Selective Double Functionalization of *meso*-Tetraphenylporphyrin Complexes on the Same Pyrrole Unit by Tandem Electrophilic/Nucleophilic Aromatic Substitution

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The mono-nitrated *meso*-tetraphenylporphyrin (TPP) complex **2** could be readily functionalized on the substituted pyrrole ring with yields of up to 83%. These transformations were achieved *via* aromatic substitution with carbanions generated from diverse functionalized compounds containing different leaving groups (**3a**–**g**, *Scheme 1*). The resulting TPP compounds **4a**–**g**, bearing two different β-substituents on the same pyrrole ring, may be further manipulated. This, in turn, should allow one to tune the solubility of TPP derivatives used in photodynamic cancer therapy.

Introduction. – Porphyrins are important compounds intensively studied in recent years [1]. From a synthetic point of view, the selective functionalization of readily available *meso*-tetraphenylporphyrin (TPP) and its derivatives is of significant importance due to their potential use as sensitizers in photodynamic cancer therapy [2]. We have recently published two papers describing a convenient method for the selective mono-nitration in β-position of Zn, Cu, Ni, and Co TPP complexes by means of 25–50% aqueous HNO_3 in $CHCl_3$ [3].

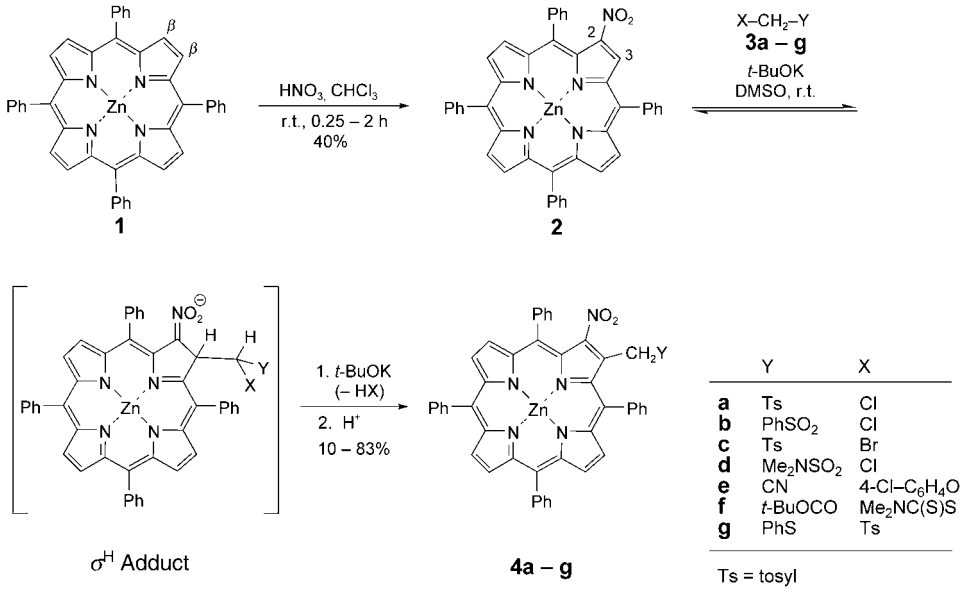
A NO_2 group in the ring makes porphyrins, as well as aromatic systems in general, susceptible to nucleophilic attack. Of particular importance is the nucleophilic aromatic substitution of a H-atom by a carbanion made from precursors of type $X-CH_2-Y$, where X and Y are leaving and stabilizing groups, respectively. Mechanistically, this kind of transformation proceeds according to the vicarious nucleophilic substitution (VNS) scheme [4]. Recently, several papers concerning this type of substitution in *meso*-aryl rings have been published [5].

Results and Discussion. – In continuation of our work, we describe herein the functionalization of TPP (**1**) by selective β-nitration to **2**, followed by nucleophilic aromatic substitution with a variety of carbanions derived from the precursors **3**. The resulting porphyrins **4** are unique in that they are doubly functionalized on *one* pyrrole ring only (*Scheme 1*).

For the generation of functionalized carbanions to be reacted with the TPP–Zn complex **2**, different aryl sulfones (**3a**–**c**), a sulfonamide (**3d**), a nitrile (**3e**), an ester (**3f**), and a sulfane (**3g**) were used. As leaving groups X, halogen atoms (Cl, Br), a 4-chlorophenoxy group (in **3e**), a dithiocarbamate function (in **3f**), or a tosyl[1]) group (in

[1]) (4-Methylphenyl)sulfonyl (Ts).

