Chemistry of Heterocyclic Compounds, Vol. 30, Nos. 11-12, 1994

FORMYLPORPHYRINS AND THEIR DERIVATIVES IN THE CHEMISTRY OF PORPHYRINS (REVIEW)

G. V. Ponomarev

Data on the synthesis and chemical transformations of formylporphyrins obtained with the Vilsmeier reaction are generalized in the review. Special attention is focused on synthesis of dimeric porphyrins.

Formylporphyrins are some of the most interesting and promising objects of investigation in the chemistry and physical chemistry of porphyrins. Data on the synthesis and transformations of formylporphyrins prepared with the Vilsmeier reaction are presented in the present review. Problems of the chemistry of meso-substituted porphyrins and chlorins are basically considered in the review. A great deal of information on synthesis of formylporphyrins by transformation of substituents already in the macrocycles ($CH=CH_2$, COOR, CH_2OH, COR, etc.) and by incorporation of a formyl group by Friedel–Crafts alkylation of metalloporphyrins with dichloromethylalkyl ethers in the presence of $SnCl_4$ or $SnBr_4$ is reported in the review in [1]. In addition, there are also data on the appearance of formylporphyrins as a result of cyclization of linear tetrapyrroles in [1, 2].

1. SYNTHESIS OF FORMYLPORPHYRINS

1.1. General Information on Use of the Vilsmeier Reaction in Porphyrin Chemistry

Several score of communications have been published over the past 30 years since the first studies on synthesis of meso-formyloctaalkylporphyrins in conditions of the Vilsmeier reaction directed by H. Inhoffen [3] and A. Johnson [4]; in summarizing them, the following conclusions can be drawn.

1. Of the many versions of the Vilsmeier reaction in porphyrin chemistry, only complexes of DMF, diisopropylformamide, or diisobutylformamide and 3-(dimethylamino)acrolein (DMA) with $POCl_3$ have been used up to now. Complexes of benzoyl chloride with DMF have been used exclusively for substitution of the primary hydroxyl in the CH_2CH_2OH group by chlorine [5, 6], for creation of a vinyl group from α-hydroxyethyl [7] or α-alkoxyethyl groups [8], and acrylic acid ester residue from the $CH(OH)CH_2COOMe$ group [9]. There are several examples of the use of more complex amides which are simultaneously substituents in porphyrin (for example, the CH_2CH_2NHAc group) in the Vilsmeier reaction for obtaining spiran derivatives and different chlorins [10].

2. Metal complexes of porphyrins, chlorins, or phlorins with most transition metals which are stable in the presence of HCl, formed as a result of the reaction, undergo formylation. On the example of formylation of metal complexes of [Co(II), Ni(II), Pd(II), Pt(II), Co(III), Mn(III), Fe(III), Al(III), Si(IV), Pt(IV)] meso-tetra(p-tolyl)porphyrin (TTP), a special study showed that the rate of formylation decreases in the order M(II) > M(III) > M(IV), and of the M(II), in the order Ni(II) > Cu(II) > Pd(II) > Pt(II) [11]. Cu(II), Ni(II), Co(II), and Fe(III)Cl complexes of porphyrins are used most frequently. The rate of formylation of octaalkylporphyrins varies as follows according to our data: Co(II) >> Cu(II) ~ Ni(II) >> Fe(III)Cl complexes, and hemins, i.e., complexes of porphyrins with Fe(III) Cl, can be used for formylation in the presence of alternative positions, for example, in β-unsubstituted porphyrins or chlorins and in vinylporphyrins for substitution in the most reactive position.

Institute of Biological and Medical Chemistry, Russian Academy of Medical Sciences, Moscow 119832. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1669-1696, November-December, 1994. Original article submitted September 26, 1994.

3. If there are vinyl groups in the porphyrin or chlorin, they primarily undergo attack by a Vilsmeier complex ($DMF/POCl_3$) with formation of a $-CH{=}CH{-}CHO$ group in the *trans* form [12]. However, the reaction of vinylchlorins with the $DMA/POCl_3$ complex only results in δ-meso-substitution [13].

4. If the porphyrin has β-unsubstituted positions, the reaction takes place at both β- and at meso positions [14]. The use of bulky diisobutylformamide instead of DMF decreases the probability of meso-substitution in the case of formylation of the Ni complex of deuteroporphyrin-IX dimethyl ester (Ni–DP–IX) [15], and only the unsubstituted β-position is formylated when diisopropylformamide is used [16]. The first term of the series – porphin, which is only formylated at the meso position in the presence of all unsubstituted both meso- and β-pyrrole positions, stands alone [17]. In our opinion, the results could perhaps be slightly different when the studies on formylation of porphin metal complexes are repeated.

5. Formylation of meso-tetraaryl(alkyl)porphyrin metal complexes, i.e., having eight β-unsubstituted pyrrole positions, only yields mono-β-formylporphyrins [18-20]. (There is only one communication [11] in which diformyl-TTP (2%) was obtained in formylation of FeCl-TTP in addition to 2-formyl-TTP (50%), and the formyl groups of diformyl-TTP are perhaps in opposite pyrrole rings.)

6. Porphyrin free bases (metal-free porphyrins) are not formylated in the conditions of the Vilsmeier reaction, although chlorination at the meso position with a low yield is possible [3].

In all cases of conducting the Vilsmeier reaction, the reaction mixture is treated with an aqueous solution of sodium acetate or dilute aqueous solution of base after the reaction ends with separation of the corresponding formylporphyrin metal complex. Our studies are an exception, as intermediate, stable imino salts which we called "phosphorus complexes" (PC) were separated. The latter have in turn been widely used for synthesis of different porphyrin and chlorin derivatives.

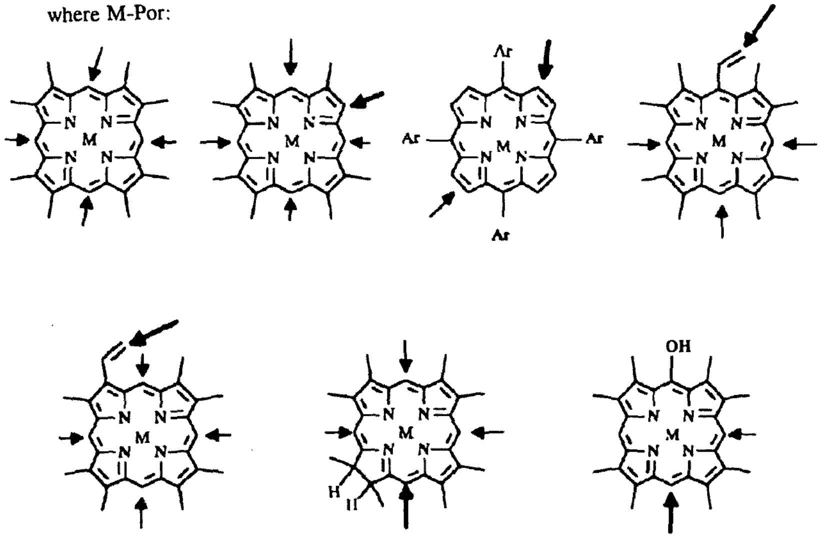
In general form, the Vilsmeier reaction can be represented as follows (the basic directions of attack by the Vilsmeier complex are indicated by the arrows):

$$\text{M-Por-H} + \left[\begin{array}{c} Me_2N^+{=}CHCl \\ (PO_2Cl_2)^- \end{array} \longleftrightarrow \begin{array}{c} Me_2N^+{=}CHOPOCl_2 \\ Cl^- \end{array}\right] \longrightarrow$$

"Vilsmeier complex"

$$\underset{\text{I (imino salt)}}{\text{M-Por-CH=N}^+\text{Me}_2\ \text{Cl}^-} \xrightarrow{OH^-} \text{M-Por-CHO}$$

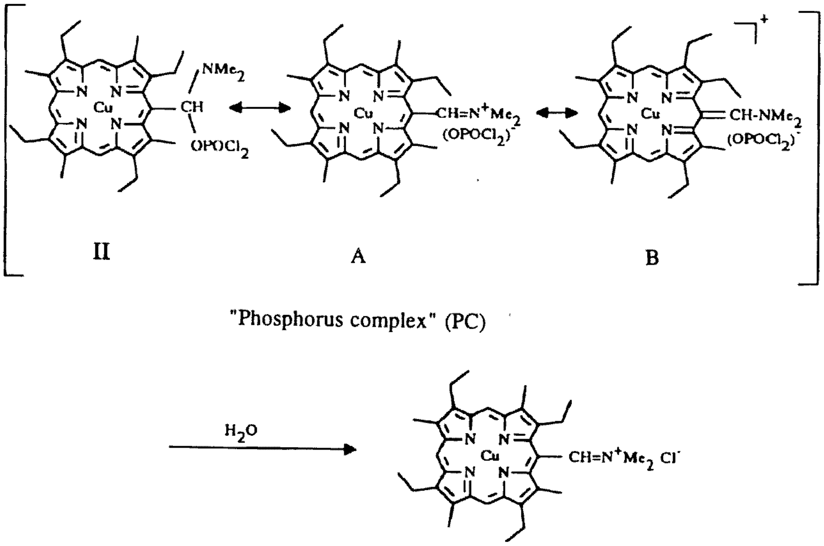
where M-Por:



It was hypothesized in [11] that intermediate imino salt I is formed as a result ot the reaction, and its hydrolysis without separation also yields the corresponding formylporphins.

Our studies [21] on formylation of etioporphyrin-I Cu complex (Cu-EP-I) showed that a crystalline complex stable in air is formed as a result of the reaction; based on analysis of the IR and UV spectra and the data from elemental analysis, structure II, where the C—O bond is "essentially" ionic and the C=N bond is "essentially" double, was proposed for it. Complexes of type II, which we called PC, are probably in two equilibrium states (A and B) whose ratio is a function of the solvent. When heated in water, PC are hydrolyzed into true imino salts which are easily converted into formylporphyrin metal complexes when treated with sodium acetate or dilute solutions of base in alcohol.

When PC are treated with aqueous solutions of ammonia or methylamine without heating, the corresponding meso-formylporphyrin aldimines or Schiff bases are formed, and reduction of PC with sodium borohydride in chloroform—methanol mixture yields meso-dimethylaminomethyl derivatives with an almost quantitative yield. However, the chemistry of Schiff bases and meso-aminomethylporphyrins is so interesting, unexpected, and vast that it will be examined in a separate review.



"Phosphorus complex" (PC)

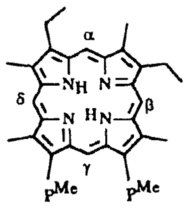
imino salt

1.2. Effect of Steric and Electronic Factors of Peripheral Substituents on the Direction and Rate of Formylation

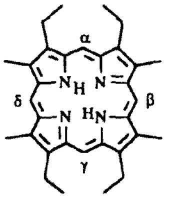
It was initially believed [12] that directed formylation was possible in the case of nonsymmetrically substituted porphyrins such as meso-porphyrin-IX dimethyl ester (MP-IX), for example, when the corresponding hemin, i.e., FeCl-MP-IX, was used. Formation of β-meso-formylporphyrin alone was postulated. In our opinion, in reality, substitution of one central atom by another could lead to some change in the ratios of the isomers formed due to a change in the overall reaction rate but nevertheless could not significantly affect the formylation process itself. According to our data [22], all four possible isomers of meso-formyl-MP-IX are formed in formylation of Cu, Ni, Co, and FeCl complexes of MP-IX, although only one of them, the most chromatographically mobile γ-formyl-MP-IX, can be relatively easily separated from a mixture of the other isomers with very close mobility by chromatographic methods, and this did not permit separating the individual substances and correctly establishing their structure [12].

