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Physicochemical Properties of the Atropisomers of *meso*-Tetra(*o*-pivalamidophenyl)porphyrin

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Four possible atropisomers of *meso*-tetra(*o*-pivalamidophenyl)porphyrin, one of which is known as the picket fence porphyrin, have been prepared and their physicochemical properties examined. The visible absorption spectra of the isomers are all different, especially in DMF. The wavelength of the absorption maxima is most blue-shifted in the $\alpha\alpha\alpha\alpha$-isomer. Phyllotype tendency, which is characterized by the relative intensity of the four bands in the visible region, was in the order $\alpha\alpha\alpha\alpha > \alpha\alpha\beta\beta \simeq \alpha\alpha\alpha\beta > \alpha\beta\alpha\beta$. This is the same order as that of the blue shift. The order is also the same as that of the reduction potentials measured in DMF. The nuclear magnetic resonance (NMR) chemical shifts of methyl protons of the pivalamido groups are distinguishable among the four isomers even in a mixture of the isomers in chloroform or toluene. These results indicate that the conformation of the porphyrin (the distribution of the pivalamido groups between the two sides of the porphyrin plane) affects the physicochemical properties of the porphyrin. Interaction between adjacent pivalamido groups is considered to be responsible for this phenomenon.

Keywords——atropisomer; porphyrin; picket fence porphyrin; reduction potential; UV; NMR

There have been several reports concerning atropisomers of tetraarylporphyrins[1] since Gottwald and Ullman first reported the atropisomerization of *meso*-tetra(*o*-hydroxyphenyl)porphyrin.[1a] Four atropisomers exist in a free base *ortho*-substituted tetraphenylporphyrin derivative (Fig. 1). Each isomer is distinguished by the distribution of the substituents between the two sides of the porphyrin plane. In this paper we call the individual isomers $\alpha\beta\alpha\beta$-, $\alpha\alpha\beta\beta$-, $\alpha\alpha\alpha\beta$-, and $\alpha\alpha\alpha\alpha$-isomer (Fig. 1), according to the notation of Collman *et al.*[1c]

Among the *ortho*-substituted tetraphenylporphyrins the picket fence porphyrin, $\alpha\alpha\alpha\alpha$-isomer of *meso*-tetra(*o*-pivalamidophenyl)porphyrin (ToPivPP), has received special attention, because its iron complex has been characterized as a good model for myoglobin or hemoglobin in view of its reversible dioxygen adduct formation at room temperature.[1c] It has been considered that the structure having the pickets on the side of the porphyrin plane is important for the reversible dioxygen adduct formation. Since the picket fence porphyrin is a unique atropisomer of ToPivPP, investigation of the properties of the other atropisomers should provide useful information for understanding the particular nature of the picket fence

