PERKIN 1 COMMUNICATION

Synthesis of novel laterally-bridged pyropheophorbide *a* dimers

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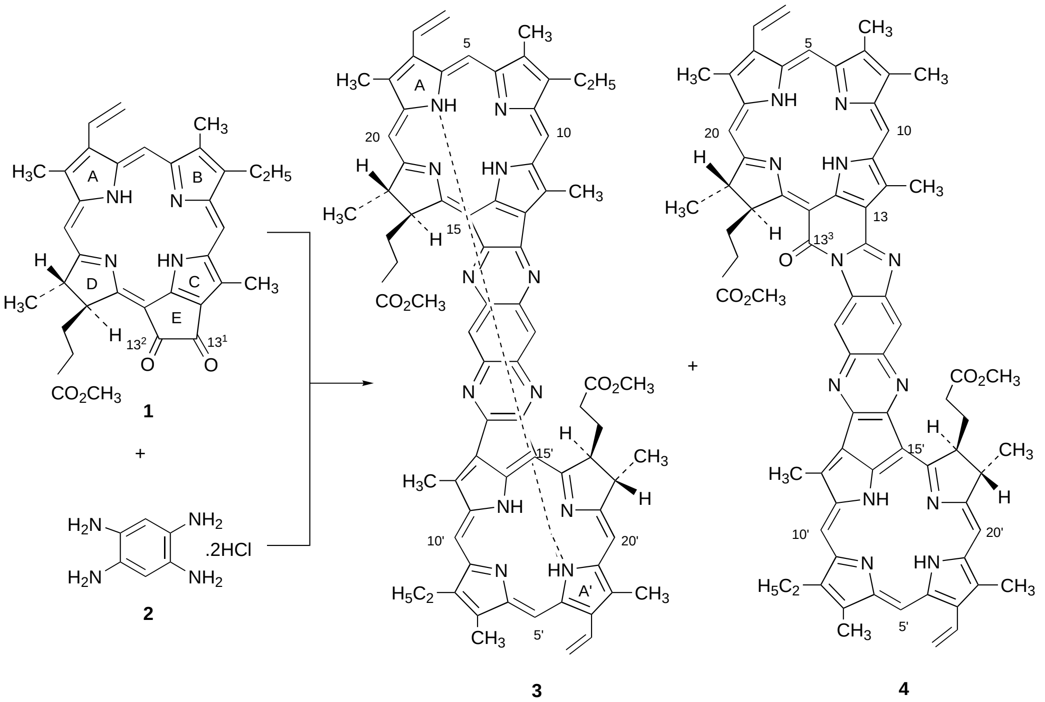
Condensation of 13^2-oxopyropheophorbide *a* with benzene-1,2,4,5-tetramine produced a bis-quinoxaline-bridged symmetrical chlorin dimer and an unsymmetrical benzimidazole/pyrazine bridged analog. Spectroscopic data of the novel conjugated dimers show a significant perturbation of the extended bis-chlorin π-system in a coplanar arrangement.

In recent years considerable attention has been focused on the development of conjugated porphyrin arrays as effective biomimetic models.[1] Poly-porphyrin systems, in which the individual porphyrin rings are either directly fused or are bridged by coplanar aromatic systems, are also expected to meet the criteria for electrical conductivity and are of interest as chemical models for physiological electron-transfer systems.[2] Crossley and co-workers recently reported the synthesis of various linearly conjugated tetrakis-porphyrin systems with or without appended phenanthroline units.[3] This chemistry provides an excellent approach by which the porphyrin π-systems can be connected to external redox centers. Although these and other porphyrins have proven to be valuable model compounds, we considered that chlorin-chlorin dimers would be a useful step toward the preparation of more biologically relevant model systems.[4]

In our approach, diketo chlorin **1**[5] was used as a building block for the synthesis of bis-chlorins by condensing with benzene-1,2,4,5-tetramine tetrahydrochloride **2**. Our initial attempts to prepare chlorin-chlorin dimers following the conditions used for the porphyrin system were unsuccessful.[3] Several attempts were made to prepare the desired dimer by varying the reaction conditions. The best results were obtained by refluxing the reaction mixture in CH_2Cl_2 for 4 days with a catalytic amount of TFA. The crude reaction product was purified by silica chromatography and preparative TLC. Besides the expected dimer **3** (*m*/*z* 1190), observed as an orange–red band (23% yield), a minor product **4** (in 8% yield) was also isolated (Scheme 1).