We have now developed a convenient method for chromatographic separation of the products of formylation in the form of meso-dimethylaminomethyl (DMAM) derivatives and the corresponding aminoborane complexes and established the basic principles for demonstration of their structure using PMR methods [22-24]. All of the questions related to the possible incorrect interpretation of the PMR spectral data and erroneous establishment of the structure of meso-formylporphyrins were eliminated as a result.

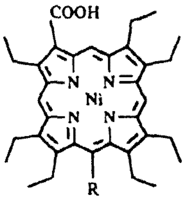
Predominant formylation in the $\beta(\delta)$-position due to the smaller shielding effect of the two neighbors with the meso position of the methyl substituents in comparison to the two ethyls in the $\alpha(\gamma)$-position was observed in the case of Cu and Ni complexes of etioporphyrin-II (EP-II) [23]. These data were obtained from both an analysis of the PMR spectrum of the reaction mixture, since separation of each isomer of β- and γ-formyl-EP-II in the individual state is a very laborious problem, and by separation of each isomer of DMAM-EP-II in the individual state.



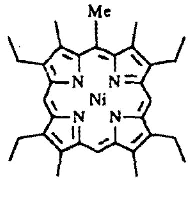
MP-IX



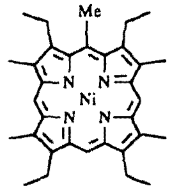
EP-II



III,IV



V



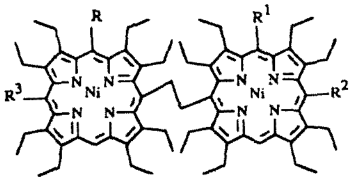
VI

Here and below: $p^{Me} = CH_2CH_2COOMe$; all not indicated R, R^1, R^2, R^3 = H; IV, R = CHO

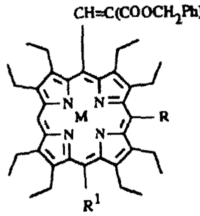
In addition to purely steric factors, the electronic (electron-acceptor or electron-donor) properties of pyrrole and meso substituents can also affect the reaction rate. Although all possible isomers are formed in formylation of complex III, formylporphyrin IV is obtained in a large amount [25].

The combined effect of the steric and electron-donor properties of meso substituents was established in formylation of two isomers of meso-methyl-EP-II – complexes V and VI [26]. The presence of a meso-methyl group in complexes V and VI significantly increases the reactivity of the molecule in electrophilic substitution, manifested by a decrease in the reaction time by 10-15 times in comparison to formylation of complexes of meso-unsubstituted EP-II [23] and causes a significant difference in the ratios of the isomers formed as a result of the reaction.

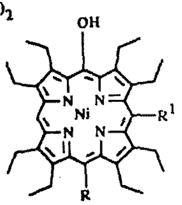
In formylation of dimer VII, which can be considered as a monomeso-substituted porphyrin, a mixture of complexes VIII-XI is formed with yields of 16, 33, 2, and 16%, respectively [27], i.e., porphyrins with formyl groups in β-meso positions adjacent to an ethane group are formed in a large amount. Other meso-substituted porphyrins, for example, complexes XII and XIII, are also formylated analogously [28]. Both neighboring β(δ)-meso positions (complexes XIV and XV) and the opposite γ-meso position (complexes XVI and XVII) are attacked. We come up against the manifestation of the directed effect of the central metal atom on the ratios of isomers formed for the first time here. Complexes XIV and XVI are separated with yields of 53 and 20%, and complexes XV and XVII are separated with yields of 19 and 53%, respectively.



VII - XI



XII - XVII



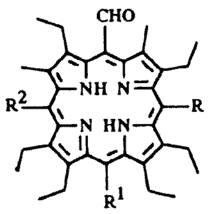
XVIII - XX

VIII R = CHO; IX R = R^1 = CHO; X R^2 = R^3 = CHO; XII M = Cu; XIII M = Ni; XIV M = Cu, R^1 = CHO; XV M = Cu, R^1 = CHO; XVI M = Ni, R = CHO; XVII M = Ni, R^1 = CHO; XIX R = CHO; XX R = R^1 = CHO

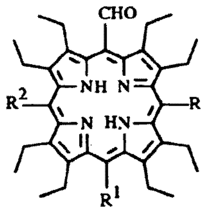
The hydroxy group in the meso position does not prevent incorporation of formyl groups. For example, in formylation of hydroxyporphyrin XVIII, two products are separated: XIX and XX [29]. In this case, the γ-position opposite the hydroxy group is most probably attacked first. As the examples show, the presence of different substituents in the meso position does not prevent the formylation reaction. The formyl group is an exception. Meso-formylporphyrins, in contrast to β-formylporphyrins, are not formylated in the conditions of the Vilsmeier reaction, as our experiment suggests. In our opinion, the protonated formyl group separated as a result of the reaction of HCl deactivates the porphyrin ring for electrophilic attack.

1.3. Polyformylation

The question of possible polyformylation has been debated for some time. In 1975, after prolonged heating of octaethylporphyrin Cu complex (Cu-OEP) with a large excess of Vilsmeier complex and demetallization, a small amount of α,γ-diformyl-OEP, whose structure was demonstrated with the PMR spectrum, was also separated together with meso-formyl-OEP in 1975 [30]. Individual compounds could not be separated in formylation of Co-OEP due to the formation of a large number of products of unknown structure as a result of the reaction. Before this [31], a substance which was probably a mixture of isomers of meso-diformyl-EP-I Co complexes was separated in formylation of Co-EP-I. However, the corresponding isomers of metal-free porphyrins could not be separated and their properties were not investigated. The data on the possibility of polyformylation were thus ambiguous and contradictory. In special studies [32-34], we were able to show for Cu, Ni, and Co complexes of EP-I and OEP that all possible products of polyformylation XXI-XXX are formed as a result of the reaction. Similar results were obtained later by K. M. Smith in polyformylation of EP-I complexes [35-36].



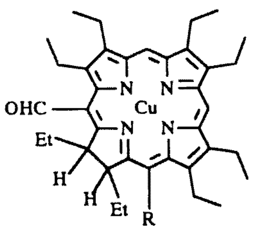
XXI — XXV



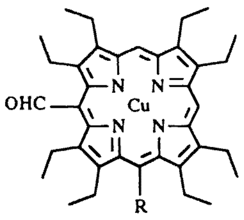
XXVI — XXX

XXII, XXVII R - CHO; XXIII, XXVIII R^1 - CHO; XXIV, XXIX R - R^1 - CHO;
XXV, XXX R - R^1 - R^2 - CHO

These studies showed that the reaction time must be increased significantly and a large excess of Vilsmeier complex must be used for obtaining polyformylporphyrins in comparison to synthesis of monoformyl derivatives. The PC formed in the initial stage of the reaction does not prevent subsequent electrophilic attacks either in the neighboring or in the opposite meso position. For this reason, the amount of α,β-diformyl-EP-I XXII is approximately two times higher than the amount of α,γ-diformyl-EP-I XXIII formed [33].



XXXI, XXXII

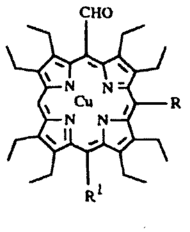


XXXIII, XXXIV

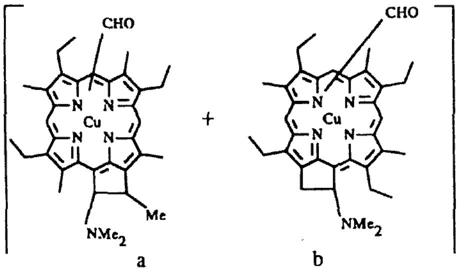
XXXII, XXXIV R - CHO

Directed synthesis of mono- and α,β-diformylporphyrins can be conducted by formylation of the corresponding chlorin with subsequent oxidation of the products obtained with dichlorodicyanobenzoquinone (DDQ). Not only complexes XXXI and XXXII but also the corresponding metalloporphyrins XXXIII and XXXIV in the form of an impurity are thus formed in prolonged treatment of octaethylchlorin Cu complex (Cu-OEC) [37, 38].

The general features of the mechanism of the polyformylation reaction are now clear. However, there are still several questions related to this process. In reality, a very large number of unidentified new substances is formed in polyformylation. The basic cause of their formation is in our opinion due to partial decomposition of the Vilsmeier complex during prolonged heating and the appearance of amines in the reaction mixture, so that synthesis of a series of secondary compounds is possible. We have separated some of them. They are complexes XXXV-XXXVII and cyclopentaneporphyrins XXXVIIIa, b [33, 34]. The structure of the complexes was established after demetallization in conc. H_2SO_4 to the corresponding porphyrins with the PMR and mass spectra.



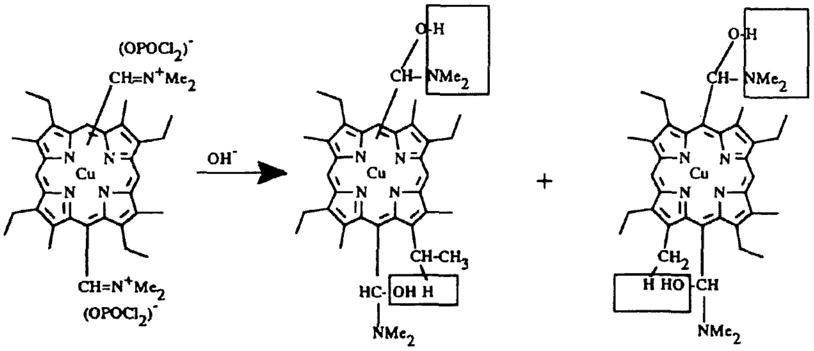
XXXV — XXXVII



XXXVIII a,b

XXXV R = Cl; XXXVII R^1 = CH=NMe

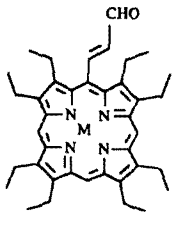
The formation of meso-chloro derivatives XXXV and XXXVI in Vilsmeier formylation is not particularly surprising. This process is observed relatively frequently in treatment of different substances with Vilsmeier complex. The formation of complex XXXVII is easily explained by the appearance of a small amount of methylamine from DMF in the reaction mixture during prolonged heating, and its reaction with the intermediate PC. Explaining the formation of complexes of the type of XXXVIIIa, b is more complicated. They are only obtained when the reaction mixture is treated with an aqueous solution of base and not with the traditional aqueous solution of sodium acetate, i.e., in more rigorous conditions of hydrolysis of PC. We propose the following scheme for this transformation:



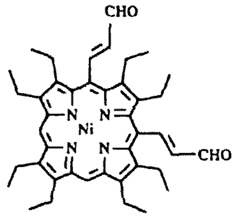
In contrast to the conditions of monoformylation in which PC is easily degraded into formylporphyrin exclusively in the presence of sodium acetate or a dilute solution of base, the probability of intramolecular cyclization with formation of cyclopentaneporphyrins is increased in the case of di-PC and even more for tri-PC due to spatial approach of the imino salt to the neighboring β-alkyl substituents. The appearance of a very large amount of very different substances during prolonged formylation is probably related to this factor. In general, as we will show below, the formation of compounds with additional rings due to β-alkyl and meso substituents is characteristic of porphyrins. (Of course, the β-alkyl substituents are transformed into reactive alkylidene substituents during cyclization.)

