THE COMPARATIVE REACTIONS OF PORPHIN, 5-BROMOPORPHIN, 2-BROMOPORPHIN AND 5-NITROPORPHIN

Louis R. Nudy, Cherylann Schieber, and Frederick R. Longo*

Chemistry Department

Drexel University

Philadelphia, PA 19104, U.S.A.

Vinod S. Agarwala

Naval Air Development Center

Warminster, PA 18914, U.S.A.

Abstract - In a continuing study of the aromaticity of the parent porphyrin, porphin, we have conducted the nitration of 5-bromoporphin and the bromination of 5-nitroporphin to determine the presence of substituent directing effects. In addition we have compared the rates of Cu(II) incorporation by these structures with the rate for porphin. Our results substantiate the Fleischer-Webb model for the π-electron pathway in porphin.

INTRODUCTION

We have previously reported studies of the electrophilic nitration and bromination of porphin[1,2,3]. All substitutions occurred at the meso positions and definite predictable directing effects were observed: A nitro group will direct to the adjacent meso position, whereas N-acetyl-amino and bromo groups activate the opposite meso position. All of our observations can be explained in terms of the Fleischer-Webb (FW) model of porphyrin aromaticity.[4] This model includes the four meso-bridge carbon atoms, the eight α-pyrryl carbon atoms and the four pyrrolenine nitrogen atoms as an inner aromatic pathway; it excludes the eight β-pyrryl carbon atoms.

In order to continue our study of the chemical behavior of porphin and examine the directing effects and aromaticity, we have extended the bromination and nitration studies; in addition we have examined the effect of meso substituents on the rate of Cu(II) incorporation.

EXPERIMENTAL

Visible absorption spectra were measured at room temperature in spectral grade solvents with the Perkin Elmer Model 320 Spectrophotometer. The NMR spectra were taken on a Joel FT 90Q, except where noted otherwise, and mass spectra were recorded with the Finnegan 4021GS/MS/DS System and the HP 5995 System.

Bromination of Porphin with DBICA. For example, to 28.6 mg of porphin (9.2×10^{-5} mol) was added 20 ml of concentrated H_2SO_4. The solution was kept at 3-5°C or at 25°C during the addition of 13.8 mg of dibromoisocyanuric acid in 20 ml of concentrated H_2SO_4. The solution was stirred at this temperature for one hour and then poured into 350 ml of ice water. After addition was complete, the solution was saturated with sodium acetate (120g). The porphyrinic materials were then extracted with toluene; this solution was dried over anh. sodium sulfate, filtered and evaporated to a volume of 100 ml. To this solution was added 100ml of hexane and the resulting mixture was separated by flash chromatography on silica gel into six distinct porphyrinic bands, which were identified in order of elution: 5,10,15,20-tetrabromoporphin 1; 5,10,15-tribromoporphin 2; 5,15-dibromoporphin 3a; 5,10-dibromoporphin 3b; 5-bromoporphin 4; and unreacted porphin. All products, other than 1 and 3b, were previously reported and were identified by visible absorption spectrometry.[3]

TABLE 1. BROMINATIONS OF PORPHIN

Reagent	Solvent	Temp/°C	Time/min	A	B	C	D	E	F
1	$CHCl_3$	1-3	10	24%	54%	0	15%	0	0
2	$CHCl_3$	2-4	10	31%	53%	0	15%	0	0
3	$CHCl_3$	1-3	10	20%	71%	0	8%	0	0
4	H_2SO_4	3-5	60	39%	31%	2.3%	4.5%	1.8%	<1%
5	H_2SO_4	25	14.5 hrs.	41%	36%	4%	3%	4%	<1%

1: Br_2. 2: Pyridiniumbromide perbromide. 3: N-bromosuccinimide. 4: DBICA 5: DBICA

A: Recovered porphin. B: 5-bromoporphin. C: 5,10-dibromoporphin. D: 5,15-dibromoporphin. E: 5,10,15-tribromoporphin. F: 5,10,15,20-tetrabromoporphin.

