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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.

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The photodynamic therapy of cancer<sup>1,2</sup> 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 transfor-

mations 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.<sup>3</sup> During the synthesis four optical isomers *RR'*, *SS'*, *RS'* and *SR'* can arise, thus giving two pairs of diastereoisomers. Silica

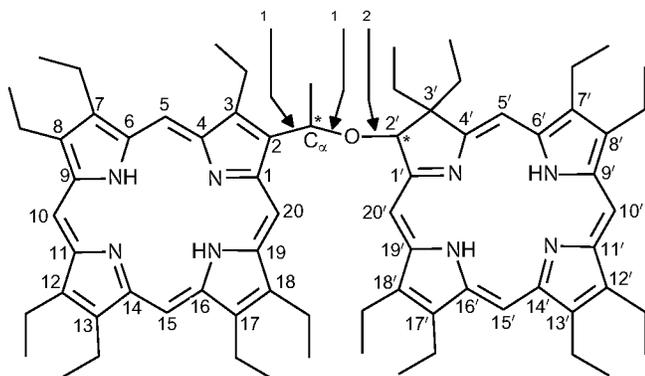


Fig. 1 Dimeric porphyrin-chlorin.

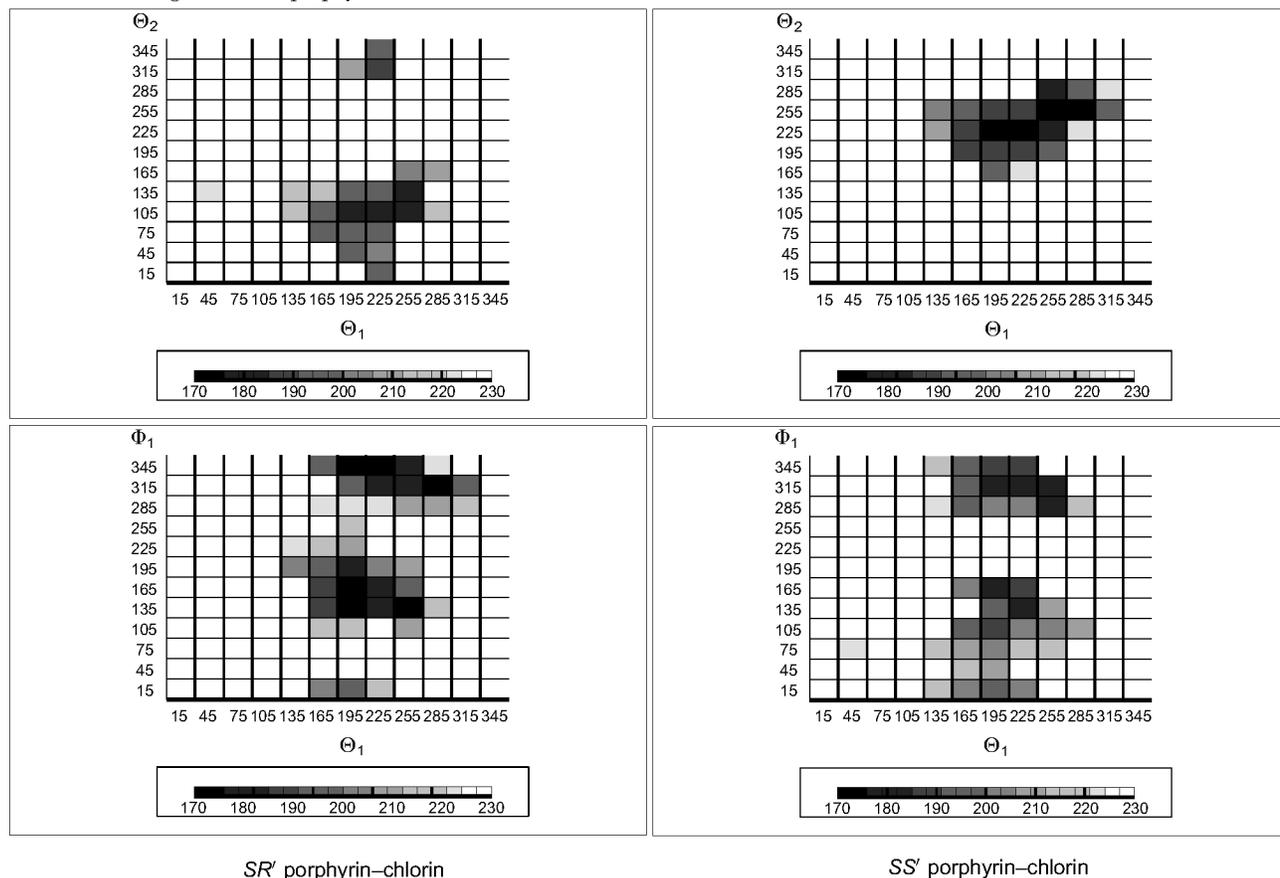


Fig. 2 Dependence of total energy (kcal mol<sup>-1</sup>) upon the geometry of the molecule.

