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Atropisomers of *meso*-Conjugated Uracyl Porphyrin Derivatives and Their Assembling Structures

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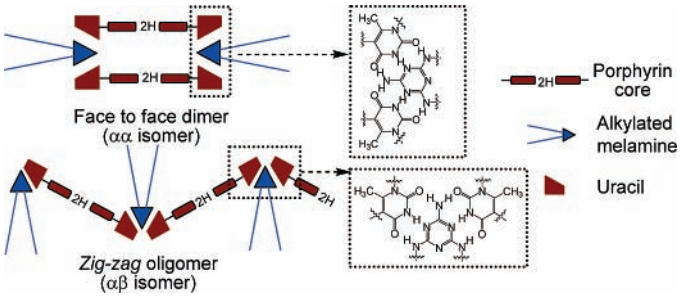
ABSTRACT



We have synthesized a 5,15 *meso*-substituted methyluracyl porphyrin derivative bearing 6-methyluracyl units directly at the *meso* positions. The atropisomerization was regulated by steric replusion between the methyl substituents. When the atropisomers were mixed with alkylated melamine as a complementary hydrogen-bonding unit, the hydrogen-bonded assemblies were analyzed by diffusion-ordered spectroscopy (DOSY) in solution, which clarified that the αα isomer formed a face-to-face dimer, whereas the αβ isomer took a zigzag structure.

Materials fabricated from self-assembled porphyrins have attracted attention for the past few decades because of their potential use in photonic devices and catalysts, based on photosynthetic chemistry or heme protein science.[1] As such, our group has synthetically targeted the active site of heme proteins via secondary interactions such as hydrophobic interaction, electrostatic interaction, or hydrogen bonding.[2] To fabricate a desirable assembly consisting of porphyrins, atropisomers are required to be regulated because the mixture of atropisomers could lead to less preorganization and thus poor control of the assembly. The atropisomers of *meso*-conjugated porphyrin generally arise via restricted rotation of the carbon−carbon bond at the *meso*-position. A general methodology to regulate atropisomerization is to introduce bulky substituent groups such as pivaloyl amide to the *ortho* position of the *meso* phenyl units or to conjugate naphthyl units at the porphyrin *meso* position.[3]

In this paper, we designed two porphyrin derivatives, of which atropisomerization was regulated at room temperature by steric hindrance; the methyl group at the *ortho* position on the *meso*-substituted uracyl units was flanked by methyl substituents at the porphyrin pyrrolic β positions. It was expected that it would be possible to isolate the atropisomers with chromatography due to the steric hindrance between the methyl groups.[4] Each atropisomer was also expected to

(1) (a) Satake, A.; Kobuke, Y. *Tetrahedron* **2005**, *61*, 13. (b) Shi, X.; Barkigia, K. M.; Fajer, J.; Drain, C. M. *J. Org. Chem.* **2001**, *66*, 6513. (c) Drain, C. M.; Batteas, J. D.; Flynn, G. W.; Milic, T.; Chi, N.; Yablon, D. G.; Sommers H. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 6498. (d) Campos, A. C.; Hunter, C. A.; Tomas, S. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 3034. (e) Drain, C. M.; Fischer, R.; Nolen, E. G.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 243.

(2) (a) Arai, S.; Ohkawa, H.; Ishihara, S.; Shibue, T.; Takeoka, S.; Nishide, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 2007.(b) Ohkawa, H.; Arai, S.; Takeoka, S.; Nishide, H. *Chem. Lett.* **2003**, *32*, 1052.(c) Ohkawa, H.; Takayama, A.; Nakajima, S.; Nishide, H. *Org. Lett.* **2006**, *8*, 2225.

(3) (a) Momenteau, M.; Reed, C. A. *Chem. Rev.* **1994**, *94*, 659. (b) Hayashi, T.; Miyahara, T.; Hashizume, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 2049.

(4) Plieger, P. G.; Burrell, A. K.; Jameson, G. B.; Officer, D. L. *J. Chem. Soc., Dalton Trans.* **2004**, 319.

