THE PHYSICOCHEMICAL CHARACTERISATION OF CYCLODEXTRIN INCLUSION COMPOUNDS WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

BY

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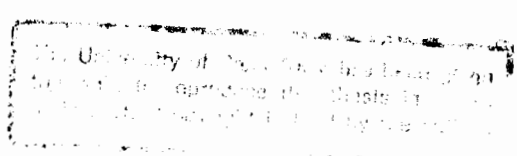

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Patent: SA Preliminary Patent Application no. 94/4446, filed February 1995, *The complexes of naproxen and ibuprofen with heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin.* G.R. Brown, M.R. Caira, V.J. Griffith, L.R. Nassimbeni, M.C. van Oudtshoorn.

ABSTRACT

The cyclodextrins and their derivatives have been utilised as complexing agents for a wide range of pharmaceutical compounds, through their ability to include small molecular weight molecules inside an annular cavity formed by linked glucose residues of varying number. The non-steroidal anti-inflammatory drugs (NSAIDs), a group of agents that share a similar therapeutic effect in the management of inflammatory processes in the body, have been studied as guest molecules for inclusion in cyclodextrins, due to a number of potential advantages that are conferred by complexation, such as improved bioavailability, modified side-effect profiles and the control of drug release from novel formulations.

This study has tested a number of commonly used NSAIDs belonging to certain structural groups, together with a number of cyclodextrins and their derivatives, and attempts have been made to prepare complexes in the solid state and characterise them using physicochemical methods. The cyclodextrins used were native seven- and eight-membered β- and γ-cyclodextrin and two methylated derivatives of β-cyclodextrin, namely heptakis(2,6-di-O-methyl)-β-cyclodextrin and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin, abbreviated as DIMEB and TRIMEB respectively. NSAIDs belonging to the salicylate, fenamate, profen, oxicam and indene structural groups were used. These included diflunisal, mefenamic acid, niflumic acid, tolfenamic acid, flufenamic acid, ibuprofen, ketoprofen, piroxicam, tenoxicam, indomethacin and sulindac.

All complexes were prepared in aqueous solution and characterised using methods such as thermal analysis (hot stage microscopy, thermogravimetric analysis, differential scanning calorimetry), X-ray powder diffraction (XRD), UV spectrophotometry, microanalysis and single crystal X-ray photography. Properties such as thermal behaviour and X-ray diffraction were used as evidence that complexation had occurred, by observing any modification in these properties of the host and guest.

A number of complexes were obtained for which thermal analysis and XRD gave confirmation of the formation of a complex, and unit cell data could be obtained for seven complexes for which single crystals of suitable size were obtained. Two

crystal structures, for the complexes of β-cyclodextrin and TRIMEB with ibuprofen, one of the profen group of NSAIDs, were solved using X-ray analysis. The guest molecule in the β-cyclodextrin complex is disordered and could not be modelled, but was located and refined in the TRIMEB complex.

Ibuprofen is a chiral molecule and the crystal used for analysis of the complex with TRIMEB was obtained from a vial containing racemic drug. Only the (S)-isomer was found to be present in the crystal. Based on these results, the possibility of racemic resolution of ibuprofen by TRIMEB was investigated and it was concluded that isomorphous complexes are formed with both isomers.

ABBREVIATIONS

NSAIDs	Non-steroidal anti-inflammatory drugs
DIMEB	heptakis(2,6-di-O-methyl)-β-cyclodextrin
TRIMEB	heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin
TGA	thermogravimetric analysis
DSC	differential scanning calorimetry
XRD	X-ray powder diffraction
UV	ultraviolet

CONTENTS

1. INTRODUCTION TO CYCLODEXTRINS

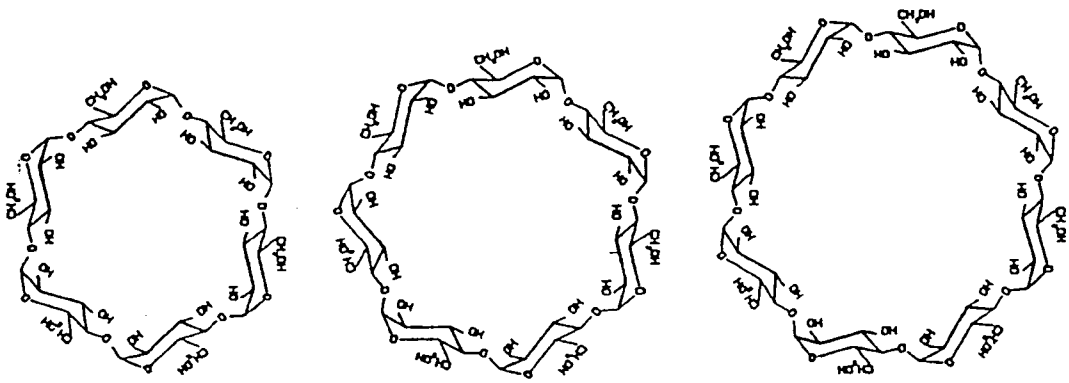
The cyclodextrins, also less commonly known as Schardinger's dextrins, cycloamyloses and cycloglucans, are naturally occurring cyclic oligosaccharides composed of six or more 1,4-linked α-D-glucopyranose units. Initially reported in 1891 by Villiers as degradation products of starch[1], their structure was investigated more fully by Schardinger[2,3], and their use as complexing agents for small molecular weight compounds that can insert into the central cavity formed by the macrocycle, and as catalysts in certain chemical reactions, as well as for racemic resolution, came to be recognised through the work of Freudenberg and French among others[4,5,6,7,8,9]. Studies in recent years have placed their focus on their application in pharmaceutical and other industries through their ability to modify the physicochemical characteristics and reactivity of substances, and a large number of review articles and books devoted to the subject are currently available[10,11,12,13].

1.1 ISOLATION AND CHARACTERISATION

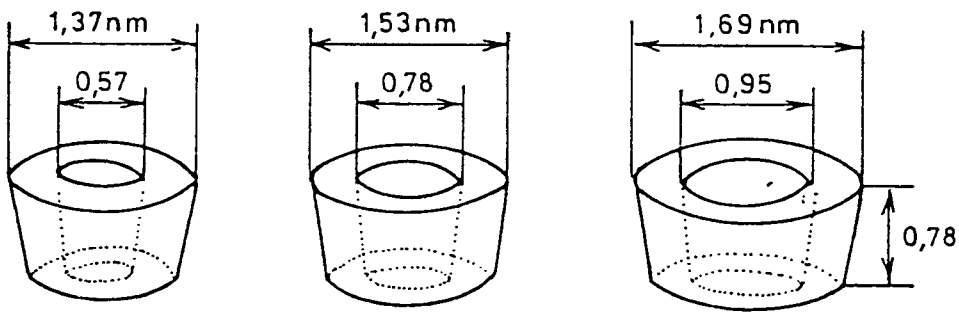
Cyclodextrins are included in a mixture of end-products formed by the action of *Bacillus macerans* amylase (cyclodextrin-transglycolase or CGT) on helical starch molecules and related compounds[2,3,9]. The enzyme does not cleave fragments of any particular size, and cyclodextrins of between six and twelve glucose units have been identified using chromatography and other separation techniques[14], with those of six, seven and eight units being the most common products. These have been designated by Greek lettering according to the number of units, namely α- (6), β- (7) and γ-cyclodextrin (8) (Fig.1.1a), having a cavity size ranging from 5-8Å into which small molecules may be inserted (Fig.1.1b). The higher-chain cyclodextrins (δ,ε and longer) have been isolated and identified in chromatography columns[14,15], though their potential use as complexing agents is seen as limited, due to a large cavity that is energetically similar to the aqueous environment and unable to effectively complex small molecules, a high water solubility and a relatively flexible structure. Cyclodextrins of four or less units are not known to exist, possibly due to steric hindrance[16].

Fig 1.1: **Structure of α-, β- and γ-cyclodextrin.** (a) macrocyclic conformation and (b) dimensions of cavities

(a)



(b)



Their applications in the pharmaceutical and food industries necessitate a high degree of purity, and the isolation of cyclodextrins from the end-products of the amylase activity of *Bacillus macerans*, and other bacterial strains known to produce CGT, has been extensively investigated, both to improve yields and to isolate cyclodextrins of specific size from acyclic dextrins and other cyclodextrins contained in the starch digests[17,18,19]. Organic compounds of a certain size may preferentially insert into a cavity of particular radius, with the resulting precipitation of an insoluble complex, though traces of potentially hazardous chemicals in the final product are a disadvantage of this method[20,21], and the use of efficient bacterial CGT is preferred[21]. Separation of cyclodextrins for analytical purposes may be effected using chromatographic and other methods, such as selective dissolution and electrophoresis[22,23,24].

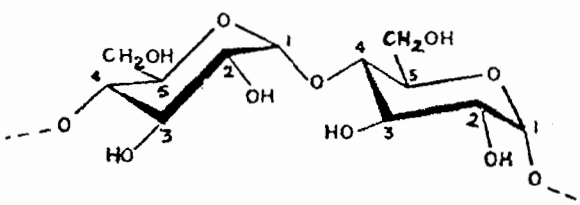
1.2 MACROCYCLIC STRUCTURE AND PROPERTIES

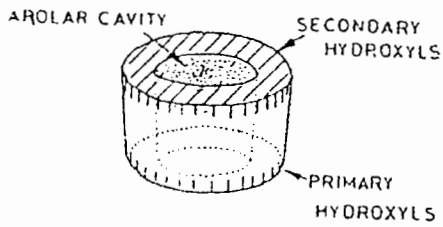
1.2.1 Structure and conformation

The repeating α-D-glucopyranose units that make up α-, β-, and γ-cyclodextrin are all present in the largely undistorted $^4C_1$ - chair conformation, joined via α-1,4 linkages to form the macrocycle (Fig. 1.2a). The spatial configuration of functional groups conferred by this conformation imparts certain features to the cyclodextrins which contribute to the mode by which guest molecules are accommodated within the cavity (Fig. 1.2b).

Fig. 1.2: (a) Conformation of glucose subunit and (b) arrangement of primary and secondary rims

(a) (b)





The two rims of the cyclodextrin ring are composed of glucose hydroxyl groups and are thus hydrophilic. The primary (1°) rim, formed of relatively free-moving C(6)-OH groups, is narrower than the secondary (2°) rim of more rigidly placed C(2)- and C(3)-OH groups, giving the macrocycle the shape of a truncated cone. Rotation of the primary hydroxyl groups can partially close off one end of the cavity. The shape adopted by the cavity is shown in Fig. 1.1. The interior of the cavity consists of glucopyranose methylene and methine groups and the O(4)-glycoside linkages, arranged as layers of C-H bonds, then glycoside oxygens, then another layer of C-H bonds, making the cavity relatively apolar.

An asymmetry in charge distribution, caused by the presence of half as many OH groups on the primary than on the secondary rim, leads to a strong dipole moment running parallel to the axis of the macrocycle, and this could be expected to affect the mode of complexation with guest molecules that contain charged species. The non-bonding electron pairs on the glycoside oxygens are inwardly directed and give the cavity a high electron-density, lending it some Lewis base character[13]. Overall, however, the cavity has a positive charge and would be expected to preferentially include neutral and anionic molecules. Studies on complexes with ionic species have shown this to be the case[25,26,27,28,29].

X-ray crystallographic studies have been used to characterise the conformations of α-, β- and γ-cyclodextrins in the solid state. They are non-hygroscopic and crystallise from aqueous solution as stable hydrates that can be stored without decomposition for many years. A number of crystal structures of parent cyclodextrins have been reported stating varying degrees of hydration and differences in positioning of water molecules within the crystal, depending on the conditions of crystallisation, such that α-cyclodextrin can have three forms (I and II, both hexahydrates[30,31], and III, with 7.57 waters[32]), β-cyclodextrin may form an undecahydrate[33] or dodecahydrate[34,35] dependent on the relative humidity of the crystal environment such that a low humidity may cause loss of water without crystal structure being destroyed[36], and γ-cyclodextrin has been reported with 11, 14 and 17 waters of crystallisation[37,38,39]. These waters are distributed within the empty cavity and in the interstitial spaces between adjacent cyclodextrin molecules.

The water molecules that are enclosed within the cavity possess a high thermal motion and tend to exhibit a degree of disorder. The displacement of these waters from this relatively apolar environment by more hydrophobic guest molecules, and the subsequent gain in energy by redistribution into the solvent bulk, is seen as part of the driving force behind complexation. This is discussed in Section 1.3.2.

A complex network of hydrogen-bonding stabilises the structure and confers certain chemical properties on the cyclodextrin molecule. Intramolecular hydrogen bonds between secondary rim C(2)- and C(3)-OH groups on adjacent residues, and intermolecular hydrogen bonds between OH groups and waters of crystallisation, both contribute to the conformation of the cyclodextrin within the crystal. The

presence of waters of crystallisation is important in determining the structure in the solid state, due to special arrangements of the atoms and the formation of a hydrogen bonding network that includes the cyclodextrin, guest and water molecules[40,41,42].

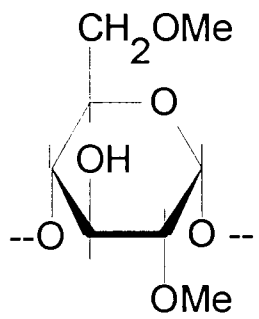
Intramolecular hydrogen bonds on the secondary face are observable in a broadening of the ν_{OH} bands in the infrared spectrum, and have been characterised in neutron diffraction studies[43,44]. The degree of distortion of the units from the coplanar model determines the degree to which these hydrogen bonds are formed and maintained. This in turn has an effect on a number of other characteristics, in particular the solubilities of the individual cyclodextrins (Section 1.3.1), and they lower the overall energy of the molecule[45,46].

1.2.2 Substituted cyclodextrins

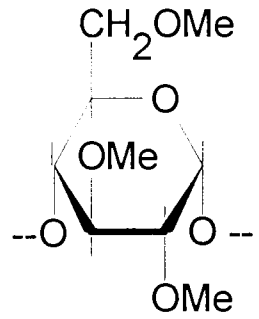
The presence of a large number of terminal OH groups lends the cyclodextrins to substitution. Those of particular interest have been the derivatives of β-cyclodextrin, due mainly to the favourable cavity volume and low aqueous solubility of the native compound. A large number of other derivatives have been prepared and are commercially available, for use as complexing agents and as enzymes, and recent studies have placed their focus on preparing cyclodextrin derivatives that may specifically interact with certain guests[47]. The difference in reactivity of the C(2), C(3) and C(6) hydroxyl groups is not great, making substitution a sometimes difficult process as yet unsuitable for the large-scale industrial production of derivatives, except in a few instances[48,49,50].

Solubility may be improved by substitution on the β-cyclodextrin macrocycle, even with hydrophobic substituents. This is notable with the most commonly studied derivatives, namely the methylated and hydroxypropylated cyclodextrins. Two methylated derivatives of β-cyclodextrin, heptakis(2,6-di-O-methyl)-β-cyclodextrin and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin, commonly abbreviated as DIMEB and TRIMEB[51], have been proposed as drug carriers in the pharmaceutical industry, and have formed part of this study. The structure of these compounds is given in Fig.1.3. However, there are limitations to their use, especially in parenteral dosage forms, due to their potential toxicity. This is discussed further in section 1.5.2.

Fig. 1.3: Structure of DIMEB and TRIMEB subunits



2,6-di-O-methyl-α-D-glucose



2,3,6-tri-O-methyl-α-D-glucose

1.3 PHYSICOCHEMICAL PROPERTIES

1.3.1 Solubility

The aqueous and other solubilities of the cyclodextrins are given in Fig.1.4. A number of chemical factors contribute to the differing solubilities, based on the conformations of the individual cyclodextrins in solution and the nature of the substituents on the derivatised cyclodextrins:

1. Hydrogen bonding. In α-cyclodextrin, one residue is distorted from the plane of the macrocycle and only four of a possible six hydrogen bonds may be formed between O(2) and O(3) groups located on the secondary rim[52]. In β-cyclodextrin, a complete belt of hydrogen bonds is formed as all the units are in an essentially undistorted conformation. The aqueous solubility of β-cyclodextrin is the lowest of the cyclodextrins, possibly because of this complete layer of hydrogen bonds. In γ-cyclodextrin, the molecule is larger and relatively more flexible, exhibiting a significant degree of non-coplanarity, such that the extent of hydrogen-bonding is less than with the other cyclodextrins and it is highly water-soluble. This increase in solubility is seen with the higher-chain cyclodextrins, which behave in a similar manner to straight-chain oligosaccharides and are extremely water-soluble.
2. Substituted cyclodextrins, particularly the methylated and hydroxypropyl derivatives, are highly water soluble, despite a predicted increase in

hydrophobic character on formation of ether groups. This may again be due to the relatively more flexible conformation of the macrocycle, and the decrease in the number of hydrogen-bonding connections between C(2)- and C(3)-OH groups.

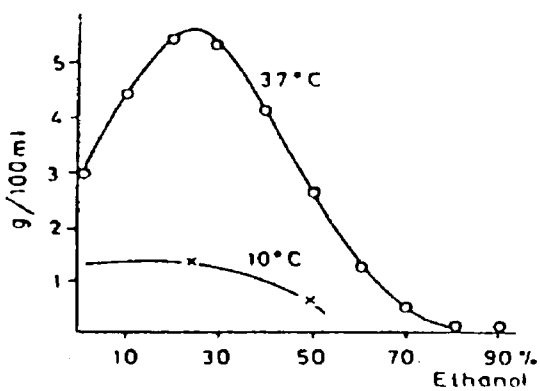
3. Temperature can have a significant effect on solubility (Fig. 1.4a). For the native cyclodextrins, solubility increases with an increase in temperature, the degree varying with each individual cyclodextrin. However, on decreasing the temperature, a hysteresis profile is followed and a supersaturated solution is obtained. This can be seen most prominently with β-cyclodextrin.
4. Cosolvents. Studies on the polarity of β-cyclodextrin, using fluorescence and other techniques, have shown that the value is similar to that of a 40% ethanol/water mixture. The solubility of β-cyclodextrin in alcohol/water mixtures is given in Fig. 1.4b and can be seen to show a maximum at approximately that percentage. Thus, a higher concentration of cyclodextrin may be brought into solution by the use of cosolvents, though the advantages of this may be limited, due to possible solvent/guest competition for the host cavity and the formation of ternary complexes[53].

Fig. 1.4: Solubilities of α-, β- and γ-cyclodextrin. (a) Aqueous solubility with temperature change and (b) solubility of β-cyclodextrin in ethanol/water mixture (reproduced from 13).

(a)

	Solubility mg CG/g water		
t°C	α	β	γ
20	90	16.4	185
25	127	18.8	256
30	165	22.8	320
35	204	28.3	390
40	242	34.9	460
45	285	44.0	585
50	347	52.7	–
55	–	60.5	–
60	–	74.9	–
65	–	101.8	–
70	–	120.3	–
75	–	148.0	–
80	–	196.6	–

(b)



1.3.2 Solid-state structure

Cyclisation should introduce a geometrical strain into the cyclodextrin, and this would be imposed on the glycoside bridge that links the residues. Thus, the glycoside C-O-C angle in α-cyclodextrin would be expected to be smaller than in the higher cyclodextrins, but conformational changes that occur in the macrocycle and induce the distortion seen in α-cyclodextrin release some of that strain, and a comparison of angles shows an agreement among the three[52,54].

A number of other geometrical parameters are used to define the conformations of cyclodextrins and their complexes, based on results obtained from X-ray analyses. These are outlined in detail below and values for α-, β- and γ-cyclodextrin are given in Table 1.1:

1. Torsion angle index[†] - this defines the differences in conformation of individual glucopyranose units and the small changes that occur on complexation.
2. The O(4)···O(4') distance is another indication of the conformation of the glucose units, and is related to the torsion angles. An increase in distance is seen from α- to γ-cyclodextrin, indicating a release in bond strain by the introduction of more units.
3. Tilt angle - the primary rim is narrower than the secondary rim, such that the glucose units are positioned at an angle to the plane of the macrocycle, as measured by a polygon described through the O(4) atoms. Specifically, the tilt angle is defined as the angle made by the plane through O(4'), C(1), C(4) and O(4) to the plane of the macrocycle. An inclination of the primary (O(6)) end of the residue toward the centre of the cavity is denoted by a positive angle. Differences in tilt angle are a measure of the degree of change in conformation to accommodate a guest molecule on complexation. Parameters for the methylated cyclodextrins differ significantly in their values, as will be discussed further on.
4. A measure of the roundness and symmetry of the cyclodextrin ring is obtained by calculating the distance of each O(4) atom from the centre of gravity of all the O(4) atoms.

[†] The torsion-angle index is defined as $|\psi(C1\text{-}C2)| + |\psi(C2\text{-}C3)| - |\psi(C3\text{-}C4)| - |\psi(C4\text{-}C5)| + |\psi(C5\text{-}O5)| + |\psi(O5\text{-}C1)|$, where $\psi(C1\text{-}C2)$ is the torsion angle O(5)-C(1)-C(2)-C(3).

Table 1.1: Crystallographic parameters for α-,β- and γ-cyclodextrin[13]

	α	β	γ
O(4)···O(4') distance (Å) *	4.31	4.36	4.50
Radius of the O(4) polygon (Å) *	4.30	5.04	5.88
Tilt angle (°) *	19	13	14
C(1')-O(4)-C(4) angle (°) *	119.0	117.7	112.6
O(2)···O(3') distance (Å) *	3.00	2.86	2.81
Crystal form	hexagonal plates	monoclinic parallelepipeds	quadratic prisms

* These are average values for all glucose residues in the asymmetric unit.

1.3.3 Structure in solution

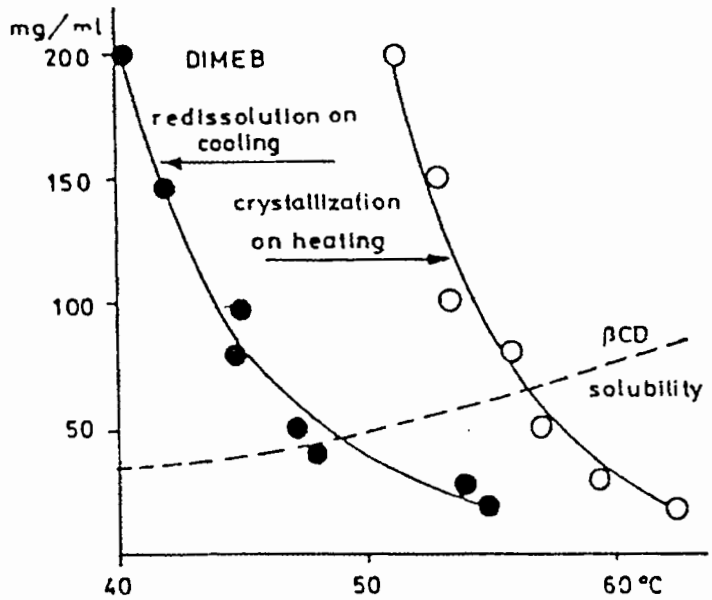
Techniques such as nuclear magnetic resonance (NMR), infrared spectroscopy (IR) and dialysis methods have been used to determine the conformation of cyclodextrins in solution. Results have shown that each glucose unit is present in the same $^4C_1$ conformation and that the macrocyclic structure is almost identical to that in the solid state, even for the relatively more flexible γ-cyclodextrin. The intramolecular hydrogen bonding network would also be identical, and this would explain the solubility properties of the cyclodextrins. It would thus be possible to state that complexes in solution are in many respects similar in structure to those determined from crystallographic studies[13].

However, there are possible differences in stoichiometry that should be noted. Whereas complexation in solution is typically characterised by insertion of the guest, or part of the guest, into the cavity, and the formation of a stoichiometric complex, the value being dependent on a number of factors such as concentration and pH, guest molecules may be located between cyclodextrin molecules in the crystalline complex, and these solid-state complexes may not be absolutely stoichiometric in composition. Furthermore, the crystal may contain "empty" cavities of cyclodextrin hydrate, with no guest present.

1.3.4 Substituted cyclodextrins

Both DIMEB and TRIMEB are highly water-soluble, though solubility does decrease with increased methylation. One unusual feature of the methylated derivatives is that solubility decreases with increasing temperature, such that crystallisation will occur rapidly at higher temperatures, dependent on concentration and within a narrow temperature range. Redissolution is just as rapid, though at a lower temperature, and the profile is characterised by a hysteresis loop. This is shown as a graph, with comparison to β-cyclodextrin, in Fig.1.5[55].

Fig. 1.5: Aqueous solubility of DIMEB with temperature (reproduced from 13)



1.4 CYCLODEXTRIN COMPLEXES

1.4.1 Uses of cyclodextrin complexes

The cyclodextrins and their polymers have found applications in a number of industries through their ability to complex molecules and modify their physicochemical characteristics. A molecule within a cyclodextrin is encapsulated and isolated from its environment, which may be advantageous in conferring stability to otherwise labile compounds[56]. This may be applied to a number of commercially useful substances such as pharmaceuticals, agrochemicals and

foodstuffs, as well as dyes, flavourants and fragrances used in a number of industries. Some of the advantages of complexation can be summarised:

1. Stabilisation of light- and oxygen-sensitive compounds and modification of chemical reactivity, thus allowing for more manageable formulation. A few examples include the pyrethrin insecticides, which are sensitive to light[57], vitamin D_3 (cholecalciferol)[58], certain prostaglandins[59,60,61], and nitroglycerin, which may be complexed with β-cyclodextrin to reduce its explosive properties and allow formulation in tablets[62].
2. Fixation of volatile substances, especially aromatic oils used as flavourants in toiletries and foodstuffs, with retention of essential properties such as taste and smell. An oil may then also be easier to manipulate as a powder or emulsion in complexes with cyclodextrin e.g. chamomile, garlic and rosemary oils, and certain toothpaste, chewing gum and bath additives[21,63,64,65,66,67]. The flavour will be released through dissociation of the complex once it comes into contact with water or saliva.
3. Modification of physicochemical characteristics, especially the aqueous solubility of poorly soluble or insoluble substances, thus allowing easier dissolution or dispersion in the aqueous medium, which is important in biological applications e.g. dispersal of tablets in the stomach upon oral administration and improvement in bioavailability[68,69,70].
4. The masking of pigments and unpleasant odour and taste may also be achieved by complexation with cyclodextrins[71,72,73,74,75,76]. Many drug substances are astringent or bitter-tasting and complexation may be especially useful in paediatric drug formulations as the cyclodextrins are relatively sweet and have a taste threshold similar to sucrose[13].
5. Improved compatibilty within multicomponent systems by the isolation of incompatible substances from each other[77,78], though care needs to be taken to avoid exposure to moisture which may partially disintegrate the complex and bring these substances into contact with each other[13].

models to mimic the action of

Other uses of the cyclodextrins, as enzymes and in racemic resolution, are beyond the scope of this study as they are utilised primarily outside of the pharmaceutical industry[56]. As catalysts, the ability to form covalent and non-covalent bonds with a number of substrates makes the cyclodextrins capable of improving rates of

reaction under specified conditions. Examples include ester and amide hydrolysis, decarboxylation and oxidation[10].

Being chiral molecules, the cyclodextrins, and especially cyclodextrin polymers, may be used to resolve racemic mixtures of substances by formation of diastereomeric pairs[79,80,81,82,83,84]. This may be applied with drugs where one isomer has a considerably greater potency than another, and where isolation may allow for a reduction in the dose required to effect a therapeutic response, with a possible reduction in side-effects and other adverse reactions that may be associated with that drug. Generally, however, the cyclodextrins have been found to be weakly selective and their usefulness in this area is still limited[85,86]. The behaviour of cyclodextrins towards the chiral non-steroidal anti-inflammatory drugs (NSAIDs), specifically the profen analogues, will be discussed further in Section 5.5.

1.4.2 Mode of complexation

A guest molecule will insert into the cavity of cyclodextrin or interact with the macrocycle and, through hydrogen bonding and other forces, an inclusion complex will be formed. The preparation and characterisation of these complexes involves an understanding of the possible mechanisms underlying the "driving force" behind complexation and how the physicochemical characteristics of the cyclodextrin and guest molecule may be modified through interaction.

The formation of an inclusion complex involves the replacement of water molecules located within the "empty" cavity of cyclodextrin by a guest molecule of suitable size and shape, thereby reducing the free energy of the system. A number of factors may be identified as contributing to the driving force that enacts this substitution in solution, and these can be summarised as follows[87]:

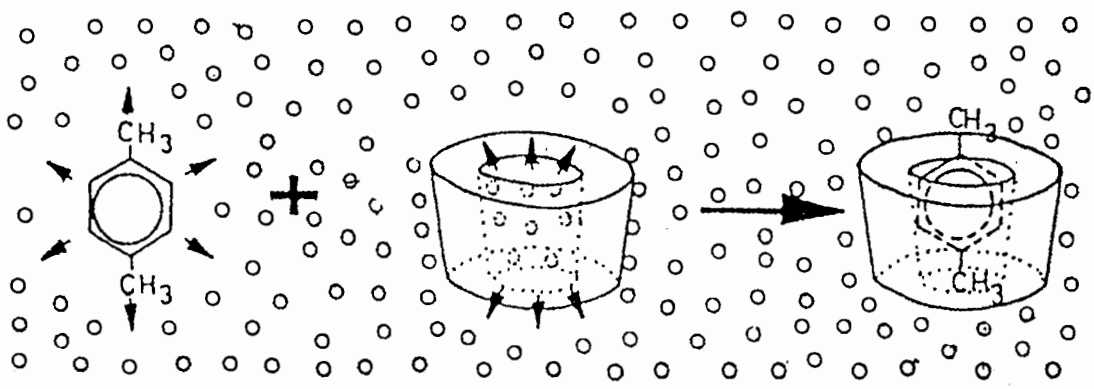
1. The size and shape of the guest molecule, as well as the properties of functional groups and the relative polarity, are seen as possibly the most important factors in determining whether complexation will proceed. A guest, or portion of a guest, must be able to insert into the cavity with minimal steric effects to hinder progress, though a tight fit in the cavity is considered important, to effect favourable distances for intermolecular interaction.

2. The energy of interaction between water and the hydrophobic cavity of cyclodextrin, and between a relatively apolar guest and solvent water, is reduced by insertion of the guest into the cavity and release of cavity-bound water into the solvent bulk. The unfavourable environment within the cavity means that water molecules are unable to satisfy hydrogen bonding potential, and their expulsion from the cavity increases their degrees of freedom, as well as decreasing the potential energy of the system, and these changes all favour complexation.
3. A number of interactions between cyclodextrin and guest, such as van der Waals forces, hydrophobic interactions within the cavity, and hydrogen bonding, impart a greater stability and lower energy to the complex[88,89]. These interactions may dominate in the formation of complexes, as well as the increased hydrogen bonding potential of waters released into the medium.
4. A decrease in ring strain, most notable in α-cyclodextrin, where conformation is more distorted and the macrocycle becomes more symmetrical on complexation than in β- and γ-cyclodextrin. This may contribute to overall complexation, but is not considered as important as other factors[52].

All of these factors may act simultaneously to effect complexation, with that contributing most being the nature of the guest, most particularly size, shape and distribution of functional groups. The chemical nature of the guest appears relatively unimportant, except where moieties are able to interact strongly with the cyclodextrin and drive the equilibrium toward complexation.

A scheme showing the steps involved in complexation is given in Fig.1.6. Expelled water molecules show an increase in energy associated with transition to the gaseous phase, as well as an increase in rotational degrees of freedom resulting from release into a more favourable environment. They condense back into the liquid phase as they are drawn into the solvent bulk. The guest molecule, shedding its hydrate coating, also assumes the properties of an ideal gas and inserts into the cavity, with a corresponding increase in host-guest interactions. Finally, water is restored around the cyclodextrin and any exposed parts of the guest.

Fig. 1.6: Scheme showing the mode of complexation of cyclodextrin with guest molecules in solution (reproduced from 13). The guest molecule is *p*-xylene, and water molecules are shown as circles.



1.4.3 Equilibrium of complexation

An equilibrium is established in solution between complexation and dissociation, which may be represented as:

$$CD + G \underset{k_d}{\overset{k_c}{\rightleftharpoons}} CD{\cdot}G$$

The rate of formation of the complex is determined by the constant k_c, and that of dissociation by k_d, and the equilibrium obtained gives a measure of the stability of the complex. The overall equilibrium constant K (= k_c/k_d) is determined by a number of factors, and these in turn determine the conditions under which a stable complex may be formed in solution:

1. Size of guest molecule - the rate of complexation and decomposition is slower with larger guests, due to a possibly stronger interaction with the cyclodextrin cavity. This may also be dependent on the type and size of substituents.
2. Ionisation of the guest molecule impedes complexation, due to an increase in possible interactions with solvent water molecules. Altering the pH of the medium may thus affect the equilibrium[90].

3. Relative concentration of guest and cyclodextrin in solution. An excess of one or the other may promote complexation. The stoichiometry of the complex may also be affected, though this could depend in part on the nature of the guest molecule and whether a 1:1 or higher complex is formed in equimolar solution.
4. Interaction between host and guest, through hydrogen bonding, van der Waals forces and hydrophobic interactions, related to the structure of the guest and the presence of certain functional groups. ~~A combination of these interactions between one or more groups may result in an energy similar to that of covalent bonding, thus promoting complexation~~.

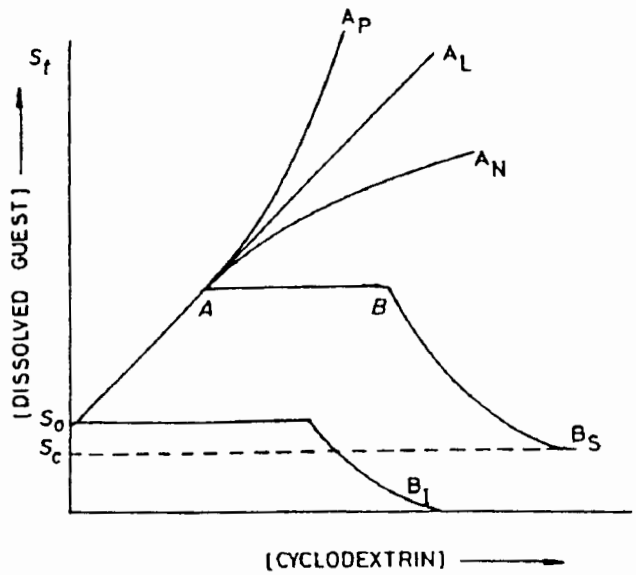
1.4.4 Solubility of the complex

Attempts to crystallise a complex from solution must take its solubility characteristics into account. Studies have shown that the stability of a complex and its solubility are independent of each other, though enhancement of the poor solubility of a guest is directly related to the ability of a complex to form in solution. Measurements of the equilibrium constant will therefore not ensure that a complex can be readily crystallised, despite high stability.

The solubility isotherm for a guest, however, gives an important indication of the possibility of precipitating a complex. A scheme, Fig.1.7, illustrates how solubility may be affected by the concentration of cyclodextrin. Complexation in solution will follow profile A. A further increase in cyclodextrin concentration can improve solubility up to a point limited by its own solubility. Where this is linear, it follows the type A_L solubility curves proposed by Higuchi and Connors[91].

If the complex is more soluble than the cyclodextrin, no precipitation will occur. Where complex solubility is limited, the isotherm will follow profile B i.e. a saturation point of guest and cyclodextrin has been reached. A greater concentration of cyclodextrin, either by addition to the medium or reduction in solvent volume, may then result in a decrease in guest solubility, indicating precipitation of the complex. Where no improvement is seen in solubility, the complex formed is insoluble and will precipitate (B_I).

Fig.1.7: Solubility isotherms for cyclodextrin complexes



S_O = saturation solubility of the guest in aqueous solution. S_C = solubility limit of complex.
S_t = concentration of dissolved guest in the free and complexed state.
(adapted from Higuchi and Connors[91])

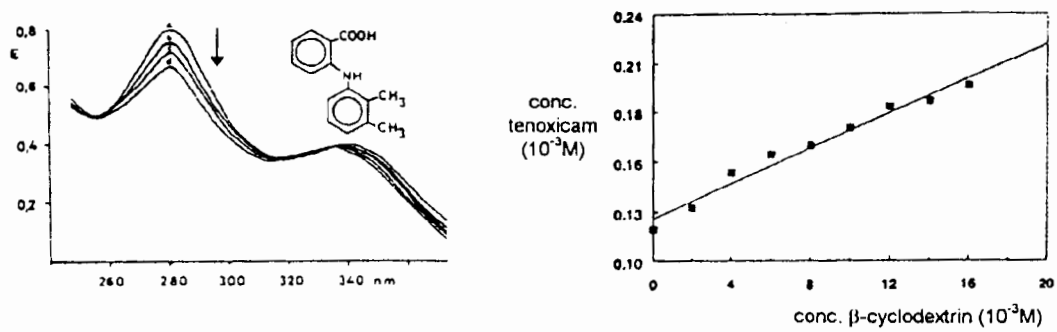
1.4.5 Complex characterisation

The solubility profile of a guest in the presence of cyclodextrin, as well as the mode of complexation, may be measured using a number of techniques that record modifications in certain physicochemical characteristics of the guest or cyclodextrin.

UV spectrophotometry may be used as the cyclodextrins do not absorb in the UV wavelength range, but will cause changes in the spectra of guests where a chromophore is shielded by the cyclodextrin cavity[92,93]. This may be used to obtain a solubility profile as shown in Fig.1.8, showing spectrum modification for mefenamic acid[94] and a plot of β-cyclodextrin-tenoxicam complex in solution, showing a type A_L solubility curve. The plots obtained may be used to calculate equilibrium constants for the reaction, using the Benesi-Hildebrand equation[95].

Fig. 1.8: UV spectrophotometry. (a) Spectral changes with β-cyclodextrin concentration[94] and (b) a plot of solubility change with increased cyclodextrin concentration[96].

(a) arrow indicates increase in cyclodextrin concentration. (b)



Induced circular dichroism is observed with achiral guests in the presence of cyclodextrin and is sensitive to the orientation of the chromophore in the cavity[97,98,99]. Other techniques measure changes in characteristics such as fluorescence and luminescence, as well as chemical shifts in proton NMR spectroscopy[93,100,101].

Most of these techniques are applied to solutions of cyclodextrin and guest, though solid-state characterisation is possible using thermal analysis and X-ray diffraction where the complex formed is crystalline. The basis of the present study is the characterisation of complexes using these techniques, and they will be discussed in more detail in the methodology (Section 2), though the thermal behaviour of cyclodextrins may be discussed here.

1.4.6 Thermal properties

The behaviour of the cyclodextrins with temperature may be analysed using a number of techniques[10,13,102,103]. Those of interest in this study have been thermogravimetric analysis (TGA), measuring mass loss over a temperature range, and differential scanning calorimetry (DSC), which records heat flow through a sample and the energy that may be absorbed or released. Changes in the thermal characteristics of a guest molecule, such as absence of a melting point endotherm

or delayed onset of decomposition, by association with cyclodextrin, may be used as an indication of complex formation.

1.4.7 Crystal structure

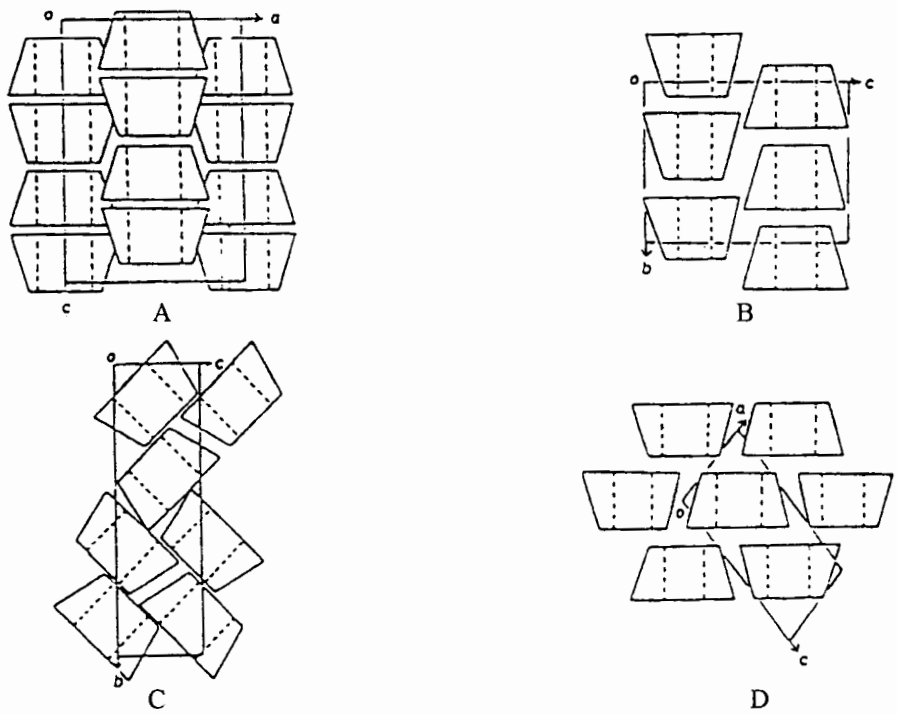
There are a number of basic modes of packing in those crystal structures that have been reported for cyclodextrins and their complexes. These may be grouped according to whether the host molecules crystallise as monomers or dimers, as shown schematically in Fig 1.9. A number of factors may account for the mode of packing, especially the intermolecular contacts, such as hydrogen bonding, that are possible between host and guest and solvent water molecules, such that all possible contacts are satisfied.

1.4.7.1 Monomeric complexes

Herringbone - this is the arrangement adopted by the hydrates of α-, β- and γ-cyclodextrin[31,32,39] and is confined mainly to complexes with very small guests that can be completely enclosed within the cavity, such as that of α-cyclodextrin with iodine[104] and *n*-propanol[105] and β-cyclodextrin with methanol[29] and ethanol[106] though larger guest molecules, such as benzyl alcohol[107] and nicotinamide[108], may also complex in this manner where they can fully insert into the cavity. Both ends of the cavity are blocked by adjacent rings and the guest is completely isolated and trapped. Adjacent cyclodextrins are related by a crystallographic two-fold screw axis.

