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Preparation and Characterization of the β-Cyclodextrin Inclusion Complex with Phenylpropiolic Acid

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Abstract. The preparation of a 1:1 complex involving β-cyclodextrin (β-CD) and phenylpropiolic acid (PPA) is reported. The new inclusion complex of β-CD has been characterized on the basis of its chemical analysis, thermal behavior, infrared spectrum, X-ray powder pattern and ^{13}C-NMR spectrum in DMSO solution.

Key words. β-cyclodextrin complex, phenylpropiolic acid, IR and ^{13}C-NMR complexation effects.

1. Introduction

One of the most interesting properties of cyclodextrins is their ability to form host–guest molecular complexes with many kinds of molecules and ions [1–3]. As a consequence of this behavior, the cyclodextrins are utilized in many fields, e.g. pharmaceutical preparations [4], separations [5–7] and model enzyme catalysis [1, 8].

β-cyclodextrin, β-CD, is a cyclic saccharide consisting of seven linked *D*(+)-glucopyranose units that have a toroidal shape, in the interior of which a hydrophobic cavity is formed [9].

Phenylpropiolic acid (PPA) has been utilized as a wholly reversible inhibitor in the deamination of *L*-phenylalanine by phenylalanine ammonia-lyase [10].

This paper reports the interaction of β-CD and PPA in the solid state. The inclusion complex formed was characterized by means of chemical analysis, thermal analysis, IR spectroscopy and X-ray diffractometry. The DMSO solution of the complex is also studied by ^{13}C-NMR spectroscopy.

2. Experimental

2.1. MATERIALS

β-cyclodextrin supplied by Aldrich was used without purification.

Phenylpropiolic acid (C_6H_5—C≡C—COOH) (PPA) was prepared from *trans*-cinnamic acid (C. Erba) through ethyl cinnamate by dibromination of the ester and subsequent dehydrobromination, according to procedures described in the literature [11]. PPA obtained as above was recrystallized from carbon tetrachloride, m.p. 135–136°C, and was characterized by its spectroscopic data [12].

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2.2. PREPARATION OF THE INCLUSION COMPLEX

Ten mL of a solution prepared by dissolution of 0.25 g (1.71 mmol) of PPA in acetone was added dropwise to a constantly stirred suspension of β-CD, which had been prepared with 0.98 g (0.86 mmol) of β-CD in 35 mL of water. The reaction mixture was heated for ten minutes at 50°C and kept for 24 hours at room temperature for complete crystallization. The white precipitate formed was removed by filtration, washed successively with water and a few millilitres of acetone, and then dried *in vacuo* at ambient temperature (yield: 70%).

The physical mixture of β-CD with PPA in a 1:1 molar ratio was prepared by mixing the components followed by a gentle grinding for ten minutes.

2.3. PHYSICAL MEASUREMENTS

TG and DSC curves were obtained on a Du Pont model 1090 DSC TGA system at a heating rate of 10°C/min under a nitrogen atmosphere.

X-ray powder patterns were obtained with a Phillips Model PW 1140 diffractometer with a monochromator of LiF(200) utilizing Cu$K\alpha$ radiation with 20 kV and 15 mA at a scan rate of 1°/min.

Infrared spectra of samples were recorded in the 4000–200 cm^{-1} region for Nujol and Fluorolube dispersions between CsI or KBr windows on a Perkin-Elmer 180 IR spectrophotometer.

^{13}C-NMR spectra were obtained in a Varian XL-100 NMR spectrometer operating at 25.2 MHz, interfaced with a Varian 620/L Fourier Transform computer. The chemical shifts ($\pm$0.05 ppm) were measured at 6 kHz spectral width, with an acquisition time of 0.6 s and a 20 μs pulse width, using an internal lock.

3. Results and Discussion

The elemental analysis suggests that the isolated solid has a β-CD:PPA molar ratio of 1 : 1.

3.1. THERMAL ANALYSIS

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) curves for β-CD, PPA, the complex β-CD·PPA and the physical mixture (molar ratio 1 : 1) are shown in Figures 1 and 2, respectively.

