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# A STUDY OF BROMOPORPHINS

LOUIS R. NUDY, HOWARD C. HUTCHINSON, CHERLYANN SCHIEBER
and FREDERICK R. LONGO*

Department of Chemistry
Drexel University
Philadelphia, Penna. 19104

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ABSTRACT - The synthesis and characterizations of 2-bromoporphin, 5-bromoporphin, 5,15-dibromoporphin, and 5, 10,15-tribromoporphin are described. Yields of the bromoporphins obtained with a variety of brominating agents are reported. Spectral properties were measured and, along with chemical properties, are presented as evidence for a preferred delocalization pathway in porphin.

## INTRODUCTION

There have been several recent publications which deal with question of the preferred path of delocalization of the $\pi$-electrons, in the porphyrin structure. Some studies support the inner 16 membered dianion while other studies support a system which includes the peripheries of opposite pyrrole residues. The bases of these arguments lie in $^{13}$C-NMR(1,2),$^{1}$H-NMR(3,4,5), crystallographic, (6) theoretical (7), and chemical studies (8).

In this manuscript we describe a study of the bromination of the parent compound porphin. We feel that the work supports the hypothesis originally proposed by Fleischer and Webb that the pathway of $\pi$-electron delocalization does not include the $\beta$-carbon atoms of the pyrrl residues.

Electrophilic substitution on porphyrins generally leads to products which are meso rather than beta substituted. Several recent reviews of such reactions contain numerous examples which confirm this general selectivity.(9,10,11) One notable exception to this general trend is the previously reported bromination of porphin. Samuels, Shuttleworth, and Stevens reported that bromination of porphin with molecular bromine in chloroform gives 2-bromoporphin, exclusively.(12) A consideration of the Fleischer-Webb hypothesis (13), that the beta pyrryl positions of the porphyrin moiety are somewhat olefinic, suggests that the formation of the 2-bromoporphin may result from $Br_2$ addition followed by HBr elimination. We attempted to test this idea but, surprisingly, all attempts to form 2-bromoporphin by direct bromination of porphin failed. The synthesis and characterization of the various bromoporphins obtained in this study are reported in this paper.

## EXPERIMENTAL

Visible absorption spectra were measured at room temperature in spectral grade solvents with the Perkin Elmer Model 320 Spectrophotometer. Spectral data for all of the new porphyrins reported in this paper are given in Table 1. Fluorescence spectra were measured with the Spex Fluorolog 222 equipped with a 450 W xenon lamp and photon counting capability; all solutions whose fluorescence was examined had optical densities of approximately 0.04 at band IV. The NMR spectra were taken on a Joel FT 90Q; we have previously communicated the NMR spectra of 5-bromoporphin, 5, 15-dibromoporphin, and 5, 10, 15-tribromoporphin.(14) Due to the low solubility of 2-bromoporphin we

were forced to use highly deuterated chloroform (99.96% atom purity) to obtain its NMR spectrum. Mass spectra were recorded with the Finnegan 4021 GS/MS/DS System and the HP 5995 GC/MS System.

5,10,15-tribromoporphin To a 5-liter flask equipped with stirrer and condenser was added 90 mg of porphin and two liters of 90% acetic acid in water at room temperature. When all the porphin had dissolved an equimolar quantity of bromine in 30 ml of the same solvent was added dropwise over a period of 5 minutes. Stirring of the solution was continued for two hours at which point the solvent was removed by rotoevaporator. The red solid was redissolved in benzene and chromatographed on a column (5cm x 120cm) packed with 4 kg of dry neutral alumina (Brockman Activity 1). After elution with benzene four major bands were apparent. The three bands which were eluted first did not fluoresce. Significant broadening of these bands occurred as they moved down the column. The first band, which moved close to the solvent front, was concentrated and allowed to crystallize from a solution of 50v:50v, hexane-benzene. The red crystals were washed with cold hexane. The mass spectrum revealed a base peak at 548 m/e. The ratio of peak heights at 544, 546, 548 and 550 m/e was 1:3.1:3.5:1.0. Taking into account only bromine isotope effects, the mass ratio expected for a tribromo compound is 1:3:3:1. The components of the next three bands in order of elution were identified as follows; 5,15-dibromoporphin, 5-bromoporphin and porphin, respectively. 5-bromoporphin and 5,15-dibromoporphin can best be prepared with other reagents (vide infra).

