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Tetraphenylporphyrins Monosubstituted with Glycerol Derivative Units in the Phenyl Rings. Synthesis and Characterization

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Summary. The synthesis and spectroscopic characterization of a series of *meso*-tetraphenyl substituted porphyrins appended with glycerol, diacetylglycerol, or isopropylideneglycerol units in *ortho*, *meta*, or *para* position of the phenylene ring is described.

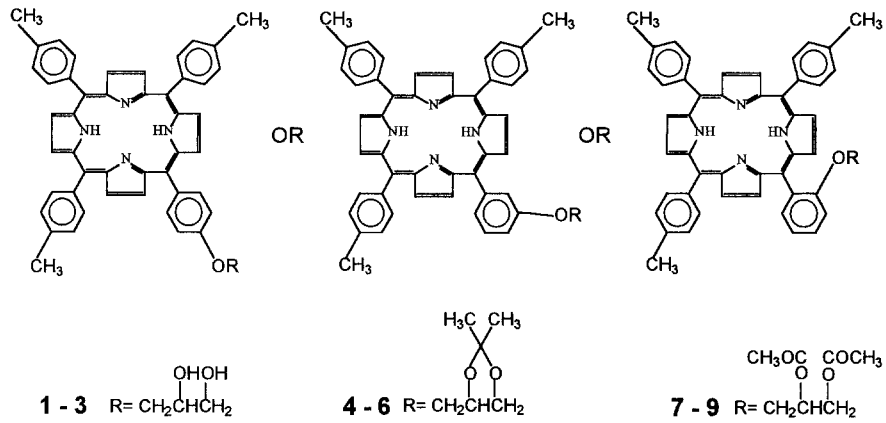
Keywords. Glycerol ethers; 1,2-Diacetylglycerols; Tetraphenylporphyrin; Tetraphenylporphyrine-glycerol.

Synthese und Charakterisierung von an den Phenylresten mit Glycerinderivaten monosubstituierten Tetraphenylporphyrinen

Zusammenfassung. Synthese und spektroskopische Charakterisierung einer Reihe von an den Phenylringen in *ortho*-, *meta*- oder *para*-Position mit Glycerin, Diacetylglycerin oder Isopropyliden-glycerin substituierten *meso*-tetraphenylsubstituierten Porphyrinen wird beschrieben.

Introduction

Porphyrin derivatives coupled with units arising from natural products have been developed and evaluated for use in the treatment of light accessible tumors during the last years. For example, the synthesis of the number of glycosylated porphyrin derivatives [1–4], porphyrins coupled with nucleoside bases [5–7] or a nucleoside [8–9], with a steroid [10], 2,3-diacylglycerol units [11], cholic acid units [12–13], guanidine and betaine units [14], or carotenoid units [15] have been described. In order to establish the effects of various substituents in the porphyrin molecule on hydrophobicity, solubility, and finally on the localization in tumor tissue, a series of new *meso*-tetraphenylporphyrin derivatives, substituted in *para*, *meta*, or *ortho* position of one phenyl moiety with glycerol (**1**–**3**), 2,3-isopropylideneglycerol (**4**–**6**), or 2,3-diacetylglycerol units (**7**–**9**) were synthesized and investigated (Scheme 1).



Scheme 2 (explanation of the values in parentheses)

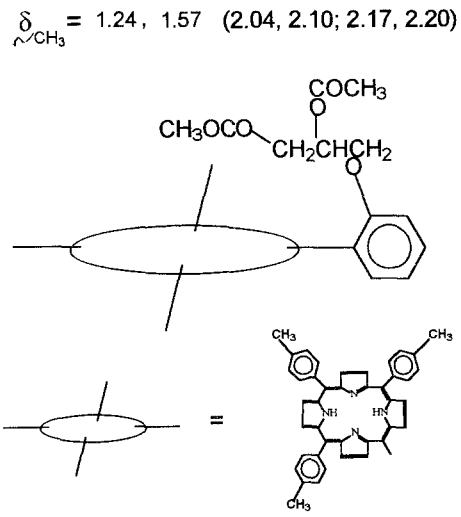
Results and Discussion

Porphyrins **1**–**3** were synthesized, respectively, by reaction of *D,L*-2,3-*iso*-propylideneglycerol tosylate [16] with *para*, *meta*, or *ortho* isomers of 5-(hydroxyphenyl)-10,15,20-*tri*-*para*-tolylporphyrin which were synthesized according to published methods [17]. The products were readily purified by alumina chromatography (dichloromethane as eluant) and then converted to the glycerol derivatives underwent hydrolysis with HCl in methanol. Porphyrins **4**–**6** were purified on alumina with ethyl acetate. Acetylation of the glycerol hydroxy groups with small excess of acetyl chloride in dichloromethane in the presence of pyridine yielded the desired compounds **7**–**9**. The structures of all compounds were confirmed by ^{1}H NMR, UV, and mass spectral data.

