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Supramolecular Systems of 5-(2-Hydroxy phenyl)-10,15,20-tris(4-methoxy phenyl) Porphyrin and 5-(4-Hydroxy phenyl)-10,15,20-tris(4-methoxy phenyl) Porphyrin with Cyclodextrins

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Supramolecular Systems of 5-(2-Hydroxy phenyl)-10,15, 20-tris(4-methoxy phenyl) Porphyrin and 5-(4-Hydroxy phenyl)-10,15,20-tris(4-methoxy phenyl) Porphyrin with Cyclodextrins

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In neutral phosphate buffer solutions of pH 7.4, the inclusion complexes of 5-(2-hydroxy phenyl)-10,15,20-tris(4-methoxy phenyl) porphyrin (o-HTPP) and 5-(4-hydroxy phenyl)-10,15,20-tris(4-hydroxy phenyl) porphyrin (p-HTPP) with α-cyclodextrin (α-CD), β-CD, heptakis (2,3,6-tri-O-methyl)-β-CD (TM-β-CD) and γ-CD have been examined by means of fluorescence and absorption spectroscopy. The inclusion ability of cyclodextrin exhibited remarkable difference for TM-β-CD. Both o-HTPP and p-HTPP can form 1:1 host-guest inclusion supramolecular with α-CD, β-CD, γ-CD. The o-HTPP can form 1:2 inclusion supramolecular with TM-β-CD, which forms 1:1 inclusion supramolecular with p-HTPP. The formation constants (K) of o-HTPP and p-HTPP for the formation of the inclusion complexes have been estimated from the absorbance and/or fluorescence intensity changes in neutral phosphate buffer solutions. The formation constants as high as $K = 3.05 \times 10^7\,M^{-2}$ in the case of TM-β-CD/o-HTPP and $2.77 \times 10^3\,M^{-1}$ in case of TM-β-CD/p-HTPP complexes were determined, whereas lower K values were given in the case of α-CD, β-CD, γ-CD/o-HTPP and α-CD, β-CD, γ-CD/p-HTPP. It suggests the strongest inclusion ability of TM-β-CD in the four cyclodextrins (α-CD, β-CD, γ-CD and TM-β-CD), which can be explained that the hydrogen bond and the different chemical structures of the guest molecular play significant roles in the inclusion process.

Keywords: Porphyrin; Cyclodextrin; Absorbance; Fluorescence; Supramolecular systems

INTRODUCTION

Porphyrins and their metalloderivatives play a significant role in biological processes and have been studied and applied in many aspects of artificial enzyme [1], catalysis [2], supramolecular assembly [3] and so on [4]. Recently, porphyrins have become accepted not only as catalysts or photosensitisers but also as anticancer drugs [5]. Cyclodextrins (CDs) are water-soluble cyclic oligosaccharides with six, seven, and eight D-glucopyranose residues, which are called α-, β- and γ-CD, respectively [6]. It is well known that, because of their unique hydrophobic cavity interior and polar or hydrophilic exterior, many organic guest molecules can be fully or partly incorporated into the cavities of CDs to form inclusion complexes in aqueous solution [7–9]. And CDs have been used as carriers to improve the aqueous solubility [10], stability against chemical and photochemical degradation [11] and to control drug release [12,13] etc.

The formation of inclusion complexes of CDs with porphyrin derivatives modifies the photochemical and photophysical properties of porphyrin derivatives [14]. The inclusion processes in solution depend on the size, shape and hydrophobicity of the guest molecule. The main forces that have to do with the processes are van der Waal interaction and hydrophobic interaction [15]. In addition, hydrogen bonding between the guest and the hydroxyl groups of the CDs [16], the relief of high energy water from the CD cavity, release of strain energy in the molecular rings and dipole–dipole [17,18] are important interactions. These weak interactions have been used to study the nature of the formation of supramolecular structures. As a result, it is very useful to examine the formation of inclusion

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complexes of CDs with porphyrin derivatives. In our previous laboratory studies, several CD-porphyrin inclusion systems were investigated by different methods [19–23].