Brick - an arrangement of layers parallel to the plane of the macrocycle, adjacent layers being displaced approximately by the radius of a cyclodextrin molecule. Both ends of the cavity are open, and the guest, either too large or too long to be fully accommodated within the cavity, is able to penetrate into the intermolecular space created between neighbouring cyclodextrins in the adjacent layer. This arrangement has so far been observed primarily in α-cyclodextrin complexes with aromatic monocyclic compounds such as pyrrolidone[109] and *p*-nitrophenol[110], and also in the β-cyclodextrin complex with triethylenediamine[111].

Fig. 1.9: Scheme showing basic packing arrangements of cyclodextrin complexes. (a) Head-to-head channel structures, (b) head-to-tail channel structures, (c) cage (herringbone) and (d) layer (brick) structures. (Reproduced from 112).



1.4.7.2 Dimeric complexes

Even where the guest molecule may be small enough to be fully enclosed within the cavity, β-cyclodextrin will preferentially crystallise as a dimer, such as in the complex with *n*-propanol[113,114]. The formation of head-to-head dimers is favoured by the establishment of O(3)···O(3') hydrogen bonds between adjacent cyclodextrins, which confer further stability to an already relatively rigid molecule. Furthermore, the cavity volume of the dimer is approximately 2.5 times that of the monomer, and thus able to accommodate larger guest molecules. These molecules are not isolated within individual cavities, and the possibility exists for interactions between them that may stabilise the complex further. The cyclodextrin molecules are also less distorted from the plane of the macrocycle than in monomeric complexes, which may further contribute to complex stability[115].

A characteristic of dimer complexes, observed with the increasing number of structures reported, is the formation of invariant layers (Fig.1.10)[115,116], differing in the relative displacement of adjacent layers:

Channel - dimers are aligned along the axis, such that endless channels are formed into which the guest is inserted. These head-to-head channels are most commonly found with β-cyclodextrin complexes[26,117], though a number of head-to-tail complexes have been reported with α-cyclodextrin and compounds such as *m*-nitroaniline[118] and benzenesulphonate[119], with hydrogen bonding between primary and secondary OH groups.

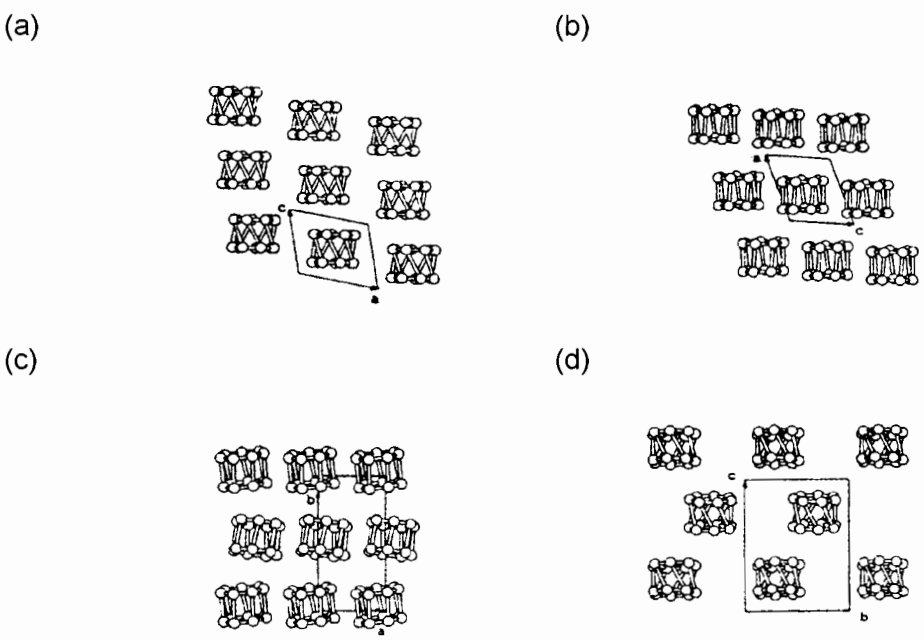
Chessboard - a lateral displacement of dimers in adjacent layers related by a two-fold screw axis, such that each dimer is located above a space filled with solvent e.g. β-cyclodextrin with benzil and phenylethylmalonic acid. This is a similar arrangement to that of the brick-type cage structure observed with monomeric complexes.

Intermediate - an arrangement between channel and chessboard, where the dimer cavity is partially closed on either end. The shift of dimers is almost equal to the inner diameter of the β-cyclodextrin cavity such that the axis of a dimer is located near the rim of the dimer below, creating a brick-like pattern similar to that found in monomeric complexes, e.g. 1-adamantane carboxylic acid complex[120].

Screw - a distorted channel arrangement where dimers are not aligned along the channel axis but displaced at an angle and related via a two-fold screw axis, forming distorted channels[115], e.g. β-cyclodextrin with racemic fenoprofen[82].

The establishment of a further hydrogen bonding network has been proposed as the reason for the arrangement of dimers in layers[116]. A primary network of intermolecular hydrogen bonds between the secondary faces of the individual monomers that make up the dimer, and a secondary network between these OH groups and solvent molecules, acting as a bridge to adjacent cyclodextrins in the same layers, act to stabilise the dimer within the layer. This arrangement has been found in the two-dimensional arrangement of all cyclodextrin dimers characterised to date.

Fig. 1.10: Packing arrangement for dimeric complexes (Reproduced from 115). Each β-cyclodextrin molecule is represented by the O(4) heptagon. (a) Channel, (b) intermediate, (c) screw channel and (d) chessboard.



The type of packing that is adopted appears to depend in large part on the nature of the guest included. Factors such as size, the character of functional groups that may interact through hydrogen bonding or hydrophobic interactions, and ionisation of the guest are all important. The crystalline complexes of α-cyclodextrin with small chain carboxylic acids, such as acetic, propionic and butyric acid, adopt the cage structure, whereas higher-chain acids will form channels[121]. Furthermore, ionisation may cause a change in arrangement e.g. molecular iodine converting from a cage-type structure in complexes with β-cyclodextrin to channels on formation of the iodide, due to a polyiodide chain positioned inside the channel[104].

The few reported structures of γ-cyclodextrin show that the nature of the guest may have very little influence on the packing arrangement. The hydrates and deuterate of γ-cyclodextrin crystallise in a cage structure very similar to that of β-cyclodextrin[37,38,122], but on complex formation a channel is assumed that is linear, even where the guest, such as *n*-propanol, is small[123,124]. Furthermore, the cyclodextrin rings are stacked in an alternating head-to-head and head-to-tail

arrangement that is unique and would appear to be characteristic more of γ-cyclodextrin than the nature of the guest molecule. Each cyclodextrin is positioned on a four-fold axis, and all structures of complexes recorded to date crystallise in the space group $P42_12$, indicating a highly rigid structure[27,123,124].

The hydrated form of δ-cyclodextrin has been characterised and this is the only structure of this nine-glucose cyclodextrin to be published to date[125], and the structure of ε-cyclodextrin has recently been elucidated[126].

1.4.7.3 Substituted cyclodextrins

The substituted cyclodextrins, specifically DIMEB and TRIMEB, have a more flexible macrocyclic structure, though a degree of rigidity is maintained in DIMEB by the formation of intramolecular O(2)···H-O(3) hydrogen bonds[127]. A comparison between the geometrical parameters of selected complexes of β-cyclodextrin, DIMEB and TRIMEB is given in Table 1.2.

Whereas β-cyclodextrin and DIMEB are similar in conformation, the macrocycle of TRIMEB deviates more significantly from planarity, due mainly to the greater inclination of the glucose moieties toward the centre of the cavity, as seen by the O(2)···O(3) distance and the tilt angle. This may be due in part to the steric effects of substitution on the O(2),O(3) rim.

The crystal structures of DIMEB pentadecahydrate and TRIMEB monohydrate have been reported[127,128]. TRIMEB is more distorted in the uncomplexed than complexed state, with six methylglucose moieties adopting the $^4C_1$ conformation and one adopting the $^1C_4$ conformation, and undergoes significant conformational changes to accommodate the guest molecule[128].

There is less difference in the hydrophilic character of the intra- and intermolecular spaces of DIMEB, due to the presence of methyl groups, and guests can be found inside and outside the cavity[131,129,130], though interaction between guests usually does not occur. The O(6) rim of TRIMEB is almost completely closed off by O(6)-methyl groups, giving the molecule a cup-shape into which the hydrophobic part of a guest molecule can insert only partially. The hydrophilic moiety protrudes and is able to interact with other TRIMEB molecules in the crystal. Unlike

Table 1.2: Geometrical parameters for β-cyclodextrin and methylated derivatives(reproduced from 112).

	β-cyclodextrin[a]	DIMEB[b]	TRIMEB[c]
O(4) hexagon radius (Å)*	5.02	5.06	4.99
O(4)···O(4') distance (Å)*	4.36	4.38	4.33
O(2)···O(3) distance (Å)*	2.86	2.91	3.46
Planarity of O(4) hexagon[d] (°)	0.16	0.09	0.44
Glycosidic O(4) angle (°)	117	117	117
Tilt-angle (°)[e]	14	14	20

* The average value for all residues
a) triethylenediamine complex[111] b) *p*-nitrophenol complex[131] c) *p*-iodophenol complex[132]
d) root-mean-square deviation e) as defined in Table 1.1.

β-cyclodextrin, each guest molecule is usually isolated within each host molecule and channel structures are not formed[131,133,134].

The complexes formed are often anhydrous, due to the hydrophobic environment of the crystal, though a few water molecules may be present to form hydrogen bonds with the host and guest molecule[131,133].

1.5 CYCLODEXTRINS AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

1.5.1 NSAIDs

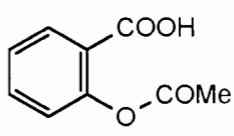
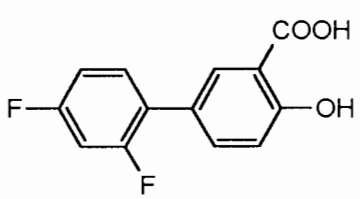
This is a group of chemically unrelated drugs, classified by structure, that share a common mechanism of action and therapeutic effect. They are anti-inflammatory, analgesic and anti-pyretic, with differences in the respective potencies of these effects between different structural classes and their analogues. The prototype for the group is aspirin (acetylsalicylic acid), originally synthesised by Hoffman in the previous century and released by Bayer in 1899, and the NSAIDs are often referred to as the aspirin-like drugs. They have been successfully employed in a number of acute and chronic conditions, primarily rheumatoid arthritis and acute gout[135].

The NSAIDs, with paracetamol as an exception, may be broadly defined as a group of heteroalkyl and -aryl alkanoic and enolic acids, possessing a common structural feature in an acid group with a large hydrophobic substituent. This appears to be important in determining the interaction with receptors in target tissues and evincing the anti-inflammatory effect. Paracetamol, a non-acidic *p*-aminophenol derivative, is primarily anti-pyretic, with a weak anti-inflammatory effect. The molecular structures of the most commonly used classes of NSAIDs are given in Table 1.3, and IUPAC nomenclature for those with which this study is concerned are given in Table 1.4.

1.5.1.1 Mechanism of action

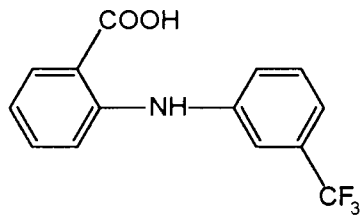
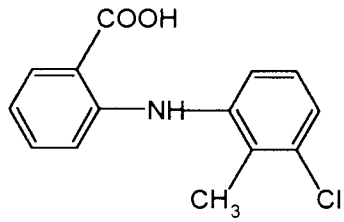
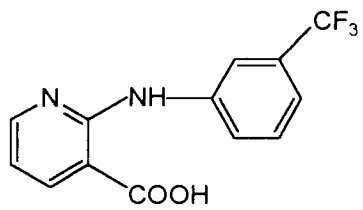
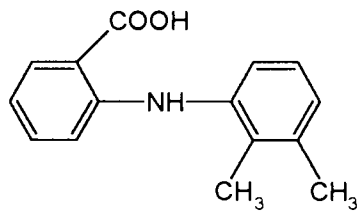
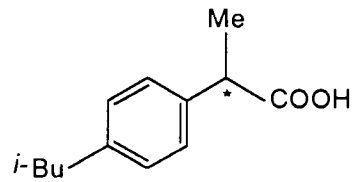
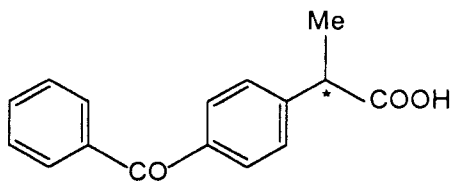
Though the precise mechanism of action is still under investigation, a common interaction with specific enzyme receptor sites is observed with the NSAIDs. They inhibit the production of prostaglandins, a series of eicosanoids which mediate in inflammatory pathogenesis and are produced at the site of trauma, by blockade of the enzyme cyclooxygenase. This action, combined with other possible interactions still to be elucidated, determines the pharmacological and side-effect profiles of this group of drugs.

Table 1.3: Structure of NSAIDs

Class	Structure	Activity
SALICYLATES		
acetylsalicylic acid (aspirin)		anti-inflammatory anti-pyretic analgesic
diflunisal		**Other examples:** aloxiprin methyl salicylate salsalate

continued....

Table 1.3 continued /2

FENAMATES flufenamic acid		anti-inflammatory analgesic anti-pyretic
tolfenamic acid		**Other examples:** meclofenamic acid diclofenac (a phenylacetic acid)
~~flufenamic acid~~		
~~niflumic~~ acid		
PROPIONIC ACIDS **(profens)** ibuprofen		**Other examples:** naproxen flurbiprofen fenoprofen fenbrufen tiaprofenic acid oxaprozin
ketoprofen	 * chiral C atom	

continued....

Table 1.3 continued /3

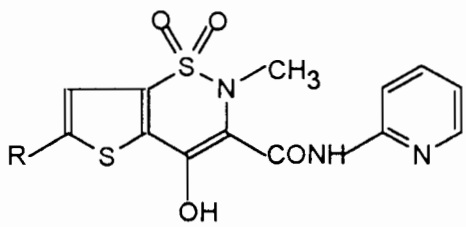
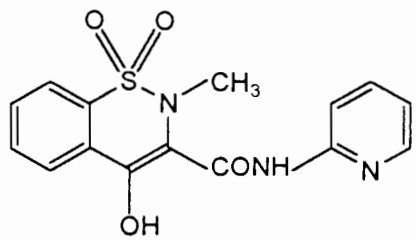
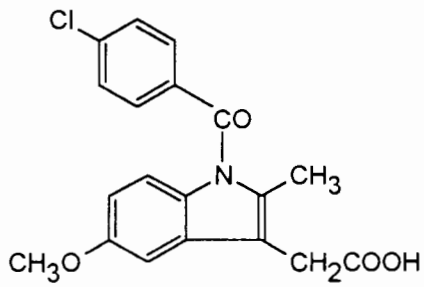
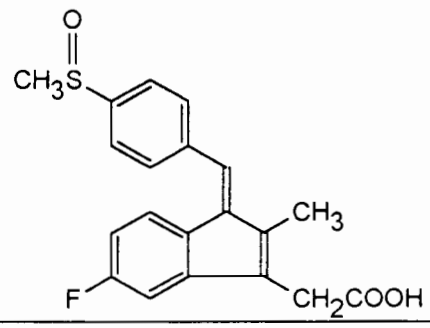
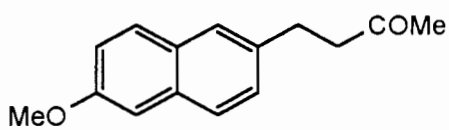
OXICAMS (enolic acids)		
tenoxicam R=H lornoxicam R=Cl		long-acting primarily anti-inflammatory
piroxicam		**Other examples:** isoxicam meloxicam
INDENES (derivatives of heterocyclic acids)		
indomethacin		
sulindac		
OTHERS		
nabumetone (a non-acidic naphthylalkanone)		Anti-inflammatory, with few gastric effects reported
pyrazoles	phenylbutazone azapropazone	No longer widely used due to potentially fatal blood dyscrasias

Table 1.4: Nomenclature for NSAIDs used in this study[136]

DRUG	NOMENCLATURE
diflunisal	2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid
flufenamic acid	2-[[3-(trifluoromethyl)phenyl]-amino]benzoic acid
tolfenamic acid	2-[(3-chloro-2-methylphenyl)-amino]benzoic acid
niflumic acid	2-[[3-(trifluoromethyl)phenyl]-amino]-3-pyridine-carboxylic acid
mefenamic acid	2-[(2,3-dimethylphenyl)amino]-benzoic acid
ibuprofen	2-(4-isobutylphenyl)propionic acid
ketoprofen	2-(3-benzoylphenyl)propionic acid
tenoxicam	4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide
piroxicam	4-hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide
indomethacin	1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid
sulindac	(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)-phenyl]methylene]-1H-indene-3-acetic acid

Related to this mode of action is an important limiting factor to the use of the NSAIDs, especially in the long-term treatment of chronic osteo- and rheumatoid arthritis. Apart from their role in inflammation, the prostaglandins, specifically PGE_2 and PGI_2, inhibit acid secretion in the stomach and promote mucous secretion that protects the cell lining of the gastric mucosa. Depletion of prostaglandins thus robs the stomach of this protection, and ulceration and bleeding may result if NSAID use is prolonged, with debilitating and potentially fatal results[135,137,138,139,140].

1.5.2 CYCLODEXTRIN INCLUSION OF NSAIDs

The NSAIDs are small molecular weight compounds possessing a hydrophobic group that may comfortably insert into the cyclodextrin cavity, and a number of complexes have been prepared and become commercially available, with notable improvements in drug behaviour.

The hydrophobic and acidic properties of the NSAIDs confer a poor aqueous solubility, especially in the acid environment of the stomach where the drug is present mainly in its unionised form. This is responsible in part for a direct irritant effect on the gastric lining with oral administration that can result in nausea, vomiting and gastric discomfort caused by hyperacidity, which, in combination with prostaglandin E_2 inhibition, may ultimately progress to ulcer formation.

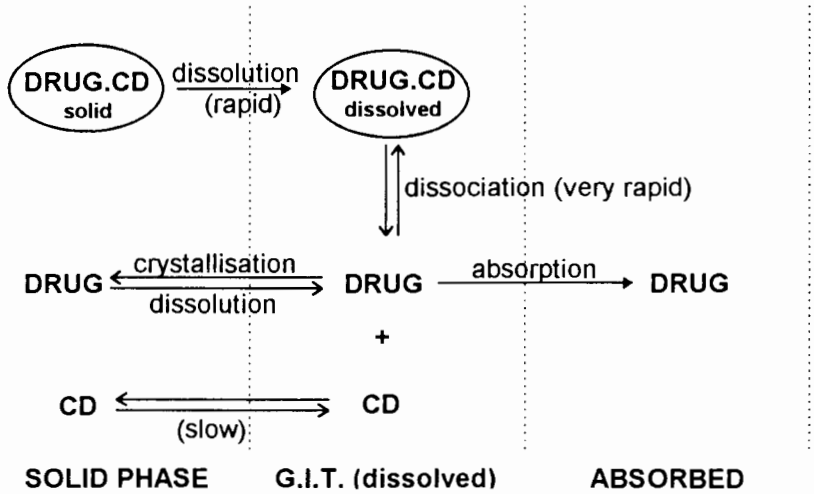
By encapsulation in a soluble host molecule, it becomes easier to disperse the drug in an aqueous medium. This has a number of potential advantages:

1. Enhanced absorption of the drug from the intestine, by delivering more to the absorbing surface. The intestinal mucosa preferentially absorbs hydrophobic molecules, and will readily dissociate the cyclodextrin-drug complex. This has a dual beneficial effect, by improving the rate of absorption and the onset of action, and by increasing the amount of drug that is potentially available for therapeutic effect[141,142,143,144,145,146,147]. A scheme showing the process of dissolution and absorption is given in Fig.1.11. The complex will dissolve and dissociate rapidly in the gastrointestinal tract and be absorbed. Drug that has dissolved in excess of the saturation concentration will then recrystallise and be dissolved as more drug is absorbed. Further studies have suggested that

cyclodextrins may also improve absorption by interaction with and modification of the mucosal membrane[148,149].

2. Reduction of gastric side effects, which are the main limiting factor in the use of NSAIDs on a long-term basis[147,150,151,152,153,154,155].
3. Dosage form modification, for example the formulation of parenterals and solutions for topical administration, such as ophthalmic and water-based (gel) preparations[156,157,158,159].

Fig. 1.11: Scheme showing dissolution and absorption of complexes in the gastrointestinal tract (G.I.T.)(adapted from 87).



1.5.2.1 Cyclodextrin toxicity

An important limitation to the use of cyclodextrins is their potential toxicity, though in general they are considered to be safe, with high LD_{50} values being reported in test animals. Absorption of the whole molecule from the gut is minimal, and it is degraded by intestinal flora in the colon after the complex has dissociated and the drug has been absorbed. The relative amounts of unmetabolised cyclodextrin that are absorbed are less than 2% for α-cyclodextrin and from 1-6% for β-cyclodextrin with γ-cyclodextrin being degraded higher up in the gastrointestinal tract so that less than 0.1% of the whole molecule is absorbed[160]. The breakdown products - glucose and short-chain oligosaccharides - are non-toxic and readily assimilated. The

potential toxicity of methylglucose, and other derivatives, may limit the use of substituted cyclodextrins.

A well-documented haemolytic effect, due to a high surface activity, with depletion of cholesterol from cell membranes, could limit parenteral administration. This is most pronounced with DIMEB and may lead to toxic effects. Furthermore, the relatively poor solubility of β-cyclodextrin, most commonly used because of its cavity size and cost-effectiveness, and its higher affinity for cholesterol than other native cyclodextrins, can lead to crystallisation and accumulation of the β-cyclodextrin-cholesterol complex in the kidneys[13].

The hydroxypropyl derivative of β-cyclodextrin has been extensively studied for use as an excipient in oral and parenteral drug formulation, for two main reasons. The derivatised molecule is more resistant to enzymatic breakdown in the gastrointestinal tract and the haemolytic effect occurs at considerably higher doses than with the unsubstituted β-cyclodextrin, being comparable to γ-cyclodextrin, which is the safest of the native cyclodextrins for parenteral use, though its wider application is inhibited by cost[13,157,161,162].

The sulphoalkylether cyclodextrins have also been studied, for use as drug carriers in formulations with a number of different routes of administration. Their safety profile is comparable to hydroxypropyl-β-cyclodextrin, and they can favourably improve bioavailability[163,164].

1.6 AIMS OF THIS STUDY

This introduction has given an overview of the structure and potential uses of the cyclodextrins as carrier molecules for a number of compounds. This study has concentrated specifically on the non-steroidal anti-inflammatory drugs as guest molecules for inclusion into cyclodextrins and their derivatives, and the application of physicochemical methods to establish that complexation has occurred. Complexes have been prepared by a number of methods, and characterised using techniques such as thermal analysis and X-ray diffraction studies, which are outlined in the methodology in Section 2.

Results for a number of complexes are given in Section 3. With a knowledge of the physicochemical characteristics of the non-steroidal anti-inflammatory in question, it becomes possible to establish that complexation has occurred. The main aim of the study was to cultivate crystals of sufficient size for single crystal X-ray analysis. Where this was successful, unit cell data have been listed. In sections 4 and 5, the results of crystal structure solution for two complexes, both with the arylpropionic acid ibuprofen, are described in detail, with discussions on the implications of complexation and racemic resolution of chiral guests.

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2. METHODOLOGY AND MATERIALS

A number of methods were used to obtain solid-state complexes, both as powders and as crystals suitable for single-crystal X-ray studies. All complexes were prepared by bringing insoluble NSAIDs into a saturated aqueous solution of cyclodextrin, with slight variations in method being attempted according to the physicochemical and other properties of the host and drug being reacted.

2.1 COMPLEXES WITH β- AND γ-CYCLODEXTRIN

The methods used to obtain complexes are summarised in Fig. 2.1 and may be explained as follows:

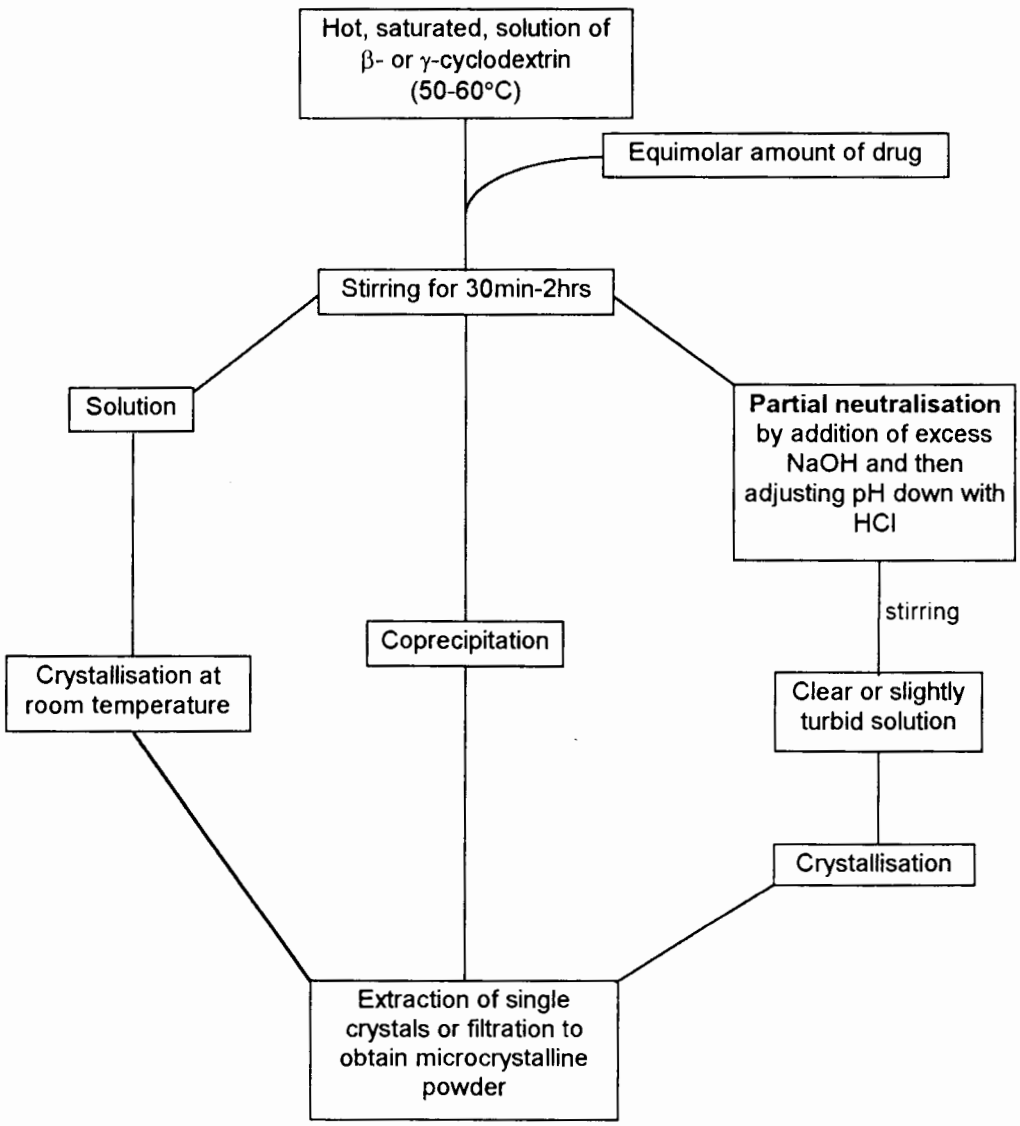
1. The main approach with all crystallisations with β- and γ-cyclodextrin was to slowly add an equimolar quantity, or other molar ratio, of drug to a hot, saturated solution of cyclodextrin, with prolonged stirring until a solution was obtained. This can be seen as an indication that the solubility of the poorly-soluble drug had been enhanced by the presence of cyclodextrin, and some interaction was occurring between the two reactants. In some cases, an excess of either drug or cyclodextrin was used in an attempt to drive the equilibrium of the reaction toward complexation. Any excess drug that did not react was then filtered off and the resultant clear solution left to crystallise.

   Complete uptake of drug from stirring alone was often not successful, and a method of partial neutralisation was then employed. The dropwise addition of 0.01M NaOH ionised the drug and brought it into solution. The pH was then adjusted down with 0.01M HCl until a turbidity was observed in the solution, indicating precipitation of the poorly soluble drug in its unionised state. Minor adjustments in pH would then produce a solution either just above or at the precipitation point, giving a clear or slightly turbid solution. Turbidity would usually disappear with further stirring and so the guest was slowly brought into solution.

2. Cosolvents, such as acetone and ethanol, were used reluctantly as cyclodextrins form complexes with many organic solvents, possibly more readily than with the guest. Ternary complexes may also be formed.

3. An interface was created between an aqueous solution of cyclodextrin and a non-miscible organic phase containing dissolved drug, with the aim of promoting crystallisation at the interface. A number of powder complexes could be obtained in this manner.

Fig 2.1: Method used to prepare complexes with β- and γ-cyclodextrin

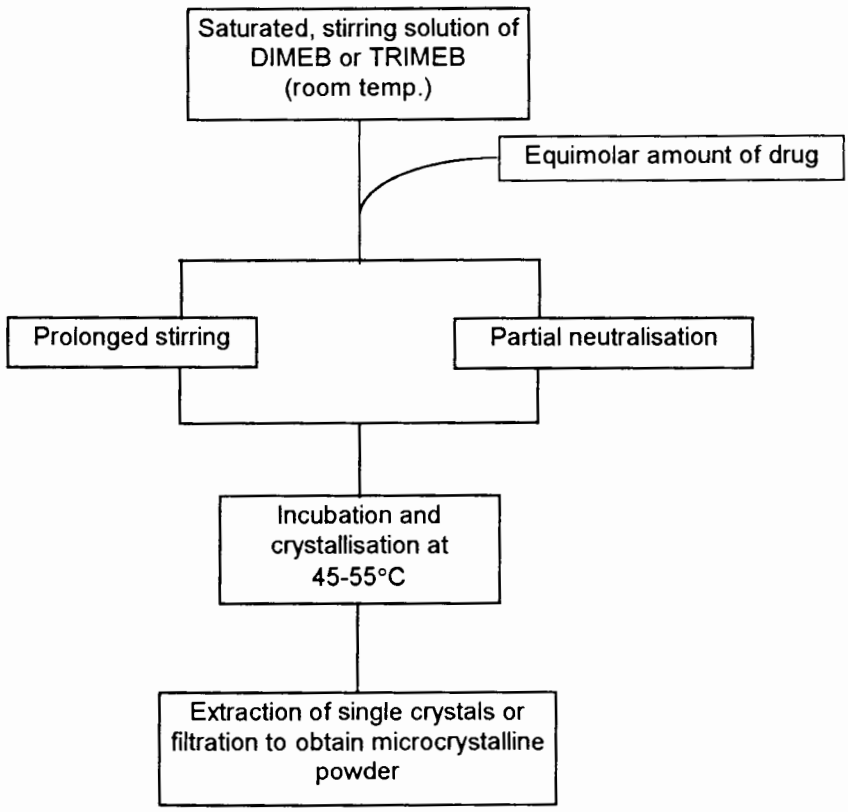


Solutions were filtered using Millex-LCR 0.5μm nylon microfilters and left to stand in specially prepared crystallisation vials. Solutions were left to incubate at temperatures ranging from 4-60°C, with slow evaporation being used to supersaturate the solution and precipitate a complex.

2.2 COMPLEXES WITH DIMEB AND TRIMEB

Due to their unique solubility characteristics, the preparation of complexes with the methylated cyclodextrins required a slightly different method, shown in Fig. 2.2, where all reactions were performed at room temperature and the resultant solution incubated at elevated temperature (45-55°C).

Fig 2.2: Method of preparation of complexes with DIMEB and TRIMEB



Care was taken that the complex formed at high temperature did not dissolve back into solution once the sample vial was removed from the incubation oven. In cases where this occurred, and where the complex was unstable in air through loss of

water from the crystal, swift action was required to extract the crystal, remove solvent traces from the crystal faces and seal the crystal against water loss. It was necessary to remove all solvent from the surface of the crystal to prevent reaction with cyanoacrylate, which was used as a sealant and opacifies on contact with water.

2.3 THERMAL ANALYSIS

2.3.1 Hot stage microscopy

Visual characterisation of crystals was performed on a Nikon SMZ-10 stereoscopic microscope, using a Linkam TH600 hot stage with a silver heating/freezing block covering a range of -200 to 600°C. A Linkam CO600 temperature controller was used to incrementally increase the temperature over the range chosen. The temperature was raised at a rate of 5-10°C/min, and events such as opacity of the crystal, fusion and the onset of degradation were recorded for comparison with data obtained for crystals of native cyclodextrin. Inspection of the morphology of the crystal under investigation also provided comparisons with uncomplexed cyclodextrin that could be used as an indication of complex formation.

Photographic records were obtained with a Nikon FX-35 camera, using a Nikon Microflex AFX-II Photomicrographic Attachment. Photographs were taken with 400ASA film, and magnifications are given.

2.3.2 Thermogravimetry (TGA) and differential scanning calorimetry (DSC)

Thermal analysis was used in conjunction with hot stage microscopy to determine the behaviour of complexes with increase in temperature, and to provide comparison with native cyclodextrin and other complexes. Thermogravimetric analysis (TGA) measures mass loss over a temperature range, and was used to determine the number of water molecules of crystallisation per host molecule for each complex. DSC determines heat flow through the sample as measured against a reference, and can be used to accurately establish the melting point and the onset of other thermal events[1].

TGA and DSC were performed on a Perkin-Elmer PC-7 series thermal analysis system. Scans were performed at 5 or 10°C/min under N_2 gas at a flow rate of 50ml/min. The temperature range over which analyses were performed was from 30-330°C for β- and γ-cyclodextrin and DIMEB complexes, and from 30-220°C for TRIMEB complexes. Samples for DSC were placed in vented aluminium pans against an empty reference pan. Calibration for TGA was performed against the Curie points of alumel (163°C) and perkalloy (596°C), and for DSC using the temperature of melting of indium (156.6°C) and zinc (419.5°C), and the enthalpy of fusion of indium (28.62J/g).

The temperature range over which experiments were conducted was dependent on the cyclodextrin involved. The onset of decomposition of β- and γ-cyclodextrin, and of DIMEB, occurs from 200°C, with complete degradation at 310-330°C, while TRIMEB has a melting point of approximately 160°C and degrades from 220°C upwards.

2.4 ULTRAVIOLET SPECTROPHOTOMETRY AND ELEMENTAL ANALYSIS

The cyclodextrins do not absorb in the ultraviolet wavelength range, and this property may be useful in determining the effect of cyclodextrin on the absorbance of chromophores on the guest molecule. A measure of the absorbance may also be used to establish the amount of guest present in a specific mass of sample to obtain complex stoichiometry though in general this method may not be sensitive.

Spectrophotometry was performed on a Philips PU8720 UV/VIS Scanning Spectrophotometer in the range of 200-600nm. Silica cuvettes were used. The apparatus was calibrated using a sample of solvent (water), and scans were run at a rate of 200nm/min. A standard calibration curve could be obtained for a guest compound using a range of known concentrations and Beer's Law was used to calculate the absorbance, against which a comparison could be made with the absorbance of the guest in a complex. Measurement of the decrease in absorption maxima for a guest in the presence of increasing concentration of cyclodextrin may also be used to quantify the dynamics of complexation and obtain a stability constant for a complex in solution, as described in Section 1.4.5.

Microanalysis was performed using a Fisons EA-1108 elemental analyser to determine the percentage of C, H, N and S in a sample of each complex.

2.5 X-RAY POWDER DIFFRACTION (XRD)

Comparison was made between the XRD traces for complexes and physical mixtures of cyclodextrin and drug. The composition of mixtures was based on the molar ratios used in the preparation of the complex.

2.5.1 Preparation of samples

Physical mixtures were prepared by shaking equimolar amounts of cyclodextrin and drug on a Wig-L-Bug Amalgamator Model 3110-3A for three minutes without ballbearings to prevent the crystallinity of the complex from being destroyed. Complexes were isolated from the mother liquor by filtration under vacuum and then finely ground using a pestle and mortar.

2.5.2 Recording of XRD patterns

XRD traces were recorded in a 2θ range of 6-40° on a Philips PW1050/80 vertical goniometer with Ni-filtered CuK_α radiation (λ=1.5418Å) generated by a Philips PW 1130/90 generator operating at 20mA and 40kV. Samples were mounted in aluminium holders and step scans (0.1° 2θ, 1s counting times) were carried out with 1° divergence and 1° receiving slits.

2.6 X-RAY PHOTOGRAPHY

2.6.1 Crystal preparation

Single crystals of suitable size, chosen for their ability to uniformly extinguish polarised light, were mounted for photography according to their stability in air. Stable crystals were mounted directly onto a glass fibre, either fully exposed or encased in cyanoacrylate to prevent any decay through slow diffusion of water from the crystal lattice. Unstable crystals were mounted naked in 0.3 or 0.5mm Lindemann capillary tubes, near a small volume of mother liquor which provided a

vapour pressure able to maintain the crystal. The glass fibre or capillary was then fixed in plasticine and mounted on a Stoe goniometer head.

2.6.2 Photography

Oscillation, Weissenberg and Buerger precession photographs were taken and, by inspection of Laue symmetries and systematic absences, it was possible to determine lattice and space group information. All photography was performed on Stoe Weissenberg and precession goniometers using Ni-filtered CuK_α radiation (λ=1.5418Å) generated by a Philips PW 1120/00 generator operating at 20mA and 40kV.

2.7 X-RAY STRUCTURE ANALYSIS

2.7.1 Data collection

Where a suitable specimen was available, and the cell dimensions obtained from photography were not considered too large (<60Å), crystal structure determination was attempted using intensity data collected from a single crystal. All attempted data collections were carried out on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated MoK_α radiation (λ=0.71069Å). Intensity data were collected at lowered temperatures. The specific conditions under which data were collected for the two structure solutions that were attempted are given in detail in sections 4 and 5.

2.7.2 Crystal structure solution

Solution of crystal structures was attempted by isomorphous replacement, using the atomic coordinates for the non-hydrogen atoms from cyclodextrin structures with similar cell parameters as found in the Cambridge Structural Database. Once the atoms of the host and guest had been located after successive Fourier difference syntheses and examination of difference electron-density maps, the structure was refined by full-matrix least-squares analyses of the positions of all atoms using the programs SHELX-76 and SHELX-93 (minimisation of $\sum w(|F_o|-|kF_c|)^2$ and of $\sum w(|F_o^2|-|kF_c^2|)^2$ respectively) [2,3], until all atoms had been placed with

acceptable temperature factors and site occupancy factors. Molecular parameters with estimated standard deviations were calculated using program PARST[4], and molecular diagrams were drawn using program PLUTO[5]. The details of structure solution and refinement for those complexes which were characterised are given in Sections 4 and 5.

2.8 MATERIALS

β-cyclodextrin and γ-cyclodextrin were obtained from Sigma Chemicals, Missouri, USA and were recrystallised from water before use.

TRIMEB and DIMEB were obtained from Cyclolab, Budapest, Hungary and recrystallised from water before use.

Diflunisal, flufenamic acid, tolfenamic acid, niflumic acid, mefenamic acid, indomethacin and sulindac were obtained from Sigma Chemicals, Missouri, USA and used as received.

Racemic ketoprofen and piroxicam were obtained from Lennon Ltd., Port Elizabeth, South Africa and used as received.

Racemic and (S)-ibuprofen were obtained from Boots Chemicals, Nottingham, England and used as received.

Tenoxicam was obtained from Labochim, Milan, Italy and used as received.

2.9 REFERENCES

1 M.E. Brown: *Introduction to Thermal Analysis Techniques and Applications*, Chapman and Hall, London (1988)

2 G.M. Sheldrick: *SHELX-76, Programme for Crystal Structure Determination*, University of Cambridge, England (1978)

3 G.M. Sheldrick: *SHELX-93; Programme for Crystal Structure Determination*, unpublished work

4 M. Nardelli: *Comput. Chem.* **7** 95 (1983)

5 . W.D.S. Motherwell: *PLUTO89*, program for plotting molecular and crystal structures, University of Cambridge, England (1989)

3. COMPLEX CHARACTERISATION

A summary of the methods used to prepare complexes, with the results obtained, is given in Table 3.1. Similar methods were followed with most crystallisations, depending on the host and drug being reacted, and a number of microcrystalline powder and single crystal complexes were obtained. More success was had with certain drugs than with others, most notably the fenamates and the profens, specifically ibuprofen, though some hosts did show an affinity for particular drugs where others did not. In some cases, no complexation or crystallisation of complex occurred at all, despite repeated efforts to idealise conditions.

In general, complexes were more readily prepared with β- and γ-cyclodextrin than with the methylated derivatives. A number of reasons may account for this, and these are discussed in greater detail in Chapter 6. Crystals would usually appear within one or two days, depending on the final concentration of the reacting solution, though in some cases a powder complex would precipitate almost immediately, indicating the formation of an insoluble complex. In other cases, a complex formed in solution but would not readily crystallise.

Initial characterisation, involving hot stage microscopy, thermal analysis and XRD, as well as UV spectrophotometry and elemental analysis when used to determine stoichiometry, confirmed whether a complex had been formed. Complexes for which X-ray intensity data were successfully collected and full or partial crystal structure solution was performed, namely those of ibuprofen with β-cyclodextrin and TRIMEB, are detailed separately in Chapters 4 and 5.

