



## Infrared Study of Solid Dispersions of $\beta$ -Cyclodextrin with Naphthalene Derivatives

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### Abstract

The inclusion complexes of  $\beta$ -cyclodextrin ( $\beta$ -CD) with naphthalene and some of its derivatives in the solid state have been studied by infrared spectroscopy. Digital subtraction, deconvolution and curve fitting have been used to investigate the interactions between the naphthalene derivatives and  $\beta$ -CD. Several preparation methods for the solid dispersions have been tested, using FTIR as an effective tool to evaluate the interactions at the molecular level. The effects of temperature and humidity on the spectra have been also analyzed. A carbonyl moiety in the guest molecule can increase the stability of the complex by establishing specific interactions with the hydroxyl groups of the CD cavity rims. The stability of the complexes is higher for 2-naphthyl acetate than that for 1-naphthyl acetate, and so is the degree of association of its carbonyl groups. On the other hand, 2-acetylnaphthalene forms very stable inclusion complexes although its carbonyl groups appear to be significantly less associated.

### Introduction

Infrared spectroscopy is one of the most frequently used techniques that provide some information of cyclodextrin complexes in the solid state. The inclusion process causes restrictions both in the vibration and the rotation of the guest molecule, yielding shifts of IR bands or provoking that either new contributions appear or some others are lost. Nevertheless, the subtle changes observed in most systems involving cyclodextrin complexes limit the applicability of this technique. For instance, a typical 1:1 complex corresponds to ca. 15 weight percent of the guest molecule. Only the most intense bands of the probe can be easily detected in the spectra of the mixtures. Moreover, the effect of the guest in the spectrum of the cyclodextrin is necessarily small, due to the number of bonds this molecule possesses. Most of the research in which infrared spectroscopy is used as a characterization tool deal with guest molecules with a carbonyl moiety, such as carboxylic acids. A shift in this vibration mode is easily explained as a change in the association via hydrogen bonding when the molecule enters the cyclodextrin cavity [1–6]. The carbonyl bands are especially useful for infrared characterizations due to their high relative absorbance and their remarkable sensitivity to the changes in the environment surrounding them. FTIR has been used to study salicylic and benzoic acids as guests in CD complexes [7–9], and to investigate the influence of the preparation method on the complexation of several drugs [1–3]. There are also several studies dealing with the analysis

of the stretching vibrations of linked O–H of CD and N–H groups of some guest molecules [10]. The changes in the CD hydroxyl bands are usually too small due to the high number of O–H bonds in the CD molecule.

Nevertheless, those are not the only modifications expected. In a recent work, we have shown that the out-of-plane bending modes of C–H aromatic bonds (ca. 700–800  $\text{cm}^{-1}$ ) can be useful to determine whether the guest molecule presents a hindrance in that vibration mode attributable to its inclusion within the CD cavity [11]. In that work, we have also investigated the influence of the preparation method on the complexation of dibenzofuran-2-carboxylic acid with  $\beta$ -CD using infrared spectroscopy as a tool.

Although the stability of CD inclusion complexes with non-polar guests is mainly attributed to van der Waals forces and the hydrophobic effect [12], it has been shown that a polar group in the guest compound can increase the stability of the complex by establishing either dipolar or hydrogen bonding interactions. A number of crystal structures of CD complexes have clearly shown the well-defined hydrogen bonds between the substrates and the hydroxyls of CDs [13].

In this work, we have performed an extensive study of the complexes of  $\beta$ -CD with naphthalene and some of its derivatives using FTIR. Among the carbonyl derivatives of naphthalene, 2-acetylnaphthalene is one of the simplest. Nevertheless, we have also analyzed both 1- and 2-naphthyl acetates, since the ester carbonyl band is somewhat displaced with respect to the ketonic one, so it does not overlap with the spectrum of  $\beta$ -CD. Besides, we were able to study the influence of the substituent position on the complexa-

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tion process. Finally, we have also analyzed the complexes with naphthalene and 2-ethylnaphthalene, two molecules whose main absorbing modes have lower absorptivities. We have used several mathematical procedures such as digital subtraction, deconvolution and curve fitting, in order to elucidate the nature of the interaction between these molecules and  $\beta$ -CD.

## Experimental methods

### Preparation of samples

Naphthalene derivatives were obtained from Aldrich (naphthalene, 2-ethylnaphthalene and 2-acetylnaphthalene) and Acros Organics (1-naphthyl acetate and 2-naphthyl acetate).  $\beta$ -cyclodextrin was kindly donated by Roquette (Laisa España S.A.). The solvents ( $\text{CCl}_4$ , 1-propanol and 2-propanol from Panreac Química S.A., Spain) were of spectrophotometric grade. All of the reagents were used as received.

Three methods were used to prepare solid dispersions of the naphthalene derivatives with  $\beta$ -CD: coprecipitation, evaporation from either water or water/cosolvent mixtures and 'sealed-container heating'.

**Coprecipitation.** In this method, the naphthalene derivative was added as a solid into a  $\beta$ -CD aqueous solution close to saturation (1.6 g/100 ml or  $1.4 \times 10^{-2}$  M) and the mixture was stirred by sonication. If a precipitate appeared, it was filtered out and dried under reduced pressure.

**Evaporation.** The inclusion complexes were prepared by mixing naphthalene derivatives and  $\beta$ -CD either in aqueous solutions (200 mL) or in 1-propanol/water or ethanol/water solutions both in an equimolar ratio ( $1.07 \times 10^{-5}$  mol and  $1.23 \times 10^{-4}$  mol of both host and guest in the pure water and water/cosolvent variants, respectively). In the latter variant, the naphthalene derivative was dissolved in 1-propanol or ethanol (5 mL) and  $\beta$ -CD in water (10 mL). These solutions were mixed and stirred by sonication. The solid dispersions were obtained by evaporation from these solutions in a 'Buchi R 3000' rotary evaporator at 75 °C in the case of aqueous solutions, and in a vacuum desiccator at a reduced pressure and 24 °C, for the 1-propanol/water and ethanol/water solutions.

**'Sealed-container heating' method.** Host and guest were mixed in an equimolar ratio (except for 1-naphthyl acetate: $\beta$ -CD, for which there was an excess of the guest), in the solid state, and kept inside a sealed container at 60 °C for different periods of time (the mixture 2-ethylnaphthalene: $\beta$ -CD was heated also at 100 °C for 12 hrs).

The three methods were used for 1-naphthyl acetate with  $\beta$ -CD in order to decide the most suitable one for the other aromatic derivatives studied. Only the evaporation from 1-propanol/water method was used for all the equimolar substrate:CD dispersions (we also prepared 1-naphthyl acetate: $\beta$ -CD in 2:1 and 1:2 molar ratios). The

other methods were used in these cases: the coprecipitation method for 2-acetylnaphthalene: $\beta$ -CD (with favorable results), the evaporation from ethanol/water solution for 2-naphthyl acetate, and the 'sealed-container heating' method for naphthalene and ethylnaphthalene.

### FTIR analysis

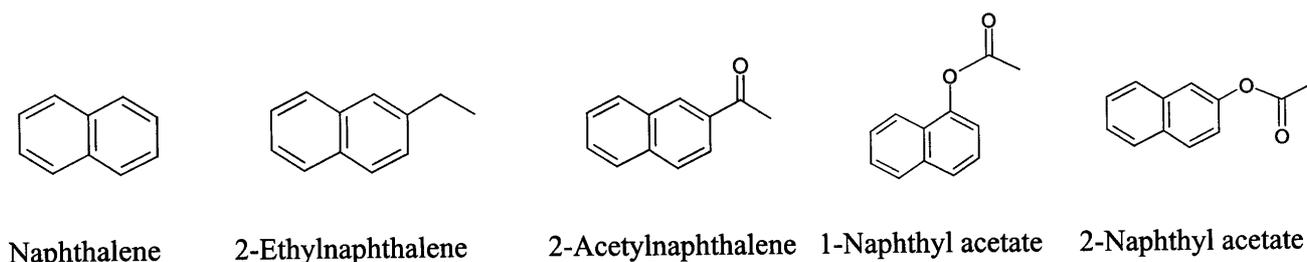
The infrared spectra were recorded using a Nicolet-FTIR Avatar 360, with OMNIC E.S.P. software [14]. The resolution was  $2 \text{ cm}^{-1}$  and the spectra were the result of averaging 100 scans. The humidity was kept constant inside the bench (ca. 40%). All measurements were carried out at  $20 \pm 1$  °C.

