Synthesis and characterization of intramolecular *N*-strapped porphyrins

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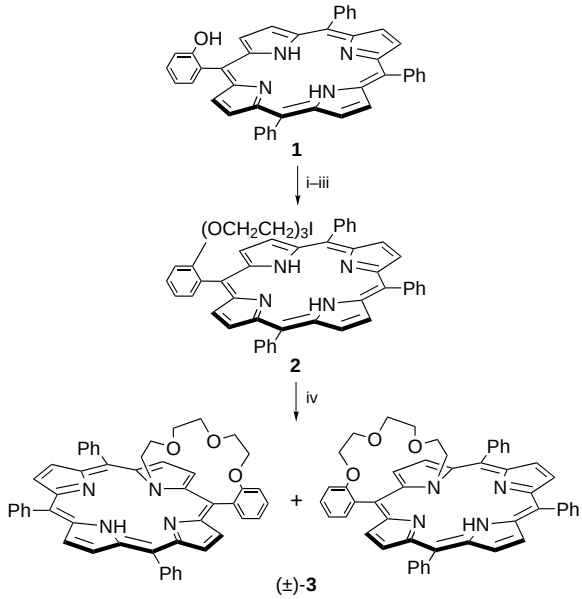
The first successful synthesis and characterization of intramolecular *N*-strapped porphyrins and the separation of a set of enantiomers are described.

The functionalization of porphyrin macrocycles has become of interest in the field of supramolecular and biomimetic chemistry. Moreover, current investigations of porphyrin chemistry have led to the construction of new structural motifs using porphyrin rings.[1,2] *N*-Alkylporphyrins have been synthesized as biologically important compounds, after having been found to be formed by the reaction of alkenes with the cytochrome P-450 in the liver of mice. The aim of the present investigation was to synthesize the *N*-alkylporphyrins with new structural properties. Accordingly, we decided upon the preparation of intramolecular *N*-strapped porphyrins, that is, with one nitrogen atom alkylated by a tris(3-oxapropylene) bridge the other end of which was joined at the 2-position of a *meso* phenyl group.

The proposed intramolecular *N*-alkylation introduced three structural motifs into the porphyrin ring. (i) The generation of an asymmetric nitrogen atom. (ii) The steric distortion of the porphyrin ring. (iii) The construction of a half crown ether type bridge. To the best of our knowledge, despite the development of various methods for the alkylation of inner nitrogen atom(s),[3] no practical synthetic methods have yet been proposed for intramolecular *N*-alkylation. Accordingly, we propose here the synthetic method shown in Scheme 1.

Compound **1** was synthesized by condensation of pyrrole, benzaldehyde and 2-hydroxybenzaldehyde in a 4 : 3 : 1 molar ratio according to the method of Little *et al.*[4] The alkyl halide, 5-[2′-(9″-iodo-1″,4″,7″-trioxanonyl)phenyl]-10,15,20-triphenylporphyrin **2** was synthesized from **1** in 73% overall yield.



Scheme 1 *Reagents and conditions*: i, NaOH, $I(CH_2CH_2O)_3THP$, dry DMSO, room temp., 12 h; ii, TsOH, MeOH–CH_2Cl_2, room temp., 12 h; iii, imidazole, I_2, PPh_3, benzene, room temp., 0.5 h; iv, $AgBF_4$, MeCN, reflux, 3 days

The detailed reaction conditions are shown in the caption to Scheme 1. The starting material **2** (0.3 mmol) and $AgBF_4$ (0.6 mmol) were stirred in refluxing dry MeCN (30 ml) for 3 days. After chromatographic purification, the desired product could be collected as a second purple band (R_f 0.2, chloroform–methanol, 97 : 3) in 50% yield. Compound **3** has a UV–VIS spectrum that is fairly typical of *N*-alkylporphyrin free base derivatives.†

The reaction of **2** with $AgBF_4$ gave carbonium ion intermediates formed by the precipitation of AgI. The resulting intermediates were readily attacked by the intramolecular pyrrolic nitrogen atom *in situ* to give the proposed compound.

