater interaction between chiral portions of the cyclodextrins and those of the guests

Modifying cyclodextrins and their complexing characteristics usually involves substitution of one or more of the C-2, C-3 and C-6 hydroxy groups The modifications may be divided into two categories In one, the hydroxy substituents are substituted in a symmetric fashion to give a single modified cyclodextrin (*e g* , all the hydroxy groups may be substituted) or at random to give a complex mixture of cyclodextrins in which the average effect is that of a symmetric substitution As we will show, this tends not to alter the symmetry of the cyclodextrin or the enantioselectivity that it displays With the other type of modified cyclodextrin, either a single substituent or a specific combination of substituents is introduced This may induce substantial changes in the asymmetry of the cyclodextrin and result in additional and more specific interactions between the chiral area of the guest and the asymmetry of the host, which restrict the geometry of binding, leading to greater enantioselectivity The additional interactions between the cyclodextrin substituent and the host may be subdivided into secondary bonding interactions, metal complexation and covalent attachment Again we will show that as the extent of the interaction between the cyclodextrin substituent and the guest increases, the magnitude of chiral discrimination often becomes greater

In choosing examples to illustrate this review, we have restricted our selection to those for which thermodynamic and/or kinetic parameters of the homogeneous solution-phase interaction between the cyclodextrin and each enantiomer of the guest have been reported We have not included results from heterogeneous systems, on the basis that they may depend on factors such as phase solubility and other medium and surface effects, and guest or cyclodextrin aggregate formation, rather than inclusion complex formation It has been noted previously that little direct correlation exists between the retention times of molecules on cyclodextrin-based chromatography columns and the thermodynamic stability of the inclusion complexes formed in solution between those molecules and cyclodextrins [3] Spectroscopic discrimination does not necessarily correlate with thermodynamic discrimination, so examples of the former are only discussed where they have been used to measure the thermodynamics of inclusion complex formation Since our aim is to compare the chiral discrimination displayed by the natural and modified cyclodextrins, we have only included details of enantioselectivity shown by natural cyclodextrins where comparative data with cyclodextrin derivatives are available

The values for cyclodextrin–guest association constants given herein are quoted directly from the primary literature It should be noted that these data arise from work in various laboratories, with the result that a range of experimental conditions has been used For this reason, key experimental parameters are indicated, to show the limits to which results from various studies are directly comparable Nevertheless, there is remarkable consistency between the various experiments, with most studies being carried out in aqueous solution, at or near 298 K Most importantly, identical conditions prevailed in all cases where comparisons are made between diastereoisomeric pairs of host–guest complexes

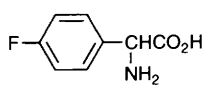
## 2 Effect of Additional Secondary Bonding Interactions

As mentioned above, symmetrically substituted cyclodextrins tend to show no greater chiral discrimination than the naturally occurring analogues This holds even where the modification results in more favourable interactions between the racemic guest and cyclodextrin host, as reflected in much higher association constants for the diastereoisomeric inclusion complexes For example, as shown in Table 1 (entries 1—12), the association constants of the inclusion

**Table 1** Association constants of cyclodextrin inclusion complexes

| Entry | Cyclodextrin | Guest | $K_R$/dm³ mol⁻¹ | $K_S$/dm³ mol⁻¹ | $K_R/K_S$[a] | Ref[b] |
|---|---|---|---|---|---|---|
| 1 | **1** | **4** + H⁺ | 7 7 ± 0 3 | 8 2 ± 0 3 | 0 94 | 4 |
| 2 | **7** | **4** + H⁺ | 54 ± 3 | 59 ± 4 | 0 92 | 5 |
| 3 | **1** | **4** − H⁺ | 21 5 ± 0 4 | 22 5 ± 0 4 | 0 96 | 4 |
| 4 | **7** | **4** − H⁺ | 49 ± 3 | 55 ± 3 | 0 89 | 5 |
| 5 | **1** | **5** | 14 4 ± 0 1 | 14 6 ± 0 1 | 0 99 | 4 |
| 6 | **7** | **5** | 451 ± 7 | 434 ± 7 | 1 04 | 5 |
| 7 | **1** | **5** − H⁺ | 13 1 ± 0 5 | 14 1 ± 0 5 | 0 93 | 4 |
| 8 | **7** | **5** − H⁺ | 80 ± 3 | 77 ± 3 | 1 04 | 5 |
| 9 | **1** | **6** | 8 3 ± 0 3 | 8 3 ± 0 3 | 1 00 | 4 |
| 10 | **7** | **6** | 142 ± 6 | 155 ± 6 | 0 92 | 5 |
| 11 | **1** | **6** − H⁺ | 12 4 ± 0 3 | 10 6 ± 0 4 | 1 17 | 4 |
| 12 | **7** | **6** − H⁺ | 143 ± 6 | 153 ± 6 | 0 93 | 5 |
| 13 | **1** | **10** | 27 ± 3 | 17 ± 4 | 1 59 | 7 |
| 14 | **2** | **10** | 1090 ± 30 | 1010 ± 40 | 1 08 | 6 |
| 15 | **7** | **10** | 220 ± 10 | 207 ± 8 | 1 06 | 7 |
| 16 | **8** | **10** | 129 ± 5 | 170 ± 10 | 0 76 | 7 |
| 17 | **2** | **10** − H⁺ | 63 ± 8 | 52 ± 5 | 1 21 | 6 |
| 18 | **9** | **10** − H⁺ | 36 ± 6 | 13 ± 7 | 2 77 | 6 |
| 19 | **13**[c] | **16** | 14 7 | 10 8 | 1 36 | 11 |
| 20 | **14**[d] | **16** | 54 0 ± 7 6 | 42 5 ± 7 3 | 1 27 | 10,11 |
| 21 | **15**[d] | **16** | 45 5 ± 8 2 | 34 5 ± 5 7 | 1 32 | 10 |
| 22 | **18** | **17** | 295 ± 3 | 629 ± 10 | 0 47 | 13 |
| 23 | **19** | **17** | 160 ± 36 | 83 ± 28 | 1 93 | 12,13 |
| 24 | **20** | **17** | 139 ± 24 | 231 ± 45 | 0 60 | 12,13 |

