THE PORPHYRINS

Volume II

Structure and Synthesis, Part B

Edited by

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ACADEMIC PRESS New York San Francisco London 1978

A Subsidiary of Harcourt Brace Jovanovich, Publishers

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Hydroporphyrins: Reactivity, Spectroscopy, and Hydroporphyrin Analogues

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I. REACTIVITY OF HYDROPORPHYRINS

A. Chlorins and Bacteriochlorins

The chlorin macrocyclic system, as compared to that of porphyrins, shows two distinct differences in reactivity. The methine positions next to the pyrroline ring have a higher electron density and are, thus, susceptible to

electrophilic attack, and chlorins are more easily oxidized both by one- and two-electron oxidants. Both features have been linked to the reactivity of chlorophylls, which are, with the exception of the chlorophylls *c*, either chlorins or bacteriochlorins. The easy isotope exchange of the δ-H in chlorophyll *a* (**1**) is a direct result of the increased electron density at this position, and especially the photooxidation to the cation radical is of eminent biological importance as the genuine light conversion step in photosystem I (see Volume II, Chapter 6; Volume IV, Chapters 3–5; and Volume V, Chapters 2 and 9).

However, chlorophyll chemistry is determined not only by the central Mg ion, but by the functional groups of the peripheral substituents. The most prominent one is probably the enolizable β-ketoester grouping at the isocyclic ring E, which is (together with the central Mg) responsible for the strong and specific self-aggregation of chlorophylls[1,2] and for which the involvement in photosystem II oxygen evolution has been discussed.[3,4] Chlorophyll chemistry and chlorophyll aggregation have been reviewed thoroughly[2,5–8] (see also Volume V, Chapter 9). Besides the basic features of the chlorin nucleus, only one special aspect of chlorophyll chemistry shall be discussed here, namely, the metalation or the free phorbin ligand with Mg. A brief summary of the recent research in chlorophyll chemistry is provided in the appendix of Chapter 1.

1. Electrophilic Substitution

The increased electron density at the methine positions next to the pyrroline ring in chlorins was first concluded by Woodward and Skarič[9] from reactivity studies. It could be shown that the product obtained on reaction of chlorins with HCl/H_2O_2 was not a dioxychlorin, as originally proposed,[10] but rather a δ-chloro-7,8-chlorin. The formation of this *meso*-substituted chlorin by a selective electrophilic attack was rationalized in a new formulation of the

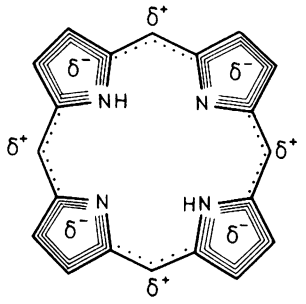


Fig. 1. Schematic representation of the porphyrin π-electron charge densities, according to Woodward.[11]

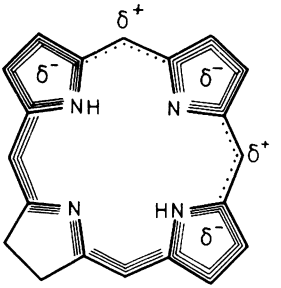
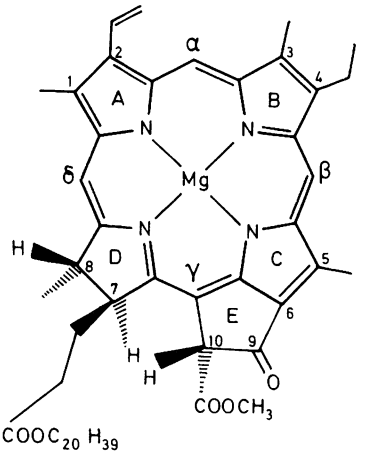


Fig. 2. Schematic representation of the chlorin π-electron charge densities, according to Woodward.[11]

porphyrin macrocycle,[11] in which the four pyrrolic subunits retain, to a certain degree, their aromaticity (= 6π systems) by borrowing electron density from the neighboring methine bridges (Fig. 1). In the chlorins, the reduced pyrroline ring can no longer be such an aromatic subunit and, thus, the electron density at the neighboring methine positions is increased (Fig. 2). This difference between the "chlorin-type" methine protons next to the pyrroline ring (γ, δ in formula **1**), and the "porphyrin-type" methine protons



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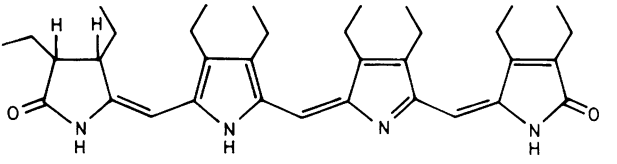
(α, β in **1**), respectively, was supported by MO calculations,[12–16] and is now an experimentally well established fact.

The chlorin-type methine protons next to the reduced ring are easily exchangeable against ^2H with acid,[9,17] while, under the same conditions, the remote porphyrin-type methine protons are nonexchangeable. This exchange

is even more pronounced in some metal complexes and proceeds in the chlorophylls already in neutral solutions.[17] The differential $^1H/^2H$ exchange of a series of pheophorbides and bacteriopheophorbides has been studied[18] in an attempt to establish the methyl substitution site in the bacteriochlorophylls *d* (chlorobium chlorophylls 660), from which substitution at α or β was suggested. The results were not equivocal, however, and there is now positive proof for a δ-substituted structure instead.[19–22] The selective electrophilic attack at the chlorin-type methine positions has been demonstrated, for example, during nitration,[23] chlorination,[9,24] bromination,[20a] and formylation (of the hemins[25]). Further support for the increased electron density comes from the oxidative cleavage of H_2(OEC) or Zn(OEC) with thallic trifluoroacetate yielding selectively the A-dihydrobiliverdin **2** via hydrolysis



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of a meso-trifluoroacetoxy intermediate[26] and cleavage of the oxochlorin phlorin.[27] The selective cleavage at 1-δ in δ-methylpheophorbides has been reported to occur photochemically in good yield.[22] Preparative difficulties arising in electrophilic substitution of pheophorbide metal complexes have been discussed.[20a]

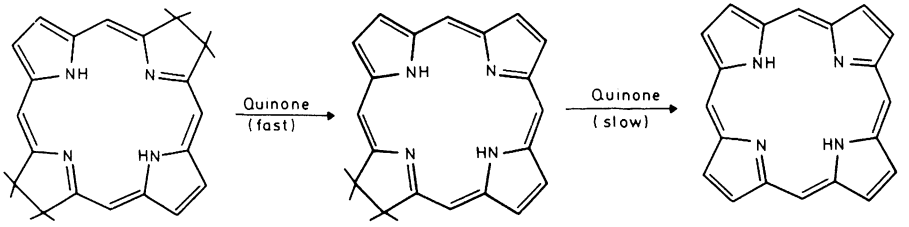
Although in the latter examples, steric factors could play an additional role, the main driving force is certainly the increased electron density at the chlorin-type methine positions. In bacteriochlorins, all methine positions are adjacent to pyrroline rings, and accordingly all three methine protons in bacteriochlorophyll *a* and its pheophorbides are exchangeable.[17,18] Spectroscopic support for the increased electron density arises mainly from the characteristic high field shift of the chlorin-type methine protons in the nmr spectra of chlorins and bacteriochlorins.[28] In chlorins, the δ- and, if present, the γ-methine protons are shielded by about 1 ppm as compared to the α- and β-protons. In the bacteriochlorins, all methine protons are comparably shielded, while in the isobacteriochlorins three sets of methine resonances are observed.

While nucleophilic attack at the *meso* positions has been demonstrated in porphyrin dications[29], no similar reaction is known for chlorins. However, cation radicals of metallochlorins can be nitrated at the methine bridge next to the pyrroline ring with nitrite.[30]

2. Oxidation to Porphyrins

The conversion of chlorins to porphyrins was a major clue in establishing the relationship between heme and chlorophyll. A variety of reactions has been worked out by Fischer and his co-workers to achieve this formal oxidation of the macrocycle.[5] There are two principal modes for this reaction: the direct dehydrogenation of the reduced ring(s), or an initial reduction to colorless hydroporphyrins, followed by reoxidation beyond the chlorin level to the porphyrin.

Chlorins can be oxidized directly to the respective porphyrins with oxidants such as O_2, I_2, Fe(III), H_2O_2[5], but the reaction is best carried out with high-potential quinones. In a comparative study, *o*-chloranil and 2,3-dichloro-4,5-dicyano-*p*-benzoquinone were found most effective for the oxidation of pheophytin *a* to protopheophytin *a*.[31] With excess quinone, the oxidation is spectroscopically almost quantitative, but the yield is often reduced due to the formation of insoluble aggregates and further oxidation during workup. Quinone oxidation has been used to prepare 2-vinyl pheoporphyrins because the sensitive 2-vinyl group in chlorophylls is not attacked during the reaction,[32] and H_2(TPC) contaminations in H_2(TPC) can be removed as well by selective oxidation with quinones[33, 33a] or even with dimethylsulfoxide[34] (see Scheme 1).



Scheme 1

Bacteriochlorins are oxidized by quinones in two kinetically well separated steps to porphyrins. The first step to the chlorin is fast and quantitative, and only an equimolar amount of the quinone is needed.[35,36] In the bacteriochlorophylls, only ring B is dehydrogenated during the first reaction (see also Fischer and Orth,[5] p. 306), this high selectivity probably being mainly due to steric factors (overcrowded periphery, Chapter 1). The subsequent dehydrogenation to the porphyrin is much slower and requires an excess of oxidant. This distinct differentiation of the two oxidation steps has been used to prepare unusually substituted chlorophylls (7,8-chlorins) from bacteriochlorophylls[35–37] and to optimize the H_2(TPC) yield in the chemical reduction of H_2(TPP) with diimide.[38] In the chlorophylls, this stability of the chlorin, as compared to the bacteriochlorin conjugation system, is probably aided by the steric strain introduced in the molecule upon oxidation of the 7,8 positions

(see Chapter 1). However, symmetrically substituted bacteriochlorins follow the same reactivity pattern,[38,39] indicating only a comparably small increase in stabilization energy upon conversion of chlorins to porphyrins.

For the alternative method of converting chlorins into porphyrins by reduction with subsequent reoxidation, either Pd/H_2 or HI in acetic acid are the reagents of choice.[5] In neutral organic solvents, chlorins are reduced with Pd/H_2 to colorless "chlorinogens," which are reoxidized by air to the starting material. In acidic solutions, porphyrins are the major reoxidation products, accompanied by small amounts of the respective chlorins.[40–43] In both cases, the recovered chlorin is fully optically active.[5,44,45] Depending on structure and conditions, 2–3 moles of hydrogen are consumed during the reduction of chlorins, in excess to the 1 mole used up by the 2-vinyl group, if present. As the 7,8-stereochemistry is unchanged, the chlorinogens are, therefore, tetra- or hexahydrochlorins, respectively. It is not clear however, if the chlorinogen is converted to a porphyrinogen and both are oxidized separately, or whether a common leuco compound is reoxidized to a different degree, depending on the solvent system. It could be shown that chlorins can be formed during the oxidation of porphyrinogens by re-reduction of previously formed porphyrin under the conditions of the Rothemund H_2(TPP) synthesis,[46] but an analogous sequence would not account for the optical activity in the Pd/H_2 reaction.

Catalytic hydrogenation followed by oxidation is suitable for converting sterically nonhindered chlorins in good yields to porphyrins, but, for sterically hindered pheophorbides, the reduction step is too slow and accompanied by reductive cleavage of ring E.[47] In this case, the HI "isomerization" reaction provides better yields in spite of a number of by-products.[44] HI is one of the most versatile reagents of Fischer's porphyrin chemistry, and the by-products are generally derived from attack of the 2-vinyl group. The mechanism of the isomerization is not known in detail, but uv-vis spectroscopic changes and by-product analysis indicate a porphodimethene intermediate.[47]

Besides being oxidable to porphyrins, chlorins and bacteriochlorins, as well as their metal complexes, can be oxidized under mild conditions with I_2, Fe(III), and similar one-electron oxidants to cation radicals. As chlorophyll cation radicals are generated in the light conversion step of photosystem I in photosynthesis, this reaction is of prime biological importance and widely investigated. The chemistry and spectroscopy of radical cations (and of radical anions) is beyond the scope of this Chapter, and the reader is referred to Volume II, Chapter 6; Volume IV, Chapters 3–5; and Volume VI, Chapters 2 and 9 for pertinent reviews.

