Chemistry of Heterocyclic Compounds, Vol. 33, No. 10, 1997

SYNTHESIS AND PROPERTIES OF DIMETHYLAMINO-METHYLPORPHYRINS. A REVIEW

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The chemistry of β- and meso-dimethylaminomethylporphyrins is reviewed. These compounds are synthesized by the reduction of intermediate immonium salts or "phosphate complexes" obtained in the Vilsmeier reaction. Special attention was given to the formation of porphyrin carbocations and porphyrin dimers covalently bound through an ethane or ethylene bridge.

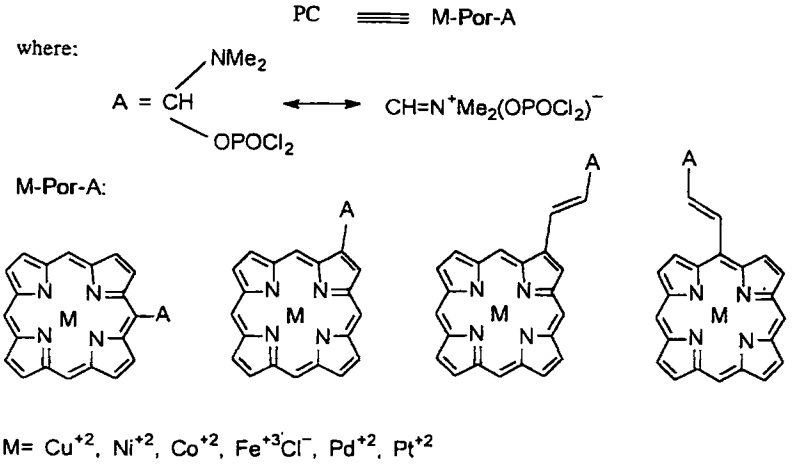
INTRODUCTION

In this review, we analyze use of the Vilsmeier reaction in porphyrin chemistry.* Intermediate imino salts termed "phosphate complexes" (PC) are formed during the Vilsmeier reaction using the Vilsmeier complex (the DMF/$POCl_3$ complex is generally used for introducing a formyl group or the complex of N,N-dimethylaminoacrolein (DMA) and $POCl_3$ is generally used for introducing a *trans*-formylvinyl group) in metal complexes of porphyrins. While aspects of the chemistry of formylporphyrins formed by mild alkaline hydrolysis of PC were examined in our first review and the chemistry of the Schiff bases of meso- and β-formylporphyrins obtained from PC upon the treatment of the latter with primary amines or ammonia was examined in our second review, the synthesis, physicochemical, and chemical properties of meso- and β-dimethylaminomethyl(DMAM)porphyrins as well as meso-DMAM-vinylporphyrins obtained upon the reduction of PC or the corresponding imino salts using $NaBH_4$ are surveyed in the present review.

These compounds hold interest as biologically active agents and are promising as intermediates for various chemical transformations. Thus, the Vilsmeier reaction may be used for the initial functionalization of porphyrins in three major approaches: 1) for the synthesis of formylporphyrins, 2) for the synthesis of the corresponding Schiff bases, and 3) for the synthesis of aminomethylporphyrins, which, in turn, can be used for various chemical transformations.

In general, the use of PC in porphyrin chemistry may be given by Scheme 1:

Scheme 1



*Previous communications, see refs. [1, 2].

Institute of Biomedical Chemistry, Russian Academy of Medical Sciences, 119832. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1299-1344, October, 1997. Original article submitted February 17, 1997.

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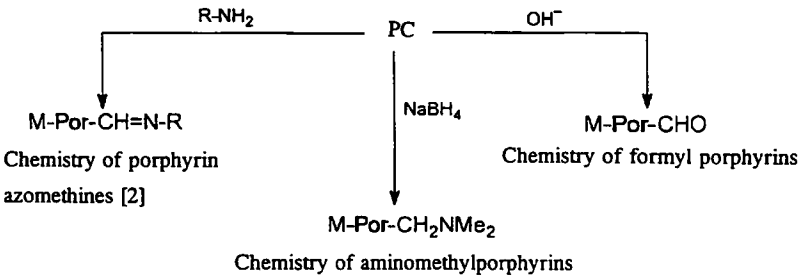


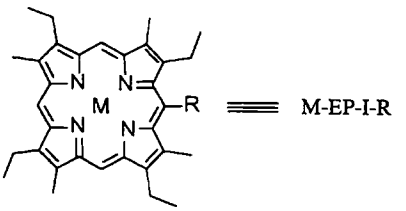
1. SYNTHESIS OF MESO- AND β-DIMETHYLAMINOMETHYLPORPHYRINS

1.1. Synthesis of Meso-DMAM-Porphyrins and Their Borane Complexes

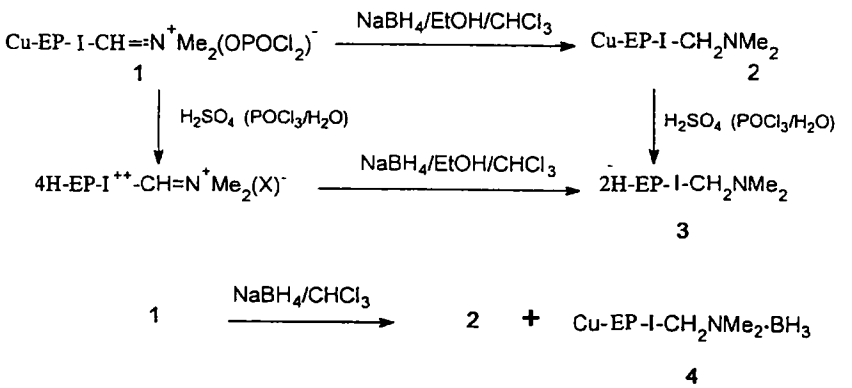
Meso-DMAM-porphyrins were first synthesized in 1973 [3], when we discovered that, in the reduction of PC **1** obtained by the formylation of the copper complex of etioporphyrin-I using sodium borohydride in a solution of chloroform and ethanol (or methanol) at room temperature, this reagent is converted after only several seconds into the corresponding copper complex **2**. Demetallation of complex **2** by sulfuric acid or $POCl_3$ previously treated with a small amount of water according to our procedure [4] leads to DMAM-porphyrin **3** in 80-90% yield. The same porphyrin can also be obtained by the careful demetallation of PC **1** under analogous conditions to the corresponding intermediate imino salt with subsequent treatment by $NaBH_4$ in chloroform–ethanol to give porphyrin **3**.

However, if the reduction of PC **1** is carried out in chloroform, a new product, aminoborane **4** is obtained in 5-15% yield, which demonstrates low polarity upon chromatography on silica gel [5]. Although the demetallation of **4** also leads to DMAM-porphyrin **3**, this reaction proceeds with relatively low yield since it occurs along with the formation of a significant amount of side-products. The generation of aminoborane complexes may also account for the formation of a certain amount of diborane in chloroform solution upon the reaction of $NaBH_4$ with the acid anion $(OPOCl_2)^-$ in the presence of traces of moisture.

Scheme 2



M-EP-I-R



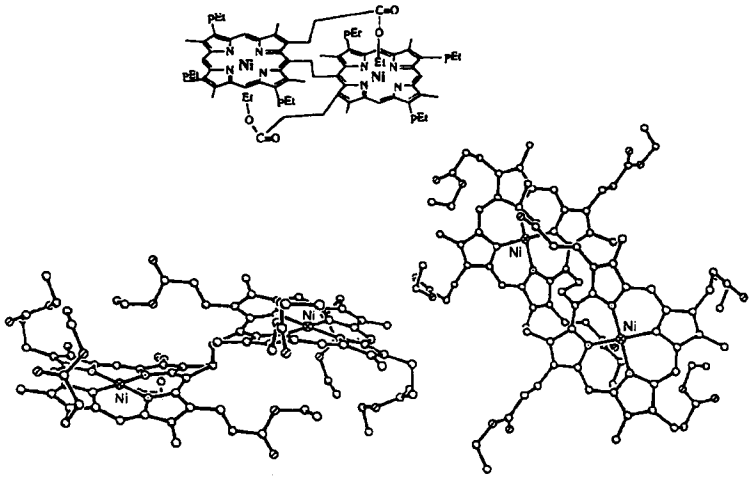


Fig. 1. Molecular structure of dimer **138** (two representations at a different angle relative to the bridging bond).

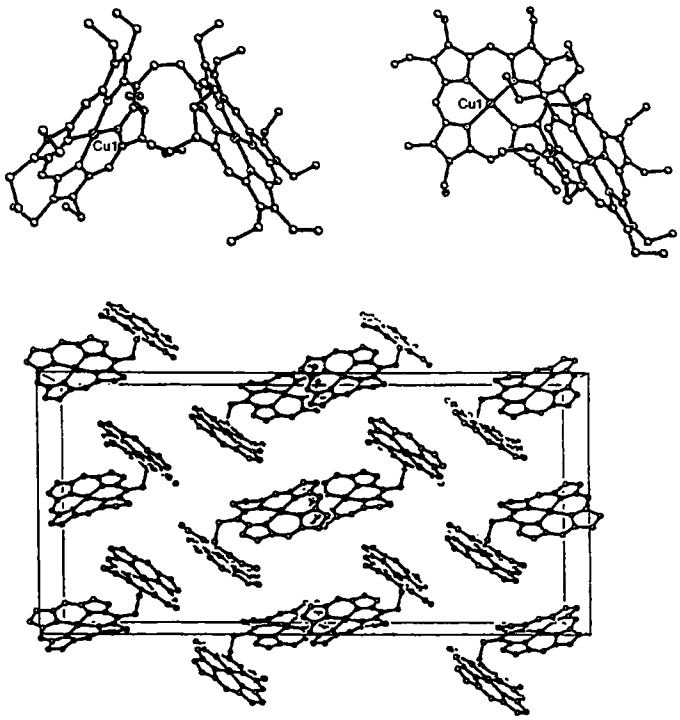
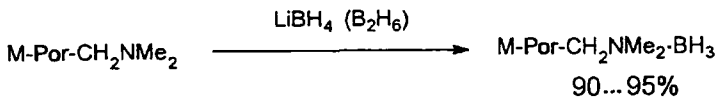


Fig. 2. Molecular and crystal structure of dimer **140** (two representations at different angles relative to the bridging bond).

Indeed, the formation of aminoboranes is one of the most important chemical properties of all meso-DMAM-porphyrins. These products are obtained readily in high yield upon the treatment of DMAM-porphyrins with $LiBH_4$ or diborane [5]. As shall be shown below, these compounds can be used to establish the structure of porphyrins using PMR spectroscopy and in the synthesis of meso-methylporphyrins.

GENERAL METHOD FOR THE PREPARATION OF PORPHYRIN AMINOBORANES

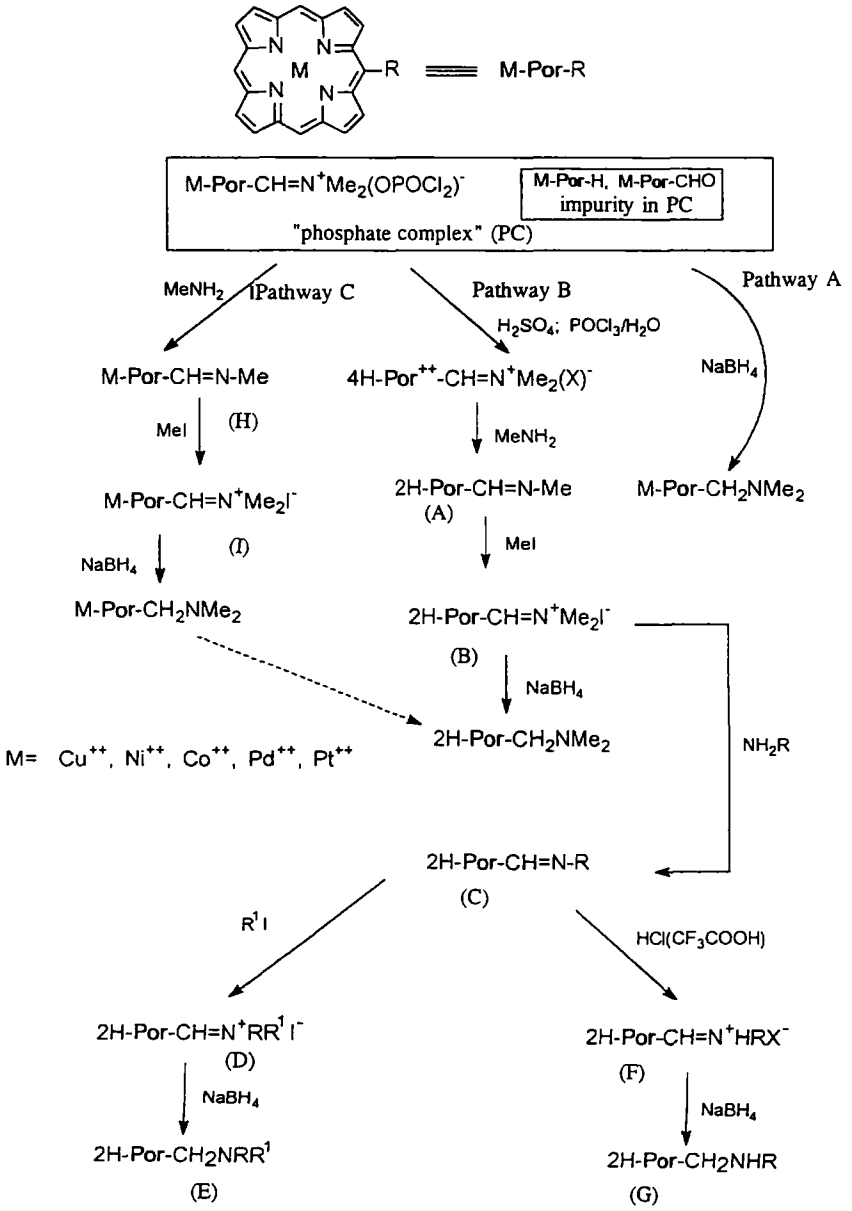


$LiBH_4$ in THF or bubbling B_2H_6 into a chloroform solution of porphyrin

However, the partial formation of aminoboranes as impurities in the direct synthesis of DMAM-porphyrins is an undesired reaction since it reduces the yield of these derivatives.

On the basis of extensive experimental work, we propose the following optimal variants for the synthesis of DMAM-porphyrins, which are summarized in Scheme 3:

Scheme 3
General Scheme for the Synthesis of DMAM-Porphyrin



Notes on Scheme 3:

1. **Pathway A.** Since PC are "crude" products, i.e., obtained directly from the reaction mixture, they always contain some impurities, mainly the starting metal complex and formylporphyrin complex. Thus, the direct reduction of PC to M-Por-CH_2NMe_2 using $NaBH_4$ may have practical significance only in the case of copper, nickel, or cobalt complexes of relatively simple porphyrins such as etioporphyrin (EP), octaethylporphyrin (OEP), coproporphyrin (CP), or tetraphenylporphyrin (TPP). In other cases, when PC cannot be isolated in relatively pure crystalline form, the following two alternative pathways may be preferred.

2. **Pathway B** involves the demetallation of PC with subsequent treatment of the intermediate imino salt without its isolation by aqueous methylamine over only 1-5 min to give the corresponding Schiff base (A), which is then converted by brief heating in a solution of MeI to give the crystalline iodomethylate 2H-Por-$CN{=}N^+Me_2I^-$ (B). (More details concerning the properties of imino salts are given in our previous review, [2]). Iodomethylate (B) may be used conveniently as the starting intermediate for the synthesis of DMAM-porphyrins, new Schiff bases (C), new immonium salts (D), and, consequently, aminomethylporphyrins (E) with various substituents at the amine nitrogen atom.

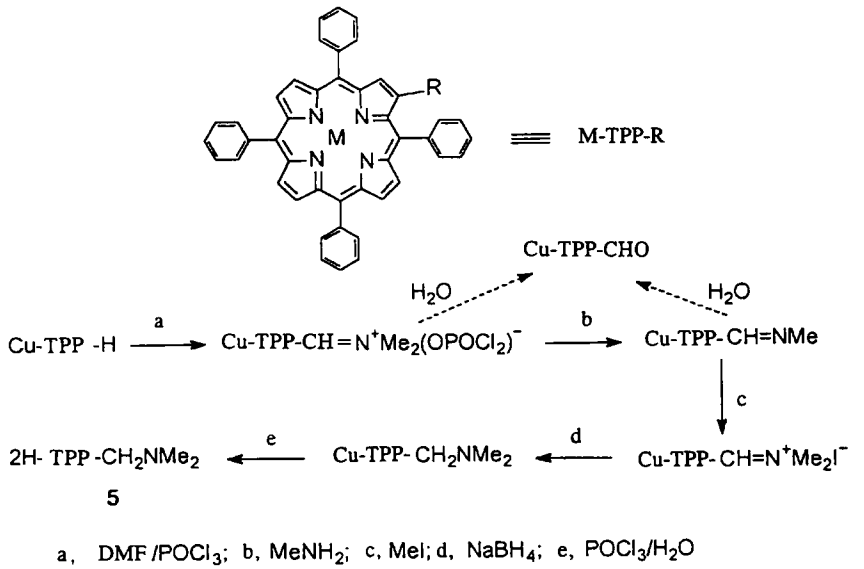
The reduction of Schiff bases (C) using $NaBH_4$ to obtain alkylaminomethylporphyrins, in contrast to PC and other imino salts, proceeds extremely slowly in neutral media and with very low yield. However, if the Schiff base is first treated with a solution in CF_3CO_2H or dry HCl in chloroform and the solvent is then removed to dryness, i.e., Schiff bases (C) are converted to the corresponding imino salts (F) and then dissolved in a suitable solvent, the reduction proceeds as rapidly as for any iodoalkylates to give 2H-Por-CH_2NHR (G).

3. **Pathway C** is convenient for the synthesis of metal complexes of DMAM-porphyrins when the PC formed are unstable and readily hydrolyze upon isolation to give the metal complexes of formylporphyrins as in the case of derivatives of TPP or octaethylchlorine (OEC). Extensive experimental data indicate that the reaction of PC with aqueous methylamine to give Schiff base (H) proceeds much more rapidly than the hydrolysis of PC under the same conditions to give formylporphyrins. Furthermore, Schiff bases and then the corresponding iodomethylate (I) are readily obtained immediately after carrying out the Vilsmeier reaction in the preparation of Pt and Pd complexes of DMAM-porphyrins since the mixture contains significant amounts of both the starting complexes and side-products due to the low reactivity of the Pt and Pd complexes of octaalkylporphyrins and the long duration of heating with the Vilsmeier complex.