3.1 OXICAMS

Numerous attempts were made to crystallise complexes with those oxicam NSAIDs that were available, using a wide pH range and other variations in vial conditions. Complexation with tenoxicam was effected in solution, though the cyclodextrin and drug tended to crystallise separately as their own hydrates. This would indicate the formation of a soluble complex that would not precipitate above the saturation concentrations of β-cyclodextrin and drug, as suggested by

Table 3.1 Summary of prepared complexes

DRUG	CD	METHOD	RESULT
tenoxicam[1] piroxicam[2]	β	**A** 1:1 mixture† stirring at 50-70°C partial neutralisation (turbidity) (pH range)†† standing (temp range)‡	[1] Separate crystallisation of CD and drug [2] Crystals - monoclinic yellow prisms (1:1)‡‡
	γ		[1,2] Crystals - tetragonal yellow prisms ([1]1:1)
	DIMEB TRIMEB	**B** 1:1 mixture stirring at room temp. partial neutralisation (turbidity) standing at 50°C	[1,2] Glass state
mefenamic acid[1] tolfenamic acid[2] flufenamic acid[3] niflumic acid[4]	β	**A**	[1,3] Powder complex (1:1) [2] Crystals - monoclinic parallelepipeds (1:1) [4] Crystals - fine needles (1:1)
	γ		[1-4] Powder complex - low yields*
	DIMEB TRIMEB	**B**	[1-4] No complexation or glass state

continued....

† A molar excess of drug or cyclodextrin was also used.
†† A pH range of 5-12 was used. A more acidic medium would accelerate hydrolysis of the CD ring. The oxicams are zwitterionic and pH may be important in inducing a polarity that may be favourable to complexation.
‡ Crystallisation temperatures were (i) room temperature, (ii) 35°C, (iii) 55-60°C and (iv) 4-6°C.
‡‡ Denotes the host:guest stoichiometry of the complex.
* Complexes obtained but not fully characterised.

Table 3.1 continued

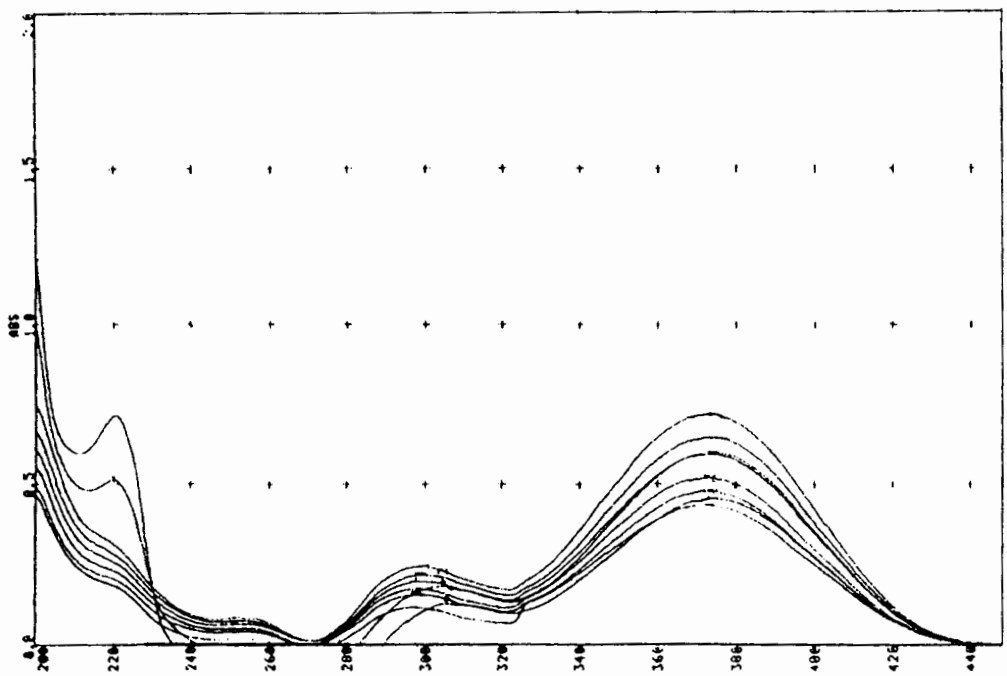
DRUG	CD	METHOD	RESULT
ibuprofen[1] ketoprofen[2]*	β	1:1 mixture stirring at 60-70°C standing at room temp and 60°C† (ibuprofen and ketoprofen melt)	[1,2] Crystals - monoclinic parallelepipeds (1:1)
	γ		[1,2] Crystals - tetragonal prisms (1:1)
	DIMEB TRIMEB	**B** (ibuprofen is taken up by DIMEB without pH adjustment)	[1,2] Crystals - orthorhombic prisms (1:1)
indomethacin[1] sulindac[2]	β γ	**A**	[1] Precipitation of powder complex* [2] No complexation
	DIMEB TRIMEB	**B**	[1,2] No complexation
diflunisal	β	**A**	Crystals - irregular hexagons (1:1)
	γ		Microcrystalline powder*
	DIMEB TRIMEB	**B**	No complexation

† Incubation at a higher temperature allowed crystallisation to occur at a slower rate and crystals of a size suitable for single crystal analysis to be obtained. Bringing the guest into solution without pH adjustment was considered desirable as ionised molecules are less readily taken up into cyclodextrin cavities than unionised molecules.

Senel *et al*[2] who show that an increase in cyclodextrin concentration will increase the amount of tenoxicam taken into solution, expressing an A_L-type solubility curve, as described originally by Higuchi and Connors[3].

A UV profile obtained for tenoxicam with varying concentrations of β-cyclodextrin is shown in Fig. 3.1. A decrease in the absorbance maximum at 373nm with increased cyclodextrin concentration is an indication that the absorbing chromophore is being shielded by the cyclodextrin, and thus that an interaction is occurring in solution, even though no solid-state complex may result.

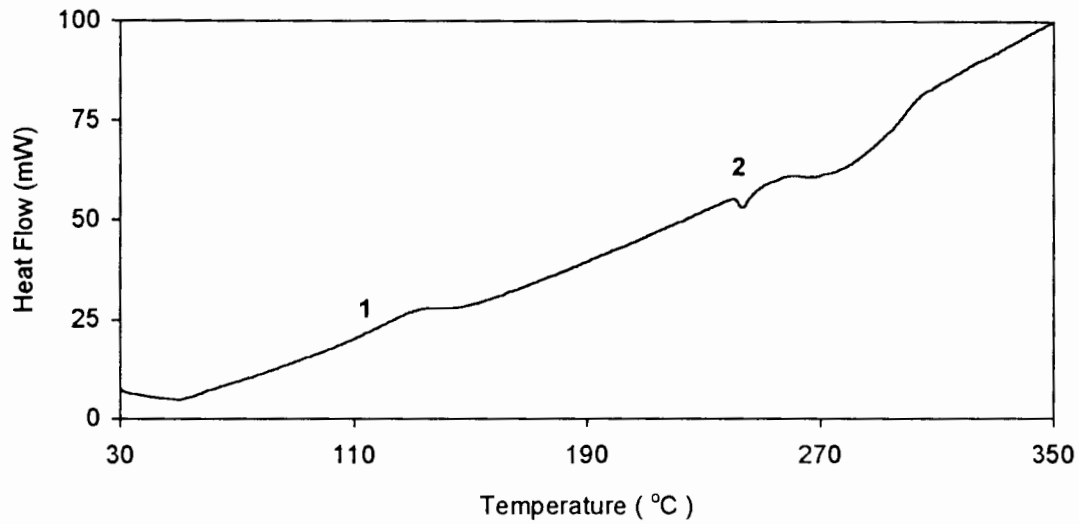
Fig.3.1 UV absorption spectrum for tenoxicam. The *x* axis gives wavelength in nm and the *y* axis gives absorbance values. The absorption maximum at 373nm decreases with increased cyclodextrin concentration.



Thermal analysis confirmed the presence of two species in the reaction vial (Fig.3.2). The fusion point of tenoxicam is at 230°C, and a characteristic exotherm is seen at that temperature (peak 2), indicating that the drug is not included in the cavity but is rather present in its free or hydrated form.

2 Ref. Chapter 1 /87 96
3 Ref. Chapter 1 /82 91

Fig. 3.2 DSC for β-cyclodextrin - tenoxicam.



Mass of sample = 2.534mg. Onset of peak 1 = 105.4°C, of peak 2 =227.2°C.

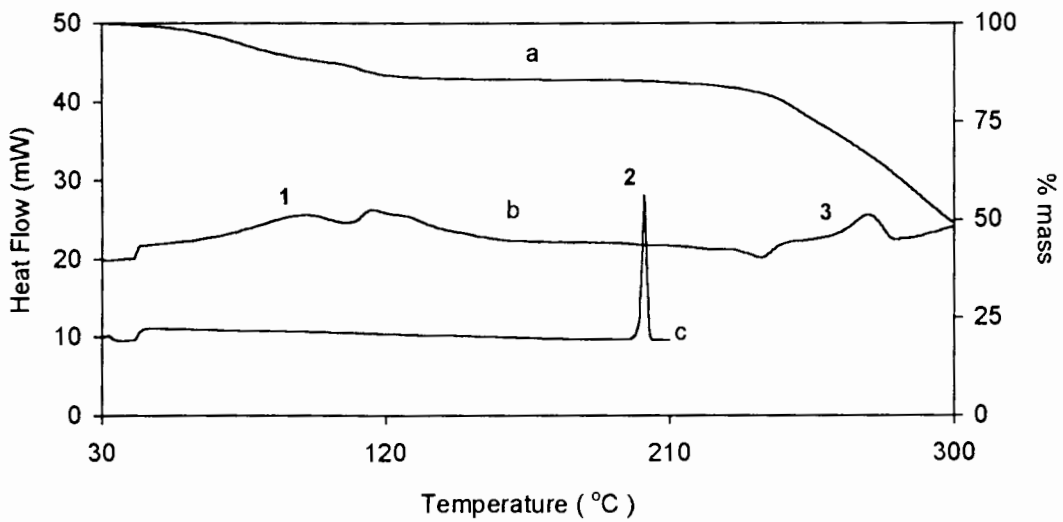
3.1.1 Piroxicam with β-cyclodextrin

A crystalline complex of β-cyclodextrin with piroxicam was obtained from a solution with pH 7, after prolonged standing at room temperature. The crystals obtained were monoclinic flat prisms with a pale yellow hue, ranging in length from 0.1 to 1.5mm, with a thickness of 0.1 to 0.6mm.

Hot stage microscopy and thermal analysis characterised the behaviour of the complex under a temperature regimen in comparison with β-cyclodextrin, and a photographic record is given in Fig. 3.4a and b, showing opacification on loss of water molecules and decompostion at higher temperatures. Results obtained for DSC and TGA (Fig. 3.3a and b) show a mass loss from 40-130°C, indicated by a broad two-stage endotherm in DSC and gradual opacification of the crystal under the microscope. This mass loss is attributed to waters of crystallisation being lost by diffusion through the crystal lattice. A mass loss of 23.8% was observed, which is equal to 26 waters of crystallisation per cyclodextrin-guest unit, based on microanalysis results that indicated a 1:1 stoichiometry of host and guest.

In Fig. 3.3b, a DSC profile for the complex is given. Water loss is indicated by the two-stage endothermic peak at 60-130°C. Suppression of the melting endotherm of piroxicam at 198-200°C (Fig. 3.3c) indicates the formation of a complex, and the onset of degradation of the complex occurs from approximately 240-250°C. These results are visualised in photographs in Fig. 3.4, showing the effect of temperature on the gross morphology and colouration of the crystals. Comparison is given with β-cyclodextrin hydrate, showing differences in crystal habit and in thermal behaviour. Whereas both crystals begin to splinter and opacify soon after removal from mother liquor, due to water loss as shown in TGA, the behaviour at higher temperatures differs. The native β-cyclodextrin crystal undergoes a characterisitc phase change at 225°C and thereafter begins to degrade. The complex with piroxicam undergoes a deepening colour change from 240°C, at which point decomposition begins.

Fig. 3.3 **Thermal analysis for β-cyclodextrin - piroxicam complex.**
(a) TGA for complex, (b) DSC for complex and (c) DSC for piroxicam powder.



Sample mass for b = 4.394mg, for c = 3.640mg
Temperature onset for peak 1 = 70.3°C, peak 2 = 200.2°C, peak 3 = 244.0°C.

CHNS microanalysis indicated the formation of a 1:1 complex in the crystal, based on the presence of sulphur. The calculated sulphur value was 2.2%, with the experimentally obtained amount being 2.3%[†].

[†] Microanalysis results, with calculated values for a 1:1 complex in parentheses, are C: 45.94% (46.67%), H: 5.54% (5.66%), N: 3.32% (2.87%) and S: 2.36% (2.24%)

Fig. 3.4 Crystal morphology and hot stage microscopy for β-cyclodextrin hydrate and complex with piroxicam.

a. Hot stage microscopy for β-cyclodextrin hydrate. Magnification x33.

(i) 30°C (ii) 75°C (iii) 130°C

(iv) 225°C (v) 310°C (vi) 350°C

b. Hot stage microscopy for β-cyclodextrin - piroxicam complex. Magnification x33.

(i) 30°C (ii) 75°C (iii) 150°C

(iv) 240°C (v) 310°C (vi) 350°C

Unit cell data were obtained for a single crystal of β-cyclodextrin - piroxicam complex, and are given in Table 3.2. The complex crystallises in the monoclinic C-centred space group C2, based on the observation of Laue 2/m symmetry and systematic absences hkl: $h+k$=2n+1 ; $h0l$: (h=2n+1) ; $0k0$: (k=2n+1) in oscillation and Weissenberg photographs. The cell dimensions obtained are unique for β-cyclodextrin in this space group and have not been reported previously. The unit cell volume and Z value calculated from these data imply the presence of one cyclodextrin and one piroxicam molecule per asymmetric unit. Though a full intensity data collection at room temperature was successfully carried out, the applications of direct methods techniques in attempts to solve the molecular structure did not yield the positions of atoms of either the host or guest. The programs SHELX86[1] and SIR92[2] were both employed, and attempts were primarily made to locate the position of the sulphur atom of piroxicam, but these were unsuccessful. The Patterson strategy in SHELX86 was also attempted, though an acceptable model for the cyclodextrin and piroxicam molecule was not obtained.

Table 3.2 Unit cell data for β-cyclodextrin - piroxicam complex

Crystal system	monoclinic
Space group	C2
a (Å)	27.2
b (Å)	12.4
c (Å)	24.8
β (°)	104.1
Vol (Å^3)	8110
Z	4

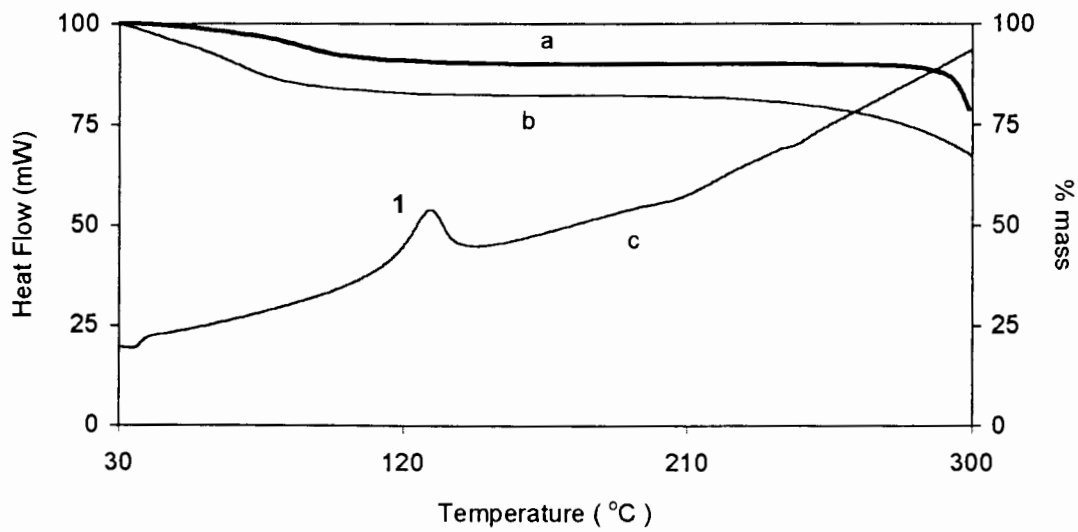
3.1.2 Oxicams with γ-cyclodextrin

The complexation of γ-cyclodextrin with oxicams was more successful, though the crystals obtained were small and yields were low. Only in the case of the complex with piroxicam was it possible to obtain enough sample for characterisation. In the complexes formed with tenoxicam and piroxicam the crystals obtained were tetragonal prisms, with a yellow colour visually related to the intensity of colour of the drug. The size was less than 0.1mm in all dimensions, even with very slow crystallisation. The crystals were stable, and showed no signs of cracking when

exposed to air. The final volume of mother liquor from which crystals were obtained was low, related to the solubility of the host, and it was noted that a layer of amorphous γ-cyclodextrin formed as a coat around the crystal on drying, possibly sealing it against water loss.

Thermal analysis and hot stage microscopy confirmed the presence of water in the crystal. The thermal analysis result for γ-cyclodextrin - piroxicam complex is given in Fig. 3.5, with the characteristic TGA profile of γ-cyclodextrin hydrate given for comparison. From the TGA result, it was possible to obtain the number of waters of crystallisation present in the complex. Compared to a value of 8.3 waters for γ-cyclodextrin hydrate, the complex was calculated to contain 19.2 waters of crystallisation per cyclodextrin unit based on microanalysis results that indicated the formation of a possible 1:1 solid-state complex between γ-cyclodextrin and piroxicam, though the values obtained could also indicate the formation of a 3:2 complex[†]. Decomposition of the complex commenced at a lower temperature than that of γ-cyclodextrin.

Fig. 3.5 **Thermal analysis for γ-cyclodextrin - piroxicam complex.**
TGA for (a) γ-cyclodextrin hydrate and (b) complex and (c) DSC for complex.



Sample mass for c = 8.434mg. Onset of peak 1 = 115.5°C

[†] Microanalysis results for γ-cyclodextrin - piroxicam complex, with calculated values for a 1:1 and 3:2 complex in parentheses, are C: 45.84% (46.46% and 45.89%), H: 5.93% (5.72% and 5.84%), N: 1,98% (2,58% and 1.84%) and S: 1,84% (1,96% and 1.41%).

3.2 FENAMATES

3.2.1 Fenamates with β-cyclodextrin

A number of complexes were successfully formed with the fenamates, all as microcrystalline powders or small crystals, with sizeable crystals being obtained with tolfenamic acid. Equimolar amounts of host and guest were used in each case, with ionisation being necessary to bring the fenamate into solution (Table 3.1).

Thermal analysis showed conclusively that complexation had occurred, through suppression of the melting endotherms for each guest under examination. An estimate of the crystal water was obtained with TGA, and a comparison of results is given in Table 3.3. Thermal analysis results are shown in Fig. 3.6 for the four fenamate NSAIDs that were part of this investigation. All show similar TGA and DSC profiles, and onset of decomposition occurs from approximately the same temperature.

Where it was possible to obtain good yields of powder complexes, X-ray powder diffraction (XRD) was performed to further establish that a complex had been formed. The XRD traces for the complexes with mefenamic acid and flufenamic acid are shown in Fig.3.7, together with XRD traces for 1:1 physical mixtures of cyclodextrin and guest prepared as outlined in section 2.6, based on the stoichiometry of each complex as determined using microanalysis. A comparison of the two traces shows that intensity peaks characteristic of β-cyclodextrin and the guest have been suppressed and that the complex has a crystal structure that differs from that of β-cyclodextrin alone.

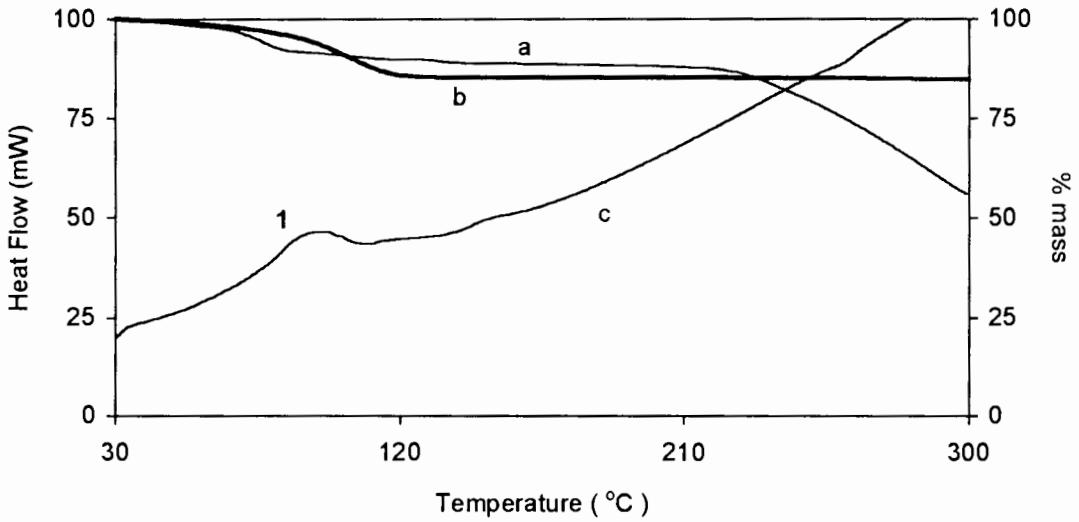
Table 3.3 TGA for fenamate complexes with β-cyclodextrin

β-cyclodextrin complex	TG mass loss (%)	No. of waters present†
mefenamic acid	13.1	11.5
tolfenamic acid	15.4	14.2
flufenamic acid	13.8	12.8
niflumic acid	14.4	13.2

† The number of water molecules per cyclodextrin molecule, based on host:guest stoichiometry calculated from microanalysis (Table 3.4).

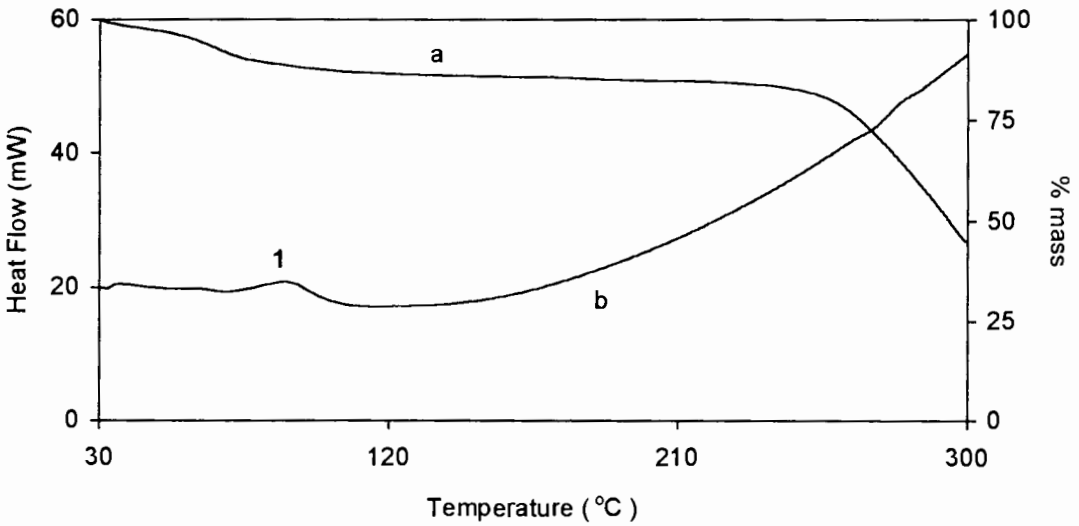
Fig. 3.6 Thermal analysis for β-cyclodextrin complexes with fenamate NSAIDs

a. mefenamic acid. TGA for (a) complex and (b) β-cyclodextrin and (c) DSC for complex.



Sample mass for c = 8.259mg. Onset of peak 1 = 71.95°C.

b. flufenamic acid. (a) TGA and (b) DSC.

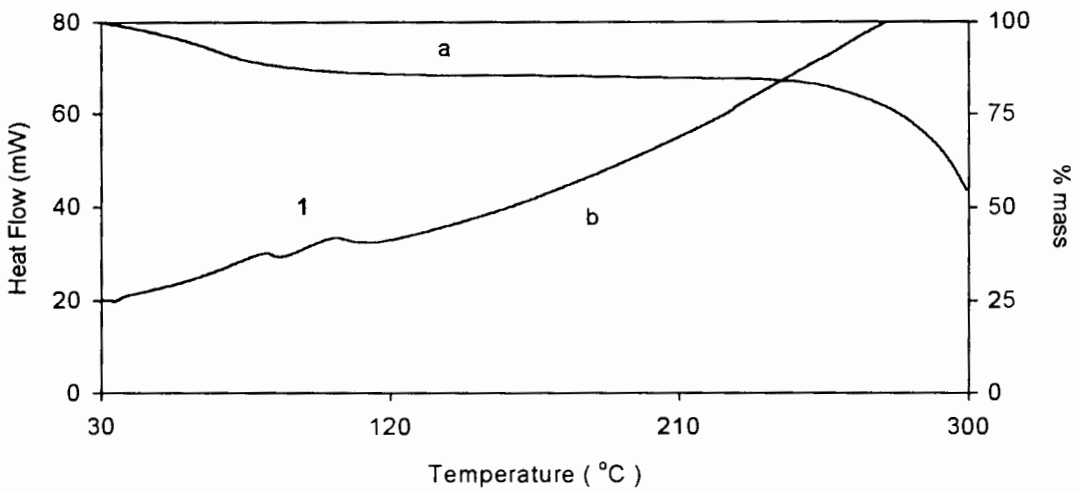


Sample mass for b = 5.534mg. Onset of peak 1 = 71.6°C.

continued....

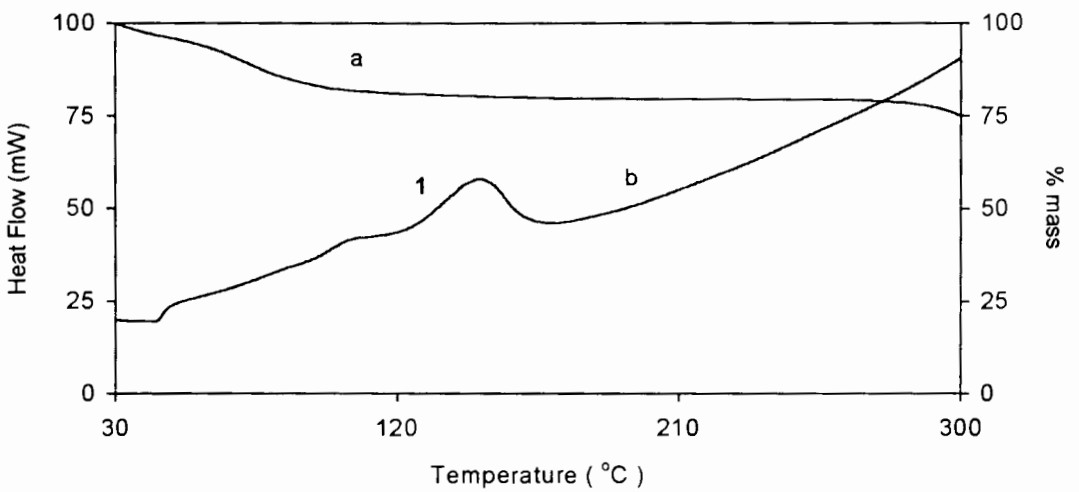
Fig. 3.6 continued

c. niflumic acid. (a) TGA and (b) DSC



Sample weight = 3.571mg. Onset of peak 1 = 62.4°C.

d. tolfenamic acid. (a) TGA and (b) DSC profile.



Sample mass for b = 7.412mg. Onset of peak 1 = 113.8°C.

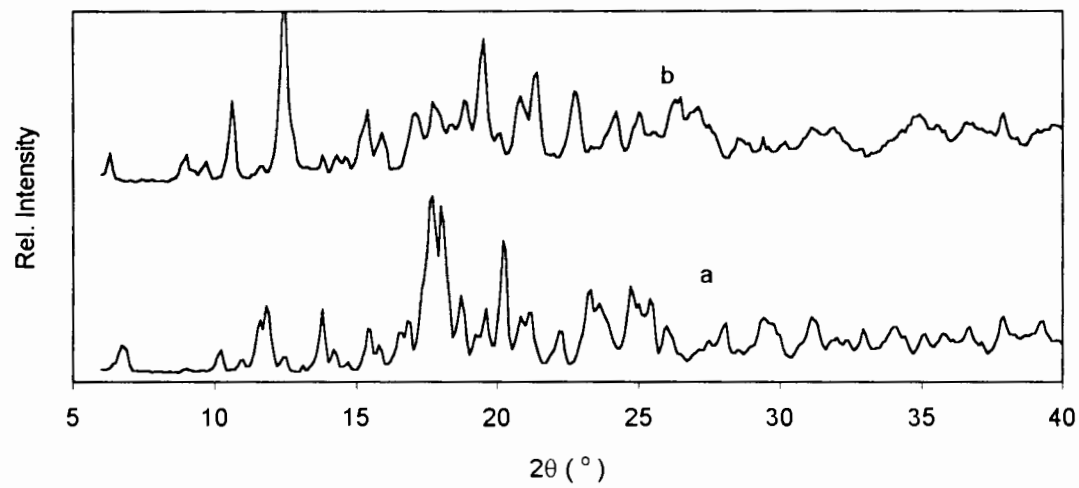
Table 3.4 Microanalysis results for 1:1 β-cyclodextrin-fenamate complexes†

	C		H		N	
	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
mefenamic acid	49.74	47.86	6.29	6.15	1.02	0.61
tolfenamic acid	48.14	47.54	5.87	5.79	1.01	0.66
niflumic acid	46.61	45.24	3.60	3.19	1.98	1.24
flufenamic acid	47.49	46.68	5.65	5.78	0.98	0.6

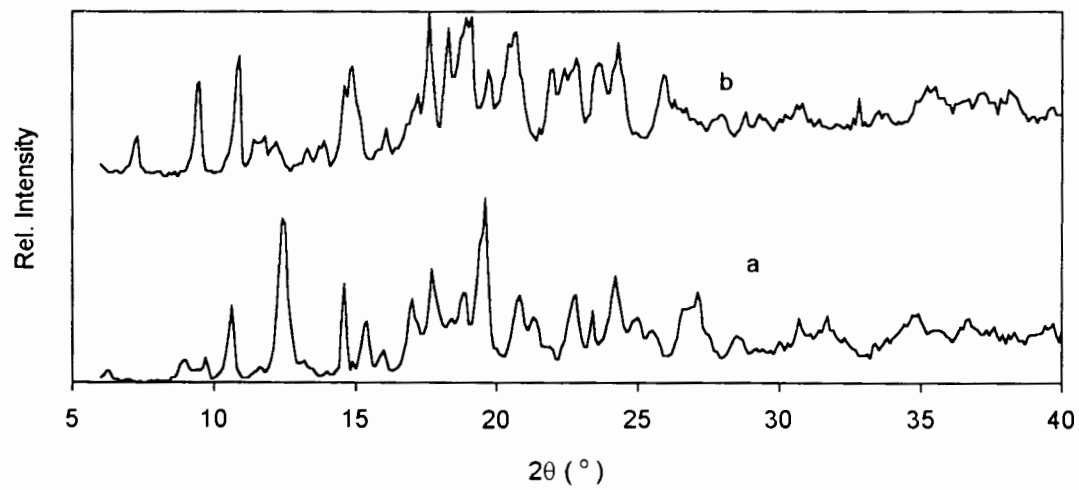
† Agreement between the observed and calculated values for each complex is not good and a number of factors may account for this, most notably the degree of hydration of each sample. This is discussed in Section 3.5.

Fig. 3.7 XRD for β-cyclodextrin complexes with fenamate NSAIDs.

a. mefenamic acid. (a) 1:1 physical mixture and (b) complex.



b. flufenamic acid. (a) 1:1 physical mixture and (b) complex.



Crystals of a suitable size for X-ray photography were obtained for the complex with tolfenamic acid. These crystallised as monoclinic parallelepipeds, with dimensions ranging from 0.1 to 0.5mm. They were labile to air and were required to be fully immersed in mother liquor in Lindemann capillaries for X-ray photography. Unit cell and space group data were obtained and are listed below in Table 3.5. The complex crystallises in the space group $P2_1$, based on the observation of Laue 2/*m* symmetry and the systematic absences *hkl*: none ; 0k0: *k*=2n+1 in oscillation and

Weissenberg photographs. The cell dimensions that were calculated for the complex are unique and have not been reported for other complexes with cyclodextrins. A screw axis parallel to the *b* axis implies the presence of three cyclodextrin molecules in the asymmetric unit though the arrangement of these units relative to each other cannot be ascertained without full structural analysis.

Table 3.5 Unit cell data for β-cyclodextrin - tolfenamic acid complex

Crystal system	monoclinic
Space group	$P2_1$
a (Å)	15.46
b (Å)	64.24
c (Å)	14.65
β (°)	129
V ($Å^3$)	11329
Z	6

The gross morphology of the β-cyclodextrin - tolfenamic acid is shown in Fig. 3.8a, and the behaviour of the complex with elevation of temperature is given in Fig. 3.8b. The crystals undergo similar visual changes to those observed with the β-cyclodextrin - piroxicam complex, with initial opacification due to loss of crystal water molecules, and then a discolouring and finally blackening of the complex that accompanies decomposition. The decomposed crystal does not melt until approximately 370°C. Crystals of the β-cyclodextrin - niflumic acid complex are shown in Fig 3.8d(ii). These crystals were too small and fragile for X-ray analysis.

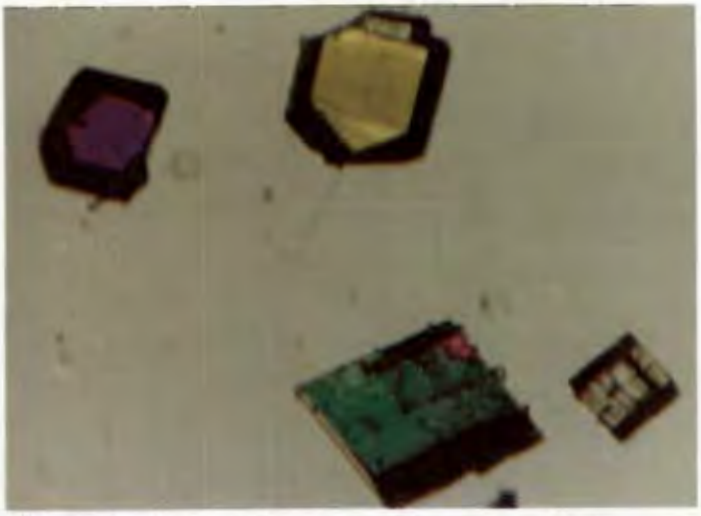
3.3 PROFENS

The most successful solid state complexations were achieved with the profens, specifically ibuprofen. The complexes of ibuprofen with β-cyclodextrin and TRIMEB are detailed in chapters 4 and 5. Unit cell data for those with γ-cyclodextrin and DIMEB are given in Table 3.6 below.

For the complex with γ-cyclodextrin, the observation of Laue 4/*mmm* symmetry, combined with systematic absences *hkl*: none ; *h*00: *h* = 2n+1, and the chiral nature of cyclodextrin, identified the space group as $P42_12$. The space group for the

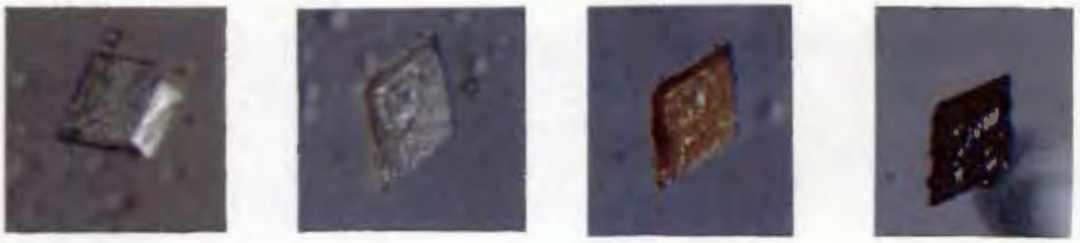
Fig. 3.8 Crystal morphology and hot stage microscopy for cyclodextrin complexes.

a. β-cyclodextrin - tolfenamic acid complex. (i) Crystal habit under polarised light, viewed parallel to the unique axis (clear and green crystals). Comparison is given to β-cyclodextrin (purple and yellow crystals). Magnification x45.

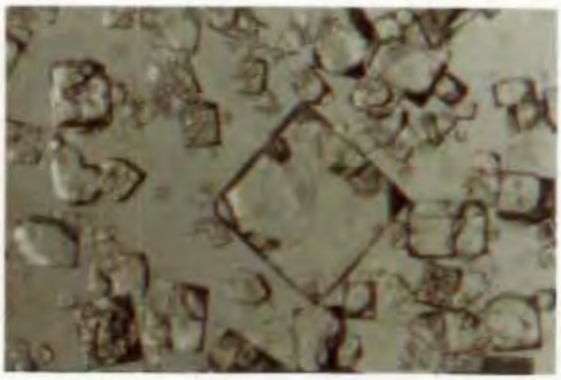


b. Behaviour of β-cyclodextrin - tolfenamic acid complex with temperature. Magnification x33.

(i) 30°C (ii) 75°C (iii) 280°C (iv) 330°C



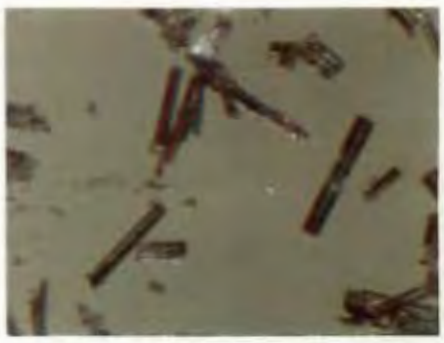
c. γ-cyclodextrin ibuprofen complex. Crystals immersed in mother liquor. Magnification x45.



d. (i) β-cyclodextrin - diflunisal complex and (ii) β-cyclodextrin - niflumic acid complex. Crystals immersed in mother liquor as viewed under polarised light. Magnification x45.

(i)

(ii)



DIMEB-ibuprofen complex was identified, based on observation of Laue *mmm* symmetry and the systematic absences *h*00: *h*=2n+1 ; 0*k*0: *k*=2n+1 ; 00*l*: *l*=2n+1, as $P2_12_12_1$.

Table 3.6 Unit cell data for ibuprofen complexes with γ-cyclodextrin and DIMEB

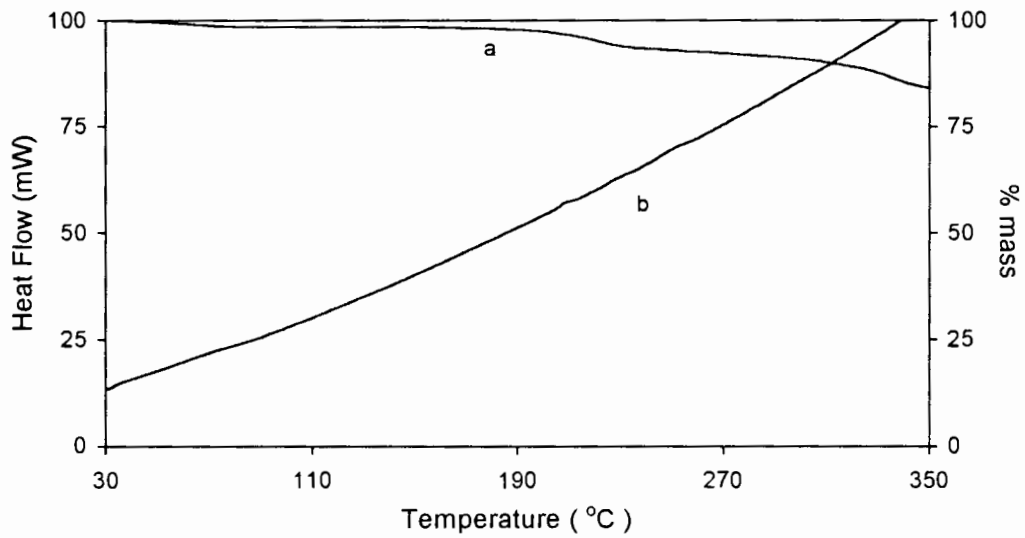
	γ-cyclodextrin	DIMEB
Crystal system	tetragonal	orthorhombic
Space group	$P42_12$	$P2_12_12_1$
a (Å)	23.7	10.1
b (Å)	23.7	15.3
c (Å)	45.9	53.6
V ($Å^3$)	25780	8280
Z	12	4

As outlined in section 1.5.2, the tetragonal arrangement of γ-cyclodextrin has been observed in all complexes reported to date, though the cell dimensions calculated for the complex with ibuprofen are unique. The tetragonal arrangement implies that all eight residues of the cyclodextrin are present in an identical conformation and the molecule is positioned on a four-fold axis parallel to *c*. The large cell volume and a *Z* value of 12 imply that six cyclodextrin molecules are stacked along the *c* axis, which is double the length of that recorded for other γ-cyclodextrin complexes. The asymmetric unit would contain six by one-eighth γ-cyclodextrin molecules, unlike three fractions as seen with other γ-cyclodextrin complexes characterised to date i.e. with *n*-propanol and the crown ether 12-crown-4[3,4]. The morphology of the crystals of the γ-cyclodextrin - ibuprofen complex is shown in Fig. 3.8c.

