# *Factors Influencing Isomer Discrimination by Modified Cyclodextrins*

by

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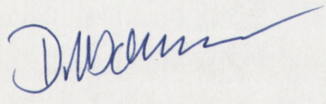

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## Publication

"Complexes of 2- and 4-Fluorobenzoate Anions and the Corresponding Methyl Esters with β-Cyclodextrin and the Conjugate Acids of $6^{A}$-Amino-$6^{A}$-deoxy-β-cyclodextrin and $3^{A}$-Amino-$3^{A}$-deoxy-($2^{A}S$,$3^{A}S$)-β-cyclodextrin in Aqueous Solution; a Fluorine-19 Nuclear Magnetic Resonance Study", Easton, C.J.; Lincoln, S.F.; Papageorgiou, J.; Schliebs, D.M.; *J. Chem. Research (S)*, **1995**, 381.

## Abstract

The susceptibility to environmental effects of the fluoro substituent of $6^A$-deoxy-$6^A$-fluoro-β-cyclodextrin was gauged, and the complexation of racemic mixtures of aromatic guests by that species was studied by $^{19}F$ nuclear magnetic resonance spectroscopy. This technique was also used to study the complexation of fluoro-substituted aromatic esters and acids by β-cyclodextrin and the conjugate acids of $6^A$-amino-$6^A$-deoxy-β-cyclodextrin and $3^A$-amino-$3^A$-deoxy-($2^AS$,$3^AS$)-β-cyclodextrin. The results of this study show that $^{19}F$ NMR spectroscopy can be employed to detect the formation of these host-guest complexes and to calculate their association constants. It was further shown that the factors affecting complexation include the charge and extent of hydration of the hosts and guests, ionic interactions between the hosts and guests and the antiparallel alignment of the dipole moments of the hosts and guests in the inclusion complexes. The orientation of host and guest which was predicted from results obtained was confirmed in two systems by the application of two dimensional rotating frame nuclear magnetic resonance spectroscopy.

Four pairs of diastereomeric amino-cyclodextrins were prepared by the action of the chiral aromatic amines 1-phenylethylamine, 1-(1-naphthyl)ethylamine, amphetamine and phenylglycinol on both $6^A$-*O*-*p*-toluenesulfonyl-β-cyclodextrin and $6^A$-deoxy-$6^A$-iodo-β-cyclodextrin. Initial indications were of diastereoselectivity in the synthesis of those compounds from the latter cyclodextrin, but upon careful investigation it was found that any selectivity is variable and greatly dependent on the presence of ternary complexes in the reaction mixtures. The four pairs of cyclodextrin diastereomers were all found to form intramolecular complexes between

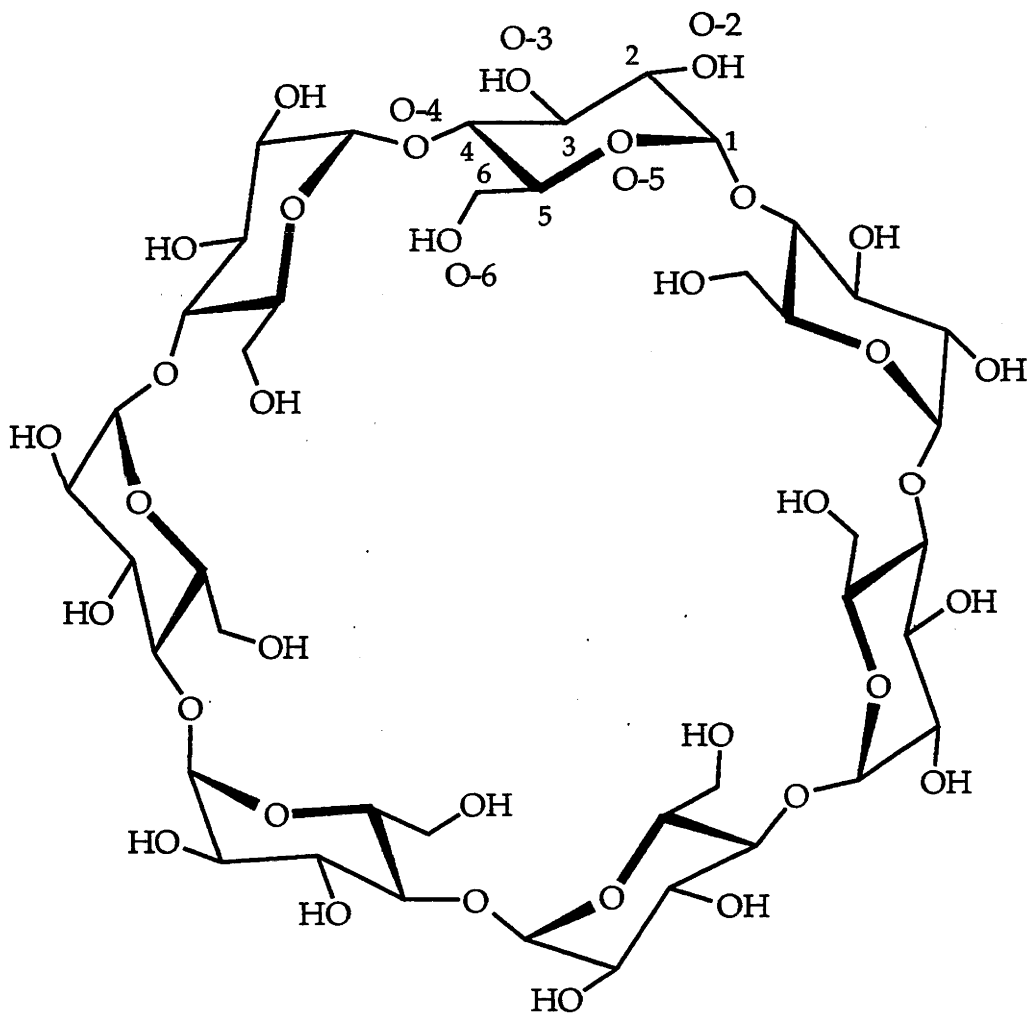
their annuli and the aromatic moieties of their substituents. The extents of self-inclusion in these complexes were found to be dependent on the chirality of the cyclodextrin substituent, and this affected the ease of displacement of those aromatic moieties from the annuli. The strongly lipophilic species adamantan-1-ol was able to disrupt the intramolecular complexes in all cyclodextrins, and so be complexed by them. In contrast the weakly lipophilic *para*-methoxybenzylalcohol was not complexed by the cyclodextrins in which there were larger extents of intramolecular complexation present. Similarly it was found that a racemate of the weakly lipophilic 2-phenylpropanoate anion was not complexed by several of the cyclodextrins while the corresponding acids and also the Ibuprofen anions and corresponding acids, all more lipophilic in nature than the 2-phenylpropanoate anions, all readily displaced the self-included aromatic moiety to form intermolecular complexes in all systems, save for those containing a cyclodextrin derived from *(R)*-amphetamine.

In order to probe factors influencing the presence of spectroscopic discrimination, and to ultimately investigate the possibility of complementary thermodynamic discrimination in the systems above which contain chiral guests, a $^{1}H$ nuclear magnetic resonance spectroscopic study of those systems was undertaken. The results of this study identified spectroscopic discrimination in many complexes. In many systems, most notably those containing the 2-phenylpropanoate anions, the presence of discrimination was found to be dependent on the extent of intramolecular complexation in the host cyclodextrin. Systems containing cyclodextrins derived from 1-phenylethylamine were considered most promising to probe the potential for complementary thermodynamic discrimination in host-guest complex formation with the chiral guests, and so $^{1}H$ nuclear magnetic

resonance spectroscopic titrations of those species were performed. However, these systems were found not to be suitable for the observation of complementary discrimination because of other overriding factors. These include the extent of intramolecular complexation in the cyclodextrin host, as influenced by the chirality of the substituent, and also the extreme lipophilicity of the Ibuprofen-derived guests, which rendered insignificant factors such as species charge and hydration and the ionic interactions between hosts and guests. However, it was significant that the cyclodextrins employed in this study, by virtue of their charge and the nature of the groups present in their substituents, were specifically designed to maximize interactions with all guests and particularly to provide for enhanced discrimination between the enantiomeric pairs of anionic guests over β-cyclodextrin, and that was indeed the case.

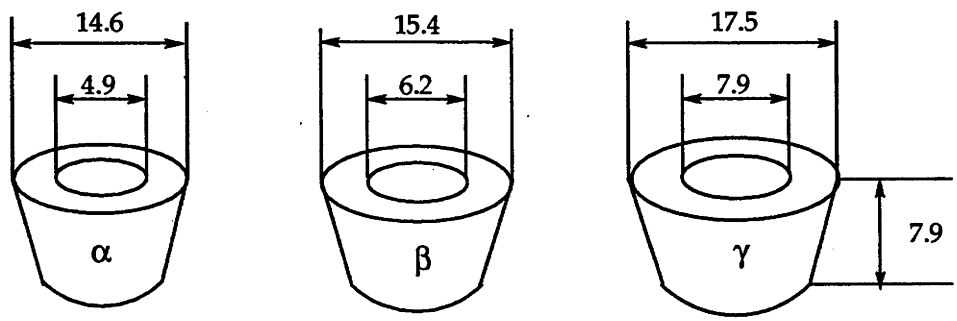
## Introduction

Cyclodextrins are naturally occurring cyclic oligosaccharides, with α-, β– and γ-cyclodextrin having 6, 7 and 8 α-1,4-linked D-glucopyranose units, respectively.[1] The individual glucose units of cyclodextrins exist in regular chair conformations and this renders the molecules toroidal in shape with each of the cyclodextrins having an axis of rotational symmetry.




1

Cyclodextrins are numbered as for other saccharides in the fashion of position one as the anomeric carbon, C-1, to the position of the primary hydroxyls on C-6. Glucose residues are then numbered alphabetically, for example as A-G in the case of β-cyclodextrin **1**. Cyclodextrins are conveniently depicted as a truncated cone, where the narrow end represents the primary hydroxyl groups attached at the C-6 positions and the wide end represents the secondary hydroxyl groups attached at the C-2 and C-3 positions.[2] The variation in the number of glucopyranose units for the cyclodextrins produces molecular weights which are multiples of 162.1,[3] namely 973, 1135 and 1297 daltons for α-, β- and γ-cyclodextrin **2**, **1** and **3**, respectively, and causes obvious differences in dimension (Figure 1), but also has other effects on the physical properties of these species such as their water solubilities, which are 14.5, 1.85 and 23.2 g / 100 ml at room temperature, and the differing specific rotations ($[\alpha]^{D}_{25}$), which are 150.5, 162.5 and 177.4 degrees, for α-, β- and γ-cyclodextrin, respectively.[4]



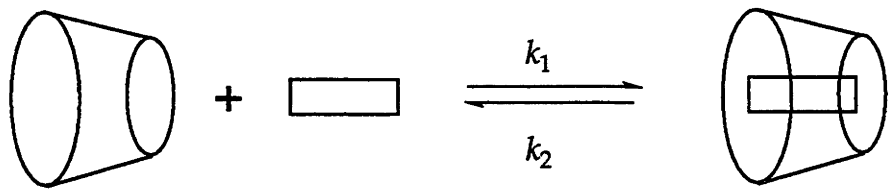

**2** **1** **3**

**Figure 1.** Dimensions of the cyclodextrins (Å).[1,5]

As a consequence of the structure of these compounds the C-3 and C-5 protons project into the cavity of the cyclodextrin, making the torus lipophilic and suitable for the inclusion of many and varied guests to form

complexes (Scheme 1).[1] This process is characterised by the association constant, *K*, which is simply the equilibrium constant for the formation of the host-guest complex (Equation 1).

$$K = k_1/k_2 = [\text{complex}].[\text{cyclodextrin}]^{-1}.[\text{guest}]^{-1} \quad 1$$



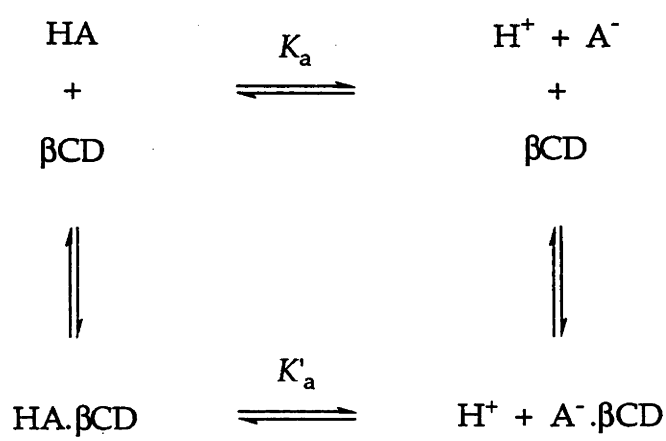

**Scheme 1**

While a binary complex, in which the cyclodextrin and guest are present in 1:1 stoichiometry, is most common there are many examples of multicomponent systems in cyclodextrin host-guest chemistry. Ternary systems in which a single cyclodextrin contains two distinct guests are well known.[6-9] Common also are 2:1 host:guest systems in which a guest is complexed by two cyclodextrins,[10-12] such as recent work which saw *iso*-phthalaldehyde complexed by two α-cyclodextrin **2** molecules and phenyl benzoate forming a 1:2 complex with β-cyclodextrin **1**.[12]

Despite the hydrophobicity of the cyclodextrin cavity, in aqueous solvent and in the absence of a guest, several high energy water molecules are included within that annulus.[1] One of the driving forces for complexation, along with hydrophobic interactions between lipophilic guests and the cyclodextrin cavity, is expulsion of those high energy waters from that cavity, but they are not always necessarily completely removed upon complexation of a guest. Thus a system thought of as being 1:1 may well

contain multiple solvent molecules co-complexed in the cyclodextrin cavity. The inclusion of multiple guests into the cavity of a cyclodextrin is not just isolated to purely aqueous environments, the effect has been noted many times in complexes in the presence of some other solvent, for example ethanol or other alcohols.[13-16]

The presence of a cyclodextrin has a significant effect on the physical properties of a bound guest. Cyclodextrins have been used to confer solubility onto organic guests with low water solubility, and can often stabilise guests so bound against oxidation, decomposition or other processes.[17] In principle, formation of complexes between a cyclodextrin and some guest may be observed by monitoring any property of either the host or the guest that is influenced by formation of a complex.[10,18-27] Thus a cyclodextrin has also been shown to alter the $pK_a$ of a bound organic acid guest (Scheme 2)[26,27] such that a simple titration will show pH variations in the vicinity of the $pK_a$ of a bound acid HA. This is clearly because $K_a$ and $K'_a$, the acid dissociation constants for the carboxylic acid in the free state



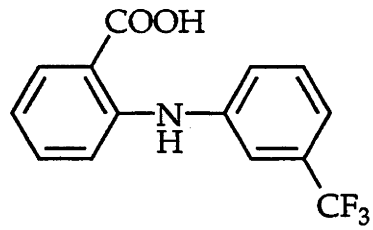

**Scheme 2**

and in the complex, are not equal (Scheme 2). This effect is a direct result of inclusion of that acid guest by the cyclodextrin.

Changes in physical properties of some species can be reflected in spectroscopic changes also, and an impressive example of that is the observation of changes in the circular dichroism of a guest upon addition of a cyclodextrin. To yield a circular dichroism response a substrate must be both chiral, and posses a chromophore which absorbs light in the ultraviolet (UV) region of the spectrum.[28] Thus cyclodextrins, which are chiral but do not posses a chromophore, yield no significant circular dichroism spectrum. Addition of a UV-absorbing guest which is achiral, and so also will not yield a circular dichroism response, will result in an induced circular dichroism spectrum for the complex.[29,30] Similarly, the inclusion of an optically active aromatic guest in a cyclodextrin will also produce changes in the existing circular dichroism spectra of that guest, due to the change in chiral environment.[31,32]

More simply, it was seen as early as 1958 by French and Thoma,[33] by inspection of variations in the spectra of an $I_2/I^-$ system upon addition of α-cyclodextrin **2**, that ultraviolet-visible (UV-VIS) spectrophotometric techniques are a powerful tool to indicate the existence and extent of complex formation. This has also been demonstrated by observation of the complexation behaviour of flufenamic acid **4**. This species **4** showed a shift in $\lambda_{max}$ from 292 to 320 nm upon addition of a large excess of cyclodextrin with accompanying changes in intensity, a result that was typical for others in the fenemate series of antiinflammatory drugs[32] and similar to that for phenothiazine tranquillizers.[31] This data was further used to calculate definitive stoichiometries for the host-guest complexes under study.

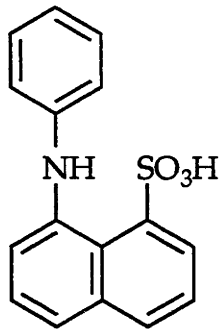
Association constants of inclusion complexes can also be derived from such systems by measuring the absorption spectra of a range of solutions comprising a standard guest concentration and varying the concentration of cyclodextrin, with data so obtained fitted to equation (1).[31,32,34-37]



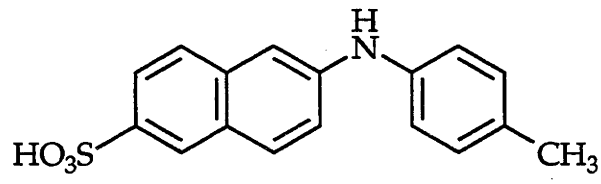

**4**

The fluorescence properties of guests have been used to great effect for detection of complexation in many systems.[10,35,38,39] It has been observed that 1-anilino-8-naphthalenesulfonate (ANS) **5** and structurally similar compounds show strong fluorescence in organic solvents such as ethanol, while in water they exhibit very low fluorescence. The result of that was when, in an aqueous system, ANS **5** formed a complex with either β- or γ-cyclodextrin **1** or **3**, there was a ten-fold increase in the fluorescence of the guest **5**, due to the lipophilicity of the host cavity. A lesser increase was noted with α-cyclodextrin **2** due to the smaller cavity of that host being unable to fully accommodate the relative large aromatic guest.[35] Similar effects have been observed with compounds such as *p*-*N*,*N*-dimethylaminobenzonitrile and 6-(*p*-toluidino)-2-naphthalenesulfonic acid (TNS) **6**, although it was found that upon expulsion from a cyclodextrin cavity, these guests experienced around one hundred-fold quenching of fluorescence.[40] It happens that this is an extremely useful facility for the detection of complex formation between a cyclodextrin and some other guest. In the event that a third species displaces a fluorophore from the

cavity of a cyclodextrin into the bulk aqueous solvent, then the complexation of that third guest is necessarily accompanied by a quenching of fluorescence.[41]




**5**




**6**

This technique is of course inferring the presence of complexation by observation of some property of a third species. Complex formation between cyclodextrins and many aromatic guests, including ANS **5**, TNS **6** and the previously discussed ternary systems involving inclusion of *iso*-phthalaldehyde and phenyl benzoate, has been shown to be able to be detected directly in the gas phase by using the sensitive technique of electrospray ionization mass spectrometry (ESI-MS).[12,42] The mildness of the electrospray ionization/desorption process enables weakly bound complexes to remain intact upon transfer to the gas phase. Clearly the presence of false-positives for inclusion complex formation, in the form of electrostatic adducts in the gas phase, is a prime concern. Recently published work[12,42] has demonstrated that such effects can be eliminated by control of the cone voltage at the instrument orifice, resulting in the ability to detect complexation and calculate stoichiometries with a high degree of confidence.

Another direct method of observing host-guest complex formation is the implementation of nuclear magnetic resonance (NMR) spectroscopy.[32,43-52] The inclusion of an aromatic guest into the cavity of a cyclodextrin has significant anisotropic effects on the environment of the cyclodextrin cavity. This will influence the magnetic environment of the nuclei of the cyclodextrin, even as the lipophilic environment of the cavity affects the magnetic environment experienced by nuclei of the guest. Therefore in principle, complexation can be detected by monitoring the NMR spectra of either the guest or the host species during complexation, and a great deal of work has been done on this utilizing $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy, amongst others. Early work by Bergeron *et al.*,[46] in 1977 showed that all protons present in sodium 3-methyl-4-nitrophenolate experienced complexation induced shifts of at least 0.2 ppm in the $^{1}H$ NMR spectrum of that species upon addition of α-cyclodextrin **2**. The variation in chemical shift with increasing cyclodextrin concentration was sufficiently regular to enable the calculation of thermodynamic data corresponding to an association constant of 28.6 ± 1.3 $dm^3\ mol^{-1}$. As mentioned above, such techniques are not limited to $^{1}H$ NMR studies; similar results have also been obtained upon inspection of the variations in the $^{19}F$ chemical shift of the trifluoromethyl substituent in flufenamic acid **4**, upon addition of β-cyclodextrin **1**.[32]

Because the changes in total environment are greater for the guest upon forming a host-guest complex, it is often easier to detect complexation by observing NMR spectral effects in the nuclei of the guest species rather than those of the host. Despite this, studies have shown there to be effects observable in the spectra of both host and guest,[32,43-52] such as a comprehensive $^{13}C$ NMR study by Gelb.[43] That work found induced $^{13}C$

chemical shift changes of up to 3 ppm in resonances of many benzoic acid and phenol derivative guests, upon complexation by α-cyclodextrin **2**, to be accompanied by complexation induced shifts of up to 0.51 ppm, in the resonances of the cyclodextrin. Similar studies have concentrated on the observation of complexation by inspection of the $^1$H NMR spectra of the cyclodextrin host only.[44,45] Over the wide range of guests used in these studies it was found that the largest complexation induced changes in cyclodextrin chemical shift were generally observed in the H-3 and H-5 proton resonances. This is not surprising because it is those protons that project inward to the cyclodextrin cavity[1] along with, to a lesser extent, H-6. It is therefore these protons that are most likely to experience environmental changes upon addition of guest. Differential changes between those two sets of resonances have also been used to infer the depth of inclusion, and even likely orientation, of various guests in cyclodextrin complexes.[46]

Although 1D NMR techniques, such as those outlined above, are able to provide a great deal of evidence for complex formation between a wide range of guest and cyclodextrin systems, modern high field NMR spectrometers with appropriate pulse sequences can give a much greater insight into host-guest complex formation. A widely used method in structure determination in organic chemistry is the exploitation of Nuclear Overhauser Enhancement (NOE) effects to indicate proximity of nuclei through space.[53] This technique has been used with varying success to gain information about intra- and intermolecular through space effects in cyclodextrin systems.[11,54,55] However, the corresponding 2D Nuclear Overhauser Enhancement Spectroscopy (NOESY) techniques are not appropriate for the investigation of cyclodextrin host-guest complexes due to

the rotational correlation times of compounds of this size typically occurring in the range where minimal NOE responses are observed.[54,56] An alternative approach for larger molecules is the implementation of Rotating Frame Overhauser Enhancement Spectroscopy (ROESY)[57,58] with that technique having been found particularly appropriate for use in systems containing cyclodextrins.[11,47,54,56,59,60] ROESY techniques are essentially equivalent to NOESY experiments, save for operating on a rotating frame of reference and so eliminating the difficulties associated with relaxation in cyclodextrin systems.[47,54,56] Nishijo *et al.*,[59] have shown that the ROESY spectrum of a sample containing β-cyclodextrin **1** and 1-naphthalenesulfonate indicated many and intense connectivities between resonances corresponding to the guest aromatic protons and those of the cyclodextrin annulus H-3, -5 and -6 protons. As has been mentioned above, the cyclodextrin H-3 and H-5 protons project into the host cavity and the observation of through space interactions between those resonances and the guest resonances is definitive evidence of the formation of the host-guest complex.[59] In similar work the ROESY spectra of 1-bromoadamantane, in the presence of α-cyclodextrin **2**, provided clear evidence of complex formation, and also indicated that the stoichiometry of the system was 1:2 guest:cyclodextrin.[11]

In addition to simply providing evidence for host-guest complex formation, the 2D ROESY experiment can also provide evidence for the orientation of a guest within a cyclodextrin.[47,11,59-61] In a study of the complexation behaviour of benzhydrylamine derivatives[47] evidence of complexation between the guest **7** and β-cyclodextrin **1** was found in the ROESY spectrum of a sample containing those species. This was observed as clear ROE interactions (ROEs) between resonances corresponding to the *ortho*-protons

of the phenyl substituent of the guest **7** ($H_o$) and the cyclodextrin **1** H-3 and H-5 protons. This was accompanied by the observation of ROEs between the resonances corresponding to the *meta*-protons of the phenyl substituent of the guest **7** ($H_m$) and those of the cyclodextrin **1** H-5 protons. The presence of these interactions, and the absence of through space interactions between other guest aromatic proton and cyclodextrin proton resonances, indicated not only complexation but was clearly evidence for the direction of orientation of the guest within the cyclodextrin annulus as depicted in Figure 2.

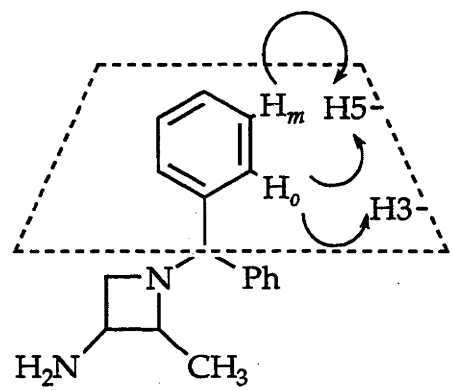
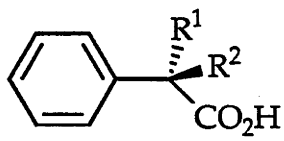
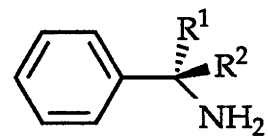



**Figure 2.** Host-guest geometry for β-cyclodextrin **1** and the guest **7**

Due to their inherent chirality, cyclodextrins form diastereomeric inclusion complexes upon addition of a racemic guest.[26,52,62-66] This may result in distinct NMR spectra being observed for each of the diastereomeric complexes, observed as doubling of species resonances (spectroscopic discrimination).[26,62,64] Differences in chirality of the guest may also result in different physical properties, such as solubility[67] or stability, of the resultant diastereomeric host-guest complexes (thermodynamic discrimination). For example, spectroscopic discrimination was observed when the guest **7** was delivered to β-cyclodextrin **1** as a racemate.[47] In

addition to the results obtained from the 2D ROESY experiment, the simple 1D $^1H$ NMR spectrum of that complex showed there to be duplication of the guest **7** methyl resonances at around δ 1.8. This spectroscopic discrimination was also observed in the $^1H$ NMR spectra of other related compounds upon complexation with β-cyclodextrin **1**.[47] Similarly, in the presence of β-cyclodextrin **1**, the methyl doublet in the $^1H$ NMR spectrum of racemic 2-phenylpropanoic acid **8** has been shown to resolve into separate signals for the enantiomers of the guest,[26] and duplication of signals has also been observed in the guest $^{19}F$ NMR spectra of a series of fluorinated amino acids in the presence of α-cyclodextrin **2**.[64] These NMR studies were, however, preceded some years by a calorimetric study in which the heats of mixing of various optically active benzene derivatives in the presence of α-cyclodextrin **2** were used to calculate enthalpy data and dissociation constants for those complexes. No selectivity was found for complexation of the isomers of amphetamine by α-cyclodextrin **2** but discrimination of 1.3 : 1 was observed in the complexation of racemic phenylalanine and racemic α-methylbenzylamine (1-phenylethylamine **9**) by the cyclodextrin **2**.[66]



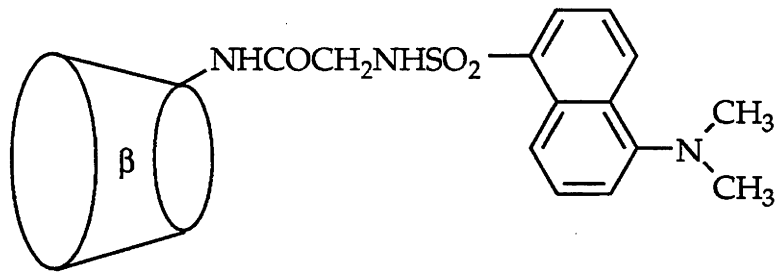

**8a** $R^1 = H, R^2 = CH_3$
**8b** $R^1 = CH_3, R^2 = H$

**9a** $R^1 = H, R^2 = CH_3$
**9b** $R^1 = CH_3, R^2 = H$

The implementation of modified cyclodextrins has been shown to provide access to many differing properties and characteristics in host-guest chemistry. Many types of modified cyclodextrins have been prepared, and their synthesis generally involves the substitution of one or more of the C-2,

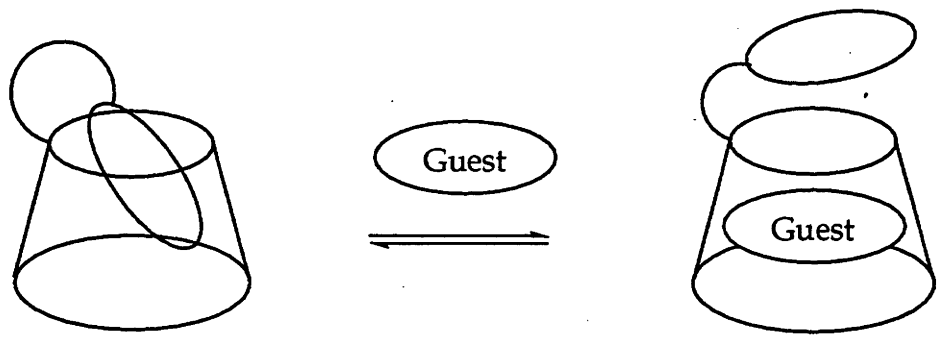
C-3 and C-6 hydroxyl groups with some other functional group.[65,68-109] There are other approaches, such as the preparation by Sakarai and co-workers,[110] of an amino-modified β-cyclodextrin derivative by the insertion of a D-glucosamine unit into the ring of α-cyclodextrin **2**. However, the previously mentioned method of targeted substitution of certain hydroxyl residues is simpler and more widely used. Such modifications may be divided into two categories. In one, the hydroxyl groups are substituted in a symmetrical fashion to give a single modified cyclodextrin (e.g., all the hydroxyl groups may be substituted) or at random to give a complex mixture of cyclodextrins in which the average effect is that of symmetric substitution.[69] This tends not to alter the symmetry of the cyclodextrin or the enantioselectivity that it displays upon complexing some guest. An example of this is the implementation of termethylated cyclodextrins, in which all of the cyclodextrin alcohol residues are converted to methyl ethers.[70] The result of this substitution is extremely enhanced lipophilicity of the cyclodextrin annulus over that of parent cyclodextrins, and also an increase in the size and flexibility of that cavity.[25]

The other type of cyclodextrin modification involves the introduction of a single substituent or a specific combination of substituents. This results in increases in the asymmetry of the cyclodextrin and may result in additional and more specific interactions. Alternatively the modification may act to convert the cyclodextrin into a spectroscopically active compound, in order to detect complexation of a guest by observing the host.[39,41,71-78] A particularly effective example of this is the exploitation of the naphthalenesulfonate moiety, which, as discussed above, fluoresces within the cavity of a cyclodextrin but that fluorescence is quenched in water.




**10**

Studies with the dansyl-glycine substituted cyclodextrin **10**[75] found that compound to exhibit a fluorescence peak at 535 nm. The aromatic side chain is clearly included into the cavity of the cyclodextrin (Scheme 3), where, due to the lipophilic micro-environment, it exhibits fluorescence behaviour. However, the fluorescence intensity was found to decrease with addition of lipophilic guests such as 1-borneol. The implication gained from this work,[75] and others,[74,79-82] is that the fluorescent "tag" is ejected from the cyclodextrin cavity to bulk solvent by the added guest (Scheme 3[74,75,82]). The result of that is of course the quenching of observable fluorescence.

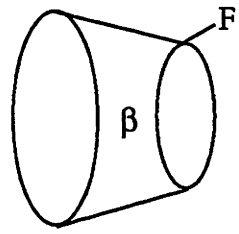



Fluorescence Observed

Fluorescence Quenched

**Scheme 3**[74,75,82]

In the present work, in order to attempt to study the effects of host-guest complex formation on the host, $6^A$-deoxy-$6^A$-fluoro-β–cyclodextrin **11** was prepared.[83] The interaction of that compound with solvent and several racemic aromatic guests was studied by $^{19}F$ NMR spectroscopy, and that work is discussed in Chapter 1 of the Results and Discussion section of this thesis.




**11**

Despite the effectiveness of using particularly modified cyclodextrins to probe complexation, they tend to be prepared in a fashion tailored to promote interactions with a known guest by judicious choice of appropriate functionality on the cyclodextrin,[76,84-88] or to take advantage of particular properties such as host solubility and charge, catalytic properties, the potential for secondary interactions, or some other factor.[25,34,89-98,110]

The synthesis of cyclodextrins substituted at one of the hydroxyl positions by an amine can allow access to many of these properties. An example of work of this type is the synthesis of $6^A$-deoxy-$6^A$-trimethylamino-β-cyclodextrin **13**, and subsequent complexation studies with a series of guests including 4-acetoxybenzoate **12**.[34] This study suggested that the electrostatic attraction between the positively charged ammonium cation and the carboxylate anion of the guest **12** served to stabilize such a complex, over a corresponding system containing β-cyclodextrin **1** and the same guest **12**. It

was further suggested that such electrostatic interactions are likely to effect the orientation of the guest within the host molecule, clearly due to preferred alignments which maximise such interactions (Figure 3).

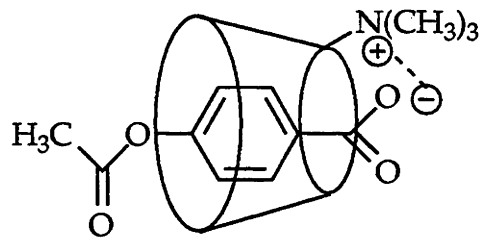
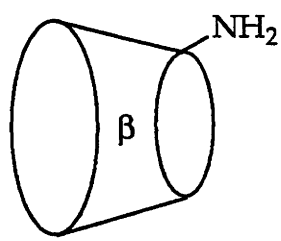



**Figure 3.** Likely orientation of the guest **12** included within the amino-cyclodextrin **13.**

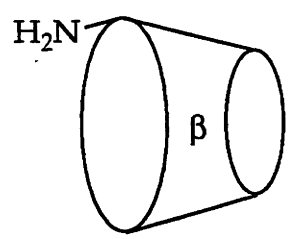
A large disadvantage of the use of natural cyclodextrins is their extremely low aqueous solubility, the lowest of which, as mentioned above, is 1.85 g / 100 ml at room temperature for β-cyclodextrin **1**.[4] It is thought that this low solubility arises from extensive hydrogen-bonding between the hydroxyl groups of individual molecules of β-cyclodextrin **1** in the crystal structure.[99] Modification of the cyclodextrin, such as in the previously mentioned termethylated cyclodextrins, results in a breakdown of the crystal lattice by disrupting this hydrogen bonding. The end result of this is that heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin has an enhanced aqueous solubility of approximately 57 g / 100 ml at room temperature.[99] Other increases in solubility have been observed in hosts such as charged modified cyclodextrins, where an associated hydration sphere about the substituent renders the species more soluble in aqueous media.[25,34,91-94,110]

All modified cyclodextrins prepared for studies presented in this thesis are singly substituted, at either a C-6 or C-3 position of one of the glucopyranose residues of the cyclodextrin. And all, save for the already-mentioned fluoro-cyclodextrin **11**, are prepared by introduction of some amine substituent.

To take advantage of solubility effects, the conjugate acids of the modified cyclodextrins $6^A$-amino-$6^A$-deoxy-β-cyclodextrin **14** and $3^A$-amino-$3^A$-deoxy-($2^AS$,$3^AS$)-β-cyclodextrin **15**, where one C-6 hydroxyl substituent of β-cyclodextrin **1** is replaced by an amino group in the former case and one C-3 hydroxyl substituent is replaced by an amino group in the latter case, were of interest. The aqueous solubilities of the conjugate acids of the C-6 substituted amine **14** and the C-3 substituted amine **15** are approximately 70 g / 100 ml and greater than 70 g / 100 ml, respectively at room temperature.[100] The $pK_a$s of the conjugate acids of the cyclodextrins **14** and **15** in aqueous media have been shown to be around 8.7[100] and 7.5,[24] respectively, and so appropriate choice of the pH of complexation studies can select the protonation state of these species.



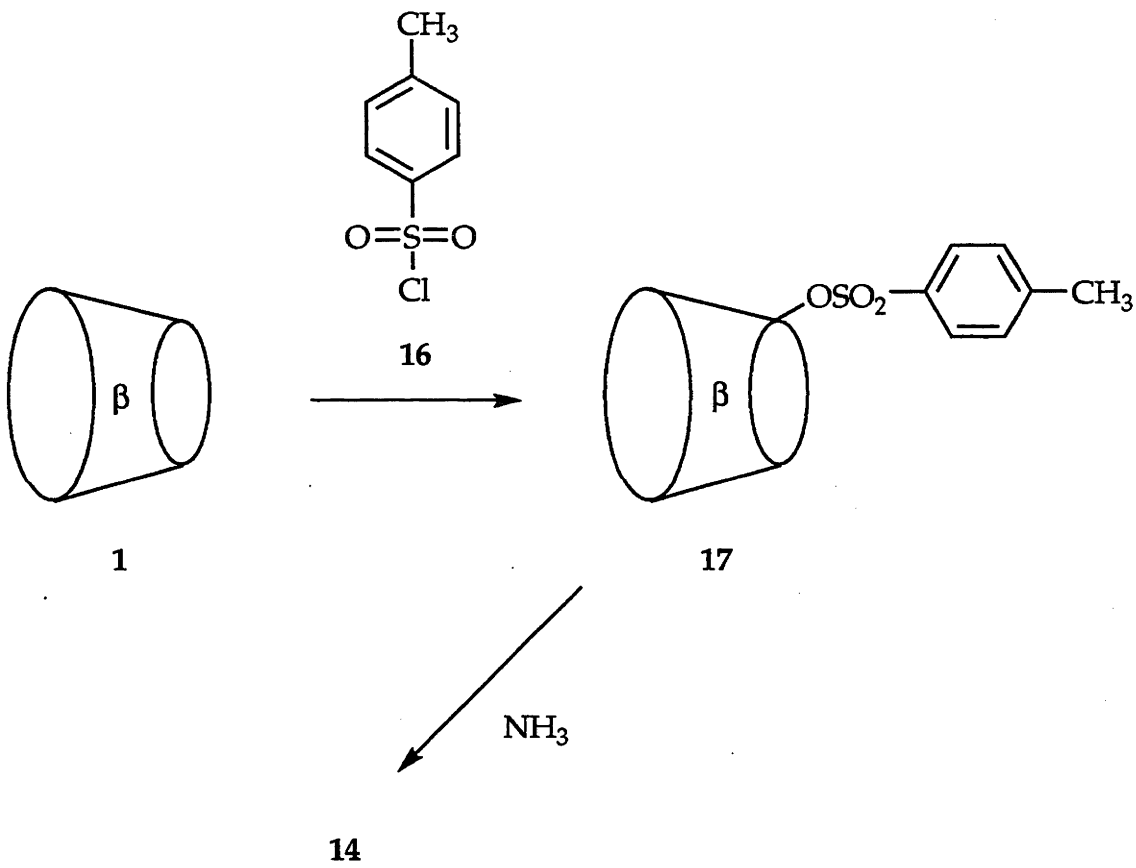

**14**




**15**

The C-6 substituted amine **14** has been synthesized previously,[101] and Easton *et al.*,[100] have reported a similar two step synthesis from β-cyclodextrin **1**. In that method β-cyclodextrin **1** has a single C-6 hydroxyl

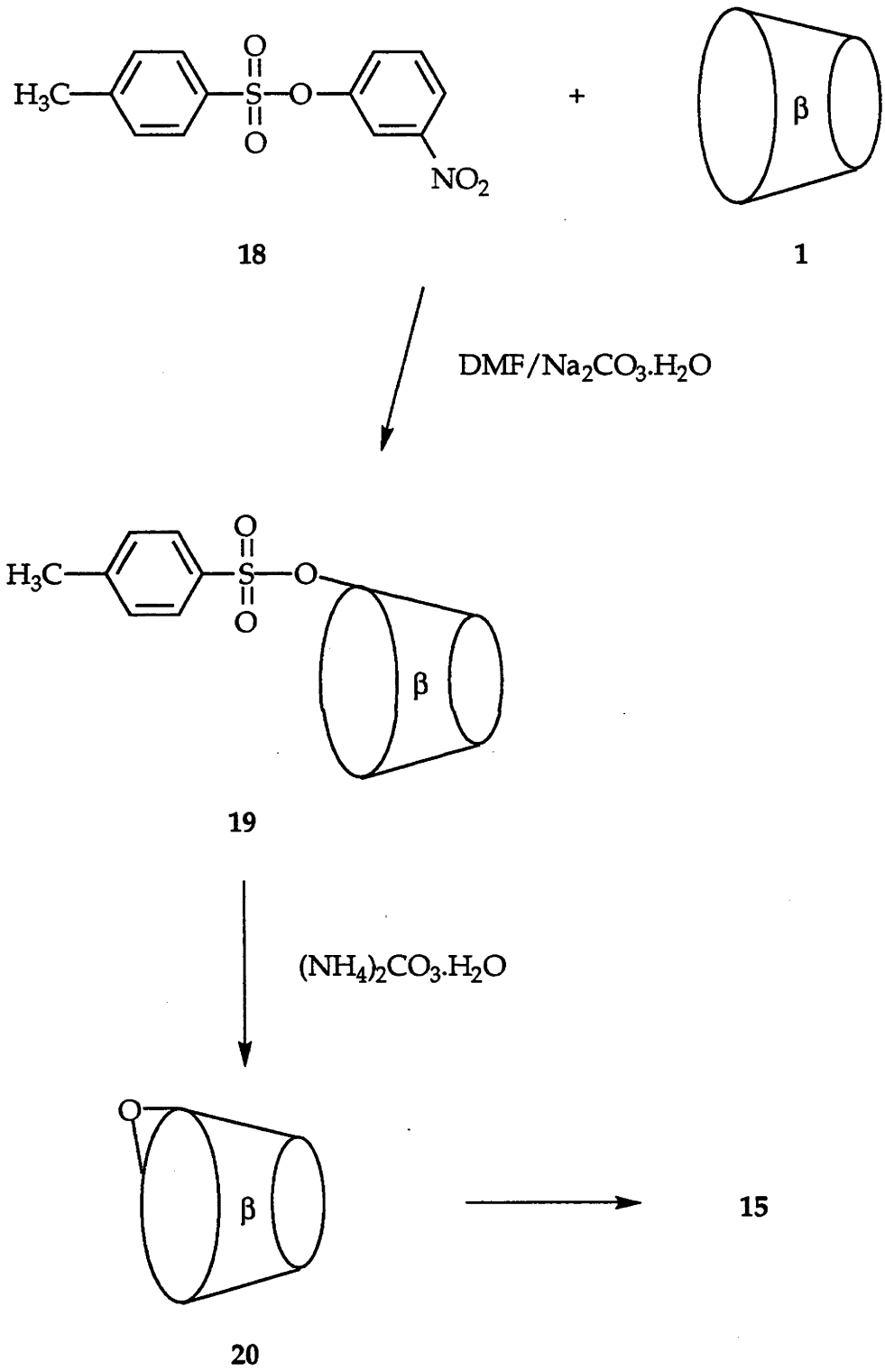
group tosylated by the action of *p*-toluenesulfonyl chloride **16** in pyridine, a process in which the reagent includes into the cyclodextrin prior to reaction. It is likely that polytosylation is limited in this process due to self-inclusion of the *p*-toluenesulfonyl group of the cyclodextrin tosylate **17** limiting the access of further tosyl chloride **16** molecules to the substrate. The tosylate **17** is then treated with condensed ammonia in *N,N*-dimethylformamide (DMF) to yield the amine **14** (Scheme 4).




**Scheme 4**

Ueno and Breslow[102] showed that selective functionalization of the secondary face of β-cyclodextrin **1** could be achieved by tosyl transfer from *m*-nitrophenyl *p*-toluenesulfonate **18** to a C-2 hydroxyl of β-cyclodextrin **1**.

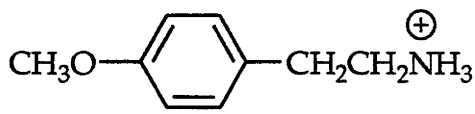
The reaction is performed in pH 9.9 carbonate buffer, in order to selectively deprotonate the C-2 hydroxyls of the cyclodextrin 1. Addition of the



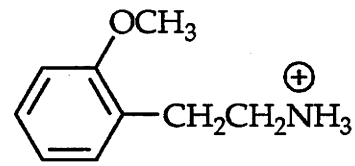

**Scheme 5**

substrate with heating yields the tosylate **19**. The C-2 substituted tosylate **17** is thought to be favoured in this process because of convenient orientation of the *m*-nitrophenyl *p*-toluenesulfonate **18**, such that the substrate's sulfonate group is held in close proximity to the deprotonated C-2 hydroxyls of the cyclodextrin **1**, thereby facilitating the formation of the required product. Murakami *et al.*,[65] reported that the action of ammonium carbonate on the tosylate **19** caused the elimination of the tosylate group to form the $2^A,3^A$-mannoepoxide **20**, which reacted with aqueous ammonia to give the C-3 substituted amine **15** (Scheme 5). The result of these reactions is the expected preparation of a cyclodextrin which has a secondary hydroxyl group substituted with an amino group, but it is important to note that this process involves the reversal of stereochemistry at the C-2 and C-3 centres of the glucopyranose residue which is modified, compared to the other residues of the cyclodextrin.[65]

In order to probe the effect of the amino-substituent, with respect to host charge and symmetry, on the complexation behaviour of these cyclodextrins **14** and **15**, it was necessary to choose appropriately substituted aromatic guests. A recent thermodynamic and NMR study by Goldberg *et al.*,[48] of a large array of aromatic guests, as complexed by α- and β-cyclodextrin **2** and **1**, showed evidence of clear steric effects. For example, in the complexation of *para*- and *ortho*-methoxyphenethylamine **21** and **22**, the stability constants

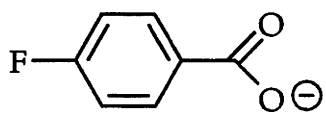



**21**

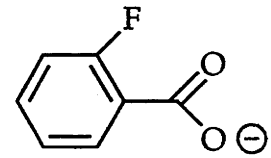



**22**

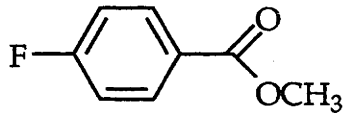
for complexation by β-cyclodextrin **1** were found to be 77.3 ± 1.5 and 8.0 ± 1.0 $dm^3\ mol^{-1}$, respectively. This corresponded to a selectivity for complexation of *para*-methoxyphenethylamine **21** over that of the *ortho*-isomer **22** of 9.7:1. This is almost certainly due to the lesser steric demand of the former, more linear, guest over that of the latter species.



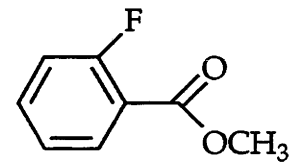
**23**



**24**



**25**



**26**

In the present study it was decided to probe several factors affecting complexation, including electronic effects, in the absence of any such steric considerations. Accordingly the guests chosen for this study were the fluorinated aromatic compounds **23 - 26**. Fluorine is of a similar size to hydrogen and so any steric effects will be limited, although the large difference in electronegativity between those two species means that the *ortho*-substituted anion and ester **24** and **26** are expected to have much greater dipole moments than the corresponding *para*-isomers **23** and **25**. This is in addition to the fact that the complexation of the guests **23 - 26** with β-cyclodextrin **1** and the conjugate acids of the amines **14** and **15** will be able to be readily monitored by $^{19}F$ NMR spectroscopy.

The guest species, *para*- and *ortho*-fluorobenzoate **23** and **24**, and the corresponding methyl esters **25** and **26**, provide convenient pairs to probe the effect of guest charge on complex formation with these cyclodextrin hosts. The presence of guest charge, and the resultant hydration of that species in aqueous media, is expected to reduce the association constant of that guest with a given cyclodextrin, in comparison to a corresponding uncharged species. This was in fact found to be the case in a study of the complexation behaviour of the conjugate acid-base pair of benzoic acid and benzoate, where the association constants of those species with β-cyclodextrin **1** were found to be 590 ± 60 and 60 ± 10 $dm^3\ mol^{-1}$, respectively, a ten-fold increase upon protonation of the benzoate guest and the corresponding loss of hydration sphere that results.[26] This effect is probed further in the systems under study, and this work is presented in Chapter 1 of the Results and Discussion section of this thesis.

Accordingly, the association constants of the inclusion complexes of β-cyclodextrin **1** and the conjugate acids of the amines **14** and **15** with the guests **23 - 26** were determined by the established NMR technique of measuring the variation in chemical shift of some resonance of the guest at constant concentration (in this case the $^{19}F$ chemical shift of the fluorine substituents) with varying amounts of cyclodextrin present.[52,61,64] That work is discussed in Chapter 1 of the Results and Discussion section of this thesis.

As discussed above, cyclodextrins are chiral, and the interaction with a racemic guest forms diastereomeric inclusion complexes which may have differing thermodynamic stability.[26,48,52,64,66] However, the extent of chiral discrimination by unmodified cyclodextrins is typically quite

modest.[26,48,52,64,66] Low selectivity may be a consequence of the inherent symmetry of cyclodextrins as each has an axis of rotational symmetry. In addition, inclusion of a guest into a cyclodextrin often occurs as a result of interaction of the hydrophobic annulus of the cyclodextrin with an achiral hydrophobic portion of the guest, and there is little interaction between the chiral centres of the cyclodextrin and those of the guest. It follows that increased chiral discrimination might be expected with modified cyclodextrins where, through the modification, the degree of asymmetry of the cyclodextrin has been increased.[69] This is in addition to the possibility of increasing the interaction between chiral portions of the guest and the host by tailoring the modified cyclodextrin to maximise any potential interactions.[65,76,103-105]

Easton *et al.*,[104] have prepared $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin, and the corresponding nickel(II) complex **27** and have studied the complexation characteristics of those species, and β-cyclodextrin **1**, with the isomers of the tryptophan anion **28**. It was found that both β-cyclodextrin **1** and $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin exhibited no discrimination in the complexation of the tryptophan anion **28**, however $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin did show a ten-fold increase in the association constant for that guest **28**. This effect was attributed to ionic interaction between the guest anion species **28** and the amine substituent of $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin, which was protonated under the conditions of the study. It was further found that the complex **27** binds the anion **28** even more strongly than $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin, indicating the presence of interactions with the former species that are even more favourable. This effect is combined with a ten-fold enantioselectivity in favour of

complexation of the *(S)*-enantiomer of tryptophan **28**, over that of the corresponding *(R)*-isomer. Clearly the metallocyclodextrin **27** has a large degree of asymmetry and, with both the tryptophan anion **28** and $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin complexed to $Ni^{2+}$, there is also likely to be a high degree of rigidity in the complex (Figure 4), resulting in the large enantioselectivity.

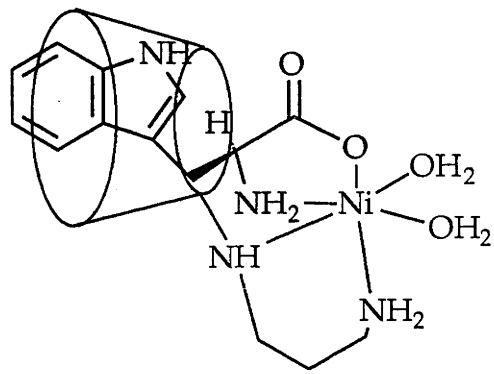
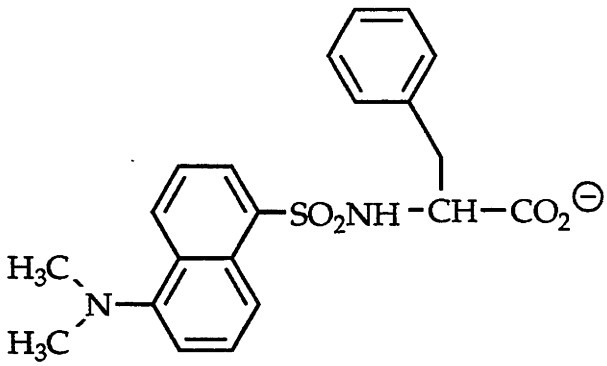


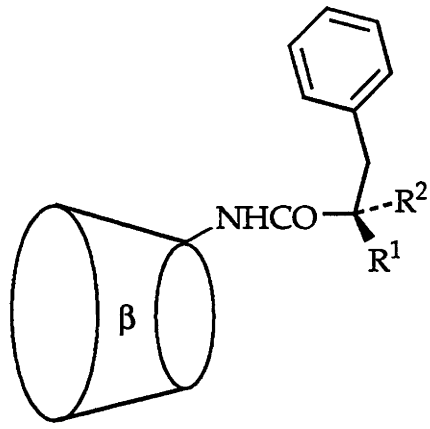

**Figure 4.** A possible structure for the complex of the metallocyclodextrin **27** and *(S)*-tryptophan **28**.

An alternative approach to achieving guest enantioselectivity upon complexation by a cyclodextrin is to add even greater asymmetry to that host species by the addition of a chiral substituent.[65,76,104,105] It follows that an increase in host asymmetry will once again lead to enantioselective complexation. Enhanced enantioselectivity, over that of β-cyclodextrin **1**, was observed in the complexation of the enantiomers of *N*-dansylphenylalanine **29** by the amino acid substituted cyclodextrin *N*-(*N'*-formyl-D-phenylalanyl)-$6^A$-amino-$6^A$-deoxy-β-cyclodextrin **30a**. β-Cyclodextrin **1** shows a modest selectivity of 1.2:1 for the D-isomer of *N*-dansylphenylalanine **29** over the corresponding L-isomer. Upon

complexation by the cyclodextrin **30a** this selectivity increases to 2.0:1, once again in favour of complexation of the D-isomer of the guest **29**.[76]




**29**



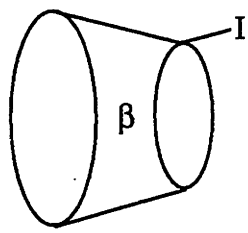

**30a** $R^1$ = NHCHO, $R^2$ = H
**30b** $R^1$ = H, $R^2$ = NHCHO

In such complexes, 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 the chiral portion of the guest.[69] This argument is supported by the observation that enantioselectivity in the complexation of the isomers of *N*-dansylphenylalanine **29** by *N*-(*N'*-formyl-L-phenylalanyl)-6$^A$-amino-6$^A$-deoxy-β-cyclodextrin **30b**, the diastereomer of the cyclodextrin **30a**, is similar in magnitude, although reversed in terms of absolute stereochemistry.[76] This effect is not commented upon by the authors, but the phenomenon constitutes a complementary discrimination between the isomers of the guest **29** by the cyclodextrins **30a** and **30b**. That is by reversing the stereochemistry of the chiral substituent the observed stereoselectivity is reversed.

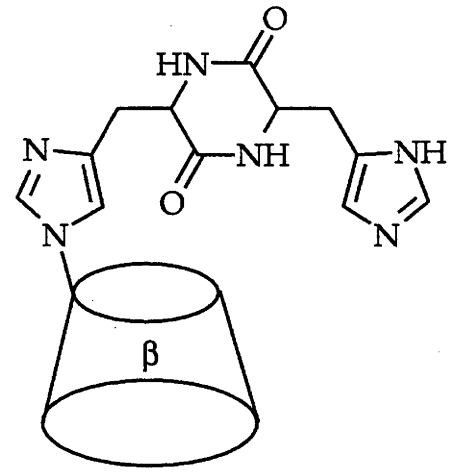
Amide-linked modified cyclodextrins of this type are prepared simply by the action of dicyclohexylcarbodiimide (DCC) on the C-6 substututed amine **14** and an appropriate acid.[39,73-76,79,105-107] The diastereomers of the cyclodextrin **30** were thus prepared from the C-6 substituted amine **14** and the appropriate enantiomer of *N*-formylphenylalanine, in the presence of DCC.[76] Similarly the dansyl modified cyclodextrin **10** has been prepared from the C-6 substituted amine **14** and *N*-dansylglycine, also in the presence of DCC.[75] This method is of course general and non-amino acid bearing fluorescent hosts such as a cyclodextrin appended with a *para*-(dimethylamino)benzoyl moiety have been prepared from *para*-(dimethylamino)benzoic acid and the C-6 substituted amine **14** .[74]

The above general method of synthesis of course uses the cyclodextrin as a nucleophile in a reaction system to produce the required species. An obvious alternative approach, analogous to the preparation of the C-6 substituted amine **14** and the C-3 substituted amine **15**, is the use of a cyclodextrin substituted with a leaving group and having a nucleophile displace that leaving group.[82,83,88,91,103,108-110] This was used effectively for the synthesis of $6^A$-aminoethylamino-$6^A$-deoxy-β-cyclodextrin from the tosylate **17** and 1,2 diaminoethane,[89] also a method used in the synthesis of the previously discussed $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin.[104] However, such an approach is not restricted to the use of the tosylate **17** and simple amines. $6^A$-Deoxy-$6^A$-iodo-β-cyclodextrin **31**, prepared by the action of sodium iodide on the tosylate **17**,[111] has also been used for alternative synthesis of modified cyclodextrins. An example of this is the synthesis of the piperazinedione-substituted cyclodextrin **32** from the complex amine *cyclo*-(L-histidyl-L-histidyl) and the iodide **31**. In this

synthesis the nucleophilic nitrogen of the imidazole ring of one of the histidine residues displaces iodide anion to yield the required product **32**.



