

# Thermoanalytical and Spectroscopic Characterization of $\beta$ -Cyclodextrin/Ketoprofen Inclusion Complexes

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**Abstract.** A method to determine the composition and hydration state of the complexes formed in aqueous solution by cyclodextrins (CD) is presented and applied to the  $\beta$ -CD/ketoprofen system; it is based on a combination of spectroscopic, calorimetric, and thermogravimetric analyses. The complexes have, on average and per  $\beta$ -CD mole, more than eleven water molecules, which are present in completely different bound states.

**Key words:**  $\beta$ -Cyclodextrin complex, ketoprofen, hydration, properties.

## 1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides whose ability to form inclusion complexes with water and a variety of other molecules is appreciated by drug developers [1, 2] and supramolecular chemists [3, 4]. This ability is due to the presence of a doughnut-shaped cavity, with diameters ranging from  $\sim 0.5$  nm (in  $\alpha$ -CD) to  $\sim 0.9$  nm (in  $\gamma$ -CD); these doughnuts may be joined together by threading them in necklace fashion with the inclusion compound itself [5–8], or by directly bonding together two or more modified CD molecules [9]. In most cases, the inclusion reaction takes place in an aqueous medium, and the obvious question is what part is played by hydration water [10] and, more generally, the solvent-induced forces? The thermodynamic mechanisms that determine the formation and stability of these complexes in aqueous solutions have been studied for a wide

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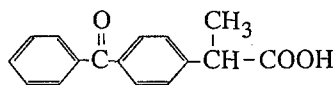
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range of cyclodextrins ( $\alpha$ ,  $\beta$ ,  $\gamma$ , or modified  $\beta$ ) and guest molecules [9, 11, 12]. It is found that the entropy of complex formation ( $\Delta S$ ) increases as the enthalpy change ( $\Delta H$ ) increases

$$T\Delta S = a\Delta H + E$$

where the parameters  $E$  and  $a$  describe large families of similar complexes; the energy  $E$  is of the order of  $\sim 10$  kJ/mol, while the coefficient  $a$  varies over the range 0.6–1. This uniform behaviour is quite puzzling in view of the different species and forces involved in the complexation processes; we suspect that the answer may involve the roles played by hydration water and by water as a solvent. Unfortunately, even the characterization of the stoichiometry of the complex in the solid state is not a trivial matter [13, 14]; in most cases, one searches for some spectroscopic signature of the complex and of the reagents, and roughly estimates the unreacted fraction in the coprecipitated sample. Here we present a method that, under favourable circumstances, allows determination of the complex stoichiometry, of the unreacted fractions of the reagents, and of the hydration state of the complex. We argue that this information is necessary for investigating the mechanisms of complex formation [10].

In this paper, we study the ternary system  $\beta$ -CD, water, ketoprofen [2-(3-benzoyl-phenyl)propionic acid], abbreviated to KETO [15, 16]



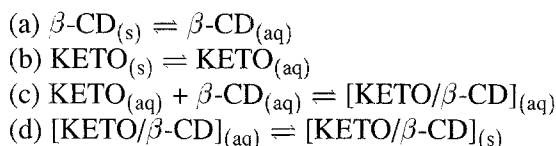
after having completed a careful analysis of the binary  $\beta$ -CD/ $\text{H}_2\text{O}$  system [17]. Complex formation takes place in stirred suspensions of water, KETO and  $\beta$ -CD. Thermogravimetry (TGA), differential scanning calorimetry (DSC) and infrared spectroscopy (FT-IR/PAS) have been used to characterize the products of reaction, and to determine the KETO/ $\beta$ -CD ratio ( $y$ ) of the complex and its hydration in the solid state. We provide evidence for the existence of two complexes, one with  $y \simeq 0.5$  and the other with  $y \simeq 1.0$ . Quite surprisingly, in both of them a KETO molecule appears to replace just one of the water molecules which are present in the fully hydrated  $\beta$ -CD form.

## 2. Experimental

### 2.1. SAMPLE PREPARATION

The starting materials are commercial  $\beta$ -CD $\cdot$ 11  $\text{H}_2\text{O}$  powder (Roquette, France; water content determined by TGA) and the anti-inflammatory drug ketoprofen (Carlo Erba Farmitalia, Italy). The inclusion complexes have been prepared starting from suspensions of the reagents in water with the following KETO/ $\beta$ -CD molar ratios: 1 : 1, 2 : 1, and 1 : 2. The suspensions were kept at 25 °C (room temperature: rt) and periodically stirred. Since both reagents and products are only moderately

soluble in water, several equilibria among solid (s) and solvated (aq) phases need to be considered:



It is expected that, due to its low water solubility, the complex formed in solution (reaction c) will precipitate (d), allowing reactions (a), (b), and (c) to move to the right; the net process results in conversion of the original solids,  $\beta\text{-CD}_{(s)}$  and  $\text{KETO}_{(s)}$ , into the solid complex (coprecipitate samples).

