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meso-Phenyl Substituted Porphocyanines: A New Class of Functionalized Expanded Porphyrins

Ross W. Boyle, Lily Yun Xie and David Dolphin*

Department of Chemistry, University of British Columbia, 2036 Main Mall
Vancouver, B.C., Canada, V6T 1Z1

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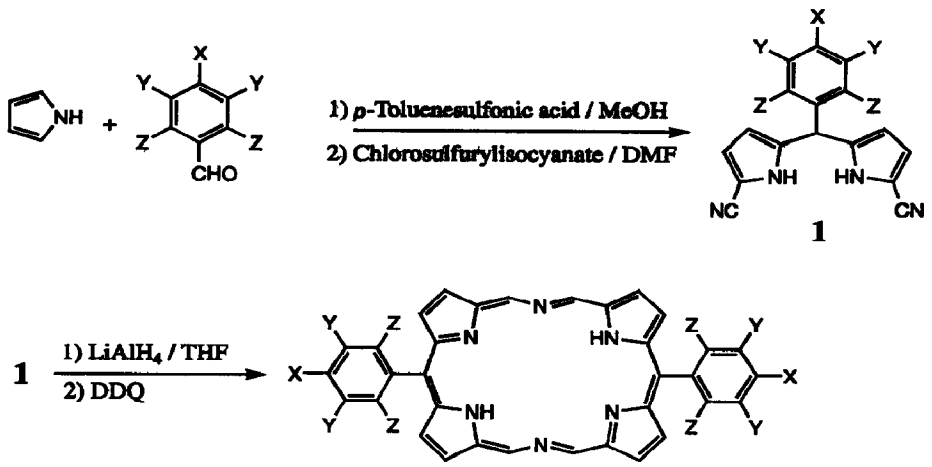
Abstract: Porphocyanines bearing phenyl substituents at both or one of the two available *meso*-positions have been synthesised. Derivatives have also been synthesised with substituents on the phenyl rings and both alkyl and unsubstituted pyrrolic β-positions.

Currently a great deal of interest is being shown in the development of novel porphyrin-like molecules with absorption bands in the far red, or near infrared, region of the electromagnetic spectrum.[1-3] It is anticipated that these molecules will allow enhancement of the photosensitized destruction of neoplastic tissue due to increased transparency of mammalian tissue at these wavelengths. Many of the new photosensitizing species, however, show limited versatility with regard to altering the pattern of substitution, which has been shown to affect biological activity.[4-6] We have, therefore, developed a strategy which allows facile interchange of functional groups on a long wavelength absorbing core. Central to our strategy is the synthesis of a novel series of compounds, the *meso*-phenyl-substituted porphocyanines. The octaethyl derivative of porphocyanine was reported recently.[7] We wish to report here the synthesis of a range of these compounds possessing different substituents at both *meso* and pyrrolic β-positions. The ability of these molecules to bring about photosensitized modification of biological substrates has been demonstrated by the photooxidation of cholesterol.

In order to attain the versatility, with regard to interchanging functional groups, that we required, we decided to synthesize porphocyanine with phenyl rings attached to the two available *meso* positions. In this way substituents could be introduced "indirectly" on the phenyl rings without the need to directly substitute the macrocycle. The key intermediate in this strategy, 1,9-dicyano-5-phenyldipyrromethane **1**, was synthesized in two steps from pyrrole and benzaldehyde (Scheme 1) in 20-30% yield depending on substitution on the benzaldehyde. Reduction of **1** using $LiAlH_4$ followed by DDQ oxidation of the unstable



