PORPHYRINS. 12.* INVESTIGATION OF THE PROTONATION OF meso-SUBSTITUTED PROPHYRINS BY PMR SPECTROSCOPY

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The dependence of the chemical shifts of the protons in the PMR spectra of meso-dimethylaminomethyl derivatives of etioporphyrin and octaethylporphyrin, as well as the Schiff bases of meso-formylporphyrins, on the concentration of trifluoroacetic acid was studied. The order of protonation of the nitrogen atoms of these compounds was determined. The effect of various solvents and acids on the ratio of the equilibria of proton transfer along the hydrogen bond and dissociation of the H complexes with the formation of solvated ions was examined. The PMR spectra of various salts of the Schiff bases of meso-formylporphyrins were studied.

Protonation processes are of great significance in the mechanism of the action of various medicinal preparations. Acid–base interactions in aqueous and nonaqueous media to a great extent determine the penetration of biologically active substances through cell membranes. The diversity of natural porphyrins and their role in the most important vital processes of organisms are attracting a great deal of attention and interest. The acid-base properties of porphyrins are determined by the presence in the molecule of two nitrogen atoms that are capable of adding protons and two nitrogen atoms that are capable of giving up or adding protons. In accordance with this, the porphyrin molecule can theoretically exist in two anionic and four cationic forms. The presence of substituents in the meso position of porphyrin changes its acid–base properties.

The aim of the present research was to study processes involving the protonation of porphyrins, one of the meso protons of which is substituted with a $-CH_2N(CH_3)_2$ or $-CH{=}N{-}CH_3$ group, since, as was recently observed, precisely these porphyrins have the greatest biological effect [2, 3].

The dependence of the chemical shifts of the protons of meso-dimethylaminomethyletioporphyrin (I) and its Ni complex (III), as well as meso-dimethylaminomethyloctaethylporphyrin (II), on the concentration of trifluoroacetic acid in various solvents was investigated.

According to modern concepts [4], an acid–base interaction in solutions proceeds through a number of successive equilibria and includes the formation of complexes due to hydrogen bonding, proton transfer from the acid to the base via an H bond, and dissociation of ion pairs as the principal processes:

$$B + HA \overset{(1)}{\rightleftharpoons} B...HA \overset{(2)}{\rightleftharpoons} B^+H...A^- \overset{(3)}{\rightleftharpoons} B^+H + A^-$$

It is usually assumed that in low-polarity media dissociation of ion pairs does not make an appreciable contribution to the reaction constant for proton transfer along a hydrogen bond [5]. The importance of the ratio of equilibria (2) and (3) has been demonstrated for azaindolines [6, 7] by PMR and IR spectroscopy. The dependence of the chemical shifts of the protons that are close to the protonation center on the molar ratio of the reagents had extrema, the extent and position of which depended on the solvent and the strength of the acid, which indicated a change in the ratio of the equilibria.

Anomalies in the character of the curves of the dependence of the chemical shifts of the protons of the N-methylene and N-methyl groups on the acid concentration were also

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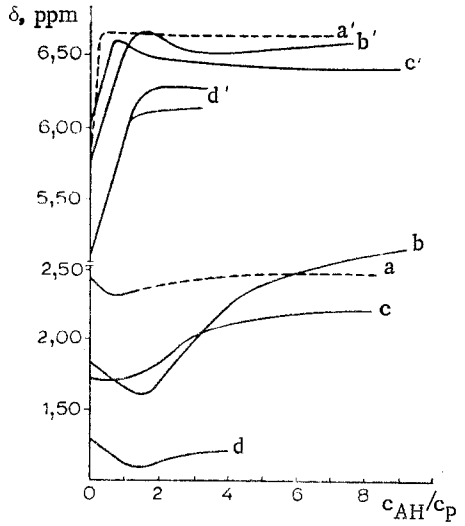

