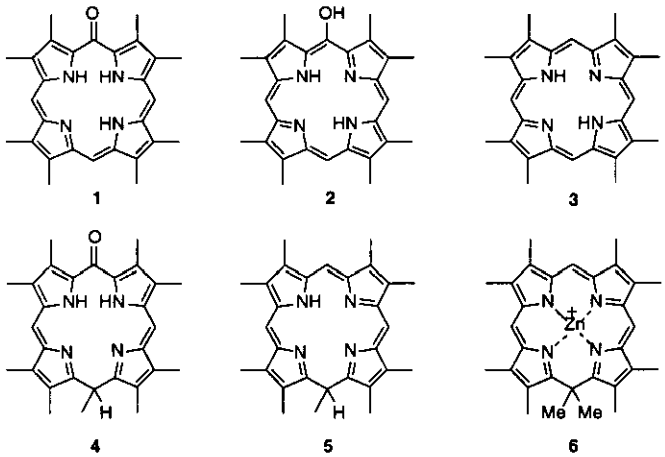
MACROCYCLES CONTAINING FIVE PYRROLE SUBUNITS: THE ISO-OXOPENTAPHYRIN SYSTEM

Richard G. Khoury, Laurent Jaquinod, Liem T. Nguyen, and Kevin M. Smith*[†]

Department of Chemistry, University of California, Davis, California 95616, U.S.A.

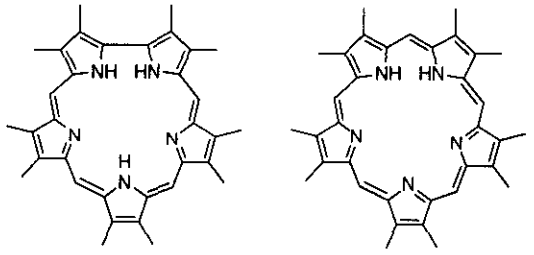
Abstract - Reaction of a 1,9-diformyl-5-dipyrroketone (**11**) with a tripyrrane (**12**) affords a novel pentapyrrolic macrocycle (**13**) characterized as an iso-oxopentaphyrin (λ_{max} 787 nm). Along with the iso-oxopentaphyrin, small amounts of oxophlorin (**20**) and porphyrin (**21**) are also produced. Mechanistic implications are discussed.

Oxophlorins (e.g. **1**) are the keto tautomers of 5-hydroxyporphyrins (**2**). The iron complexes of oxophlorins have been shown to be key intermediates in the conversion of hemes into biliverdins, catalyzed by the enzyme heme oxygenase.[1] A considerable amount of work has been published on the synthesis and chemistry of the oxophlorin system, and on the aromaticity of the system compared with, for example, porphyrins.[2] We recently showed[3] that oxophlorins (**1**) possess significantly less aromatic stabilization than do porphyrins (**3**) because the iso-oxophlorin system (e.g. **4**) (possessing no macrocyclic conjugation) can be favored to relieve the steric congestion due to abutting peripheral substituents. On the other hand, the isoporphyrin system (**5**) is highly unstable with respect to tautomerization to the aromatic porphyrin macrocycle (**3**),[4] unless geminal 5,5-substituents are present which prevent aromatization, as in **6**.[5]

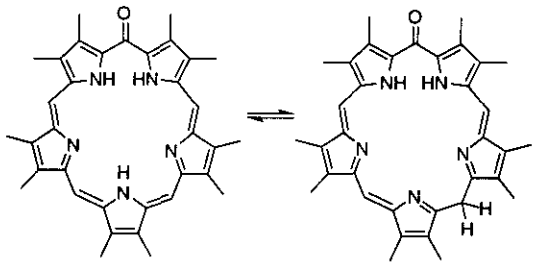


[†] Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Expanded porphyrin chromophores have attracted much attention recently,[6] and emphasis has focused on the synthesis and characterization of new compounds containing five or more pyrrole subunits; typical examples of the pentapyrrole systems are sapphyrins (**7**)[7] and pentaphyrins (**8**).[8] Their expanded π-systems allow the study of aromaticity in large conjugated systems, and their expanded core size might lead to the coordination of larger ions, thus expanding upon the coordination properties of the porphyrins. Pentaphyrins (**8**) are the pentapyrrolic analogues of porphyrins (**3**). Likewise, oxopentaphyrins (**9**) are the pentapyrrolic analogues of the oxophlorins (**1**). Bearing in mind the rich chemistry which has been uncovered in the oxophlorin series of tetrapyrroles, we felt it would be appropriate to see whether oxopentaphyrins could be synthesized, and additionally to estimate their aromaticity vis-a-vis the corresponding iso-oxopentaphyrin macrocycle (**10**).