3. Mg Insertion

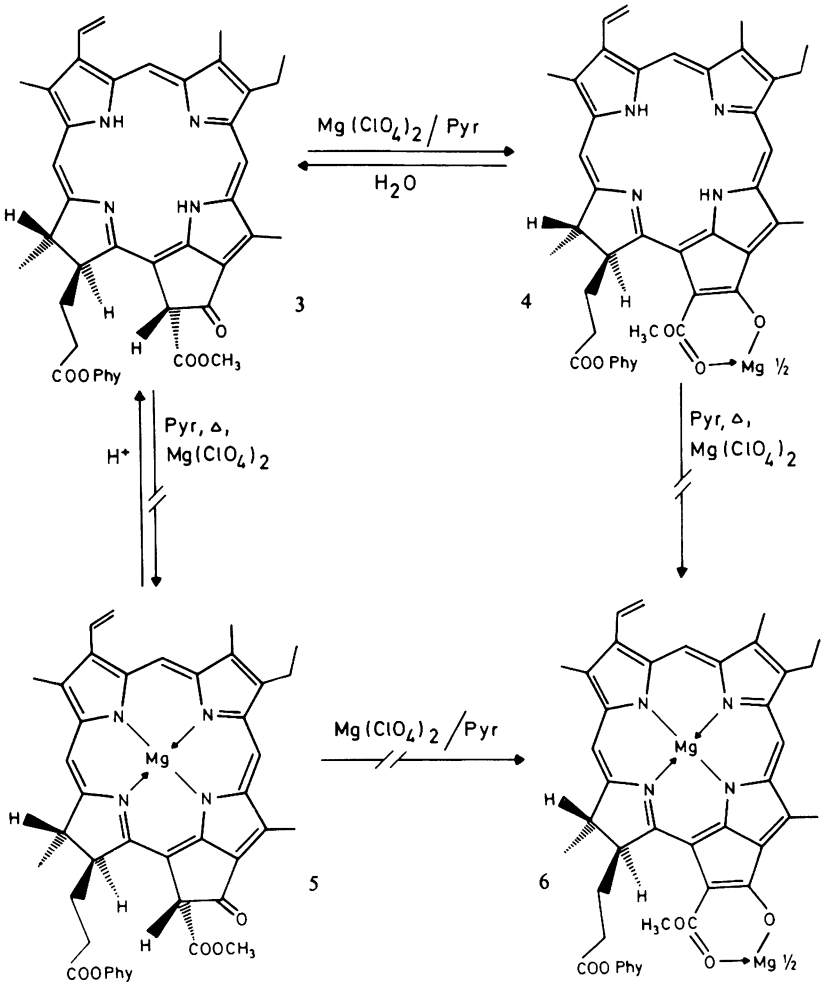
The binding of the central magnesium ion in chlorophylls and Mg porphyrins is thermodynamically unstable,[48] and the metal is lost very easily by acid catalysis[49] or photochemically (see Chapter 1).

By contrast, the remetalation of pheophytins with Mg to the corresponding chlorophylls has been a problem in chlorophyll chemistry until very recently. Alcohol-treated Grignard reagents,[49,50] Mg phenoxide, Mg viologen, MgI_2 hexapyridinate,[51] and anhydrous Mg salts in pyridine[52,53] have been used to metalate pheophytins in moderate to low yield. As porphyrins can be metalated in high yields under these conditions, this difference has been ascribed to their being chlorins, and has been rationalized on the basis of their lower basicity as compared to the porphyrins.[53] Recently, strongly sterically hindered phenoxides have been applied successfully in the metalation of pheophytins, including bacteriopheophytin *a*,* under carefully controlled conditions.[53a] This procedure is probably the method of choice for the large scale preparation of chlorophylls, since the pheophytins are usually available in large amounts and are more easily purified. The metalation of chlorins related to chlorophyll *a* has been investigated systematically by T. Urumov and M. Strell (*Justus Liebigs Ann. Chem.*, in press; T. Urumov, Ph.D. Thesis, Technische Universität München, West Germany, 1975). The authors report the insertion of Mg into methylpheophorbide *a* in refluxing DMSO, although part of the product is decarbomethoxylated. Starting with Cd-chlorins, which are easily accessible, they also obtained less readily accessible metal complexes (e.g., Mn-chlorins) by transmetalation in refluxing methanol.

H_2(OEC)[54] and certain pheophorbides[55a] have been metalated with anhydrous Mg $(ClO_4)_2$ in pyridine[53] in a reaction catalyzed by traces of water.[55a] By systematic variations of the substituents, it could be shown that the difficult metalation of pheophytin *a* (**3**) is not due to its chlorin structure, but rather to the presence of the enolizable β-ketoester system at ring E.[55] If this group is absent, as in pyropheophorbides, the metalation to the respective chlorophyllide usually proceeds in high yields. If the β-ketoester system is present, it competes successfully as a ligand for Mg with the central 4-N cavity, and peripheral complexes (cf. **4**) are formed in which the Mg is bound to the β-dicarbonyl group. Similar complexes have recently been obtained from pheophorbides containing a rigid *cis*-β-diketo group,[55b] and a Δ9,10-pheophorbide has been discussed.[20a] There appears to be a mutual exclusion of the two binding sites. Chlorophylls (= central Mg complexes, cf. **5**) do not form peripheral complexes (cf. **6**) even though the enolizable β-ketoester system is present, and the peripheral complexes of pheophorbides cannot be further metalated to the chlorophylls. Interestingly, the biosynthetic insertion of Mg takes place before the formation of the isocyclic ring bearing the β-ketoester grouping.[6,56]

This mutual exclusion seems unexpected at first, but it can be rationalized on both structural and electronic grounds. X-Ray results reveal substantial

* For the metalation of bacteriopheophytin *a*, see also M. Wasielewski, *Tetrahedron Lett.* p. 1373 (1977).



differences between chlorophyllides[57-59] and the Mg-free pheophorbides,[60,61] and similar pronounced changes are expected, too, in the rings C and E of the peripheral complexes, due to the partial double bond between C-9 and C-10. As both complexes are not very stable, the changes due to the metal at one binding site could then prevent binding of the second metal ion at the other binding site, respectively. The stability is further decreased by the electrostatic repulsion of the two proximate Mg^{2+} ions.

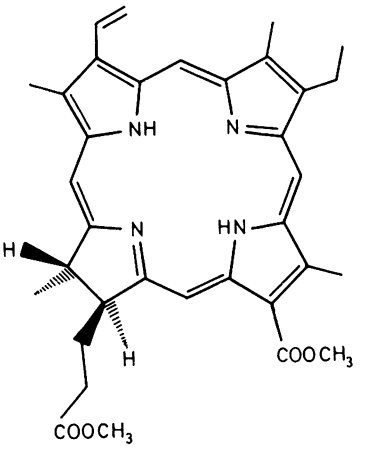
B. Phlorins

1. Oxidation to Porphyrins

Phlorins are generally easily oxidized to the corresponding porphyrins,[11,62-64] but they can be stabilized enough to be studied by conventional spectro-

scopic techniques if the parent porphyrins are sterically hindered. Thus, phlorins were first characterized during the redox reactions of a porphyrin sterically hindered by design in the course of Woodward's chlorophyll synthesis.[65,66]

The structural factors influencing the stability of phlorins were studied most systematically for a series of electrochemically generated chlorinphlorins related to chlorophylls.[63] Chlorinphlorins derived from sterically unhindered chlorins like rhodochlorin dimethyl ester (**7**) have a half-life (in aerobic



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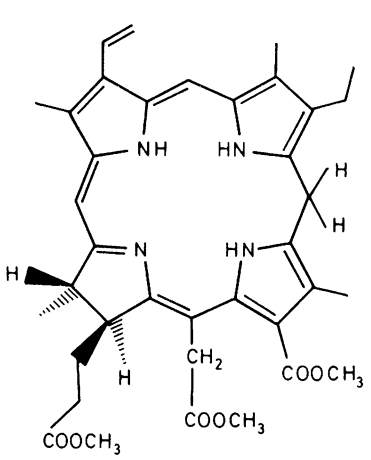
solutions) in the range of minutes. Their stability is increased by the presence of a 2-vinyl substituent, but it is strongly decreased in chlorinphlorins derived from pheophorbides. The latter compounds contain an isocyclic ring between C-6 and C-γ, by which the rigidity of the macrocyclic system is increased. On the other hand, the β-chlorinphlorins obtained by cathodic reduction of sterically hindered chlorins with substituents at C-6 and C-γ, but without the isocyclic ring (cf. **8**), have a half-life in the range of hours or even days. An isomer of **8**, the chlorinphlorin **9** obtained by photoreduction is the only phlorin as yet isolated.[67] Space filling models indicate for both isomers **8** and **9** a comparable relief of steric strain.

The oxidation of phlorins derived from unhindered porphyrins has been studied by a combination of rapid electrochemical techniques and absorption spectroscopy.[64,68–70] The oxidation is irreversible in neutral and alkaline solutions, with $E_{1/2} = -0.5$ to -0.7 V versus the saturated calomel electrode. Below pH 2, in aqueous HCl, the oxidation of **10** to **11** is reversible ($E_{1/2} = -0.04$ V[68]). Under these conditions, the phlorin cation **10** having an interrupted macrocyclic conjugation is in equilibrium with the cyclic-conjugated porphyrin dication **11**; thus, an estimate of the porphyrin resonance energy



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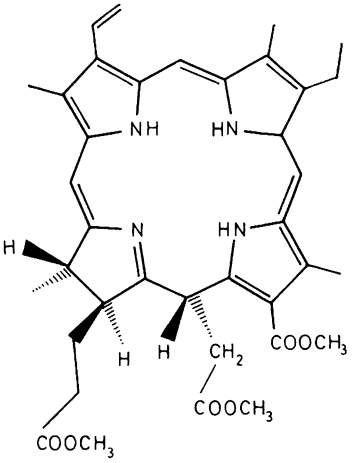

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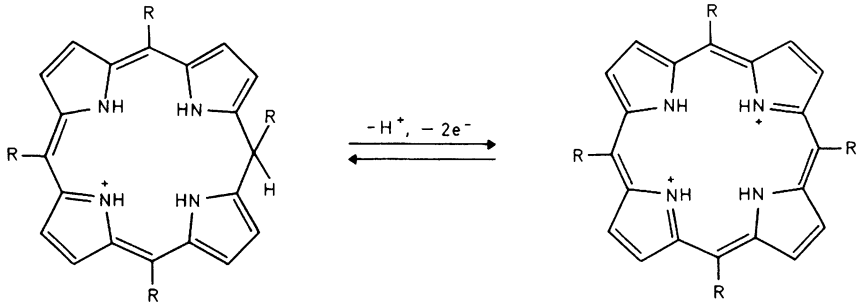
is possible from the electrochemical data (see below). Of particular interest is the formation and oxidation of the tetraphenylisophlorin anion, which is observed during cyclic voltametry of TPP in wet dimethylformamide.[69] In the dark, the isophlorin is oxidized to the parent porphyrin, but when



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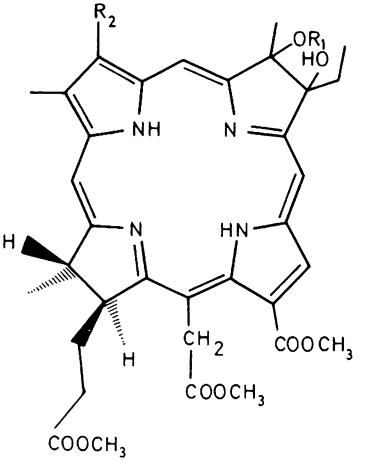
irradiated at its red absorption band (λ_{max} = 730 nm), the isoporphyrin[66,71,72] is formed instead, which subsequently tautomerizes to TPP. As a special case of oxidation, Mauzerall[62] has demonstrated the slow disproportionation of the urophlorin cation to porphyrin and porphomethene by a radical mechanism.