Structure 1 exhibited an etio spectrum with maxima at 668, 605, 560, 525, and 424 nm (Soret) and relative absorbances of 0.34, 0.33, 0.83, 1.0, and 17.2, respectively. This material was present in only trace amount; no further structural studies were attempted. However, there is virtually no doubt that 1 is 5,10,15,20-tetrabromoporphin.[6] The bathochromic shift of the Soret is greater than that of 2; it elutes before 2, and it does not fluoresce.[4] Structure 3b exhibits a phyllo spectrum, with maxima at 640, 586, 540, 508 and 415 nm (Soret) with relative absorbances of 0.10, 0.29, 0.22, 1.0, and 15.2, respectively. The mass spectrum showed peaks at 466, 468, and 470 m/z in a ratio of 1:2:2:1:2, respectively, consistent with a dibromoporphin. The proton NMR in $CDCl_3$ (99.99%) exhibited an unsymmetrical β-proton ratio of 4:1, indicating that 3b is 5,10-dibromoporphin.[7] Yields for this reaction were determined spectrophotometrically and are present in Table 1 along

with yields previously reported for other brominating agents.[2,3]

Nitration of 5-Bromoporphin. For example, to a round bottom flask immersed in an ice bath and containing 11.8 mg of 5-bromoporphin in 0.4 ml concentrated H_2SO_4, was added dropwise, over a period of 5 min, 0.7 ml of a stock solution containing 0.04 volume-% HNO_3 in H_2SO_4. The solution was filtered, $CHCl_3$ was removed by rotary evaporator and the solid product was readied for flash chromatography on silica gel by dissolution in 30 vol-% hexane in toluene. The product was separated into two bands; the first band contained only unreacted starting material as was determined by the visible spectrum and the 90 MHz NMR spectrum. The spectrophotometrically determined recovery was 14%. The second band was a mixture which was resolved into two compounds by HPLC using a 20 cm column of silica and an eluent containing 35 vol-% CH_2Cl_2 in hexane. Each component was recrystallized from a 50 vol-% solution of benzene in hexane. The mass spectra for both components were identical, consistent with that of a monobromomononitroporphin: Peaks were observed at 433 m/z and 435 m/z with percent relative intensities of 72.4 and 63.8, respectively;

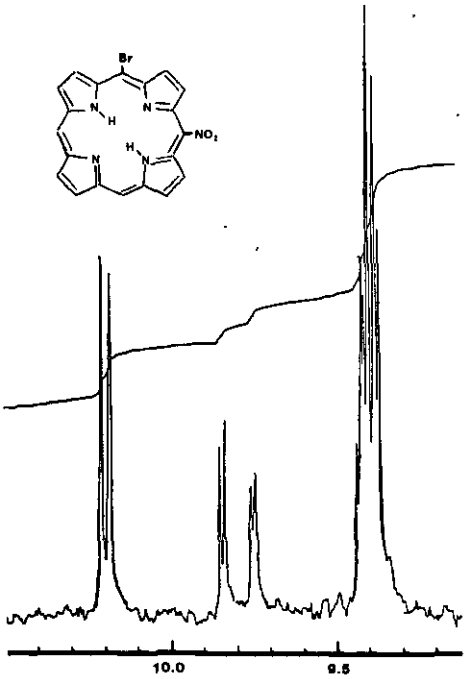

Fig. 1a. Structure and 360 MHz PMR Spectrum of 5-Bromo-10-nitroporphin.