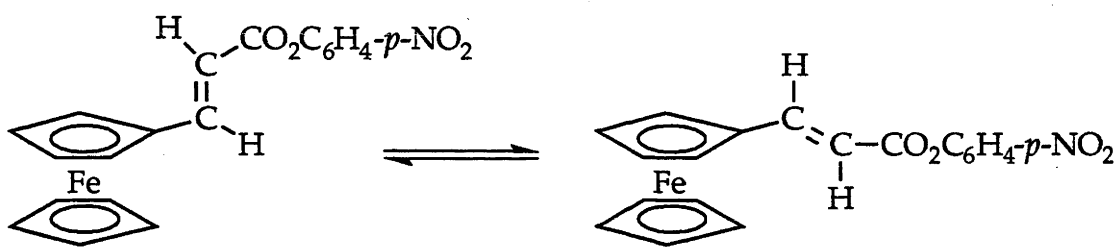

**31**



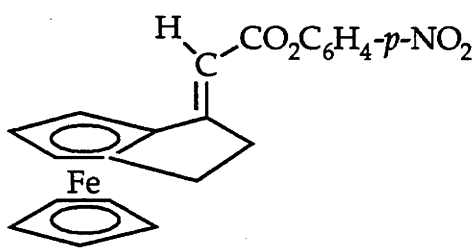

**32**

There exists scope for observing selectivity in processes involving such covalent attachment to a cyclodextrin of a species which contains chirality. Comprehensive work by Tee and co-workers,[15,16,112-114] and other groups[63,115-119] has shown cyclodextrins to catalyse the hydrolysis of aromatic esters by a mechanism which involves covalent attachment of the acyl species. The process involves the formation of a host-guest complex between the cyclodextrin and an ester, then transesterification between host and guest, followed by hydrolysis of the acylated cyclodextrin. In principle, any chiral discrimination observed in such a process could arise either from selectivity in the complexation of the isomers of guest, or differing reactivities of the guests once bound, or a combination of these effects. This has been investigated by Trainor and Breslow[120,121] by studying the β-cyclodextrin **1** catalysed hydrolysis of the *para*-nitrophenyl esters of enantiomeric ferrocene derivatives. It was found that enantioselectivity displayed by the cyclodextrin is dependent on the extent to which the

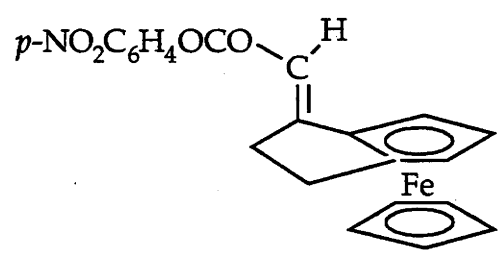
geometry of binding of the guest is restricted. β-Cyclodextrin **1** catalysed the hydrolysis of the ester **33**, which exists in two conformers, 360000-fold but without enantioselectivity. However, the enantiomeric esters **34a** and **34b** correspond to the conformers of that ester **33**, but with restricted geometries. It was found that β-cyclodextrin **1** increased the rate of hydrolysis of ester **34a** by a factor of 5900000, but increased the rate of hydrolysis of ester **34b** by a much smaller amount, namely by a factor of 95000. This is a 62-fold enantioselectivity in a reaction involving covalent attachment, and is the largest reported such selectivity for hydrolysis of an ester by a cyclodextrin.[120]




**33**



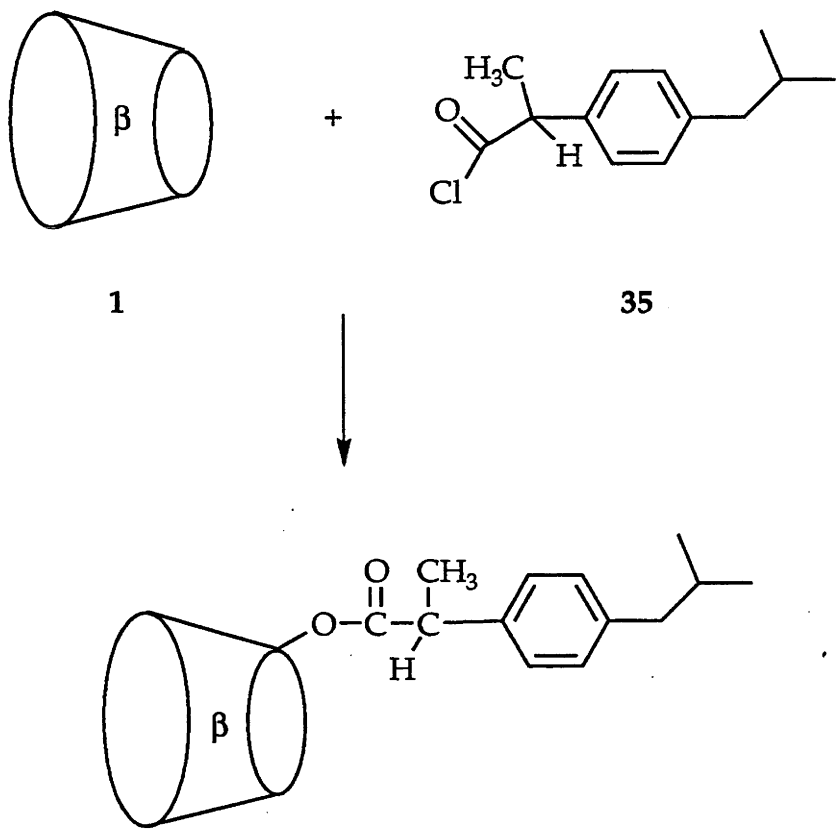

**34a**




**34b**

Enantioselectivity upon covalent attachment has also been observed, not just in processes in which cyclodextrin is the catalyst, but also in the synthesis of diastereomeric cyclodextrin compounds. Easton *et al.*,[63]

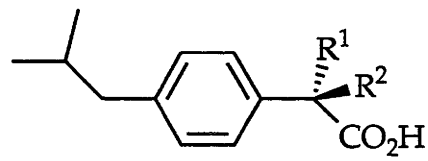
observed chiral discrimination in the preparation of a cyclodextrin derived from a racemic mixture of the 4-*iso*-butyl-α-methylphenylacetic acid (Ibuprofen acid) enantiomers **37a** and **37b** via acylation of β-cyclodextrin **1** with the enantiomeric acid chlorides of Ibuprofen **35** (Scheme 6). The diastereomers of the cyclodextrin ester **36** were produced in a ratio of 5:1 in favour of the isomer derived from the *(R)*-Ibuprofen acid **37a**.




**Scheme 6**

Previous work[122] had shown that there was a tenfold selectivity in the hydrolysis of the diastereomers of the cyclodextrin ester **36** in favour of release of the *(R)*-Ibuprofen acid **37a**. This of course corresponds to

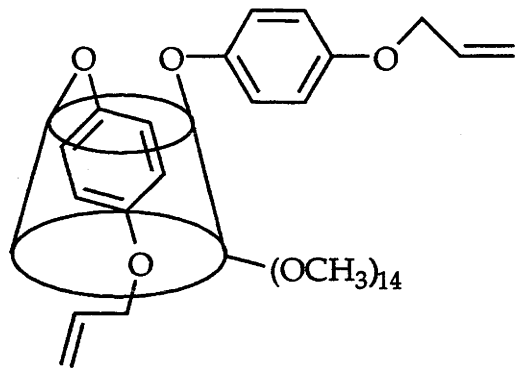
preferential hydrolysis of the isomer of the ester **36** which was most readily formed, and so constitutes an overall stereoselectivity for the two-step reaction of the acid chloride **35** of 50:1. The complementary nature of the diastereoselectivity of the synthesis and hydrolysis was attributed to similarities between the reaction transition states.




**37a** $R^1 = H, R^2 = CH_3$
**37b** $R^1 = CH_3, R^2 = H$

As has been suggested above, by discussion of work involving cyclodextrins with a fluorescent substituent,[74-76] for modified cyclodextrins with an aromatic, or some other lipophilic, substituent, there exists the possibility of intramolecular complex formation; that is, the self-inclusion of the aromatic moiety of the substituent into the cavity of the cyclodextrin. Takahashi[49] found the aromatic ring of the modified cyclodextrin **30b**, prepared from *N*-formyl-*L*-phenylalanine, was sufficiently self-included to show significant effects on the $^{13}C$ NMR spectrum of the cyclodextrin annulus. In the absence of a substituent, the $^{13}C$ NMR spectrum of β-cyclodextrin **1** shows the glucopyranose units to be equivalent, due to the axis of symmetry in the molecule, with signals corresponding to each carbon appearing as a single resonance, for example a single C-1 resonance at around δ 104 for all seven of those nuclei present. In the $^{13}C$ NMR spectrum of **30b** there exists multiple signals for the C-1 carbons, namely δ 102.80, 103.02, 103.62 and

103.79. This was attributed to the self inclusion of the aromatic ring causing magnetic environment changes on the cyclodextrin annulus carbons.[49] Such effects were also observed in a study of the $^1$H NMR spectra of that cyclodextrin **30b**, with an enormous amount of non-equivalence and shielding effects observed in the *N*-formyl-*L*-phenylalanine appended cyclodextrin **30b**, in comparison to β-cyclodextrin **1**.[107]

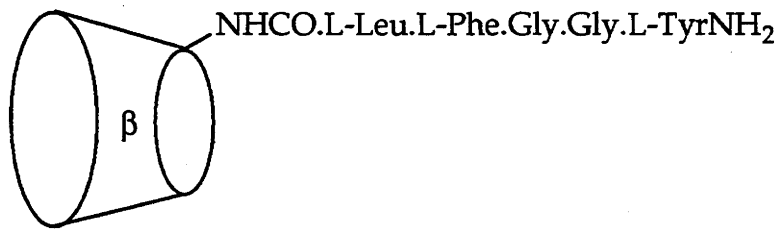



**38**

Many similar studies have also shown $^1$H NMR spectroscopy to be a very useful tool for the detection of intramolecular complex formation, with evidence for self-inclusion generally found in the $^1$H NMR spectrum of both the cyclodextrin annulus, and the substituent of the modified cyclodextrin.[49,105,123] Bradshaw *et al.*,[108] observed such effects in the $^1$H NMR spectrum of the bis-phenylether substituted cyclodextrin **38**. This particular species has two *para*-(allyloxy)-phenyl substituents in C-6$^A$ and C-6$^B$ positions and all of the secondary hydroxyl groups capped as methyl ethers. It was found that one of the phenyl substituents was self-included into the cyclodextrin cavity to form an intramolecular complex and the other aromatic moiety was directed outside the cavity. This was observed in clear anisotropic shielding of the cyclodextrin annulus H-3 and H-5 protons and the presence of extremely well resolved anomeric (C-1) proton signals

spanning δ 4.9 - 5.3, all effects of the inclusion of the substituent moiety. This was in addition to differences observed in the resonances of the two substituents, as they resolved into both two sets of signals for the allyl groups and two sets of signals for the two aromatic moieties. This was clear evidence of the exclusion of one allyloxyphenyl substituent from the cyclodextrin cavity and the inclusion of the other of those moieties, and demonstrated the effect that intramolecular complexation can have on a substituent.

The same method can be used, of course, to show that the cavity of a modified cyclodextrin is vacant. A study of the neuropeptide substituted cyclodextrin *N*-(Leu-enkephalin)-6$^{A}$-amino-6$^{A}$-deoxy-β-cyclodextrin **39**, which contains aromatic functionality on a flexible substituent side chain, showed there to be very little dispersion of the $^{1}$H NMR spectrum over that of native β-cyclodextrin **1**. The complexation behaviour of the cyclodextrin **39** was also found to be similar to that of β-cyclodextrin **1** and it was concluded that the cavity was vacant; that is there was no evidence of intramolecular complex formation.[123]




**39**

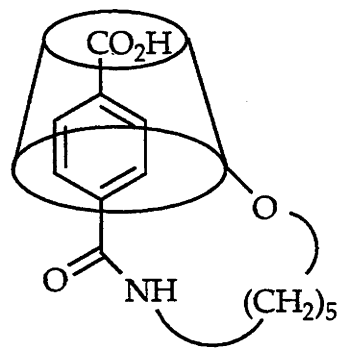
A similar approach was used by Takahashi *et al.*,[105] in the investigation of the inclusion behaviour of the previously discussed diastereomers of the *N*-formylphenylalanine appended cyclodextrins **30a** and **30b**. Both of these

species show evidence in their $^1H$ NMR spectra of self-inclusion of the aromatic ring into the cyclodextrin cavity. However it was noted that the annulus protons showed marked shielding differences, with the C-1 protons showing different splitting patterns for the diastereomers, along with the phenyl protons appearing at different chemical shifts. It is likely that such effects are caused by significant differences in the conformation of the two diastereomers **30a** and **30b**. Gelb *et al.*,[43] reported, in an earlier study, that the C-1 positions of the glucopyranose units of a cyclodextrin annulus are screened from direct interaction with any included substrate, including magnetic anisotropy effects, by neighbouring carbon and oxygen nuclei. Therefore any complexation induced shifts in NMR spectra of nuclei at the C-1 position of a cyclodextrin species are due to conformational changes. Thus the differences in the spectra of the diastereomers **30a** and **30b** are an indicator of conformational non-equivalence, consistent with differences in the extent of intramolecular complex formation.

As for intermolecular complex formation, the self-inclusion of the substituent of a modified cyclodextrin into the cavity to form an intramolecular complex is a dynamic process, with an equilibrium set up between the included and excluded forms of that species.[39,72,73,79,106,108,109] This has shown to be the case with a short-tethered naphthyl-substituted cyclodextrin, and that equilibrium was found to be temperature dependent.[72] At ambient temperatures the equilibrium was found to favour the self-inclusion of the naphthyl substituent and there was no possibility of the inclusion of some other guest species. Under these conditions the presence of TNS **6** did not result in the observation of significant fluorescence. However at higher temperatures, where the excluded form of the cyclodextrin species was present in greater quantities,

the addition of TNS **6** resulted in the observation of appreciable increases in the intensity of observable fluorescence.

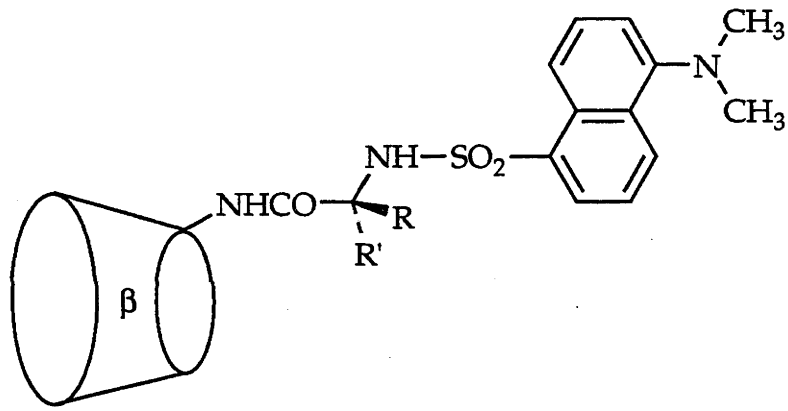
Intramolecular complexation necessarily brings the substituent into close contact with the protons of the cyclodextrin annulus. Therefore the observation of through space interactions between the substituent and the annulus by 2D NMR ROESY techniques, as for the detection of inter-molecular host-guest complexation, is a powerful tool for detecting the presence of self-inclusion.[39,56,73,108,109,124] For example in the ROESY spectrum of the modified cyclodextrin **40** with a *para*-substituted aromatic ester attached to the C-2 hydroxyl of a single glucopyranose unit, a correlation was observed between the aromatic protons and resonances in the δ 3 - 4 region of the $^1$H NMR spectra. This indicated close proximity between the aromatic protons and the H-3 and H-5 protons. The phenyl residue was therefore definitively considered to be included inside the cavity, forming the intramolecular complex **40**.[124]




**40**

Recent studies by Ueno and co-workers[39] of the ROESY spectra of modified cyclodextrins, derived from the enantiomers of *N*-dansylleucine, showed connectivities, for both isomers, between the aromatic proton resonances

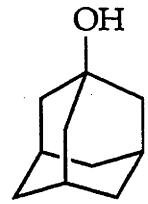
and the resonances corresponding to protons of the cyclodextrin annulus. This is, once again, direct evidence of intra-molecular complex formation between the cyclodextrin substituent and cavity for both cyclodextrin species. However, inspection of the 1D $^1$H NMR spectra of the diastereomers **41a** and **41b**, which revealed differences in the degree of the anisotropic ring current effect from the dansyl moiety on the cyclodextrin annulus protons, combined with sufficient differences in the ROESY spectra of those compounds, led to the conclusion that in fact the D-amino acid derived cyclodextrin **41a** had the dansyl substituent included more deeply into the cavity than the corresponding L-leucine derived species **41b**.




**41a** R = H, R' = *iso*-butyl
**41b** R = *iso*-butyl, R' = H

It has been established that the introduction of a competitive guest, for inter-molecular complexation, can provide valuable information about the presence, or indeed the extent of, intramolecular complex formation.[39,49,56,73,105] Thus, the above observation of inclusion of the dansyl moiety of both diastereomers of the modified cyclodextrin is well supported by competitive binding studies.[39,73] It was noted that the resonance patterns, of the $^1$H NMR spectra of the substituents of the

cyclodextrin diastereomers **41a** and **41b**, are different from each other, but that both are different from free *N*-dansylleucine. Upon addition of 1-adamantanol **42**, the $^1$H NMR spectra of the substituents become virtually identical to that of the dansyl moiety of *N*-dansylleucine. This was strong evidence that the substituent was included in the cyclodextrin cavity and then subsequently displaced upon addition of 1-adamantanol **42**. This effect was mirrored in the observation of the $^1$H NMR spectra of the cyclodextrin annulus protons of **41a** and **41b**. For example the C-1 protons of both the cyclodextrins **41a** and **41b** are a very dispersed, well resolved series of signals. Upon addition of 1-adamantanol **42** these resonances become significantly less dispersed and show a large amount of signal overlap. This was attributed to the removal of the dansyl moiety from the annulus of the cyclodextrins **41a** and **41b** upon inclusion of the guest **42**, thereby removing the anisotropic effects and releasing the conformational strain required to form that intra-molecular complex. This had obvious coalescence effects on the observed $^1$H NMR spectrum of the annulus protons.




**42**

In addition to such qualitative studies, in a similar fashion, it is possible to probe the extent of self-inclusion of the aromatic moiety of the substituent of a modified cyclodextrin by thermodynamic studies upon introduction of a competitive guest. This was the case in the study of the complexation behaviour of *N*-dansylalanine with the previously mentioned hosts **30a** and

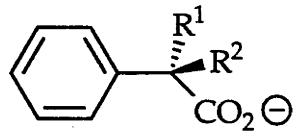
**30b**.[105] It was demonstrated that both cyclodextrins **30a** and **30b** have the aromatic moiety of the substituent substantially self-included. However, the *N*-dansylalanine guest was found to have associations constants of 42 ± 13 and 113 ± 18 $dm^3 mol^{-1}$ with the cyclodextrins **30a** and **30b**, respectively, which is consistent with the former species having a larger extent of self-inclusion of the aromatic moiety of the amino-acid substituent, thereby inhibiting intermolecular complex formation with that diastereomer **30a**.

Similarly, for cyclodextrin compounds with a self-included substituent there may be variations in the circular dichroism spectrum of that compound upon addition of a spectroscopically inert species which displaces the substituent. In studies of a fluorescent *para*-(dimethylamino)-benzoyl substituted β-cyclodextrin,[74] that species was found to have strong pair of positive and negative bands in the induced circular dichroism pattern in the 250 - 350 nm region. This response was changed to a single, simple negative band of greatly reduced intensity upon addition of 1-adamantanol **42**. This confirmed that the aromatic moiety of the substituent was substantially self-included in the absence of a guest, but was displaced from the cavity to the bulk solvent by 1-adamantanol **42**.

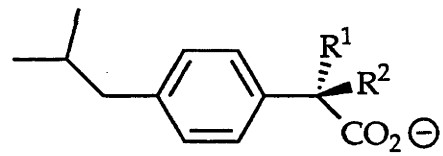
Clearly much work has been done on cyclodextrins in which one or more hydroxyl group has been replaced by an amino acid residue, however these amino acid-substituted cyclodextrins tend not to be charged due to their protection. Therefore it was decided, in order to probe the complexation and discrimination properties of modified cyclodextrins, with respect to both their charge and geometry, that cyclodextrins bearing an amine substituent containing an aromatic moiety would be studied. In order to potentially

tailor the host-guest interactions specifically it was necessary to first choose appropriate aromatic guests for study.

To that end it was decided to investigate the complexation of the 2-phenylpropanoic acid enantiomers **8a** and **8b**, and the corresponding anions **43a** and **43b**. This provides a very convenient acid-base system with which the effect on complexation of the charge and hydration of guest can be probed. To take advantage of the resultant higher solubility of charged cyclodextrin species,[25,34,91-94,110] it was intended that amino-cyclodextrins in this study would be monitored as the conjugate acids. Therefore it was also envisaged that the effects of ionic interactions in complexation might be probed by comparison of the anions **43a** and **43b** and the corresponding acids **8a** and **8b**, in studies with the conjugate acids of the cyclodextrin hosts **45 - 48**.




**43a** $R^1 = H, R^2 = CH_3$
**43b** $R^1 = CH_3, R^2 = H$



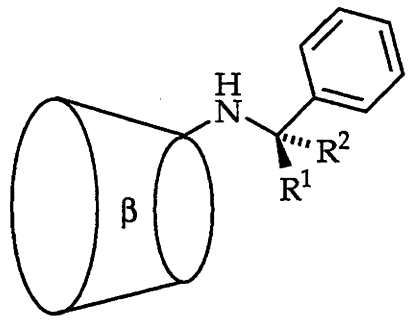

**44a** $R^1 = H, R^2 = CH_3$
**44b** $R^1 = CH_3, R^2 = H$

In addition to the guests **8a,b** and **43a,b**, it was decided to study the inclusion behaviour of cyclodextrins with the *(R)*-and *(S)*-Ibuprofen acids **37a** and **37b**, and the corresponding anions **44a** and **44b**. These species are also arylpropanoic acids, the series of compounds of which the 2-phenylpropanoic acid enantiomers **8a** and **8b** are the parents, and so allow further information to be obtained on the effects of guest hydration and

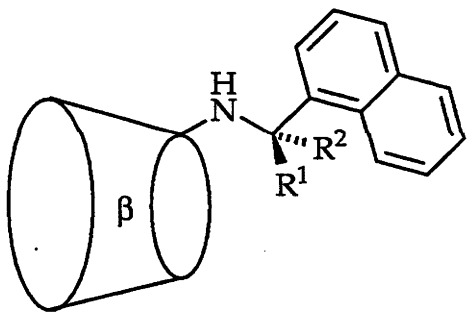
charge on complexation with cyclodextrins. Comparison of these guests allows study of the effects of changing size and apparent hydrophobicity on the complexation of guests in modified cyclodextrins. Previous studies have suggested, for example, that the addition of an alkyl substituent to a guest, such as benzoic acid, can have a profound effect on the size of the association constant of that species with cyclodextrin hosts.[25,26] This hypothesis is supported by studies which calculated the association constant of a racemte of the Ibuprofe anions **44a** and **44b** with β-cyclodextrin **1** to be 2900 ± 500 $dm^3$ $mol^{-1}$,[125] compared to that of around 55 $dm^3$ $mol^{-1}$ for each of the enantiomers of 2-phenylpropanoic acid **8a** and **8b** with that cyclodextrin **1**.[26] This effect is further investigated in the present work by comparison of relative complexation of the 2-phenylpropanoic acid enantiomers **8a** and **8b** and the Ibuprofen acid enantiomers **37a** and **37b** by the conjugate acids of the modified cyclodextrins **45a,b - 48a,b** prepared in this study.

Having chosen appropriate guests for study it was necessary to choose appropriate modifications of cyclodextrins, tailored to promote specific interactions with the guests, and chosen to probe factors such as substituent charge, size and flexibility. To that end the pairs of diastereomeric cyclodextrins **45a,b - 48a,b** were chosen for study. This series of compounds allows access to host-guest systems for complexations studies in which diastereomeric pairs of cyclodextrin hosts can be readily compared. Therefore it was expected that these compounds would be extremely suitable for checking for generality in complementarity upon complexation of racemic guests. That is, in the event that one of the hosts shows selectivity in complexation for an isomer of a given guest, it was expected that the

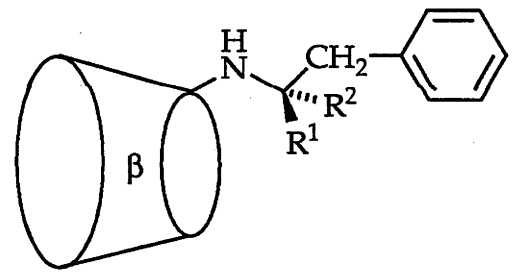
reversal of chirality of the cyclodextrin substituent might result in a reversal of the selectivity shown for the isomers of that guest.




**45a** $R^1 = CH_3$, $R^2 = H$
**45b** $R^1 = H$, $R^2 = CH_3$
**46a** $R^1 = H$, $R^2 = CH_2OH$
**46b** $R^1 = CH_2OH$, $R^2 = H$




**47a** $R^1 = CH_3$, $R^2 = H$
**47b** $R^1 = H$, $R^2 = CH_3$




**48a** $R^1 = CH_3$, $R^2 = H$
**48b** $R^1 = H$, $R^2 = CH_3$

In order to probe all of these factors discussed above, the geometries and properties of the conjugate acids of the hosts **45a,b - 48a,b** were investigated, and their conjugate acids then used in complexation studies with guests which included the 2-phenylpropanoic acid enantiomers **8a** and **8b**, and the corresponding anions **43a** and **43b**, and the Ibuprofen acid enantiomers **37a**

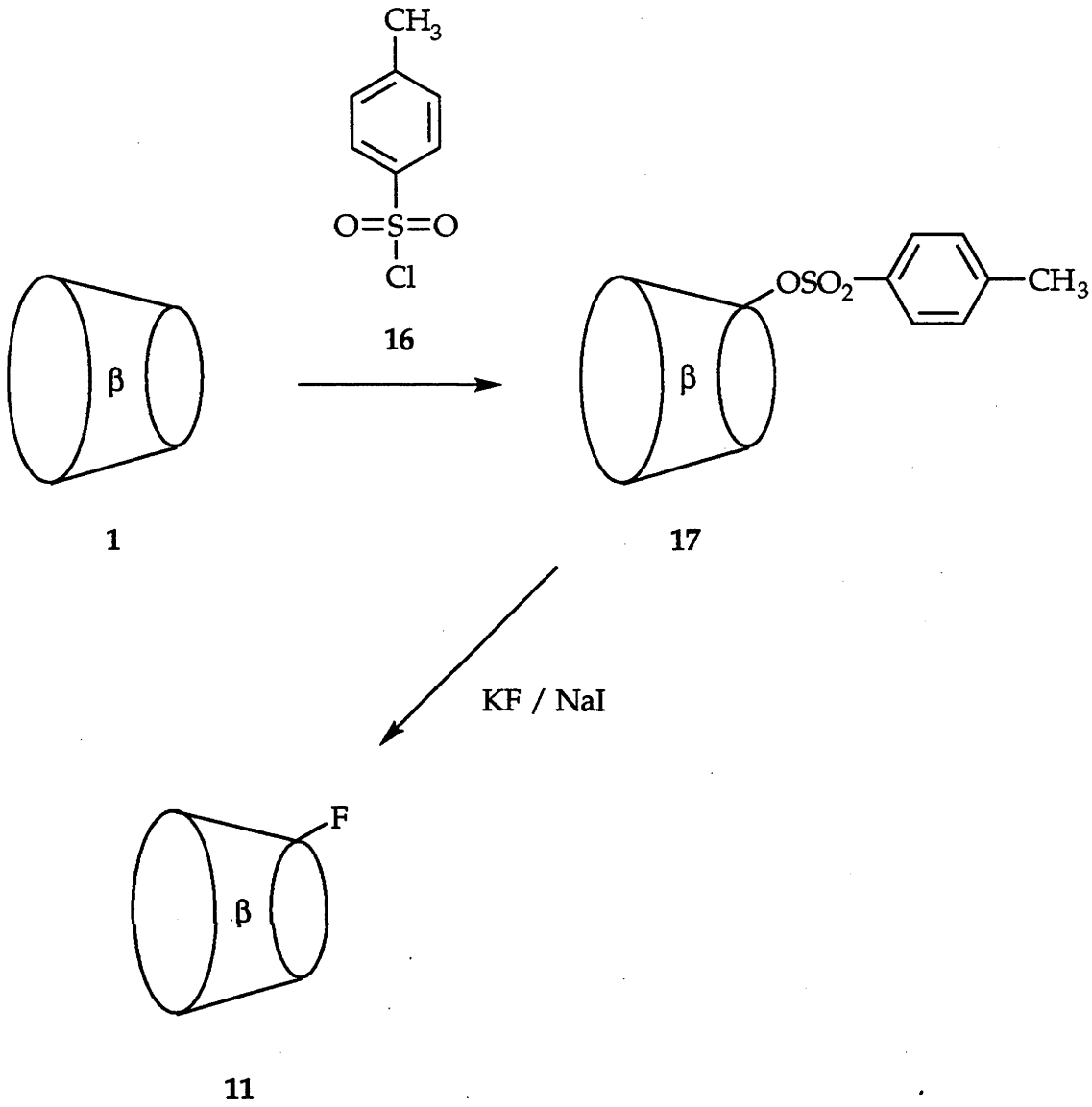
and **37b**, and the corresponding anions **43** and **44**, and that work is described in Chapters 2 to 4 of the Results and Discussion of this thesis.

## Results and Discussion Chapter 1

### Inclusion Complexes of Fluoro- and Amino-Substituted Cyclodextrins

As explained in the Introduction to this thesis, host-guest complex formation can, in principle, be monitored by inspection of the NMR spectra of particular nuclei of either the host or the guest. In order to provide a fluorinated host species, in which host-guest complexation might be monitored and discrimination detected by observation of variations in the $^{19}F$ NMR spectra of the fluoro-substituent, the cyclodextrin **11** was prepared.

$6^A$-Deoxy-$6^A$-fluoro-β–cyclodextrin **11** was synthesized using a modification of the method reported by Robyt and co-workers.[83] β-Cyclodextrin **1** was converted to the C-6 monotosylated cyclodextrin **17** by the action of *p*-toluenesulfonyl chloride **16** in pyridine.[101] The tosylate **17** was then heated at gentle reflux in ethane-1,2-diol in the presence of a catalytic amount of sodium iodide and an excess of potassium fluoride, for 20 minutes. The cooled reaction mixture was then triturated with propan-2-ol. The resultant suspension was centrifuged and a colourless solid was collected. This material was recrystallized twice from water to yield the fluoride **11** in 23% yield (Scheme 1.1). Electrospray Ionization Mass Spectroscopic (ESI-MS) analysis of the fluoride **11** gave a peak for the molecular ion plus sodium ($[M + Na]^+$) at *m/z* 1159. The $^{19}F$ NMR spectrum in deuterium oxide ($D_2O$) showed a doublet of triplets at $\delta_F$ ($CF_3CO_2H$ reference) -157.85 ($^3J_{FH}$ 29.9 Hz, $^2J_{FH}$ 47.1 Hz, which compared very favourably to the reported values of 29.3 and 47.9 Hz, respectively[83]). The $^{13}C$ NMR spectrum was essentially as for β-cyclodextrin **1**, except for the presence of a resonance at $\delta_C$ 86.3 assigned to the carbon bearing the fluorine substituent (C-$6^A$). In addition, the $^1H$ NMR




**Scheme 1.1**

spectrum of the fluoride **11** was similar to that of β-cyclodextrin **1**, save for strong line broadening in the poorly resolved H-5 and H-6 proton resonances. One major difference however, was the presence of a single-proton doublet (*J* 2.1 Hz) at $\delta_H$ 5.68 which probably corresponds to either the H-$1^A$ or H-$1^B$ proton due to the proximity of the 1-position of the A- and B-glucose residues of the cyclodextrin **11** to the fluoro-substituent in the C-$6^A$ position. This signal was adjacent to the doublet (*J* 2.1 Hz) at $\delta_H$ 5.35

corresponding to the remaining six magnetically equivalent H-1 protons. Clearly the presence of the fluorine substituent has little effect on the equivalence of the protons of the cyclodextrin **11**, and only small electronic effects on that species as a whole, compared to β-cyclodextrin **1**.

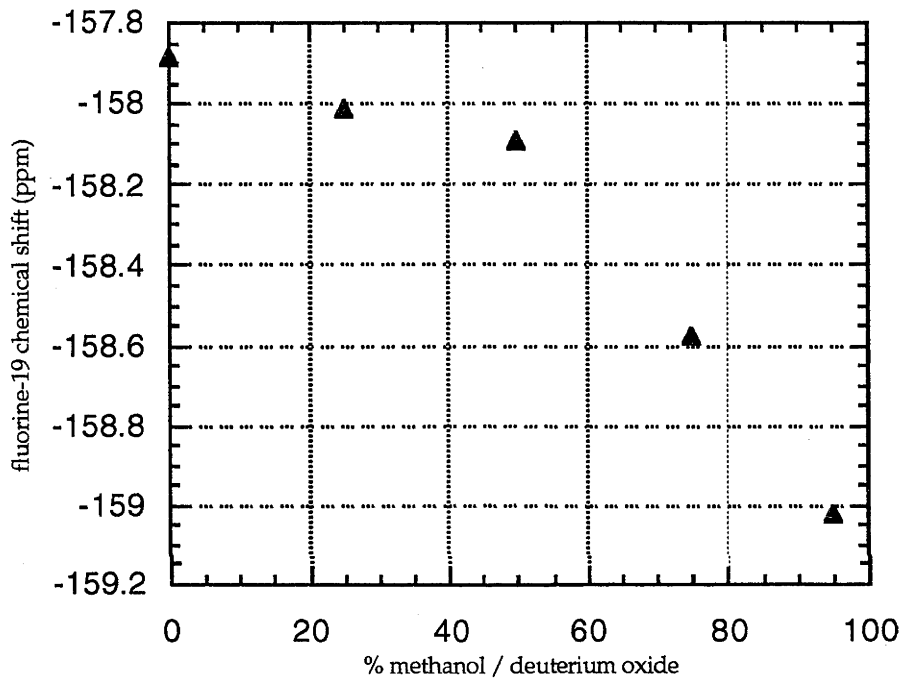



**Figure 1.1.** $^{19}F$ Chemical shift of the fluorine substituent of the cyclodextrin **11** as a function of solvent composition.

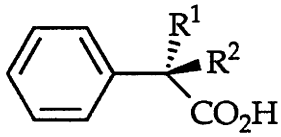
In order to test the susceptibility of the fluoro-substituent of the cyclodextrin **11** to environmental effects, a study of solvation effects on the observed chemical shift in the $^{19}F$ NMR spectrum of that cyclodextrin **11** was performed. Five samples were prepared containing $6^A$-deoxy-$6^A$-fluoro-β–cyclodextrin **11** (4.4 mM) with decreasing solvent polarity, ranging from neat $D_2O$ to 95% methanol / $D_2O$, and the $^{19}F$ NMR chemical shift of the fluorine substituent of the cyclodextrin **11** was recorded (Figure 1.1). It is clear that

environmental influences affect the fluoro-substituent of the cyclodextrin **11** sufficiently to cause a change in the $^{19}F$ chemical shift of the resonance corresponding to that nucleus of up to 1.2 ppm, across the range of solvent polarities considered. Further, the observed chemical shift change of 1.2 ppm was large enough to be measured accurately and was reproducible. It therefore follows that, should the complexation of a guest result in changes in the magnetic environment of the fluoro-substituent of the cyclodextrin **11**, then such complexation might be detected using $^{19}F$ NMR analysis of that host species.

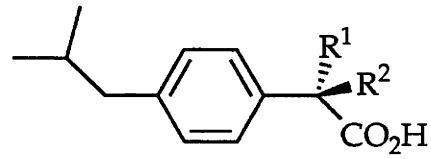
In the event of complexation of a racemic guest by some cyclodextrin host there exists the possibility that the host may discriminate between the isomers of the guest. Thermodynamic discrimination exists when the association constants (Equation 1 (Page 3)) of the complexes of two guests, be they isomers or some other discrete species, with a given cyclodextrin are not equal. This effect can be detected by calculation of association constants by many methods, as outlined in the Introduction to this Thesis. Although the two effects can be mutually exclusive, thermodynamic discrimination is often accompanied by spectroscopic discrimination; when the complexes under consideration have differing spectral properties.

In work described in this Chapter the complexation by the fluoride **11** of the racemates of the 2-phenylpropanoate anions **43a** and **43b** and the corresponding acids **8a** and **8b**, along with the racemates of the Ibuprofen anions **44a** and **44b** and the corresponding acids **37a** and **37b**, was studied. The guests **8a,b** and **43a,b** were chosen because of a previous study by Easton *et al.*,[26] of the complexation of those species by β-cyclodextrin **1**. In that work thermodynamic discrimination was observed between the enantiomers of

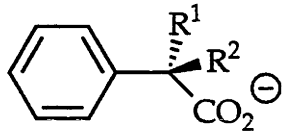
the guest **8a** and **8b** by the cyclodextrin **1**, using potentiometric titration techniques.



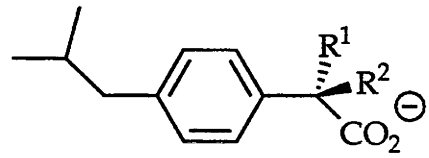
**8a** $R^1 = H, R^2 = CH_3$
**8b** $R^1 = CH_3, R^2 = H$



**37a** $R^1 = H, R^2 = CH_3$
**37b** $R^1 = CH_3, R^2 = H$



**43a** $R^1 = H, R^2 = CH_3$
**43b** $R^1 = CH_3, R^2 = H$



**44a** $R^1 = H, R^2 = CH_3$
**44b** $R^1 = CH_3, R^2 = H$

This was accompanied by spectroscopic discrimination, observed as the non-equivalence of signals corresponding to the enantiomeric acids **8a** and **8b** in the $^1H$ NMR spectra of the complexes formed with β-cyclodextrin **1**. However neither spectroscopic nor thermodynamic discrimination was observed between the enantiomers of the corresponding anions **43a** and **43b** by β-cyclodextrin **1** in that study. It was thought that thermodynamic discrimination might be observed in the complexation of the guests **8a** and **8b** by the fluorinated cyclodextrin **11**, particularly in light of the similarities between the cyclodextrins **1** and **11**, as discussed above. For completeness, the interaction of the anions **43a** and **43b** and the fluoride **11** was also studied, with the hope that discrimination might be observed in any complexation present in that system. It was hoped that spectroscopic

discrimination would be observed in the $^{19}F$ NMR signals of the host **11** fluorine substituent in the host-guest systems of this study. The Ibuprofen anions **44a** and **44b** were also chosen for study, and hence too the corresponding acids **37a** and **37b**, because the association constant of the racemate of the former species with β-cyclodextrin 1 is known to be large,[125] and therefore those guests were thought likely to be good candidates for observing complexation by the fluoride **11**, and hence possibly discrimination.

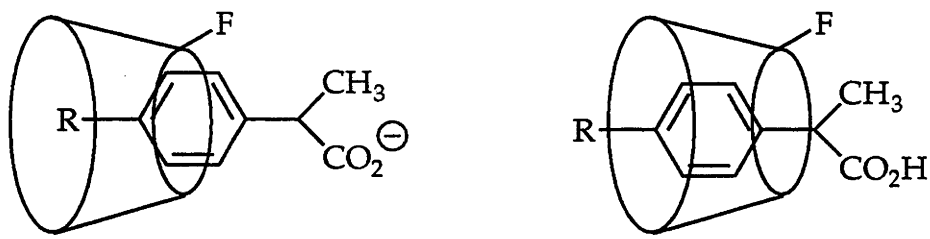
Thus the $^{19}F$ NMR spectra of samples containing the fluoro-cyclodextrin **11** (1.0 mM) and the racemates of the anions **43a,b** or **44a,b** (5.0 mM), at pH 6.0 in phosphate buffered $D_2O$ at 298 K and $I$ = 0.10 mol $dm^{-3}$, were recorded. These samples were then adjusted to pH 1.0 by the addition of 10% DCl / $D_2O$, so that the predominant guest species would be the acids **8a,b** and **37a,b**, and the $^{19}F$ NMR spectra were re-recorded. The spectra so obtained were then inspected for duplication of resonances which would have indicated discrimination between the enantiomers of the guests **8a,b**, **37a,b**, **43a,b** and **44a,b** by the cyclodextrin **11**. Spectroscopic discrimination was not observed in any of the complexes. However, the addition of the racemates of the guests **8a,b**, **37a,b**, **43a,b** and **44a,b** to the cyclodextrin **11** had the effect of causing downfield chemical shift changes of 0.030, 0.204, 0.122 and 0.636 ppm, respectively, in the $^{19}F$ resonance of the fluoro-substituent of the host **11**.

As mentioned above, the study of the complexation of the anions **43a,b** and **44a,b** was conducted at pH 6.0. Formation of inclusion complexes is known to change the $pK_a$s of organic acids.[26,27] Thus, complexation of 2-phenylpropanoic acids **8a** and **8b** by β-cyclodextrin 1 has the effect of raising

the $pK_a$ of the guest species to around 5.5.[26] This is obviously quite near the pH of samples prepared for the study of the complexation of the anionic guests **43a,b** and **44a,b**. The result of an increase in the $pK_a$ of the acid **8a** and **8b** in the presence of the cyclodextrin **11** would of course be for there to be a significant proportion of the protonated species **8a** and **8b** present at pH 6.0. Thus in experiments described above for the study of the effect of complexation of the anion **43a** and **43b** by the fluoro-cyclodextrin **11** it is likely that a significant amount of the acid **8a** and **8b** was present. However, in the event that all of the guest existed in the form of the acid **8a** and **8b**, the contribution of that guest to the observed chemical shift in the presence of the cyclodextrin **11** can only be a maximum of 0.030 ppm. Thus the observed change in chemical shift of 0.122 ppm upon addition of guest in this sample is due in large part to the influence of the anions **43a** and **43b**. By an analogous argument the chemical shift change upon complexation of the Ibuprofen anions **44a** and **44b** was the largest part of the observed shift change of 0.636 ppm in the corresponding system at pH 6.0. This is because the maximum possible contribution to that shift due to the presence of the acids **37a** and **37b** was 0.204 ppm. Any influence of the acids **8a,b** and **37a,b** on the observed chemical shift changes in systems containing the anions **43a,b** and **44a,b** could be effectively eliminated by conducting similar studies at an elevated pH. However, this was deemed unnecessary because it had been clearly demonstrated that the observed chemical shift changes in those systems were largely due to the presence of the anions **43a,b** and **44a,b**. In addition, there was no evidence of spectroscopic discrimination in the $^{19}F$ NMR spectra of any of the complexes discussed above which might justify further study of these systems.

It is interesting to note that the extent of chemical shift change upon complexation ($\Delta\delta$) appears to be dependent upon the nature of the guest. The different magnitudes of the $\Delta\delta$ values for the acid species, the 2-phenylpropanoic acids **8a,b** and Ibuprofen acids **37a,b**, of 0.030 and 0.204 ppm, respectively, appear to be a reflection of the greater lipophilicity of Ibuprofen acids **37a** and **37b** over the phenylpropanoic acids **8a** and **8b**. Similarly, the relative sizes of the $\Delta\delta$ values of 0.122 and 0.636 upon complexation of the guests **43a,b** and **44a,b**, respectively, reflect the greater lipophilicity of the latter species. That is, the more lipophilic guest species is likely to have a greater association with a cyclodextrin and hence have a greater proportion of the complexed form of the guest present (Scheme 1 (Page 3)). This will of course yield greater effects on the average chemical shift change observed in that system. However, greater lipophilicity of guest resulting in greater observed change in chemical shift does not appear to hold for comparison of the anionic species **43a,b** and **44a,b** with their more lipophilic conjugate acids **8a,b** and **37a,b**, respectively. It would appear that there is greater deshielding of the fluoro-substituent of the cyclodextrin **11** by the anion guests **43a,b** and **44a,b**, than by the corresponding acids **8a,b** and **37a,b**. This could well be due to a shallow depth of inclusion of the guests **43a,b** and **44a,b** within the cyclodextrin **11**, which acts to cause significant deshielding of the fluoro-substituent of that host by the aromatic moities of these guests (Figure 1.2, Mode I). This is consistent with work which has shown that complexation of a charged guest species by a cyclodextrin occurs with a shallow depth of inclusion, which minimises hydrophobic interactions between the ionic portion of the guest and the cavity of the cyclodextrin.[1,126] Conversely, it is possible that the uncharged acids **8a,b** and **37a,b** are included more deeply within the cavity of the cyclodextrin **11** than the corresponding anions **43a,b**

and **44a,b** (Figure 1.2, Mode II), with lesser deshielding of the fluoro-substituent of the cyclodextrin **11** in the presence of those guests the result.

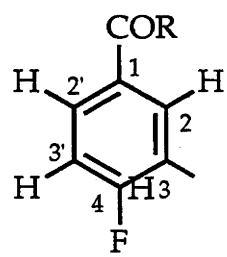



MODE I MODE II

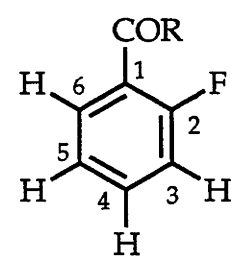
**Figure 1.2.** Possible depths of inclusion of the anions **43a,b** and **44a,b** (Mode I) and the acids **8a,b** and **37a,b** (Mode II) within the cavity of the fluorinated host **11.**

It seems unlikely that thermodynamic discrimination was not occurring in the complexation of the 2-phenylpropanoic acid enantiomers **8a** and **8b** by the fluoro-cyclodextrin **11,** due to the observation of both spectroscopic and thermodynamic discrimination in the corresponding system containing β-cyclodextrin **1** as the host.[26] This suggests that in the present work any thermodynamic discrimination was not accompanied by spectroscopic discrimination observable in the $^{19}F$ NMR spectra. However, despite the lack of spectroscopic discrimination and as mentioned above, significant complexation-induced $^{19}F$ NMR chemical shift changes were observed in the systems under study. Such $^{19}F$ NMR shift changes observed in host-guest complexes of the fluoro-cyclodextrin **11** are likely to be appropriate for monitoring complexation, and therefore calculation of association constants, with other guests.

Despite the limitations of the particular system under study which contained a fluorinated host, the above work confirmed that, as in previous studies,[52,64] host-guest complexation in cyclodextrin systems might be readily monitored using $^{19}F$ NMR spectroscopy. Therefore, complementary to the above work, it was decided to monitor host-guest complexation using an $^{19}F$ NMR technique in which it was the guest species which contained a fluoro-substituent. Further, as outlined in the Introduction to this Thesis, it was thought that charged cyclodextrin species might provide greater possibilities for observing discrimination due to the greater capacity for host-guest interactions compared to native β-cyclodextrin **1**. To that end it was decided to study the complexation of the guests **23** - **26** by β-cyclodextrin **1** and the C-6 and C-3 substituted cyclodextrins **49** and **50**. As well as allowing the monitoring of complexation by $^{19}F$ NMR techniques, it was therefore thought that this study would afford the opportunity to examine the effects of guest and cyclodextrin hydration and charge on the inclusion process. The use of the fluorine substituent for the monitoring of such electronic effects also has the advantage of limiting steric differences between isomers due to the comparable size of the fluorine substituent and hydrogen.

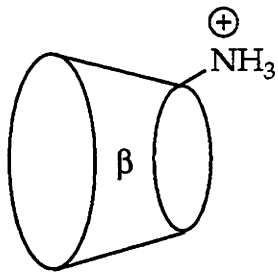



**23** R = $O^{\ominus}$
**25** R = OMe

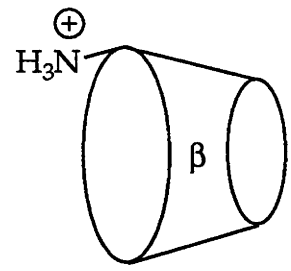



**24** R = $O^{\ominus}$
**26** R = OMe

**Figure 1.3.** Fluorinated species **23** - **26** with atom labels.

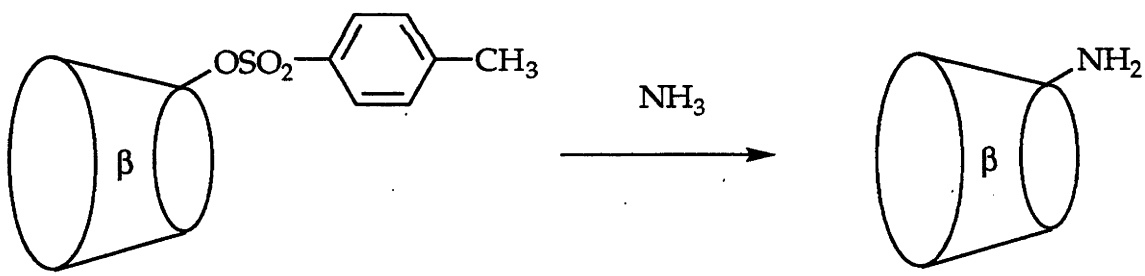



49




50

In order to carry out the work described in this section it was necessary to firstly synthesize the esters **25** and **26** and the amino-cyclodextrin **14**, using the methods described below. The acids **23** and **24** were commercially available[127] and the C-3 amino-substituted cyclodextrin **15** was received as a gift.[128]




17 14

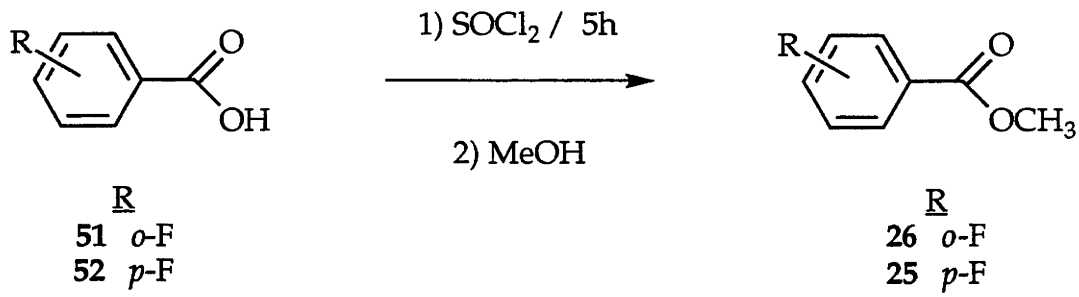
**Scheme 1.2**

Synthesis of the C-6 amino-substituted cyclodextrin **14** was carried out using a modification of the method of Melton and Slessor.[101] This published method describes preparation of the amine **14** *via* reduction of the corresponding azido-cyclodextrin which had been prepared from the corresponding tosylate **17**.[101] In the present work, the cyclodextrin tosylate **17**, prepared as described above, was treated directly with ammonia in *N,N*-

dimethylformamide (DMF) to yield the crude amine **14** (Scheme 1.2).[100] The pure amine **14** was then separated from unreacted tosylate **17** by the application of cation exchange chromatography. A column of Biorex 70™ cation exchange resin was employed to bind the amine **14**, while other cyclodextrin species were removed from the column by washing with water. The column was then eluted with aliquots of ammonia. Fractions recovered bearing the C-6 substituted amine **14** were combined and concentrated to give that material in 56% yield. HPLC analysis of the amine **14** thus obtained showed a single component, which was of greater polarity than β-cyclodextrin **1**, indicating that this compound was pure. Fast atom bombardment mass spectrometric analysis (FAB-MS) of the amine **14** gave a peak at *m/z* 1135 for the protonated molecular ion ($M+H^+$). The proton decoupled $^{13}C$ NMR spectrum of the C-6 amino-substituted cyclodextrin **14** displays a resonance at $\delta_C$ 43.0, corresponding to the C-$6^A$ carbon of the modified glucopyranose unit, and is consistent with the previously recorded data for this compound.[100]

The C-3 amino-substituted cyclodextrin **15**, which was provided by a co-worker,[128] had been synthesized using the procedure developed by Murakami *et al.*[65] In that method the tosylate **19**, prepared by the method of Breslow *et al.*,[102] was converted to the amine **15** *via* the mannoepoxide **20** (Scheme 5 (Page 19)).[65] HPLC analysis of the amino-cyclodextrin **15** showed a single compound, of greater polarity than β-cyclodextrin **1**, indicating that this compound was pure. Other physical and spectral data were consistent with that previously reported.[65]

The methyl ester **26** was prepared by initially converting the acid **51** to the corresponding acid chloride, which was then treated with methanol to give




| R | R |
|---|---|
| **51** *o*-F | **26** *o*-F |
| **52** *p*-F | **25** *p*-F |

**Scheme 1.3**

the crude ester **26** as a yellow oil. Unreacted acid **51** was removed by washing a dichloromethane solution of the crude product mixture with aqueous sodium bicarbonate. The solvent was then removed from the organic fraction and the resultant oil was distilled to give the ester **26** as a colourless clear liquid in 81% yield (Scheme 1.3). The $^{19}F$ NMR spectrum of the ester **26** in $I$ = 0.10 mol $dm^{-3}$ pH 6.0 phosphate buffer showed one peak, at $\delta$ -34.83, for the fluoro substituent. It should be noted that under the conditions of this sample preparation any unreacted acid **51** starting material would be present as the conjugate anion **24**. The $^{19}F$ NMR signal of the fluoro substituent of the anion **24** occurs at $\delta$ -38.87, however this signal was not observed in the $^{19}F$ NMR spectrum of the ester **26**, indicating the absence of starting material in that sample.

Methyl *para*-fluorobenzoate **25** was prepared and purified using the method outlined above for preparation of the ester **26** (Scheme 1.3). The ester **25** was thus obtained as a colourless clear liquid in 89% yield. The $^{19}F$ NMR spectrum of the ester **25** showed one peak, at $\delta$ -28.51, for the fluoro substituent. As above, under the conditions of the NMR sample preparation any unreacted starting material, in this case the acid **52**, would be present as the conjugate anion **23**. The $^{19}F$ NMR signal of the anion **23**

occurs at δ -32.97, however this signal was not present in the $^{19}F$ NMR spectrum of the ester **25**, which, similar to above, indicated the absence of the acid **52**.

Similar to work described above, for study of complexation by the fluoro-cyclodextrin **11**, the present study was undertaken in buffer at pH 6.0. With the complexation of aromatic guests known to elevate the $pK_a$ value of the C-6 substituted amino-cyclodextrin **14**,[26] and with $pK_a$s of 8.7[100] and 7.5,[24] respectively, the conjugate acids **49** and **50** will be the predominant forms of the corresponding modified cyclodextrins **14** and **15** at this pH. Benzoic acid has a $pK_a$ of 4.2,[26,129] which has been shown to rise to 5.1 upon complexation by β-cyclodextrin **1**.[26] The corresponding $pK_a$ of benzoic acid when measured in aqueous sulfuric acid is approximately -7.22.[130] With $pK_a$s measured in aqueous sulfuric acid of -7.60 and -7.30, respectively,[130] the acids **51** and **52** will both have $pK_a$s less than that of benzoic acid in other media. Thus in samples prepared for this study in aqueous pH 6.0 buffer there will be little protonation of the fluorobenzoate anions **23** and **24**, either in the hydrated state or when complexed by cyclodextrins. Although conducting the studies at a higher pH would eliminate the possibility of having acid present, it would also cause deprotonation of the hosts **49** and **50** due to the $pK_a$s of the amines **14** and **15**, as discussed above.

The association constants of the complexes of the guests **23** - **26** with β-cyclodextrin **1**, and the modified cyclodextrins **49** and **50** were determined using the $^{19}F$ NMR spectroscopic technique outlined in the Introduction to this Thesis.[52,61,64] $^{19}F$ NMR spectra of the appropriate guest (0.6 - 1.1 mmol $dm^{-3}$) were recorded in the presence of one of the hosts **1**, **49** or **50**, where the ratio of that chosen host to guest ranged from 0 to 15 mole equivalents.