The TG data show that the loss in weight for β-CD occurs in two steps: the first, in the region of 80–90°C, corresponds to dehydration and the second, above 300°C, to decomposition, m.p. 298–300°C [13]. Similarly, PPA presents a loss in the range of 150–200°C, m.p. 135–136°C. In the inclusion complex we have no modification at 135°C but two weight losses are observed near 190°C and 280°C. The first step can be attributed to the release of PPA and suggests that the complex obtained is stable up to this temperature, decomposing around the melting point of β-CD (the second step). If we compare the curves of β-CD complex with the physical mixture we find that, in the latter, the weight loss due to PPA begins near 140°C, that is, very close to that of the free acid. The decrease of volatility upon complexation is

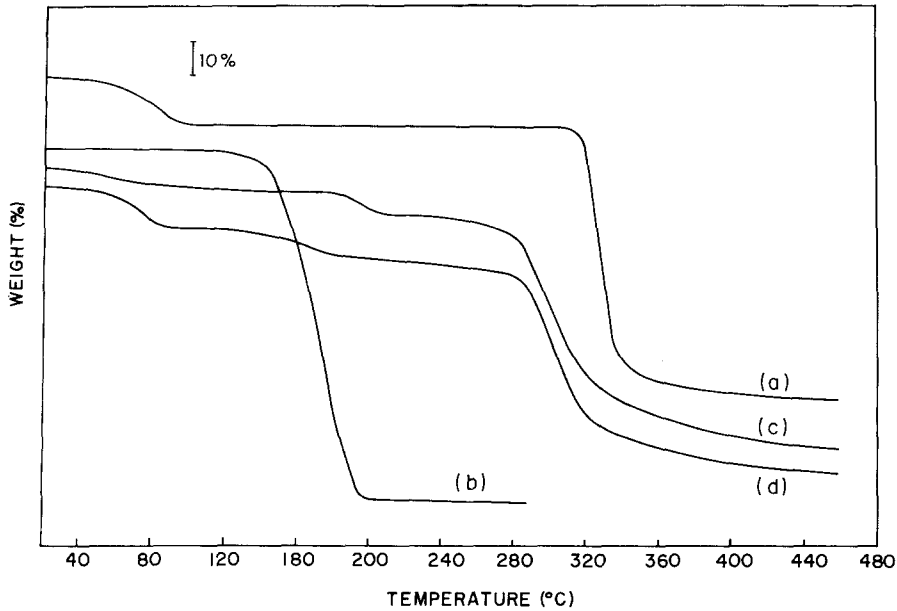


Fig. 1. TG Curves. (a) β-Cyclodextrin, β-CD; (b) phenylpropiolic acid, PPA; (c) β-CD·PPA complex; (d) physical mixture.

similar to that observed for other β-CD complexes with cinnamic acid derivatives [14].

The DSC curves, Figure 2, show a reasonable agreement with the TGA results. The significant differences between the curves of the complex and the physical mixture indicate the possible formation of a new crystalline phase in the complex.

3.2. IR SPECTRA

Generally IR techniques are not suitable for the detection of inclusion compounds because the resultant spectra have a superposition of host and guest bands [2]. Recently, Davies showed that utilizing FTIR spectral subtraction techniques one can in principle observe bands due to the guest molecule, which are obscured by the host bands [15]. Fortunately, in this study, due to the fact that PPA has some characteristic IR absorption bands in a region where β-CD does not absorb this region could be used to detect a guest interaction.

IR spectra are shown in Figure 3. The two bands at 2196 cm^{-1} and 2234 cm^{-1} in the PPA spectrum can be attributed to the carbon–carbon triple bond stretching, $\nu(C{\equiv}C)$. The splitting of this vibration is explained in terms of Fermi resonance interactions with the combinations or overtones in the region [16]. The wavenumber values of the fundamentals are markedly affected by the interaction with β-CD and this fact is revealed by the presence of a single band situated at 2226 cm^{-1} (Table I) in the spectrum of the inclusion complex.

This result, compared with that of the physical mixture, where two peaks are observed, can be taken as evidence of inclusion. Tests of crystallization of PPA from different solvents exclude the possibility of crystal effects on the splitting of ν (C≡C).

