6. K. A. Askarov, B. D. Berezin, R. P. Evstigneeva, et al., Porphyrins: Structure, Properties, and Synthesis [in Russian], Nauka, Moscow (1985).
7. A. S. Semeikin, O. I. Koifman, and B. D. Berezin, Khim. Geterotsikl. Soedin., No. 6, 798 (1986).

PORPHYRINS.

25.* USE OF THE NUCLEAR OVERHAUSER EFFECT FOR ESTABLISHMENT OF THE STRUCTURE OF ISOMERIC meso-SUBSTITUTED METALLOPORPHYRINS

G. V. Kirillova, A. M. Shul'ga, and G. V. Ponomarev

UDC 547.979.733.174:543.51'422

Nickel complexes of the dimethyl esters of meso-dimethylaminomethyl derivatives of mesoporphyrin-II and mesoporphyrin-IX are synthesized. The structure of the prepared isomeric compounds is determined by analysis of their chromatographic properties, visible spectra, as well as of their PMR spectra using the nuclear Overhauser effect.

Porphyrins which contain a dimethylaminomethyl (DMAM) group in the meso-position hold great interest as starting materials for synthesis of widely differing compounds, e.g., meso-hydroxy(alkoxy)methylporphyrins [2] and meso-methylporphyrins [3]. Besides this, certain of the DMAM porphyrins are biologically active substances [4].

We demonstrated that formation of DMAM porphyrins can be used successfully for proving the structure of formylation products in the case of simple symmetrically substituted octaalkylporphyrins, for example, etioporphyrin-II [5].

Recently, PMR spectroscopy using the nuclear Overhauser effect (NOE) has been used to establish the structure of complicated natural porphyrins of unknown structure.

The purpose of the present work is to expand the possibilities for using DMAM porphyrins for establishment of the structure of formylation products in the case of complicated unsymmetrically substituted porphyrins and to confirm independently the structures of these compounds using the NOE.

We chose mesoporphyrin-II (Ia) and mesoporphyrin-IX (IIa) for the study. Earlier it was shown that formation of all four possible meso-substituted products occurs during formylation of the copper complex of mesoporphyrin-IX. However, unambiguous and correct establishment of the structure for each of these has not been carried out [6].

The PMR spectra of porphyrins Ia and IIa were simplified by preparation of the trideuteromethyl esters of the Ni complexes Ic and IIc. The Ni complexes of the DMAM porphyrins were synthesized by a method which was developed earlier [5]. The individual isomers Id, Ie, and IVa-d were separated by preparative thin-layer chromatography on silica gel.

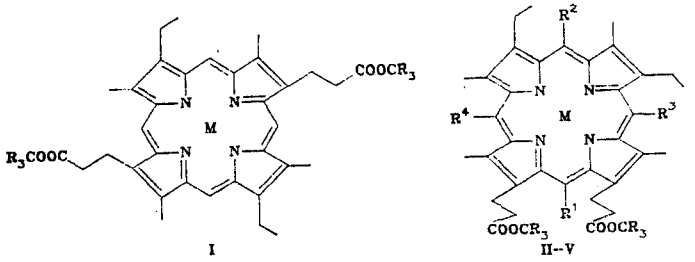
Initial data on the proposed structure of the isomers were obtained based on analysis of chromatographic mobility data. The chromatographic mobility of DMAM porphyrins is known to depend to a large extent on the screening effect of the β-pyrrole substituents next to the DMAM group [5]. Therefore, the more mobile isomer in the case of the Ni complexes of the DMAM isomers of mesoporphyrin-II was assigned structure Id. In this structure, the meso-substituent is located between the methyl and methoxycarbonylethyl group. This is in contrast to the less mobile isomer Ie, in which the DMAM group is located between the less bulky substituents.

A small bathochromic shift in comparison with compound Id is characteristic for the electronic spectrum of porphyrin Ie. This agrees with the electronic spectral data for derivatives of etioporphyrin-II [5].

*See [1] for Communication 24.

Institute of Biophysics, Ministry of Health of the USSR, Moscow 123182. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1378-1384, October, 1989. Original article submitted April 29, 1988.

