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Formation of Novel Spirochlorin and Allylidenechlorin by the Reaction of Bromovinylporphyrin with Tetracyanoethylene

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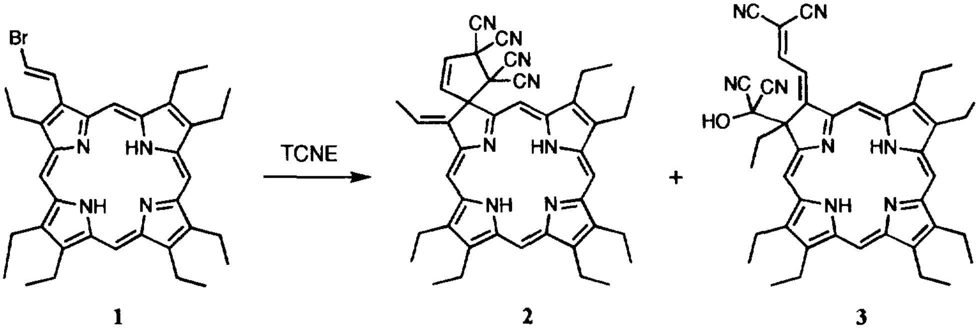
Abstracts: Treatment of bromovinylheptaethylporphyrin **1** with tetracyanoethylene leads to the formation of spirochlorin **2** and allylidenechlorin **3** *via* the initially formed Diels-Alder adduct. The former product **2** is a new class of chlorin and the latter **3** exhibits unusual long-wavelength absorption in the red region of the spectrum. Copyright © 1996 Elsevier Science Ltd

Recently, chlorins (reduced porphyrins) have attracted much interest as possible photosensitizers for the photodynamic therapy (PDT) of tumors[1] because of their strong absorption in the red region of the spectrum, where activating light will penetrate more deeply into malignant tissues.[2] It is therefore desirable to develop porphyrin photosensitizers with strong absorption near or above 700 nm in order to increase the utilization of the light as well as to take advantage of greater tissue penetration with longer wavelengths.

One approach that has led to the synthesis of chlorins utilized a vinyl-substituted porphyrin as the diene component of a Diels-Alder addition with an electron-deficient dienophile.[3] We now describe the formation of new spiro-linked chlorin **2** and ω,ω-dicyanoallylidenechlorin **3** having unusual long-wavelength absorption in the red region of the spectrum by the reaction of the known bromovinylheptaethylporphyrin[4] **1** with tetracyanoethylene (TCNE) as a dienophile.



Scheme 1

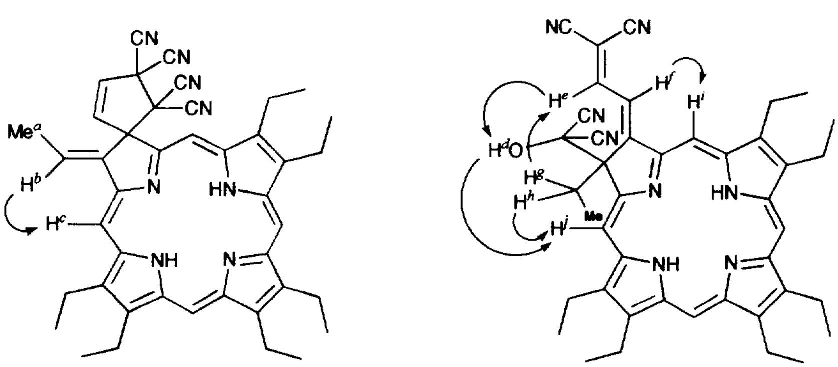
When a solution of bromovinylheptaethylporphyrin **1** and TCNE in 1,2-dichloroethane was refluxed for 6 h, the color of the solution gradually turned to dark green. After removal of the solvent, the residue was chromatographed on silica gel using hexane/dichloromethane (5:3→2:1) as eluent to give the spirochlorin **2** and ω,ω-dicyanoallylidenechlorin **3** as green solids in 22.2% and 33.3% yields respectively.[5,6] (Scheme 1) However, no reaction was observed when a less reactive dienophile such as dimethyl acetylenedicarboxylate was used under similar reaction conditions.

The novel structure of **2** thus obtained was confirmed by spectroscopic data.[7] In particular, the ^{1}H NMR spectrum indicated the presence of six ethyl groups, one vinylic methyl group (Me^a) [δ 0.71 (3H, d, J=6.8 Hz)] and one methine proton (H^b) [δ 4.98 (1H, q, J=6.8 Hz)] in an exocyclic ethylidene moiety, and a set of olefinic protons [δ 7.93 (d, J=6.3 Hz) and δ 7.96 (d, J=6.3 Hz) respectively] on a spirocyclopentene ring. The electronic spectrum showed the intense long-wavelength band at λ_{max} 672 nm with a high molar extinction coefficient (ε 30,300) characteristic of chlorins, a Soret band, and several smaller peaks.