Scheme 1



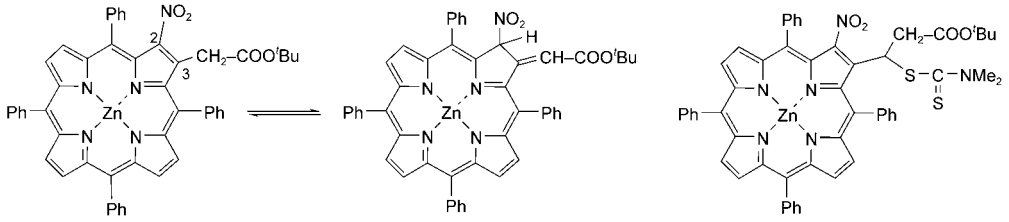
3g) were used. A similar reaction with the Br analog of **3a** has already been reported by *Malinovskii et al.* [6].

In the reaction of porphyrin complex **2** with **3a** in the presence of *t*-BuOK in DMSO at room temperature, substitution took place adjacent to the NO_2 group to afford the porphyrin **4a** in high yield (82%). Its structure was readily elucidated based on the disappearance of the diagnostic ^{1}H-NMR *singlet* for H–C(3). Analogously, in the reaction of **2** with the anions of **3b** or **3c** under the same conditions, the corresponding products **4b** (83%) and **4a** (51%) were obtained. Similarly, compounds **4d** (57%) and **4e** (76%) could be obtained. The structures of the latter two products were confirmed by spectroscopic methods. In the case of **4d**, the Me_2N group was shifted upfield (δ(H) 2.29), probably due to local-field effects generated by the ring current of the aromatic porphyrin system; in addition, this group, with its electron lone pair at the N-atom, might be partially coordinated to the Zn^{II} center of neighboring TPP molecules.

In the above transformations, the cyanomethylation to **4e** is of particular interest, since it should be possible to convert the CN group into other substituents such as COOH, $CONH_2$, CH_2NH_2, CHO, or CH_2OH, *etc.* This, in turn, would allow one to increase the hydrophilicity of TPP derivatives and to make these compounds water-soluble, a prerequisite for applications in photodynamic therapy.

The reaction of **2** with the carbanion of the *tert*-butyl acetate **3f**, expected to provide the very useful porphyrin **4f**, was unsatisfactory (14% yield). Several attempts to optimize this reaction failed. When using *t*-BuOK/DMSO at room temperature, and prolonging the reaction time from 30 min to 1 h, we observed three products by TLC. For two of them, the tautomeric structures **4f**/**4f′** were proposed on the basis of MS and ^{1}H-NMR investigations (*Scheme 2*). Although the ^{1}H-NMR spectrum of the mixture

Scheme 2



4f **4f'** **5**

was rather complicated, we managed to assign all signals to the two tautomers. This type of tautomerism has actually been reported before for (alkoxycarbonyl)methyl, cyanomethyl, hydroxy, and dichloromethyl derivatives, especially in heterocyclic systems [7].

Due to the small amount of material, the third product from the reaction leading to **4f**/**4f′** could not be isolated in pure form. However, the diagnostic ^{1}H-NMR signal at δ(H) 6.41 (*s*, CH) and the molecular ion in the mass spectrum at *m*/*z* 954 (1%; M^+) suggested compound **5**, arising from oxidative nucleophilic substitution [8], without removal of the (rather poor) dithiocarbamate-type leaving group. Mechanistically, this process could be rationalized by competing oxidation of the σ^H adduct (see *Scheme 1*) rather than base-induced β-elimination. In the reaction mixture, *ca.* 25% of the starting porphyrin **2** was found, which further explains the low yield (14%) of **4f /4f′**.

Finally, attempts at reacting **2** with the carbanion of **3g** were undertaken, which would allow the introduction of a sulfur-substituted methyl group into β-position. However, since the corresponding carbanion is relatively bulky and since both substituents are rather poor leaving groups [9], this reaction was not very successful. Several products were, thus, formed (TLC), accompanied by small amounts of the starting porphyrin **2** (12%). The desired product **4g** was isolated only in low yield (<10%). Herein, the Ts group plays the role of a leaving group, thus confirming the previously observed preferences for carbanion **3g** in the VNS process [10]. However, despite the low yields, porphyrin **4g**, as well as the other derivatives, are attractive molecules that can be further manipulated, *e.g.*, to tune the solubility of TPP derivatives used in photodynamic therapy.