1.2. Synthesis of β-DMAM-Porphyrins

The most representative synthesis of DMAM-porphyrins through pathway C is the synthesis of 2-DMAM-TPP **5** given in Scheme 4 [6, 7]:

Scheme 4



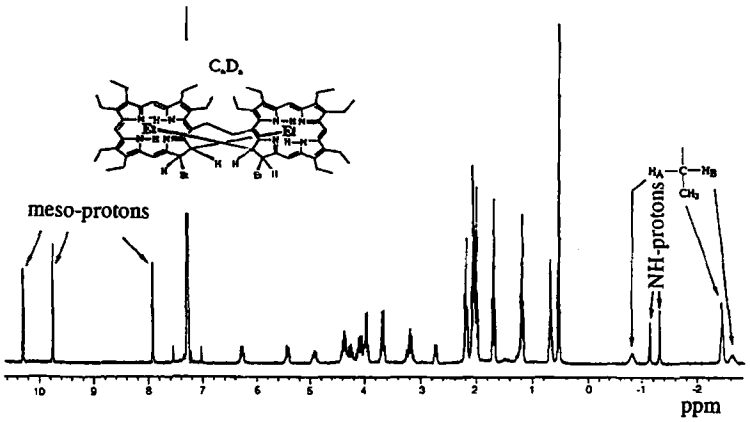


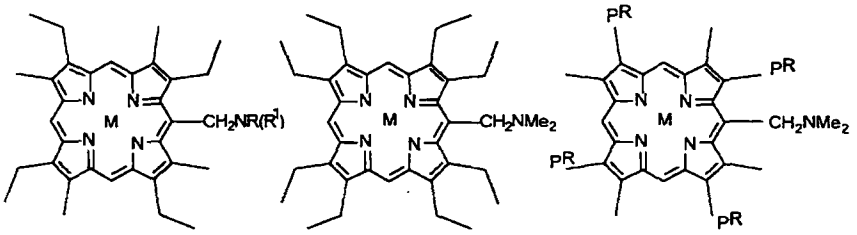
Fig. 3. PMR spectrum of dimer **141** in C_6D_6.

The direct synthesis of porphyrin **5** by demetallation of the corresponding PC with subsequent reduction of the imino salt is impossible since formylporphyrin forms immediately upon the addition of sodium borohydride to the solution of the imino salt; formylporphyrin then is readily reduced to 2-hydroxymethyl-TPP. The formation of a Schiff base from PC upon the addition of aqueous methylamine proceeds much faster than the hydrolysis of PC to Cu-TPP-CHO, while treatment of the Schiff base with MeI permits us to separate the iodomethylate from the impurity of formylporphyrin impurity.

1.3. Examples of Meso-DMAM-Porphyrins Synthesized

Examples of various meso-aminomethylporphyrins and their complexes obtained from relatively simple symmetric octaalkylporphyrins derived from EP-I (**6-22**) [3-5, 8, 9], OEP (**23-25**) [8], and ethers of CP-I (**26-31**) [10]:

Scheme 5



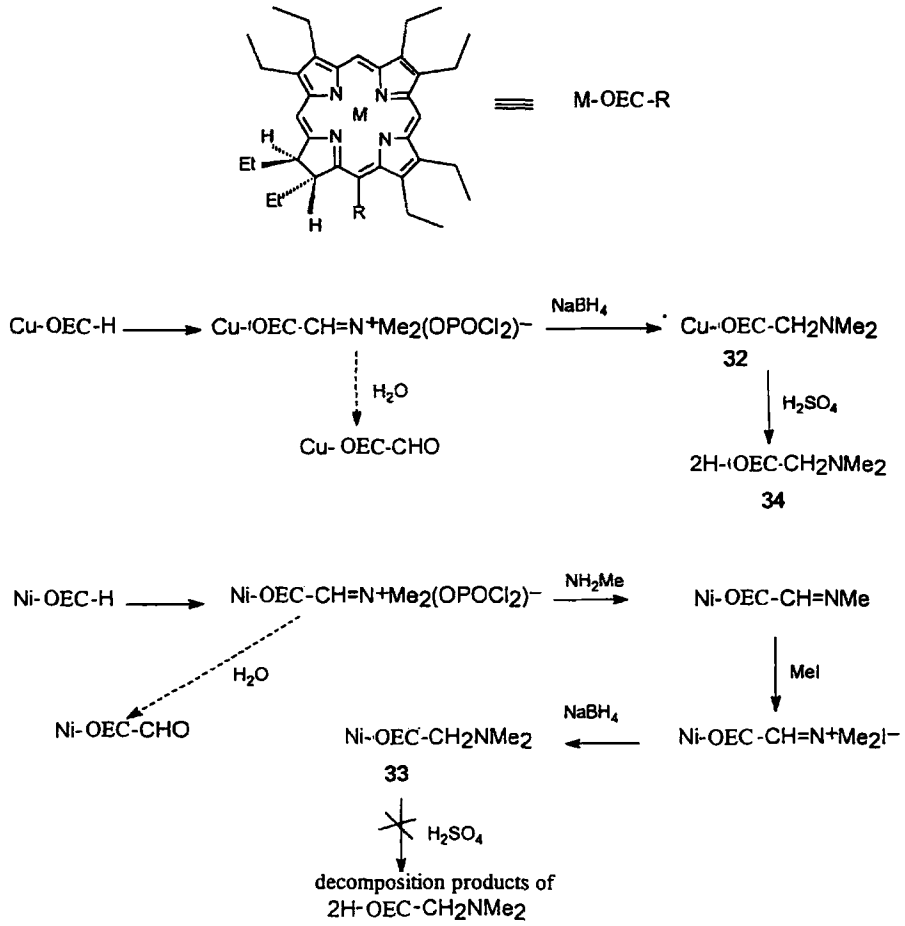
6 R = R^1 = H; 7 R = H, R^1 = Me; 8 R = H, R^1 = $(CH_2)_{11}Me$; 9 R = H, R^1 = CH_2(adamantyl-1);
10 R = H, R^1 = CH_2COOEt; 11 R = H, R^1 = CH_2CH_2COOMe; 12 R = H, R^1 = $CH_2C_6H_4COOEt$ (*p*);
13 R = H, R^1 = $(CH_2)_5COOMe$; 14 R = Me, R^1 = Et; 15 R = R^1 = Et; 16 R = R^1 = Pr; 17 R = R^1 = Bu;
18 R = Me, R^1 = CH_2CH_2OH; 19 R = Ac, R^1 = Me; 20 R = COPh, R^1 = Me; 21 R = R^1 = Me;
22 R = R^1 = Me, M = Co(II); 26 R = Et; 27 R = Et; 28 R = Et; 29 R = Me; 30 R = Me; 31 R = *i*-Pr;
6—20, 25, 28, 30 M = 2H; 21, 24, 27, 29, 31 M = Ni(II); 23, 26 M = Cu(II);
26—31 P^R = CH_2CH_2COOR

The Vilsmeier reaction was carried out in all the cases indicated above such that only a single meso-substitution product was obtained. This problem was simplified by the circumstance that there are equivalent meso positions in porphyrins **6-31**.

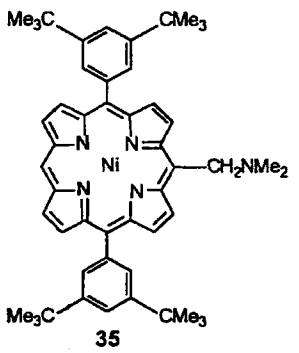
The electrophilic attack by the Vilsmeier complex in the formylation of metal complexes of octaethylchlorine (OEC) proceeds initially to the meso positions adjacent to the hydrogenated pyrrole ring and there is hardly any formation of additional isomeric substitution products.

The reaction requires only a few minutes at room temperature both for the copper and nickel complex of OEC. However, the synthesis of the corresponding DMAM derivatives **32** and **33** is a difficult problem in light of the tendency of these PC to undergo hydrolysis to the corresponding formylchlorines, especially in the formylation of Ni-OEC (shown in Scheme 6 by dashed arrows). Nevertheless, the synthesis of such compounds according to the scheme given below was accomplished and DMAM-octaethylchlorine was obtained from complex **32** by demetallation in sulfuric acid [11, 12]. The synthesis of chlorine **34** had been unsuccessfully attempted previously by Smith et al. [13].

Scheme 6



DMAM-porphyrins may also be readily obtained from meso,meso-disubstituted porphyrins by an analogous scheme. Thus, for example, our colleague D. V. Yashunskii obtained complex **35** in high yield from the corresponding nickel complex of the porphyrin kindly provided by Dr. D. P. Arnold (Q.U.T., Brisbane, Australia).



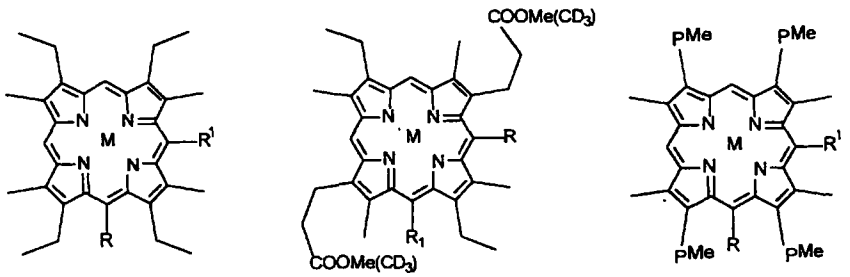
35

When two isomeric products are formed as the result of the Vilsmeier reaction, the synthesis of DMAM derivatives permits the relatively facile and rapid separation of each of the derivatives in pure form by chromatography on silica gel.

Examples are given below for DMAM-porphyrins obtained starting from type-II porphyrin isomers, namely, etioporphyrin-II (EP-II) (**36a-39a**), mesoporphyrin-II (MP-II) (**40a-43a**), and CP-II (**44a-47a**) [14, 15]. For all these compounds, the isomers containing the DMAM group at position R had higher chromatographic mobility on silica gel with chloroform–acetone as the eluent than the corresponding isomers with the DMAM group at position R^1.

The corresponding aminoborane derivatives **36b-47a** were obtained upon the treatment of DMAM-porphyrins **36b-47b** with diborane in chloroform solution.

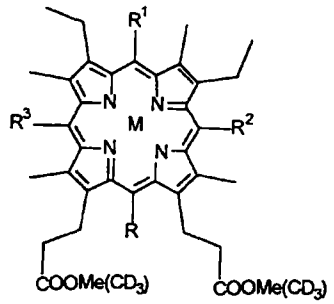
Scheme 7



36a, b - 39a, b **40a, b - 43a, b** **44a, b - 47a, b**

36a, 40a, 44a R = A, M = Ni; **37a, 41a, 45a** R = A, M = 2H; **38a, 42a, 46a** R^1 = A, M = Ni; **39a, 43a, 47a** R = A, M = 2H. In all cases, for **36b-47b**, R or R^1 = B, A = CH_2NMe_2; B = $CH_2NMe_2 \cdot BH_3$; P^{Me} = $CH_2CH_2CO_2Me$. CD_3 esters were obtained for the PMR spectral study since the signals for the ring and ester methyl groups are found in the same spectral region.

The tendency of isomeric DMAM-porphyrins and their metal complexes to differ in chromatographic mobility depending on the shielding effect of the adjacent β-alkyl substituents was used in our work on the formylation of natural asymmetrically substituted porphyrins. Thus, isomeric DMAM-porphyrins were obtained in the formylation of the dimethyl ester of mesoporphyrin-IX after reduction of the intermediate PC and then separated into pure isomers **48a-55a**, whose structure was established by comparison of the PMR spectra of both the free amines and their borane complexes **48b-55b**. The chromatographic mobility of these compounds depends on the site of the DMAM group and falls in the series $R > R^1 > R^2 > R^3$ [14, 16].



48a, b - 55a, b

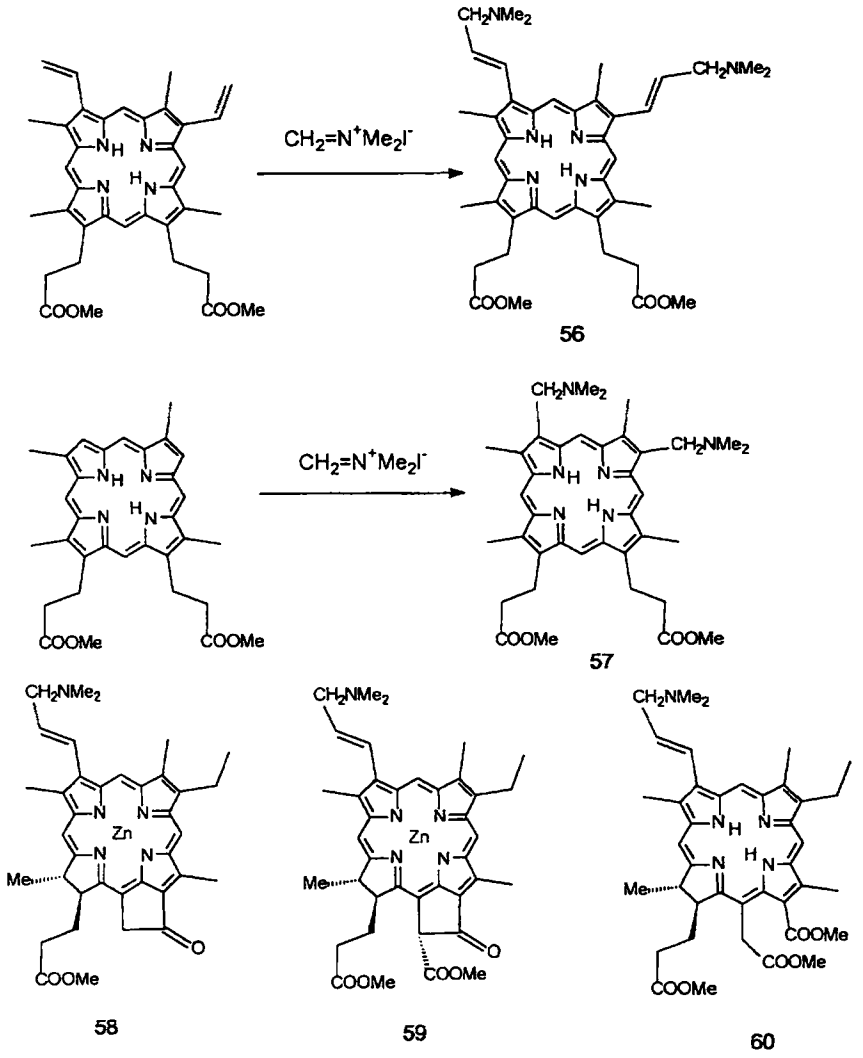
48a R = A, M = Ni; **49a** R^1 = A, M = Ni; **50a** R^2 = A, M = Ni; **51a** R^3 = A, M = Ni; **52a** R = A, M = 2H; **53a** R^1 = A, M = 2H; **54a** R^2 = A, M = 2H; **55a** R^3 = A, M = 2H; **48b-55b** — are the corresponding borane complexes of porphyrins **48a-55a** (instead of A, B)

1.4. Synthesis of DMAM-Porphyrins Using Eschenmoser Salts

A few communications have recently appeared on the use of an alternative method for introducing the DMAM group into the porphyrin macrocycle. Smith et al. [13, 17] have shown that dimethylmethylenammonium iodide (the Eschenmoser

salt) [18] may be used to introduce the DMAM group into porphyrin and chlorine molecules not only at β-unsubstituted positions of the porphyrin macrocycle or at vinyl peripheral substituents to give a *trans*-formylvinyl group. Examples of products **56-60** are given below. It is interesting that this reaction never proceeds at the meso positions not only of porphyrins but even at the hyperactive chlorine meso positions adjacent to a reduced pyrrole ring.

Scheme 8



2. PHYSICOCHEMICAL PROPERTIES OF DMAM-PORPHYRINS AND THEIR BORANE COMPLEXES

2.1. Chromatographic Properties

In the previous section, we indicated that the introduction of a DMAM group permits the facile separation of isomeric DMAM-porphyrins by chromatography on silica gel [14-16].

The chromatographic mobility of DMAM-porphyrins on silica gel depends significantly on the steric parameters of the adjacent β-pyrrole substituents. The interaction of the DMAM group with the acid surface of silica gel is enhanced and the mobility of the corresponding product is diminished with decreasing bulk of the adjacent substituents (analogous behavior was also noted for the Schiff bases of meso-formylporphyrins [2]).

We have found that the chromatographic mobility of DMAM-porphyrins on silica gel increases depending on the adjacent pyrrole substituents in the series:

$$Me, Me < Me, Et < Et, Et < Pr, Pr < Me, P^{Me} < Me, P^{Et} < P^{Me}, P^{Me} < P^{Et}, P^{Et}$$

$$P^{Me} = CH_2CH_2COOMe; P^{Et} = CH_2CH_2COOEt$$

Of course, this behavior has significance only when comparing isomeric compounds.

The formation of aminoborane complexes prevents interaction of the amine nitrogen atom with the acid surface of the adsorbent, which leads to a marked increase in mobility and levelling out of the differences in chromatographic properties.

Thus, the introduction of a DMAM group into meso positions of porphyrin macrocycles permits the separation of compounds with very similar chemical composition such as positional isomers into pure compounds, which may have great practical importance.

2.2. Electronic, IR, PMR, and Mass Spectra of DMAM-Porphyrins and Their Borane Complexes

The presence of a DMAM group in compounds is readily and reliably detected using the IR spectra obtained for KBr pellets or for solutions in CCl_4 relative to the bands at 2760 and 2810 cm^{-1} due to stretching vibrations of the C–H bonds in the dimethylamino group [19]. The existence of aminoborane groups is most clearly and unequivocally determined by finding strong bands at 2268, 2312, and 2363 cm^{-1} (for solutions in CCl_4) characteristic for the stretching vibrations of the B–H bonds in trialkylaminoboranes [20].

The many DMAM-porphyrins and their metal complexes studied display several common features in their electronic spectra. Thus, introduction of the DMAM group into the meso position of the porphyrin ring leads to:

1. A bathochromic shift of 7-10 nm of all the bands in the visible spectrum, including the Soret band, for the porphyrin free bases. The intensity of the I-band is reduced by a factor of about 1.5-2 and the general form of the spectrum, i.e., the I:II:III:IV band ratio, becomes characteristic for meso-monoalkyloctaalkylporphyrins.