The geometry of the ethylidene group was assigned to *E*-conformation with the aid of difference nuclear Overhauser effect (NOE) experiments. (Fig. 1) Thus, an NOE (9.7% enhancement) was observed at the *meso*-proton (H^c) (δ 9.12) upon irradiation of H^b, whereas no NOE was observed there upon irradiation of Me^a.

On the other hand, the structure of **3** was confirmed by spectroscopic data.[8] The ^{1}H NMR spectrum indicated the presence of seven ethyl groups, one hydroxyl proton (H^d) (δ 4.81),[9] and two olefinic protons [δ 8.42 (d, J=13.2 Hz, H^e) and δ 8.73 (d, J=13.2 Hz, H^f) respectively] in an exocylclic allylidene moiety. The methylene protons of the tertiary ethyl group were not equivalent and showed signals at δ 2.97~3.02 (H^g) and δ 3.64~3.72 (H^h), respectively.

The electronic spectrum showed the intense long-wavelength peak characteristic of chlorins, a Soret band, and several smaller peaks. Especially, the lowest energy band has λ_{max} 720 nm with a high molar extinction coefficient (ε 33,000). The spectroscopic behavior of **3** observed here is quite unusual since the chlorins all show the typical strong band (ε ~20,000) at about 650 nm.[1a] This remarkable bathochromic shift is attributed to the presence of an exocyclic allylidene moiety which plays a role in extending the conjugation system of the chlorin macrocycle and has electron-withdrawing groups conjugated with its 1,3-diene system.[10]



2

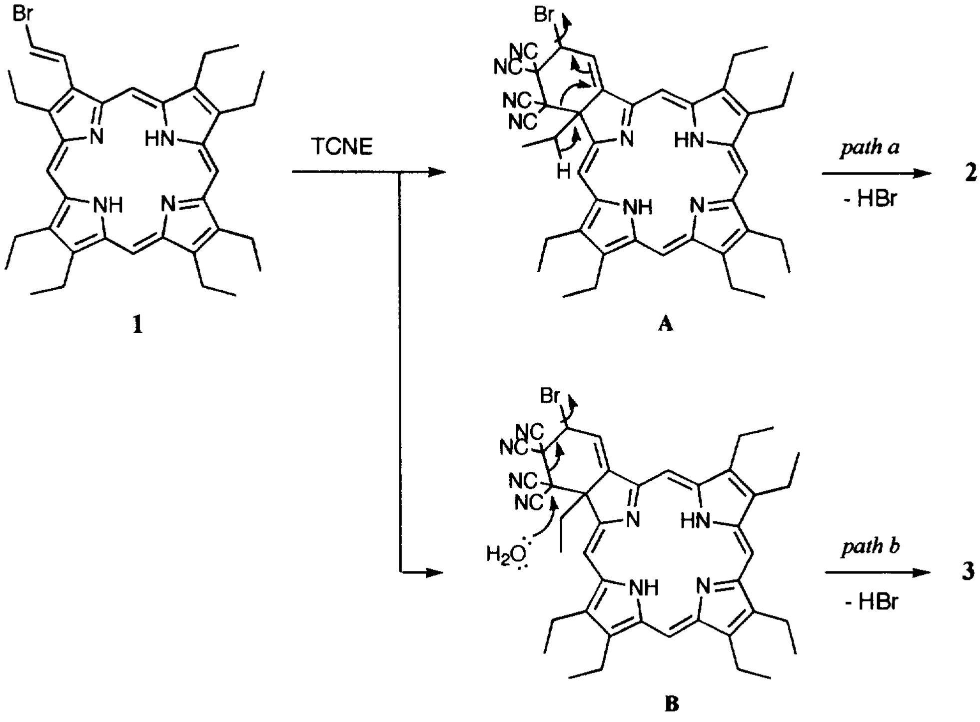
3

Fig. 1. Nuclear Overhauser enhancements observed for compounds **2** and **3**

The geometry of the conjugated diene moiety in the ω,ω-dicyanoallylidene group was assigned to s-*trans* conformation about the central single bond[11] by NOE experiments. (Fig. 1) Thus, an NOE (10.4% enhancement) was observed at the hydroxyl proton (H^d) upon irradiation of the olefinic proton (H^e), while an NOE (8.1%) was observed at the *meso*-proton (H^i) (δ 9.75) upon irradiation of the olefinic proton (H^f). Furthermore, NOEs (12.2%, 7.8%, 2.6%) were observed between the methylene proton (H^g) and H^e, between the methylene proton (H^h) and the *meso*-proton (H^j) (δ 9.36), and between H^d and H^j respectively.

As depicted in Scheme 2, it seems reasonable to assume that the facile formation of spirochlorin **2** involves a homo Wagner-Meerwein-like rearrangement of the initially formed Diels-Alder adduct with the elimination of hydrogen bromide as shown in **A**. (*path a*) On the other hand, the formation of allylidenechlorin **3** may involve a nucleophilic attack of water[12] to the Diels-Alder adduct accompanying the C-C bond cleavage as shown in **B**. (*path b*)

Further studies on the photochemical and photophysical properties of chlorins **2** and **3** are now in progress to explore their potentialities as photosensitizers for PDT.



