Pergamon

Tetrahedron Letters, Vol. 38, No. 14, pp. 2409-2412, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00369-9

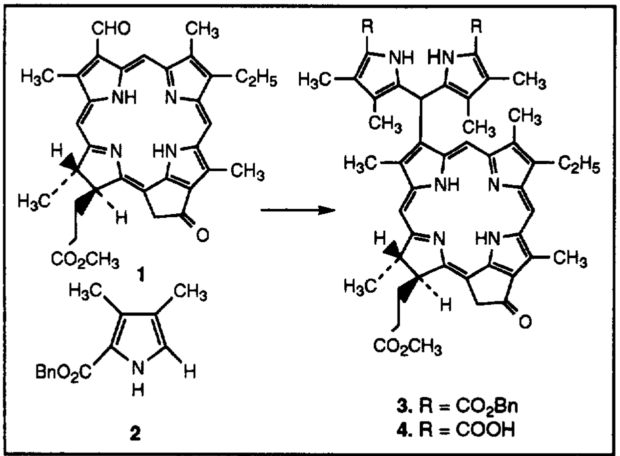
Syntheses and Spectroscopic Studies of Some Novel Porphyrin-Pyropheophorbide Dimers and Trimers with Fixed Distances[1]

Gang Zheng,[a] Ravindra K. Pandey,[a,*] Timothy P. Forsyth,[b] Andrei N. Kozyrev,[a]
Thomas J. Dougherty [a] and Kevin M. Smith[b,*]

[a]Chemistry Division, Department of Radiation Biology, Division of Radiation Medicine,
Roswell Park Cancer Institute, Buffalo, NY 14263, USA
[b]Department of Chemistry, University of California, Davis, CA 95616, USA

Abstract: *Syntheses and spectroscopic properties of pyropheophorbide-porphyrin dimers and a bis-pyropheophorbide-porphyrin trimer are described. Fluorescence spectroscopic data of the oligomers reveal that the macrocycles in the systems are only weakly coupled.* © 1997 Elsevier Science Ltd.

Porphyrin dimers and trimers have attracted considerable attention due to their potential use as models for the bacterial photosynthetic reaction center and for supramolecular photonics.[2] The preparation of arrays of covalently linked porphyrins is a popular area of research, not only for its possible application to the elucidation of natural photosynthetic mechanisms, but also for purposes of probing the fundamental physicochemical properties of the porphyrin chromophore.[3] Many elegant studies by various research groups have resulted in a number of porphyrin dimers and higher oligomers with various linkages and configurations. The nature of the linkages between each pair of macrocycles is thought to have a large influence on the observed rate of electron transfer.[4] So far, much work has been devoted to the preparation of bis-macrocycles where the two chromophores are coplanar. Since the structural determination of the structure of the reactive center in photosynthetic bacteria,[5] the dimer hypothesis has stimulated an enormous amount of research on the design and characterization of porphyrin and chlorophyll dimers in many possible configurations.[6] In addition, certain porphyrin dimers and higher oligomers have been reported to be effective photosensitizers for the treatment of tumors using photodynamic therapy (PDT).[7]

