Chemistry of Heterocyclic Compounds, Vol. 32, Nos. 11-12, 1996

SYNTHESIS AND PROPERTIES OF SCHIFF BASES OF MESOFORMYLPORPHYRINS (REVIEW)*

G. V. Ponomarev

A summary is presented on the use of intermediate immonium salts formed in the Vilsmeier reaction in porphyrin chemistry for the synthesis of various Schiff bases of mesoporphyrins. Special attention is given to the formation and properties of porphyrins with a five-membered exocycle.

This review is a logical extension of our recent review of the chemistry of formylporphyrins [1]. Intermediate immonium salts, which have been designated "phosphoric complexes" (PC), are formed in the Vilsmeier reaction. These species are usually not isolated and the reaction mixture is hydrolyzed to the corresponding formylporphyrin. However, the author was able to establish that not only may stable and, sometimes, even crystalline PC be isolated, but these intermediates may be used for various chemical transformations. While the chemistry of formylporphyrins formed by mild basic hydrolysis of PC was the subject of our previous review [1], the chemistry of the Schiff bases of meso- and β-formylporphyrins obtained treating PC with primary amines or ammonia and the use of these compounds in various new reactions are examined in the present review. The term "Schiff bases" implies all azomethines, which formally can be considered products of the reaction of formylporphyrins with any primary amines. In order to compare the scope for the use of PC relative to formylporphyrins, some information is given on the reactions of formylporphyrins with various amino compounds.

1. AZOMETHINES FROM FORMYLPORPHYRINS

1.1. Oximes and Hydrazones from β- and Mesoformylporphyrins and Chlorines

The classical reactions involving the aldehyde group, namely, the reactions with hydroxylamine and hydrazine hydrate to form the corresponding oximes and hydrazones, are characteristics for porphyrins and chlorines regardless of whether the formyl group is in the β- or meso position. Oximes are usually formed in rather high yield upon heating of the corresponding formyl derivative with hydroxylamine from several minutes to 2-3 h in aqueous pyridine often at reflux.

A series of oximes is given below derived from mesoformyltetramethyltetracarboethoxyporphyrin I [2], etioporphyrin-1 II, III [3, 4], octaethylporphyrin IV [5, 6], and its derivatives V-VII [7, 8], tetraphenylporphyrin VIII [9], mesotetra(*p*-tolyl)porphyrin IX, X [10], 2-desvinyl-γ-formyl-2-methoxycarbonylpyrrochlorine XI and the trimethyl ester of rhodine g_7 XII [11]. According to our data, di- and triformylporphyrins [12, 13] form the corresponding bis and trisoximes XIII-XVI without any difficulty.

*Dedicated to the Academician É. Lukevits on his sixtieth birthday.

Institute of Biological and Medicinal Chemistry, Russian Academy of Medical Sciences, 119832 Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1472-1493, November-December, 1996. Original article submitted October 3, 1996.

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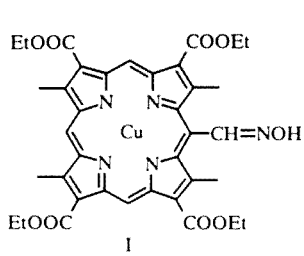
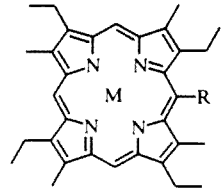


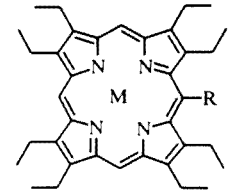
I

M-EP-R

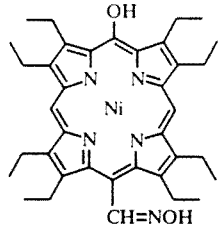


II, III

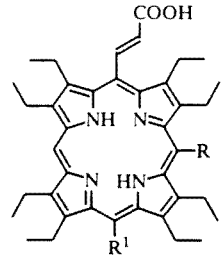
M-OEP-R



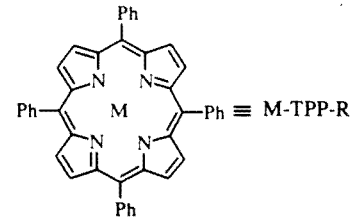
IV



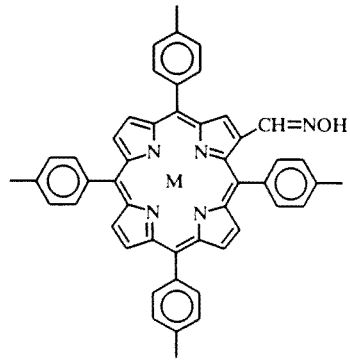
V



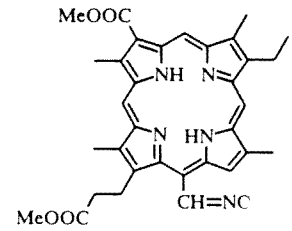
VI, VII



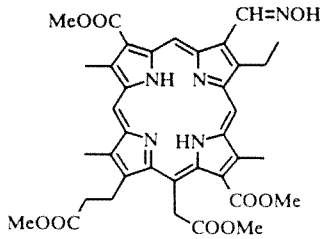
VIII, XVIII, XIX



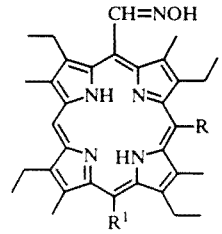
IX, X



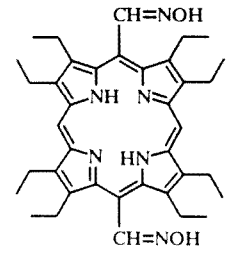
XI



XII



XIII–XV



XVI

III, M = Cu; VI, VIII, XIII, R = CH = NOH; VII, XIV, R^1 = CH = NOH; XV, R = R^1 = CH = NOH; XVIII, R = CH = NOAc; XIX, R = CN

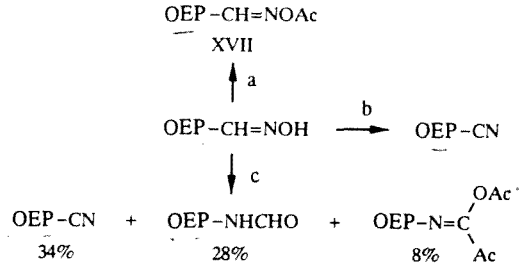
Here and subsequently, the free bases of porphyrins M—Por—R are designated Por—R and not 2H—Por—R.

The oximes hold interest as a starting material for the synthesis initially of meso- and β-cyanoporphyrins and chlorines in order to convert the latter into carboxy derivatives. Although, the corresponding nitriles were obtained in ≥50% yield from the most of the above-mentioned oximes upon heating in acetic anhydride for from several minutes to 2-3 h, the formation of these derivatives proved rather complicated.

Clezy et al. [5] studied the chemical properties of these oximes and, in the case of mesoformyloctaethylporphyrin (mesoformyl—OEP), showed that various products are formed depending on the reaction temperature and time (Scheme 1).

Scheme 1 shows that the initial step in the dehydration of the oximes to give nitriles is generation of acetoxy derivative XVII [reaction a], which then may undergo various transformations [reaction c]. In some cases, the acetoxy derivatives are so stable, for example, the derivative from tetraphenylporphyrin—CH=NOH (TPP—CH = NOH, XVIII) [9], that the corresponding nitrile XIX is formed only upon prolonged heating in acetic anhydride at reflux in very low yield.

