PORPHYRINS.

VIII.* meso-FORMYLATION OF METAL COMPLEXES OF MESOPORPHYRIN IX DIMETHYL ESTER

G. V. Kirillova, T. A. Babushkina,
V. P. Suboch, and G. V. Ponomarev

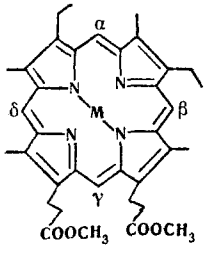
UDC 547.749.07:541.49

The Vilsmeier formylation of Cu^{2+}, Ni^{2+}, Co^{2+}, and $Fe^{3+}Cl$ complexes with mesoporphyrin IX dimethyl ester was investigated. It was established that the formylation takes place at all four meso positions of the porphyrin ring and that replacement of one metal by another affects only the rate of formylation (it has no effect on the orientation of electrophilic substitution). Four isomers of meso-dimethylaminomethylmesoporphyrin IX dimethyl ester were obtained by reduction of the intermediate immonium salts.

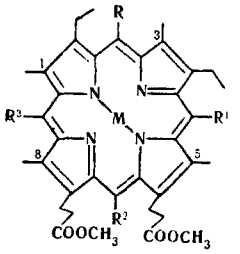
The introduction of a formyl group in the meso position of the porphyrin ring via the Vilsmeier reaction was first accomplished in 1966 in the case of copper and nickel complexes of octaalkyl-substituted porphyrins [2, 3]. This method was subsequently used frequently for the synthesis of diverse porphyrins containing a formyl group. However, up until now there have been no convincing data on the effect of the central metal atom, as well as the adjacent β substituents of the porphyrin ring, on the direction and rate of meso formylation. For example, in [4] it was established that etiohemin I is not formylated at all, whereas we were able to accomplish this reaction in high yield [5]. Formylation of the Cu complex of an unsymmetrically substituted porphyrin leads to an isomeric mixture of monoformylporphyrins [6], whereas the use of mesohemin IX dimethyl ester (Ia) leads only to β-meso-formylmesoporphyrin IX dimethyl ester (IIa) [7], which indicates the possibility of specific orientation of electrophilic substitution in the case of replacement of one central metal atom by another.

The goal of the present research was to ascertain the role of the central metal atom on the direction and rate of formylation. Mesoporphyrin IX dimethyl ester (Ib) complexes with Cu^{2+}, Ni^{2+}, Co^{2+}, and Fe^{3+} Cl were used as the subjects for the study.

All of the meso positions in porphyrin Ib are nonequivalent from the point of view of symmetry. At the same time the α-, β-, and δ-meso positions seemed equivalent to us for electrophilic substitution from the point of view of steric factors.



Ia-e



IIa-f

Unspecified M=2H and R, R^1, R^2, R^3=H; I a M=FeCl; b M=2H; c M=Cu; d M=Ni; e M=Co; II a R^1=CHO; b R=CHO; c $R^2=CH_2N(CH_3)_2$ (AM); d R^3=AM; e R^1=AM; f R=AM

We established experimentally that for the preparation of primarily monosubstituted mesoformylporphyrins it is sufficient to carry out the Vilsmeier reaction with the Co complexes of porphyrins at room temperature for 5-10 min, with the Ni and Cu complexes at 50-60°C for 15-20 min, and with the Fe complexes by refluxing the reaction mixture in dichloroethane for 3-5 h until the starting complex disappears.

*See [1] for communication VII.

Institute of Biophysics of the Ministry of Public Health of the USSR, Moscow 123182.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1215-1220, September, 1978. Original article submitted October 21, 1977.

 0009-3122/78/1409-0980$07.50

TABLE 1. PMR Spectra of Isomers of meso-Dimethylaminomethylmesoporphyrin IX Dimethyl Ester

