Monatshefte für Chemie 129, 69–79 (1998)

Monatshefte für Chemie
Chemical Monthly

Benzoylation at the *meso* Position of a Zinc(II) Deuteroporphyrin

Jordi Vázquez[1], **Maria M. González**[1], **Cristina Martí**[2], **Santi Nonell**[2,*], and **Francesc R. Trull**[1,†]

[1] Departament de Química Orgànica, Universitat de Barcelona, E-08028 Barcelona, Catalunya, Spain
[2] CETS Institut Químic de Sarrià, Universitat Ramon Llull, E-08017 Barcelona, Catalunya, Spain

Summary. By short treatment of zinc(II) deuteroporphyrin-IX dimethyl ester with benzoic anhydride/$SnCl_4$, a mixture of benzoylated derivatives was obtained from which a tribenzoyl derivative with benzoyl groups at the 2, 4, and γ-*meso* positions could be isolated in low yield. Except for the known *Vilsmeier* formylation, this constitutes the first example of a *Friedel-Crafts* acylation taking place at the *meso* position of a porphyrin chelate. The expected lack of regioselectivity of this reaction, even at low conversion rates, and the difficulty to separate the products limit, of course, its synthetic value for the preparation of the particular benzoyl derivatives. This limitation cannot be overcome by starting with a completely β-substituted porphyrin or with a symmetrically substituted porphyrin, since attempts to benzoylate Zn(II) mesoporphyrin-IX dimethyl ester lead exclusively to demetallation. However, these findings add to the knowledge of the fundamental properties of porphyrin reactivity. A rationalization based on calculations at a semiempirical level, which are in acceptable agreement with the experimental results, is presented.

Keywords. Electrophilic substitution; Benzoylation; Porphyrins; Semiempirical calculations.

Zur Benzoylierung an der *meso*-Position eines Zink(II)-Deuteroporphyrins

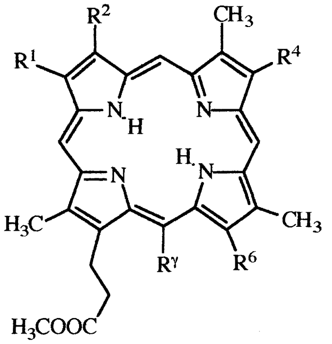
Zusammenfassung. Durch kurzes Behandeln von Zink(II)-Deuteroporphyrin-IX-dimethylester mit Benzoesäureanhydrid/$SnCl_4$ wurde ein Gemisch von benzoylierten Derivaten erhalten, aus welchen in geringer Ausbeute ein Tribenzoylderivat isoliert werden konnte, das die Benzoylgruppen in 2-,4- und γ-*meso*-Position enthält. Abgesehen von der *Vilsmeier*-Formylierung stellt diese Reaktion das erste Beispiel einer *Friedl-Crafts*-Acylierung an der *meso*-Position eines Porphyrinchelates dar. Mangelnde Selektivität der Reaktion auch bei geringem Umsatz und die Schwierigkeiten bei der Trennung der Produkte engen natürlich ihre Bedeutung für die Synthese bestimmter Benzoylderivate ein. Dieser Mangel konnte auch nicht durch Verwendung von vollständig β-substituierten oder symmetrisch substituierten Porphyrinen behoben werden, da Versuche, Zn(II)-Mesoporphyrin-IX-dimethylester zu benzoylieren, ausschließlich das entmetallierte System ergaben. Allerdings tragen diese Resultate zum Wissen über die fundamentalen Reaktionsweisen von Porphyrinen wesentlich bei. Eine Rationalisierung der Ergebnisse kann auf der Basis von semiempirischen Rechenmethoden, deren Resultate mit den experimentellen Daten im Einklang stehen, gegeben werden.

[†] Deceased on June 28, 1997 at the age of 43

Introduction

The study of the relative reactivity of the different positions in the porphyrin periphery (*i.e.*, β and *meso* positions) is an important goal of porphyrin chemistry [1], particularly because it could set the path to differently substituted porphyrins which are of general interest for the evaluation of the effects of these substituents upon the chemical behaviour of the porphyrins [2]. Among those, benzoylated porphyrins are *a priori* candidates as non-fluorescent singlet molecular oxygen ($O_2(^1\Delta_g)$) sensitizers [3].

In principle, deuteroporphyrin-IX **1a** with two free β positions should be a suitable system to study the relative reactivity of β *vs. meso* positions of porphyrins and for the subsequent preparation of their structurally related derivatives. A number of electrophilic substitution reactions of deuteroporphyrin or its iron(III) chloride have been investigated [1, 2, 4]. The results of these studies are basically in agreement with the calculated reactivity indices for a metalloporphyrin towards an electrophile: 0.29 (*meso*), 0.05 (β-pyrrole), 0.14 (α-pyrrole), 0.07 (N) [2]. Exceptional preferences for β-pyrrolic substitutions have been mostly rationalized on grounds of steric hindrance of the *meso* carbons [1]. Substitution of the two NH