Since solutions may need long times to achieve equilibrium, the suspensions were studied at times ranging from hours to many days. Fixed amounts (10 mL) of the suspensions were drawn at the following times:

H8, H32, H56, D6H8, D7H8, D8H8, D9H8, D13H8, and D16

where Hxx indicates hours and Dxx days in aqueous suspension. These samples were filtered, dried, and stored for 48 hours in a wet atmosphere ( $p_{\text{H}_2\text{O}} = 18 \text{ mm Hg}$ ) before analysis. No significant differences were found among samples after one day in suspension. All the average values refer to samples treated from one to 16 days in suspension.

Suspension-treated  $\beta\text{-CD}$  was found to have a water content (thermogravimetrically determined) of  $11.8 \pm 0.2 \text{ H}_2\text{O}$  molecules, or about one water molecule more than the as-received product. In the following, the composition of fully hydrated  $\beta\text{-CD}$  will be assumed to be  $\beta\text{-CD}^* \cdot 11.8 \text{ H}_2\text{O}$ .

## 2.2. APPARATUS AND PROCEDURES

FT-IR/PAS measurements were carried out with a Nicolet 730 FT-IR spectrometer fitted with a MTEC 200 Photoacoustic Detector. Spectra were collected with a  $4 \text{ cm}^{-1}$  resolution by adding and FFT-transforming 64 interferograms. Carbon black was used as background. Since the IR bands due to water may obscure the spectral regions of interest, spectra were collected with samples dehydrated directly in the FT-IR cell. The samples were kept for 3 h in the FT-IR spectrometer at rt under a flow of dry nitrogen ( $900 \text{ L h}^{-1}$ ) before collecting data. TGA runs confirmed that this treatment yielded nearly complete dehydration.

TGA and DSC measurements were performed with samples of about 10 mg using DuPont units 951 and 910, respectively, interfaced to a TA2000 Thermal Analysis System (TA Instruments, USA). The experiments in a wet atmosphere were carried out under a flow of  $\text{N}_2$  ( $3.6 \text{ L h}^{-1}$ ) bubbled through water at rt. Under these conditions, dehydration begins above rt, and it is usually easy to distinguish different stages of water loss. In the TGA runs made to assess the water content, the samples were heated to  $120 \text{ }^\circ\text{C}$ , at  $1 \text{ }^\circ\text{C min}^{-1}$ , and kept for 3 h at this temperature.

With this thermal treatment, full dehydration was achieved while avoiding KETO evaporation and/or decomposition, which becomes appreciable above 140 °C. The DSC runs were performed at 2 °C min<sup>-1</sup>, which yielded a reasonable compromise between the magnitude of the peaks and their resolution. The top DSC temperature was limited to 100 °C, because the last thermal phenomenon, the KETO melting endotherm, was completed at this temperature.

All thermal experiments were repeated from five to eight times. Numeric results are quoted in the format: 'mean ± standard deviation' rather than 'mean ± standard deviation of the mean'. All the errors quoted have been estimated experimentally.

### 3. Results and Discussion

#### 3.1. FT-IR/PAS MEASUREMENTS

Two spectral regions are discussed in detail:

- (i) 3500–2500 cm<sup>-1</sup>, where O—H and aliphatic C—H stretching modes are located;
- (ii) 1800–1500 cm<sup>-1</sup>, where the prominent spectral feature is the C=O stretching mode.

##### (i) 3500–2500 cm<sup>-1</sup> Region

Figure 1a shows the spectrum of pure, dehydrated  $\beta$ -CD. The major spectral features are the broad band near 3300 cm<sup>-1</sup>, assigned to the stretching vibration of linked O—H groups, and the peak at 2921 cm<sup>-1</sup>, due to the aliphatic C—H stretching vibration. Figure 1b shows the KETO spectrum in the same region: it consists of a broad band attributed to the O—H stretching vibration of the dimeric form of the carboxylic acid.

Figures 2a, 2b, and 2c report the spectra of the coprecipitate from the different suspensions. In general, the spectral features of  $\beta$ -CD are substantially more evident in these spectra than in those obtained by combining the spectra of Figure 1 according to the stoichiometric ratios of KETO and  $\beta$ -CD. In particular, the KETO presence is not obvious in the spectra of the 1 : 1 and 1 : 2 samples (Figures 2b and 2c); only in the spectrum of the 2 : 1 sample (Figure 2a) do the shoulders at 2750 and 2500 cm<sup>-1</sup> reveal the presence of some unreacted KETO. The spectra in Figure 2 give evidence for the formation of complexes in which KETO loses some of its characteristic spectral features.

##### (ii) 1800–1500 cm<sup>-1</sup> Region

The spectrum of pure hydrated  $\beta$ -CD is dominated by the absorption due to water, while the spectrum of anhydrous  $\beta$ -CD is featureless. The spectrum of pure KETO (Figure 3a) has:

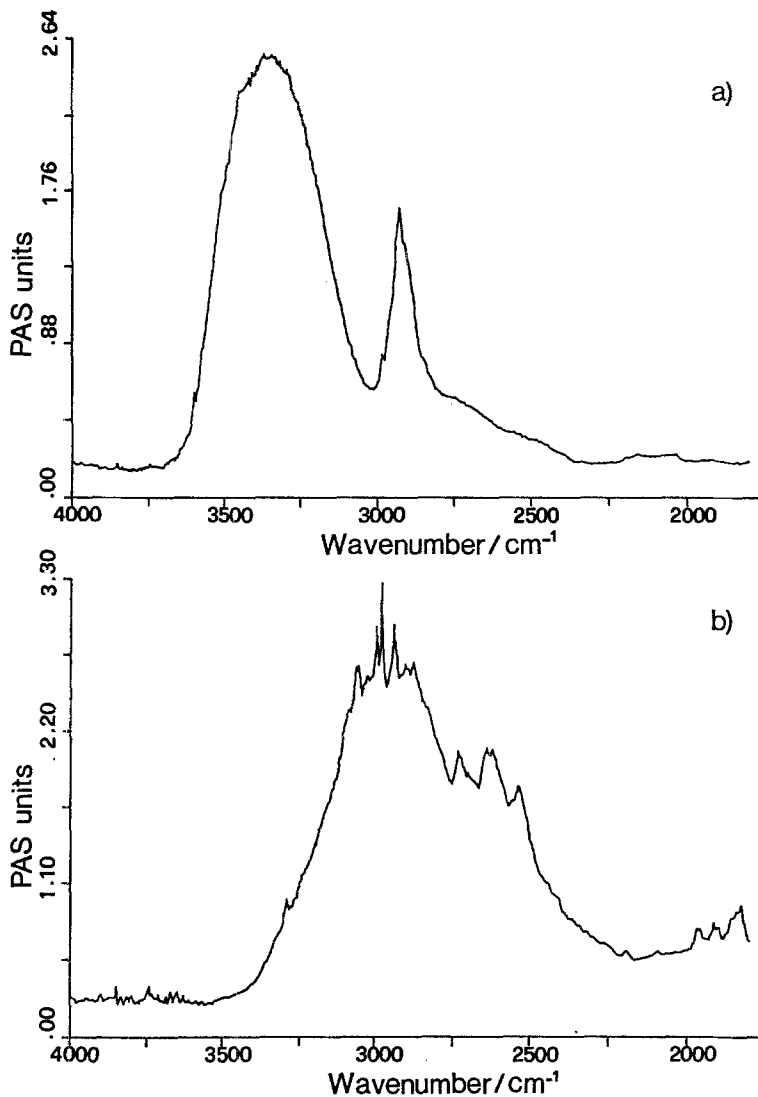


Fig. 1. FT-IR/PAS spectra (4000–2000 cm<sup>-1</sup> spectral region) collected at 4 cm<sup>-1</sup> after a dry nitrogen purge (900 L h<sup>-1</sup>) of 3 h: (a) pure  $\beta$ -CD; (b) pure KETO.

- a strong peak at 1695 cm<sup>-1</sup> due to the stretching vibration of carbonyl in the dimeric carboxylic group;
- a peak at 1655 cm<sup>-1</sup>, smaller and narrower than that at 1695 cm<sup>-1</sup>, ascribed to the stretching vibration of carbonyl in the ketonic group conjugated with two benzene rings;
- a peak at 1600 cm<sup>-1</sup> and a doublet centered at 1575 cm<sup>-1</sup>, both arising from stretching modes of the benzene ring.