Fig. 1

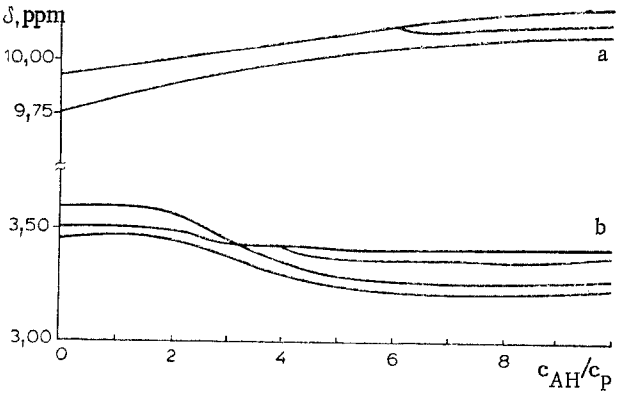

Fig. 2

Fig. 1. Dependence of the chemical shifts of the protons of the $N(CH_3)_2$ and CH_2N groups of meso-dimethylaminomethyletioporphyrin and its Ni complex on the trifluoroacetic acid:porphyrin molar ratio in $CDCl_3$ (b, b', d, and d'), $(CD_2Br)_2$ (c, c'), and DMSO (a, a') (the apostrophe pertains to the methylene protons).

Fig. 2. Dependence of the chemical shifts of the meso protons (a) and the β-CH_3 protons (b) of meso-dimethylaminomethyletioporphyrin on the trifluoroacetic acid:porphyrin molar ratio in $CDCl_3$.

observed during a PMR spectroscopic study of the protonation of I and II in chloroform. The dependence of the chemical shifts of these protons on the trifluoroacetic acid concentration in various media for I, as well as for III in chloroform, is given in Fig. 1. A distinct minimum is observed near the equimolar ratio of the reagents ($c_{AH}/c_P \sim 1$) on the curve for the protons of the $N(CH_3)_2$ group of the meso substituent, whereas a maximum is observed for the protons of the CH_2N group. The chemical shifts of the meso protons and the protons of the β substituents of porphyrin change more smoothly (Fig.2). To ascertain the reason for the appearance of extrema we investigated the dependence of the chemical shifts of the protons of the N-methylene and N-methyl groups of nickel complex III, in which there is only one proton-acceptor centor, viz., the nitrogen atom of the side chain. The protonation curves (Fig. 1, curves d' and d) in the case of addition of trifluoroacetic acid to a solution of III in $CDCl_3$ have the same form as in thecase of I (Fig. 1, curves b' and b). It may consequently be assumed that the observed curves describe monoprotonation of the nitrogen atom of the side chain. When $c_{AH}/c_P \geq 4$, changes in the chemical shifts are virtually absent, which constitutes evidence for a shift of equilibrium (3) to the right over this acid concentration range. The dissociation of the H complexes of III with the formation of solvated ions ($c_{AH}/c_P \sim 4$) leads to a decrease in the chemical shift of the $N(CH_3)_2$ protons as compared with the original chemical shift in $CDCl_3$ (δ 1.29 ppm) to $\delta^{P^+H}_{N(CH_3)_2} = 1.20$ ppm (Fig. 1, curve d).

However, in addition to a protonation center in the side chain, I also contains two proton-acceptor nitrogen atoms in the porphyrin ring. The protonation of these nitrogen atoms is manifested as a change in the chemical shifts of the β-CH_3 protons when $c_{AH}/c_P > 1$ (Fig. 2, curve b). The same process gives rise to a further increase in the chemical shifts of the $N(CH_3)_2$ protons in I after the extremum is reached, and when $c_{AH}/c_P \geq 5$, one can evidently speak of the chemical shift $\delta^{P^{3+}H}_{N(CH_3)_2} = 2.39$ ppm, which is considerably larger than the shift in pure chloroform (δ 1.82 ppm). It hence follows that the protonation of meso-substituted porphyrins that have a heteroatom in the side chain proceeds in two steps: The nitrogen atom of the substituent is protonated initially, after which the central nitrogen atoms of the porphyrin ring are protonated.