The KBr disk method has been used for the solid samples. In this procedure, the pellets were prepared by mixing the samples with KBr (1–2 mg and 100–150 mg, respectively), both dried under a lamp, with a pestle on an agate mortar and compacted with a hydraulic press. In the case of the physical mixture of 1-naphthyl acetate and  $\beta$ -CD, we introduced a modification in this method because of the low melting point of this naphthalene derivative: 1-naphthyl acetate and  $\beta$ -CD were separately dried. The aromatic derivative was ground with the suitable KBr amount and the mixture was dried under a lamp. In this process, 1-naphthyl acetate melted; the sample was then allowed to cool to room temperature so it resolidified.  $\beta$ -CD was ground and dried alone and then both solids were mixed on the mortar without further heating of the dispersion under lamp.

A ZnSe liquid cell of  $32 \times 3$  mm, with a path length of 0.5 mm, was used for the FTIR measurements in solution. The effect of the addition of 1-propanol and 2-propanol was observed by preparing solutions in  $\text{CCl}_4$  at the same carbonyl naphthalene derivative concentration ( $6.4 \times 10^{-3}$  M) and increasing the alcohol concentration 25, 50, 75 and 100 times that of the naphthalene. Several mixtures of higher alcohol ratios, 1:200 in most cases, and up to 1:400 for 2-naphthyl acetate:2-propanol solution were analyzed. We also collected the spectra in  $\text{CCl}_4$  solution for each carbonyl derivative at different concentrations between  $6.4 \times 10^{-3}$  and  $8 \times 10^{-4}$  M in order to detect any changes in the spectra due to associations (intra or intermolecular).

Multiple curve fitting using Origin 5.0 [15] was performed for the carbonyl stretching bands of the solid state spectra and also of those prepared in  $\text{CCl}_4$  solutions to study the interactions with 1 and 2-propanol. For this analysis several steps must be followed: (1) subtraction of the overlapping bands; (2) Fourier self-deconvolution, for a preliminary determination of the number of contributions for each band and their tentative locations; and (3) multiple curve fitting, after selection of the number of contributions, and their initial estimated locations, assuming Gaussian shapes. Thus, the position and width of their components as well as their areas were calculated. The last step was carried out using Origin 5.0, and the other two with OMNIC E.S.P. software.

The subtraction step is necessary in the solid mixtures of carbonyl derivatives and  $\beta$ -CD, specially for the 2-acetylnaphthalene: $\beta$ -CD dispersions, due to the overlapping of the ketonic carbonyl band and the O–H bending mode of



*Scheme 1.* Atom-and-bond representations of naphthalene derivatives.

$\beta$ -CD. The contributions of  $\text{CCl}_4$  were also subtracted from spectra in solution, because of the overlapping in the carbonyl stretching region. In all cases, an automatic smoothing using the OMNIC software feature was performed, and, for the solid state spectra, the baselines were corrected prior to the subtraction step.

## Results and discussion

### *Preparation of solid dispersions*

Several methods have been proposed in the literature to prepare solid phase cyclodextrin complexes. The two main groups of methods are those starting from liquid media (coprecipitation, evaporation or solvent casting, freeze-drying, spray-drying, and neutralization from either pure solvents or solvent/cosolvent mixtures) and those based on a solid mixture of both components (cogrinding, kneading, melting, heating in a sealed container, compactation) [3]. Three of them, coprecipitation, cosolvent evaporation and 'sealed-container heating' have been used to prepare solid dispersions of 1-naphthyl acetate with  $\beta$ -CD in order to decide the most suitable method to be used for the rest of the aromatic derivatives studied. We choose 1-naphthyl acetate as the guest compound for several reasons. As will be shown below, the ester carbonyl infrared band, which is the most sensitive to changes in the degree of association due to its hydrogen bonding capability, does not overlap with the vibration modes of  $\beta$ -CD, making the data analysis much simpler. Besides, when compared to the 2-isomer, 1-naphthyl acetate is supposed to form weaker complexes with  $\beta$ -CD. In fact, previous studies have shown that the equilibrium constant for the 1:1 complex between  $\beta$ -CD and 1-naphthyl-1-ethanol is smaller than that for 2-naphthyl-1-ethanol [16]. Once the preparation method has been optimized for this derivative, it will be used to prepare solid dispersions with the other guest molecules.

Figure 1a shows the spectra of pure  $\beta$ -CD, 1-naphthyl acetate and its mixtures in the carbonyl stretching region. As can be seen, the broad band corresponding to the HOH bending mode of water within the  $\beta$ -CD cavity does not overlap the carbonyl band of the guest compound. The spectrum of a physical mixture of the pure components should then correspond to the addition of the spectra of  $\beta$ -CD and 1-naphthyl acetate in the adequate ratio. This is indeed the case, provided that some precautions are taken when preparing the sample. The carbonyl band of a physical mixture

prepared at room temperature matches that corresponding to pure 1-naphthyl acetate. Identical results are obtained for the mathematical addition of both spectra, as expected (see Figure 1a). Nevertheless, when preparing solid dispersions in KBr pellets to be analyzed by FTIR, the common practice consists in co-grinding the products with KBr using a mortar and pestle. The sample is placed under a heating lamp, in order to dry both KBr and the organic derivatives. When using this procedure, we observed a strong displacement together with a broadening for the carbonyl band (sample labeled as 'phys. mixt. (h)' in Fig 1). This effect could be an indication of a complexation process taking place. However, the melting point of this highly volatile compound is ca. 45 °C. It is not unexpected that, during the processing of the sample, complexation occurs. We decided then to test one of the 'dry' methods to prepare the complex, known as 'heating in a sealed container' [9]. An excess of the guest compound was kept inside a sealed container with  $\beta$ -CD at 60 °C during 63 hrs. Figure 1a shows the result of an experiment using this procedure (labeled 's-c heated'). As can be seen, two bands are detected, with the two maxima well resolved in the carbonyl stretching region. We can conclude that this preparation method also produces a certain degree of intimate mixing on a molecular scale.

The evaporation method from an aqueous solution (see experimental part) did not yield the complex: the spectrum of the obtained solid dispersion corresponds to that of pure  $\beta$ -CD. We decided to use a cosolvent together with water, in order to increase the concentration of the guest compound in the mixed solution (ca.  $8 \times 10^{-3}$  M compared to that used for aqueous solutions, ca.  $5 \times 10^{-5}$  M). Both 1-propanol and ethanol were tested. The solvents should not be eliminated using a rotary evaporator: the high volatility of 1-naphthyl acetate causes its loss, and  $\beta$ -CD is the only product yielded. Valid results were reached when eliminating the solvent at a reduced pressure in a vacuum desiccator at a moderate temperature (ca. 24 °C). The two liquid mixtures employed did not yield the same result (see Figure 1a). Reproducible results are obtained when using propanol as the cosolvent. On the contrary, ethanol based mixtures produced complexes with a poorer concentration of the guest compound. A simple explanation can be given if we consider the higher volatility of ethanol relative to water (especially when compared to that of propanol). As ethanol evaporates, the aromatic derivative starts to precipitate, provided that the complex with  $\beta$ -CD either is not stable or has not been formed yet in these conditions.  $\beta$ -CD remains in a water