The cell data obtained for the complex with DIMEB are also unique. A number of crystal structures for DIMEB complexes have been reported to date, all crystallising in the orthorhombic space group $P2_12_12_1$[5,6,7,8,9]. Thermal analysis results for the complex with ibuprofen are shown in Fig. 3.9. Initial mass loss in TGA, corresponding to loss of crystal water, gives a total of one water molecule per DIMEB molecule. A second mass loss event of 4.75% from approximately

135-250°C is too small to reflect loss of guest, given a 1:1 stoichiometry in the complex, and cannot be explained with the results obtained.

Fig. 3.9 Thermal analysis for DIMEB - ibuprofen complex



Sample mass for b = 7.328mg.

Microanalysis results for the complexes of ibuprofen with γ-cyclodextrin and DIMEB indicated the possible formation of 1:1 complexes in the solid state. For the DIMEB complex, the obtained values for C and H were 54.36% and 7.67% respectively, as compared to calculated values of 53.87% and 7.79% respectively. The complex with γ-cyclodextrin gave values for C and H of 46.89% and 5.89% respectively, as compared to 48.70% and 6.52%. This latter result may not be conclusive of the formation of a 1:1 complex, as observed in the complex with piroxicam (Section 3.1.2), and this may be due to the alignment of the γ-cyclodextrin in channels and the possibility of the guest being disordered over a number of positions within these cavities (Section 1.4.7.2).

3.4 OTHER COMPLEXES

3.4.1 Diflunisal with β-cyclodextrin

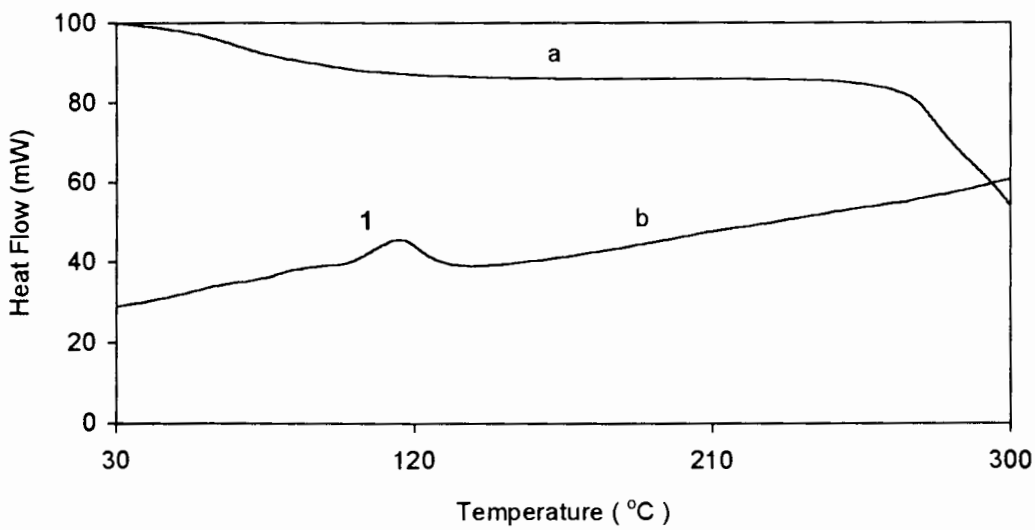
A complex of β-cyclodextrin with diflunisal was prepared as outlined in Table 3.1. Irregular hexagon-shaped crystals were obtained after overnight incubation at room

temperature, with a size range of 0.2 to 1mm and a thickness of 0.1 to 0.2mm. Most crystals appeared as thin plates fused together parallel to the thin axis and obtaining single crystals from the batches proved difficult. The morphology is shown in a photograph in Fig.3.8d(i).

Thermal analysis confirmed that a complex had been formed (Fig. 3.10). The crystals were unstable in air, due to loss of crystal water, and this is reflected by mass loss in TGA (Fig. 3.10a). A total mass loss of 14.4% was recorded from 30-190°C, corresponding to 13 waters of crystallisation per molecule of β-cyclodextrin, based on 1:1 stoichiometry obtained from microanalysis.

These results were confirmed by XRD, shown in Fig. 3.11, with a comparison made between the profile for β-cyclodextrin and that of the complex, showing suppression of the intensity peaks characteristic of β-cyclodextrin by complexation and the appearance of new peaks for the complex.

Fig. 3.10 **Thermal analysis for β-cyclodextrin - diflunisal complex.**
(a) TGA and (b) DSC



Sample mass for b = 13.411mg. Onset of peak 1 = 92.3°C.

Microanalysis results for the complex indicated the possible formation of a 1:1 complex. The obtained values of C and H were 40.29% and 5.58% respectively. This compares to calculated values of 39.74% and 5.63% for a 1:1 complex. This is

consistent with results obtained for complexation of diflunisal by β-cyclodextrin in solution[10]

Unit cell data and space group information were obtained for the complex from inspection of oscillation, Weissenberg and Buerger precession photography, and are tabulated in Table 3.7. The complex crystallises in the orthorhombic space group $P2_12_12_1$, as identified from Laue *mmm* symmetry and systematic absences as outlined for the DIMEB-ibuprofen complex, and the calculated unit cell volume, giving a *Z* value of 8, suggests that the cyclodextrin crystallises with a dimer in each asymmetric unit.

Fig. 3.11 XRD for β-cyclodextrin - diflunisal complex.
Trace for (a) β-cyclodextrin and (b) for complex.

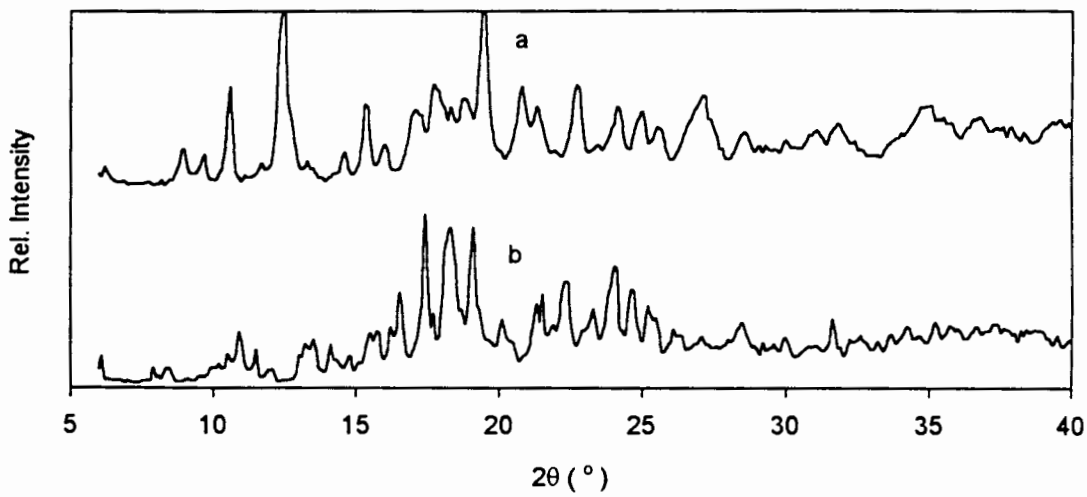


Table 3.7 Unit cell data for β-cyclodextrin - diflunisal complex

Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	15.4
b (Å)	29.0
c (Å)	29.7
V ($Å^3$)	13240
Z	8

3.5 DISCUSSION

A number of complexes were successfully prepared using the methods outlined in Sections 2.1 and 2.2. It was not possible to predict whether a host was suitable for a particular guest compound, despite the application of varying changes to the reaction conditions that might enhance complex formation.

The main aim of these experiments was to produce solid state complexes, preferably suitably-sized single crystals for X-ray structure analysis and a number of complexes were obtained during the course of experimental work that were not fully characterised as detailed characterisations have been reported in a number of instances e.g. β-cyclodextrin with indomethacin and with ketoprofen[11,12,13,14]. In certain instances, insufficient sample could be obtained for thorough analysis such as the γ-cyclodextrin complexes with the fenamates.

As has been mentioned in Section 1, the precipitation of a solid-state complex is dependent in large part on the solubility of the complex in comparison to the saturation concentrations of host and guest. Most of the NSAIDs used are practically insoluble in water, and continual stirring of a hot cyclodextrin solution over a long period was often not sufficient to bring the guest into solution. Adjustment of pH was used in the majority of cases i.e. a more basic environment to ionise the acidic NSAID molecule. Ionisation of a guest can however impede complexation, due in part to an increase in the possibility of interactions between the polar moiety on the guest and water molecules, thus affecting the stability constant as well as the solubility of the complex in solution.

The stability constant for complexation in solution, as well as the phase solubility profile for a particular cyclodextrin and drug interaction are important in determining the rate of complexation and dissociation of the complex in solution as well as whether the complex that has formed will crystallise. Values for these constants have been noted from previous studies[14].

The complexation of piroxicam in solution with β-cyclodextrin possesses a stability constant value (K_c) of $90M^{-1}$, while β-cyclodextrin - ibuprofen has a K_c value[14] of $1030M^{-1}$. Difficulty was observed in achieving the effective uptake of piroxicam into

solutions of β-cyclodextrin. Crystals of the piroxicam complex were very slow to appear (over a month) while those of the ibuprofen complex appeared relatively soon after reaction (24-36 hours) as discussed in Section 4. The complex with piroxicam follows a A-type phase solubility profile, forming a soluble complex, while the complex with ibuprofen follows a B-type solubility profile and would thus precipitate at an established solubility limit (Section 1.4.4). Crystals of the complex of γ-cyclodextrin with piroxicam have a slightly higher value for K_c and more of the drug was brought into solution during reaction time. Crystals were obtained more easily than crystals of the β-cyclodextrin complex[14].

The size of the guest may also inhibit or promote complexation. Only β- and γ-cyclodextrin, and derivatives of β-cyclodextrin, were used, due to the size of the NSAIDs under investigation. The cavity of α-cyclodextrin would be too small and complexes were not prepared using this cyclodextrin, and stability constants for complexes with NSAIDs are generally lower than for β-cyclodextrin. Complexation appeared to occur more readily with γ-cyclodextrin, though yields were often too low and crystals too small for complete characterisation to be possible. This may be due to the much greater aqueous solubility of γ-cyclodextrin and the complexes that were formed. Complexes were not isolated for any of the cyclodextrins with a large guest such as sulindac, but success was had with smaller molecules such as ibuprofen and the fenamates.

Another observation was the relative difficulty in forming complexes with the methylated cyclodextrins. Complexes were prepared with all the fenamates under investigation and β-cyclodextrin though none could be isolated with DIMEB and TRIMEB. This may be due to the incubation conditions for crystallisation. These derivatives crystallise within a narrow temperature range and the environment may have been imperfect for crystallisation to occur. Furthermore, the cavities of DIMEB and TRIMEB are deeper than that of β-cyclodextrin (11Å and 8Å respectively), and the cavities are more distorted in the uncomplexed state, which may impede the insertion of the guest.

Complex stoichiometries have been determined where possible using microanalysis. The results were fairly conclusive, though there is a margin for error based on the relatively large molecular mass of the host compounds as compared

to the guests. The hygroscopic properties of the complexes analysed also posed difficulties when attempting to obtain accurate results. Samples were used as extracted from crystallisation vials and TGA performed to establish the water content as a percentage of the sample mass. Stoichiometry was calculated from microanalysis results using the percentage of water in the sample and values for the content of C, H, N and S then calculated for each sample. In other cases the sample was first dehydrated using TGA before microanalysis was performed, with a second TGA result being used to measure any uptake of atmospheric water during the course of analysis.

Using these results it was possible to calculate the number of waters of crystallisation for each complex based on mass loss as measured using TGA. All complexes except that of TRIMEB with ibuprofen contain water molecules in the interstices between cyclodextrins in the crystal lattice and interact through hydrogen bonding with the OH groups on the primary and secondary rims of the cyclodextrin molecule. The relatively hydrophobic environment of the methylated cyclodextrin crystal structures generally excludes water molecules.

Unit cell data were obtained for a number of complexes. The cell dimensions recorded are unique for the complexes of β-cyclodextrin with piroxicam, tolfenamic acid and diflunisal, and for γ-cyclodextrin and DIMEB with ibuprofen. For these complexes, however, it was not possible to collect X-ray intensity data and attempt any solution of the crystal structure despite repeated efforts, due to a number of factors, such as inferior crystal quality and the sometimes large unit cell volumes that were calculated from X-ray photography. These dimensions do however suggest a possible extension to the number of different modes of crystal packing of cyclodextrin complexes in the solid state.

3.6 REFERENCES

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4. COMPLEX OF β-CYCLODEXTRIN WITH IBUPROFEN

4.1 PREPARATION OF COMPLEX

Crystalline complexes of β-cyclodextrin with racemic and (S)-ibuprofen were prepared using equimolar ratios in aqueous solution. Ibuprofen is insoluble in water but has a relatively low melting point of 75-77°C (50-54°C for the (R)- and (S)-isomers) and was more easily brought into solution than other NSAIDs by raising the temperature of the reacting solution to 75-80°C[1]. The resulting solution was incubated at 50-65°C, with the incubation temperature being varied in an effort to control the standing time for crystallisation and produce crystals of adequate size for X-ray analysis. A temperature of 50-55°C was found to be optimal, with crystals ranging in size from 0.2 to 1mm being obtained. Allowing the reaction solution to cool or evaporate more rapidly produced a microcrystalline powder complex that was used in X-ray powder diffraction.

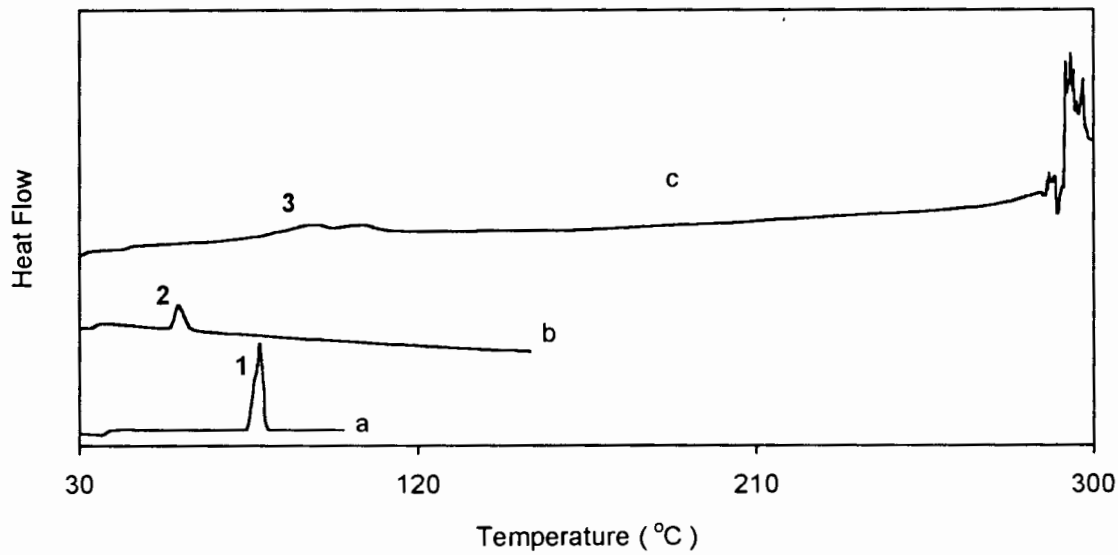
4.2 THERMAL ANALYSIS

TGA and DSC profiles obtained for the complexes with racemic and (S)-ibuprofen are shown in Fig. 4.1. Crystals removed from the mother liquor exhibited rapid cracking of the crystal surface on the hot stage microscope as a result of the loss of loosely bound interstitial water, shown by a steep mass loss in the initial stages of TGA as compared to that seen with β-cyclodextrin.

The overall percentage mass loss with temperature was 13.5% from 30-120°C. Microanalysis results for the complex indicated the presence of 48.95% C in a dehydrated sample as compared to a calculated value of 49.21% for a 1:1 complex. The mass loss in TGA thus corresponded to 12 waters of crystallisation per cyclodextrin molecule. This is represented in the DSC trace as a broad two-stage endothermic peak over a temperature range of 60-120°C, suggesting the loss of more loosely bound water molecules in the first stage of dehydration. Suppression of the melting endotherms for racemic and (S)-ibuprofen [Fig. 4.1(i)-a and -b respectively] gives proof of the formation of a complex. The onset of degradation of the complex is indicated at approximately 280°C.

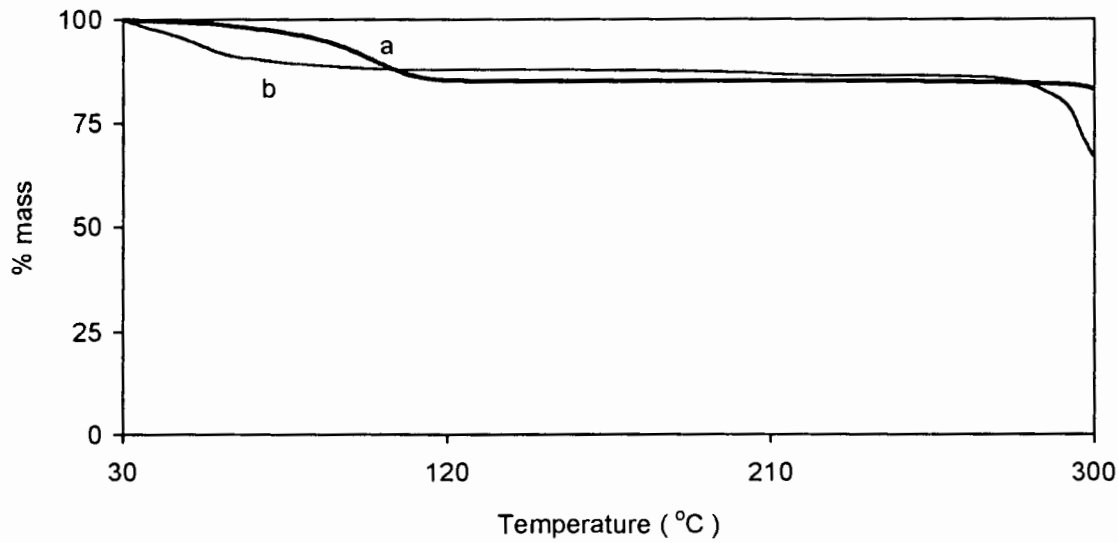
Figure 4.1 Thermal analysis for β-cyclodextrin - ibuprofen complex.

(i) DSC profile for (a) racemic and (b) (S)-ibuprofen and (c) for complex prepared with racemic ibuprofen.



Sample mass for a = 3.943mg, for b = 2.814mg and for c = 3.481mg.
Onset of peak 1 = 75.9°C, for peak 2 = 54.3°C and for peak 3 = 64.3°C

(ii) TGA for (a) β-cyclodextrin and (b) complex with racemic ibuprofen.



The morphology of the crystal and the behaviour with temperature are shown in photographs obtained from the hot stage microscope in Fig. 4.2 below. The crystallographic *b* axis runs parallel to the long diagonal (Fig. 4.2a). The crystal begins to opacify almost immediately after removal from mother liquor, and this is related to the steep initial mass loss seen on TGA (Fig. 4.1(ii)-b). The crystal begins to decompose at 280°C when the crystal begins to brown, and final melting and decomposition occur from 340°C onwards.

4.3 X-RAY POWDER DIFFRACTION

Powder samples of complexes containing β-cyclodextrin with either racemic or (S)-ibuprofen were prepared as outlined above. XRD profiles were obtained and compared with those for native β-cyclodextrin in an effort to further demonstrate the formation of a complex and the suppression of peaks characteristic of ibuprofen and β-cyclodextrin, as seen in the trace obtained for the 1:1 physical mixture of the two components (Fig. 4.3a and b).

The physical mixture of host and guest was composed according to results obtained for microanalysis, which indicated the formation of a 1:1 complex. The experimental values for C and H composition were 48.84 and 5.94% respectively, which compares reasonably with calculated values of 49.24% and 6.56%. This result is partially confirmed by crystal structure analysis.

A comparison with the XRD traces for the complex with (S)-ibuprofen shows a similarity in profiles that indicates the formation of isomorphous complexes with the racemate and pure isomer. The crystals exhibited identical morphology, and thermal behaviour under the hot stage microscope and with TGA and DSC was similar.

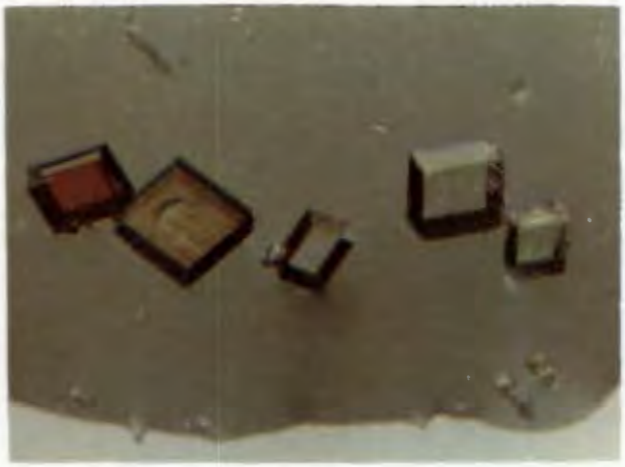
4.4 X-RAY ANALYSIS

4.4.1 Data collection and refinement

A crystal of suitable size was extracted from a batch of complex crystals prepared with β-cyclodextrin and racemic ibuprofen. The crystals formed were colourless prismatic parallelepipeds. A polarising microscope and oscillation photography

Fig. 4.2 Complex morphology and hot stage microscopy.

a. Crystals of β-cyclodextrin - (RS)-ibuprofen complex immersed in mother liquor as seen under polarised light. The unique axis is parallel to the long diagonal. Magnification x45.



b. Hot stage microscopy for complex. The crystal is photographed at 30°C, 50°C, 90°C, 280°C and 340°C. Opacification begins almost immediately after removal from mother liquor, with degradation commencing at 280-300°C. The complex fuses at 340°C. Magnification x33.

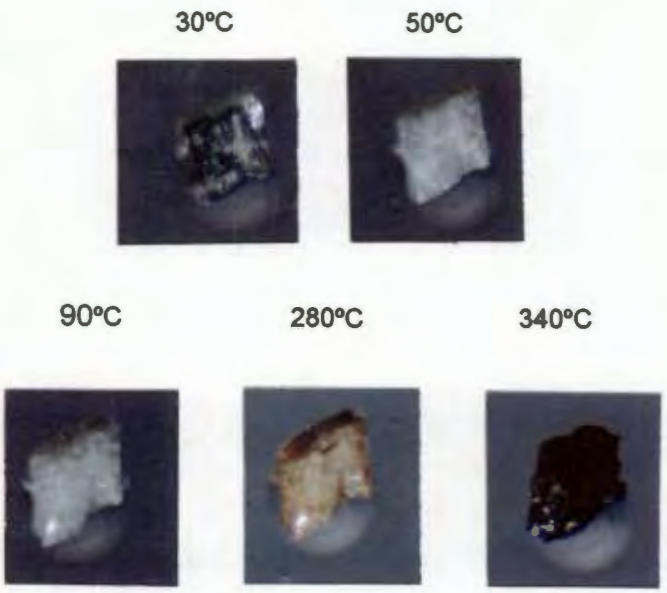
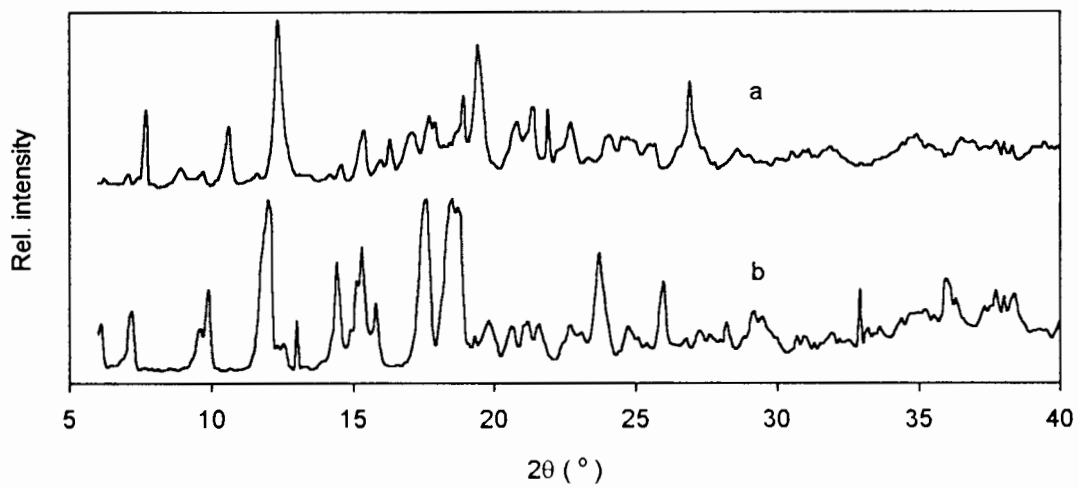
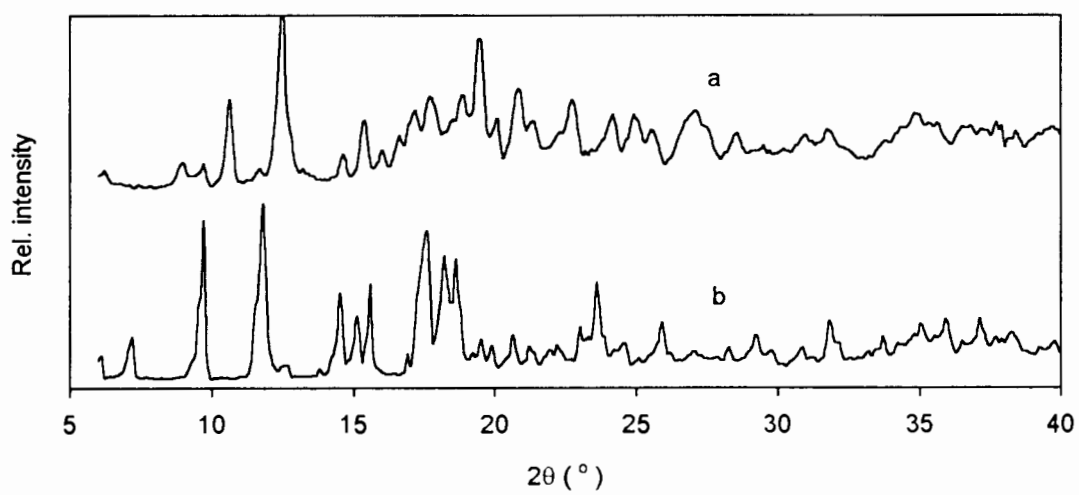


Fig. 4 3 XRD for β-cyclodextrin - ibuprofen complex

(i) XRD for β-cyclodextrin - (S)-ibuprofen. (a) 1:1 physical mixture and (b) complex.



(ii). XRD for β-cyclodextrin - (RS)-ibuprofen. (a) 1:1 physical mixture and (b) complex.



were used to determine and align the axis of symmetry. The crystals are highly unstable to air and were sealed in Lindemann capillaries, fully immersed in mother liquor. Oscillation and Weissenberg photographs showed Laue 2/*m* symmetry, and the systematic absences *hkl*: *h*+*k*=2n+1 ; *h*0*l*: (*h*=2n+1) ; 0*k*0: (*k*=2n+1), together with the absence of possible mirror planes or centres of inversion, due to the chiral nature of the cyclodextrins, confirmed the space group to be monoclinic centred C2.

The cell dimensions obtained were *a*=19.41Å, *b*=24.41Å and *c*=15.92Å (β=108.9°). This is isomorphous with a number of other β-cyclodextrin complexes with small molecular weight compounds such as potassium heptaiodide[2], benzophenone[3], biphenyl[3], 2,5-diiodobenzoic acid[4] and 3,3-dimethylbutylamine[5].

A crystal of 0.5x0.4x0.4mm was extracted from a crystallisation vial containing complex prepared with racemic ibuprofen, dried and rapidly sealed in cyanoacrylate before cracking of the crystal surface and subsequent loss of crystal integrity was allowed to occur. The sealed crystal was then attached with glue to the end of a glass fibre, sealed in a Lindemann capillary and mounted on a goniometer head. The choice of cyanoacrylate seal above immersion in mother liquor in a capillary tube was determined by the desire to collect intensity data at temperatures below 0°C, as well as the possibility of diffraction from the mother liquor which could interfere with that from the crystal.

The crystal was mounted on an Enraf-Nonius CAD4 diffractometer and intensity data were collected at 248K, as detailed in Section 2.7. Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections lying in the range $16°<\theta<17°$. The ω-scan technique was used and a pre-scan acceptance parameter of zero was chosen to force the final intensity scans up to a maximum of 100s, to ensure accurate measurement of weak reflections. Data were collected to $(\sin\theta/\lambda)_{max}$=0.595Å^{-1}. Three standard reflections were monitored hourly in the range of $15°<\theta<16°$ (13 5 1;8 12 4;7 7 7) and showed a loss of intensity of 0.8% over the period of the data collection. Orientation control was performed every 200 reflections. Data were corrected for Lorentz-polarisation effects. Data collection details are outlined in Table 4.1.

4.4.2 Structure solution

Coordinates for the non-hydrogen atoms of the cyclodextrin host in the isomorphous 3,3-dimethylbutylamine complex were used for structure solution[5] . Refinement of these atoms with full-matrix least-squares techniques [minimisation of $\Sigma w(|F_o^2|-|kF_c^2|)^2$] was performed using SHELX93[6], with subsequent successive difference Fourier syntheses being applied to reveal the positions of the atoms of the guest molecule and the waters of crystallisation present in the lattice.

All atoms of the cyclodextrin molecule were located with a site occupancy factor of 1.000, except O(6G4) which occupies two positions with site occupancies of 0.65 and 0.35, and O(6G6), which displayed high thermal motion though it occupied only one site. All atoms were assigned anisotropic temperature factors after a number of cycles of refinement. Hydrogen atoms attached to the carbon atoms on the cyclodextrin were inserted at idealised positions (C-H=0.98Å for methine groups and 0.97Å for methylene groups) and assigned a common variable isotropic temperature factor, excepting for C(6G4) where the hydroxyl group is disordered over two sites. A total of 12 water molecules of crystallisation were located and refined, some with anisotropic temperature factors. The guest could not be located beyond a diffuse electron density cloud located within the cyclodextrin cavity and could not be modelled, due to abnormal distances and angles between electron density peaks. Details of the structure refinement are given in Table 4.1 below and supplementary data such as atomic coordinates, temperature factors, bond lengths and angles, and torsion angles are presented in Appendix A. A listing of observed and calculated structure factors for the complex, given as F_o^2 and F_c^2, together with standard deviations for the observed structure factors, is given in Appendix C on disk, in ASCII format as filenames BETIBUP1.ASC and BETIBUP2.ASC.

4.4.3 Geometry and hydrogen bonding

The structure of the cyclodextrin molecule and the numbering scheme adopted for the complex, with the conformation and numbering scheme for each glucose moiety, are given in Fig. 4.4. All the glucose subunits are present in the $^4C_1$-conformation. Except for unit G4, all C($6G_n$)-O($6G_n$) bonds lie *gauche* to bonds C($4G_n$)-C($5G_n$) and O($5G_n$)-C($5G_n$), and are directed away from the cavity. The O(6) atom of G4 occupies two positions, a minor position [O(64A)] that points away from the cavity and a major position [O(6G4)] that points inward. The C(6)-O(6) bond is *gauche* to O(5)-C(5) and *anti* to C(4)-C(5).

The macrocycle shows a seven-fold symmetry based on O(4_n)···O(4_{n+1}) distances and O(4_{n-1})···O(4_n)···O(4_{n+1}) angles. These are given in Table 4.2a below, together with values for the deviation of each O(4) atom from the heptagon formed by all O(4) atoms. The similarity in O(4) lengths and angles, and the relatively small deviations indicate that a highly rigid conformation is adopted by the β-cyclodextrin molecule.

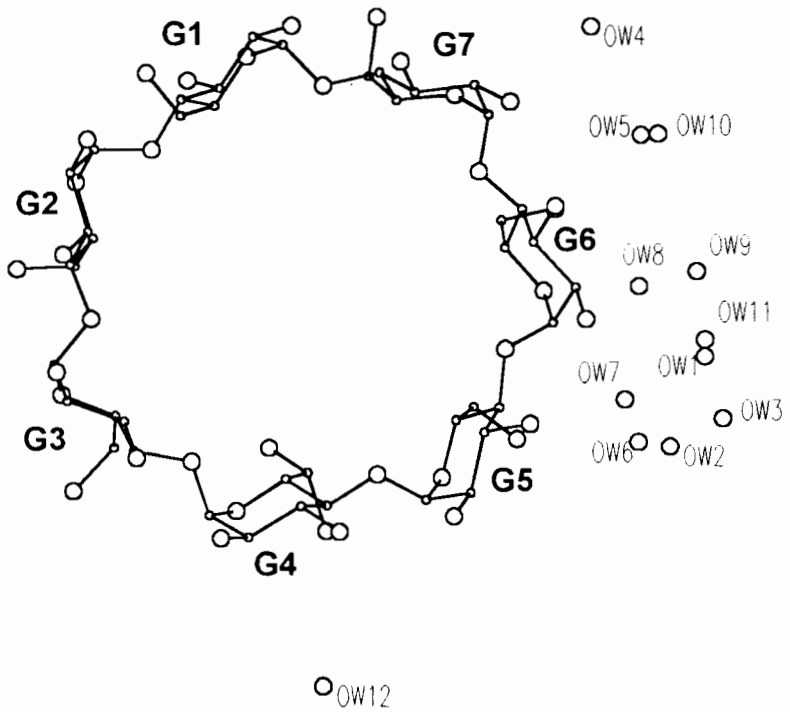
Table 4.1: Data collection and refinement details for 1:1 β-cyclodextrin-(RS)-ibuprofen complex

Molecular formula	$C_{42}H_{70}O_{35}.C_{13}H_{18}O_2.12H_2O$
M_r / $gmol^{-1}$	1557
Crystal system	Monoclinic
Space group	C2
Z	4
a (Å)	19.41(1)
b (Å)	24.41(2)
c (Å)	15.92(1)
β (°)	108.89(6)
V ($Å^3$)	7133(9)
D_c (gcm^{-3})†	1.242
Crystal dimensions (mm)	0.5x0.4x0.4
T/K	248
Range scanned θ (°)	$1 \leq \theta \leq 25$
Index range	h:0,23; k:0,28; l:-18,17
Scan width	0.8 + 0.35 tan θ
Aperture width (mm)	1.12 + 1.05 tan θ
No. reflections collected	6657
No. unique reflections	6451
No. reflections with $I > 2\sigma(I)$	4853
No. L.S. parameters	768
R1 ($I > 2\sigma(I)$)	0.111
w	$[\sigma^2(Fo)^2+(0.2770P)^2]^{-1}$ where $P = (F_o^2+2F_c^2)/3$
wR2 (F^2)	0.275
S	1.073
Shift.e.s.d. max., ave.	1.342, 0.087
$(\Delta\rho)_{max}$ final ($e Å^{-3}$)	1.31
$(\Delta\rho)_{min}$ final ($e Å^{-3}$)	-0.27

† An experimental value for the crystal density was not obtained as a suitable solvent mixture could not be found.

Fig. 4.4 Structure of β-cyclodextrin - ibuprofen complex.

a. Macrocyclic structure and numbering system of glucose residues and water oxygen molecules. Hydrogen atoms are excluded.



b. Numbering scheme and configuration for glucose moiety. C atoms are represented by numbers only.

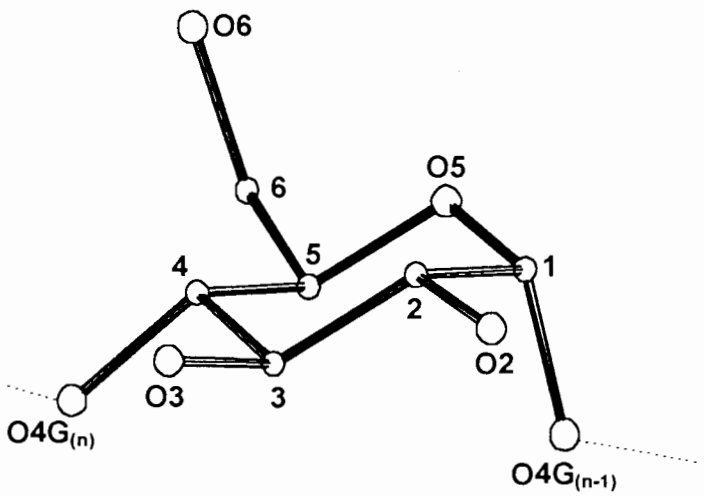


Table 4.2 Geometrical data for β-cyclodextrin.

a. Conformation of O(4) heptagon

	Glycosidic oxygen angle (°)[a]	$O(4_n)\cdots O(4_{n+1})$ distance (Å)	$O(4_{n-1})\cdots O(4_n)\cdots O(4_{n+1})$ angle (°)	Deviation[b] (Å)
G1	118.3	4.37	130.5[d]	-0.009(4)
G2	119.3	4.23	124.6	0.019(4)
G3	118.5	4.53	128.4	-0.024(4)
G4	117.4	4.34	132.2	0.012(4)
G5	120.0	4.34	125.9	0.007(4)
G6	116.5	4.34	127.1	-0.015(4)
G7	119.1	4.46[c]	130.8[e]	-0.012(4)

[a] The angle subtended at the (O)4 atom i.e. the angle between $C(4G_n)$,$O(4G_n)$ and $C(1G_{n+1})$. For G7, the angle is defined between C(4G7), O(4G7) and C(4G1).
[b] The deviation of the O(4) atom from the least squares plane formed by all O(4) atoms.
[c] The distance O(4G7)···O(4G1).
[d] The angle formed by O(4G7)···O(4G1)···O(4G2).
[e] The angle formed by O(4G6)···O(4G7)···O(4G1).

b. Tilt angles and torsion angle indices for glucose subunits.

	Radius of heptagon (Å)[a]	Tilt angle (°)		Torsion angle index[d]
G1	4.96	12.0[b]	80.4[c]	120.6
G2	5.21	12.0	80.4	121.9
G3	4.99	7.9	84.7	115.8
G4	4.86	15.6	76.6	114.4
G5	5.17	13.2	80.2	111.0
G6	5.15	10.6	82.0	116.6
G7	4.93	6.9	86.0	112.7

[a] The average value of the distance of each O4 atom from the centre of gravity of all O(4) atoms = 5.04Å.
[b] The dihedral angle between the O(4) plane and the optimum plane through $O(4_{n-1})$, $C(1_n)$, $C(4_n)$ and $O(4_n)$.
[c] The dihedral angle between the O(4) plane and the optimum plane through $C(2_n)$, $C(3_n)$, $C(5_n)$ and $O(5_n)$.
[d] As defined in section 1.5.2.

The shape of the macrocycle is defined by the tilt angles in Table 4.2b. The dihedral angles between the plane of the macrocycle and the optimum planes that define the relative position of each glucose subunit show that all have a positive tilt angle and lean toward the centre of the cavity. This gives the molecule the characteristic truncated cone appearance with the O(2), O(3) - rim being wider than the O(6) rim.

A number of intramolecular $O(3G_n)\cdots O(2G_{n+1})$ hydrogen bonds stabilise the cyclodextrin, as has been reported with other β-cyclodextrin structures. The average hydrogen bonding distance is 2.84(1)Å, and the average of the angles $C(3G_n)\text{-}O(3G_n)\cdots O(2G_{n+1})$ and $C(2G_{n+1})\text{-}O(2G_{n+1})\cdots O(3G_n)$ are 116.4° and 118.6° respectively, which are within the range required for hydrogen bonding (Table 4.3). These hydrogen bonds contribute to the rigidity and highly symmetrical conformation of the cyclodextrin.

Table 4.3 Intramolecular hydrogen bonds for β-cyclodextrin.

	Bonding distance[a] (Å)	C(3)-O(3)···O(2') angle[b] (°)	C(2')-O(2')···O(3) angle[c] (°)
G1	2.82(1)	117.8	118.5
G2	2.84(1)	115.8	117.3
G3	2.87(1)	115.2	119.4
G4	2.82(1)	117.8	117.7
G5	2.86(1)	116.7	116.8
G6	2.76(1)	116.6	117.9
G7	2.78(1)	115.7	121.7
Average	2.82(1)	116.5	118.5

[a] The distance between $O(3G_n)$ and $O(2G_{n+1})$.
[b] Angle as defined in the text above.
[c] Angle as defined in the text above.

The β-cyclodextrin molecule crystallises as a dimer in the crystal, as evidenced by the formation of hydrogen bonds between O(3) atoms on adjacent cyclodextrins related by a two-fold rotation axis parallel to *b*. The lengths and angles for these bonds are given below in Table 4.4, and the arrangement is shown schematically in Figure 4.5.

The $O(2G_n)\cdots O(3G_{8-n})$ distances average 3.11Å, and the $C(2G_n)\text{-}O(2G_n)\cdots O(3G_{8-n})$ angle has an average value of 112.6°, and this could signify the formation of weak

Table 4.4 Intradimer hydrogen bonds for β-cyclodextrin dimer.

	Bonding distance (Å)[a]	Angle (°)[b]
G1	2.83(1)	116.0
G2	2.85(1)	116.7
G3	2.72(1)	118.3
G4	2.82(1)	115.8
G5	2.72(1)	113.3
G6	2.85(1)	116.7
G7	2.82(1)	118.7
Average	2.80(1)	116.5

[a] The distance $O(3G_n)\cdots O(3G_{8-n})'$, related by the symmetry operator -x, y, -z+1.
[b] The angle $C(3G_n)\text{-}O(3G_n)\cdots O(3G_{8-n})'$.

Fig. 4.5 Arrangement of β-cyclodextrin dimer. The O(2),O(3) face is designated by larger circles. Water molecules and hydrogen atoms are shown. View is down [010], showing generation of the dimer by the two-fold rotation axis parallel to *b*.

