SYNTHESIS OF A DIFURYL ANALOG OF THE OXOPHLORINS

Timothy D. Lash* and Yanet G. Motta†

* Faculty of Chemistry, Northern State College, Aberdeen, South Dakota 57401, USA

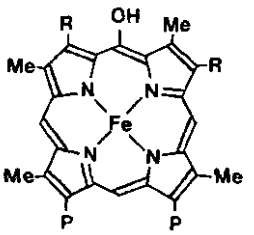
† Department of Chemistry, University of Wisconsin, River Falls, WI 54022, USA

Abstract - Condensation of 2,2'-bis(5-formylfuryl)methanone with a 2,2'-dipyrrylmethane-5,5'-dicarboxylic acid in trifluoroacetic acid afforded a macrocycle (6) analogous to the oxophlorin (oxyporphyrin) system. IR and UV spectra indicate that this compound exists as the keto tautomer (6) rather than the fully conjugated enol form (7a). (6) did not react with acetic anhydride-pyridine and the enol acetate (7b) could not be isolated, although the diperchlorate salt was formed under acidic conditions.

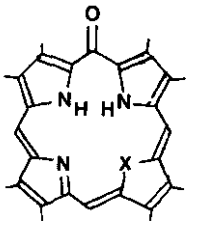
Specific oxidative cleavage of heme leads[1] to the bile pigment biliverdin. This process is believed to take place via the iron complex of a meso-hydroxyporphyrin (1a) and studies[2] with α-hydroxymesoheme (1b) support this. Metal free meso-hydroxyporphyrins (2a) have been synthesised by a variety of methods[3-5] and are important intermediates[3,4] in the total synthesis of porphyrins. These compounds afford royal blue solutions in organic solvents; the Soret band in the near ultraviolet is somewhat reduced in intensity compared to the porphyrins and this indicates that the macrocyclic ring current is diminished. IR and NMR spectra suggest[5a] that these compounds exist as the keto tautomeric species (2a) and the enol form is only favored in the metal complexes and dicationic species. They may be considered as oxo derivatives of the dihydroporphyrin phlorin, a system first discerned by Woodward[6] in the total synthesis of chlorophyll-a, and for this reason have been named[5a] oxophlorins.

The furan and thiophene oxophlorin analogs (2b) and (2c) have been synthesised[7] and the spectroscopic and chemical properties of these macrocycles presented an illuminating contrast to those of the tetrapyrrolic compounds. We were interested in extending these studies to the related macrocycle (6) and the synthesis of this compound was approached via the coupling of a dipyrrylmethane (5) and a difuryl ketone (4).

2,2'-Bis(5-formylfuryl)methanone (4) was prepared[8,9] from (3) by consecutive treatment with n-butyl lithium and ethyl N,N-dimethylcarbamate in ether at -20°C, followed by acid hydrolyses. The known 2,2'-dipyrrylmethane-5,5'-dicarboxylic acid (5; R = H)[10], prepared by hydrogenolyses of the corresponding dibenzyl ester (5; R = $-CH_2C_6H_5$), was dissolved in trifluoroacetic acid at room temperature and a molar equivalent of (4) added portionwise over 10 min. The oxophlorin analog (6) was isolated after chromatography on neutral alumina as deep purple



(1) a. R = V; b. R = Et



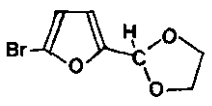
(2) a. X = NH; b. X = O; c. X = S

Me = $-CH_3$

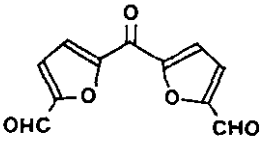
V = $-CH=CH_2$

P = $-CH_2CH_2CO_2H$

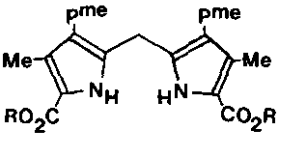
pme = $-CH_2CH_2CO_2Me$



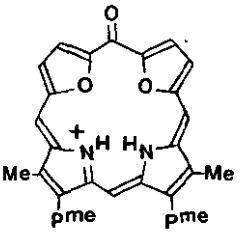
(3)



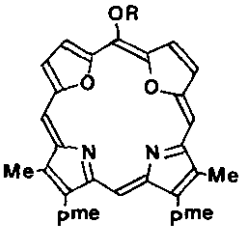
(4)