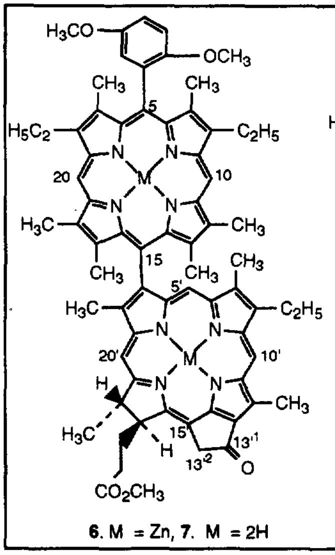


1

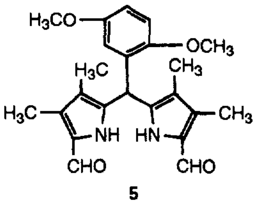
2

3. R = CO_2Bn
4. R = COOH

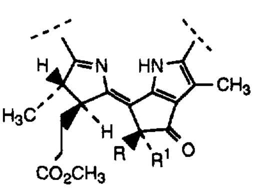
Here we report the syntheses, spectroscopic properties, and structural analyses of some novel porphyrin-pyropheophorbide dimers and of a trimer consisting of bis pyropheophorbide-porphyrin units with fixed distances between the chromophers. For our studies, 2-devinyl-2-formylpyropheophorbide-a **1**[8] was used as the starting material. Acid catalyzed condensation of **1** with benzyl 3,4-dimethyl-2-carboxylate **2**[9] produced the pyro pheophorbide-dipyrromethane **3** in 60% yield as a diastereomeric mixture; catalytic de-benzylation afforded the corresponding carboxylic acid **4**. The product obtained after reaction of **4** with diformyldipyrromethane **5**[10] was found to be a mixture of three chlorins and two porphyrins. The porphyrin mixture was separated from the chlorins by column chromatography. Among the free base chlorins (obtained after acid treatment), the faster moving band was characterized as a mixture of two isomers (compound **7**). In dimer **6** or its demetallated analogue **7** there is restricted rotation between the porphyrin and pyropheophorbide units. The ^{1}H NMR spectrum clearly indicated the presence of two isomers. The Rf values for two slow-moving chlorins were extremely close and they could be separated only by repeated preparative chromatography (solvent system: 2% MeOH/CH_2Cl_2). Both of these bands were found to be a mixture of two compounds by ^{1}H NMR spectroscopy. Interestingly, in both compounds the ABX pattern for the 13^2-CH_2 protons which is generally observed at 5.39 and 5.28 were missing. The 17^1-H and 18^1-H protons show significant shifts when compared with those in dimer **7**. The mass spectra of both the compounds showed a molecuar ion at m/z 1123 (M+1), i. e. 16 mass units more than expected for dimer **7** [m/z 1107 (M+1)]. This result diverted our attention to the earlier report of Senge *et al.* [11] concerning the formation of 13^2-hydroxy derivatives by aerial oxidation of methyl pheophorbide-a. On the basis of these results, we tentatively assigned the structure of isomers as **8a** and **8b**.



6. M = Zn, **7**. M = 2H

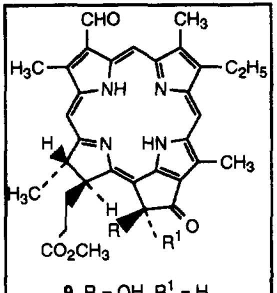


5



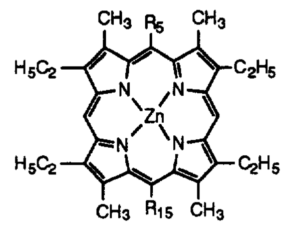
8a. R =OH, R^1 =H
8b. R = H, R^1 =OH

These structures were further confirmed by model studies. The formylpyropheophorbide **1** was converted into the Zn(II) analogue. In addition to the desired zinc complex a mixtute of another two chlorins was observed which was difficult to purify as metallated derivatives. As free bases the mixture was separated into two isomers which were characterized as the 13^2-hydroxy derivatives **9** and **10**. The mass spectra of both the isomers were identical [m/z 565, (M+1)], again suggesting the presence of an hydroxy group. The stereo isomers **9** (S) and**10** (R) showed distinctive chemical shift differences for the proton on the carbon bearing the hydroxyl group the hydroxy group. The assignments of the (R) and (S) isomers were postulated on the basis of the effect of the newly introduced 13^2-OH group, which causes the adjacent protons to move downfield in the ^{1}H NMR spectra. For example, the signal for 17-Ha- of the R-isomer was found at δ 2.88 (dddd), compared with the corresponding S-isomer proton at 3.10 (dddd). Similar effects of the 13^2 -OH group have recently been reported by Ma and Dolphin[12] for the 13^2-hydroxypheophorbide-a in their stereoselective synthesis of some chlorophyll analogues. These results are in agreement with the NMR data obtained from dimer **8a** and **8b**. The preferential formation of the R-isomer **8b** (60%, based on NMR data), might be due to preferential attack on the 13 carbon^2 atom, by molecular oxygen, from the less hindered side of the chlorin macrocycle. On the basis of NMR and HRMS analyses the structures of the two porphyrins separated from the mixture were assigned as **11** and **12**. The formation of symmetrical porphyrin **11** was probably due to self-condensation of the diformyl-dipyrromethane **5**. However, the formation of unsymmetrical porphyrin **12** suggests that the intermediate dipyrromethane-pyropheophorbide **4**, at the oxidation step [Zn(OAc)$_2$/air], cleaves the strained carbon-carbon bond joining the porphyrin-pyropheophorbide macrocycles. It is also likely that, under the acidic conditions, the pyropheophorbide-pyrromethane adduct **4** produces the dipyrromethene **13**, which on reaction with diformyldipyrromethane **5** could afford the unsymmetrical porphyrin **12** and 2-devinylchlorin **15**.