Replacement of the β-methyl group by a β-ethyl group does not introduce changes in the protonation processes. The change in the chemical shifts for all of the protons of II is similar to the behavior of the chemical shifts of the corresponding protons of I (Fig. 3).

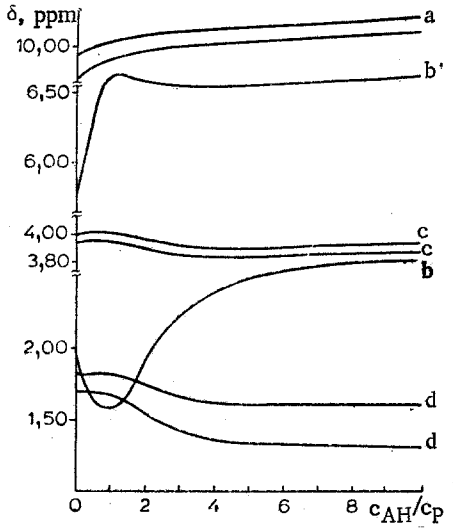

Fig. 3

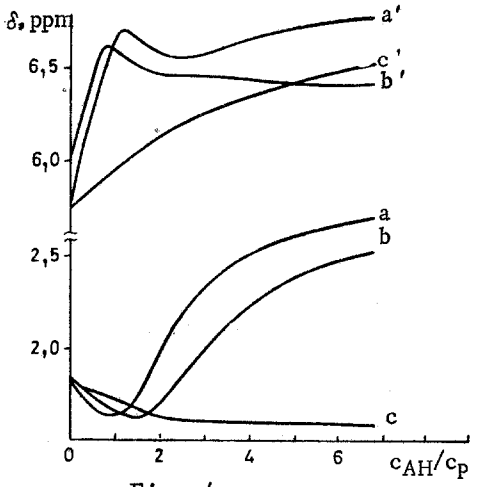

Fig. 4

Fig. 3. Dependence of the chemical shifts of the protons of meso-dimethylaminomethyloctaethylporphyrin on the trifluoroacetic acid:porphyrin molar ratio in $CDCl_3$: meso-H (a), $N(CH_3)_2$ (b), CH_2N (b'), β-CH_2CH_3 (c), and β-CH_2CH_3 (d).

Fig. 4. Dependence of the chemical shifts of the $N(CH_3)_2$ and CH_2N protons of meso-dimethylaminomethyletioporphyrin on the acid:porphyrin molar ratio: CCl_3COOH (a), CF_3COOH (b), and CH_3COOH (c) (the apostrophe pertains to the signals of the methylene protons).

Taking the material presented above into account, it may be assumed that the characteristic form of the curves of the dependences of the chemical shifts of the protons of the N-methyl and N-methylene groups on the acid concentration in solution is due mainly to the steric effect of the electrical field and the magnetic anisotropy of the trifluoroacetate group in the H complex, as in the case of azaindolines [6].

To clear up the problem of the type of complex formed in the first step of protonation, i.e., the position of equilibrium (2), we investigated the IR spectra of In in $CDCl_3$ when $c_{AH}/c_P = 1$ for trifluoroacetic and acetic acids. The spectra in the region of the stretching vibrations of the carbonyl groups of the acids were recorded. A band at 1670 cm^{-1}, which is characteristic for trifluoroacetate ions, is observed in the spectrum at an equimolar porphyrin:trifluoroacetic acid ratio. This constitutes evidence for a significant shift of equilibrium (2) to the right. A band at 1710 cm^{-1}, which corresponds to the undissociated acid, is observed in the spectrum of the porphyrin–acetic acid system. An increase in the acid concentration leads to the appearance of a band of the ionic form of the acid only at $c_{AH}/c_P > 2$. This corresponds to the formation of an undissociated H complex at an equimolar porphyrin:acetic acid ratio.

As demonstrated in [6], a shift of equilibrium (2) leads to a change in the position of the extrema on the curves of the dependence of the chemical shifts on the acidity of the solution. In conformity with the IR spectroscopic data, as the strength of the acid changes (trichloroacetic acid ~ trifluoroacetic acid > acetic acid) the extrema on the $\delta_{N(CH_3)_2} = f(c_{AH}/c_P)$ curves are shifted to the region of higher c_{AH}/c_P values, and the depth of the minimum decreases (Fig. 4). A minimum is virtually absent in the case of the curve with acetic acid.