[a] These ratios substantiate the trends referred to in the text, but it should be noted that standard deviations in the association constants of the diastereoisomeric pairs of inclusion complexes limit the reliability of the data [b] Although a range of conditions has been used in measuring the association constants cited herein, in the text comparisons are only made of data recorded under similar conditions Experimental conditions were as follows refs 4 and 5 solvent 10% aqueous $D_2O$, $I$ = 0 10 mol dm$^{-3}$, $T$ = 295 5 K, refs 6 and 7 solvent $H_2O$, $I$ = 0 10 mol dm$^{-3}$, $T$ = 298 2 K, refs 10 and 11: solvent $H_2O$, $Na_2B_4O_7$ (15 4 × 10$^{-3}$ mol dm$^{-3}$) and $H_3BO_3$ (34 6 × 10$^{-3}$ mol dm$^{-3}$), $T$ = 298 K, refs 12 and 13 solvent $H_2O$, 0 066 mol dm$^{-3}$ phosphate, $T$ = 298 K [c] Compound **13** is a mixture of the 6$^A$,6$^B$-isomers, in which the primary hydroxy groups of two adjacent glucose residues of the cyclodextrin have been substituted The association constants are the same for each isomer, within experimental error [10,11] [d] Compounds **14** and **15** are 6$^A$,6$^B$-isomers, in which the primary hydroxy groups of two adjacent glucose residues of the cyclodextrin have been substituted The structures of the 6$^A$,6$^B$-isomers **14** and **15** may be the reverse [10,11]

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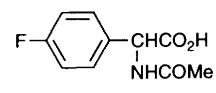


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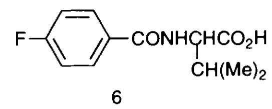


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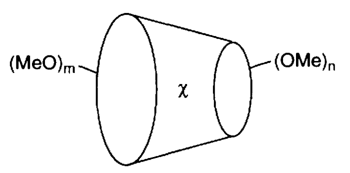
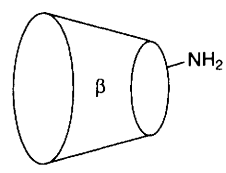



7 $\chi = \alpha$, m = 12, n = 6
8 $\chi = \beta$, m = 14, n = 7

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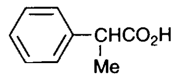


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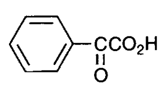
complexes of the variously protonated and deprotonated fluorinated amino acid derivatives **4—6** with termethylated $\alpha$-cyclodextrin **7** are substantially greater than those formed with the parent $\alpha$-cyclodextrin **1**, yet the enantioselectivity shown by the modified cyclodextrin **7** is little different from that displayed by $\alpha$-cyclodextrin **1** [4,5] Similarly, the extent of chiral discrimination displayed by the termethylated cyclodextrins **7** and **8** in the formation of inclusion complexes with the (*R*)- and (*S*)-enantiomers of 2-phenylpropanoic acid **10** is not much different from that exhibited by the natural cyclodextrin analogues **1** and **2** (Table 1, entries 13—16) [6,7] It is worth noting that the methyl substituents of the modified cyclodextrins **7** and **8** increase their flexibility as hosts This flexibility allows conformational change to occur more easily, to accommodate a guest and increase complex stability, but it is unlikely to favour chiral discrimination Conversely, lack of flexibility of the host and specific host–guest interactions should lead to increased enantioselectivity, but this is likely to correlate with the formation of less stable complexes The association constants of the complexes of the enantiomers of the anion of 2-phenylpropanoic acid **10** with $\beta$-cyclodextrin **2** and the corresponding amine **9** (Table 1, entries 17 and 18)[6] provide a pertinent illustration The enantioselectivity displayed by the modified cyclodextrin **9** is significantly greater but the association constants are lower, indicating a specific and unfavourable effect of the amino substituent of the host **9** on complexation of the propanoate guest The enhanced stereoselectivity displayed by the amino-substituted cyclodextrin **9** in the formation of inclusion complexes is reflected by an increase in asymmetric induction in reactions of included guests [8,9] While the sodium borohydride reduction of benzoylformic acid **11** in the presence of $\beta$-cyclodextrin **2** gave the (*R*)-enantiomer of the alcohol **12** in 4% enantiomeric excess, a 13% excess was obtained when the reaction was performed in the presence of the amino-substituted cyclodextrin **9** The effect of the modified cyclodextrin **9** was attributed to electrostatic interaction between the amino substituent of the cyclodextrin **9** and the carboxy moiety of benzoylformic acid **11**