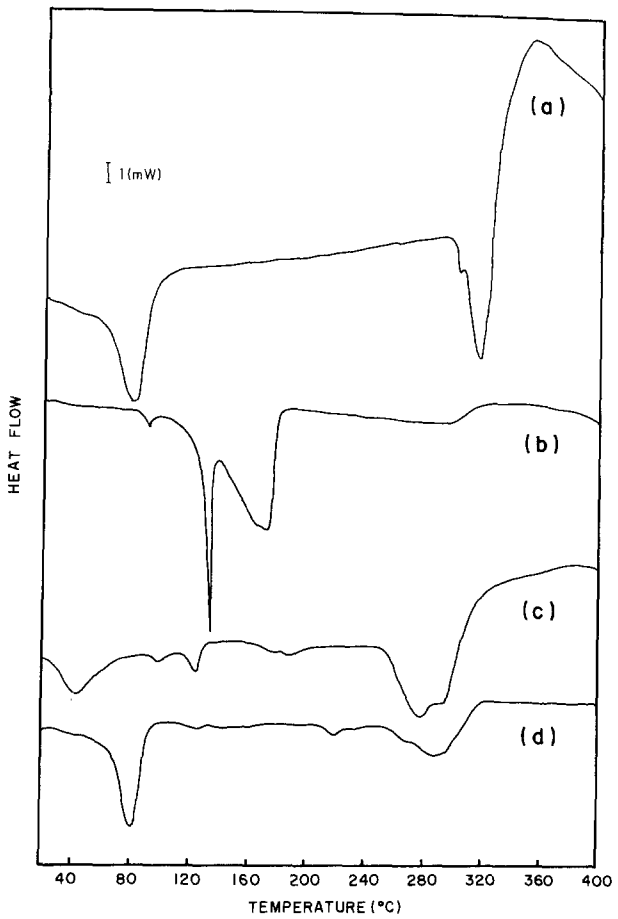


Fig. 2. DSC Curves. (a) β-Cyclodextrin, β-CD; (b) phenylpropiolic acid, PPA; (c) β-CD·PPA complex; (d) physical mixture.

Table I. IR frequencies in the $\nu(C{\equiv}C)$ region (cm^{-1})

free PPA	physical mixture	complex
2196	2200	2226
2234	2236	

3.3. X-RAY POWDER DIFFRACTION

The X-ray powder patterns for the individual components, complex and physical mixture, are reported in Figure 4.

A comparison of the β-CD·PPA diffraction pattern with that of the physical mixture reveals marked differences. The sharp peaks in the region of 13° for β-CD and near 17° for PPA (2θ) are absent in the inclusion pattern. Furthermore, the

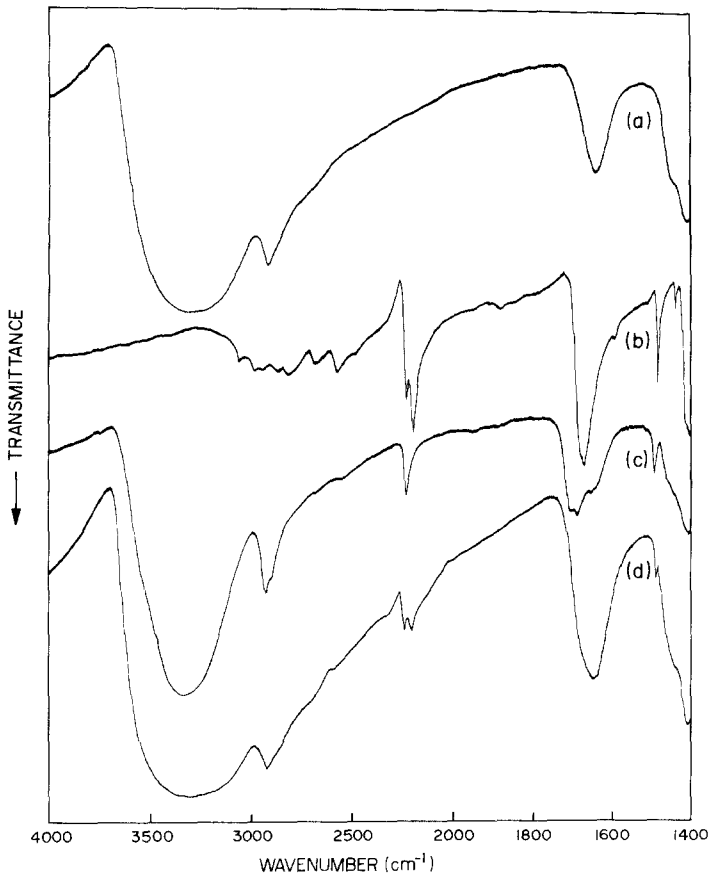


Fig. 3. Infrared Spectra (4000–1400 cm^{-1}) in fluorolube of (a) β-cyclodextrin, β-CD; (b) phenylpropiolic acid, PPA; (c) β-CD·PPA complex and (d) physical mixture.

data for the physical mixture can be interpreted as an approximate superposition of the components.

