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Regio- and stereoselective reduction of intramolecular *N*-strapped porphyrins to phlorins

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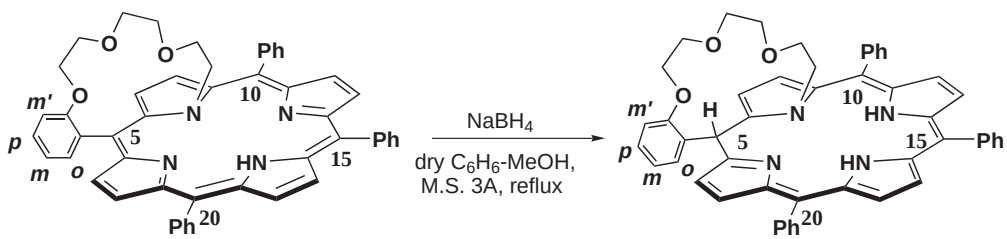
Abstract—Intramolecular *N*-strapped porphyrins were successfully reduced to *N*-alkyl phlorins regio- and stereoselectively.

We report herein the first regio- and stereoselective reduction of *N*-alkyl porphyrins to phlorins. We have recently reported new *N*-alkyl porphyrin derivatives[1] with an intramolecular loop with the aim of inducing the molecular distortion.

Dihydroporphyrins,[2] well-known nonaromatic isomers of porphyrins, have been investigated in the relation to the redox chemistry of porphyrin macrocycles by a few groups.[3] The isolation of dihydroporphyrins was demonstrated by the introduction of sterically hindered substituents at the porphyrin periphery, as well as by strongly electrophilic metal complexes. The recent advance in dihydroporphyrins has had a major impact on understanding of the structure–reactivity relationship of distorted porphyrins in terms of not only *N*,*N*-etheno bridged porphyrins reported by Setsune[4] but also a simple *N*-phenyl porphyrin reported by Callot.[5] The former porphyrin ring possesses a fixed structure with distortion, while the latter has a flexible structure. These compounds react with nucleophilic reagents at both *meso*-positions adjacent to the *N*-alkylated pyrrole.

We have previously synthesized the intramolecular *N*-strapped porphyrins **1**.[1] We have carried out the nucleophilic addition of H^- to the intramolecular *N*-strapped porphyrins (a set of enantiomers) by the following procedure (Scheme 1).

Dry benzene–methanol (18 ml : 2 ml) was successively added to a flask charged with **1** (38.0 mg, 0.051 mmol), $NaBH_4$ (96.5 mg, 2.55 mmol), and 3 A MS (ca. 1 g)† under argon. The reaction mixture was stirred at 60°C for 2 h. The color of the reaction mixture changed from green to blue. Column chromatographic purification on



1 **2**

Scheme 1. Synthetic method of **2**.

Keywords: porphyrins; strained compounds; regiospecificity; stereospecificity.

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† This reaction was very sensitive to moisture. Addition of 3 A MS is needed to reproduce the reduction of **1**.

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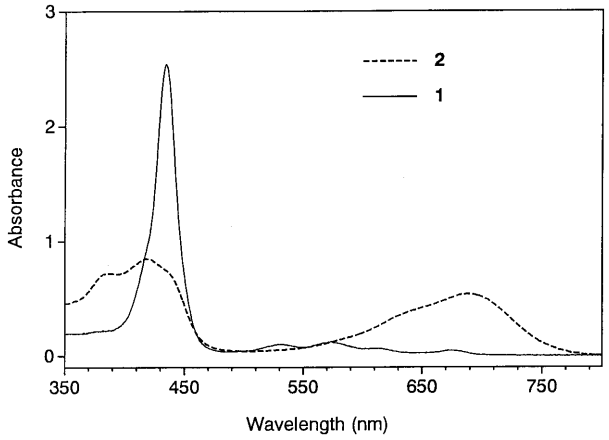

Figure 1. UV–vis spectra in $CHCl_3$ comparing **1** and **2**.

silica gel gave compound **2** in 61% yield. Surprisingly, **2** has proved to be quite stable in exposure to air. Fig. 1 shows that the Soret band characteristic of porphyrin has disappeared and broad bands appeared in the UV–vis of **2**. It strongly suggests that this compound is free base derivative of the *N*-alkyl phlorin.