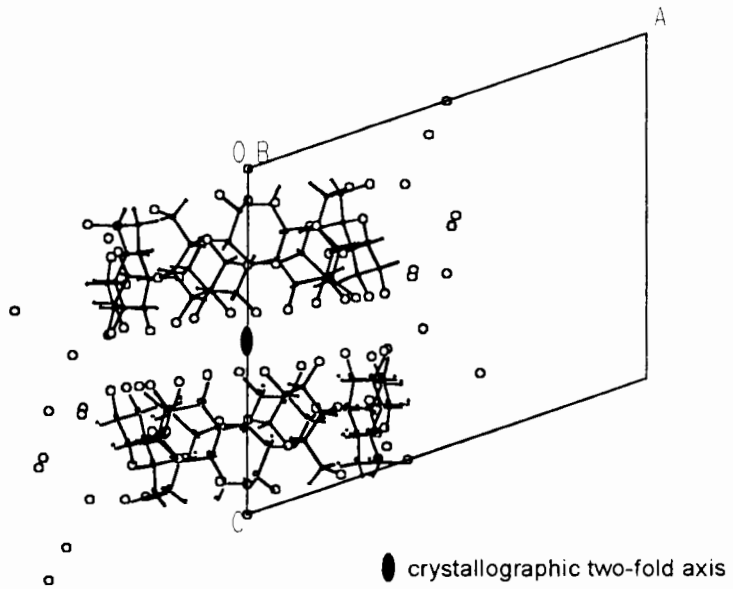
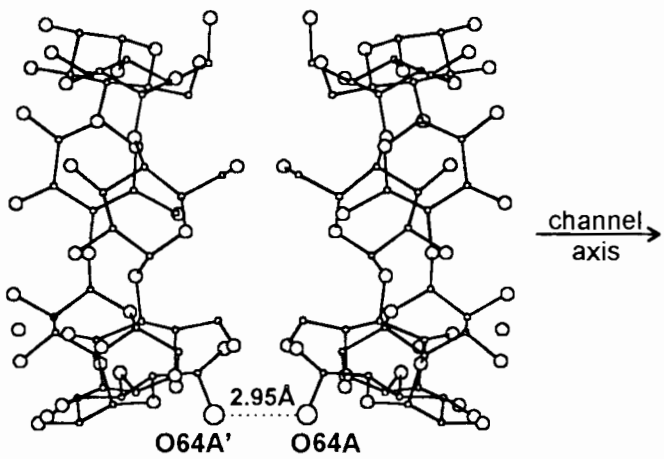


Fig. 4.6 **Hydrogen bonding between adjacent dimers parallel to *c* axis.** Head-to-head cyclodextrin molecules are related by a two-fold axis parallel to *b* along a channel axis parallel to *c*. The symmetry operation for O(64A)' is -*x*,*y*,-*z*. Water molecules are not shown.



hydrogen bonds. The angle C($3G_{8-n}$)-O($3G_{8-n}$)···O($2G_n$), however, has an average value of 159.7°, and though this is large it cannot be said that no hydrogen bonding occurs between these two OH groups in the dimer. No O($2G_n$)···O($2G_{8-n}$) hydrogen bonds are found in the complex either, despite some favourable distances.

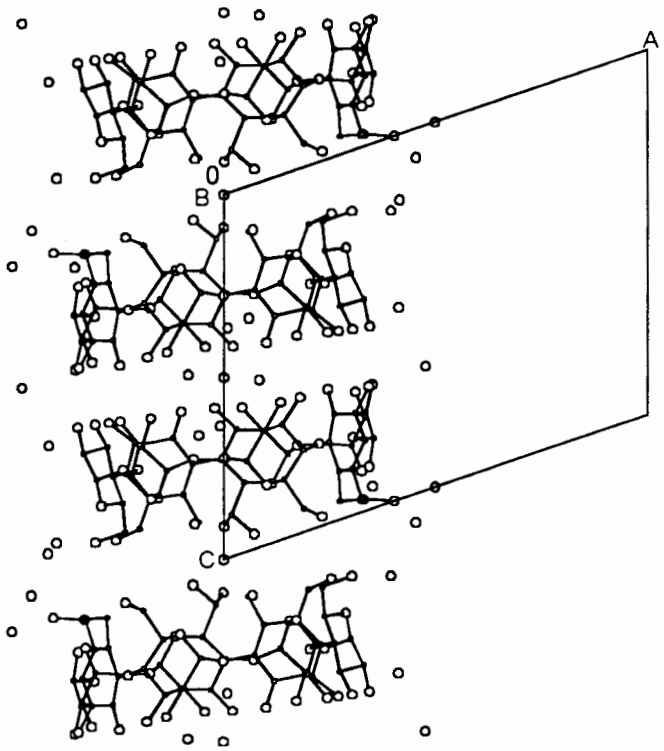
The dimers are arranged in C-centred layers and these layers are held together via a hydrogen bonding network through water molecules that link dimers within a layer and dimers of one layer to those of adjacent layers. The dimers are stacked upon each other parallel to the *c* axis to form channels. Direct hydrogen bonding between adjacent O(6) layers along the channel is found only with the minor position of O(6G4), which is bonded to a symmetry-related O(64A) atom (Fig. 4.6). The length of the bond is 2.95(5)Å, with an angle C(6G4)-O(64A)···O(64A)' of 105.7°.

Other interdimer hydrogen bonds are directed towards dimers positioned in the same layer. The hydrogen bonding distance O(2G5)···O(2G7)' is 2.73(1)Å, with an angle C(2G5)-O(2G5)···O(2G7)' of 111.1°[†]. Two hydrogen bonds between the O(6) rims of neighbouring cyclodextrin molecules lying parallel to the *xy*-plane are bonds

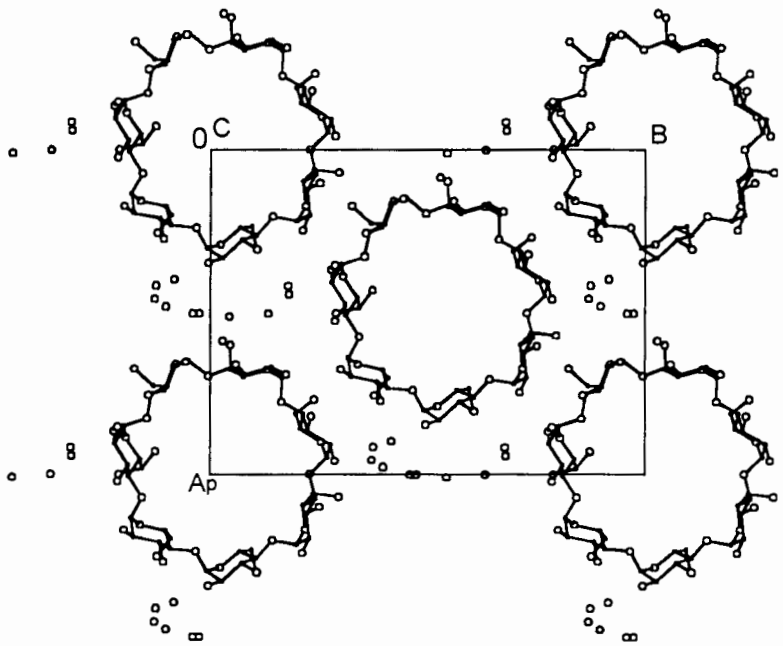
[†] The symmetry operation is -*x*+1/2, *y*-1/2, 1-*z*.

Fig. 4.7. Channel packing arrangement of complex.

a. View down [010].



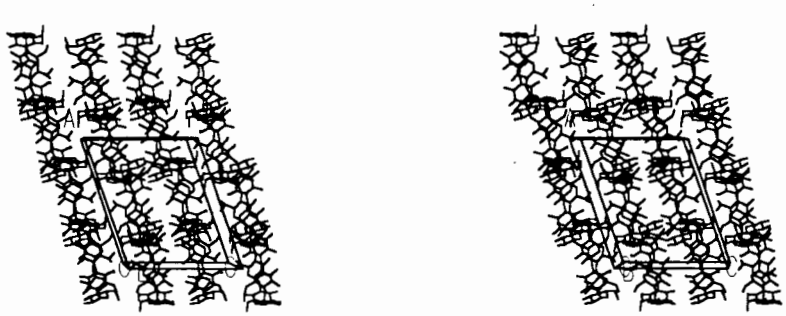
b. View down [001], showing centering parallel to the *xy* plane.



extending from (i) O(6G1)···O(6G3)" and (ii) O(6G3)···O(6G7)"'[††] . The angle for (ii) may be too large but could satisfy the conditions for hydrogen bonding.

A scheme showing the packing of β-cyclodextrin dimers in channels and the C-centering condition is given in Figures 4.7a and 4.7b respectively. Adjacent dimers that are projected along the *xy*-plane are displaced by 3.03Å relative to the axis of the channel which is almost exactly parallel to *c*. These dimers form infinite planes (Fig.4.8), with the channels and layers being connected to each other by a hydrogen bonding network through water molecules.

Fig. 4.8 **Formation of layers by cyclodextrin channels parallel to the *xy*-plane.**



Two networks of water molecules form hydrogen bonds to primary and secondary hydroxyl groups (Table 4.5). One water molecule, O(W11), does not bond directly to a cyclodextrin molecule but is connected to other water molecules. The water molecules that interact with the O(6) rim of the cyclodextrin - O(W1),O(W2), O(W4), O(W7), O(W8) and O(W12) - form bridges between adjacent dimers in the same layer, while those that interact with the O(2),O(3) rim - O(W3), O(W5), O(W6), O(W9), O(W10) and O(W11) indirectly - form part of an infinite sublayer of water molecules that runs between the cyclodextrin channels. There are no water molecules positioned inside the cyclodextrin cavity.

[††] (i) Bond length of 2.74(1)° and angle C(6G1)-O(6G1)···O(6G3)" of 118.9°. The symmetry operation is -*x*-1/2, *y*+1/2, -*z*.
(ii) Bond length of 2.89(1)Å and angle C(6G3)-O(6G3)···O(6G7)" of 131.7°. The symmetry operation is *x*-1/2, *y*-1/2, *z*.

Table 4.5 Hydrogen bonding distances and angles to water molecules

	Hydrogen bond length (Å)[a]	Angle (°)[b]	
O(6G1)···O(W4)	2.76(1)	C(6G1)-O(6G1···O(W4)	131.6
O(6G2)···O(W1)	2.80(1)	C(6G2)-O(6G2)···O(W1)	131.2
···O(W12)	2.83(1)	C(6G2)-O(6G2)···O(W12)	125.1
O(6G3)···O(W2)	2.76(1)	C(6G3)-O(6G3)···O(W2)	105.3
O(6G4)···O(W4)	2.78(1)	C(6G4)-O(6G4)···O(W4)	106.6
O(64A)···O(W4)	3.04(1)	C(6G4)-O(64A)···O(W4)	113.0
O(6G5)···O(W7)	2.76(1)	C(6G5)-O(6G5)···O(W7)	122.2
O(6G6)···O(W8)	2.79(1)	C(6G6)-O(6G6)···O(W8)	125.8
O(6G7)···O(W2)	2.78(1)	C(6G7)-O(6G7)···O(W2)	123.3
O(2G1)···O(W6)	2.71(1)	C(2G1)-O(2G1)···O(W6)	110.5
O(2G2)···O(W10)	2.66(1)	C(2G2)-O(2G2)···O(W10)	98.4
O(3G2)···O(W9)	3.03(1)	C(3G2)-O(3G2)···O(W9)	141.5
O(2G3)···O(W3)	2.68(1)	C(2G3)-O(2G3)···O(W3)	101.6
O(2G4)···O(W5)	2.74(1)	C(2G4)-O(2G4)···O(W5)	98.1
O(3G4)···O(W10)	2.91(1)	C(3G4)-O(3G4)···O(W10)	106.9
O(3G5)···O(W6)	2.82(1)	C(3G5)-O(3G5)···O(W6)	118.5
O(3G6)···O(W5)	2.96(1)	C(3G6)-O(3G6)···O(W8)	108.3

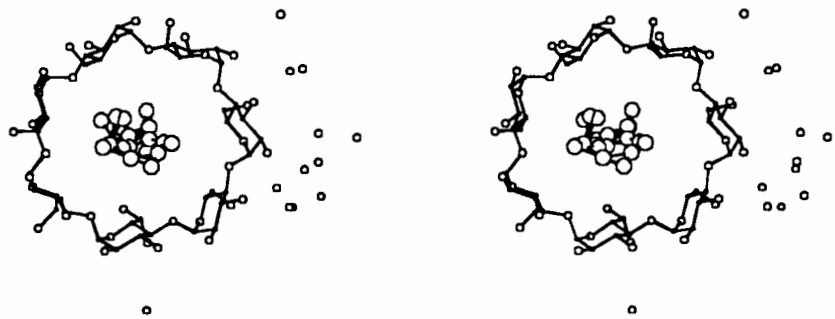
[a] A range of 2.5-3.1Å is considered to be acceptable for cyclodextrin hydrogen bonds, due to the disorder of water molecules and the inability to locate hydrogen atoms

[b] Angles within a range of 90-140° are considered as possible hydrogen bonding angles.

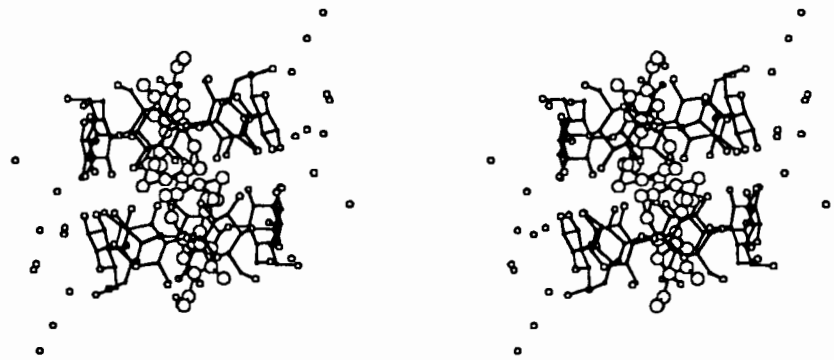
The guest molecule is located inside the cavity, but is greatly disordered and could not be visualised beyond a diffuse electron density cloud. A number of electron density peaks were located, having values of 0.5-0.7eÅ^{-3}, as compared to 1.3eÅ^{-3} and higher for water oxygen molecules, and it was not possible to model a guest molecule due to abnormal bond angles and lengths, and the mode of complexation could not be established. The positioning of this electron density cloud is shown in Fig. 4.9 by the positions of peaks that were identified, indicating the placement of the cloud in relation to the β-cyclodextrin dimer. A group of six peaks arranged in a rough hexagon could be discerned, though attempts to include these in the model

Fig. 4.9 Guest positioning inside β-cyclodextrin cavity

a. Stereoview down *c* axis. Guest molecules are shown as larger circles positioned inside the cavity.



b. Stereoview of dimer down *b* axis.



as a phenyl group were not successful. Subsequent difference electron density maps did not elucidate the presence of guest substituent groups. This disorder is not uncommon and can be compared to a number of examples of guest disorder in the channel arrangement that have been reported for β-cyclodextrin complexes[2,3,5].

Microanalysis results for a dehydrated sample of the complex revealed a carbon content of 48.84% C and 5.94% H. The calculated values for a 1:1 complex are 49.24% and 6.56%, and these values correspond reasonably despite a discrepancy in values for H due possibly to the presence of water in the sample. This result compares with other β-cyclodextrin complexes with profens, where a 2:2 dimer complex is formed in each case[7,8]. This disorder is inherent to cyclodextrin complexes of this type, and few structures have been reported where the guest is

revealed and placed. It is not possible to ascertain whether the disorder is statistical or whether the guest molecule is undergoing a high degree of thermal motion or is actually migrating though the channels, despite collecting intensity data at reduced temperatures and being able to position water molecules with site occupancy factors of 1.0. The channels formed by the cyclodextrin molecule are almost exactly linear and the guest appears to be positioned near the centre of the cavity as a long chain of overlapping peaks generated by symmetry, suggesting a number of possible positionings for the guest and possible interactions with the host.

4.5 DISCUSSION

A complex of β-cyclodextrin and racemic ibuprofen has been crystallised and the crystal structure has been elucidated. The cyclodextrin molecules crystallise as dimers and these pack in infinite head-to-head channels into which the guest molecule is inserted. Water molecules fill the interstices between these channels. The guest molecule is disordered within the channels and cannot be located from examination of electron density maps, and it is not possible to identify which enantiomers are included in the complex. A complex hydrogen bonding network between cyclodextrin hydroxyl groups and water molecules maintains the structure of the complex, and crystallinity is lost on dehydration. A series of intramolecular, intradimer and interdimer hydrogen bonds between hydroxyl groups maintain the conformation of the β-cyclodextrin molecule.

All atoms of the cyclodextrin molecule, and all water molecules, were located and were not disordered. All atoms have site occupancy factors of 1, except the O(6) group of G4, which occupies two positions with occupancy factors of 0.65 and 0.35. This disorder is important as the minor position of O(6G4) forms a hydrogen bond to its symmetry related hydroxyl group on an adjacent dimer in the next layer of the channel. This is the only direct hydrogen bond linking the dimers in the channel. The relative weakness of this bond, due to the low site occupancy, may explain in part the instability of the crystal structure.

The two-dimensional network of water molecules that maintains the structure is constructed in a similar fashion to that proposed by Le Bas and Tsoucaris[9], with the intramolecular and intradimer network of hydrogen bonds extending into the interstices. Their findings show that nine possible hydrogen bonds are formed with

water molecules by O(2) and O(3) hydroxyl groups (the secondary network of hydrogen bonds), though only eight could be located for this structure. They furthermore state that two hydrogen bonds are directed towards dimers located in the same layer, though only one of these could be identified for the secondary hydroxyl rim. Two hydrogen bonds were located from the O(6) rim (the primary network) to O(6) groups on neighbouring dimers in the same layer, and one to the adjacent layer. These differ from the number identified by Le Bas and Tsoucaris.

The geometrical parameters that define the conformation of the cyclodextrin ring in the complex are comparable to those of other cyclodextrin complexes that crystallise in the channel arrangement. In a study of conformational parameters by Lipkowitz *et al*[10], distributions of a number of parameters were plotted, and values for tilt angles, distance of O(4) groups from the centre of the cavity and deviations of O(4) groups from planarity for this complex lie within the ranges observed for β-cyclodextrin complexes.

Due to the disorder of the guest, it was not possible to establish which enantiomer was included in the complex. Complexes with both racemic and pure (S)-ibuprofen were prepared though only the complex with the racemate was characterised. XRD showed that similar complexes are formed and they showed identical behaviour with thermal analysis. The possibility of racemic resolution of ibuprofen and other profen anti-inflammatories using the cyclodextrins is discussed in section 5.5.

4.6 REFERENCES

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5. COMPLEX OF TRIMEB WITH IBUPROFEN[1,2]

5.1 PREPARATION OF COMPLEX

Preparation of the crystalline complex is outlined briefly in Table 3.1. Equimolar amounts of TRIMEB and racemic ibuprofen were dissolved in distilled water at room temperature and the resulting solution incubated at 50°C for 48h to obtain crystals. Microcrystalline complexes of TRIMEB with racemic and (S)-ibuprofen were prepared by stirring equimolar amounts of host and drug in aqueous solution for 24hrs at room temperature and filtering the insoluble powders that formed.

5.2 THERMAL ANALYSIS

Initial investigations using hot stage microscopy showed that melting of the complex occurred at approximately 185°C. This was confirmed by DSC, with a melting endotherm present at 186.3°C, as compared to fusion of TRIMEB at 159.1°C [Fig.5.1a and b respectively]. TGA showed negligible mass loss over the temperature range [Fig.5.1c]. This was attributed to loss of surface water, and it was concluded that no water molecules of crystallisation were present in the complex. This conclusion was supported by no evidence of crystal cracking under the hot stage microscope, and confirmed by X-ray analysis.

5.3 CRYSTAL STRUCTURE SOLUTION

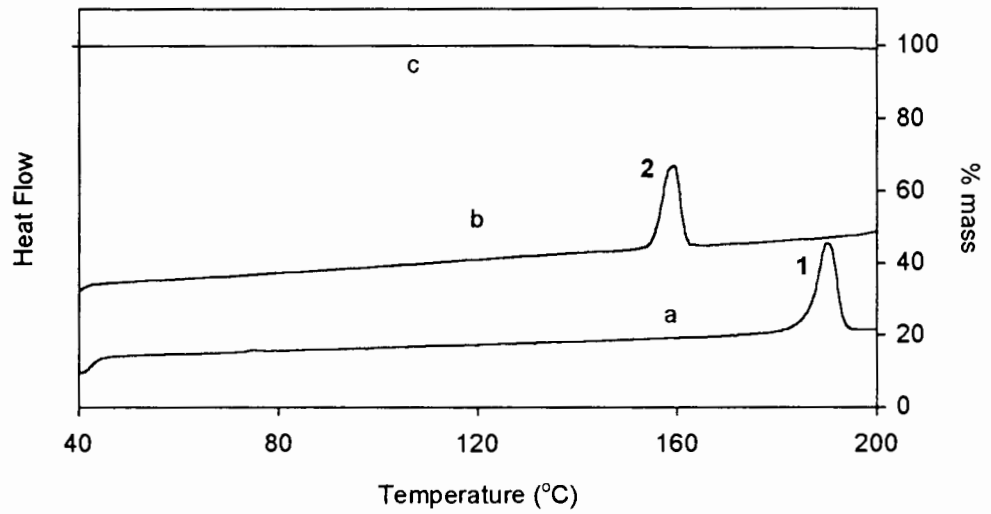
5.3.1 Photography

A crystal was removed from a batch of complex obtained with racemic ibuprofen and attached unsealed to a glass fibre, then mounted on a goniometer as outlined in Section 2.7. Oscillation and Weissenberg photography revealed Laue *mmm* symmetry, corresponding to the orthorhombic system. The systematic absences *h*00: *h*=2n+1 ; 0*k*0: *k*=2n+1 ; 00*l*: *l*=2n+1 confirmed the space group as $P2_12_12_1$.

5.3.2 Data collection and refinement

A single crystal was removed from a batch prepared from racemic ibuprofen and TRIMEB, and mounted on a diffractometer as outlined in Section 2.7. Intensity data

Fig. 5.1. Thermal analysis for TRIMEB - (RS)-ibuprofen complex.
(a) DSC for complex, with (b) comparison to TRIMEB, and (c) TGA for complex.



Sample mass for a = 13.313mg, for b = 14.706mg
Onset of peak 1 = 181.5°C, for peak 2 = 155.1°C.

were collected at 253K. Accurate cell dimensions were obtained by least squares analysis of the setting angles of 24 reflections in the range $16°<\theta<17°$C. The ω-scan technique was used and, to ensure accurate measurement of weak reflections, a pre-scan acceptance parameter of zero was chosen to force the final intensity scans up to a maximum of 100s per reflection. Data were collected to $(\sin\theta/\lambda)_{max}=0.595$Å^{-1}. Three reflections (3 15 8; 3 2 21; 5 15 6) were used as standards and were monitored hourly, showing only a 2.5% intensity decrease over the data collection period. Orientation control was performed every 200 reflections and data were corrected for Lorentz-polarisation effects. Crystal data collection and refinement details are given in Table 5.1.

5.3.3 Structure solution

The structure was solved using coordinates for the non-hydrogen atoms - excluding O(6), C(7), C(8) and C(9) for each methylglucose residue - of the isomorphous TRIMEB - (S)-naproxen complex[3]. After refinement of these atoms by full-matrix least-squares techniques [minimisation of $\sum w(|F_o|-|kF_c|)^2$ using SHELX-76[4]], successive difference Fourier syntheses revealed all remaining non-hydrogen

Table 5.1 Crystal data, experimental and refinement parameters for TRIMEB - (S)-ibuprofen complex.

Molecular formula	$C_{63}H_{112}O_{35}.C_{13}H_{18}O_2$
M_r / gmol^{-1}	1635.8
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z	4
a (Å)	15.232(7)
b (Å)	21.327(7)
c (Å)	27.597(7)
V (Å^3)	8965(5)
D_c (g cm^{-3})†	1.211
Crystal dimensions (mm)	0.3 x 0.4 x 0.5
T/K	253
Range scanned θ (°)	$1 \leq \theta \leq 25$
Index range	h:0,18; k:0,25; l:0,32
Scan width	0.8 + 0.35 tan θ
Aperture width (mm)	1.12 + 1.05 tan θ
No. reflections collected	8619
No. unique reflections	7473
No. reflections with $I > 2\sigma(I)$	4888
No. L.S. parameters	1112
R ($I > 2\sigma(I)$)	0.079
w	$[\sigma^2(F_o)]^{-1}$
R_w	0.066
S	4.029
Shift.e.s.d. max., ave.	0.921, 0.04
$(\Delta\rho)_{max}$ final (e Å^{-3})	0.15
$(\Delta\rho)_{min}$ final (e Å^{-3})	-0.11

atoms. One molecule of ibuprofen, in the (S)-configuration, was located in the cavity of TRIMEB. All atoms were assigned anisotropic temperature factors. Hydrogen atoms attached to carbon atoms on both the host and guest were inserted at idealised positions (C–H=1.00Å), with methyl hydrogen atoms on the host and guest being assigned a variable isotropic temperature factor. Other

† The density of the complex could not be obtained experimentally. A suitable solvent mixture could not be identified as TRIMEB is freely soluble in a number of solvents.

hydrogen atoms on the cyclodextrin and ibuprofen molecule were assigned common variable isotropic temperature factors. Due to abnormally long bond lengths and large bond angles for atoms of the guest isobutyl group, the position of H(13) was not idealised, and was instead obtained from a difference Fourier synthesis and allowed to refine with distance constraints to C(12), C(13) and C(14). Final fractional coordinates for all atoms of the complex are given in Appendix B. A full listing of observed and calculated structure factors (F_o and F_c), is given in Appendix C on disk, in ASCII format, under the filename TRIBUP.ASC.

5.3.4 Description of structure

The structure of the complex and the numbering system used for TRIMEB and (S)-ibuprofen are given in Fig. 5.2. The isobutyl group of (S)-ibuprofen is inserted

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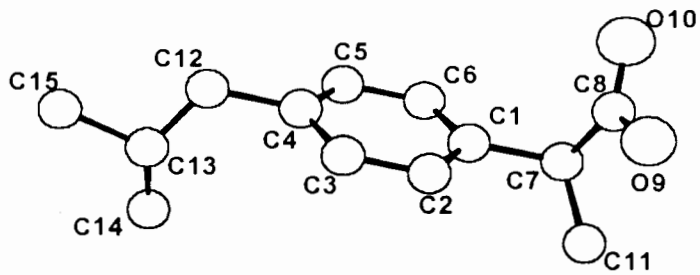
Fig. 5.2 **Structure of TRIMEB - (S)-ibuprofen complex.** (a) Numbering system and conformation of (S)-ibuprofen, (b) numbering system of cyclodextrin trimethylglucose molecules (C atoms are represented by numbers only) and (c) structure of complex showing numbering of glucose residues.

a.



b.

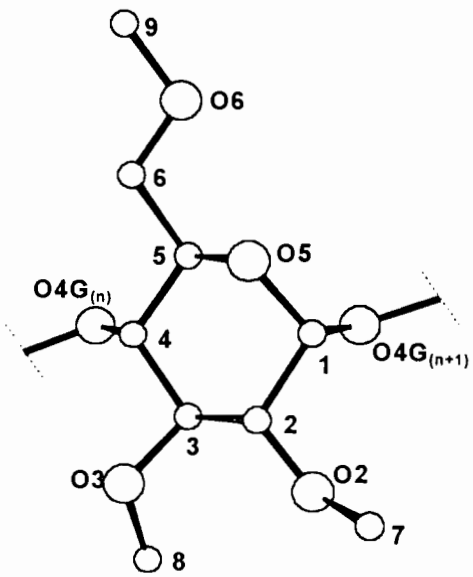


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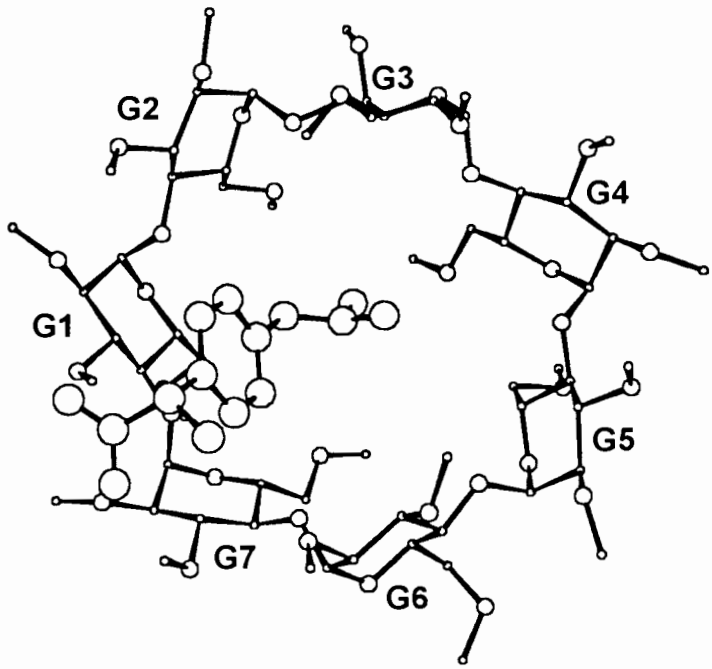
Fig 5.2 continued

c.



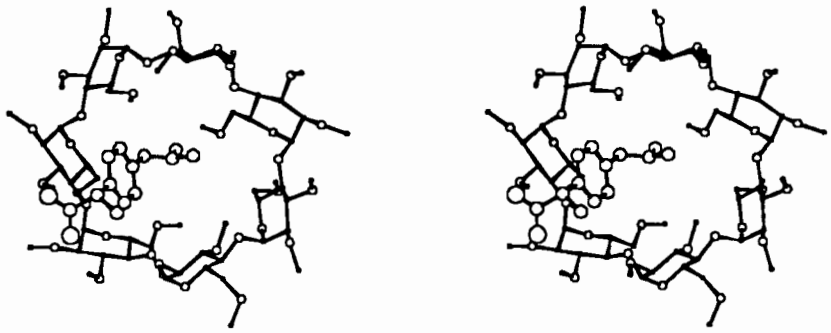
into the cavity of TRIMEB, with the propionic acid group protruding from the O(2),O(3) rim. All methylglucose groups of TRIMEB are in the $^4C_1$ conformation, with the O(2)-C(7) bonds being directed away from the cavity and the O(3)-C(8) bonds directed inward. The C(6)-O(6) bonds of residues G2, G4 and G7 are directed toward the cavity in the (+)-*gauche* conformation, and those of G1, G3, G5 and G6 are directed away in the (-)-*gauche* conformation. All O(6)-C(9) bonds are *trans* to the respective C(5)-C(6) bonds, except in G(6) where the bond lies *gauche* (Fig. 5.2). TRIMEB assumes a cup-shape into which the guest molecule is recessed, in contrast to structures with β-cyclodextrin where the cavity conforms to a more annular shape. The conformation and the extent of penetration of the guest into the cavity are shown in Fig. 5.3. There are no water molecules present in the complex.

5.3.4.1 Geometry and hydrogen bonding

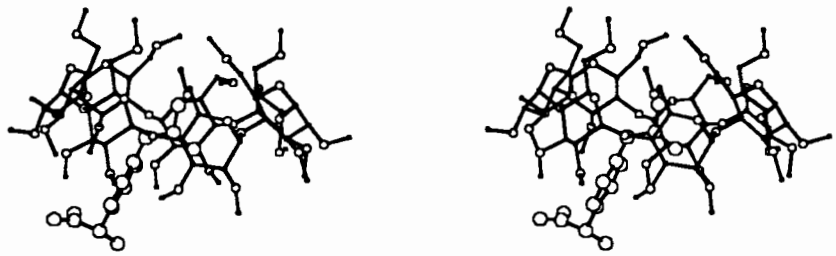
The geometrical data for TRIMEB are given in Table 5.2, based on parameters as outlined in Section 1.3.2. All the calculated parameters show good agreement with those for the complex of TRIMEB with (S)-naproxen[3], and are comparable to those

Fig. 5.3 Stereodiagram of the TRIMEB - (S)-ibuprofen complex

a. View into TRIMEB cavity parallel to *b* axis.



b. View normal to *b* axis, showing extent of guest penetration into the cavity.



for the complex formed with the (S)-isomer of flurbiprofen[5,6], both of which are analogues of ibuprofen and belong to the profen group of NSAIDs.

The conformation of the isobutyl group of (S)-ibuprofen may be defined by torsion angles τ_1, τ_2 and τ_3 , and that of the propionic acid group by τ_4, τ_5 and τ_6, as defined in Table 5.3. Comparison can be made with the conformation of free ibuprofen as the racemate and the pure (S)-isomer. (S)-ibuprofen crystallises with two molecules in the asymmetric unit, and torsion angles are outlined for both molecules[7,8]. Whereas the torsion angle values for free ibuprofen are similar, the isobutyl group in the complexed molecule is brought nearly normal to the plane of the phenyl ring. The positions of the phenyl and propionic acid groups are similar to those in free ibuprofen, as well as to those found in the TRIMEB - (S)-naproxen complex. The angle that the phenyl group makes with the least-squares plane of the O(4) atoms of the macrocycle is 20.9°, while that of TRIMEB - (S)-naproxen is 23.3°.

The carboxylic acid group interacts with an adjacent TRIMEB methoxy group to form a hydrogen bond. An O–H···O hydrogen bond is formed between O(10) and O(3G2) on a symmetry-related cyclodextrin (x+1/2, -y+1/2, -z+1) with a distance of 2.72(1)Å (Fig. 5.4). This is the only intermolecular hydrogen bond present in the crystal structure. This interaction is also observed in other TRIMEB-profen structures.

Table 5.2 Geometrical data for TRIMEB

Residue	Tilt angle (°)[a]	Deviation[b] (Å)	Torsion angle index[c]	Glycosidic oxygen angle[d] (°)	Radius of heptagon[e] (Å)
G1	28.3	0.446(6)	116.0	128.7	4.93
G2	18.7	0.208(6)	139.8	124.8	5.16
G3	-11.3	-0.511(6)	116.3	124.0	5.06
G4	41.9	-0.013(6)	139.7	137.3	4.71
G5	33.3	0.566(6)	118.4	120.4	5.17
G6	-14.1	-0.312(6)	128.6	126.5	5.06
G7	36.3	-0.383(6)	138.1	130.2	4.87
			Average	127.4	4.99

[a] As defined in Table 1.3.2.
[b] The deviation of O(4) atoms from the least-squares plane through all O(4) atoms.
[c] As defined in section 1.3.2.
[d] As defined in section 1.3.2.
[e] The radius of heptagon (Å) is the average value of the distance of each O(4) atom from the centre of gravity of seven O(4) atoms.

Table 5.3 Torsion angles. (a) Racemic ibuprofen, (b) (S)-ibuprofen and (c) TRIMEB - (S)-ibuprofen complex. Values in degrees.

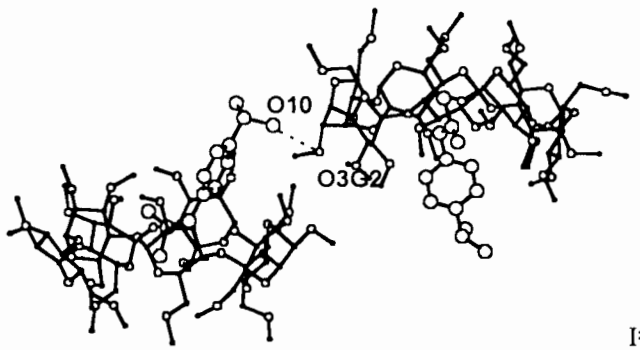
Atoms	a[†]	b(i)	b(ii)	c
τ1 C(2)-C(1)-C(7)-C(11)	42(1)	40(1)	28(1)	48(2)
τ2 C(2)-C(1)-C(7)-C(8)	-81(1)	-85(1)	-95(1)	-78(1)
τ3 C(1)-C(7)-C(8)-O(9)	-88(1)	-81(1)	83(1)	-83(1)
τ4 C(3)-C(4)-C(12)-C(13)	-102(1)	-92(1)	-79(1)	-59(2)
τ5 C(4)-C(12)-C(13)-C(14)	-170(1)	-170(1)	171(1)	-37(3)
τ6 C(4)-C(12)-C(13)-C(15)	67(1)	66(1)	-64(1)	173(1)

[†] The values for τ1, τ2 and τ3 will have opposite signs for each isomer. The values given here are for the (S)-isomer.

A series of intramolecular C–H···O hydrogen bonds maintain the conformation of the macrocycle (Table 5.4). Five C6(G_n)–H···O5(G_{n-1}) bonds stabilise the residues G1, G2, G4, G5 and G7, while the negative tilt angles of G3 and G6 are maintained by bonds C(1G3)–H···O(3G4) and C(1G5)–H···O(6G6) (Fig. 5.5). The existence of these bonds has been confirmed by previous reports in other TRIMEB complexes and in uncomplexed TRIMEB[9,10,11].

The packing arrangement of the complex in the crystal is shown in Fig. 5.6. Complex units are packed head-to-tail in a screw channel mode with axes almost parallel to the *b* axis.

Fig. 5.4 Intermolecular hydrogen bond between O(10) and O(3G2)[I].



I=*x*+1/2, -*y*+1/2, -*z*+1

Table 5.4 Intramolecular C–H···O hydrogen bonds in TRIMEB.

			Distance (Å)			Angle (°)
C	H	O	C···O	C–H*	H···O	C–H···O
C(6G1)	-H(611)	O(5G7)	3.23(1)	1.00	2.56	123.8
C(6G2)	-H(622)	O(5G1)	3.39(1)	1.00	2.47	153.0
C(1G3)	-H(1G3)	O(3G4)	3.09(1)	1.00	2.43	123.2
C(6G3)	-H(631)	O(5G2)	3.17(1)	1.00	2.38	135.7
C(1G5)	-H(1G5)	O(6G6)	3.24(1)	1.00	2.44	136.6
C(6G5)	-H(651)	O(5G4)	3.12(1)	1.00	2.42	126.4
C(6G6)	-H(661)	O(5G5)	3.20(1)	1.00	2.37	139.5

* idealised hydrogen positions inserted during refinement of crystal structure

Fig. 5.5 **View of TRIMEB showing hydrogen atoms and intramolecular C–H···O hydrogen bonds.**
Hydrogen atoms are shown. Hydrogen bonds are represented by dotted lines.

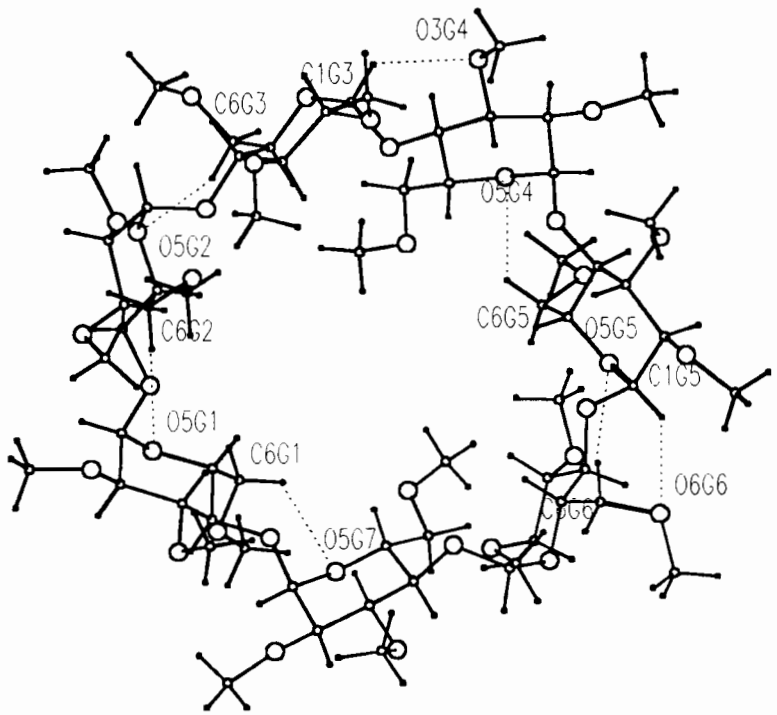
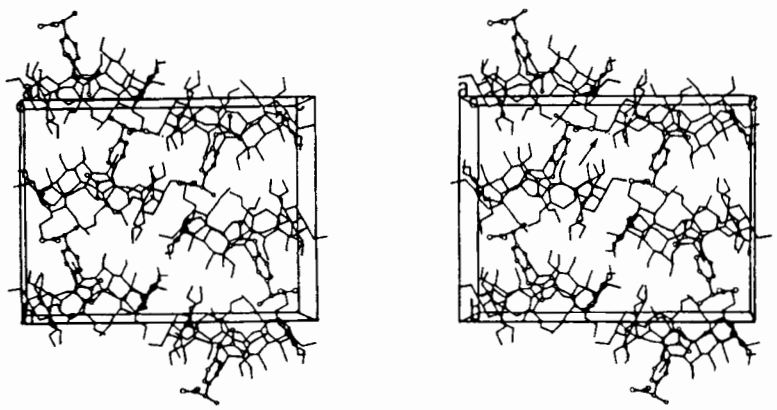


Fig. 5.6 **Stereoview of packing arrangement of complex in the crystal.**
View down *a* axis towards the origin. The intermolecular hydrogen bond is indicated by the arrow.



5.4 X-RAY POWDER DIFFRACTION (XRD)

A representative XRD pattern for the complex was generated using the program LAZY PULVERIX[12], which utilises unit cell data, atomic coordinates and thermal parameters (Fig. 5.7a). Comparison was made with experimental XRD patterns obtained as described in Section 2.7 (Fig. 5.7b and c).

