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Intramolecular Inclusion of L-tryptophan within 3-functionalized Cyclodextrins

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The synthesis of L-tryptophan attached to the C3 group of a β-cyclodextrin through amide linkages with ethylenediamine or propylenediamine is reported. Circular dichroism and fluorescence investigations were carried out showing great differences between the two derivatives. The derivative containing the propylenediamine chain shows clear self-inclusion and exhibits spectral variations upon guest inclusion detected both by circular dichroism or by fluorescence. The difference in conformation of the two derivatives could be explained on the basis of the chain length.

Keywords: Functionalized cyclodextrin, self-inclusion

INTRODUCTION

Functionalized cyclodextrins (CDs) have been widely investigated as molecular receptors [1]. Several attempts have been made to obtain more efficient and selective binding of chiral molecules such as amino acids, α-hydroxyl acids, also through the use of different metal ions assisting the molecular recognition process [2-5].

In addition to intermolecular complexes, a large number of cyclodextrin derivatives bearing hydrophobic or aromatic molecules have shown intramolecular inclusion [6-8]. Recent reports have described the attachment of amino-acids, or peptides, to cyclodextrins in the primary position and their intramolecular interaction with the cavity, using ^{1}H NMR, fluorescence and circular dichroism [9-13].

The geometric disposition of primary OH groups, their capacity to give non-covalent interactions with some functional residues of guest molecules, and the size of the narrower rim of cyclodextrins in addition to the hydrophobic features of the included molecule have been quoted to rationalize the supramolecular complex formation and self-assembly process. There are, however, comparatively much fewer examples of intramolecular inclusion of organic functional groups through attachment to the secondary face of a cyclodextrin [14]. The secondary side of the CD is more apparent in chirality, and more diverse in chemistry than the primary side. It is often the preferential site for selective binding and catalysis in native cyclodextrins, exhibiting different properties in com-

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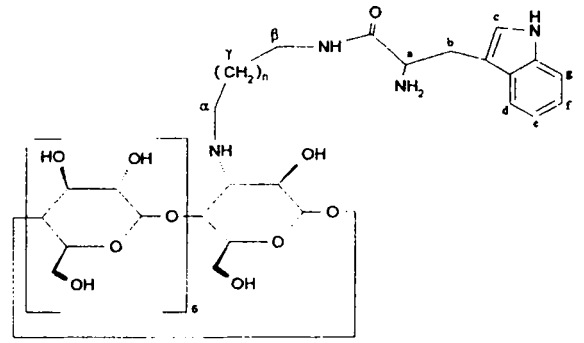
parison to the primary side. A few artificial enzymes have been prepared by modifying the secondary hydroxyl side of the β-cyclodextrin, [15,16] and selective modifications of the secondary hydroxyl group of the cyclodextrin have been reported to be an effective approach in order to increase chiral recognition [17,18].

In this paper, we have synthesised two 3-functionalized cyclodextrins, 2A(S), 3A(R)-deoxy-2A(S), 3A(R)-L-tryptophanylamidoethylamino-β-cyclodextrin (CDenTrp) **1** and 2A(S), 3A(R)-deoxy-2A(S), 3A(R)-L-tryptophanylamidopropylamino-β-cyclodextrin (CDpnTrp) **2** (chart 1), in order to generate molecules that exhibit spectral variations upon guest inclusion and that also have a chiral moiety which can effect the chiral recognition process.