The orientation of the glycerin moiety with respect to the porphyrin ring in *ortho* derivatives was compared with that of *meta* or *para* derivatives. Chemical shifts of ^{1}H NMR spectra for compounds **1**–**9** are given in Experimental and in Table 1. The porphyrin NH protons appeared in a narrow region from -2.73 to -2.80 ppm. β-Protons of the porphyrin core resonate at approximately 8.85 ppm as broad singlets for compounds **3**, **4**, **5**, and **8** and as multiplets for the residual compounds. The ring current of the porphyrin core causes substantial differentiation of signals of the protons in the glycerol moiety.

In the ^{1}H NMR spectra of *ortho*-substituted derivatives (**3**, **6**, **9**), the signals of the glycerol moiety appear at remarkably high fields compared with *meta* or *para* derivatives. Also, the signals of the methyl protons of diisopropyl compound **6** and diacetyl compound **9** show high-field shifts compared with the *meta* or *para* derivatives (0.5–0.9 ppm; see Scheme 2). The high field shifts due to the ring current effect of the porphyrin core demonstrate the conformational features in which the glycerol moiety are located above the porphyrin ring. The proton signals of *meta* isomers are comparable to those of *para* isomers in chemical shift. Selected ^{1}H NMR data for **4**–**9** are presented in Table 1.

In the mass spectra (LSIMS technique), the prominent ions correspond to the protonated molecular ion peaks at $m/e = 747$, 787, and 831 for glycerol, isopro-



Scheme 2 (explanation of the values in parentheses)

Table 1. Selected ^{1}H NMR chemical shifts of compounds **4–9**

	CH_2CHCH_2	CH_3CCH_3	$COCH_3$
4	4.60 q (1 H) 3.99–4.26 m (4 H)	1.54 s (3 H) 1.46 s (3 H)	
5	4.57 q (1 H), 4.05–4.20 m (3 H), 3.92–3.99 m (1 H)	1.45 s (3 H) 1.40 s (3 H),	
6	4.03 m (1 H), 3.80 t (1 H), 3.50 m (1 H), 2.65–2.82 m (2 H)	0.78 s (3 H), 0.82 s (3 H),	
7	5.58 m (1 H) 4.30–4.70 m (4 H)		2.20 s (3 H) 2.17 s (3 H)
8	5.47 m (1 H) 4.29–4.54 m (4 H)		2.10 s (3 H) 2.04 s (3 H)
9	4.69 m (1 H), 3.99 d (1 H) 3.39, 3.45 dd (1 H) 2.91, 2.98 dd (2 H)		1.57 s (3 H) 1.24 s (3 H)

pylideneglycerol and diacetylglycerol derivatives, respectively. These ions are formed by a proton transfer reaction in the matrix.

The UV-Vis absorption spectra of the porphyringlycerides show typical porphyrin absorption bands. For example, the spectrum of compound **3** exhibits a strong *Soret* band at 421 nm with Q bands at 519, 555, 596, and 653 nm. The position of bands differs for the individual compounds by no more than 4 nm. The relative intensities for these features are typical for *meso*-substituted porphyrins.

In summary, we have developed a synthetic route to porphyringlycerol compounds which may allow to prepare new functionalized porphyrin derivatives in which the functional groups may be linked to the porphyrin *via* a very flexible glycerol spacer.

Experimental

The proton NMR spectra were recorded with Varian VXR 300 or IBM AF-200 spectrometers; chemical shifts are given in ppm ($CDCl_3/TMS$). Electronic spectra were recorded on a Specord UV-Vis spectrophotometer (Carl Zeiss-Jena) in CH_2Cl_2 solutions. Mass spectrometry was performed on a LSIMS(+) model AMD 604 (AMD Intectra) spectrometer (NBA matrix). Thin layer chromatography (TLC) was performed with Merck Alumina $60F_{254}$ neutral (type E) or Silica $40F_{254}$ plates. The plates were precoated with 0.2 mm of alumina or 0.25 mm of silica gel. Column chromatography was performed on silica gel Kieselgel 100 (70–230 mesh, Merck) or aluminium oxide (neutral) for column chromatography (POCh – Poland). Unless specified otherwise, starting materials and solvents were reagent grade and used as received. Methylene chloride was passed through very short column of basic alumina to remove traces of hydrochloric acid.

