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Structure of Isomeric Ether-bonded Porphyrin–Chlorins

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The computation of credible spatial isomers has been performed in order to explain the difference in properties between the diastereoisomers of dimeric porphyrin–chlorin previously synthesized.

The photodynamic therapy of cancer[1,2] is a relatively new and actively developing method for the diagnosis and treatment of tumour. It is based on the tendency of certain dyes to accumulate selectively in tumour tissues. Subsequent illumination with light of a specific wavelength leads to stimulation of accumulated substance, a chain of photochemical transformations in the cell under investigation and as a result to tumour necrosis.

Recently, a dimer containing porphyrin and chlorin macrocycles (Fig. 1) was synthesized in our laboratory.[3] During the synthesis four optical isomers *RR′*, *SS′*, *RS′* and *SR′* can arise, thus giving two pairs of diastereoisomers. Silica

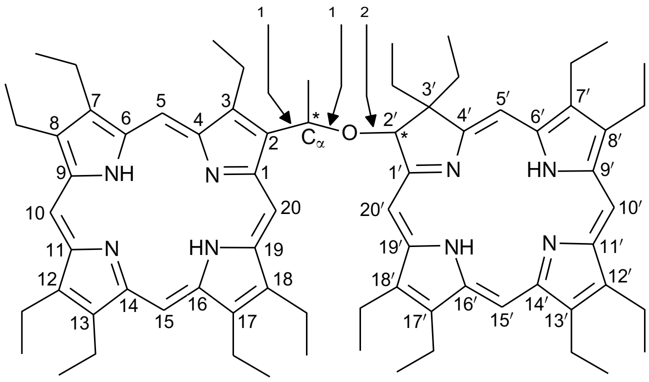
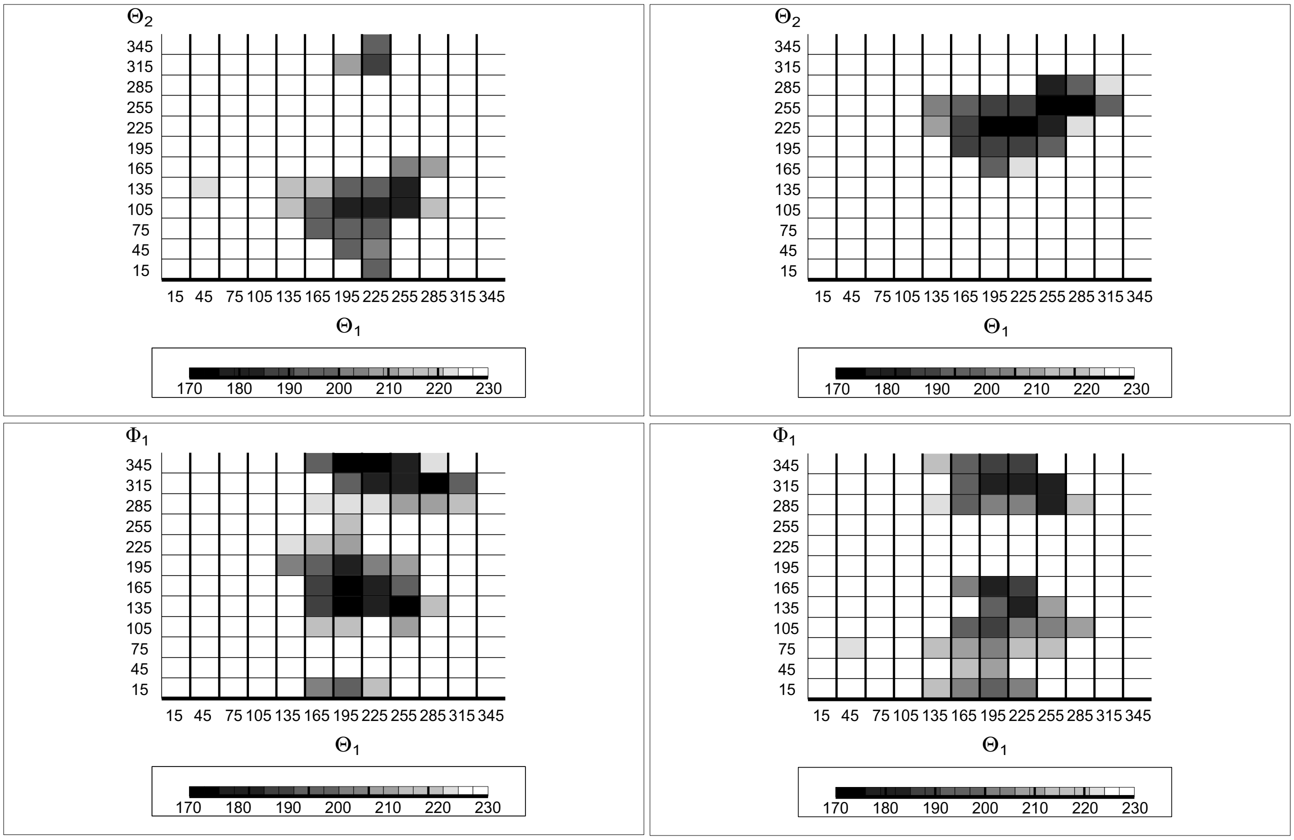