There are few literature reports concerning the complexation of cyclodextrin derivatives with o-HTPP and p-HTPP [24,25]. Both the two porphyrins are non-water soluble. Their structures are shown in Fig. 1. In this paper, the inclusion complexes between the two porphyrins (o-HTPP and p-HTPP) and CDs have been studied by absorption and fluorescence spectroscopy. Their formation constants (K) are calculated by photometry and the inclusion capacities of different CDs were compared. In addition, we have contrasted the different inclusion abilities of o-HTPP and p-HTPP. It indicates that the capacity matching between cyclodextrins and porphyrins plays important role in the inclusion procedure except for the hydrophobic effect and hydroxyl group position. Furthermore, this paper would present potential applications not only in the studies of supramolecular systems but also in pharmacokinetics and biodistribution. The results of the experiments would provide useful information for further uses of p-HTPP and o-HTPP.

EXPERIMENT

Reagent

The o-HTPP and p-HTPP were purchased from Sichuan E Mei Chemical Factory, China. 5.0×10^{-5} mol·L^{-1} stock solution of p-HTPP was prepared by 1,4-Dioxane. The same concentration stock solution of o-HTPP was prepared by N,N-Dimethylformamide (DMF). β-CD (YuNan Gourmet Factory, China) was purified by recrystallization in double distilled water. α-CD and γ-CD were obtained from Tokyo Kasei Kogyo Co., TM-β-CD was obtained from FLUKA. All the other reagents are of analytical-reagent grade made in China, and the experimental water is doubly distilled.

Apparatus

The absorption spectra are measured on TU-1901 spectrophotometer (Puxi instrument Co. Beijing, China), and all the auto-corrected fluorescence spectra are conducted on Cary Eclipse Fluorescence Spectrophotometer (USA). Both excitation and emission slit width are typically set at 10 nm. All experiments are carried out at 20 ± 1°C.

Method

1.0 mL aliquot of the stock solution (5.0×10^{-5} mol·L^{-1}) of p-HTPP in 1,4-Dioxane was transferred into a 10 mL volumetric flask, the 1.0 mL 0.1 mol·L^{-1} KH_2PO_4–Na_2HPO_4 (pH 7.4) buffer solution was added. An appropriate amount of cyclodextrins (α-CD, β-CD, γ-CD, TM-β-CD) were added, respectively. The mixed solution was diluted to final volume with distilled water and shaken thoroughly, following equilibration for 10 min. Then the spectra were recorded or fluorescence intensities and absorbance were measured. All of these procedures were similar for o-HTPP.

RESULTS AND DISCUSSION

Inclusion Complexes of TM-β-CD with p-HTPP and o-HTPP in Neutral Solution

Figure 2 showed the changes of the absorption spectra of p-HTPP and o-HTPP. The Soret band of p-HTPP is at 423 nm in absence of TM-β-CD. With the addition of TM-β-CD, the maximum absorption peak is blue shifted to 417 nm, accompanied by an