2. The bathochromic shift for copper and nickel complexes of DMAM-porphyrins is 7-10 nm for the Soret band and 15-18 nm for the α- and β-bands. The α/β band intensity ratio for the metal complexes of DMAM-porphyrins is always less than the α/β ratio of meso-unsubstituted metal complexes. Furthermore, the intensity of the Soret band and, especially, the α-band for the DMAM derivatives is reduced by a factor of about 1.5-2 relative to the corresponding unsubstituted metal complex.

3. The formation of aminoborane complexes leads to a marked bathochromic shift and redistribution of the intensities of the bands in the visible range both for the metal complexes and free bases of porphyrins, which naturally affects the color of the solutions. While the bathochromic shift for the Soret band is only 1-3 nm, the shift is 6-9 nm for the β-band and 12-13 nm for the α-band in the visible range, and the α/β band intensity ratio is always greater than this ratio for the starting DMAM-porphyrin metal complex.

4. In all cases, in comparing the spectra of isomeric DMAM-porphyrins and their metal complexes, the isomers most mobile on silica gel, i.e., having the DMAM group between the bulkier substituents, display a bathochromic shift of 2-4 nm relative to the more polar isomer. This trend is retained in the case of the corresponding aminoboranes. A bathochromic shift of 2-5 nm is found for isomers containing the DMAM·BH_3 group between the bulkier substituents relative to the less sterically hindered isomer.

Of course, a correct, unequivocal assignment of all the signals in the PMR spectra of DMAM-porphyrins may be achieved only by employing the nuclear Overhauser effect. However, simpler and more accessible PMR spectral methods may be used in many cases to establish the structure of DMAM-porphyrins, i.e., to determine the meso-substitution site in the Vilsmeier reaction. Analysis of the PMR spectra of DMAM-porphyrins, their nickel complexes, and the corresponding aminoboranes [7, 14-16] indicates the following general conclusions:

1. When the meso-DMAM or meso-DMAM·BH_3 group is found between identical substituents, all the DMAM methylene group protons appear as a narrow singlet at 5.05-5.15 ppm for the nickel complexes, 5.75-5.9 ppm for the free bases, 5.9-6.15 ppm for the aminoboranes of the nickel complexes, 6.45-6.65 ppm for the aminoboranes of the free porphyrin bases.

2. The presence of a DMAM group between two different substituents such as in derivatives of EP-I, CP-I, and MP-II leads to a marked broadening of the signal for the $\underline{CH_2}-NMe_2$ group, which appears in the corresponding aminoborane as an AB quartet with coupling constant of 14.5-15.5 Hz. Thus, the aminoboranes may be prepared to provide an unequivocal answer to the question of whether the β-pyrrole substituents adjacent to the DMAM group are identical.

3. Analysis of the spectra of isomers of meso-DMAM-MP-II (**40a-43a, 40b-43b**) indicates that

a) the introduction of the DMAM group hardly shifts the signal of the adjacent methyl group in comparison with the meso-unsubstituted porphyrin,

b) the greatest upfield shift is seen for protons of the methyl group also found in the adjacent pyrrole ring but through a single β-substituent,

c) the methylene groups in the ethyl and alkoxycarbonylelthyl substituents located in the porphyrin ring and adjacent to the meso substituent appear as an AB system coupled with a methyl or methylene group,

d) the formation of borane complexes leads to two upfield singlets due to the methyl protons of the $CH_2N\underline{Me_2}\cdot BH_3$ group.

4. Analysis of the PMR spectra of MP-IX derivatives (**48a-55a, 48b-55b**) indicates that, in addition to all the effects noted above, even when the meso substituent is found between two identical substituents (γ-meso position) and the methylene protons of the $\underline{CH_2}NMe_2\cdot BH_3$ group appear as a broadened singlet, the signals of the N-methyl protons appear as two narrow singlets. Thus, aminoborane formation may be used not only to characterize a specific meso position but also to determine whether the arrangement of the other β-substituents in the given porphyrin macrocycle is symmetrical.

5. Protonation seen when the spectra are taken for the samples in the presence of CF_3CO_2D at different concentrations leads to marked changes in the chemical shifts of both the meso and peripheral β-substituents [8], which may be used to interpret these spectra. We should take into account that the amine nitrogen atom is initially protonated followed by the nitrogen atoms of the porphyrin macrocycle.

The electron impact mass spectra of Schiff bases of meso-formylporphyrins were examined in detail in our previous review [2]. For such compounds, we find that a) the molecular ion tends to undergo intramolecular rearrangements and cyclization, and b) these molecules tend to undergo thermal decomposition in the ionization chamber of the mass spectrometer [21]. The thermal decomposition of meso-aminomethylporphyrins proceeds to even a greater extent than for other meso-substituted porphyrins. The intensity of the molecular ion peak for most of these compounds does not exceed a few percent, and special chemical modification is required for a correct interpretation of the spectra of aminomethylporphyrins [22].

The intensity of the molecular ion peak in the spectra of meso-aminomethylporphyrins decreases with increasing mass and complexity of the structure of the substituents at the nitrogen atom. In most cases, the strongest ion peak 490 for EP-I derivatives (546 for OEP derivatives) corresponds to elimination of the $NHRR^1$ amine from the meso-substituent with transfer of the hydrogen atom from the porphyrin system to the amine nitrogen.

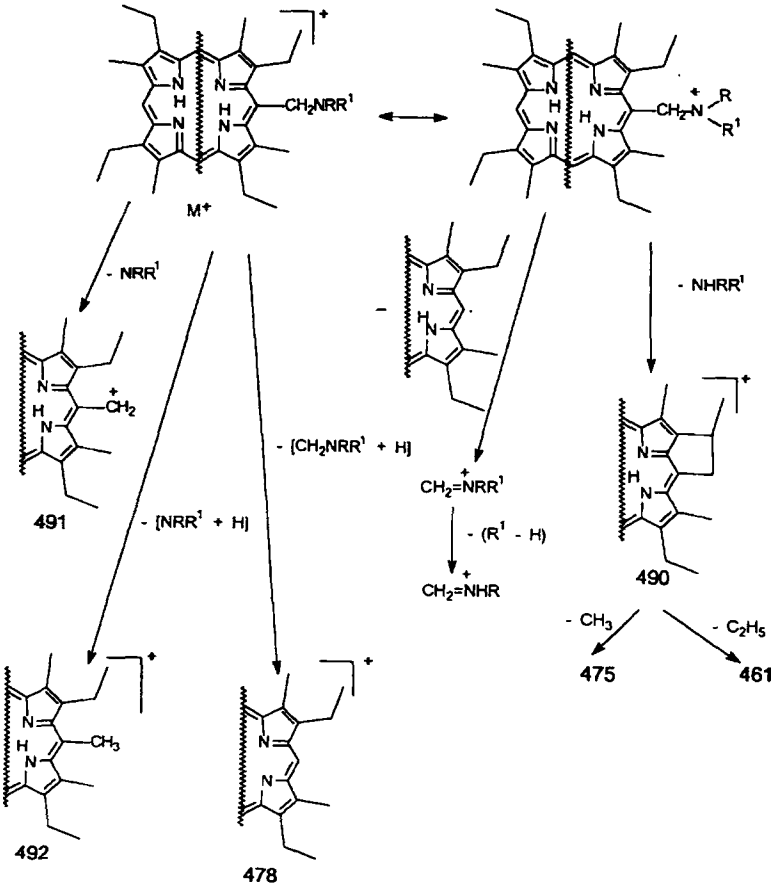
The finding of ions at 492 and 478 in the spectra of secondary and tertiary amines is attributed to thermal decomposition of the meso-substituted porphyrins to EP-I (M 478) and meso-methyl-EP-I (M 492) upon evaporation of the sample in the ionization chamber of the mass spectrometer. Similar behavior is observed for the other OEP, CP, and MP porphyrin derivatives synthesized. The possibility of such decomposition was demonstrated by chemical and mass spectral analysis of the products of the vacuum sublimation of the secondary and tertiary amine samples and their borane complexes. Furthermore, DADI analysis of mass spectra of the metastable ions of meso-aminomethylporphyrins shows that ions 492 and 478 (for EP derivatives) do not form from the molecular ions and are thus a consequence of thermolysis of the sample examined.

Strong peaks of the ions formed as a result of the loss of amine from the porphyrin ring can be seen in the low mass region. Fragmentation of the amine residue proceeds through the classical scheme [23], which permits us to use mass spectrometry for the reliable identification of the substituent at the nitrogen atom.

A general scheme for fragmentation of porphyrins containing a $-CH_2NRR^1$ group in the meso position is given below for the case of EP derivatives:

Scheme 9

Major fragmentation directions of meso-dimethylaminomethylporphyrins in electron impact mass spectrometry



This scheme shows that the major fragmentation process is related to loss of the $HNRR^1$ amine and formation of the molecular ion of a porphyrin with a cyclopentane ring. The correctness of the conclusion concerning a rearrangement is supported by the finding that sublimation of aminomethylporphyrins gives trace amounts of products, which correspond in their electronic spectra to porphyrins with a cyclopentane ring.

The acylation (acetylation or benzoylation) of secondary amines leads to a sharp increase in the intensity of the molecular ion peaks, which may be used to identify these compounds. Thus, derivatives **19** and **20** were obtained upon the acylation of porphyrin **7**. The intensity of the molecular ions in the spectra of **19** and **20** is maximal, and the most characteristic fragmentation pathway is loss of the acyl residue.

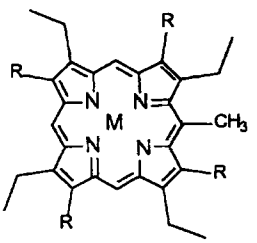
A mass spectral study of the borane complexes of DMAM-porphyrins showed that the use of rapid heating of the sample in the ionization chamber of the mass spectrometer permits us in most cases to obtain spectra containing molecular ion peaks. However, the major process occurring in the mass spectrometric analysis is thermolysis of the sample and generation of strong peaks for ions corresponding to molecular ion peaks of meso-methylporphyrins.

3. CHEMICAL PROPERTIES OF DMAM-PORPHYRINS

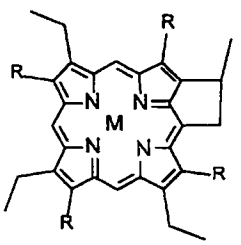
3.1. Thermolysis of Meso-DMAM-Porphyrins in Vacuum and High-Boiling Alcohols

3.1.1. Synthesis of Meso-Methylporphyrins

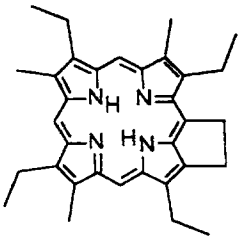
There have been several reports of the synthesis of meso-methylporphyrins and chlorines holding interest in the study of energy fixation in photosynthesizing bacteria [24-26]. All the methods for the synthesis of such compounds are rather complicated, and the starting intermediates are difficult to obtain.



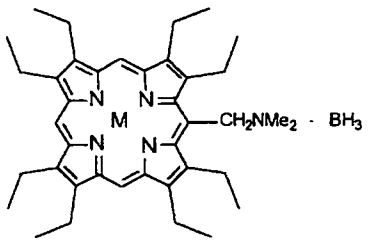
61, 64



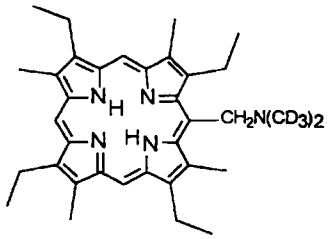
62, 65



63



66, 67



68

61, 62, 64, 65, 67 M = 2H; 61, 62 R = Me; 64, 65 R = Et; 66 M = Cu(II)

The last chapter indicated that ions $M^{+\cdot}$ $[M-CH_2NRR^1 + H]^+$ (a), $[M-NRR^1 + H]^+$ (b), $[M-NRR^1]^+$ (c), and $[M-NHRR^1]^+$ (d) are the most characteristic ions in the electron impact spectra of DMAM-porphyrins and other meso-aminomethylporphyrins [22].

DADI analysis of the mass spectra of the metastable ions showed that ions (a) and (b) are due to impurities and are not formed as a result of fragmentation of the molecular ion. These ions are most likely formed in the thermal decomposition of meso-aminomethylporphyrins to give a meso-unsubstituted porphyrin fragment (a) and meso-methylporphyrin fragment (b), respectively. Fragment (d), which gives rise to the strongest peak in the mass spectra of many aminomethylporphyrins, corresponds to a stable porphyrin containing a cyclopentane ring. Such a porphyrin can form not only from the molecular ion (see Scheme 9) but also upon thermal cyclization with loss of amine.

Meso-methylporphyrin **61** and a mixture of cyclopentaneporphyrins **62** and **63** are formed in thermolysis (250-280°C, vacuum 1.0-0.05 mm Hg, 5-10 min) of all EP-1 meso-aminomethylporphyrin derivatives, while **64** and **65** are formed from OEP.

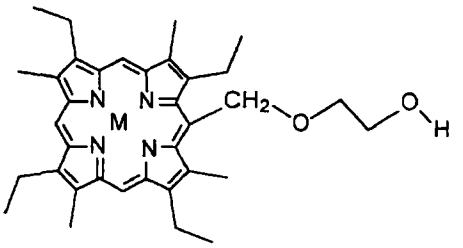
The thermolysis of aminomethylporphyrins probably proceeds through homolytic dissociation of the C−N bond and recombination of the meso-methyleneporphyrin free radical with one of the hydrogen atoms in the eliminated side-chain. Thus, the use of aminoboranes such as **66** or **67** for thermolysis markedly increases the yield of the corresponding meso-methylporphyrin up to 50-75% [27]. Mass spectrometric analysis of porphyrin **61** obtained in the sublimation of deuteroanalog **68** showed that the hydrogen atom required for recombination of the free radical is provided by residue $N(CD_3)_2$. The amount of cyclopentaneporphyrins in the thermolysis products is only 1-2%.

Thus, the major difference in the thermolytic decomposition of meso-aminomethylporphyrins from the decomposition of the radical−cations (molecular ions) involves mainly formation of meso-methylporphyrins and not porphyrins with a cyclopentane ring [22, 28-30].

3.1.2. Synthesis of Metal Complexes of Meso-Alkoxymethylporphyrins

Homolytic dissociation of the C−N bond in the DMAM group occurs upon heating metal complexes of meso-DMAM-porphyrins in solutions of high-boiling alcohols at ≥130-150°C accompanied by substitution of the dimethylamino group by an alkoxide group. For example, heating the copper and nickel complexes of meso-DMAM-EP-I in ethyleneglycol gives the corresponding ethers 69 and 70 in high yield [31]. On the other hand, heating the free bases of DMAM-porphy-

rins in high-boiling alcohols leads to a mixture of products and, thus, cannot be recommended for use in the synthesis of the corresponding meso-alkoxymethylporphyrins.



69, M=Cu; 70, M=Ni

3.2. Reaction of DMAM-Porphyrins with Nucleophiles in the Presence of Zinc Acetate

The first property encountered by chemists studying meso-DMAM-porphyrins is the mandatory appearance of the more mobile bright red spots upon their identification using thin-layer chromatography on silica gel on aluminum foil and solvents containing moisture or alcohols such as stabilized chloroform. In some cases, the silica gel used for column chromatography is absolutely unsuitable for the separation and purification of DMAM-porphyrins, since the quantitative conversion of DMAM-porphyrins into other more mobile compounds sometimes occurs upon chromatography in systems containing alcohols such as methanol or ethanol.

This analysis indicates that the mobile nonpolar compounds detected in thin-layer chromatography are zinc complexes of meso-ethoxy- or meso-methoxymethylporphyrins. Thus, the formation of zinc complexes of meso-DMAM-porphyrins leads to the loss of the dimethylamino group and its replacement by an ethoxyl or methoxyl group dependent on the elution system (chloroform–ethanol or chloroform–methanol). Thus, the isolation and purification of DMAM-porphyrins requires careful selection of the thin-layer chromatography plates and brand of silica gel for column chromatography, checking for the absence of trace amounts of zinc ions in the silica gel used for chromatography, and the replacement of methanol or ethanol by acetone to enhance the polarity of the chromatographic system. Good results are obtained upon prior conditioning of the plates with 5% aqueous EDTA. This procedure permits the complete elimination of zinc ions from the adsorbent surface and reproducible results upon chromatography of the samples. The formation of some amount of copper or nickel complexes of meso-ethoxy- or meso-methoxymethylporphyrins can also occur in the chromatography of copper or nickel complexes of meso-DMAM-porphyrins although to a lesser extent than in the chromatography of DMAM-porphyrin free bases when zinc ions are present in the silica gel.

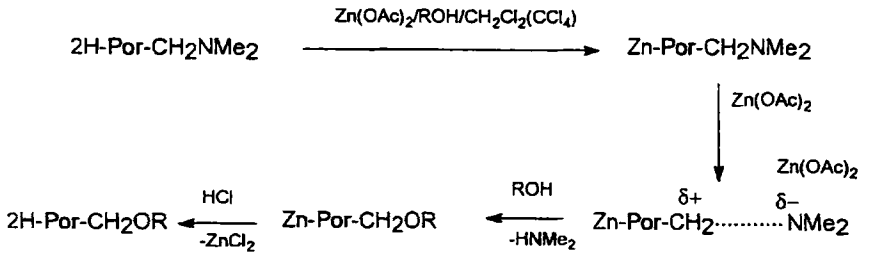
$$2H\text{-}Por\text{-}CH_2NMe_2 \xrightarrow[\text{silica gel + traces of } Zn^{+2}\ (\text{Silufol})]{CHCl_3/(MeOH \text{ or } EtOH)} Zn\text{-}Por\text{-}CH_2OMe(Et)$$

3.2.1. Reaction with Alcohols and Phenols to Give Ethers

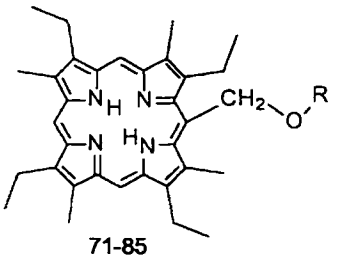
The capacity of meso-DMAM-porphyrins to undergo facile transformation to zinc complexes of meso-ethoxymethylporphyrins upon chromatography on silica gel was used in our laboratory to develop a general method for the synthesis of meso-alkoxy- and meso-aryloxymethylporphyrins involving heating of meso-DMAM-porphyrin and the corresponding alcohol in a solution of methylene chloride or carbon tetrachloride in the presence of excess zinc acetate. The reaction proceeds as follows. A zinc complex of the DMAM-porphyrin is formed initially (1-2 min), which is clearly

seen by chromatography and in the electronic spectra of the reaction mixture. The excess of zinc acetate then coordinates with the nitrogen of the DMAM group. The complex is activated due to weakening of the C−N bond upon the appearance of positive charge on the meso-methylene carbon. The cryptocarbocation formed analogous to the classical benzyl carbocation reacts with a nucleophile, in this case, with compounds possessing a hydroxyl group, to give zinc complexes of ethers. Treatment of these complexes with hydrochloric acid for only 1-2 min gives the corresponding porphyrins according to the following scheme:

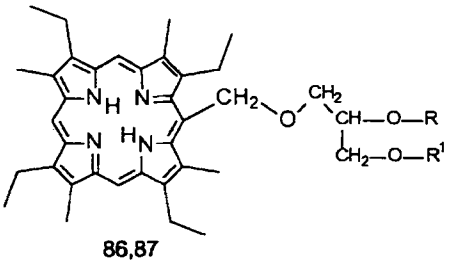
Scheme 10



Samples of such syntheses are given below [32-34]



71-85



86,87

71 R = H; 72 R = Me; 73 R = Et; 74 R = Pr; 75 R = *i*-Pr; 76 R = Bu; 77 R = *i*-Bu; 78 R = *t*-Bu; 79 R = $(CH_2)_2OH$; 80 R = $(CH_2)_2OMe$; 81 R = $(CH_2CH_2O)_2H$; 82 R = $(CH_2CH_2O)_3H$; 83 R = $(CH_2)_6OH$; 84 R = Ph; 85 R = $CH_2CH{=}CH_2$; 86 R + R^1 = CMe_2; 87 R = R^1 = H

The rate of formation of meso-alkoxymethylporphyrins for a series of lower aliphatic alcohols decreases with increasing number of methylene units in the alcohol. However, steric factors have great significance. Thus, for example, the following series is found for butanols: BuOH > *i*-BuOH > *t*-BuOH. The relatively low yield of 50-60% found for porphyrin **78** is due to its thermal instability in addition to steric factors. It is interesting that attempts to obtain porphyrin **78** by another method involving heating meso-acetoxymethyl-OEP with *tert*-butyl alcohol did not lead to the desired result at all [35].