1	R^1	R^2	R^4	R^6	R^γ
a	CH_3-	H-	H-	CH_3OOC-$(CH_2)_2$-	H-
b	CH_3-	CH_3CH_2-	CH_3CH_2-	CH_3OOC-$(CH_2)_2$-	H-
c	CH_3-	CH_3CH_2-	CH_3CH_2-	H-	H-
d	CH_3-	CH_3CH_2-	CH_3CH_2-	H-	CH_3-
e	CH_3-	CH_3CH_2-	CH_3CH_2-	PhCO-	H-
f	CH_3-	CH_3CH_2-	CH_3CH_2-	PhCO-	CH_3-
g	CH_3CH_2-	CH_3-	PhCO-	CH_3OOC-$(CH_2)_2$-	H-
h	PhCO-	CH_3-	PhCO-	CH_3OOC-$(CH_2)_2$-	H-
i	CH_3-	PhCO- or H-	H- or PhCO-	CH_3OOC-$(CH_2)_2$-	H-
j	CH_3-	PhCO-	PhCO-	CH_3OOC-$(CH_2)_2$-	H-
k	CH_3-	PhCO-	PhCO-	CH_3OOC-$(CH_2)_2$-	PhCO-
l	CH_3-	CH_3CO-	CH_3CO-	CH_3OOC-$(CH_2)_2$-	H-

protons in a porphyrin by metal ions of low electronegativity, *e.g.* Mg^{2+}, lead to porphyrin ligands of relatively high nucleophilicity. However, the acid lability of magnesium porphyrins prevents their general use in electrophilic reactions.

Previously, the synthesis of the 6-benzoyl porphyrins **1e** and **1f** has been achieved by treatment of the iron(II) complex of the corresponding 6-unsubstituted precursor (**1c**, **1d**) with benzoic anhydride using $SnBr_4$ as the *Lewis* acid [4]. Iron(III) porphyrins were chosen as substrates because metal-free porphyrins did not react. Apparently, *meso* substitution has never been observed, although similar reactions have been applied to a number of porphyrins.

Interestingly enough, *Fischer* has prepared both the 4-benzoyl porphyrin **1g** and the symmetrical 1,4-dibenzoyl porphyrin **1h** using a completely different strategy: by coupling of the two dipyrrin halves [4]. On the other hand, no benzoylated porphyrin of type IX has been reported so far.

Acetylation of copper and iron(III) porphyrins has only been described for β-pyrrolic positions. The usual product is the 2,4-diacetyl derivative, but careful control of reaction conditions led to formation of a mixture of 2- and 4-acetyl deuteroporphyrin dimethyl esters [5, 6].

In summary, non of the *Friedel-Crafts* acylations reported to date leads to *meso* substitution. On the contrary, the *Vilsmeier* formylation does so in almost quantitative yield [7]. No rationalization has been offered for these results.

Introduction of nitrogen, sulfur, and halogen substituents into the porphyrin periphery has also been achieved [1, 5, 8]. These reactions are regioselective and usually take place either at the β positions (bromination, iodination) or at the *meso* positions (nitration, chlorination), but not at both.

Because the photophysical properties of porphyrin derivatives of the benzophenone type (*i.e.* with structures like **1i**–**1k**) are of interest, we decided to further investigate *Fischer*'s benzoylation procedure upon the easily accesible deuterohemin dimethyl ester (iron(III) deuteroporphyrin-IX dimethyl ester, Fe(III)-**1a**). In addition, we extended the benzoylation reaction to zinc(II) deuteroporphyrin-IX dimethyl ester (Zn(II)-**1a**) which contains a more easily removable metal.

Results and Discussion

The product of the above reaction is a partially demetallated mixture of mainly mono-, di-, and tribenzoylated porphyrins where benzoylation at the 2 and 4β positions predominates. HPLC permits to isolate the 2,4,γ-tribenzoyl deuteroporphyrin-IX dimethyl ester **1k**. This compound constitutes the first reported *meso* substituted derivative prepared by *Friedel-Crafts* acylation of a porphyrin chelate. It is also interesting because of its low fluorescence quantum yield (*ca.* one third that of the unbenzoylated precursor). Interestingly, benzoylation of a completely β-substituted porphyrin chelate such as zinc(II) mesoporphyrin-IX dimethyl ester, Zn(II)-**1b**, under analogous conditions does not take place, and the reaction leads exclusively to demetallation. These results have been used to propose a mechanism for the benzoylation in the deuteroporphyrin series. Quantum mechanical calculations at a semiempirical level have been performed of the relative reactivity towards electrophiles of deuteroporphyrin-IX, its Zn(II) complex, and the 2-

benzoyl and 2,4-dibenzoyl derivatives of the latter. The theoretical results are compared to the experimental ones.

*Benzoylation of iron(III)-deuteroporphyrin-IX (duterohemin, Fe(III)-***1a***,* $R_6 = -(CH_2)_2\text{-COOH}$)

According to *Fischer* [4], treatment of the iron(III) complex of the β-free porphyrins **1c** and **1d** with benzoic anhydride/$SnBr_4$ for 10–12 min at 70°C, followed by a cumbersome work-up which includes as key steps treatment with ice-cooled concentrated H_2SO_4 (probably to demetallate the product) and esterification of the resulting free acid with CH_2N_2, affords the corresponding metal-free monobenzoyl porphyrin dimethyl esters **1e** and **1f**.