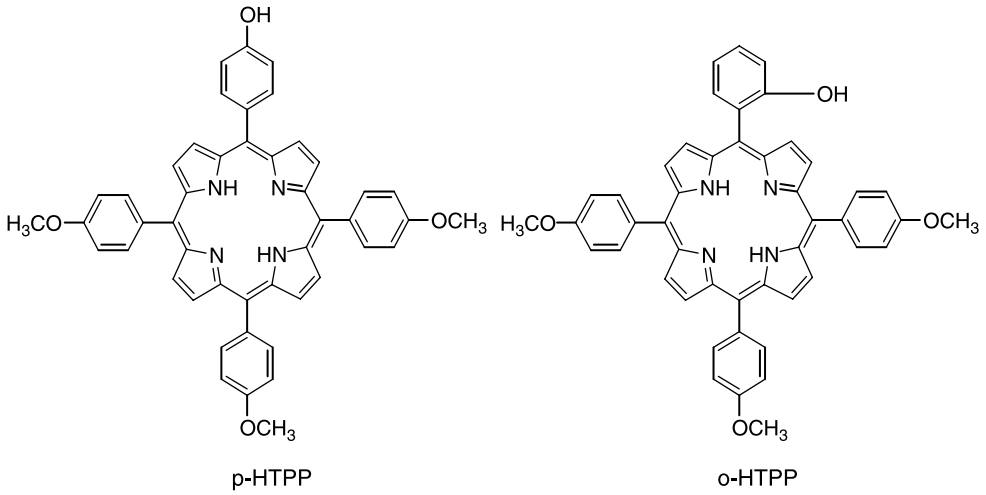

FIGURE 1 The structures of p-HTPP and o-HTPP.

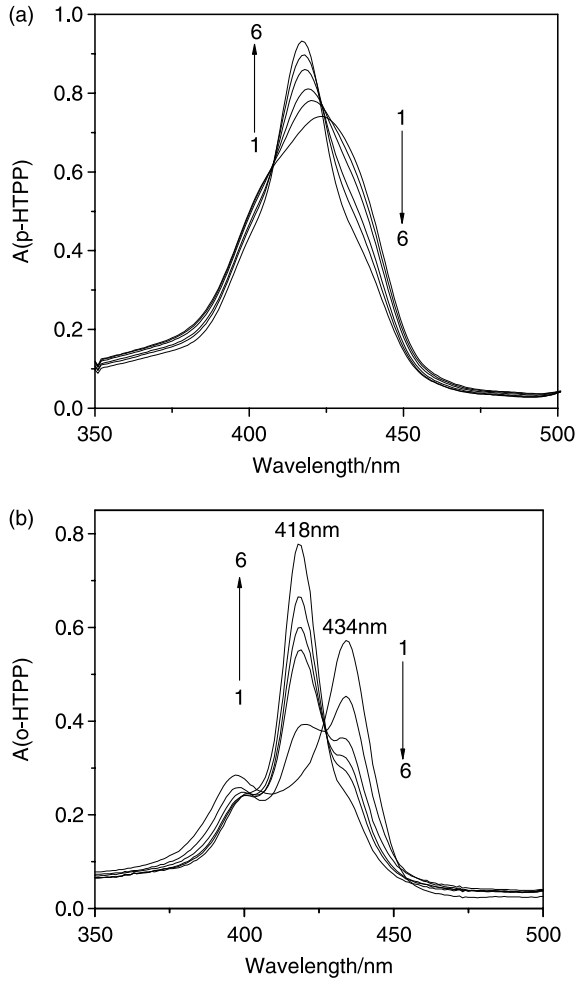

FIGURE 2 UV–vis spectra of p-HTPP and o-HTPP (5.0×10^{-6} mol·L^{-1}) containing various concentration of TM-β-CD in neutral solution (pH = 7.4).

isosbestic point at 408 nm. The absorbance (A) of o-HTPP upon increasing the concentration of TM-β-CD also showed a strong enhancement. The Soret band of o-HTPP shifted and the tendency of blue-shift was more than 16 nm (from 434 nm to 418 nm, see Fig. 2), respectively. All of these suggest that TM-β-CD can form inclusion complexes with p-HTPP and o-HTPP. On the basis of the absorption spectra, the hydrophobic cavity of TM-β-CD may prefer to bind to apolar neutral porphyrin molecules.