Starting Materials

D,L-2,3-isopropylideneglycerol tosylate [16], 5-(4-hydroxyphenyl)-, 5-(3-hydroxyphenyl)-, and 5-(2-hydroxyphenyl)-10,15,20-tritolylporphyrin [17] were prepared by procedures described earlier.

D,L-1,2-O-(5-othro-phenylene-10,15,20-tritolylporphyrin)glycerol (**3**)

To the stirred suspension of 0.79 g (1 mmol) **6** in methanol (100 ml), 1 ml of conc. hydrochloric acid was added. The green solution was stirred at room temperature for 20 h, and the methanol was removed by evaporation under reduced pressure. The crude product was dissolved in a mixture of dichloromethane and water (appr. 100 ml, 1:1). The organic layer was separated and washed with water, saturated sodium bicarbonate, and finally twice with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column with chloroform as first eluant to remove traces of **6** and with chloroform:methanol (10:1, v/v) as second eluant. After evaporation of the solvent, 0.47 g (63%) of crude product was obtained. The product was pure enough for the following reaction with acetyl chloride. For the spectroscopic studies, the crude product was rechromatographed twice on a silica gel column with ethyl acetate as eluant.
MS (*m/z*): 747 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 421$, 519, 555, 596, 653 nm; ^1H NMR (δ): 8.86 s (8H), 8.09, 7.54 dd (12H, $J = 7.8$ Hz), 7.77–7.86 m (2H), 7.62 t (1H), 7.29–7.34 m (1H), 3.95 d (2H), 3.09 m (1H), 2.69 s (9H), 2.62–2.69 m (2H), 2.62 bs (1H), 1.9–2.0 bt (1H), −2.79 bs (2H).

D,L-1,2-O-(5-meta-phenylene-10,15,20-tritolylporphyrin)glycerol (**2**)

This compound was obtained in the same way as **3**, the substrate for deprotection being **5**. The crude product was rechromatographed on alumina with ethyl acetate. Yield: 60%.
MS (*m/z*): 747 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 420$, 519, 554, 595, 650 nm; ^1H NMR (δ): 8.76–8.85 m (8H), 8.08 m (7H), 7.73–7.80 m (1H), 7.54 d (6H, $J = 7.8$ Hz), 7.44–7.25 m (2H), 4.17–4.22 m (3H), 3.81 m (2H), 2.69 s (3H), 1.26 d (1H), 0.94 t (1H), −2.74 bs (2H).

D,L-1,2-O-(5-para-phenylene-10,15,20-tritolylporphyrin)glycerol (**1**)

This compound was obtained in the same way as **3**, the substrate for deprotection being **4**. Alumina with ethyl acetate were used for the purification of the crude product. Yield: 76%.
MS (*m/z*): 747 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 420$, 518, 555, 594, 651 nm; ^1H NMR (δ): 8.85 m (8H), 8.13 d (2H, $J = 8.4$ Hz), 8.09 d (6H, $J = 7.8$) 7.54 d (6H, $J = 7.8$ Hz), 7.28 d (2H, $J = 8.4$ Hz), 4.29 m (3H), 3.95 m (2H), 2.69 s (9H), 1.55 bs (2H), −2.77 bs (2H).

D,L-1,2-O-Isopropylidene-3-O-(5-ortho-phenylene-10,15,20-tritolylporphyrin)-glycerol (**6**)

A suspension containing sodium hydride (0.12 g, 5 mmol), 1.34 g (2 mmol) of 5-(2-hydroxyphenyl)-10,15,20-tritolylporphyrin, and 0.58 g (2.5 mmol), of *D,L*-1,2-isopropylideneglycerol tosylate in 50 ml of anhydrous *DMF* was stirred at room temperature for 24 h. Then 10 ml of water was added to the reaction flask and the mixture was evaporated under reduced pressure. The residue was dissolved in a water-dichloromethane mixture. The organic layer was separated, washed with water and dried over anhydrous $MgSO_4$. The product was purified by chromatography (twice) on a silica gel column using chloroform as eluant (first fraction: product; second fraction: unreacted substrate). Yield 0.91 g (58%).
MS (*m/z*): 787 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 420$, 518, 554, 595, 650 nm; ^1H NMR (δ): 8.74–8.85 m (8H), 8.0–8.12 m (1H), 8.06 d (6H, $J = 7.9$ Hz), 7.71–7.79 m (1H), 7.54 d (6H, $J = 7.9$ Hz), 7.32–7.41 m (2H), 4.03 m (1H), 3.80 t (1H), 3.50 m (1H), 2.65–2.82 m (2H), 2.70 s (9H), 0.82 s (3H), 0.78 s (3H), −2.76 bs (2H).

