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Synthesis and self-assembling behavior of a porphyrin bearing multiple *meso*-conjugated barbiturates

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ABSTRACT

An efficient procedure through deprotection of 2,4,6-trimethoxypyrimidine derivative afforded porphyrinato zinc bearing multi-barbiturates acting as multiple hydrogen bonding sites at the *meso* positions. Addition of excess amphiphilic triaminopyrimidine derivative, as a complementary motif to the barbiturate, in an aqueous solution of porphyrin conjugated with multiple barbiturates at the *meso* positions resulted in precipitation. The cast film from the chloroform solution of the precipitate indicated the formation of a well-defined porphyrin assembly.

Recently, self-assembled porphyrins have received considerable attention because of the wide range of potential applications, such as the development of efficient catalysts and optical devices. Indeed, there are successful reports on porphyrin-assemblies via noncovalent interactions such as electrostatic interactions, hydrophobic interactions, coordination bonding, and hydrogen bonding.[1] We have focused on hydrogen bonding as a desirable means of assembling the molecular components because of their inherent directionality and selectivity.[2] In particular, we are able to construct on-target porphyrin-assemblies using a well-known complementary hydrogen bonding system between donor–acceptor–donor (DAD) and acceptor–donor–acceptor (ADA).[3,4]

In order to design a more sophisticated porphyrin-assembly, three important factors need to be considered. (i) Multipoint hydrogen bonding motifs should be incorporated into the porphyrin scaffold as a functional core for enthalpic reasons in order to maintain a stable assembly. (ii) Entropic loss involved in bringing molecules together into an assembly should be as low as possible. Indeed, a previous report describes this entropic effect for porphyrin-assembly by incorporation of hydrogen bonding motifs at the *meso* positions.[5] In this way, unfavorable entropic loss should be minimized due to an increase in structural rigidity. (iii) Regulation of atropisomers resulting from the free rotation of carbon–carbon bonds at *meso* positions enhances the control of self-assembly.[4] To meet the above requirements a porphyrin bearing four barbiturates at *meso* positions, which act as multipoint hydrogen bonding sites, was designed. Indeed, this is, a well-known component of a 2ADA type molecular assembly.[6] Multi-barbiturates incorporated into *meso* positions function as direct hydrogen bonding units on both sides of the porphyrin plane, thereby expanding the structural dimension of the assembly. Moreover, from a synthetic viewpoint, the design avoids the need to separate atropisomers.

In order to prepare the targeting porphyrin, 5-formylbarbituric acid was synthesized according to a previous report (Scheme 1).[7] The ring condensation with pyrrole and its formyl derivative was carried out using the Lindsey and Adler methods, respectively.[5,8] However, the desired *meso*-arylporphyrin could not be detected. The failure of this procedure is due, at least in part, to the poor solubility of the barbiturate derivative in the organic solvent. Additionally, 5-formylbarbituric acid adopts an enol form as a result of tautomerization, which might not be tolerated under acidic conditions.[9] Therefore, the synthetic route through deprotection of the methoxy groups of the pyrimidine was chosen because 2,4,6-trimethoxypyrimidine was expected to be converted to barbituric acid as shown in Scheme 1.

2,4,6-Trimethoxypyrimidine (**1**) was obtained by the reaction of 2,4,6-trichloropyrimidine with sodium methoxide as a nucleophilic reagent.[10] Following treatment of **1** with *n*-butyllithium, the lithio derivative was precipitated. Reaction at −70 °C with ethylformate as an electrophile then gave 5-formyl-2,4,6-trimethoxypyrimidine (**2**).[11] The ring condensation succeeded at higher concentrations of aldehyde-pyrrole (50 mM) than that of the Lindsey method using general conditions to give a 5,10,15,20-tetrakis-(2,4,6-trimethoxy-pyrimidin-5-yl)-porphyrin (**3**) at 55% yield. The methoxy groups of **3** were easily deprotected by iodotrimethylsilane to generate *meso*-conjugated barbiturates porphyrin as a free base form.[12] After insertion of zinc to the porphyrin by addition of zinc chloride, purification was performed using Sephadex LH-20 to give 5,10,15,20-tetrakis-(2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-