Scheme 2

REFERENCES AND NOTES

1. (a) Bonnett, R.; Berenbaum, M. C. Porphyrins as Photosensitizers. In *Photosensitising Compounds: Their Chemistry, Biology and Clinical Use*; Ciba Foundation Symposium No.146; John Wiley & Sons, Ltd.: Chichester, 1989; pp. 40-59. (b) Spikes, J. D. *J. Photochem. Photobiol., B: Biol.* **1990**, *6*, 259-274. (c) Morgan, A. R. Reduced Porphyrins as Photosensitizers: Synthesis and Biological Effects. In *Photodynamic Therapy*; Henderson, B. W; Dougherty, T. J. Eds.; Marcel Dekker, Inc.: New York, 1992; pp. 157-172. (d) Dougherty, T. J. *Photochem. Photobiol.* **1993**, *58*, 895-900.
2. Wan, S.; Parrish, J. A.; Anderson, R. R.; Madden, M. *Photochem. Photobiol.* **1981**, *34*, 679-681.
3. (a) Grigg, R.; Johnson, A. W.; Sweeney, A. *J. Chem. Soc., Chem. Comm.* **1968**, 697. (b) Callott, H. J.; Johnson, A. W.; Sweeney, A. *J. Chem. Soc., Perkin Trans. I* **1973**, 1424-1427. (c) DiNello, R. K.; Dolphin, D. *J. Org. Chem.* **1980**, *45*, 5196-5204. (d) Pangka, S. V.; Morgan, A. R.; Dolphin, D. *J. Org. Chem.* **1986**, *51*, 1094-1100.
4. Vicente, M. G. H.; Smith, K. M. *Tetrahedron* **1991**, *47*, 6887-6894.
5. 28.3% of starting material **1** was recovered unchanged. Prolonged reaction time caused a decrease in the yields of both chlorins **2** and **3**.
6. A similar treatment of 2-bromovinyl-7,12,17-triethyl-3,8,13,18-tetramethylporphyrin with TCNE resulted in the formation of the corresponding spirochlorin and allylidenechlorin in 3.7% and 6.5% yields, respectively. Details will be described in the full paper.
7. Spectroscopic data for **2**: ^{1}H NMR (CDCl$_3$) δ: -2.88 (1H, s), -2.86 (1H, s), 0.71 (3H, d, J=6.8 Hz), 1.80~1.88 (18H, m), 3.85~4.07 (12H, m), 4.98 (1H, q, J=6.8 Hz), 7.93 (1H, d, J=6.3 Hz), 7.96 (1H, d, J=6.3 Hz), 9.12 (1H, s), 9.49 (1H, s), 9.86 (1H, s), 9.87 (1H, s). UV-Vis (dioxane) λ_{max} nm (ε /M^{-1} cm^{-1}) : 351 (41,700), 387 (72,300), 448 (49,300), 587 (14,800), 616 (15,800), 672 (30,300). FAB-MS (3-nitrobenzylalcohol matrix) *m/z* : 658 (M$^+$).
8. Spectroscopic data for **3**: ^{1}H NMR (CDCl$_3$) δ: -2.54 (1H, s), -2.50 (1H, s), 0.51 (3H, t, J=6.8 Hz), 1.77~1.93 (18H, m), 2.97~3.02 (1H, m), 3.64~3.72 (1H, m), 3.84~3.92 (4H, m), 3.95~4.08 (8H, m), 4.81 (1H, s) 8.42 (1H, d, J=13.2 Hz), 8.73 (1H, d, J=13.2 Hz), 9.36 (1H, s), 9.72 (1H, s), 9.75 (1H, s), 9.83 (1H, s). UV-Vis (dioxane) λ_{max} nm (ε /M^{-1} cm^{-1}) : 394 (68,500), 473 (39,100), 502 (29,800), 663 (21,300), 720 (33,000). FAB-MS (3-nitrobenzylalcohol matrix) *m/z* : 676 (M$^+$), 677 (M+1)$^+$.
9. The hydroxyl proton was observed at δ 6.06 in acetone-d$_6$ as a singlet peak, which disappeared by shaking with D$_2$O.
10. (a) Chang, C. K. ; Sotiriou, C.; Wu, W. *Proc. SPIE* **1990**, *1203*, 281-286. (b) Mironov, A. F.; Kozyrev, A. N.; Perepyolkin, P. Y. *Proc. SPIE* **1993**, *2078*, 186-192.
11. Eliel, E. L. ; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. The Conformation of Acyclic Molecules. In *Conformational Analysis*; John Wiley & Sons, Inc.: New York, 1965; pp. 5-35.
12. The water participating to the formation of **3** appears to come from reagent grade 1,2-dichloroethane used as the solvent. Actually, the experiment performed under dry (not absolutely) conditions resulted in not only a decreased yield of **3** (27.9%) but also a slightly increased yield of **2** (23.6%).

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