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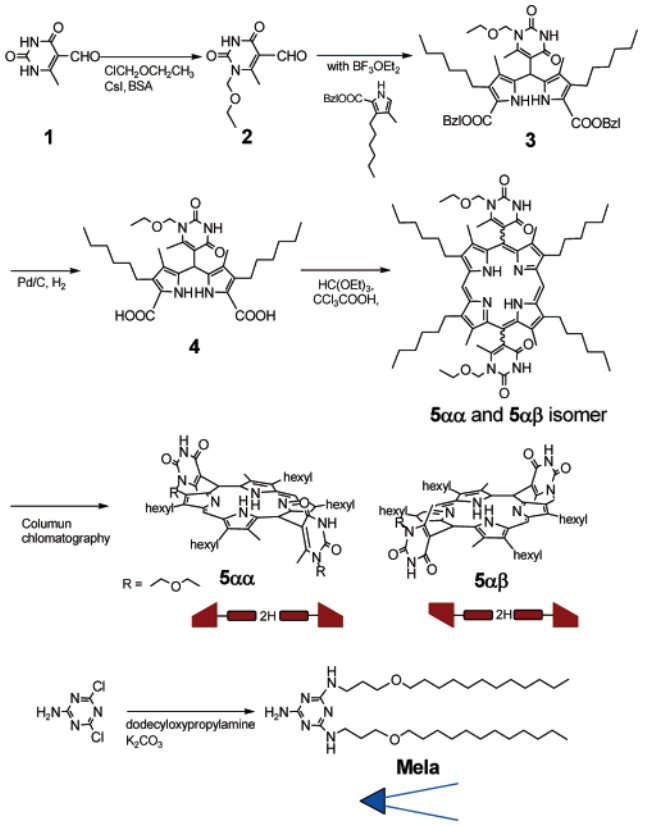
form a different self-assembling structure when mixed with a melamine derivative, a complementary unit to the uracil group.

5-Formyl-6-methyluracil (**1**) was prepared according to the previous literature.[5] A uracil derivative **2** was obtained by alkylation of **1** in the N1-position using bis(trimethylsilyl)-acetamide (BSA), chloromethyl ethyl ether, and CsI (Scheme 1).[6] The alkylation was required in order to prevent tau-

Scheme 1



tomerization and improve solubility. Dipyrrolmethane **3** was synthesized by the condensation of **2** with benzyl 3-hexyl-4-methylpyrrole 2-carboxylate in the presence of an acid catalyst. The hexyl chain introduced to the pyrrole was necessary for reasons of solubility.[7] After the catalytic reduction of **3**, **4** was condensed, using trichloroacetic acid as a catalyst, to give porphyrin **5** as a mixture of atropisomers. Careful column chromatography (silica gel 60 (63−200 μm), eluent: $CHCl_3$/MeOH = 40/1 (v/v)) resulted in the isolation of the individual atropisomers. The relative stereochemistry was assigned on the basis of the polarity; the αα isomer was more polar than the $\alpha\beta$ isomer and so eluted later than the $\alpha\beta$ isomer. ^{1}H NMR spectra of two isomers in DMSO indicated almost the same signals, except one signal ascribed to the protons on the α-carbon of the hexyl group in the 2, 8, 12, and 18 positions.

The signal corresponding to the protons on the α-carbon of the αα isomer was more complicated, whereas that in the $\alpha\beta$ isomer was a simple triplet, suggesting that the $\alpha\beta$ isomer would adopt a symmetric structure. It is noted that this phenomenon was only observed in DMSO but not in $CDCl_3$. The $\alpha\beta$ isomer, being less polar, was easily crystallized from DMSO, to form a thin needle-like crystal. The X-ray analysis provided conclusive evidence of the structure of **5**$\alpha\beta$ (Figure 1).[8] The X-ray data showed the $\alpha\beta$ orientation

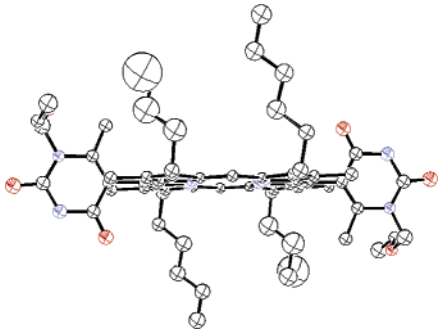


Figure 1. Solid-state structure of the **5**$\alpha\beta$ isomer. The hydrogen atoms and solvents are omitted for clarity.