1 n = 0
2 n = 1

RESULTS AND DISCUSSION

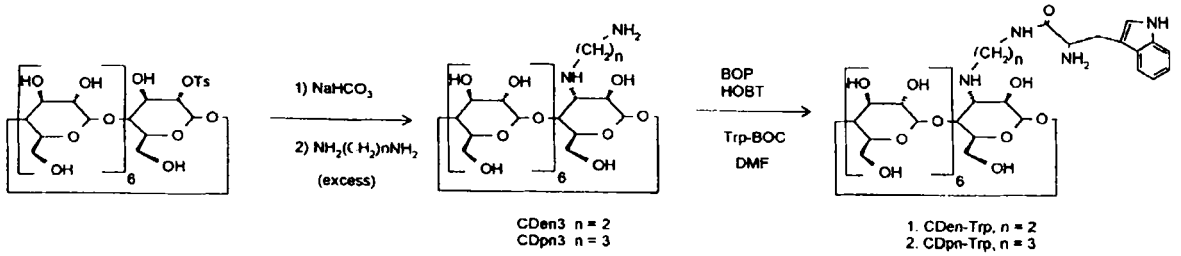
Synthesis

The 2-deoxy-2-[(*p*-tosyl)oxy]-β-cyclodextrin (2-CDOts) was prepared as previously described and was treated with an aqueous solution of $NaHCO_3$ to give 2,3-manno-epoxide [15, 19] (Scheme 1). Ethylenediamine or propylenediamine was added in excess to the mixture containing the epoxide, not isolated [15]. The solution was stirred for 5 h at 60°C under nitrogen. After purification by chromatography, we obtained the intermediary compounds 2A(S), 3A(R)-deoxy-2A(S), 3A(R)-aminoethylamino-β-cyclodextrin (CDen3) and 2A(S), 3A(R)-deoxy-2A(S), 3A(R)-aminopropylamino-β-cyclodextrin (CDpn3). As described in the literature, the ring opening of the manno-epoxide generally gives rise to a derivative in position 3 having modified altrose residue [15].

For derivatives **1** and **2**, the L-tryptophan protected by the tert-butyloxycarbonyl, was grafted to cyclodextrin derivatives using phosphonium hexafluorophosphate-hydroxybenzotriazole (BOP-HOBT) in DMF at room temperature [20]. The products were deprotected in neat trifluoroacetic acid and purified by chromatography. The purity was checked by ^{1}H NMR.

NMR Spectroscopy

^{1}H NMR spectra were assigned on the basis of the COSY spectra and for comparison with other C-3 modified cyclodextrins [21–23]. The ^{1}H NMR spectra of the CDen3 and CDpn3 show the expected signals of the diamine and cyclodextrin protons, also conforming monosubstitution in position 3. As a consequence of the 3-functionalization in addition to the two groups of peaks observed in the 4.1–3.5 region



SCHEME 1

due to the CD protons, peaks are present at 2.8 ppm and 4.3 ppm due to the H-3A and H-5A. All the other protons of the modified ring are easily assigned on the COSY spectra. At about 2.85 ppm, the signal of ethylenic protons is present on the CDen3 spectrum and at 1.75 and 2.78 ppm the signals of propylene chain on the CDpn3 spectrum can be seen.

In the case of the tryptophan derivatives, we performed the ^{1}H NMR spectra in MeOD. The spectra confirm the identity of the products. The aromatic proton peaks are present at about 7.2 ppm in both the derivatives' spectra. The anomeric proton region is present between 4.6 and 5 ppm. All the protons of the functionalized ring can be easily identified with the COSY spectra. The COSY spectrum of 1 is shown in Figure 1. The H-1A proton shows a cross peak with the H-2A at about 3.5 ppm, which shows a cross peak with the H-3A at 2.6 ppm. The H-3A shows a cross peak