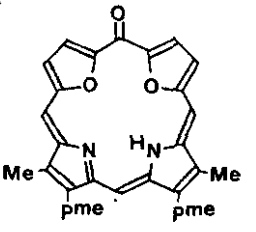
(5)



(8)



(7)



(6)

a. R = H; b. R = -COMe

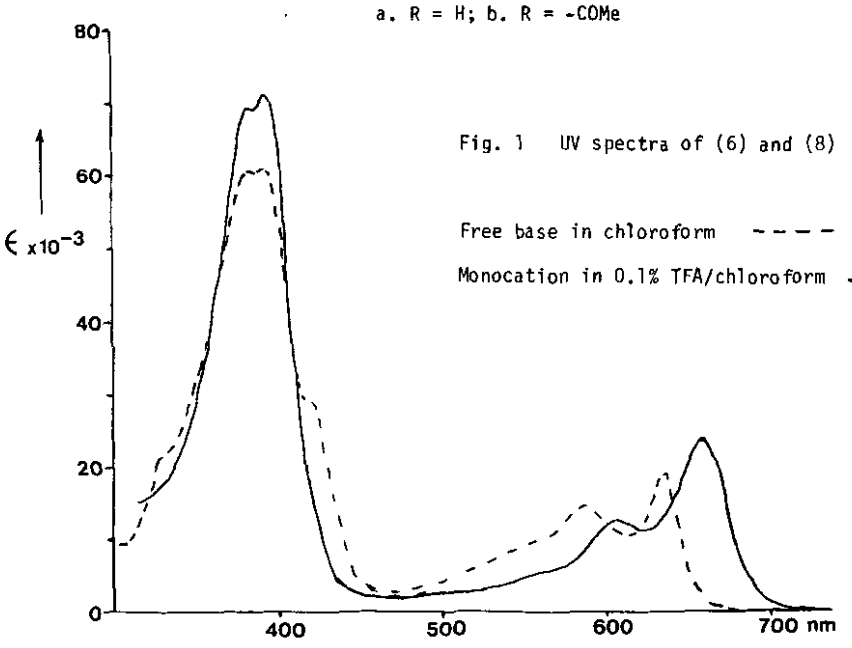


Fig. 1 UV spectra of (6) and (8)

Free base in chloroform - - - -

Monocation in 0.1% TFA/chloroform ——

crystals (mp >300°C) in 15% yield. The compound was sparingly soluble in neutral solvents forming deep blue solutions which exhibit bright red porphyrin-like fluorescence under long wave ultraviolet light. The IR spectrum of (6) did not show an absorption in the OH region, indicating that little, if any, of the enol tautomer (7a) was present, and an absorption at 1551 cm^{-1} was recorded reminiscent of that observed for the oxophlorin system (C=O stretch).

The UV spectrum in chloroform (fig. 1) gave a band of low intensity in the Soret region indicating that the conjugation of the macrocycle is significantly interupted, presumably by the cross conjugated carbonyl. Addition of small quantities of TFA lead to the formation of a discrete species showing marked bathochromic shifts of minor absorptions but little change in the Soret absorptions (fig. 1). This was ascribed to the monocationic species (8). In 10% TFA/chloroform an intense Soret band was observed at 400 nm (log ϵ 5.25) corresponding to the fully conjugated dication (9).

The very low solubility of (6) in common organic solvents precluded the attainment of the proton NMR spectrum for the free base. However the oxophlorin analog was sufficiently soluble in d-TFA and the resultant NMR spectrum (fig. 2) was consistent with the fully conjugated dication structure (9). The very low field shifts of the aromatic protons are similar to those seen for porphyrin dications; these reflect the macrocyclic ring current of the fully aromatic system together with further deshielding due to the protonated nitrogens. Careful examination of the NMR spectrum shows the presence of two doublets for two protons each (corresponding to the furan β-protons) and one singlet corresponding to two bridge protons. The third bridge proton has been lost, presumably due to exchange with the d-TFA. This might be reasonably explained if the conjugated dication (9) were in equilibrium with the C-protonated species (10). Similar proton exchange has been noted in the oxophlorins[5a].