7 **8**

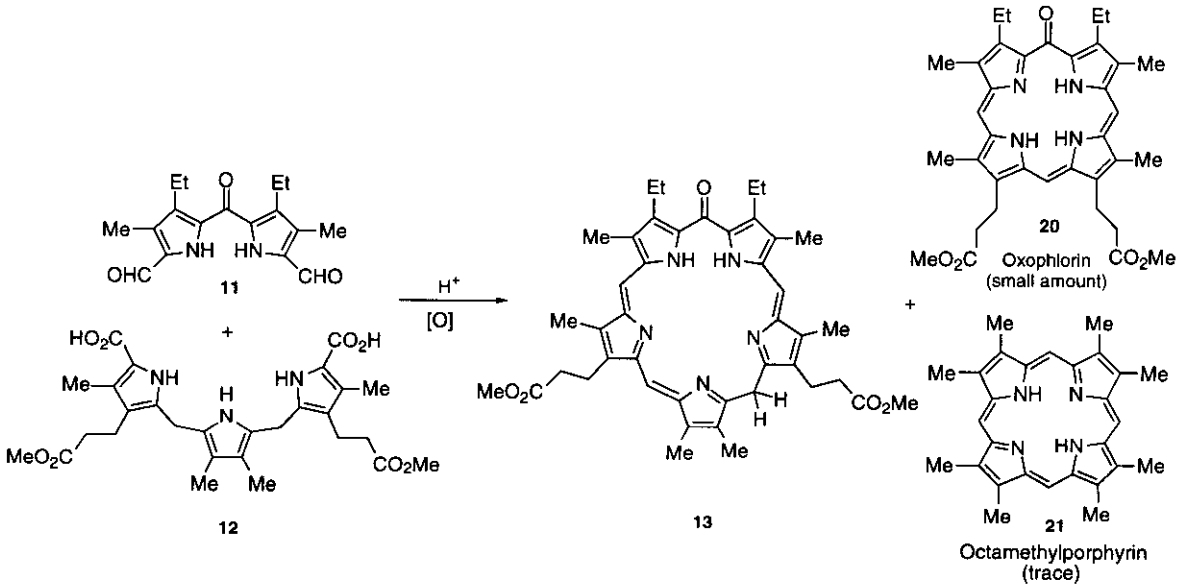


9 **10**

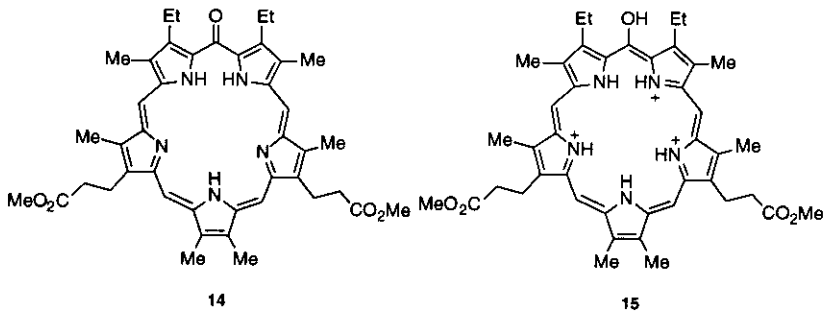
Since the optical spectra of (blue) oxophlorins are significantly red-shifted compared with (red) porphyrins, we suspected that oxopentaphyrin electronic absorption spectra should be red-shifted when compared with those of pentaphyrins. Independent of whether the pentapyrrolic macrocycle existed in the fully conjugated (**9**) or "iso" form (**10**), we felt that significantly red-shifted spectra should result anyway.