2. Synthesis of Chlorophyll *b*

7,8-Chlorin-β-phlorins (cf. **8**) are subject to a remarkable photooxidation leading to 3-methoxy-4-hydroxy- or 3,4-dioxybacteriochlorins (**12**), according



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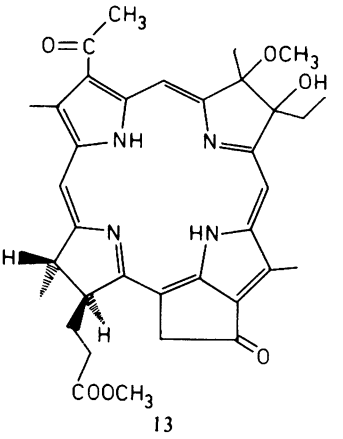
to the solvent used (methanol or water, respectively).[63] From the latter compounds, chlorins with functionalized side chains at C-3 or C-4 are available, which open a synthetic route from the chlorophyll *a*- to the *b*-series.[63a] The β-hydrogenated structure of **8** (see above), the chlorinphlorin isomer being obtained in practically quantitative yield, could be proved by *one* cycle of electrochemical reduction in deuteromethanol and subsequent reoxidation, when only the ^{1}H nmr signal of the β-methine proton was decreased by exactly 50%. Photooxygenation of β-chlorinphlorins with



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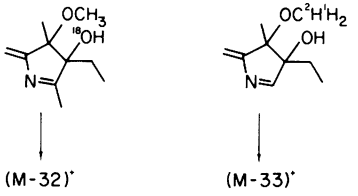
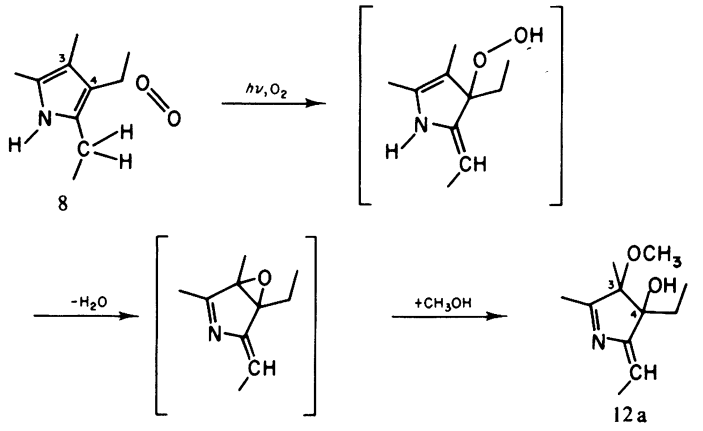
visible light, namely, irradiation of the chlorin-e_6 trimethyl ester-β-phlorin (**8**) in benzene/methanol in the presence of oxygen and boric acid produce, in moderate yield, two isomeric 3-methoxy-4-hydroxybacteriochlorins (**12a**) (R_2 = $CHCH_2$). The two new groups are presumably in a *transoid* orientation, thus accounting for the two isomers. The origin of the 4-*OH* from atmospheric oxygen could be demonstrated (in the bacteriopyromethylpheophorbide *a* series, cf. **13**) by using heavy oxygen ($^{18}O_2$) for the photooxidation. Mass spectroscopy then shows for the molecular ion of the dioxybacteriochlorin an increase of two mass units, but still an $(M-32)^+$ fragment originating from loss of "normal" methanol. Conversely, in view of the uptake of one carbon atom, the 3-OCH_3 group could be shown to be derived from the solvent. If mono-C-deutero-methanol ($C^1H_2\,{}^2HO^1H$) was used as solvent, the molecular ion shows *one* mass unit more, from which a 33 mass unit fragment is lost (Scheme 2).



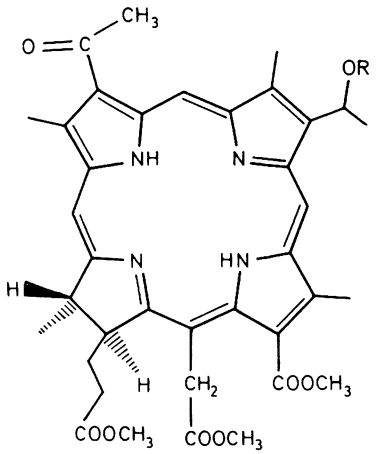
Scheme 2

Concerning the mechanism, it is probable that oxygen attacks the acidic β-phlorin hydrogen, forming a peripheral hydroperoxide. The latter loses water, producing an epoxide, which is then cleaved regioselectively by the solvent methanol. (See Scheme 3.) Accordingly, photooxidation in dioxane/water produces 3,4-diols (cf. **12b**).



Scheme 3

Treatment of the 3-methoxy-4-hydroxybacteriochlorin **12a** with alcoholic or aqueous hydrochloric acid yielded the 4a-alkoxy- and 4a-hydroxychlorins **14a** and **14b**, respectively.[63a] The mechanism of this reaction is not known in detail, but the driving force seems to be the reformation of the 3,4-double bond. Similar products are obtained from bacteriochlorophyll *b*, which bears an ethylidene group at position 4.[36] The 4a-hydroxychlorin **14b** can be converted to the 4-vinyl or 4-acetyl derivatives **15a, b** by dehydration or oxidation, respectively.



(a) R = alkyl
(b) R = H

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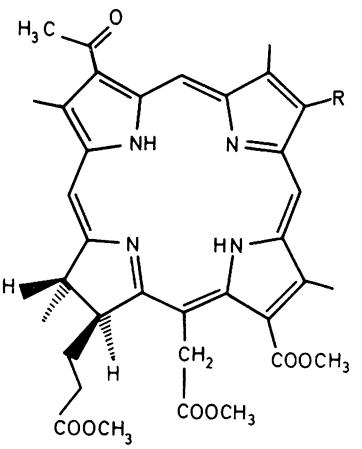


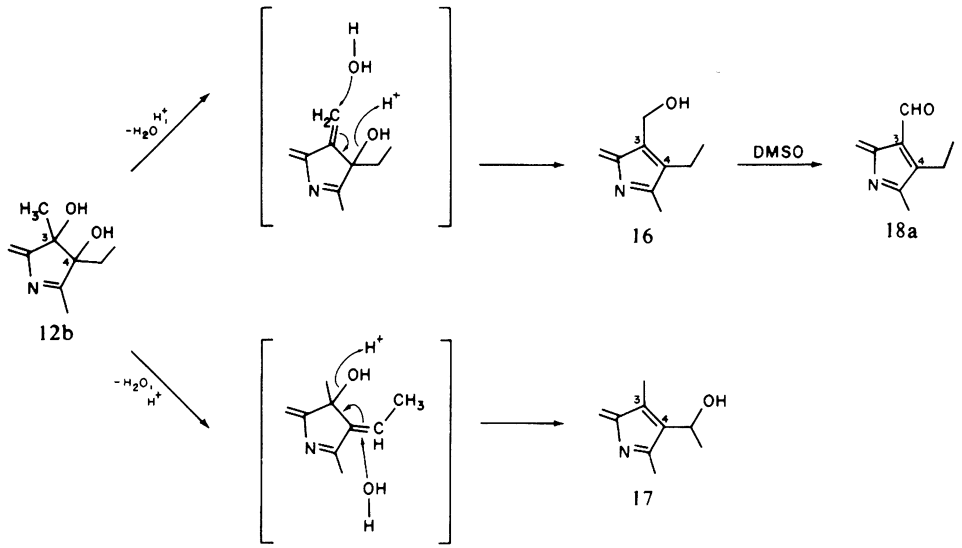
(a) R = $CH{=}CH_2$
(b) R = $COCH_3$

15

By the above reaction sequence, the 4-ethyl side chain in chlorophylls can be functionalized, but the selective methoxylation at C-3 prevents a similar reaction at C-3. However, if the photooxidation of **8** is carried out in aqueous dioxane, the epoxide cleavage leads to a mixture of 3,4-dihydroxybacteriochlorins (**12b**; $R_2 = CHCH_2$), which can then be functionalized at either position 3 or 4. By this means, derivatives of the chlorophyll *b* series bearing a 3-formyl substituent are accessible from the chlorophyll *a* series.[63a]

Acid treatment of the diol **12b** ($R = CHCH_2$) leads to a mixture of the isomers **16** and **17** (Scheme 4) bearing a hydroxy group at either C-3a or C-4a. From the isomer **16**, rhodin-g_7 trimethyl ester **18a** is obtained by oxidation with dimethyl sulfoxide, as shown in the reaction Scheme 4.

In connection with the total synthesis of chlorin-e_6 trimethylester (**18b**),[65,66] (see also Chapter 1) and the conversion of rhodin-g_7 trimethyl ester (**18a**) into chlorophyll *b* worked out by the schools of Fischer and Willstätter, this



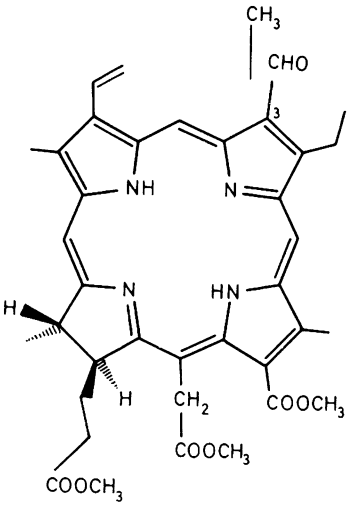
Scheme 4

partial synthesis represents the missing link in the total synthesis of chlorophyll *b*.

3. Phlorins and the Porphyrin Resonance Energy

From stability, reactivity, and spectroscopic properties, the porphyrin macrocycle has been firmly established as being an aromatic system. The most detailed information for this statement arises probably from ^{1}H nmr data. For porphyrins and hydroporphyrins with a closed macrocyclic conjugation pathway, the ^{1}H nmr spectra are dominated by the magnetic anisitropy arising from the aromatic π-system, while this effect is absent in the ^{1}H nmr spectra of hydroporphyrins with interrupted conjugation.[28] Further evidence for the aromaticity of porphyrins arises from the equal bond lengths of the inner 16-membered conjugation pathway, which is found consistently in the X-ray analysis of metalloporphyrins (Volume III, Chapters 10 and 11), from MO calculations[13,73,75,76] (Volume III, Chapter 1), from reactivity studies[76] (Chapter 5), and from the similarity between the uv-vis spectra of porphyrins and 18π-annulenes.[77] Except for a few intermediate cases, a clear and consistent differentiation is possible by either one of these methods between the aromatic porphyrins and their nonaromatic derivatives.

In spite of this general agreement, however, the amount of stabilization is uncertain because only few quantitative experimental data are available. From the heat of combustion of several porphyrins, resonance energies



(a) R = CHO
(b) R = CH_3

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between 78 and 500 kcal/mole have been calculated (see George[78]). This wide range is mainly due to the uncertainties in the bond energies, and in a critical review, using the best set of bond energies, a narrower range of 120–180 kcal/mole has been suggested recently.[78] Although in the lower range of the first estimates, this value amounts to 6.7–10 kcal/mole bond, which is comparable to that of the classical aromatic molecule, benzene (9 kcal/double bond).

A more direct approach, without the necessity to sum up a large number of bonds, would be possible by comparison with reference compounds that lack the macrocyclic conjugation, but for which the geometry, substitution pattern, etc., are comparable to the porphyrins. Phlorins and, to a lesser extent, related systems like isoporphyrins, oxophlorins, and oxaporphyrins, are useful reference compounds in this respect. So far, a direct comparison by calorimetric methods is not yet possible for the lack of stable, isolated phlorins, but equilibria between the two types have been observed in several cases: (a) between a γ-phlorinylacrylic acid and a γ-porphyrinylpropionic acid in the course of Woodward's[65] chlorophyll synthesis (see Chapter 1); (b) between the anions of octaethylchlorin and octaethylphlorin[79]; and (c) between the dication of *meso*-tetra (-4-*N*-methylpyridyl)porphyrin (**11**) and the monocation of the respective phlorin (**10**).[68] Equilibrium (a) suggests a very low resonance energy indeed, but it involves extreme structural conditions. The phlorin is not in equilibrium with a chlorin, for which a similar relief of steric

hindrance was anticipated. Instead, it is in equilibrium with a porphyrin sterically hindered by design. The concept of steric hindrance as the main driving force for phlorin formation has been recently criticized.[80] On the basis of reactivity studies with OEP derivatives, the authors discuss an electronic concept instead. The second equilibrium (b) is observed at high pH and elevated temperatures, and a correlation with normal conditions is, therefore, difficult. So far the best model is the equilibrium (c) between compounds **10** and **11**. From the redox potential of -0.041 V versus the Ag/AgCl electrode, a resonance energy of 103 kcal/mole has been calculated by George,[78] which is in the lower range of estimates obtained from heat of combustion experiments. It should be noted, however, that the phlorin cation has not been investigated well enough, by the methods mentioned above, to exclude its partial conjugation. In particular, phlorin monocations have been suggested to be somewhat intermediate between the aromatic porphyrins and the nonaromatic phlorins on the basis of ^{1}H nmr data,[81] and a similar situation in **10** would then render the resonance energy too low.

