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Sterically Hindered Porphyrins

A.V.Bogatskii and Z.I.Zhilina

Data on the chemistry of sterically hindered porphyrins as well as dimeric and trimeric prophyrins are examined and described systematically. Attention has been concentrated on sterically hindered porphyrins as synthetic models of natural oxygen-transferring agents—haemoglobin and myoglobin.
The bibliography includes 94 references.

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I. INTRODUCTION

Iron-porphyrins are classified in terms of their functions as the prosthetic groups of an important class of proteins and enzymes—haemi- and haemo-proteins[1-3]. The main function of natural haemoproteins such as haemoglobin and myoglobin is based on their ability to combine reversibly with oxygen. The structures of haemoglobin[4] and myoglobin[5] have been determined by X-ray diffraction. The studies by Perutz and Kendrew showed that the iron-porphyrin complex is located in a hydrophobic "protein pocket". The iron atoms in the molecules of both proteins are coordinated to the four nitrogen atoms of protoporphyrin-IX and to the nitrogen atom of the imidazole ring in the histidine residue forming part of the polypeptide chain of the haemoglobin molecule. In oxygenation a second azial ligand (oxygen) is added. The decisive factor in the biological function of haemoproteins is the spin state of iron. In haemoglobin and myoglobin the Fe^{II} atom is pentacoordinate in the deoxy-form. The high-spin form has an ionic radius which is too large for the Fe^{II} atoms to be accommodated within the cavity of the porphyrin. The iron atom in the high-spin state lies outside the limits of the plane of the four nitrogen atoms of porphyrin towards the "proximal" imidazole.

Whereas the Fe^{II} atom is hexacoordinate, the low-spin iron atom of the diamagnetic oxyhaemoglobin or oxymyoglobin lies within the cavity in the porphyrin ring. It can be assumed that Fe^{II} oscillates very rapidly between these states and that the part of the protein molecule linked directly to the iron atoms via the "proximal" imidazole also undergoes rapid changes[6].

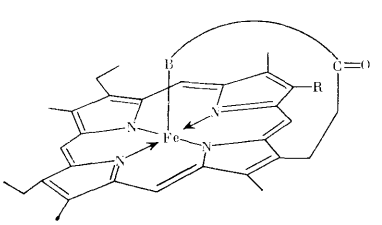
The nature of the regulation of the oxygen affinity, of the control of the axial binding, and of the means used by the protein to ensure the kinetic stability of the dioxy-form in haemoglobin and myoglobin can be most readily understood by obtaining and fully characterising model compounds which are capable of binding oxygen reversibly. In recent years the problem of such modelling has aroused much interest. Various teams of investigators have devoted their attention to problems of the modelling of natural haemoproteins based on metalloporphyrins.

In modelling account is usually taken of the following factors[7]: (1) the steric hindrance around the "active centre"; (2) the role of the "proximal" imidazole in coordination to the Fe^{II} atom in the 5-position; (3) the influence of the "distal" imidazole on the kinetic stability of the oxy-form of haemoglobin and myoglobin and the search for ways of modelling it; (4) the basicity of the "proximal" imidazole; (5) the characteristics of the stereochemistry of the "hydrophobic pocket" formed by the protein around haem and the search for ways of its chemical modelling.

By virtue of the advances in the development of bioorganic chemistry, a need has arisen for well-defined dinuclear metal complexes such as haemoerythrin, haemocyanine[6], and superoxide disnutase, which serve as models of various metalloenzymes[6,8]. Model systems which are of interest from the standpoint of the study of interionic interactions have also been synthesised[9,10]. Since 1973, the principal trend in the development of the chemistry of porphyrins has been the creation of model compounds on the basis of sterically hindered porphyrins. The present review is devoted to the analysis of the literature on this extremely interesting question published during the last seven years.

II. THE SYNTHESIS AND PROPERTIES OF STERICALLY HINDERED PORPHYRINS

In contrast to haemoglobin and myoglobin which are capable of being reversibly oxygenated, simple iron-porphyrins are rapidly and irreversibly oxidised by atmospheric oxygen. Wang[11] was the first to establish that simple porphyrins can undergo reversible oxidation when they are placed in a specially prepared polymer film. Somewhat later, a series of papers were published[12-17] describing the reversible attachment of oxygen to Fe^{II}-porphyrins (I) in solutions at a low temperature. In these experiments, compounds (I) were modified in such a way that the base was covalently bound to the carboxy-groups in the porphyrin ring:



(I)

(a) R = H, B = $-NH(CH_2)_3-$ ;

(b) R = $-CH_2CH_2COOCH_3$, B = $-NH(CH_2)_3-$ ;

(c) R = $-CH_2CH_2CONH(CH_2)_3-$ , B = $-NH(CH_2)_3-$ ;

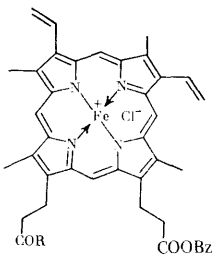
(d) R = $-CH_2CH_2COOCH_3$, B = $-O(CH_2)_3-$;

(e) R = $CH_2CH_2COO(CH_2)_3-$, B = $-O(CH_2)_3-$.

Pyrroporphyrin-*N*[3-(1-imidazolyl)propyl]amide (Ia) has been obtained[12] by treating pyrroporphyrin-XV [18] with 1-(3-aminopropyl)imidazole at room temperature in a solvent mixture (2:1:1 methylene chloride–acetone–pyridine); the amides (Ib) and (Ic) have been obtained[15] by treating the acid chloride of the monomethyl ester of mesoporphyrin-IX with 1-(3-aminopropyl)imidazole, while compounds (Id) and (Ie) [15] have been synthesised by treating the acid chloride of the monomethyl ester of mesoporphyrin-IX with 3-(3-pyridyl)-1-propanol.

In contrast to these methods, a number of workers[19–21] used the methyl ester of histidine and substituted histidine-containing peptides as ligands in iron-haemin. The peptides comprised the methyl ester of t-butoxycarbonyl-leucyl-histidine, the benzyl ester of t-butoxycarbonylhistidyl-leucylglycyl-*S*-benzylcysteine, and the benzyl ester of t-butoxycarbonyl-leucylhistidylalanyl-*S*-benzyloxycarbonyl-lysylglycyl-*N*-benzylcysteine[19–21].

A series of *C*-aminoacyl derivatives of haemin (IIb)–(IIf) have been obtained from the monobenzyl ester of haemin (IIa):[20]



(II)

(a) R=OH;

(b) R = Ala — OMe;

(c) R = His — OMe;

(d) R = Leu—His—OMe

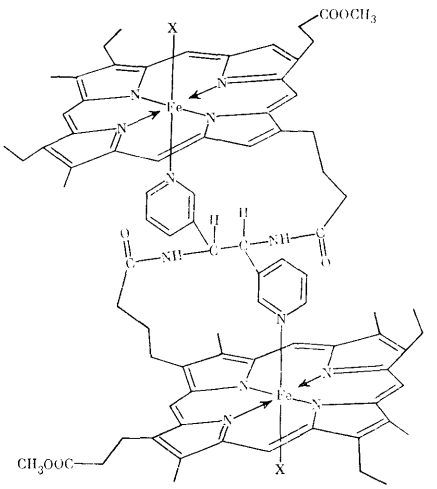
(e) R = Leu—His—Leu—Gly—Lys(Bz)—OBz

(f) R = Leu—His—Ala—Lys(Z)—Gly—Lys(Bz)—OBz.

Compounds (IIb)–(IIf) were synthesised by condensing the monobenzyl ester of haemin with the methyl esters of alanine and histidine and also with the *N*-unsubstituted di-, penta- and hexa-peptides enumerated above—by the mixed anhydride method involving interaction with ethyl chloroformate in dimethylformamide (DMF) in the presence of triethylamine. The bis-*C*-aminoacyl derivatives of haemin have been obtained analogously[19].

It has been shown[20] that the pentacoordinate complexes of iron-porphyrins, obtained by reducing compounds (IIe) and (IIf) with an aqueous solution of sodium dithionite in an atmosphere of nitrogen, are able to combine reversibly with oxygen in the course of 35–40 min at room temperature.

In order to investigate the interaction of haem molecules within a single conformational system, Traylor et al.[22] obtained the model compound (III) from the monomethyl ester of mesoporphyrin and 1,2-di-(3-pyridyl)ethylenediamine[23], in which two haem molecules are conformationally linked via the common central ethylenic linkage. Any change in the conformation of the "upper" iron-containing porphyrin ring must influence the conformation of the identical "lower" ring via this bond. Compound (III) combines reversibly with oxygen in solution, being converted into compound (IIIb), and reacts with carbon monoxide in two stages (in contrast to model monohaem compounds[24,25]), forming compound (IIIc): (a) X absent; (b) $X = O_2$; (c) X = CO.