 © 1990 Plenum Publishing Corporation



I II–V

Ic–g, IIc, IV, V R=D, M=Ni. All A=$CH_2N(CH_3)_2$, unspecified R, R^1, R^2, R^3, R^4=H. Ia M=2H; b R=D, M=2H; d R^1=A; e R^2=A; f R^1=A·BH_3; g R^2=A·BH_3. IIa M=2H; b M=Ni. IIIa R^1=A; b R^2=A; c R^3=A; d R^4=A. IVa R^1=A; b R^2=A; c R^3=A; d R^4=A. Va R^1=A·BH_3; b R^2=A·BH_3; c R^3=A·BH_3; R^4=A·BH_3

Finally, the structure of isomers Id and Ie was established by PMR. The absolute values of the chemical shifts in certain cases in the PMR spectra of porphyrins are known [7] to be capable of changing markedly depending on the concentration. This is due to the ability of porphyrins to form associates. The PMR spectra of the free mesoporphyrin bases depend greatly on the experimental conditions. Therefore, the spectra of the Ni complexes of isomeric porphyrins were obtained at identical concentrations for accurate comparison. Besides this, it was found that the chemical shifts remain practically constant for these metallocomplexes at a concentration from 0.06 mg to 6.5 mg of substance per 0.5 ml $CDCl_3$.

Figure 1 shows results of experiments which were carried out by the NOE method. Table 1 contains chemical shifts with assignment for each of the groups of protons. These data indicate that the structure of the isomers based on the study of their chromatographic mobility was assigned correctly. The following conclusions can be made by analyzing the PMR spectra. 1) Addition of DMAM groups leads to a shift of the signals for all meso-protons to strong field. The strongest shift is observed for the protons in neighboring meso positions. 2) Signals from the ring methyl group protons, as well as protons in the groups CH_2CH_3 and CH_2CH_2COOR, which are located in positions designated in Fig. 1 by the symbol ▲, are shifted to a stronger field than for the signals from analogous substituents. 3) The steric effect of the DMAM group significantly affects the shape of the signals from the neighboring methoxycarbonylethyl group. This leads to conversion of the triplet from the methylene protons of CH_2CH_2COOR into a broad featureless multiplet, which is also readily identified in the spectrum.

Additional information on the structure of meso-DMAM porphyrins can be obtained from PMR spectral data of the corresponding borane complexes [5]. Thus, the presence of an AB-quartet for the $CH_2N(CH_3)_2 \cdot BH_3$ protons for isomers If and Ig indicate that the meso-substituent is located between the two different β-substituents.

The final stage of the work was the synthesis and establishment of the structure of DMAM derivatives of mesoporphyrin-IX. The formylation reaction and reduction of the intermediate complexes were carried out on the Ni complexes of mesoporphyrin-IX IIb and IIc. After chromatographic separation of reaction products, four isomers IIIa-d and IVa-d were isolated.

In this case, chromatographic mobility data could give preliminary information on the possible structure of only two isomers. These were the more mobile γ-isomers IIIa and IVa and the less mobile δ-isomers IIId and IVd. In fact, singlets for the $CH_2N(CH_3)_2$ protons are observed in the PMR spectra of these isomers and their borane complexes Va and Vd. This indicates identical substituents in neighboring pyrrole rings. With respect to the α- and β-DMAM isomers, establishment of their structure is possible only by the NOE method. Figure 1 shows the results of NOE experiments for the three isomers, the α-, β-, and δ-isomers. The PMR spectrum of the γ-isomer differs noticeably from the spectra of the others and does not require special structural confirmation by the NOE method.

Thus, the NOE method can be used successfully for establishment of the structure of complicated unsymmetrically substituted porphyrins.

EXPERIMENTAL

IR spectra were taken as KBr pellets on a Perkin-Elmer 398 instrument. Electronic spectra were recorded using chloroform solutions in a SF-18 spectrophotometer. PMR spectra were obtained in $CDCl_3$ on a Bruker WM-360 instrument with an internal standard of TMS. Mass spectra were taken on a Varian MAT-311 spectrometer. Preparative separation of isomers of porphy-