TABLE 1: Visible Absorption Data

Wavelength in nm (extinction coeffients x $10^{-3}$)

| Porphyrin | Soret | IV | III | II | I |
|---|---|---|---|---|---|
| 5, 10, 15 - Tribromoporphin | 417(217) | 518(13.2) | 551(7.6) | 600(4.1) | 657(3.2) |
| 5, 10 - Dibromoporphin | 415(238) | 508(12.7) | 540(7.6) | 586(4.0) | 640(2.5) |
| 5 - Bromoporphin | 402(242) | 495(14.3) | 525(2.9) | 572(4.4) | 625(0.59) |
| 2 - Bromoporphin | 398(246) | 492(16.3) | 522(5.2) | 563(5.8) | 616(0.83) |
| Porphin (9) | 395(261) | 490(16.0) | 520(3.0) | 563(5.2) | 616(0.89) |

TABLE 2: BROMINATIONS OF PORPHIN

| | | PERCENT RECOVERY | |
|---|---|---|---|
| REAGENT | PORPHIN | 5-BROMOPORPHIN | 5,15-DIBROMOPORPHIN |
| Molecular Bromine | 24 | 54 | 15 |
| Pyridinium Bromide Perbromide | 31 | 53 | 15 |
| N-Bromo succinimide | 20 | 71 | 8 |

5-Bromoporphin and 5,15-Dibromoporphin The 5-bromoporphin and the 5,15-dibromoporphin can be isolated as products of the reaction of porphin with molecular bromine in $CHCl_3$, with pyridinium bromide perbromide in $CHCl_3$, or with N-bromosuccinimide in $CHCl_3$. Yields of porphyrins obtained with each of the different brominating reagents are reported in Table 2. In all cases an equimolar amount of brominating agent in solution is added over a 5 minute period to a stirred solution of porphin in the same solvent at 2°-5°C. The concentration of porphin was of the order of $10^{-4}$M. Reaction is quenched after another 5 minutes by addition of an excess amount of acetone. The solution is then washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield a red solid. Flash chromatography on silica gel (40 m average particle) diameter, supplied by Baker) with a 33v:67v hexane-toluene eluent was found to be more practical than separation on alumina. In this method two non-fluorescent bands elute first; the first band proved to be 5,15-dibromoporphin and the second, 5-bromoporphin.

The first band was concentrated and recrystallized from 50v:50v hexane-benzene producing a red solid which has a base peak in its mass spectrum at 468 m/e. The intensities of peaks at 466, 468 and 470 m/e were found in the ratio of 1:2.2: 1.2; (expected ratio for dibromoporphin: 1:2:1). The NMR spectrum in a 50% by volume mixture of $CDCl_3$ and $CF_3COOD$ showed a meso peak at 10.9 ppm from TMS and a symmetrical beta multiplet centered at 9.8 ppm. The beta to meso area ratio observed was (4.0 0.02):1; (expected for 5, 15-dibromoporphin: 4:1).

The second non-fluorescent band was isolated and recrystallized in the same fashion. The mass spectrum revealed two peaks at 388 and 390 m/e with a relative abundance of 98 and 100% respectively; expected for 5-bromoporphin: 1:1. The NMR showed a meso peak at 11 ppm and a symmetrical beta multiplet at 9.9 ppm. The beta area to meso area ratio was found to be (2.7 0.1):1 (expected for 5-bromoporphin: 2.67:1).

2-Bromoporphin A stirred solution containing 0.6 g of 4-bromo-2- methylolpyrrole (0.003 mol), obtained by the method of Anderson and Lee, (15) and 0.94 g of 2-methylol pyrrole (0.009 mol), obtained by the method of Silverstein, Ryskiewicz, and Chaikin (16) was maintained at 100°C for 24 hours. At this point the solution was cooled, filtered and evaporated to dryness on a

rotoevaporator. The resulting red solid was then dissolved in a 33v:67v heptane-toluene solution and flash chromotographed on silica gel. Two major bands, both of which fluoresce were collected and found to be porphin and 2-bromoporphin; the latter was eluted first. Spectroscopic yields of the major components were determined using Soret extinction coefficients. We obtained approximately 0.4% yield of 2-bromoporphin with a 0.6% recovery of porphin. Porphin was identified by its visible absorption spectrum. The 2-bromoporphin was identified by mass spectrometry, which gave the appropriate doublet of peaks at 388 and 390 m/e corresponding to the expected molecular ions and by NMR in deuteochloroform which revealed three peaks in the meso region centered at 10.5 ppm and a complex multiplet in the beta region centered at 9.6 ppm. The beta to meso area ratio was 1.8:1 (expected for a 2-bromoporphin 1.75:1). Figure 1 is a comparison of the NMR spectra of 5-bromo and of 2-bromoporphin.