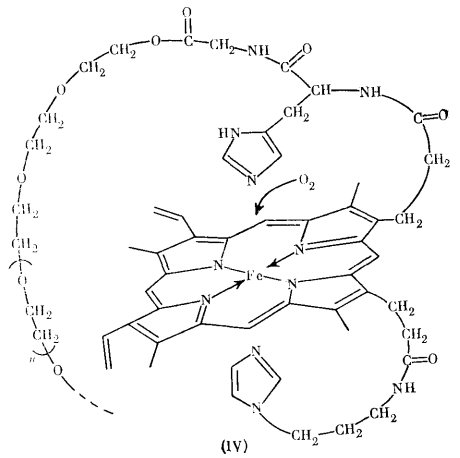
(III)

In 1977 German investigators[26] synthesised the haem polymer (IV) capable of reversible transfer of molecular oxygen. This haem polymer had the properties of the natural oxygen carrier—haemoglobin: high solubility in water, difficult irreversible oxidation of the oxygen complex by the functional polymer, and similarity to the "distal" imidazole. The principal initial polymers were poly(ethylene glycol)–bis-(glycine ester) (V) [27] and the polyurethane (VI) obtained from poly(ethylene glycol) (PEG) and di-isocyanate.

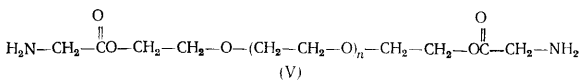
Di-t-butoxycarbonylhistidine was attached to the free amino-groups of polymers (V) and (VI) by means of liquid-phase peptide synthesis[27]. After the removal of the protecting group from histidine, poly(ethylene glycol)–bis(glycyl-histidylhaemin) (VII) and the histidylhaem derivative of the polymeric urethane (VIII) were obtained.

The histidine in the polymeric haemins (VII) and (VIII) is linked to the carboxy-group of haemin via the amide group. In this structure the optimum coordination of the imidazole nitrogen atom of histidine is sterically hindered. Consequently this histidine may be compared with the "distal" histidine in myoglobin and haemoglobin.

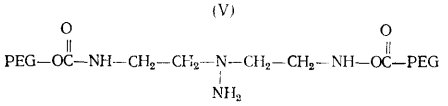
3-(1-Imidazolyl)propylamine has been attached to two carboxy-groups of the haem polymer (VII) by liquid-phase peptide synthesis[26] and compound (IV) was obtained. The imidazole residue in the polymeric haemin (IV) is optimally coordinated to the iron atom. In this haem polymer the oxygen coordination site is shielded both by histidine and by the synthetic polymer. The iron(II) complex of the haem polymer (IV) is readily soluble in water and combines reversibly with oxygen in solution. After frequent repetitions of the oxygen addition and liberation process, complex (IV) is oxidised to a haemin polymer, which, however, can be again reduced to compound (IV). The reversible oxygenation cycle is then again repeated.



(IV)



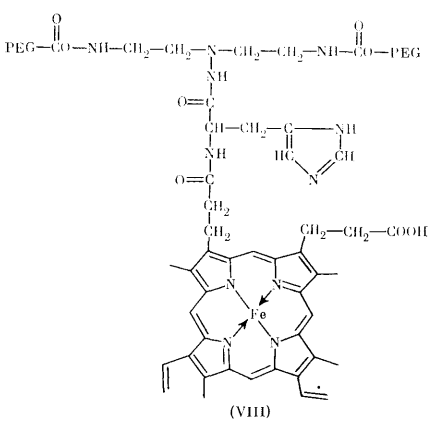
(V)



(VI)

Haem—His—Gly—PEG—Gly— His — Haem

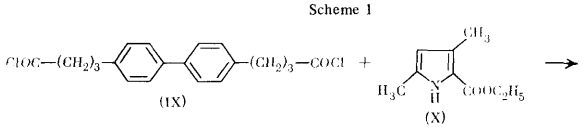
(VII)



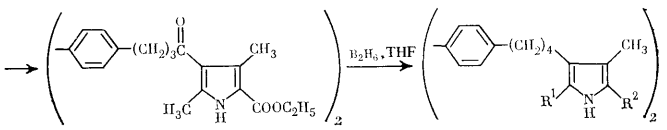
(VIII)

The copper and iron complexes of the first cyclophane (bridged) porphyrin compounds (XVI) and (XVII) were obtained for the first time by Diekman et al [28] from dipyrromethenes (XIV) linked by both ends of the aromatic chain. Friedel–Crafts acylation of 5-ethoxycarbonyl-2,4-dimethylpyrrole (X) [29] with the acid dichloride (IX) in the presence of aluminium chloride and nitrobenzene yielded dipyrrole (XI), [30] whose keto-group was reduced with B_2H_6 in tetrahydrofuran (THF) with formation of compound (XIIa): [31]

Scheme 1



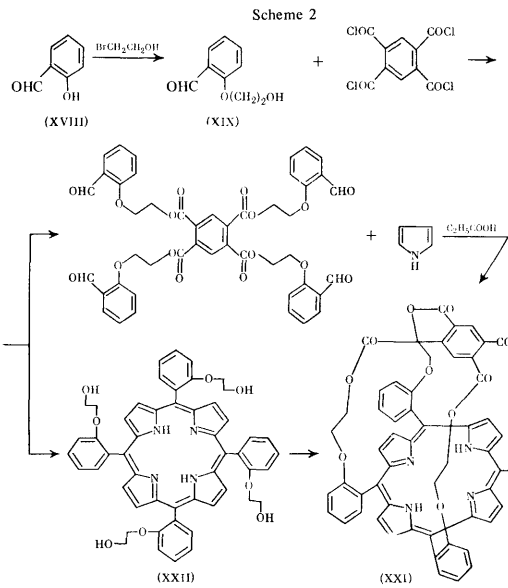
(IX) (X)



(XI) (XII)

(a) R^1=CH_3, R^2 = $COOC_2H_5$; (b) R^1=CH_3, R^2=$COOC_6H_5$; (c) R^1=CHO, R^2=$COOC_6H_5$; (d) R^1=CHO, R^2=COOH

Scheme 2

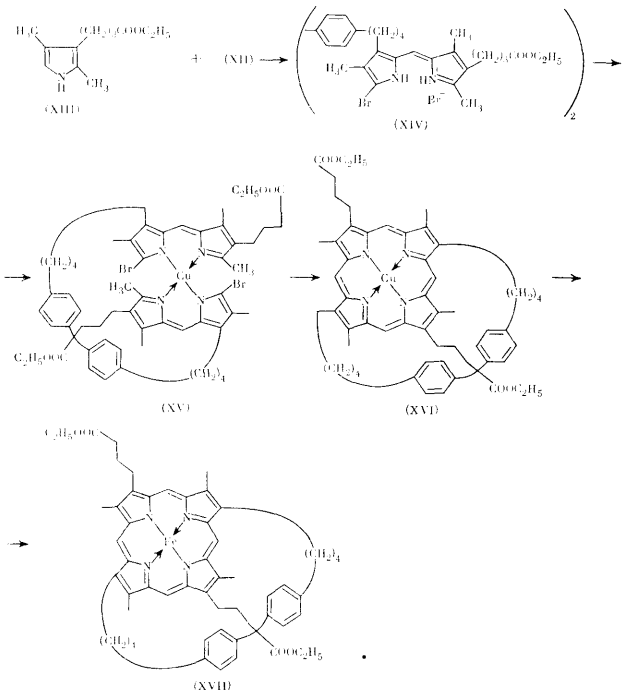


(XVIII) (XIX) (XXII) (XXI)

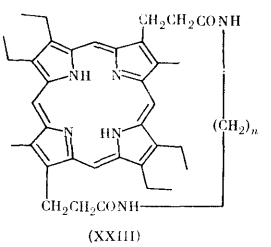
Transesterification with sodium benzilate and subsequent treatment with sulphuryl chloride in the presence of diethylamine then gave rise to the aldehyde (XIIc), the catalytic hydrogenolysis of which led to compound (XIId). [32,33] Condensation of the substituted pyrrole (XIId) with the substituted pyrrole (XIII) [34] in the acetic acid–hydrogen bromide mixture followed by bromination of the product led to the formation of dibromopyrromethene (XIV). [35] On treatment with copper acetate in the presence of ammonia, the latter forms the copper complex (XV), which cyclises on heating in xylene with formation of the copper complex of the cyclophane porphyrin (XVI). [36] The free porphyrin is formed from compound (XVI) under the influence of sulphuric acid. Complex (XVII), containing iron(III), was obtained from the free porphyrin by treatment with iron sulphate (Scheme 1).

