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Attempts of the Synthesis of Highly Functionalized Porphyrins at the β−Positions: Nitration of Exhaustively Substituted Moieties in the 'Eastern Half' and Mass−Spectral Study of the Reaction Products

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MS investigations of the products obtained by electrophilic nitration of tetrasubstituted porphyrin complexes are described. Cu(II)-Porphyrinates, exhaustively derivatized at the so-called 'eastern half' [dinitro-, bis(arylsulphonyl-methyl-)], in the reaction with 33 % nitric acid (at r.t.; reaction time – ca. 5 h) resulted in the formation of a mixture of many polynitro-substituted products. They were identified by MS-ESI and IR methods and the mode of reactivity of the substrates was explained.

Keywords: Porphyrins, electrophilic nitration, nitrenes, mass spectrometry.

Попытки синтеза порфиринов, высокофункционализированных по β−положениям: нитрование производных, полностью замещенных в «восточной половине», и масс−спектральное исследование продуктов реакции

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Описаны масс-спектральные исследования продуктов, полученных электрофильным нитрованием тетразамещенных комплексов порфиринов. Реакция Cu(II)-порфиринатов, полностью замещенных в так называемой «восточной половине» [динитро-, бис(арилсульфонилметил-)], с 33 % азотной кислотой (при комнатной температуре в течение примерно 5 ч) привела к образованию смеси полинитрозамещенных продуктов. Полученные соединения были идентифицированы методами масс-спектрометрии (электроспрей ионизация) и ИК спектроскопии; обсуждается реакционная способность субстратов.

Ключевые слова: Порфирины, электрофильное нитрование, нитрены, масс-спектрометрия.

Introduction

Porphyrins are intensively studied in recent years.[1] These systems are present in well-known biological materials, *e.g.* chlorophyll, heme, or vitamin B_{12}. On the other hand, the selective functionalization of readily available synthetic *meso*-tetraarylporphyrins is also of significant importance. For example, from this process, the hydrophobic moieties can be transformed into the hydrophilic compounds. The latters, as such, being soluble in physiological milieu, may be considered as potential PDT agents.[2]

Our ongoing research program, among others, is focused on the synthesis of highly functionalized porphyrins. Numerous reactions and various methods of activation of the system are utilized.[3-9] Previously the preparation of poly-substituted derivatives in *meso*-aryl rings was demonstrated.[3,4,7] Herein, attempts of synthesizing *β*-multifunctionalized porphyrins are reported. The first four functional groups were introduced to the ring due to tandem reactions electrophilic nitration/nucleophilic substitution of hydrogen.[10] Introduction of the next substituents (one or more NO_2 groups) was undertaken (by the direct electrophilic nitration using HNO_3) and this opportunity was verified by MS analysis of the products formed in these reactions.

Experimental

Mass spectra were measured with a 4000 Q-TRAP and API 3000 (Applied Biosystems) spectrometers (ESI–turbo-spray method); *m/z* intensity values for peaks are given as % of relative intensity. IR spectra were measured with a Shimadzu IRAffinity-1 and UV–Vis spectra with a Metertech SP-8001 spectrophotometer. TLC analysis was performed on aluminium foil plates pre-coated with silica gel (60 F-254, Merck AG). The products were isolated *via* chromatography on preparative TLC plates (silica gel 60 F_{254}, 2 mm or 0.5 mm; Merck AG). Their structures were proposed on the basis of MS method. Molecular formulas of new compounds were confirmed by comparing the isotope patterns of the ions measured (theoretical and experimental).

*Nitration of [3,7-dinitro-2,8-bis(toluene-4-sulphonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) (**2**).*

