REACTIVITY OF ZINC(II) 5-OXONIAPROTOPORPHYRIN-IX: SYNTHESIS OF THE FIRST 5-OXONIA-15-PHLORIN

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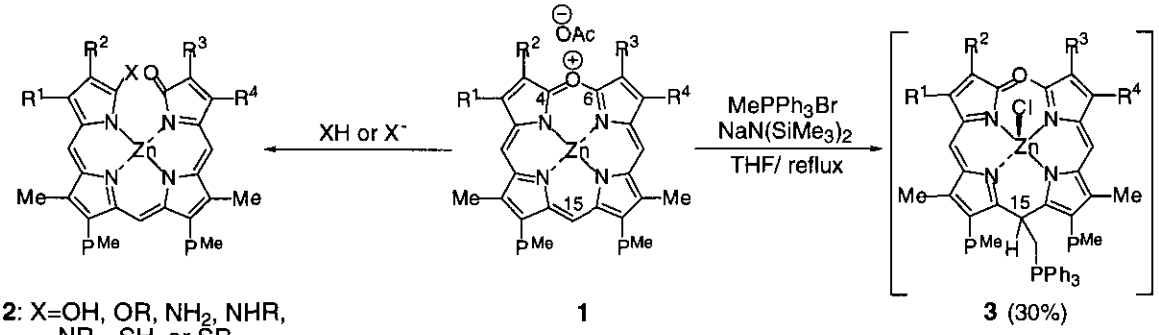
Abstract - The reactivity of zinc(II) 5-oxoniaprotoporphyrin-IX with selected carbon nucleophiles is demonstrated to be highest at the 15-C_{meso} position, enabling the first synthesis of a 5-oxonia-15-phlorin which has been isolated and studied by X-Ray crystallography.

The study of oxygen transport mediated through the blood has been a topic of considerable interest for many years. Although heme [iron(II) protoporphyrin-IX] was isolated in the mid-1800s,[1] its role in an O_2 binding capacity in hemoglobin was not confirmed until its synthesis by Fischer in the early 1900s.[2] The breakdown of hemoglobin involves the dissociation of the prosthetic heme group and the apoprotein, followed by the catabolism of heme to bile pigments which, after further degradation, are excreted from the body in the feces. Although research on heme catabolism has been carried out in the last three decades,[3] some of the putative intermediates have not been well characterized and thus, the mechanistic details are often unclear. It is postulated that one key intermediate is verdoheme [iron(II) 5-oxoniaprotoporphyrin-IX], and that the study of oxoniaporphyrin reactivity may contribute to a more complete understanding of the formation and properties of biologically significant open-chain tetrapyrroles.

Oxoniaporphyrins have been demonstrated to react regioselectively with heteroatomic nucleophiles (e.g. ^-OH, ^-OR, NH_3, NH_2R, NHR_2, ^-SH, and ^-SR) at the 4- and 6-C_α positions (see **1**) to provide 1- or 19-substituted-deoxybiliverdins (**2**).[4] However, the reactivity of carbon based nucleophiles had not been tested, and due to the aforementioned results, we assumed the most reactive position would be adjacent to the 5-*meso*-oxygen. Recently, we have reported[5] the isolation of 15-*meso*-alkylated porphyrins from the reaction of Grignard reagents with 5-*meso*-formylporphyrins. We surmised that the 5-*meso*-oxygen of an oxoniaporphyrin could have the same electronic effect on the 15-C_{meso} position as does a 5-formyl group, and that nucleophilic attack at C_{15} was probable despite experience with other nucleophiles.

