Syntheses of Cationic Porphyrins and Chlorins

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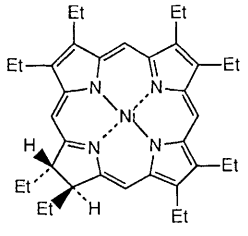
Treatment of vinyl-chlorins **2**, **4**, **5** and -porphyrins **8** with *N,N*-dimethylmethyleneammonium iodide affords the corresponding vinyl-extended Mannich adducts **3**, **6**, **7**, **9**; with deuteroporphyrin IX dimethyl ester **10** the product is the bis-Mannich base **11**; quaternization of the products is readily accomplished with methyl iodide to afford a general method for synthesis of water-soluble cationic sensitizers for use in photodynamic therapy.

Photodynamic therapy (PDT) is an experimental method for treatment of malignant tumours.[1] The clinical treatment involves administration of a compound that can localize preferentially in tumour cells and act as a photosensitizer to give a photoreaction resulting in destruction of tumour cells,[2] presumably by formation of singlet oxygen.[3] It is advantageous to use light in the red region of the visible spectrum since long-wavelength light penetrates further into tissue. Photofrin-II® is presently the only drug approved for advanced clinical testing. In recent years a number of photosensitizers that absorb in the range of 630–780 nm, such as porphyrin oligomers,[4–10] purpurins,[11] benzoporphyrins,[12] bacteriochlorophylls,[13] pheophorbides,[14] chlorins,[15] phthalocyanines,[16] naphthalocyanines[17] and oxo-chlorins[18] have been reported in the literature. Many porphyrin-type compounds investigated so far contain carboxylate functions, which are anionic in nature at physiological pH. Recently, it was demonstrated[19,20] that carcinoma cells also take up cationic molecules and retain them longer than normal cells, showing highly selective, light-induced *mitochondrial* damage and cell killing.[20] The present communication describes a procedure for transformation of readily available anionic tetrapyrroles into cationic derivatives, with the eventual aim that such photosensitizers might now target mitochondrial loci, and because of their positive charges, be somewhat more water-soluble than the anionic series.

The Mannich salt *N,N*-dimethylmethyleneammonium iodide (DMMAI) has been used for introduction of (dimethylamino)methyl side chains onto corrin and pyrrole units.[21,22] Treatment of nickel(II) octaethylchlorin **1** with up to 20 equiv. of DMMAI under variable reaction conditions gave no detectable *meso*-substituted product; the starting material **1** was re-isolated as the sole product. Reaction of chlorin e_6 trimethyl ester **2** with DMMAI gave a polar product (78% yield) after chromatography. ^{1}H NMR showed three downfield *meso* protons indicating that *meso*-substitution has not occurred, and alterations in the vinyl proton pattern showed that this moiety was the site of reaction. A J_{HH} value of 17 Hz for the 2a-H was indicative of *trans*-coupling and led to the assignment of structure **3**† for the new product. Vilsmeier formylation of metal complexes of chlorin e_6 has previously been shown to occur similarly at the vinyl position.[23] The optical spectrum of **3** was virtually identical with that of the starting material. We extended this methodology to the pheophorbide series to obtain **4** (70) and **5** (72%) (from **6** and **7**, respectively). In all cases, NMR spectroscopy showed no *meso*-substitution, and the reaction was cleanly limited only to the vinyl substituents. Protoporphyrin IX dimethyl ester **8** likewise gave the adduct **9**.

In contrast, reaction of deuteroporphyrin IX dimethyl ester **10** with DMMAI produced 2,4-bis[(dimethylamino)methyl]-deuteroporphyrin IX dimethyl ester **11** in quantitative yield.

In both the porphyrin and chlorin series described above, the rate of reaction was significantly faster when the corresponding zinc(II) complexes were used as starting materials;



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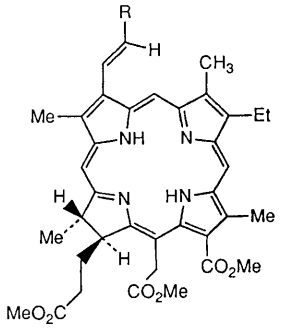
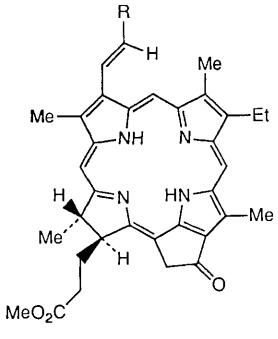
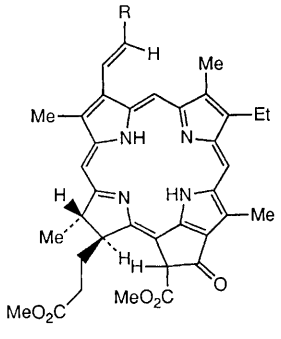


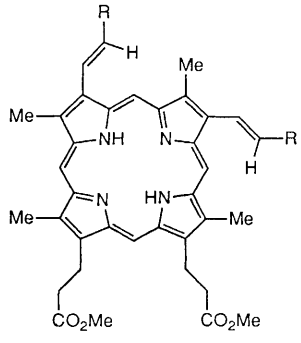
2; R = H
3; R = CH_2NMe_2
12; R = $CH_2\overset{+}{N}Me_3\ I^-$



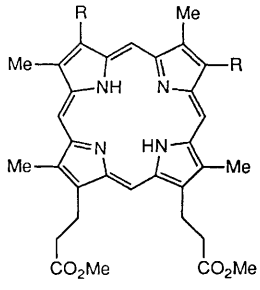
4; R = H
6; R = CH_2NMe_2
13; R = $CH_2\overset{+}{N}Me_3\ I^-$



5; R = H
7; R = CH_2NMe_2
14; R = $CH_2\overset{+}{N}Me_3\ I^-$



8; R = H
9; R = CH_2NMe_2
15; R = $CH_2\overset{+}{N}Me_3\ I^-$



10; R = H
11; R = CH_2NMe_2
16; R = $CH_2\overset{+}{N}Me_3\ I^-$

† All new compounds were characterized by ^{1}H NMR spectra, elemental combustion analyses and/or high resolution mass spectra.

demetallation using acid treatment afforded the same metal free products. The *N,N*-dimethylamino compounds **3**, **4**, **5**, **9** and **11** were converted into the corresponding water-soluble quaternary ammonium salts (**12–16**) by stirring briefly with methyl iodide in acetone. Biological studies are in progress and will be reported elsewhere.

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