The emission spectra of p-HTPP and o-HTPP both showed enhancements in fluorescence intensities in the presence of TM-β-CD, which are not given. The influence of TM-β-CD concentration on the fluorescence intensity of p-HTPP and o-HTPP in pH 7.4 buffer solution is provided in Fig. 3. The fluorescence intensities of the two porphyrins were gradually enhanced with the increasing concentration of TM-β-CD until the stable inclusion supramolecular was formed. The observation may be related to the fact that the addition of TM-β-CD reduced the chance of collision taking place between guest molecules of

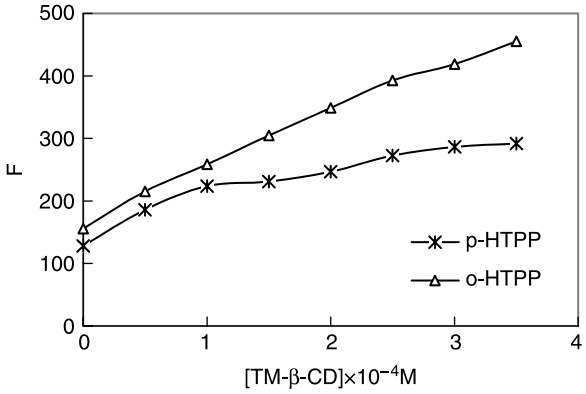

FIGURE 3 Effect of TM-β-CD concentration on the fluorescence intensities of p-HTPP and o-HTPP.

p-HTPP and o-HTPP and increased the fluorescence quantum yield, which would lead to the enhancements of fluorescence intensities.

Inclusion Complexes of p-HTPP and o-HTPP with β-CD, α-CD and γ-CD in Neutral Solution

Figure 4 showed the absorbance (A) and fluorescence intensities (F) changes of o-HTPP in the presence of β-CD. As the β-CD concentration increased, the absorbance and fluorescence intensities both decreased gradually. The trend of intensities-decreasing is opposite to TM-β-CD. The absorption and fluorescence spectra of the inclusion complexes between the other two cyclodextrins (α-CD and γ-CD) and o-HTPP are similar to each other in forms. Furthermore, all the UV–vis and emission spectra of the inclusion complexes between p-HTPP and the cyclodextrins (α-CD, β-CD, γ-CD) are similar, which indicated that the absorbance and fluorescence intensities both decreased with the increased cyclodextrins concentration (the spectra are not given). It is illustrated that the inclusion complexes were formed between the three cyclodextrins and p-HTPP, o-HTPP.

Formation Constants of Inclusion Complexes by Absorption Spectrometry

The formation constant (K) is an important parameter, which represents the inclusion capacity. The stoichiometry and binding strength of the interaction between the two porphyrins (p-HTPP and o-HTPP) and cyclodextrins are determined in this experiment. The formation constants (K) of complexes are estimated by the double-reciprocal method [26]. It can be obtained from the following equation [27]:

$$\frac{1}{(A - A_0)} = \frac{1}{a} + \frac{1}{\left(a \times k \times [CD]_0^n\right)} \quad (1)$$