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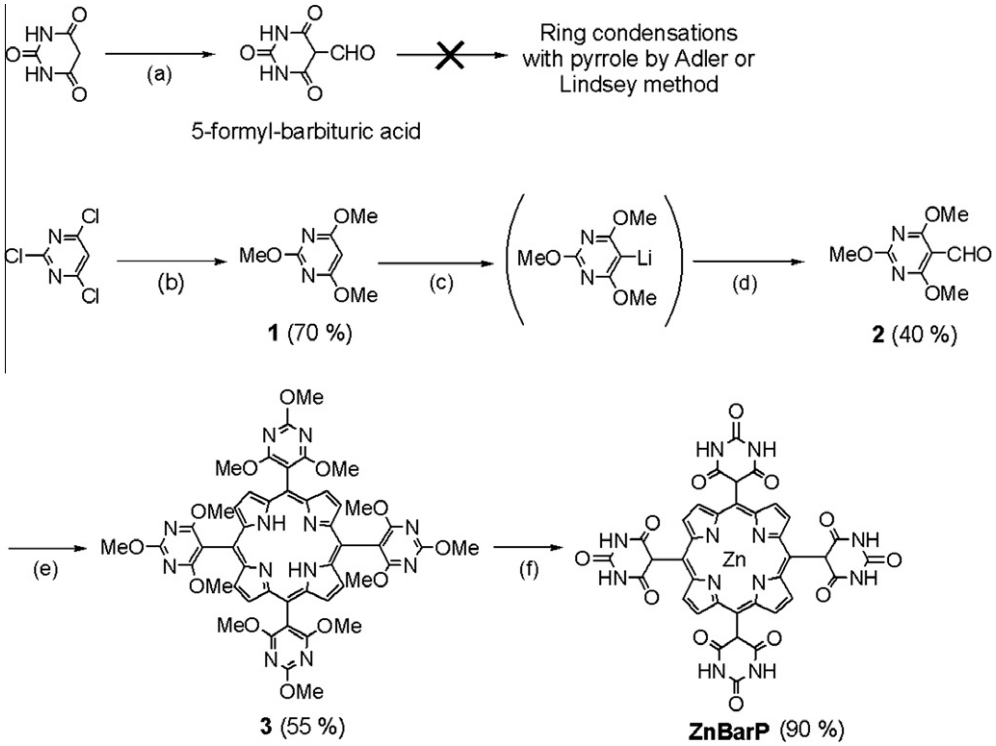

Scheme 1. Synthesis of *meso*-conjugated barbiturates porphyrin. Reagents and conditions: (a) KOH, $CHCl_3$; (b) NaOMe, toluene at reflux; (c) *n*-BuLi, Et_2O at −30 °C; (d) ethylformate, at −70 °C; (e) pyrrole, $BF_3(OEt)_2$ at rt, *p*-chloranil, CH_2Cl_2, at reflux; (f) (i) $(CH_3)_3SiI$, at 45 °C; (ii) $ZnCl_2$ at 50 °C.

porphyrinato zinc, that is, *meso*-conjugated barbiturates porphyrinato zinc (**ZnBarP**) in 90% yield. The infrared spectrum of **ZnBarP** (KBr) gave peaks corresponding to the stretching vibration of the carbonyl groups at 1698 and 1573 cm^{-1}, which are in agreement with those of typical barbituric acid derivatives.[13] The N–H-stretching vibration was also observed around 3200 cm^{-1} in a similar manner to that of barbituric acid.

