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Efficient Preparation of αβαβ-Atropisomer of *meso*-Tetra(*o*-aminophenyl)porphyrin

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Unusual abundance of αβαβ-atropisomer of *meso*-tetra(*o*-nitrophenyl)-porphyrin was observed in the thermal treatment in toluene. The reduction with $SnCl_2$ and chromatographic separation gave the corresponding atropisomer of *meso*-tetra(*o*-aminophenyl)porphyrin in 52% yield.

Collman's picket-fence porphyrin, the first porphyrin architecture, was prepared by utilizing the αααα-atropisomer of *meso*-tetra(*o*-aminophenyl)porphyrin (TAPP, Fig. 1).[1] Since then, atropisomers of TAPP were often employed to design various porphyrin compounds, which were named, for example, as basket-handle,[2] picnic-basket,[3] and gyroscope[4] porphyrins. We also successfully combined amino acid derivatives to all atropisomers of TAPP, as a starting building block for a polypeptide conjugate, and found interesting circular dichroic behaviors.[5] Furthermore, reported is the design of the bilayer membrane-compatible porphyrin compounds by employing the αααα-[6] and αβαβ-[7] isomers of TAPP.

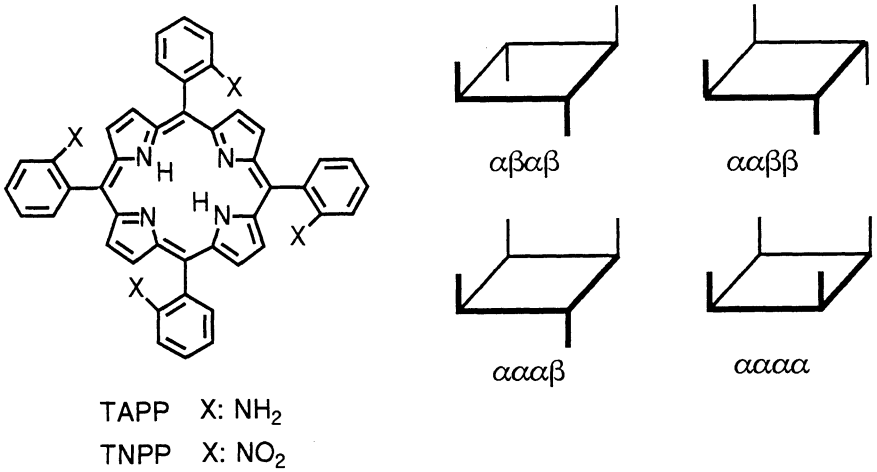

Fig. 1. Structure and illustration of atropisomers of *meso*-tetra(*o*-substituted-phenyl)porphyrin.

However, it is tedious to prepare the αβαβ-atropisomer of TAPP in quantity, because its content in the atropisomeric mixture under equilibrium is calculated to be 12.5% (The statistic ratio of the four isomers; αααα/αβαβ/ααββ/αααβ = 1/1/2/4). On the other hand, the αααα-isomer, which is also poor in content, can be obtained in quantity by the inductive treatment with silica gel in benzene.[8] Since the αβαβ-isomer has not been enriched, the poverty of this isomer limits the construction of porphyrin architecture having interesting functions.

In the literature search on the atropisomerisms of the *o*-substituted tetraphenylporphyrins, we learned that *meso*-tetra(*o*-cyanophenyl)porphyrin gives its αβαβ-isomer as much as 39% under equilibrium in $CHCl_3$.[9] The nitro group of *meso*-tetra(*o*-nitrophenyl)porphyrin (TNPP), the precursor of TAPP, is as polar as CN group. Therefore, we expected the induction of αβαβ-isomer of TNPP in a high yield under a similar condition. The following reduction would give the corresponding TAPP isomer.

The thermal atropisomerism of TNPP in CH_3CN and toluene was studied by starting with αααβ- and αβαβ-isomers separated by silica gel chromatography (Wakogel C-300, 4.0 cm x 30 cm, $CHCl_3$). The isomerization was followed by reversed-phase HPLC analysis [Waters μBondasphere C18 (3.9 mm x 150 mm), $CH_3CN/CH_3OH/H_2O$ = 7/73/20, v/v/v], as shown in Fig. 2. The time courses of isomerizations from the αααβ-isomer in CH_3CN and toluene at 353 K are given in Fig. 3A and 3B, respectively. The TNPP differently behaved in atropisomerisms in CH_3CN and toluene. In the polar solvent, the ratio of the four isomers is very close to the statistic one (the first-order rate constant, $k = 9.6 \times 10^{-5}$ s^{-1} and the activation free energy, $\Delta G^{\neq} = 114$ kJ mol^{-1}). In toluene, however, induction of the αβαβ-isomer up to 64% was observed (αααβ 22.3%, ααββ 13.7%, αααα 0%, $k = 4.0 \times 10^{-4}$ s^{-1}, $\Delta G^{\neq} = 110$ kJ mol^{-1}). The contents of isomers in the mixture were also examined by the thermal isomerization of the αβαβ-isomer in the same