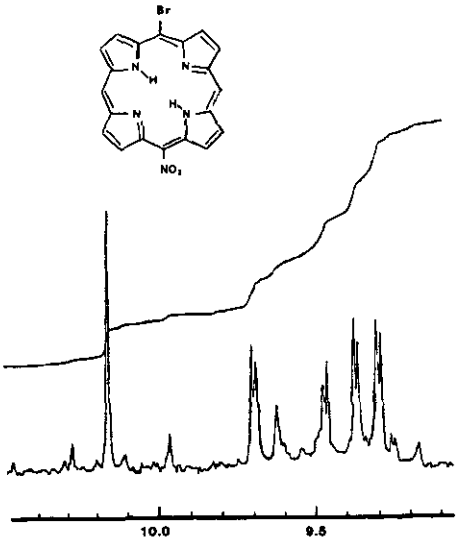

Fig. 1b. Structure and 360 MHz PMR Spectrum of 5-Bromo-15-nitroporphin.

the base peak occurred at 307 m/z.

The Bruker WH 360 MHz NMR spectrum of the first component shows two different meso proton resonance peaks whereas the second component shows a single meso resonance peak.[8] (See figures 1a and 1b). Therefore, the first component is 5-bromo-10-nitroporphin and the second component is 5-bromo-15-nitroporphin. The visible absorption spectrum of 5-bromo-10-nitroporphin is of the phyllo type and shows maxima at 638, 580, 546, 504, and 409 nm (Soret) with relative absorbances of 0.15, 0.35, 0.30, 1.0, and 11.3; the visible absorption spectrum of 5-bromo-15-nitroporphin shows maxima at 638, 580, 546, 504 and 410 nm with relative absorbances of 0.64, 0.57, 1.03, 1.0, and 16.4, respectively. The total yield of nitrated bromoporphin is 73% and the ratio of the 10-nitro to the 15-nitro is 2.5 to 1.0, assuming a Soret extinction coefficient of 2×10^5.

Bromination of 5-Nitroporphin. Attempts to brominate 5-nitroporphin with equimolar amounts of Br_2 in $CHCl_3$ failed both at 2°C and 65°C. Success was attained by use of DBICA in H_2SO_4. For example, to a solution of 12.4 mg of 5-nitroporphin in 10 ml of concentrated H_2SO_4 was added, dropwise with stirring, over a period of 5 min., a solution of 5 mg of DBICA in 18 ml of concentrated H_2SO_4. The solution was stirred an additional 10 min., after which the product solution was added to ice-water. The porphyrinic material precipitated immediately. The ice-water was neutralized with NaOAc prior to dissolution of the porphyrin in toluene. The resulting solution was dried over anh Na_2SO_4, filtered, and evaporated to dryness. The porphyrin was taken up in 750 ml of 50 vol-% toluene in hexane prior to flash chromatography on silica gel.

Upon elution three bands were readily observed. The visible spectrum of the first band, which did not fluoresce, exhibited a Soret peak at 422nm with other absorbances at 518, 560, 590, and 670 nm. As estimated from the Soret absorption, assuming a molar absorptivity of 2×10^5, this species constitutes less than 1% yield and no attempt was made at characterization.

The third band fluoresced and had a visible absorption spectrum identical to that of 5-nitroporphin indicating a 73% recovery of starting material. Under the same conditions porphin yields 84% of brominated product.

The visible absorption spectrum of the second band, which did not fluoresce, showed a Soret at 410nm. The yield of this material was estimated at 8%. A 90 MHz NMR spectrum of this material was very complex suggesting a mixture of products. Attempts at resolution utilizing thin layer chromatography on silica and alumina with a variety of solvents failed. Analysis by HPLC with a 20cm column of silica gel and an eluent containing 35 vol-% CH_2Cl_2 in hexane demonstrated the

presence of two components. The first had visible and NMR spectra identical to the 5-bromo-10-nitroporphin produced by the nitration of 5-bromoporphin. In the same manner the second component was identified as 5-bromo-15-nitroporphin. The ratio of the two isomers is 3 moles 10-nitro to 2 moles 15-nitro.

Rate Constants for Cu(II) Incorporation. In these preliminary studies we followed the incorporation of Cu(II) by 2-bromoporphin, 5-bromoporphin, and 5-nitroporphin in DMF solution at 25°C using the apparatus and procedures described previously.[5] The results of these studies are presented in Table 2. Anhydrous $CuCl_2$ was used as the source of Cu(II).