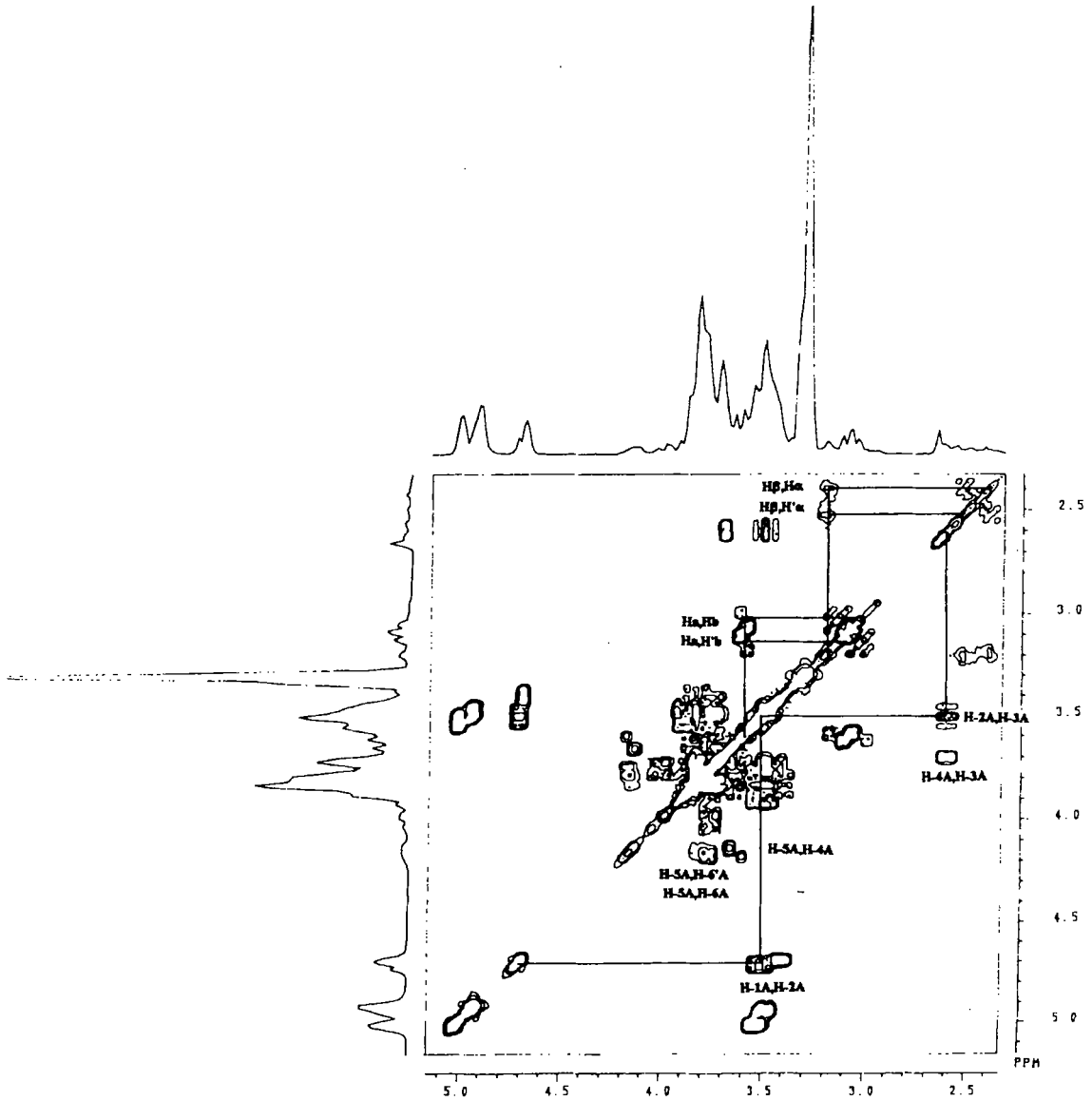


FIGURE 1 COSY spectrum of 1 in MeOD.

also with the H-4A. The H-5A shows cross peaks with the H-6A and H-6'A at 3.8 ppm and 3.6 ppm respectively and with the H-4A at about 3.8 ppm. As for the ethylenic chain, the two Hα protons are diastereotopic, and both show a cross peak with the Hβ at 3.2 ppm. At 3.05, 3.15 and 3.6 ppm, the ABX pattern of tryptophan moiety protons is present, as typically observed in the amino acid derivatives. The spectrum of **2** is very similar to the spectrum of **1**, except for the signal at about 1.5 ppm of the Hγ.

The asymmetry of the CD cavity due to substitution, and especially to the modification of C-2 and C-3 configuration of the functionalized ring, which is an altrose unit in these derivatives, can be seen in the anomeric region, as typically observed in CD derivatives. In MeOD, when the water resonance was suppressed, the coupling constant of the H-1A with H-2A could be measured. Figure 2 shows the ^{1}H NMR spectrum of **2** in MeOD. The coupling constant values between H-2A and H-1A ($J_{2A,1A} = 6.8$ Hz for **1** and 7.2 Hz for **2**) and between H-2A and H-3A ($J_{2A,3A} = 11.4$ Hz for **1** and 12 Hz for **2**) indicated that 1A, 2A, 3A protons were axial. Furthermore, the coupling

