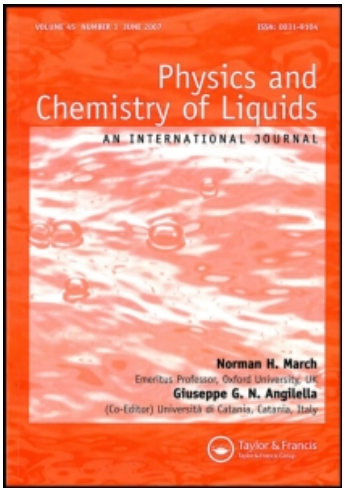

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Study on the supramolecular system of tetrakis(2-hydroxy-5-sulfonatophenyl)porphyrin with cyclodextrins by spectroscopy

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The supramolecular systems of meso-tetrakis(2-hydroxy-5-sulfonatophenyl)porphyrin (THSPP) with six cyclodextrins (CDs) have been examined by means of absorption, fluorescence and ^{1}H NMR spectroscopy in phosphate buffer (pH 7.15). The formation of inclusion complexes has been confirmed on the base of change of spectroscopy properties. Meso-tetrakis(2-hydroxy-5-sulfonatophenyl)porphyrin can form 1 : 1 inclusion complexes with the six CDs. The inclusion constants have been estimated from the absorbance and fluorescence intensity changes in neutral phosphate buffer solutions. The results show that the inclusion ability of anionic CD SBE-β-CD is weaker and the abilities of hydroxypropyl modified CDs are stronger compared to native CDs. It suggests that the interaction of hydrogen bond and charge attraction between CD and porphyrin play important roles in the inclusion procedure except for hydrophobic effect. The mechanism of inclusion interaction was carried out by ^{1}H NMR technique. Furthermore, the inclusion constants of hydroxypropyl-γ-CD with THSPP were measured at 15–30°C. The values decrease with increasing temperature and the thermodynamic parameters have been calculated.

Keywords: Porphyrin; Cyclodextrin; Supramolecular system; Inclusion constant

1. Introduction

Water-soluble porphyrins and metaloporphyrins are interesting materials in many applied fields [1]. Studies have shown that some water-soluble porphyrins are accepted not only as photosensitizers [2] but also as potential anti-cancer and anti-virus drugs [3]. It has been found that porphyrins can inhibit HIV-1 virus, the virus responsible for AIDS [4]. They were used as sensitizer in photodynamic therapy (PDT) because they tend to accumulate in neoplasm than in the surrounding normal tissue and they might be able to convert dioxygen into singlet state oxygen, which can destroy the cancer cells when irradiated by light [5]. They were also used as models for biological electron

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transport, oxygen transport and metalloenzymes [6]. Therefore, the development of porphyrin medicines has been increasingly paid attention to by scientists.

Cyclodextrins (CDs) are cyclic oligosaccharides. It is well known that, because of their unique cavity of hydrophobic interior and polar or hydrophilic exterior, many of organic or inorganic guest molecules can be fully or partly incorporated into the cavities of CD to form inclusion complexes in aqueous solution [7]. The formation of inclusion complex can apparently improve the physical and chemical properties of guests, such as stability against chemical and photochemical degradation [8], control of volatility and sublimation, physical isolation of incompatible compounds, chromatographic separations, taste modification by masking off flavors, unpleasant odor, and controlled release of drugs and flavors [9,10].

The formation of inclusion complexes of CDs with porphyrin derivatives modified the photochemical and photophysical properties of porphyrin derivatives, because CDs can provide a microscopical apolar environment around the center of a porphyrin ring and prevent self-aggregation of the porphyrin. Therefore, it is very important to examine the formation of inclusion complexes of CDs with porphyrin derivatives. Nowadays, more and more researchers have dedicated themselves to the study of supramolecular system of porphyrins with CDs [11–18].