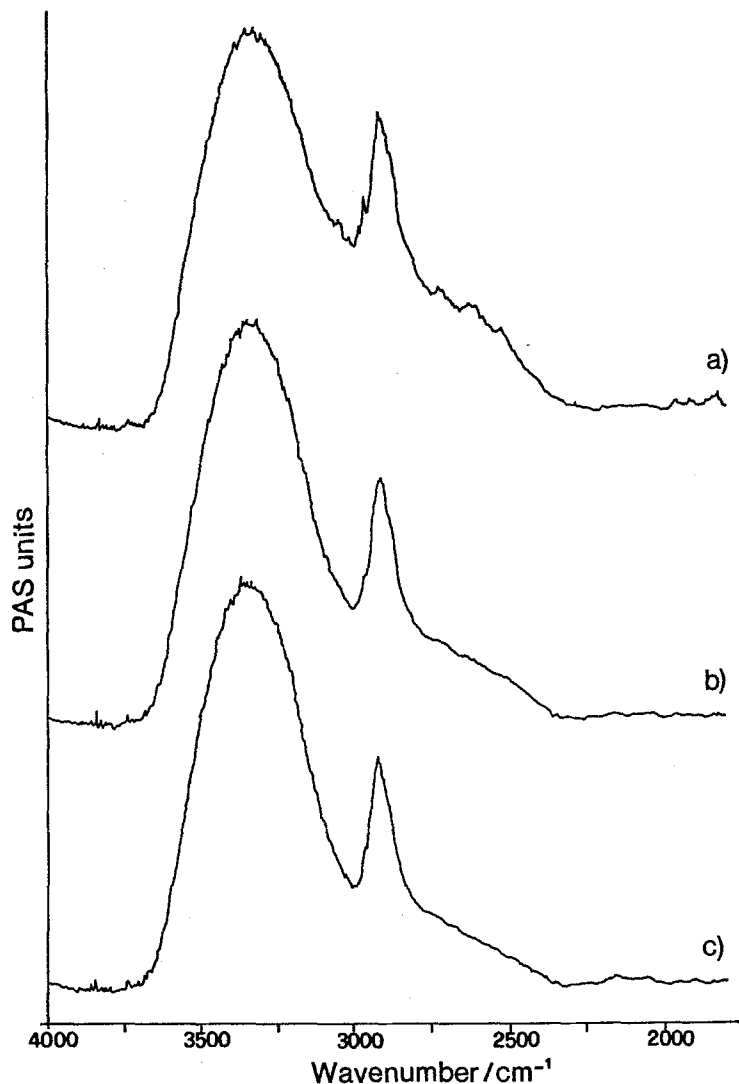


Fig. 2. FT-IR/PAS spectra of coprecipitate samples (spectral region  $4000\text{--}2000\text{ cm}^{-1}$ ) collected at  $4\text{ cm}^{-1}$  after purging in dry nitrogen ( $900\text{ L h}^{-1}$ ) for 3 h. Molar ratios of the suspensions are: (a) 2 : 1 KETO/ $\beta$ -CD; (b) 1 : 1 KETO/ $\beta$ -CD; (c) 1 : 2 KETO/ $\beta$ -CD.

The spectra of the coprecipitates from the 2 : 1, 1 : 1, and 1 : 2 KETO/ $\beta$ -CD solutions are reported in Figure 3b, 3c, and 3d, respectively. The stretching modes of the benzene ring ( $1600$  and  $1575\text{ cm}^{-1}$  peaks) are clearly evident in the spectrum of the 2 : 1 sample; the doublet has a reduced intensity in the 1 : 1 spectrum, and is nearly absent in the 1 : 2 sample. Although this trend is not a clear indication of complex formation, with increasing  $\beta$ -CD content, the stretching mode of the ketonic carbonyl at  $1655\text{ cm}^{-1}$ :

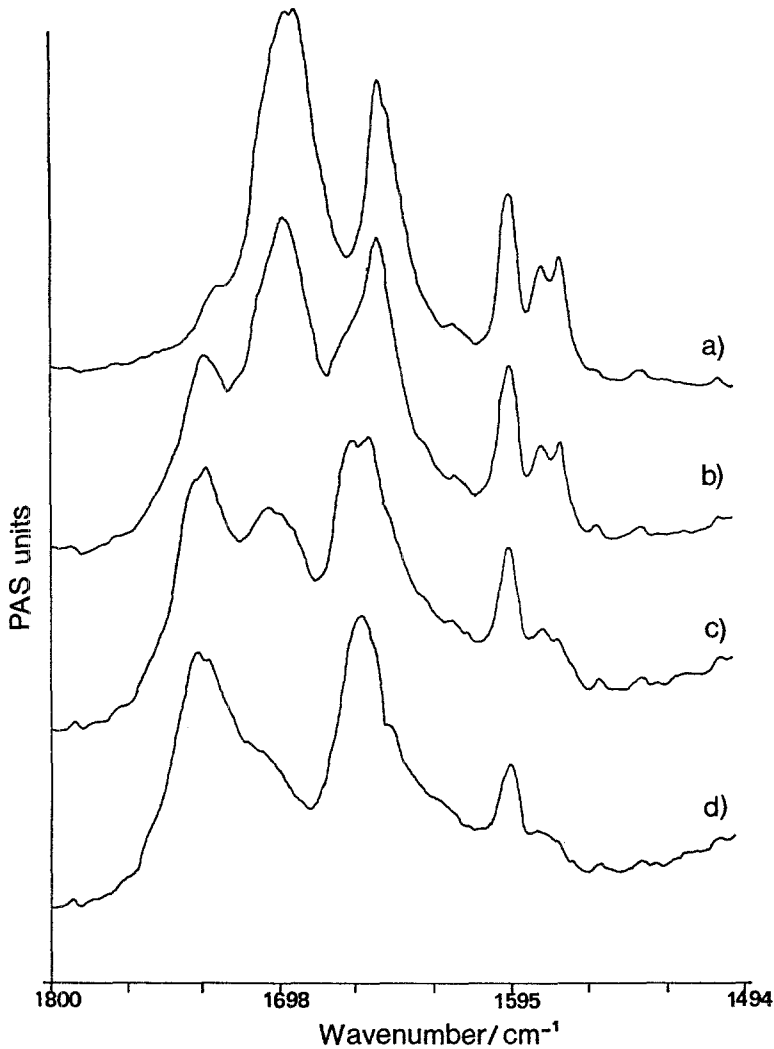


Fig. 3. FT-IR/PAS spectra (1800–1500  $\text{cm}^{-1}$  region, resolution 4  $\text{cm}^{-1}$ ) of samples purged in dry nitrogen after precipitation from suspensions with: (a) pure KETO; (b) 2 : 1 KETO/ $\beta$ -CD; (c) 1 : 1 KETO/ $\beta$ -CD; (d) 1 : 2 KETO/ $\beta$ -CD.

- becomes wider and shifts to higher frequency (2 : 1 sample, Figure 3b);
- turns into a doublet (1 : 1 sample, Figure 3c);
- evolves into a single peak, shifted to 1665  $\text{cm}^{-1}$ , with a low frequency shoulder (1 : 2 sample, Figure 3d).

