Molecular Asymmetry of an *N*-Alkylporphyrin with Enantiotopic Faces. Resolution and Spectroscopic Characterizations of Optical Antipodes of *N*-Methyletioporphyrin I

Hideo Kubo,[a] Takuzo Aida,[a] Shohei Inoue,*[a] and Yoshio Okamoto[b]

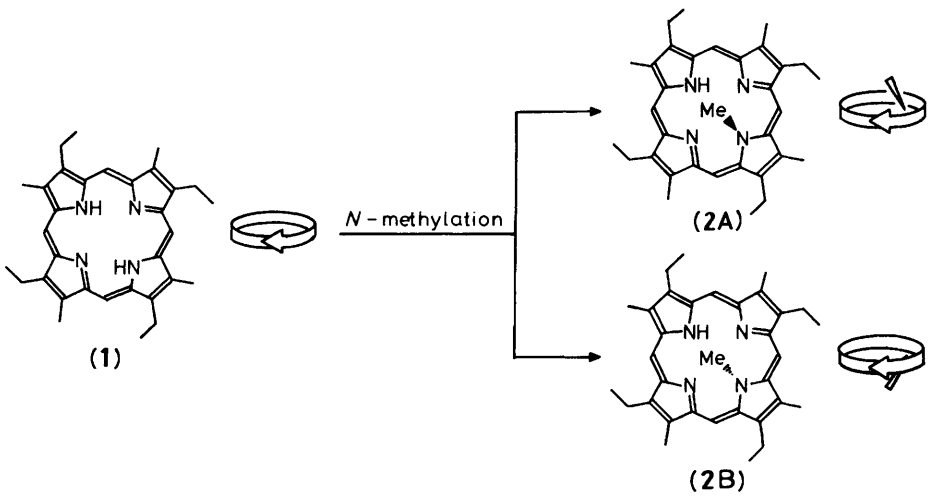
[a] *Department of Synthetic Chemistry, Faculty of Engineering, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan*

[b] *Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan*

The optical antipodes of *N*-methyletioporphyrin I were resolved and characterized as the zinc complex with a chiral axial ligand by n.m.r. spectroscopy.

The prosthetic heme group has a fundamental structure with enantiotopic faces where the front and back views are not superimposable but are mirror images with respect to each other, and thus it has no inherent optical activity. In the active centre of hemoprotein, the heme group has been indicated to adopt a chiral orientation owing to enantiotopic face recognition by the asymmetric protein cavity.[1] Recently, *N*-alkylated protoporphyrin IX isolated from the hemoenzyme inactivation process was claimed to be optically active based on its circular dichroism profile, and the metabolic oxidation process was concluded to take place exclusively on one of the two enantiotopic faces of the heme group owing to its chiral orientation in the protein.[2] We now report the first successful resolution of the optical antipodes of *N*-methyletioporphyrin I (**2**) and their characterization by circular dichroism and n.m.r. spectroscopy.

Etioporphyrin I ($EtioPH_2$) (**1**)[3] has D_{4h} symmetry owing to the alternating arrangement of two different substituents along the periphery of the porphyrin plane. Thus, *N*-methyletioporphyrin I (NMEtioPH) (**2**) has an inherent asymmetry associated with the direction of the *N*-methyl group with respect to the enantiotopic porphyrin plane (Scheme 1). H.p.l.c.[4] of NMEtioPH, prepared by the reaction of $EtioPH_2$ with methyl iodide,[5] showed two well resolved elution peaks



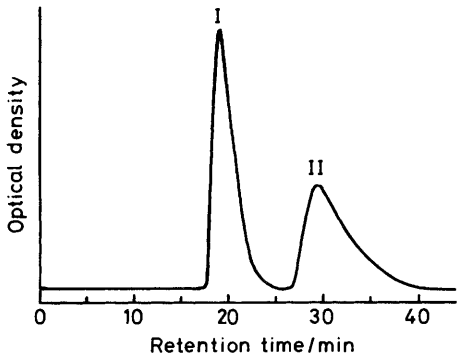


Figure 1. H.p.l.c. of *N*-methyletioporphyrin I (NMEtioPH) (**2**) on a silica gel column coated with cellulose tris(3,5-dimethylphenylcarbamate), eluant; n-hexane/propan-2-ol/diethylamine, 90:10:0.1 v/v; flow rate, 9.9 cm^3 min^{-1}, monitored at 254 nm.

with comparable peak areas, as monitored by the absorbance at 254 nm (Figure 1). The compounds corresponding to peaks I and II were fractionated, and confirmed to be identical to the original NMEtioPH by u.v.–visible, ^1H n.m.r., and fast atom bombardment mass spectrometry. On the other hand, these two compounds exhibited c.d. spectra which are perfect mirror images of each other (Figure 2). Thus, the optical antipodes of NMEtioPH (**2A**) and (**2B**), which arise from two possible directions of *N*-methylation with respect to the enantiotopic $EtioPH_2$ plane, were successfully resolved.