Fig. 1 shows ^{1}H NMR spectrum of **3**. Extraordinarily up-field shifted signals at −4.08 and −4.31 ppm due to *N*-CH_2 protons and twelve multiplet signals due to the CH protons were evidence of the intramolecular conjugation of the tris(1-oxapropylene) bridge with asymmetric nitrogen atom. Signals at 8.78 (2 H), 8.67, 8.54, 8.47, 8.44, 7.61 and 7.52 ppm were assigned to the eight β-pyrrole protons on the basis of their peak intensity and coupling constants (J 4.5 Hz). In particular, the signals at 7.61 and 7.52 ppm were strictly assigned to the *N*-alkylated β-pyrrole protons as explained by Kuila *et al.*[5] Signals at 7.66, 7.40 and 7.25 ppm were assigned to the *o*′-, *m*- and *m*′-protons of the 5-phenyl group, respectively, by 2D COSY measurement. This evidence suggested that the porphyrin ring was restrictively distorted by the introduction of an intramolecular strap.

As a result of the introduction of an intramolecular strap, two sets of enantiomers were expected to be formed at the different possible *N*-alkylation positions. Thus, a detailed two-dimensional NMR study (HMBC method) was performed to confirm which nitrogen atom is alkylated. The signal at 122.24 ppm† is correlated with the signals at 7.61 ppm due to the *N*-alkylated β-pyrrole proton and 7.66 ppm due to the *o*′-phenyl proton of the 5-phenyl group. Thus, we concluded that either the N(21) or N(22) atom of the pyrroles, which are adjacent to the 5-phenyl

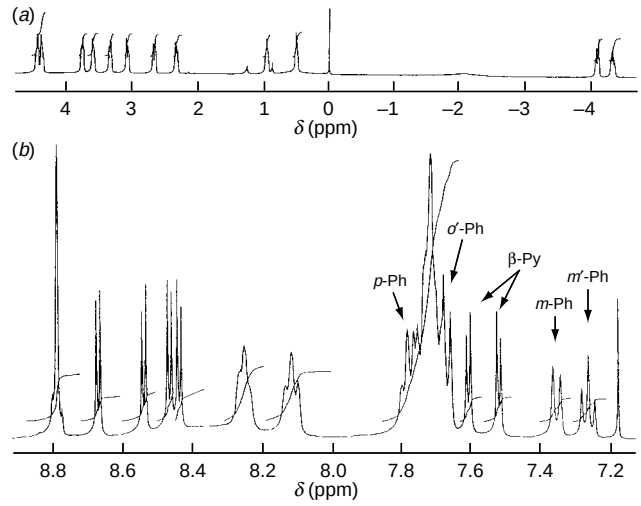


Fig. 1 Portions of the ^{1}H NMR spectrum of **3** in $CDCl_3$; (*a*) the tris(1-oxapropylene) region; (*b*) the aromatic region

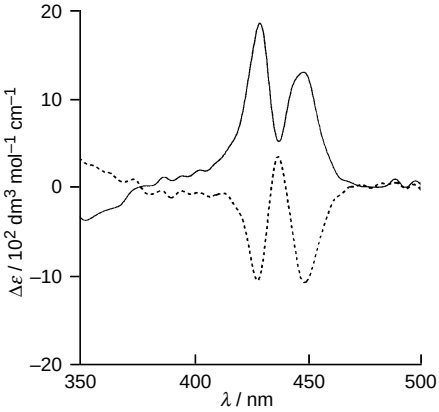


Fig. 2 CD spectra of (+)-**3** (—) and (−)-**3** (- - -) in $CHCl_3$

group attached to the tris(1-oxapropylene) side chain, were alkylated. The length of the tris(1-oxapropylene) side chain is especially well-suited for connecting the 5-phenyl group and the nitrogen atom of the adjacent pyrrole rings.

It is considered that compound **3** is a set of enantiomers with an asymmetric nitrogen atom. Consequently, separation of racemic compound **3** was attempted using chiral HPLC (CHIRALCEL OD; Daisel Co. Lt. in Japan) eluted by *n*-hexane–propan-2-ol (7 : 3). Two fractions each of 100% ee were obtained.

The separated enantiomers, (+)-**3** and (−)-**3**, show mirror-image circular dichroism spectra and a split Cotton effect in the Soret region as shown in Fig. 2.

In summary, a new type of *N*-alkylporphyrin has been synthesized and characterized. The present work provides a unique technique for controlling the distortion of porphyrinoid macrocycles through intramolecular *N*-strapping. *N*-Alkylation studies with chains of different lengths is now under way.