We obtained absorption spectra of **ZnBarP** in three different solvents, that is, DMSO, methanol, and water. From a structural viewpoint, the hydroxy form of barbituric acid dominates over the oxo form in an aqueous solution.[14] **ZnBarP** exhibited the higher solubility in water (more than 50 mg/ml) than in organic solvents such as methanol (ca. less than 0.1 mg/ml) and DMSO (ca. less than 1.0 mg/ml) because the hydroxy form existed as a mixture of mono- and dianionic states. As shown in Figure 1, the UV–vis spectrum of **ZnBarP** displays an absorption band around 250 nm, suggesting that **ZnBarP** is present as a mixture of mono- and dianionic forms of barbituric acid at the *meso* positions.[14] Interestingly, the DMSO solution showed the larger red shift of the *Soret* band (450 nm) than water (426 nm) and methanol (429 nm). It was assumed that the barbiturate moiety would take an oxo form having the proton at the C5 position of the barbiturate in DMSO, which might cause steric repulsion with the protons at pyrrolic β positions resulting in the distortion of the porphyrin plane.

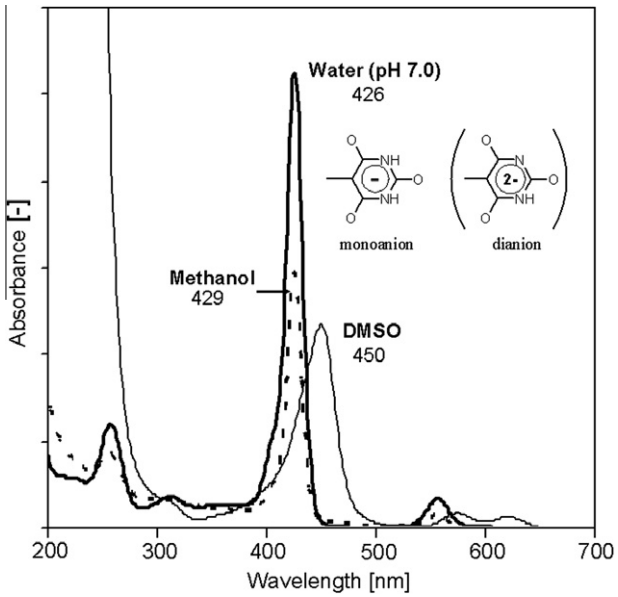

Figure 1. UV–vis spectra of **ZnBarP** (10 μM) in methanol, water and DMSO.

In order to investigate the self-assembling property of **ZnBarP**, 5-(2-{2-[2-(2-octyloxy-ethoxy)-ethoxy]-ethoxy}-ethyl)-pyrimidine-2,4,6-triamine (**C8EO4TAP**) as a 2DAD type having both hydrophilic and hydrophobic moieties was synthesized as described in a previous report.[15] When aqueous solutions of **ZnBarP** (1 mM) and **C8EO4TAP** were mixed at different molar ratios (1:1, 1:2, 1:3, 1:4, and 1:8, respectively), the amount of precipitate gradually increased as the proportion of **C8EO4TAP** increased. After the mixed solution was allowed to stand for 48 h at room temperature, the amount of precipitate was saturated. The suspension was centrifuged to isolate the precipitate. The composition of the precipitate was then characterized by ^1H NMR in $CDCl_3$ and UV–vis spectra (see the Supplementary data). Interestingly, the molar ratio of **ZnBarP**/**C8EO4TAP** was 1:4 even if excess **C8EO4TAP** was added to the **ZnBarP** aqueous solution (Fig. 2).[16]

The interaction of **ZnBarP** with **C8EO4TAP** was characterized by IR spectroscopy using a KBr sample of the precipitate. A peak corresponding to vibration of the carbonyl groups appeared at 1645 cm^{-1} after complexation of **ZnBarP** with **C8EO4TAP** (cf. peak of the unbound carbonyl group at 1698 cm^{-1}). The mechanism of