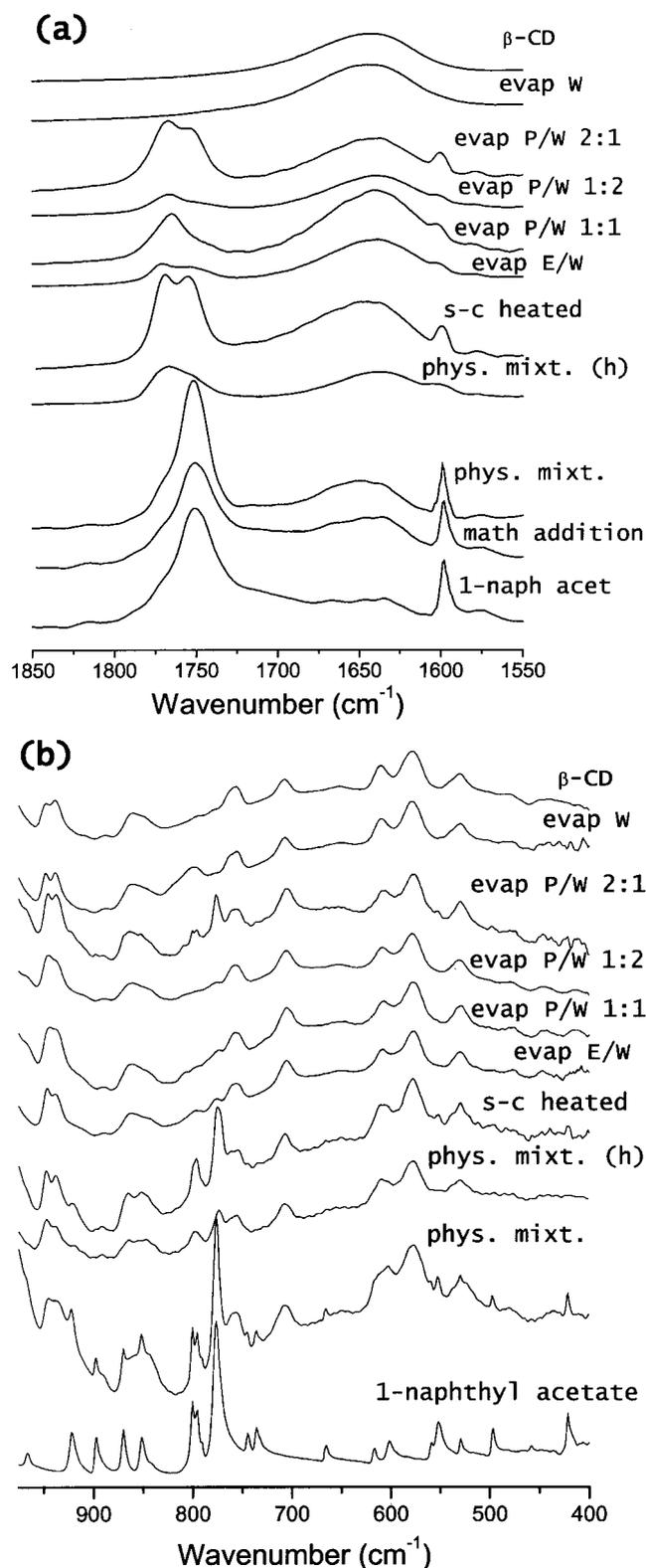


Figure 1. FTIR spectra of pure  $\beta$ -CD, 1-naphthyl acetate and their mixtures in (a) the carbonyl stretching region; (b) the 1000–400  $\text{cm}^{-1}$  region. (For abbreviations, see text. P: 1-propanol, W: water, E: ethanol.)

enriched solution, and the 1:1 complex is not fully achieved. This is not a general behavior though. Ethanol and propanol can form inclusion complexes with CDs in aqueous solutions [12]. Some authors have found that ethanol compete with other guests to form the complex in solution. Nevertheless, during the final stages of the evaporation of ethanol, true inclusion complexes with the aromatic guests were yielded in the solid state [17].

Figure 1b shows the spectra of 1-naphthyl acetate/ $\beta$ -CD mixtures in the 1000–400  $\text{cm}^{-1}$  region. The vibration mode of 1-naphthyl acetate located at 776  $\text{cm}^{-1}$  will be useful to confirm the results explained above. As can be seen, the physical mixture prepared at room temperature does present this vibration mode, while the ones heated (either ground with KBr and heated under lamp, or ‘sealed-container’ heated) show a remarkable diminishing in its intensity. The disappearing of this band could be attributed to two causes. Either the guest compound has been lost by evaporation, or this vibration mode has been hindered due to complexation. The first possibility can be ruled out by checking that some other bands are present in the spectrum, for instance, the already mentioned carbonyl stretching bands. If we analyze now the rest of the solid dispersions prepared, we see how the band at 776  $\text{cm}^{-1}$  is absent in the sample obtained after evaporation from water (no guest compound is present as mentioned above). As for the cosolvent mixtures, the one from ethanol/water presents a small contribution of this band, while the 1:1 (guest:host) dispersion from propanol/water lacks this mode. Figure 1b also shows the spectra corresponding to two other dispersions, both prepared from propanol/water mixtures but using different guest:host ratios. The one with an excess of  $\beta$ -CD (1:2) has no band at 776, while the 2:1 shows the contribution corresponding to the excess of 1-naphthyl acetate. The interest of preparing these two dispersions will be shown later, when we analyze the carbonyl bands using some mathematical procedures. This vibration mode provides then an excellent proof of the interactions at the molecular level between host and guest.

It has to be added that for all the studied complexes some subtle changes can be detected for the C–H stretching mode of  $\beta$ -CD at 2900  $\text{cm}^{-1}$ , and also for the band located ca. 950  $\text{cm}^{-1}$  (attributable to CO/CC stretching of  $\beta$ -CD [10, 18]). Nevertheless, a wider study comparing this one with some other systems should be carried out in order to confirm that these changes are a consequence of the complex formation process. We will focus the rest of our study in the carbonyl band, since some more useful information can be extracted from it.

The changes in the carbonyl band of the physical mixtures when they are prepared using different conditions have been analyzed. The spectra can be scaled using either the bending mode of  $\beta$ -CD at 1642  $\text{cm}^{-1}$  as the reference, or the CO/CC stretching modes at 1080 and 1029  $\text{cm}^{-1}$ . The latter have been chosen since the 1642  $\text{cm}^{-1}$  band is related to the water molecules attached to  $\beta$ -CD. Figure 2a shows a remarkable decrease in the relative intensity of the carbonyl band as we increase the grinding time (spectrum 1: physical

mixture; spectra 2–3: progressive grinding of 1). When the physical mixture is heated, there is also a change in the shape of this band (spectra 4–6). A new contribution, centered at  $1769\text{ cm}^{-1}$  is present, indicating a change in the association mode of the carbonyl groups, i.e., an intimate contact at the molecular level between  $\beta$ -CD and 1-naphthyl acetate is taking place. As for the stability of the complexes, we have studied the evolution of the complexes obtained from propanol/water mixtures. We can conclude that the stability is not high. As can be seen in Figure 2b, the relative intensity of the carbonyl band for the complex decreases at room temperature after several days. If the sample is kept at  $60\text{ }^{\circ}\text{C}$  this process occurs faster. Several hours suffice to evaporate part of the guest from the solid dispersion. This is not the case for  $\beta$ -CD complexes with other probes, as it will be discussed in the following sections. Moreover, the evolution is not the same for the two carbonyl bands. At room temperature, the low wavenumber band seems to maintain its intensity, while the high wavenumber band diminishes. On the other hand, at  $60\text{ }^{\circ}\text{C}$  both bands decrease, although the effects seem to be smaller for the low wavenumber peak which corresponds to the associated (hydrogen-bonded) carbonyls (see below). The guest molecules associated via hydrogen bonding seem to be attached to the cyclodextrin in a stronger fashion.

Finally, we also analyzed the influence of the humidity on the carbonyl stretching region of the spectra. As was stated above, special care must be taken when preparing the samples, due to the high volatility of this guest compound. Nevertheless, the carbonyl band is significantly affected by the presence of water in the samples. Figure 2c shows the extents of this effect. A sample of 1-naphthyl acetate/ $\beta$ -CD was prepared by evaporation of a 1-propanol/water mixture with an excess of 1-naphthyl acetate and its spectrum was collected. Then, the sample was kept for several days in a drier environment (humidity ca. 40%). A significantly different shape for the carbonyl band was detected: the contribution at high wavenumber diminishes. Then, the sample pellet was kept in a humid environment (water saturated at room temperature). The peak located at  $1642\text{ cm}^{-1}$ , which corresponds to the bending mode of HOH, gives us an idea of the hydration level of the sample pellet. The spectra taken as a function of time showed a progressive change in the relative intensity of the two carbonyl contributions. There was a remarkable decrease in the intensity of the peak located at low wavenumber, ca.  $1750\text{ cm}^{-1}$ , attributable to the associated carbonyl groups. Finally, the spectrum of the wet sample (after 30 hrs.) resembles that of the original sample. The hygroscopicity of KBr could be responsible for this effect. The hydroxyl groups of  $\beta$ -CD bind to the excess of water molecules, liberating the carbonyl groups attached to them. Consequently, in order to avoid this effect, the samples have to be kept in a desiccator at a controlled low humidity level. It has been shown that the hydration and dehydration of  $\beta$ -CD hydrates are fast processes until they reach equilibrium with atmospheric humidities [19, 20]. Consequently, no appreciable errors are expected provided that some special care in keeping the samples and measuring the spectra are taken.