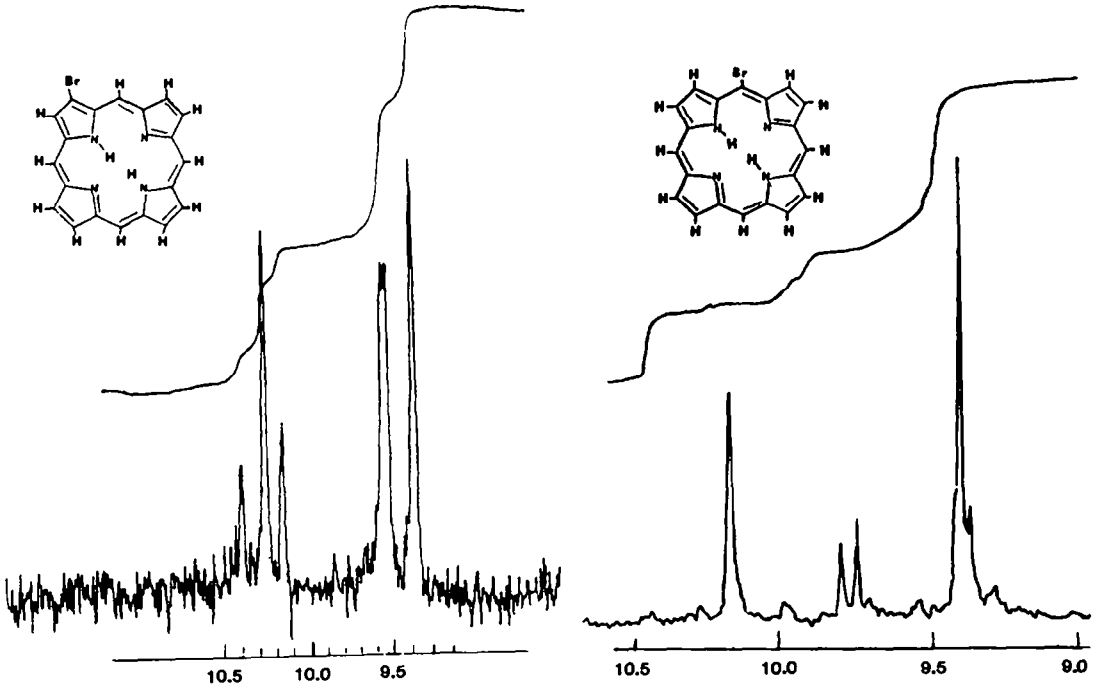


Figure 1. Proton NMR spectra of 2-bromoporphin and 5-bromoporphin in 99.96% deuterated $CHCl_3$.

## RESULTS AND DISCUSSION

The Fleischer-Webb (F-W) model in which the aromaticity does not extend to the beta pyrryl positions permits the explanation of meso nitration (17) and formylation (18) as ordinary electrophilic aromatic substitution. Initially, we devised experiments to determine the mechanism of bromination, which according to the literature, resulted in beta attack only, yielding 2-bromoporphin (12) and therefore did not appear to be in accord with the F-W Model. Beta-bromination would conform to the F-W Model provided that it take place via an addition-elimination reaction involving a $\beta$-pyrryl bond. Experiments devised to test this possibility were negative; we found that bromination of porphin can be detected only at the meso positions under the conditions of our experiments. Our observations are in agreement with the observations of Callot and Schaeffer (19) who briefly investigated the bromination of porphin in order to evaluate the competition between meso and beta-pyrryl carbon atoms. The results of our studies with different brominating systems are presented in Table 2; note that the yield of 5-bromoporphin by bromination with N-bromosuccinimide is quite high. In no case were we able to detect beta brominated species as reported by Samuels, et. al.

Indeed faint bands were noticed during the chromatographic separation of the porphyrin products of these reactions. The small yields of these materials precluded structural analysis but the presence of 2-bromoporphin can probably be ruled out: These faint bands were eluted after porphin whereas 2-bromoporphin has a greater $R_f$ than porphin under the same conditions. We estimate

using a molar absorptivity of 2 x $10^5$ in the Soret region that the total yield of porphyrins in these bands is less than 1%. These bands were fluorescent and the visible spectra were different from the spectra of the structures which we have identified.

Of the two possible meso dibromo porphins only 5,15-dibromoporphin was detected in our product mixtures. Since the dibromo species is produced from 5-bromoporphin it is obvious that the bromo-substituent at the meso position exhibits a predictable directing effect (20). We have now demonstrated that bromo, nitro, and N-acetylamino groups, substituted at the meso position of porphin, direct the next substitution in a predictable manner and we conclude that the electrophilic substitution studies on porphin (6, 9, 11, 13) support the F-W model.

