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Host–Guest Interactions of 4-Carboxyphenoxy Phthalocyanines and β-Cyclodextrins in Aqueous Media

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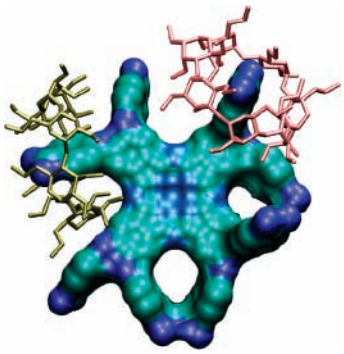
ABSTRACT



β-Cyclodextrin and its permethylated derivatives form 2:1 inclusion complexes with tetrakis- and octakis(4-carboxyphenoxy)phthalocyanines 1–4, reducing their aggregation tendency and promoting their sensitization of singlet oxygen formation in aqueous media.

Being a versatile class of functional dyes, phthalocyanines have been studied extensively over the last few decades.[1] The intriguing physical, chemical, and biological properties of these macrocycles have led to many practical applications in various disciplines.[2] For those applications involving the photosensitizing property of phthalocyanines such as photodynamic therapy[3] and photodegradation of pollutants,[4] the macrocycles have to remain in a nonaggregated state. Aggregation, however, is very common for such large hydrophobic π systems, particularly in polar media such as water.[5] Several strategies have been explored to generate hydrophilic and nonaggregated phthalocyanines, which include the introduction of bulky dendritic fragments with terminal hydrophilic groups,[6] and the use of surfactants[7] or dis-stacking agents such as polyethylene glycol.[8] Cyclodextrins are well-known for their unique inclusion property

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toward a wide range of hydrophobic species.[9] We believe that these host−guest interactions can disrupt the substantial $\pi-\pi$ stacking of phthalocyanines, rendering nonaggregated species in aqueous media. This simple approach has been reported for porphyrins,[10] which in general have a weaker aggregation tendency compared with phthalocyanines. To our knowledge, the complexation of phthalocyanines with cyclodextrins has only been little studied. Ruebner and Breslow et al. reported a series of cyclodextrin dimers which can complex and solubilize several mono-sulfonyl or carboxy phthalocyanines in water.[11] Nyokong et al. studied briefly the effects of cyclodextrins on the photophysical properties of several hydrophobic phthalocyanines in DMSO.[12] In this work, we used various spectroscopic and molecular modeling methods to show unambiguously the complexation of a series of tetrakis- and octakis(4-carboxyphenoxy) phthalocyanines with β-cyclodextrin (β-CD) and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMe-β-CD) (Figure 1), and demonstrate that

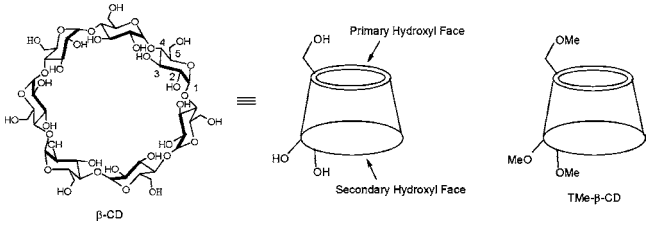

Figure 1. Schematic structures of β-CD and TMe-β-CD.

such host−guest interactions could be an effective way to reduce the aggregation of phthalocyanines in water and enhance their singlet oxygen formation.

The 4-carboxyphenoxy phthalocyanines **1**−**4** (Figure 2) were selected for the study because they could be readily soluble in alkaline aqueous media and the aryl substituents were expected to preferentially reside in the hydrophobic cavity of cyclodextrins. The metal-free phthalocyanines **1** (as a mixture of constitutional isomers) and **3** were prepared in ca. 30% yield by treating 4-(4-methoxycarbonylphenoxy)-phthalonitrile or 4,5-bis(4-methoxycarbonylphenoxy)phthalonitrile with lithium in 1-pentanol followed by in situ alkaline hydrolysis with LiOH and subsequent protonation with HCl. These compounds were then metalated with Zn(OAc)$_2$·2H$_2$O to give the zinc analogues **2** and **4** in 56% and 63% yield, respectively (characterization data and spectra for **1**−**4** are given in the Supporting Information).[13,14]

