CHEMISTRY LETTERS, pp. 279-282, 1993.

5,10,15,20-Tetrakis(2-amino-6-methoxycarbonylphenyl)porphyrin. Synthesis and Separation of Atropisomers Useful for Porphyrin Architecture

Norikazu NISHINO,* Toshiaki SAKAMOTO, Hiroshi KIYOTA,
Hisakazu MIHARA, Tomoko YANAI,† and Tsutomu FUJIMOTO
Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Tobata, Kitakyushu 804
†Shinnikka Environmental Engineering Co. Ltd., Tobata, Kitakyushu 804

5,10,15,20-Tetrakis(2-amino-6-methoxycarbonylphenyl)porphyrin was synthesized and three atropisomers in four were successfully separated. Different from the related mono-substituted tetraphenylporphyrins (2-amino- and 2-methoxycarbonylphenylporphyrins), the rotation of the bond between phenyl and porphyrin rings was totally prohibited under thermal isomerization.

Atropisomeric substituted tetraphenylporphyrins (TPP) are promising core compounds for porphyrin architecture. A number of skillful designs and syntheses have been achieved based on the atropisomers of 5,10,15,20-tetrakis(2-amino- and 2-carboxy-phenyl)porphyrins (TAPP and TCPP, respectively).1) However, to our knowledge, the synthesis and atropisomerism of doubly substituted TPP (at 2- and 6- positions of phenyl ring) with different anchoring groups have not been reported. In order to expand the design of porphyrin architecture, it is desirable to equip TPP with different condensing groups, which can be separately combined with various functional moieties. In this respect, we attempted to add chemical features of an amino acid to a porphyrin ring by introducing both amino and carboxyl groups on the phenyl rings of TPP (Fig. 1). Two anchoring groups can be utilized to bind amino acids, peptides, acyl groups, and amines through peptide bonds.

The synthetic scheme and illustration of the atropisomers are shown in Fig. 1. Methyl 2-formyl-3-nitrobenzoate was prepared *via* 4-nitro-3-methoxyphthalide2) and reacted with pyrrole according to Lindsey and Wagner.3) The increase in yield of 5,10,15,20-tetrakis(2-methoxycarbonyl-6-nitrophenyl)porphyrin (TMCNPP) was attained by the optimization of the reaction conditions. The use of 0.085 M $BF_3 \cdot OEt_2$ (1 M = 1 mol dm^{-3}) and 0.2 M aldehyde in CH_2Cl_2 gave the highest yield (20%). It is noteworthy that fairly higher concentrations of both aldehyde and catalyst (26 and 20 times, respectively) are required than those employed in the literature.3 The same conditions as in the literature gave the desired doubly substituted TPP in less than 0.5% yield. These results can be attributed to the enhanced steric hindrance by nitro and methoxycarbonyl groups. The separation of four atropisomers of TMCNPP was achieved by passing the mixture through silica gel columns several times with benzene/CH_3CN = 9/1, v/v as eluent. The R_f values on TLC and 400 MHz ^1H-NMR spectral data in $CDCl_3$ are given in Table 1. The signal of the ester methyl groups of $\alpha\beta\alpha\beta$-isomer appeared at 2.69 ppm with about 1 ppm higher field shift than regular one. This is attributed to the ring current effect on the methyl groups protruded toward the porphyrin ring.