The position of equilibrium (2) should be affected not only by the strength of the acid but also by the properties of the medium, and the ability of the solvent to form hydrogen bonds with the acid or porphyrin rather than the degree of polarity of the solvent should be of principal importance. The extrema on the curves obtained decrease on passing from $CDCl_3$ to CH_2BrCH_2Br and DMSO (Fig. 1).

It has been shown [5, 7] that equilibrium (2) is shifted to the right as the proton-donor properties of the solvent increase. It is known that chloroform can form H complexes by

TABLE 1. Chemical Shifts (δ, ppm) in the PMR Spectra of meso-Formyletioporphyrin N-Methylimine and Its Salts

Compound	Structure[a]	$-CH=N^+-$ / $(-CH=N)$	$=N^+-CH_3$ / $(=N-CH_3)$	β-CH_3	β-CH_2CH_3	β-CH_2CH_3	meso-H
IV	EP–CH=N–CH_3	(10,42 s)	(3,91 s)	3,52 s 3,47 s 3,02 s	3,93 q	1,78 t 1,45 t	9,96 s 9,95 s 9,82 s
VI	EP–CH=N^+(H)(CH$_3$)CF_3COO^-	11,78 d	4,23 s 2,99 s	3,40 m	3,92 q	1,58 t	10,19 s 10,13 s
VII	EP–CH=$N^+H_2CH_3 \cdot n$HCl$^-$	12,44 s	4,15 s 2,96 s	3,40 s 3,30 s 3,00 s	3,78 q	1,85 t	10,23 s 10,14 s
VIII	EP–CH=$N^+(CH_3)_2I^-$	12,74 s	4,73 s 2,74 s	3,41 s 3,36 s 3,32 s	3,88 q	1,59 t	9,85 s 9,78 s
IX	OEP–CH=$N^+(CH_3)_2I^-$	12,39 s	4,77 s 2,69 s		3,90 q	1,79 t	9,91 s 9,86 s
X	EP–CH=N^+(CH$_3$)CH_2CH_3 I^-	12,97 s 12,54 s	4,70 sb 2,56 s	3,40 s 3,34 s 3,28 s	3,73 q	1,74 t	9,82 s 9,73 s 9,58 s
XI	EP–CH=$N^+(CH_2CH_3)_2I^-$	10,40 s	c	3,44 s	3,92 q	1,73 t	9,85 s 9,78 s

[a]Symbols: EP is etioporphyrin, and OEP is octaethylporphyrin. [b]Two quartets of methylene protons (5.12 and 3.60 ppm) and a triplet of methyl protons (1.70 ppm) of the $N^+-C_2H_5$ group are also observed. [c]Two quartets (5.21 and 3.77 ppm) and two triplets (3.00 and 1.65 ppm) of the $N^+(C_2H_5)_2$ group are also observed.