D,L-1,2-O-Isopropylidene-3-O-(5-meta-phenylene-10,15,20-tritolylporphyrin)-glycerol (**5**)

This compound was obtained in the same way as **6**; the substrates were 5-(3-hydroxyphenyl)-10,15,20-tritolylporphyrin and 2,3-isopropylideneglycerol tosylate. The crude product was chromatographed on alumina with dichloromethane. Yield: 65%.
MS (*m/z*): 787 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 421$, 518, 554, 595, 653 nm; ^1H NMR (δ): 8.86 s (8H), 8.09 d (6H, $J = 7.9$ Hz), 7.78–7.84 m (2H), 7.62 t (1H), 7.55 d (6H, $J = 7.9$ Hz), 7.31–7.36 m (1H), 4.57 q (1H), 4.05–4.20 m (3H), 3.92–3.99 m (1H), 2.70 s (9H), 1.45 s (3H), 1.40 s (3H), −2.79 bs (2H).

D,L-1,2-O-Isopropylidene-3-O-(5-para-phenylene-10.15,20-tritolylporphyrin)-glycerol (**4**)

This compound was obtained in the same way as **6**; the substrates were 5-(4-hydroxyphenyl)-10,15,20-tritolylporphyrin and 2,3-isopropylideneglycerol tosylate. Purification as for comp. **5**. Yield: 70%.
MS (*m/z*): 787 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 420$, 519, 555, 595, 653 nm; ^1H NMR (δ): 8.85 bs (8H), 8.09 d (2H, $J = 8.4$ Hz), 8.07 d (6H, $J = 7.8$ Hz), 7.49 d (6H, $J = 7.8$ Hz), 7.21 d (2H, $J = 8.4$ Hz), 4.60 q (1H), 3.99–4.26 m (4H), 2.65 s (9H), 1.54 s (3H), 1.46 s (3H), −2.73 s (2H).

D,L-1-O-(5-ortho-phenylene-10,15,20-tritolylporphyrin)-2,3-diacetylglycerol (**9**)

Freshly distilled acetyl chloride (0.12 g, *ca.* 1.5 mmol) was added dropwise to the stirred solution of compound **3** (0.37, 0.5 mmol) in dichloromethane (15 ml) and two ml of pyridine. The resulting mixture was stirred at room temperature for 24 h. The solution was diluted with dichloromethane (*ca.* 35 ml) and washed with water (several times), with saturated sodium bicarbonate, with water, and dried over anh. $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography (two or three times) on alumina with dichloromethane as eluant to give **9** as first fraction; second and third fraction: monosubstituted derivative and unreacted diol **3**, respectively. Yield 0.2 g (48%).
MS (*m/z*): 831 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 420$, 517, 553, 594, 650 nm; ^1H NMR (δ): 8.7–8.9 m (8H), 8.0–8.2 m (7H), 7.68–7.83 m (1H), 7.54 d (6H), 7.29–7.43 m (2H), 4.69 m (1H), 3.99 d (1H), 3.39, 3.45 dd (1H), 2.91, 2.98 dd (2H), 2.70 s (9H), 1.57 s (3H), 1.24 s (3H), −2.76 bs (2H).

D,L-1-O-(5-meta-phenylene-10,15,20-tritolylporphyrin)-2,3-diacetylglycerol (**8**)

This compound was obtained in the same way as **9** (substrate: **2**). Yield *ca.* 40%.
MS (*m/z*): 831 ($M + H^+$); UV (CH_2Cl_2): $\lambda_{max} = 420$, 518, 553, 594, 649 nm; ^1H NMR (δ): 8.86 s (8H), 8.09 d (6H, $J = 7.8$ Hz), 7.6–7.9 m (3H), 7.55 d (6H, $J = 7.8$ Hz), 7.3–7.4 m (1H), 5.47 m (1H), 4.29–4.54 m (4H), 2.70 s (9H), 2.10 s (3H), 2.04 s (3H), −2.80 bs (2H).

D,L1-O-(5-para-phenylene-10,15,20-tritolylporphyrin)-2,3-diacetylglycerol (**7**)

This compound was obtained in the same way as **9** (substrate: **1**). Yield *ca.* 45%.
MS (*m/z*) (*δ*): 831 ($M + H^+$); UV (CH_2Cl_2): λ_{max} = 420, 519, 555, 595, 651 nm; ^1H NMR (*δ*): 8.85 m (8H), 8.12 d (2H, J = 8.6 Hz), 8.07 d (6H, J = 7.9 Hz), 7.55 d (6H, J = 7.9 Hz), 7.28 d (2H, J = 8.6 Hz), 5.58 m (1H), 4.30–4.70 m (4H), 2.70 s (9H), 2.20 s (3H), 2.17 s (3H), −2.78 bs (2H).

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