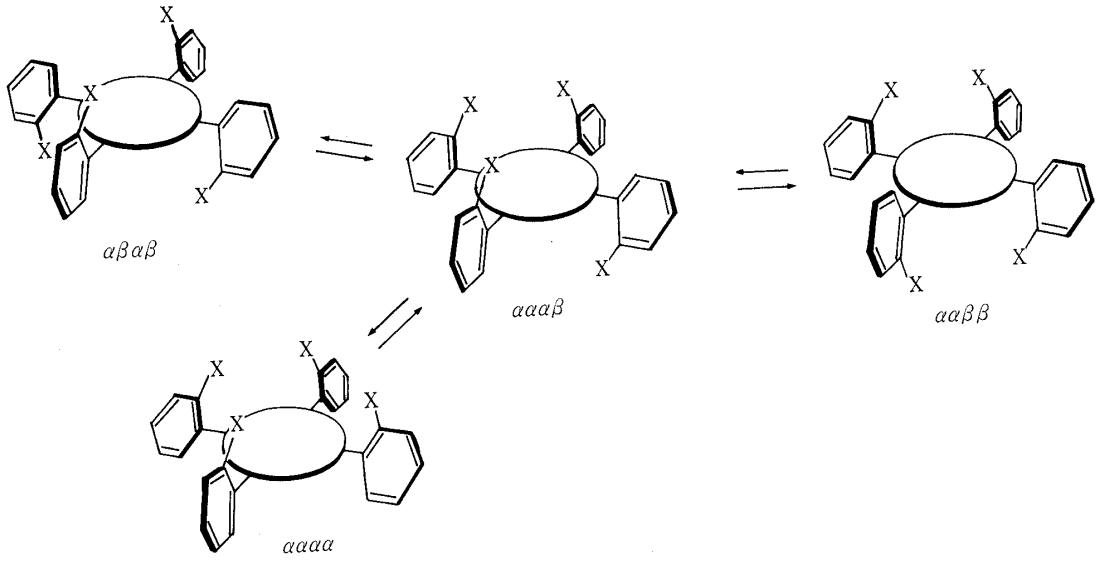

Fig. 1. Atropisomers of an *ortho*-Substituted TPP Derivative

The circle represents the porphyrin skeleton and the *ortho*-substituted phenyl groups bond to the *meso*-position of the porphyrin skeleton. The isomers are distinguished based on the distribution of the substituents (X) between the two sides of the porphyrin plane.

porphyrin.

In this paper, we report the preparation of the four possible atropisomers of ToPivPP and a comparison of the physicochemical properties in order to obtain information about the effect of the stereochemical structure of the porphyrin periphery on the nature of the porphyrin ring.

Experimental

Each isomer of ToPivPP was prepared by the reaction of the corresponding isomer of *meso*-tetra(*o*-aminophenyl)porphyrin ($ToNH_2PP$) with pivaloyl chloride according to Collman *et al.*[1c] Pivaloyl chloride was synthesized by the reaction of pivalic acid with benzoyl chloride.[2] The mixture of four atropisomers of $ToNH_2PP$ was separated by column chromatography (silica gel 60, Merck). The $\alpha\beta\alpha\beta$-isomer and $\alpha\alpha\beta\beta$-isomer were eluted in the first and second fractions with 5% diethylether in chloroform, then the $\alpha\alpha\alpha\beta$-isomer with 1% methanol, and finally the $\alpha\alpha\alpha\alpha$-isomer with 2% methanol in chloroform. *n*-Heptane was added to each fraction of the isomers and the solutions were concentrated on a rotary evaporator at room temperature until crystalline products appeared. The purity was confirmed by thin layer chromatography (TLC).

The $\alpha\beta\alpha\beta$-isomer of ToPivPP was prepared as follows. The $\alpha\beta\alpha\beta$-isomer of $ToNH_2PP$ (103 mg) was dissolved in about 200 ml of dry chloroform containing 8 ml of triethylamine. Excess pivaloyl chloride (about 2 ml) was added dropwise to the solution at room temperature with stirring. The completion of the reaction was checked by TLC after 2 h of stirring. The solution was washed with distilled water several times and then evaporated. The residue was redissolved in a small volume of chloroform, and the resulting solution was charged on a column of silica gel to remove the unreacted materials. Ethanol (about 30 ml) and heptane (about 60 ml) were added to the main fraction eluted with 5% diethylether in chloroform and the solution was concentrated. Hexane was added to the residue and left to stand overnight. The solid product (107 mg) was collected and recrystallized by slow diffusion of *n*-pentane into the chloroform solution. The preparation of the other isomers was carried out in a similar manner. All the isomers except the $\alpha\alpha\alpha\beta$-isomer were obtained as single crystals of X-ray diffraction quality. *Anal.* Calcd for $C_{64}H_{66}N_8O_4$: C, 76.01; H, 6.58; N, 11.08. Found: C, 74.71; H, 6.14; N, 11.01 for $\alpha\beta\alpha\beta$-isomer: C, 76.40; H, 6.85; N, 10.78 for $\alpha\alpha\beta\beta$-isomer: C, 74.47; H, 5.83; N, 10.78 for $\alpha\alpha\alpha\beta$-isomer: C, 74.41; H, 6.38; N, 10.84 for $\alpha\alpha\alpha\alpha$-isomer. *meso*-Tetraphenylporphyrin (TPP) was prepared and purified according to the literature.[3]

Visible, infrared (IR), and nuclear magnetic resonance (NMR) spectra were measured with a Shimadzu UV200 spectrophotometer, a JASCO IRA-2 IR spectrometer, and a JEOL FX-100 FT-NMR spectrometer, respectively. Reduction potential was measured with a Yanaco P-8 polarographic analyzer. The electrolyte system consisted of a 0.1 M solution of $(C_2H_5)_4NClO_4$ in dimethylformamide (DMF). The concentration of the porphyrin was 0.1—1.0×10^{-3} M. Ag/AgCl in 1 N LiCl gel was used as a reference electrode (MR-P3, Yanaco).