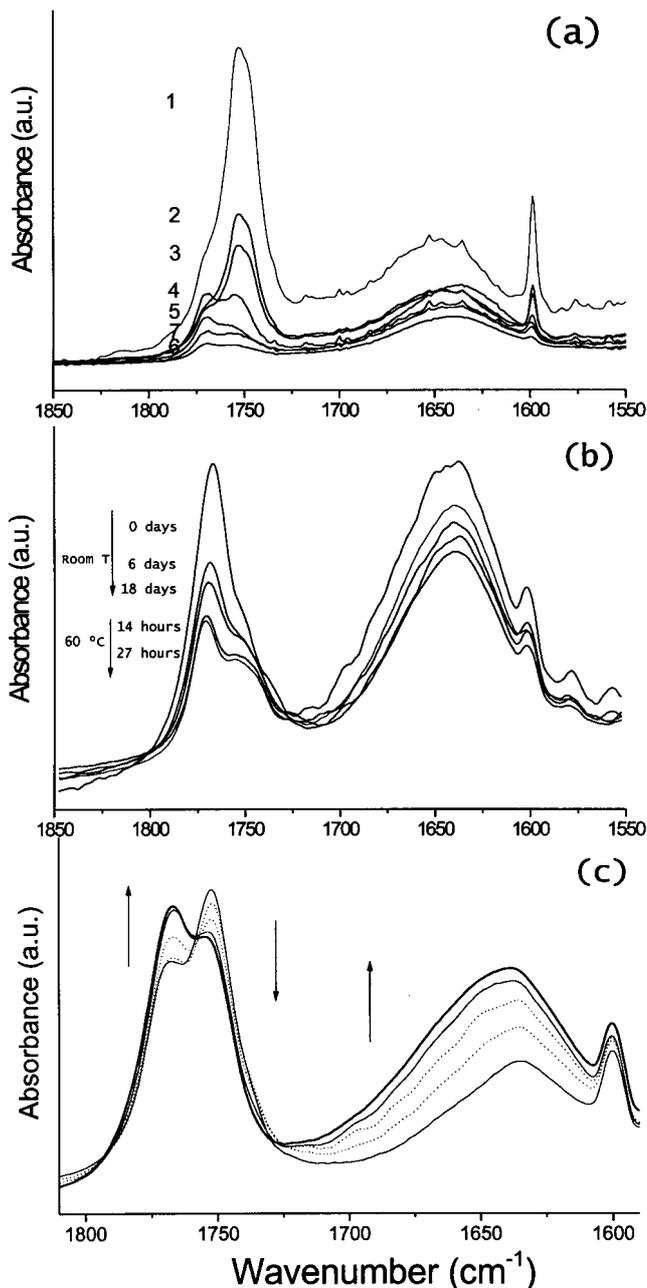


Figure 2. FTIR spectra of 1-naphthyl acetate: $\beta$ -CD in the carbonyl stretching region: (a) physical mixtures prepared using different conditions: (1) initial non-heated, (2–3) effect of progressive grinding, (4–6) effect of progressive grinding and heating, (7) sample prepared grinding under lamp; (b) evolution for a complex solid dispersion at room temperature and  $60\text{ }^{\circ}\text{C}$ ; (c) effect of the humidity on the carbonyl band for a 2:1 mixture; arrows mark the effect of increasing humidity (increasing absorbance for  $1642\text{ cm}^{-1}$  band: “dry” sample, 1.5 hours, 4.5 hours, 21 hours kept in a humid environment, “fresh” sample as prepared).

#### FTIR analysis of 1-naphthyl acetate/ $\beta$ -CD complexes

Two different environments are responsible for the two carbonyl contributions observed in these samples. As mentioned above, the low wavenumber contributions are usually attributable to the associated carbonyls. Hydrogen bonds can be formed between the carbonyl groups and the  $\beta$ -CD hydroxyls [11, 21, 22]. The ‘free’ carbonyls, i.e., those

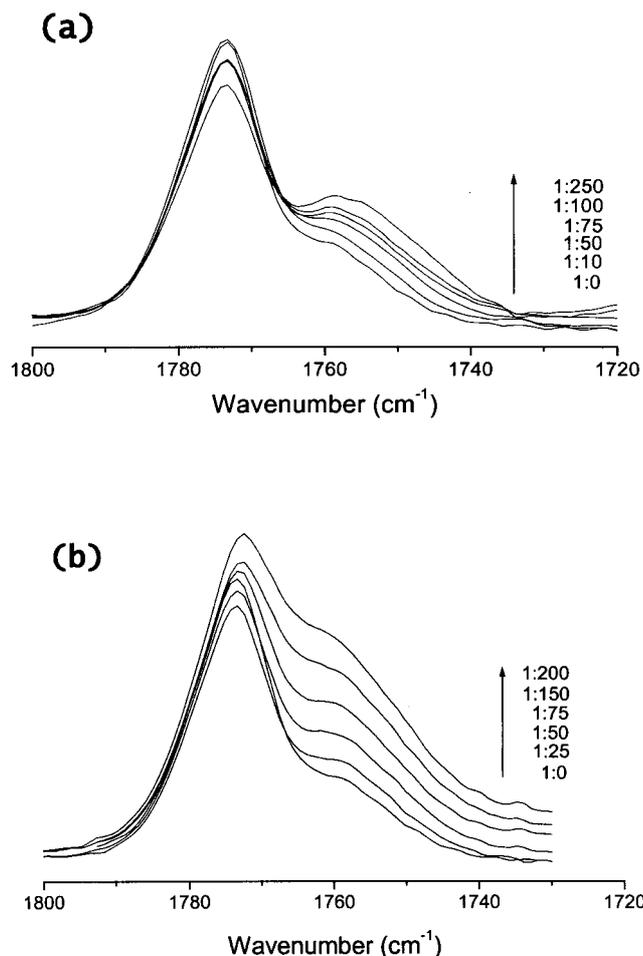


Figure 3. FTIR spectra in  $\text{CCl}_4$  solutions for different ratios 1-naphthyl acetate:propanol (a) 1-propanol; (b) 2-propanol, in the carbonyl stretching region.

not attached to hydroxyl groups, are detected at higher wavenumbers.

In order to confirm this point, we have studied the effect of adding 1-propanol or 2-propanol, as model compounds resembling the primary and secondary hydroxyls of the cyclodextrin molecules, respectively, to  $\text{CCl}_4$  solutions of the guests. The concentration of the naphthalene derivative was kept constant and different amounts of the alcohols were added. Figure 3 shows the effect on the carbonyl stretching region of 1-naphthyl acetate. An increase in the intensity of the shoulder is clearly observed as the concentration of the alcohol increases. 2-naphthyl acetate and 2-acetylnaphthalene also present a similar behavior, although the shoulder is not so well resolved (not shown). A new contribution arises that can be attributed to the formation of hydrogen bonds between the OH groups of the alcohols and the C=O groups of the naphthalene derivatives. The values observed for  $\Delta\bar{\nu}$  are in fact similar (ca. 15–17  $\text{cm}^{-1}$ ) to those detected in the solid dispersion mixtures (ca. 20  $\text{cm}^{-1}$ ), as can be seen in Table 1. Nevertheless, the peak positions of the carbonyl bands are different, as expected: they are shifted to lower wavenumbers for crystalline samples due to solid-state effects [23].