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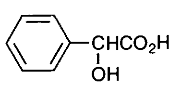


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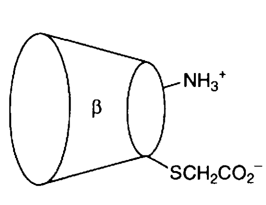
With an increase in the number of interactions between the guest and substituents introduced on to the modified host, greater chiral discrimination by the host could be expected Tabushi *et al*,[10,11] synthesised the modified cyclodextrins **13—15**, having both positively and negatively charged substituents, and investigated their behaviour as chiral artificial receptors for tryptophan **16** (Fig 1) Each of the modified cyclodextrins **13—15** displayed a modest degree of enantioselectivity (Table 1, entries 19—21) The stability

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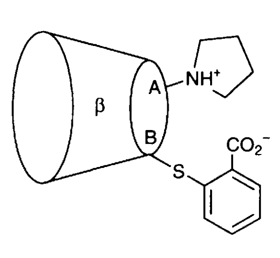


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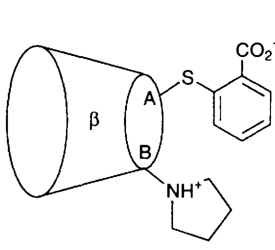


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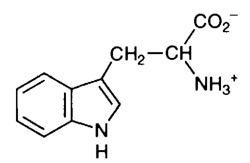


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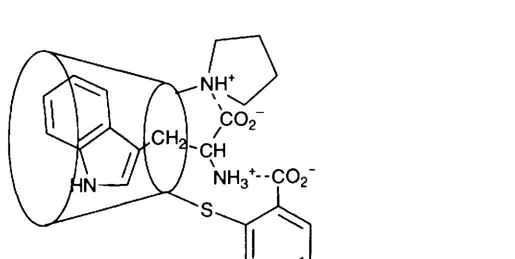
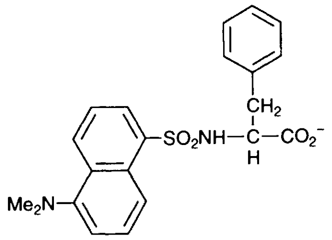



**Figure 1** Schematic representation of the complexation of tryptophan **16** by the modified cyclodextrin **14**

constants of the complexes were found to be larger in the cases of the cyclodextrins **14** and **15**, than those observed with the analogue **13**, and this was attributed to greater polar interactions between the guest and host when the host substituents were in a relatively non-polar environment The greater polar interactions were not reflected in enhanced chiral discrimination, however, as the enantioselectivity displayed by the cyclodextrins **13—15** was quite similar

An alternative facet of enantioselective guest complexation by a modified cyclodextrin was reported by Takahashi *et al* [12,13] Amino acid-substituted cyclodextrins formed diastereoisomeric complexes with the *N*-dansylphenylalanine anion **17**, in the case of the tyrosine



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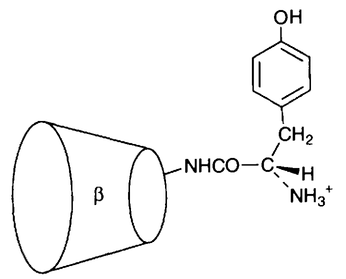

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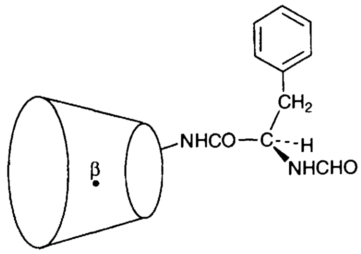

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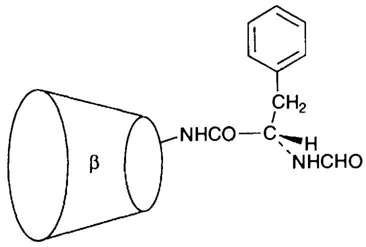

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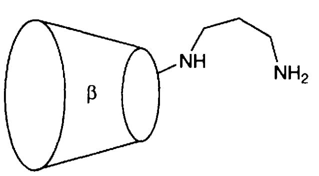
derivative **18** their association constants differed by a factor of 2.13 (Table 1, entry 22). In this case, where the substituent of the modified cyclodextrin is chiral, the cyclodextrin annulus probably serves mainly to bind the guest and contributes little towards the enantioselectivity. Instead stereoselectivity probably results from interactions between the chiral substituent of the cyclodextrin and chiral portions of the guest. Support for this interpretation comes from the observation that the enantioselectivity displayed by the modified cyclodextrin diastereoisomers **19** and **20** in complexing the *N*-dansylphenylalanine anion **17** is similar in magnitude, though reversed in terms of absolute stereochemistry (Table 1, entries 23 and 24).[12,13]

## 3 Metallocyclodextrins

The examples given above show that secondary bonding interactions between included guests and substituents of modified cyclodextrins can lead to greater stereoselectivity in the formation of inclusion complexes. Nevertheless the association constants of the diastereoisomeric inclusion complexes differ by no greater than a factor of three and generally by much less. Through metal complexation, which further increases the extent of interaction between the cyclodextrin and the guest, the diastereoselectivity can be further improved. This involves the coordination of both the cyclodextrin substituent and the guest to a metal in the host–guest complex, as a result of which the binding geometry can be quite restricted.