Samples were recorded at 298 K and $I$ = 0.10 mol $dm^{-3}$, in pH 6.0 phosphate buffer, which contained 10% deuterium oxide ($D_2O$) to provide a locking signal for the NMR spectrometer. In host-guest systems there is a dynamic equilibrium between the complexed and uncomplexed forms of the species present, rendering any observed NMR chemical shift a weighted average of the complexed and uncomplexed forms. Thus the observed $^{19}F$ NMR chemical shift of the guest substituent ($\delta_{obs}$) is determined by that of the species in the absence of cyclodextrin ($\delta_{free}$) and that of a fully complexed guest ($\delta_{complex}$), according to Equation 2. As outlined in the Introduction of this thesis, the formation of an inclusion complex in cyclodextrin chemistry is characterised by the association constant, $K$ (Equation 1 (Page 3)). The NMR shift data, obtained as described above (see Figure 1.4 for data relating to the esters **25** and **26**), was therefore fitted to Equations 1 and 2 by a non-linear regression analysis[131] and association constants were calculated (Table 1.1).[131] Also obtained *via* this method is $\delta_{complex}$, calculated here as the $^{19}F$ chemical shift of the guest substituent at infinite cyclodextrin concentration. This allows ready calculation of the change in chemical shift of the guest substituent upon complexation, $\delta_{free} - \delta_{complex}$ ($\Delta\delta$), an indication of the change in environment experienced by the substituent upon inclusion of the guest into the cavity of the cyclodextrin host (Table 1.1).

$$\delta_{obs} = (\delta_{free}[\text{free guest}] + \delta_{complex}[\text{complex}])/([\text{free guest}] + [\text{complex}]) \qquad 2$$

The association constants of the complexes formed with β-cyclodextrin **1** vary markedly with the identity of the guest. The complexes of the esters **25** and **26**, with association constants of 228 ± 7 and 253 ± 11 $dm^3$ $mol^{-1}$, respectively, are more than four times more stable than those of the corresponding benzoate anions **23** and **24**, with association constants of

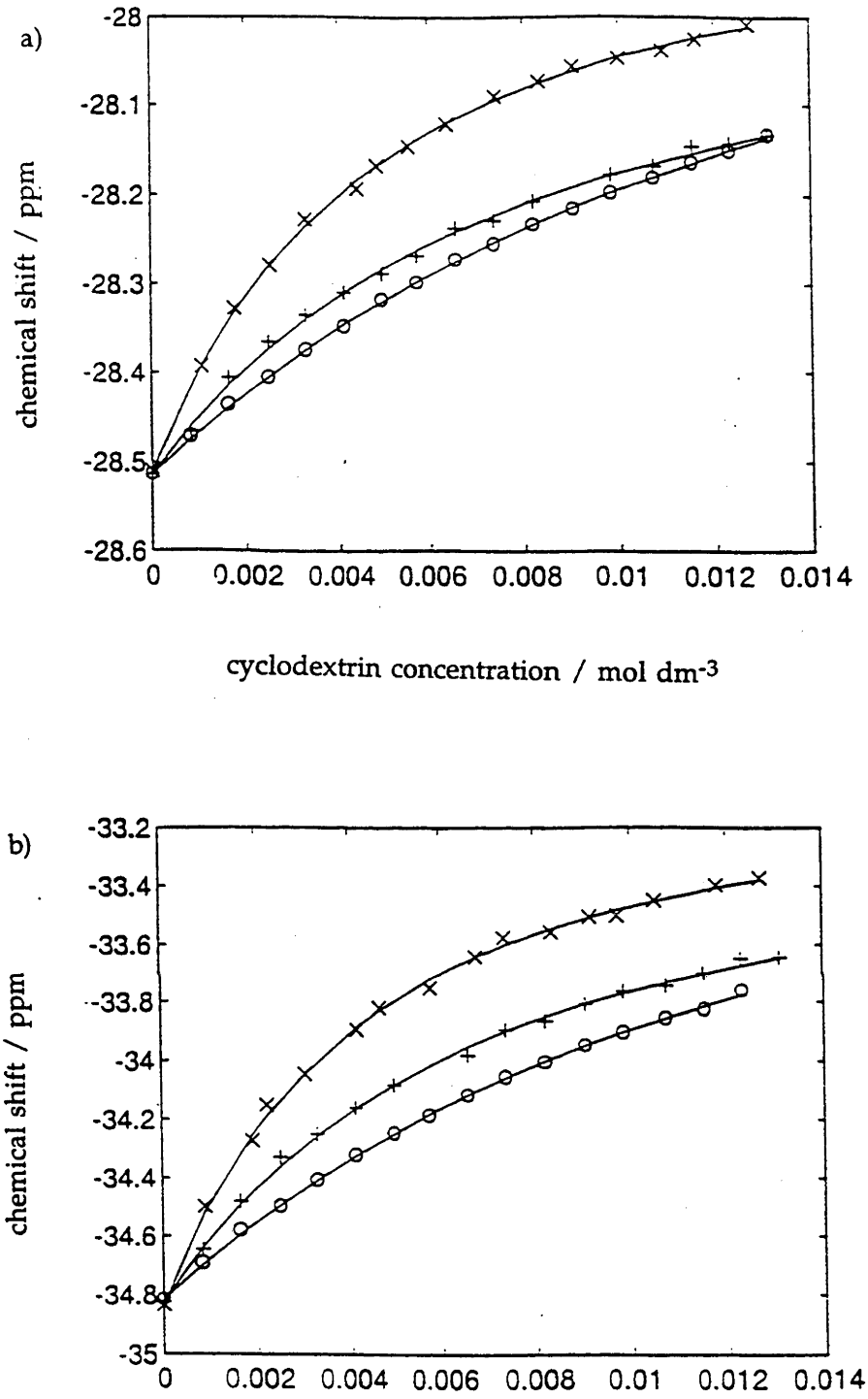



**Figure 1.4.** $^{19}F$ NMR chemical shift for the fluoro substituent of a) methyl *para*-fluorobenzoate **25** (0.76 mmol $dm^{-3}$) and b) methyl *ortho*-fluorobenzoate **26** (0.62 mmol $dm^{-3}$), in the presence of β-cyclodextrin **1** (x), the C-6 substituted cyclodextrin **49** (o) and the C-3 substituted cyclodextrin **50** (+). The solid curves represent the least-squares best fit of the $\delta_{obs}$ to equation 2.

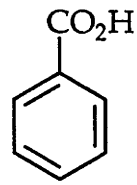
50 ± 2 and 19 ± 3 $dm^3$ $mol^{-1}$, respectively. This suggests that, although van der Waals interactions between the aromatic moieties of each of the guests and
the hydrophobic interior of the cyclodextrin annulus result in complexation, the stronger hydration of the carboxylates destabilises their inclusion complexes. In addition, as mentioned in the Introduction to this Thesis, one of the driving forces of cyclodextrin complexation is the removal of water molecules from the host cavity. Therefore hydrated species such as the anions **23** and **24** are less attractive as guests than the corresponding hydrophobic esters **25** and **26**.

The association constant of 253 ± 11 $dm^3$ $mol^{-1}$ of the complex of the ester **26** with β-cyclodextrin **1** is greater than that of 228 ± 7 $dm^3$ $mol^{-1}$ for the complex of the corresponding *para*-isomer **25**. This may be attributed to the effect of the complementary dipole moments of β-cyclodextrin **1** and the esters **25** and **26** on the inclusion complexes. Inoue and co-workers[132] reported that α-cyclodextrin **2** has a large dipole moment of 13.5 D which is directed from the face containing the primary hydroxyl groups (narrower rim) toward the face containing the secondary hydroxyls (wider rim). It was determined, by consideration of known orientations in the host-guest inclusion complexes of α-cyclodextrin **2** with benzoic acid **53**, *p*-hydroxybenzoic acid **54**[133] and *p*-nitrophenol **55**,[134] along with electrostatic potential maps of α-cyclodextrin **2**,[135] that in those complexes there is an antiparallel alignment of the dipole moments of those guests with the host α-cyclodextrin **2**. The result of this is that in the complexes of the guest **55** and the benzoic acids **53** and **54** with α-cyclodextrin **2** the electron withdrawing nitro and acid groups are oriented such that they are adjacent the primary hydroxyl groups at the narrower rim of the annulus of the

| Cyclodextrin | Guest | $K$ ($dm^3\ mol^{-1}$) | $\delta_{free}$ or $\delta_{complex}$ (ppm) | $\Delta\delta$ (ppm) |
|---|---|---|---|---|
| - | **23** | - | -32.97 | |
| - | **24** | - | -38.87 | |
| - | **25** | - | -28.51 | |
| - | **26** | - | -34.83 | |
| 1 | **23** | 50 ± 2 | - 33.49 ± 0.02 | - 0.52 |
| 1 | **24** | 19 ± 3 | - 36.44 ± 0.30 | + 2.43 |
| 1 | **25** | 228 ± 7 | - 27.83 ± 0.01 | + 0.68 |
| 1 | **26** | 253 ± 11 | - 32.91 ± 0.03 | + 1.92 |
| 49 | **23** | 69 ± 4 | - 33.35 ± 0.02 | - 0.38 |
| 49 | **24** | 65 ± 2 | - 37.29 ± 0.03 | + 1.58 |
| 49 | **25** | 128 ± 7 | - 27.90 ± 0.02 | + 0.61 |
| 49 | **26** | 152 ± 7 | - 33.04 ± 0.04 | + 1.79 |
| 50 | **23** | 19 ± 5 | - 33.72 ± 0.20 | - 0.75 |
| 50 | **24** | 32 ± 3 | - 37.20 ± 0.10 | + 1.67 |
| 50 | **25** | 59 ± 2 | - 27.64 ± 0.01 | + 0.87 |
| 50 | **26** | 69 ± 2 | - 32.52 ± 0.05 | + 2.31 |

**Table 1.1.** Association constants and $^{19}F$ chemical shifts of cyclodextrin-fluorinated guest inclusion complexes, in pH 6.0 phosphate buffered 10% aqueous $D_2O$ at 298 K and $I$ = 0.10 mol $dm^{-3}$.

cyclodextrin **2**. The orientation and magnitude of the dipole moment of β-cyclodextrin **1** is likely to be analogous to that of α-cyclodextrin **2**, and it is probable that the fluorinated esters **25** and **26** used in this study will align their dipoles antiparallel to that of β-cyclodextrin **1** in the complexes of those



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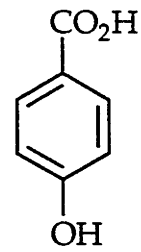

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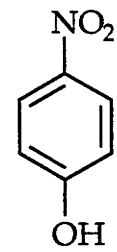

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species, with this alignment contributing to the extent of association in the corresponding complexes. As the dipole moment of the *ortho*-substituted ester **26** is greater than that of the corresponding *para*-substituted isomer **25**, the complex of the former with β-cyclodextrin **1** had the higher association constant.

Complementary to work discussed above, it was thought that more direct evidence that the inclusion of the guests **23** and **25** into the cavity of β-cyclodextrin **1** occurs with an antiparallel alignment of the cyclodextrin and guest dipole moments, such that the carboxy groups of the guests are held at the face of the host cyclodextrin annulus containing the primary hydroxyl groups, was likely to be obtained by the use of 2D NMR techniques. To this end, ROESY spectra[11,47,54,56,59,60] were employed to investigate proximity effects, and hence probe the direction of orientation, in the host-guest complexes of those species. The *para*-fluorobenzoate anion **23** and the corresponding methyl ester **25** were chosen as guests for this 2D NMR study due to the simplicity of their 1D $^1$H NMR spectra, arising as a consequence of the symmetry of those species. Degassed samples were prepared containing the appropriate guest (5.0 mmolar) and β-cyclodextrin **1** (12.5 mmolar) and the ROESY spectra of those samples were recorded at 298 K and $I$ = 0.10 mol

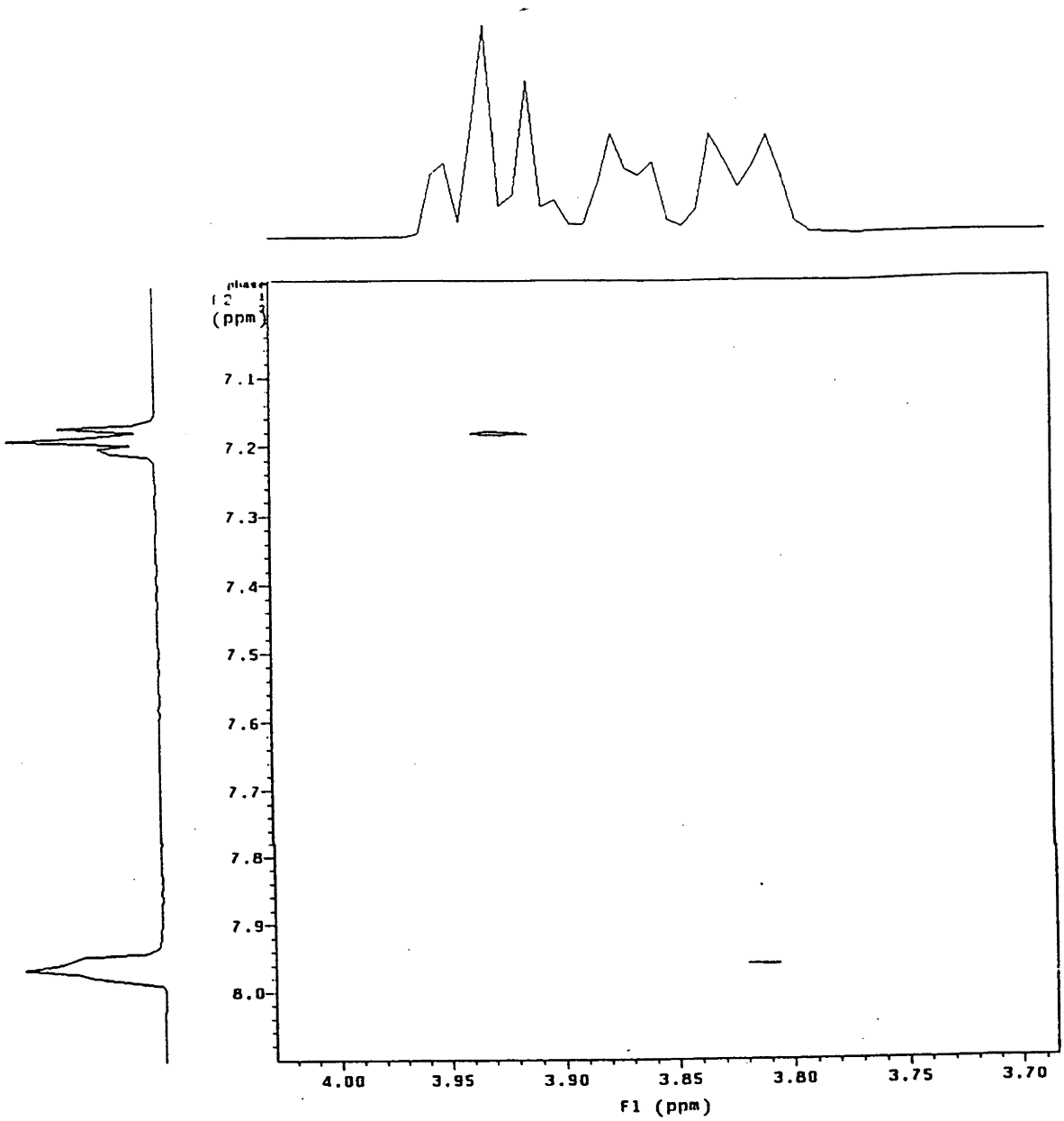



**Figure 1.5.** Partial 2D ROESY NMR spectrum of the complex of the anion **23** and β-cyclodextrin **1**.

$dm^{-3}$ in pH 6.0 phosphate buffered $D_2O$. The ROESY spectrum of the mixture of the anion **23** and β-cyclodextrin **1** shows connectivities (cross peaks) between resonances corresponding to both the H-2 and H-3 protons of the anion **23** and β-cyclodextrin **1** internal annulus proton resonances,

which confirmed the presence of the host-guest complex (Figure 1.5). The guest **23** H-2 proton resonance at δ 7.96[136] has a distinct cross-peak to the cyclodextrin signal at δ 3.81, which corresponds to the overlapping H-5 and H-6 cyclodextrin resonances. This is combined with the presence of a cross-peak between the guest **23** H-3-proton resonance at δ 7.18 and the cyclodextrin H-3 proton resonance at δ 3.93. The clear indication of this experiment is confirmation of the expected orientation of the guest **23** within the cyclodextrin cavity, such that the carboxylate group is in close proximity to the primary hydroxyl groups of the cyclodextrin **1** and the fluoro-substituent is adjacent the cyclodextrin secondary hydroxyl groups (Figure 1.6). This confirmed the hypothesised orientation of the anion **23** within the host-guest complex such that there is antiparallel alignment of the cyclodextrin and guest dipole moments.

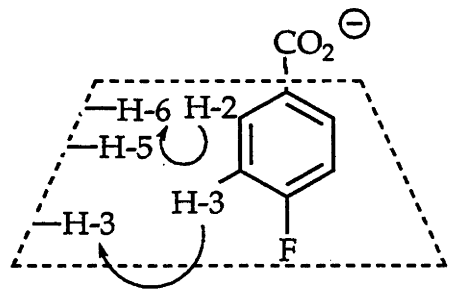



**Figure 1.6.** Geometry of the complex of the anion **23** and β-cyclodextrin **1**, with observed ROESY connectivities indicated.

The ROESY spectrum of the mixture of the ester **25** and β-cyclodextrin **1** shows connectivities between resonances corresponding to both the H-2 and H-3 protons of the ester **25** and β-cyclodextrin **1** internal annulus proton resonances, which once again confirmed the presence of the host-guest complex (Figure 1.7). An apparent connectivity seeming to originate from the resonance at δ 3.91 and giving a cross-peak to a vacant section of the

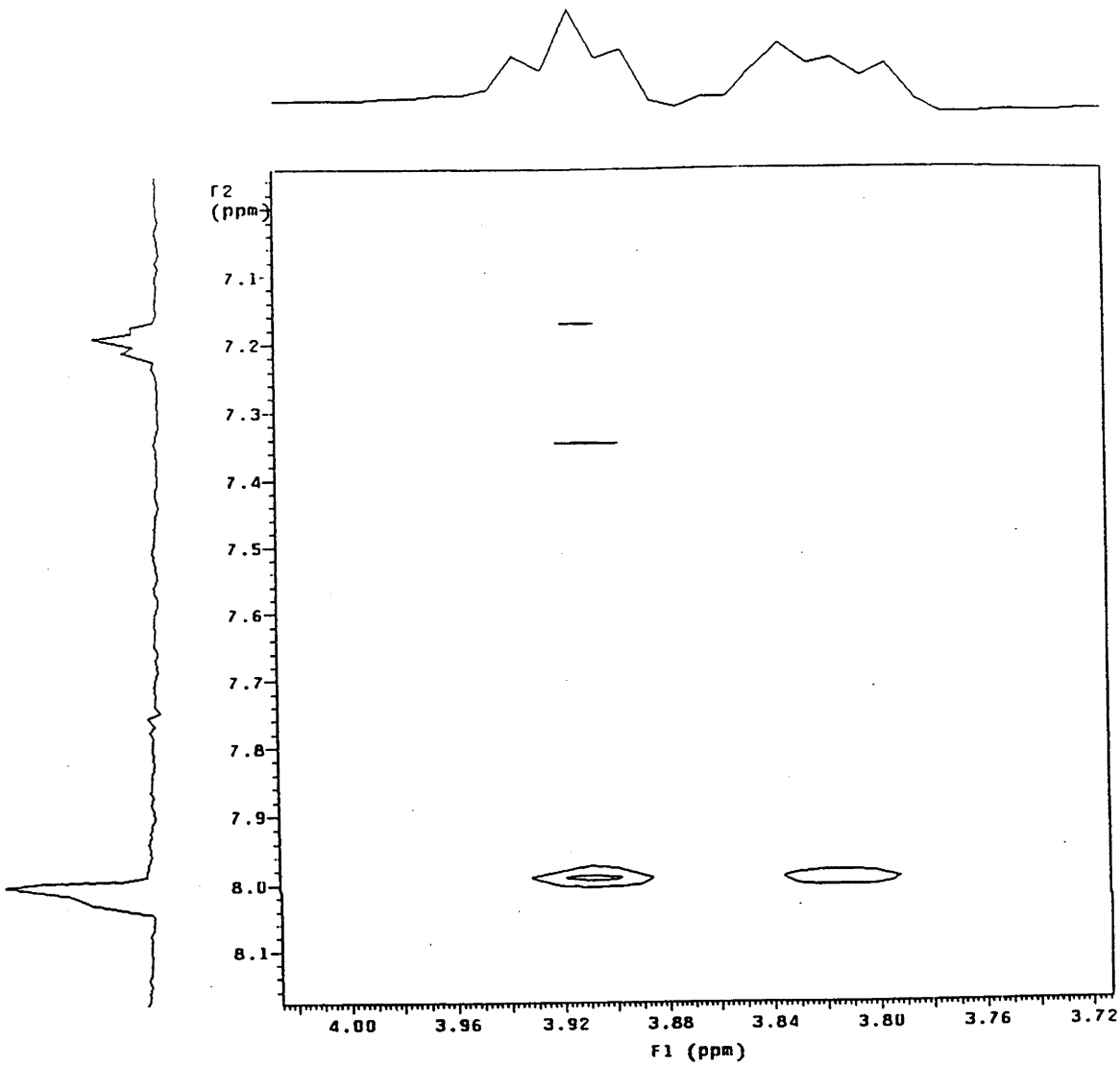



**Figure 1.7.** Partial 2D ROESY NMR spectrum of the complex of the ester **25** and β-cyclodextrin **1.**

$^1$H NMR spectrum at around δ 7.36 is a small fragment of a large line of spectral interference. Much more significantly, the guest **25** H-2 proton resonance at δ 8.01 has a distinct connectivity with the overlapping cyclodextrin H-5 and H-6 signals at δ 3.82. This, combined with a very strong connectivity between the guest **25** H-2 proton resonance at δ 8.01 and the

cyclodextrin H-3 proton resonance at δ 3.91, suggested a deep inclusion of the guest **25** into the cyclodextrin cavity such that the guest H-2 protons are held between the cyclodextrin H-3 and H-5 proton resonances in close proximity to both of those nuclei (Figure 1.8). These connectivities were combined with the presence of a weak cross-peak between the guest **25** H-3 resonance at δ 7.19 and the cyclodextrin H-3 proton resonance at δ 3.91. This confirmed the proposed orientation of the guest **25** within β-cyclodextrin **1**, as discussed above, which has the methoxycarbonyl group of the ester **25** held in close proximity to the primary hydroxyl groups of the cyclodextrin **1**. Once again this is consistent with the antiparallel alignment of the cyclodextrin and guest dipoles in the inclusion complex.

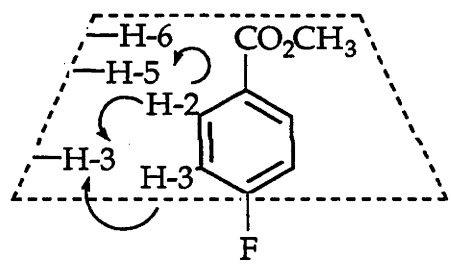



**Figure 1.8.** Geometry of the complex of the ester **25** and β-cyclodextrin **1**, with ROESY connectivities indicated.

The contribution of the dipole moment of the guest to the extent of association constants of the complexes of the esters **25** and **26** with the cyclodextrins **49** and **50**. Methyl *ortho*-fluorobenzoate **26**, with association constants of 152 ± 7 and 69 ± 2 $dm^3$ $mol^{-1}$ with the modified cyclodextrins **49** and **50**, respectively, clearly forms more stable complexes with each of the hosts, than the corresponding *para*-isomer **25**, with corresponding association constants of 128 ± 7 and 59 ± 2 $dm^3$ $mol^{-1}$, respectively. The

greater stability of complexes of methyl *ortho*-fluorobenzoate **26** over those of the corresponding *para*-isomer **25** is a reflection of the larger dipole moment of the former species. However, the greater dipole moment of the *ortho*-fluorobenzoate anion **24** compared to that of the *para*-isomer **23** is not reflected as a general trend in the association constants of the complexes with β-cyclodextrin **1**, and the cyclodextrins **49** and **50** (Table 1.1), so other factors that are not easily discerned must affect the relative extents of association of these complexes.

Of note are the association constants of the complexes of the anions **23** and **24** with the C-6 substituted cyclodextrin **49** of 69 ± 4 and 65 ± 2 $dm^3\ mol^{-1}$, respectively. These values are larger than the association constants of the corresponding complexes of the anions **23** and **24** with both β-cyclodextrin **1** of 50 ± 2 and 19 ± 3 $dm^3\ mol^{-1}$, respectively, and also the C-3 substituted cyclodextrin **50**, of 19 ± 5 and 32 ± 3 $dm^3\ mol^{-1}$, respectively. The extra stabilization in the former case may be attributed to ionic interactions between the C-6 substituted cyclodextrin **49** and the anions **23** and **24**, which are important only with this host **49**, where interaction between charged groups of the cyclodextrin and the guests is compatible with the antiparallel alignment of the dipole moments of the cyclodextrin and the guests in the inclusion complexes. That is, the antiparallel alignment of the anion guests **23** and **24** acts to hold the negative charge of these benzoates in close proximity to the positive charge of the ammonium substituent in the modified cyclodextrin **49**. This effect, and of course the resultant extra stabilization, is absent in the complexes of those guests **23** and **24** with the host β-cyclodextrin **1**, and is in fact unfavourable in the corresponding complexes with the C-3 substituted cyclodextrin **50**. This is due to the location of the ammonium substituent in that cyclodextrin **50** at the

secondary hydroxyl (wider rim) end of the annulus,[65] and thus any ionic interactions between the positive charge of the ammonium substituent of the cyclodextrin **50** and the guests **23** and **24** would necessitate an unfavourable parallel alignment of the dipole moments of those species.

The complexes of the esters **25** and **26** with the C-6 substituted cyclodextrin **49**, with association constants of 128 ± 7 and 152 ± 7 $dm^3\ mol^{-1}$, respectively, are each less stable than those with β-cyclodextrin **1**, with which those guests have association constants of 228 ± 7 and 253 ± 11, respectively. This may be a reflection of the decreased hydrophobicity of the annulus of the modified cyclodextrin **49**, resulting from the effect of hydration of the protonated amino substituent impinging on the character of the cyclodextrin cavity. The association constants of the complexes of the esters **25** and **26** with the C-3 substituted cyclodextrin **50** of 59 ± 2 and 69 ± 2 $dm^3\ mol^{-1}$, respectively, are even lower than those with the host **49**. The synthesis of the modified cyclodextrin **15** occurs with inversion of stereochemistry at C-2 and C-3 of the modified glucopyranose residue,[65] with the result that the amino substituent intrudes into the cavity of the cyclodextrin, and so too the charged ammonium substituent of the conjugate acid **50**. The consequent hydration of the substituent will decrease the hydrophobicity of the cyclodextrin annulus, to an even greater extent than for the C-6 substituted cyclodextrin **49** and the decreased association of the inclusion complexes of the esters **25** and **26** follows. The complexes of the fluorobenzoate anions **23** and **24** with the cyclodextrins **49** and **50** are each less stable than the corresponding complexes of the esters **25** and **26**. This may be attributed to the effect of hydration of the anions, as discussed above for the complexes of the guests with β-cyclodextrin **1**.

The change in the $^{19}F$ chemical shift of the fluoro substituent upon complexation of each of the guests ($\Delta\delta$) is remarkably independent of the cyclodextrin or of the association constant of the complex. This indicates that the mode of complexation by the modified cyclodextrins **49** and **50** is similar to that of β-cyclodextrin **1**. With each cyclodextrin, complexation results in the $^{19}F$ NMR signals of the *ortho*-substituted anion **24** and the corresponding ester **26** moving downfield by 1.5 - 2.5 ppm, the signal of the *para*-substituted ester **25** moving downfield by 0.6 - 0.9 ppm, and that of the *para*-substituted anion **23** moving upfield by 0.4 - 0.7 ppm. The downfield shifts of the $^{19}F$ NMR signals for the *ortho*-substituted anion **24** and both of the esters **25** and **26** indicate more extensive hydrogen bonding of the fluoro substituents, consistent with their being in close proximity to cyclodextrin hydroxy groups in the inclusion complexes.[64,137] This is likely to involve cyclodextrin primary hydroxy groups in the case of the *ortho*-isomers **24** and **26**, and cyclodextrin secondary hydroxy groups in the case of the *para*-substituted ester **25**, based on the antiparallel alignment of cyclodextrin and guest dipole moments in the inclusion complexes. The upfield shift of the signal for the *para*-substituted benzoate anion **23** indicates that in the complexes of this species the fluoro substituent is imbedded in the hydrophobic cyclodextrin annulus.[64,137] Presumably the depth of penetration of the anions **23** and **24** into the cyclodextrin cavities is less than that of the esters **25** and **26**, due to more extensive hydration of the anions **23** and **24**. This partial inclusion of the *ortho*-substituted anion **24** will maintain the fluoro substituent of that compound in a hydrophilic environment near cyclodextrin hydroxyl groups, while the effect of partial inclusion of the *para*-substituted anion **23** will be to place the fluoro substituent of that compound within the hydrophobic region of the cyclodextrin.

This conclusion is supported by the results of the 2D ROESY NMR experiments outlined above. In the ROESY spectrum of the complex of the ester **25** and β-cyclodextrin **1** (Figure 1.7), the strong connectivity observed between resonances corresponding to the H-2 protons of the ester **25** and the H-3 and H-5 protons of the cyclodextrin **1** indicated a substantial depth of inclusion of that guest into the cyclodextrin cavity (Figure 1.8). In comparison, no connectivity was observed between the resonances corresponding to the H-2 protons of the anion guest **23** and the H-3 protons of β-cyclodextrin **1** in the ROESY spectrum of the complex of those species (Figure 1.5). This indicates the lesser depth of inclusion of the hydrophilic anion guest **23** within the cavity of the cyclodextrin **1**, compared to the corresponding complex of the comparatively lipophilic ester **25** (Figure 1.6). This is consistent with the shallow depth of inclusion of the anion **23**, as suggested above, which places the fluoro-substituent of that guest within the hydrophobic region of the cyclodextrin **1**. This result is also entirely consistent with the proposed lesser inclusion of the anions **43a,b** and **44a,b** within the fluoro-cyclodextrin **11**, compared to the corresponding acids **8a,b** and **37a,b** (Figure 1.2), as outlined above and due to the greater hydration of the former anionic species. Such NMR effects, both experienced by, and caused by the presence of, some aromatic species in close proximity to a cyclodextrin annulus, can provide a great deal of information about that association. This is explored further in subsequent Chapters of this Thesis for both inter- and intra-molecular complexation.

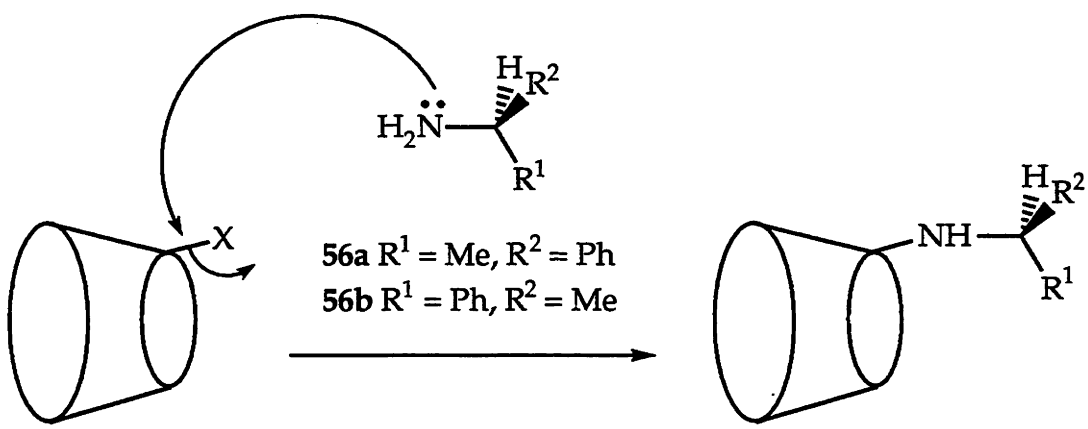
## Results and Discussion Chapter 2

### The Synthesis of a Pair of Diastereomeric Amino-Cyclodextrins

As outlined in the Introduction to this Thesis it was envisaged that studies would be undertaken to investigate factors influencing complexation of selected chiral aromatic guests by modified cyclodextrins. Chiefly it was decided to probe the potential for complementary discrimination in the complexation of chiral guests by modified cyclodextrins. That is, where there is discrimination upon the complexation of a chiral guest by a modified cyclodextrin bearing a chiral substituent, it was thought likely that the reversal of chirality of the substituent of the modified cyclodextrin might result in a reversal of the selectivity of the discrimination observed. In addition, it was apparent from work described in Chapter 1 of the Results and Discussion of this Thesis that ionic interactions between a guest and a charged host can have significant effects on the association of those species. Thus it was deemed necessary for the hosts under study to have the potential to exist in a charged form. To these ends it was therefore decided to synthesize a pair of diastereomeric cyclodextrins, in order to probe the possibility of complementary discrimination, and those cyclodextrins were to contain an amino-substituent in order to provide the potential for charged host species, through protonation of the nitrogen of that substituent.

Thus the modified cyclodextrins **45a** and **45b** were synthesised from the enantiomers of 1-phenylethylamine **56a** and **56b** (Scheme 2.1) and $6^{A}$-deoxy-$6^{A}$-iodo-β-cyclodextrin **31**, which was obtained from $6^{A}$-O-(4-methylphenylsulfonyl)-β-cyclodextrin **17**. As mentioned in the previous

Chapter, the tosylate **17** was obtained by treatment of β-cyclodextrin **1** with tosyl chloride **16** in pyridine.[101] Treatment of the tosylate **17** with excess sodium iodide in water gave the iodide **31**.[101] Thus a solution of the tosylate **17** in water containing a large excess of sodium iodide was heated at reflux for 3 h, then it was cooled and the solvent was removed to yield a crude product. Analysis of that material using HPLC showed that it contained a small amount of β-cyclodextrin **1**. This contaminant was removed by dissolving the crude product in water and adding tetrachloroethylene, with which the iodide **31** preferentially forms an insoluble complex. The resultant precipitate was collected and the complexed tetrachloroethylene was removed by heating an aqueous suspension of the collected solid on a steam bath, such that the tetrachloroethylene is distilled off as an azeotrope with water. Repeating the treatment with tetrachloroethylene liberated the pure iodide **31** in 56% yield. The iodide **31** showed physical and spectral data consistent with those previously reported.[101] FAB-MS of the iodide **31** showed a peak at *m/z* 1262




**17** X = OTs
**31** X = I

**45a** $R^1$ = Me, $R^2$ = Ph
**45b** $R^1$ = Ph, $R^2$ = Me

**Scheme 2.1**

corresponding to M + $H^+$. The $^{13}C$ NMR spectrum of the iodide **31** displayed a signal at δ 45.2, characteristic of the C-$6^A$ carbon.

Treatment of the iodide **31** with 2 mole equivalents of each of the amines **56a** and **56b** in *N,N*-dimethylformamide (DMF) yielded the corresponding modified cyclodextrins **45a** and **45b** (Scheme 2.1). Isolation of the crude cyclodextrins **45a** and **45b** was accomplished by trituration of each reaction mixture with acetone and then collection of the material which precipitated. An alternative method of preparation of the cyclodextrins **45a** and **45b** involved treatment of the tosylate **17** with 2 mole equivalents of each of the amines **56a** and **56b** in the presence of 20% sodium iodide in *N*-methylpyrrolidin-2-one (Scheme 2.1).[138] Isolation of the crude cyclodextrins **45a** and **45b** prepared by this method was accomplished by trituration of each reaction mixture with ethanol, and then collecting the precipitated cyclodextrins. Formation of the cyclodextrins **45a** and **45b** quite probably still occurs *via* the iodide **31** in the latter procedure, but it was ultimately adopted as the method of choice due to better recovery of material and hence greater ultimate yield of products. After recovering the crude products, prepared by either of the above methods, the cyclodextrins **45a** and **45b** were purified by column chromatography with Biorex 70™ cation exchange resin, followed by preparative high performance liquid chromatography (HPLC) for characterization.

Thus the *(R)*-1-phenylethylamine-derived cyclodextrin **45a** was isolated as a colourless solid and fully characterized. TLC analysis of the amine **45a** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **45a** gave a signal at *m/z* 1238.5 corresponding to M+$H^+$. High resolution electrospray ionization mass spectrometry (HRESI-

MS) gave a signal measured as *m/z* 1238.4571, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1238.4562 required for $C_{50}H_{80}NO_{34}$. Microanalytical data indicated that the cyclodextrin **45a** was complexed with an average of 3.5 water molecules, which were not removed using conventional drying methods. The proton decoupled $^{13}C$ NMR spectrum of the amine **45a** displayed resonances corresponding to carbons of the substituent of the cyclodextrin at δ 24.7 and 57.0, assigned to the methyl and methine carbons, and several signals in the range δ 126.3 - 128.5 and a single resonance at δ 146.2 assigned to the five tertiary carbons and single quaternary carbon of the aromatic moiety of that substituent, respectively. In addition to these resonances, several signals assigned to cyclodextrin annulus carbons were observed, including a resonance at δ 46.7 assigned to the C-$6^A$ carbon, along with multiple resonances in the range δ 59.8 - 60.2, assigned as corresponding to the C-$6^{B-G}$ carbons.

Similarly, the *(S)*-1-phenylethylamine-derived cyclodextrin **45b** was isolated as a colourless solid and fully characterized. TLC analysis of the amine **45b** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **45b** gave a signal at *m/z* 1238.5 corresponding to $M+H^+$ and one at *m/z* 1260.4 for the molecular ion plus sodium ($M+Na^+$). HRESI-MS gave a signal measured as *m/z* 1238.4588, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1238.4562 required for $C_{50}H_{80}NO_{34}$. Microanalytical data indicated that the cyclodextrin **45b** was complexed with an average of 8 water molecules. The proton decoupled $^{13}C$ NMR spectrum of the amine **45b** displayed resonances corresponding to carbons of the substituent of the cyclodextrin at δ 25.1 and 57.6, assigned to the methyl and methine carbons, and several signals in the range δ 126.3 - 128.3 and a single resonance at δ 146.3 assigned to the five tertiary carbons

and single quaternary carbon of the aromatic moiety of that substituent, respectively. In addition to these resonances, several signals assigned to the cyclodextrin **45b** annulus carbons were observed, including a resonance at δ 47.7, assigned to the C-$6^{A}$ carbon, along with multiple resonances in the range δ 59.0 - 59.9, assigned as corresponding to the C-$6^{B-G}$ carbons.

The diastereomers **45a** and **45b** were found to have very distinct HPLC retention times. For an eluent of 70% acetonitrile/water, with a Waters Carbohydrate Analysis column, the retention times of the *(R)*- and *(S)*-1-phenylethylamine-derived cyclodextrins **45a** and **45b** were 0.72 and 0.60, respectively, relative to β-cyclodextrin **1**. By way of comparison, the retention time of the cyclodextrin tosylate **17** was 0.5 relative to β-cyclodextrin **1**. This suggests that the presence of an aromatic ring in the tosylate **17**, and therefore exposure of that aromatic moiety to the HPLC running solvent, resulted in a shorter retention time than that of β-cyclodextrin **1** which has no such aromatic character. The corollary to that conclusion is that the cyclodextrin **45b** with a shorter retention time than the diastereomer **45a** exposes a greater amount of aromatic character to the HPLC running solvent, probably indicating a greater extent of association of the aromatic moiety of the latter species **45a** with it's annulus. This possibility will be discussed later in this Chapter.

Due to their structural similarities, there are other properties of the cyclodextrins **45a** and **45b** which are quite similar. For example, in neat $D_2O$ and at 298 K the $^{1}H$ NMR spectrum of the amine **45a** exhibits a doublet at δ 1.62, corresponding to the methyl group of the phenylethylamino substituent. This signal exactly overlaps the resonance due to the corresponding methyl group of the diastereomer **45b** in the $^{1}H$ NMR spectrum of a mixture of the isomers measured at 298 K. However, it was

found that in the $^1$H NMR spectra of an identical sample recorded at elevated temperatures, these methyl signals were no longer coincident. This resulted in those resonances being essentially baseline-resolved in the $^1$H NMR spectrum of a mixture of the cyclodextrins **45a** and **45b** recorded at 350K (Figure 2.1). Thus it was found that the relative abundance of the cyclodextrins **45a** and **45b** in a mixture could readily be estimated from the $^1$H NMR spectrum of that mixture, measured at 350 K.

In preliminary studies, when prepared from reaction of the iodide **31** and the amines **56a** and **56b** in DMF, the cyclodextrins **45a** and **45b** were isolated in yields of around 40% and only 2%, respectively. These relative yields of the cyclodextrin derivatives **45a** and **45b**, from experiments carried out under identical conditions, indicated an enantioselectivity in the reaction of the 1-phenylethylamine enantiomers **56a** and **56b** with the iodide **31**. To examine this stereoselectivity in more detail, the iodo-cyclodextrin **31** was treated with various mixtures of the amine enantiomers **56a** and **56b**.

Thus, when a competitive reaction was performed in which a sample of the iodide **31** was allowed to react in the presence of 1 mole equivalent of each of the amines **56a** and **56b**, only the cyclodextrin derivative **45a**, of the *(R)*-amine **56a**, was detected by HPLC analysis of the product mixture. The selectivity of this reaction was confirmed when $^1$H NMR spectroscopic analysis of the product mixture at 350 K, as outlined above, also failed to indicate the presence of any of the cyclodextrin **45b**, derived from the *(S)*-amine **56b**. When the crude iodide **31**, the *(R)*-amine **56a** and the *(S)*-amine **56b** were mixed in a 1 : 1 : 100 molar ratio, the cyclodextrin derivatives **45a** and **45b** were found by $^1$H NMR analysis to have been produced in the ratio 1.6 : 1. On this basis, the apparent enantioselectivity displayed in the

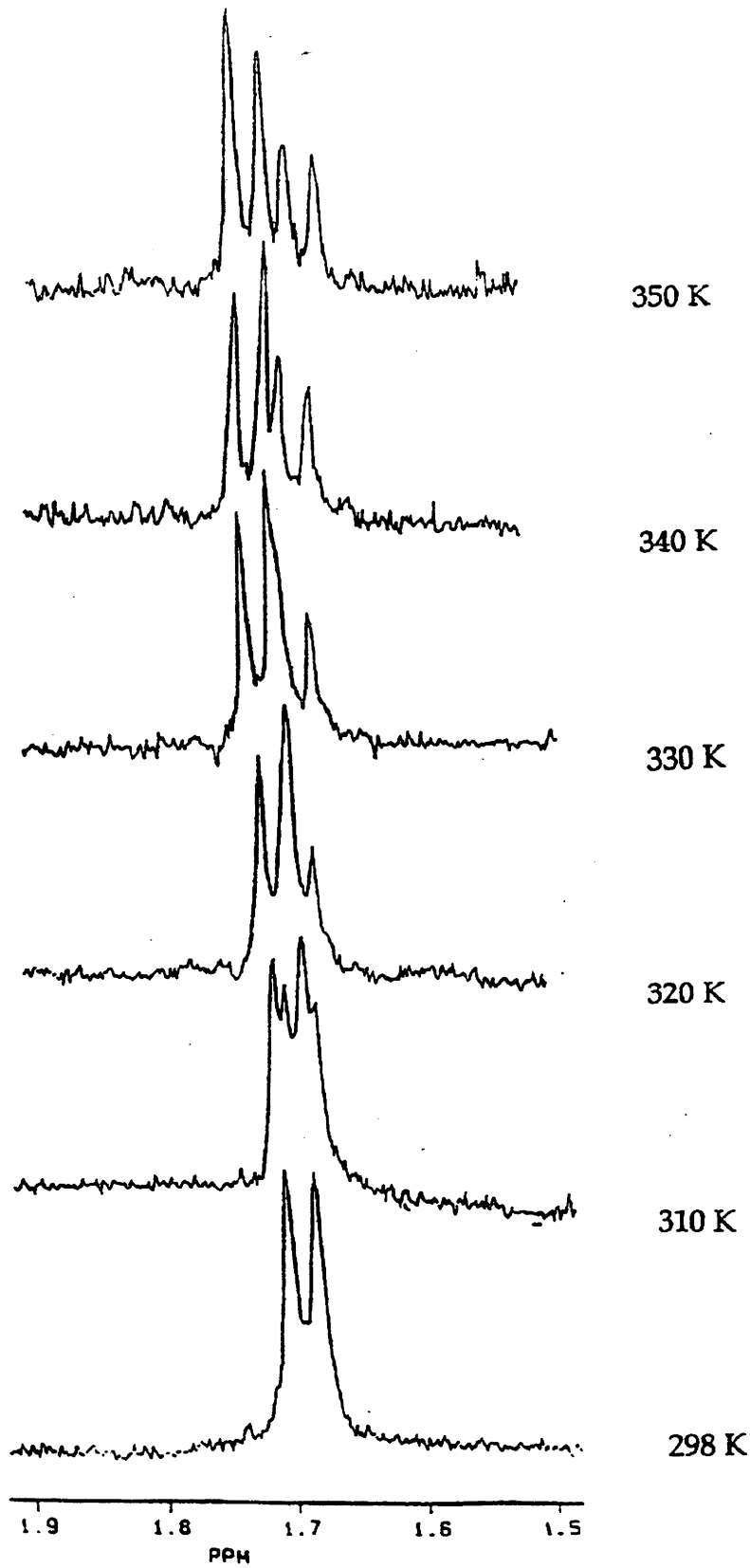



**Figure 2.1.** Partial $^1$H NMR spectra of a 2:1 mixture of the cyclodextrins **45a** and **45b** with increasing temperature.

reaction of the iodide **31** with the 1-phenylethylamine enantiomers **56a** and **56b** was determined to be a factor of one hundred and sixty, significantly larger than previously reported selectivities for covalent attachment of enantiomers to cyclodextrins.[120,121,139]

In order to confirm the resultant kinetic resolution of the amines **56a** and **56b** upon reaction with the iodide **31**, a study of the unreacted amine components of such reaction mixtures was conducted. Thus one mole equivalent each of *(R)*- and *(S)*-1-phenylethylamine **56a** and **56b** was treated with one equivalent of the iodide **31**, a reaction mixture from which any unreacted 1-phenylethylamines **56a** and **56b** were recovered. This mixture of unreacted amines **56a** and **56b** was then stirred with the acid chloride of *(S)*-2-phenylpropanoic acid **8b** to yield a mixture of diastereomeric amides. Analysis of the mixture using HPLC showed the product amides to be present in a 4.6 : 1 ratio in favour of the *(S)*-amine-derived diastereomer *N*-((*S*)-α-methylbenzyl)-*(S)*-2-phenylpropanamide), confirming the selective removal of *(R)*-1-phenylethylamine **56b** by the iodide **31**. This selectivity demonstrated an enrichment of a racemic mixture of the amine to one with an enantiomeric excess (ee) of 64% of *(S)*-1-phenylethylamine **56b**. A subsequent reaction with such a mixture yielded products that demonstrated an enrichment of *(S)*-1-phenylethylamine **56b** in that sample to 88% ee.

The reaction of the amines **56a** and **56b** with the iodo-cyclodextrin **31** most likely occurs in two discrete steps. The first step is likely to be the formation of a host-guest complex as in Scheme 1 (Page 3). The second step is of course reaction of the host cyclodextrin with the amine guest once included. In principle the enantioselectivity might derive from either or both of these processes, but the initial results of experiments with mixtures of the 1-

phenylethylamine enantiomers **56a** and **56b** indicated that the stereoselectivity may well originate from the latter process. As the amount of the *(S)*-isomer **56b** in a reaction mixture was increased, the rate of formation of both cyclodextrin products **45a** and **45b** decreased. This indicates that the *(S)*-amine **56b** competed with the *(R)*-enantiomer **56a** for binding with the iodide **31**, but did not react as easily to give product. The implication of this is that the complex containing the *(S)*-1-phenylethylamine **56b** is less reactive than that containing the *(R)*-amine **56a**. However in further experiments to prepare greater quantities of material for complexation studies outlined in this Thesis it was found that the extent of the stereoselectivity was not reproducible and in general was much lower than was at first calculated. It was found that yields of the cyclodextrin **45b** in particular increased dramatically upon the use of stringently purified reagents. Inspection of samples of the iodide **31** used in early reactions to produce the cyclodextrins **45a** and **45b**, showed that material to be contaminated by ethanol.

The yields of the reactions producing the cyclodextrins **45a** and **45b**, in the absence of any possible effects due to the presence of ethanol, are quite different from those in which ethanol is a part of the mixture. Further, and as mentioned above, any selectivity in competitive reactions of the enantiomers **56a** and **56b** with the iodide **31** is minimal. Thus in optimised reactions the purified iodide **31** was treated with *(R)*-1-phenylethylamine **56a** to yield the required product **45a** in 44% yield, with the diastereomer **45b** being produced by the identical procedure from *(S)*-1-phenylethylamine **56b** in 39% yield. Similarly, the cyclodextrins **45a** and **45b** were produced by the alternative method, also outlined above, from the tosylate **17**, sodium iodide and the amines **56a** and **56b** in 56% and 67% yields, respectively.

Reasons for the variations in the enantioselectivity in the reaction of the iodide **31** with the isomers of 1-phenylethylamine **56a** and **56b** and apparent dependence on factors such as concentration and the presence of ethanol are not clear. It is well established that simple aliphatic alcohols can form inclusion complexes with cyclodextrins, and in the presence of some other guest may form ternary complexes.[14-16,112,140-143] An example is found in a study by Hamai *et al.*,[140] of ternary complexes of β-cyclodextrin **1**, alcohols and other guests. That work showed that the presence of *iso*-propanol clearly affected the orientation of azulene in it's complex with the β-cyclodextrin host **1**.

Similarly, the ethanol present as an impurity in certain of the reaction mixtures in the present study was demonstrated to exhibit unusual complexation behaviour with the iodide **31**, particularly in the presence of the amines **56a** and **56b**. The $^1H$ NMR spectrum of a mixture containing ethanol (0.008 mmol $dm^{-3}$) in the presence of an excess of the iodide **31** (0.012 mmol $dm^{-3}$) in $D_2O$, displayed a pair of triplets at around δ1.07 corresponding to the ethanol methyl group, instead of an expected single triplet (Figure 2.2a). The presence of such a second triplet indicates that ethanol exists in two different forms in this mixture, and is exchanging sufficiently slowly on the NMR timescale between those two forms for them to yield discrete signals. These two forms of the ethanol are presumably when it is bound by the iodide **31** and when it is in free solution. The addition of approximately 0.5 equivalents of the *(R)*-amine **56a** to this mixture, with respect to the ethanol concentration, caused the minor of the ethanol triplets to be greatly reduced in area, compared to the major triplet. The major triplet was also effected by the addition of the *(R)*-amine **56**, appearing to begin to resolve into a pair of separate doublets (Figure 2.2c).

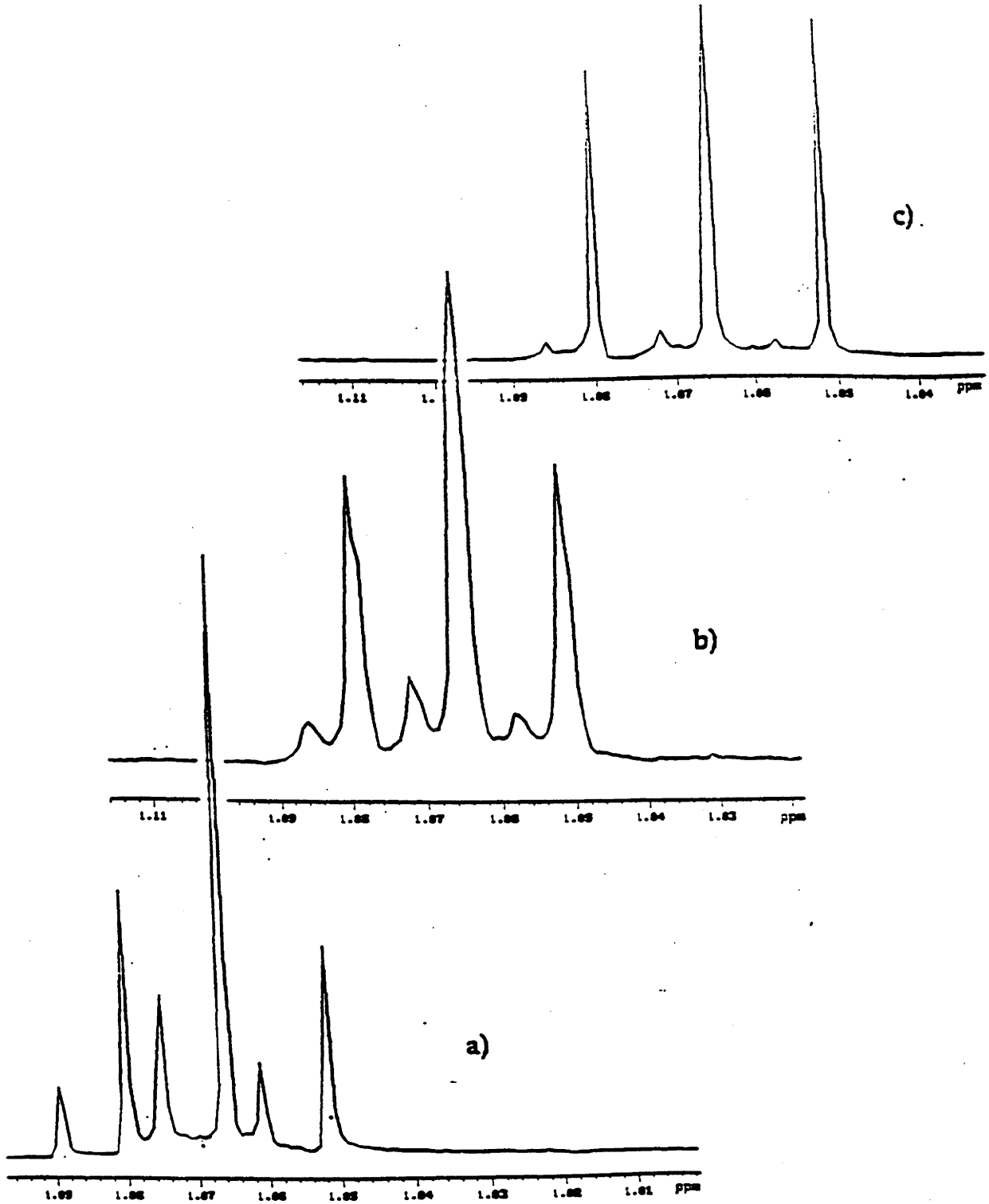


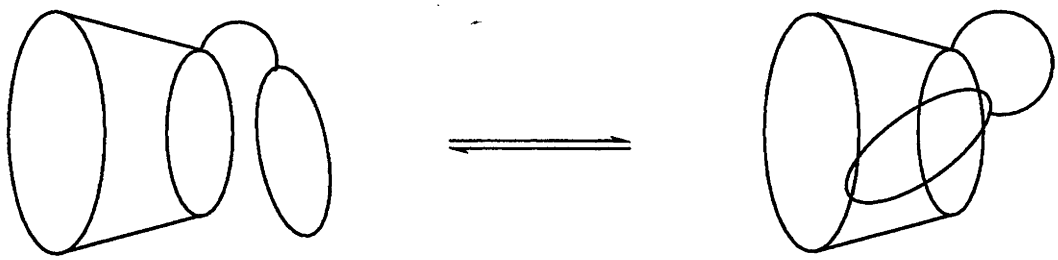

**Figure 2.2.** Partial $^1H$ NMR spectra of ethanol (0.008 mmol $dm^{-3}$) in $D_2O$ in the presence of an excess of the iodide **31** (0.012 mmol $dm^{-3}$) a) in the absence of any amines, b) in the presence of *(S)*-1-phenylethylamine **56b** (0.004 mmol $dm^{-3}$) and c) in the presence of *(R)*-1-phenylethylamine **56a** (0.004 mmol $dm^{-3}$).

This resolution of signals indicates that the adjacent protons, those of the methylene group of ethanol, are non-equivalent and so couple to the resonance of the methyl group as discrete nuclei. A potential reason for this is the formation of a ternary complex involving the *(R)*-amine **56a**, ethanol and the iodide **31** in which the ethanol, and hence it's methylene protons, is tightly bound in one specific conformation. This of course indicates that the major of the ethanol triplets is due to the bound form of ethanol, since ethanol in free solution would not exist with non-equivalent methylene protons. In the $^1$H NMR spectrum of a similar mixture, where 0.5 equivalents of the *(S)*-amine **56b**, with respect to the ethanol concentration, was added in place of the *(R)*-amine **56a**, there was also a decrease in intensity of the minor ethanol signal, although to a lesser extent than in the previous system, but still indicating a change in the ratio of bound to free ethanol (Figure 2.2b). This effect was accompanied by a modification of the major triplet as it exhibited line-broadening and relative intensity changes in the bands of the triplet.

Clearly the ethanol in all of the above mixtures is existing in two forms and the ratio of the bound to free forms of that ethanol in the system is dependent on the presence of the amines **56a** and **56b**. It was also extremely interesting that the effects of the presence of the *(R)*- and *(S)*-amines **56a** and **56b** are different. This is unambiguous evidence for the presence of ternary complexes in the amine-containing systems, complexes which differ substantially in character. As in the above mentioned work[140] this difference in character may well be due to different orientations of the amines **56a** and **56b** in their respective complexes with the iodide **31** and ethanol.

Tee and coworkers[15,16,112,144] have shown in several studies that the presence of aliphatic alcohols can retard the cleavage of *m*-nitrophenyl acetate by a series of cyclodextrins, but does not inhibit reaction of *p*-nitrophenyl acetate, and in some cases can increase the rate of reaction of that isomer up to 100-fold. It is clear from that work that orientation differences between the isomers of a guest, in their respective ternary complexes with a cyclodextrin host and an alcohol, can have profound effects on the relative rates of a subsequent reaction. The effect of formation of ternary complexes in reaction mixtures in the present study containing the iodide **31**, 1-phenylethylamine **56** and ethanol is unclear, but orientation of the guest amine **56** may be an important factor. Clearly if one isomer of the amine **56** forms a complex with a more favourable orientation for reaction than that of it's enantiomer then that former species will react at a greater rate than the latter, with selective product formation the result.

Despite the above discussion it is also possible that variable selectivities observed in reaction of the amines **56a** and **56b** with the iodide **31**, in the presence of ethanol, do simply relate to the association of guest species with the cyclodextrin **31**. The association of the isomers of 1-phenylethylamine **56a** and **56b** may be affected by the presence of ethanol, in similar fashion to work which has shown that the presence of alcohols in cyclodextrin systems can effect the association constants of aromatic guests.[143] Any differences in association constants of the isomers **56a** and **56b** with the iodide **31** in the presence of ethanol may well be reflected in differing observed rates of reaction in the resultant ternary complexes, and hence a selectivity for one of the products **45a** and **45b** would be observed.