Fig. 1 Dimeric porphyrin–chlorin.



SR′ porphyrin–chlorin

SS′ porphyrin–chlorin

Fig. 2 Dependence of total energy (kcal mol^{-1}) upon the geometry of the molecule.

gel chromatography and crystallization from hexane gave two stable isomers,[†] the electronic absorption spectra of which represent superposition of chlorin and porphyrin spectra with λ_{max} 650 and 500 nm, respectively. The computation of credible spatial isomers was performed in this work in an attempt to explain the difference in properties between the diastereoisomers obtained.

Table 1

	SR′	*SS′*
Total energy/kcal mol^{-1}	172.84	182.09
μ/D (CNDO)	3.415	2.419
μ/D (INDO)	3.631	2.369
Θ$_1$/° C(2)–C$_\alpha$–O–C(2′)	229.4	213.2
Θ$_2$/° C(1′)–C(2′)–C$_\alpha$–O	0.6	150.1
Φ$_1$/° C(1)–C(2)–C$_\alpha$–O	105.9	225.5

Molecular mechanics calculations were performed on Autodesk™ HyperChem® using the MM+ routine with default force-field parameters. Due to the complexity of the molecules considered the following technique was used for searching the optimal geometry. Since the geometry of the molecule is determined by rotation around three bonds of the ether linkage, the values of the torsion angles marked as $_1$, $_2$ and $_1$ have maximum influence on the energy of the molecule. Thus, $12^3 = 1728$ points were calculated for each molecule,[‡] the torsion angles mentioned previously being varied from 15 to 345° in 30° steps. The data obtained showed that two areas of low energy exist (Fig. 2). The latter were examined more precisely in the same manner and the conformation with lowest energy was optimized using standard routine (block-diagonal Newton–Raphson optimization method, convergence limit 0.01 kcal Å^{-1}).

[†] *Characterization data:*

Low R_f diastereoisomer: m.p. 217–220 °C; *m*/*z* 1085 (M$^+$ + H); λ_{max}, nm [10^{-3} (ε/dm^3 mol^{-1} cm^{-1})]: 392 (220), 407 (230), 499 (26), 534 (12), 570 (8), 596 (5), 624 (8) and 644 (48); fluorescence λ_{ex} 410 nm, λ_{em} 648 nm; ^{1}H NMR δ_H (200 MHz, CDCl$_3$) 11.21 (s, H, *meso*-H), 10.29 (s, H, *meso*-H), 10.19, 10.17 (s, each 1H, *meso*-H), 9.70, 9.31, 8.88 and 8.46 (s, each 1H, *meso*-H), 7.03 (s, 1H at C-2′), 6.85 [q, H, OC*H*(CH$_3$)], 3.0–4.3 (m, 30H, C*H*$_2$CH$_3$), 2.80 [d, 3H, OCH(C*H*$_3$)], 0.7–2.3 (m, 42H, CH$_2$C*H*$_3$), −1.30 (t, 3H, CH$_2$C*H*$_3$), −2.69 (br.s, 1H, NH), −3.08 (br.s, 1H, NH), −3.45 (br.s, 2H, NH).