The tenfold chiral discrimination displayed by the nickel(II) complex **22** (M = Ni) of $6^A$-(3-aminopropylamino)-$6^A$-deoxy-$\beta$-cyclodextrin **21** in the formation of inclusion complexes with the enantiomers of the anion of tryptophan **16** (Table 2, entry 3) is the largest reported for a metallocyclodextrin.[14,15] Comparison of the association constants of the inclusion complexes of the metallocyclodextrin **22** (M = Ni) with those of the complexes formed in the absence of a metal and with the parent $\beta$-cyclodextrin **2** (Table 2, entries 1—3) provides an insight into the origin of this enantioselectivity. There is no chiral discrimination in the formation of the diastereoisomeric inclusion complexes of the enantiomers of the anion of tryptophan **16** with $\beta$-cyclodextrin **2** or with the aminopropylamino-substituted cyclodextrin **21**, although the thermodynamic stability of the complexes is greater with the modified cyclodextrin **21**. The thermodynamic stability of the ternary complex of each enantiomer of the anion of tryptophan **16** with the metallocyclodextrin **22** (M = Ni) is even greater, showing the presence of even more favourable interactions. By comparison with the complexation constant for the interaction between the anion of tryptophan **16** and nickel(II) (Table 3, entry 2), the ternary complexes are less stable, however, indicating that the cyclodextrin annulus disrupts coordination of the anion of tryptophan **16** to nickel(II). The extent of these unfavourable interactions appears to depend on the chirality of the anion of tryptophan **16**, thus affecting the enantioselectivity.

The adverse effect of the cyclodextrin on the thermodynamic stability of the ternary complex is also apparent, though less marked, in the interaction of the anion of tryptophan **16** with the cobalt(II) and copper(II) complexes **22** (M = Co) and **22** (M = Cu) of the aminopropylamino-substituted cyclodextrin **21** (Table 2, entries 4 and 5, Table 3, entries 4 and 6).[15] These metallocyclodextrins also display enantioselectivity but to a lesser extent than that displayed by the nickel(II) complex **22** (M = Ni). By contrast, the



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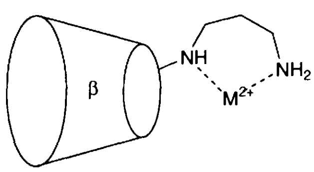

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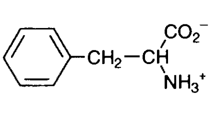

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**Table 2** Association constants of metallocyclodextrin inclusion complexes[a]

| Entry | Cyclodextrin | Guest | log ($K_R$/dm$^3$ mol$^{-1}$) | log ($K_S$/dm$^3$ mol$^{-1}$) | $K_R/K_S$ | Ref. |
|---|---|---|---|---|---|---|
| 1 | **2** | **16** − H$^+$ | 2.33 ± 0.06 | 2.33 ± 0.08 | 1.00 | 14,15 |
| 2 | **21** | **16** − H$^+$ | 3.41 ± 0.05 | 3.40 ± 0.07 | 1.00 | 14,15 |
| 3 | **22** (M = Ni) | **16** − H$^+$ | 4.1 ± 0.2 | 5.1 ± 0.2 | 0.10 | 14,15 |
| 4 | **22** (M = Co) | **16** − H$^+$ | 4.04 ± 0.03 | 4.32 ± 0.05 | 0.53 | 15 |
| 5 | **22** (M = Cu) | **16** − H$^+$ | 7.85 ± 0.07 | 8.09 ± 0.05 | 0.58 | 15 |
| 6 | **22** (M = Zn) | **16** − H$^+$ | 5.3 ± 0.1 | 5.3 ± 0.1 | 1.00 | 15 |
| 7 | **22** (M = Ni) | **23** − H$^+$ | < 3.6 | 4.4 ± 0.1 | <0.16 | 16 |
| 8 | **22** (M = Co) | **23** − H$^+$ | 3.6 ± 0.2 | 3.69 ± 0.06 | 0.81 | 16 |
| 9 | **22** (M = Cu) | **23** − H$^+$ | 7.2 ± 0.1 | 6.9 ± 0.1 | 2.00 | 16 |
| 10 | **22** (M = Zn) | **23** − H$^+$ | 4.7 ± 0.1 | 4.7 ± 0.1 | 1.00 | 16 |

[a] In $H_2O$, $I$ = 0.10 mol dm$^{-3}$, $T$ = 298.2 K.

