Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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Online publication date: 13 May 2010

To cite this Article Wang, Xiao-ping , Pan, Jing-hao , Shuang, Shao-min and Zhang, Yong(2003) 'Study on the Supramolecular System of TAPP and Cyclodextrins by Spectroscopy', Supramolecular Chemistry, 15: 4, 245 — 250
To link to this Article: DOI: 10.1080/1061027031000090389
URL: http://dx.doi.org/10.1080/1061027031000090389

Supramolecular Chemistry, 2003 Vol. 15 (4), pp. 245–250

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Study on the Supramolecular System of TAPP and Cyclodextrins by Spectroscopy

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Received (in Austin, USA) 18 October 2001; Accepted 29 April 2002

The ability of β-cyclodextrin (β-CD), γ-CD, hydroxypropyl-β-CD (HP-β-CD), trimethyl-β-CD (TM-β-CD), sulfurbutylether-β-CD (SBE-β-CD) and carboxymethyl-β-cyclodextrin (CM-β-CD) to break the aggregate of the meso-tetrakis(4-*N*-trimethylaminobenzyl)porphyrin (TAPP) and to form 2:1 inclusion complexes has been studied by absorption and fluorescence spectroscopy. The formation constants are calculated, respectively, by fluorimetry, from which the inclusion capacity of different CDs is compared and the inclusion mechanism of charged-β-CD (SBE-β-CD and CM-β-CD) is quite different from that of the parent β-CD. At lower pH, the complexation between TM-β-CD and H_2TAPP^{2+} (the form of the diprotonated TAPP) hampers the continuous protonation of the pyrrole nitrogen of TAPP and the hydrophobic cavity may prefer to bind an apolar neutral porphyrin molecule. ^{1}HNMR data support the inclusion conformation of the porphyrin–cyclodextrin supramolecular system, indicating the interaction of the meso-phenyl groups of TAPP with the cavity of CDs. For this host–guest inclusion model, cyclodextrin being regarded as the protein component, which acts as a carrier enveloping the active site of heme prosthetic group within its hydrophobic environment, provides a protective sheath for the porphyrin, creating artificial analogues of heme-containing proteins. However, for TAPP, encapsulated within this saccharide-coated barrier, its photophysical and photochemical properties changed strongly.

Keywords: Fluorimetry; Cyclodextrin; TAPP; Supramolecular system; Inclusion constants

INTRODUCTION

In the human body, heme-containing proteins participate in a range of activities, including oxygen transport and activation. The protein component acts as a carrier transporting the heme to the appropriate cellular environment. The active site of the heme prosthetic group is enveloped within a protective hydrophobic environment. In addition, porphyrin and metallaporphyrins are interesting materials in many applied fields [1]. TAPP is the most accessible anionic, water-soluble porphyrin. Many studies have concentrated on the interaction of anionic porphyrins with nucleic acid [2,3] in order to select an effective agent such as hematoporphyrin to cure cancer [4]. Recently, porphyrins have become accepted not only as catalysts or photosensitisers but also as anticancer drugs [4].

There are few literature reports concerning the complexation of cyclodextrin derivatives with porphyrins [5–7]. Only two reports studied the external assembly between meso-tetrakis(4-carboxyphenyl) porphyrin and HP-β-CD [8,9]; and in our previous research, the supramolecular system of TAPP and cyclodextrins was studied by polarography [10]. The self-assembly of β-CD, γ-CD with $TPPS_4$ and 2,6-dimethyl-β-CD with non-water soluble porphyrin has shown that porphyrins can form inclusion complexes through their meso-phenyl groups [11]. Sanyo *et al.* [12] undertook a detailed study of the inclusion complexation of $TPPS_4$ with trimethyl-β-CD and γ-CD by means of electronic absorption, fluorescence and circular dichroism method. Moisinger's study [13] confirmed that a new type of efficient $TPPS_4$-HP-β-CD sensitiser had been formed. We have studied the inclusion interactions of diprotonated $TPPS_4$ with various CDs [14]. Recently, we have published several other articles that are aimed at the synthesis of a new type of porphyrin, β-CD-sandwiched porphyrin [15,16]. Despite the growing amount of information about

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ISSN 1061-0278 print/ISSN 1029-0478 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/1061027031000090389

the interactions of porphyrin–CD complexes, the study of the complexation between TAPP and CDs is still rare.