TABLE I. Visible Spectral Data for ToPivPP Atropisomers

Solvent	Isomer	Absorption bands[a]					II/III[b]
		Soret	IV	III	II	I	
DMF	$\alpha\beta\alpha\beta$	426 (5.53)	521 (4.23)	558 (3.86)	597 (3.74)	654 (3.50)	0.76
	$\alpha\alpha\beta\beta$	421 (5.53)	516 (4.27)	550 (3.72)	591 (3.77)	649 (3.44)	1.11
	$\alpha\alpha\alpha\beta$	422 (5.52)	517 (4.27)	551 (3.75)	592 (3.77)	651 (3.51)	1.04
	$\alpha\alpha\alpha\alpha$	419 (5.53)	514 (4.28)	546 (3.64)	589 (3.77)	651 (3.47)	1.37
Chloroform	$\alpha\beta\alpha\beta$	422 (5.52)	516 (4.29)	550 (3.78)	591 (3.79)	648 (3.40)	1.03
	$\alpha\alpha\beta\beta$	420 (5.52)	514 (4.30)	546 (3.70)	587 (3.79)	645 (3.35)	1.25
	$\alpha\alpha\alpha\beta$	420 (5.52)	514 (4.30)	547 (3.72)	588 (3.80)	650 (3.45)	1.20
	$\alpha\alpha\alpha\alpha$	418 (5.53)	512 (4.31)	544 (3.65)	587 (3.79)	651 (3.49)	1.39
Benzene	$\alpha\beta\alpha\beta$	422 (5.49)	516 (4.28)	549 (3.75)	590 (3.77)	647 (3.36)	1.04
	$\alpha\alpha\beta\beta$	421 (5.51)	513 (4.31)	546 (3.70)	587 (3.80)	645 (3.35)	1.25
	$\alpha\alpha\alpha\beta$	421 (5.49)	514 (4.30)	547 (3.71)	589 (3.78)	652 (3.44)	1.18
	$\alpha\alpha\alpha\alpha$	420 (5.50)	513 (4.31)	545 (3.66)	588 (3.79)	652 (3.52)	1.32
Ethanol	$\alpha\beta\alpha\beta$	419 (5.50)	515 (4.22)	549 (3.72)	591 (3.73)	647 (3.34)	1.02
	$\alpha\alpha\beta\beta$	417 (5.55)	513 (4.29)	546 (3.69)	588 (3.80)	646 (3.38)	1.28
	$\alpha\alpha\alpha\beta$	417 (5.53)	513 (4.28)	546 (3.70)	588 (3.78)	648 (3.43)	1.22
	$\alpha\alpha\alpha\alpha$	416 (5.54)	512 (4.29)	543 (3.62)	587 (3.79)	650 (3.45)	1.45

a) Absorption peak (nm) and logarithm of extinction coefficient (in parenthesis).
b) Ratio of intensity of band II to that of band III.

Results and Discussion

The atropisomers of ToPivPP all gave identical IR spectra and elementary analysis results, confirming that all the isomers prepared have the same chemical composition. The NMR spectra indicated that none of the isomers contains any other isomer as a contaminant (*vide infra*). Formation of single crystals also suggests the purity of each isomer.