**Table 3** Metal complexation constants[a]

| Entry | Metal | Ligand | log ($K$/dm$^3$ mol$^{-1}$) | Ref. |
|---|---|---|---|---|
| 1 | $Ni^{2+}$ | **21** | 5.2 ± 0.1 | 14,15 |
| 2 | $Ni^{2+}$ | **16** − H$^+$ | 5.42 ± 0.03 | 14,15 |
| 3 | $Co^{2+}$ | **21** | 4.22 ± 0.02 | 15 |
| 4 | $Co^{2+}$ | **16** − H$^+$ | 4.41 ± 0.05 | 15 |
| 5 | $Cu^{2+}$ | **21** | 7.35 + 0.04 | 15 |
| 6 | $Cu^{2+}$ | **16** − H$^+$ | 8.11 ± 0.03 | 15 |
| 7 | $Zn^{2+}$ | **21** | 4.96 ± 0.08 | 15 |
| 8 | $Zn^{2+}$ | **16** − H$^+$ | 4.90 ± 0.04 | 15 |
| 9 | $Ni^{2+}$ | **23** − H$^+$ | 5.09 + 0.05 | 16 |
| 10 | $Co^{2+}$ | **23** − H$^+$ | 4.19 ± 0.03 | 16 |
| 11 | $Cu^{2+}$ | **23** − H$^+$ | 7.8 ± 0.1 | 16 |
| 12 | $Zn^{2+}$ | **23** − H$^+$ | 4.59 ± 0.04 | 16 |

[a] In $H_2O$, $I$ = 0.10 mol dm$^{-3}$, $T$ = 298.2 K.

diastereoisomeric ternary complexes **22** (M = Zn) of the anion of tryptophan **16**, zinc(II) and the modified cyclodextrin **21** are thermodynamically indistinguishable (Table 2, entry 6), but more stable than the binary complexes of zinc(II) with the modified cyclodextrin **21** and of the anion of tryptophan **21** with the metal ion alone (Table 3, entries 7 and 8). It seems that enantioselectivity only results from unfavourable interactions in the ternary complexes which restrict the geometry of binding.

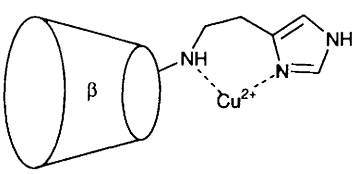
Analogous effects were observed in the formation of ternary complexes of the metallocyclodextrins **22** with the anion of phenylalanine **23** (Table 2, entries 7—10; Table 3, entries 9—12).[16] The enantioselectivity was greatest with the nickel(II) metallocyclodextrin **22** (M = Ni), decreasing in the order nickel(II) > copper(II) ≃ cobalt(II) > zinc(II). Again this order correlates with the extent to which the cyclodextrin disrupts the binding of the guest to the metal. The discrimination displayed by the nickel(II) and cobalt(II) metallocyclodextrins **22** (M = Ni) and **22** (M = Co) favours binding of the (*S*)-enantiomers of the anions of tryptophan **16** and phenylalanine **23**. The discrimination of the copper(II) metallocyclodextrin **22** (M = Cu) favours binding of the (*S*)-enantiomer of the anion of tryptophan **16** and the (*R*)-enantiomer of the anion of phenylalanine **23**.

While the work carried out to date with the metal complexes of the aminopropylamino-substituted cyclodextrin **21** has been mostly limited to studies with the anions of tryptophan **16** and phenylalanine **23** as guests, a more extensive range of amino acids has been used to investigate chiral discrimination by the copper(II) complexed histamine-monofunctionalised β-cyclodextrin **24** (Table 4).[17,18] In this case the metallocyclodextrin **24** displayed enantioselectivity in the complexation of the anions of the aromatic amino acids, tryptophan **16**, phenylalanine **23** and tyrosine **25**, with the stability constant of the complex of the (*R*)-enantiomer being the

**Table 4** Association constants of copper(II) ternary complexes of the cyclodextrin **24** with amino acid anions[a]

| Entry | Amino acid | log ($K_R$/ dm$^3$ mol$^{-1}$) | log ($K_S$/ dm$^3$ mol$^{-1}$) | $K_R/K_S$ | Ref. |
|---|---|---|---|---|---|
| 1 | **16** − H$^+$ | 16.47 ± 0.02 | 16.12 ± 0.01 | 2.23 | 17,18 |
| 2 | **23** − H$^+$ | 15.85 ± 0.01 | 15.68 ± 0.02 | 1.48 | 18 |
| 3 | **25** − H$^+$ | 15.22 ± 0.01 | 14.82 ± 0.01 | 2.51 | 18 |
| 4 | **26** − H$^+$ | 15.51 ± 0.02 | 15.53 ± 0.04 | 0.96 | 17,18 |
| 5 | **27** − H$^+$ | 14.87 ± 0.05 | 14.80 ± 0.02 | 1.17 | 18 |
| 6 | **28** − H$^+$ | 14.96 ± 0.02 | 14.89 ± 0.02 | 1.18 | 18 |

[a] In $H_2O$, $I$ = 0.10 mol dm$^{-3}$, $T$ = 298 K.