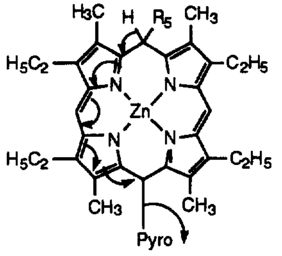


9. R = OH, R^1 = H
10. R = H, R^1 = OH

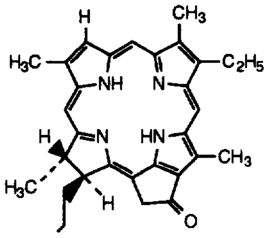
For the synthesis of trimer **17**, the methyl pyropheophorbide **1** was condensed with dipyrromethane **16**[13] under MacDonald reaction conditions.[14] Two major bands were isolated and were identified as the pyropheophorbide-porphyrin-pyropheophorbide trimer **17** and pyropheophorbide-porphyrin dimer **19**. Under the reaction conditions, the formation of dimer **19** further indicated that the carbon-carbon bond between the porphyrin-pyropheophorbide macrocycles was cleaved at the oxidation step of the intermediate porphodimethene-pyropheophorbide **14**. The structures of the trimer and dimer as their free bases, were confirmed by ^{1}H NMR and mass spectroscopy. In trimer **17** both the pyropheophorbide and porphyrin macrocycles are attached at a fixed distances and have restricted rotation about the linking bond; on the basis of the orientation of the chlorin pyrrolic rings there is a possibility of two structural isomers in which (a) the reduced rings are on the same side, or (b) the reduced rings are on opposite sides of the molecule. These results were further confirmed by ^{1}H NMR and HRMS analyses. The structure of dimer **19** was also confirmed by preliminary X-ray crystal studies (not shown).



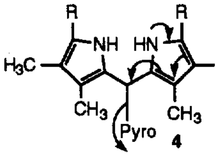
11. $R_5 = R_{15}$ = 2,5-dimethoxyphenyl
12. R_5 = 2,5-dimethoxyphenyl, R_{15} = H



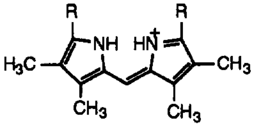
14. R_5 = 2, 5-dimethoxyphenyl



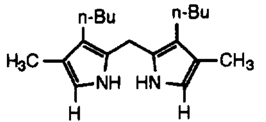
15



4

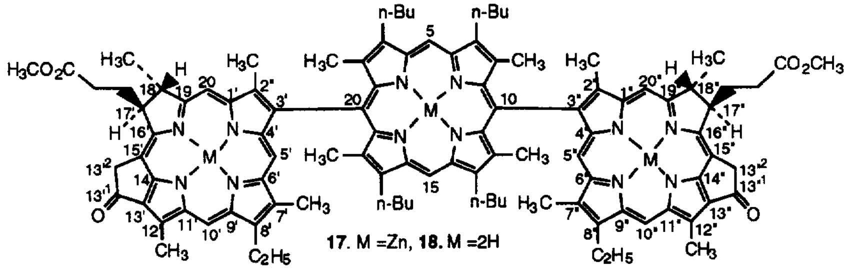


13

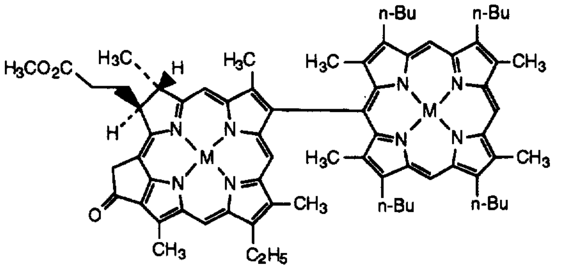


16

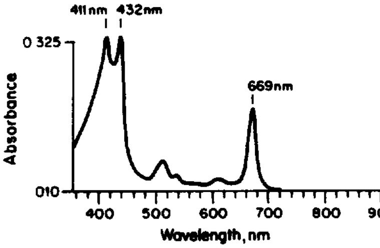
The absorption spectra of the dimers and trimers were measured in dichloromethane. The ground state absorption spectra of dimer **7** and trimer **18** were almost identical, with two Soret bands and distinct Q bands for each macrocycle. The Qy transitions of the chlorin rings in the zinc and free base complexes for dimer **6** and **7**



17. M =Zn, **18.** M =2H



19. M = Zn **20.** M = 2H



Optical spectrum (in CH_2Cl_2) of trimer **18** are observed at 654 and 663 nm, and for the trimer at 657 and 669, respectively. The Zn dimer **6** and trimer **17** showed characteristic Q bands at 510, 537, 572 and 609 nm for the porphyrin macrocycles. The prominence of the Soret bands of the chlorin and porphyrin macrocycles in dimer **6** (405 and 423 nm) and trimer **17** (405 and 429 nm) make it possible to selectively excite the molecule at two specific wavelengths.