5.5 RACEMIC RESOLUTION

In preparing crystals for structure solution, racemic ibuprofen was used. The crystal drawn for X-ray analysis revealed only the (S)-isomer in the complex, and it was decided to investigate the possibility that TRIMEB exhibits selectivity toward ibuprofen as studies have shown that only the (S)-isomer of the profen anti-inflammatories is active against cyclooxygenase, the enzyme responsible for the onset of the inflammation cascade[13].

Powder complexes with both racemic and (S)-ibuprofen were prepared (Section 5.1) and thermal analysis, XRD and polarimetry were applied to establish the composition of the complexes. Thermal analysis results were comparable for both complexes. In the prepared complexes, traces of free ibuprofen were present in the samples used for DSC and these presented as small endothermic peaks corresponding to the melting points. In the complex prepared from racemic ibuprofen, a peak was seen at 75°C only, which is the melting point of the racemate, as compared to an endotherm at 54°C for the complex with (S)-ibuprofen, corresponding to the melting point for that isomer. From this result it was possible to state that a complex is formed equally with both isomers. XRD patterns obtained for both complexes also showed a similarity that suggested the complexes formed are isomorphous (Fig. 5.8).

Measurements of optical rotation were used as confirmation of these results. Crystals isolated from the complex prepared using racemic ibuprofen were dissolved in a 40:60 ethanol:water mixture (the complex is sparingly soluble in water). This gave $[\alpha]_D$=132±3°. The mother liquor was diluted with ethanol to give the same solvent composition and the rotation measured was $[\alpha]_D$=130±3°. An ethanolic solution of mother liquor from a crystallisation using (S)-ibuprofen gave a measurement of $[\alpha]_D$=118°. It could thus be concluded from the similar results

obtained for the crystals and mother liquor of the racemate complex, and the difference with that for the pure isomer complex, that the (S)-isomer is not exclusively taken up by TRIMEB in the presence of the racemate.

Fig. 5.7 **XRD results for complex.** (a) Calculated pattern based on single crystal data, (b) experimental pattern from powder complex and (c) pattern from recrystallised TRIMEB alone.

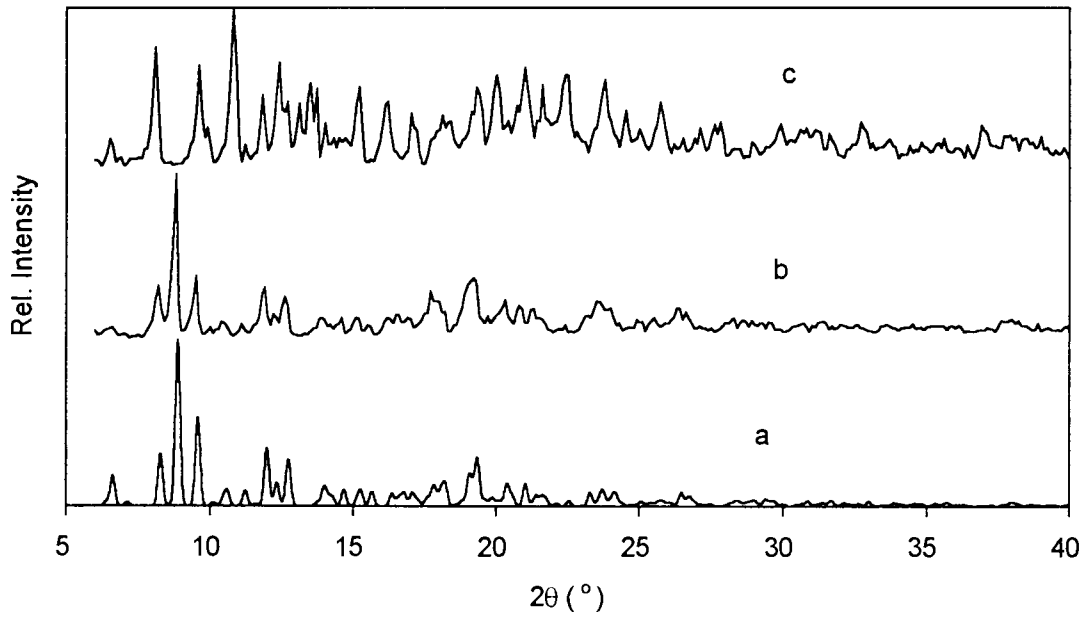
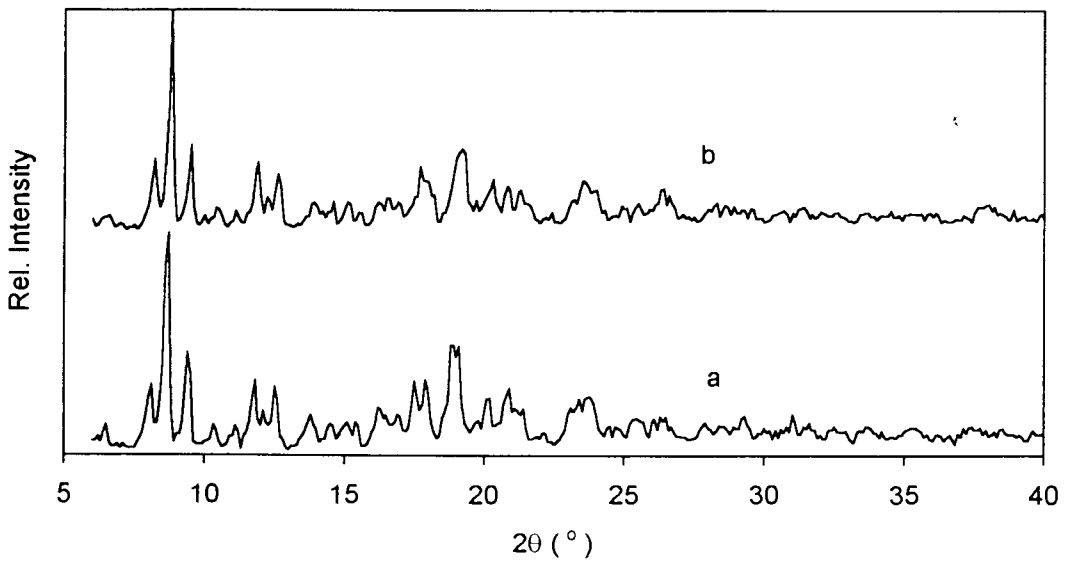


Fig. 5.8 **Comparison of XRD patterns for complexes prepared with racemic and (S)-ibuprofen.** (a) TRIMEB - (RS)-ibuprofen powder and (b) TRIMEB - (S)-ibuprofen.



5.6 DISCUSSION

The studies cited in this report using other profen anti-inflammatories as guests have made use of one or both isomers in the preparation of complexes with TRIMEB and with β-cyclodextrin. The TRIMEB-flurbiprofen complex was prepared with the drug (R)- and (S)-isomers and the racemate[6], and the results showed that isomorphous complexes are formed with each isomer, with some notable structural differences. The biphenyl group of flurbiprofen is inserted into the cavity with the propionic acid moiety protruding, and the (S)-isomer is hydrogen bonded to an adjacent cyclodextrin molecule as found here for (S)-ibuprofen in its complex. The biphenyl group is disordered within the cavity, adopting an (R) and (S) configuration. The (R)-isomer crystallises with one water molecule in the complex which forms a hydrogen bonding bridge from the carboxylic acid to a neighbouring TRIMEB molecule. The configuration of the biphenyl group is similar to that of free flurbiprofen, indicating weak binding by the cavity and the authors suggest this may be due to steric effects. The packing pattern of TRIMEB is isomorphous for both isomers. From these results, it is not, however, possible to predict in detail the mode of complexation of (R)-ibuprofen with TRIMEB.

In the complex of flurbiprofen with β-cyclodextrin, reaction with the racemate leads to a 2:2 complex being formed, with one (R)- and one (S)-isomer being enclosed in a cyclodextrin dimer[14]. Reaction with the (R)-isomer alone gives an isomorphous complex with the (S)-isomer being replaced by one (R)-isomer[15]. In a similar study concerning the complexation of fenoprofen by β-cyclodextrin[16,17], it was found that the cyclodextrin includes both the (R)- and (S)-isomer, though the modes differ significantly. The (S)-isomer is more tightly bound to the host than the (R)-isomer, due to a more favourable conformation for the carboxylic acid substituent which results in the formation of a number of hydrogen bonds to the primary and secondary hydroxyl groups of the cyclodextrin. Where the racemate was complexed, disorder of the guests was noted and the authors concluded that a 3:1 occupancy ratio of (S)- and (R)- isomers was responsible.

This suggests that the cyclodextrins may exhibit chiral selectivity toward the profen anti-inflammatories. However, these complexes are not isomorphous with the complex obtained for β-cyclodextrin and ibuprofen outlined in Section 4, and it

would not be possible to predict the mode of inclusion of the guest and its isomers from these models.

Chromatographic studies using a number of cyclodextrins and their derivatives as stationary phases have concluded that some of them, especially β-cyclodextrin and derivatives, are selective towards certain of the profens under certain conditions[18,19,20]. A β-cyclodextrin column showed chiral selectivity toward racemic ibuprofen at low pH i.e. below the pK_A value. A column containing γ-cyclodextrin showed no selectivity, suggesting that the size of the cavity is not optimal. Chiral separation would be based on the number and strength of favourable intermolecular contacts between host and guest, and a tight fit in the cavity would be required for these contacts to occur. Furthermore, a notable difference would need to be observed between the mode of interaction of each isomer, such that one isomer would preferentially interact with the host molecule, for separation to be possible.

The elucidation of the crystal structures of native β-cyclodextrin and TRIMEB with the same guest molecule - ibuprofen - allow for comparisons between the two modes of crystallisation. The structure of TRIMEB - (S)-ibuprofen is isomorphous with previously reported structures of TRIMEB complexes using analogues of ibuprofen as guest molecules. The complex with β-cyclodextrin is not isomorphous with other β-cyclodextrin - profen complexes despite packing in a channel arrangement similar to those complexes. The channels formed in the complex with ibuprofen are more linear and the guest is disordered within these channels and cannot be modelled, as has been observed with a number of complexes in the channel packing arrangement of β-cyclodextrin.

The geometrical parameters that define the conformation of the macrocycle, as shown in Tables 4.2 and 5.2 show that the ring of β-cyclodextrin adopts a more rigid relative positioning of the glucose residues, as illustrated by the radius of the heptagon, deviation of O(4) atoms from the plane of the macrocycle and glycosidic oxygen angles. This is maintained by a complex network of intramolecular and intermolecular hydrogen bonds. The macrocycle of TRIMEB is maintained by a series of C-H···O hydrogen bonds, and distortion may be due to a number of factors, such as the steric effects of the methyl substituents on each residue.

The tilt angles observed for each residue of the host molecule are a measure of the macrocyclic shape. In the TRIMEB complex, the O(6) rim of the host molecule is narrowed and the molecule assumes a cup-shaped appearance. The guest molecule is inserted into the cavity and isolated from other ibuprofen molecules in the complex. The channel packing of the β-cyclodextrin complex , with both ends of the cavity being open, suggests however that interaction is possible between guest molecules even though this could not be ascertained.

The water molecules present in the interstitial spaces are vital in maintaining the crystal structure and crystallinity is lost upon their removal. No water molecules are present in the TRIMEB complex, due to the hydrophobic environment, and the crystals are thus more stable to air and heat.

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6. CONCLUSION

Inclusion of NSAIDs by the cyclodextrins can improve a number of their physicochemical properties and thereby improve the bioavailability, side effect profile and other characteristics when administered orally or by other routes. A number of review articles have been devoted to studies of cyclodextrin complexes with NSAIDs and other drugs[1,2,3], and the main objective of this study has been the preparation of solid state complexes and their characterisation where possible using a range of physicochemical methods.

A number of complexes have been prepared and properties such as host:guest stoichiometry, water content, thermal behaviour and X-ray diffraction characteristics have been recorded. Where crystals of suitable size have been cultivated, single crystal X-ray photography and X-ray intensity data collection have been performed.

A list of all complexes for which a thorough investigation was carried out is given in Table 6.1 below. For each complex, the host:guest:water stoichiometry is given together with space group information and unit cell dimensions where these have been obtained.

Complexes were generally more easily prepared with native β- and γ-cyclodextrins than with DIMEB and TRIMEB, and a number of reasons may account for this. The conformation of DIMEB is similar to that of β-cyclodextrin, due to the formation of a network of (O)2···H-O(3) hydrogen bonds, though the cavity is deeper and the O(6) rim narrower than in β-cyclodextrin and steric effects may be important in inhibiting complex formation. The conformation of the TRIMEB molecule in the uncomplexed state tends to be more distorted and the macrocycle is more collapsed than that of either β- or γ-cyclodextrin[4,5]. It would thus be possible to state that the insertion of the guest into the cavity of DIMEB or TRIMEB, according to the established mode of complexation whereby the conformation of the ring is altered to accommodate the guest, could require greater energy than would be needed for complexation with native cyclodextrin. Simple heating of the reaction solution would not be possible due to the unusual solubility profiles of the methylated cyclodextrins whereby solubility decreases with temperature, and other factors would need to play a role in promoting complex formation.

Table 6.1 Summary of characterised complexes

HOST - GUEST	COMPOSITION (host:guest:water)	SPACE GROUP	UNIT CELL DATA*
β-cyclodextrin - piroxicam	1:1:25.8	C2	a=27.197(5)Å b=12.43(1)Å c=24.815(5)Å β=104.19(2)°
γ-cyclodextrin - piroxicam	1:1:19.2		
β-cyclodextrin - mefenamic acid	1:1:11.5		
β-cyclodextrin - flufenamic acid	1:1:12.8		
β-cyclodextrin - niflumic acid	1:1:13.2		
β-cyclodextrin - tolfenamic acid	1:1:14.2	$P2_1$	a=15.5Å b=64.2Å c=14.7Å β=129.0°
β-cyclodextrin - ibuprofen**	1:1:12.0	C2	a=19.41(1)Å b=24.41(2)Å c=15.92(1)Å β=108.9(6)°
γ-cyclodextrin - ibuprofen	1:1:18.3	$P42_12$	a=b=23.7Å c=45.9Å
DIMEB - ibuprofen	1:1:1	$P2_12_12_1$	a=10.1Å b=15.3Å c=53.6Å
TRIMEB - ibuprofen**	1:1:0	$P2_12_12_1$	a=15.232(7)Å b=21.327(7)Å c=27.597(7)Å
β-cyclodextrin - diflunisal	1:1:13.0	$P2_12_12_1$	a=15.4Å b=29.0Å c=29.7Å

* Unit cell data with standard deviations are given for those complexes where parameters were obtained diffractometrically.

** Complexes for which complete structural analysis was successfully performed.

In cases where complexation did proceed with DIMEB and TRIMEB, specifically in the case of ibuprofen, the size of the guest molecule would appear to be of importance. Relatively larger molecules such as the oxicam and indene derivatives (indomethacin and sulindac) do not form complexes with cyclodextrins as readily as the smaller profens, fenamates and salicylates, and this has been shown in numerous literature studies and been the observation in this study. Other factors, such as ionisation of the guest and the phase solubilities of complexes that may form in solution but not precipitate as solid complexes, should also be noted.

Numerous difficulties were encountered in the preparation of many complexes, and obtaining crystals of suitable quality for X-ray analysis was hampered by a number of factors such as crystal size and the inability to optimise conditions for crystallisation despite repeated efforts, and many attempts to characterise complexes failed. Where success was achieved, the unit cell dimensions and instability of the crystals outside of the mother liquor precluded intensity data collection and the solution of the structure, which was the true aim of this study.

Certain hosts showed a greater affinity for a particular guest than others. With the DIMEB-ibuprofen complex it was observed that pH adjustment or other manipulation of the reaction medium was unnecessary, and that the guest molecule was rapidly and completely taken into solution with simple stirring. This is related to the stability constant of the complex and suggests that the interaction between host and guest is enhanced by specific intermolecular interactions that would need to be elucidated. Reported stability constants for the complexes of DIMEB and β-cyclodextrin with ibuprofen give a value for the DIMEB complex that is approximately four times greater, and the authors suggest that the deeper cavity and greater closeness of fit between host and guest may be responsible for these observations[6]. The ability of the host and guest molecule to interact with each other through a number of intermolecular forces such as hydrogen bonding, van der Waals forces and hydrophobic interactions would need to be considered.

The advantages of complexation are related to these properties and have been reviewed extensively. Dispersion of NSAIDs, which are usually insoluble, especially in the acidic environment of the stomach where they are present mainly in their unionised form, can allow for more rapid dissolution and absorption, thereby

decreasing the time to peak plasma concentration and increasing the maximum plasma concentration. The anti-inflammatory activity of piroxicam is improved 2.65 times by inclusion into β-cyclodextrin[7]. The complex formed dissociates rapidly in the gastric environment and more free drug is delivered to the site of absorption. The only steady-state pharmacokinetic parameter that is modified is the T_{max} value due to this effect[8]. Gastric irritation is also considerably reduced[9].

A similar modification is noted with the β-cyclodextrin - ibuprofen complex. The improvement in aqueous solubility of ibuprofen by complexation with β-cyclodextrin is 2.1 times, and for TRIMEB it is 1.9 times[10], and the complexes formed are relatively insoluble compared to the cyclodextrin alone. This is not as great an enhancement as is observed with other compounds though it can be sufficient to significantly improve bioavailability. The amount of free drug that is absorbed is similar to that of the uncomplexed drug, but the rate of absorption is improved 2.5 times in a similar manner to the piroxicam complex[11]. Furthermore, the bitter taste and irritant effect of ibuprofen on the tongue are masked by complexation which may improve formulation of the drug[12].

In conclusion, the NSAIDs are favourable candidates for inclusion by cyclodextrins, with the aim of improving their therapeutic behaviour, and much work has been devoted to ascertaining the mode of inclusion and properties of the complexes in the solid state. Physicochemical characterisation of solid state complexes is possible using a wide range of techniques, and a number of complexes have been prepared and characterised to provide evidence for inclusion. The results of X-ray analysis for a number of complexes, and the unique cell data that were obtained, indicate that the mode of packing of cyclodextrin complexes in the solid state may be more varied than has been reported until now. The elucidation of the crystal structures of these complexes would improve the understanding of these modes and thereby enhance knowledge of the inclusion capabilities of these important compounds.

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APPENDICES

Appendix A

Supplementary data for β-cyclodextrin - (RS)-ibuprofen complex

Appendix B

Supplementary data for TRIMEB - (S)-ibuprofen complex

Appendix C - Disk

BETIBUP1.ASC and BETIBUP2.ASC:

Structure factor tables for β-cyclodextrin - (RS)-ibuprofen complex.

(ASCII format). Observed and calculated structure factors as F_O^2 and F_C^2 with standard deviations for observed structure factors ($\sigma(F_O^2)$).

TRIBUP.ASC:

Structure factor tables for TRIMEB - (S)-ibuprofen complex.

(ASCII format). Observed and calculated structure factors as F_O and F_C.

Appendix A : SUPPLEMENTARY DATA FOR β-CYCLODEXTRIN - (RS)-IBUPROFEN COMPLEX

TABLE A1. Fractional atomic coordinates (x 10^4) and thermal parameters ($Å^2$ x 10^3) with estimated standard deviations in parentheses for β-cyclodextrin - (RS)-ibuprofen complex.

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i . a_j$$

Atom	x/a	y/b	z/c	U_{eq}/U_{iso}*
C(1G1)	-546(4)	2680(4)	2465(6)	36(2)
C(2G1)	-938(5)	2757(4)	3137(6)	37(2)
O(2G1)	-431(3)	2868(4)	3987(4)	46(2)
C(3G1)	-1384(4)	2247(4)	3167(5)	33(2)
O(3G1)	-1800(3)	2323(4)	3737(4)	43(1)
C(4G1)	-1884(4)	2135(4)	2229(5)	32(2)
O(4G1)	-2268(3)	1635(3)	2257(4)	35(1)
C(5G1)	-1444(5)	2072(4)	1601(6)	38(2)
O(5G1)	-1022(3)	2560(4)	1627(4)	41(1)
C(6G1)	-1888(7)	1971(5)	642(6)	57(3)
O(6G1)	-2344(5)	2395(5)	255(5)	78(3)
C(1G2)	-3026(5)	1637(4)	1905(5)	35(2)
C(2G2)	-3340(5)	1406(4)	2593(5)	37(2)
O(2G2)	-3115(4)	1737(4)	3364(4)	45(1)
C(3G2)	-3105(5)	817(4)	2795(5)	35(2)
O(3G2)	-3427(4)	589(4)	3402(4)	47(2)
C(4G2)	-3340(5)	490(4)	1933(5)	34(2)
O(4G2)	-3060(3)	-051(4)	2126(4)	36(1)
C(5G2)	-3039(5)	751(5)	1253(6)	42(2)
O(5G2)	-3264(4)	1309(4)	1113(4)	42(1)
C(6G2)	-3275(7)	475(5)	364(6)	56(3)
O(6G2)	-4032(5)	444(5)	014(6)	74(2)
C(1G3)	-3541(5)	-500(4)	1891(5)	35(2)
C(2G3)	-3370(5)	-861(4)	2709(5)	38(2)
O(2G3)	-3509(4)	-572(4)	3420(4)	47(2)
C(3G3)	-2620(5)	-1059(4)	2966(5)	39(2)
O(3G3)	-2454(4)	-1422(4)	3706(4)	45(2)
C(4G3)	-2490(5)	-1354(4)	2193(5)	35(2)
O(4G3)	-1731(3)	-1458(4)	2431(4)	42(1)
C(5G3)	-2740(5)	-1001(5)	1336(5)	39(2)
O(5G3)	-3443(3)	-796(4)	1181(4)	38(1)
C(6G3)	-2754(5)	-1321(5)	527(5)	47(2)
O(6G3)	-3287(4)	-1753(4)	348(4)	52(2)
C(1G4)	-1499(5)	-1991(5)	2273(6)	45(2)
C(2G4)	-983(5)	-2209(5)	3142(6)	43(2)
O(2G4)	-1346(4)	-2220(4)	3792(4)	49(2)

C(3G4)	-293(4)	-1896(5)	3449(5)	36(2)	
O(3G4)	214(4)	-2151(4)	4232(4)	47(2)	
C(4G4)	050(5)	-1889(5)	2721(5)	43(2)	
O(4G4)	710(3)	-1578(4)	3017(4)	38(1)	
C(5G4)	-494(6)	-1626(6)	1890(6)	57(3)	
O(5G4)	-1143(4)	-1948(5)	1626(4)	57(2)	
C(6G4)	-209(8)	-1564(9)	1124(8)	91(5)	
O(6G4)	-712(12)	-1319(12)	469(11)	115(9)	0.57**
O(64A)*	42(17)	-2146(15)	942(23)	117(9)	0.43 **
C(1G5)	1351(5)	-1831(5)	2965(6)	41(2)	
C(2G5)	1935(5)	-1760(4)	3836(6)	40(2)	
O(2G5)	1717(4)	-1997(4)	4542(4)	50(2)	
C(3G5)	2112(5)	-1162(5)	4006(5)	37(2)	
O(3G5)	2715(3)	-1077(4)	4797(4)	46(2)	
C(4G5)	2308(5)	-917(5)	3248(5)	39(2)	
O(4G5)	2386(3)	-339(4)	3375(4)	42(2)	
C(5G5)	1742(5)	-1042(5)	2360(6)	43(2)	
O(5G5)	1556(4)	-1610(4)	2268(4)	51(2)	
C(6G5)	1972(7)	-907(7)	1569(7)	68(3)	
O(6G5)	2543(6)	-1228(7)	1527(7)	99(4)	
C(1G6)	3012(6)	-081(5)	3349(6)	47(2)	
C(2G6)	3307(5)	268(5)	4180(6)	45(2)	
O(2G6)	3445(4)	-047(4)	4963(4)	47(2)	
C(3G6)	2754(5)	721(5)	4141(5)	36(2)	
O(3G6)	3040(4)	1078(4)	4885(4)	46(2)	
C(4G6)	2603(5)	1049(5)	3293(6)	41(2)	
O(4G6)	2037(3)	1421(3)	3246(4)	34(1)	
C(5G6)	2381(7)	664(6)	2488(6)	56(3)	
O(5G6)	2887(5)	234(4)	2586(5)	63(2)	
C(6G6)	2332(11)	937(8)	1635(10)	98(6)	
O(6G6)*	3036(11)	1050(9)	1614(13)	155(6)	
C(1G7)	2161(5)	1986(4)	3151(6)	37(2)	
C(2G7)	1976(5)	2281(4)	3898(6)	38(2)	
O(2G7)	2445(3)	2115(4)	4737(4)	41(2)	
C(3G7)	1193(4)	2208(4)	3792(5)	34(2)	
O(3G7)	1006(4)	2513(4)	4459(4)	47(2)	
C(4G7)	729(4)	2403(4)	2883(5)	33(2)	
O(4G7)	-013(3)	2274(3)	2775(3)	34(1)	
C(5G7)	949(5)	2131(4)	2154(5)	38(2)	
O(5G7)	1719(3)	2183(4)	2322(4)	43(2)	
C(6G7)	586(6)	2369(5)	1243(6)	46(2)	
O(6G7)	690(4)	2953(4)	1245(4)	54(2)	
O(W1)	5000(0)	-411(5)	0000(0)	59(3)	
O(W2)	4546(4)	-1300(4)	800(4)	53(2)	

** Site occupancy factors for O(6G4) and O(64A)

O(W3)	5231(7)	-1024(7)	3419(7)	116(5)
O(W4)*	3504(7)	2860(7)	9362(9)	116(4)
O(W5)*	4159(8)	1786(8)	4540(11)	128(5)
O(W6)	4133(5)	8743(5)	4738(7)	76(2)
O(W7)	3951(5)	9163(5)	1998(6)	76(2)
O(W8)*	5863(8)	281(7)	8215(10)	117(4)
O(W9)	5112(9)	426(12)	3664(22)	234(15)
O(W10)*	4382(11)	1796(10)	6327(13)	166(7)
O(W11)	5000(0)	-245(13)	5000(0)	153(9)
O(W12)*	0000(0)	6314(13)	0000(0)	153(9)

TABLE A2. Anisotropic atoms have thermal parameters ($Å^2 \times 10^3$) of the form:

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$$

Atom	U11	U22	U33	U23	U13	U12
C(1G1)	33(4)	31(4)	40(4)	16(3)	7(3)	2(3)
C(2G1)	39(4)	23(4)	41(4)	-3(3)	1(3)	1(3)
O(2G1)	46(3)	45(3)	41(3)	-13(3)	5(3)	5(3)
C(3G1)	38(4)	31(4)	32(4)	5(3)	12(3)	5(3)
O(3G1)	46(3)	55(4)	31(3)	-6(3)	15(3)	-2(3)
C(4G1)	41(4)	24(4)	29(4)	6(3)	8(3)	-2(3)
O(4G1)	44(3)	25(3)	33(3)	4(2)	7(2)	-5(2)
C(5G1)	42(4)	40(4)	31(4)	7(3)	9(3)	-9(4)
O(5G1)	48(3)	39(3)	32(3)	12(2)	9(2)	-7(3)
C(6G1)	81(7)	60(7)	31(5)	1(4)	20(5)	-20(6)
O(6G1)	73(5)	93(7)	52(5)	23(4)	-2(4)	-10(5)
C(1G2)	45(4)	31(4)	25(4)	1(3)	6(3)	-4(3)
C(2G2)	43(4)	35(4)	31(4)	-4(3)	9(3)	-2(3)
O(2G2)	59(4)	41(3)	42(3)	-9(3)	25(3)	-8(3)
C(3G2)	46(4)	35(4)	23(4)	3(3)	10(3)	-2(3)
O(3G2)	73(4)	38(3)	38(3)	-3(3)	32(3)	-12(3)
C(4G2)	46(5)	29(4)	29(4)	2(3)	18(3)	-5(3)
O(4G2)	42(3)	31(3)	34(3)	2(2)	9(2)	-7(2)
C(5G2)	53(5)	40(4)	36(4)	6(4)	17(4)	-11(4)
O(5G2)	53(3)	36(3)	30(3)	-1(2)	2(2)	-15(3)
C(6G2)	76(7)	59(6)	32(5)	6(4)	18(5)	-16(5)
O(6G2)	94(6)	74(6)	49(4)	-10(4)	17(4)	-29(5)
C(1G3)	45(4)	39(4)	22(4)	-6(3)	11(3)	-9(4)
C(2G3)	67(6)	28(4)	27(4)	-5(3)	27(4)	-13(4)
O(2G3)	76(4)	44(3)	29(3)	-9(3)	28(3)	-12(3)
C(3G3)	72(6)	26(4)	18(3)	-1(3)	14(4)	-15(4)

O(3G3)	77(4)	33(3)	26(3)	3(2)	20(3)	-3(3)
C(4G3)	45(5)	37(4)	23(4)	-6(3)	11(3)	-11(3)
O(4G3)	46(3)	42(3)	30(3)	-8(2)	0(2)	-4(3)
C(5G3)	48(5)	46(5)	20(4)	-7(3)	8(3)	-15(4)
O(5G3)	48(3)	42(3)	20(3)	-8(2)	6(2)	-6(3)
C(6G3)	47(5)	68(6)	22(4)	-6(4)	5(3)	1(4)
O(6G3)	72(4)	50(4)	28(3)	-13(3)	8(3)	-1(3)
C(1G4)	51(5)	49(5)	28(4)	-11(4)	3(4)	-8(4)
C(2G4)	51(5)	43(5)	34(4)	-8(4)	11(4)	0(4)
O(2G4)	54(4)	54(4)	41(3)	4(3)	18(3)	1(3)
C(3G4)	43(4)	46(5)	18(3)	2(3)	10(3)	6(4)
O(3G4)	51(3)	64(4)	23(3)	6(3)	8(2)	3(3)
C(4G4)	47(5)	62(6)	19(4)	-4(4)	9(3)	-3(4)
O(4G4)	47(3)	39(3)	28(3)	-4(2)	11(2)	4(3)
C(5G4)	56(5)	85(8)	21(4)	3(4)	1(4)	-6(5)
O(5G4)	55(4)	91(6)	21(3)	-18(3)	6(3)	-6(4)
C(6G4)	79(8)	154(16)	39(6)	16(8)	18(6)	-18(9)
O(6G4)	120(15)	159(23)	46(8)	11(11)	-1(9)	-53(15)
C(1G5)	52(5)	47(5)	34(4)	1(4)	26(4)	1(4)
C(2G5)	52(5)	44(5)	31(4)	3(4)	21(4)	15(4)
O(2G5)	67(4)	52(4)	32(3)	6(3)	18(3)	8(3)
C(3G5)	39(4)	53(5)	22(3)	(3)13	0(3)	11(4)
O(3G5)	49(3)	66(4)	18(3)	5(3)	10(2)	4(3)
C(4G5)	53(5)	46(5)	24(4)	-2(3)	21(4)	15(4)
O(4G5)	47(3)	49(4)	37(3)	1(3)	24(3)	18(3)
C(5G5)	49(5)	54(5)	29(4)	3(4)	19(4)	4(4)
O(5G5)	65(4)	68(4)	25(3)	-14(3)	22(3)	-5(3)
C(6G5)	79(7)	104(1)	23(4)	-1(5)	20(5)	-24(7)
O(6G5)	101(7)	144(11)	75(6)	-37(7)	57(6)	-30(7)
C(1G6)	62(6)	50(5)	38(5)	9(4)	30(4)	23(5)
C(2G6)	54(5)	40(5)	48(5)	7(4)	27(4)	12(4)
O(2G6)	62(4)	37(3)	42(3)	8(3)	15(3)	8(3)
C(3G6)	38(4)	43(4)	27(4)	0(3)	13(3)	7(4)
O(3G6)	67(4)	36(3)	29(3)	0(2)	6(3)	13(3)
C(4G6)	36(4)	52(5)	40(5)	9(4)	19(4)	4(4)
O(4G6)	44(3)	28(3)	35(3)	6(2)	19(2)	2(2)
C(5G6)	79(7)	66(6)	33(5)	3(5)	32(5)	23(6)
O(5G6)	88(5)	71(5)	52(4)	9(4)	54(4)	24(4)
C(6G6)	160(16)	91(11)	51(7)	29(7)	46(9)	53(11)
C(1G7)	44(5)	36(4)	3(4)	11(3)	1(3)	-2(3)
C(2G7)	52(5)	24(4)	37(4)	3(3)	13(4)	-4(3)
O(2G7)	47(3)	32(3)	35(3)	1(2)	0(3)	3(2)
C(3G7)	44(4)	31(4)	27(4)	-3(3)	1(3)	-1(3)
O(3G7)	56(4)	54(4)	27(3)	-7(3)	7(3)	14(3)
C(4G7)	45(4)	24(3)	26(4)	5(3)	9(3)	-1(3)
O(4G7)	46(3)	23(3)	31(3)	3(2)	12(2)	-5(2)
C(5G7)	55(5)	32(4)	28(4)	4(3)	16(4)	4(4)
O(5G7)	48(3)	46(3)	37(3)	16(3)	15(3)	-3(3)

C(6G7)	54(5)	52(5)	28(4)	9(4)	9(4)	5(4)
O(6G7)	7(4)	5(4)	44(4)	23(3)	18(3)	9(3)
O(W1)	50(5)	58(6)	59(6)	0(0)	5(5)	0(0)
O(W2)	63(4)	51(4)	42(3)	7(3)	11(3)	7(3)
O(W3)	118(9)	149(12)	67(6)	41(7)	10(6)	-48(8)
O(W6)	63(5)	73(6)	86(6)	-25(5)	16(4)	5(4)
O(W7)	80(5)	81(6)	75(6)	1(5)	37(5)	4(5)
O(W9)	87(1)	241(27)	381(38)	-133(27)	84(16)	-37(13)
O(W11)	82(11)	159(21)	211(26)	0(0)	40(14)	0(0)

TABLE A3. Bond lengths (Å) with estimated standard deviations in parentheses for β-cyclodextrin - (RS)-ibuprofen complex.

C(1G1) - O(5G1)	1.39(1)	C(5G3) - C(6G3)	1.50(1)
C(1G1) - O(4G7)	1.40(1)	C(6G3) - O(6G3)	1.44(1)
C(1G1) - C(2G1)	1.51(1)	C(1G4) - O(5G4)	1.42(1)
C(2G1) - O(2G1)	1.42(1)	C(1G4) - C(2G4)	1.52(1)
C(2G1) - C(3G1)	1.53(1)	C(2G4) - O(2G4)	1.43(1)
C(3G1) - O(3G1)	1.41(1)	C(2G4) - C(3G4)	1.48(1)
C(3G1) - C(4G1)	1.52(1)	C(3G4) - O(3G4)	1.45(1)
C(4G1) - O(4G1)	1.44(1)	C(3G4) - C(4G4)	1.51(1)
C(4G1) - C(5G1)	1.52(1)	C(4G4) - O(4G4)	1.43(1)
O(4G1) - C(1G2)	1.40(1)	C(4G4) - C(5G4)	1.54(1)
C(5G1) - O(5G1)	1.44(1)	O(4G4) - C(1G5)	1.41(1)
C(5G1) - C(6G1)	1.51(1)	C(5G4) - O(5G4)	1.43(1)
C(6G1) - O(6G1)	1.37(2)	C(5G4) - C(6G4)	1.50(2)
C(1G2) - O(5G2)	1.44(1)	C(6G4) - O(6G4)	1.32(3)
C(1G2) - C(2G2)	1.52(1)	C(6G4) - O(64A	1.56(4)
C(2G2) - O(2G2)	1.42(1)	C(1G5) - O(5G5)	1.40(1)
C(2G2) - C(3G2)	1.51(1)	C(1G5) - C(2G5)	1.49(1)
C(3G2) - O(3G2)	1.42(1)	C(2G5) - O(2G5)	1.44(1)
C(3G2) - C(4G2)	1.53(1)	C(2G5) - C(3G5)	1.50(1)
C(4G2) - O(4G2)	1.42(1)	C(3G5) - O(3G5)	1.43(1)
C(4G2) - C(5G2)	1.52(1)	C(3G5) - C(4G5)	1.50(1)
O(4G2) - C(1G3)	1.41(1)	C(4G5) - O(4G5)	1.42(1)
C(5G2) - O(5G2)	1.43(1)	C(4G5) - C(5G5)	1.51(1)
C(5G2) - C(6G2)	1.50(1)	O(4G5) - C(1G6)	1.38(1)
C(6G2) - O(6G2)	1.39(2)	C(5G5) - O(5G5)	1.43(1)
C(1G3) - O(5G3)	1.40(1)	C(5G5) - C(6G5)	1.50(1)
C(1G3) - C(2G3)	1.52(1)	C(6G5) - O(6G5)	1.38(2)
C(2G3) - O(2G3)	1.43(1)	C(1G6) - O(5G6)	1.39(1)
C(2G3) - C(3G3)	1.46(1)	C(1G6) - C(2G6)	1.52(1)
C(3G3) - O(3G3)	1.43(1)	C(2G6) - O(2G6)	1.41(1)
C(3G3) - C(4G3)	1.51(1)	C(2G6) - C(3G6)	1.53(1)
C(4G3) - O(4G3)	1.42(1)	C(3G6) - O(3G6)	1.43(1)
C(4G3) - C(5G3)	1.55(1)	C(3G6) - C(4G6)	1.51(1)
O(4G3) - C(1G4)	1.42(1)	C(4G6) - O(4G6)	1.41(1)
C(5G3) - O(5G3)	1.40(1)	C(4G6) - C(5G6)	1.54(2)

O(4G6) - C(1G7)	1.42(1)	C(3G7) - O(3G7)	1.44(1)
C(5G6) - O(5G6)	1.41(1)	C(3G7) - C(4G7)	1.51(1)
C(5G6) - C(6G6)	1.49(2)	C(4G7) - O(4G7)	1.43(1)
C(6G6) - O(6G6)	1.40(3)	C(4G7) - C(5G7)	1.51(1)
C(1G7) - O(5G7)	1.41(1)	C(5G7) - O(5G7)	1.44(1)
C(1G7) - C(2G7)	1.53(1)	C(5G7) - C(6G7)	1.51(1)
C(2G7) - O(2G7)	1.41(1)	C(6G7) - O(6G7)	1.44(1)
C(2G7) - C(3G7)	1.49(1)		

TABLE A4. Bond angles (°) with estimated standard deviations in parentheses for β-cyclodextrin - (RS)-ibuprofen complex.

