Pergamon

Tetrahedron Letters, Vol. 35, No. 7, pp. 995-998, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0391-V

A New Porphyrin Derivative for Use as a Diene in the Diels-Alder Reaction

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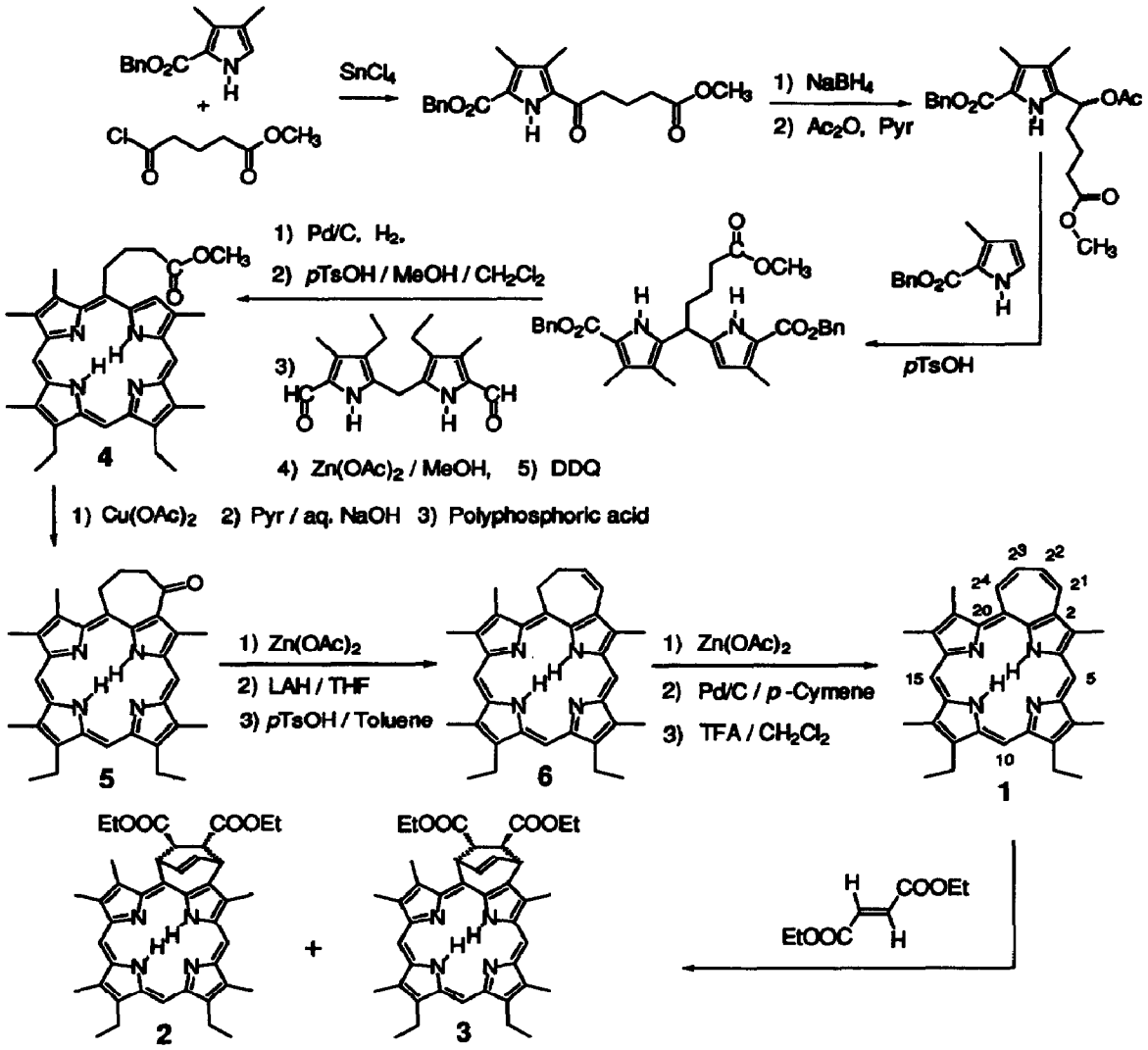
Abstract: The first representative of a new class of porphyrins featuring a tetramethine bridge joining the 2 and 20 positions of the macrocycle has been prepared and found to undergo the Diels-Alder reaction, yielding structures in which functional groups are linked to the porphyrin macrocycle through a rigid, bicyclic bridge.