2a X = Y = Z = H
2b X = Y = OCH_3, Z = H
2c X = Y = Z = F

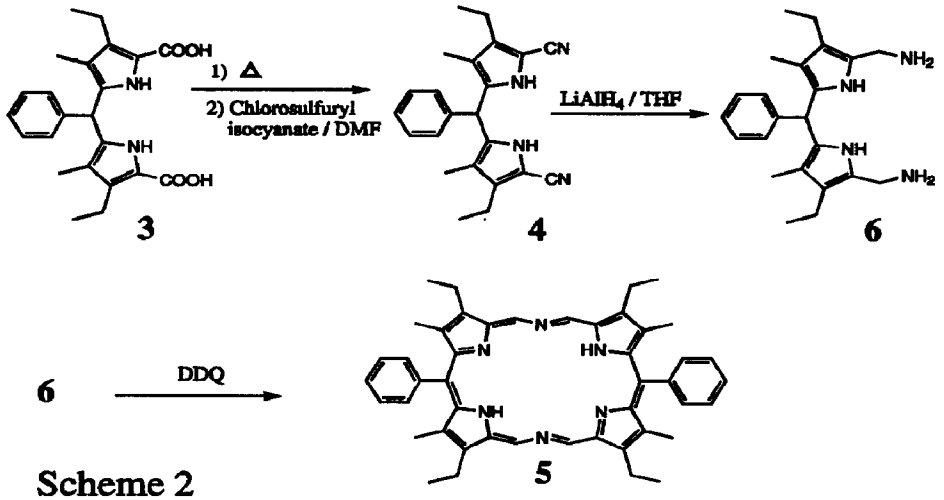
Scheme 1

product gave 12,24-diphenylporphocyanine **2a, b or c** in 30-40% yield. The optical spectrum of **2a**[8] shows a bathochromic shift of 17 nm for the major Q-band relative to octaethylporphocyanine, suggesting some degree of delocalization. Further smaller spectral shifts are also caused by substitution on the phenyl rings.[8] In order to investigate whether the bathochromic shift seen for **2a** indeed resulted from π-overlap between the phenyl rings and the macrocycle we synthesized the porphocyanine core substituted with both *meso*-phenyl and β–alkyl groups. In this way we intended to hinder rotation of the phenyl groups and limit π-overlap. Molecular modeling[9] indicated that ethyl groups adjacent to the phenyl rings would cause unacceptable steric strain on the flat, conjugated system, however, methyl groups might allow the ring to remain flat. 1,9-Dicyano-2,8-diethyl-3,7-dimethyl-5-phenyldipyrromethane **4** was synthesised in 44% yield from 1,9-dicarboxy-2,8-diethyl-3,7-dimethyl-5-phenyldipyrromethane **3** in a two step, one-pot reaction. $LiAlH_4$ reduction followed by DDQ oxidation gave 3,9,15,21-tetraethyl-2,10,14,22-tetramethyl-12,24-diphenyl-porphocyanine **5** in very low yield (<1%) (Scheme 2).

The major Q-band for **5**[10] showed a 12 nm hypsochromic shift relative to **2a**, confirming that the extension of conjugation could indeed be minimized by hindering rotation of the phenyl rings. The extremely small yield for this compound was expected as extensive "ruffling" seen in our model dramatically increased its total energy relative to **2a**. This led us to believe that, in this instance, the previously intractable 1,9-aminomethyl-5-phenyldipyrromethane **6** precursor to the porphocyanine might be isolated, and this indeed proved to be the case.[11]

As high biological activities for photochemotherapeutic agents have been correlated to amphiphilic character[12,13] we synthesized the asymmetric 2,3,21,22-tetraethyl-12-phenylporphocyanine (**7**) in 21% yield by mixed condensation (Scheme 3) and chromatographic separation.[14] The optical spectrum for **7**[15] showed the major Q-band at 804 nm, a wavelength intermediate between octaethyl and diphenylporphocyanine.

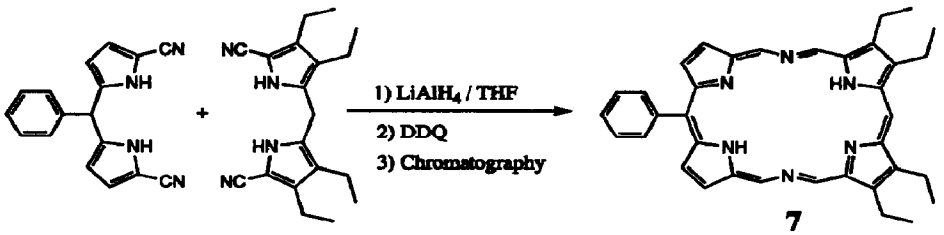
Finally, it is our intention to utilize this series of compounds as catalysts for photosensitized oxidation of biomolecules. However, it has been reported recently that photosensitizers having absorption bands greater than approximately 800 nm may be incapable of generating singlet molecular oxygen ($^1O_2$).[16] As $^1O_2$ is believed to be the cytotoxic agent responsible for the "photodynamic effect", we assayed our compounds for their ability to oxidize cholesterol to 5α-hydroperoxy cholesterol, the oxidation product specific to $^1O_2$.[17]



Scheme 2

Micromolar concentrations of all the di- and monophenyl porphocyanines described here efficiently convert cholesterol to 5α-hydroperoxy cholesterol when irradiated with light of >600nm.