The second cyclophane porphyrin (XXI), called the capped porphyrin, has been obtained by Baldwin and coworkers [37–39]. The crystalline iron(II) complex of this model undergoes reversible oxygenation in solution in pyridine or benzene containing *N*-methylimidazole; the oxygenation of the iron(II) complex of the model compound (XXI) in solution in pyridine requires 20 h. [38] The capped porphyrin (XXI) has been obtained [82] by the direct condensation of the tetra-aldehyde (XX) with pyrrole in propionic acid. The tetra-aldehyde (XX) has been obtained by alkylating salicylaldehyde (XVIII) with the aid of bromohydrin to the corresponding ester (XIX), which was converted into compound (XX) by interaction with pyromellitic acid chloride in a THF–triethylamine mixture [37] (Scheme 2). The capped porphyrin (XXI) has also been synthesised by esterifying compound (XXII) with pyromellitic

acid chloride[37]:

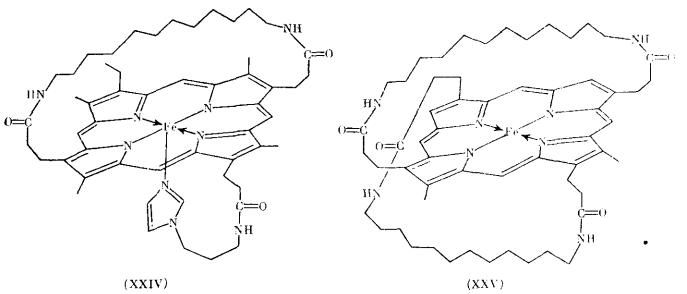


Japanese investigators[40–43] synthesised a series of cyclophane porphyrins (XXIII) with different lengths of the aliphatic bridge connecting the symmetrically located carboxy-groups of the propionic acid residues of the porphyrin:

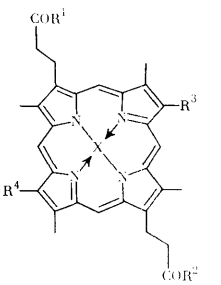


The interaction of 4,8-di-(2-carboxyethyl)-1,2,5,6-tetraethyl-3,7-dimethylporphyrin[44] with diamines $NH_2(CH_2)_nNH_2$, where n = 6, 7, 8, 9, 10, or 12, and also (for comparison) with propylamine in the presence of isobutyl chloroformate and triethylamine in THF under the conditions of high dilution, the reaction products being subsequently treated with zinc or iron acetate, yielded the corresponding complexes of cyclophane porphyrins[43].

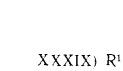
Compounds (XXIV) and (XXV), which are models of haemoglobin and myoglobin, have been obtained[45,46] from porphyrins in which the "bridges" form a belt around the porphyrin ring on either side of its plane. The necessary initial porphyrins (XXVI), (XXVII), and (XXVIII) were obtained via *ac*-biladienes[47]:

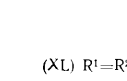


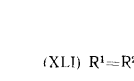
Scheme 3

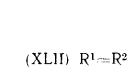


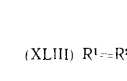
(XXVI) R^1 = OH, R^2 = OH, R^3 = R^4 = H, X = 2H;
(XXVII) R^1 = OH, R^2 = OH, R^3 = $COOC_2H_5$, R^4 = H, X = 2H;
(XXVIII) R^1 = OH, R^2 = OH, R^3 = $COOC_2H_5$, R^4 = $COOC_2H_5$, X = 2H;
(XXIX) R^1 = Cl, R^2 = Cl, R^3 = R^4 = H, X = 2H;
(XXX) R^1 = $-O(CH_2)_4C{\equiv}CH$, R^2 = $-O(CH_2)_4C{\equiv}CH$, R^3 = R^4 = H, X = 2H;
(XXXI) R^1 = $-O(CH_2)_4C{\equiv}CH$, R^2 = $-O(CH_2)_4C{\equiv}CH$, R^3 = R^4 = H, X = $Fe^{III}Cl$;
(XXXII) R^1 = R^2 = $-O(CH_2)_4C{-}C{\equiv}C{-}C(CH_2)_4O$, R^3 = R^4 = H, X = $Fe^{III}Cl$;
(XXXIII) R^1 = R^2 = $-O(CH_2)_4C{-}C{\equiv}C{-}C{-}(CH_2)_4O$, R^3 = R^4 = H, X = Cu;
(XXXIV) R^1 = R^2 = $-O(CH_2)_{12}O$, R^3 = R^4 = H, X = Cu;
(XXXV) R^1 = R^2 = $-O(CH_2)_{12}O$, R^3 = R^4 = H, X = 2H;
(XXXVI) R^1 = R^2 = $-NCH_3(CH_2)_5COOCH_3$, R^3 = R^4 = H, X = 2H;
(XXXVII) R^1 = R^2 = $-NCH_3(CH_2)_5CO(CH_2)_5NCH_3$, X = 2H;
(XXXVIII) R^1 = R^2 = $-NH(CH_2)_{12}NH$, R^3 = R^4 = H, X = 2H;

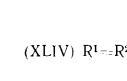
XXXIX) R^1 = R^2 = $-O(CH_2)_3$––$(CH_2)_3O$, R^3 = R^4 = H, X = 2H;

(XL) R^1 = R^2 = $-O(CH_2)_3$––$(CH_2)_3O$, R^3 = R^4 = H, X = 2H;

(XLI) R^1 = R^2 = $-O(CH_2)_3$––$(CH_2)_3O$, R^3 = R^4 = H, X = 2H;

(XLII) R^1 = R^2 = $-O(CH_2)_3$––$(CH_2)_3O$, R^3 = R^4 = H, X = $Fe^{III}Cl$;

(XLIII) R^1 = R^2 = $-O(CH_2)_3$––$(CH_2)_3O$, R^3 = R^4 = H, X = $Fe^{III}Cl$;

(XLIV) R^1 = R^2 = $-O(CH_2)_3$––$(CH_2)_3O$, R^3 = R^4 = H, X = $Fe^{III}Cl$;

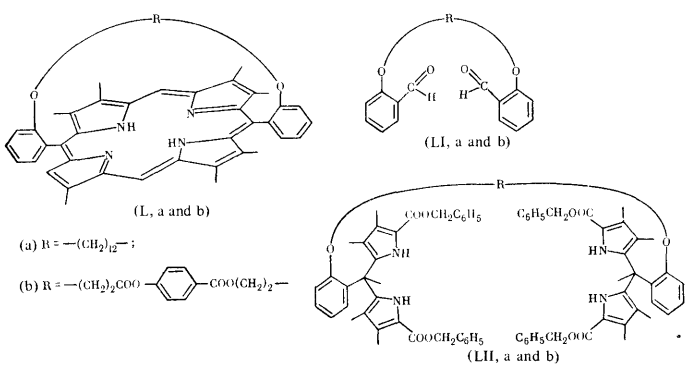
(XLV) R^1 = R^2 = $-NH(CH_2)_{12}NH$, R^3 = $-CONH(CH_2)_3$–, R^4 = H, X = 2H;

(XLVI) R^1 = R^2 = $-NH(CH_2)_{12}NH$, R^3 = $-COOC_2H_5$, R^4 = H, X = 2H;
(XLVII) R^1 = R^2 = $-NH(CH_2)_{12}NH$, R^3 = R^4 = $-CONH(CH_2)_{12}NHCO$, X = 2H;
(XLVIII) R^1 = R^2 = $-NH(CH_2)_{12}NH$, R^3 = R^4 = $-CONH(CH_2)_{12}NHCO$, X = $Fe^{III}Cl$;
(XLIX) R^1 = R^2 = $-NH(CH_2)_{12}NH$, R^3 = $-CONH(CH_2)_3$–, R^4 = H, X = $Fe^{III}Cl$.

The acid dichloride (XXIX) was made to react with hex-5-yn-2-ol [48], which led to the formation of the corresponding diester (XXX). The oxidation of the iron(III) complex of the diester (XXXI) with copper acetate in the pyridine–ether mixture leads to the bridged porphyrin (XXXII).[49] When the metal-free diester (XXX) is oxidised, the copper complex of the bridged porphyrin (XXXIII) is obtained. Reduction of the latter yielded the porphyrin (XXXIV); its demetallation leads to compound (XXXV). The diamide (XXXVI) has been obtained[50] by the reaction of the acid dichloride (XXIX) with $CH_3NH(CH_2)_5COOCH_3$. When the diamide (XXXVI) is refluxed with t-BuOK in toluene, the bridged porphyrin (XXXVII) is obtained[50]. Condensation of the acid dichloride (XXIX) with 1,12-diaminododecane at a high dilution[43] leads to the bridged porphyrin (XXXVIII) and the reaction of the acid dichloride (XXIX) with 2,6-di(γ-hydroxypropyl)pyridine, 3,5-di(γ-hydroxypropyl)pyridine, and 3,5-di(γ-hydroxypropyl)dimethylpyridine yielded the bridged porphyrins (XXXIX)–(XLI) respectively[46]. The complexes (XLII)–(XLIV) have been synthesised by a standard method[51]. The cyclophane porphyrin (XLV) with a covalently bound ligand has been obtained[46] by the reaction of the acid chloride corresponding to compound (XLVI) with 3-aminopropylimidazole. A series of successive transformations of the diethyl ester of the tetracarboxylic acid (XXVIII) led to the formation[46] of the porphyrin (XLVII) in which two "bridges" are located on either side of the plane of the porphyrin ring system (Scheme 3). The introduction of iron[51] into the bridged porphyrins (XLV) and (XLVII) made it possible to obtain the models (XLVIII) and (XLIX) of the active centres in myoglobin and haemoglobin.