It is natural that not only aliphatic alcohols can be used to obtain ethers by this scheme but also most other compounds containing a hydroxy group. The reaction proceeds very readily with quantitative yield with phenol to give **84**. The formation of an ether bond occurs at one hydroxyl group in the presence of a large excess of ethyleneglycol or triethyleneglycol. The covalent addition of porphyrin to polyethyleneglycol of various molecular weights to produce colored reagents is also possible.

Special interest is found in unsaturated alcohols, which can serve as intermediates for further chemical transformations. Thus, the reaction of porphyrin **3** with allyl alcohol gave ether **85**. The relatively low yield (50-60%) is attributed to the presence of side-products in the reaction mixture, which are formed in the reaction of the intermediate zinc complex at the double bond in allyl alcohol.

The preparation of ethers with glycerin and isopropylideneglycerin, **86** and **87**, demonstrates the broad range of this method [33]. The reaction in the case of glycerin proceeds only at the primary hydroxyl group.

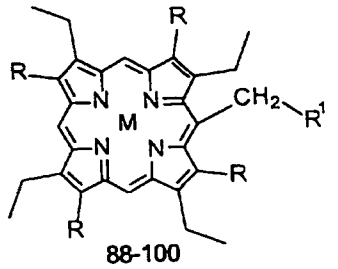
All the ethers synthesized have very similar etio-type electronic spectra regardless of the alcohol used in the reaction, which indicates the lack of a strong electronic interaction between the porphyrin ring and radical R through the ethereal oxygen atom. The IR spectra of these products display a characteristic strong band at 1150 cm^{-1} corresponding to $\nu_{(C-O)}$ for ethers.

The finding of peaks for molecular ions as well as fragments $[M - R]^+$ (a), $[M - OR + H]^+$ (b), $[M - OR]^+$ (c), and $[M - CH_2OR + H]^+$ (d) is characteristic for the mass spectra of virtually all these ethers. The M^+ peak has maximum intensity in the mass spectra with lower alkoxy groups, while the peak for ion (c) has the next highest intensity. The finding of strong ions (b) and (d), especially in the spectra of complex, nonvolatile ethers, is attributed to the formation of meso-methylporphyrins and meso-unsubstituted porphyrins upon thermolysis.

3.2.2. Reaction with CH-Acids

The hypothesis of the intermediate formation of a benzyl-type cryptocarbocation in the reaction of meso-DMAM-porphyrins with excess zinc acetate permits us to extend this reaction to the synthesis of a wide variety of meso-substituted porphyrins.

We studied one of the most important reactions, in our opinion, namely, the reaction with CH-acids [34, 36, 37], since various compounds containing groups in the porphyrin meso position bound to the macrocycle by a single C−C bond can thereby be prepared. The reaction rate is in good accord with the pK_a values of the corresponding CH-acids. Examples are given for compounds obtained in the reaction of DMAM-porphyrins with nitromethane, ethyl nitroacetate, ethyl cyanoacetate, acetone, and a series of β-diketones.



88-100

88-91, 93, 95, 98-100 R = Me; **92, 94, 96, 97** R = Et; **88, 89** R_1 = CH_2Ac; **90-92** R_1 = $CHAc_2$; **93, 94** R = CH(COPh) Ac; **95-97** R = $CH(COPh)_2$; **98** R^1 = CH_2NO_2; **99** R^1 = $CH(NO_2)COOEt$; **100** R^1 = CH(CN)COOEt; **88, 90, 96** M = Zn; other M = 2H.

Of course, the reaction with acetone proceeds most slowly. The formation of complex **88** requires heating of the reaction mixture at reflux for several hours, while the reaction with acetylacetone and other β-diketones, even sterically-hindered compounds such as dibenzoylmethane and benzoylacetone, proceed in high yield in only a few minutes. Unfortunately, there are no x-ray diffraction structural data for the β-diketonate porphyrin derivatives. Thus, we may only propose on the basis of computer modelling that one of the phenyl groups in **95** and **97** is above the porphyrin ring plane, while the other is maximally removed from the porphyrin system.

The electronic spectra of porphyrins **89**, **91-95**, and **97-100** hardly depend on the presence of electronegative groups in the meso-substituent and recall the spectra of meso-methylporphyrins, for which identical intensity is found for bands II and III in the visible region. The mass spectra of these compounds have the ordinary strong peaks for the molecular ions and ions corresponding to β-cleavage (for example, ion 491 for EP derivatives).

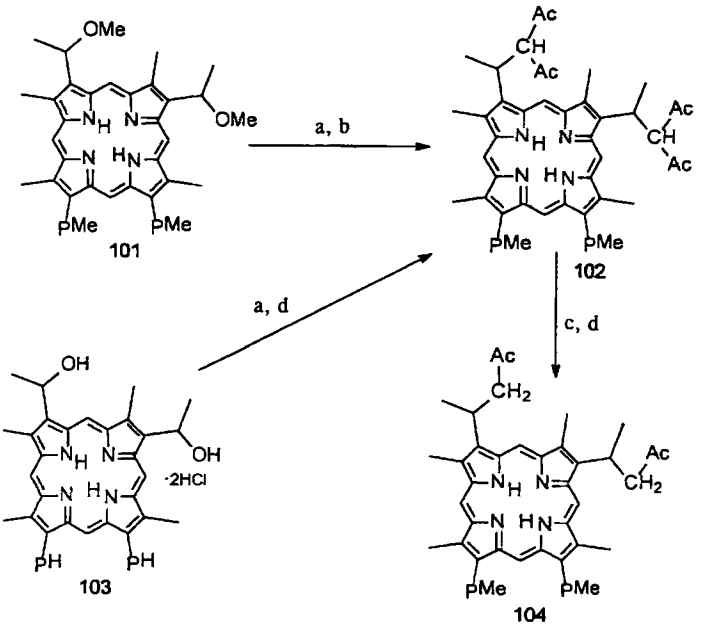
The PMR spectrum of porphyrin **99** holds interest among the products **88**. We may propose on the basis of this spectrum that the meso-substituent is found above the porphyrin ring plane in light of the strong shielding of the ester ethyl group.

3.3. Use of Zinc Acetate for Generating "Benzylic" Carbocations in the Case of Hematoporphyrin-IX Derivatives and *vic*-Dihydroxychlorines. Reaction with CH-Acid and Phenol Nucleophiles

Our studies have shown that the generation of "benzylic" carbocations using zinc acetate starter is possible not only from meso-DMAM-porphyrins but also from β-(1-alkoxyethyl)porphyrins, which is extremely important for the modification of natural porphyrins. This approach has been used in the classical chemistry of porphyrins and chlorines.

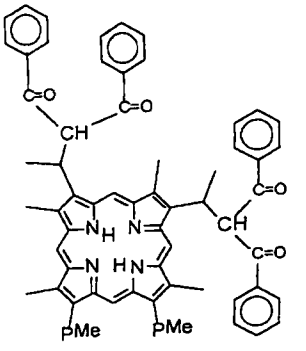
Hematoporphyrin-IX (HP) has acquired the greatest prominence among the commercially available porphyrins obtained from natural protohemin since this is the only porphyrin which is now used both independently and as an intermediate in the synthesis of drugs such as Photophryn, developed in the USA, and Photohem, developed in Russia. Both these products are used as photosensitizers in the photodynamic treatment of cancer.

Scheme 11



a, $Ac_2CH_2/Zn(OAc)_2$, 30 min, 100 °C; b, HCl, 2 min; c, NaOH/dioxane; 50°C, 2 h
d $MeOH/H_2SO_4$;

pH=CH_2CH_2COOH; pMe = CH_2CH_2COOMe

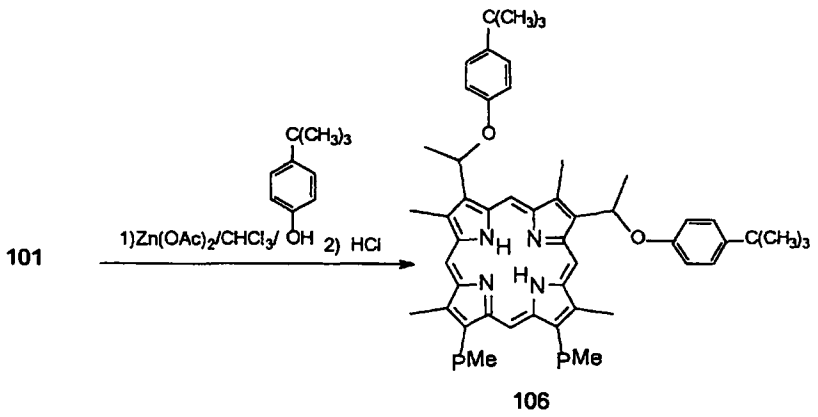


105

Porphyrin **102** was obtained in high yield from the "tetramethyl ether" of HP (**101**) [38] by heating with acetylacetone in the presence of excess zinc acetate [39]. The analogous product **102** was also isolated upon treating the complex HP·2HCl (**103**) under analogous conditions with subsequent etherification using $MeOH/H_2SO_4$. It is interesting that ketonic dissociation of the β-diketonate residues was found to occur in an attempt to obtain a water-soluble form of porphyrin **102** by alkaline hydrolysis of the methoxycarbonylethyl substituents to give a new porphyrin identified after etherification as **104**.

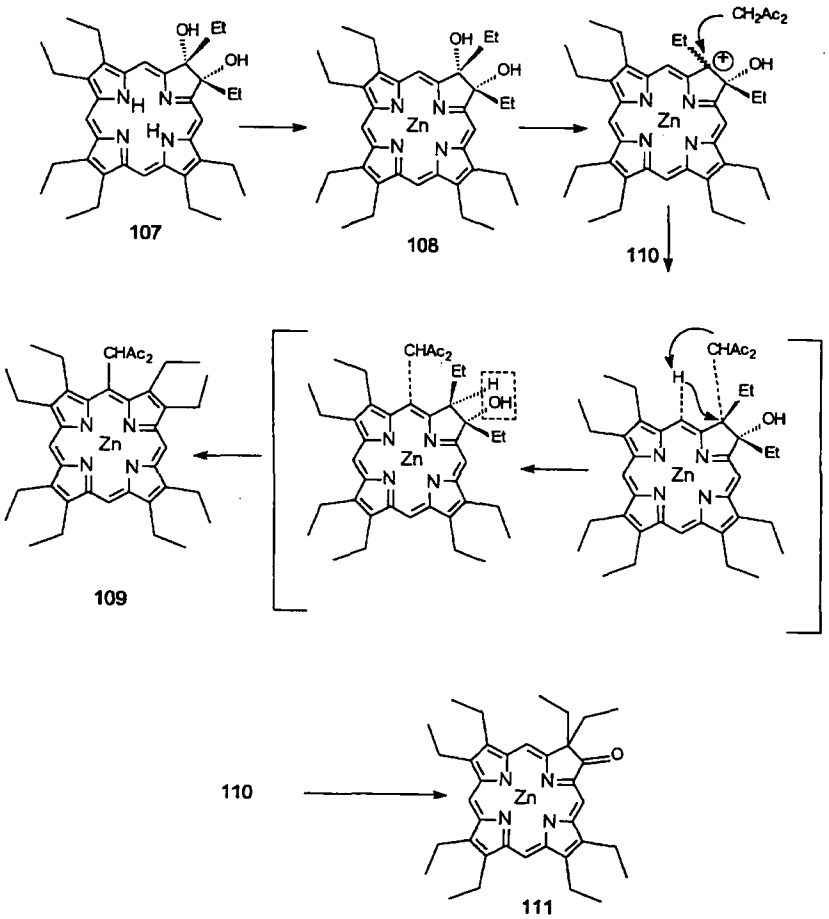
The synthesis with other β-ketones proceeds as readily. For example, heating **101**, dibenzoylmethane, and zinc acetate in carbon tetrachloride leads to porphyrin **105**.

The use of zinc acetate for carrying out reactions of porphyrins capable of giving either a meso- or β-benzylic carbocation opens great possibilities in the chemistry of physiologically active porphyrins. An example may be found in the synthesis of porphyrin **106**, which was used to study new approaches for obtaining photosensitizers for the photodynamic therapy of cancer [40].



However, when the "benzylic" carbocation may be generated from so-called *vic*-dihydroxychlorines, the use of acetylacetone and zinc acetate leads to unexpected results [41]. Thus, for example, heating diol **107** and $Zn(OAc)_2$ in acetylacetone leads initially to zinc complex **108**, which transforms to give porphyrin complex **109**. A classical pinacol rearrangement of carbocation **110** occurs simultaneously to give porphyrinketone **111**. These two processes occur at the same rate. As a result, only two products, **109** and **111**, are formed in 1:1 ratio in the reaction mixture.

Scheme 12

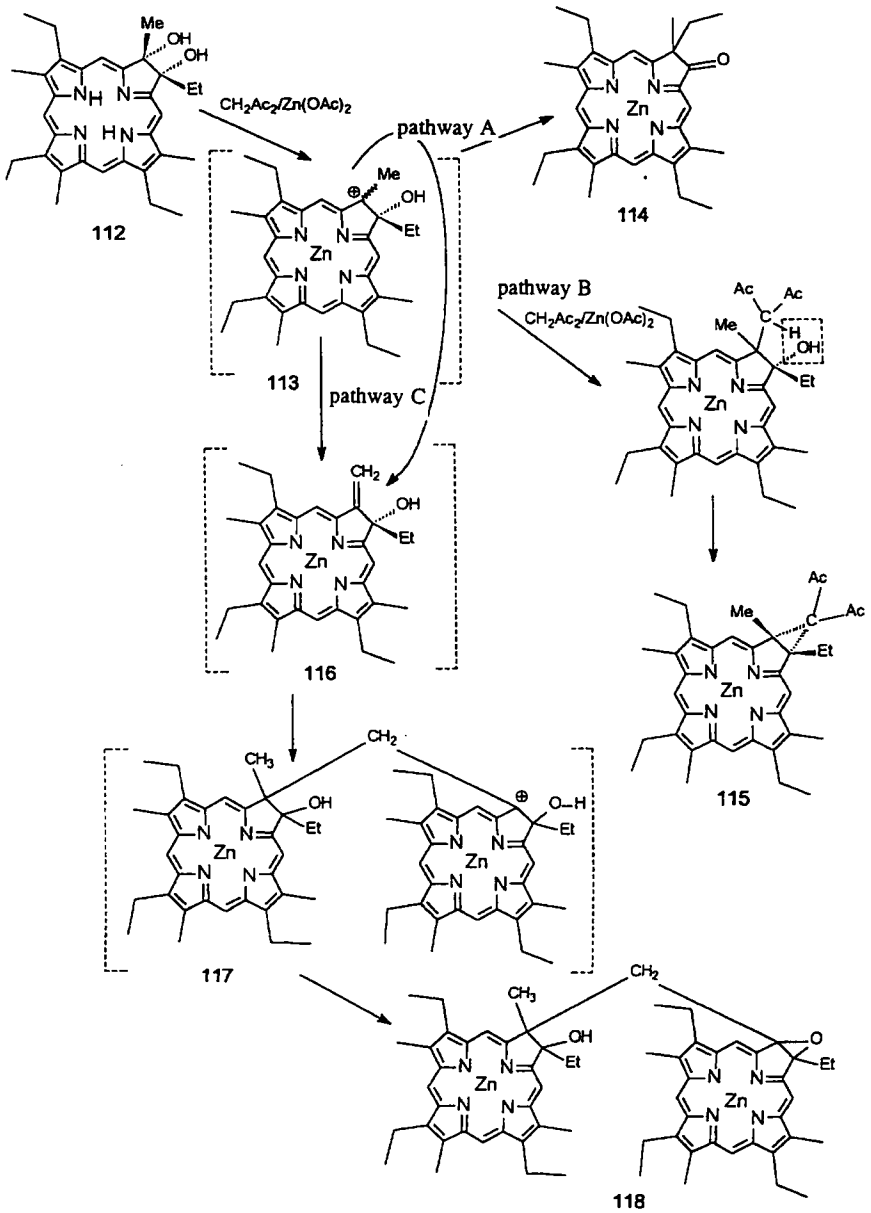


A slight change in the structure of the carbocation leads to a completely different reaction with acetylacetone. Thus, heating *vic*-dihydroxyetiochlorine-I (**112**) leads to several products. Intermediate carbocation **113** is stabilized as ketone **114**

(pathway A, pinacol rearrangement). Another type of stabilization of the carbocation involves reaction with a nucleophile to give exomethylenechlorine **116**, cation dimer **117**, and its conversion into a new type of dimer **118**. (Examples are known in porphyrin chemistry of the formation of dimers by an analogous mechanism due to the cationic dimerization of exomethyleneporphyrins or exoethylideneporphyrins in the presence of strong protic acids such as trifluoroacetic acid, sulfuric acid, or CF_3SO_3H. This behavior is also the consequence of the initial formation of the corresponding carbocations [42, 43]).