O(5G1) - C(1G1) - O(4G7)	112.0(7)	O(5G3) - C(1G3) - O(4G2)	111.2(6)
O(5G1) - C(1G1) - C(2G1)	112.1(7)	O(5G3) - C(1G3) - C(2G3)	110.1(7)
O(4G7) - C(1G1) - C(2G1)	108.9(6)	O(4G2) - C(1G3) - C(2G3)	106.3(6)
O(2G1) - C(2G1) - C(1G1)	110.2(7)	O(2G3) - C(2G3) - C(3G3)	111.6(7)
O(2G1) - C(2G1) - C(3G1)	110.6(7)	O(2G3) - C(2G3) - C(1G3)	110.3(7)
C(1G1) - C(2G1) - C(3G1)	109.9(7)	C(3G3) - C(2G3) - C(1G3)	110.7(7)
O(3G1) - C(3G1) - C(4G1)	109.9(7)	O(3G3) - C(3G3) - C(2G3)	112.0(7)
O(3G1) - C(3G1) - C(2G1)	111.2(7)	O(3G3) - C(3G3) - C(4G3)	108.9(7)
C(4G1) - C(3G1) - C(2G1)	107.7(6)	C(2G3) - C(3G3) - C(4G3)	110.1(7)
O(4G1) - C(4G1) - C(5G1)	110.0(7)	O(4G3) - C(4G3) - C(3G3)	107.5(7)
O(4G1) - C(4G1) - C(3G1)	107.1(6)	O(4G3) - C(4G3) - C(5G3)	109.7(7)
C(5G1) - C(4G1) - C(3G1)	110.4(7)	C(3G3) - C(4G3) - C(5G3)	111.4(7)
C(1G2) - O(4G1) - C(4G1)	118.3(6)	C(4G3) - O(4G3) - C(1G4)	118.5(6)
O(5G1) - C(5G1) - C(6G1)	107.3(7)	O(5G3) - C(5G3) - C(6G3)	106.9(7)
O(5G1) - C(5G1) - C(4G1)	109.5(7)	O(5G3) - C(5G3) - C(4G3)	111.3(7)
C(6G1) - C(5G1) - C(4G1)	115.0(8)	C(6G3) - C(5G3) - C(4G3)	112.4(8)
C(1G1) - O(5G1) - C(5G1)	113.4(6)	C(5G3) - O(5G3) - C(1G3)	114.9(6)
O(6G1) - C(6G1) - C(5G1)	113.9(9)	O(6G3) - C(6G3) - C(5G3)	111.2(7)
O(4G1) - C(1G2) - O(5G2)	110.3(7)	O(5G4) - C(1G4) - O(4G3)	108.5(8)
O(4G1) - C(1G2) - C(2G2)	109.1(6)	O(5G4) - C(1G4) - C(2G4)	110.8(8)
O(5G2) - C(1G2) - C(2G2)	109.6(7)	O(4G3) - C(1G4) - C(2G4)	108.2(7)
O(2G2) - C(2G2) - C(3G2)	111.8(7)	O(2G4) - C(2G4) - C(3G4)	112.1(7)
O(2G2) - C(2G2) - C(1G2)	109.2(7)	O(2G4) - C(2G4) - C(1G4)	109.4(8)
C(3G2) - C(2G2) - C(1G2)	109.9(7)	C(3G4) - C(2G4) - C(1G4)	112.3(8)
O(3G2) - C(3G2) - C(2G2)	110.3(7)	O(3G4) - C(3G4) - C(2G4)	110.5(7)
O(3G2) - C(3G2) - C(4G2)	109.7(7)	O(3G4) - C(3G4) - C(4G4)	108.6(7)
C(2G2) - C(3G2) - C(4G2)	109.0(7)	C(2G4) - C(3G4) - C(4G4)	109.1(7)
O(4G2) - C(4G2) - C(5G2)	109.5(7)	O(4G4) - C(4G4) - C(3G4)	108.8(7)
O(4G2) - C(4G2) - C(3G2)	108.0(6)	O(4G4) - C(4G4) - C(5G4)	110.7(8)
C(5G2) - C(4G2) - C(3G2)	110.4(7)	C(3G4) - C(4G4) - C(5G4)	108.3(8)
C(1G3) - O(4G2) - C(4G2)	119.3(6)	C(1G5) - O(4G4) - C(4G4)	117.4(7)
O(5G2) - C(5G2) - C(6G2)	107.3(8)	O(5G4) - C(5G4) - C(6G4)	109.7(9)
O(5G2) - C(5G2) - C(4G2)	110.0(7)	O(5G4) - C(5G4) - C(4G4)	108.5(9)
C(6G2) - C(5G2) - C(4G2)	114.4(7)	C(6G4) - C(5G4) - C(4G4)	114 (1)
C(5G2) - O(5G2) - C(1G2)	113.6(6)	C(1G4) - O(5G4) - C(5G4)	114.7(7)
O(6G2) - C(6G2) - C(5G2)	111 (1)	O(6G4) - C(6G4) - C(5G4)	108 (2)

O(6G4) - C(6G4) - O(64A	118 (2)	C(4G6) - C(3G6) - C(2G6)	110.4(7)
C(5G4) - C(6G4) - O(64A	106 (2)	O(4G6) - C(4G6) - C(3G6)	108.1(7)
O(5G5) - C(1G5) - O(4G4)	111.1(7)	O(4G6) - C(4G6) - C(5G6)	110.3(8)
O(5G5) - C(1G5) - C(2G5)	111.5(7)	C(3G6) - C(4G6) - C(5G6)	109.9(8)
O(4G4) - C(1G5) - C(2G5)	108.3(7)	C(4G6) - O(4G6) - C(1G7)	118.5(7)
O(2G5) - C(2G5) - C(1G5)	110.6(8)	O(5G6) - C(5G6) - C(6G6)	105.7(9)
O(2G5) - C(2G5) - C(3G5)	110.8(7)	O(5G6) - C(5G6) - C(4G6)	111.5(9)
C(1G5) - C(2G5) - C(3G5)	109.8(7)	C(6G6) - C(5G6) - C(4G6)	114 (1)
O(3G5) - C(3G5) - C(4G5)	107.5(7)	C(1G6) - O(5G6) - C(5G6)	115.1(7)
O(3G5) - C(3G5) - C(2G5)	111.9(7)	O(6G6) - C(6G6) - C(5G6)	110 (2)
C(4G5) - C(3G5) - C(2G5)	110.2(7)	O(5G7) - C(1G7) - O(4G6)	111.1(7)
O(4G5) - C(4G5) - C(3G5)	108.8(6)	O(5G7) - C(1G7) - C(2G7)	110.1(7)
O(4G5) - C(4G5) - C(5G5)	110.0(7)	O(4G6) - C(1G7) - C(2G7)	106.6(6)
C(3G5) - C(4G5) - C(5G5)	111.9(8)	O(2G7) - C(2G7) - C(3G7)	113.3(7)
C(1G6) - O(4G5) - C(4G5)	120.0(7)	O(2G7) - C(2G7) - C(1G7)	111.0(7)
O(5G5) - C(5G5) - C(6G5)	105.1(9)	C(3G7) - C(2G7) - C(1G7)	110.1(7)
O(5G5) - C(5G5) - C(4G5)	112.0(8)	O(3G7) - C(3G7) - C(2G7)	110.5(7)
C(6G5) - C(5G5) - C(4G5)	114.5(8)	O(3G7) - C(3G7) - C(4G7)	109.2(7)
C(1G5) - O(5G5) - C(5G5)	114.7(7)	C(2G7) - C(3G7) - C(4G7)	110.0(7)
O(6G5) - C(6G5) - C(5G5)	112 (1)	O(4G7) - C(4G7) - C(3G7)	108.1(6)
O(4G5) - C(1G6) - O(5G6)	111.9(8)	O(4G7) - C(4G7) - C(5G7)	109.5(6)
O(4G5) - C(1G6) - C(2G6)	108.5(7)	C(3G7) - C(4G7) - C(5G7)	111.4(7)
O(5G6) - C(1G6) - C(2G6)	111.2(8)	C(1G1) - O(4G7) - C(4G7)	119.1(6)
O(2G6) - C(2G6) - C(1G6)	111.9(8)	O(5G7) - C(5G7) - C(6G7)	106.2(7)
O(2G6) - C(2G6) - C(3G6)	111.1(7)	O(5G7) - C(5G7) - C(4G7)	110.7(7)
C(1G6) - C(2G6) - C(3G6)	107.9(7)	C(6G7) - C(5G7) - C(4G7)	114.1(7)
O(3G6) - C(3G6) - C(4G6)	109.1(7)	C(1G7) - O(5G7) - C(5G7)	115.3(6)
O(3G6) - C(3G6) - C(2G6)	109.1(7)	O(6G7) - C(6G7) - C(5G7)	110.9(8)

TABLE A5. Torsion angles (°) with estimated standard deviations in parentheses for β-cyclodextrin - (RS)-ibuprofen complex.

O(5G1) - C(1G1) - C(2G1) - O(2G1)	178.8(6)	C(3G1) - C(4G1) - C(5G1) - O(5G1)	-57.9(8)
O(4G7) - C(1G1) - C(2G1) - O(2G1)	54.3(8)	O(4G1) - C(4G1) - C(5G1) - C(6G1)	63.3(9)
O(5G1) - C(1G1) - C(2G1) - C(3G1)	56.7(8)	C(3G1) - C(4G1) - C(5G1) - C(6G1)	-178.8(8)
O(4G7) - C(1G1) - C(2G1) - C(3G1)	-67.8(8)	O(4G7) - C(1G1) - O(5G1) - C(5G1)	63.8(9)
O(2G1) - C(2G1) - C(3G1) - O(3G1)	62.7(8)	C(2G1) - C(1G1) - O(5G1) - C(5G1)	-58.9(9)
C(1G1) - C(2G1) - C(3G1) - O(3G1)	-175.5(6)	C(6G1) - C(5G1) - O(5G1) - C(1G1)	-175.6(8)
O(2G1) - C(2G1) - C(3G1) - C(4G1)	-176.9(7)	C(4G1) - C(5G1) - O(5G1) - C(1G1)	58.9(9)
C(1G1) - C(2G1) - C(3G1) - C(4G1)	-55.0(8)	O(5G1) - C(5G1) - C(6G1) - O(6G1)	-59 (1)
O(3G1) - C(3G1) - C(4G1) - O(4G1)	-62.2(8)	C(4G1) - C(5G1) - C(6G1) - O(6G1)	63 (1)
C(2G1) - C(3G1) - C(4G1) - O(4G1)	176.5(6)	C(4G1) - O(4G1) - C(1G2) - O(5G2)	111.5(7)
O(3G1) - C(3G1) - C(4G1) - C(5G1)	178.0(6)	C(4G1) - O(4G1) - C(1G2) - C(2G2)	-128.1(7)
C(2G1) - C(3G1) - C(4G1) - C(5G1)	56.8(8)	O(4G1) - C(1G2) - C(2G2) - O(2G2)	60.2(9)
C(5G1) - C(4G1) - O(4G1) - C(1G2)	-112.8(8)	O(5G2) - C(1G2) - C(2G2) - O(2G2)	-178.9(7)
C(3G1) - C(4G1) - O(4G1) - C(1G2)	127.3(7)	O(4G1) - C(1G2) - C(2G2) - C(3G2)	-62.8(8)
O(4G1) - C(4G1) - C(5G1) - O(5G1)	-175.9(6)	O(5G2) - C(1G2) - C(2G2) - C(3G2)	58.1(9)

O(2G2) - C(2G2) - C(3G2) - O(3G2)	61.6(9)	O(5G4) - C(1G4) - C(2G4) - O(2G4)	176.9(8)
C(1G2) - C(2G2) - C(3G2) - O(3G2)	-177.0(6)	O(4G3) - C(1G4) - C(2G4) - O(2G4)	58 (1)
O(2G2) - C(2G2) - C(3G2) - C(4G2)	-177.9(7)	O(5G4) - C(1G4) - C(2G4) - C(3G4)	52 (1)
C(1G2) - C(2G2) - C(3G2) - C(4G2)	-56.4(9)	O(4G3) - C(1G4) - C(2G4) - C(3G4)	-67 (1)
O(3G2) - C(3G2) - C(4G2) - O(4G2)	-63.9(9)	O(2G4) - C(2G4) - C(3G4) - O(3G4)	62 (1)
C(2G2) - C(3G2) - C(4G2) - O(4G2)	175.1(7)	C(1G4) - C(2G4) - C(3G4) - O(3G4)	-174.2(7)
O(3G2) - C(3G2) - C(4G2) - C(5G2)	176.3(7)	O(2G4) - C(2G4) - C(3G4) - C(4G4)	-178.5(7)
C(2G2) - C(3G2) - C(4G2) - C(5G2)	55.4(9)	C(1G4) - C(2G4) - C(3G4) - C(4G4)	-55 (1)
C(5G2) - C(4G2) - O(4G2) - C(1G3)	-114.8(8)	O(3G4) - C(3G4) - C(4G4) - O(4G4)	-60 (1)
C(3G2) - C(4G2) - O(4G2) - C(1G3)	124.9(7)	C(2G4) - C(3G4) - C(4G4) - O(4G4)	179.1(7)
O(4G2) - C(4G2) - C(5G2) - O(5G2)	-174.8(6)	O(3G4) - C(3G4) - C(4G4) - C(5G4)	179.2(8)
C(3G2) - C(4G2) - C(5G2) - O(5G2)	-56.0(9)	C(2G4) - C(3G4) - C(4G4) - C(5G4)	59 (1)
O(4G2) - C(4G2) - C(5G2) - C(6G2)	64 (1)	C(3G4) - C(4G4) - O(4G4) - C(1G5)	127.0(8)
C(3G2) - C(4G2) - C(5G2) - C(6G2)	-176.8(9)	C(5G4) - C(4G4) - O(4G4) - C(1G5)	-114.2(9)
C(6G2) - C(5G2) - O(5G2) - C(1G2)	-175.7(7)	O(4G4) - C(4G4) - C(5G4) - O(5G4)	-179.6(7)
C(4G2) - C(5G2) - O(5G2) - C(1G2)	59.3(9)	C(3G4) - C(4G4) - C(5G4) - O(5G4)	-60 (1)
O(4G1) - C(1G2) - O(5G2) - C(5G2)	59.7(8)	O(4G4) - C(4G4) - C(5G4) - C(6G4)	58 (1)
C(2G2) - C(1G2) - O(5G2) - C(5G2)	-60.4(9)	C(3G4) - C(4G4) - C(5G4) - C(6G4)	177 (1)
O(5G2) - C(5G2) - C(6G2) - O(6G2)	-67 (1)	O(4G3) - C(1G4) - O(5G4) - C(5G4)	63 (1)
C(4G2) - C(5G2) - C(6G2) - O(6G2)	55 (1)	C(2G4) - C(1G4) - O(5G4) - C(5G4)	-55 (1)
C(4G2) - O(4G2) - C(1G3) - O(5G3)	109.2(8)	C(6G4) - C(5G4) - O(5G4) - C(1G4)	-174 (1)
C(4G2) - O(4G2) - C(1G3) - C(2G3)	-131.0(7)	C(4G4) - C(5G4) - O(5G4) - C(1G4)	60 (1)
O(5G3) - C(1G3) - C(2G3) - O(2G3)	-176.7(7)	O(5G4) - C(5G4) - C(6G4) - O(6G4)	60 (1)
O(4G2) - C(1G3) - C(2G3) - O(2G3)	62.7(9)	C(4G4) - C(5G4) - C(6G4) - O(6G4)	-178 (2)
O(5G3) - C(1G3) - C(2G3) - C(3G3)	59.3(8)	O(5G4) - C(5G4) - C(6G4) - O(64A	-67 (2)
O(4G2) - C(1G3) - C(2G3) - C(3G3)	-61.3(8)	C(4G4) - C(5G4) - C(6G4) - O(64A	55 (2)
O(2G3) - C(2G3) - C(3G3) - O(3G3)	59.7(8)	C(4G4) - O(4G4) - C(1G5) - O(5G5)	106.1(8)
C(1G3) - C(2G3) - C(3G3) - O(3G3)	-177.0(6)	C(4G4) - O(4G4) - C(1G5) - C(2G5)	-131.1(7)
O(2G3) - C(2G3) - C(3G3) - C(4G3)	-179.0(6)	O(5G5) - C(1G5) - C(2G5) - O(2G5)	-179.2(7)
C(1G3) - C(2G3) - C(3G3) - C(4G3)	-55.7(8)	O(4G4) - C(1G5) - C(2G5) - O(2G5)	58.2(9)
O(3G3) - C(3G3) - C(4G3) - O(4G3)	-66.0(9)	O(5G5) - C(1G5) - C(2G5) - C(3G5)	58.1(9)
C(2G3) - C(3G3) - C(4G3) - O(4G3)	170.9(6)	O(4G4) - C(1G5) - C(2G5) - C(3G5)	-64.4(9)
O(3G3) - C(3G3) - C(4G3) - C(5G3)	173.9(7)	O(2G5) - C(2G5) - C(3G5) - O(3G5)	62.7(9)
C(2G3) - C(3G3) - C(4G3) - C(5G3)	50.7(9)	C(1G5) - C(2G5) - C(3G5) - O(3G5)	-174.8(6)
C(3G3) - C(4G3) - O(4G3) - C(1G4)	133.7(7)	O(2G5) - C(2G5) - C(3G5) - C(4G5)	-177.7(7)
C(5G3) - C(4G3) - O(4G3) - C(1G4)	-105.1(8)	C(1G5) - C(2G5) - C(3G5) - C(4G5)	-55.2(9)
O(4G3) - C(4G3) - C(5G3) - O(5G3)	-167.8(6)	O(3G5) - C(3G5) - C(4G5) - O(4G5)	-64.8(9)
C(3G3) - C(4G3) - C(5G3) - O(5G3)	-49.0(9)	C(2G5) - C(3G5) - C(4G5) - O(4G5)	173.0(7)
O(4G3) - C(4G3) - C(5G3) - C(6G3)	72.3(9)	O(3G5) - C(3G5) - C(4G5) - C(5G5)	173.4(7)
C(3G3) - C(4G3) - C(5G3) - C(6G3)	-168.8(7)	C(2G5) - C(3G5) - C(4G5) - C(5G5)	51.2(9)
C(6G3) - C(5G3) - O(5G3) - C(1G3)	177.6(7)	C(3G5) - C(4G5) - O(4G5) - C(1G6)	127.5(8)
C(4G3) - C(5G3) - O(5G3) - C(1G3)	54.5(9)	C(5G5) - C(4G5) - O(4G5) - C(1G6)	-109.6(8)
O(4G2) - C(1G3) - O(5G3) - C(5G3)	58.2(9)	O(4G5) - C(4G5) - C(5G5) - O(5G5)	-170.1(7)
C(2G3) - C(1G3) - O(5G3) - C(5G3)	-59.4(9)	C(3G5) - C(4G5) - C(5G5) - O(5G5)	-49.0(9)
O(5G3) - C(5G3) - C(6G3) - O(6G3)	-57.8(9)	O(4G5) - C(4G5) - C(5G5) - C(6G5)	70 (1)
C(4G3) - C(5G3) - C(6G3) - O(6G3)	65 (1)	C(3G5) - C(4G5) - C(5G5) - C(6G5)	-168.5(9)
C(4G3) - O(4G3) - C(1G4) - O(5G4)	114.8(8)	O(4G4) - C(1G5) - O(5G5) - C(5G5)	63 (1)
C(4G3) - O(4G3) - C(1G4) - C(2G4)	-125.0(8)	C(2G5) - C(1G5) - O(5G5) - C(5G5)	-58 (1)

C(6G5) - C(5G5) - O(5G5) - C(1G5)	177.5(8)	C(4G6) - C(5G6) - C(6G6) - O(6G6)	73(2)
C(4G5) - C(5G5) - O(5G5) - C(1G5)	53 (1)	C(4G6) - O(4G6) - C(1G7) - O(5G7)	113.5(8)
O(5G5) - C(5G5) - C(6G5) - O(6G5)	-58 (1)	C(4G6) - O(4G6) - C(1G7) - C(2G7)	-126.6(8)
C(4G5) - C(5G5) - C(6G5) - O(6G5)	65 (1)	O(5G7) - C(1G7) - C(2G7) - O(2G7)	-176.3(6)
C(4G5) - O(4G5) - C(1G6) - O(5G6)	108.5(8)	O(4G6) - C(1G7) - C(2G7) - O(2G7)	63.1(9)
C(4G5) - O(4G5) - C(1G6) - C(2G6)	-128.5(8)	O(5G7) - C(1G7) - C(2G7) - C(3G7)	57.4(9)
O(4G5) - C(1G6) - C(2G6) - O(2G6)	57.3(9)	O(4G6) - C(1G7) - C(2G7) - C(3G7)	-63.2(8)
O(5G6) - C(1G6) - C(2G6) - O(2G6)	-179.3(7)	O(2G7) - C(2G7) - C(3G7) - O(3G7)	58.6(9)
O(4G5) - C(1G6) - C(2G6) - C(3G6)	-65.2(9)	C(1G7) - C(2G7) - C(3G7) - O(3G7)	-176.4(6)
O(5G6) - C(1G6) - C(2G6) - C(3G6)	58 (1)	O(2G7) - C(2G7) - C(3G7) - C(4G7)	179.1(6)
O(2G6) - C(2G6) - C(3G6) - O(3G6)	61 (1)	C(1G7) - C(2G7) - C(3G7) - C(4G7)	-55.8(8)
C(1G6) - C(2G6) - C(3G6) - O(3G6)	-176.1(7)	O(3G7) - C(3G7) - C(4G7) - O(4G7)	-64.6(8)
O(2G6) - C(2G6) - C(3G6) - C(4G6)	-179.1(8)	C(2G7) - C(3G7) - C(4G7) - O(4G7)	174.1(6)
C(1G6) - C(2G6) - C(3G6) - C(4G6)	-56 (1)	O(3G7) - C(3G7) - C(4G7) - C(5G7)	175.0(7)
O(3G6) - C(3G6) - C(4G6) - O(4G6)	-66.2(9)	C(2G7) - C(3G7) - C(4G7) - C(5G7)	53.7(9)
C(2G6) - C(3G6) - C(4G6) - O(4G6)	173.8(7)	O(5G1) - C(1G1) - O(4G7) - C(4G7)	112.6(7)
O(3G6) - C(3G6) - C(4G6) - C(5G6)	173.4(7)	C(2G1) - C(1G1) - O(4G7) - C(4G7)	-122.9(7)
C(2G6) - C(3G6) - C(4G6) - C(5G6)	53 (1)	C(3G7) - C(4G7) - O(4G7) - C(1G1)	131.6(7)
C(3G6) - C(4G6) - O(4G6) - C(1G7)	124.4(8)	C(5G7) - C(4G7) - O(4G7) - C(1G1)	-106.8(8)
C(5G6) - C(4G6) - O(4G6) - C(1G7)	-115.4(8)	O(4G7) - C(4G7) - C(5G7) - O(5G7)	-171.1(6)
O(4G6) - C(4G6) - C(5G6) - O(5G6)	-170.7(8)	C(3G7) - C(4G7) - C(5G7) - O(5G7)	-51.5(9)
C(3G6) - C(4G6) - C(5G6) - O(5G6)	-52 (1)	O(4G7) - C(4G7) - C(5G7) - C(6G7)	69.1(9)
O(4G6) - C(4G6) - C(5G6) - C(6G6)	70 (1)	C(3G7) - C(4G7) - C(5G7) - C(6G7)	-171.2(7)
C(3G6) - C(4G6) - C(5G6) - C(6G6)	-171 (1)	O(4G6) - C(1G7) - O(5G7) - C(5G7)	60 (1)
O(4G5) - C(1G6) - O(5G6) - C(5G6)	61 (1)	C(2G7) - C(1G7) - O(5G7) - C(5G7)	-57.8(9)
C(2G6) - C(1G6) - O(5G6) - C(5G6)	-60 (1)	C(6G7) - C(5G7) - O(5G7) - C(1G7)	179.6(7)
C(6G6) - C(5G6) - O(5G6) - C(1G6)	-180 (1)	C(4G7) - C(5G7) - O(5G7) - C(1G7)	55.2(9)
C(4G6) - C(5G6) - O(5G6) - C(1G6)	56 (1)	O(5G7) - C(5G7) - C(6G7) - O(6G7)	-68.8(9)
O(5G6) - C(5G6) - C(6G6) - O(6G6)	-50 (2)	C(4G7) - C(5G7) - C(6G7) - O(6G7)	53 (1)

Table A6 Fractional co-ordinates (x 10^4) of hydrogen atoms for β-cyclodextrin - (RS)-ibuprofen complex.

H	x/a	y/b	z/c
H(1G1)	-298	3025	2426
H(2G1)	-1270	3070	2955
H(3G1)	-1056	1935	3374
H(4G1)	-2232	2437	2028
H(5G1)	-1107	1764	1808
H(611)	-1559	1905	306
H(612)	-2177	1642	608
H(1G2)	-3197	2014	1762
H(2G2)	-3873	1418	2348
H(3G2)	-2573	802	3057
H(4G2)	-3872	477	1694
H(5G2)	-2506	741	1490

H(621)	-3089	677	-41
H(622)	-3073	108	424
H(1G3)	-4045	-370	1728
H(2G3)	-3695	-1179	2562
H(3G3)	-2291	-744	3126
H(4G3)	-2756	-1702	2088
H(5G3)	-2403	-693	1404
H(631)	-2866	-1077	19
H(632)	-2277	-1478	614
H(1G4)	-1922	-2234	2055
H(2G4)	-863	-2588	3040
H(3G4)	-393	-1520	3591
H(4G4)	157	-2265	2585
H(5G4)	-618	-1260	2054
H(1G5)	1257	-2223	2856
H(2G5)	2373	-1951	3812
H(3G5)	1684	-972	4061
H(4G5)	2776	-1070	3251
H(5G5)	1301	-832	2316
H(651)	1561	-959	1032
H(652)	2114	-525	1598
H(1G6)	3374	-362	3355
H(2G6)	3764	437	4178
H(3G6)	2299	558	4163
H(4G6)	3042	1252	3306
H(5G6)	1905	505	2434
H(661)	2080	700	1142
H(662)	2057	1275	1577
H(1G7)	2674	2046	3214
H(2G7)	2058	2673	3838
H(3G7)	1097	1818	3854
H(4G7)	780	2801	2846
H(5G7)	828	1741	2140
H(671)	789	2200	823
H(672)	69	2287	1054

Appendix B : SUPPLEMENTARY DATA FOR TRIMEB-(S)-IBUPROFEN COMPLEX.

TABLE B1. Fractional atomic coordinates (x 10^4) and thermal parameters ($Å^2$ x 10^3) with estimated standard deviations in parentheses for TRIMEB - (S)-ibuprofen complex.

$$U_{eq} = (1/3)\ \Sigma_i\Sigma_j\ U_{ij}\ a_i^*\ a_j^*\ a_i.a_j$$

Atom	x/a	y/b	z/c	U_{eq}
C(1G1)	8631(6)	4637(5)	4754(4)	42(4)
C(2G1)	7917(6)	4164(4)	4917(3)	38(4)
C(3G1)	7372(6)	3943(4)	4486(3)	35(3)
C(4G1)	6980(6)	4528(4)	4251(3)	36(4)
C(5G1)	7712(6)	4970(4)	4093(3)	38(4)
C(6G1)	7403(7)	5569(5)	3869(4)	51(4)
C(7G1)	8547(7)	3736(5)	5633(4)	59(4)
C(8G1)	6664(7)	2952(5)	4435(4)	70(5)
C(9G1)	6354(9)	6358(5)	3941(4)	94(7)
O(2G1)	8282(4)	3619(3)	5147(2)	45(3)
O(3G1)	6696(5)	3547(3)	4660(2)	49(3)
O(4G1)	6473(4)	4316(3)	3846(2)	39(2)
O(5G1)	8220(4)	5141(3)	4516(2)	39(2)
O(6G1)	6731(5)	5825(3)	4154(3)	63(3)
C(1G2)	11802(6)	4178(5)	4041(3)	47(4)
C(2G2)	11517(6)	3738(5)	4457(4)	41(4)
C(3G2)	10508(6)	3725(5)	4492(3)	37(4)
C(4G2)	10141(6)	4389(5)	4517(4)	43(4)
C(5G2)	10530(6)	4805(5)	4123(4)	43(4)
C(6G2)	10304(7)	5498(5)	4184(4)	60(5)
C(7G2)	12676(8)	2992(6)	4478(5)	105(6)
C(8G2)	9856(7)	2804(5)	4826(4)	61(5)
C(9G2)	10303(11)	6451(6)	3786(6)	137(9)
O(2G2)	11765(5)	3096(4)	4387(3)	63(3)
O(3G2)	10273(4)	3389(3)	4913(2)	44(3)
O(4G2)	9205(4)	4306(3)	4435(2)	40(3)
O(5G2)	11468(5)	4765(3)	4141(2)	51(3)
O(6G2)	10506(6)	5804(4)	3749(3)	89(4)
C(1G3)	12454(7)	3908(5)	2177(3)	43(4)
C(2G3)	12454(7)	3283(5)	2437(3)	46(4)
C(3G3)	11917(7)	3332(5)	2904(4)	50(4)
C(4G3)	12162(6)	3907(5)	3201(3)	43(4)
C(5G3)	12126(6)	4495(5)	2891(3)	45(4)
C(6G3)	12355(7)	5098(5)	3134(4)	53(4)
C(7G3)	12527(15)	2280(7)	2137(6)	212(14)
C(8G3)	11266(9)	2467(6)	3304(5)	96(7)
C(9G3)	13455(8)	5616(6)	3562(5)	101(6)

O(2G3)	12162(6)	2812(4)	2134(3)	82(4)
O(3G3)	12041(5)	2768(3)	3172(3)	63(3)
O(4G3)	11528(4)	3929(3)	3594(2)	41(2)
O(5G3)	12702(4)	4402(3)	2488(2)	42(3)
O(6G3)	13194(5)	5037(3)	3360(3)	61(3)
C(1G4)	10512(6)	4540(5)	696(3)	48(4)
C(2G4)	11366(6)	4166(6)	628(4)	60(5)
C(3G4)	11644(6)	3877(5)	1102(3)	48(4)
C(4G4)	11627(6)	4341(5)	1522(3)	39(4)
C(5G4)	10813(6)	4733(5)	1537(3)	43(4)
C(6G4)	10890(7)	5286(5)	1877(4)	57(5)
C(7G4)	11272(10)	3863(7)	-194(4)	122(8)
C(8G4)	12646(9)	3037(5)	913(5)	83(6)
C(9G4)	10153(9)	6043(6)	2336(5)	102(6)
O(2G4)	11284(5)	3695(4)	289(3)	75(4)
O(3G4)	12527(4)	3666(4)	1073(2)	56(3)
O(4G4)	11628(4)	4013(3)	1972(2)	43(3)
O(5G4)	10646(4)	5011(3)	1061(2)	49(2)
O(6G4)	10085(5)	5557(4)	1972(3)	78(3)
C(1G5)	7105(7)	4029(5)	610(4)	42(4)
C(2G5)	7690(6)	3657(5)	268(4)	47(4)
C(3G5)	8614(6)	3602(5)	454(4)	41(4)
C(4G5)	8975(6)	4233(5)	591(4)	44(4)
C(5G5)	8353(6)	4572(5)	928(3)	42(4)
C(6G5)	8615(7)	5210(5)	1063(3)	47(4)
C(7G5)	6600(8)	3043(6)	-121(4)	82(6)
C(8G5)	9436(9)	2731(6)	166(5)	101(7)
C(9G5)	9136(8)	6166(6)	732(4)	76(6)
O(2G5)	7350(5)	3058(3)	179(3)	59(3)
O(3G5)	9163(5)	3358(3)	81(3)	58(3)
O(4G5)	9822(4)	4146(3)	818(2)	41(2)
O(5G5)	7504(4)	4633(3)	710(2)	37(3)
O(6G5)	8851(5)	5563(3)	638(2)	52(3)
C(1G6)	5017(7)	3582(5)	2061(4)	44(4)
C(2G6)	5333(7)	2975(5)	1840(4)	50(4)
C(3G6)	6186(7)	3065(5)	1574(4)	50(5)
C(4G6)	6125(6)	3592(5)	1222(4)	42(4)
C(5G6)	5733(7)	4177(5)	1451(4)	43(4)
C(6G6)	5536(7)	4703(5)	1108(4)	57(5)
C(7G6)	5123(9)	1944(5)	2107(4)	92(6)
C(8G6)	7293(8)	2325(5)	1341(5)	91(6)
C(9G6)	4195(7)	4436(7)	710(4)	84(6)
O(2G6)	5426(5)	2529(3)	2227(3)	62(3)
O(3G6)	6408(5)	2492(4)	1346(3)	62(3)
O(4G6)	6998(4)	3707(3)	1055(2)	48(3)
O(5G6)	4929(4)	4039(3)	1697(2)	47(3)
O(6G6)	5109(5)	4541(4)	675(3)	64(3)
C(1G7)	5654(6)	4630(5)	3765(4)	51(4)
C(2G7)	4937(7)	4143(5)	3703(3)	43(4)

C(3G7)	5090(7)	3739(5)	3255(4)	47(4)
C(4G7)	5222(7)	4147(5)	2819(3)	45(4)
C(5G7)	5835(7)	4693(5)	2920(4)	51(5)
C(6G7)	5778(9)	5187(6)	2525(4)	68(6)
C(7G7)	4579(8)	4069(6)	4549(4)	70(6)
C(8G7)	4423(7)	2731(6)	3335(4)	68(5)
C(9G7)	6758(14)	5805(10)	2168(7)	243(15)
O(2G7)	4838(4)	3731(3)	4117(2)	52(3)
O(3G7)	4347(4)	3344(3)	3166(2)	47(3)
O(4G7)	5585(4)	3779(3)	2438(2)	45(3)
O(5G7)	5662(5)	5012(3)	3361(2)	50(3)
O(6G7)	6510(9)	5563(6)	2551(4)	148(6)
C(1)	7340(7)	1749(6)	3431(4)	54(4)
C(2)	6930(8)	2164(7)	3120(4)	74(5)
C(3)	7311(10)	2750(7)	3014(5)	83(6)
C(4)	8102(11)	2922(7)	3212(4)	81(7)
C(5)	8526(8)	2491(7)	3501(4)	74(6)
C(6)	8148(8)	1907(6)	3613(4)	70(5)
C(7)	6896(8)	1097(6)	3553(4)	77(5)
C(8)	6190(9)	1270(6)	3923(7)	93(7)
O(9)	5435(7)	1339(5)	3782(4)	120(5)
O(10)	6397(6)	1331(4)	4350(3)	98(4)
C(11)	6564(9)	735(6)	3122(4)	85(6)
C(12)	8551(10)	3550(6)	3102(5)	109(7)
C(13)	8762(15)	3696(10)	2615(7)	208(15)
C(14)	9040(12)	3328(9)	2267(5)	195(13)
C(15)	9092(14)	4383(8)	2625(7)	265(15)

TABLE B2. Anisotropic atoms have thermal parameters ($Å^2 \times 10^{3)}$ of the form:

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$$

Atom	U11	U22	U33	U23	U13	U12
C(1G1)	35(6)	51(7)	41(6)	-18(6)	0(6)	-1(6)
C(2G1)	42(7)	34(6)	38(6)	0(5)	-1(5)	10(6)
C(3G1)	29(6)	43(7)	35(6)	-6(5)	11(5)	1(6)
C(4G1)	44(7)	29(6)	35(6)	-1(5)	-9(5)	9(6)
C(5G1)	44(7)	37(6)	33(6)	-5(5)	-1(5)	-6(6)
C(6G1)	66(8)	35(7)	53(7)	19(6)	-26(7)	-5(7)
C(7G1)	64(8)	64(8)	49(7)	7(6)	-15(7)	-3(7)
C(8G1)	55(8)	68(9)	88(10)	-5(8)	4(8)	-25(7)
C(9G1)	155(14)	51(8)	77(9)	13(8)	-25(10)	42(10)
O(2G1)	47(5)	43(4)	44(4)	0(4)	-5(4)	2(4)
O(3G1)	52(5)	46(5)	48(5)	-3(4)	4(4)	-6(4)
O(4G1)	37(4)	41(4)	38(4)	-9(4)	-3(4)	1(4)
O(5G1)	35(4)	40(4)	43(4)	8(4)	-8(4)	6(4)

O(5G1)	35(4)	40(4)	43(4)	8(4)	-8(4)	6(4)
O(6G1)	78(6)	54(5)	58(5)	-1(5)	-5(5)	24(5)
C(1G2)	25(6)	68(9)	48(7)	18(7)	-6(5)	-2(6)
C(2G2)	34(6)	48(7)	42(7)	0(6)	-8(5)	7(6)
C(3G2)	36(6)	49(7)	26(6)	-2(6)	0(5)	4(6)
C(4G2)	32(6)	47(7)	50(7)	2(6)	0(6)	0(6)
C(5G2)	30(7)	46(7)	52(7)	14(6)	2(6)	-1(6)
C(6G2)	54(8)	50(8)	77(9)	1(7)	10(7)	0(7)
C(7G2)	48(9)	114(12)	152(14)	47(11)	18(9)	42(9)
C(8G2)	63(8)	47(7)	73(8)	12(7)	2(7)	16(7)
C(9G2)	207(19)	48(10)	156(15)	42(10)	56(15)	28(12)
O(2G2)	48(5)	75(6)	65(5)	19(5)	11(4)	19(5)
O(3G2)	41(4)	47(5)	44(4)	1(4)	-4(4)	-2(4)
O(4G2)	36(4)	44(4)	40(4)	-4(4)	-1(4)	-4(4)
O(5G2)	43(5)	50(5)	59(5)	1(4)	0(4)	-1(4)
O(6G2)	117(8)	63(6)	87(7)	12(5)	19(6)	-3(6)
C(1G3)	47(7)	51(7)	33(6)	-8(6)	9(6)	1(6)
C(2G3)	36(6)	56(8)	47(7)	7(7)	8(6)	23(6)
C(3G3)	31(6)	58(8)	62(8)	14(7)	5(6)	3(6)
C(4G3)	27(6)	57(8)	45(7)	1(6)	7(5)	2(6)
C(5G3)	28(6)	67(8)	41(6)	17(6)	-6(5)	9(6)
C(6G3)	52(8)	49(8)	58(7)	12(6)	-9(7)	-5(7)
C(7G3)	415(38)	79(13)	141(16)	-48(13)	79(22)	8(20)
C(8G3)	127(13)	62(9)	99(11)	36(8)	9(10)	-15(10)
C(9G3)	94(11)	73(10)	135(13)	-34(10)	-37(10)	-1(9)
O(2G3)	137(9)	49(5)	59(6)	-23(5)	16(6)	-1(6)
O(3G3)	76(6)	46(5)	67(5)	16(4)	22(5)	5(5)
O(4G3)	40(4)	51(4)	33(4)	2(3)	-2(3)	-1(4)
O(5G3)	31(4)	55(5)	39(4)	17(4)	1(4)	0(4)
O(6G3)	56(5)	53(5)	74(5)	0(4)	-20(5)	8(4)
C(1G4)	53(7)	66(8)	24(6)	20(6)	-9(5)	0(7)
C(2G4)	22(6)	99(10)	60(8)	31(8)	7(6)	-7(7)
C(3G4)	36(7)	64(8)	44(7)	7(6)	-12(6)	-5(6)
C(4G4)	22(6)	55(7)	41(6)	16(6)	-7(5)	-5(5)
C(5G4)	39(7)	38(6)	53(7)	7(6)	-1(6)	-2(6)
C(6G4)	53(8)	55(8)	63(8)	12(7)	0(7)	9(7)
C(7G4)	132(14)	195(17)	39(8)	-3(10)	-1(9)	19(14)
C(8G4)	75(9)	65(9)	109(10)	-24(9)	-5(9)	13(9)
C(9G4)	115(12)	79(10)	113(12)	-7(10)	-11(11)	33(10)
O(2G4)	72(6)	112(7)	41(5)	-19(5)	-6(4)	12(6)
O(3G4)	37(4)	72(6)	59(5)	-5(4)	-2(4)	11(4)
O(4G4)	28(4)	56(5)	46(4)	7(4)	2(4)	-1(4)
O(5G4)	36(4)	57(5)	52(5)	26(4)	-8(4)	0(4)
O(6G4)	71(6)	90(6)	71(5)	-23(5)	-7(5)	17(6)
C(1G5)	34(6)	40(7)	51(7)	2(6)	-2(6)	-3(6)
C(2G5)	32(6)	71(9)	39(6)	13(6)	-7(5)	6(7)
C(3G5)	37(6)	43(7)	43(6)	6(6)	2(6)	-3(6)
C(4G5)	23(6)	72(9)	35(6)	21(6)	5(5)	16(6)
C(5G5)	51(7)	45(7)	31(6)	14(6)	-4(6)	-11(6)

C(6G5)	35(6)	76(9)	31(6)	11(7)	5(5)	19(7)
C(7G5)	60(9)	94(11)	93(10)	-28(9)	-7(8)	-9(8)
C(8G5)	104(12)	59(10)	138(13)	-31(9)	11(11)	28(9)
C(9G5)	79(10)	85(10)	63(8)	-3(8)	-18(8)	-12(9)
O(2G5)	53(5)	41(5)	84(6)	-17(4)	5(5)	-12(4)
O(3G5)	51(5)	57(5)	65(5)	-19(4)	3(4)	17(4)
O(4G5)	32(4)	52(5)	40(4)	14(4)	0(4)	-4(4)
O(5G5)	29(4)	45(5)	35(4)	3(4)	0(3)	5(4)
O(6G5)	66(5)	31(4)	59(5)	-1(4)	-17(4)	-6(4)
C(1G6)	36(7)	55(8)	41(7)	3(6)	2(6)	-16(6)
C(2G6)	56(8)	49(8)	45(7)	2(7)	-7(6)	-18(7)
C(3G6)	42(7)	66(9)	42(7)	3(7)	-8(6)	-13(7)
C(4G6)	28(6)	51(7)	46(7)	-9(6)	1(5)	-5(6)
C(5G6)	33(7)	46(7)	50(7)	18(6)	0(6)	-10(6)
C(6G6)	47(8)	65(8)	58(8)	15(7)	25(7)	6(7)
C(7G6)	129(13)	58(9)	90(10)	8(8)	-8(10)	-33(9)
C(8G6)	77(11)	50(9)	145(13)	1(9)	23(10)	11(8)
C(9G6)	41(8)	146(13)	63(8)	29(9)	0(7)	2(8)
O(2G6)	91(6)	42(5)	51(5)	3(4)	-3(5)	-27(5)
O(3G6)	69(6)	43(5)	74(6)	-8(5)	15(5)	-4(5)
O(4G6)	35(4)	57(5)	51(5)	14(4)	-4(4)	3(4)
O(5G6)	34(4)	63(5)	43(4)	17(4)	0(4)	3(4)
O(6G6)	46(5)	96(7)	49(5)	19(5)	1(4)	11(5)
C(1G7)	35(7)	65(8)	54(7)	-18(7)	-5(6)	2(7)
C(2G7)	28(6)	57(7)	44(7)	5(6)	2(5)	8(6)
C(3G7)	37(7)	54(8)	50(7)	1(6)	-9(6)	5(7)
C(4G7)	38(7)	64(8)	34(6)	7(6)	-4(6)	-1(6)
C(5G7)	48(8)	51(8)	54(8)	10(7)	1(6)	1(7)
C(6G7)	89(10)	61(8)	54(8)	10(7)	-12(8)	-7(8)
C(7G7)	74(9)	91(10)	45(8)	-4(7)	16(7)	-26(8)
C(8G7)	52(8)	83(10)	69(8)	3(8)	-2(7)	-22(8)
C(9G7)	294(33)	195(26)	240(29)	-58(23)	115(27)	147(24)
O(2G7)	49(5)	63(5)	43(4)	-3(4)	0(4)	-6(4)
O(3G7)	47(5)	41(5)	52(5)	15(4)	-5(4)	-2(4)
O(4G7)	42(4)	50(5)	41(4)	0(4)	6(4)	0(4)
O(5G7)	68(5)	53(5)	31(4)	2(4)	-5(4)	-5(5)
O(6G7)	184(13)	148(11)	110(9)	67(8)	-17(9)	-97(10)
C(1)	40(7)	77(9)	46(7)	-14(7)	20(6)	3(7)
C(2)	50(8)	98(11)	73(9)	-2(9)	8(7)	-2(9)
C(3)	81(11)	98(12)	71(9)	10(9)	8(9)	2(10)
C(4)	96(12)	104(13)	43(8)	-4(8)	17(8)	5(11)
C(5)	58(9)	97(11)	69(9)	-19(9)	9(8)	-29(9)
C(6)	68(9)	94(11)	48(7)	-13(8)	3(7)	4(9)
C(7)	52(8)	80(10)	100(11)	18(9)	48(8)	21(8)
C(8)	60(10)	60(9)	158(16)	29(11)	-43(12)	-19(8)
O(9)	101(8)	147(9)	112(8)	16(7)	27(7)	6(8)
O(10)	116(8)	127(8)	52(5)	-9(6)	-5(6)	-22(7)
C(11)	111(11)	94(10)	50(8)	-30(8)	1(8)	-17(9)
C(12)	150(15)	74(10)	103(12)	6(9)	6(11)	-52(11)

C(14)	246(24)	278(27)	62(11)	-35(14)	68(14)	116(21)
C(15)	426(38)	144(18)	224(23)	2(16)	146(25)	166(23)

TABLE B3. Bond lengths (Å) with estimated standard deviations in parentheses for TRIMEB - (S)-ibuprofen complex.