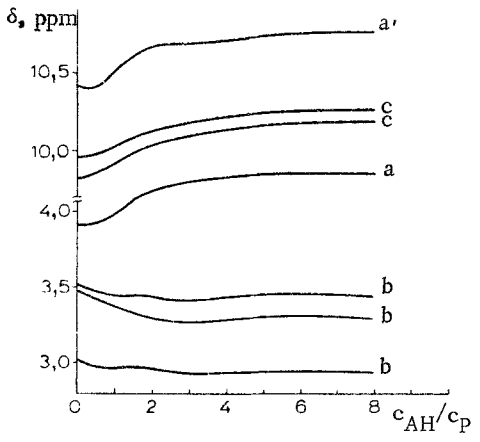

Fig. 5

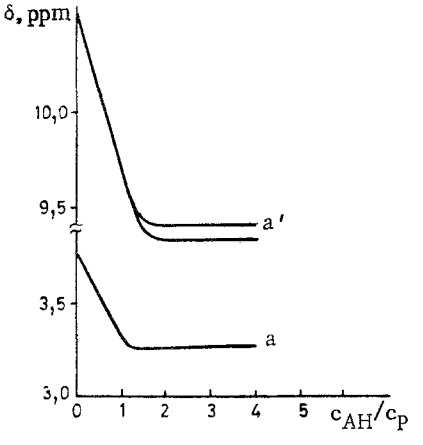

Fig. 6

Fig. 5. Dependence of the chemical shifts of the =N–CH_3 (a), CH=N (a'), β-CH_3 (b), and meso-H (c) protons of meso-formyletioporphyrin N-methylimine on the trifluoroacetic acid:prophyrin molar ratio in chloroform.

Fig. 6. Dependence of the chemical shifts of the =N–CH_3 (a) and –CH=N– (a') protons of the Ni complex of meso-formyletioporphyrin N-methylimine on the molar ratio of trifluoroacetic acid to porphyrin in chloroform.

acting as a proton donor. In addition, DMSO participates in the formation of hydrogen bonds only as a proton acceptor. The observed regularity in the change in the position of the extrema is in good agreement with the proton-donor properties of the solvents.

Let us note that the significant shift to weak field of the chemical shifts of all of the protons of I in solution in DMSO is also associated with its electron-donor properties and the large dielectric constant (ε = 45.0).

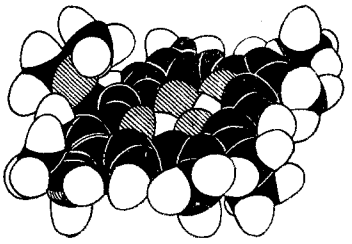

Fig. 7. Eugon model of the meso-formyletioporphyrin N-methylimine methiodide molecule.

Replacement of the dimethylaminomethyl group in the meso position of porphyrins by a $-CH=N-CH_3$ group gives rise to a number of specific pecularities in the PMR spectra that are associated with sp^2 hybridization of the nitrogen atom. Thus, the signal of the azomethine proton is found at very weak field below 10 ppm.

The dependence of the chemical shifts of the CH=N— and $=N-CH_3$ protons, as well as the meso and β-CH_3 protons, on the trifluoroacetic acid concentration in chloroform for meso-formyletioporphyrin N-methylimine (IV) is shown in Fig. 5. The signal of the proton of the CH=N group is shifted 2-Hz to strong field when the acid is added, after which it undergoes a 30-Hz shift to weak field. The chemical shift is virtually constant when acid:porphyrin $\geqslant 3$ (Fig. 5, curve a'). The change in the position of the signal of the $=N-CH_3$ protons takes place in precisely the same way: One observes an initial 1-Hz shift to strong field followed by a 30-Hz shift to weak field, while when $c_{AH}/c_P \geqslant 4$, the chemical shift is virtually constant (Fig. 5, curve a). The character of the change in the position of the signals of the meso and β-CH_3 protons (Fig. 5, curves c and b) is similar to the behavior of the protons of the corresponding groups in meso-dimethylaminomethyletioporphyrin.

To ascertain the order of the protonation of the nitrogen atoms in IV we studied the PMR spectra of the nickel complex of meso-formyletioporphyrin N-methylimine (V), in which there is only one proton-acceptor nitrogen atom in the side chain. The protonation curves of V are presented in Fig. 6. It follows from them that protonation is complete when $c_{AH}/c_P \simeq 1$, since the CH=N and $=N-CH_3$ chemical shifts are subsequently almost constant. The observed splitting of the CH=N signal when $c_{AH}/c_P > 1$ will be discussed below.

Since the shift to strong field when acid is added to a solution of IV is very small, it may be assumed that in the case of IV protonation takes place virtually simultaneously at all possible centers and is basically complete when $c_{AH}/c_P \geqslant 3$, and one can speak of a triply charged cation of porphyrin IV, viz., $P^{3+}H_3$. The mechanism of the protonation of IV is evidently similar to the mechanism observed for aminoporphyrins, the only difference being that the spatial effects of the magnetic anisotropy and the electrical field of the trifluoroacetate group in the resulting H complex are identical for the C=N— and $=N-CH_3$ groups. This explains the characteristic form of the curves of the dependences of the chemical shifts of the protons of these groups.