4. Isomerization and Substitution

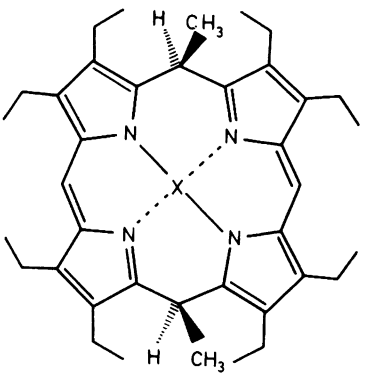
Phlorins and phlorin anions are important intermediates in porphyrin and metalloporphyrin reductions because they cannot only undergo further redox reactions but can also isomerize to chlorins or porphodimethenes (see also Chapter 1). The anion of Zn tetraphenylphlorin, which has been obtained by partial protonation of the Zn(TPP) dianion, undergoes (spectroscopically) quantitative isomerization to Zn(TPC).[81a] For the photoreduction of Sn(IV)-OEP$(OAc)_2$ to the respective chlorin, a phlorin intermediate has also been observed.[82] While in both cases the isomerization is irreversible, phlorin and chlorin anions are in equilibrium at high pH and elevated temperatures.[79] From the uv-vis data reported by Savel'ev *et al.*[83] it is likely that phlorins isomerize during metalation to porphodimethenes, and, yet, a third isomerization (isophlorin $\rightarrow$ phlorin) has been observed by Peychal-Heiling and Wilson,[69] without specification of the isophlorin structure.

The methine proton opposite to the methylene bridge is easily exchangeable in phlorins, and deprotonation of both phlorins and (metallo) porphodimethenes yields mono-*meso*- protonated anions (see Chapter 1), as evidenced by their characteristic phlorin-type spectra. Therefore, phlorins and porphodimethenes appear to be in tautomeric equilibrium at less basic conditions than required for the phlorin–chlorin equilibrium.

C. Porphodimethenes and Others

Like the isomeric (or possibly tautomeric) phlorins, porphodimethenes are easily oxidized to porphyrins and unstable toward air, but considerably

stabilized if the parent porphyrins are sterically hindered. The chemistry of the thus stabilized α,γ-dimethyl octaethyl-β,δ-porphodimethene (**19a**) and its metal complexes has been studied in some detail by Buchler *et al.*[84–86] The stability of the metal complexes toward oxidation indicates a similar dependence on the central metal as has been observed by Fuhrhop[76] for metalloporphyrins, and rationalized by an electrostatic model. Thus, the Zn complex **19b** is easily oxidized, and the stability increases in the order **19a**, **19c**, and **19d**. However, only the free base **19a** yields the expected porphyrin, while **19b**



(a) X = H_2
(b) X = Zn
(c) X = Ni
(d) X = Cu
(e) X = Fe(III)B

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yields what might be bile pigments.[84] The stability of the metal complexes toward demetalation follows the general pattern observed for porphyrins, but unlike the unsubstituted octaethyl derivatives, the extremes are more pronounced. Neither the porphodimethene (**19a**) nor its metal complexes isomerize to chlorins or phlorins, but the formation of 7,8-diethyl octamethylchlorin by reductive ethylation has been reported by Sinyakov *et al.*[87] For the Fe(III) complex **19e**, the monomer-μ-oxo-dimer equilibrium and ligand exchange reactions have been studied recently.[86] The direct oxidation of *meso*-tetraphenyl-α,γ-porphodimethene to H_2(TPP) has been studied by Dolphin.[46] Porphodimethenes and chlorinporphodimethenes formed in the Krasnovskii reduction of Zn pheoporphyrins or chlorophylls, respectively, are oxidized back to the parent compounds in the dark.[47,88,88a] For the Krasnovskii product of chlorophyll *a*, a half-life of about 1 hour under anaerobic conditions has been determined by ^{1}H nmr.[88]

The redox chemistry and the protonation–deprotonation equilibria of uroporphomethene have been studied by Mauzerall.[62] The porphomethene is more difficult to oxidize to urophlorin than the latter to uroporphyrin. With sulfite and dithionite, uroporphomethene is reduced to colorless product(s).

II. SPECTROSCOPY OF HYDROPORPHYRINS

A review on hydrophorphyrins would be incomplete without a discussion of their spectra. However, many aspects of hydroporphyrin spectroscopy are treated in the pertinent chapters on porphyrin spectroscopy, on the analysis of the porphyrin π-electron system, and on *in vivo* and *in vitro* studies of chlorophylls. Therefore, only a short summary of the characteristic features of hydroporphyrin spectroscopy is given here.

A. UV-VIS Spectra

Electron excitation ($S_0 \rightarrow S_1$) or uv-vis spectroscopy is by far the most widely applied spectroscopic method in hydroporphyrin chemistry and biochemistry. Due to the characteristic and intense absorptions of many hydroporphyrins and the large number of known spectra, the method is sensitive and selective. For a given chromophore, large shifts can be observed. These have been correlated in many cases to distinct molecular changes in substitution pattern, solvent system, aggregation, and the like by systematic structural variations, and by simultaneous investigation of defined model systems with more informative methods such as ^{1}H nmr spectroscopy. Considerable effort has also gone into a theoretical interpretation of the uv-vis spectra of hydroporphyrins.

Among the hydroporphyrins, the chlorins, bacteriochlorins, and phlorins, as well as their metal complexes, have characteristic absorption bands in the ranges between 350 and 450 nm (Soret or B-band),* and 600–900 nm (red or Q-band). In these cases, the assignment of a certain chromophoric system by uv-vis measurements is relatively safe even in reaction mixtures and biological systems. The other hydroporphyrins have less defined and less intense absorptions, around 500 nm, due to the common dipyrromethene chromophore. The assignment by uv-vis spectroscopy alone is, in these cases, ambiguous and requires support from independent techniques. In the following, the uv-vis spectroscopic features of the different hydroporphyrins

* It should be noted that, in most hydroporphyrins, the intensity of the "Soret" band is no longer an order of magnitude greater than the red band(s), but, rather, of comparable intensity. This is certainly due to the reduced symmetry in the hydroporphyrins and is especially pronounced for unsymmetric substitution.

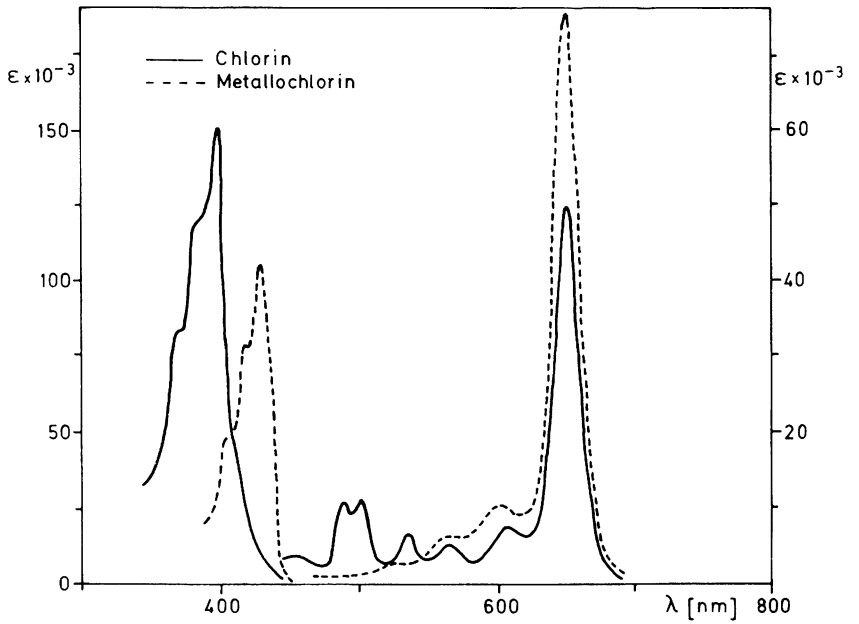


Fig. 3. Typical uv-vis spectra of pheophorbides and chlorophyllides, respectively, of the *a* series. The relative intensity of the Soret band is increased in etio-type chlorins, e.g., H_2(OEC).

are summarized. The spectra shown (Figs. 3–8) are typical for the respective etio-type compounds, if not otherwise indicated.

1. Chlorins

Chlorins have an intense narrow red band around 660 nm ($\epsilon \approx 70{,}000$), and a Soret band of about threefold intensity around 400 nm (Fig. 3). A double band in the region of 500 nm ($\epsilon \approx 15{,}000$) is typical for free-base chlorins. Upon metalation, the disappearance of this band is the most characteristic spectral change. The red band of metallochlorins is increased in intensity, and increasingly blue-shifted with increasing electronegativity of the central metal. In the chlorophyllides (Mg chlorins), its position is almost unchanged. The Soret band is decreased in intensity and blue-shifted by about 30 nm in chlorophyllides, while the effects are less pronounced for other central metals. For the spectra of chlorophyll (Chl) *a* and *b* and their derivatives, the effects of substitution, ligation, aggregation (cf. Vernon and Seely,[6] Katz,[2] and this treatise) (Volume V, Chapter 9), and stereochemical changes[44,89] have been studied. Of some interest is the extreme red shift of the long wavelength

absorption band in certain chlorophyll *a* hydrates ("crystalline chlorophyll"[15,58,89a,89b]), since similar molecular interactions have been proposed for the chl *a* "special pair"[89c] in the reaction center of photosystem I. Interestingly, a blue shift for this band has been reported recently for what has been claimed to be true chl *a* hydrate single crystals.[90] The electronic structure of chlorins has been investigated by MO calculations (for leading references, see 12–16). Recently, it has been suggested that the "isolated" C-3,C-4 double bond and the 9-carbonyl group are an integral part of the π-system and not locally excited.[90a]

2. Bacteriochlorins

Bacteriochlorins have a narrow absorption ($\epsilon \sim 80{,}000$) at about 750 nm, a split Soret band, and an absorption of intermediate intensity at about 540 nm (Fig. 4). As compared to the free base, the spectrum of the metal complexes is red-shifted. As in chlorins, the intensity of the red band increases and that of the Soret band decreases upon metalations. The structural[36] and environmental influences on the uv-vis spectra of bacteriochlorophylls have been studied *in vitro* in some detail,[2,90b] and the π electron structure has been investigated by MO calculations.[14,16,91] The uv-vis spectra of isobacteriochlorins (Fig. 5)[89,92,92a] are in the red region similar to those of the chlorins, but blue-shifted by about 30 nm for similarly substituted compounds. The Soret band of isobacteriochlorins is split as in bacteriochlorins.

3. Hypobacteriochlorins, Corphins

The uv-vis spectrum of tetraphenylhypobacteriochlorin is of the chlorin type, though considerably blue-shifted, in spite of the formal interruption of the macrocycle conjugation.[93] The hypobacteriochlorin structure had been originally assigned from mechanistic considerations and MO calculations,[93] the latter indicating a participation of the nonbonding N-electron pair as in pyrrole. Support comes from the similar uv-vis spectra of the well-characterized trioxo derivatives[94] (see Section III, B). In the corphins, the macrocyclic conjugation is efficiently interrupted by cross conjugation of one pyrrolic Cα-Cβ double bond.[95,96] Corphins have a broad absorption around 500 nm, and two bands ($\epsilon \sim 40{,}000$) between 400 and 300 nm (Fig. 5). In the corphin cation, the macrocyclic conjugation is restored, as evidenced by the reappearance of the Soret band.