The purpose of this paper is to study the inclusion complexation of TAPP and diprotonated TAPP with two ionic cyclodextrin derivatives SBE-β-CD and carboxymethyl-β-CD by means of UV–Vis adsorption and fluorescence spectroscopy besides β-CD, γ-CD and HP-β-CD. Their formation constants are calculated by fluorimetry and the inclusion capacity of different CDs was compared. Moreover, the TAPP, encapsulated within this saccharide-coated barrier, exhibited a dramatic change in its physico-chemical, photophysical and photochemical properties. The hydrophobic cavity of cyclodextrin may prefer to bind an apolar neutral porphyrin molecule rather than the polar H_2TAPP^{2+}, which is consistent with our previous study [14]. The ^{1}HNMR data support the inclusion conformation of the porphyrin–cyclodextrin supramolecular system. For this host–guest inclusion model, cyclodextrin, being regarded as an artificial analogue of proteinoid of heme, provides a protective sheath for porphyrin.

EXPERIMENTAL

Reagents

TAPP was purchased from Emeishan Yahua Drug Institute (China); β-CD (Yunan Gourment Factory, China) was purified by recrystallisation from doubly distilled water. γ-CD, TM-β-CD and HP-β-CD (MW = 1380 degree substitution (DS = 0.6)) were purchased from Aldrich; CM-β-CD and SBE-β-CD were synthesised employing the method of Reuben [17]. All other reagents were of analytical reagent grade; water was doubly distilled.

Apparatus

The absorption and fluorescence measurements were performed on a DU70 spectrophotometer (Beckman Company, USA) and RF-540 spectrofluorimeter (Shimadzu, Japan). Both excitation and emission bandwidths were set at 10 nm. All experiments were carried out at 20 ± 1°C in a model 501 superthermostat circulating water bath. The measurement of ^{1}HNMR was performed on a DKX-300 MHz (Bruker, Switzerland).

RESULTS AND DISCUSSION

Beer's Law Studies

A Beer's law titration of the TAPP at pH = 7 (disodium hydrogen phosphate, sodium dihydrogen phosphate buffer) in the presence and absence of CDs is shown in Fig. 1. The absorbance measurements were performed at 414 nm. In the absence of β-CD, γ-CD, HP-β-CD, TM-β-CD, SBE-β-CD and CM-β-CD, remarkable deviations from Beer's law are observed. This implies that the porphyrin is aggregated. In contrast to the presence of a 1000-fold excess of CDs, the photophysical properties of the porphyrin adhere to Beer's law, which means that the cyclodextrin can prevent the aggregation of TAPP. Although the aggregation interferes with the ability of the monomeric species to carry out tasks such as oxygen transport and activation, the structure of the metalloporphyrin is preserved by the protein component that prevents porphyrin–porphyrin interaction [18]. Cyclodextrin acts as protein of heme and provides a protective moiety, which precludes porphyrin–porphyrin interaction [19].

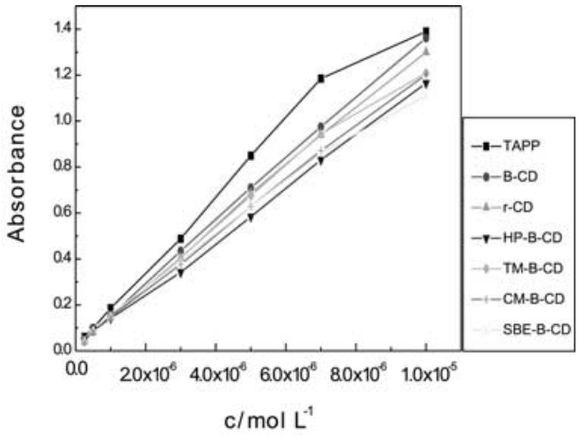

FIGURE 1 A Beer's law titration of the TAPP at pH = 7 in the presence and absence of CDs (measured at 412 nm).

Effect of β-CD Derivatives on Fluorescence of TAPP

Under the aggregation concentration 1×10^{-6} mol l^{-1}, TAPP was fixed and the concentration of cyclodextrin was varied from 5×10^{-4}–5×10^{-3} mol l^{-1}. Addition of different cyclodextrins (β-CD, γ-CD, HP-β-CD, CM-β-CD, SBE-β-CD) to an aqueous solution of TAPP produces a decrease in the emission intensity of fluorescence. In addition, both the emission wavelength (634 nm) and excitation wavelength (412 nm) shift towards longer wavelength (Fig. 2). These remarkable changes are due to the interaction between TAPP and cyclodextrins, implying the formation of TAPP-cyclodextrin inclusion complexes. However, in the presence of CM-β-CD the intensity of fluorescence at 634 nm decreases with the increase in the intensity of fluorescence at 610 nm; moreover, all the spectra pass an isostilbic point at 622 nm (Fig. 3). This suggests that CM-β-CD can form an inclusion complex with TAPP.