of the uracyl group at the *meso* position and allowed us to confirm the assignment of the early eluting porphyrin as the $\alpha\beta$ isomer. Thus, although the later eluting porphyrin could not be crystallized, it was characterized as the other isomer, that is, the αα isomer. When the porphyrin **5** was suspended in $CDCl_3$ at a high concentration (above ca. 50 mM), it aggregated due to the $\pi-\pi$ stacking and hydrogen bonding. When the alkylated melamine derivative (**Mela**),[9] a complementary unit, was added to the suspended solution of both isomers, the suspension became transparent, indicating that the complexation of **5** with **Mela** greatly increased the solubility of **5**. In the ^{1}H NMR signals of the hydrogen-bonded assembly, the signals ascribed to the ether function ($NCH_2CH_2CH_2O$) of **Mela**, which is located near the hydrogen-bonding units shifted due to the ring current effect. Interestingly, each mixture behaved differently; the ether part of **Mela** shifted upfield in **5**$\alpha\beta$/**Mela**, but downfield in **5**αα/**Mela** (Figure 2). The disparity in shifts could be caused by differences in the manner of the porphyrin-melamine assembly via hydrogen bonds. We can explain the chemical shifts if we consider the resulting assemblies are as the structures shown in Figure 3. If the porphyrin **5** and **Mela** form a face-to-face structure, it is expected that the ether

(5) Hwang, D. R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264.

(6) Petersen, L.; Pedersen, E. B.; Nielsen, C. *Synthesis* **2001**, *4*, 559.

(7) The porphyrin bearing a uracil group was synthesized by condensation of **2** and a benzyl 3,4-dimethylpyrrole 2-carboxylate instead of the 3-hexylpyrrole derivative; however, the obtained porphyrin displayed poor solubility in all solvents, which made it difficult to handle.

(8) The structure of $\alpha\beta$ isomer in detail, for example, the orientation of hexyl chain, could not be determined, although the *R* value was low due to the thin needle crystalline. The X-ray analysis provided only information of the orientation of uracil groups. The ORTEP drawing of the crystal lattice was shown in the Supporting Information.

(9) Kimizuka, N.; Kawasaki, T.; Hirata, K.; Kunitake, T. *J. Am. Chem. Soc.* **1998**, *120*, 4094.

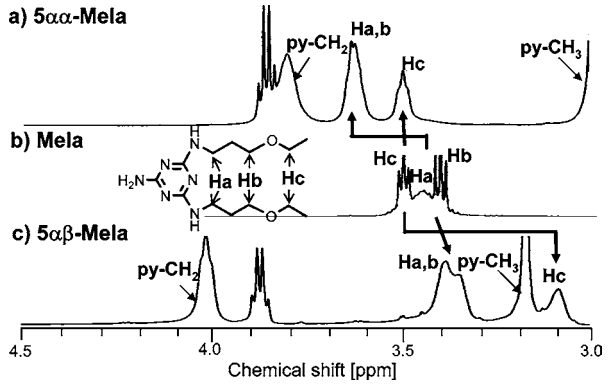


Figure 2. ^{1}H NMR spectra of the mixed chloroform solution: (a) **5**αα-**Mela** 50 mM (1:1), (b) **Mela** 50 mM, (c) **5**αβ-**Mela** 50 mM. *py-CH_2 and py-CH_3 were the signals of the protons on the α-carbon at the pyrrolic β positions of **5**αα or **5**αβ.