The same procedure was applied to iron(III)-deuteroporphyrin-IX (deuterohemin, Fe(III)-**1a**, $R_6 = -(CH_2)_2\text{-COOH}$). A mixture (by TLC) containing one or more benzoylated derivative(s) of the starting compound was obtained: the *Soret* band with a shoulder was observed near 450 nm. This should be compared with 2,4-diacetyldeuterohemin which has a *Soret* maximum at 440 nm in pyridine [9]. Phenyl signals where found near 7.9–7.2 ppm in the ^{1}H NMR spectrum (*DMSO*-d_6/NaCN), and a ketone C=O band near 1660 cm^{-1} was observed in the IR spectrum. However, all attempts to demetallate this product(s) were unsuccessful. These included treatment with: 1) concentrated H_2SO_4 at 0°C for 1 h; 2) MeOH/HCl(g) in the presence of $FeSO_4$ as described by *Caughey et al.* [5] for the one-step conversion of deuterohemin into deuteroporphyrin-IX dimethyl ester (**1a**); and 3) concentrated H_2SO_4/$FeSO_4$ at 0°C for 3 h. With the MeOH/HCl mixture, complete esterification of the components of the mixture took place (new singlet near 3.8 ppm in the ^{1}H NMR, ester C=O band near 1725 cm^{-1} in the IR).

These results indicate that iron(III) removal from the benzoylated porphyrin(s) is more difficult to achieve relative to that from the unbenzoylated precursor. The results from benzoylation reactions of Zn(II)-**1a** (see below) confirm this observation.

*Lack of reactivity of deuteroporphyrin-IX dimethyl ester (***1a***)* under the benzoylating conditions

Upon treatment of **1a** with 1) benzoyl chloride/$SnCl_4$ in CH_2Cl_2 at −3°C for 20 min following the procedure previously reported for the benzoylation of other aromatic hydrocarbons [10] and 2) benzoic anhydride/$SnCl_4$ following essentially the procedure reported by *Fischer* [4], only unreacted material was recovered even after prolonged reaction time. This confirms previous reports on the lack of reactivity of **1a** towards acylation reactions [1, 2].

*Benzoylation of the zinc(II) chelates Zn(II)-***1a** *and Zn(II)-***1b**

Starting from Zn(II)-**1a**, benzoylation took place to some extent in all attempts when $SnCl_4$ was used as catalyst (i.e. presence and absence of nitrobenzene as solvent, reaction time 15 to 30 min, 70°C). In contrast, when the more reactive catalyst but stronger *Lewis* acid $AlCl_3$ was used in *Friedel-Crafts* benzoylations

[10], no reaction took place, and the free base **1a** was recovered. Apparently, $AlCl_3$ is too strong a *Lewis* acid so that the acidic medium led to a demetallation of the substrate.

Clearly, with $SnCl_4$, demetallation of Zn(II)-**1a** occurs at a lower rate, thus allowing for the benzoylation process to take place to some extent. Indeed, with $SnCl_4$ (for additional details see Experimental), a complex mixture of Zn(II)- and free base deuteroporphyrin-IX derivatives with a variable number of benzoyl groups *per* porphyrin was obtained. In addition, whereas the metal free derivatives contain one to three benzoyl groups, up to five benzoyl units are found in the Zn(II)-compounds (by MS). This confirms that metal removal from the benzoylated porphyrin is more difficult than from the unbenzoylated precursor and that this difficulty increases with the number of benzoyl groups present on the chelate.

From the benzoylation mixture, one pure compound (2,4,γ-tribenzoyldeuteroporphyrin-IX dimethyl ester, **1k**) could be isolated. This is the first example of a *Friedel-Crafts* acylation of a porphyrin chelate occurring at one *meso* position. The structure of **1k** was established spectroscopically: high resolution mass spectrometry confirmed the tribenzoylation. The location of the three benzoyl groups was deduced from the ^{1}H NMR spectrum where the C2-H and C4-H signals are absent; in addition, substitution at the γ-*meso* position was concluded on the basis of the strong distortion of the shape and chemical shift of the -CH_2-CH_2-COOMe signals relative to both deuteroporphyrin-IX dimethyl ester (**1a**) and 2,4-diacetyldeuteroporphyrin-IX dimethyl ester (**1l**). In the UV/Vis spectrum in CH_2Cl_2, the *Soret* band is red-shifted by 19 nm and the *Q* bands by 14–17 nm relative to **1a**. These shifts are only slightly lower than those found for the 2,4-diacetyl derivative **1l** (25 nm for the *Soret* band and 19–22 nm the *Q* bands). The differences between **1k** and **1l** may be interpreted in terms of a larger deviation from coplanarity of the C=O group relative to the porphyrin in **1k**, probably imposed by steric hindrance exerted by the phenyl group. The fluorescence maximum in benzene is also red-shifted (by 21 nm) relative to **1a** and nearly coincides with that of **1l**. Interestingly, the fluorescence quantum yield of **1k** is *ca.* 0.04, *i.e.* one third of that of **1a** (one fourth of that of **1l**). These results confirm that both acetylated and benzoylated porphyrins could in principle be used as singlet molecular oxygen photosensitizers of low fluorescence.