Procedure A: In a round-bottomed flask (200 ml) [3,7-dinitro-2,8-*bis*(toluene-4-sulphonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) (**2**, 48 mg, 0.044 mmol) was dissolved in $CHCl_3$ (42 ml), and the solution was stirred under argon at room temperature. To this mixture, 33 % HNO_3 (11.5 ml, 72.3 mmol, freshly prepared from yellow nitric acid, d=1.52 g/ml) was added dropwise *via* syringe. The reaction was continued for 50 min (TLC monitoring), then the next portion of 33 % HNO_3 (8.5 ml, 53.4 mmol) was added, and after 2 h – 51 % HNO_3 (3.0 ml, 32.0 mmol, 3 h of stirring). The reaction was carried out for 5 h (total time). The mixture was poured onto water (60 ml) and the organic layer was separated, washed with water (4×50 ml), and dried with $MgSO_4/Na_2CO_3$. After evaporating the solvent, the crude mixture was separated *via* chromatography on preparative TLC plates (silica gel 60 F_{254}, 2 mm, eluent: $CHCl_3$:CH_3OH=100:1) to give five fractions which were analyzed by MS spectrometry: (a) 3.0 mg (in which isomer **7** was found); (b) 4.2 mg (containing mainly product **8**); (c) 8.4 mg (in which isomer **9** was found). The last two fractions (12 mg and 4.8 mg) did not contain defined porphyrin products.

Procedure B: As above. Modifications: 3 ml of 50 % HNO_3 was used, reaction time – 10 min. Crude post-reaction mixture (after work-up) was analyzed by MS spectrometry (ESI(+)–turbo-spray). One of the possible dinitrated isomers (or mixture of isomers) was detected (see Figure 2, n=0, m=0); *m/z* (% rel. int.): 1163 (8), 1162 (21), 1161 (47), 1160 (82), 1159 (75), 1158 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M+H)^+$ ion ($C_{60}H_{39}N_8O_{10}S_2Cu$) – found to be identical within the experimental error limits.

Data for products

Product 7. R_f=0.55 ($CHCl_3$:MeOH=50:1). m.p. > 300 ºC. IR ($CHCl_3$) ν_{max} cm^{-1}: 1732.1 s, 1714.7 s, 1672.3 m, 1647.2 m, 1555.2 m, 1516.1 m, 1514.3 m, 1465.8 s (C=N, C=C, and NO_2), 1340.0 s (NO_2), 1319.3 s (SO_2), 1153.4 s (SO_2). UV-Vis ($CHCl_3$) λ_{max} (log ε) nm: 554 (3.47), 481 (4.34, Soret), 341.5 (3.81). MS (ESI(+)–turbo-spray) *m/z* (% rel. int.): 1208 (13), 1207 (27), 1206 (49), 1205 (81), 1204 (72), 1203 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M+H)^+$ ion ($C_{60}H_{38}N_9O_{12}S_2Cu$) – found to be identical within the experimental error limits.

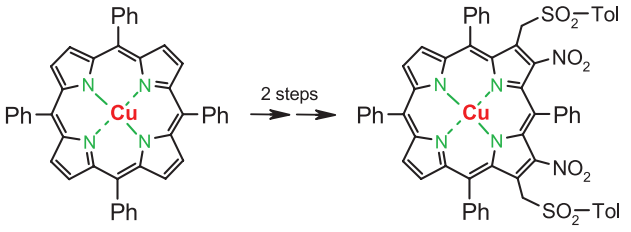
*Product **8***. R_f=0.50 ($CHCl_3$:MeOH=50:1). m.p.>300 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1734.0 s, 1716.7 s, 1647.2 m, 1597.1 w, 1561.9 w, 1543.8 m, 1521.8 w, 1458.2 s (C=N, C=C, and NO_2), 1375.3 m (NO_2), 1315.5 m (SO_2), 1159.2 s (SO_2). UV-Vis ($CHCl_3$) λ_{max} (log ε) nm: 541 (3.30), 490.5 (3.96, Soret), 419 (3.42), 350 (3.47). MS (ESI(+)–turbo-spray) *m/z* (% rel. int.): 1253 (14), 1252 (28), 1251 (52), 1250 (83), 1249 (69), 1248 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M+H)^+$ ion ($C_{60}H_{37}N_{10}O_{14}S_2Cu$) – found to be identical within the experimental error limits.

*Product **9***. R_f=0.39 ($CHCl_3$:MeOH=50:1). m.p.>300 °C. IR ($CHCl_3$) ν_{max} cm^{-1}: 1734.0 s, 1716.7 s, 1662.6 s, 1595.1 w, 1577.8 s, 1558.5 w, 1521.8 m, 1505.4 m, 1448.5 s (C=N, C=C, and NO_2), 1346.3 s (NO_2), 1315.5 s (SO_2), 1145.7 s (SO_2). UV-Vis ($CHCl_3$) λ_{max} nm: 625, 506, 461.5 (Soret), 424. MS (ESI(+)–turbo-spray) *m/z* (% rel. int.): 1208 (5), 1207 (21), 1206 (47), 1205 (78), 1204 (69), 1203 (100) [isotope $(M+H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M+H)^+$ ion ($C_{60}H_{38}N_9O_{12}S_2Cu$) – found to be identical within the experimental error limits.