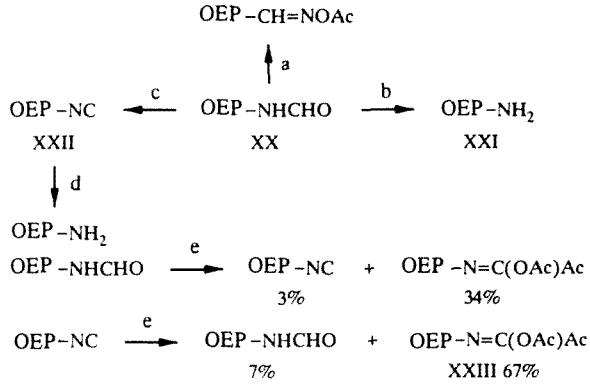
Scheme 1



a Ac_2O, 100 °C, 20 min, yield 88%; b Ac_2O, reflux 1 h, yield 57% (67%, [6]);
c Ac_2O, 120 °C, 20 min

Acetoxime XVII is capable of rearrangements and may yield meso-N-formylamino-OEP (XX), mesoamino-OEP (XXI), mesoisocyano-OEP (XXII), and 1-(N-octaethylporphyrinylimino)-2-oxopropyl acetate (XXIII) (Scheme 1). The synthesis of mesoamino-OEP is best carried out by reduction of more available mesonitro-OEP [14].

Scheme 2



a conc. H_2SO_4, 2 h, 100°C, yield 80%; b MeOH/H_2SO_4 (5 : 2), 1h, 100°C, yield 82%; c $COCl_2$, Et_3N, 0°C, 30 min; d dil. H_2SO_4, 10 min, 100°C, yield 40%; e Ac_2O, 1 h reflux

Our study, prompted by an unsuccessful attempt to obtain OEP—CO_2H from OEP—CN by analogy to the synthesis reported for etioporphyrin—CO_2H (EP—CO_2H) by the hydrolysis of EP—CN in concentrated sulfuric acid [3], resulted in a detailed examination of the properties of mesoformylporphyrin oximes. We may now concur with the conclusion of Clezy [5] concerning the impossibility of such a reaction, which leads only to stable amides. For example, only EP—$CONH_2$ and OEP—$CONH_2$ are obtained from EP—CN and OEP—CN.

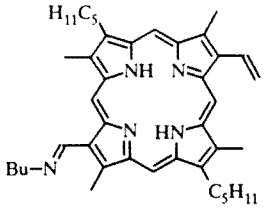
Hydrazones of mesoformylporphyrins may be obtained relatively simply by heating with hydrazine hydrate. For example, EP—CH=NNH_2 was obtained from EP—CHO by heating in the presence of hydrazine hydrate in aqueous pyridine at reflux. According to Johnson and Oldfield [3], these hydrazones were obtained as geometric syn and anti isomers. However,

we observed only one isomer in the synthesis of this and many other hydrazones. Since the hydrazones have not found any significant use for the further modification of formylporphyrins, their chemical properties were not studied.

1.2. Schiff Bases from β- and Mesoformylporphyrins

The Schiff bases of natural β-formyl pigments, namely, chlorophyll-β and cytochrome oxidase, with aliphatic amines play the major role in their biological activity. A synthetic analog XXIV was obtained to study the photophysical properties of such compounds and a study was carried out on the spectral properties upon protonation, which leads to a shift of 43 nm in the visible region and splitting of the Soret band into two components [15].

However, the classical reaction for mesoformylporphyrins with amino compounds occurs only at elevated temperature. Some examples are given for Schiff bases with aromatic amines for derivatives of EP [4] XXV-XXVI and OEP [16] XXVII-XXX.



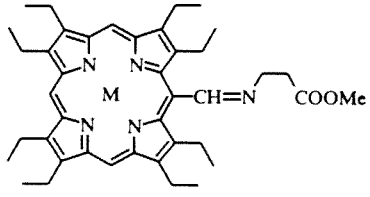
XXIV

EP -CH=N-C_6H_4-R-*p* XXV, XXVI

OEP -CH=N-C_6H_4-R-*p* XXVII–XXX

XXV R = H, XXVI R = Me, XXVII R = H, XXVIII R = Me, XXIX R = NH_2, XXX R = OEt

In 1976, Fuhrhop et al. [8] first reported the synthesis of Schiff bases of mesoformylporphyrins with aliphatic amines, indicating the difficulty of obtaining these derivatives and their lack of promise.



XXXI, XXXII

XXXI M = 2 H; XXXII M = Cu

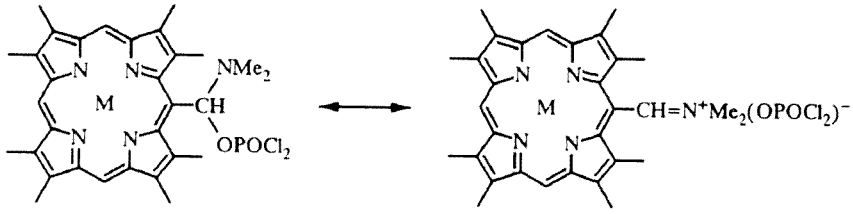
Schiff bases XXXI and XXXII were obtained in only 13-15% yield from mesoformyl—OEP, its copper complex, and β-alanine by the classical method involving heating in pyridine at reflux for 24 h; 80% of the starting porphyrin did not enter the reaction. This probably accounts for the lack of data on the chemical and physicochemical properties of the Schiff bases of mesoformylporphyrins with small aliphatic amines although we published a communication in 1975 on an extremely facile synthesis of such compounds [17]. This work has probably not been noted by workers studying porphyrin chemistry.

The subsequent sections of this review are devoted to the synthesis and chemical transformations of the Schiff bases of various mesoformylporphyrins with a broad variety of amines carried out by the author and his colleagues.

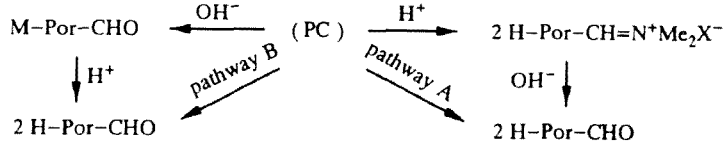
2. AZOMETHINES FROM "PHOSPHORIC COMPLEXES"

2.1. Synthesis of Schiff Bases in "Phosphoric Complexes"

An intermediate immonium salt is formed during the Vilsmeier reaction. The following structure was proposed for the so-called "phosphoric complex" (PC) [4] (more details are given in our previous review [1]).



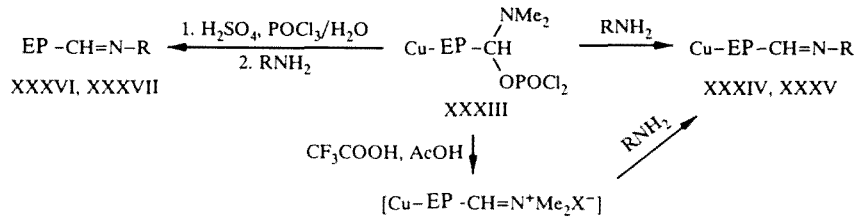
"Phosphoric complex" (PC)



In order to obtain formylporphyrins, the reaction mixture after the Vilsmeier reaction is usually heated with aqueous sodium acetate at reflux for 1-2 h, leading to hydrolysis of both the intermediate PC and Vilsmeier complex ($DMF/POCl_3$). The use of aqueous alkali in this case, especially concentrated alkali, is undesirable since a variety of side-products may be formed [18]. We should note that PC obtained in the formylation at unsubstituted pyrrole positions [9, 19, 20] are less resistant to hydrolysis to β-formylporphyrins than the derivatives obtained upon the formylation of octaalkylporphyrins.

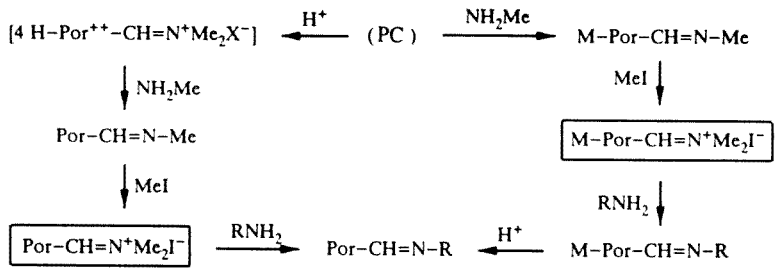
While studying the chemical properties of PC, we found that these compounds may be demetallated by dissolving both in concentrated sulfuric acid and in $POCl_3$ first treated with a small amount of water [21]. Loss of the meso substituent does not occur in this case since it is converted into a typical immonium salt ($4\text{-H—Por}^{++}\text{—CH} = \text{N}^+\text{Me}_2\text{X}^-$). Green salts were found for porphyrins and brown—green salts for chlorines. Thus, two pathways are possible for the synthesis of nonmetallic formylporphyrins, pathways A and B. When the formylporphyrin metallocomplex is demetallated to the free base without decomposition in high yield, standard pathway B may be used. However, when the metallocomplexes cannot be demetallated under standard conditions, for example, in concentrated sulfuric acid or in a mixture of sulfuric and trifluoroacetic acids, as in the case of tetraphenylporphyrin derivatives [19], pathway A may prove the ideal variant. A violet nonmetal formylporphyrin is formed upon treating a solution of the immonium salt in chloroform or chloroform—methanol with aqueous or methanolic alkali for a few minutes at room temperature.