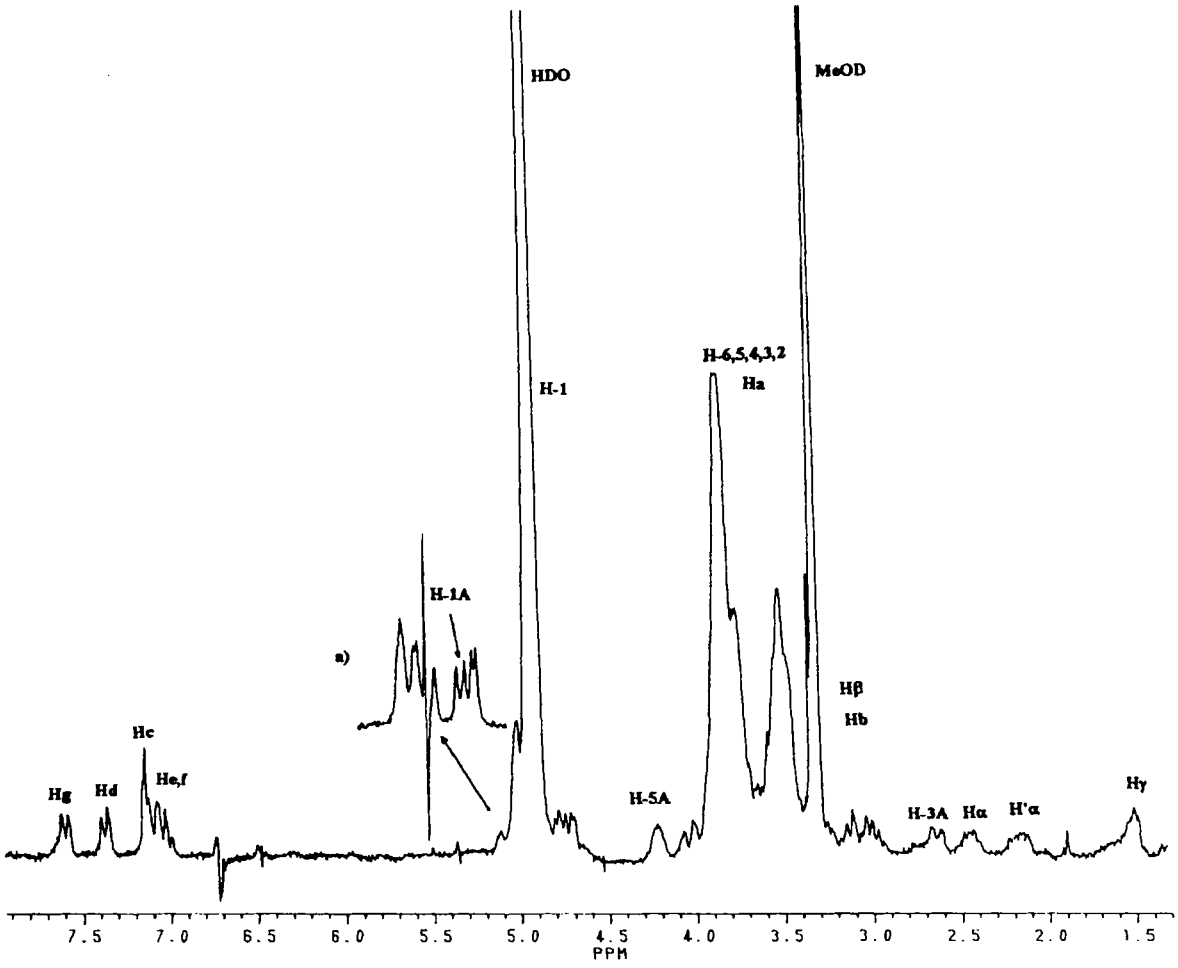


FIGURE 2 ^{1}H NMR spectrum of 2 in MeOD. (a) H-1 region when HDO was presaturated.

constant value for H-3A with H-4A ($J_{3A,4A}$ = 3.99 Hz for **1** and 2.99 Hz for **2**) indicated an equatorial orientation of the 4A proton. The data suggest that these two derivatives have the altrose residue with a mainly $^1C_4$ conformation as typically observed for this class of compounds [21–23].

Fluorescence

The location of the Trp moiety was investigated by fluorescence. It is in fact known that the fluorescence of the tryptophan is very sensitive to the microenvironment [24]. Compounds **1** and **2** show a fluorescence peak at 355 and 348 nm, respectively. The quantum yields (Φ_F = 0.29 for **1** and Φ_F = 0.48 for **2**) were higher than both those of tryptophan alone (Φ_F = 0.18) and the tryptophanamide (Φ_F = 0.11) measured in the same conditions, and this suggests that indole fluorescence is enhanced by a less polar environment [24]. The maximum wavelength emission of **2** shows a downward shift compared to the maximum wavelength emission of the tryptophanamide or of the tryptophan alone, thus suggesting strong modification of the polarity experienced by the indole upon inclusion in the relatively hydrophobic cavity of the cyclodextrin, as observed for other derivatives [25].