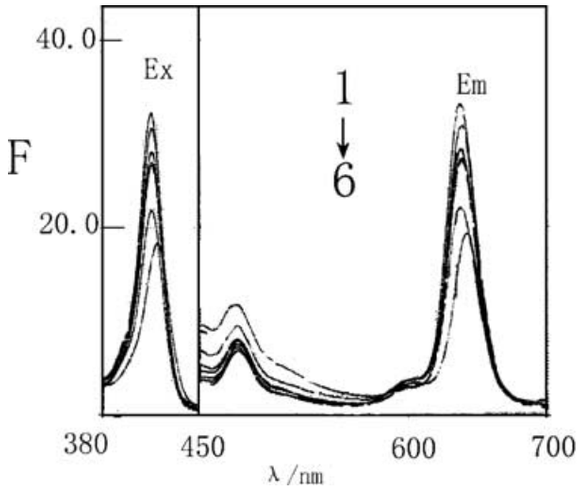

FIGURE 2 The fluorescence spectra of TAPP in the presence of different CDs: (1) TAPP; (2) β-CD; (3) γ-CD; (4) HP-β-CD; (5) TM-β-CD; (6) SBE-β-CD.

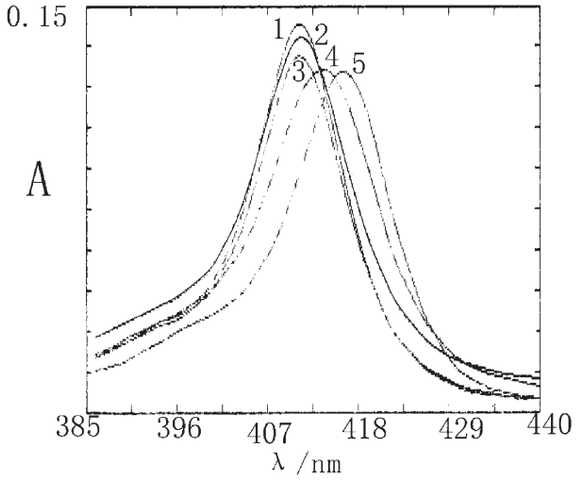

FIGURE 4 The absorption spectra of TAPP in the presence of different CDs: (1) TAPP; (2) β-CD + TAPP; (3) γ-CD + TAPP; (4) SBE-β-CD + TAPP; (5) HP-β-CD + TAPP.

Study of the UV–Vis Spectrum

From the variety of the UV–Vis spectrum of TAPP in the presence and absence of CD (Fig. 4), a similar phenomenon to that in the excitation spectra is obtained. The maximum absorption wavelength is red shifted and the absorbance also decreases. It indicates that the interactions of TAPP with cyclodextrins take place in the ground state of TAPP. Both the UV–Vis spectrum and the excitation spectra of TAPP demonstrate that in the ground state, TAPP forms complexes with cyclodextrins. The effect of temperature on the fluorescence intensity of the TAPP-CD supramolecular system shows that with the rise of temperature, the fluorescence intensity of TAPP increases slowly, which also implies the static quench that occurs between TAPP and cyclodextrin.

Inclusion Complexation of Diprotonated Porphyrin with CDs

In phosphate buffer pH = 4, TAPP forms the diprotonated H_2TAPP^{2+} (the pK_a value of TAPP is 4.8 [20]) with a Soret band at 432 nm and a fluorescence emission band at 644 nm (excitation at 432 nm). In this acid condition, the electronic absorption spectra of H_2TAPP^{2+} in the presence of TM-β-CD change with the Soret band gradually