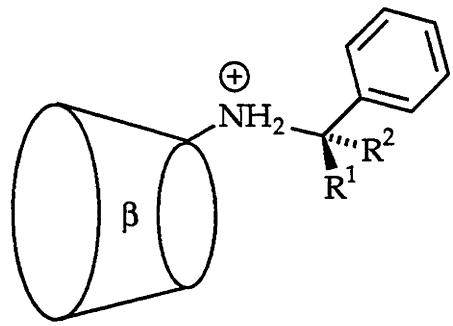
**Scheme 2.2**

As outlined in the Introduction to this Thesis, for modified cyclodextrins bearing a suitable substituent there exists the possibility of intra-molecular complex formation. Such intra-molecular association is an equilibrium, similar to the association of a guest in an inter-molecular complex in a manner discussed in the Introduction to this Thesis. One extreme of this equilibrium is the self-inclusion of a substituent, or a portion of the substituent such as an aromatic moiety, into the cavity of the cyclodextrin, or possibly capping the cyclodextrin, where the substituent moiety projects into or across the cyclodextrin cavity.[49,74-76,105,108,123] This configuration may of course preclude the possibility of any inter-molecular complex formation.[74,75,82] The other extreme that is possible in this equilibrium is the excluded form where the substituent is projected out of the cyclodextrin cavity, a geometry which of course has no such hindrance to the inter-molecular complexation of a guest. As explained in the Introduction to this Thesis, a large extent of intra-molecular association, or predominance of the self-included or capped form of the cyclodextrin, may be reflected in a greater degree of non-equivalence of resonances corresponding to cyclodextrin annulus protons in the $^1$H NMR spectrum of that species, compared to that of the unmodified β-cyclodextrin **1**.[49,105,108] Conversely, for modified cyclodextrins with a lesser extent of intra-molecular association, in which

the previously mentioned equilibrium lies in favour of the conformer in which the cyclodextrin cavity is vacant, or not capped, this may also be reflected in the $^1$H NMR spectrum of this species. Of course this is manifest as a relatively lesser degree of non-equivalence of resonances corresponding to the cyclodextrin annulus protons.

Having synthesized the modified cyclodextrins **45a** and **45b** and investigated some of their properties it was apparent that there were some significant differences between the diastereomers. Most notable were the differences between the HPLC retention times of those species, as outlined above, of which one possible explanation is that the aromatic moieties of the cyclodextrins **45a** and **45b** are self-included, and that the extents of self-inclusion are not identical. However, the cyclodextrins **45a** and **45b** are amines, and as explained above and in the Introduction to this Thesis it was envisaged that charged cyclodextrins would be employed in order to maximise the potential for ionic interactions with certain guests. Thus it was decided that all studies were to be undertaken in pH 6.0 phosphate buffered aqueous media because, by analogy with those of the amino-cyclodextrins **14** and **15**,[24,100] the $pK_a$s of the cyclodextrins **45a** and **45b** are likely to be such that the predominant form of those species at this pH will be the corresponding conjugate acids **57a** and **57b**. Thus the properties of the 1-phenylethylamine-derived cyclodextrins **57a** and **57b** were investigated, considering the potential for intra-molecular complexation in both of those species, with a view to investigating possible differences between the diastereomers **57a** and **57b**.

The $^1$H NMR spectra of the cyclodextrins **57a** and **57b** were both consistent with the attachment of a substituent bearing an aromatic moiety to a




**57a** $R^1$=$CH_3$, $R^2$=H
**57b** $R^1$=H, $R^2$=$CH_3$

cyclodextrin annulus, such that this substituent both experienced environmental changes brought about by that covalent attachment and also caused corresponding changes to the magnetic environment of the cyclodextrin annulus. These effects are evident upon comparison of the chemical shifts of the resonances corresponding to the aromatic protons of the cyclodextrins **57a** and **57b** with those of the unreacted 1-phenylethylamine **56** starting material in the 500 MHz $^1$H NMR spectra of those species. The aromatic signals of the free amine **56** appear as a narrow multiplet at δ 7.488 spanning approximately 0.04 ppm. This contrasts significantly with the appearance of the aromatic resonances of the *(S)*-amine-derived cyclodextrin **57b** which exhibit reasonably well defined signals spanning 0.073 ppm, namely resonances corresponding to the two *meta*-protons at δ 7.526 , the single *para*-proton at δ 7.511 and a two proton doublet at δ 7.467 corresponding to the *ortho*-protons. Also different to that of the amine **56**, are the aromatic signals in the $^1$H NMR spectrum of the *(R)*-amine-derived cyclodextrin **57a** which exhibit very well defined resonances spanning 0.131 ppm, namely those corresponding to the two *meta*-protons at δ 7.560, the single *para*-proton at δ 7.529 and also a two

proton doublet at δ 7.443, corresponding to the *ortho*-protons. This indicates clear and large differences between the magnetic environment of the aromatic protons of the cyclodextrins **57a** and **57b** and that of the free amine **56**. The obvious implication of a substantial change in environment of an aromatic ring upon covalent attachment to a cyclodextrin is the likely inclusion of that aromatic moiety in the cavity of the cyclodextrin, or potentially the capping of the cavity by that aromatic moiety.

The effects of intra-molecular association in the diastereomers **57a** and **57b**, either as self-inclusion of the aromatic ring of the amine side chain or possibly as capping, are also apparent upon inspection of the resonances corresponding to the protons of the cyclodextrin annulus in the $^1$H NMR spectra of those species. Intra-molecular complex formation in the modified cyclodextrins **57a** and **57b** causes the H-1 protons of the cyclodextrin (the anomeric protons of the glucopyranose units) to become substantially non-equivalent in comparison to those of native β-cyclodextrin **1**. The $^1$H NMR spectrum of β-cyclodextrin **1** indicates that the H-1 protons of that species are equivalent, with the seven proton doublet corresponding to those protons appearing at δ 5.086. This significantly differs from the $^1$H NMR spectrum of the *(S)*-phenylethylamine-derived cyclodextrin **57b** in which resonances corresponding to the anomeric H-1 protons were shifted both upfield and downfield. Thus in that spectrum the signals appear as a series of resolved doublets (δ 5.115 (d, 1H), 5.098 (d, 1H), 5.072 (d, 1H), 5.062 (d, 2H), 5.033 (d, 1H) and 5.020 (d, 1H)), spanning 0.102 ppm. Signals of the $^1$H NMR spectrum of the *(R)*-amine-derived cyclodextrin **57a** corresponding to H-1 protons are also significantly different to those of native β-cyclodextrin **1**, but also different to those of the diastereomer **57b**. Namely, in the spectrum of the cyclodextrin **57a** the H-1 resonances also appear as a series of well resolved

proton doublet signals (δ 5.161 (d, 1H), 5.129 (d, 3H), 5.038 (d, 1H), 4.983 (d, 1H) and 4.956 (d, 1H)), but spanning 0.211 ppm.

As discussed above and in the Introduction to this Thesis, work by Gelb *et al.*,[43] suggests that the C-1 position of the cyclodextrin annulus is screened from experiencing anisotropic effects caused by inclusion of species into the cyclodextrin cavity. Thus the magnetic non-equivalence of the H-1 protons of the cyclodextrins **57a** and **57b** compared to β-cyclodextrin **1** is likely to be caused chiefly by conformation differences between those modified cyclodextrins and the unmodified β-cyclodextrin **1**. This is consistent with extra ring strain in the modified cyclodextrin species as a result of accommodating geometries that allow self-inclusion of the aromatic moiety of their substituents, or perhaps capping of the cyclodextrin cavity by those substituents.

Further inspection of the $^1$H NMR spectra of the two modified cyclodextrin diastereomers **57a** and **57b** showed significant differences between those spectra in the region δ 2.7 - 4.2. Particularly striking are the differences between the spectra of β-cyclodextrin **1** and the modified cyclodextrin **57a** (Figure 2.3). Significantly the spectrum of β-cyclodextrin **1** shows resonances indicating that the seven glucopyranose units are completely equivalent. These resonances, corresponding to individual sets of equivalent protons, are also reasonably well resolved from each other and are readily assignable to individual protons within the glucopyranose structure (Figure 2.3). The $^1$H NMR spectrum of β-cyclodextrin **1** also contains no resonances upfield of δ 3.50. However, the $^1$H NMR spectra of both of the modified cyclodextrins **57a** and **57b** contain resonances upfield of δ 3.50, due to shielding of the cyclodextrin annulus protons by the presence of an aromatic ring in close

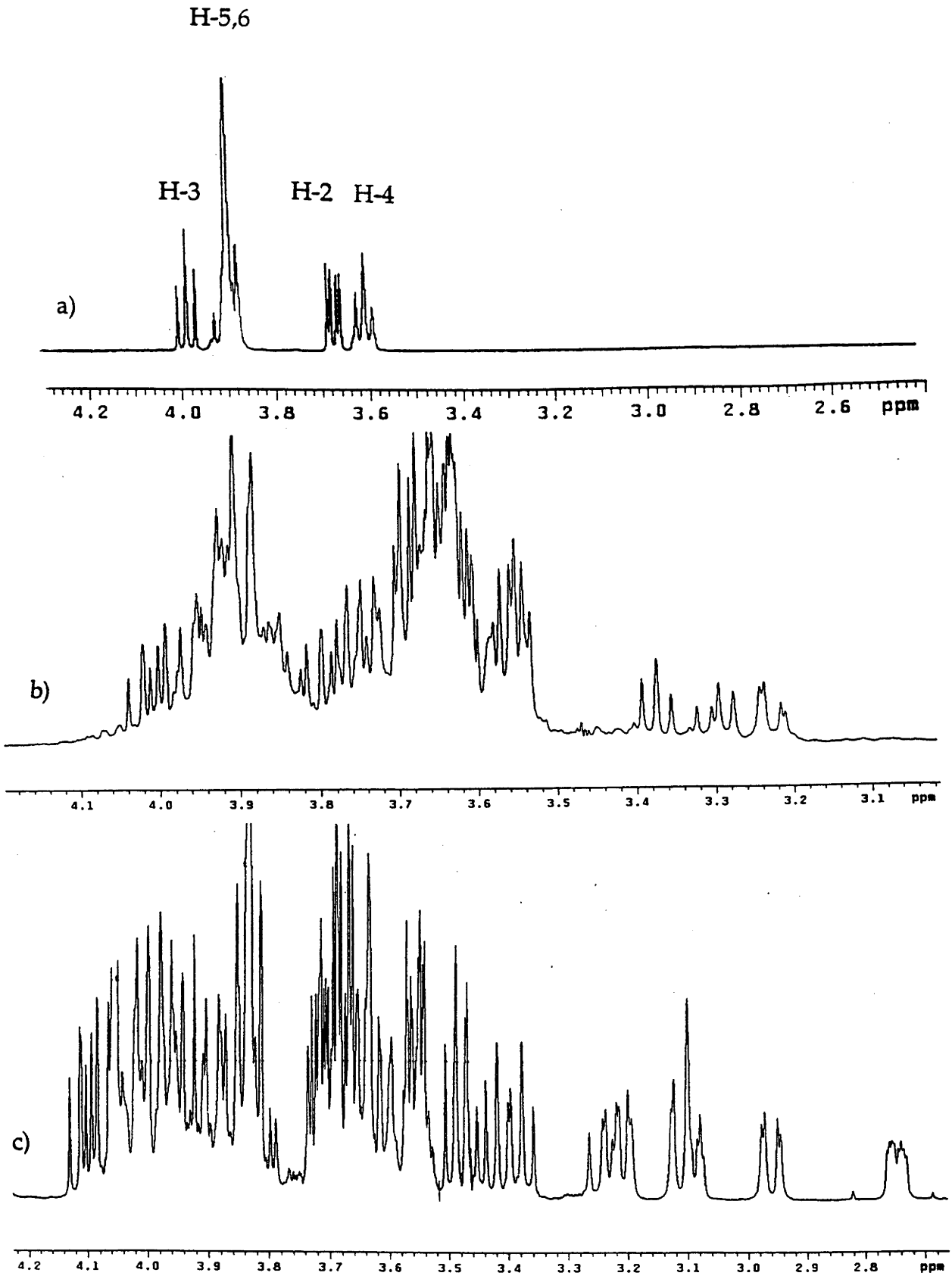



**Figure 2.3.** Partial $^1$H NMR spectra of a) β-cyclodextrin **1**, b) the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** and c) the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**.

proximity. It is clear that the greatest shielding of the cyclodextrin annulus protons takes place in the *(R)*-phenylethylamine-derived cyclodextrin **57a**. The $^1H$ NMR spectrum of the cyclodextrin **57a** gave approximately ten proton resonances upfield of δ 3.50, excluding those corresponding to the amine side chain methyl group. This is in direct contrast to the $^1H$ NMR spectrum of the *(S)*-phenylethylamine-derived cyclodextrin **57b** which contained only three resonances upfield of δ 3.50 over the same region (Figure 2.3). This greatly reduced shielding of the annulus protons of the cyclodextrin **57b** suggests that the aromatic moiety of this isomer has a lesser influence on the magnetic environment of the cyclodextrin annulus than in the corresponding *(R)*-amine-derived isomer **57a**.

Further evidence for association of the aromatic moiety of the chiral amine side chain with the cyclodextrin annulus, whether as self-inclusion or capping, was found by the employment of 2D NMR techniques. In order to gauge proximity of protons in the proposed intra-molecular complexes, individual ROESY spectra were obtained for both of the modified cyclodextrins **57a** and **57b** (0.008 mol $dm^{-3}$) at 298 K in $D_2O$. The spectra so obtained were inspected for connectivity between resonances corresponding to cyclodextrin protons. Many such cross-peaks were observed in the δ 3.00 - 4.20 region of the ROESY spectra of both cyclodextrins **57a** and **57b**. This was simply due to close proximity of hydrogens in the glucopyranose units of the cyclodextrin annulus. Of important note in the ROESY spectrum of the *(R)*-phenylethylamine-derived cyclodextrin **57a** (Figure 2.4) was the strong connectivities between resonances corresponding to all of the aromatic protons of the phenyl ring of the amine side chain around δ 7.44 - 7.56, and cyclodextrin annulus resonances over the region δ 3.80 - 4.10. This close proximity between the aromatic protons and the cyclodextrin annulus

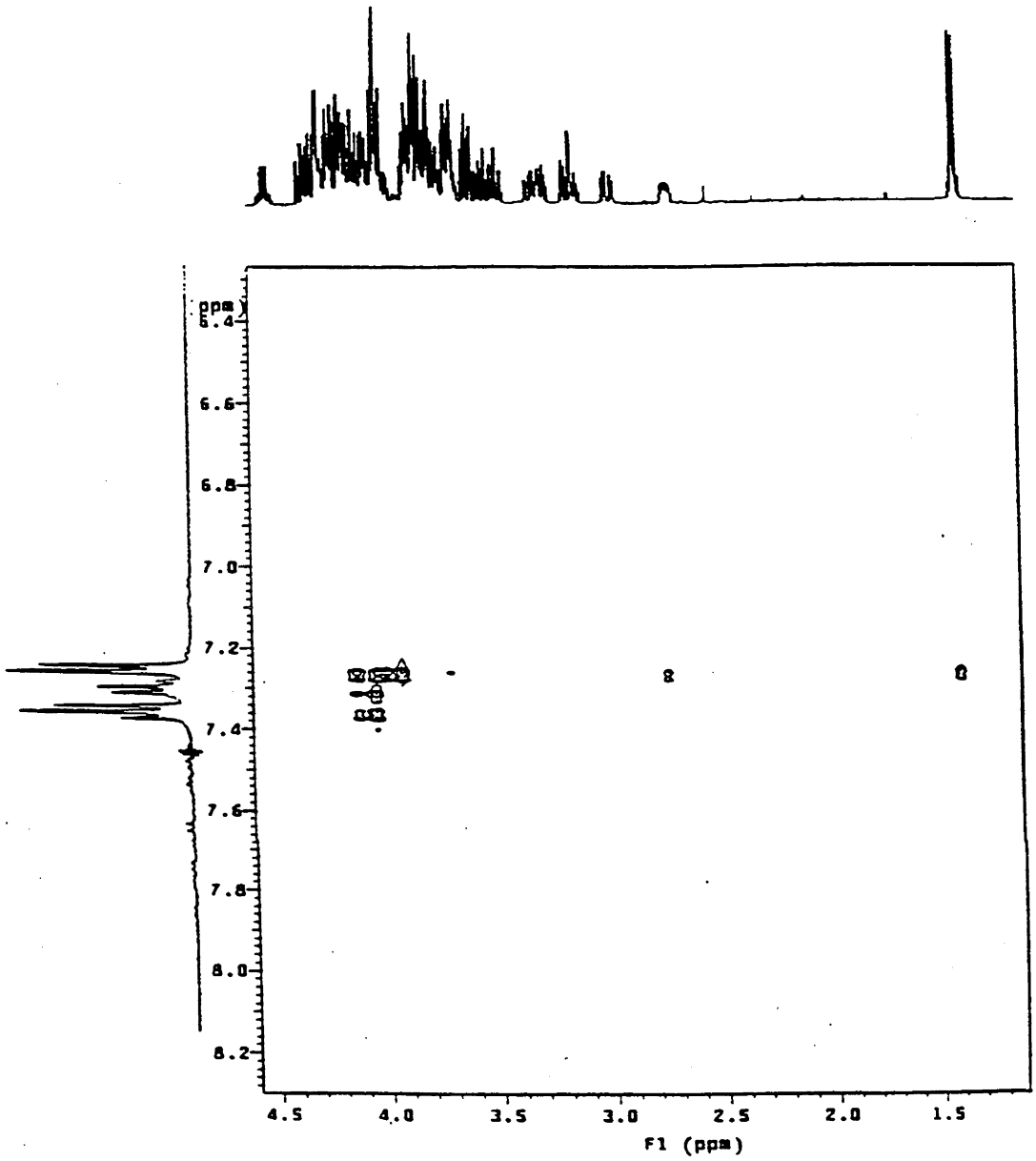



**Figure 2.4.** Partial 2D ROESY NMR spectrum of the cyclodextrin **57a**.

protons is suggestive of intra-molecular association in this species, either as inclusion of the aromatic ring in the cyclodextrin cavity, or capping of the cyclodextrin **57a** by the substituent such that the aromatic moiety is held tightly over the end of the annulus bearing the primary hydroxyl groups. This is strongly supported by the presence of the cross-peak between

resonances corresponding to the cyclodextrin annulus protons and the *para*-proton of the aromatic ring. For this aromatic proton to be close to the annulus there must be some degree of self-inclusion of the aromatic moiety, or possibly capping of the annulus by that aromatic ring. Capping was thought a possibility due to the small size of the band of cyclodextrin annulus proton resonances that give rise to cross-peaks to the resonances corresponding to the substituent aromatic moiety of the cyclodextrin **57a**. The aromatic moiety being in close proximity to a very small number of annulus protons suggests that they may well solely be the H-6 protons of the unmodified glucopyranose units, a possibility which requires a capping of the cyclodextrin annulus rather than full inclusion of the aromatic moiety. The ROESY spectrum of the cyclodextrin **57a** also showed a connectivity between the aromatic resonances of the side chain and what would be the remaining cyclodextrin annulus C-6 proton resonances at δ 2.80, namely to the C-$6^A$ protons, to which the amine moiety is directly connected.

The 2D ROESY spectrum of the *(S)*-amine-derived cyclodextrin **57b** (Figure 2.5) also showed cross-peaks between a small band of resonances in the region δ 3.90 - 4.20 and resonances corresponding to the substituent aromatic protons in the region δ 7.46 - 7.53. Once again this is indicative of the likely presence of intra-molecular association, either as self-inclusion of the aromatic moiety in the cyclodextrin annulus or possibly a capping of the cavity of that cyclodextrin by the aromatic moiety. However, strong cross peaks were only observed between the resonances corresponding to the annulus protons and those of the *ortho*-protons of the aromatic ring. The corresponding connectivities to the *meta*-protons were a good deal weaker and there was no connectivity between cyclodextrin annulus resonances and the signal corresponding to the *para*-proton of the aromatic ring. While

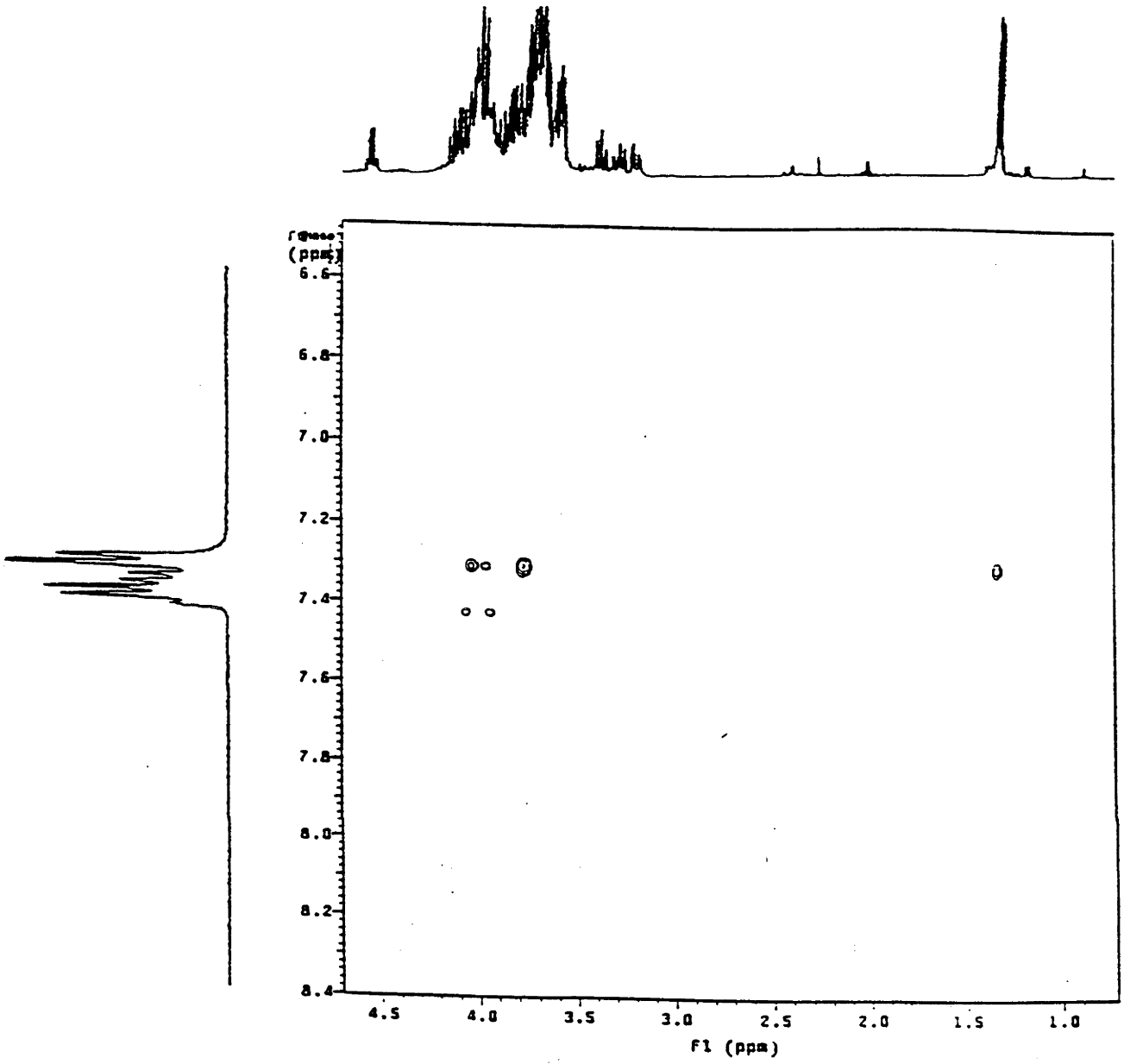
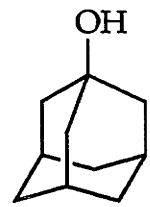



**Figure 2.5.** Partial 2D ROESY NMR spectrum of the cyclodextrin **57b**.

being consistent with some degree of intra-molecular association, such an absence is an indication that the association may be weaker in this cyclodextrin **57b** than in the previously discussed diastereomer **57a.** The connectivity observed between the cyclodextrin aromatic resonances around δ 7.50 and that of the cyclodextrin annulus C-$6^A$ resonances at around δ **2.80**

was absent for this diastereomer. Despite these differences between the diastereomers **57a** and **57b** it was confirmed that there was some degree of self-inclusion of the aromatic moiety of the substituent, or potentially capping of the cyclodextrin by that aromatic moiety, in both of those modified cyclodextrins.




**42**

Intra-molecular complexation between the aromatic moiety of the amine side chain and the cyclodextrin annulus in the modified cyclodextrins **57a** and **57b**, as discussed above, should be disrupted by the addition of a guest which complexes more strongly than the aromatic moiety of the substituent. It was expected that such inter-molecular complex formation would be observed in the $^1$H NMR spectra of these mixtures. The guest chosen for this work was adamantan-1-ol **42**. Adamantan-1-ol **42** has a high association constant of 4700 $dm^3\,mol^{-1}$ with β-cyclodextrin **1**[145] and was also expected to form strong complexes with the modified cyclodextrins of interest in this study. Therefore samples were prepared containing one of the cyclodextrins of interest, **57a** or **57b**, along with two equivalents of adamantan-1-ol **42** in pH 6.0 phosphate buffered $D_2O$, and their $^1$H NMR spectra at 298 K were recorded.

It was found that addition of adamantan-1-ol **42** (0.004 mol $dm^{-3}$) to samples containing either of the cyclodextrins **57a** or **57b** (0.002 mol $dm^{-3}$) did indeed

cause changes in the $^1$H NMR signals corresponding to the protons of the cyclodextrin species. Changes were observed in the aromatic resonances of both isomers **57a** and **57b**, with the aromatic signals significantly coalescing, indicating a decrease in the interaction of the corresponding aromatic protons with the cyclodextrin annulus. Changes were also observed in both the chemical shifts and equivalence of the H-1 proton signals of both the cyclodextrins **57a** and **57b**. As discussed above, the C-1 position of a cyclodextrin is unlikely to experience significant anisotropic effects. Thus the complexation-induced chemical shift changes experienced by resonances corresponding to the cyclodextrin H-1 protons are most likely due to the geometrical changes required to accommodate the adamantan-1-ol guest **42**.

Adamantan-1-ol **42** induced $^1$H NMR chemical shift changes were also observed in the resonances corresponding to the H-2-6 annulus protons of the cyclodextrins **57a** and **57b**, although differences were observed between the isomers, most particularly in the region from approximately δ 2.50 to 3.50. In that region the spectrum of the *(R)*-phenylethylamine-derived cyclodextrin **57a** showed very significant changes upon addition of adamantan-1-ol **42**. The ten protons that were represented upfield of δ 3.50 ppm in the spectrum of the cyclodextrin **57a** in the absence of guest became substantially less shielded, such that there were only 3 proton resonances in that region in the $^1$H NMR spectrum of the complex. It also seems likely that 2 of those remaining signals correspond to the C-6$^A$ protons. It is clear that many of the shielding effects present in the cyclodextrin **57a** in the absence of any guest are no longer present in the complex of that species with adamantan-1-ol **42**. The implication of this is that the aromatic ring of the amine side chain that was previously self-included or possibly capping the cyclodextrin, and so shielding the cyclodextrin annulus protons, is no

longer held near them; the adamantan-1-ol **42** had been complexed by the cyclodextrin **57a** precluding the aromatic ring from taking up the geometry it held in the absence of that guest.

In contrast, and despite the clear evidence of complexation gained from adamantan-1-ol **42** induced changes in resonances of the H-1 protons in the $^1$H NMR spectrum of the *(S)*-phenylethylamine-derived cyclodextrin **57b**, there were only very small changes in the resonances corresponding to the cyclodextrin annulus H-2-6 protons. In particular, the $^1$H NMR spectrum of the cyclodextrin **57b** has very few signals in the region upfield of δ 3.50, and the complexation of adamantan-1-ol **42** by this cyclodextrin left these signal virtually unchanged. Thus the magnetic environment of the cyclodextrin H-2-6 protons is minimally effected by complexation of the guest **42** into the cyclodextrin annulus, a complexation which is likely to be associated with disruption of any intra-molecular association between the aromatic moiety and the annulus. This indicates that the aromatic moiety of the cyclodextrin **57b** was only weakly associated with the annulus to begin with. This is particularly marked in comparison to the *(R)*-amine-derived diastereomer **57a** which showed substantial guest-induced changes in those resonances.

Clear evidence for disruption of some intra-molecular complexation, probably as displacement of the aromatic moiety from the cavity of the cyclodextrins **57a** and **57b**, was also found upon inspection of the circular dichroism spectra of those hosts in the presence and absence of adamantan-1-ol **42** (Figure 2.6). The inclusion of an aromatic moiety into the cavity of a cyclodextrin is known to produce an induced circular dichroism spectrum.[30-32] Thus a modified cyclodextrin in which the substituent contains an aromatic moiety which forms an intra-molecular complex with

the cyclodextrin annulus may also produce such a circular dichroism spectrum, regardless of whether the substituent contains a chiral centre or not.[29,88] Ueno and co-workers,[29] have shown that the addition of a guest such that a decrease in intensity of the circular dichroism spectrum is observed is an indication of the displacement of the self-included substituent of a modified cyclodextrin. The presence of a chiral substituent which contains an aromatic moiety in the cyclodextrins **57a** and **57b** suggests that they will yield a circular dichroism spectrum irrespective of the presence or absence of any intra-molecular association, and that is the case (Figure 2.6). The addition of adamantan-1-ol **42** caused a large decrease in the intensity of the spectra of both of the cyclodextrins **57a** and **57b** (Figure2.6), which indicated that the interaction of the substituent with the

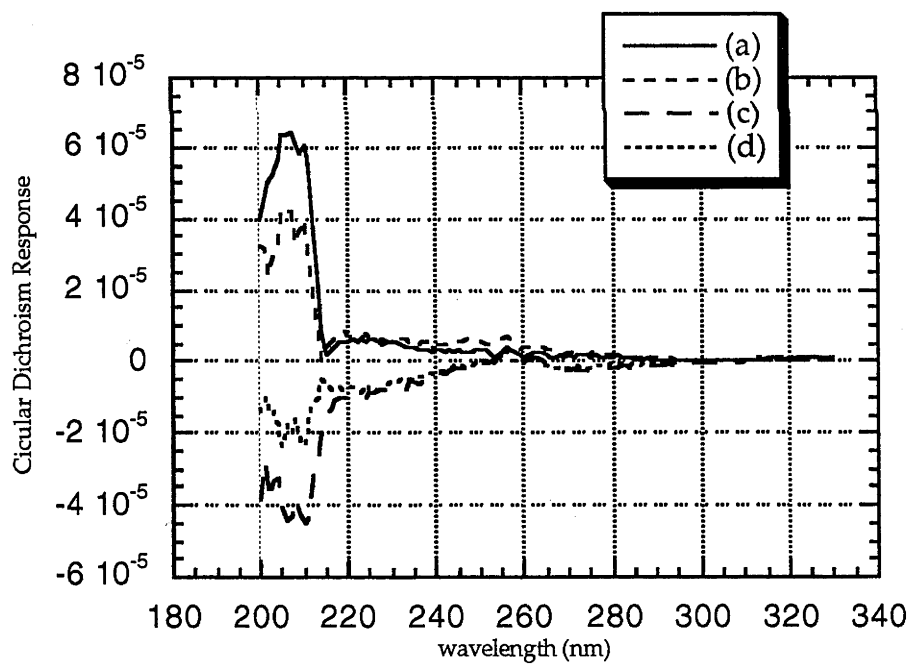


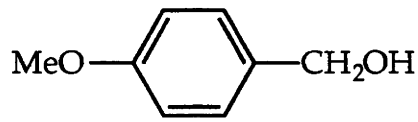

**Figure 2.6.** Circular dichroism spectra of a) *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.004 mol $dm^{-3}$), b) cyclodextrin **57a** (0.004 mol $dm^{-3}$) in the presence of adamantan-1-ol **42** (0.008 mol $dm^{-3}$), c) *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (0.004 mol $dm^{-3}$) and d) cyclodextrin **57b** (0.004 mol $dm^{-3}$) in the presence of adamantan-1-ol **42** (0.008 mol $dm^{-3}$).

annulus had been altered in those compounds. This was further confirmation that there was self-inclusion present in both of the cyclodextrins **57a** and **57b** to begin with.

To further investigate any differences in the complexation behaviour of the diastereomeric 1-phenylethylamine-derived cyclodextrins **57a** and **57b**, $^1$H NMR studies were conducted with the weakly lipophilic aromatic guest *para*-methoxybenzylalcohol **58**. This guest has the advantage of aromatic resonances that are assigned and easy to monitor in the $^1$H NMR spectra of complex mixtures. In addition, the methyl singlet of the methoxy group and the benzylic methylene singlet were also able to be easily assigned and monitored for differences in chemical shift.

It was thought that *para*-methoxybenzylalcohol **58** would be a suitable guest for highlighting differences between the two cyclodextrins **57a** and **57b** because of it's likely low hydrophobicity. Although no literature data exists for complexation of *para*-methoxybenzylalcohol **58** by cyclodextrins, the unsubstituted benzyl alcohol has an association constant of around 50 $dm^3$ $mol^{-1}$ with native β-cyclodextrin **1**,[146,147] considerably less than the 4700 $dm^3$ $mol^{-1}$ quoted for adamantan-1-ol **42** with the same cyclodextrin **1**.[145] As was shown in the studies above, adamantan-1-ol **42** is clearly sufficiently lipophilic to disrupt the intramolecular complexation present in both of the cyclodextrins **57a** and **57b**, and hence is strongly complexed by both of those hosts. This was a useful technique but it did not reveal any clear differences in behaviour between the pair of diastereomeric cyclodextrins **57a** and **57b**. It was therefore hoped that a study implementing the weakly lipophilic *para*-methoxybenzylalcohol **58** would show up any differences between the intra-molecular complexation behaviour of those hosts **57a** and **57b**. As

before, $^1$H NMR spectra of samples were recorded at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 phosphate buffered $D_2O$.




**58**

The $^1$H NMR spectrum of a sample containing the *(S)*-phenylethylamine-derived cyclodextrin **57b** (0.002 mol dm$^{-3}$) and *para*-methoxybenzylalcohol **58** (0.001 mol dm$^{-3}$) showed many complexation induced shifts in resonances corresponding to the guest **58**. In the presence of the cyclodextrin **57b** the methyl singlet of the methoxy group of the guest **58** shifted 0.013 ppm upfield and the benzylic methylene resonance of the same sample was shifted 0.006 ppm upfield, with respect to those resonances of the alcohol **58** in the absence of cyclodextrin. In addition, the distinct signals for the aromatic protons of the guest **58** were shifted upfield 0.012 and 0.015 ppm, upon addition of the *(S)*-amine-derived cyclodextrin **57b**. These changes in chemical shift upon addition of the *(S)*-amine-derived cyclodextrin **57b** indicate a change in environment of the guest **58** protons and, therefore, likely complexation by the cyclodextrin **57b**.

This conclusion is supported by inspection of the cyclodextrin resonances of the $^1$H NMR spectra of the *(S)*-phenylethylamine-derived cyclodextrin **57b** in the presence and absence of the alcohol **58**. Upon addition of the guest alcohol **58** to the cyclodextrin **57b**, the cyclodextrin aromatic signals shifted and also partially coalesced, indicating both a change in environment and an increase in equivalence, consistent with the association of the aromatic

moiety being disrupted by the alcohol **58**. This conclusion was further supported by inspection of signals corresponding to the cyclodextrin annulus H-1 protons. These resonances of the cyclodextrin **57b** annulus, upon addition of *para*-methoxybenzylalcohol **58** were shifted and also the pattern of the signals was changed. This possibly also indicated a different shielding environment experienced by the cyclodextrin annulus but, as previously discussed, is more likely an indication of the conformational change in the cyclodextrin **57b** required for complexation of the aromatic alcohol guest **58**. Whatever the reason, the above evidence clearly demonstrates the complexation of the guest **58** by the *(S)*-amine-derived cyclodextrin **57b**.

By contrast, addition of *para*-methoxybenzylalcohol **58** (0.001 mol $dm^{-3}$) to a sample containing the *(R)*-phenylethylamine-derived cyclodextrin **57a** (0.002 mol $dm^{-3}$) produced no significant changes in the $^1H$ NMR spectrum of either the alcohol guest **58** or of the cyclodextrin **57a**. Changes of 0.001 ppm upfield and 0.001 ppm downfield, observed for the guest methyl singlet and one of it's aromatic proton resonances, respectively, upon addition of the *(R)*-amine-derived cyclodextrin **57a**, were not significantly outside experimental errors of the NMR instrument. Similarly, there was no evidence of complexation in the $^1H$ NMR spectrum of the host cyclodextrin **57a**, in the presence and absence of the alcohol **58**. Changes in the chemical shifts of the cyclodextrin aromatic resonances were negligible, indicating no appreciable change in the environment of that aromatic ring upon addition of the alcohol **58**. Importantly there were no differences in the resonances of the H-1 protons of the cyclodextrin annulus; they still exhibited the same pattern for those non-equivalent protons with virtually identical chemical shifts. This indicated that the geometry of the cyclodextrin annulus was

unchanged in the presence of the alcohol **58**, suggesting that no inter-molecular complex had formed. It is likely that this lack of inter-molecular complexation is due to the strong self inclusion of the aromatic moiety of the cyclodextrin substituent in that isomer, or possibly capping of the cyclodextrin annulus by the substituent, an intra-molecular complexation that the *para*-methoxybenzylalcohol **58** is unable to disrupt.

Clearly, results obtained with the *(R)*-phenylethylamine-derived cyclodextrin **57a** are different to those obtained with the diastereomer **57b**, which readily allowed the complexation of the alcohol guest **58**. This difference supports the conclusion that there is substantially weaker intra-molecular complexation present in the *(S)*-amine-derived isomer **57b**, than in the corresponding *(R)*-amine-derived isomer **57a**.

In order to better investigate the complexation of the *para*-methoxybenzylalcohol guest **58** by the cyclodextrins **57a** and **57b**, and to further probe the relative stability of the intra-molecular inclusion complexes of those cyclodextrins, an NMR titration of the guest **58** with each of the cyclodextrins **57a** and **57b**, and β-cyclodextrin **1**, was undertaken (Figure 2.7). $^1$H NMR spectra were recorded in the presence of the guest (0.5 mmol dm$^{-3}$), where the ratio of the cyclodextrins **57a**, **57b** or **1** to the guest **58** ranged from 0 to approximately 9 mole equivalents. $^1$H NMR spectra were recorded at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 phosphate buffered $D_2O$.

Consistent with work described above, inspection of the resonance corresponding to the methyl group of the guest **58** showed no variation in the chemical shift of that signal upon addition of even many mole equivalents of the cyclodextrin **57a**, indicating a lack of complexation of the

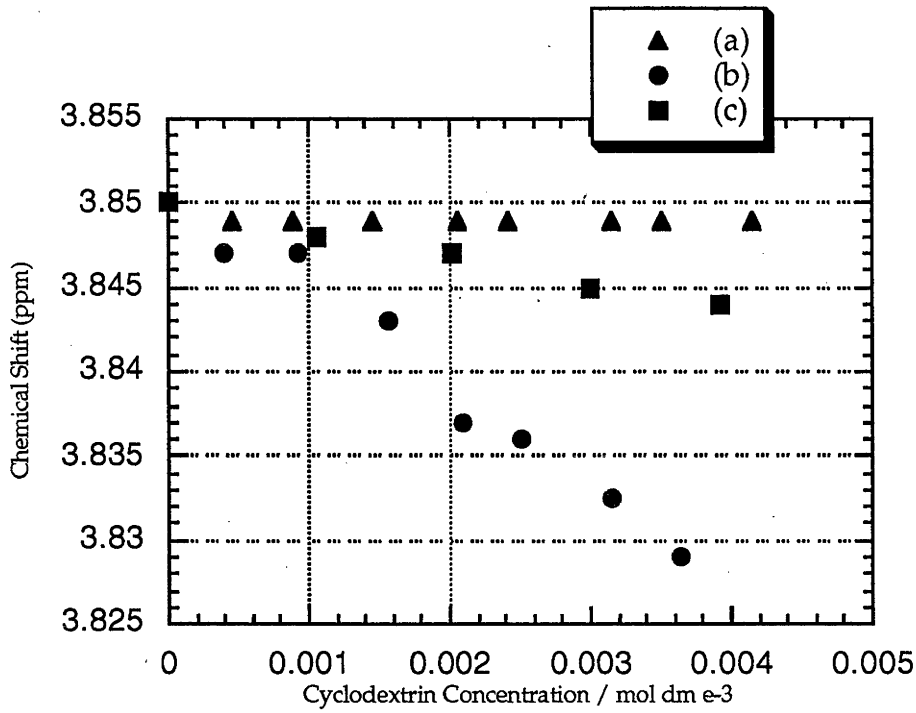



**Figure 2.7.** $^1$H NMR chemical shift of the methyl signal of *para*-methoxybenzylalcohol **58** (0.5 mmol dm$^{-3}$) in pH 6.0 phosphate buffered $D_2O$, in the presence of varying concentrations of a) the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, b) the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** or c) β-cyclodextrin **1**.

alcohol guest **58**. In contrast, in studies with the diastereomeric cyclodextrin **57b**, the chemical shift of the methyl group of the guest **58** was observed to change as a function of cyclodextrin concentration indicating the apparent complexation of the guest **58** by the cyclodextrin **57b**. Both of these results were not unexpected and confirmed the comparative hindrance to complexation of guests that is apparent in the *(R)*-amine-derived cyclodextrin **57a**. It was also noted that in studies with β-cyclodextrin **1**, the chemical shift of the guest methyl group was also seen to change as a function of cyclodextrin concentration (Figure 2.7).

Clearly the alcohol **58** is complexed by β-cyclodextrin **1** and also by the *(S)*-amine-derived cyclodextrin **57b**, but not by the *(R)*-amine-derived cyclodextrin **57a**. It is likely that the association constant of the alcohol **58** with the modified cyclodextrin **57b** is less than that with β-cyclodextrin **1**. This is because the presence of intra-molecular complexation in the modified cyclodextrin **57a** will provide a substantial hindrance to the association of the guest **58**, although this hindrance is obviously not as great as in the diastereomer **57a** which doesn't complex the guest **58** at all. The complexation of the alcohol **58** by the modified cyclodextrin **57b** produces substantially larger changes in the $^{1}H$ NMR chemical shifts of the protons of that guest than does the corresponding complexation by β-cyclodextrin **1** (Figure 2.7), but this is not inconsistent with a smaller association constant in the former system. Previous workers[51] have suggested that the magnitude of an association constant is directly related to the size of the complexation induced shift, but this by no means always holds. Table 1.1 (Page 57) indicates that the complexation of the *ortho*-fluorobenzoate anion **24** by β-cyclodextrin **1** and the C-6 substituted cyclodextrin **49** occurs with complexation-induced downfield changes in the $^{19}F$ NMR chemical shift of the guest substituents of 2.43 and 1.58 ppm, respectively, yet the association constant of that guest **24** with the latter host **49** is more than three times as large as with the former. This, and other work,[148] suggests that extent of change in chemical shift upon host-guest complexation in a system has little to do with the size of the association constant of the complex so formed; it is likely that the nature of environmental changes upon complexation is much more important.

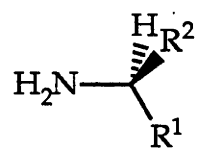
In the above work the modified cyclodextrins **45a** and **45b** were synthesized and characterized. The $^{1}H$ NMR and complexation studies of their

conjugate acids **57a** and **57b** indicate that these diastereomers have quite different properties and it is likely that this is due to a much larger extent of intra-molecular complexation in the *(R)*-amine-derived cyclodextrin **57a**, compared to the lesser, or weaker, extent of that association in the diastereomeric *(S)*-amine-derived cyclodextrin **57b**. In determining this fact, the direct comparison between complexation of both of the guests adamantan-1-ol **42** and *para*-methoxybenzylalcohol **58**, with both of the diastereomeric cyclodextrin hosts **57a** and **57b** proved extremely fruitful.

## Results and Discussion Chapter 3

### Synthesis and Properties of Related Pairs of Diastereomeric Amino-Cyclodextrins

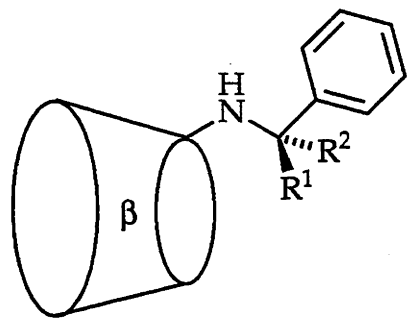
As discussed in Chapter 2 of the Results and Discussion, and outlined in the Introduction to this Thesis, in order to investigate factors influencing the complexation of selected chiral aromatic guests, it was necessary to gain access to a series of modified cyclodextrins. It was intended to probe the potential for complementary discrimination in the complexation of those chiral guests and so, as in Chapter 2 of the Results and Discussion of this Thesis, it was required that the cyclodextrins synthesized would be diastereomeric pairs. Thus the appropriate enantiomers of the amines **59a,b - 61a,b** were employed in the preparation of the modified cyclodextrins **46a,b - 48a,b**, which were then characterized and certain of their properties investigated using techniques discussed in Chapter 2 of the Results and Discussion of this Thesis.



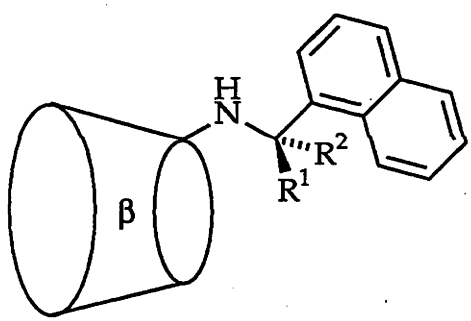

**59a** $R^1 = Ph, R^2 = CH_2OH$
**59b** $R^1 = CH_2OH, R^2 = Ph$
**60a** $R^1 = Me, R^2 = 1\text{-Naphth}$
**60b** $R^1 = 1\text{-Naphth}, R^2 = Me$
**61a** $R^1 = Me, R^2 = CH_2Ph$
**61b** $R^1 = CH_2Ph, R^2 = Me$

Due to their obvious structural similarity, the cyclodextrins **46a,b - 48a,b** were synthesized using methods identical to those outlined above for the

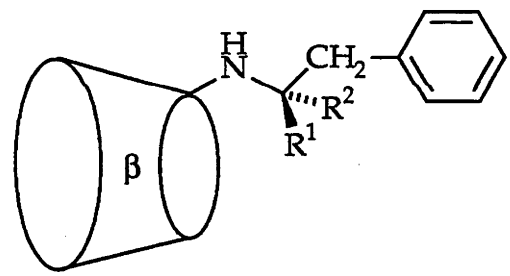
preparation of the 1-phenylethylamine-derived cyclodextrins **45a** and **45b**, namely from either the iodo-cyclodextrin **31**, or from the corresponding tosylate **17** in the presence of sodium iodide (*cf.* Scheme 2.1).




**46a** $R^1 = H$, $R^2 = CH_2OH$
**46b** $R^1 = CH_2OH$, $R^2 = H$




**47a** $R^1 = CH_3$, $R^2 = H$
**47b** $R^1 = H$, $R^2 = CH_3$




**48a** $R^1 = CH_3$, $R^2 = H$
**48b** $R^1 = H$, $R^2 = CH_3$

Thus, treatment of the tosylate **17** with 2 mole equivalents of each of the amines **59a,b**, **60a** and **61a,b** in the presence of 20% sodium iodide in *N*-methylpyrrolidin-2-one yielded the modified cyclodextrins **46a,b**, **47a** and **48a,b**, respectively. Isolation of the cyclodextrins **47a,b** and **48a,b** from their respective reaction mixtures was accomplished by trituration of those reaction mixtures with ethanol and collection of the cyclodextrins so

precipitated. The phenylglycinol-derived cyclodextrins **46a** and **46b** were found to be appreciably soluble in ethanol and so were isolated by trituration of their reaction mixtures with acetone and the cyclodextrins so precipitated were collected.

Alternatively, treatment of the iodide **31** with 2 mole equivalents of each of the amines **59a,b - 61a,b** in *N,N*-dimethylformamide yielded the corresponding modified cyclodextrins **46a,b - 48a,b**. Isolation of the cyclodextrin products **46a,b - 48a,b** was accomplished by trituration of each reaction mixture with acetone and collection of the cyclodextrin so precipitated. After recovering the cyclodextrin components the required products were purified using column chromatography with Biorex 70™ cation exchange resin followed by preparative HPLC. After purification, cyclodextrins prepared by reaction of either the tosylate **17** or the iodide **31** were found to be identical.

Thus the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **47a** was isolated as a colourless solid, in 39% and 33% yields, when prepared from the tosylate **17** or iodide **31**, respectively. TLC analysis of the amine **47a** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **47a** gave a signal at *m/z* 1288.5 corresponding to $M+H^+$. HRESI-MS gave a signal measured as *m/z* 1288.4757, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1288.4718, required for $C_{54}H_{82}NO_{34}$. Microanalytical data indicated that the cyclodextrin **47a** was complexed with an average of 9 water molecules. The proton decoupled $^{13}C$ NMR spectrum of the amine **47a** displayed resonances at δ 23.7 and 53.4, assigned to the methyl and methine carbons of the cyclodextrin substituent, along with several signals in the range δ 122.5 -

141.5 assigned to the seven tertiary and three quaternary aromatic carbons of the substituent. In addition to these resonances, several signals assigned to cyclodextrin **47a** annulus carbons were observed, including a resonance at δ 46.5, assigned to the C-$6^A$ carbon, along with multiple resonances around δ 59.9, assigned as corresponding to the C-$6^{B-G}$ carbons.

The *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **47b** was isolated as a colourless solid in 33% yield from the corresponding iodide **31**. TLC analysis of the amine **47b** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. The ESI-MS of the amine **47b** gave a signal at *m/z* 1288.5 corresponding to $M+H^+$. HRESI-MS gave a signal measured as *m/z* 1288.4688, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1288.4718, required for $C_{54}H_{82}NO_{34}$. Microanalytical data indicated that the cyclodextrin **47b** was complexed with an average of 9 water molecules. The proton decoupled $^{13}C$ NMR spectrum of the amine **47b** displayed resonances at δ 24.1 and 53.1, assigned to the methyl and methine carbons of the cyclodextrin substituent, along with several signals in the range δ 122.3 - 141.5 assigned to the seven tertiary and three quaternary carbons of the aromatic moiety of the substituent. In addition to these resonances, several signals assigned to the cyclodextrin **47b** annulus carbons were observed, including a resonance at δ 46.5, assigned to the C-$6^A$ carbon, along with multiple resonances around δ 58.7 - 59.8, assigned as corresponding to the C-$6^{B-G}$ carbons.

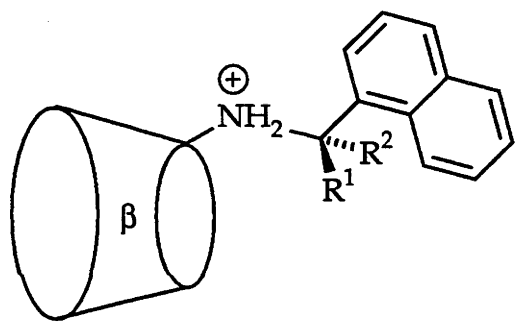
As for the 1-phenylethylamine-derived cyclodextrins **45a** and **45b**, the diastereomers **47a** and **47b** were found to have very distinct HPLC retention times. Under the previously outlined conditions these retention times of the *(R)*- and *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrins **47a** and **47b**

were 0.83 and 0.58, relative to β-cyclodextrin **1**, respectively. As discussed previously, it is apparent that the extent to which the aromatic moiety of a modified cyclodextrin is exposed to the HPLC running solvent affects the retention time of that compound. Thus, the much shorter retention time of the *(S)*-amine-derived cyclodextrin **47b** suggests that isomer has the aromatic moiety of the amine substituent substantially more exposed to the HPLC running solvent than that of the *(R)*-amine derived diastereomer **47a**.

As discussed in Chapter 2 of the Results and Discussion of this Thesis there is modest and variable selectivity which favours preparation of the *(R)*-1-phenylethylamine-derived cyclodextrin **45a** over the corresponding *(S)*-amine-derived diastereomer **45b**, when prepared from the corresponding iodide **31**. To determine if such a selectivity might be general for the preparation of the cyclodextrin diastereomers under study in this Chapter a competitive study of the reaction of the isomers of 1-(1-naphthyl)-ethylamine **60a** and **60b** with the iodide **31** was conducted. Thus the products of the reaction of one equivalent of each of the *(R)*- and *(S)*-amine enantiomers **60a** and **60b**, and the iodide **31**, were identified by HPLC analysis and the reaction was found to selectively produce the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **47a** over the corresponding *(S)*-amine-derived diastereomer **47b** in a ratio of 1.5 : 1. This is a similar result to that from the competitive reaction of *(R)*- and *(S)*-1-phenylethylamine **56a** and **56b** with the iodide **31**. In that system it was the isomer **45a**, formed by reaction of the *(R)*-amine **56a**, that was produced in preference to the cyclodextrin **45b**. The cyclodextrins **45a** and **47a**, both derived from the *(R)*-enantiomers of free amines, have longer retention times under HPLC analysis than the corresponding *(S)*-amine-derived cyclodextrins **45b** and **47b**. It is also the *(R)*-amine-derived cyclodextrins **45a** and **47a** which were

preferentially produced over their corresponding diastereomers **45b** and **47b** in the competitive reactions outlined above.

As in Chapter 2 of the Results and Discussion of this Thesis, all $^1$H NMR studies were conducted in phosphate buffered $D_2O$ at pH 6.0. These conditions were chosen because, having prepared the diastereomers **47a** and **47b**, it is likely that, as in previous systems, the predominant forms of these hosts at the pH of the study will be the conjugate acids **62a** and **62b**, giving the opportunity to study ionic host-guest interactions in systems containing charged host species.




**62a** $R^1 = CH_3, R^2 = H$
**62b** $R^1 = H, R^2 = CH_3$

Similar to those of the 1-phenylethylamine-derived compounds **57a** and **57b**, the $^1$H NMR spectra of both of the cyclodextrins **62a** and **62b** are consistent with the attachment of a substituent bearing an aromatic moiety to a cyclodextrin annulus. Attachment of such a substituent is probably accompanied by intramolecular association, where the aromatic moiety includes within, or possibly caps, the cyclodextrin annulus. This is expressed in the $^1$H NMR spectra of these species as a great deal of non-equivalence of resonances corresponding to protons of the cyclodextrin annulus.[49,105,108] The effects of intramolecular complexation can also be

observed by noting changes in the chemical shifts of other resonances, such as those corresponding to protons of the substituent, upon covalent attachment of the amine to the cyclodextrin.[105,108] Some of the signals corresponding to the aromatic protons of the free amines **60a** and **60b** in the $^1$H NMR spectrum of those species are poorly resolved. The $^1$H NMR spectrum of the *(R)*-amine **60b** contains a single hydrogen doublet, a four hydrogen multiplet and other overlapping signals, all corresponding to aromatic protons (Figure 3.1a). This is different to the spectra of both of the modified 1-(1-naphthyl)-ethylamine-derived cyclodextrins **62a** and **62b** due to significant shift changes which come about upon covalent attachment of the amine moiety to a cyclodextrin annulus. The chemical shifts of resonances corresponding to the aromatic protons of these two cyclodextrins **62a** and **62b** are in turn significantly different from each other, which also suggests that those species have differing geometries, likely due to them having unequal extents of intramolecular association (Figures 3.1b and 3.1c).

The effect of the substitution of a naphthyl moiety, as part of an amine group, on the cyclodextrin was also readily observed by inspection of the resonances in the $^1$H NMR spectra of the cyclodextrins **62a** and **62b** that correspond to their H-1 protons. The $^1$H NMR spectrum of β-cyclodextrin **1** reveals the H-1 protons of that compound to be equivalent, with the corresponding resonance appearing as a seven hydrogen doublet at around δ 5.09. This is quite unlike the $^1$H NMR spectra of the cyclodextrins **62a** and **62b** which suggest that there is significant non-equivalence of the H-1 protons in those species. These spectra have the corresponding H-1 resonances spread over 0.265 ppm in the $^1$H NMR spectrum of the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** and over 0.298 ppm in the spectrum of the corresponding *(R)*-amine derived diastereomer **62a**. As

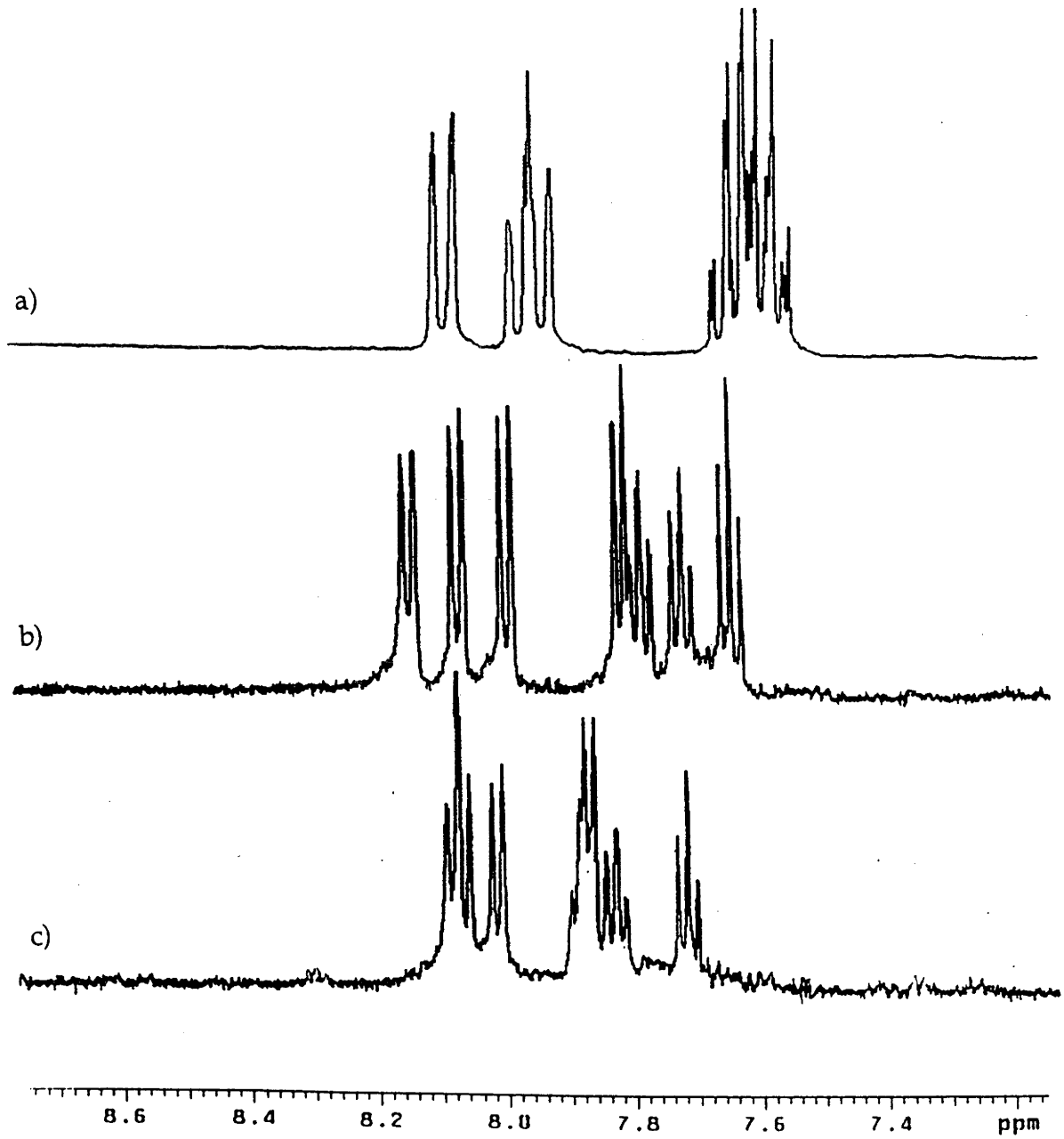



**Figure 3.1.** Partial $^{1}H$ NMR spectra of a) *(R)*-1-(1-naphthyl)-ethylamine **60a**, b) the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** and c) the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**.

discussed in the Introduction of this Thesis and in Chapter 2 of the Results and Discussion, due to the screening of the C-1 position of a cyclodextrin from any anisotropic effects that might be due to an included species,[43] it is quite likely that this effect is caused by conformational differences in the annuli of the cyclodextrins **62a** and **62b**, compared to β-cyclodextrin **1**. This is consistent with geometries required for the aromatic moiety self including in, or possibly capping, the cyclodextrin annulus. There is a slightly greater effect apparent in the spectrum of the *(R)*-amine-derived cyclodextrin **62a** than in that of the diastereomer **62b**, although it is not certain how this relates to the relative geometries of the two species.