Compound	meso-H	meso-CH_2	$N(CH_3)_2$	CH_2	CH_2	$COOCH_3$	CH_2	CH_3	CH_3	NH
IIc*	9,95 (2H) 9,78 (1H)	5,65 (2H)	1,77 (6H)	4,34 m (4H)	3,17 m (4H)	3,71 (6H)	3,95 q (2H) 3,94 q (2H)	1,77 t (6H)	[5, 8] 3,53 (6H) [1, 3] 3,51 (3H) 3,48 (3H)	−2,94
IIc†	10,25 (2H) 10,14 (1H)	6,80 (2H)	3,12 (6H)	3,89 m (4H)	2,64 m (4H)	3,35 (6H)	3,89 m (4H)	1,58 (3H) 1,54 (3H)	[5, 8] 3,27 (6H) [1, 3] 3,44 (3H) 3,40 (3H)	
IId*	9,95 (2H) 9,79 (1H)	5,73 (2H)	1,80 (6H)	4,28 t (4H)	3,18 t (4H)	3,60 (3H) 3,54 (3H)	3,99 q (4H)	1,77 t (3H) 1,67 t (3H)	[1, 8] 3,59 (6H) [3] 3,53 (3H) [5] 3,49 (3H)	−2,97
IId†	10,53 (1H) 10,22 (1H) 10,15 (1H)	6,64 (2H)	2,70 (6H)	4,18 (4H)	2,97 (4H)	3,41 (3H) 3,39 (3H)	3,76 q (2H) 3,66 q (2H)	1,32 t (3H) 1,29 t (3H)	[1, 8] 3,44 (6H) [3] 3,23 (3H) [5] 3,19 (3H)	
IIe*	9,97 (1H) 9,96 (1H) 9,80 (1H)	5,71 (2H)	1,81 (6H)	4,35 t (2H) 4,34 t (2H)	3,18 t (2H) 3,08 t (2H)	3,50 (6H)	3,96 (2H) 3,98 (2H)	1,77 (6H)	[1, 3, 8] 3,61 (6H) 3,59 (3H) [5] 3,47 (3H)	−3,02
IIe†	10,73 (1H) 10,30 (1H) 10,20 (1H)	6,73 (2H)	2,84 (6H)	4,23 t (4H)	3,02 t (4H)	3,47 (3H) 3,44 (3H)	3,99 q (2H) 3,90 q (2H)	1,56 (3H) 1,34 (3H)	[1, 8] 3,54 (3H) 3,50 (3H) [3] 3,34 (3H) [5] 3,25 (3H)	
IIf*	9,97 (1H) 9,95 (1H) 9,79 (1H)	5,77 (2H)	1,86 (6H)	4,32 t (2H) 4,33 t (2H)	3,19 t (2H) 3,07 t (2H)	3,51 (6H)	3,99 q (2H) 3,94 q (2H)	1,75 (3H) 1,67 (3H)	[1, 5, 8] 3,60 (9H) [3] 3,58 (3H)	−2,99
IIf†	10,76 (1H) 10,25 (1H) 10,18 (1H)	6,78 (2H)	2,82 (6H)	4,23 t (4H)	3,06 t (4H)	3,48 (6H)	4,00 q (2H) 3,87 q (2H)	1,57 (3H) 1,34 (3H)	[8] 3,53 (3H) [5] 3,42 (3H) [3] 3,26 (3H) [1] 3,29 (3H)	

*The PMR spectra were obtained from solutions in $CDCl_3$.

†The PMR spectra were obtained from solutions in $CDCl_3$—trifluoroacetic acid with hexamethyldisiloxane as the internal standard; the numbering of the substituents is given in brackets.

After carrying out the formylation of the FeCl, Cu, Ni, and Co complexes of Ib (Ia, Ic, Id, and Ie), demetallation, and chromatographic separation of the reaction products from the unchanged porphyrin Ib, we isolated a substance, the spectrum of which and the ratio of the intensities of the bands in the visible portion of the spectrum of both the free base in chloroform [λ_{max}: 407 (17.9), 506 (1), 539 (0.85), 576 (0.87), 628 (0.46), and 660 nm (sh)] and the protonated form in the case of dilution with trifluoroacetic acid (TFA) [λ_{max}: 422 (22.5), 573 (1), and 627 nm (0.9)] were found to be similar to the spectrum and intensity presented for porphyrin IIa [7] in chloroform [λ_{max}: 410 (19.5), 509 (1), 543 (0.83), 582 (0.84), and 631 nm (0.5)] and in HCOOH solution [λmax: 418 (23.8), 571 (1), and 625 nm (0.75)].