Table I shows the visible spectral data for the atropisomers in DMF, chloroform, benzene, and ethanol. The wavelength and the extinction coefficient of the absorption maxima are different among the isomers. All the absorption bands in the $\alpha\alpha\alpha\alpha$-isomer are most blue-shifted whereas those in the $\alpha\beta\alpha\beta$-isomer are most red-shifted. The order of blue shift is $\alpha\alpha\alpha\alpha > \alpha\alpha\beta\beta \simeq \alpha\alpha\alpha\beta > \alpha\beta\alpha\beta$. Furthermore, the relative intensity of bands I—IV (Falk's notation[4]) of the $\alpha\beta\alpha\beta$-isomer in DMF is of etio-type (IV > III > II > I), while that of the $\alpha\alpha\beta\beta$-, $\alpha\alpha\alpha\beta$-, and $\alpha\alpha\alpha\alpha$-isomers is better considered as being of phyllo-type (IV > II > III > I).[4] Although all the isomers show phyllo-type spectra in chloroform, benzene, and ethanol, the phyllo-type tendency, which is defined in terms of the ratio of the intensity of band II to that of band III, is largest in the $\alpha\alpha\alpha\alpha$-isomer and smallest in the $\alpha\beta\alpha\beta$-isomer (1.39 for $\alpha\alpha\alpha\alpha$ and 1.03 for $\alpha\beta\alpha\beta$ in chloroform). Since the observed absorption bands are due to $\pi \rightarrow \pi^*$ transition of the porphyrin ring,[4] the perturbation of the π electron level caused by the pivalamido groups differs among the isomers. The $\alpha\alpha\alpha\alpha$-isomers has the largest energy gap between the ground and the excited states.

Table II shows NMR chemical shift data for the atropisomers of ToPivPP in chloroform-d_1 ($CDCl_3$). Each signal was identified as shown in the table based upon comparisons of signal intensity, the use of the D_2O addition method to identify the exchangeable protons, and the decoupling technique. The chemical shifts of the methyl protons of pivalamido groups are distinguishable among the isomers. As is predictable from the symmetry of the $\alpha\alpha\alpha\beta$-isomer,[1g] three peaks (2 : 1 : 1 in intensity) are observed for methyl protons of the pivalamido groups. The other three isomers each show a single peak for the methyl protons, as is also predictable from the symmetry of the molecules.[1g] Figure 2 shows the methyl signals of a mixture of the

TABLE II. NMR Chemical Shifts for ToPivPP Atropisomers in $CDCl_3$[a]

	$\alpha\beta\alpha\beta$	$\alpha\alpha\beta\beta$	$\alpha\alpha\alpha\beta$	$\alpha\alpha\alpha\alpha$
β-Pyrrole	8.79	8.80	8.76	8.78
Phenyl *ortho*	8.69	8.75	—[b]	8.73
	8.61	8.66	8.64	8.64
meta	7.91	7.91	7.88	7.89
	7.83	7.83	7.80	7.81
	7.74	7.75	7.72	7.74
para	7.55	7.55	7.51	7.52
	7.48	7.46	7.44	7.45
	7.43	7.40	7.36	7.38
Amido NH	7.16	7.12	7.28	7.16
			7.16	
			7.00	
CH_3	0.23	0.13	0.20[c]	0.06
			0.14[c]	
			0.09[c]	
Ring NH	−2.54	−2.59	−2.59	−2.58

a) ppm from TMS.
b) Overlap with pyrrole signal.
c) The intensity ratio is 2 : 1 : 1.