moiety of **Mela** will be located at the deshielding region of the porphyrin ring current (face to face). If they form a zigzag structure (*J*-aggregate), the ether group will be covered by **5** and located under the shielding region (zigzag). Indeed, the mixed solution of **5**αα and **Mela** showed a downfield shift in the signals for the ether group, and that with **5**αβ and **Mela** showed upfield shifts. From a structural point of view, this implies **Mela** was located on the deshielding region of **5**αα, which suggests a face-to-face structure. On the other hand, the upfield shift suggests that the core of **5**αβ was covered with **Mela**, implying that **5**αβ and **Mela** do not form a face-to-face but a zigzag structure (Figure 3). Furthermore, the different behaviors were observed for the changes of the chemical shifts of **5**αα or **5**αβ involving in hydrogen-boned aggregation; the protons of the methyl groups (py-CH_3) and the protons on the α-carbon at the pyrrolic β positions (py-CH_2) in **5**αα/**Mela** showed the upfield shift ($\sigma = 2.98$ ppm), but experienced little change in **5**αβ/**Mela** ($\sigma = 3.16$ ppm).

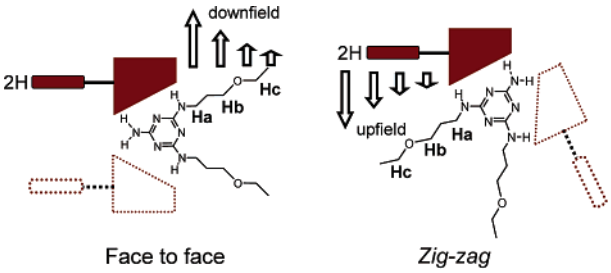


Figure 3. Model caption of the different ring current effects of **5** for the assembled structures of αα and αβ isomers.

These results also supported the above suggestion; the protons of the α carbon at the β positions of **5**αα in the face-to-face structure should be affected by the ring current effect, due to proximity between the porphyrin planes compared to that of **5**αβ in the zigzag structure.[10]

The UV−vis spectra supported these structures; the mixed toluene solution of **5**αβ and **Mela** (1 mM) showed the soret band of 412 nm compared to 410 nm in DMSO, which indicated *J*-aggregation. On the other hand, **5**αα and **Mela** (1 mM) showed the soret band of 408 and 380 nm compared to 410 nm in DMSO, which indicated H-aggregation.[10] The molecular weight for each assembly in solution was estimated by diffusion-ordered spectroscopy (2D-DOSY). This method is a useful technique for the estimation of assembly behavior in solution[2,11] because the technique does not need a large amount of sample in comparison to vapor pressure osmometry (VPO) or viscometry. In addition, gel permeation chromatography may in some cases be affected by the dissociation of hydrogen-bonded aggregates on dilution. The normalized diffusion coefficient (D_{norm}) was defined as the ratio of the observed value (D_{obs}) to $D_{\beta-CD}$, where $D_{\beta-CD}$ is the diffusion coefficient for the internal standard, heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin (β-CD).

The diffusion coefficient of the assemblies of each isomer was measured by ^{1}H NMR (Bruker 600 MHz) at a variety of concentrations, and the D_{norm} was plotted with increasing the concentration (Figure 4). The tendency shown in Figure

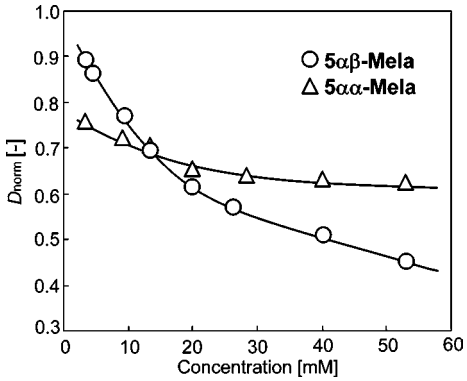


Figure 4. Concentration dependence of the normalized diffusion coefficient (D_{norm}) for the assembly of **5**αα-**Mela**(△) and **5**αβ-**Mela**(○).

4 clearly reflects the differences in the assemblies of each isomer. In a solution containing **5**αα-**Mela** mixed solution, the value of D_{norm} remained constant with increasing concentration, whereas D_{norm} decreased in a **5**αβ-**Mela** mixed solution, indicating that **5**αα and **Mela** forms a closed structure such as a dimer or a hexamer like a rosette.[12] The molecular weight in solution for each assembly was estimated

(10) See the Supporting Information that included the whole data for the NMR and UV−vis spectra.

(11) (a) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 810. (b) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520.