In contrast, treatment of zinc(II) mesoporphyrin-IX dimethyl ester (Zn(II)-**1b**) under analogous benzoylation conditions leads exclusively to demetallation, and the free base **1b** is obtained. The last compound is inert towards benzoylation, as was the deuteroporphyrin-IX dimethyl ester (*DPDME*) **1a**. The previous result is important because it indicates that when all β positions of porphyrin chelates are substituted – as in Zn(II)-**1b** – benzoylation of the *meso* position(s) competes with demetallation, the latter process apparently being more efficient and thus leading exclusively to loss of zinc(II) from the porphyrin chelate. This result is also important because it helps to rationalize the outcome of the benzoylation reaction of Zn(II)-**1a**: in this case, competition between demetallation and benzoylation also occurs. However, benzoylation of (most likely) the β position(s) is now more efficient relative to demetallation, leading to a β-benzoylated zinc(II) deuteroporphyrin dimethyl ester derivative. Secondly, and perhaps most importantly, once β-benzoylated, the porphyrin chelate is more stable towards demetallation and can therefore be further benzoylated (in *meso*). The presence of the benzoyl group(s) in β-position of the porphyrin chelate is therefore a *conditio sine qua non* for its subsequent *meso* benzoylation. In conclusion, of the three possible processes upon the original chelates (demetallation, β-benzoylation, and *meso* benzoylation, the present and previous results indicate the following order of efficiency: β-benzoylation > demetallation > *meso* benzoylation. In addition, once the original chelate has been β-benzoylated, the relative order of efficiency between demetallation and *meso* benzoylation is reversed, so that now *meso* benzoylation competes effectively with demetallation.

Calculations

The above results and those of previous authors [1, 2, 4–6] indicate that deuteroporphyrin and other free base porphyrins show only poor reactivity towards acylating agents and, in particular, towards benzoic anhydride. On the other hand, *Fischer et al.* [4] have monobenzoylated a few Fe(III) porphyrins, and the present report described the polybenzoylation of Zn(II) deuteroporphyrin-IX.

In order to check whether these results correspond with the predictions of quantum mechanical calculations, we have performed a semi-empirical investigation of the relative reactivity of deuteroporphyrin-IX, its Zn(II) complex, and the 2-benzoyl and 2,4-dibenzoyl derivatives of the last compound towards electrophiles. The regioselectivity of these reactions has also been investigated. The energy gap between the HOMO an subHOMO of the porphyrin on the one hand and the LUMO of the benzoyl cation on the other (−6.507 eV) has been chosen as a criterion for relative reactivity with the porphyrin derivative showing the smallest gap corresponding to the most reactive one. Regioselectivity, in turn, has been evaluated from the electron density maps of the HOMO and subHOMO of each porphyrin, with positions of higher electron density expectedly being the most reactive. Both criteria are based upon *Fukui*'s frontier orbital model [11].

The results of these calculations (Table 1) show that, for all the porphyrins investigated, the HOMO and subHOMO are close in energy (*ca.* 0.25 eV for deuteroporphyrin and *ca.* 0.07 eV for the three Zn(II)-porphyrins studied). In

Table 1. Energies (eV) of the most significant molecular orbitals of deuteroporphyrin-IX, Zn(II)-deuteroporphyrin-IX, Zn(II)-2-benzoyldeuteroporphyrin-IX, and Zn(II)-2,4-dibenzoyldeuteroporphyrin-IX from semi-empirical calculations

Molecular Orbital	**1a** free acid[a]	Zn(II)-**1a** free acid	Zn(II)-**1f** free acid	Zn(II)-**1g** free acid
LUMO	−1.596	−1.920	−2.012	−2.122
HOMO	−7.848	−7.746	−7.889	−7.988
subHOMO	−9.092	−7.829	−7.962	−8.045
HOMO-2	−0.395	−9.213	−9.330	−9.412
HOMO-3	−9.425	−9.394	−9.492	−9.618
HOMO-4	−9.546	−9.536	−9.633	−9.714

[a] Engergies for the N21-H, N23-H tautomer; the ordered values for the N22-H, N24-H tautomer are −1.619, −7.857, −8.107, −-9.322, −9.457, −9.544 eV

contrast, the rest of HOMOs have much lower in energy (1.4–1.5 eV for HOMO-2 in all cases). According to these results, both HOMO and subHOMO have been taken into consideration in the theoretical evaluation of the reactivity towards electrophiles of the porphyrins.

The ($E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}$) + ($E_{\mathrm{subHOMO}} - E_{\mathrm{LUMO}}$)) values (in eV) thus obtained are: deuteroporphyrin, 2.938 (average of two tautomers); Zn(II)-deuteroporphyrin, 2.561; Zn(II)-2-benzoyldeuteroporphyrin, 2.837; and Zn(II)-2,4-dibenzoyldeuteroporphyrin, 3.019. These numbers would explain why Zn(II)-deuteroporphyrin, with the smallest energy gap, is more reactive towards benzoylation than deuteroporphyrin, but not why the latter does not react under conditions where Zn(II)-2,4-dibenzoyldeurteroporphyrin, with a sightly higher energy gap, apparently does.

The regioselectivity of the benzoylation process was analyzed from the electron density (HOMO + subHOMO) maps. The following conclusions can be drawn:

1) For deuteroporphyrin, the *meso* positions are expected to be the most reactive ones; the pyrrole nitrogens display an intermediate reactivity, and the β-C2 and -C4 positions show the least reactivity.

2) For zinc(II) deuteroporphyrin, the electron densities of the *meso* and β-C2 and -C4 positions are comparable, and therefore a similar reactivity is expected for them. If steric effects are considered, one would expect reactions with electrophiles to occur preferentially at the β-C2 and/or -C4 positions.

