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SYNTHESIS OF OXYGEN ANALOGUES OF THE SULFCHLORINS

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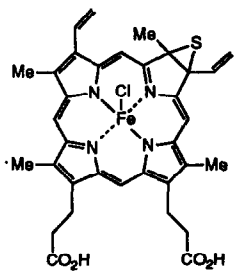
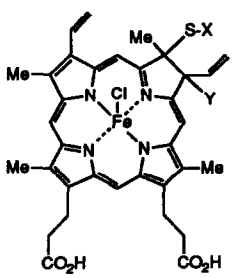
Abstract: The oxygen analogues of sulfchlorin-A and -C were synthesized from protoporphyrin-IX dimethyl ester. The developed methodology employs a modified Mitsunobu reaction and produces the first porphyrin epoxides and porphyrinones derived from protoporphyrin-IX.

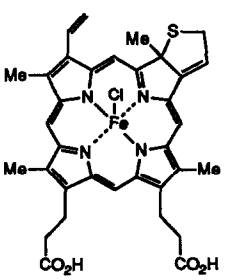
Sulfmyoglobin (SMb) and sulfhemoglobin (SHb) are heme protein derivatives of normal proteins in which the heme prosthetic group has been altered by modification of a pyrrole subunit and incorporation of a sulfur atom into the porphyrin macrocycle.[1-3] SHb is of practical medical interest, as it is formed *in vivo* under certain pathological conditions. The sulfheme prosthetic group can be extracted from the protein but has a short lifetime.[4] In 1986, Chatfield et al.[5] reported that high field ^{1}H NMR spectroscopy of SMb revealed the presence of three forms: A, B and C (designated S_AMb, S_BMb, and S_CMb in order of appearance), each with different chemical reactivity. The C form of sperm whale SMb can be extracted to give a relatively stable green heme, named sulfheme-C.[5,6] Form C was identified as the thiolene containing structure (3), the sulfheme-A precursor of which is presumably the episulfide (1). Isotope labeling of the vinyl positions confirmed that it is the 4-vinyl group that reacted in both the extracted sulfheme and in S_CMb.[7] Thus, vinyl group participation in the formation of the stable C-form was established, though it was shown that other forms of sulfmyoglobin can be formed in the absence of vinyl groups. At about the same time, Timkovich et al.[6] came to the same structural conclusions about the sulfheme-C, and were able to isolate and characterize sulfchlorin-C, the metal free derivative of (3). We present here novel syntheses of the oxygen analogues of sulfchlorin-A and sulfchlorin-C. The methodology offers a general access to novel porphyrin epoxides and to their isomeric ketochlorins.



(1)
Sulfhemin-A



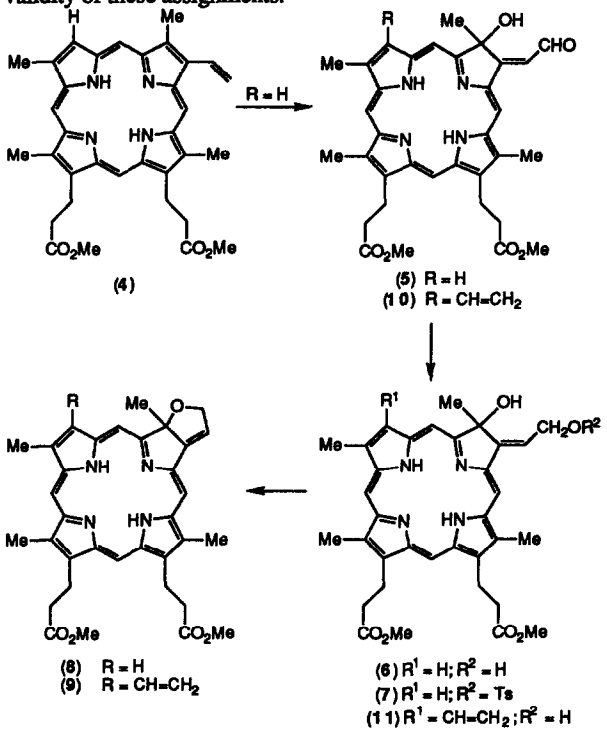
(2)
Sulfhemin-B



(3)
Sulfhemin-C

Oxygen was conveniently incorporated into the skeleton of pemptoporphyrin-IX dimethyl ester (4) by means of the so-called "photoprotoporphyrin" photo-oxidation reaction,[8] to give (5) in good yield. Subsequent borohydride reduction gave the diol (6). Tosylation took place preferentially at the secondary hydroxy group to give (7), but in the presence of 4-dimethylaminopyridine, a small amount of a relatively mobile by-product was also formed. This was isolated in a pure form and possessed an optical spectrum strikingly similar to that of Timkovich et al.[6] for their S662 sample which had been shown to bear an exocyclic thiolene ring. Low resolution mass spectra gave the highest mass peak at *m/e* 580, in complete agreement with

