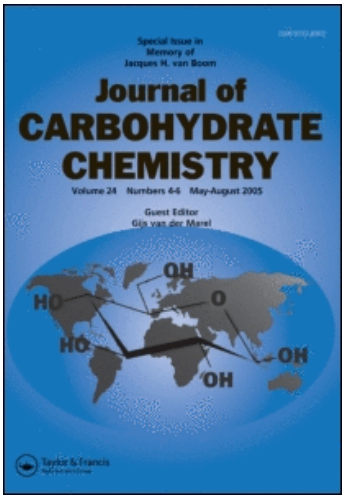

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COMMUNICATION

GLYCOSYLATED HEMATOPORPHYRINS: A NEW APPROACH IN CANCER PHOTOTHERAPY?

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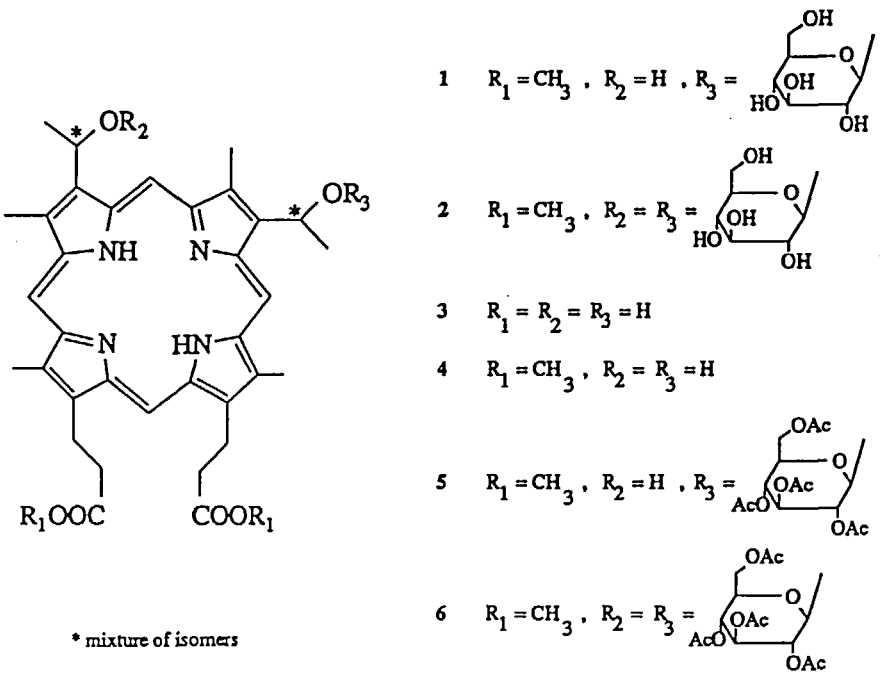
Although the phenomenon is not fully understood, it is now well established that some porphyrins have a natural tendency to concentrate more in malignant tumors than in normal tissue. This property has found an application in photodynamic therapy of cancers in which a tumor, with an enriched concentration of porphyrin, can be selectively destroyed by applying light, without damage to surrounding cells.[1]

Previous studies have shown that this accumulation could be favoured by modulating the lipophilic[2] and/or hydrophilic[3] nature of peripheral substituents of the porphyrin. Generally anionic groups such as sulfonate[4] or cationic groups (*N*-methylpyridinium)[5] are employed to increase the water solubility of the molecule. Neutral hydrophilic groups (phenol) were also used for that



Scheme

purpose.[6,7] Very recently some glycosylated porphyrins were reported in the literature [9,10] but, although they exhibited good water-solubility, absence of lipophilic substituents resulted in low penetrability across cell membranes. The synthesis of some glycosylated chlorins was also recently described.[11]

We report here the synthesis of a new class of asymmetrically modified porphyrins bearing two alkyl groups as lipophilic substituents as well as one or two glycosidic moieties as non-ionic hydrophilic substituents in compounds 1 and 2 respectively (scheme).