C(1G1) - C(2G1)	1.55(1)	C(6G3) - O(6G3)	1.43(1)
C(1G1) - O(5G1)	1.41(1)	C(7G3) - O(2G3)	1.26(1)
C(1G1) - O(4G2)	1.43(1)	C(8G3) - O(3G3)	1.39(1)
C(2G1) - C(3G1)	1.53(1)	C(9G3) - O(6G3)	1.41(1)
C(2G1) - O(2G1)	1.44(1)	C(1G4) - C(2G4)	1.54(1)
C(3G1) - C(4G1)	1.53(1)	C(1G4) - O(5G4)	1.44(1)
C(3G1) - O(3G1)	1.42(1)	C(1G4) - O(4G5)	1.39(1)
C(4G1) - C(5G1)	1.52(1)	C(2G4) - C(3G4)	1.51(1)
C(4G1) - O(4G1)	1.43(1)	C(2G4) - O(2G4)	1.38(1)
C(5G1) - C(6G1)	1.50(1)	C(3G4) - C(4G4)	1.52(1)
C(5G1) - O(5G1)	1.45(1)	C(3G4) - O(3G4)	1.42(1)
C(6G1) - O(6G1)	1.40(1)	C(4G4) - C(5G4)	1.50(1)
C(7G1) - O(2G1)	1.43(1)	C(4G4) - O(4G4)	1.43(1)
C(8G1) - O(3G1)	1.41(1)	C(5G4) - C(6G4)	1.51(1)
C(9G1) - O(6G1)	1.40(1)	C(5G4) - O(5G4)	1.46(1)
O(4G1) - C(1G7)	1.43(1)	C(6G4) - O(6G4)	1.38(1)
C(1G2) - C(2G2)	1.54(1)	C(7G4) - O(2G4)	1.38(1)
C(1G2) - O(5G2)	1.38(1)	C(8G4) - O(3G4)	1.42(1)
C(1G2) - O(4G3)	1.41(1)	C(9G4) - O(6G4)	1.45(1)
C(2G2) - C(3G2)	1.54(1)	C(1G5) - C(2G5)	1.52(1)
C(2G2) - O(2G2)	1.43(1)	C(1G5) - O(5G5)	1.45(1)
C(3G2) - C(4G2)	1.52(1)	C(1G5) - O(4G6)	1.42(1)
C(3G2) - O(3G2)	1.41(1)	C(2G5) - C(3G5)	1.50(1)
C(4G2) - C(5G2)	1.52(1)	C(2G5) - O(2G5)	1.40(1)
C(4G2) - O(4G2)	1.45(1)	C(3G5) - C(4G5)	1.50(1)
C(5G2) - C(6G2)	1.53(1)	C(3G5) - O(3G5)	1.42(1)
C(5G2) - O(5G2)	1.43(1)	C(4G5) - C(5G5)	1.51(1)
C(6G2) - O(6G2)	1.40(1)	C(4G5) - O(4G5)	1.45(1)
C(7G2) - O(2G2)	1.43(1)	C(5G5) - C(6G5)	1.47(1)
C(8G2) - O(3G2)	1.42(1)	C(5G5) - O(5G5)	1.43(1)
C(9G2) - O(6G2)	1.42(1)	C(6G5) - O(6G5)	1.44(1)
C(1G3) - C(2G3)	1.51(1)	C(7G5) - O(2G5)	1.41(1)
C(1G3) - O(5G3)	1.41(1)	C(8G5) - O(3G5)	1.42(1)
C(1G3) - O(4G4)	1.40(1)	C(9G5) - O(6G5)	1.38(1)
C(2G3) - C(3G3)	1.53(1)	C(1G6) - C(2G6)	1.51(1)
C(2G3) - O(2G3)	1.38(1)	C(1G6) - O(5G6)	1.41(1)
C(3G3) - C(4G3)	1.52(1)	C(1G6) - O(4G7)	1.42(1)
C(3G3) - O(3G3)	1.42(1)	C(2G6) - C(3G6)	1.50(1)
C(4G3) - C(5G3)	1.52(1)	C(2G6) - O(2G6)	1.44(1)
C(4G3) - O(4G3)	1.45(1)	C(3G6) - C(4G6)	1.49(1)
C(5G3) - C(6G3)	1.49(1)	C(3G6) - O(3G6)	1.42(1)
C(5G3) - O(5G3)	1.43(1)	C(4G6) - C(5G6)	1.52(1)

C(3G6) - O(3G6)	1.42(1)	C(6G7) - O(6G7)	1.38(1)
C(4G6) - C(5G6)	1.52(1)	C(7G7) - O(2G7)	1.45(1)
C(4G6) - O(4G6)	1.43(1)	C(8G7) - O(3G7)	1.39(1)
C(5G6) - C(6G6)	1.50(1)	C(9G7) - O(6G7)	1.24(2)
C(5G6) - O(5G6)	1.43(1)	C(1) - C(2)	1.38(1)
C(6G6) - O(6G6)	1.40(1)	C(1) - C(6)	1.37(1)
C(7G6) - O(2G6)	1.37(1)	C(1) - C(7)	1.58(1)
C(8G6) - O(3G6)	1.39(1)	C(2) - C(3)	1.41(2)
C(9G6) - O(6G6)	1.41(1)	C(3) - C(4)	1.37(2)
C(1G7) - C(2G7)	1.52(1)	C(4) - C(5)	1.38(1)
C(1G7) - O(5G7)	1.38(1)	C(4) - C(12)	1.53(2)
C(2G7) - C(3G7)	1.52(1)	C(5) - C(6)	1.41(1)
C(2G7) - O(2G7)	1.45(1)	C(7) - C(8)	1.53(2)
C(3G7) - C(4G7)	1.50(1)	C(7) - C(11)	1.51(1)
C(3G7) - O(3G7)	1.43(1)	C(8) - O(9)	1.22(1)
C(4G7) - C(5G7)	1.52(1)	C(8) - O(10)	1.23(2)
C(4G7) - O(4G7)	1.42(1)	C(12) - C(13)	1.41(2)
C(5G7) - C(6G7)	1.52(1)	C(13) - C(14)	1.31(2)
C(5G7) - O(5G7)	1.42(1)	C(13) - C(15)	1.55(2)

TABLE B4. Bond angles (°) with estimated standard deviations in parentheses for TRIMEB - (S)-ibuprofen complex.

O(5G1) - C(1G1) - O(4G2)	111.3(8)	C(3G2) - C(2G2) - O(2G2)	104.7(8)
C(2G1) - C(1G1) - O(4G2)	106.7(8)	C(2G2) - C(3G2) - O(3G2)	108.3(8)
C(2G1) - C(1G1) - O(5G1)	108.7(7)	C(2G2) - C(3G2) - C(4G2)	110.6(8)
C(1G1) - C(2G1) - O(2G1)	112.5(7)	C(4G2) - C(3G2) - O(3G2)	109.9(8)
C(1G1) - C(2G1) - C(3G1)	110.9(7)	C(3G2) - C(4G2) - O(4G2)	103.9(8)
C(3G1) - C(2G1) - O(2G1)	107.8(7)	C(3G2) - C(4G2) - C(5G2)	111.5(8)
C(2G1) - C(3G1) - O(3G1)	108.4(7)	C(5G2) - C(4G2) - O(4G2)	110.0(8)
C(2G1) - C(3G1) - C(4G1)	106.9(7)	C(4G2) - C(5G2) - O(5G2)	109.2(8)
C(4G1) - C(3G1) - O(3G1)	110.4(7)	C(4G2) - C(5G2) - C(6G2)	113.4(9)
C(3G1) - C(4G1) - O(4G1)	106.5(7)	C(6G2) - C(5G2) - O(5G2)	106.2(8)
C(3G1) - C(4G1) - C(5G1)	110.0(7)	C(5G2) - C(6G2) - O(6G2)	107.9(9)
C(5G1) - C(4G1) - O(4G1)	111.5(7)	C(2G2) - O(2G2) - C(7G2)	112.3(9)
C(4G1) - C(5G1) - O(5G1)	108.5(7)	C(3G2) - O(3G2) - C(8G2)	114.8(7)
C(4G1) - C(5G1) - C(6G1)	114.7(8)	C(1G1) - O(4G2) - C(4G2)	116.4(7)
C(6G1) - C(5G1) - O(5G1)	106.6(7)	C(1G2) - O(5G2) - C(5G2)	114.5(7)
C(5G1) - C(6G1) - O(6G1)	109.3(8)	C(6G2) - O(6G2) - C(9G2)	110(1)
C(2G1) - O(2G1) - C(7G1)	112.6(7)	O(5G3) - C(1G3) - O(4G4)	111.6(8)
C(3G1) - O(3G1) - C(8G1)	114.3(7)	C(2G3) - C(1G3) - O(4G4)	109.5(8)
C(4G1) - O(4G1) - C(1G7)	116.4(7)	C(2G3) - C(1G3) - O(5G3)	111.7(7)
C(1G1) - O(5G1) - C(5G1)	114.8(7)	C(1G3) - C(2G3) - O(2G3)	110.7(8)
C(6G1) - O(6G1) - C(9G1)	112.3(8)	C(1G3) - C(2G3) - C(3G3)	109.8(8)
O(5G2) - C(1G2) - O(4G3)	114.0(8)	C(3G3) - C(2G3) - O(2G3)	112.8(8)
C(2G2) - C(1G2) - O(4G3)	109.8(8)	C(2G3) - C(3G3) - O(3G3)	108.0(8)
C(2G2) - C(1G2) - O(5G2)	107.5(7)	C(2G3) - C(3G3) - C(4G3)	112.2(9)
C(1G2) - C(2G2) - O(2G2)	114.0(8)	C(4G3) - C(3G3) - O(3G3)	111.6(9)
C(1G2) - C(2G2) - C(3G2)	109.8(8)	C(3G3) - C(4G3) - O(4G3)	105.4(8)

C(3G3) - C(4G3) - C(5G3)	110.7(8)	C(3G5)-O(3G5)-C(8G5)	113.4(9)
C(5G3) - C(4G3) - O(4G3)	111.7(8)	C(1G4)-O(4G5)-C(4G5)	119.5(7)
C(4G3) - C(5G3) - O(5G3)	107.5(8)	C(1G5)-O(5G5)-C(5G5)	112.2(7)
C(4G3) - C(5G3) - C(6G3)	116.8(8)	C(6G5)-O(6G5)-C(9G5)	114.2(7)
C(6G3) - C(5G3) - O(5G3)	109.0(8)	O(5G6)-C(1G6)-O(4G7)	112.2(8)
C(5G3)-C(6G3)-O(6G3)	109.1(8)	C(2G6)-C(1G6)-O(4G7)	110.9(9)
C(2G3)-O(2G3)-C(7G3)	121(1)	C(2G6)-C(1G6)-O(5G6)	109.6(9)
C(3G3)-O(3G3)-C(8G3)	114.4(9)	C(1G6)-C(2G6)-O(2G6)	107.4(9)
C(1G2)-O(4G3)-C(4G3)	118.1(7)	C(1G6)-C(2G6)-C(3G6)	111.3(9)
C(1G3)-O(5G3)-C(5G3)	114.4(7)	C(3G6)-C(2G6)-O(2G6)	111.2(9)
C(6G3)-O(6G3)-C(9G3)	110.2(8)	C(2G6)-C(3G6)-O(3G6)	108.2(9)
O(5G4)-C(1G4)-O(4G5)	111.2(7)	C(2G6)-C(3G6)-C(4G6)	111.1(9)
C(2G4)-C(1G4)-O(4G5)	110.9(8)	C(4G6)-C(3G6)-O(3G6)	112.2(9)
C(2G4)-C(1G4)-O(5G4)	109.2(8)	C(3G6)-C(4G6)-O(4G6)	106.3(8)
C(1G4)-C(2G4)-O(2G4)	112.6(8)	C(3G6)-C(4G6)-C(5G6)	111.9(9)
C(1G4)-C(2G4)-C(3G4)	110.1(8)	C(5G6)-C(4G6)-O(4G6)	111.2(8)
C(3G4)-C(2G4)-O(2G4)	108.5(9)	C(4G6)-C(5G6)-O(5G6)	111.4(8)
C(2G4)-C(3G4)-O(3G4)	110.3(7)	C(4G6)-C(5G6)-C(6G6)	115.4(9)
C(2G4)-C(3G4)-C(4G4)	112.9(9)	C(6G6)-C(5G6)-O(5G6)	106.5(8)
C(4G4)-C(3G4)-O(3G4)	105.3(7)	C(5G6)-C(6G6)-O(6G6)	116.5(9)
C(3G4)-C(4G4)-O(4G4)	110.1(8)	C(2G6)-O(2G6)-C(7G6)	113.0(8)
C(3G4)-C(4G4)-C(5G4)	113.5(7)	C(3G6)-O(3G6)-C(8G6)	117.1(9)
C(5G4)-C(4G4)-O(4G4)	104.5(7)	C(1G5)-O(4G6)-C(4G6)	117.9(7)
C(4G4)-C(5G4)-O(5G4)	110.2(7)	C(1G6)-O(5G6)-C(5G6)	113.6(7)
C(4G4)-C(5G4)-C(6G4)	112.9(8)	C(6G6)-O(6G6)-C(9G6)	116.0(9)
C(6G4)-C(5G4)-O(5G4)	104.8(8)	O(4G1)-C(1G7)-O(5G7)	113.1(7)
C(5G4)-C(6G4)-O(6G4)	112.1(9)	O(4G1)-C(1G7)-C(2G7)	108.9(8)
C(2G4)-O(2G4)-C(7G4)	118(1)	C(2G7)-C(1G7)-O(5G7)	108.7(8)
C(3G4)-O(3G4)-C(8G4)	115.9(8)	C(1G7)-C(2G7)-O(2G7)	113.7(8)
C(1G3)-O(4G4)-C(4G4)	115.6(7)	C(1G7)-C(2G7)-C(3G7)	111.6(9)
C(1G4)-O(5G4)-C(5G4)	111.8(7)	C(3G7)-C(2G7)-O(2G7)	108.2(8)
C(6G4)-O(6G4)-C(9G4)	111.6(9)	C(2G7)-C(3G7)-O(3G7)	110.5(8)
O(5G5)-C(1G5)-O(4G6)	108.3(8)	C(2G7)-C(3G7)-C(4G7)	110.1(9)
C(2G5)-C(1G5)-O(4G6)	110.6(8)	C(4G7)-C(3G7)-O(3G7)	108.1(8)
C(2G5)-C(1G5)-O(5G5)	109.6(8)	C(3G7)-C(4G7)-O(4G7)	109.0(8)
C(1G5)-C(2G5)-O(2G5)	111.6(8)	C(3G7)-C(4G7)-C(5G7)	112.4(8)
C(1G5)-C(2G5)-C(3G5)	112.2(9)	C(5G7)-C(4G7)-O(4G7)	108.6(8)
C(3G5)-C(2G5)-O(2G5)	109.5(8)	C(4G7)-C(5G7)-O(5G7)	114.3(8)
C(2G5)-C(3G5)-O(3G5)	109.4(8)	C(4G7)-C(5G7)-C(6G7)	111.4(9)
C(2G5)-C(3G5)-C(4G5)	111.0(8)	C(6G7)-C(5G7)-O(5G7)	105.8(9)
C(4G5)-C(3G5)-O(3G5)	107.1(8)	C(5G7)-C(6G7)-O(6G7)	109(1)
C(3G5)-C(4G5)-O(4G5)	108.7(8)	C(2G7)-O(2G7)-C(7G7)	112.1(8)
C(3G5)-C(4G5)-C(5G5)	110.7(8)	C(3G7)-O(3G7)-C(8G7)	115.4(8)
C(5G5)-C(4G5)-O(4G5)	110.7(8)	C(1G6) - O(4G7) - C(4G7)	117.9(8)
C(4G5)-C(5G5)-O(5G5)	110.5(7)	C(1G7) - O(5G7) - C(5G7)	114.3(8)
C(4G5)-C(5G5)-C(6G5)	115.4(8)	C(6G7) - O(6G7) - C(9G7)	117(1)
C(6G5)-C(5G5)-O(5G5)	105.6(8)	C(6) - C(1) - C(7)	121(1)
C(5G5)-C(6G5)-O(6G5)	110.3(7)	C(2) - C(1) - C(7)	120(1)
C(2G5)-O(2G5)-C(7G5)	115.0(8)	C(2) - C(1) - C(6)	118(1)

C(1) - C(2) - C(3)	121(1)	C(8) - C(7) - C(11)	115(1)
C(2) - C(3) - C(4)	121(1)	C(7) - C(8) - O(10)	119(1)
C(3) - C(4) - C(12)	123(1)	C(7) - C(8) - O(9)	117(2)
C(3) - C(4) - C(5)	118(1)	O(9) - C(8) - O(10)	122(1)
C(5) - C(4) - C(12)	119(1)	C(4) - C(12) - C(13)	119(1)
C(4) - C(5) - C(6)	122(1)	C(12) - C(13) - C(15)	106(2)
C(1) - C(6) - C(5)	121(1)	C(12) - C(13) - C(14)	130(2)
C(1) - C(7) - C(11)	115(1)	C(14) - C(13) - C(15)	118(2)
C(1) - C(7) - C(8)	103(1)		

TABLE B5. Torsion angles (°) with estimated standard deviations in parentheses for TRIMEB - (S)-ibuprofen complex.

O(5G1) - C(1G1) - O(4G2) - C(4G2)	107.7(9)	O(4G3) - C(1G2) - O(5G2) - C(5G2)	55(1)
C(2G1) - C(1G1) - O(4G2) - C(4G2)	-133.8(8)	C(2G2) - C(1G2) - O(5G2) - C(5G2)	-67(1)
O(4G2) - C(1G1) - O(5G1) - C(5G1)	58(1)	O(5G2) - C(1G2) - C(2G2) - O(2G2)	175.8(8)
C(2G1) - C(1G1) - O(5G1) - C(5G1)	-59(1)	O(5G2) - C(1G2) - C(2G2) - C(3G2)	59(1)
O(5G1) - C(1G1) - C(2G1) - O(2G1)	177.7(7)	O(4G3) - C(1G2) - C(2G2) - O(2G2)	51(1)
O(5G1) - C(1G1) - C(2G1) - C(3G1)	57(1)	O(4G3) - C(1G2) - C(2G2) - C(3G2)	-66(1)
O(4G2) - C(1G1) - C(2G1) - O(2G1)	57.6(9)	C(1G2) - C(2G2) - O(2G2) - C(7G2)	76(1)
O(4G2) - C(1G1) - C(2G1) - C(3G1)	-63.3(9)	C(1G2) - C(2G2) - C(3G2) - C(4G2)	-52(1)
C(1G1) - C(2G1) - O(2G1) - C(7G1)	77.4(9)	C(1G2) - C(2G2) - C(3G2) - O(3G2)	-172.1(7)
C(1G1) - C(2G1) - C(3G1) - C(4G1)	-57.1(9)	C(3G2) - C(2G2) - O(2G2) - C(7G2)	-164.0(9)
C(1G1) - C(2G1) - C(3G1) - O(3G1)	-176.1(7)	O(2G2) - C(2G2) - C(3G2) - O(3G2)	65.2(9)
C(3G1) - C(2G1) - O(2G1) - C(7G1)	-160.0(7)	O(2G2) - C(2G2) - C(3G2) - C(4G2)	-174.4(8)
O(2G1) - C(2G1) - C(3G1) - O(3G1)	60.3(9)	C(2G2) - C(3G2) - O(3G2) - C(8G2)	-111.7(9)
O(2G1) - C(2G1) - C(3G1) - C(4G1)	179.3(7)	C(2G2) - C(3G2) - C(4G2) - C(5G2)	49(1)
C(2G1) - C(3G1) - O(3G1) - C(8G1)	-126.0(8)	C(2G2) - C(3G2) - C(4G2) - O(4G2)	167.3(7)
C(2G1) - C(3G1) - C(4G1) - C(5G1)	58.8(9)	C(4G2) - C(3G2) - O(3G2) - C(8G2)	127.3(8)
C(2G1) - C(3G1) - C(4G1) - O(4G1)	179.8(7)	O(3G2) - C(3G2) - C(4G2) - O(4G2)	-73.2(9)
C(4G1) - C(3G1) - O(3G1) - C(8G1)	117.2(8)	O(3G2) - C(3G2) - C(4G2) - C(5G2)	168.5(8)
O(3G1) - C(3G1) - C(4G1) - O(4G1)	-62.5(9)	C(3G2) - C(4G2) - O(4G2) - C(1G1)	134.1(8)
O(3G1) - C(3G1) - C(4G1) - C(5G1)	176.5(7)	C(5G2) - C(4G2) - O(4G2) - C(1G1)	-106.5(9)
C(3G1) - C(4G1) - O(4G1) - C(1G7)	140.3(8)	C(3G2) - C(4G2) - C(5G2) - C(6G2)	-170.3(8)
C(3G1) - C(4G1) - C(5G1) - C(6G1)	-178.5(8)	C(3G2) - C(4G2) - C(5G2) - O(5G2)	-52(1)
C(3G1) - C(4G1) - C(5G1) - O(5G1)	-59.5(9)	O(4G2) - C(4G2) - C(5G2) - O(5G2)	-166.7(7)
C(5G1) - C(4G1) - O(4G1) - C(1G7)	-99.6(9)	O(4G2) - C(4G2) - C(5G2) - C(6G2)	75(1)
O(4G1) - C(4G1) - C(5G1) - O(5G1)	-177.5(6)	C(4G2) - C(5G2) - O(5G2) - C(1G2)	64(1)
O(4G1) - C(4G1) - C(5G1) - C(6G1)	64(1)	C(6G2) - C(5G2) - O(5G2) - C(1G2)	-173.7(8)
C(4G1) - C(5G1) - O(5G1) - C(1G1)	61.2(9)	C(4G2) - C(5G2) - C(6G2) - O(6G2)	-165.9(9)
C(6G1) - C(5G1) - O(5G1) - C(1G1)	-174.9(8)	O(5G2) - C(5G2) - C(6G2) - O(6G2)	74(1)
C(4G1) - C(5G1) - C(6G1) - O(6G1)	46(1)	C(5G2) - C(6G2) - O(6G2) - C(9G2)	180(1)
O(5G1) - C(5G1) - C(6G1) - O(6G1)	-73.6(9)	O(5G3) - C(1G3) - O(4G4) - C(4G4)	90.3(9)
C(5G1) - C(6G1) - O(6G1) - C(9G1)	-174.5(8)	C(2G3) - C(1G3) - O(4G4) - C(4G4)	-145.6(8)
C(4G1) - O(4G1) - C(1G7) - C(2G7)	-130.4(8)	O(4G4) - C(1G3) - O(5G3) - C(5G3)	61(1)
C(4G1) - O(4G1) - C(1G7) - O(5G7)	108.7(9)	C(2G3) - C(1G3) - O(5G3) - C(5G3)	-62(1)
O(5G2) - C(1G2) - O(4G3) - C(4G3)	106.7(9)	O(5G3) - C(1G3) - C(2G3) - O(2G3)	176.6(8)
C(2G2) - C(1G2) - O(4G3) - C(4G3)	-132.6(8)	O(5G3) - C(1G3) - C(2G3) - C(3G3)	51(1)

O(4G4) - C(1G3) - C(2G3) - O(2G3)	53(1)	O(4G4) - C(4G4) - C(5G4) - O(5G4)	-169.9(7)
O(4G4) - C(1G3) - C(2G3) - C(3G3)	-73(1)	O(4G4) - C(4G4) - C(5G4) - C(6G4)	73(1)
C(1G3) - C(2G3) - O(2G3) - C(7G3)	140(1)	C(4G4) - C(5G4) - O(5G4) - C(1G4)	61.2(9)
C(1G3) - C(2G3) - C(3G3) - C(4G3)	-48(1)	C(6G4) - C(5G4) - O(5G4) - C(1G4)	-177.1(7)
C(1G3) - C(2G3) - C(3G3) - O(3G3)	-171.5(8)	C(4G4) - C(5G4) - C(6G4) - O(6G4)	-166.2(8)
C(3G3) - C(2G3) - O(2G3) - C(7G3)	-97(1)	O(5G4) - C(5G4) - C(6G4) - O(6G4)	74(1)
O(2G3) - C(2G3) - C(3G3) - O(3G3)	65(1)	C(5G4) - C(6G4) - O(6G4) - C(9G4)	174.0(9)
O(2G3) - C(2G3) - C(3G3) - C(4G3)	-172.0(8)	O(5G5) - C(1G5) - O(4G6) - C(4G6)	113.4(9)
C(2G3) - C(3G3) - O(3G3) - C(8G3)	-127(1)	C(2G5) - C(1G5) - O(4G6) - C(4G6)	-126.5(9)
C(2G3) - C(3G3) - C(4G3) - C(5G3)	52(1)	O(4G6) - C(1G5) - O(5G5) - C(5G5)	61(1)
C(2G3) - C(3G3) - C(4G3) - O(4G3)	173.0(8)	C(2G5) - C(1G5) - O(5G5) - C(5G5)	-60(1)
C(4G3) - C(3G3) - O(3G3) - C(8G3)	110(1)	O(5G5) - C(1G5) - C(2G5) - O(2G5)	177.2(8)
O(3G3) - C(3G3) - C(4G3) - O(4G3)	-66(1)	O(5G5) - C(1G5) - C(2G5) - C(3G5)	54(1)
O(3G3) - C(3G3) - C(4G3) - C(5G3)	173.5(8)	O(4G6) - C(1G5) - C(2G5) - O(2G5)	58(1)
C(3G3) - C(4G3) - O(4G3) - C(1G2)	148.4(8)	O(4G6) - C(1G5) - C(2G5) - C(3G5)	-66(1)
C(5G3) - C(4G3) - O(4G3) - C(1G2)	-91.4(9)	C(1G5) - C(2G5) - O(2G5) - C(7G5)	72(1)
C(3G3) - C(4G3) - C(5G3) - C(6G3)	-179.8(9)	C(1G5) - C(2G5) - C(3G5) - C(4G5)	-51(1)
C(3G3) - C(4G3) - C(5G3) - O(5G3)	-57(1)	C(1G5) - C(2G5) - C(3G5) - O(3G5)	-168.9(8)
O(4G3) - C(4G3) - C(5G3) - O(5G3)	-174.0(7)	C(3G5) - C(2G5) - O(2G5) - C(7G5)	-162.7(9)
O(4G3) - C(4G3) - C(5G3) - C(6G3)	63(1)	O(2G5) - C(2G5) - C(3G5) - O(3G5)	67(1)
C(4G3) - C(5G3) - O(5G3) - C(1G3)	63.4(9)	O(2G5) - C(2G5) - C(3G5) - C(4G5)	-175.5(8)
C(6G3) - C(5G3) - O(5G3) - C(1G3)	-169.1(8)	C(2G5) - C(3G5) - O(3G5) - C(8G5)	-109(1)
C(4G3) - C(5G3) - C(6G3) - O(6G3)	54(1)	C(2G5) - C(3G5) - C(4G5) - C(5G5)	52(1)
O(5G3) - C(5G3) - C(6G3) - O(6G3)	-68(1)	C(2G5) - C(3G5) - C(4G5) - O(4G5)	173.5(8)
C(5G3) - C(6G3) - O(6G3) - C(9G3)	175.7(9)	C(4G5) - C(3G5) - O(3G5) - C(8G5)	131.2(9)
O(5G4) - C(1G4) - O(4G5) - C(4G5)	101.6(9)	O(3G5) - C(3G5) - C(4G5) - O(4G5)	-67(1)
C(2G4) - C(1G4) - O(4G5) - C(4G5)	-136.8(8)	O(3G5) - C(3G5) - C(4G5) - C(5G5)	171.0(8)
O(4G5) - C(1G4) - O(5G4) - C(5G4)	57.5(9)	C(3G5) - C(4G5) - O(4G5) - C(1G4)	136.8(8)
C(2G4) - C(1G4) - O(5G4) - C(5G4)	-65.1(9)	C(5G5) - C(4G5) - O(4G5) - C(1G4)	-101.3(9)
O(5G4) - C(1G4) - C(2G4) - O(2G4)	178.8(8)	C(3G5) - C(4G5) - C(5G5) - C(6G5)	-176.5(8)
O(5G4) - C(1G4) - C(2G4) - C(3G4)	58(1)	C(3G5) - C(4G5) - C(5G5) - O(5G5)	-57(1)
O(4G5) - C(1G4) - C(2G4) - O(2G4)	56(1)	O(4G5) - C(4G5) - C(5G5) - O(5G5)	-177.5(7)
O(4G5) - C(1G4) - C(2G4) - C(3G4)	-65(1)	O(4G5) - C(4G5) - C(5G5) - C(6G5)	63(1)
C(1G4) - C(2G4) - O(2G4) - C(7G4)	75(1)	C(4G5) - C(5G5) - O(5G5) - C(1G5)	62(1)
C(1G4) - C(2G4) - C(3G4) - C(4G4)	-48(1)	C(6G5) - C(5G5) - O(5G5) - C(1G5)	-172.9(8)
C(1G4) - C(2G4) - C(3G4) - O(3G4)	-165.6(8)	C(4G5) - C(5G5) - C(6G5) - O(6G5)	49(1)
C(3G4) - C(2G4) - O(2G4) - C(7G4)	-163(1)	O(5G5) - C(5G5) - C(6G5) - O(6G5)	-73.5(9)
O(2G4) - C(2G4) - C(3G4) - O(3G4)	71(1)	C(5G5) - C(6G5) - O(6G5) - C(9G5)	-177.9(8)
O(2G4) - C(2G4) - C(3G4) - C(4G4)	-171.7(8)	O(5G6) - C(1G6) - O(4G7) - C(4G7)	85(1)
C(2G4) - C(3G4) - O(3G4) - C(8G4)	-90(1)	C(2G6) - C(1G6) - O(4G7) - C(4G7)	-151.9(8)
C(2G4) - C(3G4) - C(4G4) - C(5G4)	46(1)	O(4G7) - C(1G6) - O(5G6) - C(5G6)	63(1)
C(2G4) - C(3G4) - C(4G4) - O(4G4)	162.2(8)	C(2G6) - C(1G6) - O(5G6) - C(5G6)	-61(1)
C(4G4) - C(3G4) - O(3G4) - C(8G4)	147.8(9)	O(5G6) - C(1G6) - C(2G6) - O(2G6)	179.0(8)
O(3G4) - C(3G4) - C(4G4) - O(4G4)	-77.4(9)	O(5G6) - C(1G6) - C(2G6) - C(3G6)	57(1)
O(3G4) - C(3G4) - C(4G4) - C(5G4)	165.9(8)	O(4G7) - C(1G6) - C(2G6) - O(2G6)	55(1)
C(3G4) - C(4G4) - O(4G4) - C(1G3)	92.7(9)	O(4G7) - C(1G6) - C(2G6) - C(3G6)	-67(1)
C(5G4) - C(4G4) - O(4G4) - C(1G3)	-145.1(8)	C(1G6) - C(2G6) - O(2G6) - C(7G6)	138.2(9)
C(3G4) - C(4G4) - C(5G4) - C(6G4)	-166.7(8)	C(1G6) - C(2G6) - C(3G6) - C(4G6)	-52(1)
C(3G4) - C(4G4) - C(5G4) - O(5G4)	-50(1)	C(1G6) - C(2G6) - C(3G6) - O(3G6)	-175.6(9)

C(3G6) - C(2G6) - O(2G6) - C(7G6)	-100(1)	O(3G7)-C(3G7)-C(4G7)-O(4G7)	-74(1)
O(2G6) - C(2G6) - C(3G6) - O(3G6)	65(1)	O(3G7)-C(3G7)-C(4G7)-C(5G7)	165.4(8)
O(2G6) - C(2G6) - C(3G6) - C(4G6)	-171.7(8)	C(3G7)-C(4G7)-O(4G7)-C(1G6)	102.7(9)
C(2G6) - C(3G6) - O(3G6) - C(8G6)	-142(1)	C(5G7)-C(4G7)-O(4G7)-C(1G6)	-134.6(9)
C(2G6) - C(3G6) - C(4G6) - C(5G6)	49(1)	C(3G7)-C(4G7)-C(5G7)-C(6G7)	-165.3(9)
C(2G6) - C(3G6) - C(4G6) - O(4G6)	170.1(8)	C(3G7)-C(4G7)-C(5G7)-O(5G7)	-45(1)
C(4G6) - C(3G6) - O(3G6) - C(8G6)	95(1)	O(4G7)-C(4G7)-C(5G7)-O(5G7)	-166.0(8)
O(3G6) - C(3G6) - C(4G6) - O(4G6)	-69(1)	O(4G7)-C(4G7)-C(5G7)-C(6G7)	74(1)
O(3G6) - C(3G6) - C(4G6) - C(5G6)	169.9(9)	C(4G7)-C(5G7)-O(5G7)-C(1G7)	55(1)
C(3G6) - C(4G6) - O(4G6) - C(1G5)	159.3(8)	C(6G7)-C(5G7)-O(5G7)-C(1G7)	177.7(8)
C(5G6) - C(4G6) - O(4G6) - C(1G5)	-78(1)	C(4G7)-C(5G7)-C(6G7)-O(6G7)	-162(1)
C(3G6) - C(4G6) - C(5G6) - C(6G6)	-172.2(9)	O(5G7)-C(5G7)-C(6G7)-O(6G7)	73(1)
C(3G6) - C(4G6) - C(5G6) - O(5G6)	-51(1)	C(5G7)-C(6G7)-O(6G7)-C(9G7)	151(2)
O(4G6) - C(4G6) - C(5G6) - O(5G6)	-169.3(8)	C(6)-C(1)-C(7)-C(8)	105(1)
O(4G6) - C(4G6) - C(5G6) - C(6G6)	69(1)	C(2)-C(1)-C(7)-C(8)	-78(1)
C(4G6) - C(5G6) - O(5G6) - C(1G6)	58(1)	C(6)-C(1)-C(7)-C(11)	-130(1)
C(6G6) - C(5G6) - O(5G6) - C(1G6)	-175.6(8)	C(2)-C(1)-C(7)-C(11)	48(2)
C(4G6) - C(5G6) - C(6G6) - O(6G6)	45(1)	C(7)-C(1)-C(6)-C(5)	-180(1)
O(5G6) - C(5G6) - C(6G6) - O(6G6)	-78(1)	C(2)-C(1)-C(6)-C(5)	3(2)
C(5G6) - C(6G6) - O(6G6) - C(9G6)	79(1)	C(6)-C(1)-C(2)-C(3)	-4(2)
O(4G1) - C(1G7) - O(5G7) - C(5G7)	61(1)	C(7)-C(1)-C(2)-C(3)	179(1)
O(4G1) - C(1G7) - C(2G7) - C(3G7)	-64(1)	C(1)-C(2)-C(3)-C(4)	1(2)
O(4G1) - C(1G7) - C(2G7) - O(2G7)	59(1)	C(2)-C(3)-C(4)-C(5)	3(2)
C(2G7) - C(1G7) - O(5G7) - C(5G7)	-61(1)	C(2)-C(3)-C(4)-C(12)	179(1)
O(5G7) - C(1G7) - C(2G7) - O(2G7)	-177.3(7)	C(3)-C(4)-C(12)-C(13)	-59(2)
O(5G7) - C(1G7) - C(2G7) - C(3G7)	60(1)	C(3)-C(4)-C(5)-C(6)	-3(2)
C(1G7) - C(2G7) - O(2G7) - C(7G7)	63(1)	C(5)-C(4)-C(12)-C(13)	118(2)
C(1G7) - C(2G7) - C(3G7) - C(4G7)	-53(1)	C(12)-C(4)-C(5)-C(6)	-180(1)
C(1G7) - C(2G7) - C(3G7) - O(3G7)	-171.9(8)	C(4)-C(5)-C(6)-C(1)	1(2)
C(3G7)-C(2G7)-O(2G7)-C(7G7)	-172.7(8)	C(1)-C(7)-C(8)-O(9)	98(2)
O(2G7)-C(2G7)-C(3G7)-O(3G7)	63(1)	C(1)-C(7)-C(8)-O(10)	-83(2)
O(2G7)-C(2G7)-C(3G7)-C(4G7)	-178.4(8)	C(11)-C(7)-C(8)-O(10)	151(1)
C(2G7)-C(3G7)-O(3G7)-C(8G7)	-98(1)	C(11)-C(7)-C(8)-O(9)	-28(2)
C(2G7)-C(3G7)-C(4G7)-C(5G7)	45(1)	C(4)-C(12)-C(13)-C(14)	-37(3)
C(2G7)-C(3G7)-C(4G7)-O(4G7)	165.0(8)	C(4)-C(12)-C(13)-C(15)	173(1)
C(4G7)-C(3G7)-O(3G7)-C(8G7)	141.3(9)		

Table B6 Fractional co-ordinates for hydrogen atoms of the TRIMEB-(S)-ibuprofen complex.

H	x/a	y/b	z/c
H(1G1)	8972	4810	5033
H(2G1)	7543	4394	5156
H(3G1)	7731	3705	4245
H(4G1)	6602	4767	4482
H(5G1)	8054	4737	3842
H(611)	7176	5484	3536

H(612)	7903	5872	3850
H(711)	8795	3343	5776
H(712)	8029	3874	5829
H(713)	9005	4072	5637
H(811)	6174	2702	4576
H(812)	7233	2728	4490
H(813)	6567	3006	4079
H(911)	5880	6523	4157
H(912)	6098	6244	3620
H(913)	6814	6687	3897
H(1G2)	12455	4215	4018
H(2G2)	11813	3908	4752
H(3G2)	10259	3516	4198
H(4G2)	10282	4598	4832
H(5G2)	10276	4652	3810
H(621)	10657	5681	4455
H(622)	9665	5546	4257
H(721)	12818	2541	4425
H(722)	12815	3110	4820
H(723)	13033	3256	4252
H(821)	9713	2600	5141
H(822)	10260	2527	4637
H(823)	9304	2873	4638
H(921)	10450	6664	3474
H(922)	10653	6642	4055
H(923)	9663	6502	3855
H(1G3)	12898	3893	1911
H(2G3)	13069	3172	2531
H(3G3)	11283	3385	2820
H(4G3)	12776	3882	3328
H(5G3)	11495	4547	2799
H(631)	11902	5199	3385
H(632)	12376	5442	2888
H(731)	12232	2001	1897
H(732)	12479	2092	2468
H(733)	13160	2327	2049
H(831)	11410	2078	3490
H(832)	10927	2354	3007
H(833)	10907	2753	3512
H(931)	14042	5567	3719
H(932)	13015	5751	3810
H(933)	13493	5939	3300
H(1G4)	10353	4749	383
H(2G4)	11816	4472	511
H(3G4)	11219	3527	1161
H(4G4)	12155	4611	1471
H(5G4)	10337	4443	1646
H(641)	11281	5608	1726
H(642)	11153	5140	2189

H(741)	11210	3477	-398
H(742)	11834	4081	-278
H(743)	10767	4150	-257
H(841)	13245	2903	1018
H(842)	12586	2973	555
H(843)	12194	2782	1086
H(941)	9560	6228	2397
H(942)	10561	6378	2220
H(943)	10385	5858	2644
H(1G5)	6518	4084	453
H(2G5)	7701	3896	-44
H(3G5)	8603	3322	745
H(4G5)	9046	4497	294
H(5G5)	8354	4305	1226
H(651)	9130	5190	1288
H(652)	8114	5423	1230
H(751)	6404	2599	-164
H(752)	6743	3228	-444
H(753)	6118	3291	34
H(851)	9817	2588	-107
H(852)	8909	2453	189
H(853)	9774	2711	476
H(951)	9288	6381	423
H(952)	9668	6147	945
H(953)	8661	6405	902
H(1G6)	4427	3516	2212
H(2G6)	4900	2820	1595
H(3G6)	6663	3182	1806
H(4G6)	5723	3481	948
H(5G6)	6206	4319	1676
H(661)	6107	4907	1020
H(662)	5157	5012	1282
H(761)	5205	1654	2388
H(762)	5460	1782	1822
H(763)	4486	1969	2023
H(861)	7365	1914	1172
H(862)	7512	2288	1681
H(863)	7638	2654	1166
H(961)	3957	4323	384
H(962)	3899	4825	829
H(963)	4082	4084	941
H(1G7)	5546	4903	4053
H(2G7)	4385	4394	3669
H(3G7)	5623	3476	3314
H(4G7)	4637	4323	2727
H(5G7)	6427	4491	2935
H(671)	5238	5448	2575
H(672)	5750	4980	2201
H(771)	4318	3782	4796

H(772)	4126	4377	4440
H(773)	5087	4298	4695
H(871)	3875	2494	3256
H(872)	4512	2736	3694
H(873)	4936	2524	3176
H(971)	7292	6065	2230
H(972)	6281	6077	2036
H(973)	6901	5468	1928
H	6357	2046	2967
H	7000	3046	2791
H	9119	2595	3634
H	8469	1606	3827
H	7329	789	3684
H(111)	7105	706	2917
H(112)	6078	925	2927
H(113)	6389	307	3231
H(121)	9112	3558	3290
H(122)	8151	3888	3222
H	8158	3801	2499
H(141)	9652	3189	2339
H(142)	9033	3563	1953
H(143)	8648	2954	2242
H(151)	9715	4392	2737
H(152)	8720	4634	2852
H(153)	9054	4565	2292