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REGIOSPECIFIC ARYL NITRATION OF *meso*-TETRAARYL-PORPHYRINS: THE DIRECTIVE EFFECT OF *para*-SUBSTITUENT

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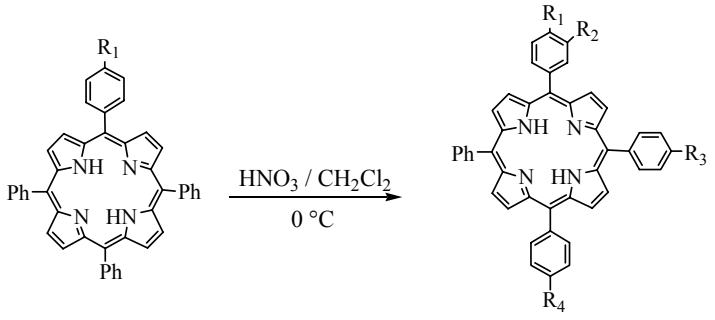
Abstract – Regiospecific nitration of single *p*-substituted tetraphenylporphyrins with excess nitric acid is reported. The directive effects of different *p*-substituents, including nitro, acetamido and hydroxy groups, were demonstrated. The electron-withdrawing *p*-nitro group was found to lead to predominant nitration at the neighboring phenyl ring, and the electron-releasing *p*-acetamido and *p*-hydroxy groups lead to adjacent nitration at the same phenyl ring.

Nitro- and amino-substituted porphyrins have served as the essential precursors to a wide range of functionalized derivatives, including synthetic analogs of hemoprotein active sites,[1] potential diagnostic and therapeutic reagents of cancer,[2,3] and versatile porphyrin-containing superstructures.[4] The classical route to *meso*-tetraarylporphyrins involves the condensation of pyrrole with corresponding aryl aldehydes by Alder-Longo approach.[5] Significant difficulty in employing this method to prepare unsymmetrically nitro-substituted tetraarylporphyrins, such as 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (**1a**) (Scheme1), is caused by low yield and tedious separation of statistical mixtures of porphyrins formed from pyrrole and mixed aldehydes. Efforts have been directed at regiospecific nitration of *meso*-tetraphenylporphyrin (TPP), the most readily available synthetic porphyrin. Whereas N_2O_4 radical nitration of TPP was found to afford substitutions at pyrrole and meso carbons of the macrocyclic ring,[6] Kruper *et al*.[7] reported the first example of regiospecific *para*-phenyl nitration of TPP with excess fuming nitric acid, obtaining mononitro-TPP (**1a**) in moderate yield (~50%) and appreciable amount of di- and tri-nitro products. Higher yields of dinitroporphyrins were achieved by Ostrowski *et al*.[8] with optimized reaction condition. Recently Luguya *et al*.[9] reported effective *para*-phenyl nitration of TPP using sodium nitrite in TFA.

We have applied Kruper's method to synthesize nitroxyl radical–substituted porphyrin for photocytotoxicity study.[10] In the practice of the reaction, nitric acid with moderate concentration (65%,

w/w, d = 1.40 g mL^{-1}) was found to be much preferable for mononitration of TPP, rather than fuming nitric acid resulting in further nitration products. Also, the preliminary inspection of obtained dinitro TPP isomers showed that the *adj*-isomer (**2a**-*adj*) was formed with large predomination over the *opp*-isomer (**2a**-*opp*) indicating the influence of the first nitro-group on the second nitration. Thus, it is of interest to make closer investigation of the substituent effect on aryl nitration in the porphyrin conjugation system.