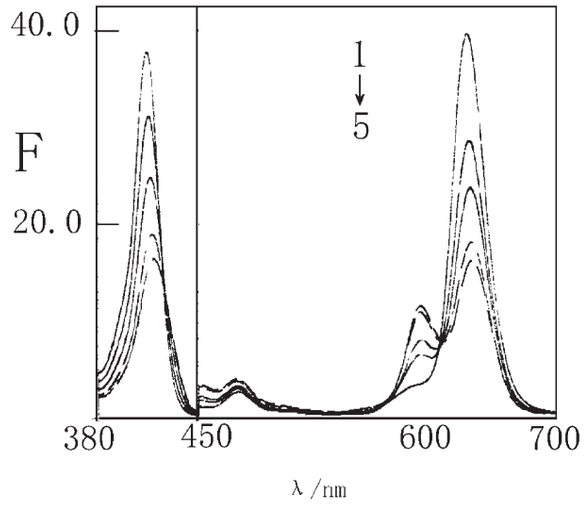

FIGURE 3 The fluorescence spectra of TAPP in the presence of CM-β-CD: (1) 3×10^{-6} mol l^{-1} TAPP; (2) 3×10^{-6} mol l^{-1} TAPP $+1\times10^{-6}$ mol l^{-1} CM-β-CD; (3) 3×10^{-6} mol l^{-1} TAPP $+2\times10^{-6}$ mol l^{-1} CM-β-CD; (4) 3×10^{-6} mol l^{-1} TAPP $+3\times10^{-6}$ mol l^{-1} CM-β-CD; (5) 3×10^{-6} mol l^{-1} TAPP $+4\times10^{-6}$ mol l^{-1} CM-β-CD.

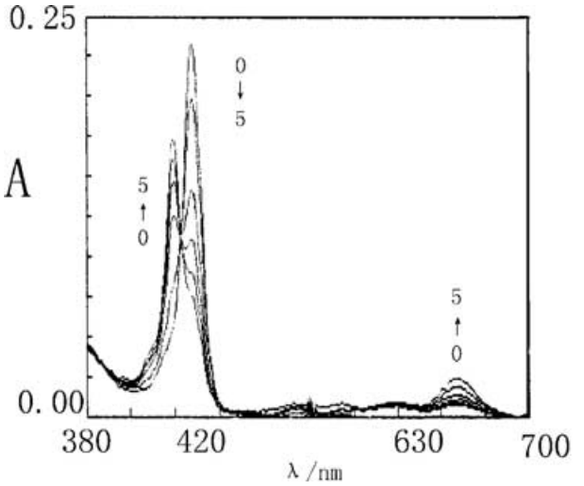

FIGURE 5 The absorption spectra of H_2TAPP^{2+} in the presence of different concentrations of TM-β-CD: (0) H_2TAPP^{2+} (3×10^{-6} mol l^{-1}); (1) (0) $+1\times10^{-6}$ mol l^{-1} TM-β-CD; (2) (0) $+2\times10^{-6}$ mol l^{-1} TM-β-CD; (3) (0) $+3\times10^{-6}$ mol l^{-1} TM-β-CD; (4) (0) $+4\times10^{-6}$ mol l^{-1} TM-β-CD; (5) (0) $+5\times10^{-6}$ mol l^{-1} TM-β-CD.

TABLE I The formation constants of TAPP with different CDs

	β-CD	β-CD	TM-β-CD	HP-β-CD	SBE-β-CD
TAPP	2.38×10^5	6.77×10^5	1.84×10^6	1.08×10^6	5.47×10^6
r	0.996	0.991	0.990	0.995	0.995
$TAPPH_4^{2+}$	1.38×10^4	5.05×10^4	2.19×10^5	7.52×10^5	1.69×10^5
r	0.984	0.992	0.993	0.991	0.997

r: The linear correlation coefficient.

shifting to 412 nm, which is the Soret band of the free-based TAPP (Fig. 5). It implies that the unprotonated form of porphyrin is increased corresponding to a decrease of protonated TAPP. The results of these experiment exhibit that much lower pH is necessary for the formation of diprotonated H_2TAPP^{2+} and the complexation between TM-β-CD and H_2TAPP^{2+} hampers the continuous protonation of the pyrrole nitrogen of TAPP. On the basis of the absorption spectra, the hydrophobic cavity of HP-β-CD may prefer to bind to an apolar neutral porphyrin molecule.