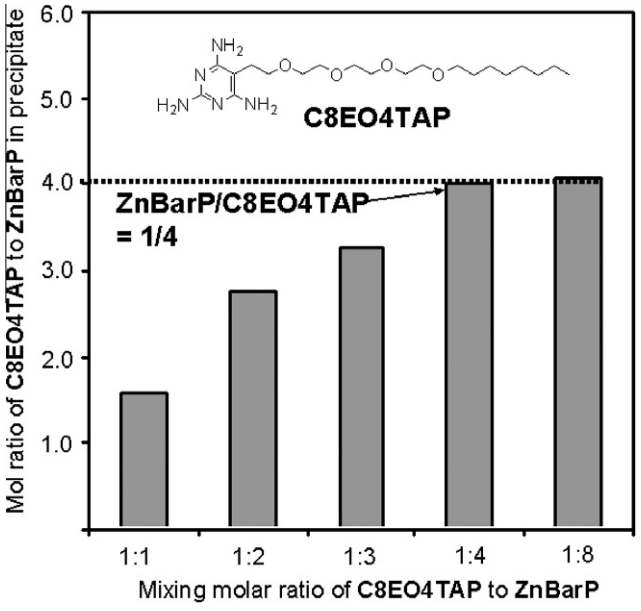

Figure 2. Analysis of the precipitation composed of **ZnBarP** and **C8EO4TAP**.

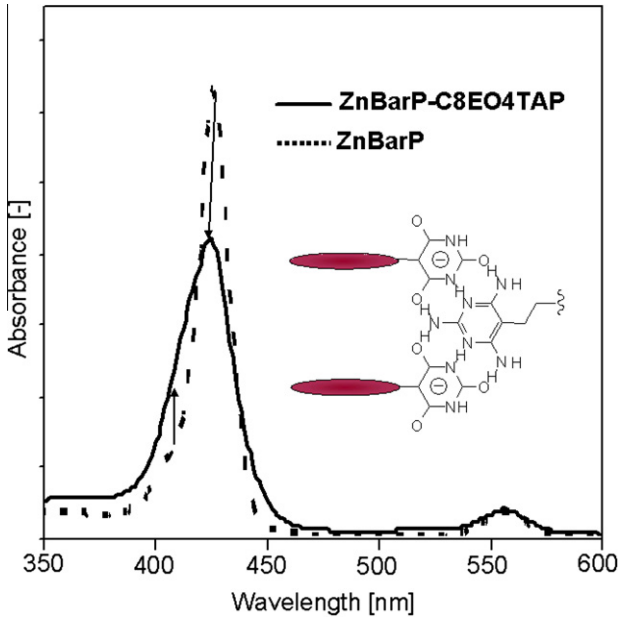

Figure 3. UV–vis spectra of **ZnBarP–C8EO4TAP** solution 1 mM using thin cell (0.1 mm).

precipitation would be as follows: units of barbituric acid specifically interact with triaminopyrimidine units to generate the complex with the hydrophobic parts of **C8EO4TAP** located toward the outside. Thus, the precipitate was highly soluble in organic solvents such as chloroform but not in water. Moreover the solution displayed a high level of viscosity. The UV–vis spectrum of the viscous chloroform solution was determined using a thin cell with a 0.1 mm pathlength. A slight blue-shift was detected indicating H-aggregation of a face-to-face type as shown in Figure 3.

This spectrum agreed with the behavior of the hydrogen-bonded face-to-face dimer as reported previously.[4] The peak half-width of the complex of **ZnBarP** with **C8EO4TAP** was broadened in comparison with the isolated state of **ZnBarP** in water, suggesting an accumulation of porphyrin at high density. In addition, the UV–vis spectra of the mixture of **ZnBarP** and **C8EO4TAP** gave the similar Q-band with the monomeric **ZnBarP** in water, indicating that the amino and pyrimidinyl groups of **C8EO4TAP** should not coordinate to the zinc core of **ZnBarP**.