1.4. Use of 3-(Dimethylamino)acrolein/POCl$_3$ Complex in Porphyrin Chemistry

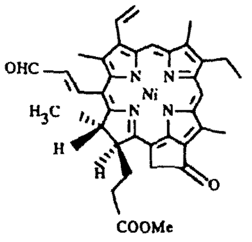
Important progress was made in using the Vilsmeier reaction for modification of porphyrins and chlorins after K. M. Smith et al. [13, 39] succeeded in showing that DMA/POCl$_3$ complex in methylene chloride as the solvent could be successfully used for synthesis of different derivatives containing an acrolein group in the meso positions of porphyrins and chlorins. The reaction takes place in soft conditions at room temperature in boiling the reaction mixture. Disubstituted products can also be formed in the last case. Some of the compounds synthesized in [13] – XXXIX-XLV – are listed below. The reaction time in hours and yield in % are shown in parentheses. It is most interesting that in the case of pyropheophorbide-*a* methyl ester Ni complex, the reaction takes place at the δ-meso position to vinylchlorin XLII, and not at the vinyl group as with use of DMF/POCl$_3$ [12]. Porphyrins containing unsubstituted pyrrole positions react exclusively at meso positions, which was demonstrated on the example of DP-IX derivatives. Complexes of 5,15-diarylporphyrins also easily form acrolein derivatives XLVI [40], XLVII, and XLVIII [41].



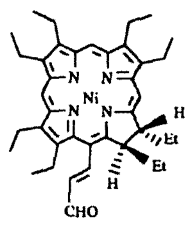
XXXIX (18 h, 57%)
XL (8 h, 85 %)



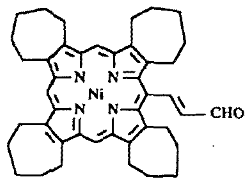
XLI (24 h, 55%)



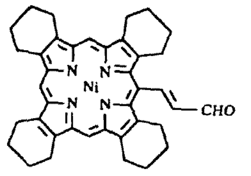
XLII (8 h, 63%)



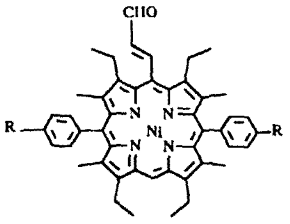
XLIII (3,5 h,81%)



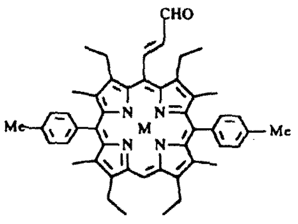
XLIV (11 h, 72%)



XLV (11 h, 65 %)



XLVI



XLVII (4 h , 65%)
XLVIII (4 h , 60%)

XXXIX, XLVIII, M = Cu; XL, XLVII, M = Ni; XLVI, R = H, Me, NMe$_2$, NO$_2$

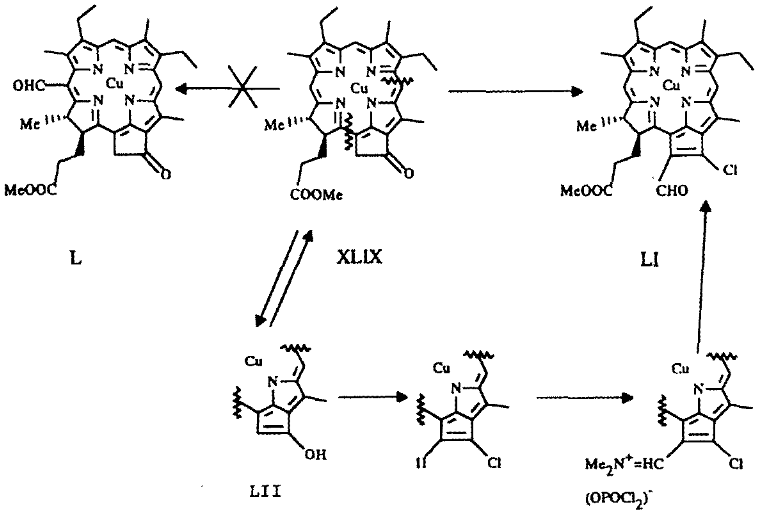
This group of different porphyrins and chlorins containing an acrolein substituent indicate the great promise of using DMA/$POCl_3$ in the chemistry of tetrapyrrole compounds, especially in comparison to the version of formylation of vinylporphyrins with DMF/$POCl_3$.

1.5. Chloroformylation of Chlorins Containing a Cyclopentane Ring

It was shown above that formation of meso-chloro-meso-formylporphyrins in the form of an impurity is possible in prolonged heating of metalloporphyrins with an excess of Vilsmeier complex. However, in the case of chlorins containing a cyclopentanone ring, this process becomes predominant.

Product of chloroformylation LI was exclusively formed in attempted formylation of methylpyropheophorbide-*a* Cu-complex XLIX to obtain the corresponding δ-formyl derivative L [42].

The formation of complex LI can be attributed to the reaction of Vilsmeier complex with tautomeric enol LII, in which a hydroxy group is easily substituted for the chlorine atom, and a vinyl proton is easily exchanged for a formyl group according to the scheme:



2. PROPERTIES OF FORMYLPORPHYRINS

2.1. Physicochemical Properties of Formylporphyrins

Before examining the chemical properties of formylporphyrins, it is necessary to present some brief information on their physicochemical properties.

Formylporphyrins containing an aldehyde group on the periphery of the macrocycle, i.e., in the β-position of the pyrrole rings, significantly differ from meso-formylporphyrins in their physicochemical properties. Although β-formylporphyrins in which the aldehyde group is conjugated with the macrocycle ($\nu_{C=O}$ 1650-1665 cm^{-1}) exhibit all of the chemical properties characteristic of arylaldehydes, meso-formylporphyrins and especially meso-polyformylporphyrins in which the aldehyde groups are significantly removed from conjugation with the macrocycle ($\nu_{C=O}$ 1695-1705 cm^{-1}) due to steric hindrances caused by neighboring pyrrole substituents have a number of unexpected new spectral and chemical properties. (The meso-formyl group in chlorins next to a reduced pyrrole ring has $\nu_{C=O}$ of 1660 cm^{-1}, since in this case the steric hindrances are much weaker, and more active reaction with the macrocycle is possible [43].)

The presence of an additional broad long-wave band in the electronic spectrum in the 650-670 nm region which becomes predominant and totally overlaps the four traditional bands in the visible region in polyformylporphyrins is a distinctive feature of meso-formylporphyrins from β-formylporphyrins. All of the characteristic features of the spectra of porphyrins are nevertheless preserved in the PMR spectra. The signals of all protons are shifted to the strong field with an increase in the number of formyl groups. In studying the PMR spectra of EP-I derivatives XXI-XXIV, it was found that the contribution of each meso-substituent to proton shielding of methyl and meso protons is additive and consists of 0.26 and 0.33 ppm, respectively [33].

Together with A. Sidorov [44] and T. Ivanova [45], we conducted a detailed study of the electronic and IR spectra of meso-formylporphyrins. We found a correlation between the absorption spectra of the different forms of association as a function of the solvating properties of the solvent, temperature, and aggregate state. It was found that the new band in the 650-680 nm region in the electronic spectra of metalloporphyrins characteristic of formylporphyrins is caused by both intermolecular association of the "metal–carbonyl" type and by the electronic interaction of the π-system of the macrocycle with the meso-formyl group.

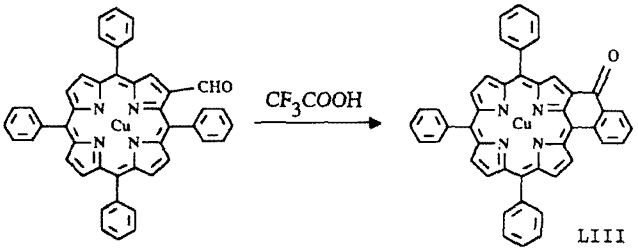
The capacity of meso-formylporphyrin metal complexes for different types of association both in solutions and in the crystalline state can significantly alter the overall shape of the IR spectrum for the same compound as a function of its crystalline form. For example, the existence of two crystalline forms – "red" with $\nu_{C=O}$ 1701 cm^{-1} and "blue" with $\nu_{C=O}$ 1700, 1602, 1572, and 1545 cm^{-1} is possible for the meso-formyl-OEP Zn complex as a function of the rate of crystallization, while several carbonyl absorption bands are always observed in the 1550-1700 cm^{-1} region in meso-formyl-EP-I Mg complex, which exists both in solution and in the crystalline state exclusively in the form of associates, and the most intense band is at 1595 cm^{-1}.

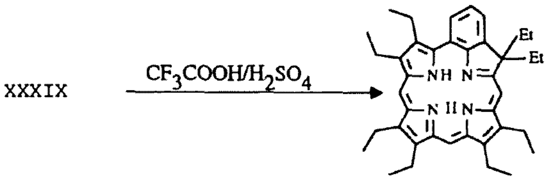
These data are reported to show that incorporation of a formyl group in the meso position can very strongly alter both the electronic and the IR spectra of porphyrins. This should always be taken into consideration in synthesis of compounds of this kind.

2.2. Demetallization of Formylporphyrin Metal Complexes

As indicated above, the corresponding formylporphyrin metal complexes are formed as a result of the Vilsmeier reaction. These are Cu and Ni complexes in the absolute majority of the cases. Co complexes are sometimes used when it is necessary to increase the reactivity of the starting metal complex, for example, for obtaining polyformylporphyrins [33, 34] or for significantly accelerating formylation in the case of β-formylation of tetraphenylporphyrin derivatives [20, 46]. In rare cases when it is desirable to exclude meso-formylation, for example, in formylation of vinylporphyrins [12] or when the formylporphyrin copper or nickel complexes formed are not demetallized in ordinary conditions, hemins are used for synthesis, and the formylhemins formed are treated with iron(II) sulfate in conc. HCl. Concentrated H_2SO_4 or $H_2SO_4-CF_3COOH$ (TPA) are usually used for demetallization of formylporphyrin Cu, Ni, and Co complexes. However, different side reactions such as deformylation [30, 47], hydrolysis of esters when they are present in the molecule, cyclization [13, 48], and sulfation at aryl residues in the case of meso-tetraphenylporphyrins, as well as oxidation of the chlorin macrocycle into a porphyrin macrocycle [38], can take place in such relative rigorous conditions. This method cannot be used for demetallization of formylhemins, and a reducing method is usually used – treatment with a saturated solution of iron(II) sulfate in conc. HCl under nitrogen. Demetallization of TPA in the presence of ethanedithiol [49] or hydrogen sulfide [50] is sometimes used for derivatives of the chlorin series, but it has not been widely used in practice.

