PORPHYRINS.

10.* NEW DATA ON THE POLYFORMYLATION OF METAL COMPLEXES OF OCTAETHYLPORPHYRIN

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

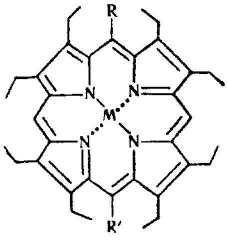
UDC 547.749

It is shown that α-chloro-γ-formyloctaethylporphyrin and porphyrins that contain a cyclopentane ring are formed along with monoformyloctaethylporphyrin and α,γ-diformyloctaethylporphyrin in the Vilsmeier formylation of the Co complex of octaethylporphyrin. Two crystalline modifications of the Zn complex of octaethylporphyrin were obtained, and their UV and IR spectra were studied.

The formation of α,γ-diformyletioporphyrin, α,β-diformyletioporphyrin, and α,β,γ-triformyletioporphyrin [1] contradicts the concept of Watanabe and co-workers [2] that secondary electrophilic substitution is directed exclusively to the γ position. For a comparison of the results we carried out the formylation of the Cu complex of octaethylporphyrin (Ia) in the same way as the formylation of the Cu complex of etioporphyrin [1] and by the method in [2]. In the first case we obtained primarily meso-formyloctaethylporphyrin (Ib) in 75-85% yield, and the yield of the α,γ-diformyloctaethylporphyrin (Ic) did not exceed 5-10%. In the second case we obtained a mixture of substances, from which we isolated a small amount of Ib and Ic in 15-20% yield. A large excess of the Vilsmeier complex and prolonged refluxing of the reaction mixture complicate the reaction process markedly, and we therefore used the considerably more reactive Co complex (Id) for the formylation, despite the fact that when Watanabe and co-workers [2] formylated it, they were unable to isolate individual compounds from the complex mixture of products and establish their structures.

Monoformyloctaethylporphyrin (Ib) is formed in 50-60% yield after 10-15 min at room temperature in the formylation of Id. Under similar conditions, porphyrin Ic was formed in 25-30% yield along with porphyrin Ib at 50°C.

In all cases we isolated an unknown compound that has a higher lability on silica gel than monoformylporphyrin Ib when we chromatographed the reaction products. An intense band at ∿1700 cm^{-1}, which corresponds to the meso-formyl group, was present in the IR spectrum of this compound. It followed from the data from the high-resolution mass spectrum that the elementary composition of the compound is $C_{37}H_{45}ClN_4O$ and that it is consequently a porphyrin in which a chlorine atom is present along with a formyl group. An analysis of the PMR spectrum makes it possible to unambiguously assign the α-chloro-γ-formyloctaethylporphyrin



I a-f

I a M=Cu, R=R′=H; b M=2H, R=CHO, R′=H; c M=2H, R=R′=CHO; d M=Co, R=R′=H; e M=2H, R=CHO, R′=Cl; f M=Zn, R=CHO, R′=H

---

*See [1] for communication 9.

Institute of Biophysics, Ministry of Public Health of the USSR, Moscow 123182. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 776-779, June, 1979. Original article submitted June 20, 1978.

0009-3122/79/1506-0630$07.50

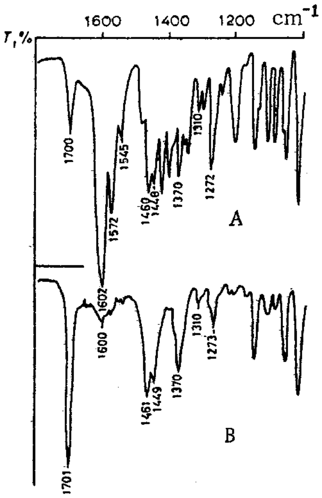


Fig. 1. IR spectra of the Zn complex (If) of meso-formyloctaethylporphyrin: A) "blue" form; B) "red" form

structure (Ie) to this porphyrin. The introduction of a chlorine atom in the Ib molecule leads to a small bathochromic shift (3-5 nm) and redistribution of the intensities of the bands in the visible portion of the spectrum, as in the case of introduction of a second formyl group. A characteristic feature in the electronic spectra of the metal complexes of Ie is the presence of a very intense additional long-wave band at 660 nm.