The effect of probable intramolecular complexation on the $^1$H NMR spectra of the diastereomeric modified cyclodextrins **62a** and **62b** is more apparent when considering the relative non-equivalence of the other protons of the cyclodextrin annuli. As for the $^1$H NMR spectra of the 1-phenylethylamine-derived cyclodextrins **57a** and **57b** discussed in the previous Chapter, the $^1$H NMR spectrum of the *(R)*-amine-derived isomer **62a** suggests a large degree of non-equivalence in the cyclodextrin annulus H-2-6 protons. That spectrum shows a great many resolved signals, with resonances corresponding to cyclodextrin annulus protons spread both upfield and downfield with respect to those in the corresponding region of the $^1$H NMR spectrum of β-cyclodextrin **1** (Figure 3.2). This is suggestive of association of the aromatic moiety with the annulus in the cyclodextrin **62a**, either as inclusion of, or capping by, the aromatic moiety of the annulus.[105,108] Similarly, the $^1$H NMR spectrum of the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** shows that the annulus protons in that species experience many shielding effects compared to β-cyclodextrin **1** (Figure 3.2). These effects are clearly caused by the presence of the aromatic substituent

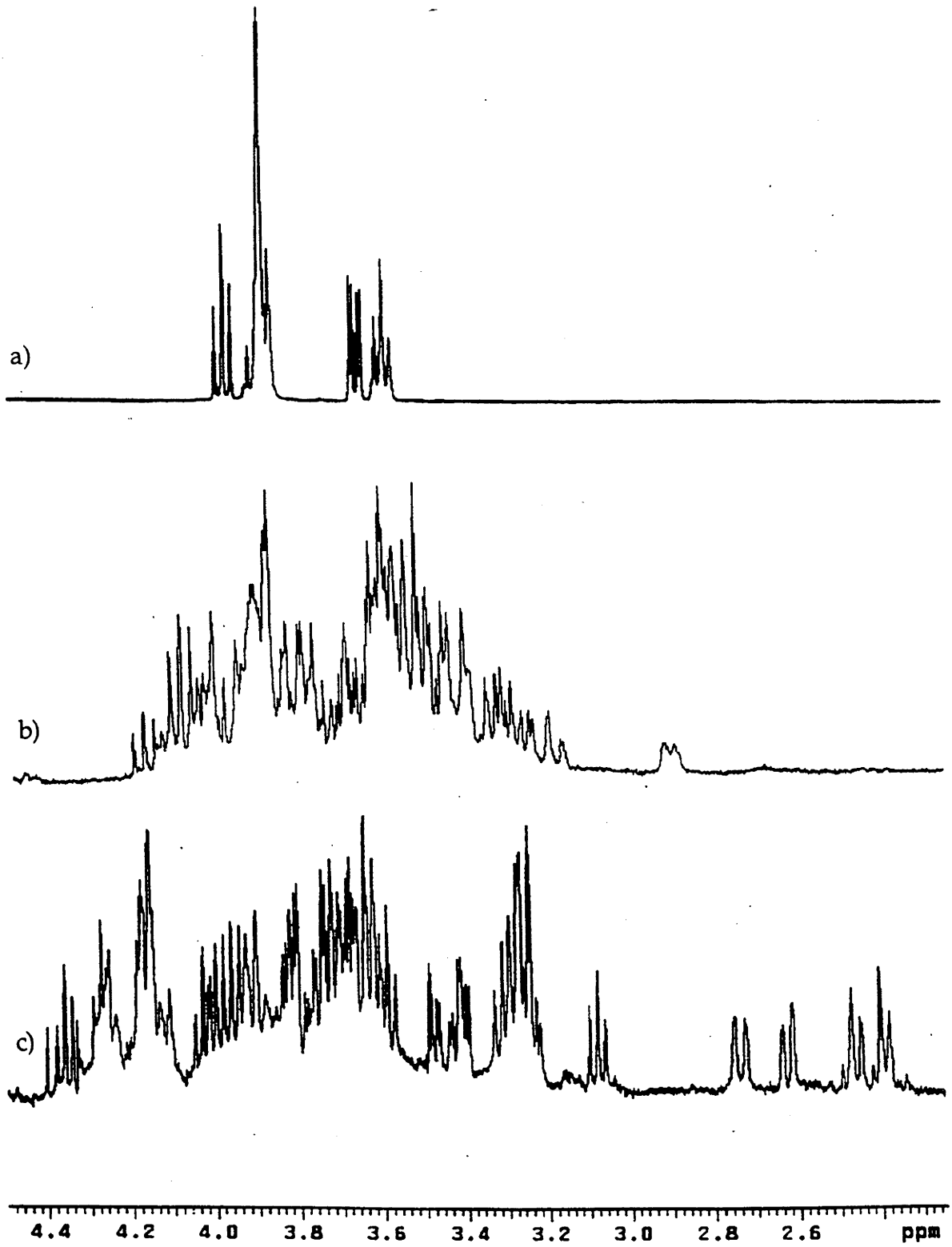



**Figure 3.2.** Partial $^{1}H$ NMR spectra, showing resonances corresponding to cyclodextrin H-2-6 annulus protons, of a) β-cyclodextrin **1**, b) the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** and c) the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**.

and are indicative of the presence of intramolecular complex formation in this cyclodextrin **62b**.

In order to gauge the ability of the cyclodextrins **62a** and **62b** to accommodate guests, the $^1$H NMR spectra of samples containing either the *(R)*- or *(S)*-1-(1-naphthyl)-ethylamine-derived species **62a** or **62b** (0.002 mol dm$^{-3}$) in the presence of two equivalents of adamantan-1-ol **42** (0.004 mol dm$^{-3}$) were recorded. The addition of adamantan-1-ol **42** to a sample containing the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** caused some minor changes to the resonances of the aromatic protons in the $^1$H NMR spectrum of that species. This indicates at least a small change in the environment of the aromatic protons of the cyclodextrin **62b** upon addition of the guest **42**, which suggests probable disruption of the intramolecular complex in that host. More marked changes were observed in the system containing the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**, where addition of the guest **42** caused significant changes to the $^1$H NMR chemical shifts of resonances corresponding to the protons of the aromatic moiety of the cyclodextrin **62a**. It was clear that the naphthyl ring aromatic protons of both of the cyclodextrins **62a** and **62b** experienced a change in environment upon addition of the adamantan-1-ol **42**. This is consistent with displacement of the naphthyl ring from the position it had previously held within, or possibly capping, the cyclodextrin annulus.

The complexation of the guest **42** was confirmed by inspection of the $^1$H NMR chemical shifts of the cyclodextrin annulus protons of the modified cyclodextrins **62a** and **62b** in the presence and absence of adamantan-1-ol **42**. Upon addition of adamantan-1-ol **42**, the cyclodextrin H-1 proton resonances were found to be changed in both of the cyclodextrin isomers **62a** and **62b**.

Examples of this include one resonance in the spectrum of the *(S)*-amine-derived cyclodextrin **62b** shifting 0.025 ppm upfield from δ 5.187 to 5.162 upon addition of the guest **42**, and other changes such as downfield shifts in resonances at δ 5.083 and 5.068. These two signals correspond to two of the H-1 protons of the cyclodextrin **62b** in the absence of guest and they coalesce to one signal at δ 5.101 in the presence of adamantan-1-ol **42**. As in the previous experiments with the cyclodextrins **57a** and **57b**, the changing of the chemical shifts of H-1 proton resonances is probably an indication of the change in geometry of the cyclodextrin annulus required to accommodate the guest **42**. This is of course accompanied by disruption of the intramolecular complex in both of the cyclodextrins **62a** and **62b**.

As mentioned above, the $^1$H NMR spectrum of the *(R)*-amine-derived cyclodextrin **62a** in the absence of guest contains many H-2-6 proton resonances upfield of those of the corresponding protons in the $^1$H NMR spectrum of β-cyclodextrin **1**. This presumably results from the shielding effects of the close proximity of the aromatic ring in the cyclodextrin **62a**, which are of course absent in the native cyclodextrin **1**.[108] The appearance of the spectrum of the cyclodextrin **62a** is greatly altered upon addition of adamantan-1-ol **42**, with an apparent decrease in the extent of observed shielding effects on the cyclodextrin annulus H-2-6 protons (Figure 3.3). This is a strong indication of disruption of the intramolecular complex in the cyclodextrin **62a** by the guest **42**, although the large amount of non-equivalence which remains suggests that the presence of adamantan-1-ol **42** does not entirely preclude intramolecular complexation in the cyclodextrin **62a**. Adamantan-1-ol **42** induced effects were also apparent upon inspection of the $^1$H NMR chemical shifts of the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** annulus H-2-6 protons (Figure 3.3). The $^1$H NMR spectrum

of the *(S)*-amine-derived cyclodextrin **62b** also contains many cyclodextrin annulus proton resonances which are significantly upfield of those of the corresponding protons in β-cyclodextrin **1** (Figure 3.2). Similar to above, addition of adamantan-1-ol **42** caused an apparent decrease in shielding of those protons in the cyclodextrin **62b** (Figure 3.3). The observed shift-changes, although not as large as those seen for complexation of the guest **42** by the *(R)*-amine-derived cyclodextrin **62a**, are indicative of a change in environment of those protons. Thus it appears that there is intramolecular complexation present in both of the cyclodextrins **62a** and **62b** and this is disrupted by the addition of the strongly lipophilic adamantan-1-ol **42** in both species.

This result is unlike that found with the less lipophilic guest *para*-methoxybenzylalcohol **58**, where addition of the *(R)*-1-(1-naphthyl)-ethylamine derived cyclodextrin **62a** (0.002 mol $dm^{-3}$) to that alcohol **58** (0.001 mol $dm^{-3}$) resulted in no significant changes to the $^1H$ NMR spectrum of either the alcohol **58** or the cyclodextrin **62a**. It seems likely that this is because of strong intramolecular complexation in the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**, either as self-inclusion of the aromatic moiety of the cyclodextrin into the cavity, or possibly capping, preventing the *para*-methoxybenzylalcohol **58** from forming an intermolecular complex. However, it was found that addition of the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** (0.002 mol $dm^{-3}$) to *para*-methoxybenzylalcohol **58** (0.001 mol $dm^{-3}$) did produce significant changes in the $^1H$ NMR spectrum of that alcohol **58**. In the presence of the cyclodextrin **62b** the resonances corresponding to the methoxy and the benzylic methylene groups, in the $^1H$ NMR spectrum of the alcohol **58**, were shifted 0.031 ppm and 0.016 ppm upfield, respectively, when compared to

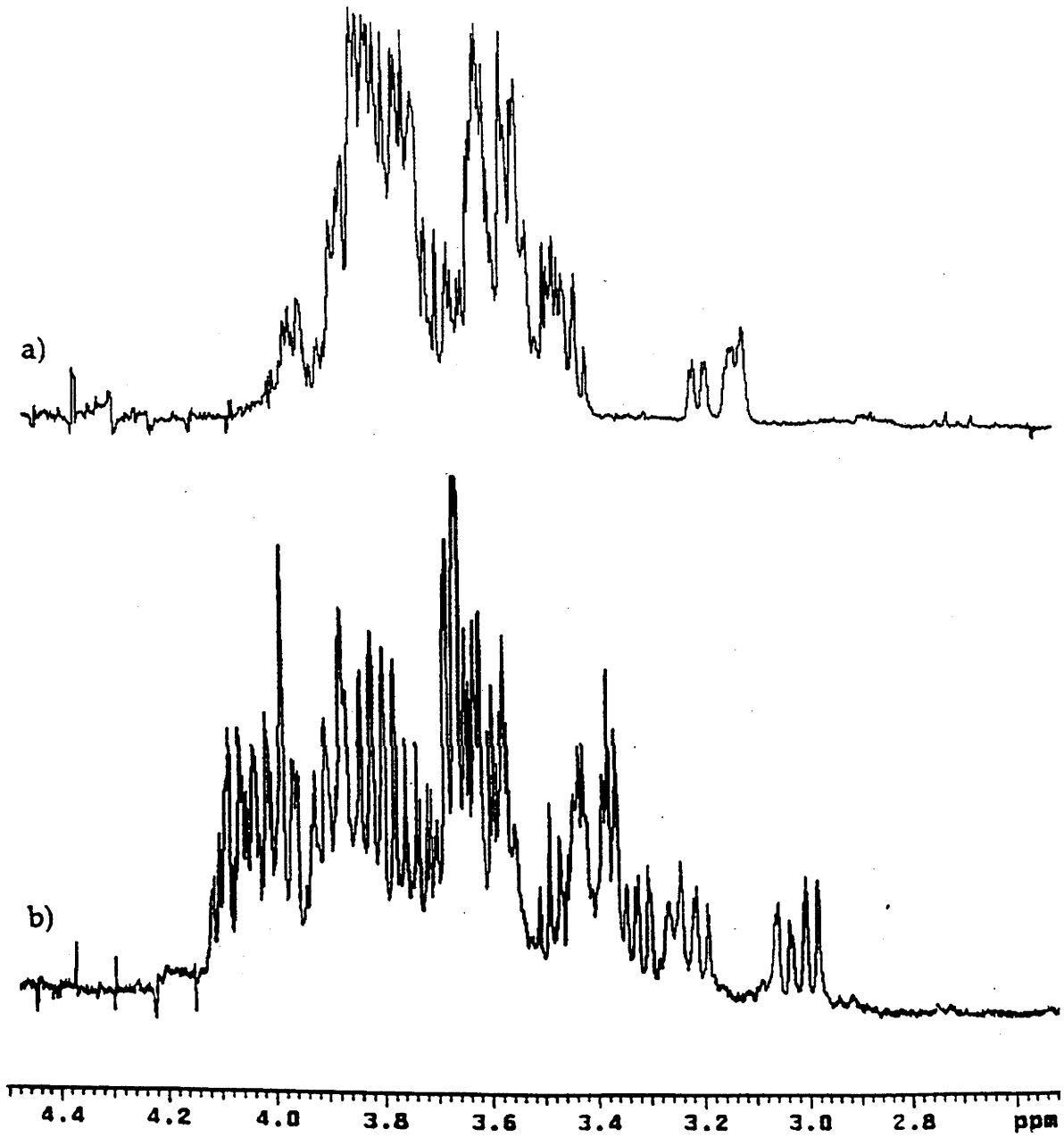



**Figure 3.3.** Partial $^1$H NMR spectra, showing resonances corresponding to cyclodextrin annulus H-2-6 protons, in the 2:1 mixtures of adamantan-1-ol **42** and either a) the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** or b) the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**.

those of the guest **58** in the absence of the cyclodextrin **62b**. This is evidence for a change in environment of those guest protons. In addition to these differences, the aromatic proton resonances were shifted 0.019 ppm and 0.025 ppm upfield, with respect to the same resonances in the absence of cyclodextrin. These changes in chemical shift indicate that not only had a change in environment of the aromatic protons occurred but also that the chemical shift difference between the resonances corresponding to the aromatic protons had changed, which suggests that their relative changes in environment were also different. This is strong evidence for complexation of the guest by inclusion within the cyclodextrin annulus. This conclusion is supported by inspection of the cyclodextrin resonances of the $^1$H NMR spectra of the *(S)*-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** in the presence and absence of the alcohol **58**. Upon addition of the guest **58** the resonances corresponding to the cyclodextrin annulus H-1 protons were shifted and the pattern of those resonances changed. This indicates that there was a change in conformation of the cyclodextrin **62b**, such as would result from accommodating the guest **58**. In contrast to the above system containing the *(R)*-amine-derived cyclodextrin **62a**, it is apparent that the *(S)*-amine-derived isomer **62b** readily complexes the alcohol **58**.

The above work is consistent with the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a** having the aromatic moiety of the substituent strongly included in, or capping, the cyclodextrin cavity. It seems likely that the *(S)*-amine-derived diastereomer **62b** forms a similar, but weaker, intramolecular complex. The greater extent of intramolecular complexation in the *(R)*-amine-derived cyclodextrin **62a**, compared to the diastereomer **62b**, is the likely reason for greater shielding effects observed in the $^1$H NMR spectrum of the former species (Figure 3.2). These results are also similar to

those obtained for the *(R)*-and *(S)*-1-phenylethylamine-derived cyclodextrins **57a** and **57b**, described in Chapter 2 of the Results and Discussion of this Thesis. In that work, evidence was observed which suggested that there was a strong association between the cyclodextrin aromatic moiety and the annulus of the *(R)*-amine-derived diastereomer **57a**. Intra molecular association was also hypothesized to occur in the *(S)*-amine-derived isomer **57b**, but probably to a lesser extent than in the diastereomer **57a**.

Synthesized using the methods outlined above for the preparation of the 1-phenylethylamine and 1-(1-naphthyl)-ethylamine derived cyclodextrins **45a,b** and **47a,b**, the *(R)*-amphetamine-derived cyclodextrin **48a** was isolated as a colourless solid in 37% and 58% yields, when prepared from the corresponding tosylate **17** or iodide **31**. TLC analysis of the amine **48a** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **48a** gave a signal at *m/z* 1252.5 corresponding to $M+H^+$. HRESI-MS gave a signal measured as *m/z* 1252.4715, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1252.4718 required for $C_{51}H_{82}NO_{34}$, and a further signal measured as *m/z* 1274.4561, which is within experimental error of the calculated value for $M+Na^+$ of *m/z* 1274.4538 required for $C_{51}H_{81}NNaO_{34}$. The proton decoupled $^{13}C$ NMR spectrum of the amine **48a** displayed resonances at δ 19.7, 42.6 and 54.5, assigned to the methyl, methylene and methine carbons of the cyclodextrin substituent. Several signals in the range δ 125.9 - 129.3 and a single resonance at δ 139.6 were assigned to the five tertiary carbons and single quaternary carbon of the aromatic ring of the cyclodextrin substituent, respectively. In addition to these resonances, several signals assigned to cyclodextrin **48a** annulus carbons were observed, including a

resonance at δ 46.9, assigned to the C-$6^{A}$ carbon, along with multiple resonances around δ 59.9, assigned as corresponding to the C-$6^{B-G}$ carbons.

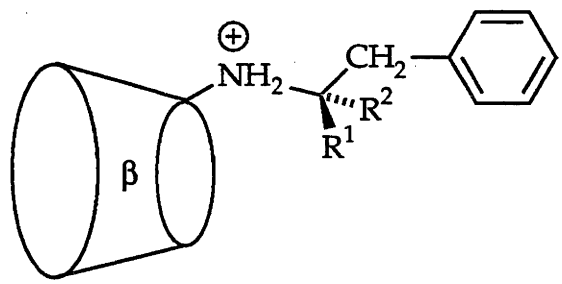
Synthesized by identical techniques to the diastereomer **48a**, above, the *(S)*-amphetamine-derived cyclodextrin **48b** was isolated as a colourless solid in 30% and 58% yields, when prepared from the corresponding tosylate **17** or iodide **31**. TLC analysis of the amine **48b** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **48b** gave a signal at *m/z* 1252.5 corresponding to $M+H^+$. HRESI-MS gave a signal measured as *m/z* 1252.4703, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1252.4718 required for $C_{51}H_{82}NNaO_{34}$, and a further signal measured as *m/z* 1274.4529, which is within experimental error of the calculated value for $M+Na^+$ of *m/z* 1274.4538 required for $C_{51}H_{81}NO_{34}Na$. Microanalytical data indicated that a mixture of this cyclodextrin **48b** and the diastereomer **48a**, isolated from a reaction mixture prepared to study the competitive rates of reaction of the amines **61a** and **61b** with the iodide **31** as outlined below, was pure save for complexing an average of 8.5 water molecules. The proton decoupled $^{13}C$ NMR spectrum of the amine **48b** displayed resonances at δ 19.1, 42.3 and 54.5, assigned to the methyl, methylene and methine carbons of the cyclodextrin substituent. Several signals in the range δ 125.9 - 129.3 and a single resonance at δ 139.3 were assigned to the five tertiary carbons and single quaternary carbon of the aromatic moiety of the amine substituent, respectively. In addition to these resonances, several signals assigned to cyclodextrin **48b** annulus carbons were observed, including a resonance at δ 46.5, assigned to the C-$6^{A}$ carbon, along with multiple resonances around δ 59.9, assigned as corresponding to the C-$6^{B-G}$ carbons.

The HPLC retention times of the *(R)*- and *(S)*-amphetamine-derived cyclodextrins **48a** and **48b** were measured under the conditions previously outlined, and found to be 0.65 and 0.64 respectively, relative to β-cyclodextrin **1**. The fact that both of these cyclodextrins **48a** and **48b** have shorter retention times than the unmodified β-cyclodextrin **1** is consistent with covalent attachment of an aromatic moiety to the cyclodextrin. The similarity in the retention times of the cyclodextrins **48a** and **48b** suggests that should these cyclodextrins form intramolecular complexes, as it seems the previously discussed pairs of diastereomers **45a,b** and **47a,b** do, the extent of association of the aromatic ring with the cyclodextrin annulus in those species may not be very different.

Similar to work described above for preparation of mixtures of the pairs of diastereomers **45a,b** and **47a,b** from the iodide **31**, the competitive reaction in which the diastereomers **48a** and **48b** were prepared from the iodide **31** was investigated for selectivity. In this case HPLC was found to be an inappropriate method for analyzing mixtures of the amphetamine-derived cyclodextrins **48a** and **48b** due to their very similar retention times. However, in the $^1$H NMR spectrum of a mixture of the diastereomers **48a** and **48b** at 298 K the resonances corresponding to the respective methyl groups of the amine substituents of those diastereomeric species are not coincident. Thus, one equivalent of each of the *(R)*- and *(S)*-amphetamine enantiomers **60a** and **60b** was heated with the iodide **31** and the product was analysed using $^1$H NMR spectroscopy at 298 K to reveal that this reaction selectively produced the *(R)*-amphetamine-derived cyclodextrin **48b** over the *(S)*-amine-derived diastereomer in a ratio of 1.5 : 1. Similar to competitive reactions previously discussed it is the *(R)*-amine-derived cyclodextrin **48a** which is produced preferentially. This further confirms

that there is some orientation of the *(R)*-enantiomers **56a**, **60a** and **61a** within the iodide **31** which is more favourable for reaction of that species to form the cyclodextrins **45a**, **47a** and **48a**.

As for systems discussed above, the $^1$H NMR studies outlined below were conducted in phosphate buffered $D_2O$ at pH 6.0. By an analogous argument to that outlined above, the predominant form of the amino-cyclodextrins in such studies will be protonated species, in this case the conjugate acids **63a** and **63b**.




**63a** $R^1 = CH_3$, $R^2 = H$
**63b** $R^1 = H$, $R^2 = CH_3$

The $^1$H NMR spectra of the amphetamine derived compounds **63a** and **63b** are consistent with attachment of a substituent bearing an aromatic moiety to a cyclodextrin annulus, with probable inclusion of that aromatic moiety within, or possibly capping, the cyclodextrin annulus. This was initially evident by comparison of the signals corresponding to the aromatic protons of the amphetamine-derived cyclodextrins **63a** and **63b** with those of the free amphetamines **61a** and **61b**, in their $^1$H NMR spectra. In the $^1$H NMR spectrum of the enantiomers **61a** and **61b**, the resonances corresponding to the aromatic protons are well resolved and appear as for a singly substituted benzene ring, namely a signal corresponding to the two *meta*-protons at δ

7.419, a signal corresponding to the *para*-proton at δ 7.370 and a two proton doublet at δ 7.324 corresponding to the *ortho*-protons.

Attachment of the amine moiety to the cyclodextrin annulus maintains the pattern of the aromatic resonances as for a singly substituted benzene ring in the $^1$H NMR spectra of the cyclodextrins **63a** and **63b**. However, the presence of the cyclodextrin annulus in these species results in major changes in the chemical shifts of their aromatic resonances, with respect to the corresponding signals in the spectra of the unsubstituted amphetamines **61a** and **61b**. Covalent attachment of *(S)*-amphetamine **61b** to the cyclodextrin annulus results in the aromatic protons of the cyclodextrin **63b** yielding resonances corresponding to the two *meta*-protons at δ 7.439 (a downfield shift of 0.020 ppm with respect to the free amine starting material), a single hydrogen aromatic *para*-proton resonance at δ 7.387 (a downfield shift of 0.017 ppm) and a two proton doublet at δ 7.331 corresponding to the *ortho*-protons (a downfield shift of 0.007 ppm). Covalent attachment of *(R)*-amphetamine **61a** to a cyclodextrin annulus results in the aromatic protons of the cyclodextrin **63a** producing resonances corresponding to the two *meta*-protons at δ 7.494 (a downfield shift of 0.075 ppm with respect to the free amine starting material), a single *para*-proton resonance at δ 7.465 (a downfield shift of 0.095 ppm) and a two proton doublet at δ 7.279 corresponding to the *ortho*-protons (an upfield shift of these resonances of 0.045 ppm). The magnetic environments of the aromatic moieties of the amines **61a** and **61b** are both significantly affected by covalent attachment to a cyclodextrin annulus upon forming the cyclodextrins **63a** and **63b**. Such a change in magnetic environment is consistent with the self-inclusion of the aromatic moiety into the cavity of the cyclodextrin, or possibly capping of the cavity by that aromatic moiety. The diastereomeric cyclodextrins **63a** and

**63b** do however exhibit significant differences in the extent of observed effects caused by that intramolecular association.

As for the other modified cyclodextrins discussed above, the likelihood of self-inclusion of the aromatic ring of the substituent into the cyclodextrin cavity, or a geometry in which the aromatic moiety caps the cyclodextrin annulus, was investigated by inspection of the resonances corresponding to the H-1 protons of the cyclodextrin annulus, in the $^1$H NMR spectra of the *(R)*- and *(S)*-amphetamine derived cyclodextrins **63a** and **63b**. In the $^1$H NMR spectrum of the *(R)*-amphetamine-derived cyclodextrin **63a**, signals corresponding to the H-1 protons are substantially resolved (Figure 3.4c), and span a region of the spectrum of 0.144 ppm. Similarly, the $^1$H NMR spectrum of the *(S)*-amphetamine-derived cyclodextrin **63b** also indicates that there is a great deal of non-equivalence of the H-1 protons of that species (Figure 3.4b). However the resonances corresponding to protons of the cyclodextrin **63b** are less well resolved than those in the spectrum of the corresponding *(R)*-amphetamine derived isomer **63a**, spanning a substantially smaller region of 0.094 ppm. The above $^1$H NMR data suggests that the cyclodextrins **63a** and **63b** both form intramolecular complexes, but also suggests that these are of differing geometries.

The $^1$H NMR spectra of the diastereomers **63a** and **63b** also exhibit differences in some resonances corresponding to the cyclodextrin H-2-6 protons of those species. The spectrum of the *(S)*-amphetamine-derived cyclodextrin **63b** contains cyclodextrin annulus proton resonances at δ 3.140, 2.940 and, partially obscured by the doublet of the methyl group of the amphetamine side chain, a further resonance at δ 1.300. Over the same

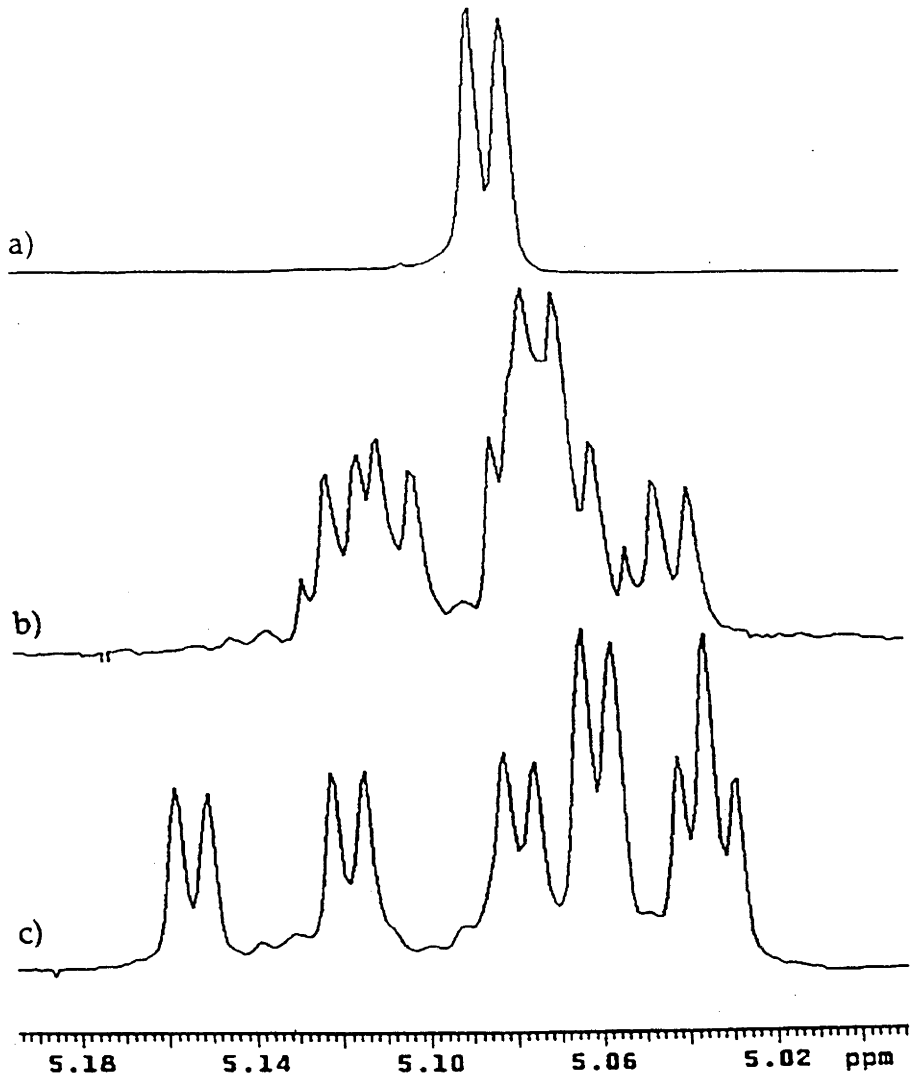



**Figure 3.4.** Partial $^1$H NMR spectra, showing the resonances corresponding to H-1 protons of the cyclodextrin annulus, of a) β-cyclodextrin **1**, b) the *(S)*-amphetamine-derived cyclodextrin **63b** and c) the *(R)*-amphetamine-derived cyclodextrin **63a**.

region, the $^1$H NMR spectrum of the *(R)*-amphetamine-derived cyclodextrin **63a** contains cyclodextrin annulus proton resonances at δ 3.104, 2.843 and 1.331.

The $^1$H NMR spectrum of each of the *(R)*- and *(S)*-amphetamine derived cyclodextrins **63a** and **63b** (0.002 mol dm$^{-3}$) in the presence of two equivalents of adamantan-1-ol **42** (0.004 mol dm$^{-3}$) was recorded. The

chemical shifts of resonances corresponding to the H-1 protons of the cyclodextrin annulus are substantially influenced by the addition of adamantan-1-ol **42**. These proton resonances are already non-equivalent prior to the addition of a guest, but the presence of adamantan-1-ol **42** causes additional chemical shift changes. As for other systems discussed above, due to the screening of the C-1 position of cyclodextrins from anisotropic effects which might be due to the complexation of a guest, these spectral changes are most likely due to a change in geometry of the cyclodextrins **63a** and **63b**. Such a change would be required to accommodate the adamantan-1-ol guest **42** and would be accompanied by disruption of any intramolecular association present in the cyclodextrins **63a** and **63b**. In addition, the remaining cyclodextrin annulus protons, namely H-2-6, which are sensitive to changes in the magnetic environment of the cavity, show slightly greater equivalence upon addition of the adamantan-1-ol guest **42** for both of the hosts **63a** and **63b**. This is consistent with the disruption of an intramolecular complex, present in both cyclodextrins **63a** and **63b**, in which the substituent aromatic moiety is affecting the magnetic environment of the cyclodextrin annulus. This is of course evidence that there were such intramolecular complexes present to begin with.

The presence of intramolecular complexation in both of the *(R)*- and *(S)*-amphetamine-derived cyclodextrins **63a** and **63b**, and thus a geometry of those species which may hinder the intermolecular complexation of a molecule less lipophilic than adamantan-1-ol **42**, was still further confirmed by complexation studies with *para*-methoxybenzylalcohol **58**. The $^{1}H$ NMR spectrum of *para*-methoxybenzylalcohol **58** (0.001 mol $dm^{-3}$) in the presence of the *(R)*-amphetamine-derived cyclodextrin **63a** (0.002 mol $dm^{-3}$) showed no shift changes in the resonances corresponding to the methoxy group, the

benzylic methylene group and the aromatic protons of the alcohol **58**, compared to those of that species in the absence of the cyclodextrin **63a**. This indicates that *para*-methoxybenzylalcohol **58** is not complexed by the *(R)*-amphetamine-derived cyclodextrin **63a**.

Addition of the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol $dm^{-3}$) to *para*-methoxybenzylalcohol **58** (0.001 mol $dm^{-3}$) did cause very small changes in the chemical shifts of resonances corresponding to the protons of the guest **58**, although no obvious changes in the $^{1}H$ NMR spectrum of the host **63b**. In the presence of the cyclodextrin **63b**, the resonances corresponding to the methyl and methylene groups of the alcohol **58** were shifted upfield by 0.008 ppm and 0.002 ppm, respectively. These small changes are similar to those of the chemical shifts of the aromatic protons of the alcohol **58**, which were moved 0.003 ppm and 0.005 ppm upfield in the presence of the cyclodextrin **63b**. The small extent of these cyclodextrin-induced changes suggests that the alcohol **58** is not substantially complexed by the cyclodextrin **63b**. This is most likely due to the presence of intramolecular complexation in the *(S)*-amphetamine-derived cyclodextrin **63b**.

Similar to the cases of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** and the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**, it is likely that it is strong intramolecular complexation in the *(R)*-amphetamine-derived cyclodextrin **63a** which prevents the complexation of *para*-methoxybenzylalcohol **58**. It seems that the *(R)*-amine-derived cyclodextrins **57a**, **62a** and **63a**, all allow a high extent of inclusion in, or capping of, the cyclodextrin annulus by their aromatic moieties. By contrast, the intramolecular complexes of the *(S)*-amine-derived cyclodextrins **57b** and

**62b** are readily disrupted by the weakly lipophilic alcohol **58**. The cyclodextrin **63b** shares the same absolute configuration in the substituent with the *(S)*-amine-derived cyclodextrins **57b** and **62b**. However, unlike those species, the *(S)*-amphetamine-derived cyclodextrin **63b** forms a sufficiently strong intramolecular complex to limit the complexation of *para*-methoxybenzylalcohol **58**. This is presumably due to extra flexibility present in the substituent.

The phenylglycinol-derived cyclodextrins **46a** and **46b** were prepared using methods outlined above. The *(R)*-phenylglycinol-derived cyclodextrin **46a** was isolated as a colourless solid in 35% and 45% yield, when prepared from the corresponding tosylate **17** or iodide **31**. TLC analysis of the amine **46a** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **46a** gave a signal at *m/z* 1254.5 corresponding to $M+H^+$ and one at *m/z* 1276.5 corresponding to $M+Na^+$. HRESI-MS gave a signal measured as *m/z* 1254.4504, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1254.4511 required for $C_{50}H_{80}NO_{35}$, and a further signal measured as *m/z* 1276.4350, which is within experimental error of the calculated value for $M+Na^+$ of *m/z* 1276.4330 required for $C_{50}H_{79}NNaO_{35}$. The proton decoupled $^{13}C$ NMR spectrum of the amine **46a** displayed a resonance at δ 57.5, assigned to the methine carbon of the substituent, and several signals in the range δ 126.1 - 128.1 and a single resonance at δ 141.8 assigned to the five tertiary carbons and single quaternary carbon of the aromatic moiety of the substituent, respectively. In addition to these resonances, several signals assigned to cyclodextrin **46a** annulus carbons were observed, including a resonance at δ 48.0, assigned to the $C\text{-}6^A$ carbon, along with multiple resonances around δ 60.0, assigned as corresponding to the $C\text{-}6^{B\text{-}G}$ carbons.

The *(S)*-phenylglycinol-derived cyclodextrin **46b** was isolated as a colourless solid in 47% or 52% yield, when prepared from the corresponding tosylate **17** or iodide **31**. TLC analysis of the amine **46b** revealed only one spot, for a compound of higher $R_f$ than β-cyclodextrin **1**. ESI-MS of the amine **46b** gave a signal at *m/z* 1255.5 corresponding to $M+H^+$. HRESI-MS gave a signal measured as *m/z* 1254.4503, which is within experimental error of the calculated value for $M+H^+$ of *m/z* 1254.4511 required for $C_{50}H_{80}NO_{35}$, and a further signal measured as *m/z* 1276.4389, which is within experimental error of the calculated value for $M+Na^+$ of *m/z* 1276.4330 required for $C_{50}H_{79}NNaO_{35}$. Microanalytical data indicated that a mixture of the cyclodextrin **46b** and the diastereomer **46a**, isolated from a reaction mixture prepared to study the competitive rates of reaction of the amines **59a** and **59b** with the iodide **31** as outlined below, was pure, save for complexing an average of 5.5 water molecules. The proton decoupled $^{13}C$ NMR spectrum of the amine **46b** contained a resonance at δ 58.5, assigned to the methine carbon of the substituent, and several signals in the range δ 127.0 - 128.3 and a single resonance at δ 141.9 assigned to the five tertiary carbons and single quaternary aromatic carbon of the substituent, respectively. In addition to these resonances, several signals assigned to cyclodextrin **46b** annulus carbons were observed, including a resonance at δ 48.4, assigned to the C-$6^A$ carbon, along with multiple resonances around δ 60.0, assigned as corresponding to the C-$6^{B-G}$ carbons.

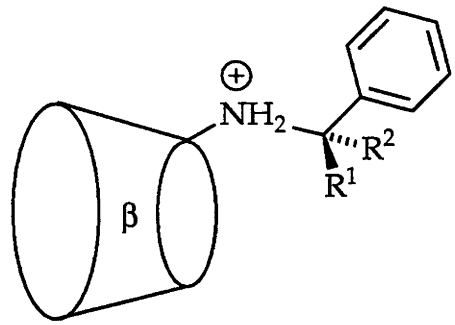
The HPLC retention times of the *(R)*- and *(S)*-phenylglycinol-derived cyclodextrins **46a** and **46b**, under the conditions previously outlined, were recorded and found to be 0.74 and 0.82, respectively, with respect to β-cyclodextrin **1**. The shorter retention time of the *(R)*-phenylglycinol-derived cyclodextrin **46a** places it in the group of cyclodextrins which include the *(S)*-

1-phenylethylamine- and *(S)*-1-(1-naphthyl)-ethylamine-derived species **45b** and **47b**, both of which have shorter HPLC retention times than their corresponding diastereomers **45a** and **47a**. These cyclodextrins **45b** and **47b**, are the species which are hypothesized above to have a weaker extent of intramolecular complexation than their diastereomers **45a** and **47a**. Simply by analogy with those systems it is possible that the cyclodextrin **46a** has a lesser extent of intramolecular complexation than the diastereomer **46b**.

Similar to work described above for preparation of mixtures of the pairs of diastereomers **45a,b**, **47a,b** and **48a,b** from the iodide **31**, the competitive reaction in which the diastereomers **46a** and **46b** were prepared from the iodide **31** was investigated for selectivity. Thus a competitive reaction was performed in which one mole equivalent of each of the enantiomers of phenylglycinol **59a** and **59b** was treated with the iodide **31**, and the products were isolated. HPLC analysis showed that the *(S)*-phenylglycinol-derived cyclodextrin **46b** and the *(R)*-phenylglycinol-derived diastereomer **46a** were produced in a ratio of approximately 1.3 : 1.

The $^1$H NMR studies outlined below were conducted in pH 6.0 phosphate buffered $D_2O$. By an analogous argument to that outlined above, for studies conducted at pH 6.0 the predominant form of the cyclodextrins **46a** and **46b** will be the corresponding conjugate acids **64a** and **64b**.

The $^1$H NMR spectra of the *(S)*- and *(R)*-phenylglycinol-derived cyclodextrins **64b** and **64a** reveal that covalent attachment of the amino alcohol moiety to the cyclodextrin annulus produces many changes in the magnetic environment of both the cyclodextrin annulus protons and those of the substituent. The aromatic protons of *(R)*-phenylglycinol **59a** in pH 6.0




**64a** $R^1 = H, R^2 = CH_2OH$
**64b** $R^1 = CH_2OH, R^2 = H$

phosphate buffered $D_2O$ give rise to a series of poorly resolved resonances in the $^1H$ NMR spectrum of that species (Figure 3.5a). The corresponding region of the spectrum of the *(R)*-phenylglycinol-derived cyclodextrin **64a** containing resonances corresponding to aromatic protons, while superficially similar in appearance to that region in the spectrum of the unreacted amine **59a**, shows changes in chemical shift which indicate that there are substantial differences in the shielding of those protons (Figure 3.5b). This is reflected in a difference upon covalent attachment, of 0.043 ppm downfield and 0.013 ppm upfield for resonances corresponding to the *para*- and *ortho*-aromatic protons of the cyclodextrin **64a**, respectively, compared to the amino alcohol **59a**. Similar effects on the aromatic protons of the *(S)*-phenylglycinol-derived cyclodextrin **64b** result in a very similar $^1H$ NMR spectrum for that isomer (Figure 3.5c).

The $^1H$ NMR spectra of the *(R)*- and *(S)*-phenylglycinol-derived cyclodextrins **64a** and **64b** show more substantial effects on resonances corresponding to the H-1 protons of the cyclodextrin annulus upon covalent attachment of the substituents. As in previous examples in this series, the

resonances corresponding to the H-1 protons of the modified cyclodextrins **64a** and **64b** show a great deal of non-equivalence in comparison to the resonance corresponding to the seven equivalent H-1 protons of unmodified β-cyclodextrin **1**. Resonances corresponding to the H-1 protons of the *(S)*-phenylglycinol-derived cyclodextrin **64b** include a two proton doublet at δ 5.122, a three proton multiplet at δ 5.069, and a pair of single proton doublets at δ 5.037 and 5.010. This is similar to the corresponding region of the $^1$H NMR spectrum of the *(R)*-amine derived cyclodextrin **64a**. As for work discussed previously, the non-equivalence of the resonances of the annulus protons in the $^1$H NMR spectra of the cyclodextrins **64a** and **64b** indicates the likely presence of conformational changes consistent with intramolecular complexation such as the aromatic moiety self-included within, or perhaps capping, the cyclodextrin cavity.

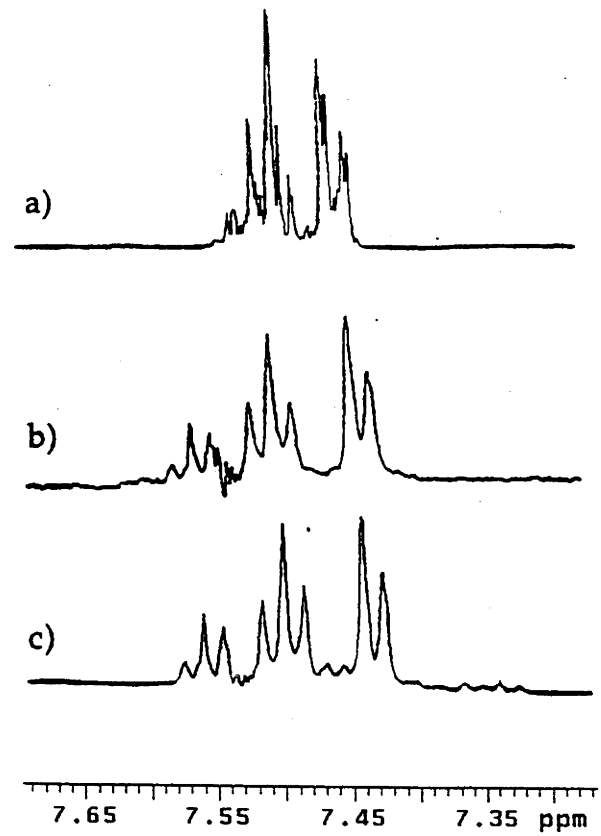



**Figure 3.5.** Partial $^1$H NMR spectra, showing the aromatic region, of a) *(R)*-phenylglycinol **59a**, b) the *(R)*-phenylglycinol-derived cyclodextrin **64a** and c) the *(S)*-phenylglycinol-derived cyclodextrin **64b**.

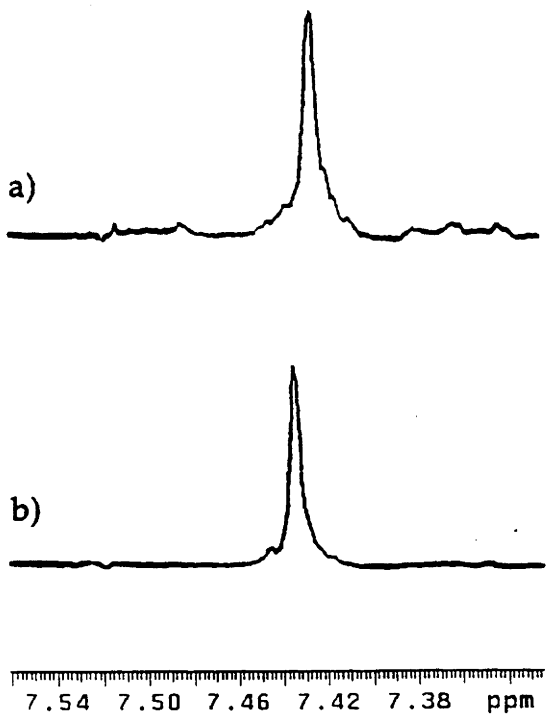



**Figure 3.6.** Partial $^1$H NMR spectra, showing resonances corresponding to aromatic protons, in the 2:1 mixtures of adamantanol **42** with a) the *(R)*-phenylglycinol-derived cyclodextrin **64a** and b) the *(S)*-phenylglycinol-derived host **64b**.

The $^1$H NMR spectra of the *(R)*- and *(S)*-phenylglycinol-derived hosts **64a** and **64b** (0.002 mol dm$^{-3}$) in the presence of two equivalents of adamantan-1-ol **42** (0.004 mol dm$^{-3}$) were recorded (Figure 3.6). These spectra indicate that addition of adamantan-1-ol **42** to the modified cyclodextrins **64a** and **64b** causes very major changes in the magnetic environment of many protons in both of the host species. Most obvious was the effect of the presence of the guest **42** on the aromatic protons of both of the cyclodextrins **64a** and **64b**. Addition of the guest **42** resulted in the signals corresponding to aromatic protons in the $^1$H NMR spectrum of those compounds **64a** and **64b** collapsing to completely unresolved singlets (Figure 3.6). It seems that the adamantan-1-ol **42** forms very strong intermolecular complexes with both of the cyclodextrins **64a** and **64b**, completely disrupting any intramolecular association between the cyclodextrin aromatic ring and annulus.

Complexation between adamantan-1-ol **42** and the *(S)*-phenylglycinol-derived cyclodextrin **64b** was further confirmed upon inspection of the

resonances corresponding to the H-1 protons of the cyclodextrin annulus in the $^1$H NMR spectrum of the complex. Upon addition of adamantan-1-ol **42** the chemical shifts of the resonances corresponding to the H-1 protons of the cyclodextrin **64b** were appreciably changed, ranging from δ 4.996 to 5.134, compared to δ 5.010 to 5.122 in the absence of guest. A smaller effect was also observed upon addition of adamantan-1-ol **42** to the *(R)*-phenylglycinol-derived cyclodextrin **64a**, where the resonances corresponding to the H-1 protons range from δ 4.992 to 5.127, compared to δ 5.010 to 5.123 in the absence of guest. As explained above, these differences upon addition of adamantan-1-ol **42** indicate the conformational change required in the cyclodextrin annulus to accommodate that guest **42**.

In order to investigate the complexation behaviour of the phenylglycinol-derived cyclodextrins **64a** and **64b** with the more weakly lipophilic *para*-methoxybenzylalcohol **58**, samples were prepared containing the alcohol **58** (0.001 mol dm$^{-3}$) and two equivalents of the *(R)*- or *(S)*-phenylglycinol-derived cyclodextrin **64a** or **64b** (0.002 mol dm$^{-3}$).

Changes were noted in the signals corresponding to the protons of the *(R)*-phenylglycinol-derived cyclodextrin **64a** in the $^1$H NMR spectrum of that species upon addition of the alcohol **58**. Resonances corresponding to the aromatic protons of the cyclodextrin **64a**, which resonated at δ 7.509 and 7.560 in the absence of the guest **58**, became a poorly resolved 3 hydrogen multiplet at around δ 7.481 upon addition of the alcohol **58**. This corresponds to changes in the chemical shifts of those signals of 0.028 and 0.079 ppm upfield, respectively. Several other noteworthy effects were produced on the $^1$H NMR spectrum of the host **64a** upon addition of the alcohol **58**, such as the change in the chemical shift of the resonance

corresponding to the methine proton of the substituent. That resonance, with a chemical shift of δ 4.196 in the absence of the cyclodextrin **64a**, had moved upfield at least 0.150 ppm to be obscured by signals corresponding to annulus protons of the cyclodextrin **64a** in the spectrum of the complex (Figures 3.7c and 3.7d). Another obvious change in the $^1$H NMR spectrum of the cyclodextrin **64a** upon addition of the guest **58** was an upfield shift of approximately 0.12 ppm in a complex overlapping set of resonances at around δ 3.20 which may correspond to the cyclodextrin annulus C-6$^A$ protons, along with other changes (Figures 3.7c and 3.7d), all consistent with the complexation of the guest **58**. In contrast, upon addition of *para*-methoxybenzylalcohol **58**, only small upfield changes of around 0.014 ppm were observed in the aromatic resonances of the *(S)*-phenylglycinol-derived cyclodextrin **64b**, and there were no significant effects on the resonances corresponding to the annulus protons of the cyclodextrin **64b** (Figures 3.7a and 3.7b). This indicates that there is little complexation of the alcohol **58** by the cyclodextrin **64b**.

It is apparent from the above work that the two phenylglycinol-derived cyclodextrins **64a** and **64b** both form intramolecular complexes between their aromatic moieties and annuli. This intramolecular complexation was able to be readily disrupted by adamantan-1-ol **42** for both of the cyclodextrins **64a** and **64b**. However *para*-methoxybenzylalcohol **58** was only able to significantly disrupt the intramolecular complex in the *(R)*-phenylglycinol-derived cyclodextrin **64a**, indicating that the intramolecular complex in the *(S)*-phenylglycinol-derived cyclodextrin **64b** is stronger.

These results are consistent with other work outlined above because, despite the absolute conformations of the species, the geometry of the substituent of

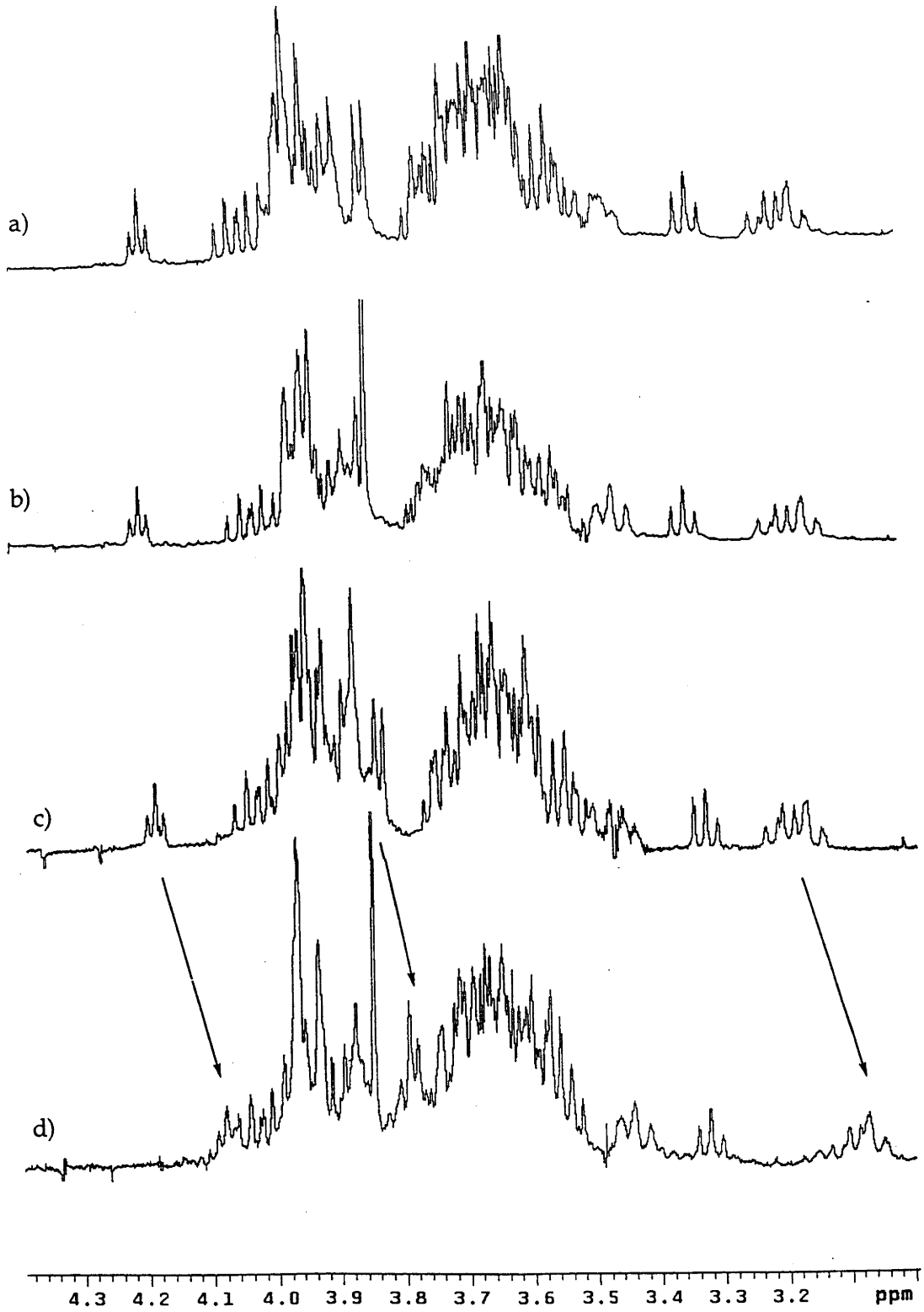



**Figure 3.7.** Partial $^{1}H$ NMR spectra, showing the resonances corresponding to the H-2-6 protons of the cyclodextrin annulus, of a) the *(S)*-phenylglycinol-derived cyclodextrin **64b**, b) the cyclodextrin **64b** plus two equivalents of *para*-methoxybenzylalcohol **58**, c) the *(R)*-phenylglycinol-derived cyclodextrin **64a** and d) the cyclodextrin **64a** plus two equivalents of *para*-methoxybenzylalcohol **58**.

the *(S)*-phenylglycinol-derived cyclodextrin **64b** is the same as for the *(R)*-amine-derived cyclodextrins **57a**, **62a** and **63a**. That is, the orientation of the aromatic moiety with respect to the methyl group in the cyclodextrins **57a**, **62a** and **63a** is the same as the orientation of the phenyl group with respect to the hydroxymethyl group in the cyclodextrin **64b**. Of course by an analogous argument, the *(R)*-phenylglycinol-derived cyclodextrin **64a** shares a similar geometry of like groups in the substituent with the *(S)*-amine-derived cyclodextrins **57b**, **62b** and **63b**.