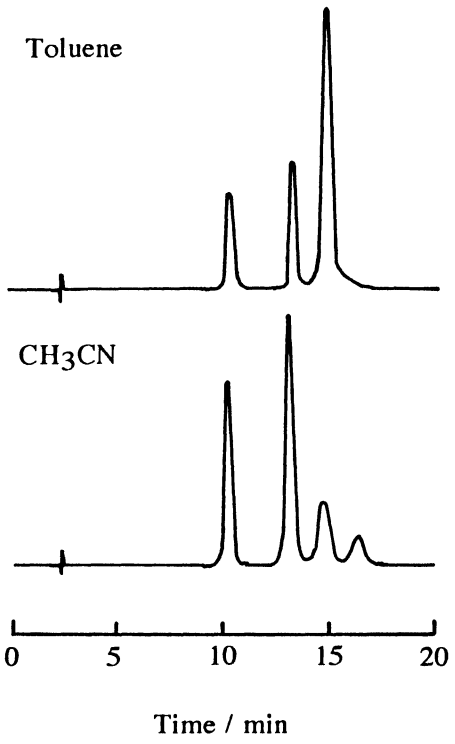

Fig. 2. HPLC profiles of the atropisomeric mixture of TNPP after the thermal treatments in CH_3CN and toluene. The isomers eluted in the order of ααββ, αααβ, αβαβ, and αααα. Column, μBondasphere C18 (3.9 mm x 150 mm); eluent, $CH_3CN/CH_3OH/H_2O$ = 7/73/20, v/v/v; flow rate, 1.0 ml/min; detection, 420 nm.

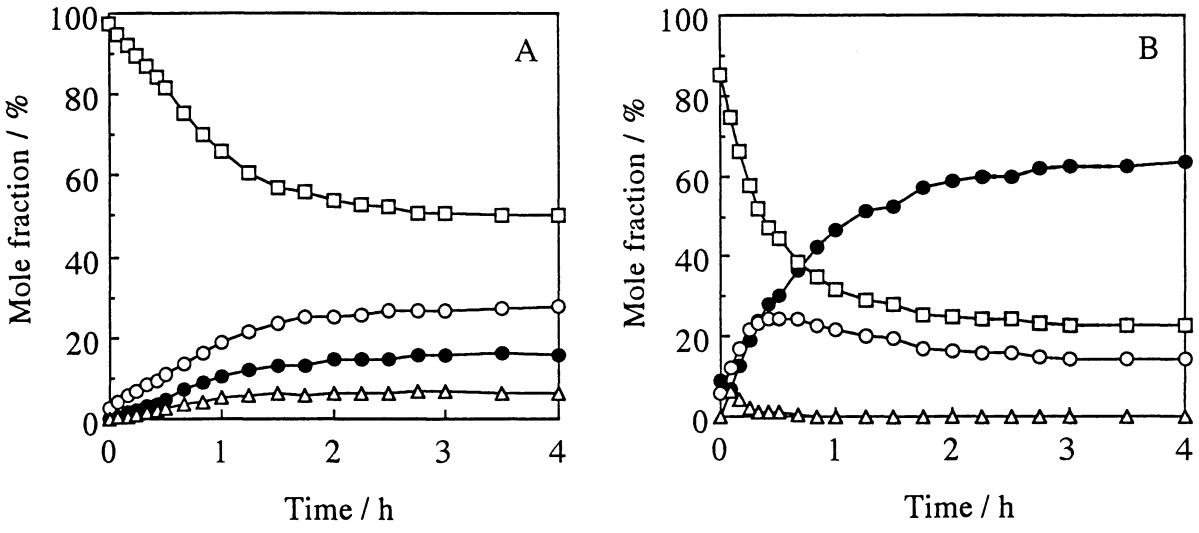

Fig. 3. Time courses of the thermal isomerizations from αααβ-TNPP in (A) CH_3CN and (B) toluene at 353 K. (●) αβαβ, (○) αα$\beta\beta$, (□) αααβ, (△) αααα.

solvent, and the same ratio of four isomers was reprodued (αβαβ 63.7%, αααβ 22.5%, αα$\beta\beta$ 13.6%, αααα 0.2%).

Since we found the unusual abundance of αβαβ-TNPP in the thermal treatment, enrichment of the αβαβ-isomer of TAPP was carried out as follows. Crude TNPP[1a] (0.50 g) was suspended in toluene (2.0 dm^3) and refluxed for 5 h. The solution was filtered and concentrated to dryness. The residual crystalline material (0.25 g) was suspended in 12 M (1 M = 1 mol dm^{-3}) HCl (15 ml) and reacted with $SnCl_2 \cdot 2H_2O$ (1.1 g) for 5 h at room temperature.[10] The reduction product was extracted with CH_2Cl_2 after neutralization. The HPLC analysis of the mixture of TAPP after the reduction showed the content of αβαβ-isomer as high as 57%, that is, there was no significant isomerizaton during the reduction. The mixture was separated by silica gel chromatography with benzene/ether (10/1, v/v) to afford 0.11 g of αβαβ-TAPP (52%). Spectroscopic properties of the isomer such as absorption and fluorescence spectra were identical to those of the authentic sample. When the original TNPP mixture was converted to the corresponding TAPP without the thermal induction, the chromatographic separation afforded 5-8% overall yield for desired αβαβ-TAPP.

It is noteworthy that the insoluble portion of TNPP in toluene consisted mainly of αα$\beta\beta$- and αααβ-isomers, 40 and 50%, respectively. The reduction may give the atropisomeric mixture of TAPP similarly enriched with αα$\beta\beta$-isomer, possibly useful one in further construction of a hybrid of peptides with the porphyrin.

In conclusion, the useful αβαβ-atropisomer of TAPP could be prepared in good yield after enrichment in its precursor. Facile preparation in quantity may encourage further design of functional porphyrin compounds.

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