A comment is then necessary, regarding the differences between the positions of the free carbonyls in the complexes and in pure 1-naphthyl acetate shown in Figure 1a. The band located at low frequency for the spectra of the complexes can be related to those molecules of the guest which are forming hydrogen bonds with the CD hydroxyls. The other band, located at a higher wavenumber is assigned to those carbonyls not bonded (i.e., 'free' carbonyls). It could be expected that this band corresponds to that of pure 1-naphthyl acetate. This is not the case for the carbonyl guest derivatives studied in this work. The 'free' carbonyls in CD complexes are shifted to higher wavenumber (ca. 8–15  $\text{cm}^{-1}$ ). These shifts can be attributed to the different environment of the carbonyl groups in both cases. For the crystalline solids, the C=O bond loses part of its double bond character due to the interactions that stabilize the crystalline network, causing a diminution in its frequency [18]. In the solid dispersions of the complexes, where the carbonyls are totally 'free', the situation is different. The shifts are analogous to those observed for the spectra in solution (see above). The frequencies for  $\nu(\text{C}=\text{O})$  of the pure guest derivatives studied in  $\text{CCl}_4$  solutions are either the same or slightly higher than those of the 'free' carbonyls in the CD solid complexes.

A quantitative analysis of the association degree of the carbonyl groups can be performed using the methods proposed in the experimental part, i.e., subtraction of the spectral contribution of the second component ( $\beta$ -CD), deconvolution to locate the initial estimates for the peak locations, and curve fitting of the bands.

Although in most cases it is clear that only two contributions are present, in some occasions three peaks must be considered. For these samples, the expected errors are more important. Figure 4a shows the deconvolution of several spectra in the carbonyl stretching region (after the  $\beta$ -CD contribution has been subtracted, although the overlapping is minimal for these mixtures). Once the approximate peak positions have been located, the curve fittings shown in Figure 4b can be obtained. An interesting comparison can be made between the solid dispersions labeled as 1:2 and 2:1 (guest: $\beta$ -CD). A 1:1 complex is expected to occur in the first case, with an excess of free  $\beta$ -CD. Two carbonyl bands are observed, corresponding to free and associated carbonyl groups. On the contrary, the 2:1 dispersion is composed of the 1:1 complex and an excess of the crystalline guest, whose carbonyl groups appear at a wavenumber intermediate between those of the 'free' and associated carbonyls of 1-naphthyl acetate in the CD complex. We should notice that the 'free' carbonyl of 1-naphthyl acetate is shifted to higher wavenumbers from its position in the crystalline state. In fact, its location is closer to that detected in  $\text{CCl}_4$  solutions. Thus, three bands are present as can be seen in Figure 4. The results for all the samples analyzed (positions and relative areas) are displayed on Table 1. When we exclude the carbonyls corresponding to pure 1-naphthyl acetate from the calculation, a remarkable result is obtained: the percentages of free and associated carbonyls after the curve fitting for the evaporated mixtures using different proportions of 1-naphthyl acetate and  $\beta$ -CD (1:2, 1:1, and 2:1) are approx-

Table 1. Curve-fitting results for carbonyl stretching bands in 1-naphthyl acetate/ $\beta$ -CD mixtures

Sample	Free carbonyl band		Associated carbonyl band		$F_{\text{assoc}}$
	Wavenumber ( $\text{cm}^{-1}$ )	Relative area (%)	Wavenumber ( $\text{cm}^{-1}$ )	Relative area (%)	
<b>1-naphthyl acetate</b>	1751	100	–	–	–
phys. mixt.	1752	100	–	–	–
Evap. P/W 1:1	1765	88	1744	12	0.08
Evap. P/W 1:2	1767	86	1746	14	0.10
Evap. P/W 2:1*	1766	86	1746	14	0.10
2:1 (evap 1:1+ 1-naphthyl acet.)*	1768	81	1742	19	0.13
Evap. P/W 2:1 20 days*	1768	85	1745	15	0.11
sealed-container heated*	1770	76	1750	24	0.17
1-naphthyl acetate ( $\text{CCl}_4$ )	1774	100	–	–	–
1-naphthyl acet. – 1-propanol ( $\text{CCl}_4$ )	1774	67	1757	33	0.25
1-naphthyl acet. – 2-propanol ( $\text{CCl}_4$ )	1774	55	1759	45	0.35

\* Areas excluding the contribution of pure 1-naphthyl acetate (see text).

imately the same. This result corroborates the hypothesis of a 1:1 stoichiometric ratio for 1-naphthyl acetate: $\beta$ -CD complexes in the solid dispersion, the same as the one found in solution [12]. Notice also that the sample prepared using the sealed-container heating method does not yield the same result. It seems that, at least in these conditions, this is not the best procedure to yield full complexation. Probably, higher temperatures or contact times should be used.

The evolution of the evaporated 2:1 sample when heated at 60 °C was also analyzed. In the first stage, the carbonyl distribution of the sample becomes analogous to that of the 1:1 solid dispersion, and after that, both evolve in a similar way. A physical mixture of the evaporated 1:1 complex and an excess of pure 1-naphthyl acetate was also prepared to compare its spectra with that of the 2:1 solid dispersion with regard to their carbonyl distributions. The band shapes are similar, although the curve fitting results were not totally coincident. As it was mentioned, the fitting of three contributions is complicated, and the expected errors are higher. The percentage of associated carbonyls is 14% for the 2:1 obtained by evaporation and 19% for the physical mixture of pure 1-naphthyl acetate and the 1:1 complex. These two results confirm that 2:1 solid dispersions consist of 1:1 stable mixtures plus an excess of pure 1-naphthyl acetate.

The relative areas of the ‘free’ and associated carbonyl bands do not correspond to the amounts of free and associated groups due to their different absorption coefficients. The  $\nu(\text{C}=\text{O})$  in acetate groups have a relative absorptivity 1.5 times that of free carbonyls [24]. The fraction of associated carbonyls could be calculated as:

$$F_{\text{assoc}} = A_{\text{assoc}} / (A_{\text{assoc}} + A_{\text{free}} \cdot 1.5)$$

where  $A_{\text{assoc}}$  and  $A_{\text{free}}$ , are the areas of the two contributions. The results from these calculations are given on Table 1.

Some authors [10, 21] have found that the decrease of the intensity of the  $\beta$ -CD mode located at 1642  $\text{cm}^{-1}$ , attributed to HOH bending, can be used as an indication of water molecules eliminated from the CD cavity because of the inclusion of the guest molecules. The  $\beta$ -CD complexes with polycyclic aromatic derivatives substituted in position

1 studied in those works do not lose the water molecules included within their cavities due to the shallow inclusion of the guest. As Figure 5 shows, that could be the case for 1-naphthyl acetate. Using the CD band at 1029  $\text{cm}^{-1}$  as the reference, the three complex samples prepared with 1:2, 1:1 and 2:1 host:guest ratios show similar areas for the band at 1642, i.e., the amount of water seems to be practically the same irrespective of how many CDs have a 1-naphthyl acetate molecule attached to them. The crystallization water molecules associated to CDs are the ones included within the cavities but also those located on the outside, i.e., the interstitial water molecules [19]. The presence of each particular guest can obviously modify the occupancy levels in a different fashion. Nevertheless, it is evident from Figure 2c that the hygroscopicity of KBr is an important factor that must be also considered when analyzing this vibration mode, and it can lead to erroneous conclusions if the humidity level of the samples is not carefully controlled.

#### FTIR spectra of 2-naphthyl acetate/ $\beta$ -CD and 2-acetylnaphthalene/ $\beta$ -CD complexes

Two other carbonyl naphthalene derivatives have also been studied: 2-naphthyl acetate, isomer of 1-naphthyl acetate, and 2-acetylnaphthalene, the simplest ketonic derivative of naphthalene. Figures 6 and 7 show their respective infrared spectra in the carbonyl stretching region and in the 1000–400  $\text{cm}^{-1}$  region. For 2-naphthyl acetate, the spectra of its solid dispersions with  $\beta$ -CD prepared from both ethanol/water and 1-propanol/water seem to match in both regions, in clear contrast with what was observed for 1-naphthyl acetate. The band at 825  $\text{cm}^{-1}$ , attributed to out-of-plane vibrations of aromatic C–H, is absent in the complexes but is easily detected in the physical mixture (see Figure 6a). The other characteristic bands of 2-naphthyl acetate in this region are difficult to analyze because of their overlapping with  $\beta$ -CD modes. The differences in the carbonyl stretching region appear to be less important for this derivative. Once we perform a quantitative analysis we will show that this is not the case though.