The trends in the visible absorption and florescence data for the bromoporphins can be explained in terms of the F-W model also. The effect of a bromine substituent on the optical properties of the porphyrins is shown in Table 1. Listed are the absorption maxima and molar absorptivities for the porphyrins which we have synthesized. These data demonstrate that the bonding of a bromine atom to a peripheral position results in bathochromic shifts of absorption maxima and diminutions of the Soret molar absorptivities. Both of these effects are much smaller for 2-bromoporphin than for 5-bromoporphin. The shifts and diminutions increase with increasing meso-bromination.

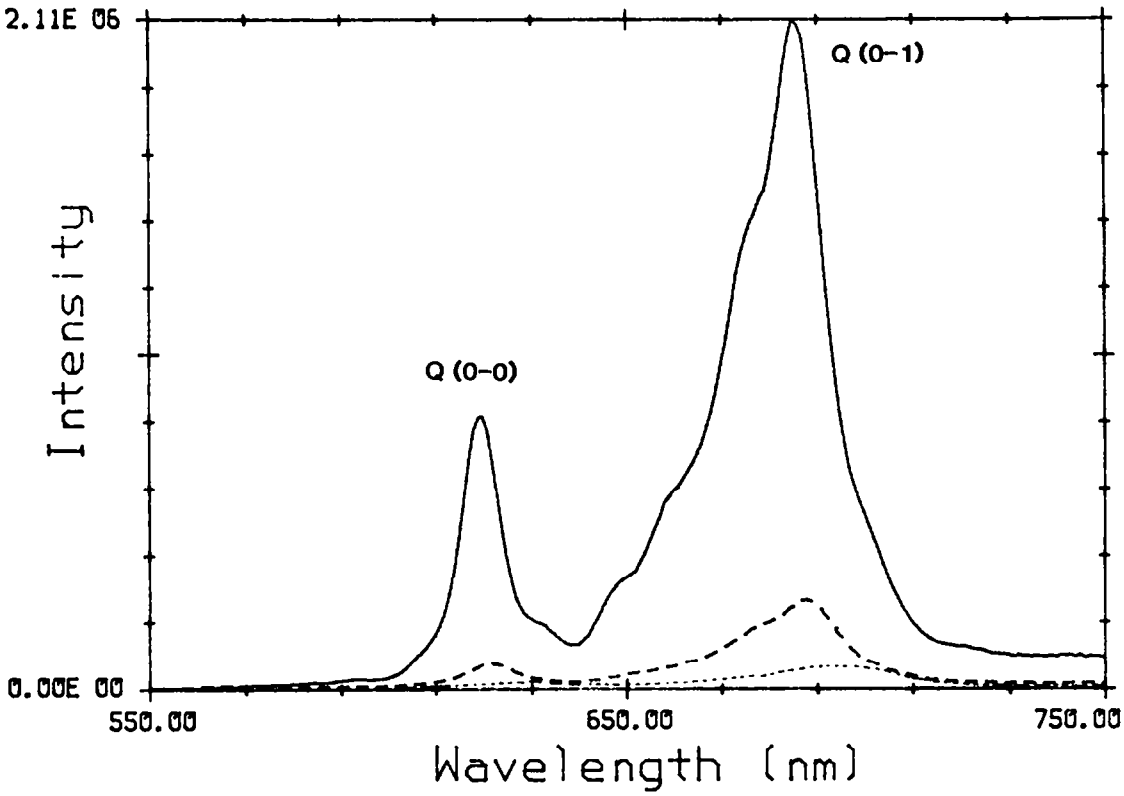


Figure 2. Fluorescence spectra: porphin indicated by solid line, 2-bromoporphin by dashed line, and 5-bromoporphin by dotted line.

The corrected fluorescence spectra of porphin, 2-bromoporphin, and 5-bromoporphin are shown in Figure 2. Considering the Q(0-0) transition which occurs at 625 nm, it appears that the intensity of fluorescence for porphin is 10 times greater than that of 2-bromoporphin and 50 times greater than that of 5-bromoporphin. Gouterman and Khalil (21) have examined the effect of bromine and iodine on the luminescence of various metal free porphyrins. They found that the fluorescence intensity of mesoporphyrin IX dimethyl ester in EPA (ethyl ether: isopentane: ethanol in a volume ratio of 5:5:2) was 7 times greater than the fluorescence from a solution which was 90 EPA/10 ethyl iodide and 32 times greater than from a solution which was 25 EPA/75 ethyl iodide. It appears, considering the fact that the atomic spin-orbit coupling constant for I is 5.4 times greater than that for Br, that a bromine atom bonded to a beta position on the porphin periphery is no more effective a quencher than

an external heavy atom.

Our studies of the bromoporphins continue to demonstrate that it is possible with the F-W model to predict and explain the chemical and physical properties of the parent porphyrin.

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