1

1a $R_1 = NO_2$
1b $R_1 = NH_2$
1c $R_1 = NHCOCH_3$
1d $R_1 = OH$

2

2a-*adj* $R_3 = NO_2$, R_2, $R_4 = H$
2a-*opp* $R_4 = NO_2$, R_2, $R_3 = H$
2c $R_2 = NO_2$, R_3, $R_4 = H$
2d $R_2 = NO_2$, R_3, $R_4 = H$

Scheme1 Regiospecific nitration of single *para*-substituted tetraphenylporphyrins

To clarify the stepwise nitration of TPP, mononitro-TPP (**1a**) was prepared and isolated, and then subjected to nitration with the use of excess nitric acid in dichloromethane at 0°C. As shown in Table 1, the nitration of **1a** was much less pronounced when the molar ratio of fuming nitric acid (95%, w/w, d = 1.53 g mL^{-1}) to **1a** was lower than 8. The most favorable molar ratio for the yield of dinitro products was found to be around 16. The declined yield at larger excesses of fuming nitric acid was attributed to the macrocycle degradation of porphyrins. It was noted that the nitration of **1a** was not observed in the case of nitric acid with moderate concentration (65%, w/w, d = 1.40 g mL^{-1}). In comparison with the fact that TPP could be nitrated facilely in the same condition,[10] the deactivating effect of nitro group on mononitro-TPP (**1a**) was obvious.

The nitration of **1a** afforded two dinitro products with similar R_f detected by thin layer chromatography (TLC). To obviate the difficulty of separation, the obtained dinitro products were reduced completely with $SnCl_2$ / HCl to the corresponding diaminoporphyrin isomers,[9] which were facilely separated by flash column chromatography on silica gel. The molar ratio of **2a**-*adj* to **2a**-*opp* was estimated from the isolated amounts of the diaminoporphyrins.

Starting from **1a**, **2a**-*adj* is resulted from the neighboring phenyl *para*-nitration whereas **2a**-*opp* is resulted from the opposite phenyl *para*-nitration, and the statistic ratio of **2a**-*adj* to **2a**-*opp* is 2:1. The observed ratio, however, was much higher, as shown in Table 1. The reactivity of the neighboring phenyl

ring was estimated to be about 5 times high as that of the opposite one. The data reveal that the second nitration takes place predominantly at the neighboring phenyl ring, which is compatible with the result reported by Ostrowski *et al*.[8]

Table 1 Nitration of **1a**[a]

Entry	HNO_3 / **1a**[b]	Yield[c] %	**2a**-*adj* / **2a**-*opp*[d]
1	4	0	
2	8	15	10
3	12	37	9
4	16	58	10
5	19	46	11
6	25	28	10
7	16[e]	0	
8	25[e]	0	

[a] Nitration in dichloromethane at 0°C for 2 h with fuming nitric acid (95%, w/w) except those noted. [b] Molar ratio of HNO_3 and **1a**. [c] Isolated total yield of dinitroporphyrins after silica gel chromatography. [d] Molar ratio of **2a**-*adj* to **2a**-*opp*. [e] nitric acid (65%, w/w).

In order to investigate the effect of other kind of substituents, **1a** was reduced to corresponding monoamino-TPP (**1b**) with $SnCl_2$ / HCl.[7] Since the direct nitration of **1b** with excess nitric acid was failed due to the oxidation degradation, it was treated with acetic anhydride to give acetamido-TPP (**1c**). Moreover, **1b** was converted to hydroxy-TPP (**1d**) by diazotization and consequent acidic hydrolysis[11] in 78% yield.

Porphyrins (**1c**) and (**1d**) were nitrated with excess 65% (w/w) nitric acid in the same condition as Entry 7 in Table 1. In both cases, TLC of the reaction mixture showed a major spot with much higher R_f than that of the starting porphyrin, which was isolated as the *meta*-nitroporphyrins (**2c**) and (**2d**), respectively, in 75-80% yield. The nitration position was determined according to comparative analysis of ^{1}H NMR spectra of the starting porphyrins (**1c**, **1d**) and resulting porphyrins (**2c**, **2d**). It was found that the peaks in the range of 8.19-8.22 and 7.71-7.78 ppm, corresponding to the *ortho* and *meta/para* protons of 10,15,20-triphenyl rings, respectively, displayed the constant integration ratio of 6:9 for the four porphyrins. On the other hand, observation of downfield shifts and integration ratio variation were made for the *para*-substituted aryl protons after nitration. Especially, the resonances of the amino proton of **2c** and hydroxyl proton of **2d** appeared at much higher δ value (>10 ppm) than that of their parent porphyrins, which were attributed to the large deshielding effect of the neighboring nitro group and consequent intramolecular hydrogen bonding between acetamido-nitro groups in **2c** and hydroxy-nitro groups in **2d**. The structure of intermolecular hydrogen bonding was also evidenced by the relative low polarities of **2c** and **2d** detected by TLC. Thus, the nitration of **1c** and **1d** was concluded to take place at

