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SELF-ASSEMBLY OF A HYDROPHOBIC GROOVE

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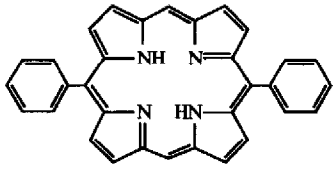
Abstract: Heptakis(2,6-di-O-methyl)-ß-cyclodextrin interacts with 5,15-diphenylporphine to produce a 2:1 complex in dimethyl sulfoxide. This complex possesses a hydrophobic groove that circumscribes the metal binding site of the porphyrin moiety.

Ribosomes, mitochondria, cells, and other multicomponent entities are assembled and maintained *via* noncovalent interactions.[1] Since these species are constructed under aqueous conditions, it is not surprising that their assembly is primarily driven by "hydrophobic forces".[1] Polar aprotic solvents also display a natural ability to promote the association of hydrophobic compounds.[2] In both cases, self-assembly liberates polar solvent molecules from energetically unfavorable states, a process which enhances favorable solvent-solvent interactions. In this paper we describe the assembly and characterization of a trimeric complex in dimethyl sulfoxide (DMSO). This species contains a hydrophobic groove that circumscribes a porphyrin moiety. Such an architectural feature may serve as a binding site for exogenous compounds and thus should endow the complex with the potential to participate in activities that are characteristic of many porphyrin-dependent proteins.[3]

The diphenylporphyrin **1** (synthesized from dipyrrylmethane and benzaldehyde in 92% yield) contains opposing phenyl substituents, which are of the proper size and shape to bind within the hydrophobic cavity of heptakis(2,6-di-O-methyl)-ß-cyclodextrin[4] ("Me-CD") **2**. Under the appropriate conditions, these components should associate to



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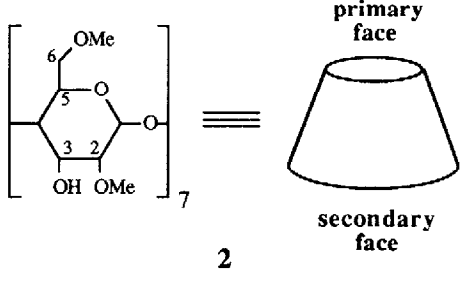

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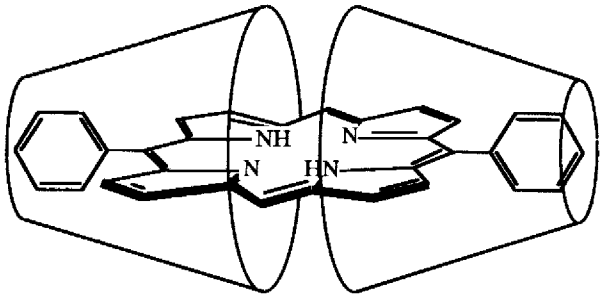
form the supramolecular complex **3**. Our selection of the cyclodextrin derivative **2** as the encapsulating agent was based on three factors. First, Me-CD is more soluble in organic solvents than the unmethylated parent cyclodextrin.



3

Second, the methyl groups on the secondary alcohol face should enhance the hydrophobicity of the groove in compound **3**. Finally, the methylated primary face is sterically congested and consequently the phenyl substituents of the porphyrin should enter the Me-CD cavity through the less hindered secondary face.

The diphenylporphyrin exhibits optical activity in the presence of **2**. Such behavior is a common phenomenon associated with cyclodextrin-dye inclusion compounds and is generally taken as compelling evidence for encapsulation of a guest molecule by a cyclodextrin host.[5] We employed Job's method of continuous variations to assess the stoichiometry of this complex.[6] A plot of induced ellipticity (ΔE) versus mole fraction of Me-CD is provided in figure 1. Under the equilibrium depicted in equation (i), the mole fraction of Me-CD (f) that induces maximal ellipticity is given by $f = \frac{n}{n+1}$.[7] The results provided in the figure ($f = 2/3$) indicate that a 2:1 Me-CD:por-

$$\text{(i)} \quad \text{Porphyrin} + n\text{Me-CD} \rightleftharpoons \text{Porphyrin(Me-CD)}_n$$