It seems that complex formation shifts the stretching vibration of the ketonic carbonyl to higher frequency. If this is so, the presence of 'free' KETO is signaled by the residual absorption at 1655  $\text{cm}^{-1}$ ; Figure 3d suggests that the 1 : 2 sample is fully reacted, and the complex has the composition 0.5 KETO  $\cdot$   $\beta$ -CD.

The inclusion in the  $\beta$ -CD cavity of the benzene ring bearing the ketonic group is expected to produce a hydrogen bond between the carbonyl group and an O—H group of  $\beta$ -CD. On the other hand, formation of an H-bond should decrease the carbonyl stretching frequency and increase the conjugation between carbonyl and benzene rings, which also would decrease the C=O stretching frequency. The increase of the ketonic carbonyl peak from 1655 to 1665  $\text{cm}^{-1}$ , which accompanies the formation of the complex, probably indicates that some twisting or bending of the KETO molecule occurs, which leads to a loss of conjugation and then to a more rigid C=O bond. This is also confirmed by the disappearance of the 1575  $\text{cm}^{-1}$  stretching peak of the benzene ring, which is known to be a consequence of loss of conjugation of the benzene ring [18].

The formation of the inclusion complex may also be monitored by following the evolution of the stretching mode of the carbonyl bond in the carboxyl group, which, in pure KETO, occurs at 1695  $\text{cm}^{-1}$ ; this peak progressively decreases from the 2 : 1 sample (Figure 3b) to the 1 : 1 sample (Figure 3c), and has disappeared in the 1 : 2 sample (Figure 3d). Such a decrease is accompanied by the growth of a new peak, slightly above 1730  $\text{cm}^{-1}$ , which is assigned to the carbonyl stretching of the monomeric acid.

The conversion of the acid to the monomeric form is confirmed by the gradual disappearance of the 970  $\text{cm}^{-1}$  peak (not shown in the figures) due to OH $\cdots$ O out-of-plane deformation, which has been taken as strong evidence of the acid dimeric form [18]. All this implies that, in the dominant complex, both the benzene ring and the ketonic group are inside the  $\beta$ -CD cavities, and the monomeric carboxyl group is outside. We stress that the interpretation suggested for the shifts of the ketonic and carboxyl C=O stretching frequencies implies that the 1 : 2 KETO/ $\beta$ -CD molar ratio is the most likely composition of the inclusion complex.

### 3.2. THERMOGRAVIMETRIC MEASUREMENTS

Figure 4 shows the dynamic portion of a TGA run for a  $\beta$ -CD sample from an aqueous suspension, while Figure 5 refers to the coprecipitated 1 : 1 sample. The derivatives (curves b) of the TGA traces (curves a) are also shown to better display the different stages of dehydration. Overall weight losses were accurately determined by comparing the initial weight with the stable weight at the end of the high temperature isothermal annealing. The standard deviations of these losses were estimated from repeated measurements, and have been found to be consistently less than 0.1% (see Section 2).

Pure KETO does not display weight losses from rt to 100 °C. All samples from  $\beta$ -CD/KETO suspensions yield TGA curves which are very similar to that of Figure 5. As we will see later, this agrees with the fact that no unreacted  $\beta$ -CD is present in these suspensions, and that all  $\beta$ -CD/KETO complexes have nearly the same overall composition.

We call attention to the following:



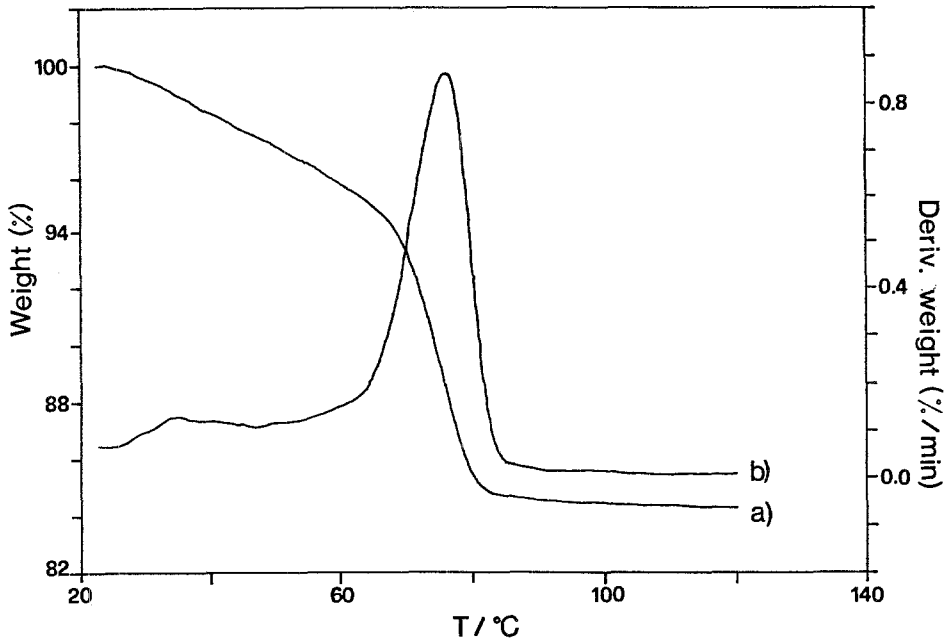


Fig. 4. TGA curve (a) and its derivative (b) for a  $\beta$ -CD sample treated in aqueous suspension. The native  $\beta$ -CD samples yield similarly shaped curves with slightly smaller weight losses.