The bridged ("belted") porphyrins (L) (Scheme 4) have been obtained[52] by the direct condensation of the dialdehydes (LI, a and b) with the benzyl ester of 3,4-dimethylpyrrole-2-carboxylic acid in the presence of hydrogen chloride with subsequent catalytic debenzylation of the intermediate (LII).[53] The dialdehyde (LIa) has been synthesised by the condensation of salicylaldehyde with 1,12-dibromododecane and the dialdehyde (LIb) has been obtained from *o*-(β-hydroxyethyl)-benzaldehyde by reaction with terephthalic acid dichloride[52].

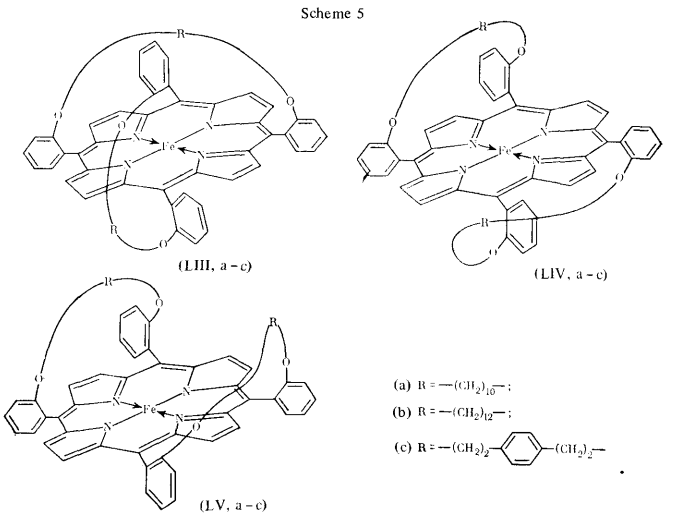
Scheme 4



The acid condensation of 1,10-di(2′-formylphenoxy)decane, 1,12-di(2′-formylphenoxy)dodecane, and 1,4-di[γ-(2′-formylphenoxy)propyl]benzene with pyrrole by the method of Kim et al.[54] yielded porphyrins of the "basket handle" type[55]. The three isomers (LIII), (LIV), and (LV) with crossing *trans*-binding, adjacent *trans*-binding, and adjacent *cis*-binding respectively, have been isolated by preparative chromatography (Scheme 5).

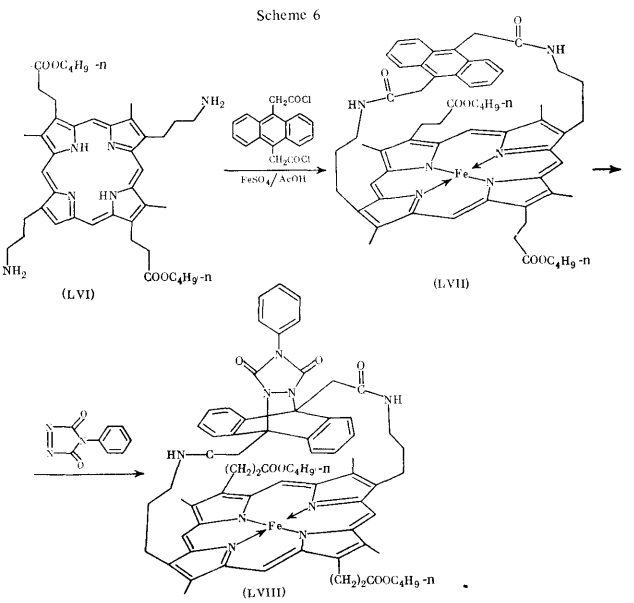
If the solution contains *N*-methylimidazole, then the iron(II) complexes of compounds (LIII), (LIV), and (LV) initially combine with two *N*-methylimidazole molecules, forming hexacoordinate complexes. The formation of these complexes with the isomers (LIII, a–c) requires a large excess of *N*-methylimidazole, apparently due to steric hindrance. When atmospheric oxygen is passed into a solution containing these complexes, one of the ligands (*N*-methylimidazole) is displaced by the oxygen. The oxygenating complexes formed are extremely stable[55].

Scheme 5



In order to increase the steric effects of the "distal" side of compounds modelling haemoglobin and myoglobin, the cyclophane porphyrins (LVII) and (LVIII) have been obtained[56] (Scheme 6).

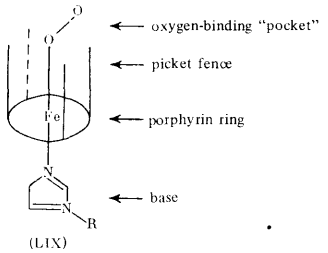
Scheme 6



The model compound (LVII) has been synthesised by the reaction of the diamino-derivative of the porphyrin (LVI) with the dichloride of anthracene-9,10-dicarboxylic acid[57]. The effect of the steric shielding of the "distal" side of the

model compound (LVIII) has been enhanced by the Diels–Alder reaction of the model compound (LVII) with 1-phenyltriazine-2,5-dione.

New sterically hindered porphyrins of the so-called "picket fence" type (LIX) have been synthesised[58–68]:



The acid condensation of *o*-nitrobenzaldehyde and pyrrole followed by the reduction of the product yielded *meso*-tetra-(*o*-aminophenyl)porphyrin (LX), which is a mixture of four atropisomers[59]. All the isomers have been isolated by preparative chromatography and have been identified on the basis of the results of Gottwald and Ullman[69] as the α,β,α,β-atropisomer (LXI), the α,α,β,β-atropisomer (LXII), the α,α,α,β-atropisomer (LXIII) and the α,α,α,α-atropisomer (LXIV).

The tetra-amides (LXV)–(LXVIII) have been synthsised by the reaction of *meso*-tetra-α,α,α,α-(*o*-aminophenyl)porphyrin with the chlorides of isophthalic, trimethylacetic, toluene-*p*-sulphonic, and nicotinic acids[58] (Scheme 7).

The interaction of compound (LXIV) with a limited amount of the chloride of trimethylacetic acid resulted in the formation of *meso*-tri-α,α,α-(*o*-pivalamidophenyl)-β-(*o*-aminophenyl)porphyrin (LXIX). Treatment of compound (LXIX) with 4-(*N*-imidazolyl)butyl chloride and 5-(*N*-imidazolyl)-penyl chloride led to the formation of the amides (LXX) and (LXXI) respectively[68] (Scheme 8).

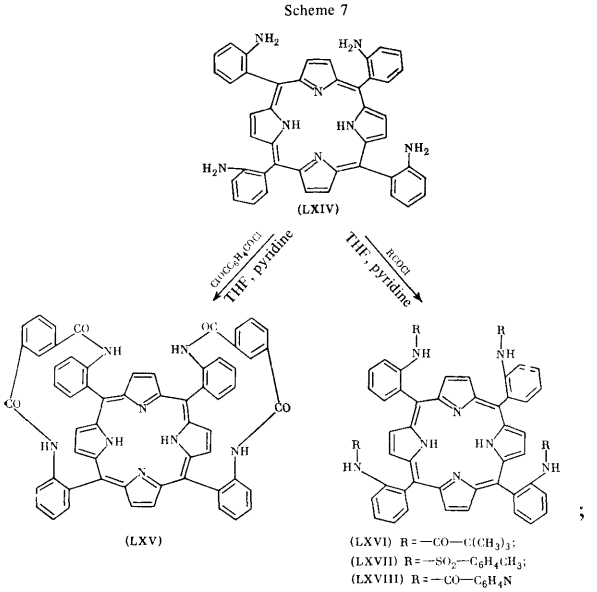
The iron(II) complexes of compounds (LXV)–(LXVIII), (LXX) and (LXXI) have been obtained by reducing the corresponding iron(III) complexes with chromium acetylacetonate. Their pentacoordinate and hexacoordinate compounds with axial ligands have also been obtained. After isolation, the crystalline oxygenating complexes of compounds (LXVI), (LXX), and (LXXI) are stable for a long time both in the solid state and in solution[58,68].

The iron(II) complexes of compounds (LXX) and (LXXI), in which one of the substituents is a base, namely 4-(*N*-imidazolyl)butyl or 5-(*N*-imidazolyl)pentyl, are of special interest. The length and conformation of this substituent can be controlled, which has a significant influence on the oxygen affinity.