Phenyl porphocyanines then, seem to offer the prospect of long wavelength absorbing photosensitizers which are well characterized, non-isomeric, single substances. The ability to easily change substituents on the phenyl groups allowing the biological activity to be maximized, makes this system especially attractive. Experiments to determine the optimal array of substituents for photodynamic therapy are underway in our laboratory.



Scheme 3

ACKNOWLEDGEMENTS

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8. Spectroscopic data for **2(a)**: ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 6H), 8.44 (m, 4H), 9.38 (d, J = 5.7 Hz, 4H), 9.8 (d, J = 5.7Hz, 4H), 12.95 (s, 4H); UV-vis: λ 452, 598, 640, 814 nm in CH_2Cl_2; HRMS (EI) for $C_{34}H_{24}N_6$ (M^+) calcd. 516.2062, found 516.2058. **2(b)**: ^{1}H NMR ($CDCl_3$) δ 4.1 (s, 12H), 4.25 (s, 6H), 7.67 (s, 4H), 9.44 (d, J = 4.8 Hz, 4H), 9.8 (d, J = 4.8 Hz, 4H), 12.95 (s, 4H); UV-vis: λ 460, 602, 644, 818 nm in CH_2Cl_2; HRMS (EI) for $C_{40}H_{36}N_6O_6$ (M^+) calcd. 696.2696, found 696.2690. **2(c)**: ^{1}H NMR ($(D_3C)_2CO$) δ 9.55 (dd, J = 15.22 Hz, J = 4.15 Hz, 4H), 10.1 (d, J = 4.15 Hz, 4H), 13.24 (s, 4H); ^{19}F NMR ($(D_3C)_2CO$) δ 60.53, 60.92, 61.45 referenced to F_3CCOOH; UV-vis: λ 442, 582, 624, 814 nm in acetone; HRMS (EI) for $C_{34}H_{14}N_6F_{10}$ (M^+) calcd. 696.1120, found 696.1124.
9. Biosym Insight II, San Diego, California.
10. Spectroscopic data for **5**: UV-vis: λ 462, 604, 642, 802 nm in CH_2Cl_2; HRMS (EI) for $C_{46}H_{48}N_6$ (M^+) calcd. 684.3940, found 684.3932.
11. Spectroscopic data for **6**: ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7.4 Hz, 6H), 1.85 (s, 6H), 2.35 (q, J = 7.4 Hz, 4H), 2.7 (brs, 4H), 3.6 (m, 4H), 5.5 (s, 1H), 7.05 (m, 3H), 7.2 (m, 3H), 8.35 (brs, 2H); HRMS (DCI) for $C_{23}H_{32}N_4$ calcd. 364.2627, found 364.2626.
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14. Preparative HPLC (C_{18} reversed phase) isocratic elution with 0.1% aqueous trifluoroacetic acid/0.1% trifluoroacetic acid in acetonitrile (1:4), R_t (**2a**) = 4.6 min; R_t (**7**) = 8.17 min; R_t (octaethylporphocyanine) = 14.94 min.
15. Spectroscopic data for **7**: ^{1}H NMR ($CDCl_3$) δ 2.05 (t, J = 7.5 Hz, 3H), 2.07 (t, J = 7.5 Hz, 3H), 4.21 (q, 7.5 Hz, 2H), 4.32 (q, 7.5 Hz, 2H), 7.88 (m, 3H), 8.41 (m, 2H), 9.31 (d, J = 4.5 Hz, 2H), 9.7 (d, J = 4.5 Hz, 2H), 10.3 (s, 1H), 12.72 (s, 2H), 12.96 (s, 2H); UV-vis: λ 456, 592, 632, 804 nm in CH_2Cl_2; HRMS (EI) for $C_{36}H_{36}N_6$ (M^+) calcd. 552.3001, found 552.2996.
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