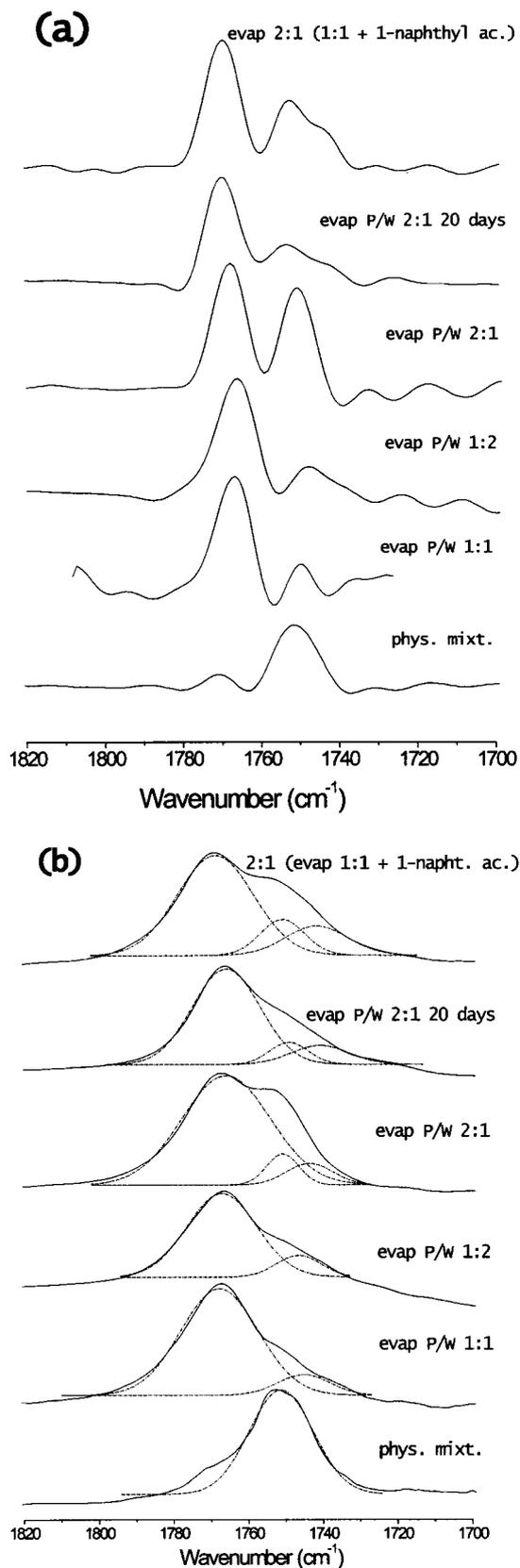


Figure 4. (a) deconvolution of several 1-naphthyl acetate: $\beta$ -CD spectra in the carbonyl stretching region after the  $\beta$ -CD contribution has been subtracted. (b) curve fitting of carbonyl contribution of the same spectra (see text).

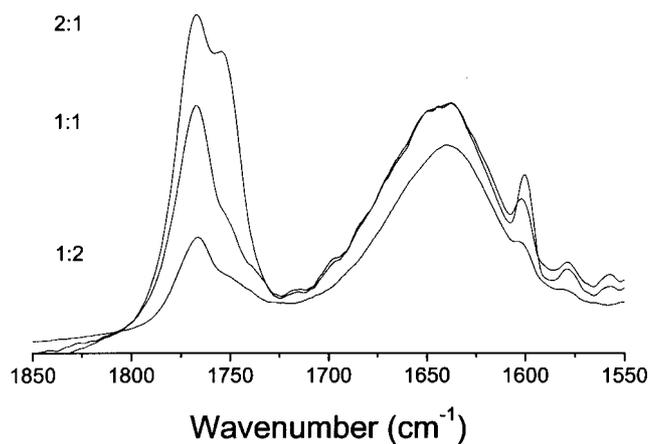


Figure 5. FTIR spectra of 1-naphthyl acetate: $\beta$ -CD complex samples prepared with 1:2, 1:1 and 2:1 host:guest ratios. The spectra were scaled using the CD band at  $1029 \text{ cm}^{-1}$  as the reference.

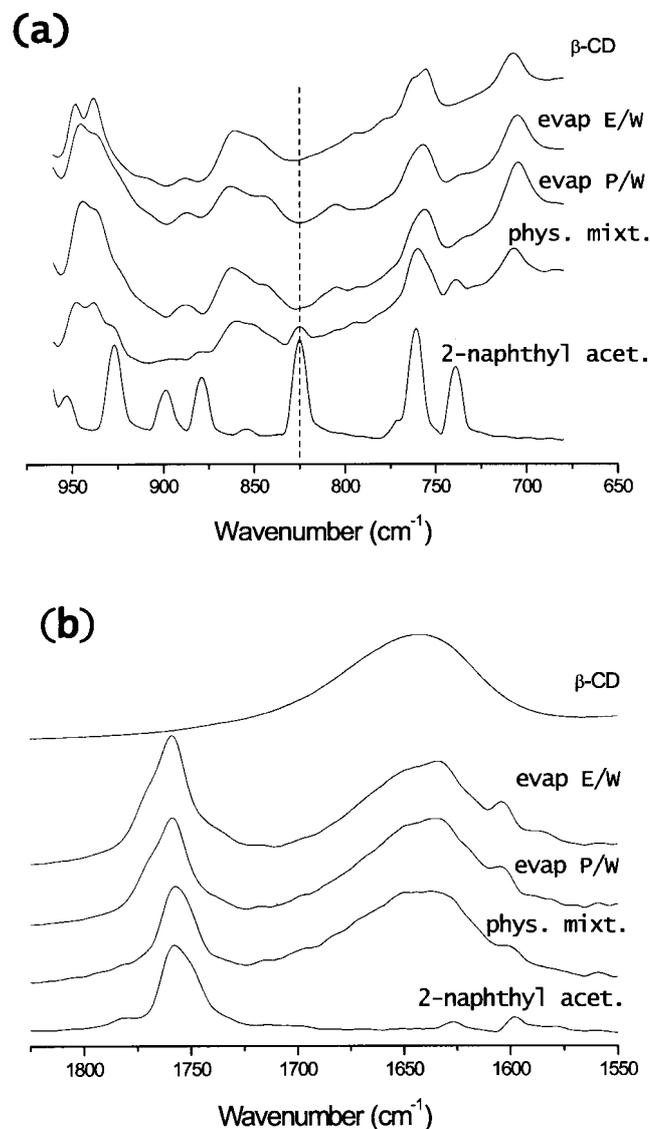


Figure 6. FTIR spectra of 2-naphthyl acetate: $\beta$ -CD in (a) the  $1000\text{--}700 \text{ cm}^{-1}$  region (broken line: mode at  $825 \text{ cm}^{-1}$ ), and (b) the carbonyl stretching region (spectra scaled using the CD band at  $1029 \text{ cm}^{-1}$  as the reference).