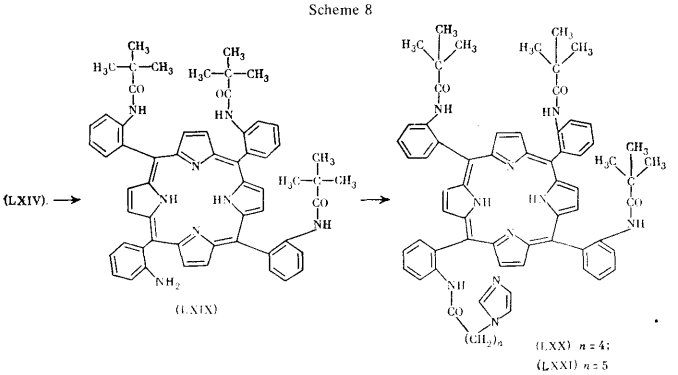
Bogatskii et al.[70] synthesised the "picket fence" and "belted" porphyrins (LXXII) and (LXXIII).

The steric shielding of one side of the porphyrin ring in the model compounds *meso*-tetra-α,α,α,α-(*o*-adamantamidophenyl)porphyrin (LXXIIa), *meso*-tetra-α,α,α,α-[*o*-3,4,5-trimethoxybenzamido)phenyl]porphyrin (LXXIIb), *meso*-tetra-α,α,α,α-(*o*-trimethylacetoamidophenyl)porphyrin (LXXIIc),[58] *meso*-tetra-α,α,α,α-(*o*-aminoacetamidophenyl)porphyrin (LXXIId), and *meso*-tetra-α,α,α,α-(*o*-acetamidophenyl)-porphyrin (LXXII) has been achieved using acid residues of different bulk (Scheme 9).

Scheme 7

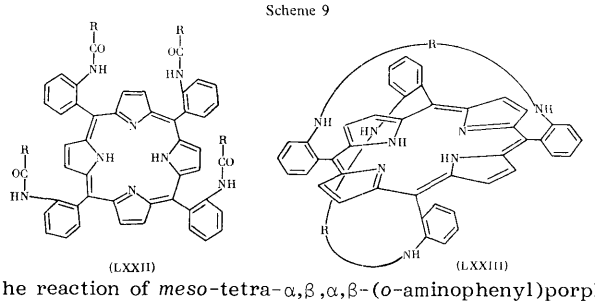


Scheme 8



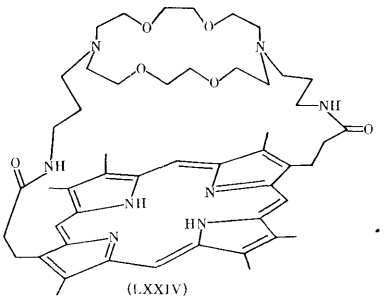
The tetra-amides (LXXII, a–e), where R = adamantyl for (a), R = 3,4,5-$(CH_3O)_3C_6H_2$ for (b), R = $C(CH_3)_3$ for (c), R = CH_2NH_2 or $-COCH_2OCH_2CH_2OCH_2CO-$ for (d), and R = CH_3 for (e), have been obtained by the reaction of *meso*-tetra-α,α,α,α-(*o*-aminophenyl)porphyrin (LXIV) [58] with the chlorides of adamantanecarboxylic, 3,4,5-trimethoxybenzoic, acetic, aminoacetic, and trimethylacetic acids in a THF–pyridine mixture at room temperature.

Scheme 9



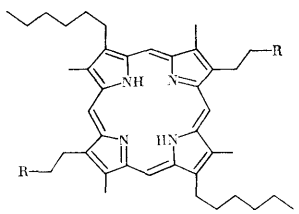
The reaction of *meso*-tetra-α,β,α,β-(*o*-aminophenyl)porphyrin (LXI) with the acid dichloride of triethyleneglycolic acid in a THF–pyridine mixture at a high dilution[43] yielded the cyclophane porphyrin (LXXIII) in which the two "bridges" form a belt around the porphyrin on either side. These porphyrins also form complexes capable of reversible oxygenation.

The crown-porphyrin (LXXIV) was obtained by Chang[57]. This dinuclear ligand permits the subsequent synthesis of composite complexes with both identical and different metals.



(LXXIV)

Dihexyldeuteroporphyrin (LXXVb) was chosen as the initial porphyrin for the synthesis of compound (LXXIV) because of its high solubility in organic solvents, which is very important for the successful separation and purification of the final bicyclic products from the starting material.

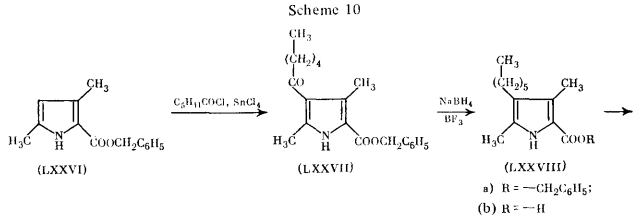


(LXXV)

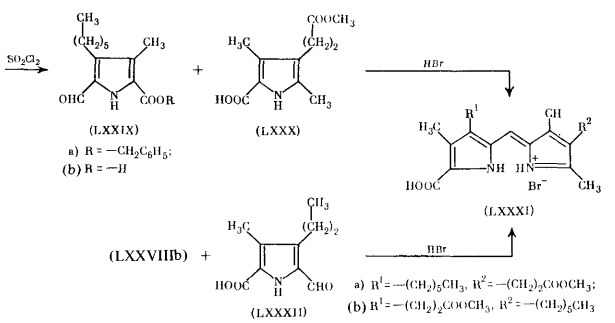
(a) R = —$COOCH_3$;
(b) R = —COOH;
(c) R = —COCl;
(d) R = —$CH_2OSO_2CH_3$;
(e) R = —$CH_2NH(CH_2)_3CH_3$;
(f) R = —$CH_2NHCH_2C_6H_5$

The hexyl side chains were introduced into the pyrrole components by acylating the pyrrole (LXXVI) in the presence of tin(IV) chloride with subsequent reduction of the resulting pyrrole (LXXVII).[71] Treatment of the pyrrole (LXXVIII) with sulphuryl chloride at high dilution yielded[72] the pyrrolealdehyde (LXXIX). After catalytic debenzylation, the free acid (LXXIXb) was mixed with an equimolar amount of the acid (LXXX) [73] and was treated with 48% hydrobromic acid at the boiling point. The pyrromethene (LXXXI) was formed instantaneously. After the removal of the solvent, the pyrromethene was subjected to self-condensation in hot formic acid in the presence of an excess of bromine, which resulted in the formation of the porphyrin (LXXVa); the latter can also be obtained in a high yield by condensing the pyrrole (LXXVIIIb) and the pyrrolealdehyde (LXXXII) via the intermediate dipyrromethene (LXXXI) [57] (Scheme 10).

Scheme 10



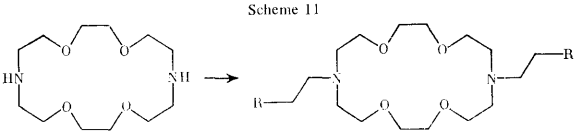
(LXXVI) (LXXVII) (LXXVIII)
a) R = —$CH_2C_6H_5$;
(b) R = —H



(LXXIX) (LXXX) (LXXXI)
a) R = —$CH_2C_6H_5$;
(b) R = —H
(LXXVIIIb) + (LXXXII)
a) R^1 = —$(CH_2)_5CH_3$, R^2 = —$(CH_2)_2COOCH_3$;
(b) R^1 = —$(CH_2)_2COOCH_3$, R^2 = —$(CH_2)_5CH_3$

The crown-ether component was synthesised from diaza-18-crown-6 derivative (LXXXIII).[74] The cyanoacetylene side chains were introduced by stirring the initial compound (LXXXIII) in acrylonitrile for 72 h. The diaminopropyl derivative of compound (LXXXIV) was obtained by reducing the cyano-group of compound (LXXXIV) in the presence of Raney nickel in a methanol solution of ammonia. The two ligands were coupled under the conditions of high dilution[57]. Compounds (LXXXVc) and (LXXXIVb) were poured simultaneously into a stirred 1 : 1 benzene–methylene chloride mixture over a period of 4 h. The crown-porphyrin (LXXIV) was isolated by column chromatography (Scheme 11):

Scheme 11



(LXXXIII) (LXXXIV) a) R = —CN;
(b) R = —CH_2NH_2

In the presence of *N*-methylimidazole and *N*-isobutylimidazole the iron(II) complex of the model compound (LXXIV) gives rise to a visible absorption spectrum typical for a hexacoordinate haemochrome compound. For a larger ligand, such as 1-triphenylmethylimidazole, the visible spectrum differs appreciably from the haemochrome spectrum; the oxygen-saturated specimen is stable at 25 °C for 1 h.[57]

III. PORPHYRIN DIMERS AND TRIMERS

Dimeric porphyrins of the "face-to-face" type (LXXXVII) and (LXXXIX) were first obtained by Collman et al.[75] Condensation of pyrrole (2 equivalents) with benzaldehyde (1 equivalent) and 2-nitrobenzaldehyde (1 equivalent) yielded a mixture of mono-di-, tri-, and tetra-(*o*-nitrophenyl)-porphyrin isomers and atropisomers. The reduction of the mixture of dinitroporphyrins, isolated by preparative chromatography, with tin(II) chloride led to a mixture of diaminoporphyrins, whose separation yields the α,α-*cis*-diaminoporphyrin (LXXXV)† and the *trans*-isomer (LXXXVIII).