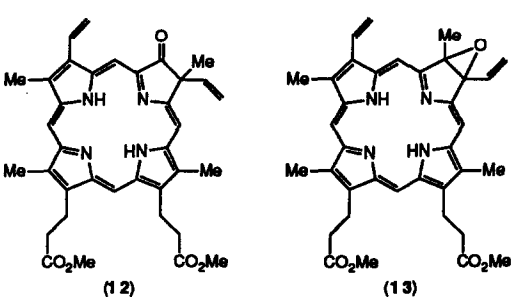
the cyclized structure (8). The ^{1}H NMR spectrum also provided evidence in favor of the oxasulfchlorin-C analogue. The two single proton doublet of doublets at 5.4 and 5.6 ppm and the triplet at 7.1 ppm are assigned to the diastereomeric methylene protons and the vinylic proton attached to the saturated ring. A series of decoupling experiments verified the validity of these assignments.



We next directed our attempts towards converting the diol (**11**), derived from isophotoprotoporphyrin-IX (**10**) into thiol via a thiolester.[9] The reaction involved addition of the diol-thiolacetic acid mixture to the preformed adduct of Ph_3P/di-isopropylazodicarboxylate (DIAD). Despite producing a substance which could not be chromatographed, it prompted us to more fully explore the Mitsunobu reaction and its variations.[10] When DIAD was added dropwise to the mixture of (**11**) and Ph_3P at 0°C in the absence of an acidic component,[11] a highly mobile brown and a less mobile green chromatographic band were almost immediately apparent on a thin layer chromatography plate.

The optical spectra showed, for both chlorins, absorption maxima at 650 nm (brown) and 648 nm (green), respectively. The ^{1}H NMR spectra, in addition to offering characteristic chlorin evidence, such as split NH resonances and nicely resolvable propionates, confirmed in both the presence of a vinyl group attached to a reduced ring. Moreover, mass spectrometry indicated that the two structures were isomeric.

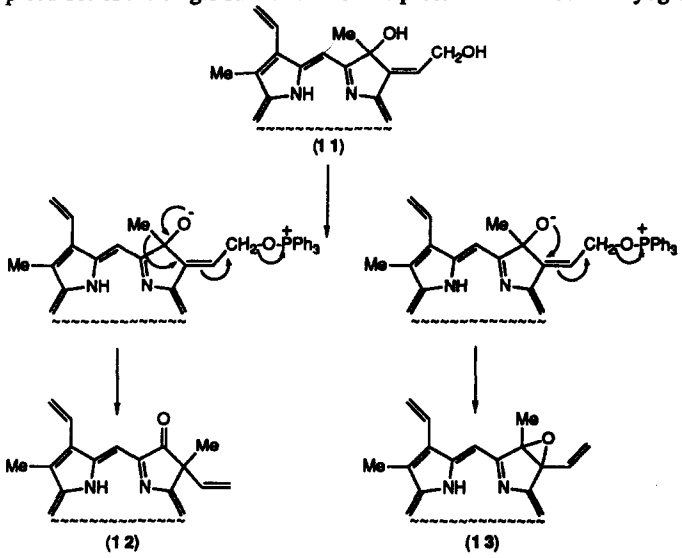
The brown band was unequivocally assigned to the porphyrinone (**12**) on the basis of its characteristic visible spectrum, the typical ^{1}H NMR 3H:1H pattern[12,13] in the meso proton region, and its carbonyl stretching frequency in the IR spectrum ($\nu_{C=O}$ 1710 cm^{-1}). This is the first example of a porphyrinone obtained in a way other than by using the H_2O_2/H_2SO_4 or the OsO_4 procedures. It is also the first ketochlorin derived from protoporphyrin-IX; notably, the vinyl groups are retained in our approach, but the much harsher conditions of previous methods could not accomplish this.



The low field region of the proton NMR of the green product is shown in Figure 1. The β-vinyl protons of the aliphatic vinyl appear at 6.09 (*cis*) and 6.25 ppm (*trans*), exhibiting an approx. 0.7 ppm downfield shift compared with the analogous resonances in the porphyrinone molecule (**12**). The α proton from the same vinyl group appears at 6.73 ppm, showing a 0.4 ppm shift. Finally, a methyl singlet at 2.51 ppm, assigned to the methyl on the reduced ring, is also shifted downfield by 0.3 ppm.

The above results, together with ^{13}C-NMR data, point to the epoxide structure (**13**), the isomer of porphyrinone (**12**). Scheme 1 shows a possible mechanism for the formation of

the porphyrinone (12) and the epoxide (13) from (11). Only a single other case of a β–β epoxide has been reported in the porphyrin literature,[14] this being a meso-substituted nickel complex obtained under irrational circumstances. Most importantly, the protoporphyrin-IX epoxide of ring B is indeed the oxygen analogue form of sulfchlorin-A, the proposed precursor of the single stable form of the prosthetic form of sulfmyoglobin, sulfheme-C.[5]



Scheme 1: Formation of the porphyrinone (12) and epoxide (13) from (11).