We observed a film cast from the viscous chloroform solution of **ZnBarP** and **C8EO4TAP** using a polarized optical microscope (POM) as shown in Figure 4.

When **C8EO4TAP** alone was cast from aqueous or chloroform solutions on a glass plate, no anisotropy was observed. By contrast, the polarized microscopic image of a mixture of **ZnBarP** and **C8EO4TAP** did show anisotropy that was different from the texture of the **ZnBarP** crystal. If the composition ratio of **ZnBarP** and **C8EO4TAP** in the assembly changed during an evaporation process involved in cast from the chloroform solution onto the glass, the POM image arising from **ZnBarP** (crystal) or **C8EO4TAP** (isotropy) alone as shown in Figure 4 would be observed in the mixed sample with **ZnBarP** and **C8EO4TAP**. We can conclude that the composition ratio of the assembly on the solid surface should be 1–4, reflecting the ratio determined in the solution state as shown in Figure 2. When the film consists of **ZnBarP** and **C8EO4TAP** was analyzed by X-ray diffraction, the peak of 3 nm ascribed to the packing of the alkyl chain was observed (see the Supplementary data). Noncovalent interactions presumably promote the adoption of a face-to-face arrangement of the porphyrin where the hydrophobic alkyl chains are positioned on the outside, resulting in a highly ordered structure via the packing of the alkyl chain. Future optimization of the length and flexibility of the chains using triaminopyrimidine derivatives will improve the stability of the rod-like structure and facilitate the construction of highly ordered arrays via chain packing.

In conclusion, we have demonstrated an efficient synthetic route to a water-soluble porphyrin bearing multi-barbituric acids (**ZnBarP**) and discuss the complementary 2DAD type self-assembling possibilities induced by amphiphilic triaminopyrimidine derivatives. Although some previous reports describe porphyrins bearing heterocyclic compounds at the *meso* positions,[8] this is

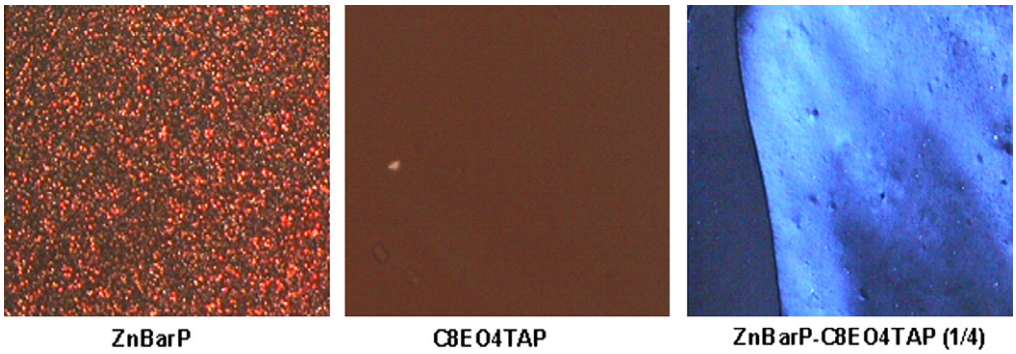

Figure 4. Polarlized microscope images of **ZnBarP**, **C8EO4TAP**, and **ZnBarP–C8EO4TAP** on a glass plate.

the first such report to use barbituric acid. **ZnBarP** is a promising candidate for synthetic strategies where introduction of multiple barbiturate moieties is required for construction of supramolecular assemblies based on other hydrophobic functional molecules, such as phthalocyanines or triphenylenes. The film composed of a porphyrin assembly, based on the complementary system of barbiturate and triaminopyrimidine, has a dense array of aligned active sites provided by the central metals of the porphyrin. Such an assembly can be used in a variety of applications (e.g., catalysts, membranes or novel functional materials), especially if different metals are inserted into the porphyrin ring system.

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Supplementary data

Supplementary data (General experimental method, experimental details, and characterization data for compounds **1–3**, and **ZnBarP**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.139.

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