4. Phlorins

In contrast to the preceding hydroporphyrins with closed macrocyclic conjugation, the phlorins have broadened uv-vis spectra with less fine

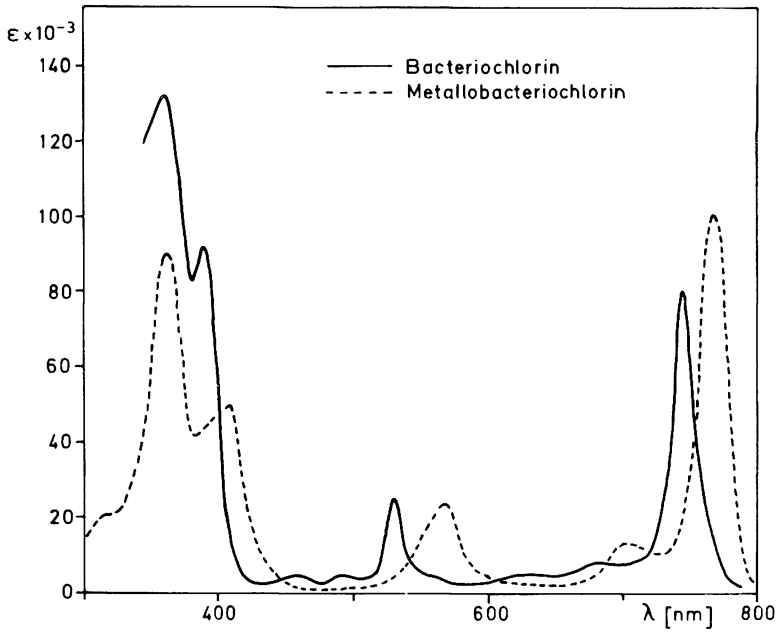


Fig. 4. Typical uv-vis spectra of bacteriopheophorbides and bacteriochlorophyllides, respectively, of the *a* or *b* series. The relative intensity of the Soret band is increased in etio-type bacteriochlorins.

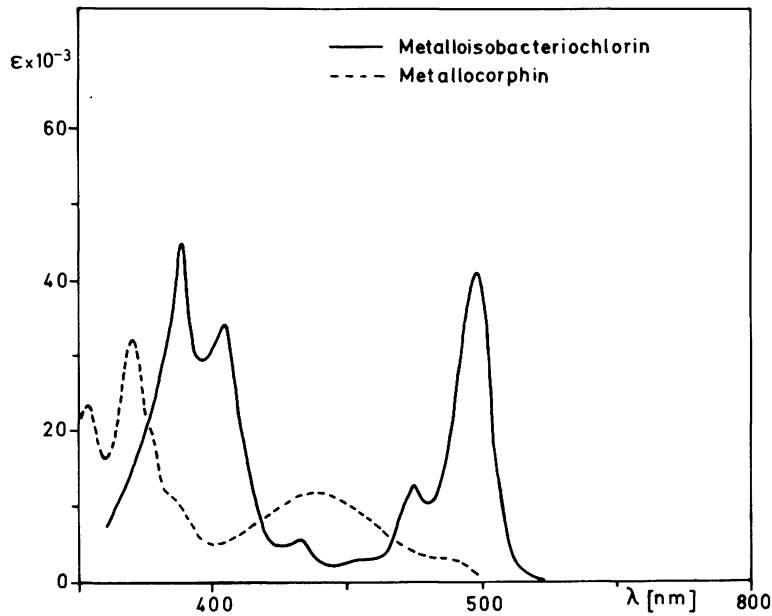


Fig. 5. Typical uv-vis spectra of metalloisobacteriochlorins (e.g., see Mengler[92]) and metallocorphins (e.g., see Johnson *et al.*[95]).

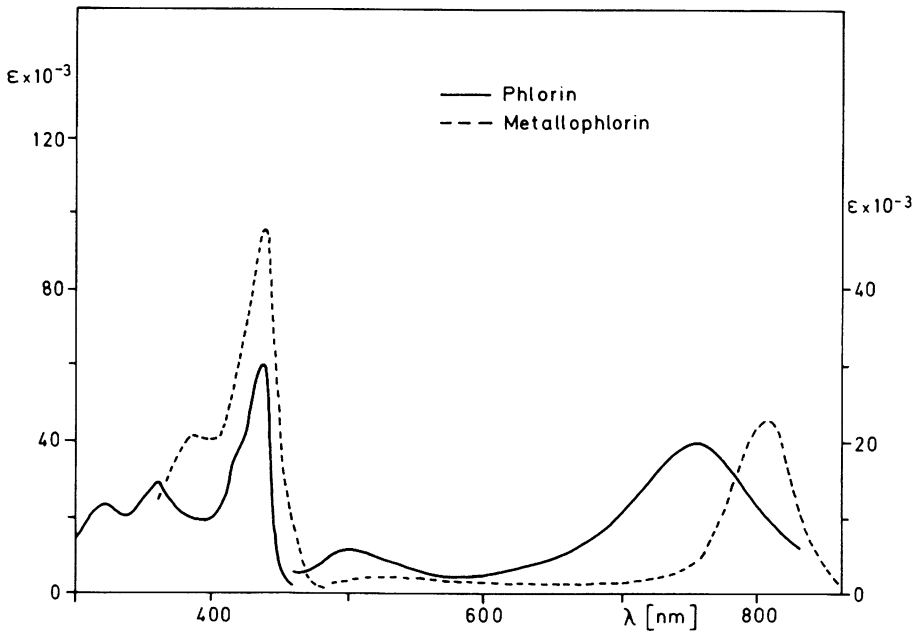


Fig. 6. The uv-vis spectra of tetraphenylphlorin and Zn tetraphenylphlorin anion (e.g., see Lanese and Wilson[70]).

structure (Fig. 6). The extinction coefficients of both the red band and the Soret band are considerably reduced, although the oscillator strength of the red band is comparable to that of the former compounds. The red band of free-base phlorins occurs around 650 nm, and a shift to 750 nm upon cation formation is characteristic for the phlorin chromophore.[62] Metallophlorins, which are probably always anions, have a considerably more intense Soret band, and the red band is shifted to the 900-nm range.[1,70,76] The spectra of chlorinphlorins (Fig. 7) are shifted about 150 nm to the blue, as compared to that of phlorins.[63] For a series of chlorinphlorins related to chlorophylls, a single, broad band between 550 and 600 nm ($\epsilon \sim 30{,}000$) has been observed.[63]

5. Porphodimethenes and Porphomethenes

Porphodimethenes generally have a weak absorption around 500 nm and an intense one around 430 nm, the double band system probably arising from the two interacting parallel dipyrromethene chromophores. This spectral type has been observed in various metalloporphodimethenes.[47,84–86,88,97–101] However, on the basis of relative intensity variations, the possibility of the two bands arising from chemically different species has been discussed.[97,102] In the case of the Krasnovskii photoreduction product of chlorophyll *a* with

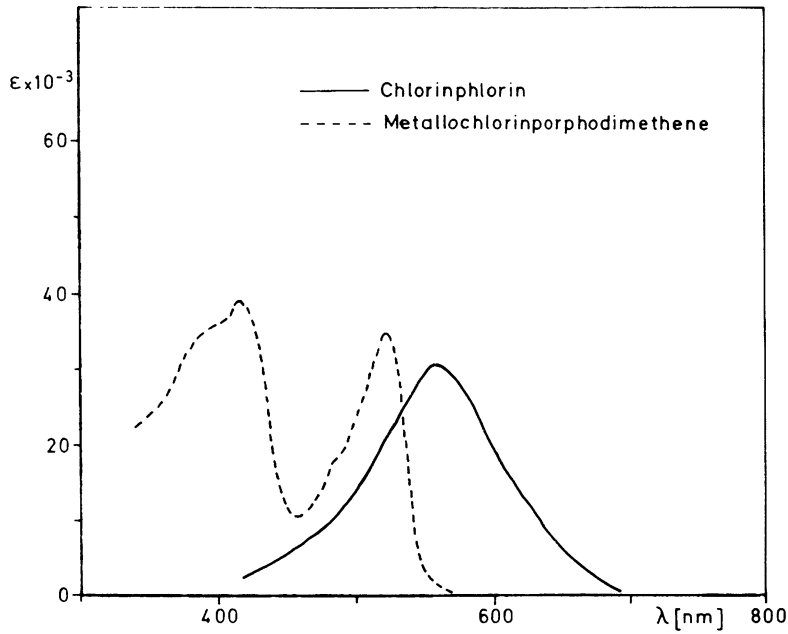


Fig. 7. The uv-vis spectra of chlorinphlorins and of the Krasnovskii photoreduction product of chlorophyll *a*,[88] a chlorinporphodimethene.

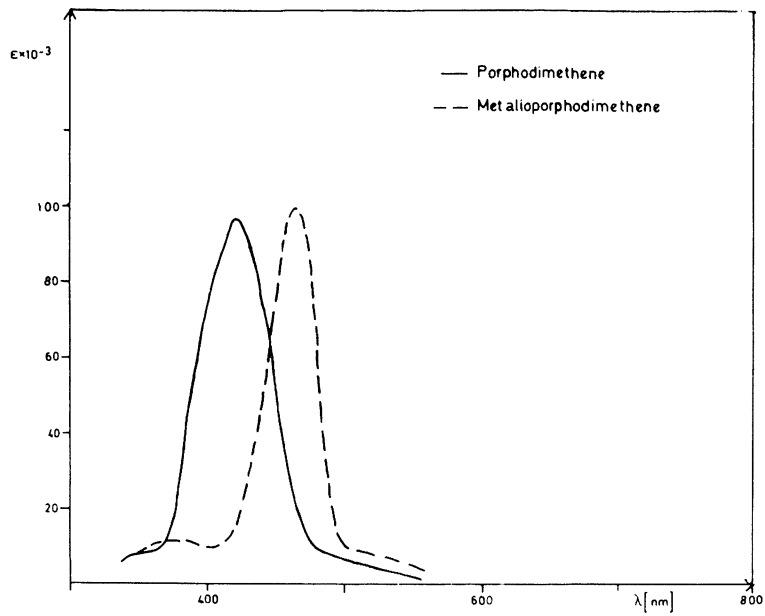


Fig. 8. The uv-vis spectra of α,γ-dimethyloctaethyl-β,δ-porphodimethene and its Zn complex (e.g., see Buchler and Puppe[84]).

H_2S, the origin of the bands from a single species has been demonstrated by ^1H nmr studies.[88] In the latter compound, a Mg chlorinporphodimethene, the two bands are of comparable intensity (Fig. 7), due to the lower symmetry. The 500-nm band is decreased to a shoulder in the dimethylporphodimethene **19a** and its metal complexes (Fig. 8).[84-86] The rooflike structure possibly favors an interaction of the two chromophores. Having only one dipyrromethene chromophore, porphodimethenes show a single intense absorption around 500 nm followed by a weak uv band.[62]

B. Fluorescence Spectra

Monomolecular chlorins and bacteriochlorins, as well as the chlorophylls, are highly fluorescent. The strong $0 \rightarrow 0$ band is often accompanied by a red shoulder, which is possibly related to aggregation. The fluorescence is efficiently quenched in chlorophyll aggregates (Volume V, Chapter 9), which can be used to study the state of chlorophylls *in vivo*.[103] The loss of fluorescence has also been observed in the phase test intermediates of chlorophylls (enolate anions), and in the peripheral Mg complexes of pheophorbides,[55] and related diketones[55b] and is probably due to chelation.[104] Delayed fluorescence of chlorophylls, which arises from population of S_1 states in the photosynthetic reaction centers through dark channels, has been observed in photosynthetic systems.[105,106] The *in vitro* photochemiluminescence of chlorophylls has been studied and reviewed recently by Krasnovskii and Litvin.[107] The intrinsic lifetimes of the fluorescence of chlorophyll *a* and bacteriochlorophyll *d* have been estimated to be 16 and 18 nsec, respectively, by Festisova and Borisov,[108] based on a critical examination of the absorption spectra.