Thus, the presence of a peripheral methyl group in the starting porphyrindiol molecule is important in stabilizing the intermediate carbocation. For example, major products **120**, **121**, and **122** were isolated upon heating *vic*-diol **119** obtained from the corresponding tetraethyl ether of CP-1 and found to be similar in structure to the products obtained starting from diol **112**.

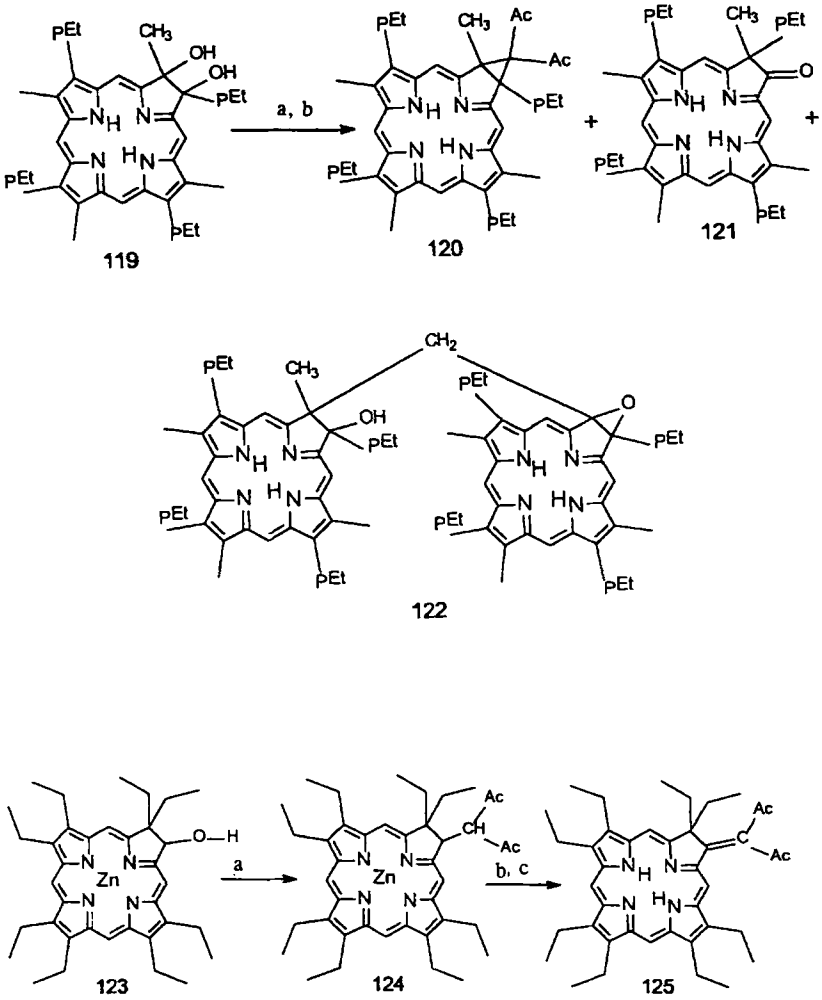
Scheme 13



The addition of a nucleophile in the presence of zinc acetate can also be accomplished for monohydroxychlorines. Thus, the reduction of ketone **111** by $NaBH_4$ gave hydroxychlorine **123**, which was converted by heating with acetylacetone under the conditions described above to give diacetylmethyl derivative **124**, whose characteristic feature is a tendency to

oxidize upon chromatography on silica gel plates to give product **125** [44]. (The capacity of porphyrins to undergo oxidation on the highly developed silica gel surface was noted in our previous work [45, 46]).

Scheme 14



a) $CH_2Ac_2Zn(OAc)_2$, b) HCl, c) multiple thin-layer chromatography on silica gel in methylene chloride. Drying of the plates for thin-layer chromatography in the air in the dark.

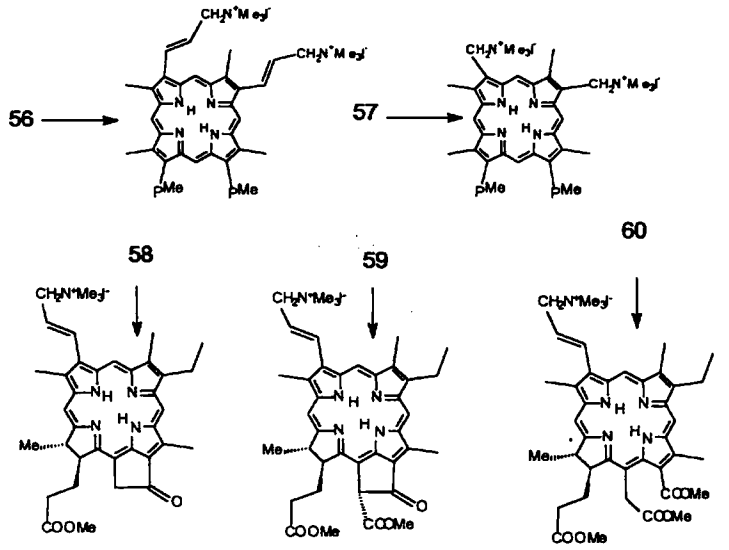
The information in sections 3.2 and 3.3 on the use of zinc acetate in the presence of various nucleophiles for modifying porphyrins and chlorines both in the meso and β-positions clearly indicates the broad possibilities for this method in the synthesis of a wide variety of products.

3.4. Chemical Properties of β- and Meso-DMAM-Porphyrin Iodoalkylates

3.4.1. Properties of β-DMAM-Porphyrin Iodoalkylates

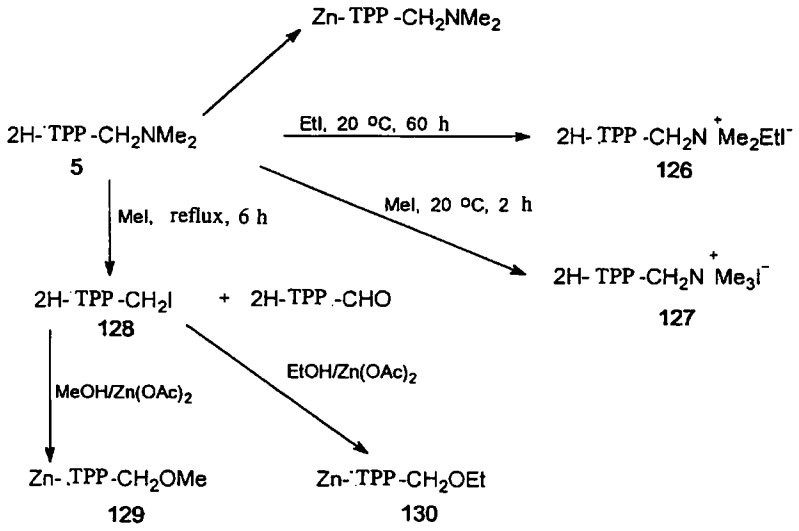
The formation of quaternary ammonium salts often leads to the formation of water-soluble physiologically active compounds. It is thus not surprising that when a compound contains an amine group, an attempt is made to alkylate this group in order to study the chemical and biological properties of such salts.

Several iodomethylates shown below were recently synthesized with the aim of creating water-soluble photosensitizers and compounds capable of targeting cancer cells [13]. These compounds were obtained by treating the corresponding DMAM derivatives **56-60** with MeI. However, the chemical properties of these compounds were not studied.



We obtained iodoalkylates **76** and **77** from porphyrin **5** in a study of the chemical properties of β-DMAM-porphyrins [7]. These results are given in the scheme below.

Scheme 15



The following major conclusions may be drawn from the study of the chemical properties of porphyrin **5**:

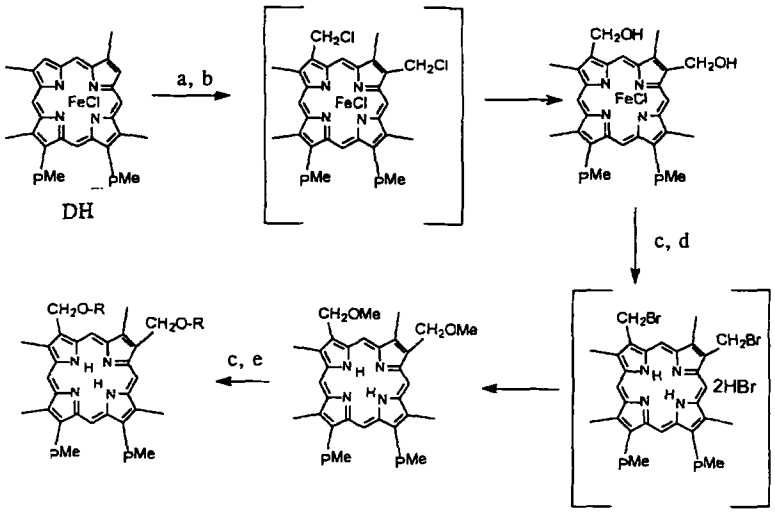
1) the corresponding zinc complex is formed upon treating porphyrin **5** with $Zn(OAc)_2$ in chloroform–methanol with noticeable formation of 2-methoxyethyl-TPP.

2) β-DMAM-porphyrin iodoalkylates are readily formed upon maintaining DMAM-porphyrins in MeI or EtI solution at room temperature. These salts are stable and may be isolated in the crystalline state. However, upon prolonged heating

in MeI at reflux, they gradually eliminate tetramethylammonium iodide to form reactive β-iodomethylporphyrin **128**. A side-reaction also occurs involving oxidation to give 2-formyl-TPP. Porphyrin **128** reacts readily and in quantitative yield with alcohols, especially in the presence of zinc acetate, to give zinc complexes of ethers **129** and **130**.

We note that the preparation of β-chloroethyl- or β-bromoethylporphyrins with subsequent transformation into various β-alkoxymethyl derivatives is rather frequently employed in porphyrin chemistry. The introduction of a β-chloromethyl group is usually carried out by the Friedel-Crafts reaction, treating β-unsubstituted hemin with chloromethyl methyl ether in the presence of $SnCl_4$. We have developed a synthesis for a series of ethers starting from deuterohemin-IX (DH) through Scheme 16 [47]:

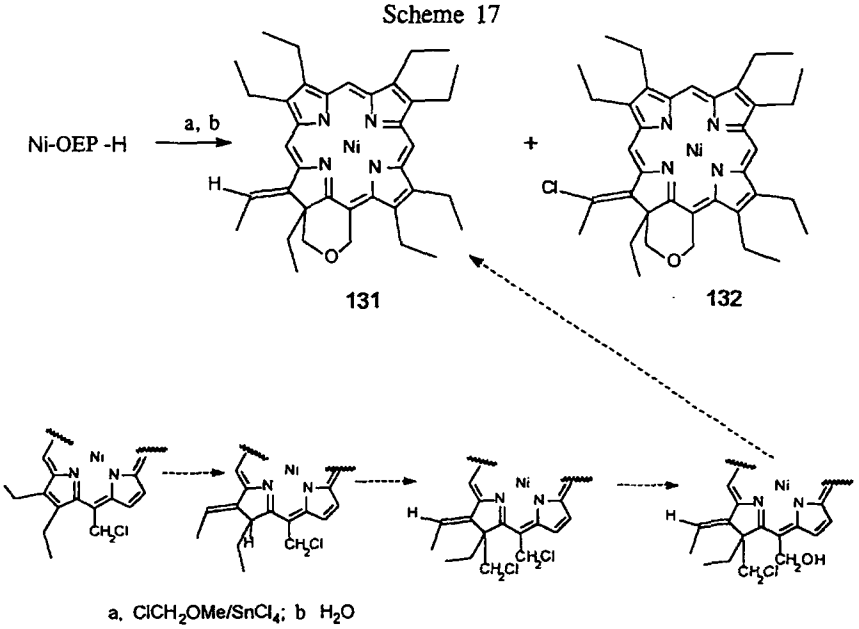
Scheme 16



a, $ClCH_2OMe/SnCl_4$, 0°C, 5 min; b, H_2O, AcONa; c, AcOH/HBr (d = 1.45); d, MeOH; e, ROH; R = i-Pr, CH_2CH_2OH, $(CH_2CH_2O)_2H$

We should note that the analogous reaction with octaalkylporphyrins leads to chlorines [48]. Thus, the alkylation of the nickel complex of OEP using $ClCH_2OCH_3/SnCl_4$ gives chlorines **131** and **132**, whose formation probably occurs through double chloromethylation, partial hydrolysis to hydroxymethylchlorine, and dehydrochlorination as shown in Scheme 17.

Scheme 17



a, $ClCH_2OMe/SnCl_4$; b H_2O

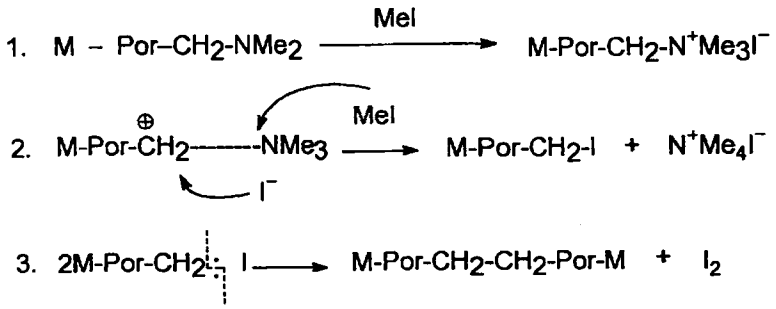
3.4.2. Properties of Meso-DMAM-Porphyrin Iodomethylates

In contrast to β-DMAM-porphyrins, for which rather stable iodoalkylates may be prepared and isolated in crystalline form, the reaction of meso-DMAM-porphyrins and their metal complexes with MeI or EtI in the cold leads to very labile quaternary salts, which must be used without isolation. A wide variety of chemical reactions has been carried out using these species. Some of these reactions are discussed below. The formation of iodomethylates or iodoethylates may be detected spectrophotometrically using the bathochromic shift of the visible bands and chromatographically relative to the formation of a product more polar than the starting porphyrin.

3.4.2.1. Synthesis of Ethanebisporphyrins and Ethanebischlorines. Dimerization of Meso-DMAM-Porphyrins and Meso-DMAM-Chlorines in MeI and EtI

Analysis of the products formed upon heating copper and nickel complexes of meso-DMAM-porphyrins in MeI showed that the corresponding metal complexes of ethanebisporphyrins are formed [49]. The dimer yields were 70-90%, which is twice or thrice the yields achieved previously for such compounds [50-54]. In a continuation of this work, we found that not only metal complexes of meso-DMAM-porphyrins, but also metal complexes of meso-DMAM-chlorines and even several DMAM-porphyrin free bases may form dimers. The mechanism of this reaction is extremely simple and was established relative to two characteristic features: 1) tetramethylammonium iodide begins to precipitate out of the reaction mixture upon heating in MeI after only a few minutes, and 2) the methyl iodide solution obtained after this volatile liquid is distilled off the reaction mixture is yellowish, due to the presence of iodine.

In our opinion, the dimerization occurs in three steps:



M=2H, Cu, Ni, Zn; Por= EP-I, OEP, OEC

LP-I tetraethyl or tetraisopropyl ether

A quaternary salt is formed in the first step, which is unstable as a result of considerable steric strain due to the proximity of the adjacent β-substituents, leading to weakening of the C–N bond and formation of a carbocation. The second step, features loss of tetramethylamine as tetramethylammonium iodide and formation of a labile meso-iodomethyl-porphyrin or meso-iodomethylchlorine. Homolytic cleavage of the C–I bond occurs in the third step followed by dimerization of the radicals to give ethanebisporphyrins and iodine.

Ethyl iodide should be used in the dimerization of DMAM-porphyrin free bases in order to exclude the possibility of alkylation at the pyrrolic nitrogen atoms.

The simplicity and reproducibility of these experiments and availability of the starting DMAM-porphyrins permit us to obtain a wide variety of ethanebisporphyrins such as:

2H-OEP-CH_2CH_2-OEP-2H (**133**),
Cu-OEP-CH_2CH_2-OEP-Cu (**134**),
Ni-OEP-CH_2CH_2-OEP-Ni (**135**),
Cu-EP-I-CH_2CH_2-EP-I-Cu (**136**),
Cu-CP-I-CH_2CH_2-CP-I-Cu octaethyl ether (**137**),
Ni-CP-I-CH_2CH_2-Cp-I-Ni octaethylether (**138**),

Ni-CP-I-CH_2CH_2-Cp-I-Ni octaisopropyl ether (**139**),
and Cu-OEC-CH_2CH_2-OEC-Cu (**140**).

The syntheses of dimers **134**, **136**, and **140** was also carried out using previously reported techniques from the corresponding copper complexes of meso-hydroxymethyl-OEP, meso-hydroxymethyl-EP-I, and OEC [54], while dimer (**137**) was obtained from the copper complex of meso-hydroxymethyl-CP-I according to our procedure [55]. The crystal and molecular structures of **138** and **140** were determined by Dr. M. O. Senge in the laboratory of Prof K. M. Smith at the University of California at Davis by x-ray diffraction analysis (Figs. 1 and 2) [10, 56].

The dimer shown in its crystalline state in Fig. 2 has a centrosymmetric elongated structure, in which the carboethoxy group of one of the ethoxycarbonylethyl residues of each of the porphyrin macrocycles is found directly above or below the plane of the other macrocycle. PMR spectroscopy indicates that this dimer in chloroform solution is mainly found in cisoid form [55]. Thus, conclusions concerning the arrangement of the macrocycles relative to each other in solution should not be drawn only from the x-ray diffraction structural data.

The presence of chlorine rings fundamentally alters the arrangement of the macrocycles in the dimer. Thus, an x-ray diffraction structural analysis of dimer **140** showed that the macrocycles are in a synclinal twist conformation [56] analogous to one of the two conformations found also by x-ray diffraction structural analysis for the free base 2H-OEC-CH_2CH_2-OEC-2H (**141**) [57].

Although the synthesis of dimer **141** was reported 15 years ago [51], no PMR spectral data have yet been reported for this compound. In our opinion, this circumstance may be attributed to the presence of trace amounts of paramagnetic copper ions in the samples studied, remaining after demetallation of complex **140**, which prevent the recording of high-quality PMR spectra.

We attempted to obtain a high-quality sample of dimer **141** and study its conformation in solution using PMR spectroscopy.