In this article, the supramolecular systems of meso-tetrakis(2-hydroxy-4-sulfonatophenyl)porphyrin (THSPP) with β-CD, γ-CD, heptakis (2,6-di-*o*-methyl-)β-CD (DM-β-CD), sulfurbutylether-β-CD (SBE-β-CD), hydroxypropyl-β-CD (HP-β-CD) and hydroxypropyl-γ-CD (HP-γ-CD) have been examined by means of absorption, fluorescence and ^{1}H NMR spectroscopy. The stoichiometry and inclusion constants of THSPP with the six CDs were determined by ''the double reciprocal method''. The results show that THSPP can form 1 : 1 inclusion complexes with the six CDs. The inclusion capacity of different CDs was compared and the interaction mechanism was discussed. In the supramolecular system, CD, being regarded as the protein component, which acts as a carrier enveloping the active site of heme prosthetic group within its hydrophobic environment, provide a protective sheath for porphyrin, creating artificial analogues of heme-containing proteins. Furthermore, the inclusion constants of HP-γ-CD with THSPP were measured in the range of 15–30°C. The values decrease with increasing temperature, which indicates that increase in temperature does not benefit in the formation of inclusion complexes. The results of this article present potential application not only in supramolecular systems but also in pharmacokinetics and biodistribution studies. Meso-tetrakis(2-hydroxy-4-sulfonatophenyl)porphyrin is a water-soluble substance and its supramolecular system with CD is seldom found in literature. The structure of THSPP is shown in figure 1.

2. Experiment

2.1. *Reagent*

Meso-tetrakis(2-hydroxy-5-sulfonatophenyl)porphyrin was purchased from Si chuan E Mei Chemical Factory, China. $1.0 \times 10^{-4}\,\mathrm{mol\,L^{-1}}$ stock solution of THSPP was prepared by double distilled water. β-CD (Yu Nan Gourmet Factory, China) was purified by recrystallization in double distilled water. γ-CD and DM-β-CD were purchased from Sigma Co. HP-γ-CD and HP-β-CD were from Aldrich Co.

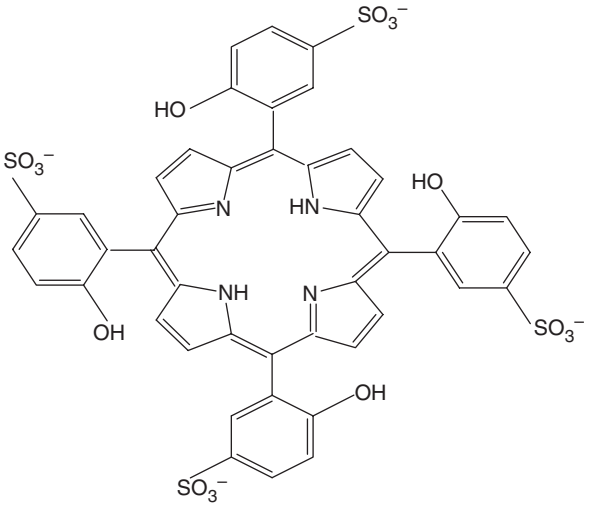

Figure 1. The structure of THSPP.

SBE-β-CD was synthesized following ref. [19]. The other reagents were of analytical reagent grade and water was doubly distilled.

2.2. *Apparatus*

The absorption and fluorescence measurements were performed on a TU-1901 Spectrophotometer (Puxi instrument Company, Beijing, China) and Varian Fluoresence Spectrophotometer (USA). Both excitation and emission band widths were set at 5 nm. The measurement of ^{1}H NMR was performed on DKX-300 MHz (Bruker, Switzerland).

2.3. *Method*

First, 1.0 mL aliquot of the stock solution (1.0×10^{-4} mol L^{-1}) of THSPP was transferred into a 10 mL volumetric flask. Then 1.0 mL 0.1 mol L^{-1} KH_2PO_4–Na_2HPO_4 (pH 7.15) buffer solution and appropriate amount of CDs were added. The mixed solution was diluted to final volume with distilled water and shaken thoroughly, following which it was equilibrated for 10 min. The spectra were recorded or fluorescence intensities and absorbance were measured. Unbuffered D_2O solution was used for ^{1}H NMR experiment.

3. Results and discussion

3.1. *Confirmation of the inclusion complexes by absorption spectra*

Meso-tetrakis(2-hydroxy-5-sulfonatophenyl)porphyrin displays an absorption maximum at 414 nm. In the presence of CDs, the maximum absorption wavelength is

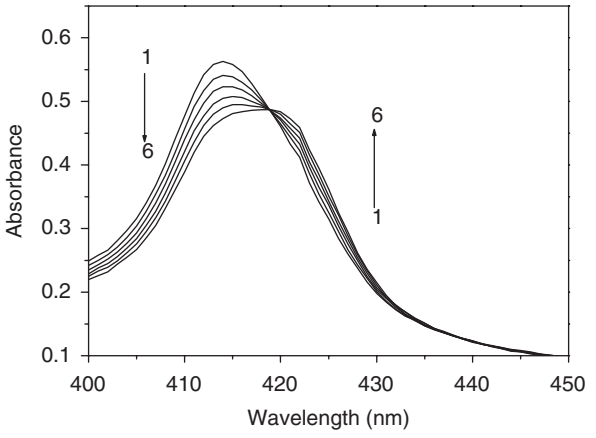

Figure 2. The absorption spectra of THSPP (1.0×10^{-5} mol L^{-1}) in pH 7.15 buffers containing different concentrations of β-CD. Concentration of β-CD: (1) 0; (2) 1.0×10^{-4}; (3) 2.0×10^{-4}; (4) 3.0×10^{-4}; (5) 4.0×10^{-4}; (6) 5.0×10^{-4} (mol L^{-1}).