C. Triplet Spectra of Chlorophylls

Due to the key role of chlorophylls in the light conversion reaction of photosynthesis, there is growing interest in other excited states besides the first excited singlet (S_1). This is especially true for the lowest triplet states (T_1), which have been discussed as possible intermediates in photosynthesis. After earlier optical studies, the detailed knowledge of the triplet state has been extended recently by the application of magnetic resonance and double resonance techniques (Volume IV, Chapter 5). Triplet–triplet absorption spectra of chlorophyll *a* and *b* and their pheophytins were first obtained by Livingston *et al.*[109-111] by flash techniques, and the influences of solvent and aggregation state have especially been studied.[112-116] The triplet spectra of the chlorophylls and the respective pheophytins in disaggregated solutions are similar. They consist of three broad and overlapping bands centered around

420 ($\epsilon \sim 6 \times 10^4$), 500 ($\epsilon \sim 2 \times 10^4$) and 670 nm ($\epsilon \sim 5 \times 10^3$)[116] with a shoulder extending above 1000 nm. For two of the bands, in-plane polarization of the absorption dipoles has been suggested from dicroic spectra.[117] Even in disaggregated (= fluorescent) solution, the quantum yield of singlet–triplet conversion (intersystem crossing) is high (chlorophyll *a*:$\Phi = 0.49$;[117] pheophytin *a*: $\Phi = 0.95$).[116] The phosphorescence (= triplet emission) of chlorophylls has first been detected by Kautsky and Hirsch[118] in deoxygenated aggregates. Due to efficient radiationless decay by vibronic coupling, the phosphorescence is very weak. Recent data determined directly are $\lambda_{max} =$ 985 nm for chlorophyll *a*, and $\lambda_{max} = 940$ nm for pheophytin *a*.[119] Both the relative order and the energy range have been supported[120] by an nmr technique,[121] in which the selective broadening of resonances arising from that component of a mixture with the lowest triplet energy is monitored. The recent success in investigating the triplet state of chlorophylls[121a] and related compounds by esr techniques is reviewed elsewhere in this treatise (Volume IV, Chapter 5).

D. Vibrational Spectra

An ir band at about 1615 cm^{-1}, which was first reported by H. Golden *et al.*,[122] occurs in chlorins, but not in porphyrins and bacteriochlorins. This "chlorin band" had been tentatively assigned to a skeleton vibration, but, from Raman spectroscopic studies, a C=N vibration has been suggested.[123] The aggregation of chlorophylls *in vitro* has been studied by ir spectroscopy, mainly by analysis of the C=0 region[124–126] (see Volume V, Chapter 9). These studies have been recently extended by resonance Raman spectroscopy.[127] The latter technique is both sensitive and selective and, thus, principally suited for *in vivo* studies. Due to fluorescence and apparative limitations, resonance Raman spectra have been obtained so far only by excitation in a narrow range at the long wavelength side of the Soret band. From intensity changes, depending on the excitation wavelength, a separation of the contributions from chlorophyll *a* and *b*, as well as of the different chlorophyll aggregates observed *in vivo*, seems possible.

E. Polarimetric Spectra

The ORD/CD spectra of a series of chlorins related to the chlorophylls *a* and *b* have been studied and reviewed.[45] Most of the cotton effects are related to $\pi \rightarrow \pi^*$ absorptions of the aromatic macrocycle. From systematic variations of the peripheral substituents, the macrocycle has been proposed to be inherently dissymmetric. This dissymetry arises from the steric hindrance between the substituents at C-7 and C-γ, and is thus determined by the configuration at C-7[44,45] (for the stereochemistry of chlorins, see also

Chapters 1 and 9 and Scheer and Katz[28]). Superimposed on this basic ORD/CD spectrum are incremental spectra that reflect the configurations at C-10, and, to a lesser extent, at C-8 and C-9. The configuration determination at C-7 and C-10 is possible by ORD/CD alone, while the increments from asymmetric substitution at C-8 and C-9 are too small and require independent support (^{1}H nmr, ir) for the assignment.[44,45,128,129] In the ORD/CD spectra of pheophorbides bearing the 10-$COOCH_3$ group characteristic for most chlorophylls, an additional strong cotton effect has been observed which is not related to aromatic $\pi \rightarrow \pi^*$ transitions. Instead, it arises from the β,γ-unsaturated ester system. As only certain conformations are possible for the 10-$COOCH_3$ group, this cotton effect allows an independent determination of the configuration at C-10.[44,45,130]

The ORD/CD spectra of chlorophyll aggregates have been studied *in vivo* and *in vitro* and interpreted by an exciton model.[131,132] From correlation with transition moment calculations, a noncoplanar geometry of chlorophyll aggregates has been concluded[133,134] in agreement with results obtained by nmr spectroscopy.[135] The magnetic CD spectra of a series of chlorins related to chlorophyll *a* have been reported by Briat *et al.*[136] The red band has been analyzed in terms of the molecular symmetry, while an analysis of the Soret region is complicated by the complex structure of this band system.

F. Nuclear Magnetic Resonance Spectra

As in the ^{1}H nmr spectra of porphyrins, the spectra of the chlorins and bacteriochlorins are dominated by the ring-current-induced shifts (RIS)[28] of the aromatic macrocycle. This effect is absent in the spectra of hydroporphyrins with interrupted macrocyclic conjugation, and the spectra are, therefore, similar to those of the linear tetrapyrrolic bile pigments. (For recent reviews, see Scheer and Katz,[28] and Janson *et al.*, this treatise.)

Chlorins and bacteriochlorins are the hydroporphyrins which have been most thoroughly investigated by ^{1}H nmr. As compared to porphyrins, the most distinct differences are (a) slight reduction of the aromatic ring-current; (b) a pronounced high-field shift of the methine proton(s) next to the reduced ring(s), which is due to the increased electron density at these positions (see below); (c) decreased RIS and increased spin–spin couplings for the substituents at the reduced "chlorin" positions which both complicate a complete analysis (for details see Scheer and Katz[28]).

The ^{13}C nmr spectra of several chlorins related to chlorophylls have been reported recently,[20,21,137–139] culminating in the complete analysis of chlorophyll *a* and methylpheophorbide *a*[140]. On the other hand, the common model systems have received little attention. Ring-current and electron density (diamagnetic) contributions are less important in ^{13}C nmr spectroscopy.

Although the effects listed above for ^1H nmr are also operative,[27] the state of hybridization is much more important. For example, the chlorin C atoms, C-7 and C-8, resonate at a much higher field than the quaternary pyrrolic C atoms due to their sp^3 hybridization. The most important difference of chlorins (as compared to porphyrins) is the distinction between rings A and C, and B and D, respectively.[140] The α- and β-pyrrolic C atoms of the former rings correspond to those in pyridines, while the ones in ring B, and especially in ring D, are pyrrolelike. This difference between the two types of rings is even more clearly visible in the ^{15}N nmr spectra. The ^2H nmr spectrum of chlorophyll a-$^2H_{35}$ has been analyzed for isotope shifts.[141] Recently, ^{14}N and ^{25}Mg nuclear quadrupole resonance (nqr) spectra have been reported for chlorophyll a.[142]

G. Mass Spectra and X-Ray Photoelectron Spectra

The mass spectra of porphyrins are dealt with in detail elsewhere in this treatise (Volume III, Chapter 9). The main feature of chlorin spectra is the loss of the entire substituents at the chlorin C atoms by benzylic type fragmentation. In the porphyrins, a fragment smaller by 14 mass units is lost, due to the more extended aromatic systems. Chlorins are subject to dehydrogenation in the mass spectrometer (M-2 fragments), which is more pronounced in the *cis* than in the *trans* isomers.[44] The X-ray photoelectron (esca) spectra of chlorins have been studied recently by Falk *et al.*[143] As in porphyrins, two N_{1s} bands are distinguishable; these correspond to the aza and pyrrole nitrogens. Surprisingly, the difference between these two types of N atoms is decreased in the chlorins, and even smaller in the bacteriochlorins. The apparent conflict with nmr results[140] is possibly due to the much faster time scale of esca.

III. OXY AND OXO ANALOGUES OF THE HYDROPORPHYRINS

Oxidative degradation of porphyrins has been one of the early analytical tools to study their substitution pattern. While during these exhaustive oxidation reactions the macrocycle is broken down to yield cyclic imides, a variety of less vigorous methods has been developed by the schools of Fischer, Lemberg, and others, in which the macrocycle is retained in the oxidation products. Although well characterized some 40 years ago, only one of the structures could be established unambigously at that time.[144] The course of the reactions and the structure of the products have been reinvestigated during the past decade. It was shown that oxidative attack of etio-type

porphyrins usually occurs at the methine positions to yield *meso*-oxo analogues of the phlorins, porphodimethenes, porphomethenes, and porphyrinogens. However, by oxidation of the dications, and by oxidation with OsO_4, the attack is directed to the β-pyrrolic positions yielding oxy- and oxoderivatives of chlorins, bacteriochlorins, hypobacteriochlorins, and corphins.

A. *Meso*-oxygenated Hydroporphyrins

1. Oxophlorins

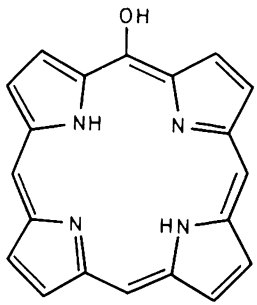
During heme catabolism, the porphyrin macrocycle is opened to bile pigments, while the α-methine C atom is lost as CO.[145,146] From studies of a model reaction, namely, the coupled oxidation of porphyrins with ascorbic acid and hydrogen peroxide,[147,148] oxidative attack, at the methine position via a *meso*-oxygenated iron porphyrin,[149] was proposed as the reaction mechanism. The *meso*-hydroxy structure **20a** or its tautomer **20b** was suggested for the demetalation product of one of the intermediates of the coupled oxidation.[150] Similar products were obtained by oxidation of hemochromes with hydrogen peroxide in pyridine, and a mono-*meso*-oxygenated structure was supported by combustion analysis[151] and benzoylation.[144] The *meso*-oxygenated structure was confirmed by a direct comparison of OEP-oxophlorin **20c** obtained by benzoylation of H_2(OEP) and hydrolysis, with a synthetic product.[152]

Oxophlorins can be prepared either by synthesis, by oxidation of porphyrins or by selective reduction of more highly oxygenated porphyrins. The synthetic approach to oxophlorins has been opened by Jackson *et al.* (see Volume I, Chapter 6),[153,154] with their oxobilane route to porphyrins. Oxophlorins are intermediates in this synthesis, and the method has been used by Clezy *et al.* (see Chapter 4 for a review) to prepare a wide variety of oxophlorins.

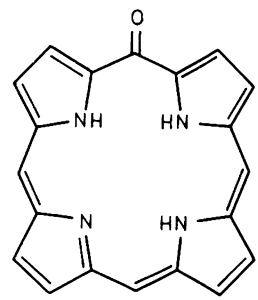
The direct oxidation of metalloporphyrins to oxophlorins can be carried out by coupled oxidation with oxygen and ascorbic acid,[148] or by reaction with H_2O_2.[155] For the latter reaction, the dependence of the central metal has been studied.[152] Among the first-row transition metals, the oxidation is only possible if the metal ion has a readily available higher oxidation state (Fe(II), CO(II), Mn(II), (Mn(III)). The oxidation of free-base porphyrins is possible with lead tetraacetate[156] or with benzoyl peroxide,[81] and subsequent hydrolysis of the *meso*-acylated porphyrin. While these reactions proceed, probably by a radical mechanism, oxidation is possible[27] too using the electrophilic reagent thallic trifluoroacetate.[157] The latter reaction, which proceeds via a *meso*-trifluoroacetoxy intermediate, is probably the best synthetic approach to octaethyloxophlorin and similar structures for which no isomerism is possible.[27] The third pathway to oxophlorins is via the reduction of higher

meso-oxygenated porphyrins, particularly the xanthoporphyrinogens.[144,156] These reactions have less synthetic value, but they were important chemical clues in the structure determination of the latter compounds.