Fluorescence intensity must change upon addition of a guest if the indole is really inside the cavity, since the location inside the relatively hydrophobic cavity enhances tryptophan fluorescence [26, 27]. In order to verify intramolecular inclusion, the 1-adamantanecarboxylic acid (ACA) was used as a competitive guest. Figure 3 shows the fluorescence spectra of **1** and **2**,

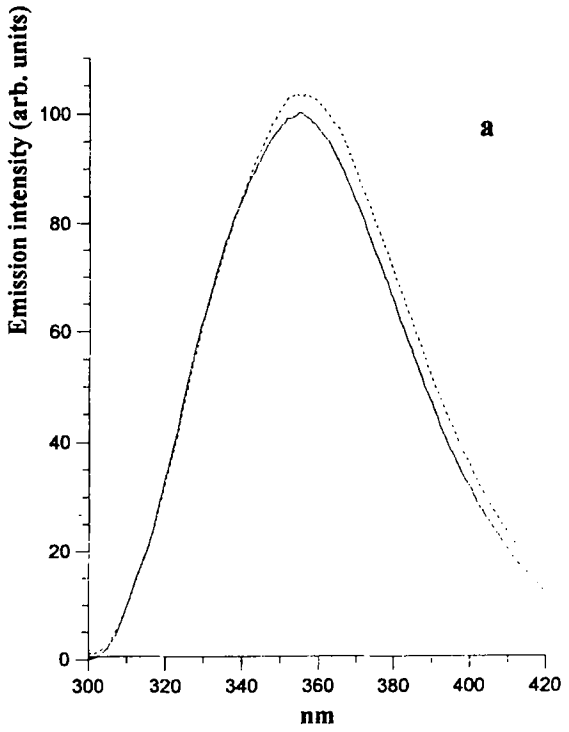


FIGURE 3 Fluorescence spectra of (a) **1** ($5\cdot10^{-5}$ M) and (b) **2** ($5\cdot10^{-5}$ M) in buffer pH 7 alone (—) and with 1-adamentanecarboxylic acid $1\cdot10^{-3}$ M (- - -). Excitation wavelength was 280 nm.

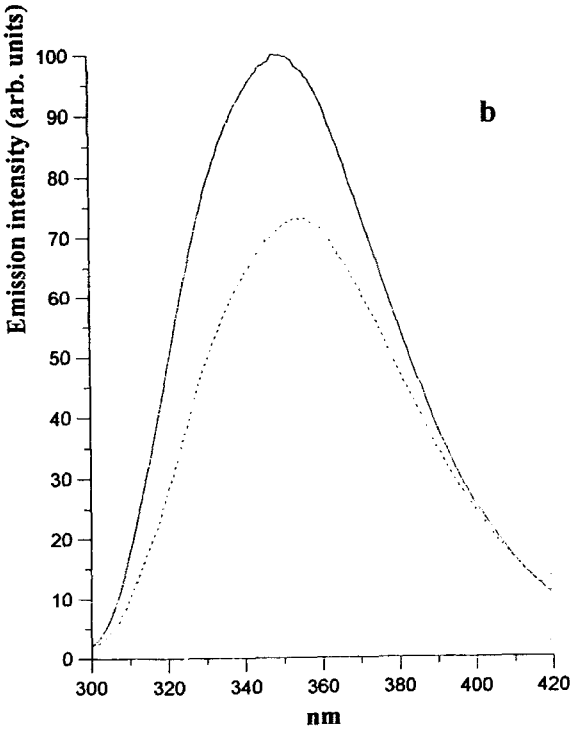


FIGURE 3 (Continued).

together with the spectra in the presence of 1-adamantanecarboxylic acid in phosphate buffer pH 7.

For **2**, fluorescence intensity diminishes by 25% and the maximum wavelength emission changes from a shorted ($\lambda = 348$ nm) to a longer one ($\lambda = 355$ nm) due to the modification of the indole environment. These results suggest that for **2**, the location of the indole changes from inside to outside the cavity in order to accommodate the guest molecules in the cavity. For **1**, no significant variation of fluorescence intensity occurs.