A solution of the diaminoporphyrin isomer (LXXXV) in benzene containing traces of pyridine was treated with phosgene and the excess phosgene was then removed. The

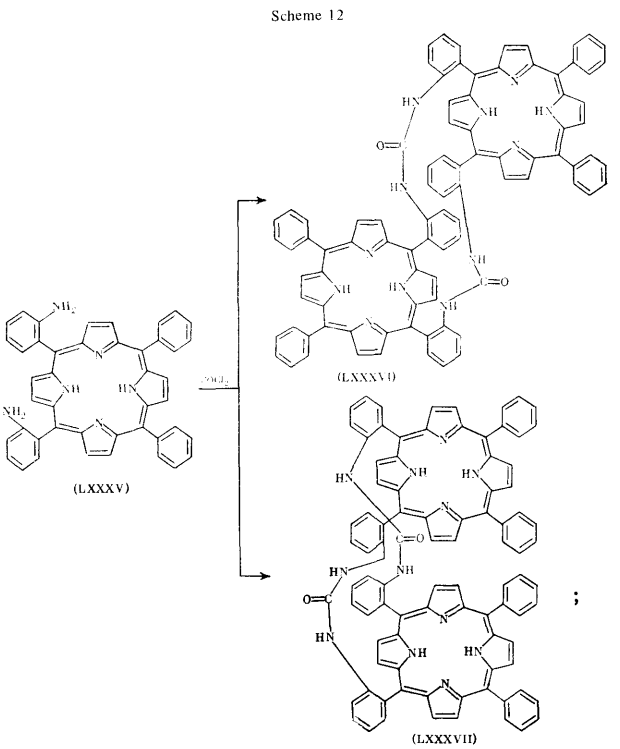
†The symbols α and β denote the opposite surfaces of the porphyrin plane; the *cis*- and *trans*-positions denote the adjoining and opposite *meso*-positions in tetraphenylporphyrins. Thus compound (LXXXV) is called 5-α-10-α-di(2-aminophenyl)-15,20-diphenylporphyrin or α,α-*cis*-diaminoporphyrin.

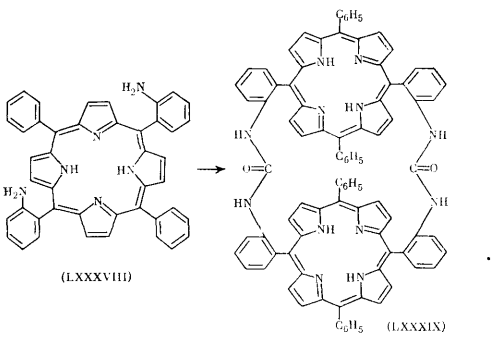
resulting solution was treated with an equivalent amount of a benzene solution of compound (LXXXV) (in nitrogen at 25 °C). Two diporphyrins, (LXXXVI) and (LXXXVII), linked by two urea "bridges", were obtained in this way. The porphyrin rings in the diporphyrin (LXXXVI) are located on different sides relative to one another, while in compound (LXXXVII) the porphyrin rings are arranged one above the other (Scheme 12). When α,α-*trans*-diaminoporphyrin (LXXXVIII) is used as the starting compound, only a single diporphyrin (LXXXIX) is formed. Two of the binary porphyrins (LXXXVII) and (LXXXIX) obtained are in the "face-to-face" conformation. The distance between the porphyrin rings in the copper and cobalt complexes of these compounds is approximately 6.5–6.8 Å.[75]

Diporphyrins of type (XC) [76–78] have been obtained similarly to compound (LXXIV), by the gradual introduction of equimolar amounts of the diamino-derivatives (LXXV, e and f) and the acid dichloride (LXXVc) in a methylene chloride–benzene mixture. The diporphyrin (XC) exists in the *syn*- and *anti*-isomeric forms; attempts to separate them by thin-layer chromatography were unsuccessful[76] (Scheme 13).

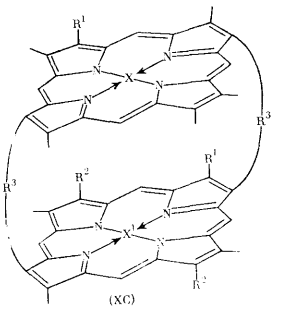
The dinuclear bimetallic complexes (XCc), (XCd), and (XCe), containing two identical metal atoms, have been obtained by a standard method[79]. The diporphyrin complex (XCf), containing only one copper atom, has been obtained[76] by the reaction of the copper complex (LXXVe) with the acid dichloride (LXXVc). The bimetallic complex (XCg) has been synthesised by introducing iron into the monometallic complex (XCf).[79]

Scheme 12





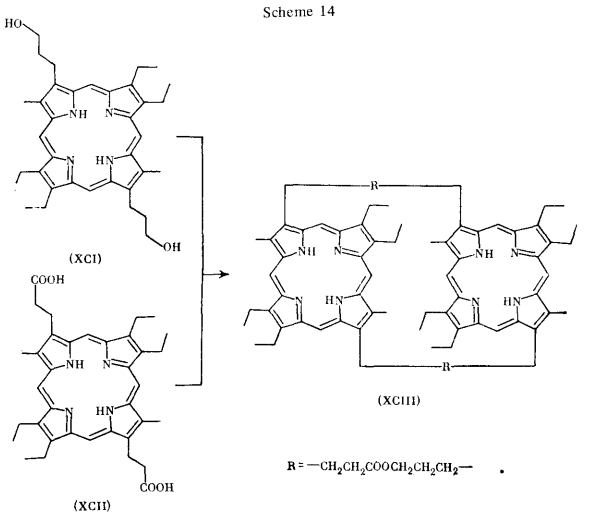
Scheme 13



(a) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(n\text{-}C_4H_9)(CH_2)_3$, $X=X^1=2H$;
(b) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(CH_2C_6H_5)(CH_2)_3$, $X=X^1=2H$;
(c) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(n\text{-}C_4H_9)(CH_2)_3$, $X=X^1=Fe^{III}Cl$;
(d) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(n\text{-}C_4H_9)(CH_2)_3$, $X=Cu$, $X^1=Fe^{III}Cl$;
(e) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(n\text{-}C_4H_9)(CH_2)_3$, $X=X^1=Zn$;
(f) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(n\text{-}C_4H_9)(CH_2)_3$, $X=2H$, $X^1=Cu$;
(g) $R^1=R^2=-(CH_2)_5CH_3$, $R^3=-(CH_2)_2CON(n\text{-}C_4H_9)(CH_2)_3$, $X=Fe^{III}Cl$, $X^1=Cu$.

The dimeric porphyrin (XCIII),[80] in which the two porphyrin rings are joined together by an ester fragment, has been obtained by treating a solution of the 3-hydroxypropyl derivative (XCI) and the carboxyethyl derivative (XCII) with isobutyl chloroformate in THF (Scheme 14). The attempt to separate the diester (XCIII) into the *syn*- and *anti*-isomers was unsuccessful, as before.

Scheme 14

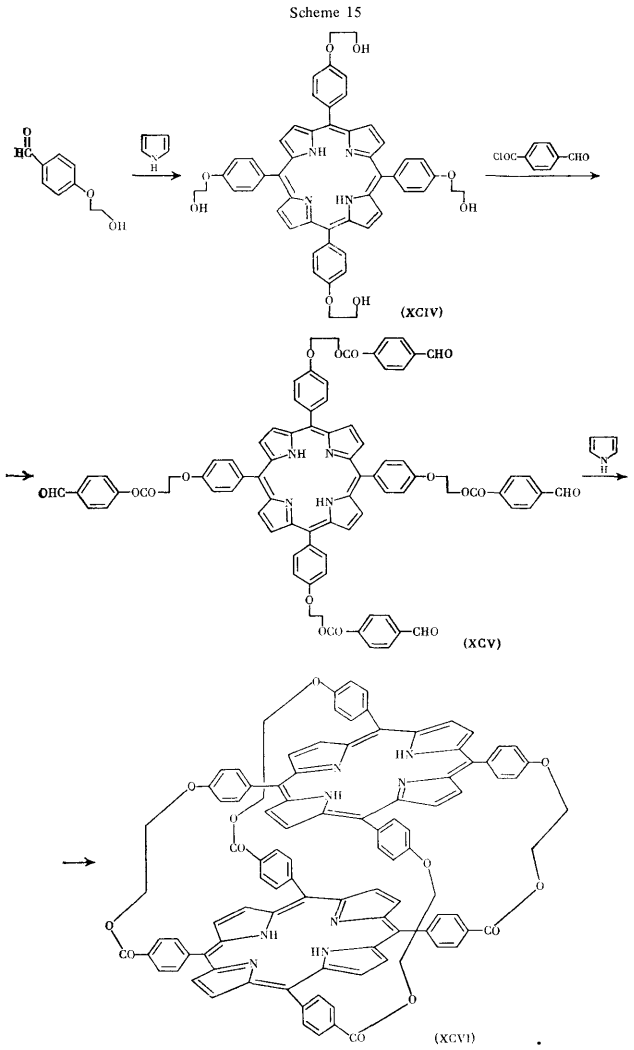


$R=-CH_2CH_2COOCH_2CH_2CH_2-$.