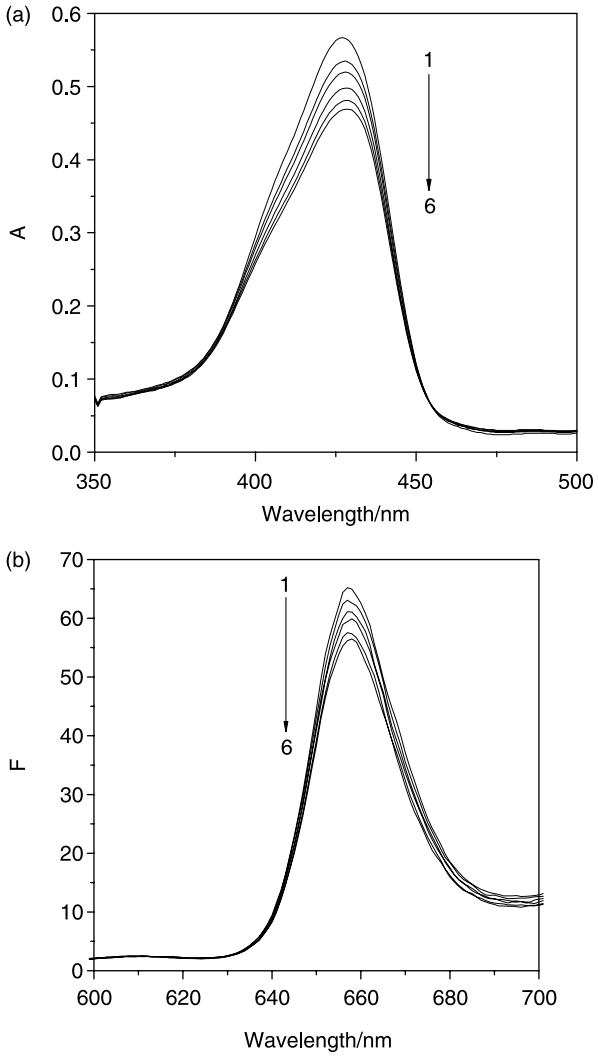

FIGURE 4 UV–vis spectra and fluorescence spectra of o-HTPP (5.0×10^{-6} mol·L^{-1}) containing various concentration of β-CD in neutral solution (pH = 7.4).

Here, A, A_0, a, k and $[CD]_0$ are the absorbance in the presence of the cyclodextrin, that in the absence of CDs, a constant, the equilibrium constant for the formation of 1:n porphyrin–CD inclusion supramolecular, and the initial concentration of CDs, respectively. Equation (1) holds under the experimental conditions of much higher concentrations of CDs than that of porphyrins.

Figure 5 shows the double reciprocal plots of $1/(A - A_0)$ vs. $1/[CD]_0^2$ for o-HTPP complexed with TM-β-CD. The plot exhibited good linearity (the linear correlation coefficient r = 0.9994). This implied the formation of inclusion complexes with a stoichiometry of 1:2. A Job plot of absorbance changes vs. mole fraction of CD is provided in Fig. 6. It has been indicated from Fig. 7 that the stoichiometric ratio between p-HTPP and TM-β-CD is 1:1. The same stoichiometric ratio (1:1) was obtained for the inclusion complexes between α-CD, β-CD , γ-CD and the two porphyrins.

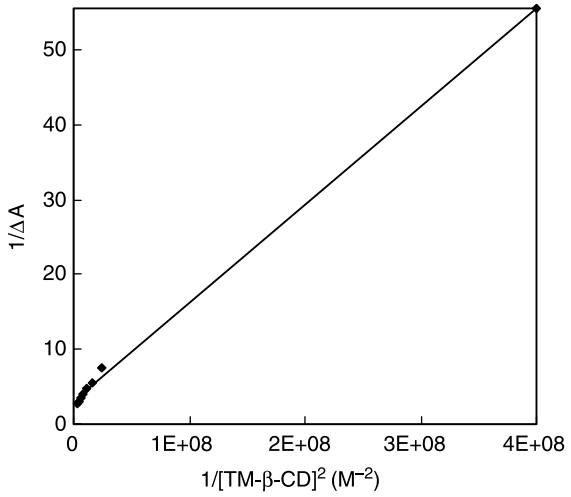

FIGURE 5 Double reciprocal plots for o-HTPP (5.0×10^{-6} M) inclusion supramolecular to TM-β-CD at pH 7.4 media.

The inclusion formation constants are listed in Table I. The K values, which are the formation constants for the formation of the o-HTPP and p-HTPP with TM-β-CD, are much larger than those of the other host-guest inclusion complexes. The results suggest that different chemical modifications have changed CD's supramolecular capacity, owing to larger and flexible cavities compared with parent CDs. The linear correlation coefficient (r) illustrated the good linearity, proving the stoichiometric ratio of inclusion complexes between different cyclodextrins and the porphyrins (p-HTPP, o-HTPP).