gel chromatography and crystallization from hexane gave two stable isomers,<sup>†</sup> the electronic absorption spectra of which

<sup>†</sup> Characterization data:

Low *R<sub>f</sub>* diastereoisomer: m.p. 217–220 °C; *m/z* 1085 (M<sup>+</sup> + H); λ<sub>max</sub>, nm [10<sup>-3</sup> (ε/dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 392 (220), 407 (230), 499 (26), 534 (12), 570 (8), 596 (5), 624 (8) and 644 (48); fluorescence λ<sub>ex</sub> 410 nm, λ<sub>em</sub> 648 nm; <sup>1</sup>H NMR δ<sub>H</sub> (200 MHz, CDCl<sub>3</sub>) 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, OCH(CH<sub>3</sub>)], 3.0–4.3 (m, 30H, CH<sub>2</sub>CH<sub>3</sub>), 2.80 [d, 3H, OCH(CH<sub>3</sub>)], 0.7–2.3 (m, 42H, CH<sub>2</sub>CH<sub>3</sub>), -1.30 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), -2.69 (br.s, 1H, NH), -3.08 (br.s, 1H, NH), -3.45 (br.s, 2H, NH).

High *R<sub>f</sub>* diastereoisomer: m.p. 267–268 °C; *m/z* 1086 (M<sup>+</sup> + 2H); λ<sub>max</sub>, nm [10<sup>-3</sup> (ε/dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 403 (370), 498 (25), 534 (10), 570 (5), 595 (3), 624 (5), 643 (48); fluorescence λ<sub>ex</sub> 400 nm, λ<sub>em</sub> 640 nm; <sup>1</sup>H NMR δ<sub>H</sub> (200 MHz, CDCl<sub>3</sub>) 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, OCH(CH<sub>3</sub>)], 3.5–4.6 (m, 30H, CH<sub>2</sub>CH<sub>3</sub>), 2.95 [d, 3H, OCH(CH<sub>3</sub>)], 1.2–2.1 (m, 39H, CH<sub>2</sub>CH<sub>3</sub>), 0.41 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 0.20 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), -2.40 (br.s, 2H, NH), -3.64 (br.s, 2H, NH).

Table 1

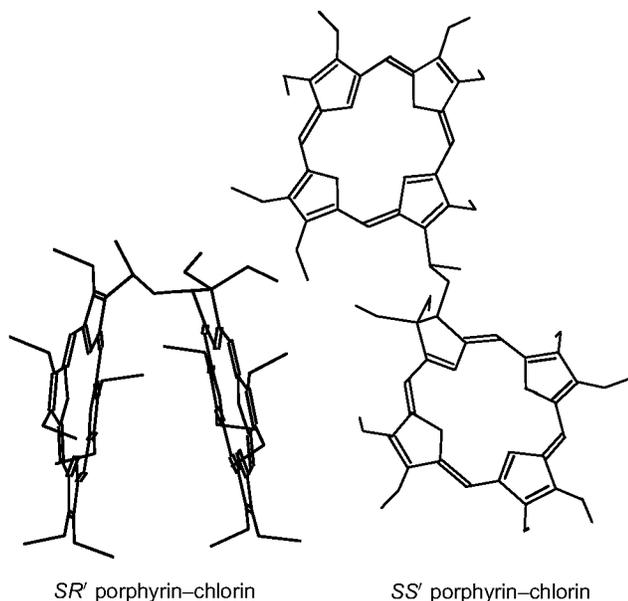
	SR'	SS'
Total energy/kcal mol <sup>-1</sup>	172.84	182.09
μ/D (CNDO)	3.415	2.419
μ/D (INDO)	3.631	2.369
Θ <sub>1</sub> /° C(2)–C <sub>α</sub> –O–C(2')	229.4	213.2
Θ <sub>2</sub> /° C(1')–C(2')–C <sub>α</sub> –O	0.6	150.1
Φ <sub>1</sub> /° C(1)–C(2)–C <sub>α</sub> –O	105.9	225.5

represent superposition of chlorin and porphyrin spectra with λ<sub>max</sub> 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.

Molecular mechanics calculations were performed on Autodesk<sup>TM</sup> HyperChem<sup>®</sup> 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 θ<sub>1</sub>, θ<sub>2</sub> and φ<sub>1</sub> have maximum influence on the energy of the molecule. Thus, 12<sup>3</sup> = 1728 points were calculated for each molecule,<sup>‡</sup> 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<sup>-1</sup>).

<sup>‡</sup> SR' and SS' isomers were taken into account.



**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  $\Theta_1$  and  $\Theta_2$  torsion angles and *two* areas on the  $\Theta_1$ – $\Phi_1$  diagram explained by a  $180^\circ$  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.<sup>3</sup> In accordance with computation results the molecule in the 'folded' conformation has a greater dipole moment and therefore less chromatographic mobility.

In the  $^1\text{H}$  NMR spectrum of the low  $R_f$  isomer one of the porphyrin ethyl triplets is located in an unusually high magnetic field:  $\delta -1.3$  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.<sup>4</sup>

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