By comparing the results obtained in the formylation of the complexes of etioporphyrin [1] and octaethylporphyrin one can note the considerable difficulty involved in the incorporation of a second meso substituent in the octaethylporphyrin complexes as compared with the etioporphyrin complexes. At the same time, the monoformylation of the complexes of both etioporphyrin and octaethylporphyrin proceeds with identical ease. In our opinion, this is explained by the fact that free rotation of the methyl groups of the ethyl substituents relative to the C—C bond is hindered after incorporation of a bulky substituent into the octaethylporphyrin molecule, and this creates steric hindrance to reaction of the Vilsmeier complex with the other meso-carbon atom. Since the greatest steric hindrance develops in the adjacent β- and δ-meso positions, the second electrophilic substitution takes place in the γ position, since it is the least shielded, rather than because of electronic factors, as proposed in [2].

In the formylation of Id, in addition to the porphyrins that we identified, small amounts of side products are formed, and their yields increase as the reaction time is increased.

The following conclusions can be drawn from an analysis of the IR, PMR, and mass spectra of the three principal compounds isolated from the reaction mixture in the chromatographically individual state: 1) all of the porphyrins belong to the class of porphyrins that contain at least one meso-formyl group and a substituent of unknown structure in one of the remaining meso positions; 2) the presence of two or three singlet signals of the protons of methyl groups in the PMR spectra is characteristic for all of the compounds; 3) according to the mass-spectral data, all of the compounds have ion peaks in the region of lower m/e values than the expected molecular peak of the possible disubstituted octaethylporphyrin derivatives. These facts can only be explained by the participation of the ethyl groups of the porphyrin ring in reactions involving the formation of cyclopentane rings. The absence of such reactions in the formylation of the Co complex of etioporphyrin [1] is explained by the greater spatial freedom of the substituents in the meso position than in the case of the octaethylporphyrin complexes.

Most of the metal complexes of meso-formyloctaethylporphyrin have somewhat better solubilities in chloroform than the corresponding complexes of meso-formyletioporphyrin. As a result of this peculiarity, it is possible to obtain meso-formyloctaethylporphyrin complexes

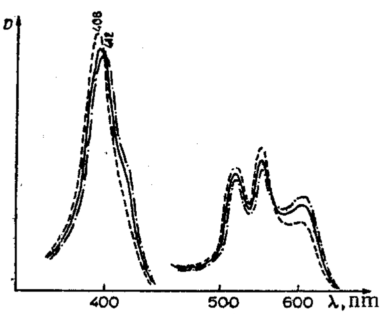


Fig. 2. UV spectra of the Zn complex (If) of meso-formyloctaethylporphyrin at 20°C (———), 15°C (- - - - -), and 40°C (—·—·—).

in various crystalline modifications, depending on the rate of crystallization. Thus, for example, the zinc complex (If) of meso-formyloctaethylporphyrin in the case of slow crystallization from chloroform forms large prismatic crystals with a bluish tint (the "blue" form), whereas fine bright-red crystals (the "red" form) are obtained in the case of rapid crystallization when a large amount of ethanol is added to the hot chloroform solution. These two forms have different solubilities in chloroform. Thus the "blue" form dissolves with considerably greater difficulty than the "red" form. In addition, the IR spectra of KBr pellets of these two forms were found to be completely different in the 600-1800 cm^{-1} region (Fig. 1).

The presence of several bands of carbonyl absorption is characteristic for the "blue" form, and this corresponds to several types of interaction between the metal of one molecule with the carbonyl group of another molecule in the metalloporphyrin crystal. We observed a similar phenomenon for the Mg complex of meso-formyletioporphyrin [3], for which a strong intermolecular interaction of the "metal—carbonyl" type is characteristic.