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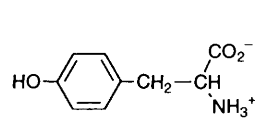


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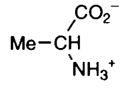


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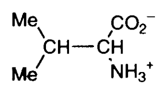


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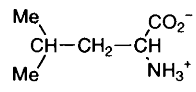


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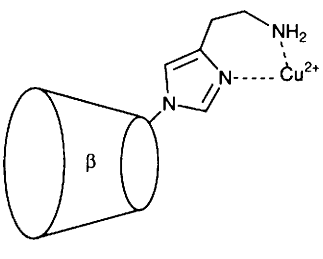
larger in each case By comparison, the diastereoisomeric pairs of ternary complexes of the anions of the aliphatic amino acids **26**—**28** showed only small differences in thermodynamic stability In this work, calorimetric studies were carried out in order to examine the factors contributing to the enantioselectivity The overall complexation process for each of the amino acids was found to be enthalpically and entropically favoured For the complexes of aromatic amino acids, however, the enthalpy contribution was found to be more favourable for the (*R*)-enantiomers, while the entropy factor was less favourable This indicates that the geometry of complexation of the (*R*)-enantiomers is more restricted but the binding interactions in the complexes are stronger, and is consistent with a model in which the complexation of the (*R*)-enantiomers is favoured by the preferential inclusion of their aromatic side chains in the cyclodextrin cavity

The histamine-substituted metallocyclodextrin **24** also displayed spectroscopic and chromatographic chiral discrimination in the complexation of amino acid anions, and the extent of chromatographic discrimination for various amino acids paralleled the thermodynamic enantioselectivity [17,18] Interestingly the isomeric metallocyclodextrin **29** showed even greater enantioselectivity when used in chromatography with the anion of tryptophan **16**[19] but no thermodynamic data for this discrimination have been reported The copper(II)-complexed aminoethylamino-substituted cyclodextrin **30** also displayed chromatographic and spectroscopic discrimination in complexing the anion of tryptophan **16**, but there was no thermodynamic enantioselectivity in this case [20] Again this illustrates the lack of correlation between thermodynamic, and chromatographic and spectroscopic effects In this regard, while the spectroscopic discrimination displayed by lanthanide–cyclodextrin complexes[21] and the enantiodiscriminating oxygenation of $\alpha$-pinene using a porphyrin-substituted cyclodextrin[22] are interesting examples of exploitation of the enantioselectivity displayed by metallocyclodextrins, they are difficult to evaluate further in the absence of thermodynamic data

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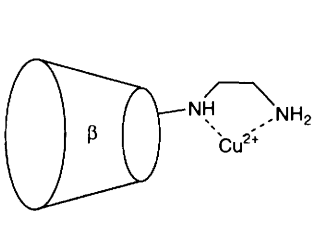


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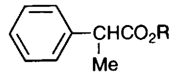
Although only a limited number of studies of chiral discrimination by metallocyclodextrins have been reported, they are sufficient to support the hypothesis, stated above, that coordination of both the cyclodextrin and the guest to a metal, which increases the extent of interaction between the cyclodextrin and the guest, will generally increase the enantiodiscrimination It is likely that even greater stereoselectivity can be expected where the substituent attached to the cyclodextrin and coordinating the metal is chiral, thus increasing the asymmetry of the complex, though this has yet to be tested

## 4 Covalent Interactions

An alternative form of interaction between cyclodextrins and guests, which also leads to enhanced enantioselectivity, involves the formation of a covalent bond between the host and guest in the inclusion complex The hydrolysis of esters by cyclodextrins has been intensively studied as a model of covalent catalysis by enzymes [23] The process involves the formation of a host–guest complex between a cyclodextrin and an ester, then transesterification between host and guest, followed by hydrolysis of the acylated cyclodextrin The interest in cyclodextrins as enzyme mimics stems from the fact that they enhance the rates of reaction of included esters and they show enantioselectivity in the case of chiral derivatives [24–32] In principal, the chiral discrimination could arise either from stereoselectivity in the formation of the host–guest complexes or from different reactivities of the guests in the diastereoisomeric complexes, or from a combination of these processes In practice, more substantial stereoselectivity has usually arisen from differences in the reactivity of the complexed species [25–30] This is illustrated by the association constants for complexation of the phenylpropionates **31** by $\alpha$- and $\beta$-cyclodextrin **1** and **2** and the rate constants for the reactions of the complexed species (Table 5) [26] An overall enantioselectivity of 19 0 was observed for the interaction of the ester **31b** with $\beta$-cyclodextrin **2**, that figure comprising factors of 1 2 for the complexation and 15 5 for the reactions of the complexed species

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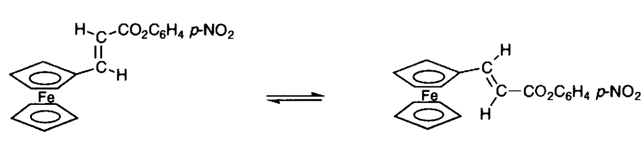
a) R = $C_6H_4$-*p*-$NO_2$
b) R = $C_6H_4$-*m*-$NO_2$