3) For zinc(II) 2-benzoyldeuteroporphyrin, perhaps surprisingly, the most reactive position is not C4 but the *meso* positions and, more specifically, the β and γ bridges. Even though the consideration of steric effects might alter this theoretical order of reactivity, benzoylation of the β and γ bridges probably occurs as proven by the obtention of a mixture of dibenzoylated products.

4) For zinc(II) 2,4-dibenzoyldeuteroporphyrin, the γ-*meso* position displays the highest electron density and therefore one should expect benzoylation to occur preferentially at this position; however, other dibenzoyl deuteroporphyrin isomers are expected to be benzoylated at different positions, and as a result, a mixture of tribenzoylporphyrins has to be expected.

Experimental

Chemicals

Deuteroporphyrin-IX dimethyl ester (**1a**) and mesoporphyrin-IX dimethyl ester (**1b**) were prepared from hemin (Aldrich) as reported previously [5]. 2,4-Diacetyldeuteroporphyrin-IX dimethyl ester (**1l**) was obtained from deuterohemin as described [5]. Zinc(II) mesoporphyrin-IX dimethyl ester (Zn(II)-**1b**) was prepared as previously reported [12]. Benzoic anhydride (m.p.: 42°C), benzoyl chloride (both from Aldrich), aluminum chloride (Merck), and stannic chloride (Fluka) were purified as reported [13]. All solvents and solutions were rendered oxygen-free and argon saturated by several cycles of evacuation at room temperature under magnetic stirring followed by argon saturation. Reactions were typically carried out in the dark and under argon.

Calculations

Quantum mechanical calculations were performed at a semiempirical level using the SPARTAN computer program, version 4.1.1, installed on a Silicon Graphics Power Indigo 2 work station [14].

All structures were optimized at the RHF/PM3 level [15] using the following criteria: maximum gradient 1.0×10^{-4} a.u., maximum shift 3.0×10^{-5} nm, maximum energy difference 4.18×10^{-3} kJ · mol^{-1}. No restrictions were used in the optimization of the geometries.

Analytical methods

Analytical thin layer chromatography (TLC) was carried out on Merck 60 F_{254} silica gel plates (0.2 mm layer). Preparative thin layer chromatography (PTLC) was carried out on home-made Merck 60 H silica gel plates (0.5 mm layer, 20 × 20 cm). Column chromatograpyhy was performed on basic Al_2O_3 (activity I, Merck; 70–230 mesh). Analytical HPLC was carried out on a home-made Nucleosil-120 silica column (0.46 × 25 cm; particle size: 3 µm) with a Shimadzu LC-7A pump (for bio liquid chromatography; 1 ml/min) using a Shimadzu SPD-M6A photododide array detector and a toluene : *n*-heptane : MeOH = 40:60:1 (v/v/v) solvent system. Preparative HPLC was performed on a Chromasil-100 (MZ-Analysentechnik Mainz) silica column (2 × 25 cm; particle size: 5 µm) with a Shimadzu LC-8A pump (7 ml/min) using a Shimadzu SPD-6AV UV/Vis detector (detection at 400 nm) and a toluene:*n*-hexane:MeOH = 40:60:1 (v/v/v) solvent system.

Melting points (not corrected) were determined on a Kofler-Reichert micro-hot stage apparatus. For Zn(II)-**1l**, it could only be obtained under rapid heating; otherwise, decomposition occured, and the product did not melt below 350°C. UV/Vis spectra were recorded on a Varian Cary 5E instrument. Fluorescence spectra were determined with an Aminco-Bowman Series 2 luminescence spectrometer using air-saturated benzene or CH_2Cl_2 solutions of the porphyrins. Emission spectra were recorded exciting at the maximum of the *Soret* band. Absorbances at the excitation wavelength were optically matched ($A \leq 0.1$; concentrations ≤ 0.7 µ*M*). Fluorescence quantum yields (Φ_f) for the free base porphyrins were calculated from the integration of the complete corrected fluorescence spectrum and comparison to mesoporphyrin-IX dimethyl ester (**1b**) solutions of equal absorbance at the excitation wavelength and taking the literature value (0.12) for Φ_f of this compound [16]. Φ_f values for the Zn(II)-porphyrin complexes were obtained similarly by comparison to Zn(II)-mesoporphyrin-IX dimethyl ester ($\Phi_f = 0.05$) [16]. ^{1}H and ^{13}C NMR spectra were run on a Varian Gemini XL-200 (200.6 MHz) or a Varian Unity-300 (300 MHz) spectrometer using tetramethylsilane (*TMS*) as internal standard. Immediately before sample preparation, the solvent ($CDCl_3$) was filtered through a short column of basic Al_2O_3 (Act. I, Merck), and the first few drops were discarded. IR spectra were determined in a Fourier-Transform Nicolet spectrophotometer. Mass spectra were run on a Hewlett-Packard 5988A instrument equipped for FAB analysis with a Capillaritron Frasor (Xe) or on a VG QUATTRO (Fisons) instrument. Nitrobenzyl alcohol (*NBA*) was used as matrix. High resolution mass measurements were carried out with an AutoSpec-Q instrument using the FAB technique at resolution 5000, and with *NBA* as matrix. The cesium gun energy was 20 KV.