Preparation of our target oxopentaphyrin was approached (Scheme 1) *via* a MacDonald type ("3+2") condensation of a 1,9-diformyldipyrroketone (**11**)[9] with a tripyrrane 1,14-dicarboxylic acid (**12**).[10] The product which resulted (64% yield) when the reaction was carried out in the presence of oxygen was the iso-oxopentaphyrin (**13**)[11] [^{1}H-NMR (triprotonated iso-macrocycle) δ: meso-H 5.98, 6.83, 7.05; meso-CH_2 3.93, NHs 8.28, 8.84, 9.55, 10.34, 10.77]; two other minor products were also isolated (see below). Figure 1A shows the optical spectrum of the iso-oxopentaphyrin (**13**). An attempt to form a fully conjugated system (**14**) by reacting the iso-oxopentaphyrin (**13**) with acetic anhydride in pyridine, as performed for oxophlorins[12] and iso-oxophlorins[3] was unsuccessful. It seems clear that, as with certain

oxophlorin systems bearing sterically demanding peripheral substituents,[3] the aromatization energy which would be gained by assumption of the fully conjugated system (**14**) is not measurably larger than the steric flexibility afforded by the sp^3 hybridized meso carbon. Mild acid accomplished protonation of the central imine nitrogens of the iso-oxopentaphyrin system, but strong acid afforded the fully conjugated tricationic oxopentaphyrin species (**15**) which possessed a very strong "Soret-type" absorption (Figure 1B) and upfield NH protons in the ^{1}H-NMR spectrum [NHs -0.80 (br, 2H), -1.21 (3H); meso-Hs 10.30 (2H), 10.08 (2H) ppm]. Both the optical and ^{1}H-NMR spectral changes were fully reversible upon neutralization. These data caused us to eliminate the possibility (Scheme 2) that the products from our oxopentaphyrin synthesis might be the dihydroiso-oxopentaphyrin compound (**16**), obtained by simple tautomerism from the initially formed macrocycle (**17**) in the MacDonald reaction; macrocycle (**16**) [and the conjugated tautomer (**18**)] would afford a non-aromatic 24 π-electron species (**19**) upon protonation, which would not demonstrate either the strong "Soret-type" band, or the shielded NH protons. In contrast, formation of **13** requires an oxidation step (commonly accomplished with air in the MacDonald reaction) compared with formation of **16** and **17**.



Scheme 1: MacDonald Reaction to Give Iso-oxopentaphyrin and Oxophlorin and Porphyrin By-products.