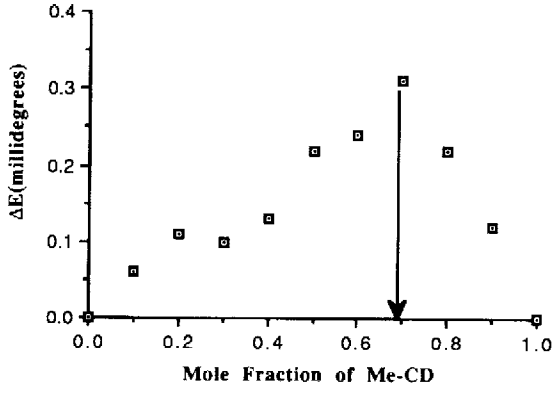


Figure 1. Induced ellipticity as a function of mole fraction of Me-CD. Experiments were conducted on a Jasco J41C circular dichroism spectrophotometer at 406.5 nm. A constant combined concentration (0.25 mM) of Me-CD and porphyrin in DMSO was employed.

phyrin complex is formed.

One dimensional nuclear Overhauser enhancement (NOE) experiments were conducted to establish the orientation of the Me-CD moiety relative to the porphyrin nucleus. The cyclodextrin component could encapsulate the phenyl groups of **1** *via* the primary face, the secondary face, or an indiscriminate combination of both. Most importantly, the mode of encapsulation determines the structure of the hydrophobic groove. As mentioned above, our rationale for employing the cyclodextrin derivative **2** was based, in part, upon the desire to direct the phenyl substituents through the secondary face of the cyclodextrin. The results of the NOE experiments, provided in the table below, confirm that the binding process occurs in the desired fashion. Irradiation of the Me-CD ^{2}OMe groups

Table 1. 300 MHz NOEs*

	porphyrin NOEs				
Me-CD protons irradiated	meso	$^{1}H_{\beta}$	$^{2}H_{\beta}$	ortho	meta & para
^{2}OMe	-16%	0%	0%	0%	0%
^{3}H & ^{5}H	0%	0%	-25%	-1.2%	-11.7%
^{6}OMe	0%	0%	0%	+1.9%	-3.5%

*** NMR sample: 0.015 M porphyrin and 0.076 M Me-CD in DMSO-d_6 with an external CH_2Cl_2 standard. Estimated precision of NOE values is ±3%.**

produced a decrease in intensity of the porphyrin meso proton resonance [negative NOEs are typically observed for large molecules (mw>1000 g/mol) possessing relatively long correlation times[8]]. This confirms that the secondary face of the Me-CD lies adjacent to the meso protons of **1**. Due to the close proximity of the ^{3}H and ^{5}H resonances of **2** and the meta and para proton resonances of the phenyl substituents on the porphyrin, it was not possible to separate the NOE effects for the individual protons. However, the sizable NOE (-11.7%) between the

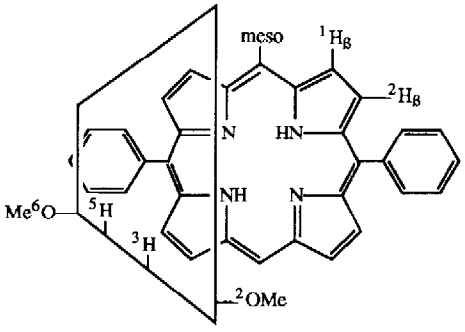


Figure 2. Schematic of the porphyrin(Me-CD) inclusion complex.

two proton groups demonstrates that the phenyl moieties are encapsulated by the Me-CD. While these results are consistent with the schematic depicted in figure 2, and circular dichroism verifies the formation of a 2:1 complex, it is important to stress that under these experimental conditions it is unlikely that all porphyrin molecules are encapsulated by two Me-CD moieties. Indeed, nearly 150 equivalents of cyclodextrin are necessary to drive the assembly of **3** to completion, as assessed by changes in the uv-vis absorption (407 nm) for the porphyrin at a concentration of 0.042 mM (data not shown). In contrast, we have found that for an analogous system in aqueous media 10 equivalents of Me-CD are sufficient to produce the desired complex.[9] The salient feature is that under the appropriate conditions a structurally well-defined trimeric complex possessing a hydrophobic groove is formed. We have recently constructed a related supramolecular complex in which the cyclodextrin components are unable to dissociate from the porphyrin moiety.[9] The proficiency with which these species mimic the activities of heme-dependent proteins is currently under investigation.

Acknowledgements

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