By means of preparative thin-layer chromatography (TLC) on a fixed layer of silica gel we established that the product of formylation is a mixture of substances, which were separated into three fractions; two of them (the more mobile fractions) actually corresponded to isomers of meso-formyl-Ib, according to the data from the IR and mass spectra. The electronic spectra of these two fractions were identical and did not differ from the known spectra of meso-formylporphyrins. The last (least mobile) fraction had an "oksorodo"* type of electronic spectrum in chloroform [λ_{max}: 423 (15.1), 514 (1), 558 (2.1), 580 (1.55), and 644 nm (0.3)], which was very similar to the spectra of pheoporphyrin-a_5 and phylloerythrin methyl esters [8] and, according to the PMR-spectral data, corresponded to a complex mixture of isomeric products. The IR spectrum of the compounds of this fraction contained intense bands at 1737, 1715, and 1677 cm^{-1}; this indicates the possibility of intramolecular cyclization of the formylation products and the formation of isomers of porphyrins that contain a cyclopentanone ring.

From the PMR spectral data it was ascertained that the compound from the first fraction is an individual isomer of meso-formyl-Ib and that the second fraction consists of an inseparable mixture of isomers of meso-formylmesoporphyrin.

The structure of the α or γ isomer can be assigned to meso-formyl-Ib, the only compound isolated in the individual state. It is more logical to assign the structure of the α isomer to it, since in this case the pronounced difference in the position of the PMR signal of one of the methyl substituents on dilution with TFA and the difference in the signals of both the CH_2 and CH_3 groups for both ethyl groupings are understandable (see the experimental section).

We were able to confirm the formation of all four meso-monosubstituted products of formylation of porphyrin Ib by reduction with sodium borohydride of the intermediate phosphorus complexes to the corresponding metal complexes of meso-dimethylaminomethylmesoporphyrin IX by the method in [9] and subsequent demetallation and separation of silica gel of the isomeric mixture of meso-dimethylaminomethylporphyrins into individual compounds; on the basis of an analysis of the PMR spectra of the isomers with R_f values 0.71, 0.59, 0.52, and 0.44 we proposed the γ-meso-dimethylaminomethyl-Ib (IIc), δ-meso-dimethylaminomethyl-Ib (IId), β-meso-dimethylaminomethyl-Ib (IIe), and α-meso-dimethylaminomethyl-Ib (IIf) structures, respectively.

In our examination of the PMR spectra of isomers IIc-f (see Table 1) we used the fact that protonation of the dimethylaminomethyl group changes the chemical shifts of the adjacent β substitutents considerably as a basis. The most pronounced shift of the signals of the methylene protons of the residues of propionic acid esters as compared with the spectra of other isomers is observed in the PMR spectrum of isomer IIc; this indicates unambiguously that the meso substitent is in the γ position. A distinctive feature in the spectra of isomers IIe and IIf is the pronounced difference in the chemical shifts of the two methyl groups of the ethyl substitutents in the 2 and 4 positions of the porphyrin ring when trifluoroacetic acid is added to solutions of the compounds in chloroform. These shifts are possible when there is a bulky dimethylaminomethyl group, which is protonated in trifluoroacetic acid, in the α and β positions.

The remaining isomer with R_f 0.59 is thus δ isomer IId.

The structures of IIc-f are confirmed by data on the chromatographic mobility on silica gel and by the quantitative ratio of the isomers in the mixture. In fact, attack at the

*A direct transliteration from the Russian; no equivalent known in English — Consultant's Bureau.

least accessible γ position leads to the formation of isomer IIc in the lowest yield. At the same time, isomer IIc has the greatest mobility of all four isomers owing to the shielding effect of the propionic acid residues on the basic dimethylaminomethyl group. Isomer IIf, which is the most polar isomer, is obtained in large amounts because of the absence of shielding effects of the adjacent and remote β-pyrrole substitutents. The unambiguous establishment of the structures of isomers IId and IIe is evidently possible only by specific chemical synthesis. Nevertheless, the important conclusion that follows from our experiments on the formylation of complexes of Ib is that when the first formyl group is introduced in octaalkyl-substituted porphyrins, one cannot obtain the effect of specific electrophilic substitution by changing the central metal atom under the conditions, of course, of approximately identical steric effects of the substituents in the adjacent pyrrole rings on each of the four meso positions. The data [7] on the production of only porphyrin IIa from mesohemin Ia should therefore be regarded as insufficiently accurate.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in chloroform were recorded with a Shimadzu MPS-50L spectrometer. The IR spectra of KBr pellets of the compounds were obtained with a UR-10 spectrometer. The PMR spectra were obtained with Varian HA-100 and Bruker WH-90 spectrometers. The mass spectra were recorded with a Varian MAT-311 spectrometer. The chromatographic separation of the isomers of the porphyrins was accomplished on 20 × 20 cm plates with Merck GF-254 silica gel in a loose layer 1-mm thick.