(12) Successful rosettes have been reported by many researchers, for example: Mathias, J. P.; Simanek, E. E.; Zerkowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4316. Drain, C. M.; Russell, K. C.; Lehn, J. M. *Chem. Commun*. **1996**, 337. Bielejewska, A. G.; Marjo, C. E.; Prins, L. J.; Timmerman, P.; Jong F.; Reinhoudt, D. N. *J. Am. Chem. Soc*. **2001**, *123*, 7518.

from the calibration curve based on polystyrene standards for GPC (Figure 5).

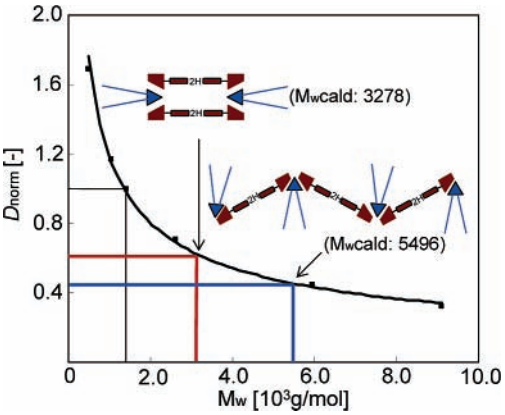


Figure 5. Calibration curve of polystyrene vs the molecular weight of the assembling for **5**αα or **5**αβ with **Mela** in $CDCl_3$ (50 mM). The red line was **5**αα and **Mela**. The blue line was **5**αβ and **Mela**.

The value of D_{norm} for **5**αβ-**Mela** (50 mM) was 0.45, which implies a trimer with an estimated M_w 5600 (the calculated M_w 5496). That of **5**αα-**Mela** (50 mM) was a constant value of 0.62, which suggests a dimer not a hexamer with an estimated M_w 3100 (the calculated M_w 3278).

In order to investigate the effect of metal insertion into the assemblies, metalloporphyrins of **5**αα**(Zn)** and **5**αβ(Zn) were synthesized, and the resulting solutions, once mixed with **Mela**, were analyzed by ^{1}H NMR. The ^{1}H NMR spectrum for the **5**αβ(Zn)-**Mela** (1:1 molar ratio) mixed solution at a high concentration state (above 10 mM) was complicated due to the competition between the coordination of **Mela** to the zinc and formation of the assembly through hydrogen bonding. On the other hand, the ^{1}H NMR spectrum for **5**αα**(Zn)-Mela** (1:1) showed the same behavior as that of the free base, which indicated that the insertion of zinc could not prevent hydrogen-bonded bis-porphyrin. Furthermore, by the equimolar addition of 3,5-dimethoxybenzylimidazole to the bis-porphyrin **5**αα**(Zn)-Mela** (2:2), the binding of the two imidazole units was confirmed by ^{1}H NMR and a UV−vis measurement.[13] By the addition of excess imidazole, the ^{1}H NMR signals of the protons ascribed to the amide and amino groups of **5**αα and **Mela** showed the same downfield shift as before the addition of the imidazole. These results mean the addition of the imidazole did not result in the collapse of the hydrogen bonded aggregate, which implies the formation of a stable hydrogen-bonded bisporphyrin.

In summary, we have synthesized an atrop-regulated porphyrin derivative which bears 6-methyluracyl units at the *meso* position. When each was mixed with *N*,*N*-bis(dodecyloxypropyl)melamine (**Mela**), a complementary hydrogen-bonding unit, analysis by NMR of the resulting hydrogen-bonded assembly in solution indicated that the αα isomer formed a dimer-like face-to-face bisporphyrin, whereas the αβ isomer preferentially adopted a zigzag structure. The two assemblies have different possible applications respectively; for example, the zigzag structure of the *J*-aggregate as an optical device and the stable and selective face-to-face dimeric structure as a catalyst for dioxygen reductions.

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Supporting Information Available: Synthetic details of the porphyrin derivatives, 2D-NMR experiments, and the imidazole titration experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) 3,5-Dimethoxybenzylimidazole was chosen to coordinate to the bisporphyrin on the outer side not on the inner side.