Cyclization can also take place in treatment of formylporphyrin metal complexes with TPA or $TPA-H_2SO_4$. For example, complex LIII, whose structure was established with the data from x-ray structural analysis (XSA) [48], is formed from β-formyl-TPP Cu complex, while complex XXXIX is cyclized into octaethylbenzochlorin LIV in addition to demetallization [13]. As these two examples show, treatment of meso-formylporphyrin metal complexes with conc. H_2SO_4 or a mixture of conc. H_2SO_4 and TPA in different proportions can yield very unexpected products. For this reason, using this mixture for treatment of porphyrins, chlorins, and their metal complexes requires special precautions.





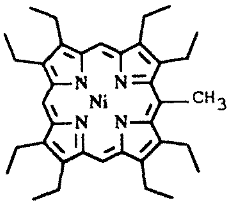
LIV

Our method of demetallization of Cu, Ni, Co, Pd, FeCl, and probably many other metal complexes is free of most of these drawbacks; it consists of briefly holding the corresponding metalloporphyrin in a solution of $POCl_3$ previously treated with a small amount of water [51]. The advantage of this method is the ease of dissolving almost any metal complex in the system (metalloporphyrins frequently dissolve slowly in conc. H_2SO_4 due to the high viscosity of the solvent). In addition, the reduction in the demetallization time decreases the number of by-products. This method is especially convenient in demetallization of relatively large amounts (more than 1-2 g) of metalloporphyrins and in demetallization of derivatives of the meso-tetraphenylporphyrin series [20, 52], where use of conc. H_2SO_4 can lead to the formation of different sulfated derivatives even at room temperature. It is highly recommended for demetallization of the most varied meso-substituted porphyrins, particularly PC, Schiff bases of meso-formylporphyrins, meso-aminomethylporphyrins, and different chlorins. The demetallizing effect of a mixture of phosphorus oxychloride with water is probably due to two causes: first, formation of a powerful complexing agent in the mixture on addition of water—polyphosphoric acid derivatives, and second, the presence of a high concentration of HCl. This method is somewhat similar to the version proposed by M. Momenteau et al. [19], consisting of treating copper complexes of substituted tetraphenylporphyrins in moist (containing up to 1% water) chloroform with gaseous HCl. However, the applicability of this method for other metal complexes is not known.

2.3. Reducing Dimerization of Formylporphyrins

One intensely developed direction in porphyrin chemistry is the synthesis of dimeric porphyrins and chlorins to obtain adequate models for the "special pair" for studying transfer and conversion of solar energy in photosynthesis and for creating different photosensitizers used in photodynamic treatment of cancer similar to PHOTOFRIN II or catalysts of multielectron transfer which model natural processes (see the detailed review by D. Dolphin [53]). In these studies, an important role is attributed to the study of dimerization of formylporphyrins and their derivatives.

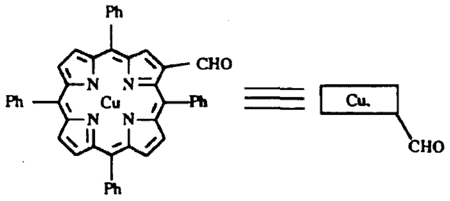
Dimerization of formylporphyrin metal complexes was first detected by D. Arnold [27] in treating meso-formyl-OEP nickel complex with $LiAlH_4$. In addition to dimer VII, a small amount of meso-methyl-OEP Ni complex LV was also formed. In addition, significant deformylation of the starting complex to Ni-OEP also took place. For this reason, the method has not been used in synthesis of dimeric porphyrins. When labile substituents or ester groups are present in the porphyrins, this method cannot be used in principle.

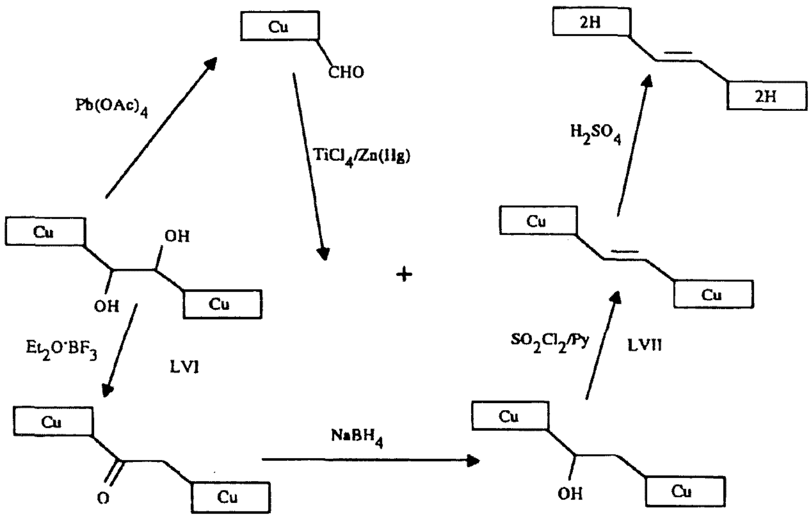


LV

The research by the Odessa scientists Z. Zhilina and Yu. Ishkov [54, 55] and K. M. Smith et al. [13, 56] made an important contribution to the study of dimerization of formylporphyrins.

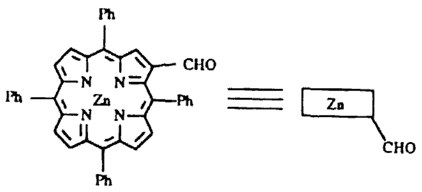
The possibility of dimerization of metalloporphyrins with aldehyde groups under tne effect of low-valence titanium in the $TiCl_4/Zn(Hg)$ system was investigated for the first time in [54, 55] on the example of different tetraarylporphyrin derivatives. The basic directions of the chemical transformations in dimerization of 2-formyl-TPP Cu and Zn complexes are shown in the scheme below.

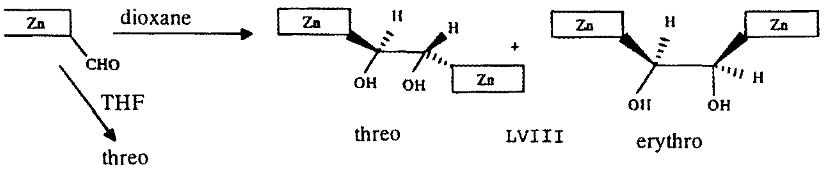


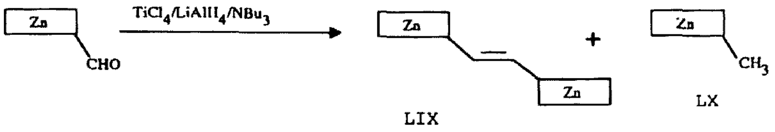


As the scheme shows, two basic products are formed as a result of the reaction – dimeric diol LVI and ethylenebisporphyrin LVII. Since the appearance of the corresponding ethylene in the *trans* form during the reaction is traditional in the study of dimerization of different aldehyde compounds in the presence of low-valence titanium, dimer LVII was assigned the structure of a *trans*-isomer.

The central metal atom and solvent have a large effect on the dimerization reaction. In the same conditions, Zn-TPP-CHO is dimerized into diol LVIII with a yield of 28%, while the yield is up to 57% in the presence of triethylamine. Substitution of dioxane by THF decreases the yield to 28%. However, although a mixture of *threo-* and *erythro*-isomers is formed in dioxane, only the chromatographically more mobile *threo*-isomer is formed in THF! It was hypothesized that the ability of titanium to form bulkier complexes with THF than with dioxane is the cause of this difference.



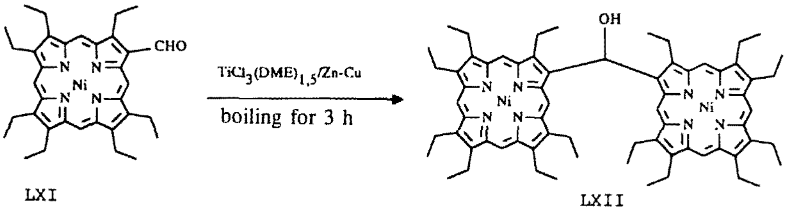




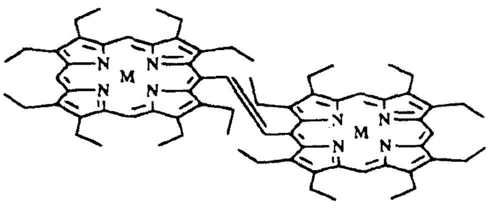
Dimerization in the presence of low-valence titanium can lead to both glycols and ethylenebisporphyrins. For example, only *trans*-isomer LIX is formed with a yield of 57% and 2-methyl-TPP Zn complex LX are formed in the TiCl$_4$/LiCl$_4$/NBu$_3$ system.

K. M. Smith et al. [13, 56] used the McMurry method [57] for dimerization of formylporphyrins; it consists of using TiCl$_3$/(DME)$_{1.5}$ solvate in the presence of Zn−Cu vapor in dry 1,2-dimethoxyethane (DME).

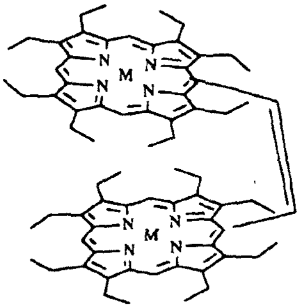
Not surprisingly, the reaction of dimerization of β-formylheptaethylporphyrin LXI, which could be considered the closest analog of the β-formyl-TPP metal complexes examined above, takes place according to another mechanism resembling self-condensation of pyrrolaldehydes. Bisporphyrinylcarbinol LXII is formed as a result of this reaction. Its structure was established with the data from x-ray structural analysis [58] and the PMR and mass spectra. (In conducting this synthesis, partial deformylation of the starting complex perhaps took place as a result of liberation of HCl during the reaction, and the formylporphyrin reacted with β-unsubstituted porphyrin which acted as a CH acid.)