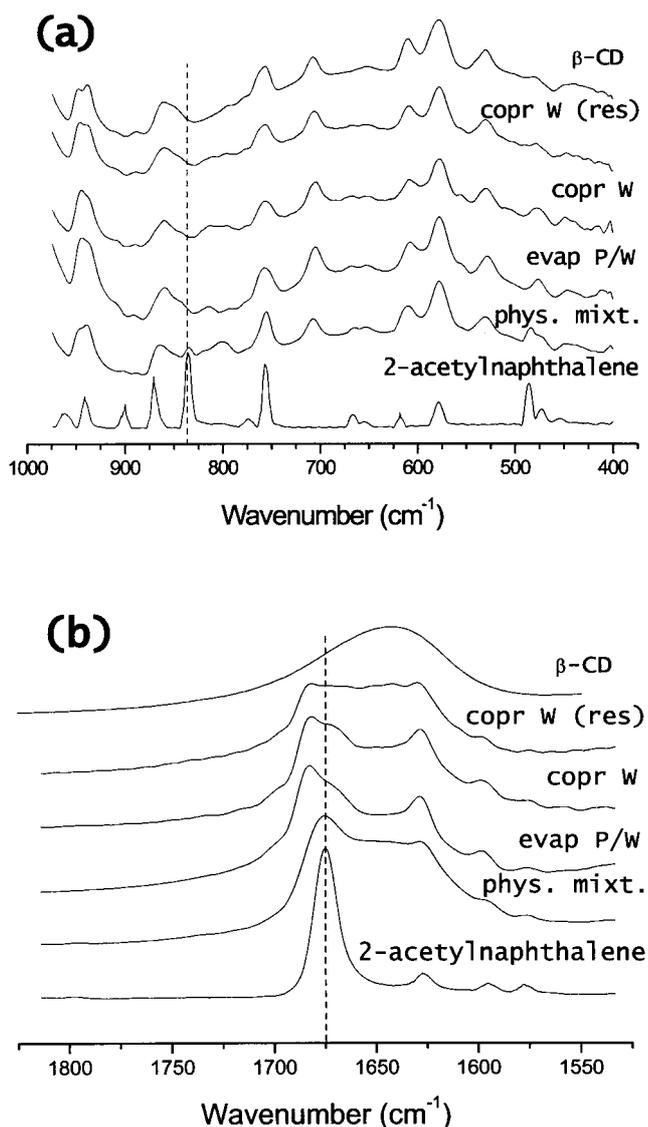


Figure 7. FTIR spectra of 2-acetylnaphthalene: $\beta$ -CD, physical mixture, evaporated from propanol/water, and coprecipitated from water (see text) in (a) the 1000–400  $\text{cm}^{-1}$  region (broken line: mode at 836  $\text{cm}^{-1}$ ), and (b) the carbonyl stretching region (broken line: mode at 1675  $\text{cm}^{-1}$ ; spectra scaled using the CD band at 1029  $\text{cm}^{-1}$  as the reference).

Figure 7 shows the corresponding spectra for 2-acetylnaphthalene. In this case, besides the propanol/water evaporation method, we could also prepare solid dispersions by precipitation from water solutions. In fact, this was the only system for which a solid precipitate was obtained when mixing the aqueous solutions of  $\beta$ -CD and the guest compound. The supernatant solution remaining, once the precipitate was separated by filtration, was concentrated using a rotary evaporator. The solid residue was also analyzed. Its spectrum ('copr W (res)' in Figure 7) turned out to be very similar to that of the precipitate. As in the previous systems, Figure 7a allows us to detect the changes in the aromatic C–H bands. The band at 836  $\text{cm}^{-1}$  is especially useful. Its presence is only detected for the physical mixture. The carbonyl stretching region (Figure 7b) is more difficult to study because of the overlapping of the ketonic carbonyl band of 2-acetylnaphthalene with the  $\beta$ -CD mode ( $\delta$ -HOH)

centered at 1642  $\text{cm}^{-1}$ . The two spectra corresponding to the samples obtained from aqueous solutions are very similar. In contrast, more important differences are found between those two and that corresponding to the sample prepared from propanol/water. Their shapes are different although the maxima are all located at ca. 1683  $\text{cm}^{-1}$ , somewhat displaced from the peak of both pure 2-acetylnaphthalene and its physical mixture with  $\beta$ -CD (located at 1675  $\text{cm}^{-1}$ ). Nevertheless, the contributions must be analyzed using the methods described above.

The stability of the complexes for these two carbonyl derivatives is much higher than that of 1-naphthyl acetate. In fact, both complexes were kept at room temperature and their spectra remained unchanged for months. When heated at 60  $^{\circ}\text{C}$ , the complex with 2-naphthyl acetate does not change after a week, although subtle changes start after two weeks. For the complex with 2-acetylnaphthalene, there is some loss due to volatilization, although it is not comparable to that observed for 1-naphthyl acetate. On the other hand, the spectra of their physical mixtures after the same time periods matched that of pure  $\beta$ -CD, a clear indication of the complete loss of the aromatic derivatives from the mixtures. The complexation with  $\beta$ -CD either avoids or hinders the evaporation of volatile chemicals, and this is obviously one of the applications of CD complexes [25].

A quantitative analysis of the carbonyl stretching region can be also performed for the complexes with both naphthalene derivatives. Figure 8 shows the spectra of 2-naphthyl acetate and its mixtures with  $\beta$ -CD in the carbonyl stretching region after subtraction of the  $\beta$ -CD contribution. For pure 2-naphthyl acetate, the carbonyl band seems to be slightly asymmetric, although only a single contribution could be expected. In fact, the band for the physical mixture looks quite symmetric. This result was also observed for 2-indanone [21]. The interactions implicating the carbonyl moiety in the complex are not the same as in the crystalline phase. The carbonyl group of a molecule entrapped in a CD cavity is involved only in short-range dipole interactions with  $\beta$ -CD. The results for the complexes from the cosolvent mixtures show a shoulder located at higher wavenumbers (ca. 1770  $\text{cm}^{-1}$ ). Both spectra (for ethanol or 1-propanol systems) are identical, in contrast to those what were obtained for 1-naphthyl acetate. We can conclude that the ethanol/water mixture is adequate to prepare the complexes with 2-naphthyl acetate although it was not useful to prepare 1-naphthyl acetate: $\beta$ -CD solid dispersions. The displacement of the free carbonyl contribution toward higher wavenumbers in the complexes with respect to the location for the pure solid sample of the naphthalene derivative is similar to that observed for 1-naphthyl acetate (ca. 15  $\text{cm}^{-1}$ ). Consequently, the  $\Delta\nu$  value is lower for 2-naphthyl acetate (12  $\text{cm}^{-1}$ , while is 21  $\text{cm}^{-1}$  for 1-naphthyl acetate). There is also a remarkable difference in the degree of association of the carbonyls of both acetate isomers. The amount of associated carbonyls is much higher for the 2-substituted naphthalene. This result could be explained assuming that the 2-naphthyl acetate: $\beta$ -CD complex possesses the most adequate geometry for the interaction between the non-polar

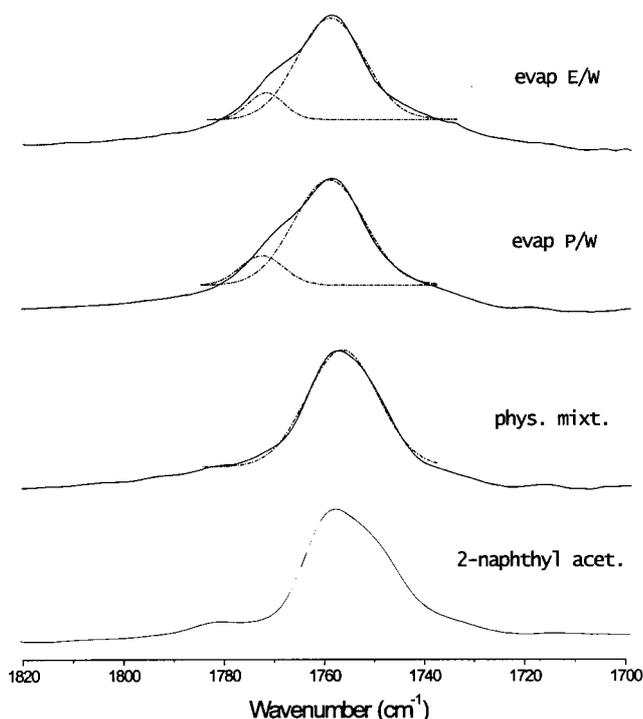


Figure 8. FTIR spectra and curve fitting results of 2-naphthyl acetate mixtures with  $\beta$ -CD in the carbonyl stretching region after subtraction of the  $\beta$ -CD contribution (pure 2-naphthyl acetate is shown for comparison).

part of the guest and the CD cavity on one side, and the polar part of the guest with the hydroxyl groups of the cyclodextrin rims on the other side [26]. The differences in the binding orientations for 1- and 2-substituted naphthalenes have been also studied for other molecules with [16, 21, 27, 28] or without [29] H-bonding capability.

Figure 9 corresponds to the curve fitting analysis of 2-acetylnaphthalene samples. Once the  $\beta$ -CD contribution has been subtracted from the spectra, it becomes obvious that their analysis is possible. The results corresponding to the relative areas of 'free' and associated contributions for the complexes with 2-acetylnaphthalene and 2-naphthyl acetate are displayed on Table 2. Assuming an absorptivity ratio of 1.5 for both derivatives, we can also calculate the fractions of 'free' and associated carbonyls (see Table 2). The associated carbonyl contributions of the 2-acetylnaphthalene: $\beta$ -CD complexes are considerably smaller than those of 2-naphthyl acetate. The geometry of the 2-naphthyl acetate molecule is indeed more favorable for the interaction. The extra oxygen atom between the naphthyl group and the carbonyl provides an additional degree of rotational freedom, so the double interaction between host and guest can be facilitated. For 2-naphthyl acetate, the carbonyl can be hydrogen bonded to the rim hydroxyls while the non-polar part of the guest (i.e., the naphthyl group) is perfectly accommodated within the cavity of the host molecule. In fact, the results of the complexation constants in solution as measured by fluorescence also point to a more favorable interaction for 2-naphthyl acetate (García-Zubiri et al., unpublished results).