It has been pointed out [2] that when a chloroform solution of the If complex is evaporated rapidly, one obtains a noncrystalline amorphous "green" form that has an IR spectrum that is similar to the spectrum of the "blue" form, whereas the electronic spectrum differs appreciably from that of the "red" form. We were unable to obtain the amorphous "green" form, since only the crystalline "blue" form is formed in all cases when the chromatographically pure substance and freshly distilled destabilized chloroform are used.

In contrast to Watanabe and co-workers [2], we were unable to observe any anomaly whatsoever in the electron spectra of the "red" and "blue" forms in the case of strict thermostatting. It is apparent from Fig. 2 that the spectrum of the If complex is very sensitive to changes in the temperature because of the capacity for the facile formation of associates of the metal—carbonyl type. This evidently explains the difference in the electronic spectra of the "red" and "green" forms of the If complex observed by Watanabe and co-workers [2], which they incorrectly interpreted as the ability of the various crystalline forms to give different electronic spectra.

EXPERIMENTAL

The methods used for the isolation and purification of the compounds and their spectral characteristics were presented in [1]. The PMR spectra of solutions of the compounds in $CDCl_3$ containing three to five drops of trifluoroacetic acid to suppress possible aggregation of the porphyrin molecules were recorded.

Formylation of the Co Complex (Ia) of Octaethylporphyrin. Method A. A mixture of 150 mg of complex Ia and the Vilsmeier complex [from 1 ml of dimethylformamide (DMF) and 1.2 ml of $POCl_3$] was heated in 25 ml of dichloroethane at 20°C for 10 min, after which 25 ml of a saturated solution of sodium acetate was added, and the mixture was refluxed for 1 h. It was then cooled, and the organic layer was separated and filtered through a layer of aluminum oxide. The filtrate was evaporated in vacuo, and the residue was dissolved in 10 ml of concentrated H_2SO_4 at 40°C. After 1 h, the mixture was poured into 100 ml of cold water, and the aqueous mixture was brought up to pH 3-5 with ammonium hydroxide. The substance was extracted with chloroform, and three fractions were isolated after chromatographic separation in plates coated with silica gel. The first and most mobile fraction contained 10 mg of octaethylporphyrin. The second red-lilac fraction contained, after crystallization (from chloroform—methanol), 5 mg of α-chloro-γ-formyloctaethylporphyrin. High-resolution mass spectrum: found M^+ 596.3238. $C_{37}H_{45}N_4OCl$. Calculated: M 596.3271. Mass spectrum, m/e (%): 596 (M^+, 100), 568 (93), 553 (33), 539 (31). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 413 (150), 513 (9.46), 553 (6.4), 585 (8.04), 644 (4.02), 660 sh; dication: 438 (171), 588 (10.11), 639 nm (9.95). PMR spectrum, δ: 12.47 (1H, CHO), 9.88 (2H, meso-H), 4.04 (4H, q), 3.91 (4H, q), 3.86 (4H, q), 3.74 (4H, q), CH_2CH_3; 1.76 (6H, t), 1.73 (12H, t), 1.63 (6H, t), CH_2CH_3; in $CDCl_3$ + trifluoroacetic acid (TFA): 12.08 (1H, CHO), 9.81 (2H, meso-H), 3.64 (4H, q), 3.57 (8H, q), 3.29 (4H, q), CH_2CH_3; 1.44, 1.28, 1.23, and 1.13 ppm (amounting to 6H), CH_2CH_3. IR spectrum: ν(C=O) 1702 cm^{-1}. The corresponding copper complex was obtained by heating the porphyrin with copper acetate in chloroform—methanol with subsequent crystallization from chloroform—methanol. Mass spectrum for $C_{37}H_{33}{}^{35}Cl^{63}CuN_4$, m/e (%): 657 ($M^+$, 100), 628 (11), 623 (19). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 415 (137), 428 sh (107), 545 (6.43), 588 (7.14), 648 nm (8.57). Workup of the third fraction gave 124 mg of meso-formyloctaethylporphyrin in the form of red crystals (chloroform—methanol). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 407 (129), 507 (8.42), 540 (6.33), 576 (6.25), 628 (4.0), 660 sh (2.75); dication: 426 (190), 575 (8.42), 630 (8.92). Mass spectrum, m/e (%): 562 (M^+, 58), 547 (5), 534 (100), 519 (30), 505 (20), 489 nm (7). PMR spectrum, δ: 12.70 (1H, CHO); 9.98 (2H), 9.87 (1H, meso-H), 3.96 (8H, q), 3.85 (4H, q), 3.80 (4H, q), CH_2CH_3; 1.82 (12H, t), 1.78 (6H, t), and 1.65 (6H, t), CH_2CH_3; − 2.94 ppm (2H, NH).