Synthesis of Isomers of meso-Formylmesoporphyrin IX Dimethyl Ester. A) From Mesohemin IX Dimethyl Ester (Ia). A solution of 65 mg of porphyrin Ia in 25 ml of dry dichloroethane was added to the complex prepared from 1 ml of dimethylforamide (DMF) and 1.2 ml of $POCl_3$, and the mixture was refluxed for 2 h. The solvent was removed in vacuo, 50 ml of a saturated solution of sodium acetate was added, and the mixture was heated on a water bath for 2 h. The reaction product was extracted with chloroform, and the extract was washed with water, dried with sodium sulfate, and evaporated. The residue was dissolved in 50 ml of acetic acid, 4 ml of a saturated solution of $FeSO_4$ in concentrated HCl was added dropwise in a nitrogen atmosphere, and the mixture was stirred for 1 h. A saturated solution of sodium acetate (80 ml) was added, and the product was extracted with ether. The organic layer was washed with water, dried, and evaporated. The residue was esterified with an ether solution of diazomethane and chromatographed with a column filled with Al_2O_3 (elution with chloroform). Workup of the first fraction yielded 11 mg (19.5%) of porphyrin Ib. The second fraction was separated on plates with silica gel in a chloroform—ether system (95:5) to give three principal fractions. Workup of the first fraction and crystallization from chloroform—methanol gave 3.1 mg of α- or γ-formylmesoporphyrin IX dimethyl ester (IIb) with R_f 0.51 in 5.2% yield. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 407 (137.9), 509 (10.0), 541 (7.1), 579 (6.9), 633 (4.55), and 660 sh (2.87); in chloroform—TFA: 424.5 (350), 575 (10.2), and 630 nm (10.8). IR spectrum, ν_{CO}: 1705 and 1740 cm^{-1}. PMR spectrum (ppm): CHO, 12.55, s (1H); 9.85 (1H), 9.83 (1H), 9.80 (1H), all s, meso-H; 4.22, t (4H), $CH_2CH_2COOCH_3$; 3.15, t (4H), $CH_2CH_2COOCH_3$; 3.84, q (2H) and 3.64, q (2H), CH_2CH_3; 1.69, t (3H) and 1.56, t, CH_2CH_3; 3.22 (3H), 3.39 (3H), 3.57 (3H), 3.58 (3H), all s, ring CH_3; 3.43 (3H), 3.47 (3H), all s, OCH_3. Mass spectrum, m/e (%): M^+ 622 (58), 594 (100), 579 (19), 563 (4), 549 (3), 535 (12), 521 (31), 507 (7). Workup of the second fraction gave 12.1 mg (20.4%) of a mixture of isomers of monoformylmesoporphyrin IX with R_f 0.44. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 407 (126), 509 (8.55), 541 (6.33), 579 (6.3), 633 (4.1), 660 sh nm (2.88). Mass spectrum, m/e (%): 622 (13), 594 (100), 579 (11), 563 (3), 535 (4), 521 (15), 507 (3). Found: C 71.7; H 6.9; N 9.0%. $C_{37}H_{42}N_4O_5$. Calculated: C 71.4; H 6.8; N 9.0%. Workup of the third fraction gave 5 mg of a substance, the spectral characteristics of which are presented in the text of the paper.