The formation constants (K) for different parent CDs with p-HTPP obey the following order: α-CD > β-CD > γ-CD, while the order for o-HTPP is: β-CD > γ-CD > α-CD (Fig. 8). It indicated that p-HTPP preferred to form inclusion supramolecular with β-CD more easily than the other two parent CDs and o-HTPP preferred to α-CD because of the

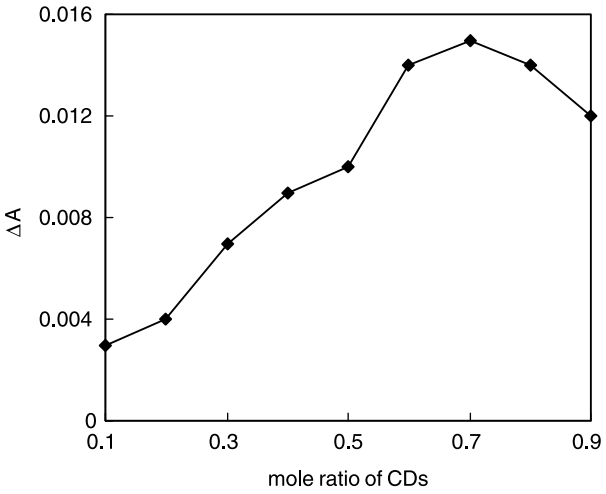

FIGURE 6 The inclusion stoichiometry of o-HTPP-TM-β-CD complexes (Job plot).

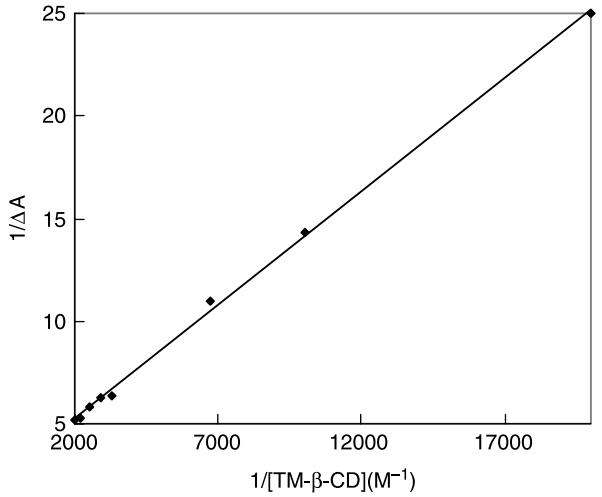

FIGURE 7 Double reciprocal plots for p-HTPP (5.0×10^{-6} M) inclusion supramolecular to TM-β-CD at pH 7.4 media.

hydrophobic effect, capacity matching and hydroxyl group position of the two porphyrins.

Discussion of Interaction Mechanism

It is shown that TM-β-CD exhibits the strongest inclusive ability among the concerned cyclodextrins (α-CD, β-CD, γ-CD and TM-β-CD) not only for p-HTPP but also for o-HTPP, implying that the cavity of TM-β-CD provides a better protective micro-environment. Strong inclusive ability can be explained by the substitution of tri-o-methyl group leading to the enlargement of the bigger opening, the reduction of the smaller opening and the destruction of the strong hydrogen bond network, which makes it easier for guest molecules to gain access to the TM-β-CD cavity and have a bigger inclusion constant. In addition, the result is partly because the two isomers p-HTPP and o-HTPP have similar chemical structures.