Attempts to react (6) with acetic anhydride-pyridine under a variety of conditions failed to afford the enol acetate (7b), although oxophlorins readily undergo this reaction. However treatment of the oxophlorin analog (6) in acetic anhydride with perchloric acid led to the precipitation of the diperchlorate salt of (7b) as bright red crystals, mp 240°C (decomp.). ν_{max} 1773, 1732 cm^{-1}; λ_{max} (log ϵ) (chloroform) 377 (4.61), 393 (4.56), 512 (3.66), 578 (3.60), 629 (3.14) nm. Attempts to isolate the free base led to elimination of acetic acid and reformation of (6). (6) also failed to complex with zinc, copper (II), nickel and cobalt (II) salts, in variance with the tetrapyrrolic compounds. Further studies are now in progress and the synthesis of a dithienyl analog is in hand.

ACKNOWLEDGEMENTS The authors thank Dr. Bruce Murray (River Falls) for his encouragement. YGM gratefully acknowledges support from the Fundacion Gran Mariscal de Ayacucho (Venezuela).

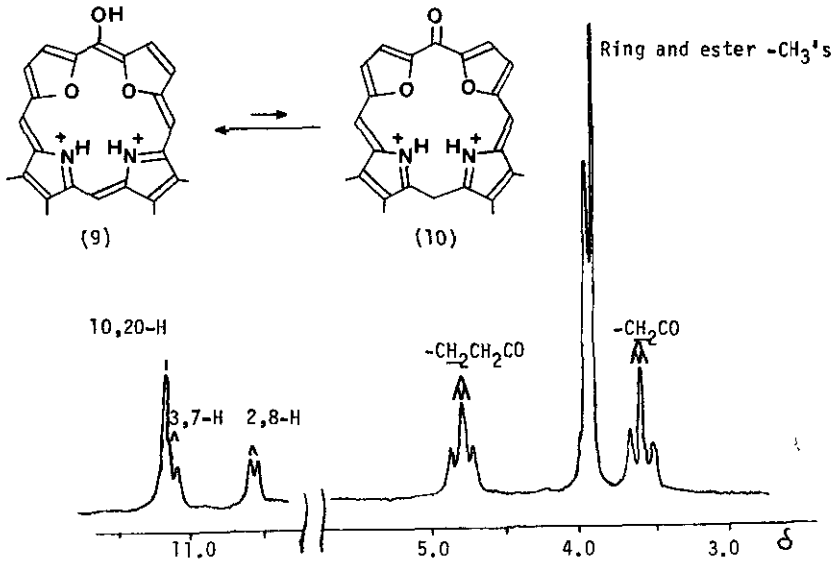


Fig. 2. Proton NMR (90 MHz) of dication (9) in d-TFA

REFERENCES

1. A. H. Jackson in "Iron in Biochemistry and Medicine", eds. A. Jacob and M. Wormwood, Academic Press, London, 1974, p. 145.
2. T. Kondo, D. C. Nicholson, A. H. Jackson and G. W. Kenner, Biochem. J., 1971, 121, 601.
3. A. H. Jackson and G. W. Kenner, Nature, 1967, 215, 1126; P. S. Clezy and A. H. Jackson, in "The Porphyrins", ed. D. Dolphin, Academic Press, 1978, Vol. 1, p. 265.
4. P. S. Clezy in "The Porphyrins", ed. D. Dolphin, Academic Press, 1978, Vol. 2, p.103.
5. a. A. H. Jackson, G. W. Kenner and K. M. Smith, J. Chem. Soc. (C), 1968, 294;
   b. P. S. Clezy, F. D. Looney, A. W. Nichol and G. A. Smythe, Aust. J. Chem., 1966, 19, 1481.
6. R. B. Woodward, Pure Appl. Chem., 1961, 2, 383; ibid., Ind. Chim. Belge, 1962, 1293.
7. P. S. Clezy and V. Diakiw, Aust. J. Chem., 1971, 24, 2665.
8. T. M. Cresp and M. V. Sargent, J. C. S. Perkin Trans., 1973, 2961.
9. U. Michael and A.-B. Hornfeldt, Tetrahedron Lett., 1970, 5219.
10. A. F. Mironov, T. R. Ovsepyan, R. P. Evstigneeva and N. A. Presbrazenskii, Zhur. Obshch. Khim., 1965, 35, 324.

Received, 12th July, 1983