One oxoniaporphyrin that could be readily synthesized from commercially available sources, with a substitution pattern similar to verdoheme, was 5-oxoniaprotoporphyrin-IX dimethyl ester. The starting

point of our synthesis was naturally occurring bilirubin, which was converted according to published procedures into biliverdin[4a] and then into zinc(II) 5-oxoniaprotoporphyrin-IX dimethyl ester.[4b] Proton NMR spectroscopy revealed that it contained a slight impurity (*ca.* 15-20%) of the so-called type-XIII regioisomer. We believe that this impurity, as previously observed,[6] was formed during the bilirubin oxidation step. Since this minor component simply involved the juxtaposition of a methyl and a vinyl group, and it would not affect the reactivity of the sample, we proceeded with our studies using the oxoniaporphyrin -IX and -XIII mixture (**1**). Initially, we chose a phosphorus ylide, a nucleophile that would react with a ketone functionality but not with an ester. The simplest Wittig reagent, methylene-triphenylphosphorane, was prepared by reacting $MePPh_3Br$ (1 eq.) and $NaN(SiMe_3)_2$ (1 eq.) in dry THF under argon, followed by addition of the oxoniaporphyrin (Scheme 1).



2: X=OH, OR, NH_2, NHR, NR_2, SH, or SR

1

3 (30%)

R^1=R^3=Me, R^2=R^4= vinyl (type-IX isomer), or R^2=R^3=Me, R^1=R^4=vinyl (type-XIII)

P^{Me} = $CH_2CH_2CO_2Me$

Scheme 1

A red-purple product (**3**) was isolated in 30% yield after column chromatography (silica gel, 20% MeOAc/CH_2Cl_2) and recrystallization (CH_2Cl_2/cyclohexane). It was clearly not a 1- or 19-substituted deoxybiliverdin, as evidenced by UV-visible spectroscopy [λ_{max} 462 nm (sharp)]; thus, nucleophilic attack did not occur in the 4- or 6-C_α positions. At this point, we believed that the ylide must have reacted at the 15-C_{meso} position, but the exact structure could not be ascertained from the spectral data at hand.[7] Subsequent X-Ray diffraction analysis[8] revealed the structural nature of the product, and it was indeed substituted in the C_{15} position (Figure 1). Overall, the molecule (**3**) is neutral, but in order to depict the structure it is necessary to show four bonds to the zinc ion, and an oxonium oxygen and a tetravalent phosphorus; hence the structure (**3**) is shown in square brackets. The major regioisomer present in the crystal is the -XIII isomer, and this is due to the relative instability of the type-IX isomer when subjected to silica gel chromatography. We speculate that this destabilization is due to the *exo*-vinyl substituent, as has been noted for other systems by McDonagh *et al.*[6a,c] Some interesting features of **3** are the sp^3 hybridized *meso*-carbon and the fully conjugated (through the *meso*-oxygen) tetrapyrrole unit. Scheme 2 shows a plausible mechanistic explanation for formation of **3**, involving nucleophilic attack at C_{15} followed by restoration of the conjugation pathway to afford the tetrapyrrole fragment. In an effort to determine if the regioselectivity observed was simply a result of the bulkiness of the ylide, the reactivity of **1** with MeMgBr

(1.2 eq.) was tested. Once again, a product was isolated, of which the type-IX isomer was unstable, that was in all respects similar spectroscopically [$\delta_{15\text{-}meso\text{-}H}$, 4.57 (q, 1H); λ_{max} 462 nm (sharp), 495 nm (sh); MS m/z 670.2 (M^+), 655.2 (M^+- CH_3)] to **3**.