Indeed, the demetallation of complex **140** in concentrated sulfuric acid proved extremely difficult due to the formation of numerous oxidation products with similar chromatographic mobility, containing chlorines and porphyrins as both metal complexes and free bases. Nevertheless, we isolated two dimers from the reaction mixture which proved suitable for PMR study, namely, dimer **141** and 2H-OEP-CH_2CH_2-OEC-2H (**142**), which has fundamental importance for understanding the physicochemical properties of ethanebisporphyrins. Dimer **142** contains both porphyrin and chlorine macrocycles. The PMR spectra of dimers **141** and **142** are presented for the first time in this review.

G. V. Ponomarev, D. V. Yashunskii, and D. P. Arnold have shown that dimer **141** exists in the synclinal twist conformation not only the crystalline state but also in chloroform and benzene solution. One of the ethyl groups of a reduced pyrrole ring in each of the macrocycles in this conformation is located near the center of the opposite chlorine macrocycle. Analysis of the PMR spectra indicates that all the signals of the two ethyl groups are found upfield relative to the signals of the pyrrole NH protons due to the strong effect of the macrocycle ring current. The uniqueness of this case lies in the position of the methyl proton triplet of the ethyl group at -2.4 ppm between the signals of the methylene protons appearing as a doublet of quartets at -0.8 and -2.75 ppm, i.e., one of the CH_2 group protons is even closer to the center of the adjacent chlorine than the methyl group. The finding of only three meso-proton signals in the PMR spectrum of this dimer indicates that only one atropisomer exists in solution (see Fig. 3).

PMR spectroscopy indicates that dimer **142** exists in C_6D_6 solution at 20°C also in a synclinal twist conformation, in which one of the chlorine ethyl groups is near the porphyrin macrocycle. Only slight twisting of the macrocycles relative to each other occurs upon heating to 70°C, as indicated by the downfield shift of the ethyl group signals and broadening of the signals of all the NH protons and two meso-protons of the chlorine ring.

3.4.2.2. Synthesis of Mono-DMAM-Derivatives of Porphyrin Dimers. Synthesis of Tetramers Bound by Ethane Bridges

A major advantage of dimerization starting from DMAM-porphyrins in the presence of MeI or EtI relative to our previous method starting from copper complexes meso-hydroxy- and meso-alkoxymethylporphyrins [54, 55] is the possibility of dimerizing specifically nickel complexes of DMAM-porphyrins, which permits the PMR study of the dimer complexes in solution immediately after demetallation along with higher yields of the final products.

The capacity of the dimeric metal complexes to undergo selective demetallation of only one of the central metal atoms [52, 54] permitted us to synthesize the mono-DMAM-derivative of ethanebisporphyrin. Thus, complex **135** was used

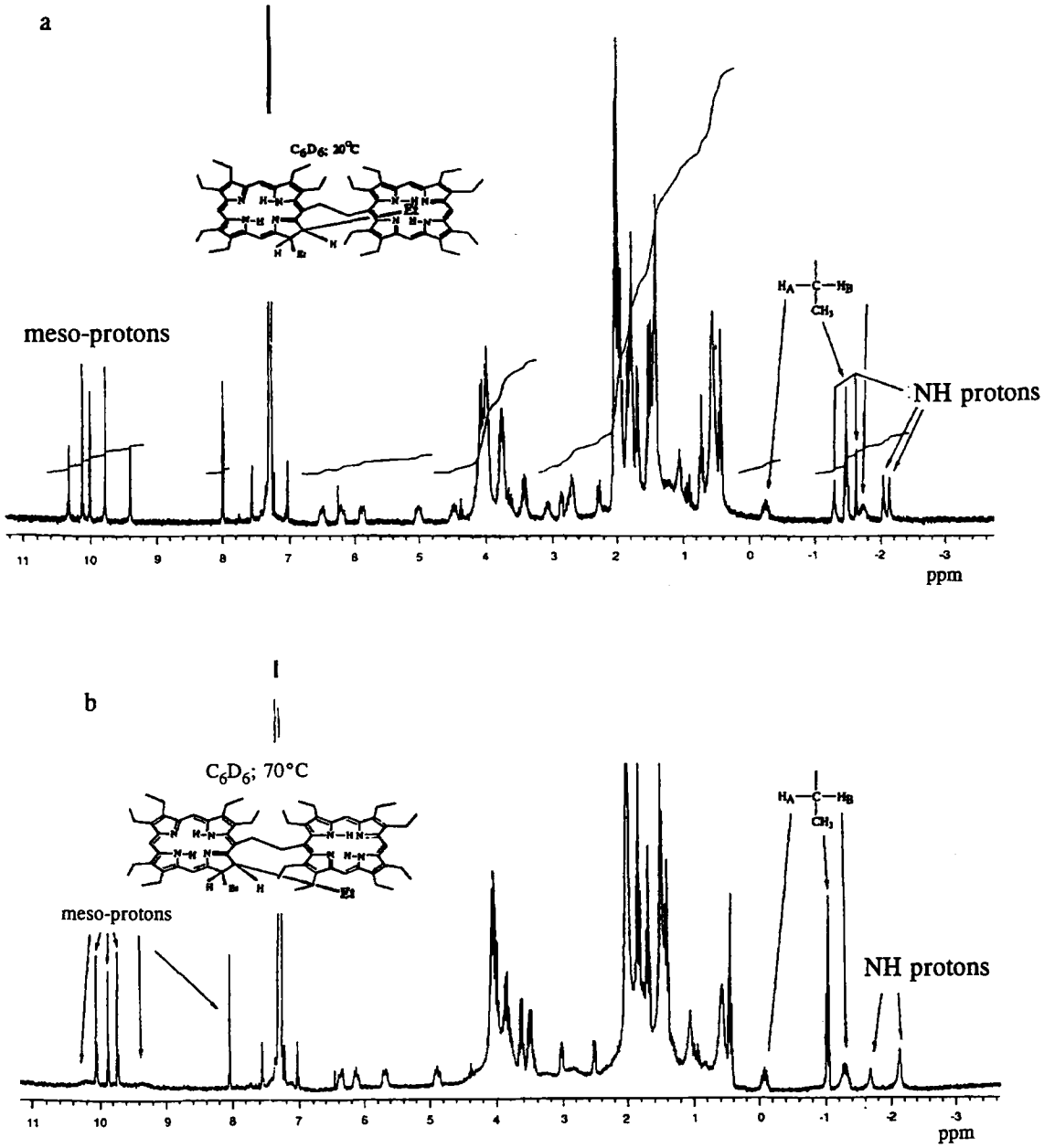
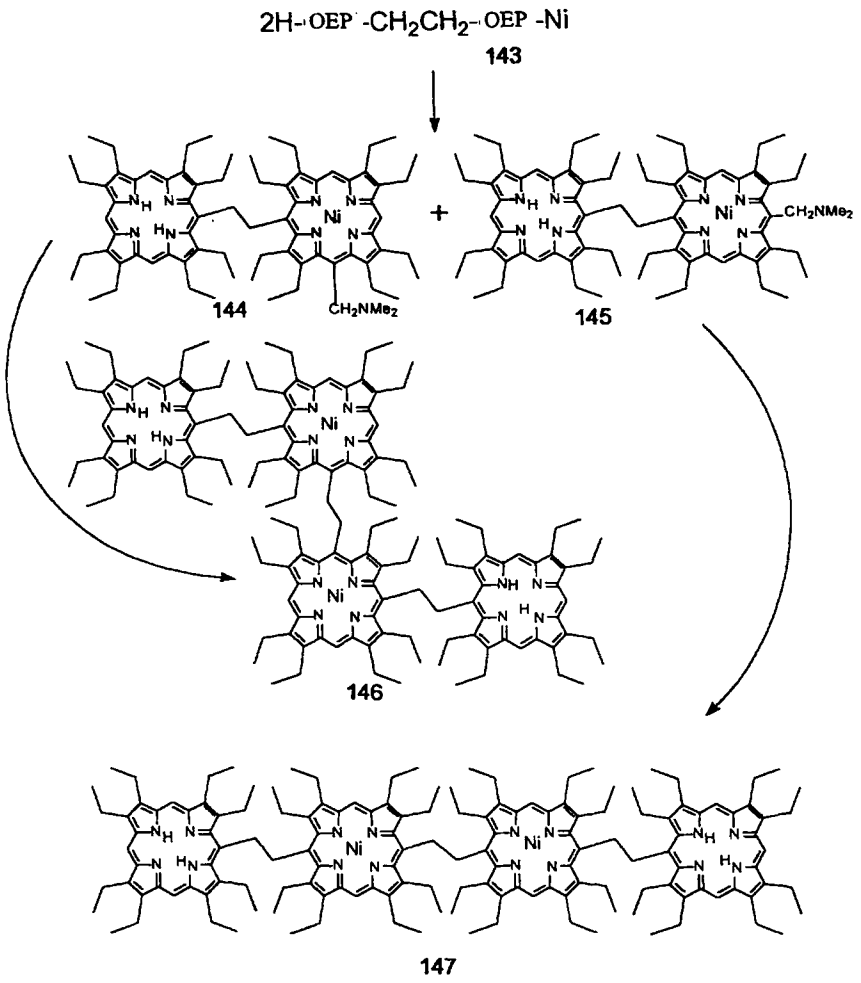


Fig. 4. PMR spectra of dimer **142** in C_6D_6: a) at 20°C; b) at 70°C.

to obtain 2H-OEP-CH_2CH_2-OEP-Ni (**143**). Formylation of **143** with subsequent reduction of the intermediate PC gave a mixture of products, from which pure isomers **144** and **145** were isolated in 4:1 ratio after chromatography on silica gel. Thus, use of the mononickel complex of the dimer permitted a facile solution of the problem concerning the site of electrophilic attack. As assumed, dimer **143** may be seen as a complex of a mono-meso-alkylporphyrin, whose formylation proceeds predominantly at the adjacent meso-positions [1]. Heating of each of these isomers in MeI gave the corresponding tetramers **146** and **147** [58].

Scheme 18

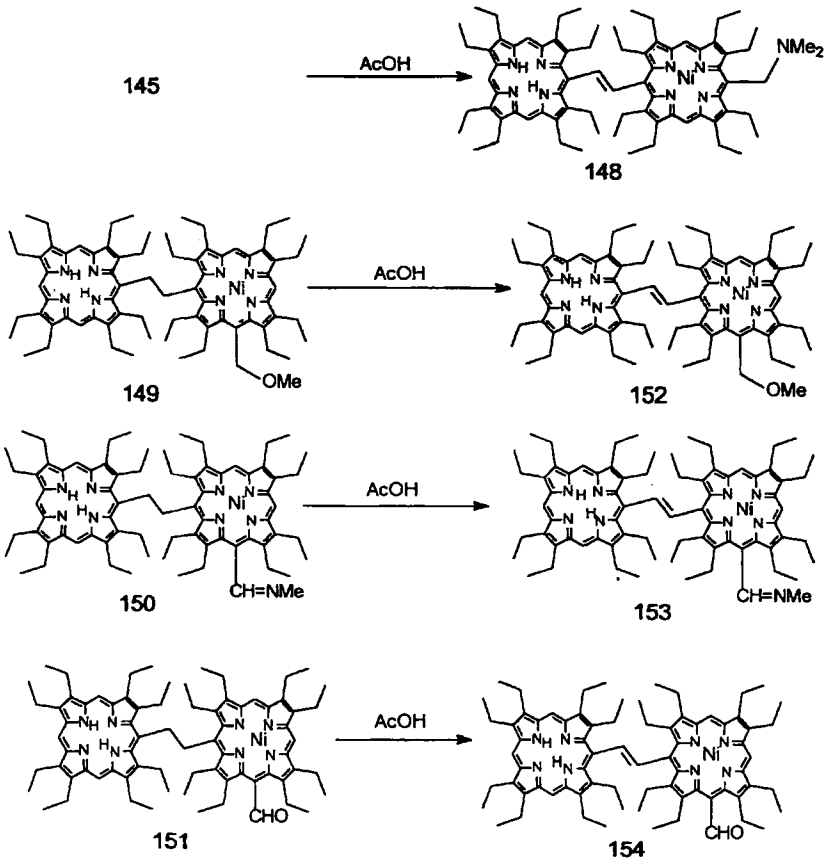


3.4.2.3. Oxidation of Mono-DMAM-Ethanebisporphyrins and other Ethanebisporphyrins and Ethanebischlorines in Acetic Acid by Atmospheric Oxygen. Oxidation Mechanism

One of the most remarkable properties of ethanebisporphyrins was discovered in our "accidental" oxidation of these compounds upon maintenance in acetic acid [54, 59] and then in other fatty acids [60] to give *trans*-ethylenebisporphyrins and the transformation of the latter to the *cis* form [61]. The mechanism for this process is not yet completely clear, but undoubtedly the oxidation of the ethane bridge to an ethylene bridge involves some transformations related to monoprotonation of one or simultaneously two porphyrin rings in weak organic acids.

In a study of the chemical properties of DMAM-dimers **144** and **145**, only one of these dimers (**145**) [sic] [the text gives "C" but this makes no sense and Scheme 19 shows **145** → **148**] in acetic acid solution was found to undergo facile oxidation to give the corresponding *trans*-ethylene dimer **148**, while the other dimer is highly unstable and converts to a complex mixture of products although other related meso-substituted dimers, **149**, **150**, and **151**, obtained from the corresponding PC by methods described above, are converted into *trans*-ethylenebisporphyrins **152-154**.

Scheme 19



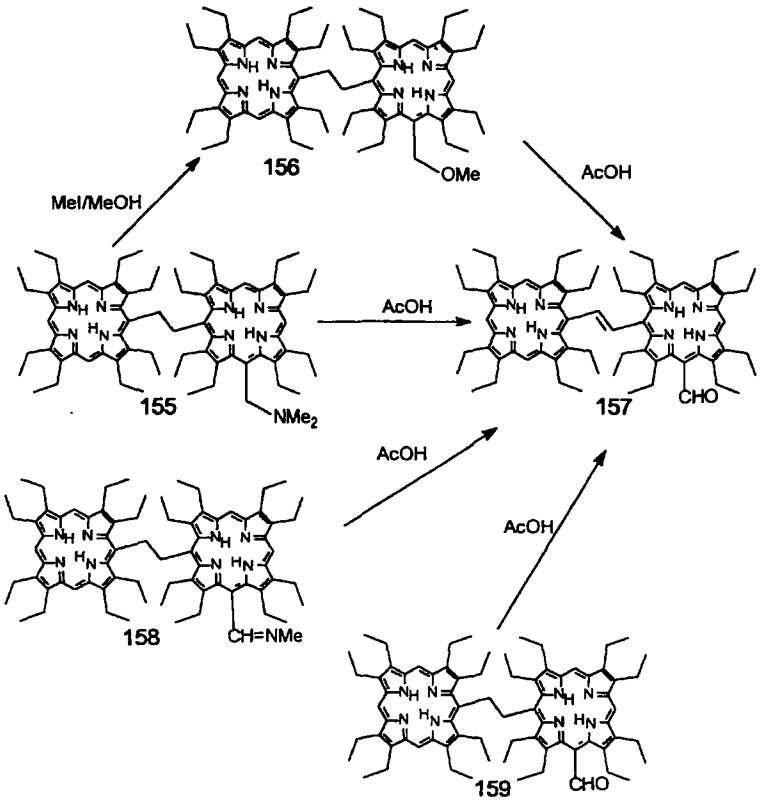
It is interesting that the free bases of dimers **155** and **156** are oxidized to *trans*-isomer **157** with the simultaneous oxidation of the DMAM and methoxymethyl groups to aldehyde groups. The oxidation of dimer **158** proceeds with hydrolysis of the azomethine bond, while dimer **159** is converted quantitatively into dimer **157** without any complications. These results are summarized in Scheme 20 [62].

In recent work [63], we have found that monocomplexes of meso-unsubstituted dimers also are capable of undergoing oxidation in acetic acid to give ethylenebisporphyrins albeit at higher temperature, which leads to the generation of both *trans* and *cis* forms in solutions. Thus, *trans*-ethylene **160** (45%) and *cis*-ethylene **161** (5%) were obtained from ethane **143** after heating for 6 h at 100°C in acetic acid and separation of the unreacted starting ethane dimer (42%). The syntheses of metal complexes of *cis* and *trans*-ethylene dimers were previously carried out by the standard procedure starting from the corresponding free bases of the *cis*-dimers [64] or the redox-induced transformation of *cis* isomers to *trans* isomers [65]. It is most important to note that in contrast to ethanebischlorine **141**, which proved rather stable under these conditions, porphyrinchlorine dimer **142** was readily oxidized to the corresponding *trans*-ethylenemonochlorine **162**. This dimer already had an extended form in comparison to ethane analog **142**, as indicated by the downfield shift of the signals of the protons of the ethyl groups located in the reduced pyrrole ring.

These findings indicate that oxidation of the ethane bridge to give a *trans*-ethylene bridge initially requires monoprotonation specifically of the porphyrin macrocycle as the free base. We propose a possible mechanism below for the oxidation of ethanebisporphyrins, which completely accounts for the experimental findings now reported.

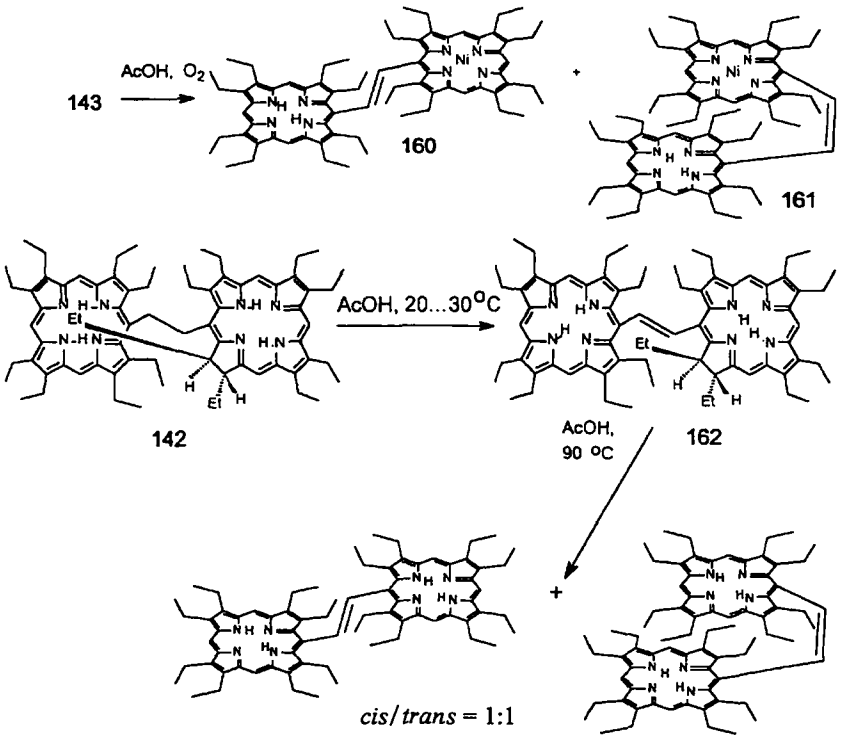
This mechanism involves a transformation in the first step due to prototropic rearrangement of monocation A to give cation-phlorine B, which is stabilized to give reactive exoalkylidene C. The latter is oxidized by the atmospheric oxygen dissolved in acetic acid to give intermediates D and E, which are then oxidized to give *trans*-ethylenedimers F.