Treatment of the dimeric porphyrin (XCIII) with zinc acetate yielded[79] the corresponding bimetallic complex, for which the distance between the porphyrin rings was calculated and proved to be approximately 7 Å.

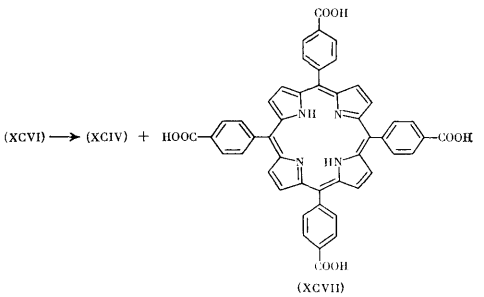
A layer (strati) diporphyrin (XCVI) has been obtained[81] by condensing the modified tetra-aldehyde (XCV) with pyrrole by the method of Adler et al.[82] The tetra-aldehyde (XCV) was obtained by the reaction of tetrahydroxyporphyrin (XCIV) with formylbenzoyl chloride[37] (Scheme 15).

Scheme 15



The structure of compound (XCVI) was proved[81] by identifying the products of its acid hydrolysis. Hydrolysis yielded only two products—compound (XCIV) and tetracarboxyporphyrin (XCVII) (Scheme 16).

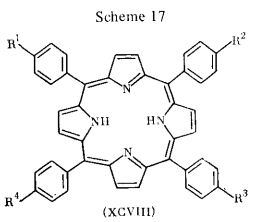
Scheme 16



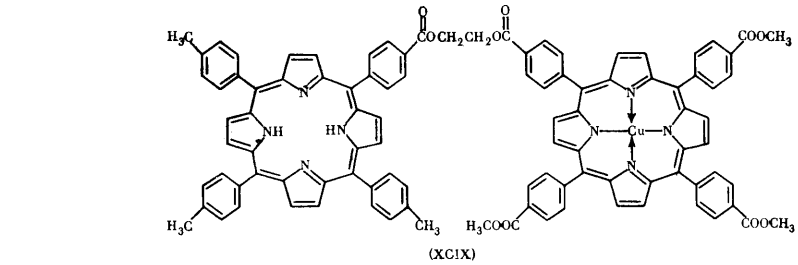
The synthesis of covalently linked porphyrins—the dimer (XCIX) and the trimers (C) and (CI)—has been achieved[83–85] and the transfer of the energy of the excited states between the two centres of the porphyrins has been investigated.

Transesterification of the tetramethyl ester (XCVIIIa) with ethylene glycol[84] leads to five isomers (XCVIII, b–f) after chromatographic separation. The condensation of 0.5 mole of *p*-toluic aldehyde, 0.1 mole of *p*-carboxybenzaldehyde, and 0.6 mole of pyrrole yielded a mixture of substituted *meso*-tetraphenylporphyrins, from which compound (XCVIIg) was isolated chromatographically[84]. The dimer (XCIX) has been obtained by the reaction of the acid chloride (XCVIIIh), synthesised by treating the corresponding acid (XCVIIIg) with oxalyl chloride, with the copper complex of 5-[4-(2-hydroxyethoxy)carbonylphenyl]-10,15,20-tri(4-methoxycarbonylphenyl)porphyrin[83]. The trimers (C) and (CI) have been obtained analogously from the copper complexes of substituted *meso*-tetraphenylporphyrins (XCVIIIc) and (XCVIIIf) respectively and the acid chloride (XCVIIIh) [84,85] (Scheme 17).

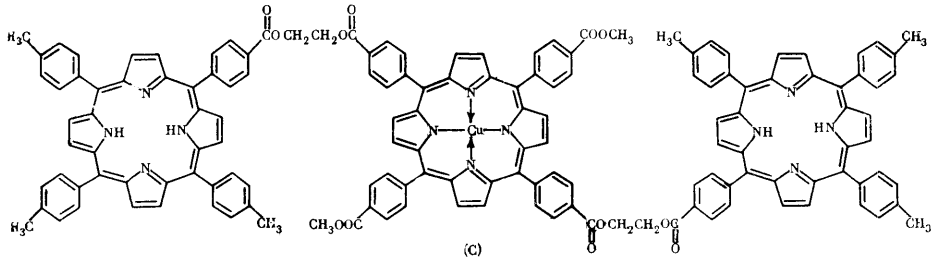
Scheme 17



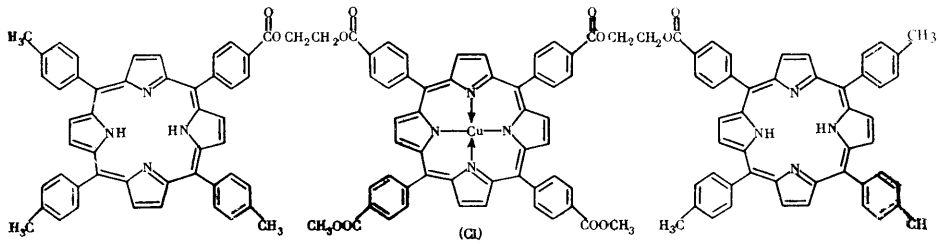
(a) $R^1=R^2=R^3=R^4=-COOCH_3$;
(b) $R^1=-COOCH_2CH_2OH$, $R^2=R^3=R^4=-COOCH_3$;
(c) $R^1=R^3=-COOCH_2CH_2OH$, $R^2=R^4=-COOCH_3$;
(d) $R^1=R^2=R^3=-COOCH_2CH_2OH$, $R^4=-COOCH_3$;
(e) $R^1=R^2=R^3=R^4=-COOCH_2CH_2OH$;
(f) $R^1=R^2=-COOCH_2CH_2OH$, $R^3=R^4=-COOCH_3$;
(g) $R^1=-COOH$, $R^2=R^3=R^4=-CH_3$;
(h) $R^1=-COCl$, $R^2=R^3=R^4=-CH_3$



(XCIX)

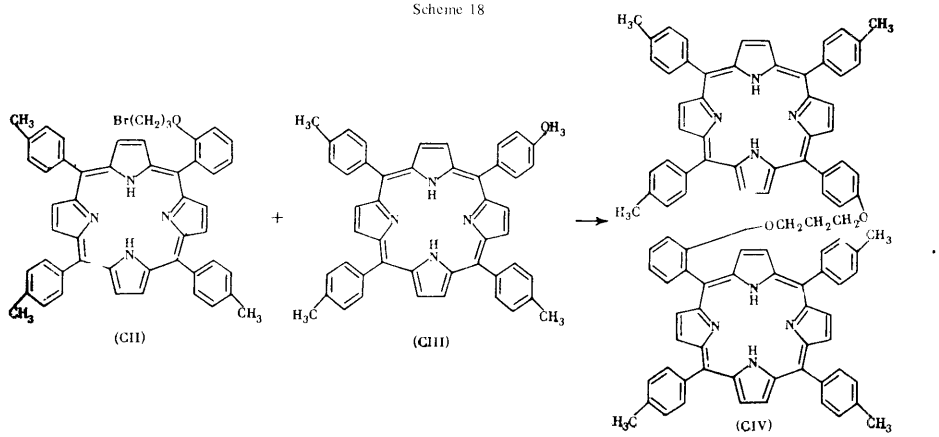


(C)



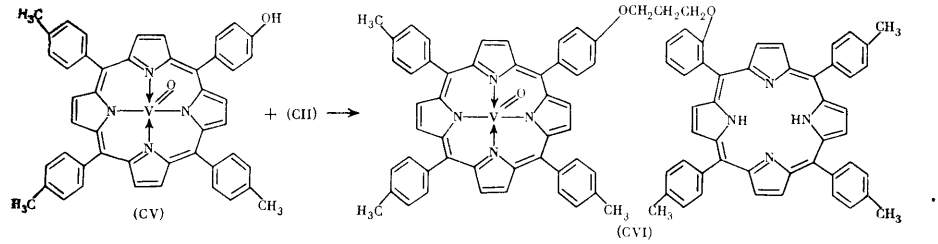
(CI)

Scheme 18



(CII) (CIII) (CIV)

Scheme 19



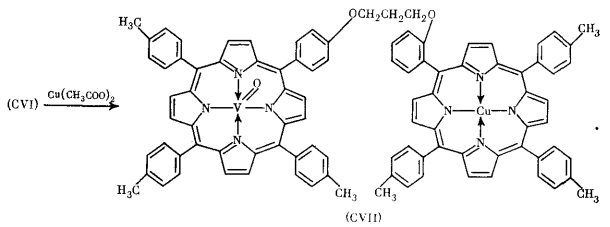
(CV) (CVI)

The covalently linked dimer (CIV) has been obtained[86] by the reaction of 5-[*o*-(3-bromopropoxy)phenyl]-10,15,20-tritolylphenylporphyrin (CII) with one equivalent of 5-(*p*-hydroxyphenyl)-10,15,20-tritolylphenylporphyrin (CIII) [87] (Scheme 18).