In Chapters 2 and 3 of the Results and Discussion of this Thesis the synthesis and properties of the related pairs of diastereomeric cyclodextrins **57a,b** and **62a,b - 64a,b** is discussed. It has been found that the cyclodextrins **57a,b** and **62a,b - 64a,b** all form intramolecular complexes between their aromatic moieties and annuli, although the strengths of these complexes vary. The strongly lipophilic species adamantan-1-ol **42** is able to disrupt the intramolecular complexes present in all of the cyclodextrins **57a,b** and **62a,b - 64a,b** and therefore form intermolecular complexes with all of them. As mentioned in the Introduction to this Thesis, the formation of intramolecular complexes in modified cyclodextrins is a dynamic process, with the associated and non-associated forms of that species existing in equilibrium.[39,72,73,79,106,108,109] In the presence of a guest there is of course an extra equilibrium set up between the vacant cyclodextrin, free guest and the host-guest intermolecular complex.[39,72,73,106] In systems containing the strongly lipophilic adamantan-1-ol **42** this equilibrium strongly favours the formation of intermolecular complexes, and this is reflected in the $^1$H NMR spectra of the complexes.

However in systems containing the much more weakly lipophilic *para*-methoxybenzylalcohol **58** the evidence for intermolecualr complexation is not so clear. This species is less likely to strongly influence the equilibrium between the intramolecularly associated and non-associated forms of the cyclodextrins **57a,b** and **62a,b - 64a,b**. In the systems containing *para*-methoxybenzylalcohol **58** and the cyclodextrins **57a,b** and **62a,b - 64a,b** only gross effects were observed and so only substantial complexation of the guest **58**, and hence significant disruption of the intramolecular complexes of the cyclodextrins **57a,b** and **62a,b - 64a,b** is able to be reported. It was observed that the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, the *(R)*-1-(1-naphthyl)-ethylamineamine-derived cyclodextrin **62a**, the *(R)*-amphetamine-derived cyclodextrin **63a** and the *(S)*-phenylglycinol-derived cyclodextrin **64b** each do not significantly complex the alcohol **58**, and this is due to the strong intramolecular complexes of those species. The *(S)*-amphetamine-derived cyclodextrin **63b**, also does not substantially complex the alcohol **58** despite sharing a common orientation of like groups in their substituents with the cyclodextrins **57b**, **62b** and **64a**, all of which are postulated to have comparatively weak extents of intramolecular complexation. This apparent larger extent of intramolecular complexation in the *(S)*-amphetamine-derived cyclodextrin **63b** is likely due to the extra flexibility in the substituent of that species. In contrast the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**, the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** and the *(R)*-phenylglycinol-derived cyclodextrin **64a** all do complex *para*-methoxybenzylalcohol **58** because of their above-mentioned comparatively weak extents of intramolecular complexation.

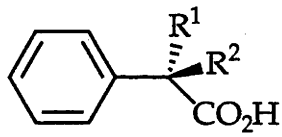
## Results and Discussion Chapter 4

### Chiral Discrimination in Inclusion Complexes of Amino-Cyclodextrins

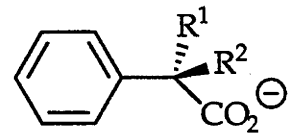
With access to the cyclodextrins **57a,b** and **62a,b - 64a,b**, their interaction with the enantiomers of 2-phenylpropanoate **43a** and **43b**, and the corresponding acids **8a** and **8b**, along with the Ibuprofen anion enantiomers **44a** and **44b**, and the corresponding acids **37a** and **37b**, was studied using $^1$H NMR spectroscopy. The guests **8a,b**, **37a,b**, **43a,b** and **44a,b** were chosen in order to probe factors which affect complexation and discrimination, such as the lipophilicity and hydration of the guest and the charge of species in host-guest complexes with modified cyclodextrins. To allow control of the protonation state of the guests, the host-guest systems discussed below were studied in pH = 6.0 and 1.0 phosphate buffered $D_2O$. These are systems in which the anions **43a,b** and **44a,b**, and the corresponding acids **8a,b** and **37a,b** will predominate, respectively.[26] The cationic cyclodextrins **57a,b** and **62a,b - 64a,b** will be the dominant host forms at both pH = 1.0 and, as previously discussed, pH = 6.0. This allows the opportunity to study ionic host-guest interactions in systems containing charged host species, also as previously discussed.

It was therefore decided to employ $^1$H NMR analysis to the systems of interest, with the expectation that complexation of racemates of the guests **8a,b**, **37a,b**, **43a,b** and **44a,b** by the cyclodextrins **57a,b** and **62a,b - 64a,b** would result in the observation of spectroscopic discrimination. It was decided to initially study the interaction of the acids **8a** and **8b**, and the anions **43a** and **43b**, with the cyclodextrins **57a,b** and **62a,b - 64a,b**. It was found that inspection of the resonances corresponding to the methyl groups of the

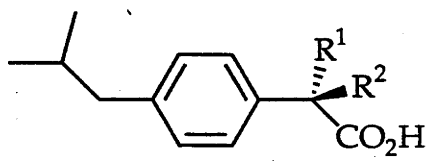
guests **8a,b** and **43a,b**, in their $^1$H NMR spectra in the presence of the cyclodextrins **57a,b** and **62a,b - 64a,b**, provided a ready method to determine either the presence or absence of complexation and discrimination in a given system. Other resonances corresponding to protons of the guests **8a,b** and **43a,b** were unsuitable because they were obscured by resonances corresponding to protons of the cyclodextrins **57a,b** and **62a,b - 64a,b** in many of the systems under study.



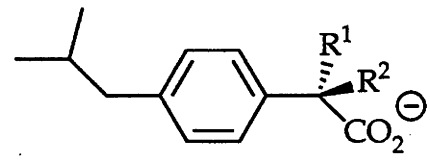

**8a** $R^1 = H, R^2 = CH_3$
**8b** $R^1 = CH_3, R^2 = H$




**43a** $R^1 = H, R^2 = CH_3$
**43b** $R^1 = CH_3, R^2 = H$




**37a** $R^1 = H, R^2 = CH_3$
**37b** $R^1 = CH_3, R^2 = H$




**44a** $R^1 = H, R^2 = CH_3$
**44b** $R^1 = CH_3, R^2 = H$

Thus, the complexation behaviour of the modified cyclodextrins **57a,b** and **62a,b - 64a,b** with the 2-phenylpropanoate enantiomers **43a** and **43b** and the enantiomeric acids **8a** and **8b**, as monitored by $^1$H NMR spectroscopy at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 and 1.0 phosphate buffered $D_2O$, respectively, was investigated.

Upon examination of the $^1$H NMR spectrum of a sample containing the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol dm$^{-3}$) and the phenylpropanoate enantiomers **43a** and **43b** (0.0005 mol dm$^{-3}$ each) there was no spectroscopic discrimination observed. In that spectrum the doublet corresponding to the methyl groups (Figure 4.1b) and the resonances corresponding to the aromatic protons of the guests **43a** and **43b** showed no evidence of splitting and no significant changes in chemical shift due to the cyclodextrin **57a**. Similarly there were no significant changes in either the appearance or the chemical shift of the resonances corresponding to the cyclodextrin **57a**, also indicating that there was no complexation. This is consistent with results discussed in Chapter 2 of this Thesis, which suggest that the aromatic moiety of the substituent of the modified cyclodextrin **57a** forms a strong complex with the annulus of that species. This intramolecular complex could not be disrupted by the weakly lipophilic anions **43a** and **43b**, and thus no discrimination was observed.

Unlike the previous system which contained the *(R)*-phenylethylamine-derived cyclodextrin **57a**, spectroscopic discrimination was observed in the interaction between the *(S)*-phenylethylamine-derived cyclodextrin **57b** (0.002 mol dm$^{-3}$) and the phenylpropanoate enantiomers **43a** and **43b** (0.0005 mol dm$^{-3}$ each) at pH 6.0. In the $^1$H NMR spectrum of this system, the methyl proton resonances corresponding to the *(S)*- and *(R)*-anions **43b** and **43a** were shifted significantly upfield, namely 0.036 and 0.032 ppm, respectively (Figure 4.1c). The extent of this discrimination is slight and the separation of the signals corresponding to the enantiomers **43a** and **43b** was lost when, in an effort to elucidate the identity of the signals in the spectrum, further *(S)*-2-phenylpropanoate **43b** (0.001 mol dm$^{-3}$) was added to the sample. It was intended that the identification of resonances which

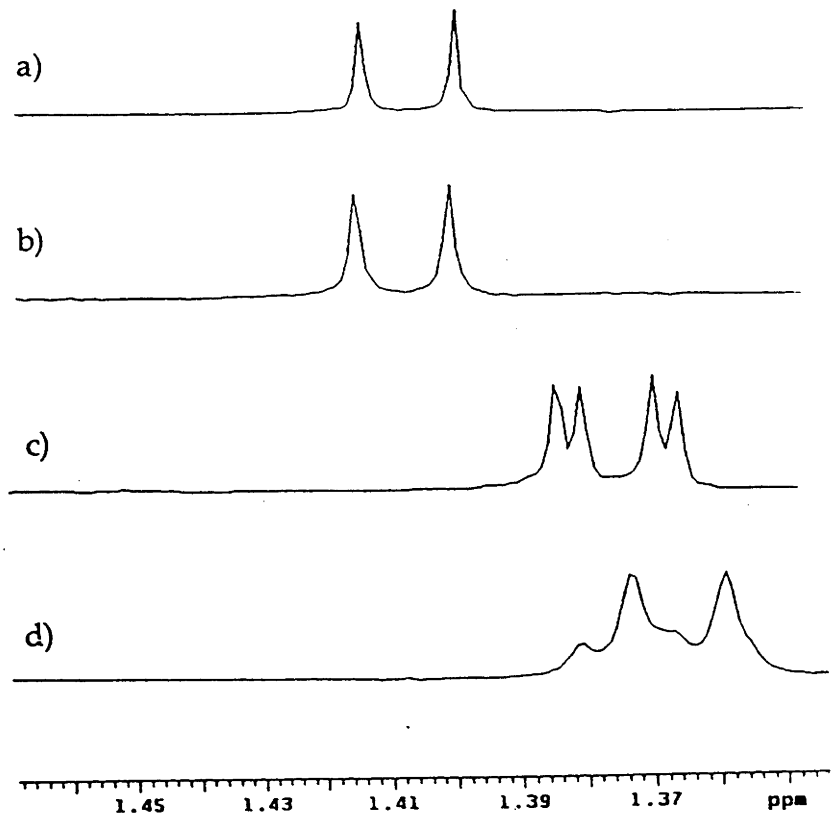



**Figure 4.1.** Partial $^1$H NMR spectra, showing resonances corresponding to the methyl groups of a) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol dm$^{-3}$ each) at pH 6.0, b) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol dm$^{-3}$) at pH 6.0, c) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (0.002 mol dm$^{-3}$) at pH 6.0, and d) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol dm$^{-3}$ each) with added *(S)*-2-phenylpropanoate **43b** (0.001 mol dm$^{-3}$) in the presence of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (0.005 mol dm$^{-3}$) at pH 6.0.

correspond to the enantiomers **43a** and **43b** in the $^1$H NMR spectrum of the complex with the guest **57b** would be made by the addition of extra *(S)*-2-phenylpropanoic acid **43b** to the existing sample, and noting the relative increase in the amplitude of one of the guest resonances.[26] In order to overcome the loss of discrimination, a sample was prepared which contained a higher concentration of the cyclodextrin **57b** (0.005 mol dm$^{-3}$) in

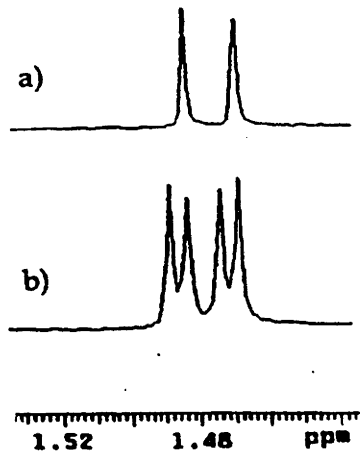



**Figure 4.2.** Partial $^1$H NMR spectra, showing resonances corresponding to the methyl groups of a) *(R)*-and *(S)*-2-phenylpropanoic acid **8a** and **8b** (0.0005 mol dm$^{-3}$ each) at pH 1.0, and b) *(R)*-and *(S)*-2-phenylpropanoic acid **8a** and **8b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol dm$^{-3}$) at pH 1.0.

the presence of a racemate of the phenylpropanoates **43a** and **43b** (0.0005 mol dm$^{-3}$ each) with added *(S)*-2-phenylpropanoate **43b** (0.001 mol dm$^{-3}$). In this sample the signals were sufficiently separated to allow positive identification of the resonances of the enantiomers (Figure 4.1d) and yielded the assignments above.

Spectroscopic discrimination was also observed in the $^1$H NMR spectrum of a sample containing the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoic acid enantiomers **8a** and **8b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. Upon addition of the cyclodextrin **57a**, the methyl groups corresponding to the guests **8a** and **8b** resolved slightly into two distinct signals (Figure 4.2b). Similar to the previous example, addition of further *(S)*-2-phenylpropanoate **8b** resulted in this slight discrimination being lost; the signals for the respective guest isomers became coincident once more. A further sample was prepared containing the racemate of the

enantiomers **8a** and **8b** (0.0005 mol $dm^{-3}$ each) with added *(S)*-2-phenylpropanoate **8b** (0.001 mol $dm^{-3}$), once again in the presence of a greater amount of the cyclodextrin **57a** (0.005 mol $dm^{-3}$) at pH 1.0. The $^1H$ NMR spectrum was recorded, and the resonances corresponding to the enantiomers **8a** and **8b** were found to be resolved and their relative abundances noted (Figure 4.3).

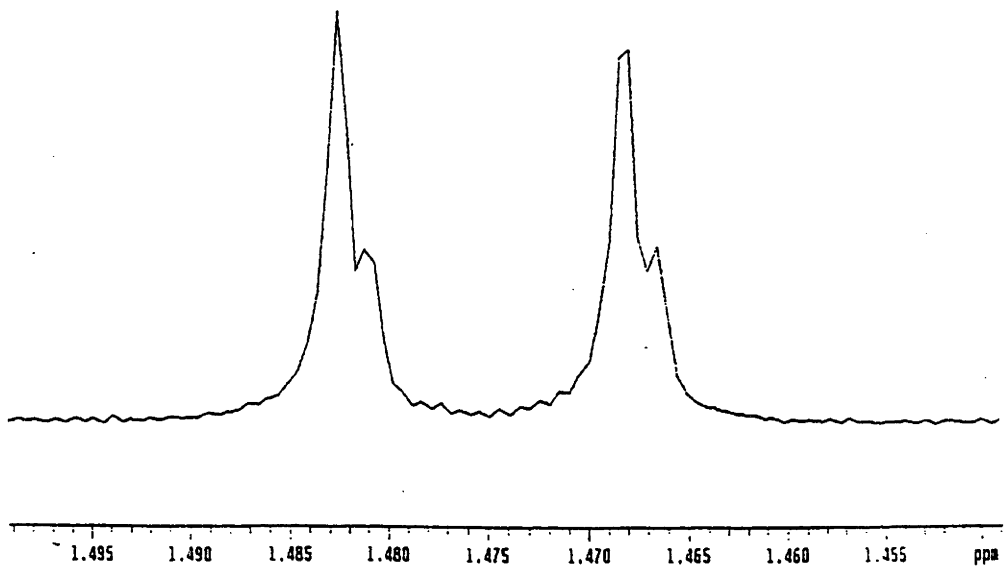



**Figure 4.3.** Partial $^1H$ NMR spectra, showing resonances corresponding to the methyl groups of the *(R)*-and *(S)*-2-phenylpropanoic acid enantiomers **8a** and **8b** (0.0005 mol $dm^{-3}$ each) with added *(S)*-2-phenylpropanoic acid **8b** (0.001 mol $dm^{-3}$) in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.005 mol $dm^{-3}$) at pH 1.0.

Discrimination was also observed in the $^1H$ NMR spectrum of a sample containing the 2-phenylpropanoic acid enantiomers **8a** and **8b** (0.0005 mol $dm^{-3}$ each) and the *(S)*-phenylethylamine-derived cyclodextrin **57b** (0.002 mol $dm^{-3}$) at pH 1.0. The spectroscopic discrimination in this system was very strong and was observed as shifts of 0.024 ppm upfield and 0.004 downfield for resonances corresponding to methyl groups of *(R)*- and *(S)*-2-

phenylpropanoic acid **8a** and **8b**, respectively. The extent of discrimination was sufficient in this spectrum that identification of enantiomers in the $^1H$ NMR spectrum of the complex was simply achieved by addition of further *(S)*-2-phenylpropanoic acid **8b** (0.002 mol $dm^{-3}$) and noting the increase in amplitude of the resonance corresponding to the methyl group of the guest **8b**.

For completeness and ease of comparison, the $^1H$ NMR spectra of the above samples, and all the subsequent ones in this study, were measured under identical conditions, with a 2:1 ratio of cyclodextrin to guest. The method of identification of the resonances corresponding to the individual isomers of the guest in a sample by adding a further amount of either the *(S)*-propanoate **43b**, or the *(S)*-acid **8b** as appropriate, and as outlined above, was adopted in all subsequent samples in this study. This allowed elucidation of the identity of resonances corresponding to the enantiomeric guests **8a,b** or **43a,b** in the $^1H$ NMR spectra of most complexes under investigation.

The loss of observable discrimination in the $^1H$ NMR spectrum upon addition of further guest in several samples in this study is a consequence of the change in relative concentrations of host and guest. As is outlined in Chapter 1 of the Results and Discussion of this Thesis, assuming a change in the chemical shift of some guest resonance upon complexation, the observed chemical shift of a species, $\delta_{obs}$, is a weighted average of the chemical shift due to free and complexed species, $\delta_{free}$ and $\delta_{complex}$, respectively (Equation 2).

$$\delta_{obs} = (\delta_{free}[\text{free guest}] + \delta_{complex}[\text{complex}])/([\text{free guest}] + [\text{complex}]) \qquad 2$$

In the systems under study here the guests are present as a pair of enantiomers **8a** and **8b**, or **43a** and **43b**, in samples which also contain one of the cyclodextrins **57a,b** and **62a,b - 64a,b**. Thus there are four species contributing to the observed chemical shifts of resonances corresponding to the protons of those guests, namely the *(R)*-isomer of guest when free and bound, and those of the *(S)*-isomer of guest when free and bound. Due to the achiral environment of the solution, the chemical shifts of the enantiomers of free guest are of course identical, $\delta_{free}$, but if chemical shifts of the *(R)*- and *(S)*-enantiomers of guest when bound are non-equivalent, then the result is spectroscopic discrimination. The extent of spectroscopic discrimination, that is the difference between the observed chemical shifts of the two isomers, $\delta_{obs(R)}$ and $\delta_{obs(S)}$, is dependent on cyclodextrin concentration. As the concentration of the cyclodextrin host increases, the concentrations of the host-guest complexes also increase. It is clear from equation 2 that the influence of $\delta_{complex}$ on $\delta_{obs}$ will then become more significant. Thus, as the concentration of cyclodextrin increases, the difference between $\delta_{obs(R)}$ and $\delta_{obs(S)}$ will be greater, and so the observed extent of spectroscopic discrimination will increase. The corollary to this is of course that as the relative concentration of guest increases the extent of observable discrimination in the system will decrease. In several samples in this study this effect was sufficiently large to totally remove the observable spectroscopic discrimination in samples which had a further quantity of the *(S)*-isomer of the guest **8b** or **43b** added in an attempt to identify the resonances of those species.

This effect of guest concentration on the extent of observable spectroscopic discrimination is readily illustrated by the following system. A sample was prepared containing the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**

(0.002 mol $dm^{-3}$) and the enantiomers of 2-phenylpropanoic acid **8a** and **8b** (0.005 mol $dm^{-3}$ each); a system observed to show large spectroscopic discrimination. $^1H$ NMR spectra were recorded in either the absence or presence of additional *(S)*-2-phenylpropanoic acid **8b** (0.005 mol $dm^{-3}$) (Figure 4.4). The signals corresponding to the methyl doublets of the *(R)*- and *(S)*-enantiomers **8a** and **8b** in the presence of cyclodextrin **57b** were a clearly resolved pair of doublets with the *(R)*-acid **8a** signal having been shifted upfield 0.012 ppm, and the doublet corresponding to the *(S)*-acid **8b** remaining unchanged. In the presence of an additional amount of *(S)*-acid **8b**, as expected there was observed a change in relative intensities in amplitude of the doublets which of course revealed the identity of the

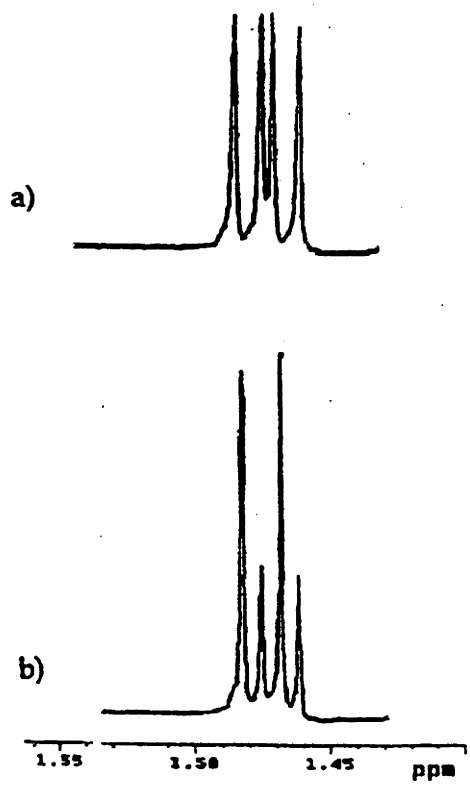



**Figure 4.4.** $^1H$ NMR spectra of the methyl groups of a) *(R)*-and *(S)*-2-phenylpropanoic acid **8a** and **8b** (0.005 mol $dm^{-3}$ each) in the presence of the cyclodextrin **57b** (0.002 mol $dm^{-3}$) at pH 1.0, and b) *(R)*-and *(S)*-2-phenylpropanoic acid **8a** and **8b** (0.005 mol $dm^{-3}$ each) with added *(S)*-2-phenylpropanoic acid **8b** (0.005 mol $dm^{-3}$) in the presence of the cyclodextrin **57b** (0.002 mol $dm^{-3}$) at pH 1.0.

resonance corresponding to the methyl group of *(S)*-2-phenylpropanoic acid **8b**. However, in addition to this, the signals for the methyl group of the guest enantiomers **8a** and **8b** were not as widely separated. In this sample, the resonance corresponding to the *(R)*-acid **8a** was found only 0.005 ppm upfield of that of the *(S)*-acid **8b**. The increased relative amount of free guest had caused a decrease in the extent of observed spectroscopic discrimination.

Similar to work described above, where there was shown to be no discrimination and no complexation of the 2-phenylpropanoate isomers **43a** and **43b** by the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, the $^1$H NMR spectrum of a sample containing the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin host **62a** (0.002 mol dm$^{-3}$) and the propanoates **43a** and **43b** (0.0005 mol dm$^{-3}$ each) at pH 6.0 also showed no evidence of discrimination or complexation in that system. The resonance corresponding to the methyl groups of the enantiomers **43a** and **43b** remained as a single doublet which had neither changed chemical shift, nor resolved into discrete signals for the guest enantiomers **43a** and **43b**, upon addition of the cyclodextrin **62a**.

Conversely, the $^1$H NMR spectrum of a sample containing the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoate enantiomers **43a** and **43b** (0.0005 mol dm$^{-3}$ each) at pH 6.0, showed discrimination and significant evidence of complexation. Upon addition of the cyclodextrin **62b**, the resonances corresponding to the methyl groups of the *(R)*- and *(S)*-2-phenylpropanoates **43a** and **43b** resolved into duplicate signals, experiencing upfield shifts of 0.082 and 0.077 ppm, respectively. This effect, combined with large upfield shifts and increases in complexity for resonances corresponding to the aromatic protons of the

guests **43a** and **43b**, indicates the existence of strong complexation in this system. Complexation was further evident in changes in resonances corresponding to the cyclodextrin host **62b** in the presence of the guests **43a** and **43b**. The presence of discrimination and complexation in this system is an indication of the relatively weak extent of intramolecular complexation present in the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b**.

As discussed above, the likelihood of the formation of a complex of a given cyclodextrin and the 2-phenylpropanoic acid enantiomers **8a** and **8b** was expected to be greater than for the anions **43a** and **43b**. This proved to be the case upon inspection of the $^1$H NMR spectrum of a sample containing the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoic acid isomers **8a** and **8b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. In this $^1$H NMR spectrum, the doublets corresponding to the methyl groups of the guests **8a** and **8b** were resolved, however this effect was not large, leaving the two signals only 0.002 ppm apart (Figure 4.5b). Due to the small separation of the signals the resonances were unable to be assigned to the enantiomers **8a** and **8b**, but the existence of discrimination in the $^1$H NMR spectrum, combined with an increase in complexity of the resonances corresponding to the aromatic protons of the guests **8a** and **8b**, is an indication of intermolecular complex formation.

Significant discrimination and complexation was observed in the $^1$H NMR spectrum of a sample containing the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoic acid enantiomers **8a** and **8b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. Upon addition of the cyclodextrin **62b** the signals corresponding to the methyl groups of the *(R)*- and *(S)*-enantiomers **8a** and **8b** resolved, shifting upfield 0.027 and 0.013

ppm, respectively. The relatively large extent of spectroscopic discrimination in this system allowed the ready identification of the resonances corresponding to the *(R)*-and *(S)*-acid enantiomers **8a** and **8b**.

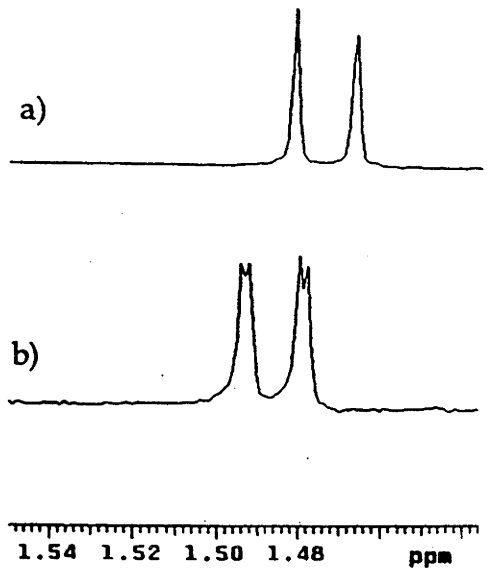



**Figure 4.5.** $^{1}H$ NMR spectra of the methyl groups of a) *(R)*-and *(S)*-2-phenylpropanoic acid **8a** and **8b** (0.0005 mol $dm^{-3}$ each) at pH 1.0, and b) *(R)*- and *(S)*-2-phenylpropanoic acid **8a** and **8b** (0.0005 mol $dm^{-3}$ each) in the presence of the *(R)*-1-(1-naphthyl)ethylamine-derived cyclodextrin **62a** (0.002 mol $dm^{-3}$) at pH 1.0.

Inspection of the $^{1}H$ NMR spectrum of a sample containing the *(R)*-amphetamine-derived cyclodextrin **63a** (0.002 mol $dm^{-3}$) and *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol $dm^{-3}$ each) at pH 6.0 showed no evidence of complex formation. In that spectrum, the resonances corresponding to the methyl groups of the guests **43a** and **43b** were coincident with that of the methyl group of the substituent of the cyclodextrin **63a**, however it was clear that there was no splitting apparent in those signals. In addition there was no shifting or duplication of the resonances corresponding to the aromatic protons of the guests **43a** and **43b** which also might have indicated complex formation. Lack of

intermolecular complexation in this system is consistent with the presence of a strong intramolecular complex in the cyclodextrin **63a**.

Inspection of the $^1H$ NMR spectrum of a sample containing the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol $dm^{-3}$) and the 2-phenylpropanoate enantiomers **43a** and **43b** (0.0005 mol $dm^{-3}$ each) at pH 6.0, showed significant spectroscopic discrimination. This was once again observed in the resonances corresponding to the methyl groups of the enantiomeric guests **43a** and **43b**, those signals resolving and shifting upfield 0.007 and 0.024 ppm, respectively (Figure 4.6a). The assignments of the resonances to the enantiomers of the guests **43a** and **43b** was accomplished using the previously outlined technique (Figure 4.6b). The complexation of the guests **43a** and **43b** in this system is interesting since, as discussed in Chapter 3 of the Results and Discussion of this Thesis, the cyclodextrin **63b** displayed no complexation of the alcohol **58**.

As for the above system containing the *(R)*-amphetamine-derived cyclodextrin **63a** and the 2-phenylpropanoate enantiomers **43a** and **43b** at pH 6.0, there was no evidence of complexation in the $^1H$ NMR spectrum of a sample containing the corresponding acid isomers **8a** and **8b** (0.0005 mol $dm^{-3}$ each) and the cyclodextrin **63a** (0.002 mol $dm^{-3}$) at pH 1.0. In this spectrum the resonances corresponding to the methyl protons of the substituent of the cyclodextrin **63a** were not coincident with those of the acids **8a** and **8b**, but there was no evidence of resolution of those signals. There was also no evidence of discrimination or complexation in any other resonances corresponding to protons of either the acid enantiomers **8a** and **8b**, or the cyclodextrin **63a**. Clearly the aromatic moiety of the cyclodextrin **63a** forms a sufficiently strong intramolecular complex with the annulus to

preclude the formation of an intermolecular complex, even with species as lipophilic as the 2-phenylpropanoic acid enantiomers **8a** and **8b**. This result was unexpected because the other *(R)*-amine-derived cyclodextrins, namely the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** and *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a**, both complexed the acid isomers **8a** and **8b**, despite also forming intramolecular complexes. As discussed in Chapter 3 of the Results and Discussion of this Thesis, the amphetamine-derived cyclodextrins **63a** and **63b** have greater flexibility in their substituents than the other cyclodextrins in this series. The effect of this flexibility, combined with the convenient chirality for strong intramolecular association that is apparently present in this series of *(R)*-amine-derived cyclodextrins **57a**, **62a** and **63a**, obviously gave special stability to the intramolecular complex in the cyclodextrin **63a**, allowing no intermolecular complexation of the lipophilic acids **8a** and **8b**.

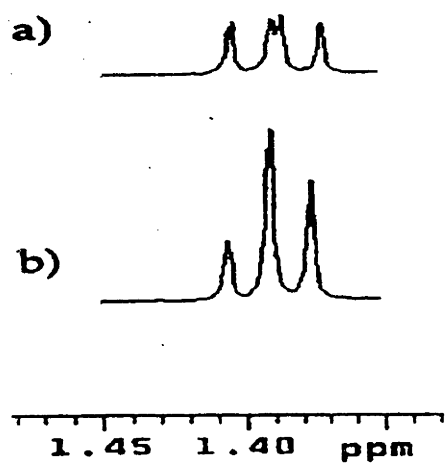



**Figure 4.6.** $^{1}H$ NMR spectra of the methyl groups of a) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol $dm^{-3}$ each) in the presence of the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol $dm^{-3}$) at pH 6.0, and b) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol $dm^{-3}$ each) with added *(S)*-2-phenylpropanoate **43b** (0.001 mol $dm^{-3}$) in the presence of the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol $dm^{-3}$) at pH 6.0.

Unlike the preceding system, marked spectroscopic discrimination was observed in the $^1$H NMR spectrum of a mixture of the 2-phenylpropanoic acid enantiomers **8a** and **8b** (0.0005 mol dm$^{-3}$ each) and the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol dm$^{-3}$) at pH 1.0. The resonances corresponding to the methyl groups of the *(R)*- and *(S)*-isomers **8a** and **8b** were observed to resolve into separate signals and move 0.026 ppm downfield and 0.058 ppm upfield, respectively. The presence of intermolecular complexation and thus discrimination in this system, but not the preceding one, confirms the lesser extent of intramolecular complexation in the cyclodextrin **63b** compared to the cyclodextrin **63a**.

The $^1$H NMR spectrum of a sample containing the *(S)*-phenylglycinol-derived cyclodextrin **64b** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoate enantiomers **43a** and **43b** (0.0005 mol dm$^{-3}$ each) at pH 6.0 showed no evidence of spectroscopic discrimination. The resonance corresponding to the methyl groups of the enantiomers **43a** and **43b** remained as a single doublet in the presence of the cyclodextrin **64b**. Although the proximity of signals corresponding to aromatic protons of the cyclodextrin **64b** made positive identification of resonances corresponding to the aromatic protons of the guests **43a** and **43b** difficult, there was no evidence of discrimination. Due to the apparent strength of the intramolecular complex in the cyclodextrin **63b**, as discussed above, the lack of intermolecular complexation of the guests **43a** and **43b** at pH 6.0 was as expected.

The $^1$H NMR spectrum of a sample containing the *(R)*-phenylglycinol-derived cyclodextrin **64a** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoate enantiomers **43a** and **43b** (0.0005 mol dm$^{-3}$ each) at pH 6.0 also provided no evidence of spectroscopic discrimination. The resonance corresponding to

the methyl group of the propanoate enantiomers **43a** and **43b** showed no splitting, and the aromatic signals showed only very small changes in chemical shift upon addition of the cyclodextrin **64a**. In addition, in the presence of the guests **43a** and **43b** the resonances corresponding to the H-2-6 protons of the annulus of the cyclodextrin **64a** were also virtually unchanged. There was no evidence of either discrimination or complexation in this system.

In the $^1$H NMR spectrum of a sample containing the *(S)*-phenylglycinol-derived cyclodextrin **64b** (0.002 mol dm$^{-3}$) and the 2-phenylpropanoic acid enantiomers **8a** and **8b** (0.0005 mol dm$^{-3}$ each) at pH 1.0, there was a great deal of spectroscopic discrimination in resonances corresponding to protons of both the aromatic and methyl groups of the guests **8a** and **8b**. Most obviously, upon addition of the cyclodextrin **64b** the doublets corresponding to the methyl groups of the *(R)*- and *(S)*-isomers of the guest **8a** and **8b** were shifted 0.035 and 0.014 ppm upfield, respectively.

The $^1$H NMR spectrum of a sample containing the *(R)*-phenylglycinol-derived cyclodextrin **64a** (0.002 mol dm$^{-3}$) and the phenylpropanoic acid isomers **8a** and **8b** (0.0005 mol dm$^{-3}$ each) at pH 1.0 also revealed spectroscopic discrimination. This discrimination was once again most readily observed by inspection of the resonances corresponding to the methyl groups of the guests **8a** and **8b**. Doublets for these resonances in the spectrum of the *(R)*- and *(S)*-enantiomers of phenylpropanoic acid **8a** and **8b** were found to shift 0.027 ppm and 0.040 ppm downfield, respectively, in the presence of the cyclodextrin **64a**. Clearly the increased hydrophobicity of the 2-phenylpropanoic acid isomers **8a** and **8b** compared to the anion

enantiomers **43a** and **43b**, results in complexation, and hence discrimination at pH 1.0 where there had been no such complexation at pH 6.0.

As is outlined in the Introduction to this Thesis, given thermodynamic discrimination upon complexation of either the acid enantiomers **8a** and **8b** or the anions **43a** and **43b**, by one of the cyclodextrin pairs **57a,b** and **62a,b - 64a,b**, it was hoped that this discrimination would be complementary. That is, given the observation of discrimination, it was hoped that the reversal of the stereochemistry in the substituent of the cyclodextrin would result in a reversal of the observed selectivity. This was predicted because, as is outlined previously, it was expected that the cyclodextrin moiety of the hosts **57a,b** and **62a,b - 64a,b** would provide a hydrophobic cavity suitable for the complexation of the aromatic guests **8a,b** and **43a,b**, and that the asymmetry present in the chiral substituent would provide interactions which would result in discrimination between those isomers of the guests **8a,b** and **43a,b**. Many of the systems discussed above are unsuitable to test such an hypothesis due either to lack of host-guest complex formation, or insufficient extent of spectroscopic discrimination upon complexation. However it was thought that the systems containing the 1-phenylethylamine-derived cyclodextrins **57a** and **57b** would afford the best opportunity to investigate complementary discrimination, due to sufficient spectroscopic discrimination to unambiguously assign resonances in the $^{1}H$ NMR spectra of the complexes of the guests **8a** and **8b** with both of the cyclodextrins **57a** and **57b**. The interaction of the cyclodextrins **57a** and **57b** with the corresponding anionic species **43a** and **43b** was also studied for comparison.

Thus, in order to determine association constants found in systems containing the 1-phenylethylamine-derived cyclodextrins **57a** and **57b**, an NMR titration of both of the 2-phenylpropanoate enantiomers **43a** and **43b**, and the 2-phenylpropanoic acid enantiomers **8a** and **8b**, at pH 6.0 and 1.0, respectively, with each of the hosts **57a** and **57b**, was conducted.[131] $^1$H NMR spectra were recorded in the presence of a racemic mixture of the appropriate guest (0.0005 mol dm$^{-3}$ in each isomer), where the ratio of the modified cyclodextrin **57a** or **57b** to the racemate of the acids **8a** and **8b**, or the anions **43a** and **43b**, ranged from 0 - 30 mole equivalents. As for the complexation studies above, the spectra of samples containing the propanoate enantiomers **43a** and **43b** were recorded at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 phosphate buffered $D_2O$. Similar samples were prepared in which the acidity of the solutions had been adjusted by the addition of DCl / $D_2O$ mixture as required, to yield samples containing the acid enantiomers **8a** and **8b** at pH 1.0, after which the $^1$H NMR spectra of the samples were recorded.

Spectra recorded in the presence of the *(R)*-and *(S)*-2-phenylpropanoates **43a** and **43b** with increasing concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** showed substantial changes in the resonances attributable to both the cyclodextrin annulus and substituent. In addition, the chemical shifts of resonances corresponding to the propanoates **43a** and **43b** altered as a function of the concentration of the cyclodextrin **57b**. In particular, signals corresponding to the methyl groups of the propanoates **43a** and **43b** moved upfield and resolved into duplicate signals, indicating the formation of diastereomeric host-guest complexes (Figure 4.7). As discussed above, these signals represent the environmental average of the free and complexed species (Equation 2 (Page 56)), and variations in the

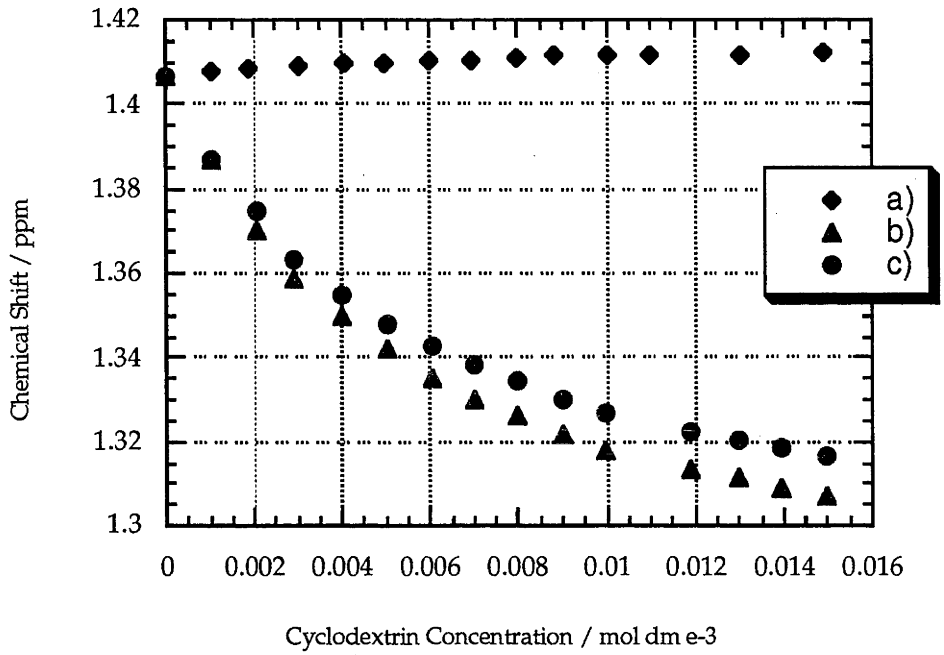



**Figure 4.7.** Chemical shift of the methyl resonances in the $^1$H NMR spectra of a) *(R)*-and *(S)*-2-phenylpropanoate **43a** and **43b** (0.0005 mol dm$^{-3}$ each) in the presence of varying concentrations of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, and b) *(R)*-2-phenylpropanoate **43a** (0.0005 mol dm$^{-3}$) or c) *(S)*-2-phenylpropanoate **43b** (0.0005 mol dm$^{-3}$), in the presence of varying concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 phosphate buffered $D_2O$.

chemical shifts in the presence of the host **57b** were used to calculate the association constants for the complexes of the *(R)*-and *(S)*-propanoates **43a** and **43b** with the cyclodextrin **57b**, of 193 ± 11 and 191 ± 11 dm$^3$ mol$^{-1}$, respectively. By contrast the presence of the 2-phenylpropanoate enantiomers **43a** and **43b** had no effect on the $^1$H NMR spectrum of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, and *vice versa*. This indicates that the intermolecular inclusion complexes did not form in this case and the association constant for this system is therefore zero. This is readily seen by inspection of the plot of the chemical shifts of the signals corresponding

to the methyl groups of the 2-phenylpropanoate enantiomers **43a** and **43b** against the concentration of the cyclodextrin **57a** (Figure 4.7a).

In the corresponding study of samples containing the propanoic acid enantiomers **8a** and **8b** at pH 1.0, with each of the cyclodextrins **57a** and **57b**, the signals for the methyl groups of the racemic guests **8a** and **8b** resolved into duplicate signals with increasing cyclodextrin concentrations in both systems (Figure 4.8). The resolution arose from a change in chemical shift of the signal for the *(R)*-acid **8a** complexed by the *(S)*-1-phenylethylamine-

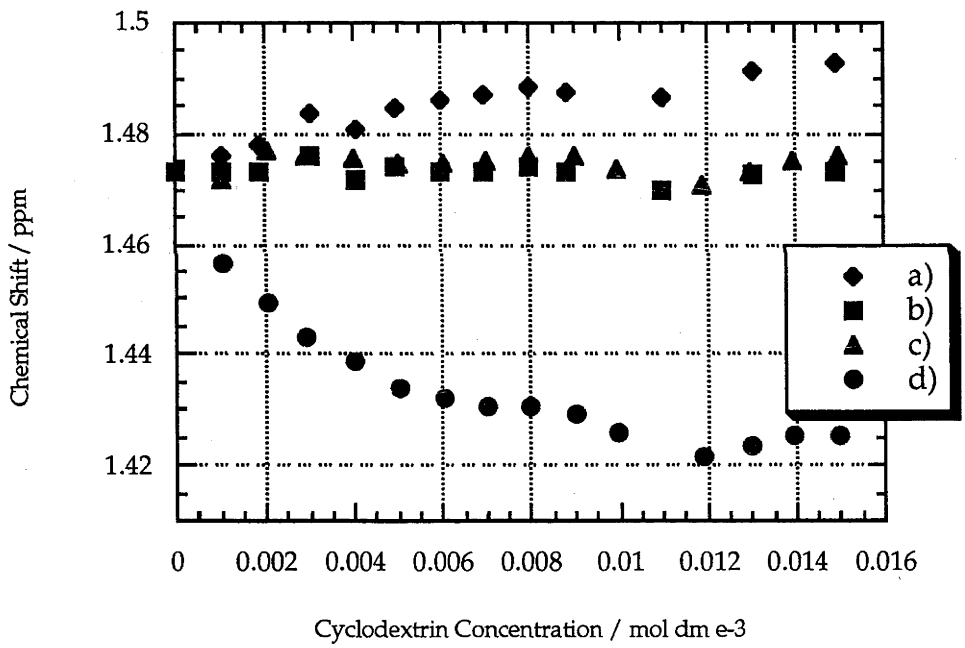



**Figure 4.8.** Chemical shift of the methyl resonances in the $^1H$ NMR spectrum of a) *(S)*-2-phenylpropanoic acid **8b** (0.0005 mol $dm^{-3}$) or b) *(R)*-2-phenylpropanoic acid **8a** (0.0005 mol $dm^{-3}$), in the presence of varying concentrations of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, and c) *(S)*-2-phenylpropanoic acid **8b** (0.0005 mol $dm^{-3}$) or d) *(R)*-2-phenylpropanoic acid **8a** (0.0005 mol $dm^{-3}$), in the presence of varying concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** at 298 K and $I$ = 0.10 mol $dm^{-3}$, in pH 1.0 phosphate buffered $D_2O$.

derived cyclodextrin **57b** and also from the *(S)*-acid **8b** complexed by the *(R)*-1-phenylethylamine derived cyclodextrin **57a**, and these changes were used to calculate association constants for the corresponding complexes of 455 ± 18 and 101 ± 16 $dm^{-3}$ mol, respectively. Due to the lipophilicity of the *(R)*- and *(S)*-acids **8a** and **8b**, it is extremely unlikely that there is no complexation of those species with the cyclodextrins **57a** and **57b**, respectively. Instead, the lack of apparent change in both the signal corresponding to the *(R)*-acid **8a** in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** and also that for the *(S)*-acid **8b** in the presence of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** appears to be due to a lack of change in the average magnetic environment of the methyl group, on guest binding.

This was confirmed by the use of single enantiomers of the guests **8a** and **8b** in conjunction with the cyclodextrins **57a** and **57b**, respectively, and examining changes in the $^1H$ NMR spectra of those hosts, in which manner it was established that the *(S)*-propanoic acid **8b** was indeed complexed by the *(S)*-amine derived cyclodextrin **57b**, and so too was the *(R)*-propanoic acid **8a** complexed by the *(R)*-amine derived cyclodextrin **57a**.

Thus, the hypothesis of observing complementary discrimination in the complexation of a chiral guest by a modified cyclodextrin was unable to be tested by employing the guests **8a,b** or **43a,b** in studies with the cyclodextrins **57a** and **57b**. While the cyclodextrins **57a** and **57b** both complex the guests **8a** and **8b**, the unsuitability of the $^1H$ NMR titration data for the calculation of the association constants of the complexes of *(R)*-2-phenylpropanoic acid **8a** with the *(R)*-amine-derived cyclodextrin **57a**, and also of *(S)*-2-phenylpropanoic acid **8b** with the *(S)*-amine-derived cyclodextrin **57b**, means

that no comparison of these systems is possible. In addition, discussion of interactions of the guests **43a** and **43b** with the cyclodextrins **57a** and **57b** is not possible since the cyclodextrin **57a** does not complex those guests, likely due to the presence of strong intramolecular complexation in that species.

As discussed above, the hope for the observation of complementary discrimination upon complexation of chiral guests by modified cyclodextrins was based on an assumption that the cavities of the modified cyclodextrins would merely act to provide suitable sites for complexation, and the chirality of the substituents of the cyclodextrins would act to provide enhanced chiral discrimination over native cyclodextrins. In systems containing the species **8a,b** and **43a,b** and the cyclodextrins **57a,b** and **62a,b - 64a,b**, clearly other important factors render this assumption invalid. Chief amongst these factors is the presence of intramolecular complexation in many of the cyclodextrins **57a,b** and **62a,b - 64a,b** which limit the complexation of the guests **8a,b** and **43a,b** in some of the systems under study here. It was thought that there would be a greater chance of complex formation in systems containing the Ibuprofen acids **8a** and **8b**, and the corresponding anions **44a** and **44b**, in the presenec of the cyclodextrins **57a,b** and **62a,b - 64a,b**, due to the high lipophilicity of the former species.

Similar to the previously discussed systems containing the guests **8a,b** and **43a,b** it was found that inspection of the resonances corresponding to the α-methyl groups of the guests **37a,b** and **44a,b**, in their $^1$H NMR spectra recorded in the presence of the cyclodextrins **57a,b** and **62a,b - 64a,b** provided a ready method to determine the presence or absence of complexation and discrimination in many of those systems. In addition, inspection of the resonances corresponding to the methylene groups of the 4-*iso*-butyl

substituents of the guests **37a,b** and **44a,b** in those spectra often gave an indication of the presence of discrimination in many systems. Other resonances corresponding to protons of the guests **37a,b** and **44a,b** were unsuitable either because they were obscured by resonances corresponding to protons of the cyclodextrins **57a,b** and **62a,b - 64a,b**, or because they showed little or no spectroscopic discrimination thus not enabling identification of the resonances corresponding to individual isomers of the guests **37a,b** and **44a,b**.

Thus, also similar to work described above in which the complexation of the species **8a,b** and **43a,b** were studied, the complexation of the individual pairs of cyclodextrins **57a,b** and **62a,b - 64a,b** with the Ibuprofen enantiomers **37a** and **37b**, and the corresponding anions **44a** and **44b**, was monitored in $^1$H NMR studies with spectra recorded at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 1.0 and 6.0 phosphate buffered $D_2O$, respectively, for all systems.

The $^1$H NMR spectrum of the Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol dm$^{-3}$) at pH 6.0 revealed discrimination between the isomers of the guest upon complexation. The doublet corresponding to the benzylic methylene groups of the guest enantiomers **44a** and **44b** resolved, experiencing downfield shifts of 0.034 and 0.025 ppm for the resonances corresponding to the *(R)*- and *(S)*-isomers **44a** and **44b**, respectively. This left the signal corresponding to the *(R)*-enantiomer **44a** downfield with respect to the resonance of the *(S)*-isomer **44b** (Figure 4.9). There were also changes in chemical shifts upon complexation in other guest signals of the $^1$H NMR spectrum of the complex, such as 0.038 ppm upfield for the resonance corresponding to the α-methyl groups of the

anions **44a** and **44b**, although this was not accompanied by spectroscopic discrimination. Upon addition of the guest enantiomers **44a** and **44b**, resonances corresponding to the cyclodextrin **57a** *meta*- and *ortho*-aromatic protons were observed to undergo complexation-induced shifts of 0.023 ppm downfield and 0.013 upfield, respectively. This effect indicates disruption of the intramolecular complex between the cyclodextrin aromatic moiety and annulus. Observation of complexation and discrimination in this system is significant because of the apparent strength of the intramolecular complex in the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, which acted to limit the intermolecular complexation of the propanoate enantiomers **43a** and **43b**. As expected the more lipophilic Ibuprofen anion enantiomers **44a** and **44b** were complexed by the cyclodextrin **57a** and discrimination was observed.

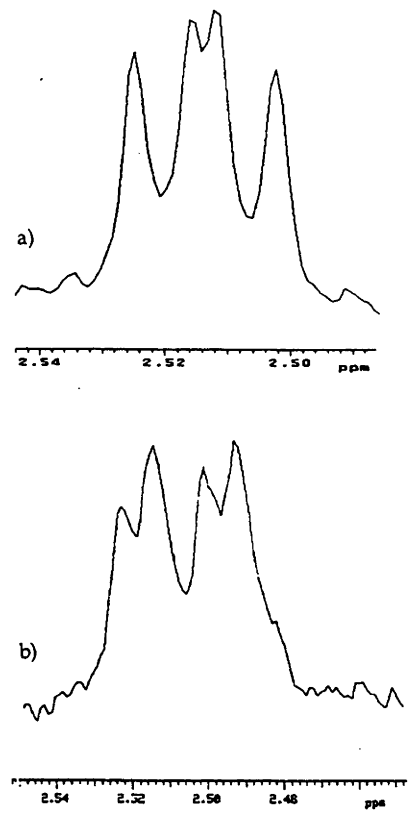



**Figure 4.9.** Partial $^1$H NMR spectra, showing resonances corresponding to the benzylic methylene protons of a) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol dm$^{-3}$) at pH 6.0, and b) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) with added *(S)*-Ibuprofen anion **44b** (0.0005 mol dm$^{-3}$) in the presence of the *(R)*-amine-derived host **57a** (0.002 mol dm$^{-3}$) at pH 6.0.

Spectroscopic discrimination was also noted on complexation of the Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol $dm^{-3}$ each) by the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (0.002 mol $dm^{-3}$) at pH 6.0. In the $^1H$ NMR spectrum of that sample signals corresponding to the guest α-methyl groups shifted upfield 0.083 and 0.070 ppm for resonances corresponding to the *(S)*- and *(R)*-isomers **44b** and **44a**, respectively. Once again changes upon complexation were noted in the guest benzylic methylene resonance, notably a shift downfield of 0.006 ppm and one upfield of 0.001 ppm for resonances corresponding to the *(S)*- and *(R)*-isomers **44b** and **44a**, respectively (Figure 4.10). The last observation is significant because, in the complexation of the racemic Ibuprofen anion enantiomers **44a** and **44b** by the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**, it is therefore the resonance corresponding to protons of the *(S)*-isomer of the guest **44b** that is shifted the greatest amount downfield upon complexation. In the corresponding

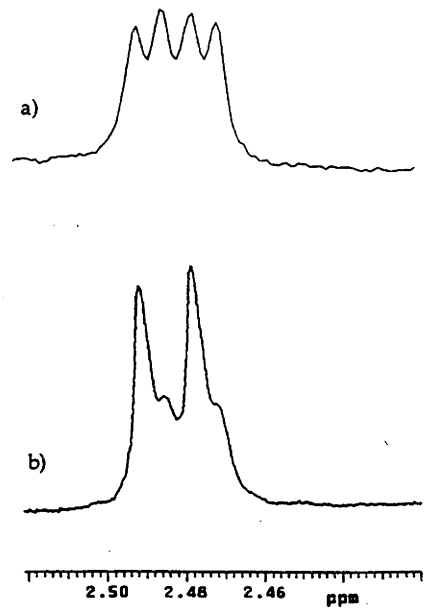



**Figure 4.10.** Partial $^1H$ NMR spectra, showing resonances corresponding to the benzylic methylene protons of a) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol $dm^{-3}$ each) in the presence of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (0.002 mol $dm^{-3}$) at pH 6.0, and b) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol $dm^{-3}$ each) with added *(S)*-Ibuprofen anion **44b** (0.001 mol $dm^{-3}$) in the presence of the *(S)*-amine-derived host **57b** (0.002 mol $dm^{-3}$) at pH 6.0.

complexation of the Ibuprofen anion enantiomers **44a** and **44b** by the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** it was the *(R)*-isomer of the guest **44a** that was shifted the greatest amount downfield upon complexation. This effect is a change in selectivity of the spectroscopic discrimination for the guest enantiomers **44a** and **44b** upon changing from being complexed by the cyclodextrin **57a** to being complexed by the cyclodextrin **57b**. That is, by reversing the stereochemistry at the chiral centre of the amine side chain of the cyclodextrin, the selectivity of the spectroscopic discrimination was also reversed, however this is not necessarily reflected as complementary thermodynamic discrimination

Complexation and discrimination was also observed in a sample containing the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** (0.002 mol $dm^{-3}$) and the racemic Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol $dm^{-3}$ each) at pH 1.0. In the $^1H$ NMR spectrum of this system, discrimination was observed with the resonances corresponding to the benzylic methylene of the guest enantiomers **37a** and **37b** shifting upfield 0.001 and 0.007 ppm, respectively. Similar to the complexation of the corresponding anion enantiomers **44a** and **44b** by this cyclodextrin **57a** at pH 6.0, this rendered the signal for the resonance corresponding to the protons of the *(R)*-Ibuprofen acid **37a** downfield of that of the *(S)*-isomer **37b**. Discrimination was also noted in the resonances corresponding to the methine proton of the *iso*-butyl group of the guests **37a** and **37b** but this was too slight to assign. The signal in the $^1H$ NMR spectrum of the complex corresponding to the α-methyl groups of the guest enantiomers **37a** and **37b**, also resolved, shifting upfield 0.049 and 0.044 ppm for signals corresponding to the *(R)*- and *(S)*-isomers of the guest **37a** and **37b**, respectively.

The $^1$H NMR spectrum of a sample containing the Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) and the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (0.002 mol dm$^{-3}$) at pH 1.0 revealed there to be discrimination present in resonances corresponding to the cyclodextrin **57b** aromatic protons, with those signals clearly splitting upon formation of the diastereomeric complexes. This was one of only a very few systems in this study where discrimination was so unambiguously observed in resonances corresponding to the cyclodextrin host. Discrimination was also noted in resonances corresponding to the α-methyl groups of the guest enantiomers **37a** and **37b**, with those signals shifting upfield 0.090 and 0.070 ppm, respectively, upon complexation. Similarly, strong shifts in the guest benzylic methylene resonances were observed, with the signals corresponding to the *(R)*- and *(S)*-isomers of the guest **37a** and **37b** being shifted upfield 0.035 and 0.044 ppm, respectively. This rendered the resonance corresponding to the *(R)*-isomer of guest **37a** downfield of that of the *(S)*-isomer **37b**, as for the corresponding complexation by the *(R)*-amine-derived cyclodextrin **57a**. Therefore, unlike the complexation of the guests **44a** and **44b** by the cyclodextrins **57a** and **57b**, the reversal of stereochemistry of the substituent of the cyclodextrins **57a** and **57b** did not reverse the selectivity of the spectroscopic discrimination in this system.

The $^1$H NMR spectrum of a sample containing the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a** (0.002 mol dm$^{-3}$) and the Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) at pH 6.0 provided no notable discrimination but some evidence of complex formation. Inspection of the resonance corresponding to the α-methyl groups of the guest enantiomers **44a** and **44b** showed no evidence of splitting, although

there was a change in the chemical shift of that resonance. Other resonances of the guest enantiomers **44a** and **44b** also showed changes in chemical shift in the presence of the cyclodextrin **62a**, such as 0.035, 0.019 and 0.059 ppm downfield for resonances corresponding to the methine, methylene and methyl protons of the *iso*-butyl moieties of the Ibuprofen anion enantiomers **44a** and **44b**, respectively, but without spectroscopic discrimination. Changes in chemical shift of the aromatic signals of the guests **44a** and **44b** were also noted in the presence of the cyclodextrin **62a**, resulting in changes in the span of the resonances. Shifts such as these are obviously an indication of change in environment of those protons and therefore evidence of the formation of an inclusion complex, although without any observable spectroscopic discrimination.