All spectroscopic measurements were performed at room temperature.

Zinc(II)-deuteroporphyrin-IX dimethyl ester (Zn(II)-**1a**; $C_{32}H_{32}N_4O_4Zn$)

A modification of the procedure previously reported for the conversion of mesoporphyrin-IX dimethyl ester into its zinc(II) complex was used [12]. A pinky red solid (96% yield; one spot on TLC (SiO_2, CH_2Cl_2:MeOH = 10:1; $R_f = 0.85$) was obtained which was spectroscopically identified as the title compound.

M.p.: 253–256°C (decomposition); ^{1}H NMR ($CDCl_3$, δ, ppm): 9.50, 9.49, 9.31, 9.28 (4 × s, 4H, $=C^{\alpha,\beta,\gamma,\delta}H$-), 8.80, 8.67 (2 × s, 2H, $=C^{2,4}H$-), 4.20, 4.12 (2 × t, 4H, -$CH_2CH_2CO_2$-), 3.66, 3.65 (2 × s, 6H, -CO_2CH_3), 3.60, 3.51, 3.47, 3.34 (4 × s, 12H, $C^{1,3,5,8}$-CH_3), 3.12, 3.06 (2 × t, 4H, -$CH_2CH_2CO_2$-); ^{13}C NMR ($CDCl_3$, δ, ppm): 173.6 (-CO_2CH_3), 148–138 ($C^{\alpha,\beta}$-pyrrole), 129.1, 128.0 ($=C^{2,4}H$-), 100.5, 99.75, 97.0, 95.8 ($=C^{meso}H$-), 51.6 (-CO_2CH_3), 37.0 (-$CH_2CH_2CO_2$-), 21.7 (-$CH_2CH_2CO_2$-), 13.5, 11.5, 11.4 ($C^{1,3,5,8}$-CH_3); IR (KBr, ν, cm^{-1}): 3440, 2915, 1730 (ester

C=O); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 400 (344000), 530 (14600), 566 (18000) nm; fluorescence (benzene): λ_{exc} = 400 nm, λ_{em} = 570, 623 nm; Φ_f = 0.045; MS (FAB): *m/z* = 604, 602, 600 (M^+ ^{68}Zn, ^{66}Zn, ^{64}Zn).

Zinc(II)-2,4-diacetyldeuteroporphyrin-IX dimethyl ester (Zn(II)-**1l**; $C_{36}H_{36}N_4O_6Zn$)

Zn(II)-**1l** was prepared by brief treatment of 2,4-diacetyldeuteroporphyrin dimethyl ester (**1l**) with zinc(II) acetate as reported previously for the conversion of mesoporphyrin-IX dimethyl ester into its zinc(II) complex [9]. A greenish red solid (quantitative yield; one spot on TLC (SiO_2, CH_2Cl_2:MeOH = 10:1; R_f = 0.83) was obtained.

M.p.: 258–262°C (*vide supra*); ^1H NMR ($CDCl_3$, δ, ppm): 10.45, 10.31, 9.6, 9.5 (4 × s, 4H, $=C^{\alpha,\beta,\gamma,\delta}H$-), 4.26, 4.24 (2 × t, 4H, -$CH_2CH_2CO_2$-), 3.77, 376, 3.66, 3.65, 3.50, 3.46 (6 × s, 18H, $C^{1,3,5,8}$-CH_3,-CO_2CH_3), 3.26, 3.23 (2 × s, 6H, CH_3CO-), 3.16, 3.14 (2 × t, 4H,-$CH_2CH_2CO_2$-); ^{13}C NMR ($CDCl_3$, δ, ppm): 199.5, 199.0 (-$COCH_3$), 173.4 (-CO_2CH_3), 146–136 ($C^{\alpha,\beta}$-pyrrole), 104–101 ($=C^{meso}H$-), 51.7 (-CO_2CH_3), 36.6 (-$CH_2CH_2CO_2$-), 33.1 (-$COCH_3$), 21.55 (-$CH_2CH_2CO_2$-), 14.2 11.6 ($C^{1,3,5,8}$-CH_3); IR (KBr, ν, cm^{-1}): 3430, 2925, 2855, 1740 (ester C=O), 1650 (ketone C=O); UV/Vis (CH_2Cl_2): λ_{max} (ε) = 424 (91000), 550 (7500), 587 (7000) nm; fluorescence (benzene): λ_{exc} = 416 nm, λ_{em} = 597, 646 nm; Φ_f = 0.03; MS (FAB): *m*/z = 688, 686, 684 (M^+ ^{68}Zn, ^{66}Zn, ^{64}Zn).