Since hematoporphyrin derivatives, a complex mixture of porphyrins, are currently employed in photodynamic therapy of tumors,[1] hematoporphyrin 3 was chosen as a model substrate in this study.

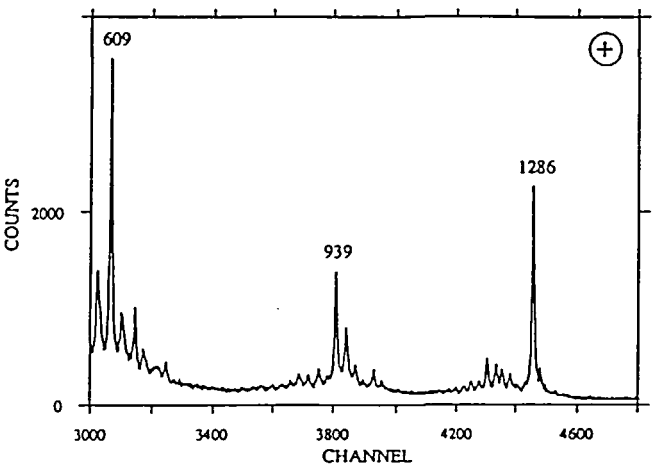


FIGURE 1. Positive ions P.D. mass spectrum of compound 6. The abscissas are proportional to the square root of the mass.

Hematoporphyrin dimethyl ester 4 was prepared by esterification of 3 with methanol in the presence of dry HCl,[12] purified by preparative thin-layer chromatography (ethyl acetate/hexane 4:1) and characterized by ^{1}H NMR.

Glycosylation of 4 was realized with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide 7 in the presence of mercuric salts.[13] In a typical experiment, at 55°C a solution of 7 in nitromethane was added to a mixture of 4, $HgBr_2$ (2.5 molar eqts), $Hg(CN)_2$ (17 molar eqts) and 3A molecular sieves in toluene-nitromethane (2/1). Even after long reaction time (24 h), the reaction was not complete and TLC and HPLC analysis indicated the formation of two new compounds. When two molar equivalents of 7 were employed, monoglycosylated porphyrin 5 was the major compound after 6 h of reaction and was isolated by preparative TLC in 30% yield. When a larger excess of 7 was used (4 molar eqts), the diglycosylated porphyrin 6 was isolated in 52% yield.

Due to their high molecular weight, compounds 5 and 6 were characterized by plasma desorption mass spectrometry (PDMS).[14] In both cases the molecular ion was detected (m/z 956 and 1286 for compound 5 and 6 respectively) together

with strong peaks corresponding to the loss of one or two acetylated sugar units [m/z 609 for 5-OR_3, 939 for 6-OR_2 and 609 for 6-OR_2-R_3 $+H^+$] (Figure). Absorption spectra of compounds 5 and 6 in dichloromethane show a broad and strong Soret band at 410 nm together with the four other bands usually observed for such porphyrins (505, 525, 572 and 625 nm).

The proton NMR spectra of 5 and 6 in deuterochloroform (500 MHz) show only the expected signals, although these ones are rather poorly resolved. This is often the case with porphyrins because of their aggregation in solution as well as, in this case, the presence of several diastereoisomers in the carbon skeleton of the porphyrin.[15] Moreover, examination of the signal of anomeric protons of the sugar moiety indicated β configuration for the glycosidic bond.[16]

Deacetylation of 5 and 6 was possible without cleaving the methyl ester function. It was carried out at room temperature with KCN (0.6 molar eqts in methanol, 24 h) or MeONa (10 molar eqts in methanol, 24 h) to afford deacetylated porphyrins 1 and 2 in 70-80% yield.

The study of the cellular uptake of these modified porphyrins is in progress. Moreover some malignant cells are selectively enriched with carbohydrates receptors,[17] so these glycosylated porphyrins could improve the selectivity of targeting in phototherapy of tumors.

Acknowledgments: Dr. Jean-Marc Valéry is gratefully acknowledged for recording the ^1H NMR spectra.

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