The ^{1}NMR spectrum of **2** (Fig. 2) demonstrates the presence of the *meso*-H signal at δ 5.95, as well as the disappearance of the ring current effects of the porphyrin macrocycle. Eight doublets ($J = 4.8$ Hz) at δ 7.20, 6.79, 6.77, 6.48, 6.46, 6.42, 6.12 and 6.09 were associated with the β-pyrrole protons. The signals at δ 8.16, 7.14, 6.98 and 7.28 are assigned to the *o*-, *m*-, *m′*- and *p*-protons on the 5-*meso*-phenyl group, respectively, by HH COSY measurement. The complex and

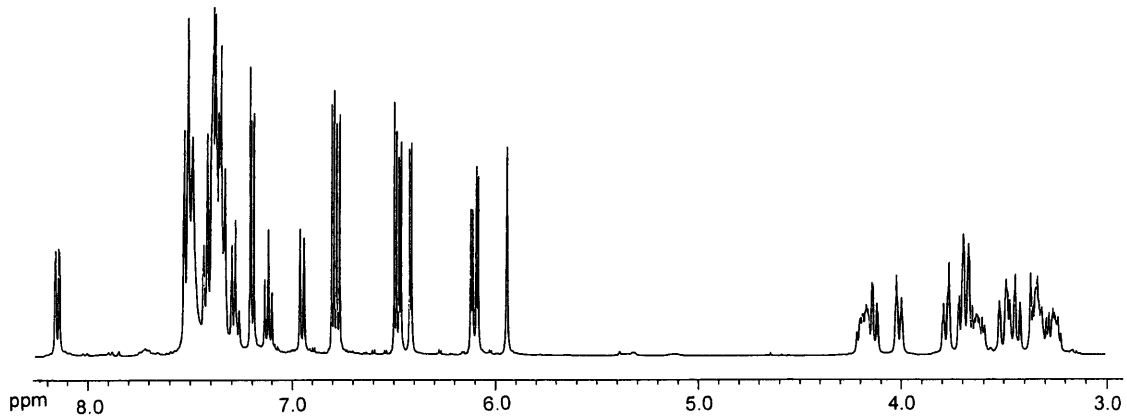

Figure 2. ^{1}H NMR spectrum of **2**.

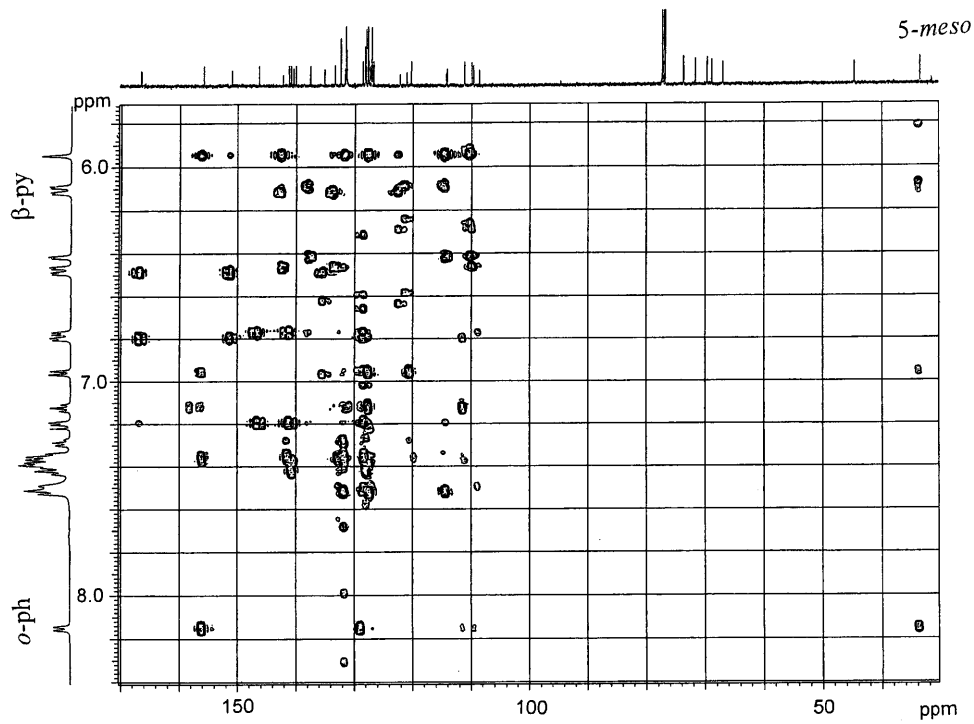

Figure 3. HMBC NMR spectrum of **2**.