The use of TiCl$_3$ was more predictive in other cases. In dimerization of meso-formyl-OEP copper and nickel complexes, ethylenebisporphyrin complexes LXIII-LXVI [13] were obtained, for which the conformation of *trans*-isomers traditional for this method was initially proposed. The situation was different in reality. The dimerization reaction in the case of meso-formylporphyrin metal complexes takes place nonstereoselectively and yields a mixture of *cis*- and *trans*-ethylenebisporphyrins in the ratio of 1:1 [58], from which the more soluble *cis*-isomer LXVI could be separated and good crystals could be obtained and investigated by XSA. It was found that the porphyrins are almost parallel in this isomer. The dihedral angle between the two planes drawn through the four nitrogen atoms of each macrocycle is a total of 1.9°, while the distance between planes is 3.36 Å. However, in studying the structure of *trans*-isomer LXIII, difficulties were encountered in obtaining crystals suitable for XSA. Independently and parallel to these studies, we succeeded in obtaining them by another directed method starting from the corresponding metal-free dimer in the form of a solvate with CHCl$_3$ [59, 60], and XSA was conducted in the Department of Applied Chemistry at Osaka University [61]. It follows from the XSA data for dimer LXIII that the molecule is centrosymmetric relative to the central bridging double bond. The distance between two parallel planes drawn through the nitrogen atoms of each porphyrin is 4.27 Å, and the distance between the nickel atoms is 10.07 Å. XSA of dimer LXIII, but in the form of a solvate with toluene, is now being conducted at the University of California at Davis by Dr. M. O. Senge (personal communication).



LXIII, LXIV

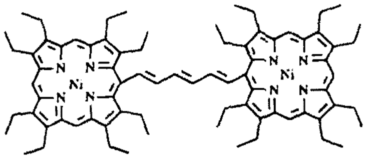


LXV, LXVI

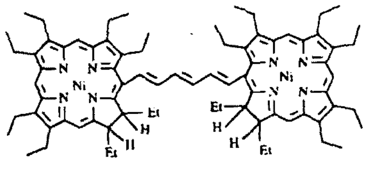
LXIII, LXV, M = Ni; LXIV, LXVI , M = Cu

McMurry dimerization with porphyrin and chlorin meso-acrolein derivatives takes place much more easily. Ni complexes containing bridges with a *trans,trans,trans*-1,3,5-hexatriene bond, compounds LXVII-LXXI, are formed [13].

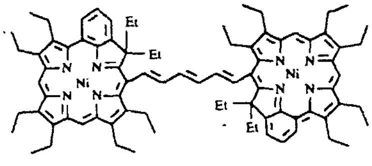
Yu. Ishkov and Z. Zhilina [62], K. M. Smith et al. [63], and German investigators [64] investigated dimerization of many porphyrins containing an aldehyde group in the *meta*, *ortho*, and *para* positions of the phenyl substituent in the presence of low-valence titanium, but these studies investigated the classic reaction of dimerization of arylaldehydes and are not examined in this review.



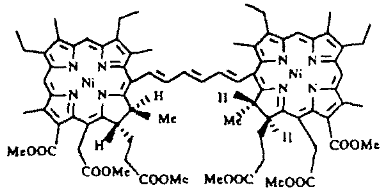
LXVII



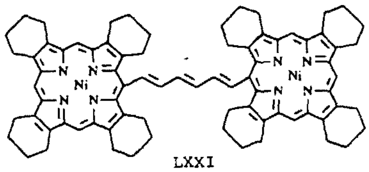
LXVIII



LXIX



LXX



LXXI

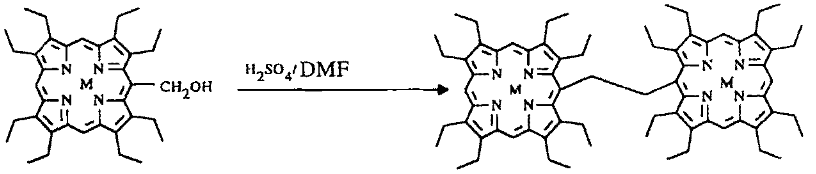
2.4. Reduction of Formyl Derivatives to Meso-hydroxymethylporphyrins and Meso-hydroxymethylchlorins with Metal Hydrides and Their Chemical Properties

Formylporphyrins and their metal complexes are easily reduced to the corresponding hydroxymethyl derivatives with a high yield. Reduction is usually conducted with $NaBH_4$ with boiling in THF solution [3] or without heating in methylene chloride–methanol for several hours [65]. Based on our experience in obtaining many meso-hydroxymethylporphyrins, the best version is addition of a rapidly prepared solution of sodium borohydride in methanol to a solution of porphyrin in chloroform. In this version, the reaction takes place in several minutes and heating is not required.

Meso-hydroxymethylporphyrins and meso-hydroxymethylchlorins have been widely used in synthesis of the most varied derivatives – dimers, ethers, meso-methylporphyrins or chlorins, etc. Synthesis of ethanebisporphyrins and ethanebischlorins is the most interesting.

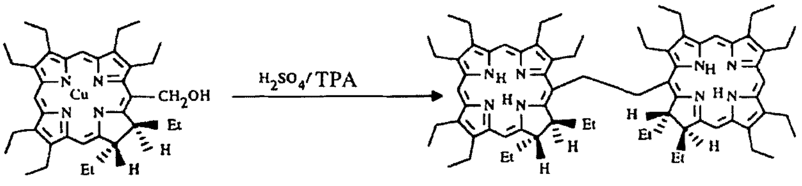
2.4.1. Dimerization of Meso-hydroxymethylporphyrins and Meso-hydroxymethylchlorins

D. Arnold [27] found for the first time in 1977 that Cu and Ni complexes of meso-hydroxymethyl-OEP LXXII and LXXIII are dimerized into the corresponding ethanebisporphyrin metal complexes when heated in DMF in the presence of catalytic quantities of conc. H_2SO_4 with yields from 13% for copper complex LXXIV to 45% for nickel complex VII. They hypothesized that the ability of the central metal atom to change valence, i.e., to participate in redox processes in which *exo*-methyleneporphyrin radicals are formed, could play the determining role in dimerization of carbocations of *exo*-methyleneporphyrin metal complexes. This hypothesis was based on the fact that metal-free porphyrins are not dimerized in these conditions, but copper complex LXXII was dimerized with a lower yield than for nickel LXXIII. The molecular structure was determined for complex VII with XSA data and it was shown that the molecule in the crystalline state has a stretched hindered conformation with the center of symmetry on the ethane bridge, while the porphyrin macrocycles are plane-parallel [66]. The crystal cell parameters and distances between the nickel atoms and porphyrin planes were very close to the *trans*-ethylenebisporphyrin LXIII which we synthesized [61]. However, no one has reproduced these results yet and no other dimers have been obtained with this method, probably due to the complexity of separating the intermediate products and the ambiguity of the results in conducting such a process.



LXXII, LXXIII VII, LXXIV

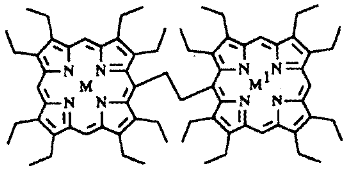
LXXII, VII, M = Ni; LXXIII, LXXIV, M = Cu



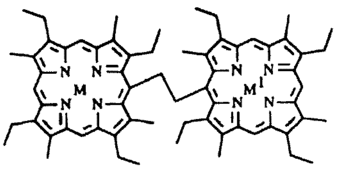
LXXV LXXVI

Meso-hydroxymethylporphyrin metal complexes cannot be demetallized in H_2SO_4−TPA, perhaps because dimers are formed [65]. Chlorine derivatives can also be dimerized in these conditions. Dimer LXXVI [38] was obtained from complex LXXV without separation of intermediate copper bis- and monocomplexes; based on the XSA data, it was found that it forms two crystalline forms, and the macrocycles in each of these forms are rotated by some angle relative to each other and are noncoplanar [67], in contrast to ethanebisporphyrin VII [66]. There are no published PMR data for bischlorin LXXVI, and the conformation of this dimer in solution is not known.

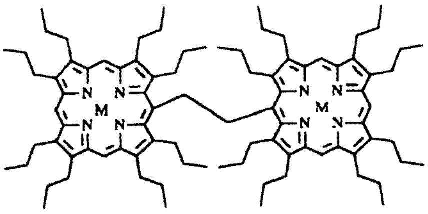
We found that dimerization of meso-hydroxymethylporphyrin copper complexes takes place more rapidly in TPA [68-70], while the corresponding nickel complexes form a difficult to separate mixture of labile products with similar chromatographic mobility, including very insignificant amounts of dimers. For this reason, dimerization of copper complexes alone was subsequently investigated. As a function of the metalloporphyrin−TPA ratio, both ethanebisporphyrins LXXIV, LXXVII-LXXIX and the corresponding ethers LXXX, LXXXI can be formed. Dimeric ethers are formed in a larger amountin dilute solutions, i.e., with a metalloporphyrin−TPA ratio of more than 1:100 (0.1 g of complex in 10 ml and more of TPA). Holding the complexes in TPA for several minutes with a metalloporphyrin−TPA ratio of 1:5-10 basically causes formation of ethanebisporphyrin copper complexes with a yield of 45-55%. Use of H_2SO_4−TPA mixture causes the formation of dimers containing only one copper atom − LXXXII, LXXXIII − or nickel atom − LXXXIV [70].



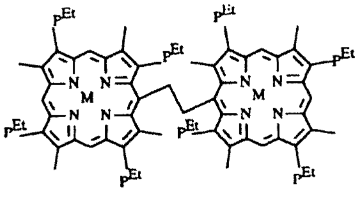
LXXIV, LXXXII, LXXXIV, LXXXV



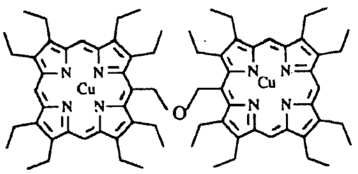
LXXVII, LXXXIII,LXXXVI



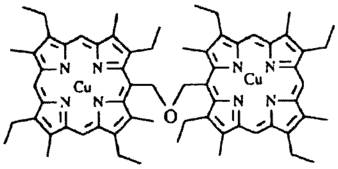
LXXVIII, LXXXVII



LXXIX, LXXXVIII



LXXX



LXXXI

p^{Et} - CH_2CH_2COOEt

LXXIV, LXXVII, LXXVIII, LXXIX M - M^1 - Cu; LXXXII, LXXXIII M - Cu, M1 - 2H;
LXXXIV M - Ni, M^1 - 2H; LXXXVI M - M^1 - 2H; LXXXVII, LXXXVIII M - 2H

The formation of ethers in dilute solutions of TPA can easily be explained by the reaction of the initially formed corresponding carbocation with the unprotonated initial complex present in the solution according to the classic scheme:

$$\text{Cu-Por—CH}_2\text{OH} + \text{CF}_3\text{COOH} \rightarrow \text{Cu-Por—CH}_2\text{—O}^+\text{H}_2 + \text{CF}_3\text{COO}^-$$

$$\text{Cu-Por—CH}_2\text{—O}^+\text{H}_2 \rightarrow \text{Cu-Por—CH}_2^+ + \text{H}_2\text{O}$$

$$\text{Cu-Por—CH}_2^+ + \text{Cu-Por—CH}_2\text{OH} \rightarrow \text{Cu-Por—CH}_2\text{OCH}_2\text{—Por-Cu} + \text{H}^+$$