Experimental Part

General. (5,10,15,20-Tetraphenylporphyrinato)zinc(II) (**1**) was obtained in 98% yield as described in [11]. Compounds **3a** [12], **3b**,**c** [13], **3d** [14], **3e** [15], **3f** [16], and **3g** [10] were prepared according to literature procedures. TLC analysis was performed on Al plates pre-coated with silica gel *60F$_{254}$* (*Merck*). Column chromatography (CC) was performed on silica gel (200–300 and 230–400 mesh; *Merck*). UV/VIS Spectra were recorded on a *Beckman DU-68* spectrophotometer; in λ_{max} (log ε). ^{1}H-NMR Spectra were recorded on a *Varian GEMINI-200* spectrometer operating at 200 MHz; chemical shifts δ in ppm rel. to $CHCl_3$ (7.26 ppm), coupling constants *J* in Hz. Mass spectra were recorded on an *AMD 604* (*AMD Intectra GmbH*; Germany) spectrometer in electron-impact (EI) mode, or on a *MARINER* (*PerSeptive Biosystems*) spectrometer in the ESI-TOF mode; in *m/z* (rel. %).

(2-Nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**2**). This compound was obtained by direct nitration of **1** with 25% aq. HNO_3 in $CHCl_3$ according to a previous publication [3b]. Yield: 33%.

General Procedure for the Synthesis of Functionalized Porphyrins **4**. In a round-bottomed, light-protected 25-ml flask equipped with a septum, *t*-BuOK (52 mg, 0.46 mmol; 104 mg for **3f**) was dissolved in anh. DMSO (10 ml) and stirred under Ar gas at r.t. To this mixture, a soln. of **2** (48 mg, 0.066 mmol) and **3** (0.14 mmol) in anh. DMSO (5 ml) was added dropwise *via* syringe over a period of *ca.* 5 min, and the mixture was stirred at r.t. for 30 min (60 min for **3f** and **3g**; TLC monitoring). The mixture was poured into ice-cold 3% aq. HCl soln. (100 ml). The precipitate was filtered off, washed with H_2O, dissolved in $CHCl_3$ (30 ml), dried ($MgSO_4$), and evaporated. The resulting residue was purified by CC to afford **4a** [=**4c**; 82% from **3a**, 51% from **3c**; CC (1. $CHCl_3$/hexane 2:1, 2. $CHCl_3$/MeOH 100:1)]; **4b** [83%; CC (1. $CHCl_3$/hexane 3:1, 2. $CHCl_3$/MeOH 100:1)]; **4d** (57%; eluent as above); **4e** (76%; eluent as above); **4f/4f′** [14%; prep. TLC ($CHCl_3$/hexane 3:1); **2** partly recovered]; **4g** [($\leq$10%; prep. TLC (as above); **2** partly recovered)].

(3-{[(4-Methylphenyl)sulfonyl]methyl}-2-nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**4a**). M.p. >300°. UV/VIS ($CHCl_3$): 640.5 (4.15), 582.0 (3.93), 453.0 (5.20; *Soret*). ^{1}H-NMR (200 MHz, $CDCl_3$)[2]): 8.87 (*d*, *J* = 4.8, 1 H$^{\beta}$ (pyr)); 8.78 (*s*, 2 H$^{\beta}$ (pyr)); 8.77–8.67 (*m*, 3 H$^{\beta}$ (pyr)); 8.28–8.12 (*m*, 8 arom. H (Ph)); 7.91–7.58 (*m*, 12 arom. H (Ph), 4 arom. H (tol)); 4.55 (*s*, CH_2); 2.26 (*s*, Me). ESI-MS: 918 (4), 917 (8), 916 (12), 915 (11), 914 (20), 913 (12), 912 (21) ([*M* + Na]$^+$ isotopes); 895 (4), 894 (7), 893 (9), 892 (10), 891 (13), 890 (13), 889 (5) (*M*$^+$ and [*M* + H]$^+$ isotopes); 740 (11), 739 (21), 738 (48), 737 (40), 736 (65), 735 (54), 734 (100) ([*M* – Ts]$^+$ isotopes); 722 (16), 721 (27), 720 (28), 719 (37), 718 (24), 717 (52), 708 (14), 707 (13), 706 (14), 705 (22), 704 (33), 703 (30), 702 (33), 701 (23), 700 (38), 695 (15), 694 (18), 693 (28), 692 (33), 691 (37), 690 (34), 689 (44), 688 (41). HR-ESI-MS: 912.1579 ([*M* + Na]$^+$, $C_{52}H_{35}N_5NaO_4SZn^+$; calc. 912.1599). The molecular formula was also confirmed by comparing the theor. and exper. isotope patterns for the [*M* + Na]$^+$ ion.