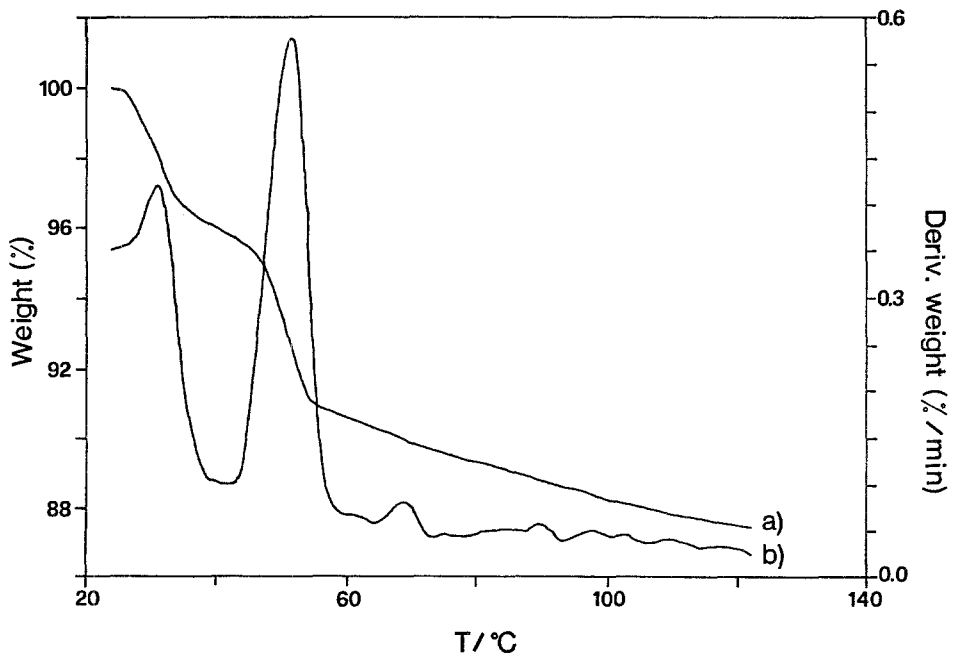
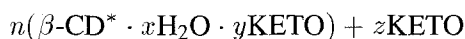


Fig. 5. TGA curve (a) and its derivative (b) for a coprecipitate sample (KETO/ $\beta$ -CD molar ratio 1 : 1). Coprecipitate samples from different suspensions (2 : 1 and 1 : 2) give very similar traces.

- (i) dehydration of  $\beta$ -CD is complete near 90 °C, apparently in a single stage, with nearly one-third of the water being released below 64 °C;
- (ii) in the coprecipitated samples, there are at least three stages: the first two are complete at 40 °C and 60 °C, respectively. The last one begins near 75 °C, but it is still underway at 120 °C and eventually terminates during the hours-long isothermal annealing. Although most of the water in the complex is released at substantially lower temperatures than in  $\beta$ -CD, the complex also has some tightly bonded water.

The FT-IR data imply that samples obtained from the 1 : 2 KETO/ $\beta$ -CD composition contain nearly 'pure' complex and that increasing amounts of excess KETO should be present in coprecipitate samples prepared by the 1 : 1 and 2 : 1 physical mixtures. Therefore, the composition of the samples may be written as:



where no hydration water is present in the  $z$  moles of the free KETO. To determine  $n$ ,  $x$ ,  $y$ , and  $z$ , the following relationships are used

- (i) the total weight  $M_h$  of the hydrated sample is

$$M_h = n(\beta\text{-CD}^* \cdot x\text{H}_2\text{O} \cdot y\text{KETO}) + z\text{KETO} \quad (1)$$

where the symbols of the compounds here represent their molar weight;

- (ii) the weight loss during dehydration  $\Delta M = M_h - M_d$  ( $M_d$  = weight of the fully dehydrated sample) is

$$\Delta M = n \cdot x \cdot \text{H}_2\text{O} \quad (2)$$

- (iii) the proportion  $\alpha = [\text{KETO}]/[\beta\text{-CD}^*]$  in the stirred suspension has been maintained in the precipitate; i.e.,

$$\alpha = (ny + z)/n \quad (3)$$

- (iv) the amount of free KETO is determined from the area  $\Delta H$  of the DSC peak around 90 °C and the molar heat of melting  $\Delta H_m$  of KETO (see below):

$$z = \Delta H / \Delta H_m \quad (4)$$

### 3.3. DSC MEASUREMENTS

Figures 6 and 7 report the DSC curves obtained with  $\beta$ -CD and three samples from different mixtures. The DSC trace of pure KETO shows only the melting peak of the substance, which yields a well-reproducible heat of fusion

$$\Delta H_m = (28.2 \pm 0.2) \text{ kJ mol}^{-1}.$$

The  $\beta$ -CD curve (Figure 6) has a single, asymmetric peak, extending from 30 to 90 °C, which agrees with the TGA datum of Figure 4. The DSCs of the coprecipitate samples reveal the following features:

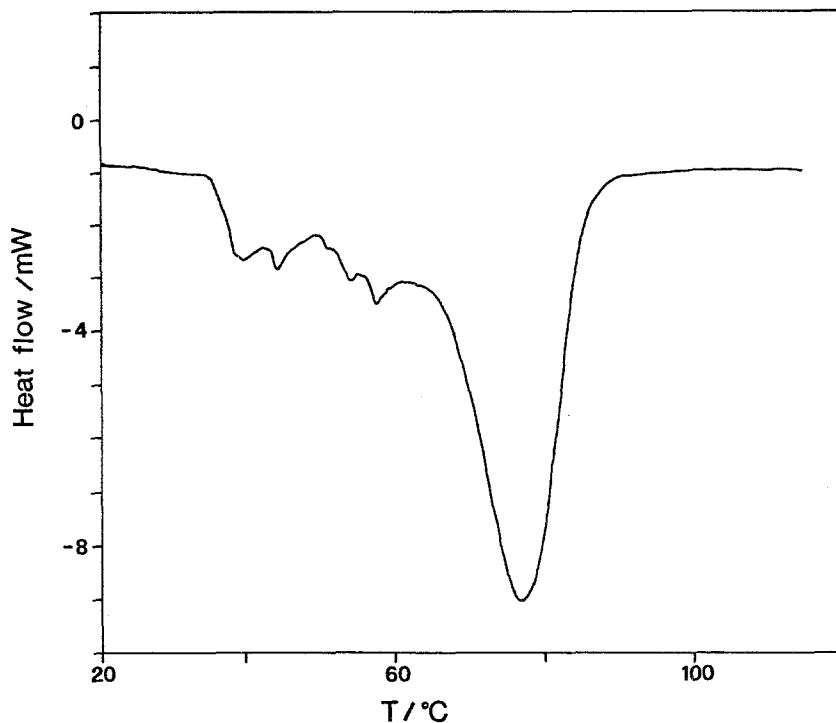


Fig. 6. DSC curve of a pure  $\beta$ -CD sample treated in aqueous suspension.

- (i) an endothermic drift of the baseline occurs between 10–15 °C and 25 °C, which is certainly not due to a change of hydration;
- (ii) the DSC peaks from 30 °C to 80 °C agree with the positions of the peaks in the derivative of TGA and are assigned to dehydration;
- (iii) while dehydration continues above 80 °C, the main feature above this temperature is the melting peak of KETO, which is apparent in both the 2 : 1 and 1 : 1 samples;
- (iv) corresponding dehydration peaks in Figure 7 have slightly different shapes, but almost the same positions and the same areas, i.e. energies, when normalized to one  $\beta$ -CD mole.

Although the different trends of the TGA and DSC curves may provide details about the dehydration kinetics, they make the evaluation of the dehydration enthalpies quite uncertain. The only feature of the DSC curves that is easy to analyze quantitatively is the melting peak of the KETO. This peak is absent in the 1 : 2 samples, in agreement with the IR evidence, and its area is proportional to the amount of 'free' KETO (see Equation 4). For the 1 : 2 samples there is no evidence of free KETO ( $z = 0$ ); it follows that  $y = 0.5$ , i.e. one KETO is complexed with two  $\beta$ -CD molecules.