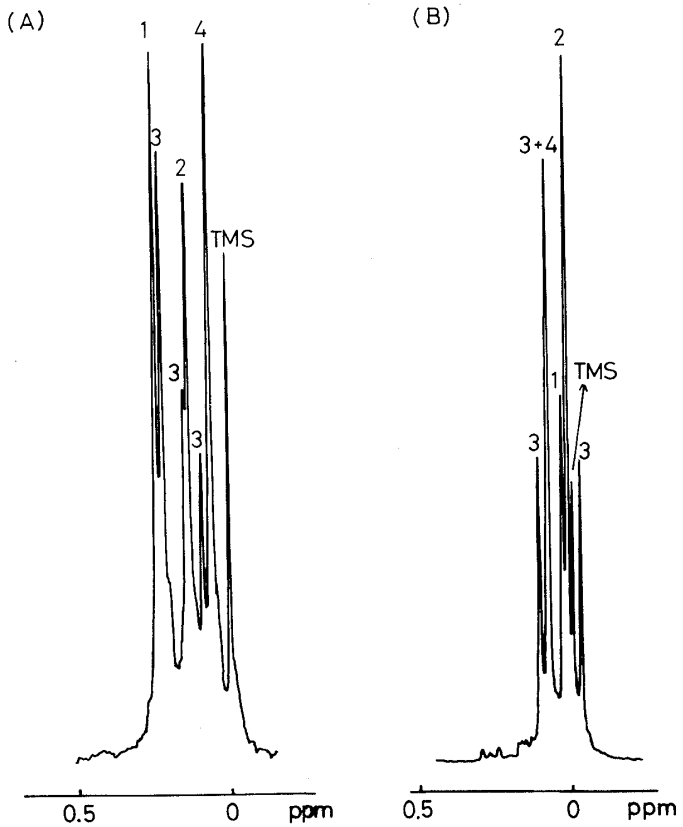

Fig. 2. NMR Spectra in the Methyl Proton Region for the Mixture of ToPivPP Atropisomers in $CDCl_3$ (A) and Toluene-d_8 (B)

1, $\alpha\beta\alpha\beta$; 2, $\alpha\alpha\beta\beta$; 3, $\alpha\alpha\alpha\beta$; 4, $\alpha\alpha\alpha\alpha$.

four atropisomers in $CDCl_3$ and toluene-d_8. Each signal is readily assigned based upon the chemical shifts from tetramethylsilane (TMS) for individual isomers. They are well separated in chloroform, while in toluene the peak of $\alpha\alpha\alpha\alpha$ overlaps with one of the three peaks of $\alpha\alpha\alpha\beta$.

TABLE III. Reduction Potentials of ToPivPP Atropisomers in DMF[a)]

	$E_{1/2}$ (1)	$E_{1/2}$ (2)	$\Delta E_{1/2}$
$\alpha\beta\alpha\beta$	−1.03 V	−1.40 V	0.37 V
$\alpha\alpha\beta\beta$	−0.98	−1.37	0.39
$\alpha\alpha\alpha\beta$	−0.99	−1.37	0.38
$\alpha\alpha\alpha\alpha$	−0.96	−1.34	0.38
TPP	−1.14	−1.53	0.39

a) *vs.* Ag/AgCl in 1 N LiCl gel.

The signal of β-pyrrole protons is split by about 0.07 ppm (equal intensity) for $\alpha\alpha\beta\beta$ and $\alpha\alpha\alpha\beta$ in toluene, while no splitting is observed for $\alpha\beta\alpha\beta$ and $\alpha\alpha\alpha\alpha$ in toluene or for any isomer in chloroform (data not shown). The splitting arises from the existence of two different magnetic environments for β-pyrrole protons in $\alpha\alpha\beta\beta$ and $\alpha\alpha\alpha\beta$ in toluene, as is easily understood by a consideration of the symmetry of the molecules. Similar splitting of β-pyrrole proton signals due to non-equivalence has been reported for the atropisomers of *meso*-tetra(2-methoxy-1-naphthyl)porphyrin.[1g)] The effect of different magnetic environments around β-pyrrole protons may be diminished in chloroform.

Table III shows the electrochemical reduction potentials of the isomers in DMF. The reduction potential of TPP was measured as a reference. Both the first and the second reduction potentials are lowest in $\alpha\beta\alpha\beta$ (−1.03 and −1.40 V) and highest in $\alpha\alpha\alpha\alpha$ (−0.96 and −1.34 V). The order of the reduction potential is $\alpha\alpha\alpha\alpha > \alpha\alpha\beta\beta \simeq \alpha\alpha\alpha\beta > \alpha\beta\alpha\beta$. This is the same order as the blue shift or phyllo-type tendency observed in the visible spectra. Thus, we can say that the $\alpha\alpha\alpha\alpha$-isomer is most reducible and most blue-shifted, while the $\alpha\beta\alpha\beta$-isomer is the least so. When the reduction potentials of TPP and the $\alpha\alpha\alpha\alpha$-isomer obtained here are compared with reported values,[5)] the values of this study are about 0.42 V higher than the reported ones. The difference can be attributed to the difference in the reference electrode; Ag/AgCl in this study and $Ag/AgNO_3$ in the previous reports.[5)]