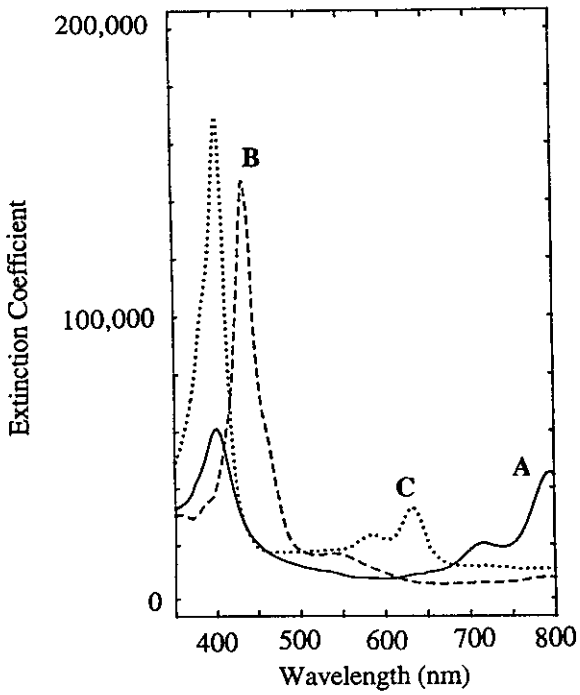
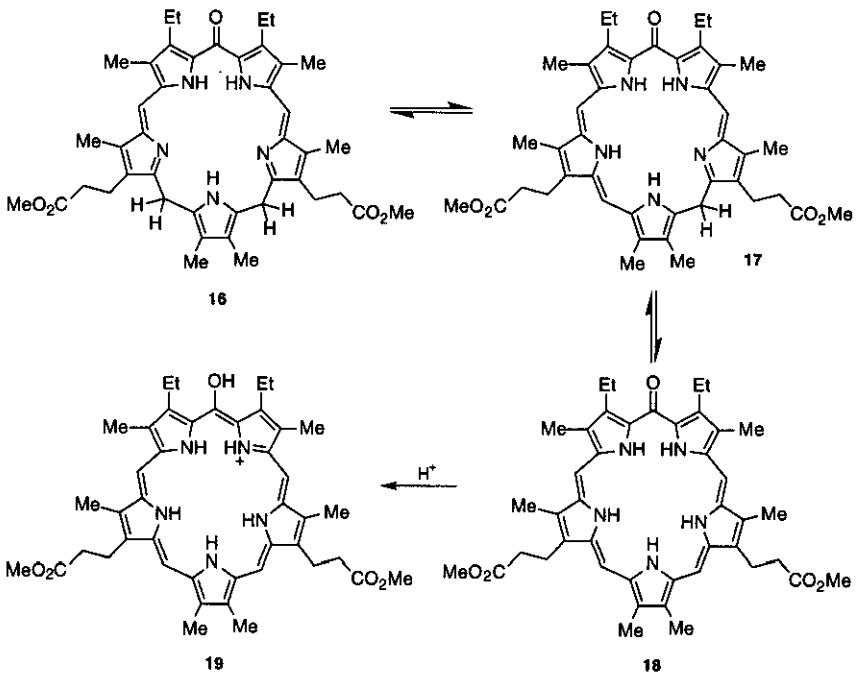
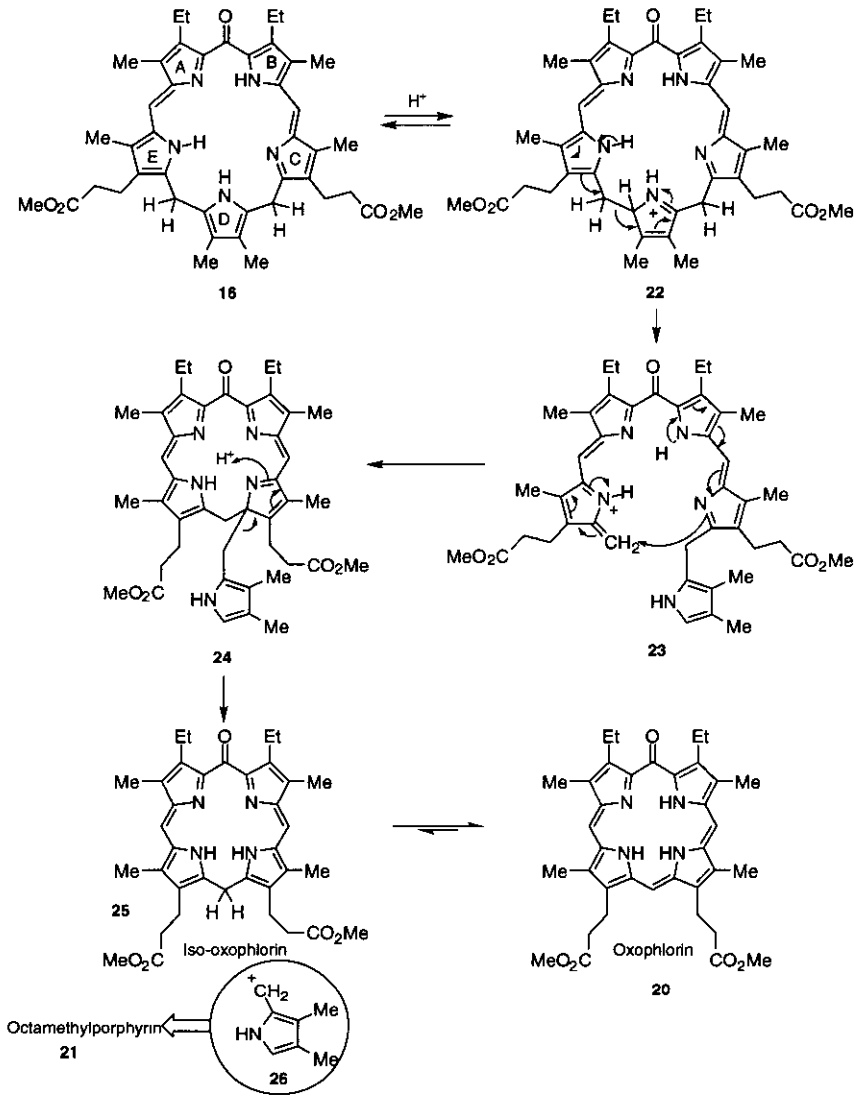


Figure 1: Optical Spectra (in CH_2Cl_2) of (A) Iso-oxopentaphyrin free base (**13**); (B) Oxopentaphyrin trication (**15**); and (C) Oxophlorin free base (**20**).