Determination of Formation Constant

The stoichiometry and binding strength of the interaction between TAPP and cyclodextrin are determined in this experiment. The formation constants of complexes are estimated by the double-reciprocal method [21]. The good linearity of the 2:1 complex in Table I suggests that a 2:1 CD–porphyrin complex is formed. The formation constant can be obtained from the following equation [22]

$$\frac{[G]_0}{\Delta F} = \frac{1}{K \cdot k \cdot Q} \frac{1}{[\mathrm{CD}]^n} + \frac{1}{k \cdot Q}$$

where $[G]_0$ is the initial concentration of TAPP, [CD] is the equilibrium concentration of cyclodextrin, ΔF is the change of fluorescence intensity in the presence of cyclodextrin, k is an instrumental constant, n is the stoichiometry of the complex, K is the formation constant and Q is the quantum yield for the complex. K can be calculated from a plot of $1/F$ vs. $1/[\mathrm{CD}]^n$. As found in our study above, 2:1 complexes are formed between CD and TAPP [10]. Furthermore, the stoichiometry of complex is assessed by equimolar variation method. A Job plot of fluorescence intensity vs. mole fraction of CDs is provided in Fig. 6. Plotting $1/F$ vs. $1/[\mathrm{CD}]^2$ gives a good linearity of the plots, which verifies the 2:1 complexation stoichiometry (Table I and Fig. 7). The formation constants of TAPP with β-CD, γ-CD, HP-β-CD and SBE-β-CD are calculated by the ratio of intercept over slope, respectively, and are listed in Table I, implying the strong inclusion ability of SBE-β-CD and the weak inclusion ability of β-CD. The result of the strong inclusion ability of anionic cyclodextrin SBE-β-CD with anionic porphyrin TAPP suggests that the charge attraction between cyclodextrins and TAPP plays an important role in the inclusion procedure except for the hydrophobic effect.

Conformation Analysis by NMR Spectroscopy

Additional evidence for the formation of the TAPP-CD complex can be obtained from changes of

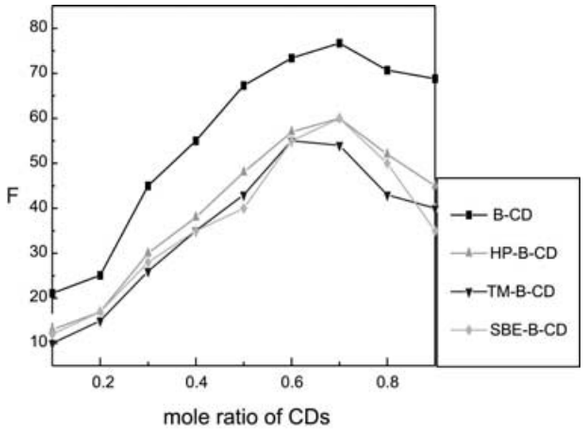

FIGURE 6 The inclusion stoichiometry of $TPPS_4$-CD complexes (Job plot).

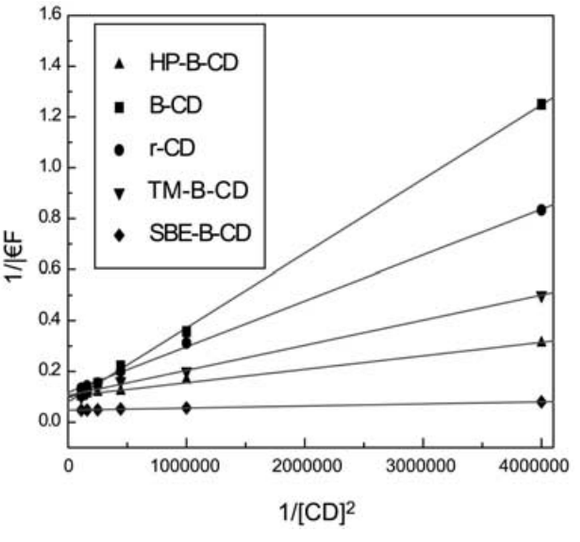

FIGURE 7 The linear plot for the determination of inclusion constants of the TAPP–cyclodextrin supramolecular system.