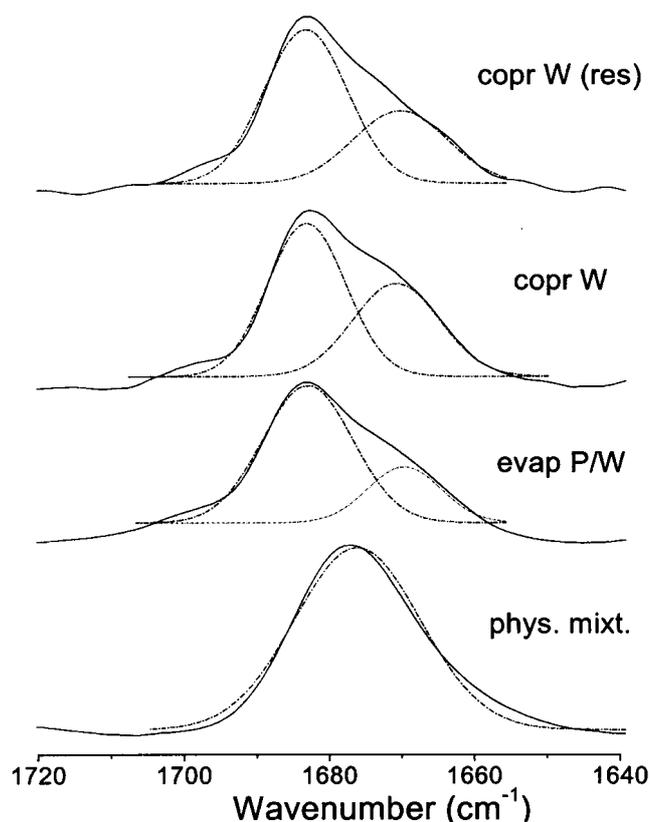


Figure 9. FTIR spectra and curve fitting results of 2-acetylnaphthalene: $\beta$ -CD samples in the carbonyl stretching region after subtraction of the  $\beta$ -CD contribution.

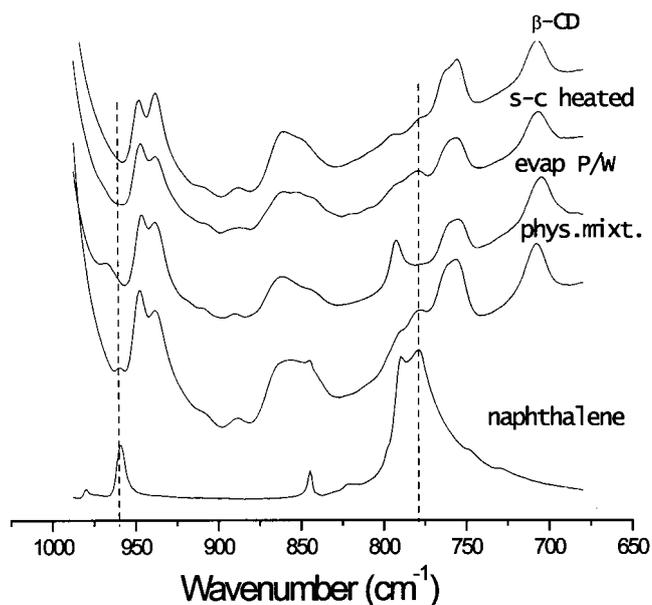


Figure 10. FTIR spectra of naphthalene: $\beta$ -CD mixtures in the 1000-700  $\text{cm}^{-1}$  region (broken lines: modes at 960 and 780  $\text{cm}^{-1}$ , see text).

Table 2. Curve-fitting results for carbonyl stretching bands in 2-naphthyl acetate, 2-acetylnaphthalene and its mixtures with  $\beta$ -CD.

Sample	Free carbonyl band		Associated carbonyl band		$F_{\text{assoc}}$
	Wavenumber ( $\text{cm}^{-1}$ )	Relative area (%)	Wavenumber ( $\text{cm}^{-1}$ )	Relative area (%)	
<b>2-naphthyl acetate</b>	1756	100	–	–	–
phys. mixt.	1757	100	–	–	–
Evap. P/W 1:1	1771	15	1759	85	0.79
Evap. E/W 1:1	1772	12	1759	88	0.83
<b>2-acetylnaphthalene</b>	1675	100	–	–	–
phys. mixt.	1676	100	–	–	–
Evap. P/W 1:1	1683	73	1670	27	0.20
Copr. W	1683	59	1671	41	0.32
Copr. W (res)	1683	61	1671	39	0.30

### FTIR Spectra of $\beta$ -CD with naphthalene and 2-ethylnaphthalene

Because of the high volatility of naphthalene and 2-ethylnaphthalene, one needs to take a special care when preparing these samples. Both chemicals are easily lost from their physical mixtures with  $\beta$ -CD. Moreover, some of the molecules could diffuse within the  $\beta$ -CD cavities during sample processing. It is obviously more difficult to study the complexation of  $\beta$ -CD with molecules that lack carbonyl groups, such as naphthalene or 2-ethylnaphthalene. Nevertheless, some subtle changes can be detected in the spectra. In the 1000-600  $\text{cm}^{-1}$  region (Figure 10), the naphthalene modes located at 780 and 960  $\text{cm}^{-1}$  can be observed in a physical mixture but they are absent in the spectrum of the complex. In fact, a new peak seems to appear at 967  $\text{cm}^{-1}$  in the complex. In contrast, the 790  $\text{cm}^{-1}$  naphthalene band is undoubtedly present in the complex, so it cannot be argued that the naphthalene has been lost during the processing of the sample. A spectrum taken for a physical mixture kept for 4 days inside a vial at 60 °C is also shown for comparison (labeled 's-c heated' in Figure 10). As can be seen, these conditions are not efficient enough to achieve the complexation of naphthalene within the  $\beta$ -CD cavities. Probably, higher temperatures would help to obtain better results. The mixtures with 2-ethylnaphthalene are even more difficult to analyze. Some preliminary experiments showed no bands corresponding to 2-ethylnaphthalene for either the physical mixture or the dispersion prepared from 1-propanol/water. In contrast, the dispersion obtained from heating the 1:1 sample in a sealed container at 100 °C did show evidence of 2-ethylnaphthalene bands. The results were similar for samples kept for 3 or 6 days. Some slight changes have been detected in the position of the vibration modes located at 850 and 890  $\text{cm}^{-1}$ , indicating some kind of interaction at the molecular level.

### Conclusions

Infrared spectroscopy can be employed to study the complexes between cyclodextrins and aromatic derivatives in the solid state. Although this technique should be used in con-

junction with others in order to prove that a true inclusion complex has been formed, significant information can be extracted from the analysis of the infrared spectra, especially in systems in which specific interactions are also present. The degree of complexation achieved using different preparation methods can be compared as shown above. FTIR has proven to be a convenient technique to evaluate the interactions at the molecular level in these systems. To accomplish this task, some mathematical procedures such as baseline corrections, digital subtraction, Fourier self-deconvolution, and curve fitting should be employed.

Thus, we have shown that the dispersions in KBr prepared by mixing these volatile compounds with  $\beta$ -CD can yield the complex, depending on the conditions of the grinding process. Besides, the effects of temperature and humidity on the spectra have been also analyzed. The stability of the dispersions can be studied as a function of time and temperature, following the evolution of the area and shape of the carbonyl bands.

The presence of a carbonyl moiety in the guest molecule can help us to analyze the interactions with the host. This is a vibration mode strongly influenced by changes in the vicinity. Although the formation of hydrogen bonds increases the stability of the complexes, these specific interactions are not as important as van der Waals and hydrophobic interactions, the main driving forces of the complexation process [13]. The differences in the association degrees via H-bonding for the 2-substituted carbonyl derivatives studied in this work seem to confirm this point.

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