Circular Dichroism

In order to further examine intramolecular inclusion, we also obtained circular dichroism spectra of the products alone and in the presence of the competitive guest (Fig. 4). When a chiral molecule interacts with the chiral cavity of a cyclodextrin, a modification of the c.d. spectrum can be observed, this being dependent on the disposition of the guest with respect to the cavity [28]. For **1**, a positive band at 219 nm arising from the tryptophan residue was observed, while for **2**, a positive band at 205 nm and a negative band at 228 nm were observed. The higher intensity observed for **2** might be attributed to a deeper inclusion of the indole in the cavity of the cyclodextrin. This assumption is supported by the competition complexation experiments. The addition of the guest (ACA) induces the intensity of the c.d. signal of **2** to diminish suggesting that the location of the indole ring changes upon guest addition, the indole is driven out of the cavity by the guest. In contrast, the addition of the guest does not modify the c.d. spectrum of **1**, confirming the fluorescence results.

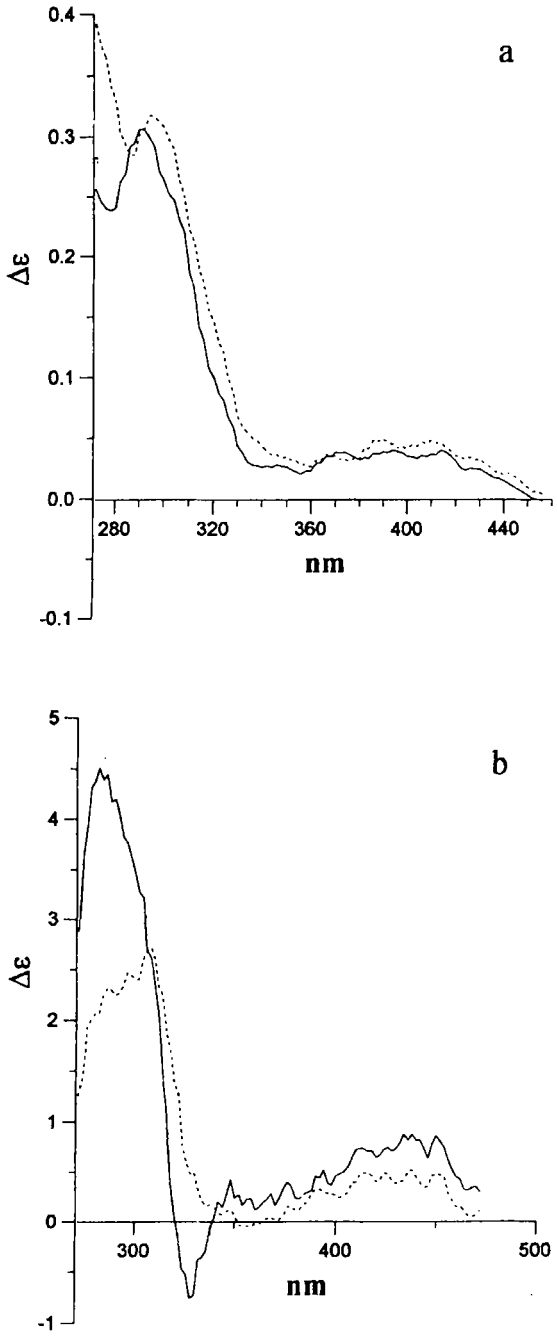


FIGURE 4 Circular dichroism spectra of (a) **1** ($5 \cdot 10^{-4}$ M) and (b) **2** ($5 \cdot 10^{-4}$ M) in buffer pH 7 alone (—) and with 1-adamentanecarboxylic acid $1 \cdot 10^{-3}$ M (---).

CONCLUSION

We have carried out the synthesis of new derivatives of tryptophan-modified-cyclodextrin functionalized in position 3 and spectroscopic investigations on the intramolecular inclusion of tryptophan. The studies show that 3-functionalized cyclodextrins can give rise to good sensory systems that exhibit spectral variations upon guest inclusion detected both by circular dichroism and by fluorescence. The difference in conformation of the two molecules could be explained on the basis of the chain length. The propylenic chain is long enough to allow the deep self-inclusion of the indole in the cavity, while the ethylenic chain is not and the location of the tryptophan for this compound may be at the edge of the cavity. The CPK model confirms this hypothesis.