{2-Nitro-5,10,15,20-tetraphenyl-3-[(phenylsulfonyl)methyl]porphyrinato}zinc(II) (**4b**). M.p. >300°. UV/VIS ($CHCl_3$): 631.5 (4.10), 582.5 (3.90), 453.5 (5.16; *Soret*). ^{1}H-NMR (200 MHz; $CDCl_3$)[2]): 8.92 (*d*, *J* = 4.9, 1 H$^{\beta}$ (pyr)); 8.83 (*d*, *J* = 4.8, 1 H$^{\beta}$ (pyr)); 8.80 (*s*, 2 H$^{\beta}$ (pyr)); 8.79–8.71 (*m*, 2 H$^{\beta}$ (pyr)); 8.24–8.12 (*m*, 8 arom. H (Ph)); 7.81–7.60, 7.50–7.39, 7.27–7.14 (3*m*, 12 arom. H (Ph), 5 arom. H (SO_2Ph)); 4.71 (*s*, CH_2). ESI-MS: 904 (3), 903 (4), 902 (9), 901 (10), 900 (19), 899 (11), 898 (18) ([*M* + Na]$^+$ isotopes); 881 (3), 880 (9), 879 (11), 878 (13), 877 (16), 876 (17), 875 (12) (*M*$^+$ and [*M* + H]$^+$ isotopes); 740 (6), 739 (18), 738 (42), 737 (37), 736 (87), 735 (48), 734 (100) ([*M* – SO_2Ph]$^+$ isotopes)]; 721 (5), 719 (11), 717 (8), 690 (6), 688 (8), 413 (8). HR-ESI-MS: 875.2538 (*M*$^+$, $C_{51}H_{33}N_5O_4SZn^+$; calc. 875.1545). The molecular formula was also confirmed by comparing the theor. and exper. isotope patterns for the *M*$^+$ and [*M* + Na]$^+$ ions.

(3-{[(Dimethylamino)sulfonyl]methyl}-2-nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (**4d**). M.p. >300°. UV/VIS ($CHCl_3$): 636.5 (4.26), 580.5 (4.09), 449.0 (5.29; *Soret*). ^{1}H-NMR (200 MHz, $CDCl_3$)[2]): 8.95 (*d*, *J* = 4.9, 1 H$^{\beta}$ (pyr)); 8.85 (*d*, *J* = 4.9, 1 H$^{\beta}$ (pyr)); 8.80 (*s*, 2 H$^{\beta}$ (pyr)); 8.78 (*d*, *J* = 4.8, 1 H$^{\beta}$ (pyr)); 8.74 (*d*, *J* = 4.8, 1 H$^{\beta}$ (pyr)); 8.30–8.12 (*m*, 8 arom. H (Ph)); 7.84–7.65 (*m*, 12 arom. H (Ph)); 4.58 (*s*, CH_2); 2.29 (*s*, Me_2N). ESI-MS: 872 (4), 871 (11), 870 (21), 869 (46), 868 (47), 867 (58), 866 (51), 865 (76) ([*M* + Na]$^+$ isotopes); 850 (5), 849 (11), 848 (22), 847 (42), 846 (83), 845 (76), 844 (100), 843 (77), 842 (76) (*M*$^+$ and [*M* + H]$^+$ isotopes); 740 (11), 739 (22), 738 (42), 737 (45), 736 (62), 735 (55), 734 (91) ([*M* – Me_2NSO_2]$^+$ isotopes). HR-ESI-MS: 842.1685 (*M*$^+$, $C_{47}H_{34}N_6O_4SZn$; calc. 842.1654). The molecular formula was also confirmed by comparing the theoretical and exper. isotope patterns for the [*M* + Na]$^+$ ion.