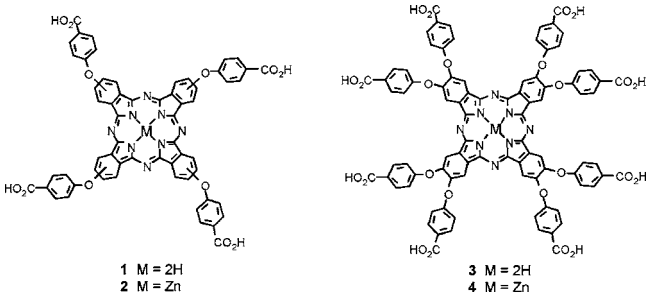

Figure 2. Structures of phthalocyanines **1**−**4**.

The UV−vis spectra of **1**−**4** in THF showed (a) very sharp and intense Q-band(s), which followed the Lambert−Beer law very well (see Figures S1 and S2 in the Supporting Information). The results suggested that these compounds are essentially nonaggregated in this solvent. In the presence of NaOH, these compounds were soluble in water, and the Q-band(s) became significant broadened and shifted to the blue, particularly for the tetrasubstituted analogues. This is a strong indication of the formation of face-to-face or H-aggregates.[15]

The complexation of **3** and β-CD in an alkaline aqueous medium (pH 12) was first studied by fluorescence spectroscopy and the stoichiometry determined by a continuous variation method.[16] The spectra of mixtures of these two compounds in different ratios (total concentration = 10 μM) showed an emission at ca. 710 nm with different intensity. By plotting the area of the fluorescence peak versus the mole fraction of **3**, the curve clearly showed a maximum at 0.34 (see Figure S3 in the Supporting Information). This suggested that phthalocyanine **3** complexes with β-CD in a 1:2 manner.

Figure 3 shows the changes in the UV−vis spectrum of **3** in water (pH 12) upon addition of β-CD (from 8- to 183-fold). It can be seen that at higher β-CD concentrations, the Soret band at 333 nm shifts to 355 nm, while the broad Q-band at 643 nm becomes a sharp band at 684 nm.[17] This shows that β-CD can disrupt the aggregation of this phthalocyanine probably through host−guest interactions. According to a 1:2 binding model, eq 1 can be derived and used to determine the stepwise binding constants K_1 and K_2 by a nonlinear regression method:[18]

$$I = \frac{I_0 + I_1K_1[\beta\text{-CD}]_0 + I_2K_1K_2[\beta\text{-CD}]_0^2}{1 + K_1[\beta\text{-CD}]_0 + K_1K_2[\beta\text{- CD}]_0^2} \qquad (1)$$

where I is the intensity (either the absorbance at a particular

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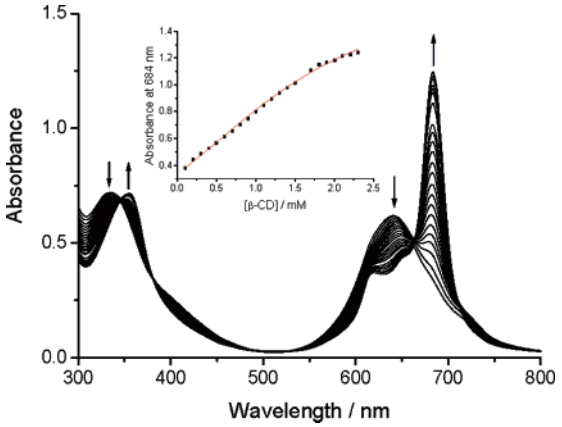

Figure 3. Change in absorption spectrum of **3** (12 μM) upon adding of β-CD (from 0.1 to 2.2 mM) in water (pH 12). The inset plots the change in absorbance of the Q-band at 684 nm versus the concentration of β-CD. The solid line represents the best fit according to eq 1.

position or the fluorescence intensity) at a given β-CD concentration, while I_0, I_1, and I_2 are the intensities in the absence of β-CD and for the 1:1 and 1:2 complexes, respectively.