The spectroscopy and chemistry of oxophlorins is discussed in detail in Chapter 4 and briefly here. The characteristic features of mono-*meso*-oxygenated porphyrins are their pH-dependent tautomerism between the hydroxyporphyrin structure (cf. **20a**) and the oxophlorin structure (cf. **20b**)

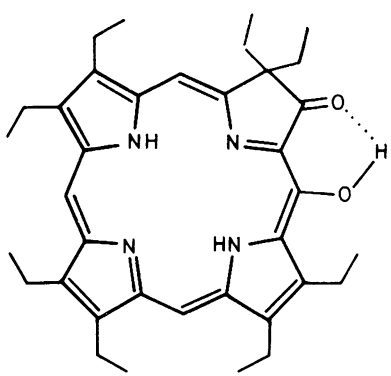


20a = IX type substitution
20c = octaethyl substitution



20b = IX type substitution
20d = octaethyl substitution

and the facile oxidation of the oxophlorins to their reactive radicals. Both have considerably complicated their structural analysis. In neutral solutions, the oxophlorin form (**20b**) is generally predominant.[81,152–154] This is evident from the ir spectra (strong CO band at about 1570 cm^{-1}, characteristic for pyrroketones), the uv-vis spectra [phlorin-type spectrum (Fig. 9)], and the ^1H nmr spectra (no ring-current effects). However, the *meso*-hydroxy tautomer **20c** is stabilized in *meso*-oxygenated furan and thiophen analogues,[158] and in OEP-β-hydroxygeminiporphyrin-4-ketone **21**.[159] In the former, tautomerization to the oxophlorin is precluded by the bivalent heteroatoms;



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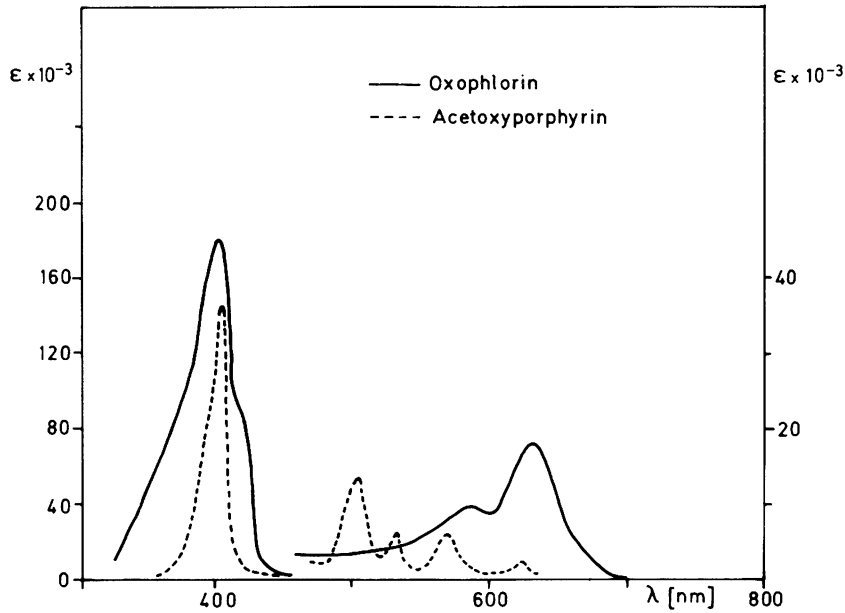


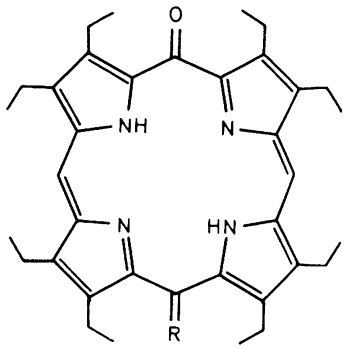
Fig. 9. The uv-vis spectra of octaethyloxophlorin and *meso*-acetoxy-OEP (e.g., see Bonnett *et al.*[81]).

in the latter the *meso*-OH is stabilized by intramolecular hydrogen bonding to the neighboring CO group.

From protonation–deprotonation studies it has been concluded that oxophlorins are both stronger acids and bases than the corresponding porphyrins.[81,154] Free-base oxophlorins are extremely sensitive to air. The redox potential of the oxophlorins is considerably lower than that of porphyrins, and the former are always contaminated with the oxophlorin radical formed by one electron oxidation and deprotonation. These paramagnetic impurities have been responsible for broadened and sometimes undetectable ^{1}H nmr spectra,[81,152,154,158] due to rapid spin exchange. The radical of OEP-oxophlorin has been obtained quantitatively by photooxidation in benzene, and its esr spectrum and reactivity have been studied. It appears that the high reactivity of oxophlorins is due primarily to the easy oxidation to and the subsequent reactions of the cation radical.[76,160]

2. Dioxoporphodimethenes

Further oxidation of porphyrins or oxophlorins[161,162] leads to α,γ-dioxo-β,δ-porphodimethenes like **229**. The best preparative procedure is again the oxidation with thallium trifluoroacetate.[161] From ^{1}H/^{2}H exchange experiments, the methine bridge opposite to the hydrogenated one in phlorins has



(a) R = O
(b) R = NH

22

been shown to be susceptible to electrophilic attack. This selectivity is less pronounced in the oxophlorins,[81] and α,β-dioxoporphodimethenes have been obtained as by-products of **22a**.[163,164] The iminooxoporphodimethene **22b** has been obtained by Fuhrhop[162] by oxidation of the *meso*-amine. The uv-vis spectra of the dioxoporphodimethenes are of the dipyrromethene type (Fig. 10), indicating an efficient separation of the two subunits by the oxo

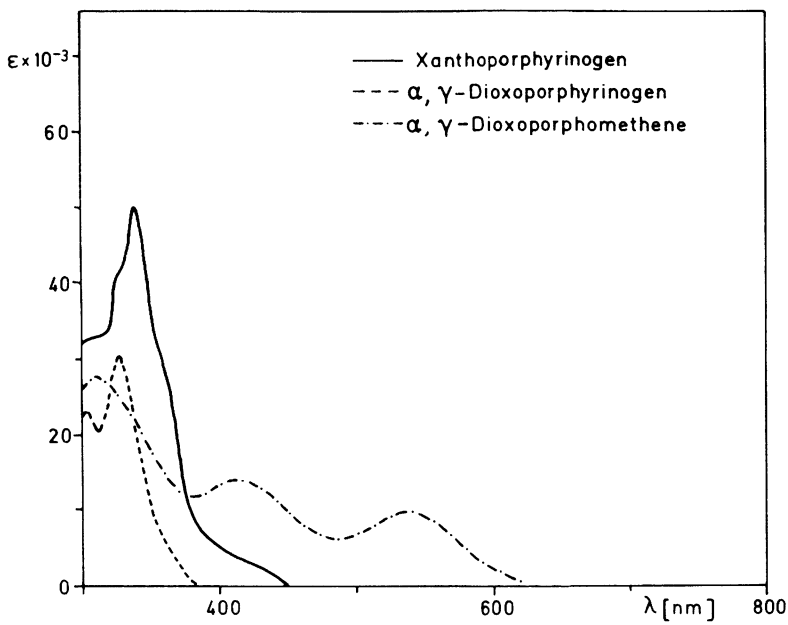
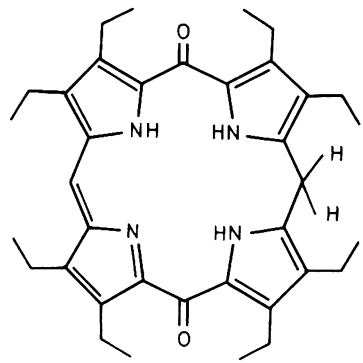


Fig. 10. The uv-vis spectra of *meso*-oxygenated octaethyl porphodimethenes, porphomethenes, and porphyrinogens.[156]

bridges. This is supported by the ^1H nmr spectra (no ring-current effects), and by the ir spectra (strong CO, no OH).

3. Oxo-porphomethenes

During the reduction studies on xanthopophyrinogens (see below), Fischer and Treibs[165] noticed the rapid oxidation of the dioxoporphyrinogen **25** to a red product. The structure of the latter was established by Inhoffen *et al.*[156] as the dioxoporphomethene **23** on the basis of ir, nmr, and ms data.

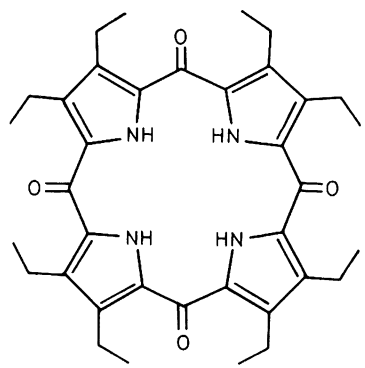


23

The opposite position of the carbonyl groups was concluded from the mass-spectroscopic fragmentation pattern.

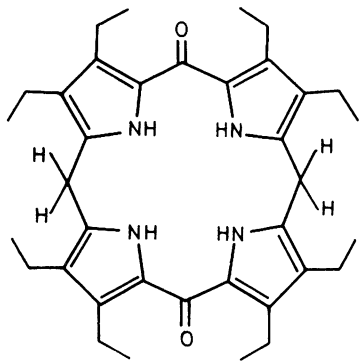
4. Oxoporphyrinogens

In 1927, in an attempt to distinguish between the indigoid and macrocyclic structures proposed for porphyrins, Fischer and Treibs[165] obtained a yellow tetraoxygenated product from the lead dioxide oxidation of porphyrins. Although Fischer and Orth[5] discussed the tetraoxoporphyrinogen **24** as a



24

possible structure, this was not proved until 25 years later by Inhoffen *et al.*[156] The difficulties in assigning structure **24** were mainly due to the puzzling chemistry of the molecule: the steric hindrance of the neighboring β-pyrrolic substituents, which interferes with derivatization of the *meso*-carbonyl groups; the strong binding of two water or solvent molecules[5] in the chlathrate-type crystals[166]; and the differential reduction of two, three, or four of the carbonyl groups. The reduction with sodium amalgam[165] or lithium aluminum hydride[156] yields the porphyrins; reduction with zinc in acetic yields the α,γ-dioxoporphyrinogen **25**.[156,165] The latter compound is unstable toward



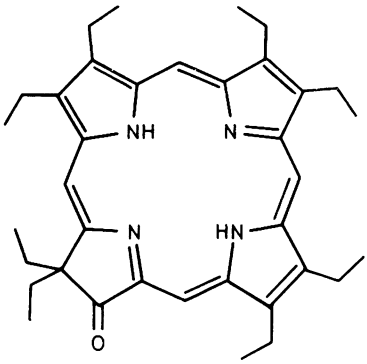
25

air[165] and oxidizes to the dioxoporphomethene **23**, which can also be obtained directly from the xanthoporphyrinogen with sodium borohydride.[156] Finally, reduction of **24** in a closed vessel with hydrogen bromide/acetic acid yields OEP-oxophlorin **20d**.[155] The reduction of **24** to **19** and subsequent benzoylation was the first definite proof of at least one oxygen of **24** in a *meso*-position.[144]

The spectra of octaethylxanthoporphyrinogen and the products derived from it by reduction have been discussed by Inhoffen *et al.*[156] (Fig. 10).