Cyclic tetrapyrroles such as porphyrins and chlorophylls play important roles in many aspects of biological energy flow including photosynthesis and respiration. For this reason, various model systems consisting of porphyrins covalently linked to donor or acceptor moieties have been prepared in order to study electron, singlet energy and triplet energy transfer.[1-5] The rates of energy and electron transfer processes are functions of donor-acceptor separation and orientation. In natural systems, these structural factors are controlled by covalent and/or non-covalent interactions with proteins, whereas in model systems, covalent linkages often supply the constraints. The synthetic linkages studied to date typically contain at least one single bond, and thus torsional motion is possible, although it can be reduced by buttressing effects. The problem has been overcome in one case by a cleverly designed rigid porphyrin-quinone linkage,[6] but this system extends the porphyrin π-electron system through a fused quinoxalino moiety and thus alters the properties of the porphyrin macrocycle to some extent.

An ideal linkage would incorporate a polycyclic hydrocarbon bridge between the porphyrin and the donor or acceptor moiety in order to preclude large-scale torsional motions. Such linkages are conveniently made by the Diels-Alder cyclization. Although some Diels-Alder reactions have been carried out on the porphyrin macrocycle,[7-10] reported examples involve alteration of the porphyrin π-electron system, and are therefore not optimal for construction of model systems involving the intact porphyrin chromophore.

We now report the synthesis and characterization of **1** and its successful employment as a diene in a Diels-Alder reaction to yield **2** and **3**. The synthetic pathway is outlined in the scheme. Porphyrin **4**, which bears a *meso*-methyl butyrate side chain, was prepared as shown using a modified MacDonald approach.[11-13] Copper was introduced into **4** by stirring a solution of the porphyrin in chloroform and methanol (3 : 1) with copper (II) acetate at 55 °C for 7 h (97 % yield). The resulting methyl ester was saponified by refluxing for 4 h in pyridine containing 22% 0.2 M aqueous NaOH (100% yield). Heating the resulting acid in polyphosphoric acid for 40 min at 120 °C led to cyclization of the acid side chain to the 20-position and removal of the copper to yield free base porphyrin **5** (91% yield). Zinc was introduced by stirring **5** for 20 h with excess zinc acetate in 8 : 1 chloroform : methanol (91% yield). The ketone was reduced by stirring for 0.5 h with excess lithium aluminum hydride in THF. After the work-up, the crude alcohol was dissolved in toluene containing 0.05M *p*-toluenesulfonic acid and heated for 1 h to give alkene **6** in quantitative yield. The alkene was metallated with zinc as described above, dissolved in *p*-cymene, and refluxed for 19 h with a catalytic amount of 10% palladium on carbon under a nitrogen atmosphere. The resulting crude zinc diene was isolated and demetallated in a solution of dichloromethane and trifluoroacetic acid to give diene **1** in 49 % yield.



Analysis of 1 by high resolution fast atom bombardment mass spectrometry gave a mass of 487.2847 for the parent ion plus one proton (calculated for $C_{33}H_{35}N_4$, 487.2861). All resonances in the 500-MHz ^{1}HNMR spectrum of 1 were assigned with the aid of COSY and NOESY (2-dimensional nuclear Overhauser effect) experiments.[14] The four protons of the tetramethine group bridging the 2 and 20 positions were easily identified. Of particular note is the appearance of the 2^4 resonance downfield at 9.92 ppm as the result of strong deshielding by the porphyrin ring current. The diene in conjugation with the porphyrin π-electron system results in a perturbed absorption spectrum (Fig. 1). In dichloromethane, the Soret band is broad, with a maximum absorbance at 408 nm and a strong shoulder at 435 nm. Four Q-bands appear at 536, 578, 602 and 658 nm. The corrected fluorescence emission spectrum in the same solvent has maxima at 660 and 729 nm (Fig. 1). The fluorescence quantum yield in dichloromethane, determined using *meso*-tetra-*p*-tolylporphyrin in toluene as a standard ($\Phi_f = 0.11$),[15,16] was 0.14. The lifetime of the first excited singlet state of 1 in

dichloromethane, measured by the single photon timing method,[15] is 7.7 ns (χ^2 = 1.24), which is typical for a porphyrin macrocycle.

To investigate the suitability of **1** as a diene in the Diels-Alder reaction, the porphyrin was sealed under nitrogen in a glass ampoule with a large excess of diethyl fumarate and heated to 198 °C for 10.5 h. The excess diethyl fumarate was removed by distillation at reduced pressure, and the residue was chromatographed on silica gel (toluene containing 2% ethyl acetate) to yield a mixture of diastereomers **2** and **3** (77% yield). The two diastereomers were separated by chromatography on silica gel to give **2** and **3**, each as a racemic mixture.