To establish the general applicability of the above methodology, a number of model epoxides and porphyrinones were synthesized starting from the simplest symmetric porphyrins, such as octaethylporphyrin (OEP; **15**) and etioporphyrin-II. As a first step the appropriate monovinyl derivative was prepared.[15] In the case of OEP (**15**), treatment with osmium tetroxide afforded the *vic*-dihydroxychlorin, along with the tetrahydroxy bacteriochlorin. Acid treatment of these resulted in the vinylheptaethylporphyrin (**16**) and the mixture of 1,6 and 1,5 divinylhexaethy porphyrins (**17**) and (**18**) respectively. Photooxidation, borohydride reduction and subsequent dehydration under the aforementioned conditions generated the corresponding ketochlorins (**19**), (**20**) and (**21**) and the epoxides (**22**), (**23**) and (**24**), which perfectly matched the spectroscopic characteristics of the analogous compounds in the protoporphyrin-IX series.

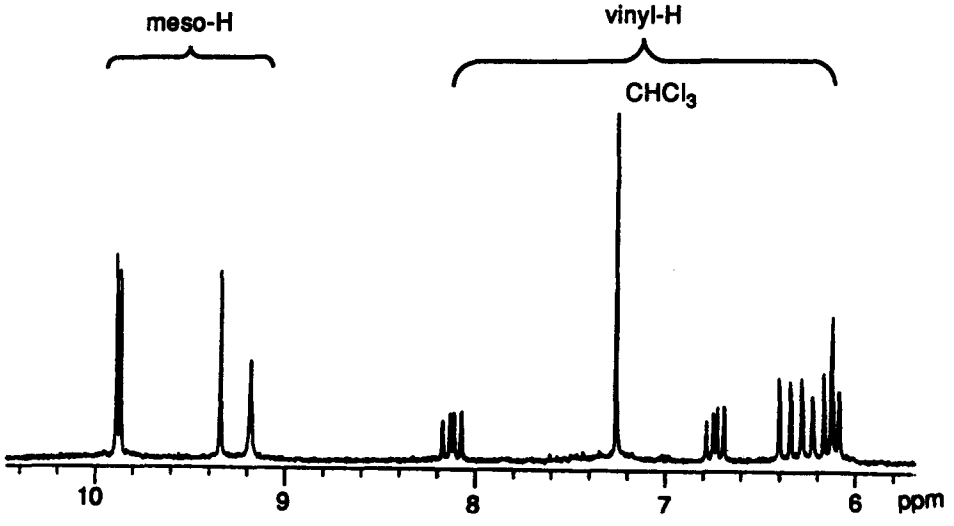
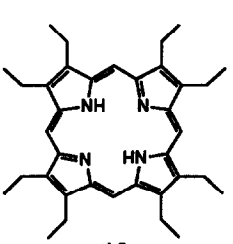


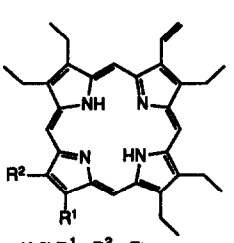
Figure 1: Low field (meso, vinyl proton) region of the proton NMR spectrum, in $CDCl_3$, of epoxide (13).

Having synthesized the analogues of sulfchlorin-A and -C, we then proceeded to investigate methods for ring-opening of the epoxide (13) to give a oxasulfchlorin-B analogue similar to (2). We chose to investigate epoxide opening

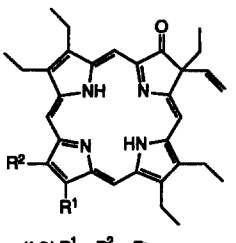
on an alumina surface.[16] After forming a slurry of alumina in CH_2Cl_2, water was added (4% by weight of alumina) as a "doping" agent and the slurry was stirred for 20 h at room temperature, after which time no epoxide was left. The product was shown to be the ring-expanded product (**9**), clearly demonstrating the feasibility of the S_AMb to S_CMb transformation already observed in proteins.[5,7]



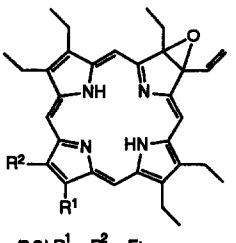
(15)



(16) $R^1 = R^2 = Et$
(17) $R^1 = Et; R^2 = CH{=}CH_2$
(18) $R^1 = CH{=}CH_2; R^2 = Et$



(19) $R^1 = R^2 = Et$
(20) $R^1 = Et; R^2 = CH{=}CH_2$
(21) $R^1 = CH{=}CH_2; R^2 = Et$



(22) $R^1 = R^2 = Et$
(23) $R^1 = Et; R^2 = CH{=}CH_2$
(24) $R^1 = CH{=}CH_2, R^2 = Et$

Acknowledgements.

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