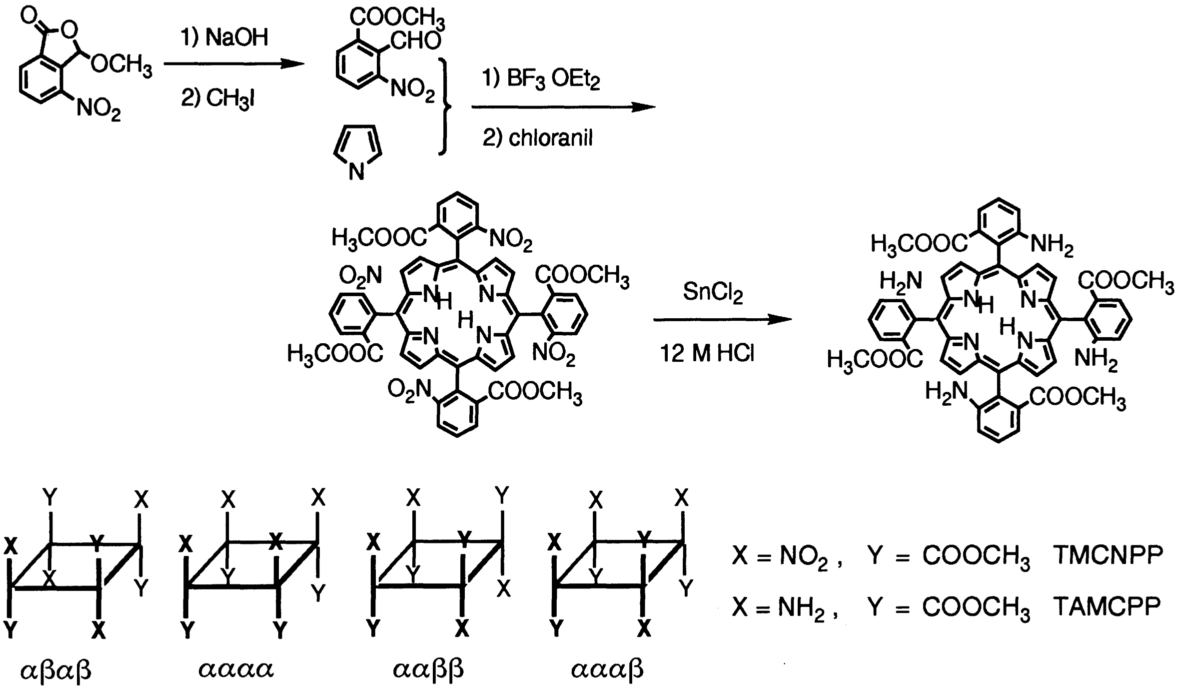

Fig. 1. Synthetic scheme of TMCNPP and TAMCPP, and illustration of the atropisomers.

The reduction of the nitro groups of TMCNPP was then carried out with $SnCl_2 \cdot 2H_2O$ in 12 M HCl according to the literature[4] for 18 h at room temperature. The desired product, 5,10,15,20-tetrakis(2-amino-6-methoxycarbonylphenyl)porphyrin (TAMCPP) was extracted into CH_2Cl_2 and isolated in 82% yield after passing through a silica gel column with CH_2Cl_2/CH_3OH, 9/1, v/v. Though the hydrolysis of ester moiety is generally unavoidable under the conditions, the particular ones in TAMCPP were very stable and retained intact. Three atropisomers of TAMCPP (αβαβ, ααββ, and αααβ) were separated by silica gel chromatography with CH_2Cl_2/CH_3CN = 9/1, v/v.[5] The R_f values on TLC and 400 MHz ^{1}H-NMR spectral data in $CDCl_3$ were summarized in Table 2.

The atropisomers of TMCNPP showed very similar electron spectra each other in CH_2Cl_2.[6] The atropisomers of TAMCPP also gave similar spectra with a blue shift by several nm.[6] In the fluorescence spectra, TAMCPP showed an emission peak at 656 nm by excitation at 424 nm (Soret band), although TMCNPP generated no emission in the fluorescence spectrum.

Among the properties which we have observed on these new doubly substituted TPP, the most important one is remarkable stability against the thermal isomerism. Refluxing of αβαβ-TAMCPP in toluene for 8 h caused no appearance of any other isomers on TLC analysis. This property may promise that this atropisomer of TAMCPP is stable enough to endure under severe synthetic conditions.

Thus, we have succeeded in the synthesis of TAMCPP *via* TMCNPP, which was obtained in good yield in porphyrin ring cyclization. Lindsey and Wagner reported some examples of the synthesis of 2,6-disubstituted TPPs (dichloro- and difluoro-TPPs) and 2,4,6-trisubstituted TPPs (trimethyl- and trimethoxy-TPPs) in about 30% yield.[3] However, they are never the candidates for further derivation to porphyrin architectures. The amino groups of TAMCPP, in contrast, are reactive to activated carbonyl groups. Modification of porphyrin compound with amino acid was further demonstrated as follows. To a

Table 1. TLC and ^{1}H-NMR Data of TMCNPP in $CDCl_3$

	αβαβ	αααα	ααββ	αααβ
R_f a)	0.33	0.14	0.30	0.29
^{1}H-NMR assignment b)				
pyrrole NH	-2.31, s (2H)	-2.34, s (2H)	-2.36, s (2H)	-2.34, s (2H)
ester CH_3	2.69, s (12H)	2.65, s (12H)	2.51, s (12H)	2.42, s (3H) 2.55, s (3H) 2.71, s (6H)
phenyl H	8.05, t (4H)	8.04, t (4H)	8.05, t (4H)	8.04, t (4H)
	8.36, dd (4H)	8.42, dd (4H)	8.40, dd (4H)	8.37, dd (1H) 8.39, dd (2H) 8.42, dd (1H)
	8.50, dd (4H)	8.43, dd (4H)	8.46, dd (4H)	8.43, dd (1H) 8.46, dd (2H) 8.50, dd (1H)
pyrrole βH	8.52, s (8H)	8.52, s (8H)	8.53, s (8H)	8.53, s (8H)

a) Benzene/CH_3CN = 9/1, v/v. b) JEOL JNM GX-400 spectrometer.