Results and Discussion

In this paper, attempts of synthesizing *β*-multifunctionalized porphyrins are reported. As a model compound for the investigations we used [3,7-dinitro-2,8-*bis*(toluene-4-sulphonylmethyl)-5,10,15,20-tetraphenylporphyrinato] copper(II) (**2**), in which all the positions at the 'eastern half' are substituted. It was previously obtained from the corresponding dinitro-porphyrin derivative by *vicarious nucleophilic substitution* methodology (Scheme 1).[8,10] Thus, the introduction of the next NO_2 group(s) ought to result in the functionalization of one or two the remaining pyrrole units. These groups should allow again the vicarious nucleophilic substitution of hydrogen reaction leading to the hexa- or even octasubstituted porphyrins at the *β*-positions. Such a diversely highly 'decorated' systems may be compounds of interesting value in many fields of porphyrins utilization.

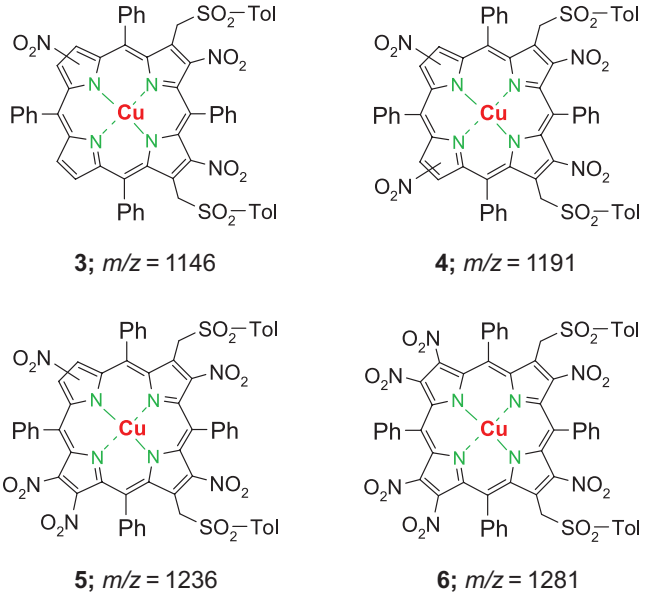
In the first experiments a 33 % HNO_3 was used and the reactions carried out for 5 h. In most of them we observed (on TLC) full consumption of the substrate and formation of several products. They were the same



1 **2**

Scheme 1.

products (from various experiments); only their ratios were differentiated. We isolated some fractions (single compounds and mixtures) by preparative TLC and all of them were analyzed by mass spectrometry (MS-ESI(+) method). Unfortunately, the expected products (their ions) were not found: *m/z*=1146 (mononitration; **3**) or *m/z*=1191 (dinitration; **4**). The ions originating from the higher nitrated compounds were also not observed (**5**, **6**; Figure 1).



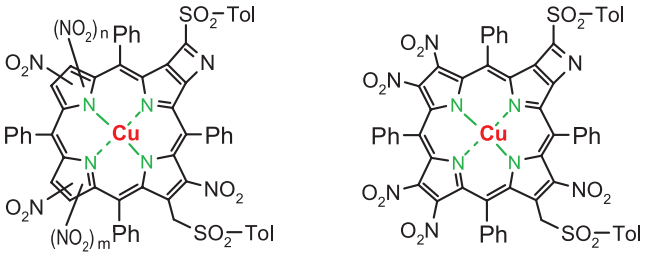
3; *m/z* = 1146 **4**; *m/z* = 1191

5; *m/z* = 1236 **6**; *m/z* = 1281

Figure 1. The expected products of electrophilic nitration of **2**.

From the best experiment five fractions were isolated, however only three of them contained defined porphyrinoid products. In the spectra of the first and the third fraction the same pseudomolecular ion was detected, *m/z*=1203. One can suppose it is originating from two isomers of the same compound. In the second fraction an ion *m/z*=1248, $[M+H]^+$, was observed.