Table 2

Rate Constants Obtained for the Reactions

$$Cu(II) + H_2P \xrightarrow[25\text{-}0.1°C]{DMF} CuP + 2H^+$$

Porphyrin	$k_2/(M^{-1}S^{-1})$	k_2/k_2 (Porphin)
Porphin	0.00760[5]	1.0
2-Bromoporphin	0.00563	0.74
5-Bromoporphin	0.00962	1.27
5-Nitroporphin	0.00413	0.544

RESULTS AND DISCUSSION

The results of the bromination of 5-bromoporphin and the nitration of both 5-nitroporphin and 5-N-acetylaminoporphin previously reported[1,2,3] can be rationalized in terms of the FW model of porphin aromaticity.[4] Grossly speaking, the results of the present study are in accordance with this model also. All of the electrophilic reactions reported here result in substitution at meso positions. However, the directing effects predicted by the model are not strictly observed. Thus the reaction of 5-bromoporphin with DBICA/H_2SO_4 does not yield, a preponderance of 5,15-dibromoporphin; instead, it yields comparable amounts of 5,10- and 5,15-dibromoporphin. We conclude that DBICA is such a powerful brominating agent that selectivity in electrophilic substitution is not observed.

The nitration of 5-bromoporphin was expected to yield a preponderance of 5-bromo-15-nitroporphin (over the 5-bromo-10-nitroporphin). However, our studies indicate the opposite result.

The bromination of 5-nitroporphin, unsurprisingly, does not take place when molecular bromine,

pyridinium bromide perbromide, or N-bromosuccinimide were used a reagents. DBICA, however, does produce a low yield of brominated product. In this case theory would suggest that 5-bromo-10-nitroporphin would be favored over the 5,15-isomer and this is observed. However, in view of the fact that the nitration of 5-nitroporphin yields only the 5,10-dinitroporphin we expected that the 5-bromo-10-nitroporphin would form in greater preponderance over the 5,15 derivative. The fact that this is not the observed result is probably again due to the use of a powerful brominating agent which obliterates selectivity.

The rate of incorporation of metal ions by free base porphyrins must be strongly influenced by the electron density of the pyrrolenine nitrogen atoms. Rate studies on porphin and phenyl-substituted tetraarylporphins show that the reaction is first order in both metal and in porphyrin in DMF. The substituents have a predictable effect on the rate constants and activation parameters. We have studied the rate of incorporation of Cu(II) by some of the simple derivatives in DMF, a solvent system for which there is a great body of kinetics data. All reactions were found to be 2nd order, 1st order in porphyrin and in Cu(II). Table 2 summarizes the results of our studies at 25°C. Each k_2- entry is the average of at least four determinations and we estimate that the uncertainty in the rate constants to be less than 7%.

In these studies we compared nitro and bromoporphins with porphin. The nitro group is electron withdrawing both by inductive and resonance effects. This substituent should cause a decrease in electron density at the pyrrolenine nitrogens and it is not surprising that k_2 for the Cu(II) incorporation by 5-nitroporphin is appreciably lower than the value for porphin.

The k_2-values obtained for 2-bromoporphin and 5-bromoporphin are very revealing. Bromine as a substituent on an aromatic system can deactivate inductively and activate by resonance. Evidently, the presence of bromine at the 2-position causes an inductive deactivation of the ring, since k_2 for 2-bromoporphin is smaller than k_2 for porphin. The fact that the 5-bromoporphin exhibits a higher k_2-value than that of porphin means that there is an activating resonance effect when bromine is at a bridge position. According to the FW model the meso position is part of the aromatic system (whereas the B-position is not). Hence, bromine substituted at the meso position could be activating but at the non-aromatic pyrryl position this is not possible. Hence, the Cu(II)

incorporation studies strongly support the contention that meso positions are aromatic and that the pyrryl positions are not.

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