NMEtioPH can be converted into the zinc carboxylate complex by reaction with dialkylzinc ($ZnEt_2$)[6] followed by a carboxylic acid (RCO_2H) in benzene at room temperature in the dark [reactions (1) and (2)].

$$\text{NMEtioPH} + ZnEt_2 \longrightarrow (\text{NMEtioP})ZnEt + EtH \quad (1)$$

$$(\text{NMEtioP})ZnEt + RCO_2H \longrightarrow (\text{NMEtioP})ZnO_2CR + EtH \quad (2)$$

When a carboxylic acid bearing an asymmetric element in the R group is used, the resulting (NMEtioP)*ZnO_2CR* should be diastereoisomeric owing to the presence of two chiral elements in the molecule. In the 400 MHz ^1H n.m.r. spectrum in C_6D_6 of racemic (NMEtioP)*ZnEt treated with L-2-methoxypropionic acid [L-Me(MeO)C*HCO_2H] at 22 °C, two sets of signals with comparable intensities were observed, respectively, for the resonances of the axial carboxylate group [Me: δ −0.279 and −0.257 (d); MeO: δ 1.905 and 1.901 (s)] and the porphyrin moiety [N–Me: δ −4.490 and −4.498 (s)] due to the formation of a mixture of two diastereoisomeric complexes. On the other hand, when optically pure NMEtioPH fractionated by the process in Figure 1 was used for the same reaction, only one of the above two sets of signals appeared in each case because of the formation of a single diastereoisomer. Based on the chemical shift data, the former set is due to the complex carrying NMEtioPH antipode I and the latter set the complex carrying NMEtioPH antipode II. Unlike $EtioPH_2$, tetraphenylporphyrin has no enantiotopic face because of the presence of uniform peripheral substitution, and the zinc L-2-methoxypropionate complex of *N*-methyltetraphenylporphyrin, accordingly, exhibited no diastereoisomeric signal splitting [Me: δ −0.120 (d), MeO: δ 2.064 (s), N–Me: δ 3.919 (s) in C_6D_6 at 22 °C]. Thus, the inherent chirality of NMEtioPH was demonstrated by n.m.r. spectroscopy for the zinc complex upon diastereoisomeric axial ligation.

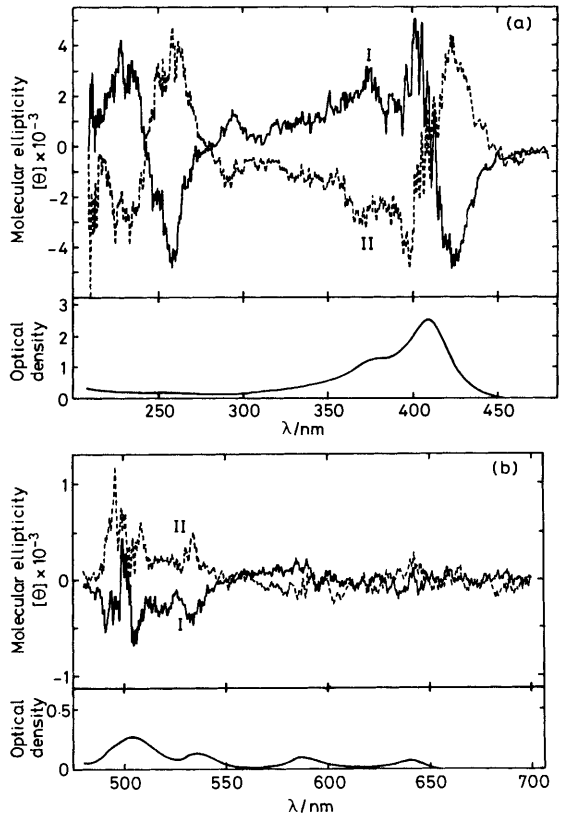


Figure 2. C.d. and u.v.–visible spectral profiles of the optically resolved antipodes of NMEtioPH (**2**) in n-hexane/propan-2-ol/diethylamine (90:10:0.1 v/v). I and II correspond to the antipodes I and II in Figure 1, respectively. C.d. spectra were recorded on a JASCO-J600 spectrometer accumulated 5 times, using cells of 1 cm and 10 cm path lengths for (a) and (b), respectively.