The ^1H NMR studies of the major component suggested a dimeric structure with diagonal symmetry between the pyrrolic rings A and A′ of the chlorin units (assigned as **3**). A similar diagonal arrangement of chlorin units has recently been reported for a completely conjugated bis-pyropheophorbide *a* as a more favourable structure due to the steric hinderance of the propionic ester side chain.[4a] A variable temperature ^1H NMR study† of dimer **3** clearly showed the distinctive singlet of the equivalent hydrogen atoms of a bis-quinoxaline bridge at δ 7.89 and had some unique characteristics. For example, compared to the parent compound **1**, the resonances for various protons generally appeared to be broader and the resonances representing the *meso* protons as singlets showed a remarkable downfield shift ($\Delta\delta$ = 0.8–1.2 ppm). All the resonances of the methyl protons were unusually collapsed into a sharp singlet observed at



Scheme 1

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† The best resolution of low field resonances was observed at −30 °C.

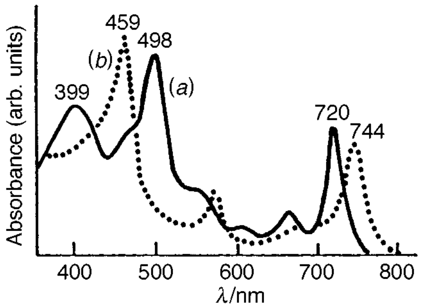
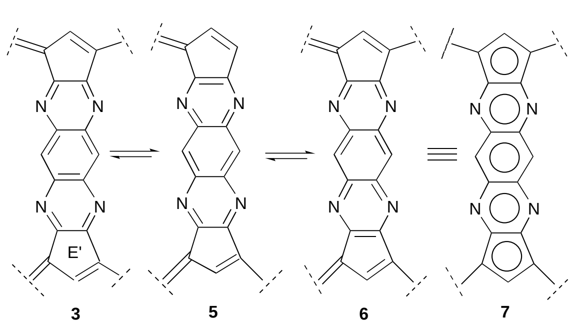


Fig. 1 Electronic absorption spectra (in CH_2Cl_2) of dimers (*a*) **3** and (*b*) **4**

δ 3.62.‡ Interestingly, similar dramatic changes have also been reported in the NMR spectra of certain chlorophyll enolates.[6] Comparative absorption spectroscopy among such compounds revealed that the UV–VIS spectrum of dimer **3** was almost identical to the pheophytin *a* enolate[6] with a characteristic split and red shifted Soret band (Fig. 1). Based on these observations, we propose the enolic-type resonance structures **5**–**7** for symmetrical dimer **3**, which more adequately explain the localization of double bonds and the hybridization distribution of electron density in the bis-quinoxaline bridge system (Scheme 2). Due to the intramolecular π-electron distribution, the 13^1–13^2 carbon–carbon bonds in isocyclic rings E and E′ show the characteristics of a double bond, which in fact is of an enolic type. Extended conjugation of pyropheophorbide *a* macrocycles through the bis-pyrazine/benzene spacer showed a profound effect on the delocalization of the π-electrons. The remarkable chemical shifts of various protons in the NMR spectrum reflect a marked reduction of the ring current caused by 'electron delocalization'[4a] and 'enolization increment'[6] effects.



Scheme 2

Similar to most of the chlorophyll enolates, dimer **3** was found to be unstable and sensitive to oxygen. Thus, under the reaction conditions used, the formation of unsymmetrical dimer **4** as a minor product could possibly be explained by oxidation of dimer **3** with molecular oxygen.§ The proposed structure for the minor product **4** was confirmed by mass (*m*/*z* 1206) and NMR data.¶ In the ^{1}H NMR spectrum, as expected, the resonances of two different chlorin units were observed, which were most distinctive for the 17/17′ and 18/18′ protons. The position of the oxo functionality at 13^3-position was tentatively assigned on the basis of the specific chemical shift of the 17-H doublet at δ 6.74.[7] The preferential formation of the 13^3-oxo derivative (instead of the related 13^1-oxo analog) might be due to steric hindrance caused by the propionic ester side chain. Interestingly, the electronic absorption spectrum of dimer **4** did not show the absorption peaks observed by the independent chlorin chromophores, but produced a single red-shifted Soret band at 459 nm and Q_y-band at 745 nm, which indicates that the unsymmetrical dimer **4** is behaving as one large conjugated system.