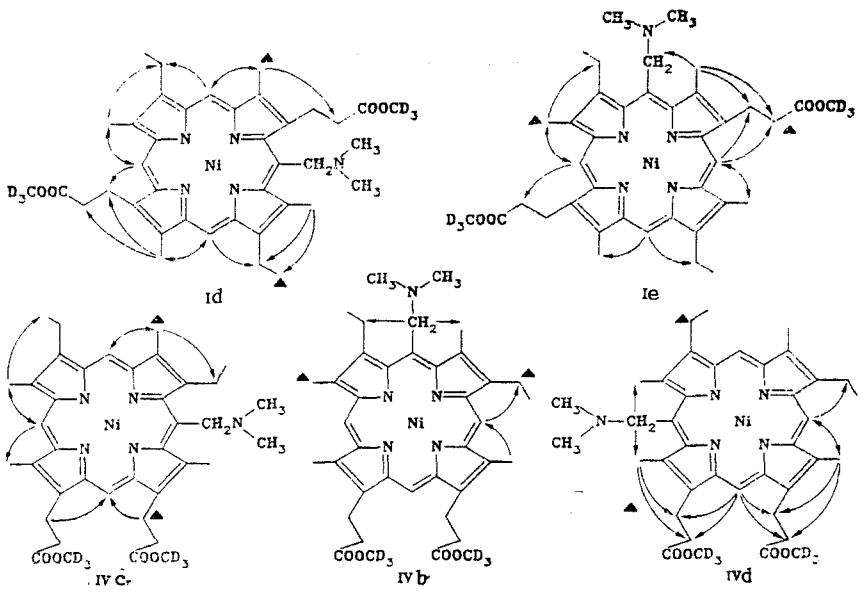


Fig. 1. Porphyrins, structures which were confirmed by the NOE. Experiments were carried out at a metalloporphyrin concentration of 4 mg in 0.5 ml $CDCl_3$. Arrows show the principal interactions between groups of protons which are necessary for establishment of the structure.

rins was carried out on 20 × 20 cm plates with a fixed Merck GF-254 silica gel layer of thickness 1 mm using the system chloroform–ether–alcohol (87:10:3). TLC data are given for Silufol UV-254 plates.

Nickel Complex of 2,7,12,17-Tetramethyl-3,13-diethyl-8,18-di(2-trideuteromethoxycarbonylethyl)porphyrin (Ic). A solution of 100 mg (0.17 mmole) porphyrin Ia in 30 ml 5% D_2SO_4 in CD_3OD was stored for 24 h, diluted with water (150 ml), and neutralized with a saturated solution of sodium acetate. The precipitate which formed was filtered off and chromatographed on a column with silica gel, eluting with chloroform. The product was separated and crystallized from a mixture of chloroform–methanol. Yield 95.5 mg (94%) porphyrin Ib. Mass spectrum ($C_{36}H_{36}D_6N_4O_4$), m/z (%): 600 (M^+, 100).

A mixture of 90 mg (0.15 mmole) porphyrin Ib, 50 mg (0.28 mmole) nickel acetate, 10 ml acetic acid, and 60 ml chloroform was heated. After 20 min (chromatographic monitoring), 100 ml water was added. The organic layer was washed several times with water, dried, chromatographed on a column with Al_2O_3, and then crystallized from a mixture of chloroform–methanol. Yield 95.7 mg (97%) porphyrin Ic. Mass spectrum ($C_{36}H_{34}D_6N_4O_4{}^{58}Ni$), m/z (%): 656 ($M^+$, 100).

Nickel Complexes of meso-N,N-Dimethylaminomethyl-2,7,12,17-tetramethyl-3,13-diethyl-8,18-di(2-trideuteromethoxycarbonylethyl)porphyrin (Id, e). A mixture of 100 mg (0.15 mmole) compound Ic and the complex which was prepared from 1 ml (0.013 mole) DMF and 1.2 ml (0.013 mole) $POCl_3$ in 60 ml dichloroethane (chromatographic monitoring) was heated at 70°C. After 20 min, the solvent was removed and the residue was poured into cold water (150 ml). The precipitate which formed was filtered off and dissolved in a mixture of 100 ml chloroform and 10 ml alcohol. A 100 mg portion of sodium borohydride was added. After 5 min, 150 ml water was added. The organic layer was washed with water and dried over sodium sulfate. The solvent was removed in vacuum. The residue was repeatedly separated on silica gel plates. Two isomers were obtained.

Isomer Id, yield 35.9%, R_f 0.43. IR spectrum: 1735 (CO), 2760, 2810 cm^{-1} (NMe_2). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 410 (165.8), 539 (8.8), 580 nm (13.4). Mass spectrum ($C_{39}H_{41}D_6N_5O_4{}^{58}Ni$), m/z (%): 713 ($M^+$, 8), 670 (86), 669 (84), 668 (100).