**Table 5** Thermodynamic parameters[a] for interaction of the esters **31** with cyclodextrins[26]

| Cyclodextrin | Ester | $K_R/K_S$[b] | $k_{cR}/k_{cS}$[c] | $(k_{cR}K_R)/(k_{cR}K_S)$ |
|---|---|---|---|---|
| **1** | **31a** | 1 33 | 1 2 | 1 6 |
| **1** | **31b** | 1 07 | 8 7 | 9 3 |
| **2** | **31a** | — | 9 5 | — |
| **2** | **31b** | 1 22 | 15 5 | 19 0 |

[a] In $H_2O$ 0 2 × $10^{-3}$ mol $dm^{-3}$ sodium carbonate buffer $T$ = 298 K [b] Ratio of the association constants for the enantiomers [c] Ratio of the rate constants for the reactions of the complexed species

It has been clearly demonstrated that the enantioselectivity displayed by the cyclodextrin depends on the extent to which the geometry of binding and transesterification has been restricted Trainor and Breslow[28] showed that freezing out residual rotational degrees of freedom in the acylation transition state increased the enantioselectivity shown by the cyclodextrin The enantiomers **33** and **34** correspond to one of the preferred conformers of the ester **32**, and $\beta$-cyclodextrin **2** was found to accelerate their rates of reaction to extents approximately ten times and one half, respectively, of that observed with the ester **32** (Table 6) The esters **35** and **36** correspond to the enantiomers of the other preferred conformer of the ester **32**, and the enantioselectivity observed in their reactions with $\beta$-cyclodextrin **2** was much less A further minor modification to the geometry of the cyclodextrin acylation, in the reactions of the esters **37** and **38**, resulted in a 62-fold enantioselectivity (Table 6) [29] This is the largest reported for hydrolysis of an ester by a cyclodextrin

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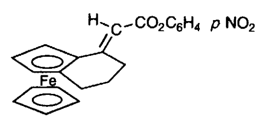


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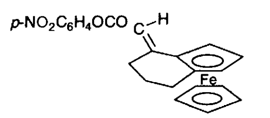


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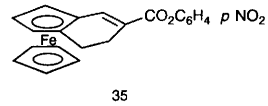


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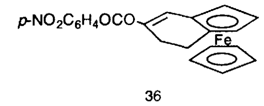


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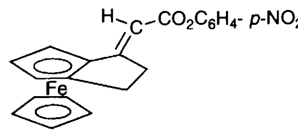
**Table 6** Rate accelerations for reactions of esters complexed by $\beta$-cyclodextrin **2**[a]

| Ester | $k_c/k_{un}$ ($\times 10^{-4}$) | Ref |
|---|---|---|
| 32 | 36 | 28 |
| 33 | 16 | 28 |
| 34 | 320 | 28 |
| 35 | 1 0 | 28 |
| 36 | 6 6 | 28 |
| 37 | 590 | 29 |
| 38 | 9 5 | 29 |

[a] In 60% $Me_2SO$ / 40% $H_2O$ (v/v) T = 303 K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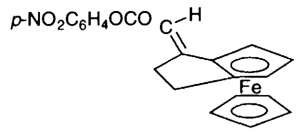
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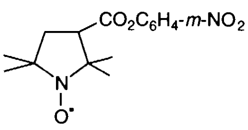
Frequently, studies of the interactions of cyclodextrins with esters have concentrated on the formation of the host–guest complexes and the subsequent transesterification, and the possibility of diastereoselective hydrolysis of the acylated cyclodextrins has often not been examined Deacylation of the cyclodextrin **40** was investigated as part of a study of the reaction of the ester **39** with $\alpha$-cyclodextrin **1** [30]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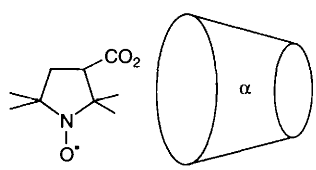
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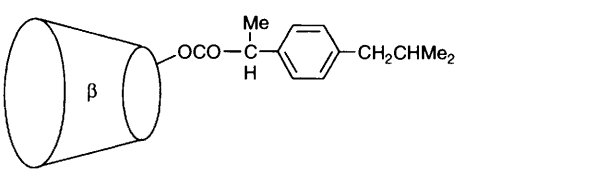
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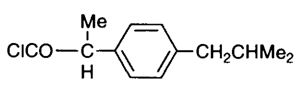
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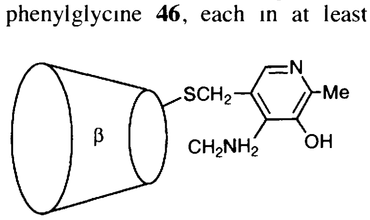
The reaction occurred without diastereoselectivity, as was the case with formation of the inclusion complexes between the ester **39** and $\alpha$-cyclodextrin **1**, although the rates of reaction of the included enantiomers of the ester **39**, to give the acylated cyclodextrin **40**, differed by a factor of 7 More recently, we reported a tenfold diastereoselectivity in the hydrolysis of the cyclodextrin **41** [31,32] The synthesis of the ester **41** through reaction of the Ibuprofen acid chloride **42** with $\beta$-cyclodextrin **2** afforded a 5 1 mixture of the diastereoisomers, in favour of the isomer derived from (*R*)-Ibuprofen, and that diastereoisomer was also the most readily hydrolysed Consequently the overall stereoselectivity for the two-step reaction of the acid chloride **42** is *ca* 50 1 The complementary nature of the diastereoselectivity of the synthesis and hydrolysis was attributed to similarities between the reaction transition states The contrast in diastereoselectivity in the reactions of the esters **40** and **41** is not surprising, given the differences between these systems The acyl substituents of the esters **40** and **41** are bound *via* secondary and primary hydroxy groups, respectively In addition, the acyl group of the Ibuprofen derivative **41** is more hydrophobic and is more likely to interact with the cyclodextrin annulus