High R_f diastereoisomer: m.p. 267–268 °C; *m*/*z* 1086 (M$^+$ + 2H); λ_{max}, nm [10^{-3} (ε/dm^3 mol^{-1} cm^{-1})]: 403 (370), 498 (25), 534 (10), 570 (5), 595 (3), 624 (5), 643 (48); fluorescence λ_{ex} 400 nm, λ_{em} 640 nm; ^{1}H NMR δ_H (200 MHz, CDCl$_3$) 11.08 (s, H, *meso*-H), 10.17, 10.12, 10.08 (s, each 1H, *meso*-H), 9.78 (s, H, *meso*-H), 9.71, 9.70 (s, each 1H, *meso*-H) and 8.40 (s, H, *meso*-H), 7.01 (s, H at C-2′), 6.97 [q, H, OC*H*(CH$_3$)], 3.5–4.6 (m, 30H, C*H*$_2$CH$_3$), 2.95 [d, 3H, OCH(C*H*$_3$)], 1.2–2.1 (m, 39H, CH$_2$C*H*$_3$), 0.41 (t, 3H, CH$_2$C*H*$_3$), 0.20 (t, 3H, CH$_2$C*H*$_3$), −2.40 (br.s, 2H, NH), −3.64 (br.s, 2H, NH).

[‡] *SR′* and *SS′* isomers were taken into account.

SR′ porphyrin–chlorin *SS′* porphyrin–chlorin

Fig. 3 The geometry of porphyrin–chlorin molecules (hydrogen atoms not shown).

Dipole moments were computed using a single point CNDO and INDO calculation method with convergence limit 0.1.

The results obtained are summarized in Table 1.

As shown in Fig. 3, the *SR′* isomer has a 'folded' conformation, while the *SS′* isomer has an 'expanded' geometry. It is noticeable that the stacked isomer has no tendency to take an opened configuration and *vice versa*, as one may see in Fig. 2: there is a *single* area of low energy corresponding to Θ_1 and Θ_2 torsion angles and *two* areas on the Θ_1–Φ_1 diagram explained by a 180° rotation of the flat porphyrin macrocycle.

The experimental data obtained support the calculation results. During the synthesis of dimeric porphyrin–chlorin the formation of two pairs of diastereoisomers was observed, and they were separated *via* silica gel chromatography.[3] In accordance with computation results the molecule in the 'folded' conformation has a greater dipole moment and therefore less chromatographic mobility.

In the ^{1}H NMR spectrum of the low R_f isomer one of the porphyrin ethyl triplets is located in an unusually high magnetic field: δ −1.3 ppm. In the molecule of *SR′* isomer with a 'folded' conformation the methyl group of the ethyl substituent at C18 is disposed at 2.25 Å from the plane of the chlorin macrocycle, leading to an upfield shift due to shielding. Moreover, the experiments show that in the case of the low R_f isomer energy transfer from porphyrin to chlorin ring takes place owing to the steric proximity of the macrocycle centres.[4]

References

1 A. Mironov, A. Krasnovskii and E. Chernyaeva, *Itogi Nauki Tekh. Ser. Sovremennye problemy lazernoi fiziki*, VINITI, 1990, **3**, 224 (in Russian).

2 *Photosensitizing Compounds: Their Chemistry, Biology and Clinical Use*, Ciba Foundation Symposium 146, John Wiley & Sons, Chichester, 1989.

3 E. G. Levinson, A. N. Nizhnik and A. F. Mironov, *Mendeleev Commun.*, 1992, 95.

4 O. Lobanov, S. Arjantsev, E. Levinson and A. Mironov, *SPIE*, 1993, **2078**, 180.

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Cambridge, 5th April 1995; Com. 5/01747E