Isomer Ie, yield 36.6%, R_f 0.33. IR spectrum: 1740 (CO), 2765, 2810 cm^{-1} (NMe_2). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 410 (169.2), 537 (9.3), 577 nm (14.4). Mass spectrum ($C_{39}H_{41}D_6N_5O_4{}^{58}Ni$), m/z (%): 713 ($M^+$, 5), 670 (84), 669 (100), 668 (98).

TABLE 1. PMR Data for Derivatives of Mesoporphyrin-II and Mesoporphyrin-IX*

Compound	meso-H	meso-CH_2—	$N(CH_3)_2$	—CH_2—CH_2—$COOCD_3$		CH_2—CH_3		CH_3 ring
				CH_2—	CH_2CO	CH_2—	CH_3	
Ic	9,75 (2) 9,73 (2)	—	—	4,24	3,16	3,90	1,77	3,48 (6) 3,47 (6)
Id	[20] 9,39 [15] 9,35 [5] 9,33	[10] 5,11	1,37	[8] 4,17 [18] 4,15	[8] 3,21 [18] 3,11	[3, 13] 3,77	[3] 1,70 [13] 1,63	[12] 3,43 [17] 3,36 [2] 3,35 [7] 3,32
Ie	[15] 9,40 [10] 9,35 [20] 9,33	[5] 5,11	1,36	[8, 18] 4,12	[18] 3,10 [8] 2,98	[3] 3,84 [13] 3,80	[3] 1,80 [13] 1,72	[7] 3,48 [17] 3,37 [12] 3,34 [2] 3,30
If	9,46 9,42 9,41	6,11d 5,81d $J = 15,1$ Hz	0,86 s 0,82 s	4,18 4,10	3,21 3,12	3,78	1,71 1,61	3,52 3,37 (6) 3,35
Ig	9,45 9,42 9,40	6,10d 5,90d $J = 15$ Hz	0,88 s 0,82 s	4,10	3,10 2,99	3,87	1,89 1,73	3,53 3,39 3,35 3,31
IIc	9,74 (f) 9,73 (3)	—	—	4,24 4,23	3,17 3,15	3,89 3,88	1,76 1,75	3,48 3,47 3,45 3,44
IVa	[5] 9,38 9,34 9,33	5,08	1,35	4,16	3,19	3,78	1,71 1,70	3,37 3,34 [12, 18] 3,32 (6)
IVb	[15] 9,39 (1) [10, 20] 9,35 (2)	[5] 5,12	1,36	4,14	3,12 3,11	[3] 3,84 [8] 3,78	[3] 1,79 [8] 1,60	[7] 3,45 [12, 18] 3,36 (6) [2] 3,29

IVc	[20] 9,39 [15] 9,36 [5] 9,33	[10] 5,13	1,41	[13, 17] 4,12	[17] 3,10 [13] 2,99	[8] 3,84 [3] 3,78	[8] 1,79 [3] 1,69	[12] 3,48 [18] 3,37 [2] 3,34 [7] 3,29
IVd	[10] 9,40 [15] 9,37 [5] 9,36	[20] 5,14	1,39	[13, 17] 4,12	[13] 3,12 [17] 2,99	[8] 3,80 [3] 3,78	[8] 1,71 [3] 1,62	[18] 3,48 [2] 3,45 [12] 3,38 [7] 3,34
Va	9,44 9,42 9,41	5,84 s	0,82 s 0,79 s	4,26 4,16	3,26	3,84 3,75	1,73 1,71	3,36 3,35 (6) 3,34
Vb	9,48 (1) 9,41 (2)	6,12 d 5,90 d $J = 15$ Hz	0,91 s 0,82 s	4,17 4,11	3,13	3,90 3,80	1,89 1,51	3,51 3,37 3,36 3,30
Vc	9,47 9,45 9,39	6,10 d 5,91 d $J = 14,4$ Hz	0,89 s 0,83 s	4,11	3,13 3,00	3,91 3,74	1,89 1,71	3,53 3,39 3,36 3,30
Vd	9,47 (2) 9,42 (1)	6,12 s	0,90 s 0,88 s	4,10	3,13 3,00	3,80	1,73 1,62	3,54 3,52 3,39 3,35

*The number of protons is shown in parentheses. The position of the substituent is shown in square brackets.