red-shifted and the absorbance decreases. Figure 2 shows the absorbance (A) change of THSPP in the presence of β-CD. As the β-CD concentration increased, the absorbance intensity decreased gradually accompanied by an isosbestic point at 418 nm. The absorption spectra of the inclusion complexes between the six CDs (β-CD, γ-CD, HP-β-CD, CM-β-CD, DM-β-CD, SBE-β-CD, HP-γ-CD) and THSPP are similar to each other in forms. The others are not given. These suggest that CDs can form inclusion complexes with THSPP. On the basis of the absorption spectra, the hydrophobic cavity of CDs may prefer to bind with an apolar neutral porphyrin molecule.

3.2. *Confirmation of the inclusion complexes by fluorescence*

The concentration of 1.0×10^{-5} mol L^{-1} THSPP was fixed and the concentration of CD was varied from 1.0×10^{-4} to 5.0×10^{-4} mol L^{-1}. The maximum excitation wavelength was set at 414 nm. With the increasing concentration of CDs, a decrease in the emission intensity of fluorescence and the wavelength shift towards longer wavelengths were observed. These changes are due to the interaction between THSPP and CDs, implying the formation of THSPP–CD inclusion complexes. Figure 3 shows the fluorescence intensity changes of THSPP in the presence of β-CD. The others are not given.

3.3. *Determination of inclusion constant by absorbance*

The inclusion constant (K) is an important parameter, which represents the ability of inclusion interaction. The stoichiometry and inclusion constants of the interaction between THSPP and CDs are determined in this experiment. The inclusion constants of the complexes are estimated by the following equation [20]:

$$\frac{1}{\Delta A} = \frac{1}{\alpha} + \frac{1}{\alpha K [\mathrm{CD}]_0^n} \tag{1}$$

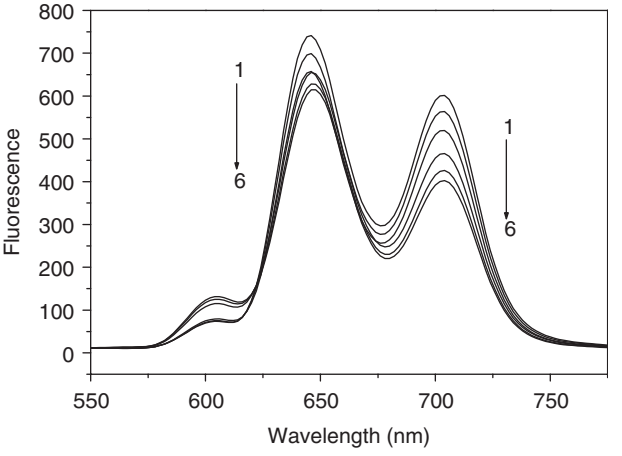

Figure 3. The fluorescence spectra of THSPP (1.0×10^{-5} mol L^{-1}) in pH 7.15 buffers containing different concentrations of β-CD. Concentration of β-CD: (1) 0; (2) 1.0×10^{-4}; (3) 2.0×10^{-4}; (4) 3.0×10^{-4}; (5) 4.0×10^{-4}; (6) 5.0×10^{-4} (mol L^{-1}).

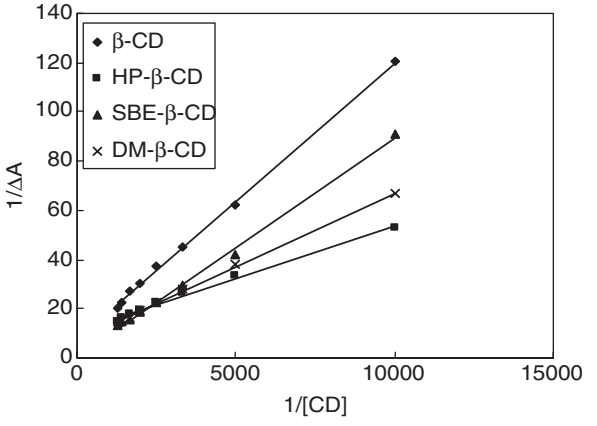

Figure 4. Double reciprocal plots for THSPP (1.0×10^{-5} mol L^{-1}) complexes to CDs at pH 7.15 media.