Derivative **2** may be used for detecting organic compounds through fluorescence variations, even if the compounds are optically inert. Furthermore, in comparison with the cyclodextrin functionalized with an a chiral fluorophore, the amino acid antenna may enhance chiral recognition and the enantioselective detection of chiral compounds. The ability of **2** to act as fluorescent sensor can be considered the first example of a chiral fluorescent sensor obtained through 3-functionalized cyclodextrins.

MATERIALS AND METHODS

Commercially available reagents were used directly unless otherwise noted: β-CD was dried in vacuo (10 mm Hg) for 24 h at 80°C using a P_2O_5 trap. Tlc was carried out on silica gel plates 60F-254 (Merck). Cyclodextrin derivatives were detected with UV light and the anisaldehyde reagent. Merck lichroprep RP-8 (40–60 mm) was used for reversed phase column chromatography.

Fluorescence spectra were measured on a Jasco FP-777 spectrofluometer using a 10 mm quartz cell. The emission and excitation widths were set at 1.5. Measure of quantum yields were made in water. The concentrations were $5 \cdot 10^{-5}$ M for the derivatives and 10^{-3} M of guest. No smoothing was applied to the spectra. Electronic and c.d. spectra were recorded on a Beckam DU 650 spectrophotometer and on a JASCO J-600 dichrograph, respectively. Calibration of the c.d. instrument was performed with a 0.60% solution of ammonium camphorsulfonate in water ($\Delta\epsilon = 2.40$ at 290.5 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Brucker spectrometer without reference compound.

2A(S), 3A(R)-deoxy-2A(S), 3A(R)-amino (ethylenamino)-β-cyclodextrin (CDen3)

A solution of 500 mg of 2-CDOts and 970 mg of $NaHCO_3$ in 7 ml of water was stirred at 60°C for 3.5 h. The epoxide which was formed was not isolated. The ethylenediamine in excess (about 1 ml) was added to the solution. The reaction mixture was stirred under nitrogen at 60°C during 5 h. The solvent was evaporated to dryness in vacuo and acetone was added to the residue. The solid was collected by filtration and purified by column chromatogrphy of CM-sephadex C-25 column (35 × 900 NH_4^+ form) by elution with water (1 l) and then with a 0–0.25 M NH_4HCO_3 linear gradient (total volume 2 l). The appropriate fractions were concentrated to give CDen3, $R_x = 0.23$, PrOH/H_2O/NH_3 5:3:2, yield: 45%. FAB/MS m/z: 1178 (M + 1).

^{1}H NMR (MeOD, 200 MHz): δ 2.6–2.8 (*m*, 4H, — CH_2 —), 2.9–2.96 (*m*, 1H, H-3A), 3.34–4.05 (*m*, 39H, H-2, H-4, H-5, H-6, H-3), 4.23 (*m*, 1H, H-5A), 4.76 (*d*, 1H, H-1A, $J_{1A,2A} = 7.45$ Hz) 4.9–5.02 (*m*, 6H, H-1)).

2A(S), 3A(R)-deoxy-2A(S), 3A(R)-amino (propylamino)-β-cyclodextrin (CDpn3)

The product was obtained following the same procedure previously described for CDen3,

using the propylenediamine. CDpn3 was obtained with 37% yield, $R_x = 0.18$ PrOH/H_2O/NH_3 5:3:2 FAB/MS m/z: 1192 (M + 1).

^{1}H NMR (MeOD, 200 MHz): δ 1.75 (*m*, 2H, —CH_2—), 2.66–2.78 (*m*, 4H, —CH_2NH, —CH_2NH_2), 2.9–3.0 (*m*, 1H, H-3A), 3.34–4.07 (*m*, 39H, H-2, H-4, H-5, H-6, H-3), 4.23 (*m*, 1H, H-5A), 4.73 (*d*, 1H, H-1A) 4.9–5.01 (*m*, 6H, H-1).