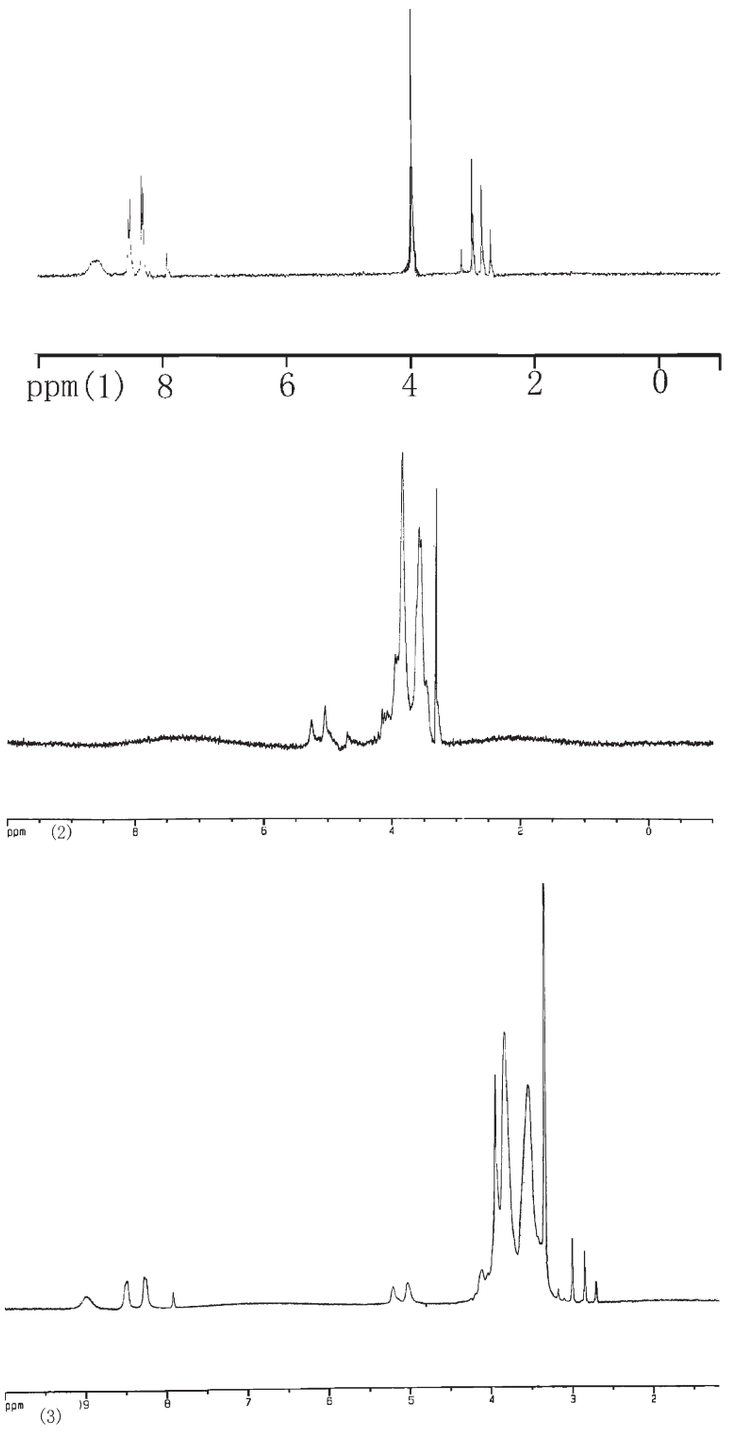

FIGURE 8 ^{1}HNMR spectra of CM-β-CD and TAPP in D_2O: (1) 1×10^{-3} M TAPP; (2) 2×10^{-3} M CM-β-CD; (3) CM-β-CD containing 1×10^{-3} M TAPP.

the chemical shifts of the ^{1}HNMR spectra at 300 MHz in D_2O solution. The ^{1}HNMR spectrum of CM-β-CD, TAPP and their complexes are shown in Fig. 8. As shown in Fig. 8, the chemical shift of the interior protons H-3 and H-5 move upfield by 0.11 ppm and 0.06 ppm (Table II), which is perhaps due to the direct interaction of these protons with the TAPP molecule. By contrast, the chemical shifts of the outer

TABLE II The chemical shifts CM-β-CD and TAPP-CM-β-CD complexes

	Chemical shifts of inner and outer protons of cyclodextrin cavity			
	H_2	H_3	H_4	H_5, H_6
CM-β-CD	3.65	3.98	3.45	3.85–3.79
TAPP-CM-β-CD complex	3.74	3.87	3.49	3.79

protons H-2 and H-4 move upfield by 0.09 and 0.04 ppm, which is less than the chemical shift of the interior protons H-3. This indicates that the interaction occurs inside the cavity instead of outside the torus, involving the encapsulation between TAPP and the secondary face of CM-β-CD. Furthermore, the downfield (0.12 ppm) chemical shift of the β-pyrrole protons and the upfield (0.05 ppm) chemical shift of the phenyl protons indicate that the meso-phenyl groups of TAPP enter the cavity of CM-β-CD. The unchanged chemical shifts of the trimethylamine groups imply that the trimethylaminobenzyl group penetrates the cavity of CDs leaving the trimethylamine outside.

Acknowledgements

This work was supported by the National Natural Science Foundation of China and by the National Natural Science Foundation of Shanxi province of China.

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