Here, ΔA, α, K and $[CD]_0$ are the change of absorbance of THSPP in the presence of CD, a constant, the equilibrium constant for the formation of the 1 : n THSPP–CD inclusion complex, and the initial concentration of CDs, respectively. Equation (1) holds under the experimental conditions of much higher concentrations of CDs than that of THSPP. Figure 4 exhibits double reciprocal plots for THSPP solution containing CDs. The good linearity of the 1 : 1 inclusion complexes suggests that 1 : 1 THSPP–CDs supramolecular systems are formed. The inclusion constants of THSPP with the six CDs are calculated by the ratio of intercept over slope, respectively, and are listed in table 1, implying the strong inclusion ability of HP-β-CD, HP-γ-CD and the weak inclusion ability of SBE-β-CD compared to their parent β-CD.

Table 1. The inclusion constants K ($L\,mol^{-1}$) of THSPP with six CDs by absorbance.

	β-CD	γ-CD	HP-β-CD	SBE-β-CD	DM-β-CD	HP-γ-CD
K	660	2.18×10^3	2.56×10^3	93	1.25×10^3	6.88×10^3

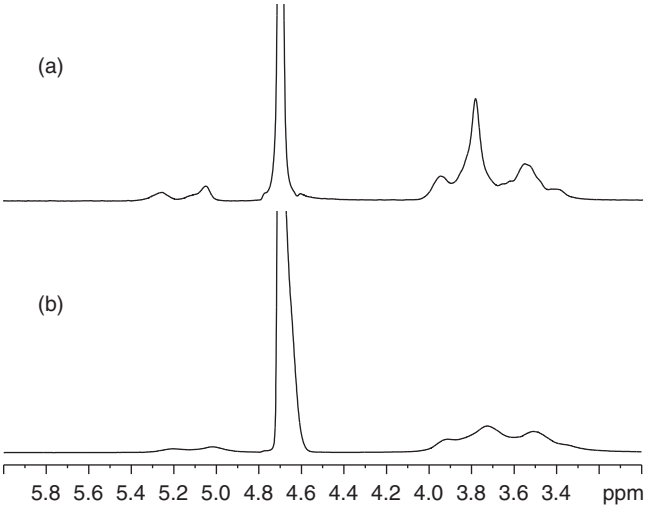

Figure 5. ^{1}H NMR spectra (300 MHz, 20□, D_2O) of (a) HP-γ-CD and (b) THSPP–HP-γ-CD.

3.4. *Conformational analysis of THSPP–CD by ^{1}H NMR spectroscopy*

Additional evidence for the formation of THSPP–CD complex can be obtained from changes of the chemical shifts of ^{1}H NMR spectra at 300 MHz in D_2O solution. The ^{1}H NMR spectra of HP-γ-CD and THSPP–HP-γ-CD are shown in figure 5. The HP-γ-CD protons showed different chemical shifts after inclusion with THSPP. By comparing these shifts, we can find the shifts of H-5, H-6 (0.063 ppm) protons larger than those of H-3 protons (0.037 ppm), indicating that THSPP may enter the cavity of HP-γ-CD from the narrow side. We propose the spatial configuration about the THSPP–HP-γ-CD inclusion complex, as shown in figure 6.

3.5. *Study on the characters of thermodynamics*

The thermodynamic parameters ($\Delta G, \Delta H, \Delta S$) of interactions of THSPP with HP-γ-CD have been determined using the method of fluorimetric titration. The inclusion constants of complexes are estimated at different temperatures. The K values can be obtained by means of [21,22].

$$\frac{[G]_0}{\Delta F} = \frac{1}{K \times K \times Q}\frac{1}{[CD]^n} + \frac{1}{K \times Q} \tag{2}$$