Vanadylporphyrin (CV), obtained by the usual methods[51,88], readily reacts with the porphyrin (CI) to form the vanadium-containing dimer (CVI) (Scheme 19).

The mixed copper–vanadium complex (CVII) can be synthesised by Falk's method[51] involving the treatment of compound (CVI) with copper acetate in pyridine (Scheme 20).

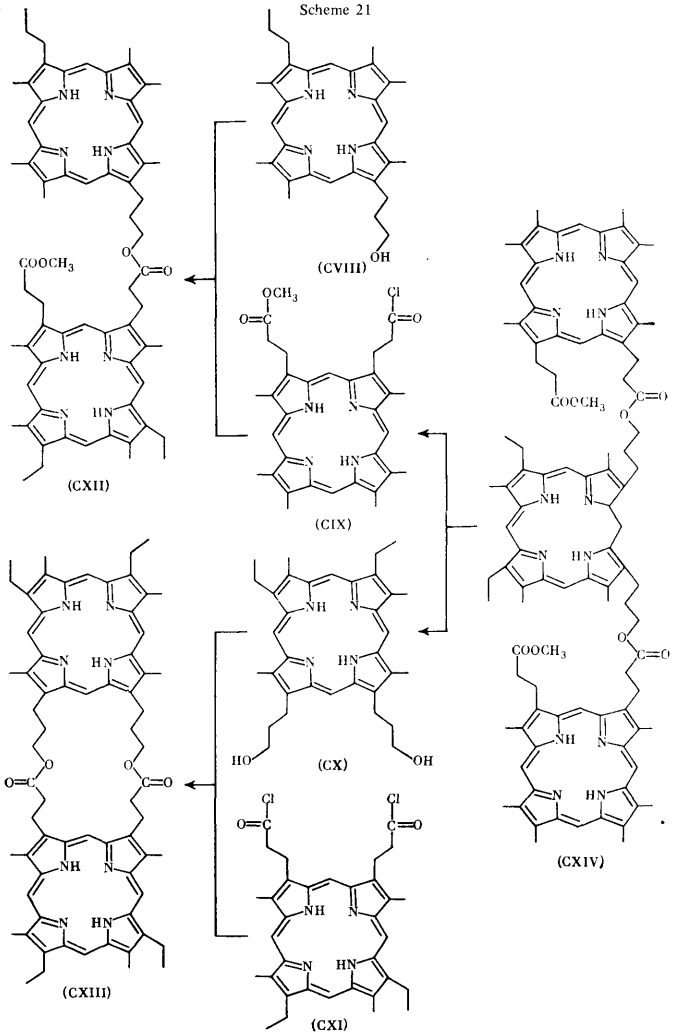
Scheme 20



(CVII)

Japanese investigators[89,90] obtained the covalently linked dimers (CXII) and (CXIII) and the trimer (CXIV) of natural porphyrins (Scheme 21).

Scheme 21



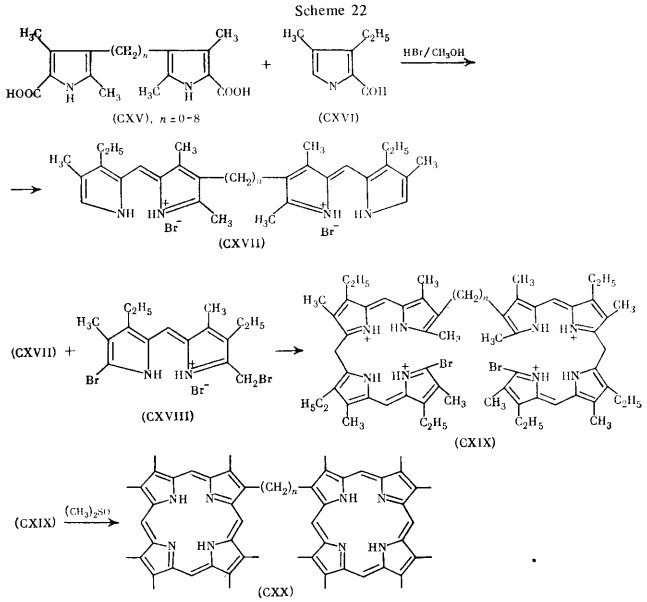
(CXI)

2-(2-Ethoxycarbonylethyl)-3,7,8,17,18-hexamethyl-12-propylporphyrin has been synthesised by Johnson's method[91] and then converted by hydrolysis into the acid; reduction of the latter[92] leads to the 3-hydroxypropyl derivative (CVIII). The dimethyl ester of mesoporphyrin-IX has been converted by partial hydrolysis into a mixture of two isomers of the monomethyl ester of mesoporphyrin-IX and then into the acid chloride (CIX) by treatment with thionyl chloride. Reduction of the dimethyl ester of mesoporphyrin-IX yielded di(3-hydroxypropyl)porphyrin (CX), [92] while treatment with thionyl chloride afforded the dichloride (CXI).

The covalently linked dimer (CXII) has been obtained by the reaction of the 3-hydroxypropyl derivative of the porphyrin (CVIII) with the acid chloride (CIX) in methylene chloride in the presence of triethylamine at a high dilution. The diporphyrin (CXIII) has been obtained analogously from the dihydroxy-derivative (CX) and the acid dichloride (CXI), while the trimer (CXIV) has been synthesised from two moles of the acid chloride (CIX) and one mole of the dihydroxy-derivative (CX). [89]

The covalently linked diporphyrin (CXX) has been obtained[93] from the dipyrrole (CXV). Condensation of the dipyrroles (CXV) with 2-formylpyrrole (CXVI) in a mixture of acetic and hydrobromic acids yielded the corresponding dihydrobromides of bisdipyrrolylmethenes (CXXII), from which the bisporphyrins (CXX) were obtained by reaction with the hydrobromide of the bromo-derivative of dipyrrolylmethene (CXVIII) and the Johnson cyclisation[91] of the intermediate bisbiladienes (CXIX) [93] (Scheme 22).

Scheme 22



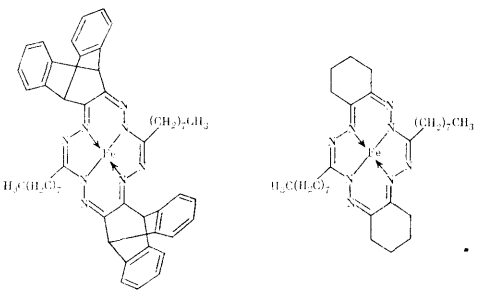
(CXX)

IV. CONCLUSION

The data presented show that in recent years there has been a rapid development of the research into the synthesis of sterically hindered porphyrins. Attention has been concentrated on the preparation of stereochemical models of the "hydrophobic pocket", the size of which has been estimated as 5.6–6.0 Å.

In this connection attempts have been made at a wider employment of the ideas of such modelling. Thus Baldwin and Huff[94] proposed models of the tetra-aza-compounds (CXXI) and (CXXII), which are not porphyrins but have

"hydrophobic pockets" of different depth, in order to demonstrate the validity of the approach under discussion. Baldwin showed that compound (CXXI), which has a 5.0 Å "hydrophobic pocket", is capable of reversible oxygenation, while the related compound (CXXII), where the "pocket" is less deep (~2.2 Å) is incapable of such oxygenation:



(CXXI) (CXXII)

We believe that the study of Baldwin and Huff[94] is extremely important, since it demonstrates the universality of the stereochemical approach to the problem of the reversible oxygenation and leads to extensive possibilities for molecular design in this field. The creation of stereochemical models of this kind on the basis of different macrocyclic tetra-aza-compounds might give rise to a new additional field of research in the synthesis of effective oxygen transferring agents.

Further development of studies on the synthesis of new models of sterically hindered porphyrins and the investigation of their properties appear to be exceptionally important both for physicochemical biology and for catalysis, the chemistry of biologically active substances, and the chemistry of medicinal preparations. It may be hoped that compounds effectively modelling not only the work of haemoglobin but also that of chlorophyll will be synthesised in the immediate future.

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The Physicochemical Institute,
Academy of Sciences of Ukrainian SSR,
Odessa

Mechnikov Odessa State University