Scheme 2: Formation of a 24 π-Electron System (**19**) by Protonation of Dihydro-oxopentaphyrins (**17**) or (**18**).



Scheme 3: Proposed Mechanism for Formation of Oxophlorin (**20**) and Porphyrin (**21**) By-products.

As mentioned above in connection with Scheme 1, two by-products were obtained in the synthesis of the iso-oxopentaphyrin (**13**); these were the oxophlorin (**20**) (optical spectrum - Figure 1C), and a very small amount of octamethylporphyrin (**21**). MS and ^{1}H-NMR spectroscopy showed the oxophlorin (**20**) to be uniquely one compound, and this was incompatible with intervention of pyrrole redistribution reactions[13] in the acid catalyzed reaction between the tripyrrane (**12**) and the dipyrroketone (**11**) (Scheme 1). Formation of **20** requires one pyrrole subunit to be extruded either during, or after, the formation of the pentapyrrolic macrocycle. We suspect that the pyrrole ring is lost uniquely after the macrocyclization reaction because only one oxophlorin is obtained. This interpretation was aided by our choice of substituent array on the tripyrrane; when 3,7,8,12-tetraethyl-2,13-dimethyltripyrrane-1,14-dicarboxylic acid was used we obtained 3,7,13,17,18,22-hexaethyl-2,8,12,23-tetramethyl-iso-5-oxopentaphyrin[14] along with 3,7,13,17-tetraethyl-

2,8,12,18-tetramethyl-5-oxophlorin[15] and octaethylporphyrin as by-products. Scheme 3 outlines a proposed mechanism for the formation of both the oxophlorin and porphyrin in these reactions.

By analogy with known dipyrromethane scrambling mechanisms,[13] protonation would be expected to take place on ring D of the dihydroiso-oxopentaphyrin (**17**), adjacent to the methylene carbon, to give (**22**); bond cleavage to give **23**, followed by recyclization to a thermodynamically more stable tetrapyrrole macrocycle (**24**) would be expected to give uniquely the iso-oxophlorin (**25**) after methylenepyrrolium ion elimination. Tautomerization would then give oxophlorin (**20**). The 2-methylene-3,4-dimethylpyrrolium cation (**26**) would then afford octamethylporphyrin (**21**) through standard tetramerization procedures.[16] Similar pyrrole subunit scrambling reactions have previously been reported in syntheses of pentapyrrolic macrocycles.[8a]

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (HL-22252) and the National Science Foundation (CHE-96-23117). Mass spectrometric analyses were performed by the UCSF Mass Spectrometry Facility (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614.

REFERENCES

1. (a) P. O' Carra, in 'Porphyrins and Metalloporphyrins', ed. by K. M. Smith, Elsevier, Amsterdam, 1975, pp. 123-150 and references therein. (b) R. Tenhunen, H. S. Marver, and R. Schmid, *Proc. Natl. Acad. Sci. U.S.A.*, 1968, **61**, 748. (c) R. Tenhunen, H. S. Marver, and R. Schmid, *J. Biol. Chem.*, 1969, **244**, 6388.

2. A. H. Jackson, G. W. Kenner, and K. M. Smith, *J. Chem. Soc. (C)*, 1968, 302.

3. R. G. Khoury, L. Jaquinod, D. J. Nurco, and K. M. Smith, *Chem. Commun.*, 1996, 1143.

4. R. B. Woodward, *Pure Appl. Chem.*, 1961, **2**, 383; *Ind. Chim. Belge.*, 1962, **27**, 1293.

5. E.g. H. Xie and K. M. Smith, *Tetrahedron Lett.*, 1992, **33**, 1197. K. M. Barkigia, M. W. Renner, H. Xie, K. M. Smith, and J. Fajer, *J. Am. Chem. Soc.*, 1993, **115**, 7894. S. Gentemann, S. H. Leung, K. M. Smith, J. Fajer, and D. Holten. *J. Phys. Chem.*, 1995, **99**, 4330.