Scheme 20

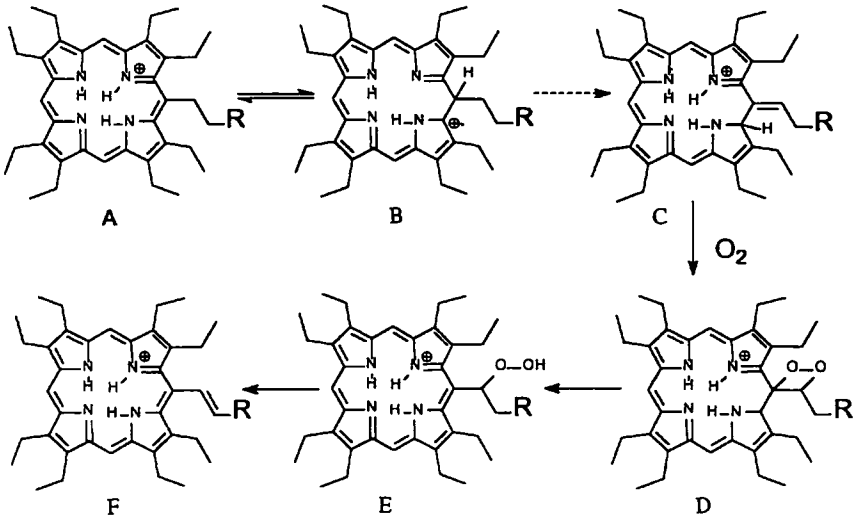


We should note that partial redistribution of positive charge between monocation A and cation B occurs in the case of chlorines. Cation B is stabilized to give labile dihydroporphyrin C capable of undergoing oxidation by means of atmospheric oxygen through intermediates D and E to give porphyrin F as shown in the scheme below.

Scheme 21



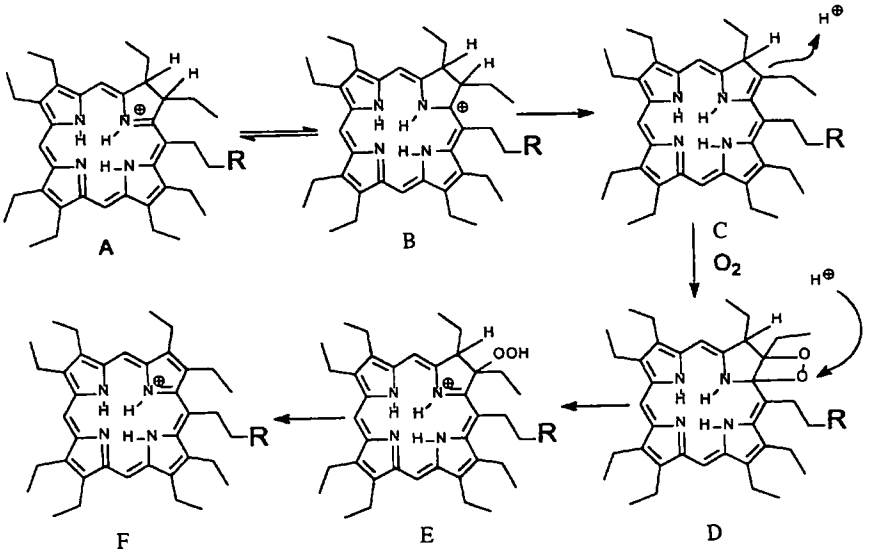
Scheme 22



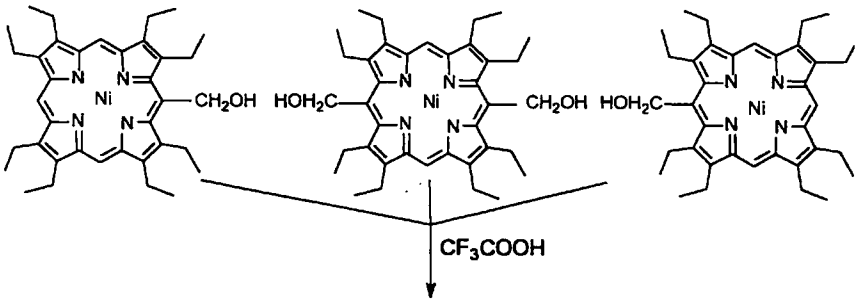
R = Por; M-Por; Chl; M-Chl

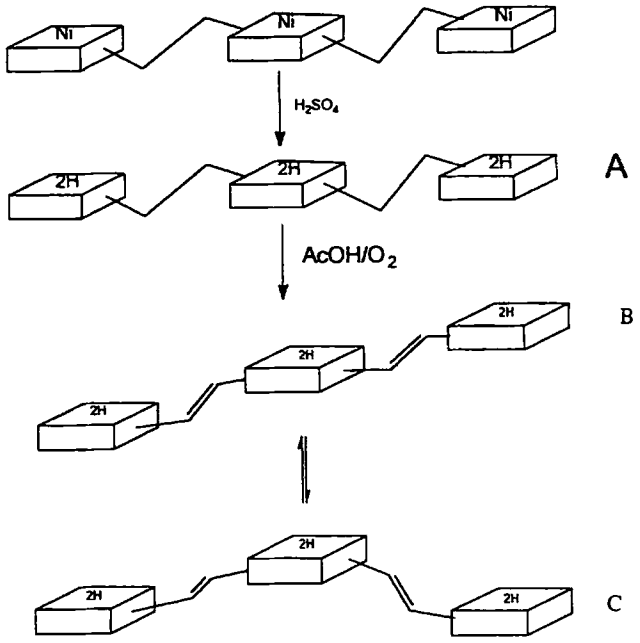
The transformations of ethanebisporphyrins and ethanebischlorines into ethylenebisporphyrins and ethanebischlorines using acetic acid have been studied by Smith [66, 68] and Higuchi [67]. For example, the oxidation of trimer A in acetic acid leads to two forms of *trans,trans*-ethylenetrimer B and C [67]. The oxidation of *trans*-chlorine D leads to the corresponding ethylenebisporphyrin E with *cis* configuration of the ethylene bridge [68].

Scheme 23

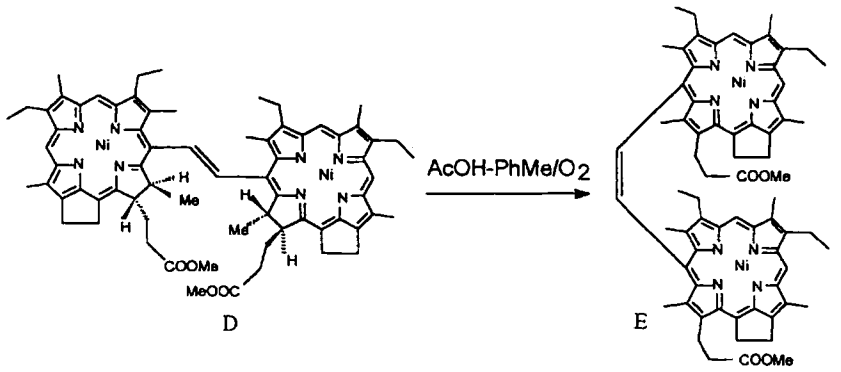


Scheme 24





The study of the *cis-trans* isomerism of ethylenebisporphyrins and their metal complexes may further our understanding of energy transfer to the active site in the photosynthetic apparatus and lead to catalysts for one- and multiple-electron transfer.

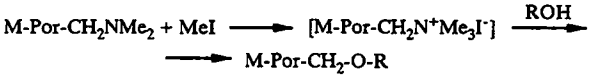


3.4.3. Reaction of Meso-DMAM-Porphyrins with Nucleophiles in the Presence of MeI

As noted above, iodomethylates of meso-DMAM-porphyrins and their complexes are extremely unstable and readily transform into both the corresponding metal complexes of ethanebisporphyrins or ethanebischlorines and numerous other products, especially in the case of free bases. Thus, study of the reaction of meso-DMAM-porphyrins with nucleophiles in the presence of MeI opens a whole new area of the chemistry of meso-substituted porphyrins. This area of chemistry could also be formulated as the reactions of exomethyleneporphyrin cation with nucleophiles.

3.4.3.1. Reaction with Alcohols to give Meso-Alkoxy-methylporphyrins

Both metal complexes and free bases of meso-DMAM-porphyrins readily form the corresponding ethers in alcohol solution upon the addition of MeI or EtI [31] since the reactive iodomethylate generated reacts immediately with the nucleophile according to the following scheme:

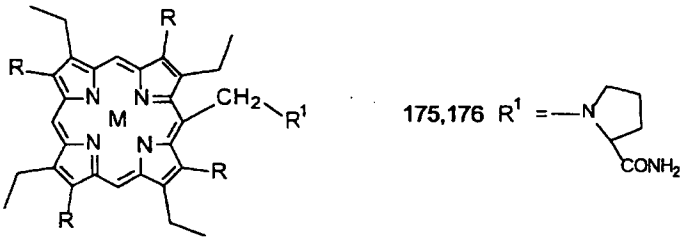


In our opinion, this method can yield many hydroxyl-containing compounds. The reaction with primary and secondary alcohols, especially the lower homologs, proceeds very rapidly and with yields close to quantitative. Probably only steric hindrance can reduce the reaction rate and yield of porphyrin ethers. We shall not present examples of the synthesis of meso-alkoxymethylporphyrins in this review since they have all been discussed previously (see Section 3.2.1).

It is difficult to find a preference for one of our two methods for the preparation of ethers from meso-DMAM-porphyrins 1) in the presence of zinc acetate and 2) in the presence of MeI. It can only be stated with certainty that each of these methods is much more convenient than the reported synthesis of ethers from meso-acetoxymethylporphyrins [24].

3.4.3.2. Reaction with Primary and Secondary Amines

Despite the facility of the decomposition of DMAM-porphyrin iodomethylates to give radicals and their dimerization to give ethanebisporphyrins, the addition of a four- or five-fold excess of primary or secondary amine as the nucleophile to a solution of DMAM-porphyrin and MeI or EtI in chloroform or dichloroethane at reflux leads to the formation of new N-substituted meso-aminomethylporphyrins **163-176** in high yields [69]. This method is also efficient for the preparation of peptides labelled at the N-terminus by a porphyrinmethyl residue. When hydrochloride salts of amino acids are used, triethylamine (1.5 equivalents) is also added.



163-177

163-173, 175 R = Me; **174, 176, 177** R = Et; **163-172, 175** M = Ni;
173, 174, 176, 177 M = 2H;
163 R^1 = $N(i\text{-}Pr)_2$; **164** R^1 = $NBzl_2$; **165** $N(CH_2CH_2)_2O$; **166** $NHCH_2-C_6H_4-NO_2\text{-}p$;
167 R^1 = NHBu-*t*; **168, 173** R^1 = $NHCH(COOMe)CH_2CHMe_2$;
169, 174 R^1 = $NHCH(CONH_2)CHMe_2$;
170 R^1 = $NHCH(COOMe)CH_2-C_6H_4-OH\text{-}p$;
171 R^1 = $NHCH(CH_2CHMe_2)CONHCH_2COOMe$;
172 R^1 = $NHCH(COOMe)CH_2SBn$; **177** R^1 = $NHCH_2CH_2CH_2$-Im(1)

The method described above for transamination for the synthesis of various aminomethylporphyrins is, of course, more convenient and holds greater promise than the synthesis already reported for such compounds by heating the amine with meso-acetoxymethylporphyrin as in the synthesis of porphyrin **177** [35].

3.4.3.3. Reaction with Triphenylphosphine and Properties of Phosphonium Salts. Synthesis of Meso-Methylporphyrins and Metal Complexes of Ethanebisporphyrins

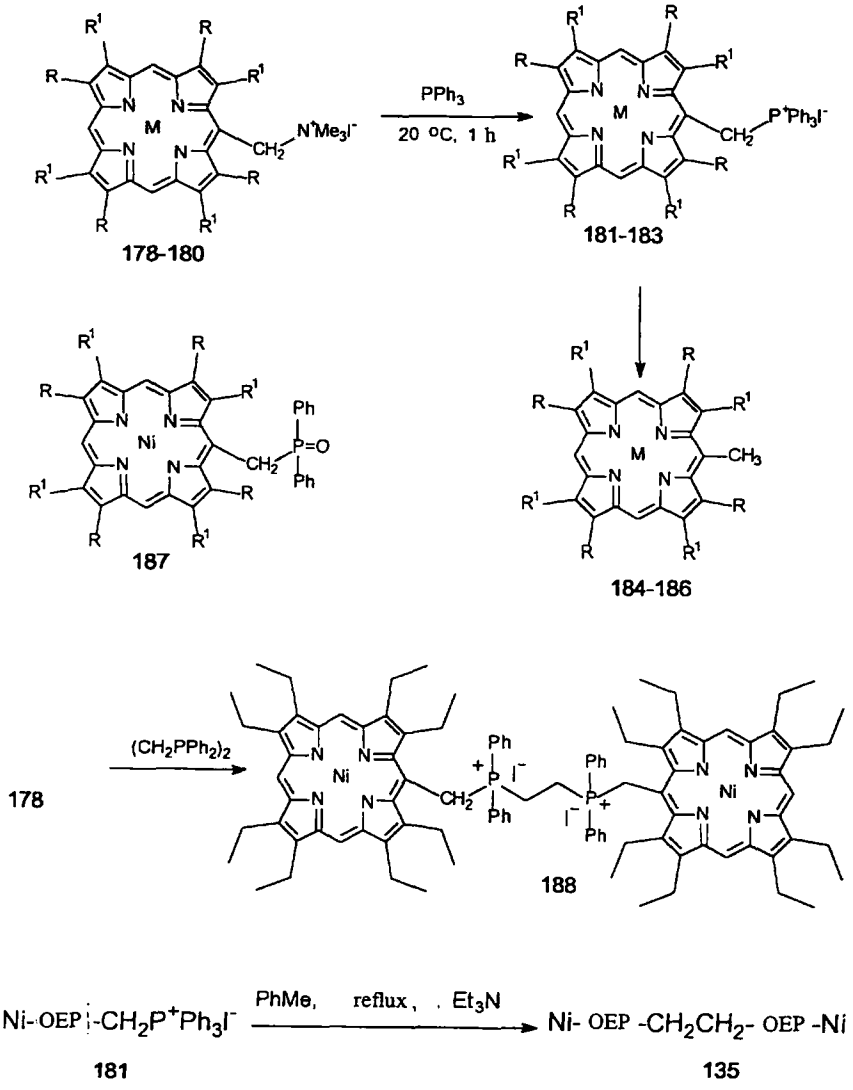
The reactive iodomethylates of metal complexes of meso-DMAM-porphyrins (trimethylporphyrinylmethylammonium iodides) obtained upon maintaining the corresponding DMAM-porphyrins and MeI in methylene chloride at room tempera-

ture readily react with triphenylphosphine after removal of the solvent to give the corresponding triphenylporphyrinylmethylphosphonium iodides in quantitative yield. These phosphonium salts, in contrast to the starting iodomethylates, are rather stable and can be isolated in crystalline form [70]. This is the first example, in which a $CH_2P^+Ph_3I^-$ group is located in the meso-position of a porphyrin ring, although the insertion of this group into the β-position of the porphyrin ring has been accomplished by the classical method by the reaction of β-chloromethyl-TPP with triphenylphosphine [71].

Phosphonium salts **181-183** were obtained from iodomethylates **178-180**. A characteristic feature of these phosphonium salts is the formation of complexes of meso-methylporphyrins **184-186** upon treatment with alkali in methanol in virtually quantitative yield. Although there are other methods for the synthesis of meso-methylporphyrins (reduction of meso-formyl- and meso-acetoxymethylporphyrins as well as meso-formyl- and meso-acetoxymethylchlorines [24, 25, 50], thermolysis of meso-DMAM-porphyrins and their borane complexes [27], and electrochemical reduction from the zinc complexes of meso-alkoxymethylporphyrins [26]), the synthesis from phosphonium salts is probably most convenient. However, this method has certain limitations. We have not yet been able to obtain meso-methyl-OEc starting from meso-DMAM-OEC through the corresponding phosphonium salt.

Attempts to obtain ylids in aprotic solvents have been unsuccessful. The classical preparation of ylids for ordinary phosphonium salts by treatment of salt **181** by NaH in DMF leads only to diphenylporphyrinylphosphine oxide **187**.

Scheme 25



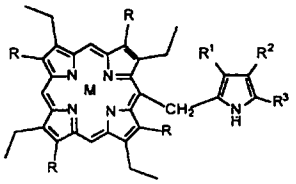
Bisphosphonium salt **188** was obtained upon prolonged treatment of bisdiphenylphosphinoethane with excess iodomethylate **178**.

However, the most remarkable property of these phosphonium salts is their thermal dimerization to give metal complexes of ethanebisporphyrins. Thus, heating **181** in toluene in the presence of triethylamine leads to dimer **135** in almost quantitative yield. In the absence of base, a mixture of products is formed, among which the dimer, meso-methyl-OEP, and OEP are found.

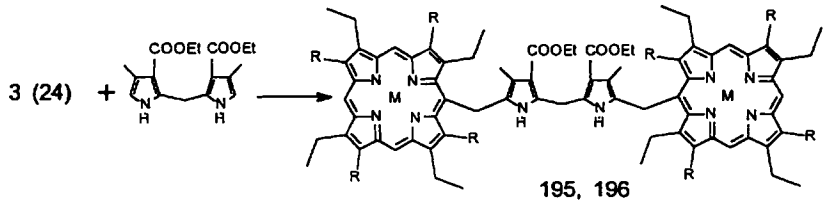
3.4.3.4. Reaction with α-Unsubstituted Pyrroles and Dipyrrylmethanes

In Section 3.2.2, we showed that zinc complexes of meso-DMAM-porphyrins activated by zinc acetate react readily with CH-acids with the loss of dimethylamine and formation of a C−C bond. DMAM-porphyrins and their metal complexes react through virtually the same mechanism with α-unsubstituted pyrroles and α,α-unsubstituted dipyrrylmethanes, acting as CH-acids in the presence of MeI or EtI [72, 73].