These observations reinforce the evidence from IR analysis that the precipitated solid is a new crystalline phase associated with the formation of an inclusion complex [2].

3.4. ^{13}C-NMR

The ^{13}C-NMR spectrum of the mechanical mixture of β-CD and PPA showed only the sum of the signals observed in the non-complexed compounds (Figures 5a and 5b), and the non-protonated carbons of phenylpropiolic acid were observed in the broad band off resonance decoupled spectrum. The signal of C-β of the acid is clearly shown in the spectrum of the complex β-CD·PPA (Figure 6a), while in the mechanical mixture (Figure 6b) that signal is concealed by the C-4 absorption of β-cyclodextrin.

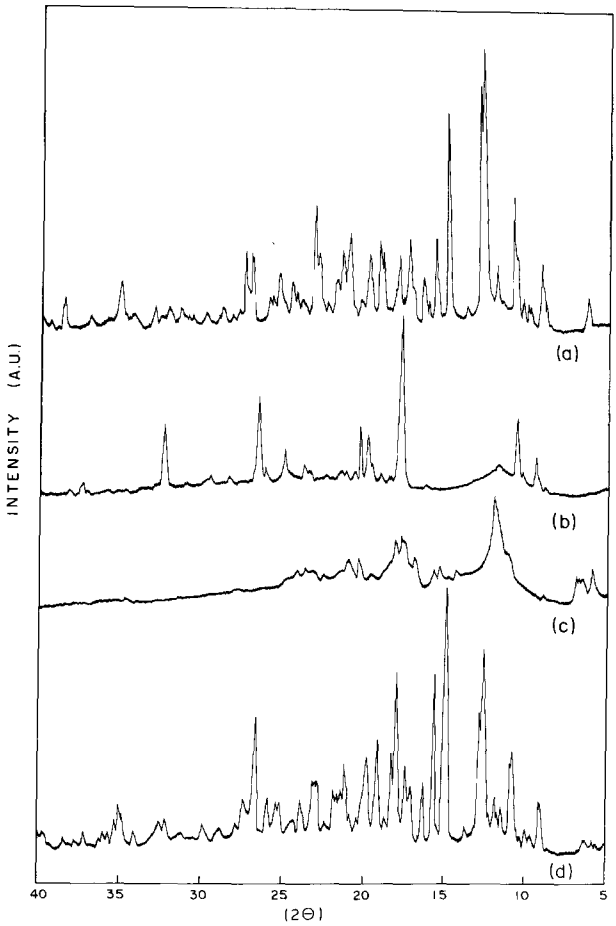


Fig. 4. X-ray diffraction patterns of (a) β-cyclodextrin, β-CD; (b) phenylpropiolic acid, PPA; (c) β-CD·PPA complex and (d) physical mixture.

The ^{13}C-NMR spectral analysis showed that the carbons of β-cyclodextrin in the complex (Table II) were shielded at most positions, with chemical shift changes of 0.15 to 0.27 ppm, and the carbons of the phenyl group of complexed PPA exhibited slight deshielding. These results corroborate the formation of the β-CD·PPA complex with the inclusion of the phenyl moiety in the cavity [18].

A more significant change was observed in the chemical shift of one of the carbons of the triple bond, where C-β showed a shielding of 2.54 ppm in comparison with the same carbon in the free acid [19]. When phenylpropiolic acid is accommodated in the cavity of β-cyclodextrin the chemical shifts of the phenyl group do not change significantly. The acetylenic system, however, seems to be sensitive to spacial interactions with the host, as indicated by the upfield shift of C-β.