The o-HTPP can form 1:2 inclusion supramolecular with TM-β-CD, which forms a 1:1 inclusion supramolecular with p-HTPP. It is mainly because of the different position of hydroxy substituents in their molecular structures. The hydroxy is ortho-position in o-HTPP, while it is in the para-position in p-HTPP. The 5-, 10-, 15-, 20-phenyl substituents all lie in the vertical plane of porphin ring and the hydroxy group is in one plane with phenyl groups. When TM-β-CD interacted with o-HTPP, the hydrogen bond is formed between the ortho-hydroxy of 5-phenyl in o-HTPP and the hydroxy group of TM-β-CD. Then the 1:2 inclusion supramolecular is formed after TM-β-CD interacted with 10-, 20-methoxy phenyl. The hydroxy group of p-HTPP is in the para-position so that it is more difficult to form a hydrogen bond with the hydroxy of TM-β-CD. It probably interacts with 15-methoxy phenyl.

TABLE I The values of K and r of o-HTPP and p-HTPP with different CDs by UV–vis spectroscopy

CDs	Porphyrin	K	r
TM-β-CD	p-HTPP	2.77×10^3	0.9992
	o-HTPP	3.05×10^7	0.9994
α-CD	p-HTPP	1.81×10^3	0.9996
	o-HTPP	3.02×10^2	0.9971
β-CD	p-HTPP	1.20×10^3	0.9987
	o-HTPP	2.27×10^3	0.9985
γ-CD	p-HTPP	1.18×10^3	0.9985
	o-HTPP	4.66×10^2	0.9953

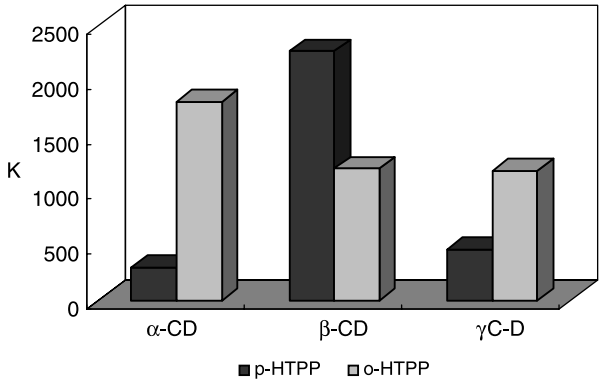

FIGURE 8 The K of different CDs with o-HTPP and p-HTPP.

The K values for different parent CDs with p-HTPP obey the order: α-CD > β-CD > γ-CD, which shows that the inclusive ability of α-CD with p-HTPP is the strongest among the three native CDs. The cavity of α-CD is narrower than that of β-CD and γ-CD. The hydroxy of p-HTPP is situated para position, which results in small steric hinder. It makes the cavity of α-CD have the best size to match to p-HTPP and it can most effectively include p-HTPP.

The magnitude of the K values for o-HTPP obeys the order: β-CD > γ-CD > α-CD. This trend reflects the degree of the fit in size between the cyclodextrin cavity and o-HTPP. β-CD has the narrower cavity than γ-CD and wider cavity than α-CD. It has the best size to match to o-HTPP to form 1:1 inclusion supramolecular with o-HTPP. The compared results indicated the major factors affecting inclusive ability are size matching between CDs and guest, the hydrophobicity and the chemical structures of the guest molecule.

CONCLUSION

The supramolecular systems between p-HTPP, o-HTPP and different cyclodextrins (α-CD, β-CD, γ-CD and TM-β-CD) have been confirmed and compared by spectrometry. The double reciprocal method has been used to determine the formation ratio and formation constants. In neutral solution, TM-β-CD formed 1:1 and 1:2 host-guest inclusion

complexes with p-HTPP and o-HTPP. And the biggest values of formation constants suggested that TM-β-CD has the strongest inclusive ability with p-HTPP and o-HTPP among the four cyclodextrins. α-CD, β-CD and γ-CD can form 1:1 inclusion complexes with both p-HTPP and o-HTPP. The K values for p-HTPP increased in the order: γ-CD < β-CD < α-CD, while the order is: α-CD < γ-CD < β-CD for o-HTPP. This finding can be interpreted in terms of the size matching between host and guest molecules, the hydrophobicity and the different chemical structures of the guest molecules.

Acknowledgements

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