In a study of the physicochemical properties of PC XXXIII [17, 22], we found that treating a solution of this species in chloroform or dichloroethane with aqueous ammonia or methylamine for 1-2 min leads to a very rapid color change from brown—green to bright red related to formation of Schiff bases XXXIV and XXXV. The formation of aldimine XXXV is much faster if the PC is initially treated with an acid such as acetic, trifluoroacetic, or hydrochloric acid. This species is probably converted into a true immonium salt, which reacts with ammonia or aqueous methylamine in a few seconds at room temperature. Nonmetal Schiff bases may be obtained by demetallation of the PC using $POCl_3/H_2O$ with subsequent treatment with aqueous ammonia or methylamine to give XXXVI or XXXVII.



XXXIV, XXXVI R = H; XXXV, XXXVII R = Me

During separation of the PC from the reaction mixture or corresponding immonium salt upon its demetallation, the corresponding formylporphyrins may form, which complicates the isolation of the Schiff bases since further chromatographic purification of the reaction products is required. The conversion of formylporphyrins is only a few percent but this amount is chromatographically significant. Thus, the following method is more convenient for preparation of the Schiff bases:



OEP- $CH=N^+Me_2I^-$ XXXVIII

EP $-CH=N^+Me_2I^-$ XXXIX

The PC (the copper or nickel complexes are usually employed) or the corresponding immonium salt in chloroform or methylene chloride solution is treated with aqueous methylamine. The Schiff base obtained containing an impurity of formylporphyrin and unreacted starting porphyrin is heated without additional purification for 1 h in methyl iodide. A stable crystalline iodomethylate free of impurities precipitates quantitatively from the solution and may be used for the synthesis of any Schiff bases. Iodomethylates XXXVIII and XXXIX were used most often in our studies.

This method is used for the synthesis of Schiff bases not only with aliphatic amines but also with hydroxylamine, hydrazines, and some amino acids, with the exception of α-amino acids, which do not enter this reaction due to steric hindrance. The yields of the azomethines obtained by this method are generally 70-90%.

Since the reactivity of amino acids is lower than the lower aliphatic amines, a two- or three-fold excess of the amino acid hydrochloride, anhydrous solvents, and prolonged heating of the reaction mixture at reflux are required to prepare the Schiff bases. Amino acid hydrochlorides are first dissolved in a small amount of methanol with excess triethylamine due to their poor solubility in chloroform.

The following Schiff bases were prepared: XL-LIII derived from mesoformyl—EP, LIV-LX derived from mesoformyl—OEP, LXI-LXIV derived from etioporphyrin-II, LXV-LXVIII derived from isomers of mesomethyl-etioporphyrin-II, LXIX and LXX derived from cyclopentaneporphyrins, LXXI-LXXIII derived from coproporphyrin-I, LXXIV and LXXV derived from coproporphyrin-II, LXXVI derived from octapropylporphyrin, LXXVII and LXXVIII derived from octaethylchlorine complexes, and LXXIX derived from a bis-Schiff base [22-27]. This method is also suitable for the synthesis of Schiff bases of β-formylporphyrin XL [28].

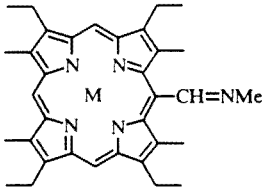
Examples of porphyrins obtained in our laboratory using this scheme are given below:

M-EP-CH=N-R

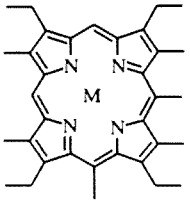
XL-LIII

M-OEP-CH=N-R

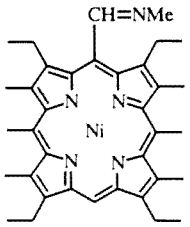
LIV-LX



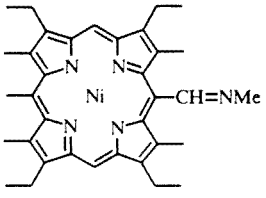
LXI, LXII



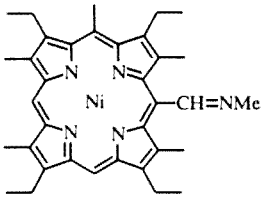
LXIII, LXIV



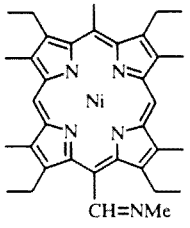
LXV



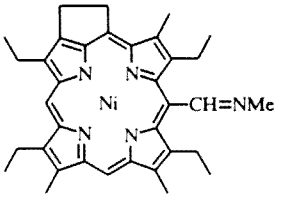
LXVI



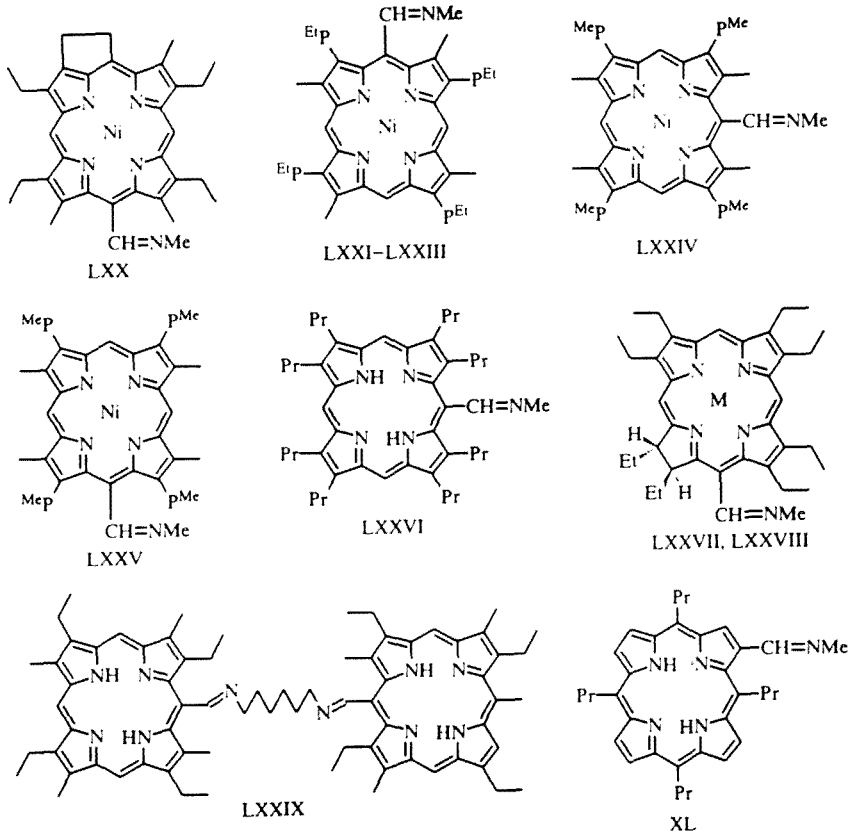
LXVII



LXVIII



LXIX



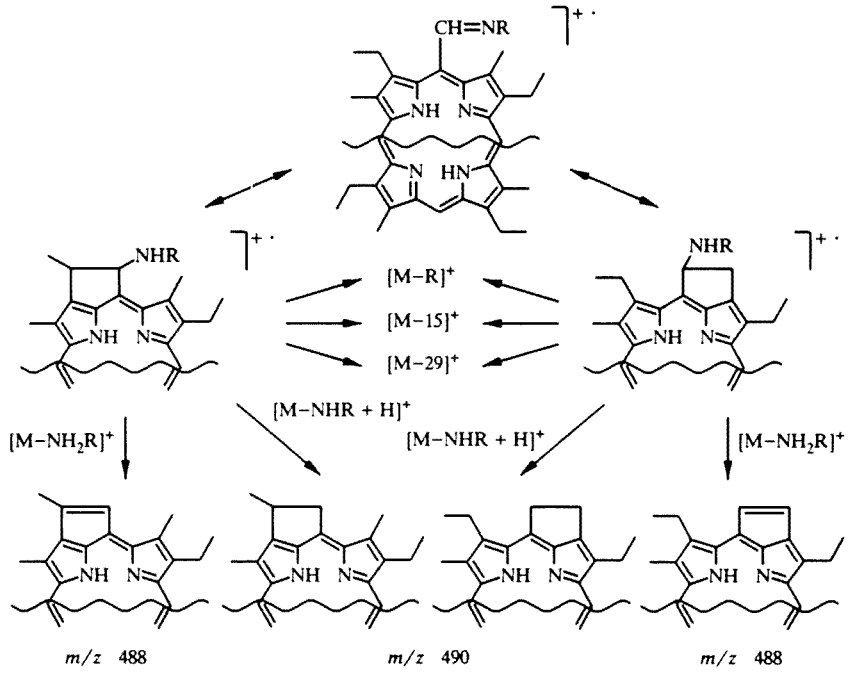
XL R = Et; XLI, XLII R = Pr; XLIII R = *i*-Pr; XLIV, XLV, LVIII R = cyclohexyl ; XLVI R = $-CH_2CH_2COOEt$; XLVII R = $CH_2CH_2C_6H_4$-OH-4; XLVIII R = $CH_2CH_2C_6H_4$-OMe-4; XLIX R = $-CH_2$-(1-adamantyl); L, LI R = CH_2CH_2OH; LII R = $(CH_2)_5COOMe$; LIII R = $CH_2C_6H_4COOEt$-4; LIV, LX, LXXI R = Me; LV, LXXII R = CH_2Ph; LVI, LVII R = *i*-Bu; LXXIII R = CH_2CH_2Ph; XLII, XLV, LI, LVI, LXXVII M = Cu; LXXVIII M = Ni; other M = 2H; P^{Et} = CH_2CH_2COOEt; P^{Me} = CH_2CH_2COOMe

2.2. Mass Spectra of Schiff Bases of Mesoformylporphyrins

Clezy [5] carried out the first mass spectrometric study of meso-substituted porphyrins and showed that an OEP^+ ion is present in the mass spectra of all meso-substituted OEP derivatives, i.e., elimination of the meso substituent occurs in the ion source of the mass spectrometer with the intermolecular addition of hydrogen. On the basis of this finding, Clezy made the pessimistic conclusion that "thermal instability leads to unsatisfactory electron impact spectra for such compounds and prevents the further study of their fragmentation reactions."

Furthermore, in a study of the mass spectra of many sterically hindered porphyrins and chlorines, Budzikiewicz [29] proposed that the fragmentation of these compounds may involve complex rearrangements, but special studies to verify this conclusion were not carried out. Thus, undertaking a study of the mass spectra of the Schiff bases of mesoformylporphyrins, we paid special attention to the possibility of decomposition and intramolecular rearrangements during the mass spectral process. A large number of Schiff bases of a very broad range of porphyrins permitted us to carry out a thorough study of the mass spectra of these compounds [30].

The major feature of the mass spectra of the above-mentioned porphyrins is the finding of strong $[M-NR]^+$ and $[M-NH_2R]^+$ ions and greatest intensity for the latter ion is found for almost all these compounds. Since decomposition of the molecular ion of a Schiff base with loss of amine and simultaneous transfer of two hydrogen atoms from the porphyrin ring to the amine residue is inconceivable, intramolecular rearrangement of the molecular ion to a cyclic species likely occurs in the initial fragmentation step. Decomposition of such a cyclic species may be explained by the experimental data. The most typical pathways for the fragmentation of the molecular ions for any Schiff bases are given below for the example of etioporphyrin derivatives according to the following scheme:



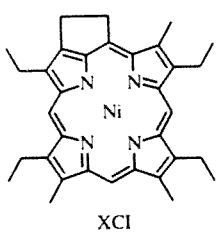
Mass spectrometric fragmentation of Schiff bases of mesoformyletioporphyrin

The presence of $[M-NR]^+$ and $[M-NH_2R]^+$ ions with mass numbers 490 and 488 in all the spectra for etioporphyrin derivatives, 546 and 544 for octaethylporphyrin derivatives, and 658 and 656 for octapropylporphyrin derivatives, respectively, indicates thermal decomposition of the Schiff bases in the mass spectrometer ion source to give new porphyrins containing a five-membered exocycle using direct analysis of daughter ion (DADI) data. Thus, a detailed analysis of the mass spectra of Schiff bases indicated a remarkably simple and elegant procedure for obtaining cyclopentaneporphyrins.

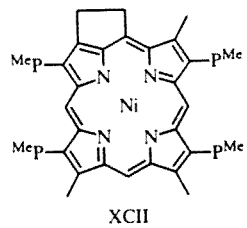
2.3. Thermolysis of Schiff Bases. Synthesis of Porphyrins Containing a Cyclopentane Ring

Thermolysis of many Schiff bases under conditions similar to those in the ion source of a mass spectrometer and under milder conditions, i.e., at 250-300°C (1.0-0.1 torr) over 3-5 min gave various cyclopentaneporphyrins XC-CVI [25-28, 31-33] with yields far exceeding the yields in the reported syntheses of similar porphyrins [34-44]. According to Clezy [45], who devoted many years to the synthesis of natural petroporphyrins, no satisfactory synthesis existed for these compounds despite the passage of sixty years since the first synthesis of their most important representative, desoxophylloerythroetioporphyrin (DPEP, CVII) [35]. The unavailability of cyclopentaneporphyrins prevented the detailed study of the chemistry of these compounds.

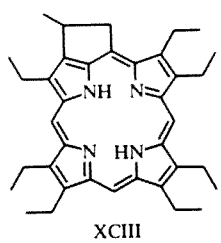
Structures of the cyclopentaneporphyrins synthesized by thermolysis of the corresponding Schiff bases are given below:



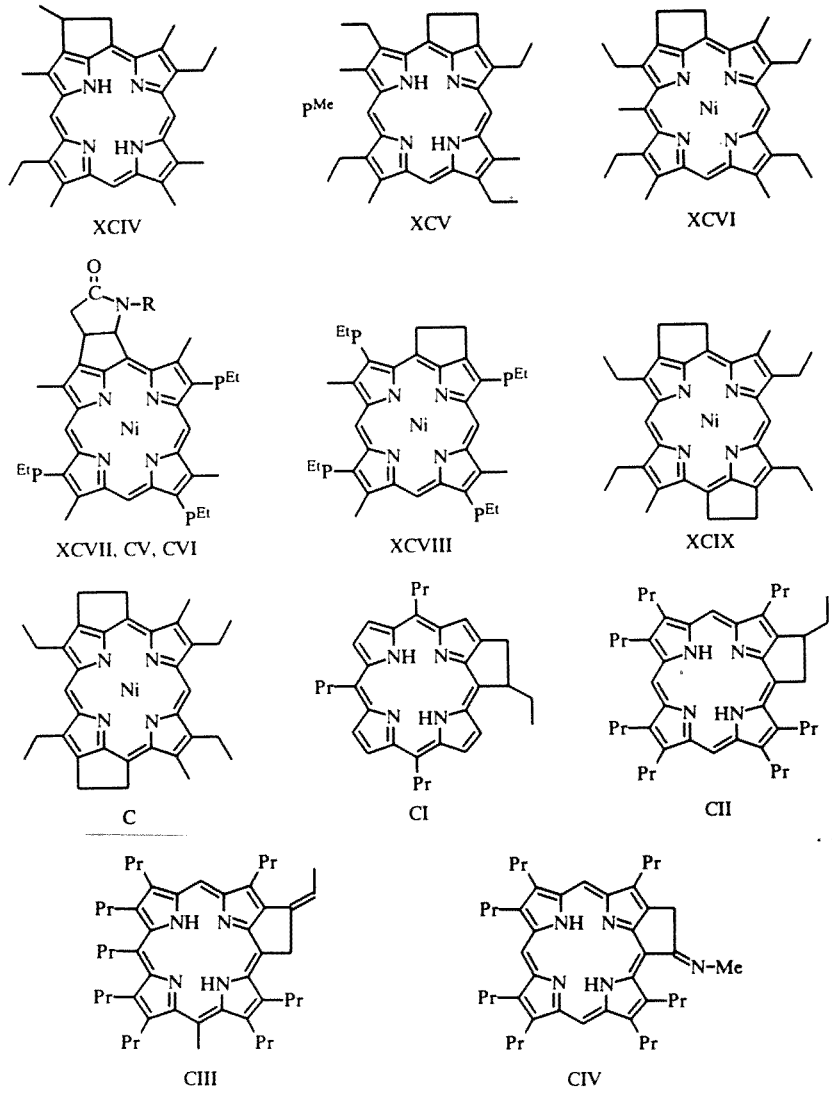
XCI



XCII



XCIII



Analysis of these results indicated the following general conclusions:

1. The fragmentation ions and major thermolysis products have much in common. However, the behavior seen in the mass spectra appears much simpler due to the lack of side processes related to additional decomposition reactions.

2. The free bases (nonmetal porphyrins) and metallocomplexes undergo thermolysis by the same mechanism though less side-products are formed in the thermolysis of metallocomplexes. Furthermore, the demetallation of the metallocomplexes of porphyrins with a cyclopentane ring proceeds readily in quantitative yield in contrast to the metallocomplexes of the Schiff bases. All these findings support the use of the Schiff base metallocomplexes for the thermolysis.

3. The formation of the exocycle in all cases is a consequence of the initial transfer of an α-proton (hydrogen atom) of the adjacent alkyl substituent such as a methyl, ethyl, propyl, or more complex group such as an alkyloxycarbonylethyl group to the nitrogen atom of the azomethine group to give a reaction intermediate containing an exocycle with a secondary amino group.

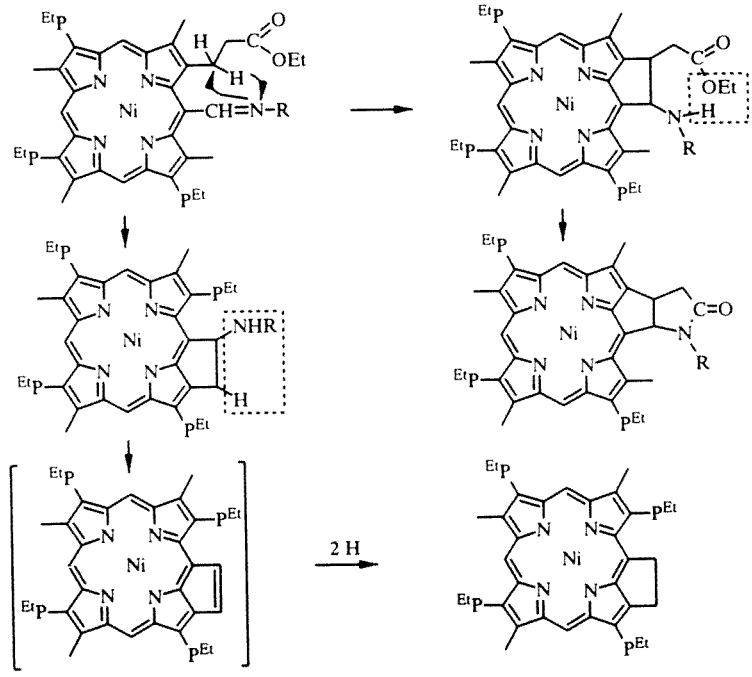
4. The course of the cyclization depends not only on the adjacent substituents but also the activating effect of other peripheral substituents:

a) if the adjacent β-substituents are methyl groups as in the case of porphyrins LXI and LXIII, only porphyrins with an unsubstituted cyclopentane ring are formed, namely, XCI and XCII;

b) in the case of etioporphyrin-I derivatives, two isomers are formed in approximately equal amounts, XCIV and XCV;

c) in the case of mesomethyletioporphyrin-II derivatives such as LXV, one isomer (XCVI) is formed predominantly. This behavior is undoubtedly related to the electron-donor properties of the mesomethyl group and the proximity of the β-methyl group and the azomethine nitrogen atom;

d) if there is a possibility of additional stabilization of the intermediate aminocyclopentane derivative, thermolysis is markedly shifted toward the more stable final reaction product. For example, the formation of cyclopentaneporphyrin XCVII in the thermolysis of the Schiff bases of coproporphyrin-I LXXI is favored by a factor of about two relative to cyclization to give a porphyrin with an unsubstituted exocycle XCVIII. The scheme shows that only loss of an alcohol molecule is required for generation of the lactam of the cyclopentaneporphyrin. This thermolysis scheme clearly supports the concept of initial isomerization of the molecular ion to give an ion with a cyclopentane ring;



Thermolysis of coporphyrin-I derivatives

e) the thermolysis of Schiff bases with various substituents at the azomethine nitrogen atom may be used to obtain lactams containing a wide variety of substituents at the lactam nitrogen atom. For example, lactams CV and CVI were obtained from complexes LXXII and XXLIII. A characteristic feature of these lactams is fixation of the position of the phenyl ring relative to the plane of the porphyrin macrocycle as indicated by analyzing the PMR chemical shifts of the phenyl protons. The phenyl ring in lactam CV is twisted away from the porphyrin macrocycle, while approximation of the phenyl ring and porphyrin macrocycle is noted in lactam CVI;

f) the cyclopentane ring in the position opposite to the azomethine substituent probably hardly affects the direction of the cyclization (porphyrins XCIX and C are formed in equal amounts from complex LXX);

g) the presence of long-chain or bulky substituents in the azomethine residue likely permits a much lower thermolysis temperature (the thermolysis of Ni—OEP—CH=NMe proceeds at 290-310°C, while the thermolysis of Ni— or Cu—OEP—CH=N-*i*Bu proceeds at only 250-260°C);

h) formation of the cyclopentane ring is independent of whether the azomethine residue is in the β- or meso position of the porphyrin macrocycle. The presence of an alkyl substituent containing an α-methyl group in the adjacent β- or meso position is important (cyclopentaneporphyrin CI is obtained from porphyrin XL);

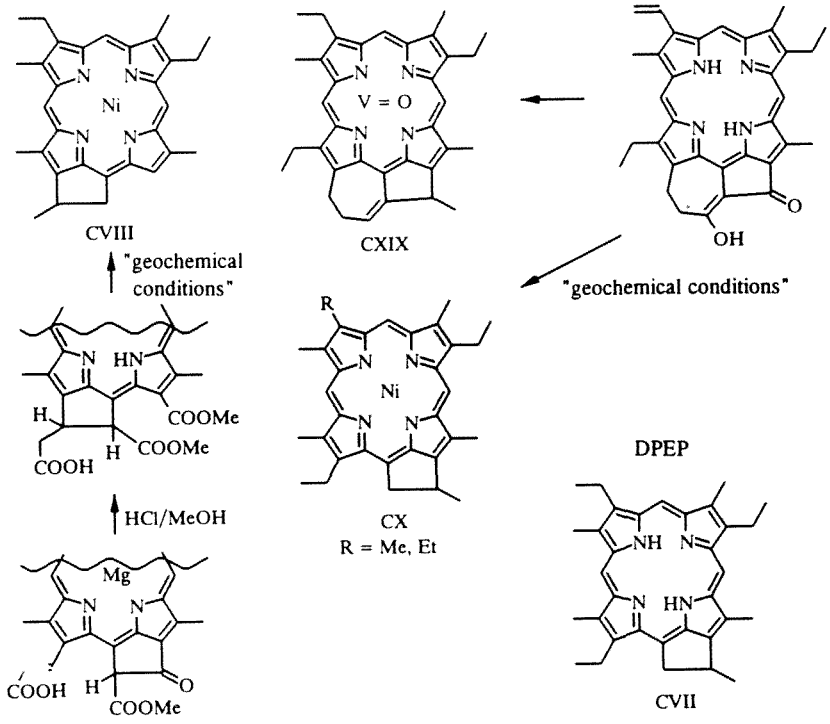
i) an increase in the length of the aliphatic chain of the peripheral β-substituents facilitates stabilization of the thermolysis products. For example, three stable porphyrins, CII, CIII, and CIV, were isolated in the thermolysis of the Schiff base from octapropylporphyrin LXXXVI and characterized;