Benzoylation of Zn(II)-deuteroporphyrin-IX dimethyl ester (Z(II)-**1a**)

Zn(II) deuteroporphyrin-IX dimethyl ester (150 mg, 0.25 mmol) was heated to 70°C in the presence of an excess of benzoic anhydride (2.7 g, 12 mmol) in a 10 ml flask equipped with a reflux condenser and a $CaCl_2$ tube. The anhydride melted and eventually dissolved the Zn(II)-porphyrin. $SnCl_4$(2.0 ml) was then added dropwise resulting in a gradual change in colour from purple to dark green of the contents of the flask which also solidified. The mixture was reacted in the dark at 70°C for a total of 30 min. After cooling to room temperature, CH_2Cl_2 (100 ml) was added, and the mixture was washed with water (6 × 50 ml), filtered through paper, and evaporated. A dark brown solid was obtained from which benzoic anhydride benzoic acid were removed by repeated washing with hexane. Subsequent column chromatography of the resulting mixture over basic Al_2O_3 afforded four fractions. Fraction 1, eluted with CH_2Cl_2, corresponded to deuteroporphyrin dimethyl ester (**1a**; 38 mg; one spot on TLC; SiO_2, CH_2Cl_2:MeOH = 10:1; R_f = 0.85). Fraction 2, eluted with CH_2Cl_2:MeOH = 500:1, consisted of a mixture of metal free, benzoylated porphyrins plus **1a** (66 mg; one spot on TLC; SiO_2, CH_2Cl_2:MeOH = 10:1; $R_f \approx 0.8$). Fraction 3, eluted with CH_2Cl_2:MeOH = 100:1, corresponded to a mixture of zinc(II) deuteroporphyrins with one to five benzoyl groups (see below; 16 mg in total; one long spot on TLC; SiO_2, CH_2Cl_2:MeOH = 10:1; R_f = 0.65–0.5). Fraction 4, eluted with CH_2Cl_2:MeOH = 10:1, was not further investigated (11 mg; several spots on TLC; SiO_2Cl_2:MeOH = 10:1; R_f = 0.4–0.25).

Fraction 2 was dissolved in ether and washed repeatedly with 2% (w/w) aqueous HCl. The acid retained **1a**, and the ether fraction showed five main peaks by HPLC with R_t in min (in brackets: relative integration): 6.59 (6%), 7.00 (+7.6, shoulder; 4.6%), 7.93 (34%), 11.67 (8.4%), (12.3, shoulder +) 12.55 (45.7%). UV/Vis spectra in the mobile phase: 395, 486, 517, 555 nm (R_t = 6.59); 399, 490, 526, 560 nm (R_t = 7.00); 403.5, 495, 529, 564 nm (R_t = 7.93); 405, 495, 527, 564 nm (R_t = 11.67); and 407, 497, 528, 565 nm (R_t = 12.55). Under identical conditions, **1a** has R_t = 5.71 min and UV/Vis: 389, 481, 509, 555 nm. MS (FAB): *m/z* : 747 (53%), 643 (100%) (R_t = 6.59); 747 (79%), 643 (100%) (R_t = 7.00); 851 (30%), 747 (100%), 643 (75%) (R_t = 7.93); 851 (69%), 747 (100%), 643 (48%) (R_t = 11.67); and 851 (100%), 745.5 (70%) (R_t = 12.55). ^1H NMR ($CDCl_3$, δ, ppm): for all the components, except that with R_t = 12.3 (below), spectra with a larger number of peaks than expected for pure compounds were obtained.

2,4,γ-Tribenzoyldeuteroporphyrin-IX dimethyl ester (**1k**; $C_{53}H_{46}N_4O_7$)

Isolated from fraction 2 (see above) by preparative HPLC ($R_t = 12.3$ min in analytical HPLC).

M.p.: 105–108°C; ^{1}H NMR ($CDCl_3$, δ, ppm): 10.20, 10.19, 10.17 ($3 \times$ s, 3H, $=C^{\alpha,\beta,\delta}H$-), 8.2–7.1 (m, 15H, $=C^{2,4}H$-), 4.43, 4.25 (t + dt, 4H, -$CH_2CH_2CO_2$-), 3.65, 3.64, 3.61, 3.59 ($4 \times$ s, 12H, $C^{5,8}$-CH_3,-CH_2CH_3), 3.30, 3.09 ($2 \times$ t, 4H, -$CH_2CH_2CO_2$-), 3.13, 2.86 ($2 \times$ s, 6H, $C^{1,3}$-CH_3), −2.99, −3.04 ($2 \times$ s, 2H, NH); IR (KBr, ν, cm^{-1}): 3429 (C-H), 2990, 2929, 1752 (ester C=O), 1652 (benzoyl C=O), 1256, 1177, 1160, 1098, 1017; UV/Vis (CH_2Cl_2): λ_{max} (ε) = 418 (138600), 512 (12700), 547 (6600), 583 (5800), 635 (2100) nm; fluorescence (benzene): $\lambda_{exc} = 416$ nm; $\lambda_{em} = 644$, 710 nm; $\Phi_f = 0.04$; high resolution MS (FAB): $m/z = 851.3446$ (calculated: 851.3445; error: −0.2 ppm), corresponds to an elemental composition of $C_{53}H_{47}N_{47}O_7$ ($M^+ + 1$).