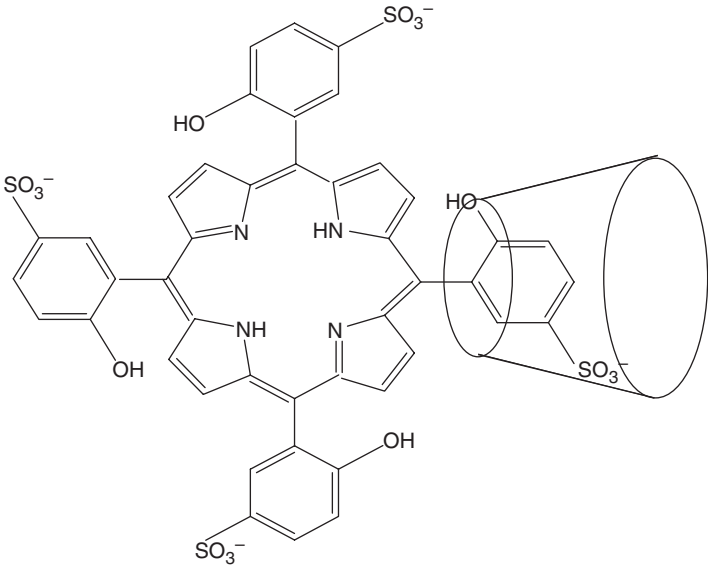

Figure 6. The possible geometry of the THSPP–HP-γ-CD complex.

Table 2. The thermodynamic parameters of THSPP–HP-γ-CD inclusion complexes.

t (□)	K (L mol^{-1})	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
15	18,000	−23.47	−178.3	−535.0
20	8600	−22.07		
25	3140	−19.95		
30	415	−15.19		

where, $[G]_0$ is the initial concentration of THSPP, [CD] is the equilibrium concentration of CD, ΔF is the change of fluorescence intensity in the presence of CD, K is an instrumental constant, n is the stoichiometry of the complex, K is the inclusion constant, and Q is quantum yield for the complex. K can be calculated from a plot of $1/\Delta F$ *versus* $1/[\mathrm{CD}]^n$. The inclusion constants are calculated by the ratio of intercept over slope and are listed in table 2. The experimental result proves that in the range of 15–30°, the inclusion constants decrease when temperature increases. The thermodynamic parameters (ΔG, ΔH, ΔS) are obtained according to

$$\Delta G = -2.303RT \lg K \tag{3}$$

$$\lg K = -\frac{\Delta H}{2.303RT} + \frac{\Delta S}{2.303R} \tag{4}$$

respectively, and listed in table 2.

As can be seen from table 2, in the range of 15–30°, both ΔG and ΔH are negative, which indicates that the supramolecular system can proceed spontaneously and the procedure is exothermic. It also indicates that increasing temperature is not beneficial to the formation of inclusion complexes.

3.6. *Discussion of interaction mechanism*

The magnitude of the K value for THSPP increases in the order SBE-β-CD < β-CD < DM-β-CD < γ-CD < HP-β-CD < HP-γ-CD. This trend reflects the degree of the fit in size between the cavity of CDs and THSPP. It shows that the inclusive ability of native γ-CD with THSPP is stronger than native β-CD. This is because the cavity of γ-CD has better size match to THSPP and it can more effectively include THSPP. The experimental results also show that HP-β-CD and HP-γ-CD exhibits stronger inclusive ability than their native CDs implying that the cavity of the hydroxypropyl modified CDs provide a better protective microenvironment. However the inclusion constant of THSPP with SBE-β-CD is smaller than native β-CD, which suggests that the inclusive ability of anionic CD (SBE-β-CD) with anionic porphyrin THSPP is weaker. From the above discussion, we can conclude that the interaction of hydrogen bond and charge attraction between CD and porphyrin play important roles in the inclusion procedure except for hydrophobic effect. In the range of 15–30°C, the inclusion constants of HP-γ-CD with THSPP decrease with increasing temperature and both ΔG, ΔH are negative, which indicates that the supramolecular system can proceed spontaneously, the procedure is exothermic, and rising temperature is not beneficial to the formation of inclusion complex.

4. Conclusion

The supramolecular systems of THSPP with β-CD, γ-CD, DM-β-CD, SBE-β-CD, HP-β-CD and HP-γ-CD has been examined by means of absorption, fluorescence and ^{1}H NMR spectroscopy. THSPP can form the 1 : 1 inclusion complexes with the six CDs. HP-β-CD and HP-γ-CD exhibit stronger inclusive ability than their native CDs. But the inclusive ability of anionic CD (SBE-β-CD) with anionic porphyrin is weaker than native β-CD. All the above illustrate that the interaction of hydrogen bond and the charge attraction between CD and porphyrin play important roles in the inclusion procedure except for hydrophobic effect. The mechanism of inclusion interaction was carried out by ^{1}H NMR technique and THSPP may enter the cavity of HP-γ-CD from the narrow side. The inclusion procedure is spontaneous and exothermic. Moreover, increasing temperature does not benefit to the formation of inclusion complexes.

Acknowledgements

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