By monitoring the change in absorbance of the band at either 684 or 643 nm, the corresponding fit converged well with a correlation coefficient $r^2 > 0.99$ (see the inset of Figure 3). The values of K_1 and K_2 were determined to be $(5.3 \pm 1.6) \times 10^2$ and $(6.2 \pm 0.3) \times 10^2$ M^{-1}, respectively, which are of the same magnitude with those for the binding of β-CD with benzoic acid (130−1820 M^{-1})[19] and 5,10,15-tris(3,5-dicarboxyphenyl)-20-phenylporphyrin [$(1.2 \pm 0.1) \times 10^3$ M^{-1}].[20] Although the binding is not particularly strong, it is still strong enough to break the aggregation of this phthalocyanine.

Due to aggregation, compound **3** did not fluoresce in water (at pH 12). Upon addition of β-CD, a fluorescence emission appeared. The band shifted from 687 to 696 nm and increased in intensity when the concentration of β-CD increased (see Figure S4 in the Supporting Information). The results also showed that the aggregation of **3** is reduced upon complexation with β-CD. The change in fluorescence data could also be used to fit into eq 1. The binding constants K_1 and K_2 derived from the best fit were comparable with those determined with the absorption data.

The complexation of other phthalocyanines with β-CD and TMe-β-CD was also studied in a similar manner. For compounds **1** and **2**, both the absorption and fluorescence spectra were virtually unchanged upon addition of β-CD. It is likely that the interactions between these species are not sufficiently strong to overcome the higher aggregation tendency of these compounds. However, by replacing β-CD with TMe-β-CD, which shows a stronger binding with some meso-arylporphyrins,[20] the spectra were changed giving features corresponding to the nonaggregated species. The complexations of **3** and **4** with β-CD as well as **1**−**4** with TMe-β-CD all behaved similarly. Table 1 summarizes the

Table 1. Binding Constants for the Complexation of **1**−**4** with β-CD and TMe-β-CD in Alkaline Aqueous Media (pH 12)

	β-CD		TMe-β-CD	
	$K_1/\times 10^3$ M^{-1}	$K_2/\times 10^3$ M^{-1}	$K_1/\times 10^3$ M^{-1}	$K_2/\times 10^3$ M^{-1}
1			6.6 ± 0.7	3.4 ± 0.4
2			6.4 ± 0.4	1.8 ± 0.4
3	0.53 ± 0.16	0.62 ± 0.03	2.8 ± 0.9	2.4 ± 1.6
4	0.42 ± 0.27	1.1 ± 0.3	3.7 ± 0.1	2.1 ± 0.2

binding constants for these systems derived from the changes in UV−vis spectral data. It can be seen that TMe-β-CD, in general, exhibits stronger binding interactions than β-CD to these phthalocyanines, and apparently the strongest interactions arise from the binding between the tetrasubstituted analogues and TMe-β-CD.

The inclusion of these phthalocyanines into the cavity of β-CD or TMe-β-CD could be shown by 2D NMR spectroscopy. For example, in the ROESY spectra of the 1:2 inclusion complexes **3**-(β-CD)$_2$ and **4**-(β-CD)$_2$ in D_2O with a drop of 20% NaOD in D_2O (see Figure S5 in the Supporting Information), cross-peaks were clearly seen for the *p*-phenylene OC_6H_4 protons of **3** and **4** (at ca. δ 7.1 and 7.7) and the β-CD protons (at ca. δ 3.2−3.4 for H_2 and H_4, and δ 3.6−3.8 for H_3, H_5, and H_6). Based on these data, it was, however, difficult to determine whether the carboxyphenoxy group enters the β-CD cavity from the primary or secondary hydroxyl face.

The structure of the host−guest complex between **3** and β-CD was also studied by molecular dynamics (MD) simulations, using the AMBER 8.0 program (the details are given in the Supporting Information). Figure 4a shows the initial configuration of **3**-(β-CD)$_2$, in which two intervening carboxyphenoxy groups are fully encapsulated by two β-CD molecules separately with the secondary hydroxyl face toward the phthalocyanine core. The complex was solvated by a rectangular solvent box of 3145 water molecules. After 2 ns of constant-pressure MD simulations, both β-CD molecules started to depart from the carboxyphenoxy groups (Figure 4b). A similar result was obtained for the model in which two adjacent carboxyphenoxy groups are trapped by two β-CD molecules (see Figure S6 in the Supporting Information). The results suggested that the encapsulation and de-encapsulation of the carboxyphenoxy group by/from β-CD are relatively facile processes.