However, a totally different reaction is characteristic of concentrated solutions, and either disproportionation of the intermediate carbocation or cationic dimerization of *exo*-methyleneporphyrin according to the following scheme probably takes place as a result:

$$\text{M-Por—CH}_2^+ \rightarrow [\text{M-Por}]^+\text{=CH}_2 \rightarrow [\text{M-Por—CH}_2\text{—CH}_2\text{—Por-M}]^{++}$$

$$[\text{M-Por—CH}_2\text{—CH}_2\text{—Por-M}]^{++} + 2e^- \rightarrow \text{M-Por—CH}_2\text{—CH}_2\text{—Por-M}$$

or

$$2\text{M-Por—CH}_2^+ + 2e^- \rightarrow 2\text{M-Por—CH}_2^{\cdot} \rightarrow \text{M-Por—CH}_2\text{—CH}_2\text{—Por-M}$$

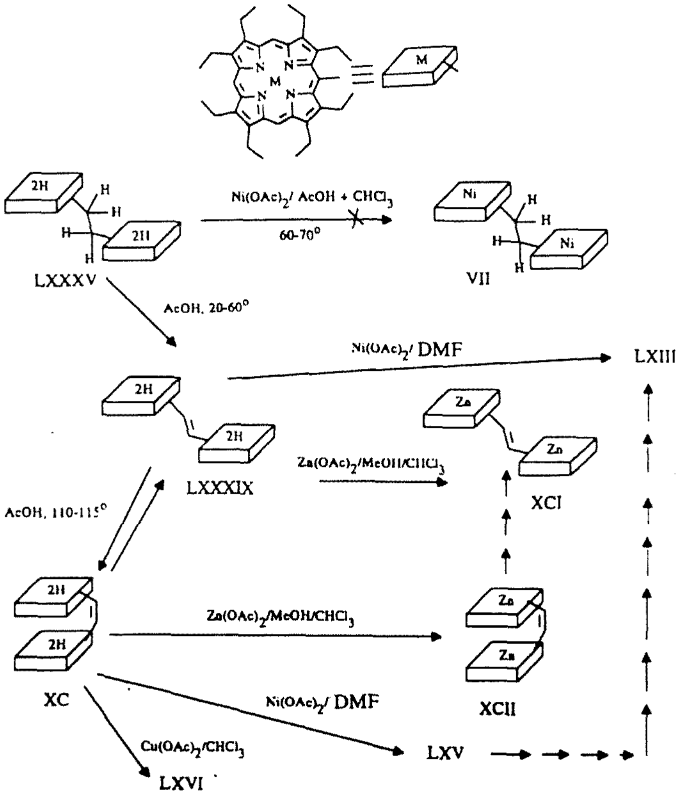
Electron transfer to the bisporphyrin dication or the carbocation can take place due to disproportionation of the intermediate products formed from the carbocations. For this reason, the yield of final dimers does not exceed 45-55%.

Obtaining dimers containing only one copper atom or any other metal atom as a result of the reaction is of some interest. Such compounds can be used for fabricating catalysts of multielectron transfer, creating models of the photosynthesis "special pair," and for other purposes, for example, for subsequent formylation.

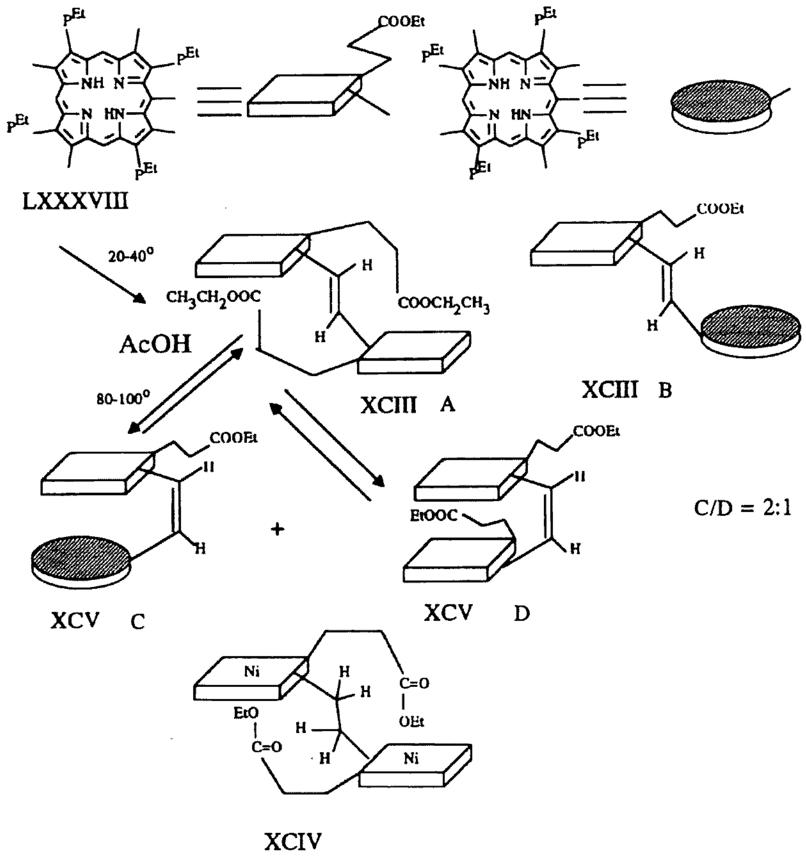
The corresponding free bases LXXXV-LXXXVIII are obtained from metal complexes of the dimers by demetallization in conc. H_2SO_4. Although it is known that meso-monoalkylporphyrins are demetallized extremely easily in conc. H_2SO_4 or H_2SO_4–TPA, rapid demetallization (in several minutes) of only one metal atom takes place in the case of ethanebisporphyrin copper and nickel complexes. Demetallization of any other metal ion takes place extremely slowly. Up to 5-6 h is required in some cases for exhaustive demetallization, for example, in obtaining dimer LXXXVIII. The intermediate dication of the ethanebisporphyrin metal monocomplex probably prevents the approach of another two protons and demetallization of the remaining copper or nickel atom.

A totally unexpected property of ethanebisporphyrins and ethanebischlorins was their capacity for quantitative conversion into the corresponding *trans*-ethylenebisporphyrins and chlorins in acetic and other lower fatty acids [59, 70-72], although this process virtually does not take place in sulfuric, TPA, or formic acid. This conversion was very accidentally detected. To confirm the structure of dimer LXXXV, it was decided to obtain complex VII from it in ordinary conditions, i.e., by heating with nickel acetate in chloroform – AcOH solution, and to compare its physicochemical properties with the published data [27, 66]. However, some new process took place in conducting this reaction so that a product with an unusual electronic spectrum having an intense absorption band at 508 nm and a broad band in the 700-750 nm region was formed. The PMR and mass spectral data showed that the product obtained is *trans*-ethylenebisporphyrin LXXXIX. A detailed study of this process showed that any ethanebisporphyrins and chlorins in a solution of AcOH and other lower fatty acids are converted into *trans*-ethylene dimers in the presence of air with a quantitative yield at 20-60°C. However, in the initial stage of the study, when the temperature conditions of this reaction were not accurately known, it was observed that boiling dimer LXXXV in AcOH significantly decreases the yield of the corresponding *trans*-dimer LXXXIX, and a new product which has similar chromatographic mobility to the starting ethanebisporphyrin appears. This product had a totally new type of electronic spectrum in which the broadened Soret band virtually overlapped the four classic bands in the visible part of the spectrum traditional for all porphyrins known up to now. After a detailed study of the process, it was found that the product is *cis*-isomer XC, where the methylene protons of the ethyl substituents in its PMR spectrum were in the form of eight sextets, i.e., each methylene proton was an AB system which reacted with the protons of the methyl group. These data unambiguously indicated the *cis* position of the macrocycles. The *cis-trans*-isomerism was thus totally accidentally detected at first glance, but it should nevertheless have obligatorily and ineluctably been found in the detailed study of the properties of ethanebisporphyrins.

cis-trans-Isomerism takes place in ethylenebisporphyrin molecules not only in solutions of lower fatty acids, but also in any high-boiling solvents. However, this process takes place at a lower temperature in fatty acids. As a consequence, in addition to the thermodynamic factor, protonation also plays an important role in isomerization, i.e., a chemical factor. The formation of nickel LXIII, copper LXIV, and zinc XCI complexes stabilizes the *trans*-form of dimer LXXXIX, and the conditions of transformation into *cis*-dimers have not yet been found. At the same time, nickel LXV and zinc XCII complexes of *cis*-isomer XC are spontaneously isomerized gradually in solutions into the corresponding *trans*-isomers. An exception is copper complex LXVI, which is stable in different solvents for a long time and does not tend to spontaneously isomerize [60].



Oxidative transformation of ethanebisporphyrins into *trans*-ethylenebisporphyrins takes place stereoselectively. Using conversion of ethane dimer LXXXVIII into *trans*-ethylene XCIII, we found [73] that of the two theoretically possible atropisomers of *trans*-dimer XCIII (A and B), only isomer A is formed. Its structure was established from an analysis of the PMR spectrum, which contained a triplet of two ethyl ether methyl groups in the region of −0.07 ppm, which indicated their reciprocal symmetric location very close to the centers of the macrocycles. It is interesting that in the crystalline state, the molecule of the nickel bis-complex of bis(coproporphyrinyl-I)ethane octaethyl ether XCIV is also a centrosymmetric structure similar in structure to the corresponding *trans*-dimer XCIII, which follows from the XSA data of complex XCIV obtained by Dr. M. O. Senge and Prof. K. M. Smith (University of California at Davis, personal communication). This conformation is optimum from the point of view of the mutual position of the substituents. At the same time, conversion of *trans*-dimer A into *cis*-isomer XCV on heating in AcOH takes place with formation of two atropisomers C and D in the ratio of 2:1. It is interesting that when *trans*-dimer XCIII is heated in AcOH, the equilibrium is shifted toward formation of the *cis*-isomer (up to 70%). In our opinion, this is due to mutual interlacing of the side substituents of the adjacent porphyrin rings with formation of a compact, thermodynamically stable coil.



Since ethylenebisporphyrins are only formed in weak fatty acids but are virtually not formed in sulfuric, TPA, or formic acids, formation of monocations in each macrocycle is initially required for oxidation of ethanebisporphyrins, since neither the bis- nor the monometal complex is oxidized into the corresponding ethylene dimers. Based on the data from the kinetic study of conversion of ethanebisporphyrins into ethylenebisporphyrins, hypotheses were advanced concerning the mechanism of the oxidation reaction in [72].

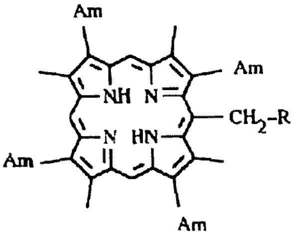
2.4.2. Chemical Properties of Meso-acetoxyhydroxymethylporphyrins

Treatment of meso-hydroxymethylporphyrins with Ac_2O in pyridine yields the corresponding reactive acetoxymethyl derivatives which easily form a "benzyl" carbocation [38, 65, 74]. They can be used for synthesis of very different compounds, since they easily react with nucleophiles, but they are primarily used for synthesis of meso-methylporphyrins and chlorins. For example, meso-methylporphyrin XCVII is formed by boiling porphyrin XCVI with tetrabutylammonium borohydride in dichloroethane for 5 min, although tetrabutylammonium borohydride can also be used for direct reduction of the meso-formyl group to a methyl group [38].