j) facile scaling up is the most important feature of the thermolysis reaction, i.e., increasing the charge of the initial Schiff base up to significant amounts (1-5 g) does not reduce the yield of the final thermolysis products. This permits the production of several grams of cyclopentaneporphyrin complexes in only a few minutes, which is absolutely impossible through the other reported chemical methods.

Ofcourse, we were not the only workers to use this thermolysis procedure to obtain cyclopentaneporphyrins, since the capacity of various substituents in porphyrins to undergo different types of intramolecular cyclization is quite characteristic in

porphyrin chemistry. Thus, the heating of porphyrins containing β-cyanoethyl groups at 250°C in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene [44] or upon the thermolysis of vinylporphyrins in TsOH/*o*-dichlorobenzene for up to 8 h may be used to obtain porphyrins with an unsubstituted cyclopentane ring [43]. However, the yields in these cyclizations do not exceed 10-20% and the multistep synthesis of the corresponding starting porphyrins is also a rather difficult problem.

Product XCIII, which is a porphyrin with a methylcyclopentane ring, holds a special place among the cyclopentaneporphyrins synthesized in our laboratory [25, 31, 32]. After this synthesis was accomplished, we proposed that such compounds are likely found in nature. Indeed, several years later, a nickel complex of a porphyrin with a cyclopentane ring CVIII was isolated as the major derivative in the porphyrin fraction of bituminous shale from Darmstadt, Germany [46], for which the authors proposed an origin from chlorophyll C. A vanadium complex of porphyrin CIX and nickel complexes of homologs of desoxophylloerythroetioporphyrin (DPEP) CX found in hilsonite asphalts, whose precursor is chlorophyll A, were isolated from marine deposit shales in Switzerland [47].



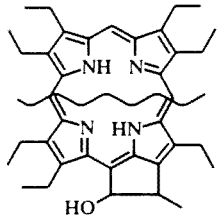
Porphyrins with two cyclopentane rings may exist among the minor series of natural petroporphyrins of the [M-4] series [48, 49]. The synthesis of such compounds XCIX and C was also carried out in our laboratory [26] not by thermolysis of the corresponding bis-Schiff bases, which proved thermally unstable, but by thermolysis of Schiff monobases LXX.

Thus, the synthesis of porphyrins with cyclopentane rings starting from Schiff bases may serve as a realistic approach for obtaining model compounds for the study of the chemical and physicochemical properties of natural petroleum porphyrins (petroporphyrins). The presence of cyclopentaneporphyrins in petroleums suggests their origin from chlorophylls and the generation of petroleum only through a biogenic pathway. However, our results on the extremely facile formation of cyclopentaneporphyrins by the thermolysis of Schiff bases indicates the possibility of an abiogenic pathway through the formation of such porphyrins in petroleum and other natural geological materials. For example, the formation of porphyrin-like compounds during volcanic activity has been demonstrated rather rigorously [50, 51] and a significant number of $[M-2]^+$ ions are found in the mass spectra of porphyrins subjected to heat treatment on a montmorillonite surface [52]. In our opinion, these findings are also evidence for the generation of cyclopentaneporphyrins under vigorous, prebiological conditions. In turn, during geological evolution, cyclopentaneporphyrins may have become precursors of chlorophyll compounds and, thus, photosynthesis, which suggests the possibility of an alternative, abiogenic pathway for the formation of petroleum on Earth.

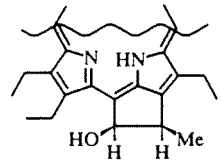
2.3.1. Chemical Properties of Cyclopentaneporphyrins. Oxidation of Cyclopentaneporphyrins on the Silica Gel Surface

In a study of petroporphyrins, among which metalloporphyrins are widely represented, containing an exocyclic cyclopentane ring of the so-called [M-2] series or the DPP series, Clezy et al. [41] found that some irreversible decomposition of the porphyrins occurs upon the chromatographic purification on silica gel, which may affect the precision and accuracy of the results of analyses of the component parts of porphyrin fractions isolated from natural sources. Thus, these authors recommended the use of chromatography on alumina, on which there is less porphyrin decomposition, for isolation of "geological" porphyrins.

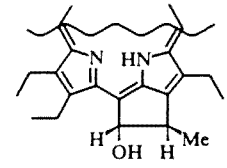
In an independent study of the chemical properties of cyclopentaneporphyrins, we found that a new polar porphyrin is formed in 30-35% yield upon the chromatographic purification of cyclopentaneporphyrin XCIII on silica gel plates after repeated chromatography of these plates. The structure of this new porphyrin corresponded to 15′-hydroxycyclopentaneporphyrin CXI. After chromatographic separation of porphyrin CXI on an alumina column, pure *cis*-CXI and *trans*-CXI were isolated in 1:9 ratio [53, 54]. Other cyclopentaneporphyrins are also regioselectively oxidized by atmospheric oxygen on a highly developed silica gel surface at position 15′. Thus, hydroxyporphyrins CXII and CXIII were obtained from porphyrins XCI and CII.



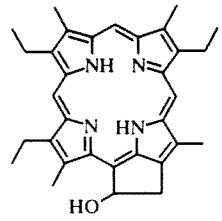
CXI



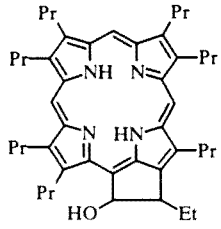
cis- CXI



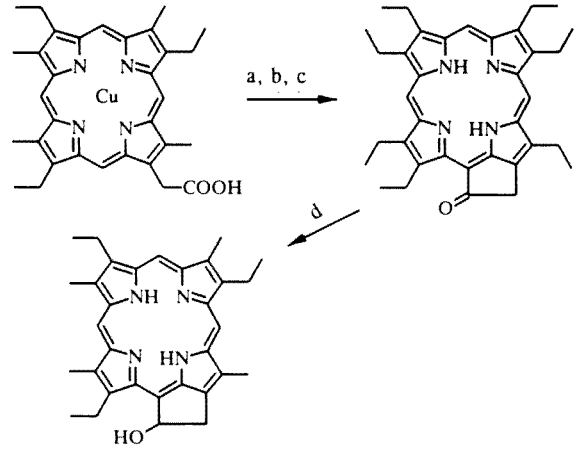
trans- CXI



CXII



CXIII

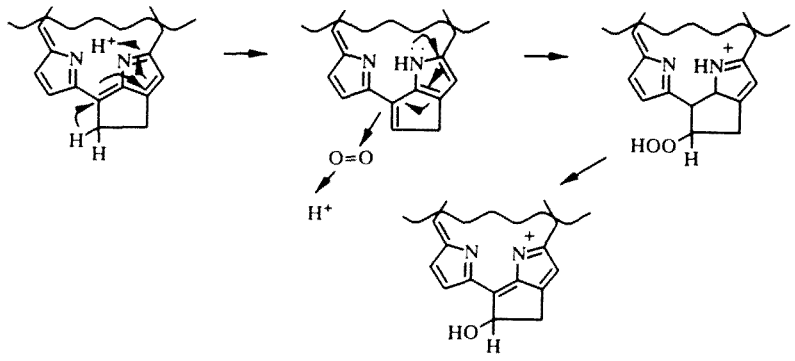


CXIV

a $(COCl)_2$, b $SnCl_4$, c H_2SO_4 (10% yield), d $NaBH_4$

Following these studies, hydroxydesoxophylloerythroetioporphyrin CXIV was isolated directly from a mixture of natural petroporphyrins. The structure of CXIV was established using the nuclear Overhauser effect [49]. The planned synthesis of this compound was then carried out starting from a porphyrin containing acetate residue by cyclization of the corresponding

acid chloride under Friedel—Crafts reaction conditions using $SnCl_4$ with subsequent reduction of the cyclopentaneporphyrin using sodium borohydride [55]. The finding of hydroxyporphyrins among petroporphyrins is an artefact in the opinion of Clezy et al. [56]. These compounds are most likely formed during the chromatographic purification. Our own studies unequivocally support this hypothesis. A mechanism for the formation of these compounds has recently been proposed. The selectivity of the oxidation of DPEP and their analogs is based on the attack of the pseudophlorine system found in equilibrium with the porphyrin species by molecular oxygen as follows:



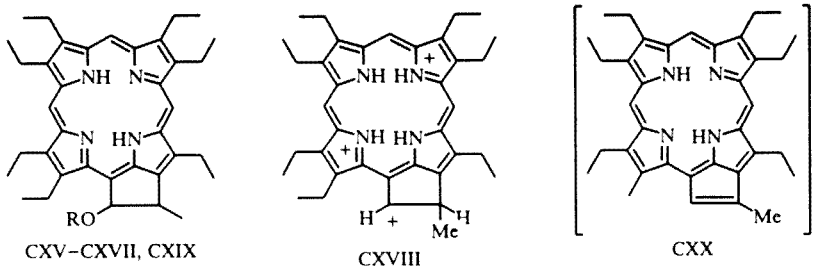
Thus, the regioselective oxidation of the methylene group of the cyclopentane ring on a highly developed silica gel surface is important for the development of chromatographic separation methods and establishing the structure of "geological" porphyrins. We have found that cyclopentaneporphyrins are readily oxidized on montmorillonite and other alumosilicates formed in volcanic activity (an example is the soil samples taken from the lava flows in the vicinity of the Klyuchevskii volcanic peak in Kamchatka). The corresponding nickel or vanadium complexes are oxidized much more slowly and we hardly ever encountered significant formation of hydroxycyclopentaneporphyrin complexes in our work on metallocyclopentaneporphyrins.

2.3.2 Chemical Properties of Hydroxycyclopentaneporphyrins

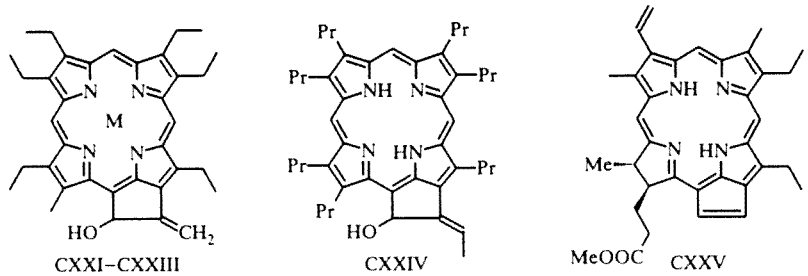
2.3.2.1 Acylation, Ether Formation, and Dehydration Combined with Prototropic Rearrangement

Hydroxycyclopentaneporphyrins are very similar in their chemical properties to the well-known mesohydroxymethylporphyrins [1]. Thus, porphyrin CXI is silylated quantitatively by various reagents to give trimethylsilyl derivative CXV. The molecular ion peak is the major peak in the mass spectrum of this compound. The corresponding highly reactive acetate CXVI is formed from CXV and acetic anhydride in pyridine. Upon chromatography on silica gel using chloroform—ethanol as the eluent, CXVI is quantitatively converted to ether CXVII. The high reactivity of acetate CXIII toward nucleophilic substitution is related to the facile formation of benzyl carbocation CXVIII, which hardly differs in its activity from reported mesoacetoxymethylporphyrins [57].

The conversion of hydroxyporphyrin CXI upon heating in trifluoroacetic acid at 60°C through the formation of intermediate trifluoroacetate CXIX not to cyclopentaneporphyrin CXX, which would seem most likely at first glance, but to stable exomethylenecyclopentaneporphyrin CXXI is the most important property of CXI. Porphyrin CXXI may be seen both as a cyclopentaneporphyrin and as a substituted monovinylporphyrin. Indeed, splitting of the α and β bands, corresponding to a bathochromic shift between the cyclopentaneporphyrins and vinylporphyrins, is found in the electronic spectra of the dication of the porphyrin and its copper CXXII and zinc complexes CXXIII. Analogously, porphyrin CIII is formed in virtually quantitative yield from porphyrin CXIII. As shown above, a small amount of porphyrin CIII is formed directly in the thermolysis of Schiff base LXXVI.



CXV–CXVII, CXIX CXVIII CXX



CXXI–CXXIII CXXIV CXXV

CXV R = $SiMe_3$, CXVI R = Ac, CXVII R = Et, CXIX R = $COCF_3$, CXXI M = 2H, CXXII M = Cu, CXXIII M = Zn

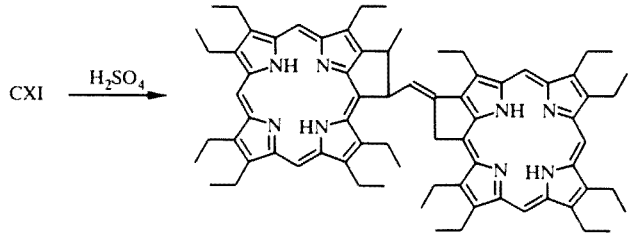
The formation of exomethyleneporphyrin CXXI, as in the case of exoethylideneporphyrin, from hydroxycyclopentaneporphyrins results from a prototropic rearrangement of the corresponding cations CXVIII due to stabilization of the less strained pentane exocycle in comparison with the cyclopentene ring (in the case of hypothetical porphyrin CXX). Of course, if stabilization due to prototropic rearrangement is impossible as in the case of hydroxyporphyrin CXII, the unstable cyclopentaneporphyrin CXXIV formed decomposes completely in trifluoroacetic acid solution.

Although a compound with an unsubstituted cyclopentene ring CXXV was specially synthesized for less strained chlorine macrocycles [58], this compound had unusual spectral characteristics due to the existence of both 18π and 20π electron systems in the macrocycle.

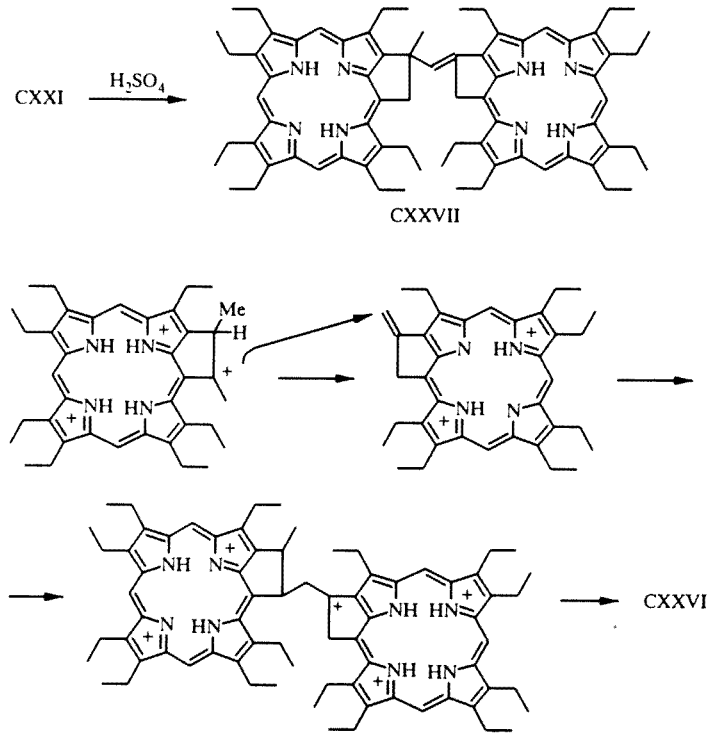
A prototropic rearrangement in porphyrins CXXI or CIII was confirmed by deuterium exchange results using CF_3CO_2D shown in the scheme.