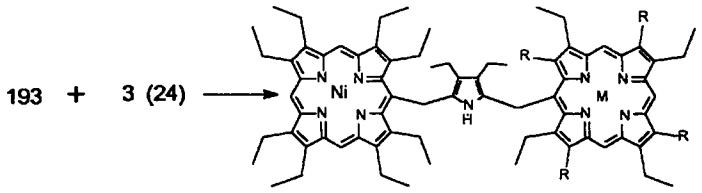
Scheme 26



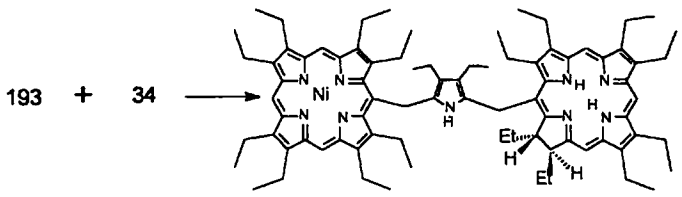
189-194



195, 196



197, 198

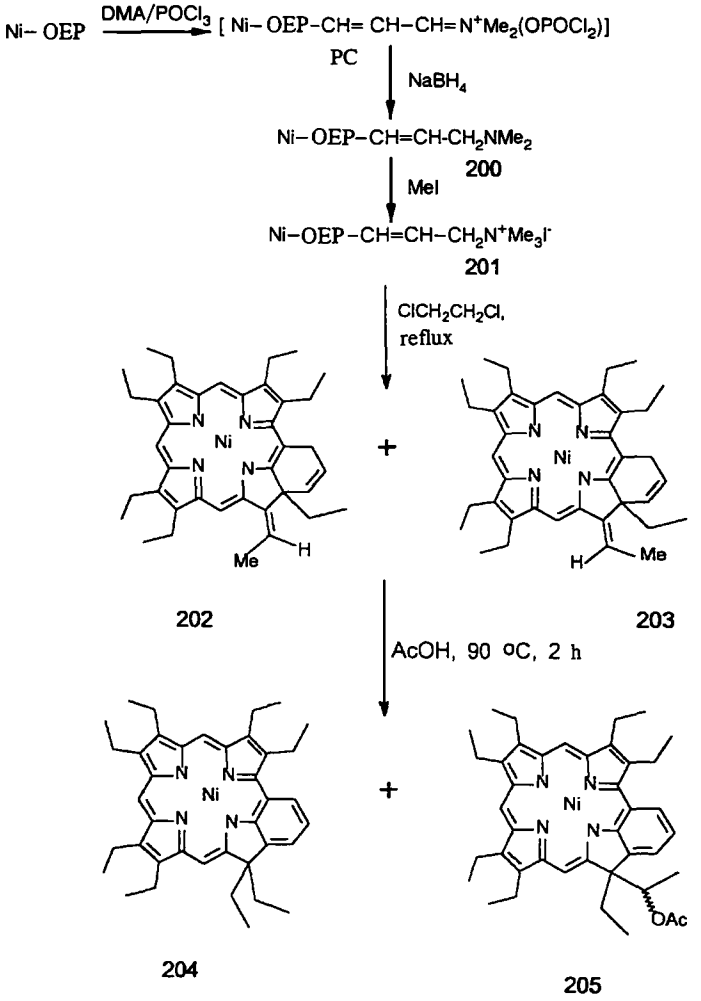


199

189 R = Me, $R^1 = R^2 = R^3$ = H, M = 2H; **190** R = Me, $R^1 = R^2 = R^3$ = H, M = Ni; **191** R = Me, $R^1 = R^3$ = Me, R^2 = COOEt, M = 2H; **192** R = Me, $R^1 = R^3$ = Me, R^2 = COOEt, M = 2H; **192** R = Et, $R^1 = R^2$ = Et, R^3 = H, M = 2H; **194** R = Me, $R^1 = R^2$ = Et, R^3 = H, M = 2H; **195**, **197** R = Me, M = 2H; **196**, **198** R = Et, M = Ni

Heating DMAM-porphyrins and their nickel complexes with excess pyrrole, 3,4-diethylpyrrole, or 2,4-dimethyl-3-ethoxycarbonylpyrrole in methylene chloride or destabilized chloroform at reflux in the presence of excess MeI yields the corresponding meso-(2-pyrrolylmethyl)porphyrins **189-194** in 80-90% yield. Only products of addition at one of the α-positions is formed (for pyrrole and 3,4-diethylpyrrole). The reaction may be carried out such that the porphyrinylmethyl group adds immediately at two α-unsubstituted positions. Thus, the reaction of porphyrins **3** and **24** with 4,4′-dimethyl-3,3′-diethoxycarbonyl-2,2′-dipyrrolylmethane gives unique dimeric products **195** and **196**, while the reaction of pyrrolylporphyrinylmethane **193** with DMAM-porphyrins and DMAM-chlorines **3**, **24**, and **34** leads to dimers **197-199**. In almost all cases, the reaction of DMAM-porphyrins with pyrroles and dipyrrolylmethanes at the unsubstituted α-position proceeds under rather mild conditions in high yield and is never accompanied by dimerization to give ethanebisporphyrins.

Scheme 27



3.5. Synthesis and Properties of Meso-Dimethylamino Propenylporphyrin Derivatives

The use of the complex of 3-(dimethylamino)acrolein (DMA) and $POCl_3$ instead of DMF/$POCl_3$ in order to introduce a formylvinyl group in the Vilsmeier reaction holds great promise for all porphyrin chemistry. The present data [74-77] indicate the following general conclusions:

a) the introduction of the acrolein group is possible only at the meso-positions of the porphyrin or chlorine ring when a β-vinyl group is present in the macrocycles,

b) treatment of nickel or copper complexes of meso-formylvinylporphyrins in sulfuric acid leads, depending on the conditions, to demetallation products or benzochlorines, and

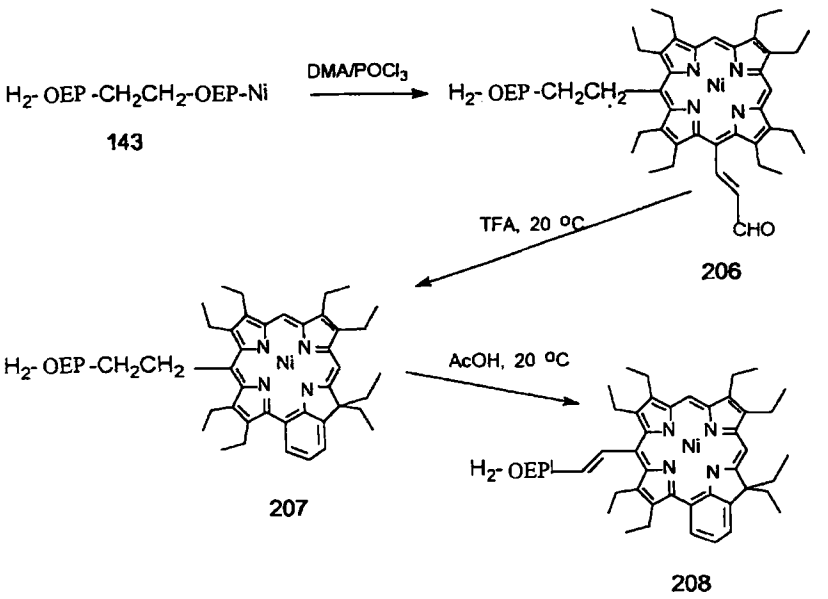
c) there have been no studies on the synthesis and chemical properties of meso-dimethylamino-propenyl(DMAP)-porphyrins (vinylogs of meso-DMAM-porphyrins).

The preliminary results of a study of the chemical properties of DMAP-porphyrins reduce to the following [78].

Treatment of PC obtained after carrying out the Vilsmeier reaction starting from the nickel complex of OEP and $DMA/POCl_3$ using $NaBH_4$ leads to amine **200**, which readily reacts with MeI to give the corresponding iodomethylate **201**. Thermolysis of this salt in dichloroethane at reflux leads to intramolecular cyclization of the meso-substituent to give chlorines **202** and **203**, which we have termed "autralochlorines" [78]. Heating these derivatives in acetic acid at 90°C leads to the reported benzochlorine **204** and acetate **205** in 1:3 ratio.

The transformations shown in Scheme 28 starting from complex **143** were carried out to obtain dimers containing both porphyrin and benzochlorine macrocycles.

Scheme 28



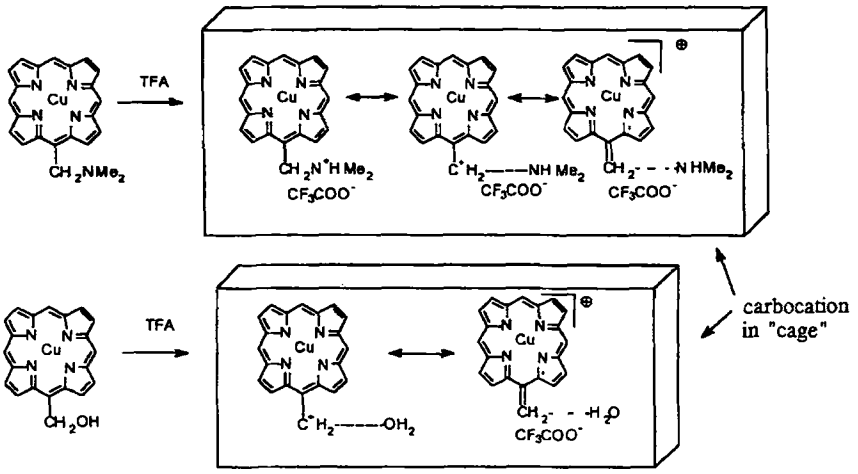
This scheme shows that the Vilsmeier reaction with $DMA/POCl_3$ proceeds exclusively at the meso-position adjacent to the ethane bridge to give a single isomer **206** (in contrast to the case of $DMF/POCl_3$), which cyclizes regioselectively in trifluoroacetic acid to give benzochlorine **207**. The latter is oxidized readily over 15 min at room temperature to give *trans*-dimer **208**.

Thus, even the first preliminary experiments on the use of $DMA/POCl_3$ for the synthesis of DMAP-porphyrins and various derived chlorines carried out in our laboratory have yielded extremely interesting and unexpected results and may hold not less interest than the study of DMAM-porphyrins.

3.6. Formation and Spectral Properties of Stabilized Meso-Methyleneporphyrin Carbocations. Protonated Porphyrin Forms

In this review, we have used the concept of a benzyl-type or benzylic carbocation or exomethyleneporphyrin carbocation to explain the chemical properties of DMAM-porphyrins and their metal complexes in reactions with nucleophiles although their reactions with alcohols or CH-acids in the presence of zinc acetate or alkyl halide do not cause any special external effects. Nevertheless, the state of the carbocation for several metal complexes of DMAM-porphyrins such as the copper and nickel complexes may be readily visualized since, in the case of porphyrins, the stabilization of the carbocation occurs due to redistribution of positive charge over the entire macrocycle as shown in Scheme 29.

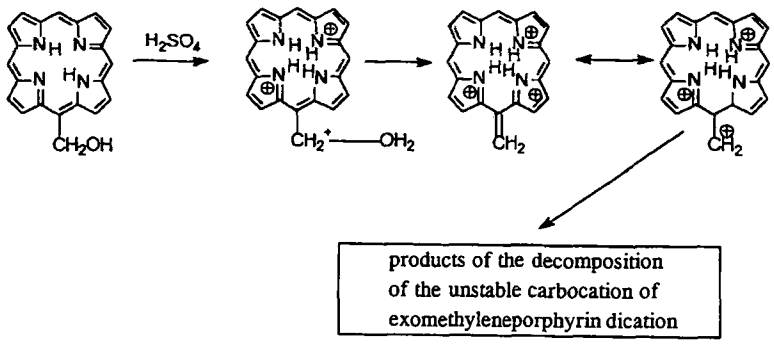
Scheme 29



The stabilized carbocation is formed, for example, upon the addition of trifluoroacetic acid to a dilute solution of Cu-Por-CH_2NMe_2 in chloroform, carbon tetrachloride, or dichloroethane. The color of the solution abruptly changes from red, which is common for most metal porphyrins, to yellow with λ_{max} 380, 452, and 1015 nm. The finding of a strong near-IR band at 1015 nm was attributed to the formation of a charge-transfer complex, i.e., a carbocation stabilized by a solvation shell consisting of solvent molecules. Absolutely the same spectrum arises upon the addition of trifluoroacetic acid to solutions of Cu-Por-CH_2OR, indicating the identical nature of the stabilized carbocations formed in both cases [31]. We especially refer to the concept of a "dilute solution," in which the carbocations are stabilized by a solvation shell. In the absence of solvating solvent (CCl_4), for example, when Cu-Por-CH_2OR is dissolved in a minimal amount of trifluoroacetic acid, disproportionation of the carbocation occurs with generation of numerous products, among which metal complexes of ethanebisporphyrins are the most interesting.

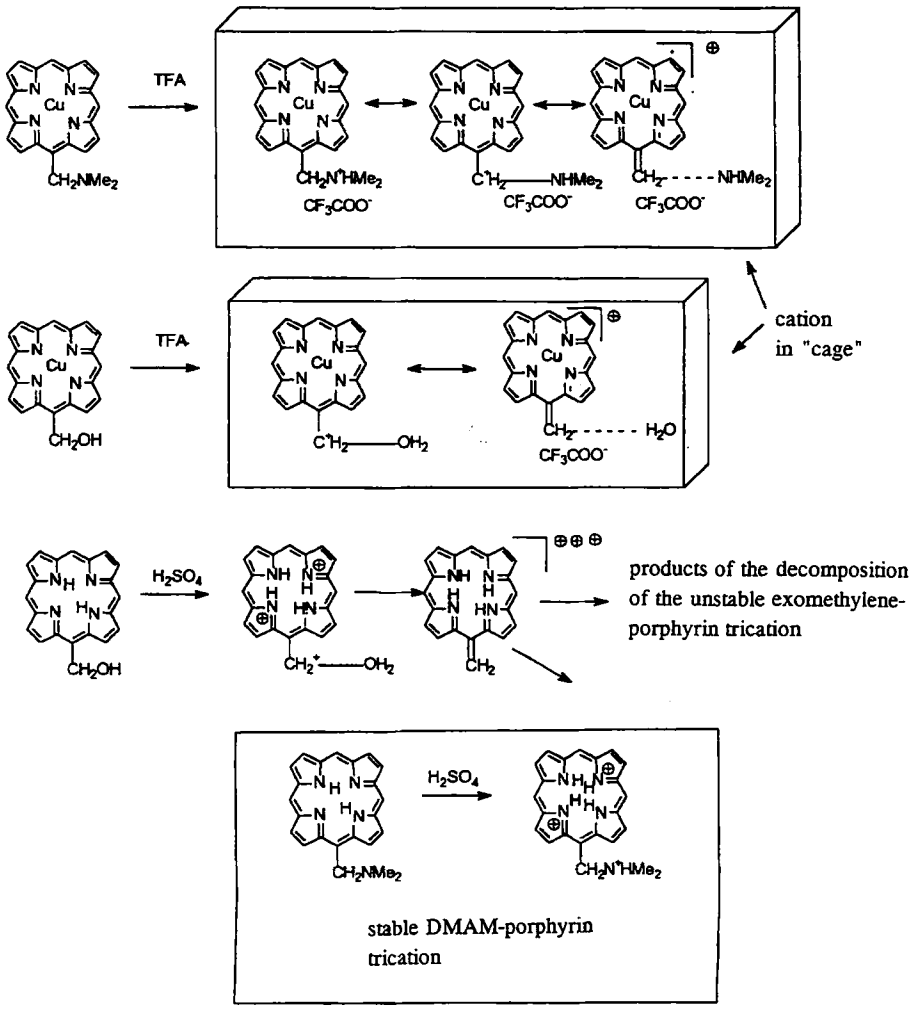
The carbocation of nonmetallic meso-methyleneporphyrin as a trication may be observed initially by the yellow color arising upon dissolving meso-alkoxymethylporphyrins in sulfuric acid, in which there is protonation not only of the central pyrrole nitrogen atoms but also of the ethereal oxygen atom to give an oxonium ion. Loss of alcohol or water gives the carbocation of the exomethyleneporphyrin dication, which decomposes into a wide variety of numerous products. Theoretical justification was found for the generation of this carbocation. A CNDO/S quantum chemical calculation showed that about a third of the positive charge is found on the exo-methylene carbon and a quarter of this charge is found on the meso-carbon atoms, while the remaining positive charge is distributed over the entire macrocycle [79].

On the other hand, dissolving meso-DMAM-porphyrins in sulfuric acid gives the classical protonation product at three nitrogen atoms (one amine and two pyrrole nitrogen atoms) without transformation of the carbocation, which accounts for the stability of these nonmetallic porphyrins under acid conditions such that chemistry of DMAM-porphyrins is possible.



CONCLUSIONS

Some conclusions drawn from our study of the Vilsmeier reaction in porphyrin chemistry, mainly for the synthesis of meso-DMAM-porphyrins and investigation of the chemical properties of these compounds, over the past 25 years are offered in this review. In addition to many remarkably varied chemical transformations, which can be carried out using DMAM-porphyrins, these compounds themselves hold great practical significance. For example, the introduction of the pharmocogenic DMAM group into the porphyrin macrocycle leads to a marked increase in the radioprotective properties of porphyrins [9, 80-83], among which the greatest radioprotective effect is seen for water-soluble meso-DMAM-MP-IX salts. The formation of DMAM-porphyrins may be recommended for establishing the structure of new porphyrins or determination of the isomeric purity of porphyrins formed by monopyrrole cyclotetramerization since isomeric DMAM-porphyrins are readily and rapidly identified by thin-layer chromatography. Our discussion has shown that the presence of a DMAM group in porphyrins facilitates the ready covalent addition of such porphyrins and their complexes to obtain immobilized catalysts [84]. The use of DMAM-porphyrins for the synthesis of dimeric ethanebisporphyrins has provided a practical solution for the synthesis of these compounds. Thus, it may be stated in all certainty that further work on the chemistry of aminomethylporphyrin derivatives will provide many additional interesting results.



The author expresses his gratitude to the Russian Basic Research Fund for financial support of studies on porphyrin chemistry (Project Code No. 96-03-32102a/110).

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