B) From the Copper Complex of Mesoporhyrin IX Dimethyl Ester (Ic). A mixture of 100 mg of Ic, the Vilsmeier complex (from 1 ml of DMF and 1.2 ml of $POCl_3$), and 30 ml of dichloroethane was heated at 70°C for 20 min, after which the solvent was removed in vacuo, 50 ml of a saturated solution of sodium acetate was added, and the mixture was refluxed for 1.5 h. The reaction product was extracted with chloroform and chromatographed with a column filled with Al_2O_3 (elution with chloroform). The product was crystallized from chloroform—methanol to give 75.6 mg of a mixture of the Cu complexes of meso-formylmesoporphyrin IX dimethyl ester. Found: C 65.0; H 5.9; N 8.1%. $C_{37}H_{40}N_4O_5Cu$. Calculated: C 64.9; H 5.9; N 8.2%. A 75.6 mg sample of the mixture of Cu complexes was dissolved in 10 ml of concentrated H_2SO_4, and the solution was stirred for 1 h. It was then poured over ice, and the mixture was made

alkaline to pH 5-6 with ammonium hydroxide. The precipitate was removed by filtration and separated on silical gel to give 8.2 mg (8.6%) of porphyrin IIb and 32.3 mg (33.9%) of a mixture of isomers. The spectra of the compounds were identical to the spectra of the products obtained by method A.

C) From the Nickel Complex of Mesoporphyrin IX Dimethyl Ester (Id). A 100 mg sample of Id yielded (after the reaction mixture was heated for 30 min) (method B) 15.4 mg (16.1%) of porphyrin IIb and 29.5 mg (30.9%) of a mixture of isomers.

D) From the Cobalt Complex of Mesoporphyrin IX Dimethyl Ester (Ie). A solution of 50 mg of Ie and the Vilsmeier complex (from 0.5 ml of DMF and 0.6 ml of $POCl_3$) in 20 ml of dry dichloroethane was maintained at 20°C for 3 min, after which it was worked up by method B to give 11.1 mg (23.3%) of porphyrin IIb and 20 mg (42%) of a mixture of isomers.

Isomers (IIc-f) of meso-Dimethylaminomethylmesoporphyrin IX Dimethyl Ester. A mixture of 100 mg of Ic, the Vilsmeier complex (from 1 ml of DMF and 1.2 ml of $POCl_3$), and 25 ml of dichloroethane was refluxed for 20 min, after which the solvent was removed in vacuo, the oily residue was poured into 150 ml of cold water, and the product was extracted with chloroform. The organic layer was washed with water, dried with sodium sulfate, and evaporated. The residue was dissolved in 50 ml of ethanol, 200 mg of sodium borohydride was added, and the mixture was treated with 200 ml of water after 5 min. The precipitate was removed by filtration, dried, and chromatographed with a column filled with Al_2O_3 (elution with chloroform) to give 83 mg (76.4%) of a mixture of Cu complexes of isomers of meso-dimethylaminomethylmesoporphyrin IX. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 409 (150), 542 (9.24), 585 nm (11.1). Found: C 65.8; H 6.6; N 9.7%. $C_{39}H_{47}N_5O_4Cu$. Calculated: C 65.7; H 6.6; N 9.8%. An 83 mg sample of the mixture of Cu complexes was dissolved in 10 ml of concentrated H_2SO_4, and the solution was stirred at 30°C for 40 min. It was then poured over ice, and the mixture was neutralized with ammonium hydroxide. The precipitate was removed by filtration, dried, and chromatographed with a column filled with activity IV Al_2O_3 (elution with chloroform) to give 55 mg (72%) of a mixture of isomers IIc-f. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 409 (168), 509 (11.4), 543.5 (6.63), 579 (5.2), 629 (2.35); chloroform—TFA: 419 (238), 565.5 (10.5), 613 nm (8.47). IR spectrum, ν: 1740 and 2770 cm^{-1}. Found: C 71.8; H 7.44; N 10.7%. $C_{39}H_{49}N_5O_4$. Calculated: C 71.9; H 7.6; N 10.8%. Separation by means of TLC on silica gel in a chloroform—ether—methanol system (8.5:1.0:0.5) gave 8.2 mg (8.3%) of IIc; mass spectrum, m/e (%): M^+ 651 (7), 607 (61), 606 (100), 594 (7), 533 (9), 519 (5) , 8.8 mg (8.9%) of IId; mass spectrum, m/e (%): 651 (8), 607 (40), 606 (100), 594 (20), 547 (5), 533 (10), 519 (6) , 8.2 mg (8.3%) of IIe; mass spectrum, m/e (%): 651 (10), 607 (62), 606 (100), 594 (17), 576 (4), 547 (3), 533 (9), 521 (6), 519 (5) , and 11.3 mg (11.4%) of IIf; mass spectrum, m/e (%): 651 (9), 607 (64), 606 (100).

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