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Footnotes and References

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† *Selected data* for **3**: $\delta_H(CDCl_3)$ 8.78 (×2), 8.67, 8.54, 8.47, 8.44, 7.61, 7.52 (8 × d, 8 × 1 H, β-Py), 8.1–8.5 (3 × br, 3 × 2 H, *o*-Ph), 7.66 (d, 1 H, *o*′-Ph), 7.40 (d, 1 H, *m*-Ph), 7.25 (t, 1 H, *m*′-Ph), 7.7–7.8 (m, 10 H, *o*-, *p*-, *p*′-Ph), 4.36, 4.42 (2 × m, 2 × 1 H, 2″-CH_2), 3.73, 3.59 (2 × m, 2 × 1 H, 3″-CH_2), 3.31, 3.07 (2 × m, 2 × 1 H, 5″-CH_2), 2.67, 2.33 (2 × m, 2 × 1 H, 6″-CH_2), 0.96, 0.51 (2 × m, 2 × 1 H, 8″-CH_2), −4.08, −4.31 (2 × m, 2 × 1 H, 9″-CH_2), −2.11 (br, 1 H, NH); $\delta_C(CDCl_3)$ 126.11, 122.24, 119.54, 118.95 (*meso*-C). These signals were assigned to the four *meso* carbons on the basis of peak intensity and in comparison with the results of previous work (ref. 6). $\lambda_{max}(CHCl_3)$ (log ε) 675 (3.68), 574 (4.09), 533 (4.01), 434 (5.41), 421 (5.62); *m*/*z* (FAB) 744 (M^+, $C_{50}H_{40}N_4O_3$) (Calc. for $C_{50}H_{40}N_4O_3H_2O$: C, 78.72; H, 5.55; N, 7.34. Found: C, 78.42; H, 5.37; N, 7.26%).

1 For reviews, see J. L. Sessler, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1348; B. Franck and A. Nonn, *ibid.*, 1995, **34**, 1795; E. Vogel, *Pure Appl. Chem.*, 1996, **68**, 1355.

2 E. Vogel, M. Kocher, H. Schmickler and J. Lex, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 257; J. L. Sessler and A. K. Burrell, *Top. Curr. Chem.*, 1991, **161**, 177; H. Furuta, T. Asano and T. Ogawa, *J. Am. Chem. Soc.*, 1994, **116**, 767; P. J. Chmielewski, L. Latos-Grazynski, K. Rachlewicz and T. Glowiak, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 779; J. L. Sessler, *ibid.*, 1994, **33**, 1348; T. D. Lash, *ibid*., 1995, **34**, 2553; J. L. Sessler, S. W. Weghorn, Y. Hishaeda and V. Lynch, *Chem. Eur. J.*, 1995, **1**, 56; B. Franck and A. Nonn, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1795; T.. D. Lash and S. T. Chaney, *Chem. Eur. J.*, 1996, **2**, 944; T. D. Lash and M. J. Hayes, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 840; K. K. Dailey, G. P. A. Yap, A. L. Rheingold and T. B. Rauchfuss, *ibid.*, 1996, **35**, 1833.

3 D. K. Lavallee, *The Chemistry and Biochemistry of N-Substituted Porphyrins*, VCH, Weinheim, 1987 and references cited therein; H. J. Callot, R. Cromer, A. Louati, B. Mets and B. J. Chevrier, *J. Am. Chem. Soc.*, 1987, **109**, 2946; A. L. Balch, C. R. Cornman, L. Latos-Grazynski and M. M. Olstead, *ibid.*, 1990, **112**, 7552; K. Konishi, Y. Takahata, T. Aida and S. Inoue, *ibid.*, 1993, **115**, 1169; J.-i. Setsune and H. Takeda, *Tetrahedron Lett.*, 1995, **36**, 5903.

4 R. G. Little, J. A. Anton, P. A. Loach and J. A. Ibers, *J. Heterocycl. Chem.*, 1975, **12**, 343.

5 D. Kuila, D. K. Lavallee, C. K. Schauer and O. P. Anderson, *J. Am. Chem. Soc.*, 1984, **106**, 448.

6 H. Scheer and J. J. Katz, in *Porphyrin and Metalloporphyrins*, ed. K. M. Smith, Elsevier, Amsterdam, 1975, p. 487; D. K. Lavallee, I. Morgenstern-Badarau, M. Lange and P. Gans, *Inorg. Chem.*, 1979, **18**, 1776.

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