To clear up the problem of the type of complex formed when $c_{AH}/c_P = 1$ we investigated the IR spectra of IV in solution in $CDCl_3$ with trifluoroacetic acid in the region of the stretching vibrations of the carbonyl group of the acid. A band at 1670 cm^{-1}, which is characteristic for trifluoroacetate ions, is observed in the spectrum at an equimolar porphyrin:acid ratio. This constitutes evidence for a significant shift of a equilibrium (2) to the right [6].

An additional singlet line at 3 ppm, the intensity of which increases while the position shifts slightly to strong field as the amount of acid is increased, appears in the PMR spectrum when acid is added to a solution of IV in $CDCl_3$. When $c_{AH}/c_P > 8$, the intensity of this line becomes comparable to the intensity of the signal of the $=NCH_3$ group at 4.23 ppm. Let us note that a significant amount of acid in the solution leads to partial decomposition of IV to meso-formyletioporphyrin (the appearance of a signal at δ 12.47 from the meso-formyl group). A similar picture is observed for Ni complex V. An additional line appears at 2.09 ppm, and when $c_{AH}/c_P \geqslant 1.5$, the overall intensity of this line and of the $=N-CH_3$ signal is 3H. A small degree of splitting of the signal of the CH=N proton is simultaneously observed. Decomposition of Ni complex V is observed when $c_{AH}/c_P \sim 2$.

A study of the PMR spectra of various salts of IV (Table 1) shows doubling of the signals from the $=\overset{+}{N}RR'$ group in all cases with a significant difference (1-2 ppm) in the chemical shifts. An examination of three-dimensional models of the Eugon type makes it possible to conclude that there are two possible orientations of the R and R' groups relative to the plane of the porphyrin ring (Fig. 7). Two signals are therefore observed in the spectra of "symmetrical" salts where R = R' because of different orientations of the R and R' groups, whereas two signals from each of the substituents R and R' are observed in the spectra of "unsymmetrical" salts ($R \neq R'$) because of the presence of two isomers with different spatial orientations of the substituents. Thus, for example, salt VII gives a PMR spectrum with two signals of the $=N^{+}H-CH_3$ group at 2.96 and 4.15 ppm with equal intensities of 1.5H, whereas doubled signals from the CH_3 and CH_2CH_3 groups are observed in the PMR spectrum of salt X.

The existence of two isomers for the salt of Ni complex V also leads to splitting of the signal of the azomethine proton.

Replacement of the β-methyl groups by β-ethyl groups, i.e., the transition from substituted etioporphyrins to substituted octaethylporphyrins, does not affect the three-dimensional structures of the corresponding salts (Table 1).

The reversibility of the protonation is confirmed by the isolation of the starting compounds by neutralization.

EXPERIMENTAL

The PMR spectra of solutions of the investigated systems with a porphyrin concentration of 0.04 mole/liter and various acid concentrations were obtained with an HA-100D spectrometer and hexamethyldisiloxane as the internal standard. The IR spectra of solutions of the compounds were recorded with a UR-20 spectrometer. Dilution of the porphyrin solutions to $CDCl_3$ < 0.04 mole/liter did not lead to a change in the chemical shifts of the porphyrin protons, in contrast to what was observed for meso-unsubstituted etio- and octaethylporphyrins [8].

The synthesis of dimethylaminomethyletioporphyrin was described in [9], and the synthesis of dimethylaminomethyloctaethylporphyrin was described in [1].