To investigate the possibility of trapping two adjacent carboxyphenoxy groups with a β-CD molecule, we also

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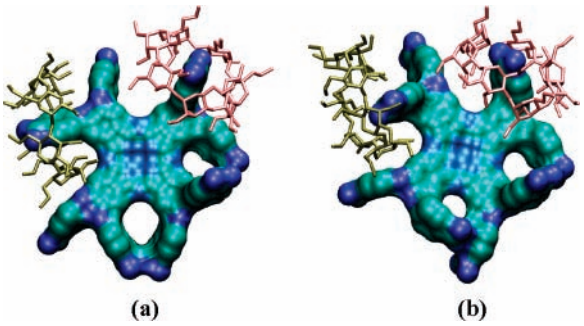

Figure 4. The initial (a) and final (b) configurations of **3**-(β-CD)$_2$ (two β-CD rings trapping two intervening carboxyphenoxy groups), revealing the incipient departure of the β-CD rings in explicit water solvent molecules (being omitted for clarity) after 2 ns MD simulation with use of AMBER 8.0. The phthalocyanine and the β-CD molecules are rendered as a molecular surface and stick representation, respectively.

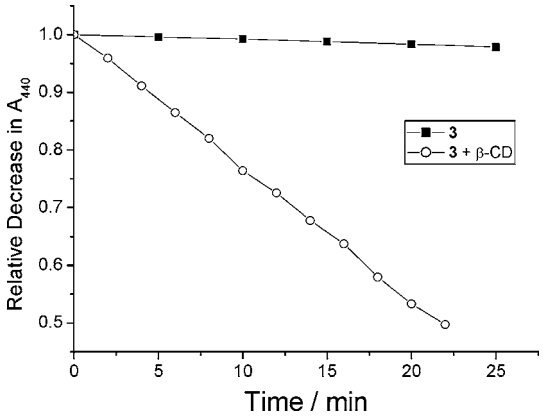

Figure 5. Comparison of the rates of decay of RNO (initial concentration = 50 μM) as monitored by the decrease in absorbance at 440 nm, using **3** (10 μM), in the absence and presence of β-CD (5 mM) as the photosensitizer ([imidazole] = 10 mM, pH 9).

performed MD simulations for such a model (see Figure S7 in the Supporting Information). It was found that in a similar time range, the β-CD molecules still entrap the carboxyphenoxy groups, showing that the energy barriers for the encapsulation and de-encapsulation processes are higher for the doubly encapsulated mode. Hence it is more likely that each β-CD ring traps only one carboxyphenoxy group in the complex.

Having a lower aggregation tendency, the cyclodextrin-encapsulated phthalocyanine systems were expected to be better photosensitizers than the parent macrocycles. We examined this aspect by comparing the singlet oxygen formation efficiency of **3** and **4** in the absence and presence of β-CD using the method reported by Kraljic and El Mohsni.[21] In this method, imidazole was added to induce the bleaching of 4-nitrosodimethylaniline (RNO) as followed spectrophotometrically at 440 nm. Figure 5 shows the results for compound **3**. It can be seen that in the absence of β-CD, the decay of RNO is negligible. However, in the presence of β-CD, the decay rate is significantly increased showing that phthalocyanine **3** can generate singlet oxygen more effectively upon complexation with β-CD. The rate of photobleaching of RNO with **4** as the sensitizer is comparable with that for **3**.

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In conclusion, we have demonstrated that tetrakis- and octakis(4-carboxyphenoxy) phthalocyanines **1**−**4** can be partially encapsulated into the cavity of β-CD and TMe-β-CD in alkaline aqueous media, by which their aggregation is greatly reduced. This supramolecular approach could be an effective way to generate hydrophilic and nonaggregated phthalocyanines, improving their photosensitizing properties in aqueous media.

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Supporting Information Available: Characterization data and spectra for **1**−**4** including UV−vis spectra in THF; Job's plot for the complexation of **3** and β-CD; change in fluorescence spectrum of **3** upon addition of β-CD; ROESY spectra of **3** and **4** in the presence of β-CD; some other simulated structures of **3**-(β-CD)$_2$; and the details of MD simulations. This material is available free of charge via the Internet at http://pubs.acs.org.

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