Table 2. TLC and ^{1}H-NMR Data of TAMCPP in $CDCl_3$

	αβαβ	αααα c)	ααββ d)	αααβ
R_f a)	0.65	0.18	0.36	0.26
^{1}H-NMR assignment b)				
pyrrole NH	-2.29, s (2H)		-2.44, s (2H)	-2.37, s (2H)
ester CH_3	2.93, s (12H)		2.81, s (12H)	2.90, s (3H) 2.85, s (6H) 2.51, s (3H)
phenyl H	7.19, dd (4H) 7.63, t (4H) 7.78, dd (4H)		7.1-7.7 (12H)	7.0-7.8 (12H)
pyrrole βH	8.71, s (8H)		8.63, s (4H) 8.55, s (4H)	8.69, s (4H) 8.67, s (4H)

a) CH_2Cl_2/CH_3CN = 9/1, v/v. b) JEOL JNM GX-400 spectrometer.
c) We could not obtained pure αααα-isomer. Ref. 5. d) In $(CD_3)_2SO$ due to poor solubility in $CDCl_3$.

chilled solution of αβαβ-TAMCPP in CH_2Cl_2 was added a solution of symmetrical anhydride (2.0 equiv.) of Boc (*t*-butyloxycarbonyl)-L-Ala-OH prepared with dicyclohexylcarbodiimide in CH_2Cl_2. The coupling reaction was carried out at room temperature for 24 h in the darkness. The conjugate, (Boc-L-Ala-)$_4$-αβαβ-TAMCPP, was isolated in 70% yield and purified by silica gel chromatography ($CH_2Cl_2/CH_3CN = 3/1$, v/v) in 57% yield. The structure was confirmed by FAB-MS; m/z 1591 (M^+) and 400 MHz ^{1}H-NMR measurements.7) The induced CD by L-Ala residues was observed at Soret band of porphyrin ring.8)

In conclusion, TMCNPP and TAMCPP have been synthesized for the first time and the separated atropisomers were characterized by spectroscopic measurements. High stability of each atropisomer was observed, which is a benefit for further modification of porphyrin ring. As an example, the condensation with Boc-L-Ala-OH was demonstrated in high yield.

References

1) J. P. Collman, R. R. Gange, C. A. Reed, T. R. Halbert, G. Lang, and W. T. Robinson, *J. Am. Chem. Soc.*, **97**, 1427 (1975); J. T. Groves and R. S. Myers, *ibid.*, **105**, 5791 (1983); M. Momenteau, J. Mispelter, B. Loock, and J.-M. Lhoste, *J. Chem. Soc., Perkin Trans. 1,* **1985**, 221; D. Mansuy, P. Battioni, J.-P. Renaud, and P. Guerin, *J. Chem. Soc., Chem. Commun.*, **1985**, 155; J. P. Collman, J. I. Brauman, J. P. Fitzgerald, P. D. Hampton, Y. Naruta, J. W. Sparapany, and J. A. Ibers, *J. Am. Chem. Soc.*, **110**, 3477 (1988); B. Boitrel, A. Lecas, Z. Renko, and E. Rose, *J. Chem. Soc., Chem. Commun.*, **1985**, 1820; T. Fujimoto, T. Umekawa, and N. Nishino, *Chem. Lett.,* **1992**, 37; N. Nishino, H. Mihara, R. Hasegawa, T. Yanai, and T. Fujimoto, *J. Chem. Soc., Chem. Commun.,* **1992**, 692; Y. Matsushita, E. Hasegawa, K. Eshima, and E. Tsuchida, *Chem. Lett.,* **1983**, 1387; J. T. Groves and R. Neumann, *J. Am. Chem. Soc.,* **111**, 2900 (1989).

2) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Am. Chem. Soc.,* **87**, 4545 (1965); C. Brown and M. V. Sargent, *J. Chem. Soc., C,* **1969**, 1818.

3) J. S. Lindsey and R. W. Wagner, *J. Org. Chem.,* **54**, 828 (1989).

4) A. Lecas, B. Boitrel, and E. Rose, *Bull. Soc. Chim. Fr.,* **128**, 407 (1991).

5) Since the $\alpha\alpha\alpha\alpha$-atropisomer of TAMCPP could not be obtained with high purity, the properties are not described in this paper.

6) λmax, nm (ε) in CH_2Cl_2: $\alpha\beta\alpha\beta$-TMCNPP; 428 (249000), 523 (17500), 558 (5700), 603 (6600), 661 (2200); $\alpha\beta\alpha\beta$-TAMCPP; 424 (360000), 519 (27600), 552 (11700), 596 (11700), 650 (7500).

7) ^{1}H-NMR (400 MHz in $CDCl_3$) (δ, ppm): -2.29 (2H) pyrrole NH, 0.92 (48H) Boc $(CH_3)_3$ and Ala CH_3, 3.05 (16H) ester CH_3 and Ala CαH, 3.38 (4H) Ala NH, 7.16 (4H) 7.92 (4H) 8.21 (8H) phenyl H, 8.57 (8H) pyrrole βH, 8.70 (4H) phenyl NH.

8) (Boc-L-Ala-)$_4$-$\alpha\beta\alpha\beta$-TAMCPP: $[\theta] = +70000$ deg·cm^2·dmol^{-1} at 429 nm in MeOH.

(Received November 10, 1992)