Fraction 3

^{1}H NMR ($CDCl_3$, δ, ppm): 10.28, 10.21, 10.15, 10.10, 10.08 ($=C^{meso}H$-), 8.0–6.8 (PhCO-), 4.42, 4.40 (-$CH_2CH_2CO_2$-), 3.71–3.62, 2.95 ($8 \times$ s, C^{β}-CH_3, -CO_2CH_3), 3.41, 3.39 (-$CH_2CH_2CO_2$-), 2.56 (not assigned): ^{13}C NMR ($CDCl_3$, δ, ppm): 199.55, 199.18 (-*C*OPh), 173.63 (-CO_2CH_3), 150–138 ($C^{\alpha,\beta}$-pyrrole), 133.0, 129.9, 128.2 (*Ph*CO-), 100–98 ($=C^{meso}H$-), 51.76 (-CO_2CH_3), 37.06, 36.89 (-$CH_2CH_2CO_2$-), 21.97, 21.81 (-$CH_2CH_2CO_2$-), 15.19, 11.74 (C^{β}-CH_3); IR (KBr, ν, cm^{-1}): 3440 (C-H), 2925, 1737 (ester C=O), 1665 (benzoyl C=O), 1260; UV/Vis (CH_2Cl_2); λ_{max} (ε) = 418 (128000), 545 (10000), 581 (7600) nm; fluorescence (benzene): $\lambda_{exc} = 416$ nm; $\lambda_{em} = 595$ nm; $\Phi_f =$ 0.04; MS (FAB): $m/z = 915.4$, 914.5, 913.6, 912.8 (100%), 810.5, 809.5, 808.6, 807.7 (100%), 706.6, 705.6, 704.6, 703.6 (25%).

In one run, this fraction (10 mg) dissolved in CH_2Cl_2 (100 ml) was demetallated with 3 *M* aqueous HCl (50 ml) during 2 h at room temperature under argon. The solution was then neutralized with 0.5 *M* aqueous $NaHCO_3$, washed with water, and dried. The recovered sample was esterified with CH_2N_2 in ether for 2 min at RT, purified by PTLC (SiO_2, CH_2Cl_2:MeOH = 10:1), and the fraction with $R_f \approx 0.4$ was analyzed.

MS (FAB): $m/z = 641.6$ (26%), 745.8, 746.9 (77%), 851.6 (100%), 955.7 (7.4%), 1058.9 (27.5%); UV/Vis (CH_2Cl_2): $\lambda_{max} = 414$, 509, 545, 579, 634 nm.

Acknowledgements

This work has been supported by a grant (QFN 94-4613-CO2) from the CICYT and the *Generalitat de Catalunya*. We thank Dr. *M. Pericás* (Univ. Barcelona) for allowing us to use his work station. Special thanks are due to Prof. *S. E. Braslavsky* (Max Planck Insitut für Strahlenchemie, Mülheim a.d. Ruhr, Germany) for help with the HPLC separation and subsequent spectroscopic analysis. *C.M.* thanks the spanish *Ministerio de Educación y Cultura* for a fellowship.

References

[1] Fuhrhop J-H (1979) In: Dolphin D (ed) The Porphyrins, vol 2. Academic Press, New York, p 131
[2] Smith KM (1975) Porphyrins and Methalloporphyrins. Elsevier, Amsterdam, Holland
[3] (a) Matsumoto T, Sato M, Hirayama S (1972) Chem Phys Lett **13**: 13; (b) Bensasson R, Land EJ (1977) Nouveau Journal de Chimie **2**: 503
[4] Fischer H, Orth H (1937) Die Chemie des Pyrrols, vol I. Akademische Verlagsgesellschaft, Leipzig, p 297
[5] Caughey WS, Alben JO, Fujimoto WY, York L (1966) J Org Chem **31**: 2631
[6] Inhoffen HH, Bliesener C, Brockmann Jr H (1967) Tetrahedron Lett 727
[7] (a) Inhoffen HH, Fuhrhop J-H, Voigt H, Brockmann Jr H (1966) Liebigs Ann Chem **695**: 133; (b) Oldfied D, Johnson AW (1966) J Chem Soc C 794

[8] (a) Fischer H, Orth H (1937) Die Chemie des Pyrrols, vol I. Akademische Verlagsgesellschaft, Leipzig, p 230; (b) Gradyushko AT, Kozhich DT, Sokolev KN, Tsvirko MP (1974) Opt Spectrosc **37**: 510; (c) Treibs A (1952) Naturwissenschaften **39**: 281; (d) Minnetian OM, Morris IK, Snow KM, Smith KM (1989) J Org Chem **54**: 5567; (e) Bonnett R, Campion-Smith IH, Kozyrev AN, Mironov AF (1990) J Chem Res (M) 1015

[9] Dinello RK, Chang CK (1979) In: Dolphin D (ed) The Porphyrins, vol 1. Academic Press, New York, p 294

[10] (a) Reeves PC (1988) Organic Syntheses Coll **VI**: 625; (b) Gore PH, Hoskins JA (1964) J Chem Soc 5666; (c) Kulka M (1954) J Am Chem Soc **76**: 5469

[11] Fukui K, Yonezawa T, Nataga C (1957) J Chem Phys **26**: 831

[12] Fuhrhop J-H, Smith KM (1975) In: Smith KM, Porphyrins and Metalloporphyrins. Elsevier, Amsterdam, Holland, p 798

[13] Perrin DD, Armarego WLF, Perrin DR (1988) Purification of Laboratory Chemicals, 2nd edn. Pergamon Press, New York

[14] Spartan version 4.1.1, Wavefunction, Inc. 18401, Von Karman Ave. 370. Irvine, CA 92715 USA, 1995

[15] (a) Stewart JJP (1989) J Comp Chem **10**: 209; (b) Stewart JJP (1989) J Comp Chem **10**: 221

[16] Darwent JR, Douglas P, Harriman A, Porter G, Richoux M-C (1982) Coord Chem Rev **44**: 83

Received June 23, 1997. Accepted (revised) July 23, 1997