the *meta*-position of the *para*-substituted phenyl ring. The result is agreeable to the *ortho-para* directive effect of electron-releasing group in the aromatic system, suggesting the nitration mechanism of electrophilic substitution.

In summary, we have demonstrated the different directive effects of *para*-substituents on the nitration of *meso*-tetraarylporphyrins with excess nitric acid. The electron-withdrawing *p*-nitro group leads to predominant nitration at the neighboring phenyl ring. The electron-releasing *para*-acetamido and *para*-hydroxy groups lead to adjacent nitration at the same phenyl ring. The regiospecific reaction affords well-defined nitroporphyrins for further transformation.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Bruker Avance DMX500 spectrometer with TMS as internal standard. MS spectra were obtained by a Bruker Esquire 3000 Plus spectrometer. UV-VIS spectra were recorded with an Analytikjena SPECORD 2000 spectrometer. Elemental analysis was performed at an EA-1112 elemental analyzer. Precoated silica gel plates (HGF_{254}) were used for analytical TLC, and silica gel (G60, 200-300 mesh) were used for column chromatography. All solvents were purified by standard procedures. 5-(4-Nitrophenyl)-10,15,20-triphenylporphyrin (**1a**) and its reduction product 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (**1b**) were prepared according to the reported method.[7,10]

5-(4-Acetamidophenyl)-10,15,20-triphenylporphyrin (1c) To a solution of porphyrin (**1b**) (250 mg, 0.40 mmol) in CH_2Cl_2 (20 mL) was added acetic anhydride (1 mL, 10 mmol) and acetic acid (1 mL). The mixture was refluxed for 1 h before being poured into cold water (20 mL). The mixed solution was basified with concentrated ammonium hydroxide to pH 8 in aqueous solution. The organic layer was washed with water twice and dried over anhydrous Na_2SO_4. The obtained solution was concentrated under vacuum and the residue was recrystallized from methanol, yielding **1c** (254 mg, 95%) as red purple powder, mp > 300°C (decomp). R_f = 0.18 ($CHCl_3$ / hexane, 3/1, v/v); UV-VIS ($CHCl_3$) λ_{max}: 420.0, 516.0, 551.0, 590.5, 646.5 nm; ^{1}H NMR ($CDCl_3$) δ ppm 8.85-8.84 (m, 8H), 8.21-8.19 (m, 6H), 8.13 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.78-7.71 (m, 9H), 7.47 (s, 1H), 2.29 (s, 3H), -2.74 (br, 2H); MS (ESI) *m/z* 672.8 $(M + H)^+$; Anal. Calcd for $C_{46}H_{33}N_5O$: C 82.24, H 4.95, N 10.42. Found: C 82.61, H 4.90, N 10.51.

5-(4-Hydroxylphenyl)-10,15,20-triphenylporphyrin (1d) Porphyrin (**1b**) (250 mg, 0.40 mmol) was dissolved in a solution of sulfuric acid (98%, 2 mL) and 4 mL of water at 0°C. A solution of sodium nitrite (138 mg, 2.0 mmol) in 4 mL of water was added dropwise to the porphyrin solution with stirring in 10 min at 0-5°C. The reaction was continued at rt for 20 min, and then 20 mL of diluted sulfuric acid (15%) was added. The mixture was heated to 100°C for 10 min before being cooled to rt. The solution was basified with concentrated ammonium hydroxide to pH 8 and extracted with $CHCl_3$ (3×25 mL). The