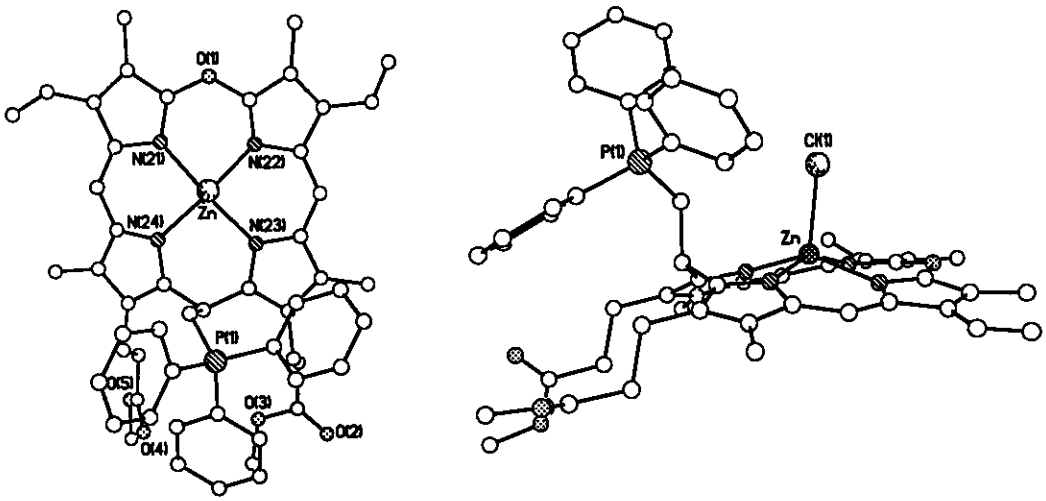
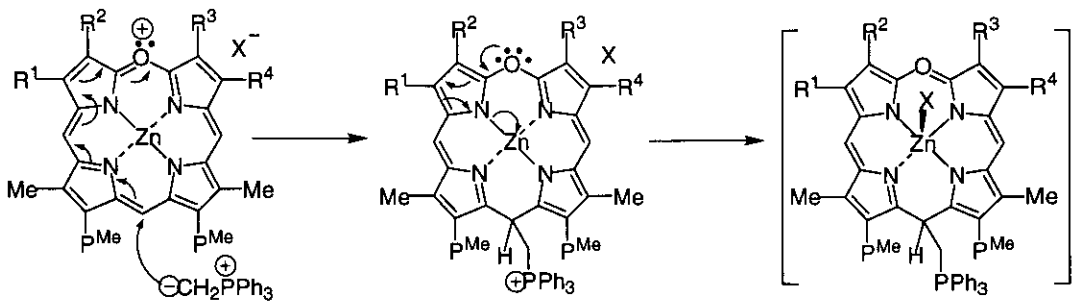


Figure 1: Top and side views of the molecular structure of Zinc(II) 5-oxonia-15-triphenylphosphoniummethylphlorin chloride (**3**). Hydrogen atoms have been omitted for clarity and only the major type-XIII component is shown.



Scheme 2

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7. For the -IX and -XIII type-isomer mixture of **3**: ^{1}H-NMR ($CDCl_3$): δ 2.15, 2.16, 2.17, 2.36, 2.45 (all s, 12H, 4x β-CH_3), 2.27 (m, 8H, 2x β-$CH_2CH_2CO_2CH_3$), 3.59 (s, 6H, 2x -CO_2CH_3), 4.44 (m, 2H, -CH_2PPh_3), 4.97 (m, 1H, 15-*meso*-H), 5.31, 5.46, 5.63, 6.01, 6.81, 7.04 (all m, 6H, 2x β-CH=CH_2), 7.36, 7.44, 7.45 (all s, 2H, 2x *meso*-H), 7.54, 7.60, 7.65 [all m, 15H, -$CH_2P(C_6H_5)_3$]; MS m/z (rel. intensity %) 931.4 (M^+- Cl, 96), 655.2 (M^+- CH_2PPh_3, 100).

8. Crystal Data (**3**): $C_{54}H_{49}N_4O_5ClPZn$, monoclinic, $P2_1/n$, a = 9.152(8), b = 31.62(2), c = 16.275(12) Å, β = 99.65(6)°, V = 4643(6) Å^3, Z = 4, ref. F^2, R1 [$I>2.0\sigma(I)$] = 0.0618, w$R2$ = 0.1649. Complete data have been deposited with the Cambridge Crystallographic Data Centre.
Selected structural data: Zn-N(21) 2.109(5) Å, Zn-N(22) 2.105(5) Å, Zn-N(23) 2.081(5) Å, Zn-N(24) 2.079(4) Å, Zn-Cl(1) 2.335(2) Å, C(4)-O(1) 1.355(7) Å, C(6)-O(1) 1.369(7) Å, C(15)-C(151) 1.559(7) Å, C(151)-P(1) 1.805(5) Å.

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