A similar effect was observed upon inspection of the $^1$H NMR spectrum of a sample containing the *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62a** (0.002 mol dm$^{-3}$) and the Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. Upon addition of the cyclodextrin **62a** none of the resonances corresponding to the Ibuprofen acid enantiomers **37a** and **37b** showed any evidence of spectroscopic discrimination. Similar to the previous system, despite the lack of observable discrimination, resonances corresponding to protons of the *iso*-butyl groups of the guest enantiomers **37a** and **37b** were shifted downfield up to 0.054 ppm upon addition of cyclodextrin **62a**, and similar shifts were observed in the resonances corresponding to the aromatic protons of the guests **37a** and **37b**. In addition, certain of the resonances corresponding to cyclodextrin annulus H-2-6 protons, were significantly deshielded with respect to those of the cyclodextrin **62a** in the absence of guest. In this system, similar to the

previous one, it is clear that the guests **37a** and **37b** are complexed by the cyclodextrins **62a**, although this occurs without spectroscopic discrimination.

Discrimination was observed in the $^1$H NMR spectrum of a system containing the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** (0.002 mol dm$^{-3}$) and Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) at pH 6.0, along with a great deal of other evidence of host-guest complex formation. Inspection of the benzylic methylene resonances of racemic guest enantiomers **44a** and **44b** showed that upon complexation they were shifted an average of 0.051 ppm upfield, and exhibited discrimination between enantiomers. However, this complexation was accompanied by large broadening which rendered assignment of these signals to protons of the guest isomers **44a** and **44b** impossible, but does suggest complex formation.[149] A great deal of broadening and splitting was also evident in the resonances corresponding to the α-methyl groups of the guest enantiomers **44a** and **44b**, accompanied by a large average upfield shift of 0.185 ppm. All of these factors of course indicate the formation of a host-guest complex.

Discrimination and evidence of complexation was also observed in many signals in the $^1$H NMR spectrum of a sample containing the *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin **62b** (0.002 mol dm$^{-3}$) and the Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. In particular, discrimination and a large degree of broadening upon complexation were observed once more in resonances corresponding to the benzylic methylene of the guest enantiomers **37a** and **37b**. This was accompanied by an average complexation-induced downfield shift in those

signals of 0.132 ppm, which, along with other complexation-induced shifts, indicates the formation of a host-guest complex.

Inspection of the $^1$H NMR spectrum of the *(R)*-amphetamine-derived cyclodextrin **63a** (0.002 mol dm$^{-3}$) in the presence of the Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) at pH 6.0, revealed complexation induced shifts in several resonances, along with the observation of discrimination in resonances corresponding to the protons in the aromatic H-2 position of the *(R)*- and *(S)*-enantiomers of the Ibuprofen anion **44a** and **44b**, which moved 0.043 and 0.034 ppm upfield, respectively, in the presence of the cyclodextrin **63a** (Figure 4.11). This of course left the signal corresponding to the *(R)*-isomer **44a** upfield of that of the *(S)*-isomer **44b**.

The $^1$H NMR spectrum of a mixture of the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol dm$^{-3}$) and Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) at pH 6.0 also contained many resonances in which strong spectroscopic discrimination was observed. Discrimination was most obviously observed upon noting upfield shifts of 0.029 and 0.043 ppm for the resonances corresponding to the α-methyl groups of the *(R)*- and *(S)*-isomers **44a** and **44b**, respectively, upon addition of the cyclodextrin **63b**. Discrimination was also observed in resonances corresponding to the protons in the aromatic H-2 position of the *(R)*- and *(S)*-enantiomers of the Ibuprofen anion **44a** and **44b**, with those signals moving 0.050 and 0.035 ppm upfield, respectively, upon addition of the cyclodextrin **63b** (Figure 4.12). This left the signal corresponding to the *(R)*-isomer **44a** upfield of that of the *(S)*-isomer **44b**. Thus the selectivity of this spectroscopic discrimination was as for the previous system.

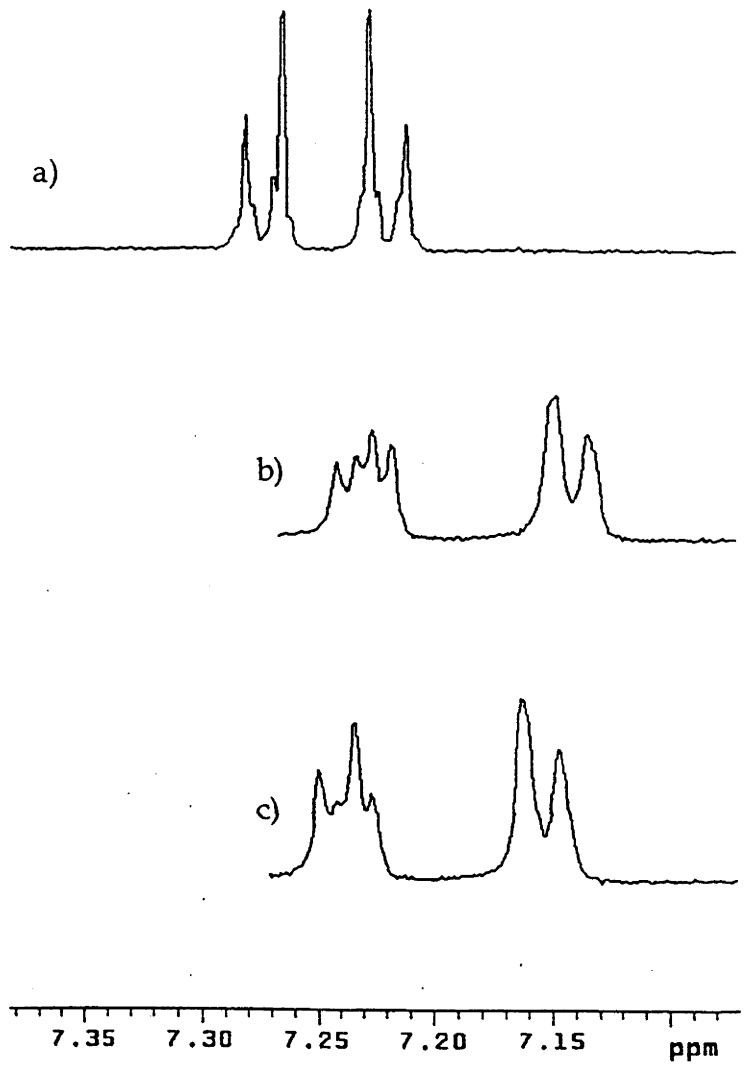



**Figure 4.11.** Partial $^{1}H$ NMR spectra, showing resonances corresponding to the protons of the aromatic moieties of a) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol $dm^{-3}$ each) at pH 6.0, b) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol $dm^{-3}$ each) in the presence of the *(R)*-amphetamine-derived cyclodextrin **63a** (0.002 mol $dm^{-3}$) at pH 6.0, and c) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol $dm^{-3}$ each) with added *(S)*-Ibuprofen anion **44b** (0.0005 mol $dm^{-3}$) in the presence of the *(R)*-amphetamine-derived cyclodextrin **63a** (0.002 mol $dm^{-3}$) at pH 6.0. Resonances not corresponding to aromatic protons of the guests **44a** and **44b** have been omitted for clarity.

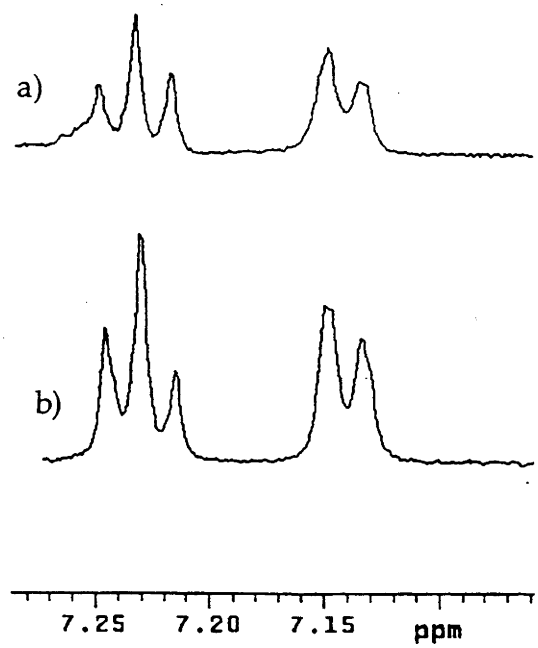



**Figure 4.12.** Partial $^1$H NMR spectra, showing resonances corresponding to the protons of the aromatic moieties of a) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol dm$^{-3}$) at pH 6.0, and b) the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) with added *(S)*-Ibuprofen anion **44b** (0.0005 mol dm$^{-3}$) in the presence of the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol dm$^{-3}$) at pH 6.0.

Similar to the above system containing the Ibuprofen anion enantiomers **44a** and **44b** and the *(R)*-amphetamine-derived cyclodextrin **63a** at pH 6.0, there was only slight discrimination apparent in the $^1$H NMR spectrum of the *(R)*-amphetamine-derived cyclodextrin **63a** (0.002 mol dm$^{-3}$) and Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. Upon addition of cyclodextrin **63a** a slight resolution of the resonances corresponding to the benzylic methylene protons of the racemic guest enantiomers **37a** and **37b** was noted. The signals, which were coincident doublets in the absence of the cyclodextrin **63a**, split by 0.003 ppm in the $^1$H NMR spectrum of the host-guest complex, leaving the signal corresponding to the *(S)*-isomer of guest **37b** slightly upfield of that of the *(R)*-isomer **37a**. It was also noted that the resonance corresponding to the 4-*iso*-butyl methine

group of the guest enantiomers **37a** and **37b** showed shift changes of 0.001 ppm upfield and 0.003 ppm downfield for the *(S)*- and *(R)*-isomer **37b** and **37a**, respectively. These shifts, although small, indicate the formation of the intermolecular host-guest complex in this system.

Very much greater complexation-induced shifts were observed in the $^1$H NMR spectrum of a sample containing the *(S)*-amphetamine-derived cyclodextrin **63b** (0.002 mol dm$^{-3}$) and the Ibuprofen acid guest enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) at pH 1.0. All resonances corresponding to protons of the *iso*-butyl group of the Ibuprofen enantiomers **37a** and **37b** showed both discrimination and complexation induced shifts of up to 0.080 ppm downfield, although the extent of spectroscopic discrimination observed was small. Upon forming the host-guest complex the signals in the $^1$H NMR spectrum corresponding to the α-methyl groups of the *(R)*- and *(S)*-isomer of guest **37a** and **37b** also resolved, experiencing downfield shifts of 0.092 and 0.139 ppm, respectively.

A great deal of discrimination and complexation induced changes in chemical shifts was noted in the $^1$H NMR spectrum of a sample containing the *(S)*-phenylglycinol-derived cyclodextrin **64b** (0.002 mol dm$^{-3}$) and the Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) at pH 6.0. In the presence of the cyclodextrin **64b** the signals corresponding to the α-methyl groups of the Ibuprofen anion enantiomers **44a** and **44b** shifted upfield 0.061 and 0.075 ppm, respectively. Several other signals, including those corresponding to both the aromatic H-2 and aromatic H-3 protons of the guests **44a** and **44b** resolved, also indicating the presence of the host-guest complex in this system.

Spectroscopic discrimination, and other evidence of complexation, was also observed in the $^1$H NMR spectrum of the Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(R)*-phenylglycinol-derived cyclodextrin **64a** (0.002 mol dm$^{-3}$) at pH 6.0. In this spectrum resonances corresponding to the α-methyl groups of the Ibuprofen anion *(R)*-and *(S)*-enantiomers **44a** and **44b** resolved into separate signals, shifting an average of 0.055 ppm upfield upon addition of the cyclodextrin **64a**, however this discrimination was very slight and the resonances were unable to be assigned (Figure 4.13). Discrimination was also observed in the aromatic H-2 resonances of the guest enantiomers **44a** and **44b**, with shifts of 0.062 and 0.069 ppm upfield, respectively, in the presence of the cyclodextrin **64a**.

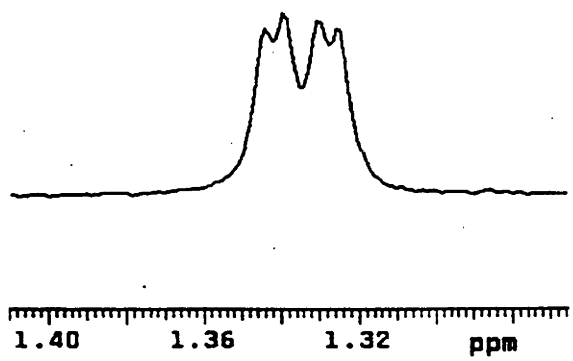



**Figure 4.13.** Partial $^1$H NMR spectra, showing resonances corresponding to the α-methyl groups of the *(R)*-and *(S)*-Ibuprofen anion enantiomers **44a** and **44b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(R)*-phenylglycinol-derived cyclodextrin **64a** (0.005 mol dm$^{-3}$) at pH 6.0.

In the $^1$H NMR spectrum of the Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) in the presence of the *(S)*-phenylglycinol-derived cyclodextrin **64b** (0.002 mol dm$^{-3}$) at pH 1.0 complexation-induced shifts were noted in many resonances corresponding to protons of the guest *(R)*-

and *(S)*-enantiomers **37a** and **37b**. Most noteworthy, discrimination was observed in the α-methyl resonances of the guest enantiomers **37a** and **37b**, with the signals shifting upfield 0.142 and 0.126 ppm, respectively, in the presence of the cyclodextrin **64b**. The $^1$H NMR spectrum of a sample containing the *(R)*-phenylglycinol-derived cyclodextrin **64a** (0.002 mol dm$^{-3}$) and the Ibuprofen acid enantiomers **37a** and **37b** (0.0005 mol dm$^{-3}$ each) at pH 1.0, also showed spectroscopic discrimination in the resonances corresponding to the α-methyl protons of the guest *(R)*-and *(S)*-enantiomers **37a** and **37b**, with those signals shifted 0.107 and 0.093 ppm upfield, respectively. Similar to work previously discussed, the observation of discrimination in the spectra of these systems indicates the formation of host-guest complexes in both cases.

Thus all of the above systems containing the cyclodextrins **57a,b** and **62a,b - 64a,b** and the guests **8a,b** and **43a,b** were shown to contain intramolecular host-guest complexes between those species, with the $^1$H NMR spectra of many of these systems exhibiting assignable spectroscopic discrimination. However the interactions between the cyclodextrins **57a** and **57b** and the guests **8a,b** and **43a,b** are of particular interest due to the reversal of the selectivity of the observed spectroscopic discrimination in the complexation of the guests **44a** and **44b** upon changing from the *(R)*-amine-derived cyclodextrin **57a** to the isomer **57b**. This consideration, combined with a desire to provide continuity with work outlined above which discusses the interactions between the aromatic species **8a,b** and **43a,b** and the cyclodextrins **57a** and **57b**, meant that it was decided to investigate the corresponding complexation of the guests **37a,b** and **44a,b** by those hosts **57a** and **57b**.

As previously discussed, it was hoped that upon obtaining association constant data for these systems, any thermodynamic discrimination observed would be complementary. Also as previously discussed, this is based on the expectation that the annuli of the cyclodextrins **57a** and **57b** would simply provide a suitable site for complexation of the guests **37a,b** and **44a,b**, while chiral interactions between those guests and the substituents of the cyclodextrin hosts **57a** and **57b** would result in discrimination. Thus it would be reasonable to expect that a change in the chirality in the substituents of the hosts **57a** and **57b** might result in a change in the selectivity of any thermodynamic discrimination in the complexation of the pairs of enantiomers **37a,b** and **44a,b**.

In order to determine association constants of complexes formed in systems containing the 1-phenylethylamine-derived cyclodextrins **57a** and **57b**, $^1$H NMR titrations of both of the racemic guests Ibuprofen enantiomers **37a** and **37b**, and the corresponding anion enantiomers **44a** and **44b**, at pHs 1.0 and 6.0 respectively, with both of those cyclodextrins **57a** and **57b** were conducted.[131] Spectra were recorded in the presence of appropriate racemic guest (0.0005 mol dm$^{-3}$ in each isomer), where the ratio of either of the modified cyclodextrins **57a** and **57b** to the racemic mixtures of the guests **37a,b** and **44a,b** ranged from 0-15 mole equivalents. As for previous complexation studies samples were recorded at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 and pH 1.0 phosphate buffered $D_2O$.

The $^1$H NMR spectra recorded in the presence of the Ibuprofen anion enantiomers **44a** and **44b** with increasing concentrations of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** showed substantial changes in the resonances attributable to both the cyclodextrin annulus and amine

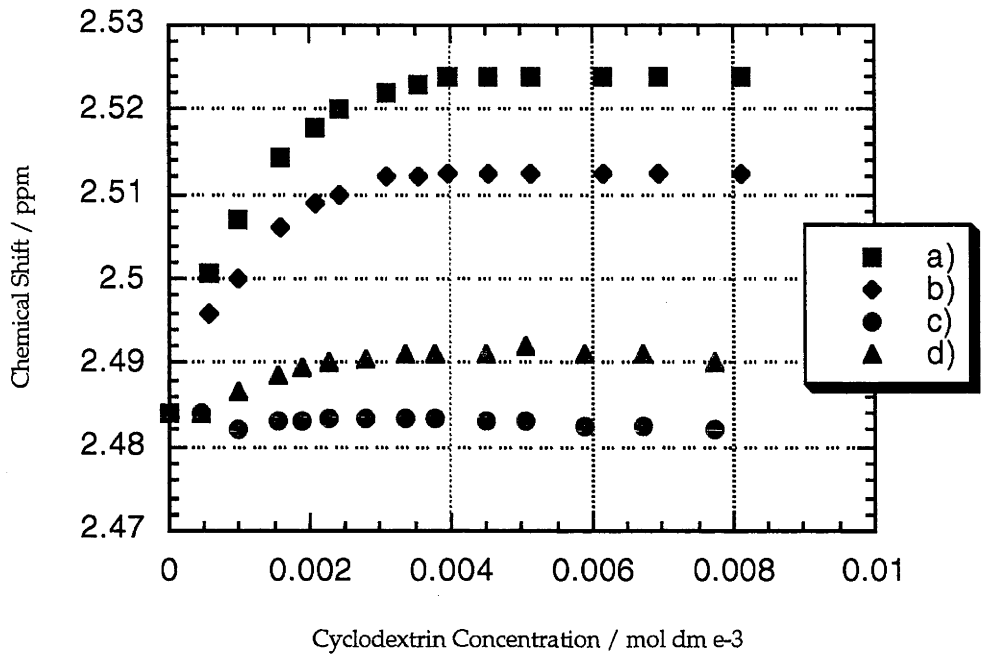



**Figure 4.14.** The chemical shift of the guest benzylic methylene resonances in the $^1$H NMR spectrum of a) the *(R)*-Ibuprofen anion **44a** (0.0005 mol dm$^{-3}$) or b) the *(S)*-Ibuprofen anion **44b** (0.0005 mol dm$^{-3}$), in the presence of varying concentrations of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, and c) the *(R)*-Ibuprofen anion **44a** (0.0005 mol dm$^{-3}$) or d) the *(S)*-Ibuprofen anion **44b** (0.0005 mol dm$^{-3}$), in the presence of varying concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 6.0 phosphate buffered $D_2O$.

substituent. In addition, the chemical shift of resonances corresponding to the Ibuprofen anion enantiomers **44a** and **44b** altered as a function of the concentration of the cyclodextrin **57a**, moving downfield and resolving (Figure 4.14). This data was used to calculate the association constants, $K$, of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a** with the *(R)*- and *(S)*-Ibuprofen anion, which are presented in Table 4.1. As mentioned in the studies of samples at a single concentration above, spectroscopic discrimination was also observed in the complexation of racemic Ibuprofen

anion enantiomers **44a** and **44b** by the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**. This was because the resonance corresponding to the *(S)*-Ibuprofen anion guest **44b** moved downfield as a function of cyclodextrin **57b** concentration (Figure 4.14d). However the chemical shift of the resonance corresponding to the *(R)*-Ibuprofen anion **44a** did not alter significantly as a function of the concentration of the host **57b**. This did not enable the calculation of an association constant from this data (Figure 4.14c). However, spectroscopic discrimination and complexation induced changes in chemical shift were also evident in the resonances of the α-methyl groups of Ibuprofen anion enantiomers **44a** and **44b** in the presence of increasing concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** (Figure 4.15). This data did enable the calculation of the association constants of both of the Ibuprofen anions **44b** and **44b** with the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**, and these are presented in Table 4.1. It is worth noting that, despite observable spectroscopic discrimination between the isomers of the Ibuprofen anion enantiomers **44a** and **44b** by inspection of their benzylic methylene resonances in the presence of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, there was no corresponding discrimination observed in the guest α-methyl resonances (Figure 4.15a).

The complexation of the Ibuprofen acid enantiomers **37a** and **37b** by the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, as observed in the $^1$H NMR spectrum of the system at pH 1.0, resulted in ready observation of discrimination in many of the resonances corresponding to protons of the guest enantiomers **37a** and **37b**, however it was the signal corresponding to the protons of the α-methyl groups of those guests **37a** and **37b** which proved most suitable for the calculation of association constants. Those

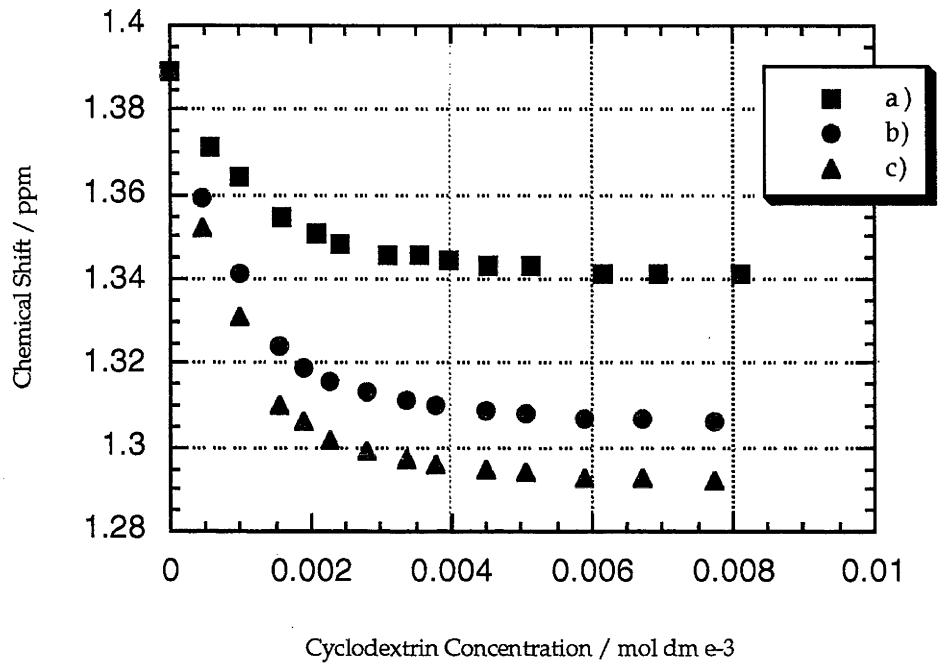



**Figure 4.15.** The chemical shift of the guest α-methyl resonances in the $^1H$ NMR spectrum of a) the *(R)*-and *(S)*-Ibuprofen anions **44a** and **44b** (0.0005 mol $dm^{-3}$ each) in the presence of varying concentrations of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, and b) the *(R)*-Ibuprofen anion **44a** (0.0005 mol $dm^{-3}$) or c) the *(S)*-Ibuprofen anion **44b** (0.0005 mol $dm^{-3}$), in the presence of varying concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** at 298 K and $I$ = 0.10 mol $dm^{-3}$, in pH 6.0 phosphate buffered $D_2O$.

signals moved upfield as a function of concentration of the cyclodextrins **57a** and **57b**, resolving into duplicate signals for each enantiomer of guest **37a** and **37b** in all systems (Figure 4.16). This enabled the calculation of the association constants of *(R)*- and *(S)*-Ibuprofen **37a** and **37b** with the *(R)*-and *(S)*-1-phenylethylamine-derived cyclodextrins **57a** and **57b** and that data is presented in Table 4.1.

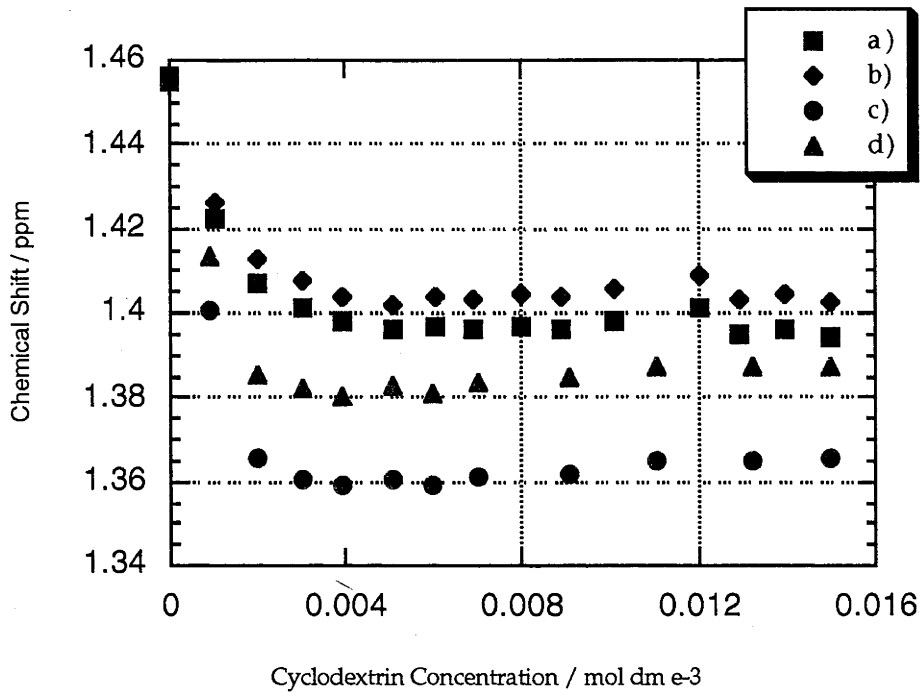



**Figure 4.16.** The chemical shift of the guest α-methyl resonances in the $^1$H NMR spectrum of a) the *(R)*-Ibuprofen acid **37a** (0.0005 mol dm$^{-3}$) or b) the *(S)*-Ibuprofen acid **37b** (0.0005 mol dm$^{-3}$), in the presence of varying concentrations of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, and c) the *(R)*-Ibuprofen acid **37a** (0.0005 mol dm$^{-3}$) or d) the *(S)*-Ibuprofen acid **37b** (0.0005 mol dm$^{-3}$), in the presence of varying concentrations of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b** at 298 K and $I$ = 0.10 mol dm$^{-3}$, in pH 1.0 phosphate buffered $D_2O$.

Inspection of the association constant data (Table 4.1) reveals the stability of the complexes of the anions **44a** and **44b** with the *(R)*-amine-derived cyclodextrin **57a** to be equal, and therefore despite the presence of spectroscopic discrimination in this system there is no thermodynamic discrimination; that is there is no selectivity. Similarly there is no selectivity in the complexation of the guests **44a** and **44b** by the *(S)*-amine-derived cyclodextrin **57b**, and thus there is no complementary discrimination in these systems, despite the previously mentioned reversal

| Cyclodextrin | pH | Guest | K ($dm^3$ $mol^{-1}$) |
|---|---|---|---|
| **57a** | 6.0 | **44a** | 1924 ± 215 |
| **57a** | 6.0 | **44b** | 2020 ± 277 |
| **57b** | 6.0 | **44a** | 2043 ± 152 |
| **57b** | 6.0 | **44b** | 2318 ± 191 |
| **57a** | 1.0 | **37a** | 1883 ± 220 |
| **57a** | 1.0 | **37b** | 2059 ± 332 |
| **57b** | 1.0 | **37a** | 3314 ± 1068 |
| **57b** | 1.0 | **37b** | 3526 ± 1319 |

**Table 4.1.** Association Constants, Calculated from Selected Guest Resonances in the $^1H$ NMR Spectra of Cyclodextrins-Guest complexes at 298 K and $I$ = 0.10 mol $dm^{-3}$, in pH 6.0 or 1.0 phosphate buffered $D_2O$.

of selectivity in the observed spectroscopic discrimination. Similarly there is no thermodynamic discrimination in the complexation of the acids **37a** and **37b** by the cyclodextrins **57a** and **57b**, and therefore of course no complementary discrimination. In fact, the data from Table 4.1 indicates that the association constants of the complexes of all of the guests **37a,b** and **44a,b** with the cyclodextrin **57a** are essentially all equal, within error, to those with the cyclodextrin **57b**. That is, unlike the corresponding complexation of the guests **8a,b** and **43a,b**, there is no influence of the chirality of the substituent of the cyclodextrins **57a** and **57b** on the stability of their complexes with the guests **37a,b** and **44a,b**. Comparison of the association constants of the complexes of the cyclodextrins **57a** and **57b** and the anions **44a** and **44b** with those with the acids **37a** and **437b** yields the surprising result that these values too are essentially all equivalent. Once again this is

unlike the complexation of the propanoate anions **43a** and **43b**, and the corresponding anions **8a** and **8b** by the cyclodextrins **57a** and **57b**, and indicates that there is no effect of the protonation or non-protonation of the guests **37a,b** and **44a,b** on their association constants with those hosts.

These results suggest that the presence of the 4-*iso*-butyl group in the guests **37a,b** and **44a,b**, that is the lipophilicity of those species, outweighs all other factors in complex formation with the cyclodextrins **57a** and **57b**. As outlined previously, it was expected that due to the greater lipophilicity of the species **37a,b** and **44a,b**, compared to the species **8a,b** and **43a,b**, the former species would be more likely be complexed by the cyclodextrins **57a,b** and **60a,b - 62a,b**. This of course proved to be the case. However this greater lipophilicity has rendered factors such as hydration of the guest, the presence of intramolecular complexation and the chirality of the substituent of the host, unimportant in the complexation of the guests **37a,b** and **44a,b** by the cyclodextrins **57a** and **57b**. This means that the systems containing the guests **37a,b** and **44a,b**, like those containing the guests **8a,b** and **43a,b**, are unsuitable for the examination of the potential for complementary discrimination in host-guest complexes with the cyclodextrins **57a** and **57b**.

In the above work, in which the complexation of the guests **8a,b**, **37a,b**, **43a,b** and **44a,b** by the cyclodextrins **57a,b** and **62a,b - 64a,b** was investigated, an assumption was made that a modified cyclodextrin might be considered as a simple species with the cyclodextrin annulus providing a hydrophobic cavity suitable for complexation of a guest while specific, tailored chiral interactions in the substituent of that cyclodextrin would result in discrimination between guest isomers. It was further hoped that the any discrimination so observed might be complementary for diastereomeric

pairs of cyclodextrin hosts. However, factors other than above, such as lipophilicity and hydration of the guest, charge of both species in the complex and the presence of intramolecular complexation in the host, the latter influenced by the chirality and flexibility of the substituent of that host, all proved to be extremely important. Thus the assumption of a simple cyclodextrin host was found not to hold, because many factors contributed to the presence or absence of intramolecular host-guest complexation.

In addition to the study of factors effecting complexation as discussed above, some observations were made on the factors effecting discrimination in the complexation of chiral guests by cyclodextrins. Unmodified β-cyclodextrin **1** is known not to discriminate between the 2-phenylpropanoate enantiomers **43a** and **43b**,[26] nor the Ibuprofen anion enantiomers **44a** and **44b**,[125] likely due to the inherent symmetry of that host **1**. The cyclodextrins **57a,b** and **62a,b - 64a,b** were prepared specifically in the hope of exhibiting enhanced discrimination upon the complexation of those guests **43a,b** and **44a,b**, and also the corresponding acids **8a,b** and **37a,b**. Thus they were designed to contain extra asymmetry in the form of chirality in their substituents, and were further designed to maximise interactions with the guests **8a,b**, **37a,b**, **43a,b** and **44a,b**, by having an arrangement of groups in their substituents similar to those guests. The potential interaction between the hosts **57a,b** and **62a,b - 64a,b** and especially the anions **43a,b** and **44a,b**, were further maximized by modifying the conditions of the study to ensure the hosts existed as charged species, thus maximizing the potential for ionic or dipole interactions. Thus the acids **37a** and **37b** were complexed by all of the cyclodextrins **57a,b** and **62a,b - 64a,b**, and the acids **8a** and **8b** by many of them, while most of the cyclodextrins **57a,b** and **62a,b - 64a,b** showed

enhanced spectroscopic discrimination over β-cyclodextrin **1** in the complexation of the anions **43a,b** and **44a,b**, although this was not necessarily reflected as thermodynamic discrimination.

## Conclusion

The solvation and complexation studies conducted with $6^A$-deoxy-$6^A$-fluoro-β-cyclodextrin **11** described in Chapter 1 of this Thesis indicate that while the fluorine-substituent of the cyclodextrin **11** is susceptible to environmental effects, and changes in the $^{19}F$ NMR chemical shift of the substituent can indicate complex formation in the presence of suitable guests, the systems under study are not appropriate for the observation of spectroscopic discrimination. However it was determined that the extent of chemical shift change upon complexation is dependent upon the nature of the guest, with the greater extent of chemical shift changes upon complexing the anions **43a,b** and **44a,b** compared to the corresponding acids **8a,b** and **37a,b** being due to an average shallower depth of inclusion of the former species. Lesser inclusion of the anions **43a,b** and **44a,b** results in the fluorine substituent of the cyclodextrin **11** residing in a more deshielding environment. In addition, such complexation-induced changes in the $^{19}F$ NMR chemical shift of the fluorine substituent of a host in the presence of a guest is suitable for the calculation of association constants in many systems.

In further work described in Chapter 1 of this Thesis such changes in $^{19}F$ NMR chemical shift were employed to calculate association constants of host-guest complexes, although in this case the fluorine nucleus was a substituent of the guest species rather than of the host. Thus it was determined that the complexes of the esters **25** and **26** with the cyclodextrins **1, 49** and **50** are up to four times more stable than those of the corresponding benzoate anions **23** and **24**. This was attributed to the stronger hydration of the carboxylates **23** and **24**, which rendered them less attractive to the hydrophobic cavities of the cyclodextrin hosts **1, 49** and **50**. It was further

determined that the association of the methyl esters **25** and **26** is greater with β-cyclodextrin **1** than with the charged C-6 substituted cyclodextrin **49**. This may be a reflection of the decreased hydrophobicity of the annulus of the modified cyclodextrin **49**, resulting from the effect of the hydration of the protonated amino substituent impinging on the character of the cyclodextrin cavity. The association constants of the esters **25** and **26** with the C-3 substituted cyclodextrin **50** are even lower than those with the host **49**. This is likely due to the inversion of stereochemistry at C-2 and C-3 in the synthesis of that species,[65] which results in the protonated amine group pointing directly into the cavity of the cyclodextrin **50**. This doubtless further decreases the hydrophobicity of the cavity of the cyclodextrin **50**.

These studies also indicated that the *ortho*-substituted ester **26** forms more stable complexes than the corresponding *para*-isomer **25** with the cyclodextrins **1, 49** and **50**. This was attributed to the effect of the complementary dipole moments of the cyclodextrins **1, 49** and **50** and those of the guests **25** and **26** in their inclusion complexes. Given the likelihood of an orientation of the complex in which the dipoles of the host and guest are anti-parallel,[133,135] this alignment will contribute to the extent of association in those complexes. As the dipole moment of the *ortho*-substituted ester **26** is greater than that of the corresponding *para*-substituted isomer **25**, the complexes of the former with the cyclodextrins **1, 49** and **50** have the higher association constants. The anti-parallel alignment of the ester **25** and the anion **23** in their complexes with β-cyclodextrin **1** was confirmed by the use of 2D ROESY NMR spectroscopy, in which the cyclodextrin annulus proton resonances gave clear connectivities with certain of the resonances corresponding to protons of the guests **23** and **25**, confirming the proposed orientation.

The work described in Chapters 2 and 3 of this Thesis shows that reaction of the amines **56a,b** and **59a,b - 61a,b** with $6^A$-deoxy-$6^A$-iodo-β-cyclodextrin **31** or the corresponding tosylate **17** readily yields the amino-cyclodextrins **45a,b - 48a,b**. Apparent enantioselectivity in the synthesis of the pairs of diastereomers when prepared from the iodide **31** was found to be variable and at least in the case of the preparation of the 1-phenylethylamine-derived cyclodextrins **45a** and **45b**, to be due to the presence of ethanol, an impurity in some reactions mixtures. This selectivity was likely a consequence of the formation of ternary complexes in those systems. The properties and complexation behaviour of the charged cyclodextrins **57a,b** and **62a,b - 64a,b**, conjugate acids of the amines **45a,b**, **47a,b**, **48a,b** and **46a,b**, respectively, were studied and found to be largely influenced by the presence of intramolecular complexation between the annuli and the aromatic moities of their substituents. The presence of intramolecular complexation in the cyclodextrins **57a** and **57b** was confirmed by the implementation of 2D ROESY NMR and circular dichroism spectroscopy. The extent of intramolecular complexation in the cyclodextrins **57a,b** and **62a,b - 64a,b** was found to be dependent on the chirality of the cyclodextrin substituent, and this affected the ease of displacement of the aromatic moieties from the annuli. The strongly lipophilic species adamantan-1-ol **42** was able to disrupt these intramolecular complexes in all cyclodextrins, and so be complexed by them. In contrast the weakly lipophilic *para*-methoxybenzylalcohol **58** was not complexed by the cyclodextrins which contained larger extents of intramolecular complexation.

Work described in Chapter 4 of this Thesis to probe the factors influencing the presence of spectroscopic discrimination shows that the 2-phenylpropanoic acid enantiomers **8a** and **8b** are complexed by all of the

modified cyclodextrins **57a,b**, **62a,b**, **63b** and **64a,b**, with spectroscopic discrimination being observed in all cases. The *(R)*-amphetamine-derived cyclodextrin **63a** did not complex these lipophilic species, presumably due to particularly strong intramolecular complexation in that species as a consequence of the flexibility of it's substituent. The propanoate anions **43a** and **43b** were not complexed by either the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**, the *(R)*-1-(1-naphthyl)ethylamine-derived cyclodextrin **62a**, the *(R)*-amphetamine-derived cyclodextrin **63a**, or the *(S)*-phenylglycinol-derived cyclodextrin **64b**, all of which share a common geometry in their substituents. This lack of intermolecular complexation is presumably due to the presence of intramolecular complexation which is sufficiently strong to preclude complexation of the weakly lipophilic anions **43a** and **43b**. In addition the *(R)*-phenylglycinol-derived cyclodextrin **64a** also did not complex the anions **43a** and **43b**. In contrast, the anions **43a** and **43b** did form complexes with the *(S)*-amine-derived cyclodextrins **57b**, **62b** and **63b**, with the associated observation of spectroscopic discrimination. Guests complexation in these systems was likely due to the presence of only weak intramolecular complexation in the cyclodextrins **57b**, **62b** and **63b**. It was found that the much more lipophilic Ibuprofen anions **44a** and **44b**, and the corresponding acids **37a** and **37b**, were complexed by all of the cyclodextrins **57a,b**, and **62a,b** - **64a,b**, with spectroscopic discrimination being observed in all systems except those containing the *(R)*-1-(1-naphthyl)ethylamine-derived cyclodextrin **62a**. However, despite the observation of spectroscopic discrimination in many of these systems this was not reflected as thermodynamic discrimination in any of the systems chosen for closer study which contained the cyclodextrins **57a** and **57b** and the guests **8a,b**, **37a,b**, **43a,b** and **44a,b**. The presence of significant spectroscopic discrimination in many of these systems is significant since the cyclodextrins **57a,b**, and **62a,b** -

**64a,b** were designed specifically to maximize interactions with the guests **8a,b**, **37a,b**, **43a,b** and **44a,b**, and especially to provide enhanced discrimination in the interactions with the guests **43a,b** and **44a,b**, compared to their corresponding complexation by β-cyclodextrin **1**, and that indeed was the case.

## Experimental

### General

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker 300, Varian 300 or Varian VXR 500S spectrometer. Sample temperatures were controlled using a Bruker B-VT1000 variable temperature unit to within ± 0.3 K. Proton nuclear magnetic resonance ($^{1}H$ NMR) spectra were recorded at 500 MHz, unless otherwise specified, carbon nuclear magnetic resonance ($^{13}C$ NMR) spectra were recorded at 75.5 MHz and fluorine nuclear magnetic resonance ($^{19}F$ NMR) spectra were recorded at 282 MHz. $^{1}H$ NMR spectra were either recorded in deuterochloroform using $\delta_H$ 7.26 as an internal standard, or in deuterium oxide, neat or as a buffered solution as indicated, using a 10 % solution of sodium 3-(trimethylsilyl)-1-propane in deuterium oxide as an $\delta_H$ 0.0 external standard. 13C NMR spectra were recorded in $d_6$-deuterated dimethylsulfoxide using $\delta_C$ 49.7 as an internal standard. $^{19}F$ NMR spectra were recorded in buffered deuterium oxide / water solutions as indicated, using 2 % trifluroacetic acid in deuterium oxide as an $\delta_F$ 0.0 external standard. Coupling constant values $J$ between either protons or proton and fluorine atoms are given in hertz. Multiplicities are abbreviated to; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Elemental analyses were carried out by the Research School of Chemistry Microanalytical Service at the Australian National University.

Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer as a nujol mull or neat liquids between sodium chloride plates.

Circular Dichroism spectra were recorded on a Jobin Yvon CD6 as aqueous buffered solutions as indicated in the text.

Fast atom bombardment mass spectra (FAB-MS) were recorded on a VG-ZAB 2HF mass spectrometer. Electrospray mass spectra (ESI-MS) were recorded on a VG Quatro triple quadrapole mass spectrometer.

Analytical thin layer chromatography was preformed using Merck Kieselgel 60 $F_{254}$ silica on aliminium backed plates. High performence liquid chromatography (HPLC) was carried out using a Waters 510 solvent pump, a Rheodyne 200 µl injector, a Waters model 486 tunable absorbence detector and a Waters model 410 differential refractometer, in conjunction with a Digital Electronics Corporation Data Station running Millennium chromatography manager. Analyses were perfomed using either a Waters Carbohydrate Analysis column or a 10µl Porasil Rad Pak, eluting with solvents as indicated.

All solvents and reagents were purified using standard methods. Organic extracts were dried by the addition of anhydrous magnesium sulfate, unless otherwise indicated.

## Experimental Details of Work Described in Chapter 1

### Synthesis

#### $6^A$-Deoxy-$6^A$-fluoro-β–cyclodextrin 11

The C-6 fluoro-substituted cyclodextrin **11** was prepared according to a modification of the reported synthesis.[83]

The tosylate **17** (1.00 g, 0.78 mmol), potassium fluoride (0.36 g, 6.2 mmol) and sodium iodide (0.080 g, 0.53 mmol) were dissolved in ethylene glycol (50 $cm^3$) and heated at gentle reflux for 20 min. The reaction mixture was allowed to cool to room temperature and then triturated with cooled propan-2-ol (500 $cm^3$), centrifuged and the resultant solid recrystallized twice from water, to yield the fluoride **11** as a colourless powder (0.14 g, 16 %). (Found: C, 38.79; H, 6.30. $C_{42}H_{69}FO_{34}.10H_2O$ requires C, 38.30; H, 6.80); HPLC $t_R$ 0.67 relative to β-cyclodextrin 1; $^1H$ NMR (300 MHz, $D_2O$) δ 3.54 (7H, m, H-4), 3.60 (7H, dd, *J* 9.8 and 3.6 Hz, H-2), 3.84 (21H, m, H-5,6), 3.92 (7H, t, *J* 9.4 Hz, H-3), 5.03 (6H, d, *J* 4.0 Hz, H-$1^{B-G}$), 5.06 (1H, d, *J* 4.0 Hz, H-$1^A$); $^{13}C$ NMR (dmso) δ 66.4 ($C6^{B-G}$), 78.0 - 79.2 (C2, C3, C5), 86.3 ($C6^A$), 87.3 (C4), 108.1 (C1); $\delta_F$ ($D_2O$) -157.847 (1F, dt, $^2J_{FH}$ 47.1 Hz, $^3J_{FH}$ 29.9 Hz); *m/z* (ESI-MS) 1159 (M + $Na^+$); HRESI-MS Found 1159.3552. $C_{42}H_{69}O_{34}Na$ requires 1159.3552.

#### $6^A$-Amino-$6^A$-deoxy-β-cyclodextrin 14

The C-6 amino-substituted cyclodextrin **14** was prepared according to the reported synthesis.[100]

The tosylate **17** (1.0 g, 0.78 mmol) was dissolved in DMF (50 $cm^3$) in a 400 $cm^3$ Parr pressure reaction vessel. Condensed ammonia (100 $cm^3$) was added and the vessel sealed. The mixture was then allowed to warm to room temperature. After the mixture was stirred for 18h at room temperature, the pressure was released, allowing the excess ammonia to evaporate, and the residual solution was concentrated under reduced pressure. The residual solid was dissolved in water (10 $cm^3$) and the solution was concentrated under reduced pressure, then the process was repeated to remove residual DMF. The remaining solid was dissolved in water (20 $cm^3$) and the solution was added to a column of Biorex 70™ Cation exchange resin (10g, $H^+$ form), pre-wetted. The column was then eluted with water (200 $cm^3$) to remove unreacted tosylate **17**. Subsequent elution of the column with aqueous ammonia (20 %, v/v) and concentration of the eluent under reduced pressure gave the pure C-6 substituted amine **14** as a colourless powder (0.58 g, 56%). HPLC $t_R$ 1.30 relative to β-cyclodextrin **1**; $^{13}C$ NMR (dmso) δ 43.0 ($C6^A$), 63.1 ($C6^{B-G}$), 74.5 - 75.2 (C2, C5), 75.6 - 75.9 (C3), 83.9 - 84.0 (C4), 104.0 ($C1^A$), 104.6 ($C1^{B-G}$); *m/z* 1135 ($M + H^+$).

**$6^A$-*O*-*p*-Toluenesulfonyl-β-cyclodextrin 17**

The C-6 monotosylated cyclodextrin **17** was prepared according to a modification of the reported synthesis.[100,101]

β-Cyclodextrin **1** (5.0 g, 4.4 mmol) was dried to constant weight over phosphorous pentoxide, then dissolved in pyridine (100 $cm^3$) and 4-methylphenylsulfonyl chloride **16** (1.0 g, 5.4 mmol) was added to the stirred

solution over one hour. The mixture was stirred at room temperature for 24 hours. The solution was reduced to approximately 5 $cm^3$ under reduced pressure and the residue pipetted into cold, stirred acetone (100 $cm^3$). The resulting precipitate was collected and recrystallized from water twice, dried to constant weight over phosphorous pentoxide, to yield the tosylate **17** as a colourless powder (2.3 g, 41%). HPLC $t_R$ 0.53 relative to β–cyclodextrin **1**. These and other spectral and physical properties were consistent with those reported.[100]

**Methyl *para*-fluorobenzoate 25**

A mixture of *para*-fluorobenzoic acid **50** (4.0 g 28.6 mmol) and thionyl chloride (20.0 g, 202 mmol) was stirred and heated at reflux for 4 h. The resultant solution was then cooled to room temperature and excess thionyl chloride removed under reduced pressure. The resultant yellow residue was then added to dry methanol (100 $cm^3$) dropwise and the resultant solution stirred and heated at reflux for a further 4 h. Removal of the solvent under vacuum afforded the crude ester **25** which was then redissolved in dichloromethane (100 $cm^3$) and washed with water (2 x 100 $cm^3$) and then aqueous sodium bicarbonate (2 x 100 $cm^3$). The organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure to give a clear yellow oil. Distillation of the oil yielded the ester **25** as a colourless clear liquid (3.4 g, 77%), b.p. 137-139°C / 28 mm (Lit.[150] 209°C). $^1H$ NMR (pH 6 $D_2O$ buffer) δ 3.92 (3H, s, $-OCH_3$), 7.28 (2H, t, *J* 5.3 Hz, H-3,3'), 8.11 (2H, dd, J 5.3 and 3.0 Hz, H-2,2'); $^{19}F$ NMR (pH 6 $D_2O$ buffer) δ -28.51 (1F, s, Ar-F).

**Methyl *ortho*-fluorobenzoate 26**

The ester **26** derived from the acid **49** was made according to the procedure described above for preparation of the ester **25**. Reaction of *ortho*-fluorobenzoic acid **49** (4.0 g, 28.6 mmol) with thionyl chloride (20g, 202 mmol) and then methanol (100cm$^3$) yielded the ester **26** as a colourless clear liquid (3.4 g, 77 %), b.p. 137 - 139°C / 28 mm (Lit.[150] 209°C). $^1$H NMR (300 MHz, pH 6 $D_2O$ buffer) δ 3.81 (3H, s, -$OCH_3$), 7.30 (1H, t, *J* 4.8 Hz, H-3), 7.35 (1H, t, *J* 4.8 Hz, H-5), 7.98 (1H, dd, J 4.8 and 4.4 Hz, H-5); $^{19}$F NMR (pH 6 $D_2O$ buffer) δ -34.83 (1F, s, Ar-F).

**Complexation Sudies with the Fluoro-Cyclodextrin 11**

**Preparation of $^{19}$F NMR samples for the investigation of solvent effects**

All samples were prepared by dissolving the fluoride **11** (10.0 mg, 8.8 mmol) in solvent consisting of a methanol / $D_2O$ mixture (2.0 cm$^3$), varying to a maximum of 95 % methanol to ensure that sufficient $D_2O$ remained to provide a locking signal for the NMR spectrometer. The $^{19}$F NMR spectra of the samples were recorded and the chemical shifts of the fluorine substituents noted (Figure 1.1).

**Phosphate buffered $D_2O$ pH 6.0 ($I$ = 0.1)**

Potassium dihydrogen phosphate (0.966 g) and disodium hydrogen phosphate (0.138 g) was dissolved in $D_2O$ and the total volume was made up to 100 cm$^3$ with $D_2O$. The pH of the solution was checked and found to be as required.

**Preparation of stock solutions of the guests 43 and 44**

Racemic Guest **43**. Racemic 2-phenylpropanoic acid **8** (19.6 mg) was dissolved in pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.1), the total volume was then made up to 25.0 $cm^3$ (5.1 mmol $dm^{-3}$) with the above buffered $D_2O$.

Racemic Guest **44**. Racemic Ibuprofen acid **37** (25.8 mg) was dissolved in pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.1), the total volume was then made up to 25.0 $cm^3$ (5.0 mmol $dm^{-3}$) with the above buffered $D_2O$.

**$^{19}F$ NMR samples containing the cyclodextrin 11 and the guests 43 and 44**

Samples were prepared by preweighing the fluoride **11** (2.5 mg) into 2 $cm^3$ volumetric flasks and the total volume made up to 2.0 cm3 with the appropriate guest solution.

**$^{19}F$ NMR samples containing the cyclodextrin 11 and the guests 8 and 37**

The above pH 6.0 samples containing the cyclodextrin **11** and the guests **43** or **44** were adjusted to pH 1.0 with 10 % DCl / $D_2O$ solution to ensure that the predominant form of the guest were the corresponding acids **8** and **37**, respectively and their $^{19}F$ NMR spectra re-recorded.

## Complexation of the Guests 23 - 26 with the Cyclodextrins 1, 51 and 52

### Preparation of samples for $^{19}F$ NMR analysis

### Phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2)

Stock A. Potassium dihydrogenphosphate (68.046 g) was dissolved in water, and the total volume was made up to 1.0 $dm^3$ (0.5 mol $dm^{-3}$) with water.
Stock B. Disodium hydrogenphosphate (35.492 g) was dissolved in water, and the total volume was made up to 500 $cm^3$ (0.5 mol $dm^{-3}$) with water.

Phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2). To stock A (265 $cm^3$), stock B (44.8 $cm^3$) was added, the total volume was then made up to 1 $dm^3$ with water. The pH of the solution was checked and found to be as required.

### Preparation of stock solutions of the guests 23 - 26

Stock Guest **23**. *Para*-fluorobenzoic acid **50** (29.2 mg) was dissolved in phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2), the total volume was then made up to 100 $cm^3$ (2.09 mmol $dm^{-3}$) with the above buffer.

Stock Guest **24**. *Ortho*-fluorobenzoic acid **49** (31 mg) was dissolved in phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2), the total volume was then made up to 100 $cm^3$ (2.21 mmol $dm^{-3}$) with the above buffer.

Stock Guest **25**. Methyl *para*-fluorobenzoate **25** (23.2 mg) was dissolved in phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2), the total volume was then made up to 100 $cm^3$ (1.51 mmol $dm^{-3}$) with the above buffer.

Stock Guest **26**. Methyl *ortho*-fluorobenzoate **26** (18.8 mg) was dissolved in phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2), the total volume was then made up to 100 $cm^3$ (1.22 mmol $dm^{-3}$) with the above buffer.

**Preparation of the stock solution of the cyclodextrin 52.**

Stock cyclodextrin **52**. The C-3 amino-substituted cyclodextrin **15** (0.375 g) was dissolved in phosphate buffer 0.2 mol $dm^{-3}$ pH 6.0 ($I$ = 0.2), the total volume was then made up to 10 $cm^3$ (33.04 mmol $dm^{-3}$) with the above buffer.

**Sample preparation.**

Samples containing β-cyclodextrin **1** or the C-6 amino-substituted cyclodextrin **51** were prepared by weighing out the appropriate mass of either β-cyclodextrin **1** or the amine **14** into 2 $cm^3$ volumetric flasks to which the appropriate guest stock solution (1.0 $cm^3$) and $D_2O$ (0.2 $cm^3$) was added. A total volume of 2 $cm^3$ was achieved by adding the necessary amount of water. Samples containing the C-3 amino-substituted cyclodextrin **52** were prepared by adding the appropriate guest stock solution (1.0 $cm^3$) to 2 $cm^3$ volumetric flask containing $D_2O$ (0.2 $cm^3$), and then adding the required volume of the amine **52** stock solution. A total volume of 2 $cm^3$ was achieved by adding the necessary amount of water.

**Association Constants of the Guests 23 - 26 with β-Cyclodextrin 1**

| Mass of Host **1** (mg) | [Host **1**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **23** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -32.967 |
| 1.866 | 0.001 | -32.988 |
| 3.732 | 0.002 | -33.005 |
| 5.598 | 0.002 | -33.023 |
| 7.464 | 0.003 | -33.040 |
| 9.330 | 0.004 | -33.053 |
| 11.196 | 0.005 | -33.066 |
| 13.062 | 0.006 | -33.079 |
| 14.928 | 0.007 | -33.092 |
| 16.793 | 0.007 | -33.105 |
| 18.659 | 0.008 | -33.118 |
| 20.525 | 0.009 | -33.126 |
| 22.391 | 0.010 | -33.135 |
| 24.257 | 0.011 | -33.144 |
| 26.123 | 0.012 | -33.152 |
| 27.989 | 0.012 | -33.161 |
| 29.855 | 0.013 | -33.174 |

**Table 1.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the acid guest **23** as a function of the concentration of β-cyclodextrin **1**. The association constant of the guest **23**, with the cyclodextrin **1** was calculated as $50 \pm 2$ $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as $-33.49 \pm 0.02$ ppm.

| Mass of Host **1** (mg) | [Host **1**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **24** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -38.867 |
| 1.865 | 0.001 | -38.828 |
| 3.731 | 0.002 | -38.798 |
| 5.596 | 0.002 | -38.759 |
| 7.462 | 0.003 | -38.733 |
| 9.327 | 0.004 | -38.694 |
| 11.193 | 0.005 | -38.660 |
| 13.058 | 0.006 | -38.625 |
| 14.923 | 0.007 | -38.595 |
| 16.789 | 0.007 | -38.569 |
| 18.654 | 0.008 | -38.543 |
| 20.520 | 0.009 | -38.496 |
| 22.385 | 0.010 | -38.481 |
| 24.251 | 0.011 | -38.452 |
| 26.116 | 0.012 | -38.426 |
| 27.981 | 0.012 | -38.400 |
| 29.847 | 0.013 | -38.396 |

**Table 2.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the acid guest **24** as a function of the concentration of β-cyclodextrin **1**. The association constant of the guest **24**, with the cyclodextrin **1** was calculated as $19 \pm 3$ $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as $-36.44 \pm 0.30$ ppm.

| Mass of Host **1** (mg) | [Host **1**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **25** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -28.510 |
| 2.400 | 0.001 | -28.393 |
| 4.000 | 0.002 | -28.328 |
| 5.700 | 0.003 | -28.280 |
| 7.400 | 0.003 | -28.229 |
| 10.000 | 0.004 | -28.194 |
| 11.000 | 0.005 | -28.168 |
| 12.600 | 0.006 | -28.146 |
| 14.500 | 0.006 | -28.121 |
| 16.800 | 0.007 | -28.090 |
| 18.900 | 0.008 | -28.073 |
| 20.500 | 0.009 | -28.056 |
| 22.800 | 0.010 | -28.047 |
| 24.700 | 0.011 | -28.038 |
| 26.400 | 0.012 | -28.025 |
| 28.800 | 0.013 | -28.008 |

**Table 3.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the ester guest **25** as a function of the concentration of β-cyclodextrin **1**. The association constant of the guest **25**, with the cyclodextrin **1** was calculated as 228 ± 7 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -27.83 ± 0.01 ppm.

| Mass of Host **1** (mg) | [Host **1**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **26** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -34.834 |
| 2.000 | 0.001 | -34.497 |
| 4.300 | 0.002 | -34.272 |
| 5.000 | 0.002 | -34.151 |
| 6.800 | 0.003 | -34.043 |
| 9.400 | 0.004 | -33.896 |
| 10.500 | 0.005 | -33.822 |
| 13.100 | 0.006 | -33.753 |
| 15.400 | 0.007 | -33.645 |
| 16.700 | 0.007 | -33.580 |
| 19.000 | 0.008 | -33.559 |
| 20.800 | 0.009 | -33.507 |
| 22.100 | 0.010 | -33.503 |
| 23.800 | 0.010 | -33.451 |
| 26.800 | 0.012 | -33.399 |
| 28.900 | 0.013 | -33.373 |

**Table 4.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the ester guest **26** as a function of the concentration of β-cyclodextrin **1**. The association constant of the guest **26**, with the cyclodextrin **1** was calculated as 253 ± 11 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -32.91 ± 0.03 ppm.