A detailed analysis of the latter product led us to the conclusion that it is a result of introduction of the four new NO_2 groups, however it entered in the subsequent reaction, because mass loss is observed (ΔM=1281–1247=34). In this reaction probably one NO_2 group was involved and two oxygen as well as two hydrogen atoms left the molecule. Moreover, the difference of the molecular mass of this product and the molecular mass of two isomers found in the fraction-1 and fraction-3 is equal ΔM=45 (equivalent of NO_2 group; $[M–NO_2+H]$). That means they are a result of introduction NO_2 group in three *β*-positions (one *β*-position is still unsubstituted), and the subsequent reaction undergoing according to the same pattern observed for exhaustively substituted moiety (discussed above). The question is about the structure of the products. On the basis of MS studies these structures were proposed (Figure 2), and one can suppose that the key-intermediate herein is the nitrene species.



two isomers (n=0, m=1 or n=1, m=0); one isomer in fraction-1 (R_f=0.55; **7**), another one in fraction-3 (R_f=0.39; **9**); *m/z* = 1203, $[M+H]^+$

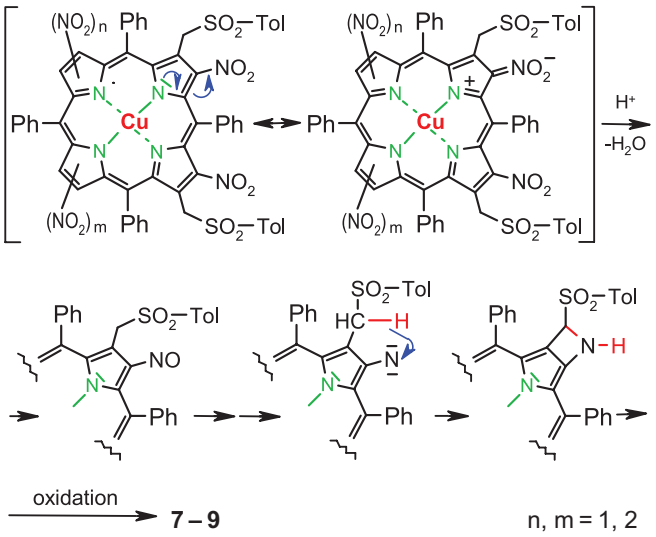
8
(fraction-2; R_f=0.50)
m/z = 1248, $[M+H]^+$

Figure 2. The structures of the products proposed on the basis of mass-spectrometry data.

There are many examples in the literature of conversion of nitroaromatic compounds into nitrenes, however, the reactions required the use of deoxygenation agents such as trivalent phosphorous compounds (phosphines, trialkyl phosphites, *etc.*) or transition metal moieties.[11,12] There are also some reports involving well-known organometallic reagents (*e.g.* Grignard compounds).[13,14] Leaving aside the detailed discussion on the mechanism, one can accept such organometallic assistance in the transformations described herein because porphyrinates are organometallic compounds. Partially they undergo 'degradation' under the reaction conditions, thus allowing (with small yield; *ca.* 15 % or below) conversion of some other moieties to the nitrene-derivatized intermediates. Two more works should be mentioned in this respect.[15,16] The reactions of α-nitronaphthalene derivatives with dimethyl phosphite anion were carried out in basic conditions, however the Authors postulated the deoxygenative mechanism (conversion of the NO_2 group into nitrene species) as possible protonation/dehydration step.

In the light of the above discussion, the nitrene formation is very likely herein. It can immediately enter the insertion reaction involving the neighbouring C–H bond and giving rise to formation of unstable four-membered ring (see Scheme 2). This type of intermediates could undergo oxidation to give final products (M=1202 or 1247). Thus, the three compounds we observed should have structures as above (**7**-**9**). The reaction is similar to the fused heterocycles formation pathway (especially indole derivatives).[11,12,14,17]

These products are extremely unstable, however, the attempts to confirm their structures by other methods were undertaken. Further manipulation on the moieties to remove paramagnetic Cu^{2+} cation and to record NMR spectra for free-base porphyrinoids failed. In this situation we tried to collect more other spectral data confirming the proposed



Scheme 2.