[3-(Cyanomethyl)-2-nitro-5,10,15,20-tetraphenylporphyrinato]zinc(II) (**4e**). M.p. >300°. UV/VIS ($CHCl_3$): 612.0 (3.95), 565.0 (4.03), 429.5 (5.30; *Soret*). ^{1}H-NMR (200 MHz, $CDCl_3$)[2]): 8.86 (*s*, 2 H$^{\beta}$ (pyr)); 8.85–8.81 (*m*, 3 H$^{\beta}$ (pyr)); 8.66 (*d*, *J* = 4.8, 1 H$^{\beta}$ (pyr)); 8.26–8.09 (*m*, 8 arom. H (Ph)); 7.84–7.59, 7.47–7.35 (2*m*, 12 arom. H (Ph)); 3.30 (*s*, CH_2). ESI-MS: 789 (7), 788 (18), 787 (44), 786 (33), 785 (66), 784 (42), 783 (100) ([*M* + Na]$^+$ isotopes); 767 (5), 766 (9), 765 (19), 764 (24), 763 (26), 762 (33), 761 (44), 760 (23) (*M*$^+$ and [*M* + H]$^+$ isotopes); 734 (5, [*M* – CN]$^+$), 720 (9, [*M* – CH_2CN]$^+$), 675 (8), 674 (8), 414 (12), 413 (45). HR-ESI-MS: 783.1428 ([*M* + Na]$^+$, $C_{46}H_{28}N_6NaO_2Zn^+$; calc. 783.1463); 761.1609 ([*M* + H]$^+$, $C_{46}H_{29}N_6O_2Zn^+$; calc. 761.1643).

*(3-{[(*tert*-Butoxy)carbonyl]methyl}-2-nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II)* (**4f**)[3]). UV/VIS: not recorded, mixture of compounds. ^{1}H-NMR (200 MHz, $CDCl_3$)[2]): 9.08 (*s*, CH–NO_2 of **4f′**)[4]); 8.96–8.67 (*m*, 6 H$^{\beta}$ (pyr)); 8.28–8.05 (*m*, 8 arom. H (Ph)); 7.84–7.66 (*m*, 12 arom. H (Ph)); 6.98 (*s*, =CH–CO of **4f′**)[4]); 4.23 (*s*, CH_2 of **4f**); 1.43 (*s*, *t*-Bu). ESI-MS: 783 (2), 782 (3), 781 (5), 780 (9), 779 (9), 778 (14) ([*M* – *t*-Bu]$^+$ isotopes); 777 (7); 739 (1), 738 (4), 737 (11), 736 (12), 735 (21), 734 (14) ([*M* – CO_2*t*Bu]$^+$ isotopes); 733 (34),

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[2]) Abbreviations: Ph, phenyl; pyr, pyrrole; tol, tolyl; Ts, tosyl.

[3]) Tautomeric mixture with **4f′** (see *Scheme 2*).

[4]) Signals may be interchanged.

696 (1), 695 (2), 694 (2), 693 (4), 692 (5), 691 (5), 690 (2), 689 (2), 688 (3), 414 (12), 413 (100), 379 (2), 303 (11). HR-ESI-MS: 734.1560 ($[M - CO_2{}^t\text{Bu}]^+$, $C_{45}H_{28}N_5O_2Zn^+$; calc. 734.1534).

{2-Nitro-5,10,15,20-tetraphenyl-3-[(phenylsulfanyl)methyl]porphyrinato}zinc(II) (**4g**). Impure sample. UV/VIS ($CHCl_3$): 635.5, 563.5, 431.5 (*Soret*). ^{1}H-NMR (200 MHz; $CDCl_3$)[2]): 9.01–8.90 (*m*, 6 H^β (pyr)); 8.32–8.15 (*m*, 8 arom. H (Ph)); 7.92–7.72 (*m*, 12 arom. H (Ph)); 7.62–7.53, 7.49–7.25 (2*m*, PhS); 4.72 (*s*, CH_2). EI-MS: 724 (1.5), 723 (1.5), 722 (1), 721 (2), 720 (1) ($[M - PhSCH_2]^+$ isotopes); 123 (100, $[PhSCH_2]^+$), 44 (34, $[CO_2]^+$). ESI-MS: 846, 845, 844 (all $< 1\%$; $[M + H]^+$ isotopes); 302 (8), 301 (100).

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