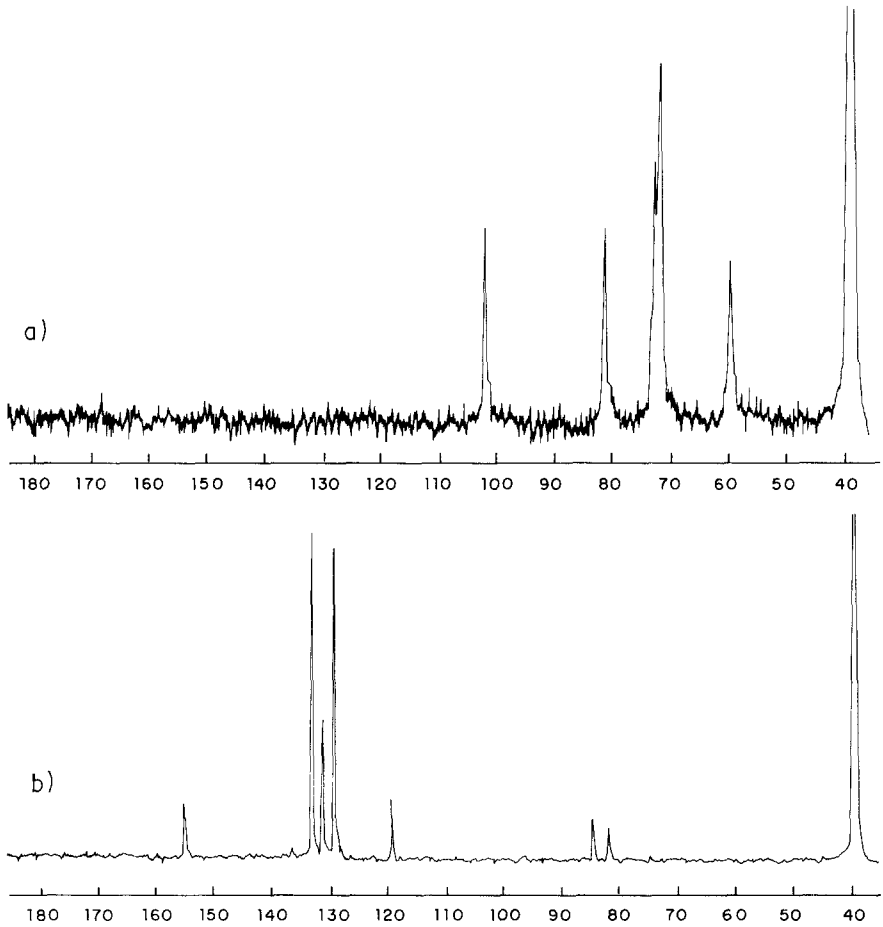


Fig. 5. ^{13}C-NMR spectra in DMSO of (a) β-cyclodextrin, β-CD and (b) phenylpropiolic acid, PPA.

Table II. Chemical shifts (ppm) of β-cyclodextrin (β-CD), phenylpropiolic acid (PPA) and the β-CD·PPA complex in DMSO[a, b]

Carbon		β-CD[c] (δ)	*β-CD*·PPA (Δδ)[e]	PPA[d] (δ)	β-CD·*PPA* (Δδ)[e]
β-CD	PPA				
1	1′	102.29	−0.15	119.10	−0.03
2	2′; 6′	72.62	+0.02	129.06	+0.12
3	3′; 5′	73.46	−0.18	132.63	+0.05
4	4′	81.69	−0.10	130.94	+0.09
5	(α)	72.51	−0.21	84.65	+0.02
6	(β)	60.52	−0.27	81.91	−2.54
	(C=O)	–	–	154.34	+0.11

[a] The spectra were obtained from solutions of approximately 0.4 mmol sample in 1 mL of DMSO at ambient temperature.
[b] The ^{13}C resonance of DMSO was used as the internal reference and converted to the Me_4Si scale by the following correction: (Me_4Si) = DMSO + 40.5.
[c] The assignments are based on Reference 18.
[d] The assignments are based on Reference 19.
[e] + and − indicate deshielding or shielding, respectively.