Method B. Similarly, when the formylation was carried out at 50°C for 10 min, demetallation and chromatographic separation on plates coated with silica gel gave 5 mg of porphyrin Ie, 10 mg of porphyrin Ib, and, after crystallization from chloroform, 30 mg (20%) of porphyrin Ic. Electronic spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 411 (134.7), 511 (7.03), 550 sh (6.40), 580 (7.35), 645 (4.95), 660 sh (4.1); dication: 437 (160), 601 (6.1), 658 nm (12.7). PMR spectrum, δ: 12.61 (2H, CHO), 10.00 (2H, meso-H), 3.84 (8H, q), 3.74 (8H, q), CH_2CH_3; 1.78 (12H, t), 1.62 (12H, t), CH_2CH_3; in $CDCl_3$ + TFA: 12.26 (2H, CHO), 10.10 (2H, meso-H), 3.64 (8H, q) and 3.32 (8H, q), CH_2CH_3; 1.28 (12H, t) and 1.15 ppm (12H, t), CH_2CH_3. Mass spectrum, m/e (%): 590 (M^+, 100), 562 (74), 547 (15), 535 (70), 534 (41), 533 (34), 519 (12). The corresponding Cu complex was obtained in quantitative yield by heating porphyrin with copper acetate in chloroform—methanol with subsequent chromatographic purification on silica gel and crystallization from chloroform. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 409 (132.5), 540 (4.17), 579 (6.67), 647 nm (6.43). Mass spectrum for $C_{38}H_{44}N_4O_2{}^{63}Cu$, m/e (%): 651 ($M^+$, 66), 637 (61), 624 (86), 610 (66), 596 (100), 595 (83).

Preparation of the "Blue" and "Red" Crystalline Modifications of the Zinc Complex (If) of Monoformyloctaethylporphyrin. A solution of 100 mg of zinc acetate in 10 ml of methanol was added to a solution of 50 mg of porphyrin Ib in 20 ml of chloroform, and the mixture was heated for 10 min. It was then evaporated to dryness, and the residue was dissolved in chloroform and chromatographed with a column filled with silica gel. The eluate was evaporated to 20 ml. After 12 h, large blue crystals of the If complex precipitated from the solution. The yield in the preparation of the "blue" and "red" forms was quantitative. Found: C 70.77; H 6.95; N 8.87%. $C_{37}H_{44}N_4OZn$. Calculated: C 70.97; H 7.08; N 8.95%. For recording of the electronic spectra, samples of the complexes in chloroform were first heated at 40°C for 10 min until they had dissolved completely, after which the solutions were cooled to 20°C, and the spectra were recorded after 30 min. The spectra of the "red" and "blue" forms were identical. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 410 (164), 541 (8.0), 579 (8.88), 644 nm (5.81).

LITERATURE CITED

1. G. V. Ponomarev, G. V. Kirillova, G. B. Maravin, T. A. Babushkina, and V. P. Suboch, Khim. Geterotsikl. Soedin., No. 6, 767 (1979).
2. E. Watanabe, S. Nishimura, H. Ogoshi, and Z. Yoshida, Tetrahedron, 31, 1385 (1975).
3. G. V. Ponomarev and A. N. Sidorov, Khim. Geterotsikl. Soedin., No. 7, 919 (1977).