**Calculation of the Association Constants of the Guests 23 - 26 with the Cyclodextrin 49**

| Mass of Cyclodextrin **14** (mg) | [Host **49**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **23** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -32.971 |
| 1.865 | 0.001 | -32.988 |
| 3.731 | 0.002 | -33.005 |
| 5.596 | 0.002 | -33.023 |
| 7.462 | 0.003 | -33.040 |
| 9.327 | 0.004 | -33.053 |
| 11.193 | 0.005 | -33.062 |
| 13.058 | 0.006 | -33.070 |
| 14.923 | 0.007 | -33.083 |
| 16.789 | 0.007 | -33.096 |
| 18.654 | 0.008 | -33.101 |
| 20.520 | 0.009 | -33.109 |
| 22.385 | 0.010 | -33.118 |
| 24.251 | 0.011 | -33.126 |
| 26.116 | 0.012 | -33.135 |
| 27.981 | 0.012 | -33.139 |

**Table 5.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the acid guest **23** as a function of the concentration of the cyclodextrin **49**. The association constant of the guest **23**, with the cyclodextrin **49** was calculated as $69 \pm 4$ $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as $-33.35 \pm 0.02$ ppm.

| Mass of Cyclodextrin **14** (mg) | [Host **49**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **24** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -38.867 |
| 1.865 | 0.001 | -38.794 |
| 3.731 | 0.002 | -38.720 |
| 5.596 | 0.002 | -38.660 |
| 7.462 | 0.003 | -38.599 |
| 9.327 | 0.004 | -38.556 |
| 11.193 | 0.005 | -38.504 |
| 13.058 | 0.006 | -38.457 |
| 14.923 | 0.007 | -38.413 |
| 16.789 | 0.007 | -38.383 |
| 18.654 | 0.008 | -38.331 |
| 20.520 | 0.009 | -38.301 |
| 22.385 | 0.010 | -38.266 |
| 24.251 | 0.011 | -38.240 |
| 26.116 | 0.012 | -38.210 |
| 27.981 | 0.012 | -38.189 |

**Table 6.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the acid guest **24** as a function of the concentration of the cyclodextrin **49**. The association constant of the guest **24**, with the cyclodextrin **49** was calculated as $65 \pm 2$ $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as $-37.29 \pm 0.03$ ppm.

| Mass of Cyclodextrin **14** (mg) | [Host **49**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **25** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -28.514 |
| 1.860 | 0.001 | -28.466 |
| 3.720 | 0.002 | -28.406 |
| 5.579 | 0.002 | -28.367 |
| 7.439 | 0.003 | -28.337 |
| 9.299 | 0.004 | -28.311 |
| 11.159 | 0.005 | -28.289 |
| 13.018 | 0.006 | -28.268 |
| 14.878 | 0.007 | -28.237 |
| 16.738 | 0.007 | -28.229 |
| 18.598 | 0.008 | -28.207 |
| 22.317 | 0.010 | -28.177 |
| 24.177 | 0.011 | -28.168 |
| 26.037 | 0.011 | -28.146 |
| 27.896 | 0.012 | -28.142 |
| 29.756 | 0.013 | -28.133 |

**Table 7.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the ester guest **25** as a function of the concentration of the cyclodextrin **49**. The association constant of the guest **25**, with the cyclodextrin **49** was calculated as 128 ± 7 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -27.90 ± 0.02 ppm.

| Mass of Cyclodextrin **14** (mg) | [Host **49**] (mol $dm^{-3}$) | Chemical Shift ($\delta_{obs}$) for guest **26** (ppm) |
|---|---|---|
| 0.000 | 0.000 | -34.825 |
| 1.860 | 0.001 | -34.644 |
| 3.720 | 0.002 | -34.480 |
| 5.579 | 0.002 | -34.328 |
| 7.439 | 0.003 | -34.250 |
| 9.299 | 0.004 | -34.160 |
| 11.159 | 0.005 | -34.082 |
| 14.878 | 0.007 | -33.982 |
| 16.738 | 0.007 | -33.896 |
| 18.598 | 0.008 | -33.866 |
| 20.457 | 0.009 | -33.809 |
| 22.317 | 0.010 | -33.766 |
| 24.177 | 0.011 | -33.745 |
| 26.037 | 0.011 | -33.701 |
| 27.896 | 0.012 | -33.650 |
| 29.800 | 0.013 | -33.645 |

**Table 8.** $^{19}F$ NMR Chemical shifts of the fluorine substituent of the ester guest **26** as a function of the concentration of the cyclodextrin **49**. The association constant of the guest **26**, with the cyclodextrin **49** was calculated as 152 ± 7 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -33.04 ± 0.04 ppm.

**Calculation of the Association Constants of the Guests 23 - 26 with the Cyclodextrin 50.[151]**

The association constants of the guests **23 - 26**, with the cyclodextrin **50** were calculated by the technique outlined above for the hosts **1** and **49**, save for the difference that the host **50** was supplied by addition of appropriate amounts of stock solution (33.04 mmol $dm^{-3}$). The association constant of the guest **23**, with the cyclodextrin **50** was calculated as 19 ± 5 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -33.72 ± 0.20 ppm. The association constant of the guest **24**, with the cyclodextrin **50** was calculated as 32 ± 3 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -37.20 ± 0.10 ppm. The association constant of the guest **25**, with the cyclodextrin **50** was calculated as 59 ± 2 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -27.64 ± 0.01 ppm. The association constant of the guest **26**, with the cyclodextrin **50** was calculated as 69 ± 2 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as -32.52 ± 0.05 ppm.

## 2D ROESY NMR Study of the Complexation of the Guests 23 and 25 with β-Cyclodextrin 1.

### Preparation of 2D ROESY NMR samples

Stock Guest **23**. *Para*-fluorobenzoic acid **23** (29.2 mg) was dissolved in $I$ = 0.1 mol $dm^{-3}$ pH 6.0 phosphate buffered $D_2O$, the total volume was then made up to 100 $cm^3$ (2.09 mmol $dm^{-3}$) with the above buffer.

Stock Guest **25**. Methyl *para*-fluorobenzoate **25** (23.2 mg) was dissolved in $I$ = 0.1 mol $dm^{-3}$ pH 6.0 phosphate buffered $D_2O$, the total volume was then made up to 100 $cm^3$ (2.09 mmol $dm^{-3}$) with the above buffer.

β-cyclodextrin **1** (28.4 mg, 0.025 mmol) was weighed into into 2 $cm^3$ volumetric flasks to which appropriate amounts of stock solutions of the guests **23** and **25** was added. A total volume of 2.0 $cm^3$ was achieved by adding the necessary amount of pH 6.0 phosphate buffered $D_2O$. The samples were sparged with argon for 4h., and then further degassed under reduced pressure in a vacuum sealed NMR tube. The samples were then sealed under argon and their 2D ROESY spectra recorded .

## Experimental Details of Work Described in Chapters 2 and 3

### Synthesis

### $6^A$-Deoxy-$6^A$-iodo-β-cyclodextrin 31

The tosylate **17** (3.0 g, 2.3 mmol) was dried to constant weight over phosphorous pentoxide, then dissolved in water (150 $cm^3$) and sodium iodide (6.0 g, 40.0 mmol) was added to the solution. The mixture was heated at reflux for 5 hours. The solution was reduced to approximately 5 $cm^3$ under reduced pressure and the residue pipetted into cold, stirred acetone (100 $cm^3$). The resulting precipitate was collected and dissolved in hot water, and then evaporated to dryness under reduced pressure. Analysis by HPLC showed the product to be contaminated with β-cyclodextrin **1**. The material obtained was dissolved in hot water (20 $cm^3$) and then cooled to 0°C. Tetrachloroethylene (TCE) (2 $cm^3$) was added and the mixture stirred vigorously for 30 minutes. The resultant precipitate was collected by filtration onto a kenite pad and rinsed with water (2 x 10 $cm^3$), acetone (2 x 10 $cm^3$), ether (2 x 10 $cm^3$) and dried by water pump suction. The dry cake of precipitate and kenite was suspended in water (50 $cm^3$) and the TCE removed by steam distillation. The hot residue was filtered and the vessel rinsed with hot water (2 x 20 $cm^3$). The combined filtrates were reduced to approximately 5 $cm^3$ under reduced pressure and the residue pipetted into cold, stirred acetone. The precipitate was collected and dissolved in water (50 $cm^3$) and then evaporated to dryness under reduced pressure. This procedure was repeated, the solid collected and dried to constant weight over phosphorous pentoxide, yielding the iodide **31** as a white powder (2.4 g, 83%). HPLC $t_R$ 0.65 relative to β–cyclodextrin **1**; $^{13}C$ NMR (dmso) δ 45.2

($C6^A$); *m/z* 1262 ($M + H^+$). These and other spectral and physical properties are consistent with those previously reported.[111]

**Amino-cyclodextrins 45a,b - 48a,b.**

**Method A.**

β-Cyclodextrin iodide **31** (1.0 g, 0.80 mmol) was desiccated to constant weight over phosphorous pentoxide, then dissolved in dry *N,N*-dimethylformamide (10 $cm^3$) and the appropriate free amine starting material (1.6 mmol) was added with stirring. The reaction mixture was stirred at 70°C for 2 days after which the solution allowed to cool to room temperature and then pipetted into cold, stirred acetone (250 $cm^3$). The resulting precipitate was collected, dissolved in hot water (*ca.* 50 $cm^3$) and then evaporated to dryness under reduced pressure. The collected solid was dissolved in water (20 $cm^3$) and loaded on to a column of Biorex 70™ ion exchange resin (20mm x 150 mm, 100-200 mesh, $H^+$ form). The column was then washed with water (1000 $cm^3$) to wash off non-amine cyclodextrin components. The amino-cyclodextrin product was then liberated from the resin by washing with ammonia liquor (5 x 100 $cm^3$ fractions). The amino-cyclodextrin bearing fractions were then combined, filtered with millipore HPLC filters, and the solution evaporated to dryness under reduced pressure and the resultant solid freeze dried from water (*ca.* 50 $cm^3$) to constant weight. The solid was stored prior to use over phosphorous pentoxide.

**Method B.**

β-Cyclodextrin tosylate **17** (1.0 g, 0.78 mmol) was desiccated to constant weight over phosphorous pentoxide, then dissolved in *N*-methylpyrrolidin-2-one (5 $cm^3$) which contained sodium iodide (0.025g, 0.16 mmol). To this

mixture, the appropriate free amine starting material (1.6 mmol) was added with stirring. The reaction mixture was stirred at 70°C for 12 hours after which the solution allowed to cool to room temperature and then pipetted into ethanol (100 $cm^3$). The resulting precipitate was collected, dissolved in hot water (50 $cm^3$) and then evaporated to dryness under reduced pressure. The collected solid was dissolved in water (*ca.* 20 $cm^3$) and loaded on to a column of Biorex 70™ ion exchange resin (20mm x 150 mm, 100-200 mesh, $H^+$ form). The column was then washed with water (1000 $cm^3$) to wash off non-amine cyclodextrin components. The amino-cyclodextrin product was then liberated from the resin by washing with ammonia liquor (5 x 100 $cm^3$ fractions). The amino-cyclodextrin bearing fractions were then combined, filtered with millipore HPLC filters, and the solution evaporated to dryness under reduced pressure and the resultant solid freeze dried from water (*ca.* 50 $cm^3$) to constant weight. The solid was stored prior to use over phosphorous pentoxide.

**The *(R)*-1-phenylethylamine-derived cyclodextrin 45a**

The title compound **45a** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(R)*-(+)-α-phenylethylamine **57a** (0.20 $cm^3$, 0.19 g, 1.60 mmol), and was isolated as a colourless solid (0.43 g, 44%). The title compound **45a** was also prepared using Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(R)*-(+)-α-phenylethylamine **57a** (0.20 $cm^3$, 0.19 g, 1.58 mmol), and was isolated as a colourless solid (0.55 g, 56%). The cyclodextrin **45a** when prepared using either Method A or Method B was found to be identical in every respect. (Found: C, 46.11; H, 6.81; N, 1.33. $C_{50}H_{79}NO_{34}.3.5H_2O$ requires C, 46.15; H, 6.66; N, 1.08); HPLC $t_R$ 0.72 relative

to β-cyclodextrin **1**; $^1$H NMR (500 MHz, pH 6 $D_2O$ buffer) δ 1.65 (3H, d, *J* 7.0 Hz, CH(Ph)-C<u>H</u>$_3$), 4.25 (1H, q, *J* 7.0 Hz, C<u>H</u>(Ph)CH$_3$), 7.44 (2H, d, *J* 7.0 Hz, -Ph, *ortho*-<u>H</u>), 7.53 (1H, d, *J* 7.0 Hz, -Ph-*para*-<u>H</u>), 7.56 (2H, t, *J* 7.0 Hz, -Ph-*meta*-<u>H</u>); $^{13}$C NMR (dmso) δ 24.7 (-CH(Ar)<u>C</u>H$_3$), 46.7 (C6$^A$), 47.9 (unassigned), 57.0 (-<u>C</u>H(Ar)CH$_3$), 59.8 - 60.2 (C6$^{B-G}$), 70.2 - 73.3 (C2, C3, C5), 81.2 - 81.7 (C4$^{B-G}$), 84.7 (C4$^A$), 101.9 - 102.5 (C1), 126.3 - 128.5 (3$^o$ Ar), 146.2 (4$^o$ Ar); *m/z* 1239 (M + H$^+$) and 1261 (M + Na$^+$); HRESI-MS Found 1238.4571. $C_{50}H_{80}NO_{34}$ requires 1238.4562.

**The *(S)*-1-phenylethylamine-derived cyclodextrin 45b**

The title compound **45b** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(S)*-(+)-α-phenylethylamine **57b** (0.20 cm$^3$, 0.19 g, 1.60 mmol), and was isolated as a colourless solid (0.38 g, 39%). The title compound **45b** was also prepared using Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(S)*-(+)-α-phenylethylamine **57b** (0.20 cm$^3$, 0.19 g, 1.58 mmol) and was isolated as a colourless solid (0.66 g, 67%). The cyclodextrin **45b** when prepared using either Method A or Method B was found to be identical in every respect. (Found: C, 43.70; H, 6.78; N, 1.13. $C_{50}H_{79}NO_{34}.8H_2O$ requires C, 43.44; H, 6.94; N, 1.01); HPLC $t_R$ 0.60 relative to β-cyclodextrin **1**; $^1$H NMR (500 MHz, pH 6 $D_2O$ buffer) δ 1.65 (3H, d, *J* 7.0 Hz, CH(Ph)-C<u>H</u>$_3$), 4.38 (1H, q, *J* 7.0 Hz, C<u>H</u>(Ph)CH$_3$), 7.47 (2H, d, *J* 7.0 Hz, -Ph-*ortho*-<u>H</u>), 7.51 (1H, d, *J* 7.0 Hz, -Ph-*para*-<u>H</u>), 7.53 (2H, t, *J* 7.0 Hz, -Ph-*meta*-<u>H</u>); $^{13}$C NMR (dmso) δ 25.1 (-CH(Ar)<u>C</u>H$_3$), 47.7 (C6$^A$), 57.6 (-<u>C</u>H(Ar)CH$_3$), 59.0 - 59.9 (C6$^{B-G}$), 70.8 - 73.3 (C2, C3, C5), 80.7 - 81.8 (C4$^{B-G}$), 83.9 (C4$^A$), 101.9 - 102.4 (C1), 126.3 - 128.3 (3$^o$ Ar), 146.3 (4$^o$ Ar); *m/z* 1239 (M + H$^+$) and 1261 (M + Na$^+$); HRESI-MS Found 1238.4588. $C_{50}H_{80}NO_{34}$ requires 1238.4562.

**The *(R)*-phenylglycinol-derived cyclodextrin 46a**

The title compound **46a** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(R)*-phenylglycinol **58a** (0.22 g, 1.60 mmol), and was isolated as a colourless solid (0.45 g, 45%). The title compound **46a** was also prepared according to Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(R)*-phenylglycinol **58a** (0.22 g, 1.60 mmol), with the modification that the trituration with ethanol step was replaced by a trituration with acetone (100 $cm^3$), and the cyclodextrin **46a** was isolated as a colourless solid (0.35 g, 35%). The cyclodextrin **46a** when prepared using either Method A or Method B was found to be identical in every respect. HPLC $t_R$ 0.74 relative to β-cyclodextrin **1**; $^1H$ NMR (500 MHz, pH 6 $D_2O$ buffer) δ 4.22 (1H, t, *J* 6.5 Hz, C<u>H</u>(Ar)$CH_2OH$), 7.44 (2H, d, *J* 7.5 Hz, -Ph-*ortho*-<u>H</u>), 7.51 (2H, t, *J* 7.5 Hz, -Ph-*meta*-<u>H</u>), 7.56 (1H, d, *J* 7.5 Hz, -Ph-*para*-<u>H</u>); $^{13}C$ NMR (dmso) δ 48.0 ($C6^A$), 56.1 (unassigned), 58.5 (-<u>C</u>H(Ar)$CH_2OH$), 59.9 ($C6^{B-G}$), 63.4, 64.8, 66.9, 70.8, 72.1 - 73.3 (C2, C3, C5), 80.3 - 81.9 ($C4^{B-G}$), 84.4 ($C4^A$), 101.5 - 102.4 (C1), 125.5 - 128.6 ($3^o$ Ar), 141.8 ($4^o$ Ar); *m/z* 1255 ($M + H^+$) and 1276 ($M + Na^+$); HRESI-MS Found 1254.4504. $C_{50}H_{80}NO_{35}$ requires 1254.4511. Found 1276.4350. $C_{50}H_{79}NO_{35}Na$ requires 1276.4330.

**The *(S)*-phenylglycinol-derived cyclodextrin 46b**

The title compound **46b** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(S)*-phenylglycinol **58b** (0.22 g, 1.60 mmol), and was isolated as a colourless solid (0.52 g, 52%). The title compound **46b** was also prepared according to Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(S)*-

phenylglycinol **58a** (0.22 g, 1.60 mmol), with the modification that the trituration with ethanol step was replaced by a trituration with acetone (100 $cm^3$), and the cyclodextrin **46a** was isolated as a colourless solid (0.47 g, 47%). The cyclodextrin **46b** when prepared using either Method A or Method B was found to be identical in every respect. (For a mixture of the cyclodextrins **46a** and **46b**, found: C, 44.05; H, 6.66; N, 1.44. $C_{50}H_{79}NO_{35}.5.5H_2O$ requires C, 44.37; H, 6.70; N, 1.04); HPLC $t_R$ 0.82 relative to β-cyclodextrin **1**; $^1H$ NMR (500 MHz, pH 6 $D_2O$ buffer) δ 4.19 (1H, t, *J* 6.0 Hz, C<u>H</u>(Ar)$CH_2OH$), 7.44 (2H, d, *J* 7.5 Hz, -Ph-*ortho*-<u>H</u>), 7.51 (2H, t, *J* 7.5 Hz, -Ph-*meta*-<u>H</u>), 7.56 (1H, d, *J* 7.5 Hz, -Ph-*para*-<u>H</u>); $^{13}C$ NMR (dmso) δ 48.4 ($C6^A$), 58.5 (-<u>C</u>H(Ar)$CH_2OH$), 60.0 ($C6^{B-G}$), 64.9, 67.0, 70.9 - 72.4 (C2, C3, C5), 80.3 - 82.0 ($C4^{B-G}$), 84.5 ($C4^A$), 101.6 - 102.5 (C1), 127.0 - 128.3 ($3^o$ Ar), 141.9 ($4^o$ Ar); *m/z* 1255 ($M + H^+$); HRESI-MS Found 1254.4503. $C_{50}H_{80}NO_{35}$ requires 1254.4511. Found 1276.4389. $C_{50}H_{79}NO_{35}Na$ requires 1276.4330.

**The *(R)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin 47a**

The title compound **47a** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(R)*-(+)-1-(1-naphthyl)-ethylamine **59a** (0.26 $cm^3$, 0.27 g, 1.60 mmol), and was isolated as a colourless solid (0.34 g, 33%). The title compound **47a** was also prepared using Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(R)*-(+)-1-(1-naphthyl)-ethylamine **59a** (0.26 $cm^3$, 0.27 g, 1.60 mmol), and was isolated as a colourless solid (0.40 g, 39%). The cyclodextrin **47a** when prepared using either Method A or Method B was found to be identical in every respect. (Found: C, 44.65; H, 6.56; N, 0.91. $C_{54}H_{81}NO_{34}.9H_2O$ requires C, 44.72; H, 6.88; N, 0.97); HPLC $t_R$ 0.83 relative to β-cyclodextrin **1**; $^1H$ NMR (500 MHz, pH 6 $D_2O$ buffer) δ 1.80 (3H, d, *J* 6.5 Hz,

CH(Ar)-C<u>H</u>$_3$), 5.10 (1H, q, *J* 7.0 Hz, C<u>H</u>(Ar)CH$_3$), 7.73 (1H, t, *J* 7.5 Hz, -Ar-<u>H</u>), 7.84 (1H, t, *J* 7.5 Hz, -Ar-<u>H</u>), 7.89 (2H, m, -Ar-<u>H</u>), 8.02 (1H, d, *J* 8.0 Hz, -Ar-<u>H</u>), 8.07 (1H, d, *J* 8.5 Hz, -Ar-<u>H</u>), 8.09 (1H, d, *J* 8.5 Hz, -Ar-<u>H</u>); $^{13}$C NMR (dmso) δ 23.7 (-CH(Ar)<u>C</u>H$_3$), 46.5 (C6$^{A}$), 53.4 (-<u>C</u>H(Ar)CH$_3$), 59.9 (C6$^{B\text{-}G}$), 72.0 - 73.1 (C2, C3, C5), 81.5 (C4), 102.0 (C1), 122.5 - 141.5 (7 x 3$^{o}$ Ar, 3 x 4$^{o}$ Ar); *m/z* 1289 (M + H$^{+}$); HRESI-MS Found 1288.4757. $C_{54}H_{82}NO_{34}$ requires 1288.4718.

**The *(S)*-1-(1-naphthyl)-ethylamine-derived cyclodextrin 47b**

The title compound **47b** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(R)*-(+)-1-(1-naphthyl)-ethylamine **59b** (0.26 cm$^3$, 0.27 g, 1.60 mmol), and was isolated as a colourless solid (0.36 g, 35%). (Found: C, 44.22; H, 6.31; N, 0.72. $C_{54}H_{81}NO_{34}.9H_2O$ requires C, 44.72; H, 6.85; N, 0.97); HPLC $t_R$ 0.58 relative to β-cyclodextrin **1**; $^{1}$H NMR (500 MHz, pH 6 $D_2O$ buffer) δ 1.75 (3H, d, *J* 7.0 Hz, CH(Ar)-C<u>H</u>$_3$), 5.16 (1H, q, *J* 7.0 Hz, C<u>H</u>(Ar)CH$_3$), 7.66 (1H, t, *J* 8.0 Hz, -Ar-<u>H</u>), 7.73 (1H, t, *J* 7.0 Hz, -Ar-<u>H</u>), 7.80 (1H, t, *J* 8.5 Hz, -Ar-<u>H</u>), 7.83 (1H, d, *J* 7.0 Hz, -Ar-<u>H</u>), 8.00 (1H, d, *J* 8.0 Hz, -Ar-<u>H</u>), 8.08 (1H, d, *J* 8.5 Hz, -Ar-<u>H</u>), 8.15 (1H, d, *J* 9.0 Hz, -Ar-<u>H</u>); $^{13}$C NMR (dmso) δ 24.1 (-CH(Ar)<u>C</u>H$_3$), 46.5 (C6$^{A}$), 47.9 (unassigned), 53.1 (-<u>C</u>H(Ar)CH$_3$), 58.7 - 59.8 (C6$^{B\text{-}G}$), 70.8 - 73.1 (C2, C3, C5), 80.4 - 84.0 (C4), 101.7 - 102.4 (C1), 122.3 - 141.5 (7 x 3$^{o}$ Ar, 3 x 4$^{o}$ Ar); *m/z* 1288 (M$^{+}$) and 1289 (M + H$^{+}$); HRESI-MS Found 1288.4688. $C_{54}H_{82}NO_{34}$ requires 1288.4718. Found 1326.4171. $C_{54}H_{81}NO_{34}Na$ requires 1326.4277.

**The *(R)*-amphetamine-derived cyclodextrin 48a**

The title compound **48a** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(R)*-amphetamine

**60a** (0.22 g, 1.60 mmol), and was isolated as a colourless solid (0.57 g, 58%). The title compound **48a** was also prepared using Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(R)*-amphetamine **60a** (0.22 g, 1.60 mmol), and was isolated as a colourless solid (0.37 g, 37%). The cyclodextrin **48a** when prepared using either Method A or Method B was found to be identical in every respect. HPLC $t_R$ 0.65 relative to β-cyclodextrin **1**; $^1$H NMR (500 MHz, pH 6 $D_2O$ buffer) δ 1.33 (1H, m, unassigned cyclodextrin annulus), 1.41 (3H, d, *J* 7.0 Hz, $CH(CH_2Ph)$-$C\underline{H}_3$), 7.28 (2H, d, *J* 7.5 Hz, -Ph-*ortho*-H), 7.47 (1H, d, *J* 7.5 Hz, -Ph-*para*-H), 7.49 (2H, t, *J* 7.5 Hz, -Ph-*meta*-H); $^{13}$C NMR (dmso) δ 19.7 (-$CH(CH_2Ar)\underline{C}H_3$), 42.6 (-$CH(\underline{C}H_2Ar)CH_3$), 46.9 ($C6^A$), 54.5 (-$\underline{C}H(CH_2Ar)CH_3$), 59.9 ($C6^{B\text{-}G}$), 70.7 - 73.1 (C2, C3, C5), 81.2 - 81.6 ($C4^{B\text{-}G}$), 83.6 ($C4^A$), 101.9 - 102.1 (C1), 125.9 - 129.2 ($3^o$ Ar), 139.6 ($4^o$ Ar); *m/z* 1252 ($M^+$) and 1253 ($M + H^+$); HRESI-MS Found 1252.4715. $C_{51}H_{82}NO_{34}$ requires 1252.4718. Found 1274.4561. $C_{51}H_{81}NO_{34}Na$ requires 1274.4538.

**The *(S)*-amphetamine-derived cyclodextrin 48b**

The title compound **48b** was synthesized using Method A, outlined above, through reaction of the iodide **31** (1.0 g, 0.80 mmol) and *(S)*-amphetamine **60b** (0.22 g, 1.60 mmol), and was isolated as a colourless solid (0.57 g, 58%). The title compound **48b** was also prepared using Method B, outlined above, through reaction of the tosylate **17** (1.0 g, 0.78 mmol) and *(S)*-amphetamine **60b** (0.22 g, 1.60 mmol), and was isolated as a colourless solid (0.30 g, 30%). The cyclodextrin **48b** when prepared using either Method A or Method B was found to be identical in every respect. (For a mixture of the cyclodextrins **48a** and **48b**, found: C, 43.57; H, 6.91; N, 0.94. $C_{51}H_{81}NO_{34}.9H_2O$ requires C, 43.31; H, 7.05; N, 0.99); HPLC $t_R$ 0.64 relative to β-cyclodextrin **1**;

$^1$H NMR (500 MHz, pH 6 $D_2O$ buffer) δ 1.27 (1H, m, unassigned cyclodextrin annulus), 1.31 (3H, d, *J* 6.0 Hz, CH($CH_2$Ph)-C$\underline{H}_3$), 7.33 (2H, d, *J* 7.5 Hz, -Ph-*ortho*-$\underline{H}$), 7.39 (1H, d, *J* 7.5 Hz, -Ph-*para*-$\underline{H}$), 7.44 (2H, t, *J* 7.5 Hz, -Ph-*meta*-$\underline{H}$); $^{13}$C NMR (dmso) δ 19.1 (-CH($CH_2$Ar)$\underline{C}H_3$), 42.3 (-CH($\underline{C}H_2$Ar)$CH_3$), 46.5 ($C6^A$), 54.5 (-$\underline{C}$H($CH_2$Ar)$CH_3$), 59.9 ($C6^{B-G}$), 72.1 - 73.1 (C2, C3, C5), 81.5 ($C4^{B-G}$), 83.3 ($C4^A$), 102.0 (C1), 125.9 - 129.3 (3° Ar), 139.3 (4° Ar); *m/z* 1252 ($M^+$) and 1253 (M + $H^+$); HRESI-MS Found 1252.4703. $C_{51}H_{82}NO_{34}$ requires 1252.4718. Found 1274.4529. $C_{51}H_{81}NO_{34}Na$ requires 1274.4538.

## Studies of the Properties and Complexation Behaviour of the Cyclodextrins 57a,b and 62a,b - 64a,b

### Variable temperature $^1$H NMR study of the diastereomers 45a and 45b

A sample containing the *(R)*-1-phenylethylamine-derived cyclodextrin **45a** (5.0 mg, 0.004 mmol) and the *(S)*-1-phenylethylamine-derived cyclodextrin **45b** (2.5 mg, 0.002 mmol) in $D_2O$ (1.0 $cm^3$) was prepared and it's 300 MHz $^1$H NMR spectrum at 298 K recorded. The temperature of the sample was raised to 310 K, the sample allowed to equilibrate for 5 minutes, and the 300 MHz $^1$H NMR spectrum re-recorded. Subsequent $^1$H NMR spectra were recorded in intervals of 10 K to a maximum of 350 K.

### Competitive reactions of the amines 56a and 56b with the iodide 31

β-Cyclodextrin iodide **31** (10.0 mg, 0.008 mmol) was desiccated to constant weight over phosphorous pentoxide, then dissolved in dry *N,N*-dimethylformamide (1.0 $cm^3$) and *(R)*-(+)-α-phenylethylamine **56a** (0.001 $cm^3$, 0.9 mg, 0.008 mmol) was added with stirring, followed by an

appropriate amount of *(S)*-(+)-α-phenylethylamine **56b** to yield the required ratio of those amine starting materials. The reaction mixture was stirred at 70°C for 24h after which the solution allowed to cool to room temperature and then freeze dried. The resulting solid was dissolved in hot water (50 $cm^3$) and freeze dried to remove any residual DMF, to yield a mixture of the diastereomers **45a** and **45b**, and the iodide **31**, as a powder. A portion of the mixture (ca. 5 mg) was dissolved in $D_2O$ and the $^1H$ NMR spectrum was recorded at 350 K and inspected to deduce relative proportions of the diastereomers **45a** and **45b** in the product mixture.

**HPLC detection of *(R)*- and *(S)*-1-phenylethylamine 56a and 56b**

A solution of *(S)*-2-phenylpropanoic acid **8b** in hexane (0.025 $cm^3$, 12 mmol $dm^{-3}$) was added to a small pressure vessel containing hexane (0.1 $cm^3$) which had been pre-treated with thionyl chloride (0.002 $cm^3$, X mmol), the vessel sealed and heated at 70°C for 2 h. The reaction mixture was allowed to cool to room temperature and divided into two. To one of the aliquots of reaction mixture *(S)*-1-phenylethylamine **56b** in hexane (0.05 $cm^3$, 0.165 mmol $dm^{-3}$) was added, the vessel resealed and stirred at room temperature for a further 2h, after which 3 molar sulfuric acid (0.5 $cm^3$) was added to ensure the there was no unreacted acid chloride remaining. This acidic mixture was extracted with hexane (2 x 2 $cm^3$) and the combined organic fractions dried ($MgSO_4$) and analyzed directly by HPLC (5 % propan-2-ol / hexane, 10 μm Porasil Rad Pak, 2 $cm^3$ $min^{-1}$, UV visualization at 220 nm). The compound derived from *(S)*-1-phenylethylamine **56b** was found to have a $t_R$ of 7.6 min. under these conditions. To the other aliquot of acid chloride solution was added *(R)*-1-phenylethylamine **56a** in hexane (0.05 $cm^3$, 0.165 mmol $dm^{-3}$) which was reacted and analyzed exactly as outlined

above for analysis of the *(S)*-isomer **56b**. The compound derived from *(R)*-1-phenylethylamine **56b** was found to have a $t_R$ of 5.2 min. under these conditions.

**HPLC analysis of the unreacted 1-phenylethylamine isomers 56a and 56b**

β-Cyclodextrin iodide **31** (10 mg, 0.008 mmol) was dissolved in dry *N,N*-dimethylformamide (1.0 $cm^3$) and *(R)*-(+)-α-phenylethylamine **56a** (0.001 $cm^3$, 0.9 mg, 0.008 mmol) was added with stirring, followed by an appropriate amount of *(S)*-(+)-α-phenylethylamine **56b** to yield the required ratio of those amine starting materials. The reaction mixture was stirred at 70°C for 24h after which the solution allowed to cool to room temperature and then pipetted into cold, stirred acetone (100 $cm^3$). The resultant mixture was centrifuged, the supernatant liquid decanted and the solvent removed under slight vacuum, to yield a mixture of the unreacted amines **56a** and **56b**. Concurrently to the above, a solution of *(S)*-2-phenylpropanoic acid **8b** in hexane (0.025 $cm^3$, 12 mmol $dm^{-3}$) was added to a small pressure vessel containing hexane (0.1 $cm^3$) which had been pre-treated with thionyl chloride (0.002 $cm^3$, 0.014 mmol), the vessel was sealed and heated at 70°C for 2 h. The reaction mixture was allowed to cool to room temperature and an aliquot of the above mixture of unreacted amines (0.05 $cm^3$) was added, the vessel resealed and stirred at room temperature for a further 2h, after which 3 molar sulfuric acid (0.5 $cm^3$) was added to ensure the there was no unreacted acid chloride remaining. This acidic mixture was extracted with hexane (2 x 2 $cm^3$) and the combined organic fractions dried ($MgSO_4$) and analyzed directly by HPLC by the method outlined above for the relative abundance of *(R)*- and *(S)*-1-phenylethylamine **56a** and **56b** derived compounds.

**$^1$H NMR study of the iodide 31 in the presence of ethanol**

Three samples were prepared containing the iodide **31** (15.0 mg, 0.012 mmol) in the presence of ethanol (0.009 mmol) in $D_2O$ (1.0 $cm^3$). To two of the samples an aliquot of $D_2O$ solution (0.041 mol $dm^{-3}$) of either *(R)*- or *(S)*-1-phenylethylamine **56a** or **56b** (0.13 $cm^3$, 0.005 mmol) was added. The $^1$H NMR spectra of the three samples were recorded and the presence of resonances corresponding to the methyl group of ethanol noted.

**Preparation of samples for $^1$H NMR spectroscopy**

Each of the cyclodextrins **45a,b - 48a,b** (5.0 mg, ca. 0.004 mmol) was dissolved in $I$ = 0.10 mol $dm^{-3}$ pH 6.0 phosphate buffered $D_2O$ (1.0 $cm^3$) to yield solutions containing the cyclodextrins **57a,b** and **64a,b, 62a,b** and **63a,b,** respectively and the $^1$H NMR spectra of the samples recorded.

**Preparation of samples for 2D ROESY NMR spectroscopy**

Each of the cyclodextrins **45a** and **45b** (10.0 mg, 0.008 mmol) was dissolved in $D_2O$ (1.0 $cm^3$), the samples sparged with argon for 4h., and then further degassed under reduced pressure in a vacuum sealed NMR tube. The samples were sealed under argon and the 2D ROESY spectra was recorded.

**Preparation of samples containing the cyclodextrins 57a,b and 62a,b - 64a,b and the guest 42 for $^1$H NMR studies.**

The cyclodextrins **45a,b - 48a,b** (5.0 mg, ca. 0.004 mmol) were each added to a 2.0 $cm^3$ volumetric flask into which adamantan-1-ol **42** (1.2 mg, 0.008 mmol) had been preweighed and the volume made up to 2.0 $cm^3$ with the above pH 6.0 phosphate buffered $D_2O$.

**Preparation of samples containing the cyclodextrins 57a and 57b and the guest 42 for circular dichroism spectroscopy.**

The cyclodextrins **45a** and **45b** (5.0 mg, 0.004 mmol) were each added to a 2.0 $cm^3$ volumetric flask into which adamantan-1-ol **42** (1.2 mg, 0.008 mmol) had been preweighed and the volume made up to 2.0 $cm^3$ with pH 6.0 phosphate buffer.

**Preparation of samples containing the cyclodextrins 57a,b and 62a,b - 64a,b and the guest 58.**

Stock Guest **58**. *para*-Methoxybenzylalcohol **58** (7.0 mg) was dissolved in $I$ = 0.10 mol $dm^{-3}$ pH 6.0 phosphate buffered $D_2O$ (ca. 5.0 $cm^3$), the total volume was then made up to 25.0 $cm^3$ (2.0 mmol $dm^{-3}$) with the above buffered $D_2O$.

All $^1$H NMR samples were prepared by adding guest **58** stock solution (1.0 $cm^3$) to 2.0 $cm^3$ volumetric flasks into which one of the cyclodextrin hosts **45 - 48** (5.0 mg, ca. 0.004 mmol) had been preweighed and the volume made up to 2.0 $cm^3$ with the above pH 6.0 phosphate buffered $D_2O$, yielding solutions containing the guest **58** and the cyclodextrins **57a,b** and **64a,b, 62a,b** and **63a,b**.

## $^1$H NMR Study of the Complexation of the Guest 58 by β-Cyclodextrin 1 and the Cyclodextrins 57a and 57b

**Preparation of $^1$H NMR samples.**

All $^1$H NMR samples were prepared by adding the above guest **58** stock solution (1.0 $cm^3$) to 2.0 $cm^3$ volumetric flasks into which an appropriate amount of one of the cyclodextrin hosts **45a, 45b** or β-cyclodextrin **1** had been preweighed and the volume made up to 2.0 $cm^3$ with the above pH 6.0 phosphate buffered $D_2O$.

| Mass of cyclodextrin **45a** (mg) | [Host **57a**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **58** (ppm) |
|---|---|---|
| 0 | 0 | 3.850 |
| 1.1 | 0.4 | 3.849 |
| 2.2 | 0.9 | 3.849 |
| 3.6 | 1.5 | 3.849 |
| 5.1 | 2.1 | 3.849 |
| 6.0 | 2.4 | 3.849 |
| 7.8 | 3.2 | 3.849 |
| 8.7 | 3.5 | 3.849 |
| 10.3 | 4.2 | 3.849 |

**Table 9.** $^1$H NMR Chemical shifts of the methyl group of the guest **58** as a function of the concentration of the conjugate acid of the *(R)*-1-phenylethylamine-derived cyclodextrin **45a**.

| Mass of cyclodextrin **45b** (mg) | [Host **57b**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **58** (ppm) |
|---|---|---|
| 0 | 0 | 3.850 |
| 1.0 | 0.4 | 3.847 |
| 2.3 | 0.9 | 3.847 |
| 3.9 | 1.6 | 3.843 |
| 5.2 | 2.1 | 3.837 |
| 6.2 | 2.5 | 3.836 |
| 7.8 | 3.2 | 3.833 |
| 9.0 | 3.6 | 3.829 |

**Table 10.** $^1H$ NMR Chemical shifts of the methyl group of the guest **58** as a function of the concentration of the conjugate acid of the *(S)*-1-phenylethylamine-derived cyclodextrin **45b**.

| Mass of cyclodextrin **1** (mg) | [Host **1**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **58** (ppm) |
|---|---|---|
| 0 | 0 | 3.850 |
| 2.5 | 1.0 | 3.848 |
| 4.7 | 1.9 | 3.847 |
| 7.4 | 3.0 | 3.845 |
| 9.9 | 4.0 | 3.844 |

**Table 11.** $^{1}H$ NMR Chemical shifts of the methyl group of the guest **58** as a function of the concentration of β-cyclodextrin **1**.

## Experimental Details of Work Described in Chapter 4

### Complexation of the Guests 8a,b, 37a,b, 43a,b and 44a,b with the Cyclodextrins 57a,b, and 62a,b - 64a,b

**Preparation of stock solutions of the guests 43a,b and 44a,b**

Stock of the racemate of the guests **43a** and **43b**. The racemate of the 2-phenylpropanoic acids **8a** and **8b** (4.2 mg, 0.028 mmol) was dissolved in pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.10 mol $dm^{-3}$), the total volume was then made up to 25.0 $cm^3$ (1.1 mmol $dm^{-3}$) with pH 6.0 phosphate buffered $D_2O$.

Stock of the *(S)*-isomer of guest **43b**. *(S)*-2-phenylpropanoic acid **8b** (1.5 mg, 0.010 mmol) was dissolved in pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.10 mol $dm^{-3}$), the total volume was then made up to 2.0 $cm^3$ (4.9 mmol $dm^{-3}$) with pH 6.0 phosphate buffered $D_2O$.

Stock of the racemate of the guests **44a** and **44b**. The racemate of the Ibuprofen acids **37a** and **37b** 10.3 mg, 0.050 mmol) was dissolved in pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.10 mol $dm^{-3}$), the total volume was then made up to 25.0 $cm^3$ (2.0 mmol $dm^{-3}$) with pH 6.0 phosphate buffered $D_2O$.

Stock of the *(S)*-isomer of guest **44b**. The *(S)*-Ibuprofen acid **37b** (2.0 mg, 0.010 mmol) was dissolved in pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.10 mol $dm^{-3}$), the total volume was then made up to 2.0 $cm^3$ (4.9 mmol $dm^{-3}$) with pH 6.0 phosphate buffered $D_2O$.

**Sample preparation**

**Samples containing anion guests 43a,b and 44a,b.** All samples were prepared by adding the appropriate guest stock solution (1.0 $cm^3$) to 2 $cm^3$ volumetric flasks into which an appropriate mass of the cyclodextrin host had been preweighed. The total volume was then made up to 2.0 $cm^3$ by the addition of further pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.10 mol $dm^{-3}$).

**Samples containing acid guests 8a,b and 37a,b.** All samples were prepared by adding the appropriate guest stock solution (1.0 $cm^3$) to 2 $cm^3$ volumetric flasks into which an appropriate mass of the cyclodextrin host had been preweighed. A small amount (*ca.* 0.8 $cm^3$) of pH 6.0 phosphate buffered $D_2O$ ($I$ = 0.10 mol $dm^{-3}$) was added to the sample, followed by sufficient 10 % DCl / $D_2O$ solution to yield a solution of pH 1.0, the total volume was then made up to 2.0 $cm^3$ by the addition of further of the above buffer if required. The pH was checked to ensure that it remained as required.

**Determing the identity of guest resonances.** In samples for which spectroscopic discrimination was observed in the $^1H$ NMR spectrum, and for which an identification of guest resonances was required, the identity of resonances belonging to the *(S)*-isomer of the respective guests was made by addition of the appropriate stock solution of the single *(S)*-isomer **43b** or **44b** (0.1 $cm^3$, ca. 5 x $10^{-4}$ mmol), re-recording the $^1H$ NMR spectrum of the sample and noting the change in relative intensity of guest resonances. Further additions of stock solution of the *(S)*-isomers **43b** or **44b** (0.1 $cm^3$, ca. 5 x $10^{-4}$ mmol), were made as and if required.

**Calculation of the Association Constants of the Guests 8a,b and 43a,b with the Cyclodextrins 57a and 57b.**

| Mass of cyclodextrin **45a** (mg) | [Host **57a**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) anions **43a** and **43b** (ppm) |
|---|---|---|
| 0 | 0 | 1.407 |
| 2.6 | 1.1 | 1.408 |
| 4.7 | 1.9 | 1.409 |
| 7.5 | 3.0 | 1.409 |
| 10.0 | 4.0 | 1.410 |
| 12.3 | 5.0 | 1.410 |
| 14.8 | 6.0 | 1.411 |
| 17.2 | 6.9 | 1.411 |
| 19.7 | 8.0 | 1.411 |
| 21.9 | 8.8 | 1.412 |
| 24.8 | 10.0 | 1.412 |
| 27.2 | 11.0 | 1.412 |
| 32.3 | 13.0 | 1.412 |
| 37.0 | 14.9 | 1.413 |

**Table 12.** $^1H$ NMR Chemical shifts of the methyl group of the racemate of the guests **43a** and **43b** as a function of the concentration of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**. The association constant of the racemate of the guests **43a** and **43b** could not be determined because there was insufficient complexation, and is assumed to be approximately zero.

| Mass of cyclodextrin **45b** (mg) | [Host **57b**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **43a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **43b** (ppm) |
|---|---|---|---|
| 0 | 0 | 1.407 | 1.407 |
| 2.5 | 1.0 | 1.387 | 1.387 |
| 5.1 | 2.1 | 1.375 | 1.371 |
| 7.2 | 2.9 | 1.364 | 1.359 |
| 9.9 | 4.0 | 1.355 | 1.350 |
| 12.4 | 5.0 | 1.348 | 1.342 |
| 15.0 | 6.1 | 1.343 | 1.335 |
| 17.3 | 7.0 | 1.338 | 1.330 |
| 19.8 | 8.0 | 1.335 | 1.326 |
| 22.3 | 9.0 | 1.330 | 1.322 |
| 24.7 | 10.0 | 1.327 | 1.318 |
| 29.5 | 11.9 | 1.323 | 1.314 |
| 32.1 | 13.0 | 1.321 | 1.312 |
| 34.6 | 14.0 | 1.319 | 1.309 |
| 37.1 | 15.0 | 1.317 | 1.307 |

**Table 13.** $^1H$ NMR Chemical shifts of the methyl group of the guests **43a** and **43b** as a function of the concentration of the *(S)*-1-phenylethylamine-derived cyclodextrin **45b**. The association constants of the guests **43a** and **43b**, with the cyclodextrin **45b** were calculated as 193 ± 11 and 191 ± 11 $dm^3$ $mol^{-1}$ respectively, with the chemical shifts of the resonance of the fully bound guests ($\delta_{complex}$) were calculated as 1.286 and 1.273 ppm, respectively.

| Mass of cyclodextrin **45a** (mg) | [Host **57a**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **8a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **8b** (ppm) |
|---|---|---|---|
| 0 | 0 | 1.473 | 1.473 |
| 2.6 | 1.1 | 1.473 | 1.476 |
| 4.7 | 1.9 | 1.473 | 1.478 |
| 7.5 | 3.0 | 1.476 | 1.484 |
| 10.0 | 4.0 | 1.472 | 1.481 |
| 12.3 | 5.0 | 1.474 | 1.485 |
| 14.8 | 6.0 | 1.473 | 1.486 |
| 17.2 | 6.9 | 1.473 | 1.487 |
| 19.7 | 8.0 | 1.474 | 1.489 |
| 21.9 | 8.8 | 1.473 | 1.488 |
| 27.2 | 11.0 | 1.470 | 1.487 |
| 32.3 | 13.0 | 1.473 | 1.492 |
| 37.0 | 14.9 | 1.473 | 1.493 |

**Table 14.** $^1H$ NMR Chemical shifts of the methyl group of the guests **8a** and **8b** as a function of the concentration of the *(R)*-1-phenylethylamine-derived cyclodextrin **45a**. The association constant of the guest **8b**, with the cyclodextrin **45a** was calculated as 101 ± 16 $dm^3$ $mol^{-1}$, with a calculated $\delta_{complex}$ of 1.505 ppm. The association constant of the guest **8a**, with the cyclodextrin **45a** was unable to be calculated.

| Mass of cyclodextrin **45b** (mg) | [Host **57b**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **8a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **8b** (ppm) |
|---|---|---|---|
| 0 | 0 | 1.473 | 1.473 |
| 2.5 | 1.0 | 1.457 | 1.472 |
| 5.1 | 2.1 | 1.450 | 1.477 |
| 7.2 | 2.9 | 1.443 | 1.476 |
| 9.9 | 4.0 | 1.439 | 1.476 |
| 12.4 | 5.0 | 1.434 | 1.475 |
| 15.0 | 6.1 | 1.432 | 1.475 |
| 17.3 | 7.0 | 1.431 | 1.475 |
| 19.8 | 8.0 | 1.431 | 1.476 |
| 22.3 | 9.0 | 1.429 | 1.476 |
| 24.7 | 10.0 | 1.426 | 1.474 |
| 29.5 | 11.9 | 1.422 | 1.471 |
| 32.1 | 13.0 | 1.424 | 1.473 |
| 34.6 | 14.0 | 1.426 | 1.475 |
| 37.1 | 15.0 | 1.426 | 1.476 |

**Table 15.** $^1H$ NMR Chemical shifts of the methyl group of the guest **8a** and **8b** as a function of the concentration of the *(S)*-1-phenylethylamine-derived cyclodextrin **45b**. The association constant of the guest **8a**, with the cyclodextrin **45b** was calculated as 455 ± 18 $dm^3$ $mol^{-1}$, with a calculated $\delta_{complex}$ of 1.415 ppm. The association constant of the guest **8b**, with the cyclodextrin **45b** was unable to be calculated.

**Association Constants of the Guests 37a,b and 44a,b with the Hosts 57a, 57b.**

| Mass of cyclodextrin **45a** (mg) | [Host **57a**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for anions **44a** and **44b** (ppm) |
|---|---|---|
| 0 | 0 | 1.389 |
| 1.4 | 0.6 | 1.371 |
| 2.4 | 1.0 | 1.364 |
| 3.9 | 1.6 | 1.355 |
| 5.1 | 2.1 | 1.351 |
| 6.0 | 2.4 | 1.348 |
| 7.7 | 3.1 | 1.346 |
| 8.8 | 3.6 | 1.346 |
| 9.8 | 4.0 | 1.345 |
| 11.2 | 4.5 | 1.344 |
| 12.7 | 5.1 | 1.342 |
| 15.2 | 6.1 | 1.341 |
| 17.2 | 7.0 | 1.341 |
| 20.1 | 8.1 | 1.341 |
| 22.6 | 9.1 | 1.341 |
| 24.9 | 10.1 | 1.341 |

**Table 16.** $^1H$ NMR Chemical shifts of the α–methyl group of the racemate of the guests **44a** and **44b** as a function of the concentration of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**. The association constant of the racemate of the guests **44a** and **44b**, with the cyclodextrin **57a** was calculated as 2362 ± 112 $dm^3$ $mol^{-1}$, with the $\delta_{complex}$ value calculated as 1.338 ppm.

| Mass of cyclodextrin **45a** (mg) | [Host **57a**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **44a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **44b** (ppm) |
|---|---|---|---|
| 0 | 0 | 2.484 | 2.484 |
| 1.4 | 0.6 | 2.501 | 2.496 |
| 2.4 | 1.0 | 2.507 | 2.500 |
| 3.9 | 1.6 | 2.515 | 2.506 |
| 5.1 | 2.1 | 2.518 | 2.509 |
| 6.0 | 2.4 | 2.520 | 2.510 |
| 7.7 | 3.1 | 2.522 | 2.512 |
| 8.8 | 3.6 | 2.523 | 2.512 |
| 9.8 | 4.0 | 2.524 | 2.513 |
| 11.2 | 4.5 | 2.524 | 2.513 |
| 12.7 | 5.1 | 2.524 | 2.513 |
| 15.2 | 6.1 | 2.524 | 2.513 |
| 17.2 | 7.0 | 2.524 | 2.513 |
| 20.1 | 8.1 | 2.524 | 2.513 |
| 22.6 | 9.1 | 2.524 | 2.513 |
| 24.9 | 10.1 | 2.523 | 2.512 |

**Table 17.** $^1H$ NMR Chemical shifts of the benzylic methylene group of the guests **44a** and **44b** as a function of the concentration of the *(R)*-1-phenylethylamine-derived cyclodextrin **45a**. The association constants of the guests **44a** and **44b**, with the cyclodextrin **45a** were calculated as 1924 ± 215 and 2020 ± 277 $dm^3$ $mol^{-1}$ respectively, with the $\delta_{complex}$ values calculated as 2.528 and 2.515 ppm, respectively.

| Mass of cyclodextrin **45b** (mg) | [Host **57b**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **44a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **44b** (ppm) |
|---|---|---|---|
| 0 | 0 | 2.484 | 2.484 |
| 1.1 | 0.4 | 2.484 | 2.484 |
| 2.4 | 1.0 | 2.482 | 2.487 |
| 3.8 | 1.5 | 2.483 | 2.489 |
| 4.7 | 1.9 | 2.483 | 2.490 |
| 5.6 | 2.3 | 2.484 | 2.490 |
| 6.9 | 2.8 | 2.484 | 2.491 |
| 8.3 | 3.4 | 2.484 | 2.491 |
| 9.3 | 3.8 | 2.484 | 2.491 |
| 11.1 | 4.5 | 2.483 | 2.491 |
| 12.5 | 5.1 | 2.483 | 2.492 |
| 14.6 | 5.9 | 2.483 | 2.491 |
| 16.6 | 6.7 | 2.483 | 2.491 |
| 19.2 | 7.8 | 2.482 | 2.490 |
| 21.2 | 8.6 | 2.481 | 2.489 |

**Table 18.** $^1H$ NMR Chemical shifts of the benzylic methylene group of the guests **44a** and **44b** as a function of the concentration of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**. The association constant of the guest **44b**, with the cyclodextrin **57b** was calculated as 1731 ± 287 $dm^3$ $mol^{-1}$ with a calculated $\delta_{complex}$ of 2.488 ppm. The association constant of the guest **44a** with the cyclodextrin **57b** was unable to be calculated.

| Mass of cyclodextrin **45b** (mg) | [Host **57b**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **44a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **44b** (ppm) |
|---|---|---|---|
| 0 | 0 | 1.389 | 1.389 |
| 1.1 | 0.4 | 1.359 | 1.352 |
| 2.4 | 1.0 | 1.341 | 1.331 |
| 3.8 | 1.5 | 1.324 | 1.310 |
| 4.7 | 1.9 | 1.319 | 1.306 |
| 5.6 | 2.3 | 1.316 | 1.302 |
| 6.9 | 2.8 | 1.313 | 1.299 |
| 8.3 | 3.4 | 1.311 | 1.297 |
| 9.3 | 3.8 | 1.310 | 1.296 |
| 11.1 | 4.5 | 1.309 | 1.295 |
| 12.5 | 5.1 | 1.308 | 1.294 |
| 14.6 | 5.9 | 1.307 | 1.293 |
| 16.6 | 6.7 | 1.307 | 1.293 |
| 19.2 | 7.8 | 1.306 | 1.292 |
| 21.2 | 8.6 | 1.306 | 1.292 |

**Table 19.** $^1H$ NMR Chemical shifts of the α–methyl group of the guests **44a** and **44b** as a function of the concentration of the *(S)*-1-phenylethylamine-derived cyclodextrin **45b**. The association constants of the guests **44a** and **44b**, with the cyclodextrin **45b** were calculated as 2043 ± 152 and 2318 ± 191 $dm^3$ $mol^{-1}$ respectively, with the $\delta_{complex}$ values calculated as 1.299 and 1.285 ppm, respectively.

| Mass of cyclodextrin **45a** (mg) | [Host **57a**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **37a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **37b** (ppm) |
|---|---|---|---|
| 0 | 0 | 1.457 | 1.457 |
| 2.4 | 1.0 | 1.423 | 1.427 |
| 4.9 | 2.0 | 1.407 | 1.413 |
| 7.5 | 3.0 | 1.402 | 1.408 |
| 9.7 | 3.9 | 1.398 | 1.404 |
| 12.5 | 5.0 | 1.396 | 1.402 |
| 15.0 | 6.1 | 1.397 | 1.404 |
| 17.1 | 6.9 | 1.396 | 1.403 |
| 19.8 | 8.0 | 1.397 | 1.405 |
| 22.0 | 8.9 | 1.397 | 1.404 |
| 24.9 | 10.0 | 1.398 | 1.406 |
| 32.0 | 12.9 | 1.395 | 1.403 |
| 34.5 | 13.9 | 1.396 | 1.405 |
| 37.1 | 15.0 | 1.394 | 1.403 |

**Table 20.** $^1H$ NMR Chemical shifts of the α-methyl group of the guest **37a** and **37b** as a function of the concentration of the *(R)*-1-phenylethylamine-derived cyclodextrin **57a**. The association constants of the guests **37a** and **37b**, with the cyclodextrin **57a** were calculated as 1883 ± 220 and 2059 ± 332 $dm^3\ mol^{-1}$ respectively, with the $\delta_{complex}$ values calculated as 1.392 and 1.400 ppm, respectively.

| Mass of cyclodextrin **45b** (mg) | [Host **57b**] (mmol $dm^{-3}$) | Chemical shift ($\delta_{obs}$) for guest **37a** (ppm) | Chemical shift ($\delta_{obs}$) for guest **37b** (ppm) |
|---|---|---|---|
| 0 | 0 | 1.457 | 1.457 |
| 2.3 | 0.9 | 1.403 | 1.416 |
| 5.0 | 2.0 | 1.368 | 1.388 |
| 7.5 | 3.0 | 1.363 | 1.384 |
| 9.7 | 3.9 | 1.361 | 1.383 |
| 12.6 | 5.1 | 1.363 | 1.385 |
| 14.8 | 6.0 | 1.361 | 1.383 |
| 17.4 | 7.0 | 1.363 | 1.386 |
| 22.5 | 9.1 | 1.364 | 1.387 |
| 27.4 | 11.1 | 1.367 | 1.389 |
| 32.7 | 13.2 | 1.367 | 1.389 |
| 37.1 | 15.0 | 1.367 | 1.389 |

**Table 21.** $^1H$ NMR Chemical shifts of the α-methyl group of the guest **37a** and **37b** as a function of the concentration of the *(S)*-1-phenylethylamine-derived cyclodextrin **57b**. The association constants of the guests **37a** and **37b**, with the cyclodextrin **57b** were calculated as 3314 ± 220 and 3526 ± 1319 $dm^3$ $mol^{-1}$ respectively, with the $\delta_{complex}$ values calculated as 1.357 and 1.381 ppm, respectively.

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