Stereoselectivity has also been observed in a variety of other reactions where the guests become covalently bound to the cyclodextrins Enantioselectivity has been found in the acylation of cyclodextrins with 5(4*H*)-oxazolones,[33,34] in reactions which are mechanistically quite similar to those of esters interacting with cyclodextrins A variety of Schiff base derivatives of cyclodextrins has been synthesised and studied as models of pyridoxal phosphate-dependent enzymes Breslow *et al*,[35] reported the synthesis of the pyridoxamine derivative **43** and showed that in the reaction of this compound with phenylpyruvic acid **44**, phenylalanine **23** was produced as a 5 1 mixture of the (*S*)- and (*R*)-enantiomers With the related cyclodextrin derivative **45**, Tabushi *et al*,[11,36] reported much higher stereoselectivity in the reactions of ketoacids, producing the (*S*)-isomers of phenylalanine **23**, tryptophan **16** and phenylglycine **46**, each in at least 90% enantiomeric excess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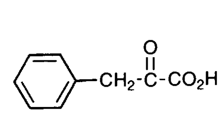
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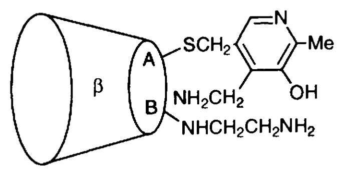
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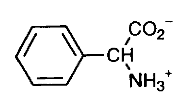
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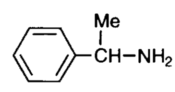
Recently we reported high enantioselectivity in the reactions of 2-phenylethylamine **47** with the iodocyclodextrin **48** to give the diastereoisomers of the amine **49** [37] In further experiments aimed to elucidate the thermodynamic parameters of those interactions, we have now found that the extent of the stereoselectivity is highly irregular, however, and is generally much less than was observed originally Currently we are examining the possibility that ternary complexes may be involved in these processes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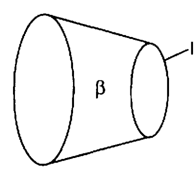
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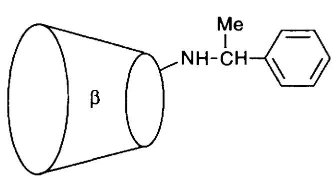
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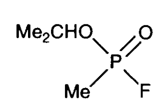
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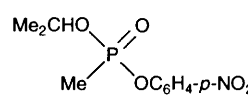
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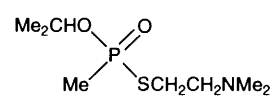
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With Sarin **50**, the compound used recently in terrorist attacks in Japan, the reaction with α-cyclodextrin **2** proceeds by inclusion complex formation, followed by phosphonylation of the cyclodextrin, and each of these processes is stereoselective (Table 7) [38,39] The reactions of α-cyclodextrin **1** with the related phosphonate **51** and phosphonothioate **52** are also highly stereoselective (Table 7) [39,40] The high enantiomeric selectivity reported in the cleavage of organophosphates may be attributed to the fact that the reaction takes place directly at the chiral centre, further supporting the hypothesis developed throughout this review, that higher stereoselectivity will result from a more intimate interaction between the chiral centres of the cyclodextrins and the guests

**Table 7** Thermodynamic parameters[a] for interaction of α-cyclodextrin **1** with the organophosphorus compounds **50**–**52**[38–40]

| Guest | $K_R/K_S$[b] | $k_{cR}/k_{cS}$[c] | $(k_{cR}K_R)/(k_{cS}K_S)$ |
|---|---|---|---|
| **50** | 0 15 | 3 5 | 0 52 |
| **51** | 0 38 | ≥ 76 | ≥ 29 |
| **52** | 1 91 | > 100 | > 191 |

[a] In $H_2O$, $I = 0$ 10 mol $dm^{-3}$ $T = 298$ K [b] Ratio of the association constants for the enantiomers [c] Ratio of the rate constants for the reactions of the complexed species

## 5 Conclusion

In summary, it is apparent from the work reviewed here that the naturally occurring cyclodextrins show only limited enantioselectivity in their interactions with chiral guests, because they form inclusion complexes in which there is only minimal interaction between chiral centres of the cyclodextrin and chiral substituents of the guests As the extent of interaction between these groups is increased, as a result of modification to the cyclodextrin, the stereoselectivity is often increased The immediate result of this improved stereoselectivity is that, whereas separation of racemic guests using the naturally occurring cyclodextrins requires multiple interactions between the host and guest, more efficient, practical and larger-scale resolutions should be possible with the modified cyclodextrins

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