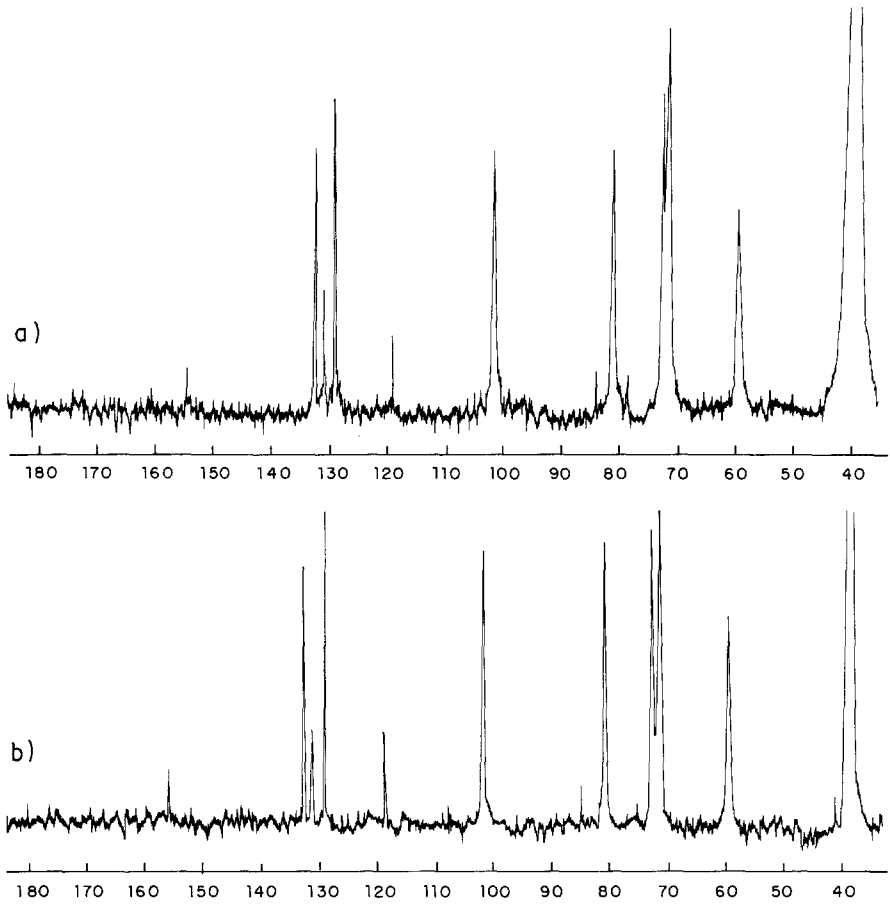
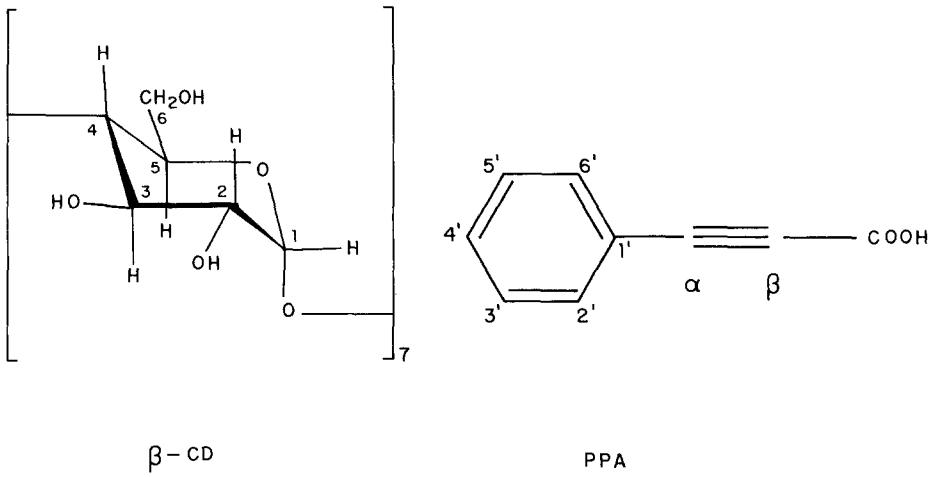


Fig. 6. ^{13}C-NMR spectra in DMSO of (a) β-CD·PPA complex and (b) physical mixture.



β – CD PPA

Fig. 7. Structures of (a) β-cyclodextrin, β-CD and (b) phenylpropiolic acid, PPA.

4. Conclusions

β-CD can readily accommodate molecules of different types in its cavity. The thermal analysis, IR spectra and powder X-ray diffraction results reported here indicate the formation of a stable 1 : 1 complex of β-CD : PPA in the solid state. The ^{13}C-NMR measurements in DMSO also confirm the existence of the complex in solution.

As proposed for similar complexes, the mode of inclusion is by the entry of the phenyl moiety of PPA into the cavity of β-CD [17]. Studies of the interaction of β-CD with substances containing phenyl groups with oxygenated substituents are currently in progress in our laboratory.

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