2A(S),3A(R)-deoxy-2A(S), 3A(R)-L-trypto phanylamidoethylamino-β-cyclodextrin (1)

The tert-butyloxycarbonyl-L-tryptophan (52 mg) was added to a solution of CDen3 (200 mg), in DMF in the presence of benzotriazolyl-*N*-oxy-tris-(dimethylamino) phosphonium hexafluorophosphate (BOP) (75 mg) and *N*-l-hydroxybenzotriazole (HOBT) (26 mg). The reaction mixture was stirred vigorously at room temperature under nitrogen over 2 h. The solvent was evaporate to dryness in vacuo, and purified by elution from a column (20 × 600 mm) of CM-sephadex C-25 (NH_4^+ form) firstly with 400 ml water, then with a 0–0.2 M NH_4HCO_3 linear gradient (total volume 1.1 l). For deprotecting step, the product was dissolved in neat trifluoroacetic acid. The solution was stirred at room temperature for 1 h and the solvent was evaporated. The product was purified by chromatography as described above. The appropriate fractions were concentrated to give **1** with 10% yield. $R_f = 0.48$ (PrOH/H_2O/AcOEt/NH_3 5:3:1:1).

^{1}H NMR (MeOD, 200MHz): 2.4–2.5 (*m*, 2H, Hα), 2.6 (*dd*, 1H, H-3A, $J_{2A,3A} = 11.4$ Hz, $J_{3A,4A} = 3.99$ Hz), 2.95–3.6 (*m*, Hb, Hβ, Ha, H-2, H-4), 3.7–4.05 (*m*, H-5, H-6, H-3), 4.16 (*m*, 1H, H-5A), 4.72 (*d*, 1H, H-1A, $J_{1A,2A} = 6.8$ Hz) 4.6–5 (*m*, 6H, H-1), 6.98–7.14 (*m*, 2H, He, Hf), 7.14 (*s*, 1H, Hc), 7.36 (*d*, 1H, Hd, $J_{d,e} = 7.6$ Hz), 7.58 (*d*, 1H, Hg, $J_{g,f} = 8.1$ Hz). ^{13}C NMR (D_2O, 50.33 MHz): δ 32.9 (Cβ), 33.5 (Ca), 41.7 (Cα), 58.4 (C-3A, Cb), 60.9 (C-6A), 62.9 (C-6), 72.3 (C-2A), 71–76 (C-2, C-3, C-5), 78.3 (C-5A), 82.4 (C-4A), 83.5 (C-4), 103.8–105 (C-1), 106 (C-1A), 112.2, 114.2, 121, 121.8, 124.4, 129.8, 138.8 (C aromatic ring). FAB/MS m/z: 1364 (M + 1).

2A(S),3A(R)-deoxy-2A(S),3A(R)-L-tryptophanylamidopropylamino-β-cyclodextrin (2)

The product was obtained following the same procedure described above for CDenTrp, using CDpn3. CDpnTrp was obtained with 13% yield: $R_f = 0.46$ (PrOH/H_2O/AcOEt/NH_3 5:3:1:1).

^{1}H NMR (MeOD, 200 MHz): δ 1.51 (*m*, 2H, Hγ), 2.15 (*m*, 1H, Hα), 2.4 (*m*, 1H, H′α), 2.63 (*dd*, 1H, H-3A, $J_{2A,3A} = 12$ Hz, $J_{3A,4A} = 2.96$ Hz), 2.99–3.2 (*m*, 3H, Hb, Hβ), 3.3–4.1 (*m*, Ha of trp, Hβ, H-2, H-4, H-5, H-6, H-3), 4.21 (*m*, 1H, H-5A), 4.75 (*d*, 1H, H-1A, $J_{1A,2A} = 7.2$ Hz) 4.7–5.02 (*m*, 6H, H-1), 7.01–7.11 (*m*, 2H, He, Hf), 7.13 (*s*, 1H, Hc), 7.37 (*d*, 1H, Hd, $J_{d,e} = 7.7$ Hz), 7.59 (*d*, 1H, Hg, $J_{g,f} = 6.9$ Hz). ^{13}C NMR (D_2O, 50.33 MHz): δ 33.5 (Cb, Cβ), 39.9 (Cγ), 46.4 (Cα), 58 (Ca), 59.3 (C-3A), 60.8 (C-6A), 62.8 (C-6), 72.1 (C-2A), 72.5–76.5 (C-2, C-3, C-5), 78.7 (C-5A), 82.9 (C-4A), 83–83.8 (C-4), 104–105 (C-1), 105.9 (C-1A), 112.8, 114.07, 121.33, 123.9, 130.4, 138.7 (C aromatic ring), 178.57 (CO). FAB/MS m/z : 1378 (M + 1).

Acknowledgments

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