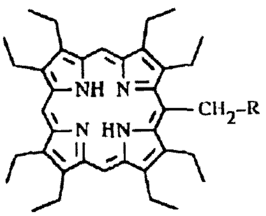
The meso-acetoxymethyl group is also easily reduced to a methyl group by hydrogenation on Pd/C in THF, but copper, or better, zinc complexes of meso-acetoxymethylporphyrins must be used for this [38].

It was shown in [74] that free bases can react with alcohols, but although the corresponding ethers are formed with methanol or ethanol during recrystallization, the reaction of porphyrin XCVIII with hexane-1,6-diol takes place only on melting to ether XCIX without formation of even traces of the dimeric ether. Meso-acetoxymethylporphyrins do not react in general with *tert*-butanol, attributed to steric causes. (In our opinion, the reaction with *tert*-butanol was unsuccessful due to the insufficient reactivity of meso-acetoxymethylporphyrins, since we succeeded in obtaining porphyrin C, but with another method [75].)

Meso-acetoxymethylporphyrins form the corresponding derivatives when heated with imidazole and 1-(3-aminopropyl)imidazole: CI and aminomethyl CII, and with butylmagnesium bromide, meso-amyl-OEP with yields of 64, 92, and 64%, respectively.



XCVI, XCVII



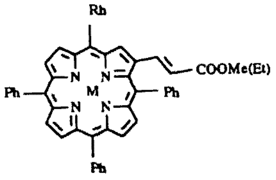
XCVIII — CII

XCVI, XCVIII R = OAc; XCVII R = H; XCIX R = O$(CH_2)_6$OH; C R = OBu-*t*;
CI R = Im; CII R = NH(CH_2)—Im
Im = 1-imidazolyl; Am = amyl

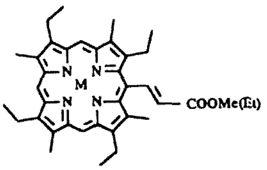
2.5. Wittig Reaction of Formylporphyrins with Phosphorus Ylides and Knoevenagel Reaction with Malonic Acid Derivatives

The Wittig reaction of formylporphyrins and their metal complexes with different ylides is one of the most successful and accessible methods of modification of meso- and formylporphyrins [20, 76-78].

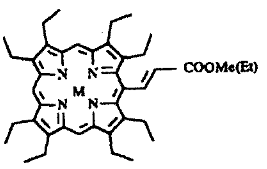
Either a stable Wittig reagent – methoxy(ethoxy)carbonylmethylenetriphenylphosphorane, or the corresponding ylides prepared *in situ* directly from the corresponding phosphonium salts and PhLi are usually used for synthesis of acrylic derivatives. The reaction is conducted by boiling nickel or copper porphyrin complexes with the corresponding ylide in xylene for 10-24 h. The yields are usually no less than 60-80%. Of the many compounds synthesized, acrylic acid derivatives CIII-CX are most frequently used for further chemical transformations.

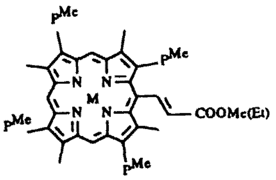


CIII,CIV



CV, CVI



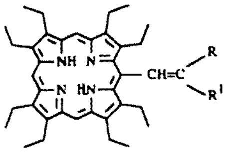


CVII, CVIII

CIX, CX

CIII, CV, CVII, CIX, M= Cu or Ni; CIV, CVI, CVIII, CX, M= 2H

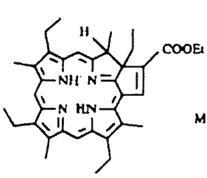
The Knoevenagel reaction is another promising reaction for modification of formylporphyrins into the corresponding acrylic acid derivatives. The reaction with β-formylporphyrins takes place in the classic version (in the presence of bases), but in the case of meso-formylporphyrins, which are easily deformylated in these conditions, using $TiCl_4$ as the catalyst is the best version [28]. (This reaction is usually used for obtaining vinyl derivatives or for obtaining acrylic acid derivatives.) The corresponding derivatives CXI-CXVI are obtained with a high (up to 70-90%) yield by reacting meso-formyl-OEP with malonic acid and its dimethyl, diethyl, dibenzyl, methylethyl, and monoethyl esters, while meso-vinyl-OEP and *trans*-meso-ethoxycarbonylvinyl-OEP are obtained with a 50-60% yield from CXI and CXVI by hydrogenation over Pd/C in AcOH.



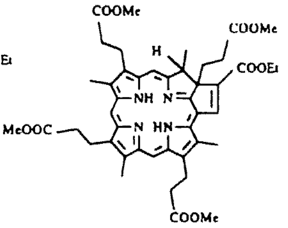
CXI-CXVI

CXI $R = R^1 = COOH$; CXII $R = R^1 = COOMe$; CXIII $R = R^1 = COOEt$; CXIV $R = R^1 = COOCH_2Ph$; CXV $R = COOMe$, $R^1 = COOEt$; CXVI $R = COOH$, $R^1 = COOEt$

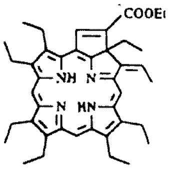
Rearrangement into purpurins on heating in AcOH is the most interesting feature of these porphyrins. Purpurins are of interest as promising photosensitizers with an intense absorption maximum in the 700 nm region for use in photodynamic treatment of cancer [78]. Cyclization of the meso-acrylic substituent always takes place opposite the neighboring methyl β-pyrrole substituent. This characteristic has been confirmed by cyclization of porphyrins CVI and CX into corresponding purpurins CXVII and CXVIII. However, prolonged heating of OEP−CH=CH−COOEt in AcOH in the presence of air yields ethylidene derivative CXIX [79].



CXVII

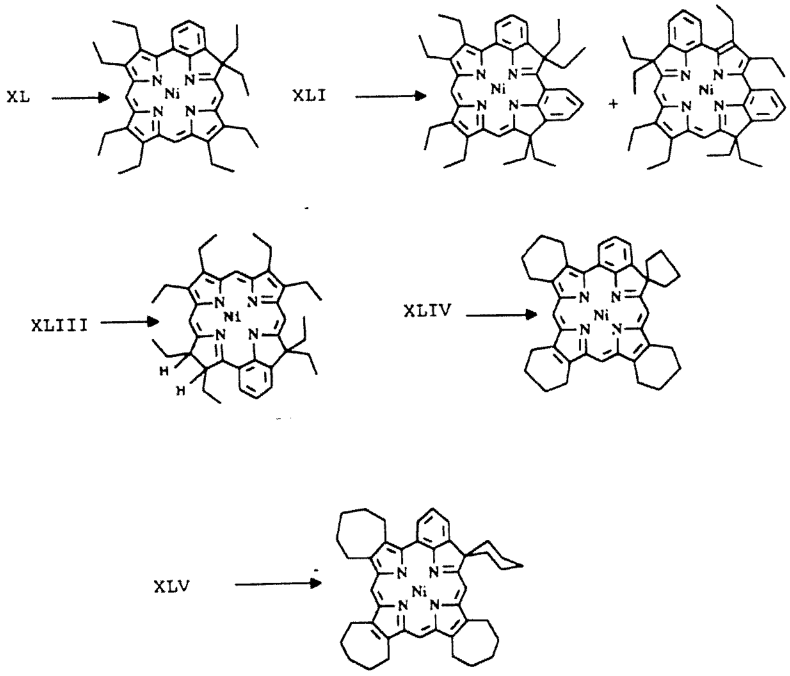


CXVIII



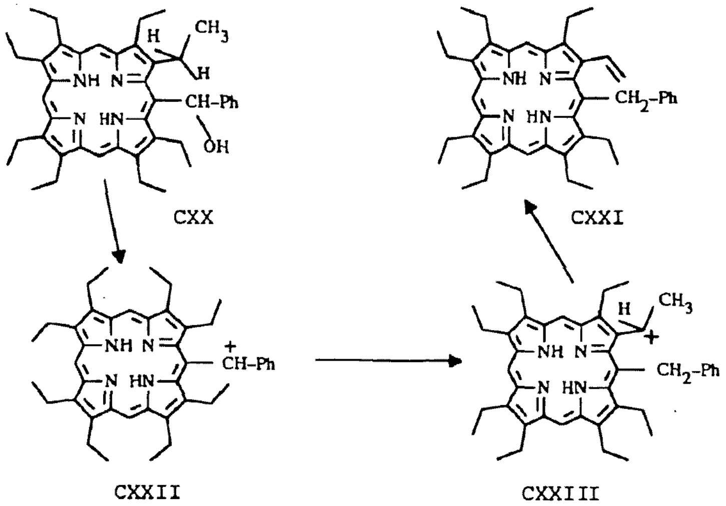
CXIX

Although free bases of porphyrins containing an acrylic acid residue in the meso position are cyclized or more accurately isomerized, in prolonged heating in AcOH, the corresponding copper and nickel porphyrin complexes with a meso-formylvinyl group are transformed into benzochlorins when held in sulfuric acid. This process was investigated in detail in [13]. Some of the transformations are shown below.



2.6. Reaction of Formylporphyrins with Grignard Reagents

Meso-formylporphyrins react with Grignard reagents with formation of the corresponding secondary alcohols, but due to steric factors and perhaps other causes, this reaction takes place somewhat slowly. For example, when meso-formyl-OEP is heated with MeMgI in ether, a formylporphyrin Mg complex is formed without significant formation of meso-(1-hydroxyethyl)-OEP [44]. At the same time, Ni-OEP-CHO heated for a long time with MeMgI forms an unstable alcohol Ni-OEP-CH(OH)Me, and its dehydration with TsOH in benzene yields meso-vinyl-OEP Ni complex with a yield of 50% [79]. Alcohol CXX is formed in the same conditions in the reaction with PhMgI. When heated in DMF in the presence of catalytic quantities of sulfuric acid, i.e., in conditions of dimerization of meso-hydroxymethylporphyrin complexes [80], CXX is dehydrated with complex rearrangement into complex CXXI via intermediate carbocations CXXII and CXXIII according to the scheme:



CONCLUSION

We have only covered a few aspects of the chemistry of formylporphyrins. The different derivatives obtained from formylporphyrins are promising for further investigation in very different areas of science, medicine, and technology. Many meso-substituted porphyrins have a radioprotective action. Purpurins and benzoporphyrins, which exhibit intense absorption in the 650-740 nm region, are of great interest as photosensitizers for photodynamic treatment of cancer. Dimeric porphyrins and their metal complexes with different metals are widely used in photophysical experiments for modeling photosynthesis and as catalysts of multielectron charge transfer.

The size of this review does not allow us to completely demonstrate the almost unlimited synthetic possibilities of using the Vilsmeier reaction in porphyrin chemistry. This basically concerns the study of the chemical properties of meso-dimethylaminomethylporphyrins and Schiff bases of meso-formylporphyrins prepared directly from PC, but this will be the subject of the next review.