Molecular building (SYBYL 6.3 program on a Silicon Graphic Indigo 2R10,000 computer) indicated that the symmetrical dimer **3** has a fully conjugated planar structure, which is about 24 Å in length. The chlorin units are separated by the spacer by 10 Å (C15–C15′ atoms). Space filling showed that the symmetrical dimer **3** is less strained than the unsymmetrical analog **4**, and is energetically favored by 18 kcal mol^{-1}.

At present, the preparation of related heterometallated analogs of dimers **3** and **4** as well as other heterosystems (*e.g.* chlorin-porphyrin, chlorin-bacteriochlorin, bacteriochlorin-bacteriochlorin) is in progress.

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‡ *Selected data* for compound **3**: $\lambda_{max}(CH_2Cl_2)$/nm (ε/dm^3 mol^{-1} cm^{-1}) 399 (82 000), 498 (10 900), 549 (41 000), 665 (26 000), 720 (70 500); δ_H(600 MHz, $CDCl_3$) −1.41 (4H, br s, NH), 1.24 (6H, t, CH_2CH_3), 1.90–2.64 (8H, m, 17a/17a′, 17b/17b′-H), 1.92 (6H, d, *J* 7.4 Hz, 18/18′-CH_3), 3.62 (24H, br s, OCH_3 and ring CH_3), 3.64 (4H, q, CH_2CH_3), 4.67 (2H, dq, *J* 7.4 Hz, 18/18′-H), 5.42 (2H, dd, *J* 7.8 Hz, 17/17′-H), 6.28 (2H, d, *J* 12 Hz, 3a/3a′-H), 6.37 (2H, d, *J* 16 Hz, 3a/3a′-H), 7.88 (2H, br s, central bridge-H), 8.08 (2H, dd, *J* 12, 16 Hz, 3b/3b′-H), 8.34 (2 H, s, 20/20′-H), 8.79 (2H, s, 5/5′-H), 8.94 (2H, br s, 10/10′-H); *m*/*z* (FAB$^+$) 1192 (MH$^+$, 100%), 1045 (21%) [HRMS: Found 1191.5653 (MH$^+$). $C_{74}H_{70}N_{12}O_4$ requires (MH$^+$) 1191.5670].

§ A similar 13^3-oxo derivative was formed on the condensation of chlorin **1** with *o*-phenylenediamine (A. N. Kozyrev, J. L. Alderfer and R. K. Pandey, unpublished results).

¶ *Selected data* for compound **4**: $\lambda_{max}(CH_2Cl_2)$/nm (ε/dm^3 mol^{-1} cm^{-1}) 378 (58 000), 459 (125 000), 567 (28 000), 678 (14 000), 744 (62 000); δ_H(400 MHz, $CDCl_3$) −1.22 (2H, br s, NH), −0.74 (2H, br s, NH), 1.29 (6H, m, CH_2CH_3), 1.88 (6H, m, 18/18′-CH_3), 1.90–2.60 (8H, m, 17/17′-a, b-H), 3.65 (28H, m, OCH_3, ring CH_3, CH_2CH_3), 4.60 (1H, q, 18′-H), 4.68 (1H, q, 18-H), 5.52 (1H, m, 17′-H), 5.78 (1H, m, 17-H), 6.29 (2H, m, 3a/3a′-H), 6.40 (2H, m, 3a/3a′-H), 7.90 (2H, m, 3b, 3b′-H), 8.12 (2H, br s, 20/20′-H), 8.20 (1H, br s, central bridge-H), 8.54 (1H, br s, central bridge-H), 8.68 (1H, s, 5′-H), 8.70 (1H, s, 5-H), 8.76 (1H, br s, 10′-H), 8.81 (1H, br s, 10-H); *m*/*z* (FAB$^+$) 1207 (MH$^+$, 100%), 1179 (12%), 1118 (23%) [HRMS: Found 1207.5702 (MH$^+$). $C_{74}H_{70}N_{12}O_5$ requires (MH$^+$) 1207.5646].

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