combined organic layer was washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was applied to a silica column and eluted with CH_2Cl_2 to give **1d** (195 mg, 78%) as a purple powder, mp > 300°C (decomp). R_f = 0.28 (CH_2Cl_2 / hexane, 3/1, v/v); UV-VIS ($CHCl_3$) λ_{max}: 421.0, 517.0, 553.0, 591.0, 646.5 nm; ^{1}H NMR ($CDCl_3$) δ ppm 8.86-8.84 (m, 8H), 8.22-8.21 (m, 6H), 8.04 (d, *J* = 8.1 Hz, 2H), 7.77-7.73 (m, 9H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.29 (s, 1H), -2.74 (br, 2H); MS (ESI) *m/z* 631.7 $(M + H)^+$; Anal. Calcd for $C_{44}H_{30}N_4O$: C 83.79, H 4.79, N 8.88. Found: C 84.02, H 4.65, N 9.01.

General procedure for the nitration of single *para*-substituted tetraphenylporphyrins. Porphyrin (**1a**) (200 mg, 0.30 mmol) was dissolved in dry CH_2Cl_2 (60 mL), and the solution was stirred under nitrogen and cooled to 0°C. To the solution fuming nitric acid (0.20 mL, 4.86 mmol, d = 1.53 g mL^{-1}) was added *via* syringe. After 2 h the mixture was extracted with 5×60 mL portions of water, and the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent the residue was applied to a silica column and eluted with $CHCl_3$ / hexane (3/2, v/v) to give the fraction containing 5,10-bis(4-nitrophenyl)-15,20-diphenylporphyrin (**2a-*adj***) (R_f = 0.77) and 5,15-bis(4-nitrophenyl)-10,20-diphenylporphyrin (**2a-*opp***) (R_f = 0.79) in total yield of 58% (120 mg). The structure assignments of **2a-*adj*** and **2a-*opp*** were made after tin chloride reduction as reported.[9]

Nitrations of porphyrins (**1c**) and (**1d**) were carried out in the same method as described above except nitric acid (65%, w/w, d = 1.40 g mL^{-1}) was used as the nitrating reagent. The crude products were purified with column chromatography to give porphyrins (**2c**) and (**2d**), respectively, in 75-80% yield as a dark purple powder.

5-(3-Nitro-4-acetamidophenyl)-10,15,20-triphenylporphyrin (2c) mp > 300°C (decomp); R_f = 0.60 ($CHCl_3$ / hexane, 3/1, v/v); UV-VIS ($CHCl_3$) λ_{max}: 419.0, 515.5, 551.0, 596.6, 645.4 nm; ^{1}H NMR ($CDCl_3$) δ ppm 10.67 (s, 1H), 9.20 (d, *J* = 8.6 Hz, 1H), 9.06 (s, 1H), 8.90-8.79 (m, 8H), 8.52 (m, 1H), 8.22-8.20 (m, 6H), 7.78-7.72 (m, 9H), 2.49 (s, 3H), -2.74 (br, 2H); MS (ESI) *m/z* 717.8 $(M + H)^+$; Anal. Calcd for $C_{46}H_{32}N_6O_3$: C 77.08, H 4.50, N 11.72. Found: C 77.67, H 4.40, N 11.86.

5-(3-Nitro-4-hydroxylphenyl)-10,15,20-triphenylporphyrin (2d) mp > 300°C (decomp); R_f = 0.89 (CH_2Cl_2 / hexane, 3/1, v/v); UV-VIS ($CHCl_3$) λ_{max}: 421.0, 516.5, 552.5, 598.0, 646.5 nm; ^{1}H NMR ($CDCl_3$) δ ppm 11.0 (s, 1H), 8.94-8.79 (m, 8H), 8.43 (d, *J* = 7.6 Hz, 1H), 8.22-8.21 (m, 6H), 7.77-7.76 (m, 9H), 7.55 (d, *J* = 8.4 Hz, 2H), -2.74 (br, 2H); MS (ESI) *m/z* 676.7 $(M + H)^+$; Anal. Calcd for $C_{44}H_{29}N_5O_3$: C 78.21, H 4.33, N 10.36. Found: C 79.02, H 4.21, N 10.48.

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