REFERENCES

1. G. V. Ponomarev and G. V. Kirillova, Porphyrins: Structure, Properties, Synthesis [in Russian], N. S. Enikolopyan (ed.), Nauka, Moscow (1985), p. 238.
2. K. M. Smith and O. M. Minnetian, J. Org. Chem., **50**, 2073 (1985).
3. H. H. Inhoffen, J. H. Fuhrhop, H. Voight, and H. Brockmann Jr., Ann., **695**, 133 (1966).
4. A. W. Johnson and D. Oldfield, J. Chem. Soc. (C), No. 8, 794 (1966).
5. P. S. Clezy, C. J. R. Fookes, and S. Sternhell, Aust. J. Chem., **31**, 639 (1978).
6. K. M. Smith, G. M. F. Bisset, and J. J. Bushell, J. Org. Chem., **45**, 2218 (1980).
7. P. S. Clezy and C. J. R. Fookes, Aust. J. Chem., **30**, 1799 (1977).

8. G. V. Kirillova, G. B. Maravin, and G. V. Ponomarev, USSR Inventor's Certificate No. 1,476,865; Byull. Izobr., No. 10 (1989).
9. I. A. Chaudhry, P. S. Clezy, and V. Diakiv, Aust. J. Chem., **30**, 879 (1977).
10. G. L. Collier, A. H. Jackson, and G. W. Kenner, J. Chem. Soc. (C), No. 1, 66 (1967).
11. J. W. Buchler, C. Dreher, and G. Herget, Ann., No. 1, 43 (1988).
12. A. W. Nichol, J. Chem. Soc. (C), No. 7, 903 (1970).
13. M. G. H. Vicente and K. M. Smith, J. Org. Chem., **56**, 4407 (1991).
14. H. Brockmann Jr., K. M. Bliesener, and H. H. Inhoffen, Ann., **718**, 148 (1968).
15. K. M. Smith and K. C. Langry, J. Chem. Soc., Perkin Trans. I, No. 2, 439 (1983).
16. K. M. Smith, E. M. Fujunary, K. C. Langry, D. W. Parish, and H. D. Tabba, J. Am. Chem. Soc., **105**, 6638 (1983).
17. R. Shlözer and J. H. Fuhrhop, Angew. Chem., **87**, 388 (1975).
18. H. J. Callot, Tetrahedron, **29**, 899 (1973).
19. M. Momenteau, B. Look, E. Bisagni, and M. Rougee, Can. J. Chem., **57**, 1804 (1979).
20. G. V. Ponomarev and G. B. Maravin, Khim. Geterotsikl. Soedin., No. 1, 59 (1982).
21. G. V. Ponomarev and B. V. Rozynov, Khim. Geterotsikl. Soedin., No. 9, 1172 (1973).
22. G. V. Kirillova, T. A. Babushkina, V. P. Suboch, and G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 9, 1215 (1978).
23. G. V. Ponomarev, G. V. Kirillova, L. B. Lazukova, and T. A. Babushkina, Khim. Geterotsikl. Soedin., No. 11, 1507 (1982).
24. G. V. Kirillova, A. M. Shul'ga, and G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 10, 1378 (1989).
25. A. R. Morgan, S. H. Selman, G. M. Garbo, and R. W. Keck, U.S. Patent No. 4,877,872 (Oct. 31, 1989).
26. G. V. Ponomarev and A. M. Shul'ga, Khim. Geterotsikl. Soedin., No. 7, 922 (1987).
27. D. Arnold, A. W. Johnson, and M. Winter, J. Chem. Soc., Perkin Trans. I, No. 14, 1643 (1977).
28. J. H. Fuhrhop, L. Witte, and W. S. Sheldrick, Ann., No. 9/10, 1537 (1976).
29. J. H. Fuhrhop, S. Besecke, J. Subramanian, Chr. Mengersen, and D. Riesner, J. Am. Chem. Soc., **97**, 7141 (1975).
30. E. Watanabe, S. Nishimura, H. Ogoshi, and Z. Yoshida, Tetrahedron, **31**, 1385 (1975).
31. R. Grigg, G. Shelton, A. W. Johnson, and A. Sweeney, J. Chem. Soc., Perkin Trans. I, No. 14, 1789 (1972).
32. G. V. Ponomarev, G. V. Kirillova, and G. B. Maravin, Khim. Geterotsikl. Soedin., No. 10, 1427 (1976).
33. G. V. Ponomarev, G. V. Kirillova, G. B. Maravin, T. A. Babushkina, and V. P. Suboch, Khim. Geterotsikl. Soedin., No. 6, 767 (1979).
34. G. V. Ponomarev, G. V. Kirillova, G. B. Maravin, T. A. Babushkina, and V. P. Suboch, Khim. Geterotsikl. Soedin., No. 6, 777 (1979).
35. K. M. Smith, G. M. F. Bisset, J. J. Case, and H. D. Tabba, Tetrahedron Lett., **21**, 3747 (1980).
36. K. M. Smith, G. M. F. Bisset, and H. D. Tabba, J. Chem. Soc., Perkin Trans. I, No. 2, 581 (1982).
37. M. J. Bushell, B. Evans, G. V. Kenner, and K. M. Smith, Heterocycles, 7, 67 (1977).
38. K. M. Smith, G. M. F. Bisset, and M. J. Bushell, Bioorg. Chem., **9**, 1 (1980).
39. M. G. H. Vicente, I. N. Rezzano, and K. M. Smith, Tetrahedron Lett., **31**, 1365 (1990).
40. M. J. Gunter, B. C. Robinson, J. M. Gulbis, and E. R. T. Tiekink, Tetrahedron, **47**, 7853 (1991).
41. A. Osuka, Y. Ikawa, and K. Maruyama, Bull. Chem. Soc. Jpn., **65**, 3322 (1992).
42. K. M. Smith, D. A. Goff, and D. J. Simpson, J. Am. Chem. Soc., **107**, 4946 (1985).
43. U. Jurgens and H. Brockmann Jr., Ann., No. 3, 472 (1982).
44. G. V. Ponomarev and A. N. Sidorov, Khim. Geterotsikl. Soedin., No. 7, 919 (1977).
45. G. V. Ponomarev and T. M. Ivanova, Bioorg. Khim., **2**, 542 (1976).
46. G. B. Maravin, G. V. Ponomarev, V. G. Yashunskii, and N. M. Morlyan, USSR Inventor's Certificate No. 881,673; Byull. Izobr., No. 47, 109 (1981).
47. H. J. Callot, Bull. Soc. Chim. France, No. 12, 3413 (1973).
48. K. Henric, P. G. Owston, R. Peters, and P. A. Tasker, Inorg. Chim. Acta Lett., **45**, 161 (1980).
49. A. R. Battersby, K. Jones, and R. J. Snow, Angew. Chem., **95**, 742 (1983).
50. R. J. Snow, C. J. R. Fookes, and A. R. Battersby, J. Chem. Soc., Chem. Commun., No. 11, 524 (1981).
51. G. V. Ponomarev and V. G. Yashunskii, USSR Inventor's Certificate No. 458,551; Byull. Izobr., No. 4, 51 (1975).

52. I. G. Rish, V. S. Pshezhetskii, K. A. Askarov, and G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 7, 936 (1985).
53. D. Dolphin, J. Hiom, and J. B. Paine III, Heterocycles, **16**, 417 (1981).
54. Yu. V. Ishkov, Z. I. Zhilina, I. S. Voloshanovskii, and S. A. Andronati, Dokl. Akad. Nauk, **303**, 377 (1988).
55. Z. I. Zhilina, Yu. V. Ishkov, I. S. Voloshanovskii, and S. V. Fel'dman, Zh. Org. Khim., **25**, 2444 (1989).
56. M. G. H. Vicente and K. M. Smith, Synlett., No. 4, 579 (1990).
57. J. E. McMurry, Chem. Rev., **89**, 1513 (1989).
58. M. O. Senge, K. R. Gerzevske, M. G. H. Vicente, T. P. Forsyth, and K. M. Smith, Angew. Chem. Int. Ed. Engl., **32**, 750 (1993).
59. G. V. Ponomarev, V. V. Borokov, K. Sugiura, Y. Sakata, and A. M. Shul'ga, Tetrahedron Lett., **34**, 2153 (1993).
60. G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 10, 1339 (1993).
61. R. Kitagawa, Y. Kai, G. V. Ponomarev, K. Sugiura, V. V. Borovkov, T. Kaneda, and Y. Sakata, Chem. Lett., No. 6, 1071 (1993).
62. Yu. V. Ishkov, Z. I. Zhilina, and A. M. Shul'ga, Zh. Org. Khim., **27**, 1087 (1991).
63. R. K. Pandey, T. P. Forsyth, K. R. Gerzevske, J. J. Lin, and K. M. Smith, Tetrahedron Lett., **33**, 5315 (1992).
64. R. Cosmo, C. Kautz, K. Meerholz, J. Heinze, and K. Müllen, Angew. Chem., **101**, 638 (1989).
65. K. M. Smith and G. M. F. Bisset, J. Org. Chem., **44**, 2077 (1979).
66. P. B. Hitchcock, J. Chem. Soc., Dalton Trans., No. 9, 2127 (1983).
67. M. O. Senge, H. Hope, and K. M. Smith, J. Chem. Soc., Perkin Trans. II, No. 1, 11 (1993).
68. G. V. Ponomarev and A. M. Shul'ga, USSR Inventor's Certificate No. 1,172,922; Byull. Izobr., No. 30, 99 (1985).
69. G. V. Ponomarev and A. M. Shul'ga, USSR Inventor's Certificate No. 1,172,923; Byull. Izobr., No. 30, 99 (1985).
70. A. M. Shul'ga and G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 3, 339 (1988).
71. G. V. Ponomarev and A. M. Shul'ga, Khim. Geterotsikl. Soedin., No. 2, 278 (1986).
72. V. V. Borovkov, G. V. Ponomarev, A. Ishida, T. Kaneda, and Y. Sakata, Chem. Lett., No. 8, 1409 (1993).
73. G. V. Ponomarev and A. M. Shul'ga, in: Proceedings fov the Third All-Union Conference on the Chemistry and Biochemistry of Macrocyclic Compounds [in Russian], Ivanovo (1988), p. 159.
74. K. M. Smith and G. M. F. Bisset, J. Chem. Soc., Perkin Trans. I, No. 9, 2625 (1981).
75. G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 7, 943 (1980).
76. H. Callot, Bull. Soc. Chim. France, 3413 (1973).
77. D. P. Arnold, R. Gaete-Holmes, A. W. Johnson, A. Smith, and G. A. Williams, J. Chem. Soc., Perkin Trans. I, No. 12, 1660 (1978).
78. A. R. Morgan, A. Rampersaud, G. M. Garbo, R. W. Keck, and S. H. Selman, J. Med. Chem., **32**, 904 (1989).
79. A. R. Morgan and N. C. Tertel, J. Org. Chem., **51**, 1347 (1986).
80. D. P. Arnold, A. W. Johnson, and M. Mahendran, J. Chem. Soc., Perkin Trans. I, No. 4, 366 (1978).