Nickel Complex of 2,7,12 18-Tetramethyl-3,8-diethyl-13,17-di(2-methoxycarbonylethyl)-porphyrin (IIb, $C_{36}H_{40}N_4O_4Ni$). This was prepared in quantitative yield by heating porphyrin IIa in a mixture of chloroform-acetic acid in the presence of nickel acetate. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 393 (196.3), 518 (11.2), 553 nm (30.2).

Nickel Complex of 2,7,12,18-Tetramethyl-3,8-diethyl-13,17-di(2-trideuteromethoxycarbonylethyl)porphyrin (IIc). This was prepared analogously to complex Ic starting from porphyrin IIa. Yield 70%. Mass spectrum ($C_{36}H_{34}D_6N_4O_4{}^{58}Ni$), m/z (%): 656 ($M^+$, 100).

Isomers of Nickel Complexes of meso-N,N-Dimethylaminomethyl-2,7,12,18-tetramethyl-3,8-diethyl-13,17-di(2-methoxycarbonylethyl)porphyrin (IIIa-d). These were prepared analogously to complexes Id and Ie. Mixtures of isomers IIIa-d (88 mg, 81%) were obtained from 100 mg (0.05 mmole) of porphyrin IIb. After repeated separation on silica gel plates, four isomers were isolated:

Isomer IIIa, 10.7 mg (9.8%), R_f 0.61. Mass spectrum ($C_{39}H_{47}N_5O_4{}^{58}Ni$), m/z (%): 707 ($M^+$, 2), 664 (100), 663 (30), 662 (42).

Isomer IIIb, 19 mg (17.5%), R_f 0.51. Mass spectrum ($C_{39}H_{47}N_5O_4{}^{58}Ni$), m/z (%): 707 ($M^+$, 5), 664 (100), 663 (36), 662 (42).

Isomer IIIc, 12.6 mg (11.6%), R_f 0.45. Mass spectrum ($C_{39}H_{47}N_5O_4{}^{58}Ni$), m/z (%): 707 ($M^+$, 5), 664 (100), 663 (39), 662 (66).

Isomer IIId, 26 mg (23.9%), R_f 0.37. Mass spectrum ($C_{39}H_{47}N_5O_4{}^{58}Ni$), m/z (%): 707 ($M^+$, 8), 664 (100), 663 (46), 662 (77).

Nickel Complexes of meso-N,N-Dimethylaminomethyl-2,7,12,18-tetramethyl-3,8-diethyl-13,17-di(2-trideuteromethoxycarbonylethyl)porphyrin (IVa-d). These were prepared analogously to complexes Id-e, starting with porphyrin IIc. After repeated separation on plates, the individual isomers IVa-d were isolated. The complete deuterium exchange was checked using PMR spectra (Table 1). UV spectra, λ_{max} ($\varepsilon \cdot 10^{-3}$): IVa, 408 (150), 539 (7.6), 579 nm (13); IVb, 407 (153), 536 (7.8), 575 nm (13.1); IVc, 407 (159), 536 (8.0), 575 nm (14); IVd, 406 (157), 534 (7.9), 572 nm (14).

Amineborane Complexes (If-g, Va-d) were prepared by the method of [5] with yields of 80-90% starting from the individual isomers Id, Ie, and IVa-d. The purity of the amineborane complexes was determined by TLC on silufol plates and by IR spectral data in the ranges 2250-2400 cm^{-1} and 2750-2810 cm^{-1}. The PMR data are given in Table 1.

LITERATURE CITED

1. G. B. Maravin and G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 6, 780 (1988).
2. G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 7, 943 (1980).
3. G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 6, 777 (1979).
4. L. T. Stroganova and T. N. Tuzhilkova, in: Materials of the IIIrd All-Union Conf. on Chemistry and Biochemistry of Porphyrins [in Russian], Izd. Samarkand Gos. Univ., Samarkand (1983), p. 116.
5. G. V. Ponomarev, G. V. Kirillova, L. B. Lazukova, and T. A. Babushkina, Khim. Geterotsikl. Soedin., No. 11, 1507 (1982).
6. G. V. Kirillova, G. V. Ponomarev, T. A. Babushkina, and V. P. Suboch, Khim. Geterotsikl. Soedin., No. 9, 1215 (1978).
7. H. Scheer and J. J. Katz, in: Porphyrins and Metalloporphyrins, K. M. Smith (editor), Elsevier, Amsterdam (1975), p. 399.