Nickel Complex of meso-Dimethylaminomethyletioporphyrin (III). A mixture of 550 mg of the nickel complex of etioporphyrin and the complex obtained from 3 ml of $POCl_3$ and 2.6 ml of dimethylformamide (DMF) was heated in 200 ml of dry dichloroethane for 20 min, after which the solvent was evaporated in vacuo, and 0.5 liter of cold water was added to the residue. The precipitate was removed by filtration, dried in air, and dissolved in 150 ml of hot ethanol, and a 0.5-g sample of sodium borohydride was added in several portions. After 1 h, 200 ml of water was added gradually to the solution, and the precipitate was removed by filtration, dried, and dissolved in a small amount of chloroform. The chloroform solution was chromatographed with a column filled with silica gel to give, after crystallization from chloroform–ethanol, 420 mg (70%) of nickel complex III. Electronic spectrum in dichloroethane, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 411 (150.7), 539 (9.0), and 579 (13.6); in dichloroethane + 1% CF_3COOH: 411 (144.0), 542 (7.9), and 585 (14.0); in dichloroethane + excess CF_3COOH: 410 (113.8), 552 (6.4), and 591 (12.3). Found %: C 70.7; H 7.4; N 11.8. $C_{35}H_{43}N_5Ni$. Calculated %: C 71.0; H 7.3; N 11.8.

meso-Formyletioporphyrin N-Methylimine (IV). This compound was obtained by the method in [10]. Its nickel complex was prepared in quantitative yield by reaction with nickel acetate in acetic acid. Electronic spectrum in chloroform, λ_{max} ($\varepsilon \cdot 10^{-3}$): 525 (14.1), 562 (17.4), and 405 nm (37.3).

meso-Formyletioporphyrin N-Methylimine Hydrochloride (VII, Table 1). This compound precipitated in quantitative yield when dry HCl was added to a solution of the porphyrin in CCl_4 that did not contain traces of moisture and alcohols.

meso-Formyloctaethylporphyrin N-Methylimine Methiodide (IX, Table 1). A 773-mg sample of meso-formyloctaethylporphyrin imine was refluxed in 20 ml of methyl iodide for 3 h, after which an equal volume of hexane was added to the mixture, and the resulting precipitate was removed by filtration. Recrystallization from benzene–hexane gave 580 mg (60%) of iodide IX. Electronic spectrum in chloroform, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 383 (75.5), 399-440 (67.8), 514 (6.1), 549 (5.2), 584 (6.6), 633 (6.4), and 660 (5.7); in chloroform + 1% CF_3COOH: 437 (148.8),

581 (6.6), and 659 (9.2). Found %: C 65.4; H 7.3; N 9.8. $C_{39}H_{52}IN_5$. Calculated %: C 65.3; H 7.3; N 9.8.

meso-Formyletioporphyrin N-Methylimine Methiodide (VIII, Table 1). This compound was similarly obtained in 75% yield.

meso-Formyletioporphyrin N-Ethylimine Methiodide (X, Table 1). A 60-mg sample of imine IV was refluxed in 20 ml of ethyl iodide for 1 h, and the resulting precipitate was removed by filtration and recrystallized from benzene–hexane to give 60 mg (77%) of X. Electronic spectrum in chloroform, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 642 (5.0), 540 (5.6), 550 (4.9), 517 (6.3), 442 (54.7), and 383 (80.0); in chloroform + 1% CF_3COOH: 645 (8.0), 585 (6.0), and 438 (129.2). Found %: N 10.0. $C_{36}H_{46}IN_5$. Calculated %: N 10.4.

meso-Formyletioporphyrin N-Ethylimine Methiodide (XI, Table 1). A solution of 100 mg of meso-formyletioporphyrin N-ethylimine in 25 ml of ethyl iodide was refluxed for 2 h, and the resulting precipitate was removed by filtration and recrystallized from xylene–hexane to give 106 mg (82%) of salt XI. Electronic spectrum in chloroform, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 641 (4.8), 588 (5.7), 550 (5.0), 516 (6.2), 440 (58.7), and 383 (77.9); in chloroform + 1% CF_3COOH: 642 (8.2), 583 (6.3), and 437 (132.1). Found %: C 64.0; H 7.0; N 10.1. $C_{37}H_{48}IN_5$. Calculated %: C 64.4; H 7.0; N 10.2.

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