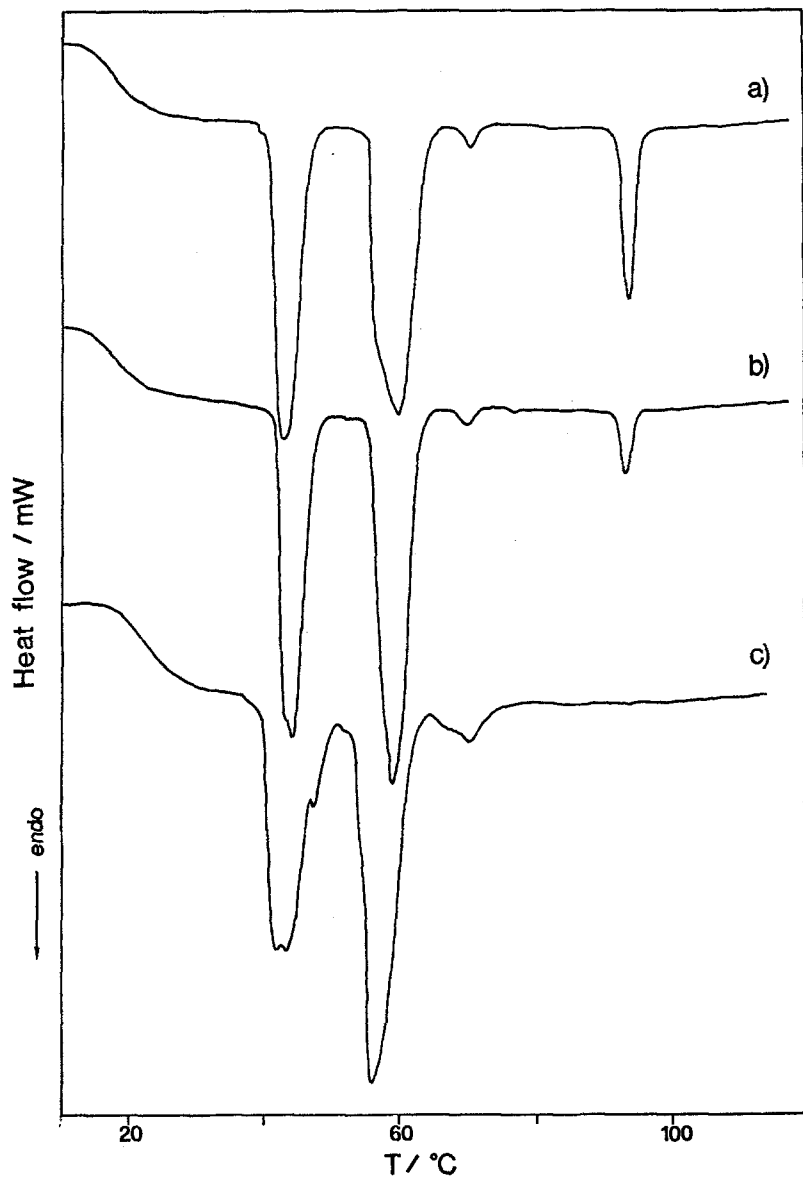


Fig. 7. DSC curves of coprecipitate samples from the suspensions: (a) 2 : 1 KETO/ $\beta$ -CD; (b) 1 : 1 KETO/ $\beta$ -CD; (c) 1 : 2 KETO/ $\beta$ -CD.

The mean values of  $y$  for the 1 : 1 and 2 : 1 samples have been determined to be  $0.58 \pm 0.07$  and  $0.56 \pm 0.08$ , respectively. These values are the same, within the experimental uncertainty, and their average of 0.57 would be obtained if 75% of the KETO molecules are bonded to two  $\beta$ -CD molecules, and the remaining 25% to one  $\beta$ -CD. The mean hydration value of the precipitates is  $x = 11.10 \pm 0.05$ ; if it is assumed that the KETO  $\cdot$   $\beta$ -CD complex 'loses' (relative to  $\beta$ -CD) two times more

water than  $\text{KETO} \cdot 2\beta\text{-CD}$ , it is found that, within the experimental uncertainty, each KETO molecule replaces a single  $\text{H}_2\text{O}$  when the complex is formed.

#### 4. Conclusions

It has been shown that  $\beta\text{-CD/KETO}$  inclusion complexes are obtained by coprecipitation from aqueous suspensions containing both components. The mean composition of the complex averaged over the preparations made with excess KETO (2 : 1 and 1 : 1) is 11.10  $\text{H}_2\text{O}$  : 0.57 KETO : 1  $\beta\text{-CD}^*$ . We suggest that the lack of a simple stoichiometry is due to formation of two complexes with  $\text{KETO}/\beta\text{-CD}^*$  ratios of 0.5 and 1. A 1 : 1 complex seems reasonable from a steric point of view. The 1 : 1 complex may imply formation of two H-bonds between the ketonic and a hydroxyl  $\beta\text{-CD}$  group, and the rupture of two H-bonds of the acid dimeric unit. In the 1 : 2 complex, both the benzene and ketonic group may be enclosed in adjacent  $\beta\text{-CD}$ s. This structure should be energetically favoured, because  $\beta\text{-CD}$  bonds preferentially with hydrophobic residues.

The average hydration state of the  $\text{KETO}-\beta\text{-CD}$  complexes has been determined; it is found that the number of absorbed water molecules per mole of CDs is barely changed by complexation, but that the bonding states of water are substantially modified. A similar result was found in a recent kinetic study [19] of decomposition of the complexes between  $\beta\text{-CD}$  and aromatic compounds. In this study, the energy of dissociation of dehydrated complexes with one mole of  $\beta\text{-CD}$  was found to be of the order of  $150 \text{ kJ mol}^{-1}$ , which is quite comparable with the energy required to extract the 6.5  $\text{H}_2\text{O}$  molecules within the cavity [16]. This means that direct host-guest bonding energies within the  $\beta\text{-CD}$  cavity tend to change little with changing guest molecule and that the thermodynamic balance should take into account other factors. In particular:

- (i) conformational changes within the macromolecular rings of CDs may substantially release its strain energy and are expected to play a major role in the enthalpy balance; they are probably related to the shifts of the vibrational frequencies of the ketonic  $\text{C}=\text{O}$ ;
- (ii) the main effect of the hydration of the complex is of inhibiting the dissociation reaction, and reducing the decrease in entropy expected from desolvation, thus stabilizing the complex.

A tentative microscopic picture of the entropy–enthalpy compensation mechanism may be as follows: substitution (partial or total) of cavity water with a guest molecule is a process assisted by formation of a hydration shell; the lower the hydration of the precipitate, the larger are likely to be the conformational changes of the CDs rings and the enthalpy term. On the other hand, the effect of desolvation becomes more favourable (or less unfavourable) to complex formation the higher the level of hydration. If these two terms dominate, the level of hydration determines both enthalpy and entropy of formation, and explains the mechanism

of compensation. Obviously, a careful study of hydration in large families of complexes would be needed to confirm this picture.

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