6. J. L. Sessler and A. K. Burrell, *Topics Curr. Chem.*, 1991, **161**, 177.

7. A. K. Burrell, B. Hemmi, V. Lynch, and J. L. Sessler, *J. Am. Chem. Soc.*, 1991, **113**, 4690.

8. (a) H. Rexhausen and A. Gossauer, *J. Chem. Soc., Chem. Commun.*, 1983, 275. (b) A. Gossauer, *Chimia*, 1983, **37**, 341; 1984, **38**, 45. (c) J. L. Sessler, S. J. Weghorn, Y. Hiseada, and V. Lynch, *Chem. Eur. J.*, 1995, **1**, 56. (d) 'The Porphyrins', ed. by D. Dolphin, Vols. I-VII, Academic Press, New York, 1978.

9. P. S. Clezy, A. J. Liepa, and G. A. Smythe, *Aust. J. Chem.*, 1970, **23**, 589.

10. J. L. Sessler, T. Marai, V. Lynch, and M. Cyr, *J. Am. Chem. Soc.*, 1988, **110**, 5586

11. mp 207-210°C. ^{1}H-NMR (trication iso-oxopentaphyrin): δ ppm, 1.19 (t *J* = 6.8 Hz, 3H), 1.32 (t *J* = 7.0 Hz, 3H), 1.78 (s, 3H), 2.05 (s, 3H), 2.26 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 2.69 (s, 3H), 2.88(m, 2H), 3.12 (m, 4H), 3.16 (m, 4H), 3.77 (s, 3H), 3.85 (s, 3H), 3.93 (s, 2H), 5.98, 6.83, 7.05 (each s, 1H), 8.28, 8.84, 9.55, 10.34, 10.77 (each s, 1H). UV-VIS: λ_{max} nm, 422 (ε 67 200) , 717 (25 900), 787 (58 100). HRMS (FAB), Calcd for $C_{43}H_{51}N_5O_5$: 717.3889; found 717.39101. Anal. Calcd for $C_{43}H_{51}N_5O_5$•1.5 H_2O: C, 69.33; H, 7.31; N, 9.40. Found: C, 69.59; H, 7.20; N, 9.13.

12. A. H. Jackson, G. W. Kenner, G. McGillivray, and K. M. Smith, *J. Chem. Soc. (C)*, 1968, 294.

13. K. M. Smith, in 'Porphyrins and Metalloporphyrins', ed. by K. M. Smith, Elsevier, Amsterdam, 1975, pp. 36-38.

14. mp 203-205°C. ^{1}H-NMR: δ ppm, 1.22 (t *J* = 6.5 Hz, 3H), 1.38 (m, 15H), 2.11 (s, 3H, 1-CH_3), 2.33 (s, 6H), 2.41 (s, 3H, 1-CH_3), 2.78(m, 12H), 3.95 (s, 2H), 6.07, 6.78, 6.99 (each s, 1H), 8.35, 8.74, 9.64, 10.39, 10.65 (each s, 1H, NH). UV-VIS: λ_{max} nm, 424 (ε 65 500), 717 (26 900), 789 (58 200). HRMS (FAB), Calcd for $C_{41}H_{49}N_5O$: 627.3; found 627.3. Anal. Calcd for $C_{41}H_{49}N_5O$•2.5 H_2O: C, 73.17; H, 8.09; N, 10.41. Found: C, 72.89; H, 7.93; N, 10.46.

15. mp 300°C. ^{1}H-NMR: δ ppm (dication in $CDCl_3$/TFA), 1.45 (t *J* = 7.0 Hz, 6H), 1.88 (t *J* = 6.9 Hz, 6H), 3.38 (s, 6H), 3.42 (s, 6H), 3.96 (m, 8H), 9.84 (s, 1H), 10.19 (s, 2H). UV-VIS: λ_{max} nm = 402 (ε 182 500) , 554 (29 350), 618 (65 400). HRMS (FAB), Calcd for $C_{32}H_{38}N_4O$: 494.3045; found 494.3049. Anal. Calcd for $C_{32}H_{38}N_4O$•H_2O: C, 76.31; H, 7.80; N, 11.12. Found: C, 76.59; H, 7.56; N, 11.07.

16. K. M. Smith, in 'Porphyrins and Metalloporphyrins', ed. by K. M. Smith, Elsevier, Amsterdam, 1975, pp. 32-33.

Received, 28th April, 1997