Visible, IR, and NMR spectra were also measured for $ToNH_2PP$ atropisomers (data not shown), and no difference was observed in the spectra of $ToNH_2PP$ atropisomers. Among ToCNPP atropisomers, a distinct but very small difference (< 1 nm) in visible spectra has been observed between the $\alpha\beta\alpha\beta$ and $\alpha\alpha\alpha\alpha$ isomers.[6)] In ToPivPP, we have found distinct differences among the isomers in visible spectra, NMR spectra, and reduction potentials. Although there are reports of chemical shift differences due to atropisomerization in *meso*-tetra(*o*-methylphenyl)porphinatonickel(II),[1b] *meso*-tetra(*o*-methoxyphenyl)porphyrin,[1d)] and *meso*-tetra(2-methoxy-1-naphthyl)porphyrin,[1g)] no special difference among the atropisomers has been observed in the visible absorption spectra. If the pivalamido groups at the *ortho* position were independent or if no interaction existed between the groups within the time scale of the experiments, there would be no difference in visible spectra or reduction potentials among the isomers of ToPivPP, as in the case of $ToNH_2PP$. The finding that the visible spectra and the reduction potentials differ among the isomers indicates that the difference is caused not by the intrinsic nature of individual pivalamido groups but by the mutual interactions among the groups. In other words, gathering of the four pivalamido groups on the same side of the porphyrin plane causes the $\alpha\alpha\alpha\alpha$-isomer to show a blue shift in the visible spectrum and an increase of the reduction potential (in the direction of zero).

Two kinds of interaction can be considered among the pivalamido groups of ToPivPP; the interaction between adjacent groups at the same side of the porphyrin plane (*cis*-interaction) and that between opposite groups at the same side of the porphyrin plane (*trans*-interaction). There are 4 *cis*- and 2 *trans*-interactions in $\alpha\alpha\alpha\alpha$, 2 *cis*-interactions in $\alpha\alpha\beta\beta$, 2 *cis*-

and 1 *trans*-interactions in $\alpha\alpha\alpha\beta$, and only 2 *trans*-interactions in $\alpha\beta\alpha\beta$. The observed order of the blue shift, phyllo-type tendency, or reduction potentials is $\alpha\alpha\alpha\alpha > \alpha\alpha\beta\beta \simeq \alpha\alpha\alpha\beta > \alpha\beta\alpha\beta$. This suggests that *cis*-interaction is responsible for the effects on the visible spectra and the reduction potentials. However, systematic ordering among the isomers is lacking in the chemical shift of β-pyrrole protons or central NH protons on the porphyrin plane. The chemical shifts appear to be affected much more by the solvent than by the conformation of the isomers. However, both the visible spectra and the reduction potentials correlate with the excited electronic state, while the NMR signals reflect predominantly the ground electronic state, and this may account for the lack of a simple correlation between the NMR spectra and the visible spectra or the reduction potentials. Although a theoretical explanation is difficult at this stage, interactions among the pivalamido groups must be responsible for the observed effects. Since the difference in the visible spectra and the chemical shift in the NMR spectra depend on the solvent, interactions among the substituent groups through the solvent are also very important.

In a visible spectral study of the effect of axial ligation to ZnTPP, Nappa and Valentine[7] showed that the red shift of the spectrum derives from the amount of negative charge transferred from the ligand to the porphyrin ring *via* the zinc atom. It has been pointed out by Kim *et al.*[8] that when there is an electron-withdrawing substituent in the *ortho* position of TPP derivatives the extinction coefficients at bands I and III are diminished. This means that an electron-withdrawing substituent increases the phyllo-type tendency in the visible spectrum. These reports imply that visible spectral changes are correlated to the electron density change in the porphyrin ring, especially in the excited electronic state. Similarly, the blue shift and phyllo-type tendency in the $\alpha\alpha\alpha\alpha$-isomer of ToPivPP may be related to the electron density in the porphyrin ring. The results of the reduction potential experiments also suggest differences in the electron density in the porphyrin ring among the isomers.

This is the first report that shows distinct difference in physicochemical properties among atropisomers. The fact that subtle difference in the stereochemical structure of the porphyrin periphery changes the nature of the porphyrin-ring is interesting in relation to the role of the protein moiety in hemoproteins.

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