2.3.2.2. Cation Dimerization of Hydroxycyclopentane- and Exomethylenecyclopentaneporphyrins

The formation of two different carbocations in hydroxycyclopentane- and exomethylenecyclopentaneporphyrins arising in sulfuric acid due to prototropic rearrangement is clearly illustrated by the formation of dimers CXXVI and CXXVII, which differ in structure but have similar electronic absorption spectra and chromatographic mobility, upon dissolving porphyrins CXI and CXXI in sulfuric acid [59] according to our mechanism. The copper complexes of these porphyrins upon dissolution in trifluoroacetic acid also form the corresponding dimers. A characteristic feature of the electronic spectra of these dimers, as for the corresponding free bases in protonated form, is good splitting of the α and β bands in the visible region and of the Soret band into two components separated by 10-12 nm, corresponding to the presence of apparently two weakly interacting macrocycles in the dimer, namely, β-vinylporphyrin and octaalkylporphyrin.

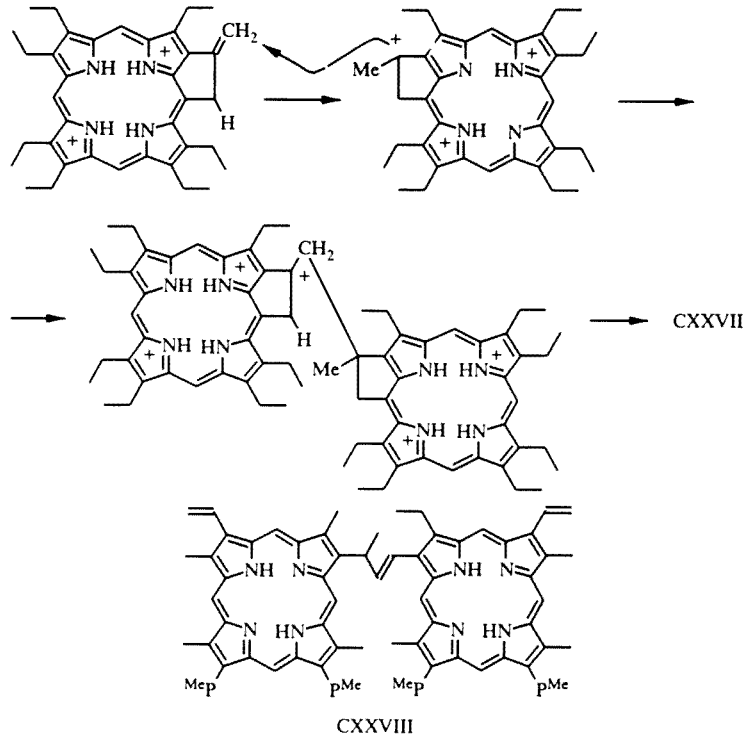


CXXVI

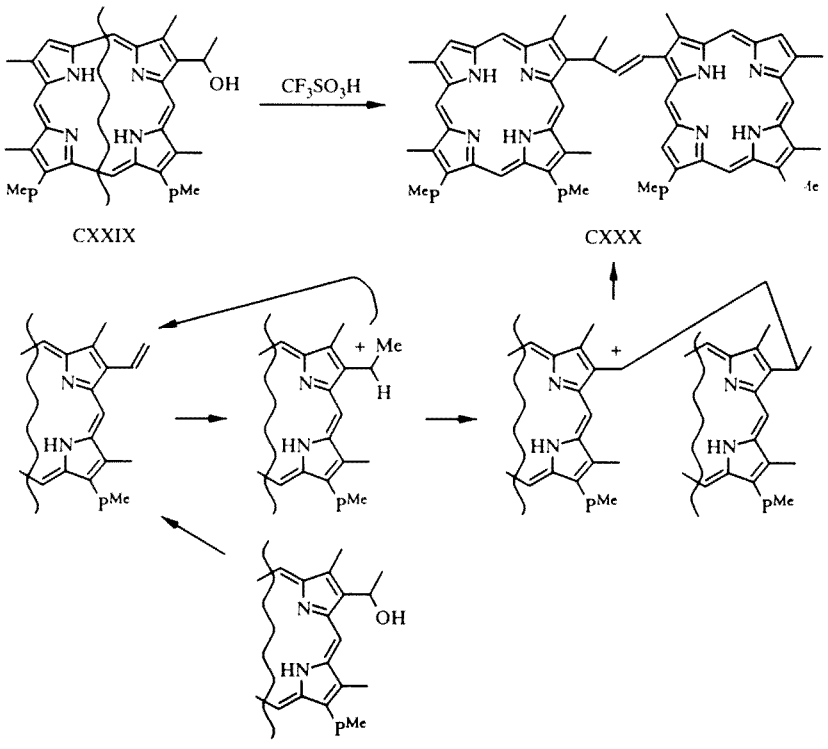


Zen'kevich et al. [60-68] studied the spectroscopic properties of cyclopentaneporphyrins, exomethylenecyclopentaneporphyrins, and covalently bound dimers and their metallocomplexes synthesized in our laboratory.

Evidence for the cationic dimerization of hydroxycyclopentane- and exomethylenecyclopentaneporphyrins was unexpectedly found in the preparation of an important drug derived from porphyrins, photophrin II, commonly used in photodynamic cancer therapy. One of the major components of this preparation obtained from hematoporphyrin is dimer CXXVIII [69], which may be formed only by cationic dimerization.



The synthesis of two C—C dimers (one of which, CXXX, is shown below [70]) was carried out starting from model 2(4)-(1-hydroxyethyl)deuteroporphyrin CXXIX using trifluoromethylsulfonic acid as the catalyst. The mechanism for the formation of such dimers by the authors was identical to the mechanism for dimerization of cyclopentaneporphyrins.



2.4. Synthesis of Schiff Base Iodoalkylates (Immonium Salts)

The most important chemical property of the Schiff bases is their capacity to react with alkyl halides, actually with lower alkyl halides, to form the corresponding methylenimmonium salts. These compounds, including well-known PC, XXXVIII and XXXIX, are used mainly for the synthesis of the corresponding aminomethylporphyrins, whose chemistry is not less interesting than the chemistry of the Schiff bases discussed here. However, this is the subject of our next review.

The following iodoalkylates were prepared starting from etioporphyrin derivatives [22, 24]:

$$EP{-}CH{=}N^{+}(Me)EtI^{-},\ EP{-}CH{=}N^{+}Et_2I^{-},\ EP{-}CH{=}N^{+}Pr_2I^{-},$$
$$EP{-}CH{=}N^{+}Bu_2I^{-},\ EP{-}CH{=}N^{+}(Me)CH_2CH_2OHI^{-}$$

A characteristic feature of all the Schiff base iodoalkylates formed is the presence of two different PMR signals for each substituent at the imine nitrogen atom differing sometimes by 2 ppm due to their different position relative to the plane of the porphyrin macrocycle. The substituent found in the field of the ring current, i.e., above the macrocycle plane, has signals at higher field.

All the iodoalkylates readily react with compounds containing a primary amino group to give an azomethine bond, which may be used for practical purposes such as the production of heterogeneous catalysts [71] or immobilization of phosphorescent labels. The derived aminomethylporphyrins may be used for the synthesis of biologically active compounds [24].

In analyzing these results, we may conclude that these Schiff bases fall among the most promising derivatives in porphyrin chemistry for the preparation of a virtually unlimited variety of tetrapyrrole compounds. The study of their chemical properties is continuing and we are certain that promising new reactions will be discovered in this area in the near future, possibly having importance not only in porphyrin chemistry but also for all heterocyclic chemistry.

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

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