Analysis of **2** and **3** by high resolution fast atom bombardment mass spectrometry gave a mass of 659.3597 for the parent ion plus one proton in each case (calculated for $C_{41}H_{47}N_4O_4$, 659.3597). The 500-MHz ^{1}H NMR spectra of **2** and **3** were assigned with the aid of COSY, NOESY and HMBC (heteronuclear multiple-bond correlation) results.[17] The isomers were identified on the basis of the strong shielding of the 2^3 ethoxy group of **3** resulting from conformations in which it is located above the center of the porphyrin ring. The aromatic ring current effect of the porphyrin also causes the two diastereotopic methylene protons of this group to appear as doubled quartets separated by 0.56 ppm. These effects are not seen in **2**, where neither of the ethoxy groups can assume such a conformation. The 2^4 protons in both isomers appear below 7 ppm because of deshielding by the porphyrin ring current in the plane of the macrocycle.

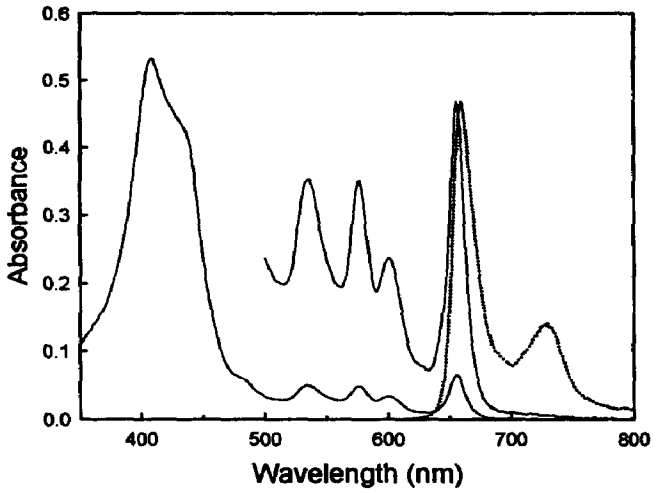


Fig. 1 Absorption (———) and fluorescence emission (.....) spectra of diene **1** in dichloromethane. The absorption values in the inset have been multiplied by 7, and the intensity of the emission maximum has been scaled to the longest-wavelength absorption band.

In dichloromethane, **2** and **3** have virtually identical phyllo-type absorption spectra, with a Soret band at 406 nm and Q-bands at 508, 544, 576 and 630-nm in the ratios 125 : 9.4 : 4.2 : 4.2 : 1.0. The distortion of the Soret band and unusual ratios of Q-bands observed for **1** (Fig. 1) are absent in **2** and **3**. The fluorescence emission spectra of **2** and **3** in dichloromethane with 590-nm excitation are also essentially the same, with maxima at 632 and 700 nm. The fluorescence quantum yield was 0.06 for each molecule. The first excited singlet states of **2** and **3** in dichloromethane decay as single-exponentials, with time constants of 9.9 ns (χ^2 = 1.23) and 10.1 ns (χ^2 = 1.24), respectively, as determined from singlet photon timing experiments with excitation at 590 nm and emission at 699 nm.

Porphyrin **1** can thus be synthesized in reasonable yield, and functions as a diene in the Diels-Alder reaction. In the example investigated here, the resulting adducts possess normal porphyrin first excited singlet state properties. This suggests that **1** can be used as a versatile building block for the construction of multicomponent models, for photosynthesis and other biological processes, in which porphyrins are linked to electron acceptors such as quinones or to other cyclic tetrapyrroles.

Acknowledgments: This research was supported by the National Science Foundation (CHE-8903216). This is publication 171 from the Arizona State University Center for the Study of Early Events in Photosynthesis. The Center is funded by DOE Grant DE-FG02-88ER13969 as part of the U. S. Department of Agriculture-Department of Energy-National Science Foundation Plant Science Center Program.