Excitation of dimer **6** at 405 and 423 nm gave a fluorescence emission band at 663 nm. Similarly, excitation at 405 and 429 nm in trimer **17**, afforded an emission at 666 nm. Excitation of the related free base analogues; dimer **7** at 411 and 423 nm produced emission band at 664 nm, and excitation of the trimer **18** at 411 and 432 nm produced fluorescence emission at 675 nm. The small differences in the fluorescence emission between the free base and Zn(II) complexes of the dimers and trimers suggest that the conjugated systems of the two macrocycles are only weakly coupled. Further studies with these compounds are in progress.

Acknowledgments:

This work was supported by grants from the National Institutes of Health (CA 55791, HL 22252) the National Science Foundation (CHE-96-23117), and the Oncologic Foundation of Buffalo. Mass spectrometric analyses were performed at the Mass Spectrometry Facility, Michigan State University, East Lansing. Assistance provided by Dr. James Alderfer, NMR Facility, Department of Biophysics, Roswell Park Cancer Institute, Buffalo (Grant CA 16056) is greatly appreciated.

References and Notes:

1. Part of this work was presented at the *210th ACS National Meeting, Chicago, August 20-25,* **1995**, (Abstract no. Orgn. 070).
2. (a) Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435-461, and references therein. (b) Wagner, R. W.; Lindsey, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 9759.
3. (a) Sessler, J. L.; Capuano, V. L. *Tetrahedron Lett.* **1993**, *34*, 2287. (b) Arnold, D. P.; Nitschinsk, L. J. *Tetrahedron* **1992**, *48*, 8781. (c) Lin, V. S. -Y.; DiMagno, S. G.; Thieren, M. J. *Science*, **1994**, *264*, 1105. (d) Susumu, K.; Shimidzu, T.; Tanaka, K.; and Segawa, H. *Tetrahedron Lett.* **1996**, *37*, 8399.
4. (a) Chang, C. K.; Abdalmuhdi, I. *J. Org. Chem.* **1983**, *48*, 5388. (b) Sessler, J. L.; Hugdahl, J.; Johnson, M. R. *J. Org. Chem.* **1986**, *51*, 2838. For a review see: (c) Gust, D.; Moore, T. A., Eds., *Tetrahedron*, **1989**, *45* (15), and references therein. (d) Pandey, R. K.; Shiau, F. -Y.; Isaac, M.; Ramaprasad, S.; Dougherty, T. J.; Smith, K. M. *Tetrahedron Lett.* **1992**, *33*, 7815.
5. (a) Deisenhofer, J.; Epp, O.; Miki, K.; Huber, R.; Michel, H. *J. Mol. Biol.* **1984**, *180*, 385. (b) Allen, J. P.; Feher, G. *Proc. Natl. Acad. Sci., USA* **1984**, *81*, 4795.
6. (a) Paolesse, R.; Pandey, R. K.; Forsyth, T. P.; Jaquinod, L.; Gerzevske, K. R.; Nurco, D. J.; Senge, M. O.; Licoccia, S.; Boschi, T.; Smith, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3869. (b) Jaquinod, L.; Nurco, D. J.; Medforth, C. J.; Pandey, R. K.; Forsyth, T. P.; Olmstead, M. M.; Smith, K. M., *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1013. (c) Khoury, R. G.; Jaquinod, L.; Nurco, D. J.; Pandey, R. K.; Senge, M. O.; Smith, K. M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2496.
7. (a) Pandey, R. K; Shiau, F.- Y.; Medforth, C. J.; Dougherty, T. J.; Smith, K. M., *Tetrahedron Lett.* **1990**, *51*, 7399. (b) Pandey, R. K.; Shiau, F. -Y.; Dougherty, T. J.; Smith, K. M., *Tetrahedron* **1991**, *47*, 9571.
8. Wasielewski, M. R.; Johnson, D. G.; Niemczyk, M. P.; Gains III, G. L.; O'Neil, M. P.; Svec, W. A. *J. Am. Chem. Soc.* **1990**, *112*, 6482.
9. Smith, K. M. and Kehres, L. A., *J. Chem. Soc. Perkin Trans. I*, **1983**, 2329.
10. Forsyth, T. P., Ph. D. Dissertation, University of California, Davis, **1996**.
11. Senge, M. O.; Struck, A.; Dornemann, D.; Scheer, H.; Senger, H. Z. *Naturforsch.* **1988**, *43c*, 515.
12. Ma, L.; Dolphin, D. *J. Org. Chem.* **1996**, *61*, 2501.
13. Sessler, J. L.; Johnson, M. R.; Creager, S. F.; Fettinger, J. C.; Ibers, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9310.
14. Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384.

(*Received in USA* 3 *February* 1997; *accepted* 18 *February* 1997)