$EtioPH_2$ itself is devoid of any inherent asymmetry, but the metal complex is asymmetric when unsymmetrical axial ligation with respect to the enantiotopic porphyrin disk is present. A typical example is a metal complex with a trivalent metal, in which the axial ligand is bonded to the metal centre from one side, and the other side is vacant. Thus, the introduction of another element of chirality as the axial ligand makes the complex diastereoisomeric, as for the chiral zinc complex of NMEtioPH. For example, the ^1H n.m.r. spectrum of the aluminium methyl complex of $EtioPH_2$ [(EtioP)Al*Me] following reaction with the chiral carboxylic acid L-2-methoxypropionic acid clearly showed two sets of diastereoisomerically split signals for the product (EtioP)Al*O_2CC*H(OMe)Me [reaction (3)][7] [for the axial group, Me: δ −1.513 and −1.530 (d), MeO: δ 1.446 and 1.431 (s), CH; δ −0.614 and −0.742 (q) in $CDCl_3$ at 22 °C]. A similar diastereoisomeric signal splitting was observed for the aluminium alkoxide complex (EtioP)Al*OC*H(Me)CO_2Me, prepared by the reaction of the methoxy complex (EtioP)Al*OMe with methyl L-lactate [reaction (4)][8] [for the axial group, Me: δ −1.889 and −1.915 (d), O_2CMe: δ 2.424 and 2.413 (s), CH: δ −2.365 and −2.451 (q) in $CDCl_3$ at 22 °C]. On the other hand, neither the corresponding alumi-

$$(\text{EtioP})Al^*Me + Me(MeO)C^*HCO_2H \longrightarrow (\text{EtioP})Al^*O_2CC^*H(OMe)Me + MeH \quad (3)$$

$$(\text{EtioP})Al^*OMe + MeO_2C(Me)C^*HOH \longrightarrow (\text{EtioP})Al^*OC^*H(Me)CO_2Me + MeOH \quad (4)$$

nium carboxylate nor alkoxide complexes of tetraphenylporphyrin showed diastereoisomeric signal splitting, because of the absence of any inherent chirality at the aluminium porphyrin.

Thus, N-substitution and trivalent metal insertion provide the EtioPH$_2$ molecule with chirality originating from its enantiotopic faces. The inherent chirality and optical activity of naturally occurring compounds are of general interest in view of the importance of regio- and/or stereo-specificity of biological processes. Thus, the above finding is of fundamental significance for elucidating the biological functions of specifically oriented or organized metalloporphyrins in living systems.

H. K. is on leave from Nippon Soda Co., Ltd., Tokyo, Japan.

Received, 21st March 1988; Com. 8/01133H

References

1 Y. P. Myer and A. Pande, in 'The Porphyrins,' ed. D. Dolphin. Academic. New York and London, 1978, vol. 3, p. 271.
2 P. R. Ortiz de Montellano, K. L. Kunze, and H. S. Beilan, *J. Biol. Chem.*, 1983, **258**, 45. K. L. Kunze, B. L. K. Mangold, C. Wheeler, H. S. Beilan, and P. R. Ortiz de Montellano, *ibid.*, 1983, **258**, 4202.
3 C. H. Barnett and K. M. Smith, in 'Porphyrins and Metalloporphyrins,' ed. K. M. Smith, Elsevier, New York, 1975, p. 765.
4 Y. Okamoto, M. Kawashima, and K. Hatada, *J. Chromatogr.*, 1986, **363**, 173.
5 J. A. S. Cavaleiro, M. F. P. N. Condesso, A. H. Jackson, M. G. P. M. S. Neves, K. R. N. Rao, and B. K. Sadashiva, *Tetrahedron Lett.*, 1984, **25**, 6047.
6 S. Inoue, M. Nukui, and F. Kojima, *Chem. Lett.*, 1984, 619.
7 T. Aida and S. Inoue, *J. Am. Chem. Soc.*, 1985, **107**, 1358.
8 S. Asano, T. Aida, and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1985, 1148. T. Aida, Y. Maekawa, S. Asano, and S. Inoue, *Macromolecules*, in the press.