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14. ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 10.31 (1 H, s, 5-H), 10.14 (1 H, s, 15-H), 9.92 (1 H, d, *J* 12 Hz, 2^4-H), 9.69 (1 H, s, 10-H), 9.16 (1 H, d, *J* 12 Hz, 2^1-H), 7.98 (1 H, m, 2^3-H), 7.95 (1 H, m, 2^2-H), 4.08 (2 H, q, *J* 8 Hz, 8-C*H*$_2$CH$_3$), 3.99 (3 H, s, 3-CH$_3$), 3.94 (2 H, q, *J* 8 Hz, 12-C*H*$_2$CH$_3$), 3.73 (3 H, s, 18-CH$_3$), 3.69 (3 H, s, 7-CH$_3$), 3.63 (3 H, s, 17-CH$_3$), 3.53 (3 H, s, 13-CH$_3$), 1.87 (3 H, t, *J* 8 Hz, 8-CH$_2$C*H*$_3$), 1.84 (3 H, t, J 8 Hz, 12-CH$_2$C*H*$_3$), -2.11 (1 H, s, NH), -2.54 (1 H, s, NH).
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17. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.04 (1 H, s, 15-H), 9.99 (1 H, s, 5-H), 9.84 (1 H, s, 10-H), 7.23 (1 H, dd, *J* 8, 8 Hz, 2^1-CH=C*H*-), 7.16 (1 H, dd, *J* 8, 8 Hz, 2^1-C*H*=CH-), 7.05 (1 H, d, *J* 8 Hz, 2^4-H), 5.32 (1 H, ddd, *J* 1, 4, 8 Hz, 2^1-H), 4.34 (2 H, q, *J* 7 Hz, 2^2-OC*H*$_2$CH$_3$), 4.21 (1 H, d, *J* 7 Hz, 2^3-H), 4.10 (1 H, dd, *J* 4, 7 Hz, 2^2-H), 4.03 (2 H, q, *J* 8 Hz, 8-C*H*$_2$CH$_3$), 3.97 (2 H, q, *J* 8 Hz, 12-C*H*$_2$CH$_3$), 3.92 (2 H, q, *J* 7 Hz, 2^3-OC*H*$_2$CH$_3$), 3.81 (3 H, s, 18-CH$_3$), 3.65 (3 H, s, 17-CH$_3$), 3.61 (3 H, s, 7-CH$_3$), 3.58 (3 H, s, 3-CH$_3$), 3.55 (3 H, s, 13-CH$_3$), 1.83 (3 H, t, *J* 8 Hz, 8-CH$_2$C*H*$_3$ or 12-CH$_2$C*H*$_3$), 1.82 (3 H, t, *J* 8 Hz, 12-CH$_2$C*H*$_3$ or 8-CH$_2$C*H*$_3$), 1.38 (3 H, t, *J* 7 Hz, 2^2-OCH$_2$C*H*$_3$), 1.04 (3 H, t, *J* 7 Hz, 2^3-OCH$_2$C*H*$_3$), -3.19 (1 H, s, NH), -3.19 (1H, s, NH). For **3**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.04 (1 H, s, 15-H), 10.04 (1 H, s, 5-H), 9.86 (1 H, s, 10-H), 7.37 (1 H, ddd, *J* 1, 8, 8 Hz, 2^1-CH=C*H*-), 7.12 (1 H, dd, *J* 7, 8 Hz, 2^4-H), 7.05 (1 H, dd, *J* 8, 8 Hz, 2^1-C*H*=CH-), 5.37 (1 H, dd, *J* 2, 8 Hz, 2^1-H), 4.44 (1 H, dd, *J* 4, 7 Hz, 2^3-H), 4.38 (2 H, q, *J* 7 Hz, 2^2-OC*H*$_2$CH$_3$), 4.11 (1 H, dd, *J* 2, 4 Hz, 2^2-H), 4.06 (2 H, q, *J* 8 Hz, 8-C*H*$_2$CH$_3$), 3.97 (2 H, m, 12-C*H*$_2$CH$_3$), 3.82 (3 H, s, 18-CH$_3$), 3.66 (3 H, s, 3-CH$_3$), 3.65 (3 H, s, 17-CH$_3$), 3.62 (3 H, s, 7-CH$_3$), 3.55 (3 H, s, 13-CH$_3$), 3.01 (2 H, dq, *J* 11, 7 Hz, 2^3-OC*H*$_2$CH$_3$), 2.45 (2 H, dq, *J* 11, 7 Hz, 2^3-OC*H*$_2$CH$_3$), 1.83 (3 H, t, *J* 8 Hz, 8-CH$_2$C*H*$_3$), 1.81 (3 H, t, *J* 8 Hz, 12-CH$_2$C*H*$_3$), 1.43 (3 H, t, *J* 7 Hz, 2^2-OCH$_2$C*H*$_3$), -0.02 (3 H, t, *J* 7 Hz, 2^3-OCH$_2$C*H*$_3$), -3.21 (2 H, br s, NH).

(*Received in USA* 22 *October* 1993; *revised* 19 *November* 1993; *accepted* 10 *December* 1993)