structures. The measurements using MALDI-MS technique and some MS spray techniques in negative ions mode were unsuccessful, and did not give definitive proof. Finally, it was found that IR spectra were very helpful (Figure 3). Comparing the bands of the substrate **2** and product **9** in the most interesting region (1400–1800 cm^{-1}; absorption of C=C and C=N bonds) one can see big difference. The first spectrum is rather symmetrical, with strong band at 1527.6 cm^{-1} and a smaller one at 1595.1 cm^{-1}. They are originating from C=C and C=N double bonds. Additionally, the first band is probably overlapped with $\nu(NO_2)$. It is rather surprising because C=N imine stretching bands usually occur in the region 1620–1690 cm^{-1}. Herein, occurring at the lower frequency is due to high conjugation of the system. After the reaction this conjugation is partially destroyed and C=N bonds (including new azet-diene four-membered ring) are considerably differentiated, thus giving many bands, up to 1734 cm^{-1} (Figure 3). The situation in other spectra is similar.

It needs to be mentioned that products obtained bearing several NO_2 groups and two SO_2 groups should reveal in the spectrum characteristic strong bands of these groups. Indeed, it was a case in the spectra of all compounds.

For these products one could propose alternative structures. Due to large strains in the small four-membered rings, their expansion to seven-membered rings may be observed. There are a number of papers in the literature, in which similar aromatic nitrene reactivity is described (*via* expansion of fused azirine or aziridine).[11,12,15,17-19] Thus, this reaction scheme may also be taken under reconsideration.

The more complex elucidation of the structures was not possible due to: (a) paramagnetic Cu^{2+} cation in the core ring (the recorded NMR spectra are not clear) and (b) very small amounts of the compounds obtained. For one product the decomplexation was carried out and the free-base porphyrin obtained was examined by ^1H NMR, but the spectrum was completely unreadable due to overlapped signals of *ca* 30 aromatic protons.

In further experiments carried out to obtain the desired products, the post-reaction mixtures were examined by MS

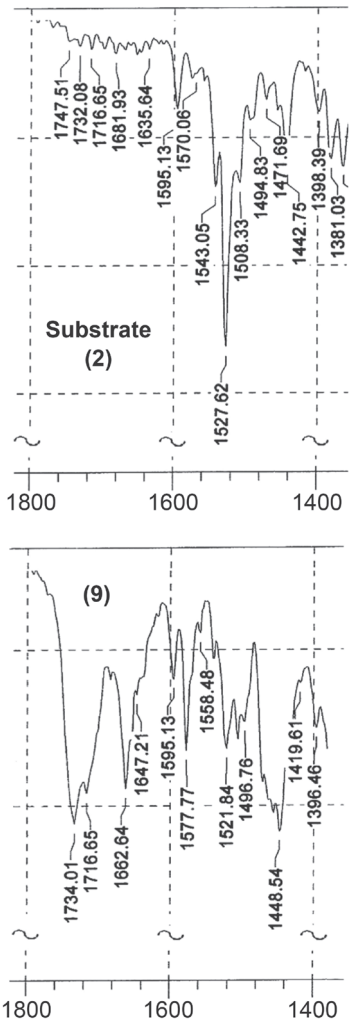


Figure 3. IR spectra (region 1400–1800 cm^{-1}) of substrate **2** (above) and product **9** (below) in $CHCl_3$ solution.

directly after work-up. We have not found the expected porphyrins in these mixtures. Interestingly, in the reaction when time was shortened to 10 min (50 % HNO_3), one more analogous product was observed, *m/z*=1158 ($[M+H]^+$), which is a consequence of dinitration (Figure 2; n=0, m=0).

From the above discussion is clearly seen that nitration of the described herein tetrasubstituted in 'eastern half' porphyrins led unselectively to a mixture of products (di-, tri-, and tetranitrated). Moreover, they underwent subsequent reactions. Despite all the yields are rather low, the observed mode of reactivity is very interesting. One cannot exclude that the products are formed according to another transformation pathway or they have another structures. Some optimization attempts (by changing the amount and concentration of HNO_3 or shortening the reaction time) did not enter into selectivity or increasing the yields of the products.

Conclusions

The conclusions from these investigations are quite clear. The nitration of exhaustively substituted in the so-called 'eastern half' porphyrinates cannot be realized by this way. Thus, another approach should be applied, as it is important

task in the synthesis of highly functionalized very attractive porphyrin intermediates, of potential utility in many fields. Currently, we are in the midst of exploring this area.

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