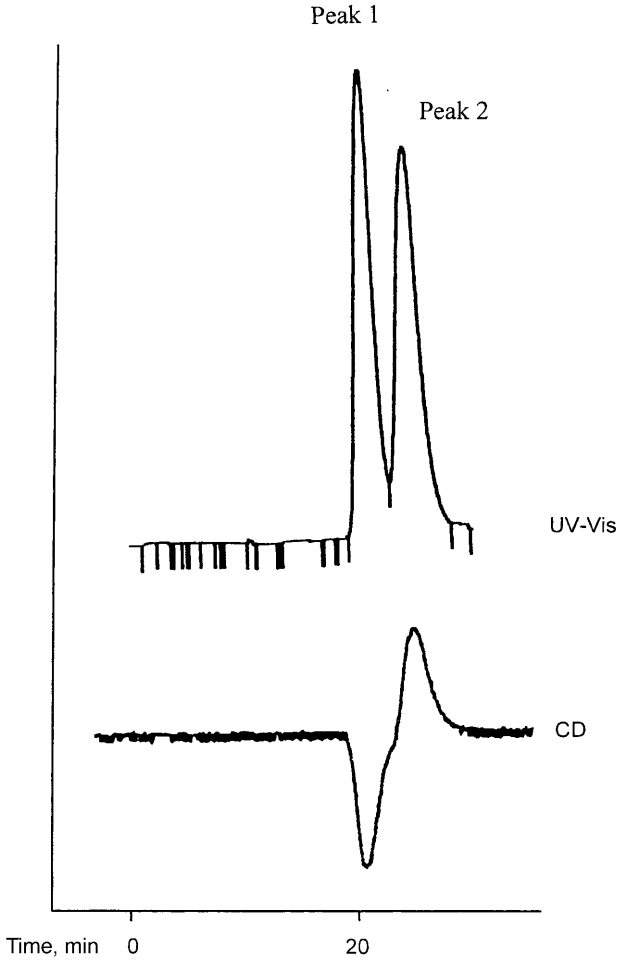

Figure 4. HPLC results of **2** by OD-H chiral column.

broad signals at δ 3.2–4.3 were fully assigned to the trioxyethylene protons by CH COSY NMR spectra.‡

We have confirmed which *meso*-carbon is reduced by HMBC spectra as Fig. 3 shows. The signals at δ 6.09 and δ 8.16 due to the β-proton of the *N*-alkylated pyrrole and the *o*-proton of the 5-*meso*-phenyl substituent, respectively, are correlated to that of the reduced *meso*-carbon (δ 33.5). The HMBC spectra provided support for the regioselective reduction of a *meso* carbon at the 5-position in this compound. The strain of this compound **1** plays an important role of this regioselectivity in comparison with that of the simple *N*-substituted porphyrin.[5]

‡ Selected data for **2**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20, 6.79, 6.77, 6.48, 6.46, 6.42, 6.12, 6.09 (8×d, 8×1H, β-Py), 8.16 (dd, 1H, *o*-Ph), 6.98 (dd, 1H, *m*-Ph), 7.14 (dt, 1H, *m*′-Ph), 7.28 (t, 1H, *p*-Ph), 7.4–7.6 (m, 9H, *o*-, *p*-Ph), 5.95 (s, 1H, *meso*-H), 4.11, 3.95 (2×m, 2×1H, 2″-CH_2), 3.70, 3.62 (2×m, 2×1H, 3″-CH_2), 3.62, 3.42 (2×m, 2×1H, 5″-CH_2), 3.48, 3.35 (2×m, 2×1H, 6″-CH_2), 4.17, 3.25 (2×m, 2×1H, 8″-CH_2), 3.60, 3.28 (2×m, 2×1H, 9″-CH_2-*N*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 131.4 (*o*′-Ph), 120.3 (*m*-Ph), 111.2 (*m*′-Ph), 33.5 (*meso*-C), 66.9 (2″-CH_2), 69.6 (3″-CH_2), 73.6 (5″-CH_2), 68.8 (6″-CH_2), 71.6 (8″-CH_2), 44.6 (9″-CH_2-*N*); UV–vis ($CHCl_3$) λ_{max} (log ε) 675 (3.68), 574 (4.09), 533 (4.01), 434 (5.41), 421 (5.62); MS (FAB): $C_{50}H_{42}N_4O_3$ *m*/*z*: 746 (M^+); anal. calcd for $C_{50}H_{42}N_4O_3H_2O$: C, 78.51; H, 5.80; N, 7.32; found: C, 78.56; H, 5.76; N, 7.03.

In contrast to the phlorin reported by Callot, the remarkable shifts of the *meso*-proton (about 1.6 ppm) downfield may be attributed to the deshielding effects due to the oxygen atoms. In addition, the correlation between the introduced proton and the oxyethylene ones in the NOESY spectrum of **2** suggests that the hydride anion attacks the porphyrin macrocycle only on the same side of the *N*-alkyl strap.

We have succeeded in detection of a set of enantiomers using HPLC with a chiral preparative column [CHIRALCEL OD-H; (Daisel)] eluted by *n*-hexane–propan-2-ol (7:3 v/v). HPLC data analyzed by a circular dichroism (CD) detector (JASCO CD-1595) are shown in Fig. 4. There are two peaks in the chromatogram with UV–vis detector at 256 nm and also each peak which is recorded by a CD detector at 400 nm is proved to be the enantiomers.

In conclusion, the hydride anion attacked regio- and stereoselectively only to one *meso*-position. Details of the structure and reactivity of **1** toward various nucleophiles are now underway.

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