B. Hydroporphyrins Oxygenated at β-Pyrrolic Positions

Oxidation of etio-type porphyrins with hydrogen peroxide in concentrated sulfuric acid leads to oxochlorins of type **26**. Although first characterized in 1930, the proof of the structure of **26** had again to await almost 40 years.[81,94,167] The reaction can be rationalized as an electrophilic attack on the porphyrin β-pyrrolic positions, possibly leading to the β,β′-dioxychlorin **27** and subsequent pinacol–pinacolone rearrangement. Obviously, the electron density distribution is changed by dication formation to direct the electrophilic attack from the methine to β-pyrrolic positions. An alternative approach to β-hydroxylated porphyrins is by treatment with OsO_4 and subsequent



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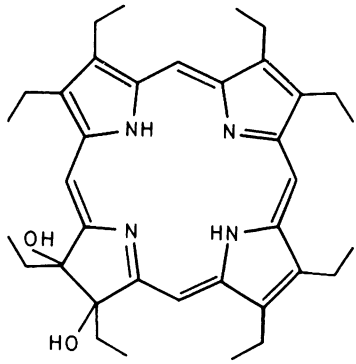
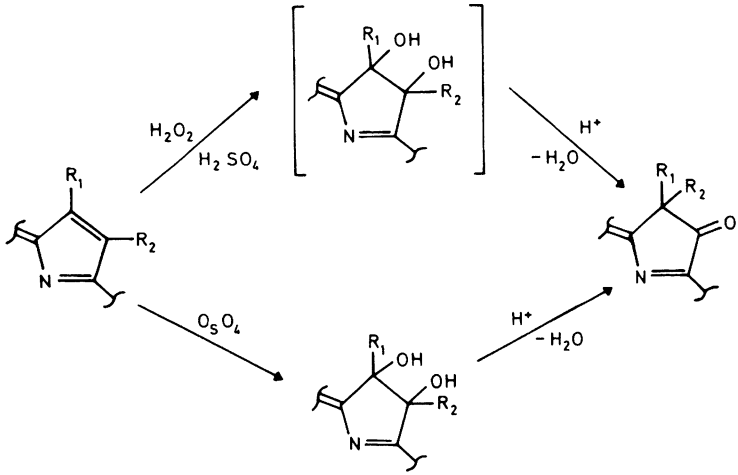


27

hydrolysis,[94,168,169] to dihydroxychlorins of type **27**. The success of this reaction again demonstrates the partial isolation of the peripheral double bond(s) from the macrocyclic conjugation pathway. The β,β'-dihydroxychlorins can be isomerized in concentrated H_2SO_4 to geminiketones, which are thus accessible by two alternate routes (Scheme 5). Both reactions have



Scheme 5

been used by Inhoffen and Müller[170] in a new approach to the corphins,[95,171] which are useful model compounds for corrins, and which principally open an alternative synthetic route[171,172] to the corrin macrocyclic system. One of the major synthetic problems is posed by the quaternary β-pyrrolic C atoms in the corphyrins and corrins. The geminiporphinketones are suitable intermediates, because alkylation of the β-pyrrolic carbonyl groups is possible with lithium organic reagent.[94,170]

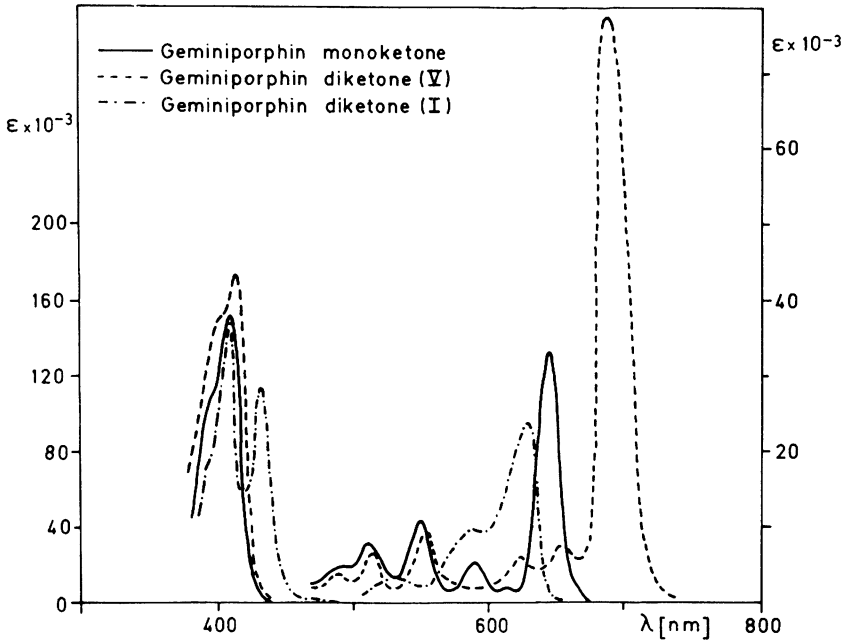


Fig. 11. The uv-vis spectra of octaethyl geminiporphyin mono- and diketones.[94]

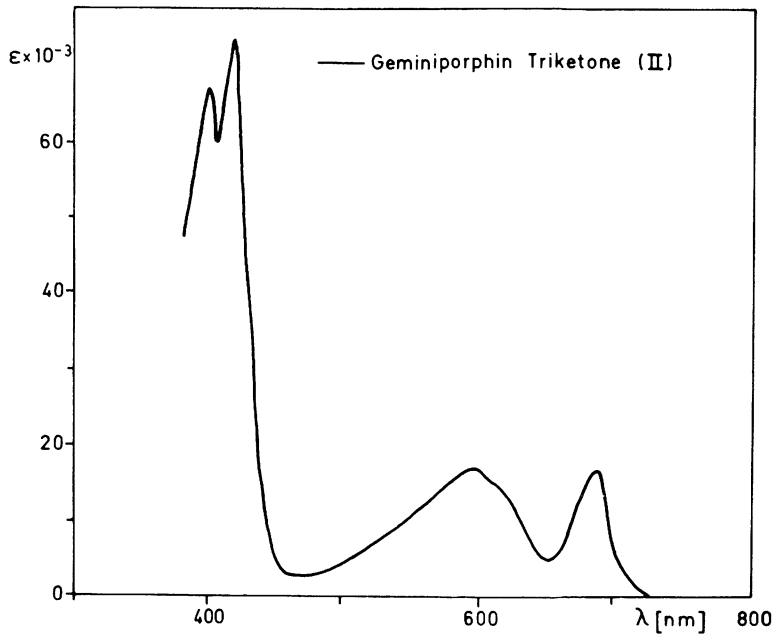
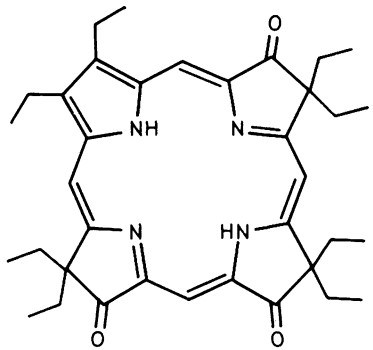


Fig. 12. The uv-vis spectrum of an octaethyl geminiporphin triketone.[94]

In exploring the H_2O_2/H_2SO_4 oxidation of H_2(OEP), it was noted[81,94] that the geminiporphin monoketone **26** is always accompanied by minor amounts of di- and triketones. Starting from H_2(OEP), all five geminiporphin diketones and two of the four possible triketones have been isolated and characterized.[94] The uv-vis spectra of these oxo compounds are similar to those of the respective hydroporphyrins (Figs. 5, 11 and 12), and all structures could be assigned from ^{1}H-nmr arguments and structural correlations between the di- and triketones. The product distribution seems to be controlled by steric hindrance: the missing triketones are the ones with two bulky geminal diethyl groups next to each other (**28**, **29**), and the diketone obtained



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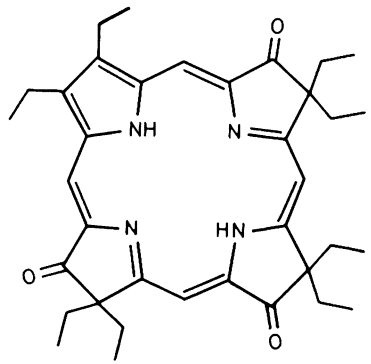
in lowest yield is the one with two of these groups next to an ethyl substituent (**30**). The yield of the triketones can be increased by treatment of the mono- and suitable diketones with OsO_4 and subsequent pinacol rearrangement. However, quaternization of the β-pyrrolic positions of the fourth pyrrole ring is not possible by further oxidation. Instead, the corphin macrocyclic system is accessible by primary reduction of the monoketone **26** with lithium phenyl



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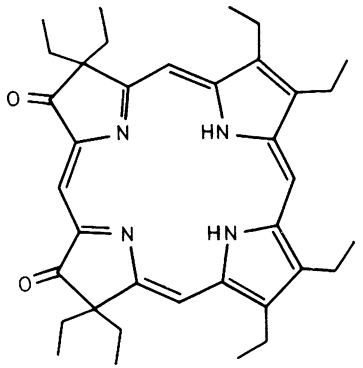
and dehydration of the metal complexes to salts of the type **31**, and subsequent treatment with OsO_4, followed by pinacol rearrangement to **33**. The



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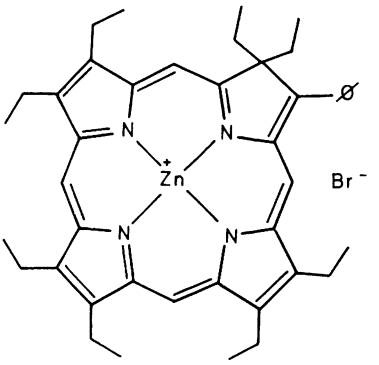
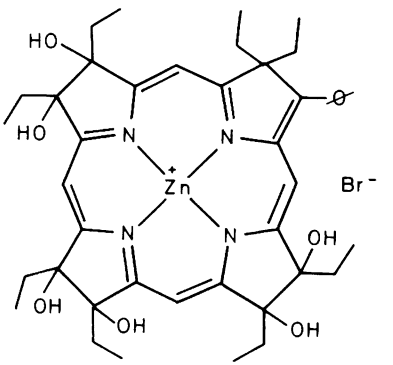


31

macrocyclic conjugation in the salts of type **31** is essentially interrupted by the cross conjugation of the 4,4a double bond, and OsO_4 hydroxylation of the three peripheral double bonds isolated from the inner olefinic conjugation system yields the hexahydroxycorphin **32**. The uv-vis spectrum of **32** is of the corphin type.[95,96] By isomerization with H_2SO_4, two of the possible eight isomeric corphin-triketones of the type **33** have been obtained in moderate yield.[170]



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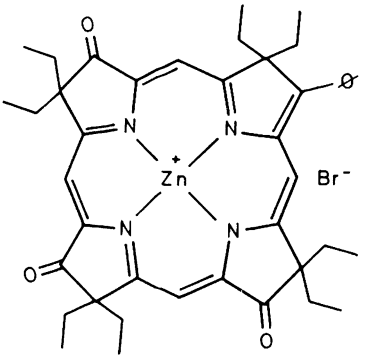

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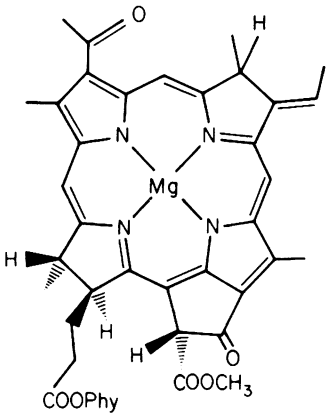
C. Analogues of Hydroporphyrins

In addition to the oxygenated hydroporphyrins, a variety of C analogues of chlorins and bacteriochlorins has been characterized recently which contain either exocyclic double bonds or two substituents at the reduced positions. In both cases, the macrocycle is in a higher formal oxidation state

than indicated by the spectra. Isomerization to this state proceeds readily by prototropic rearrangement if an exocyclic double bond and at least one proton at the neighboring reduced position are present.[36]

The only natural C analogue known is bacteriochlorophyll *b* (**34**) bearing an ethylidene group at position 4.[36] Compound **34** is rather unstable and rearranges by acid catalysis to its endocyclic isomer, 2-desvinyl-2-acetyl-chlorophyll *a* (**35**). This isomerization is irreversible *in vitro*, but the possibility



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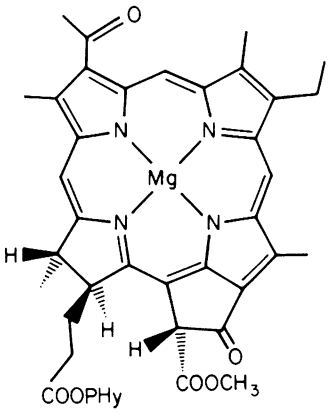

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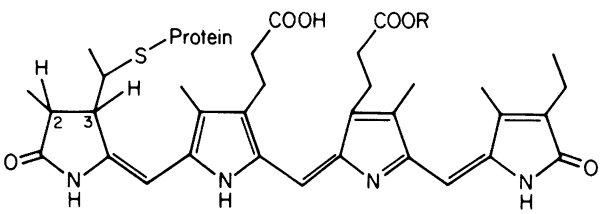
of an *in vivo* back reaction is tempting. Ethylidene derivatives such as **34** are possible intermediates during the *in vivo* hydrogenation of peripheral double bonds in chlorins and porphyrins. Hudson and Smith[173] have proposed such isomerization of Mg porphyrins into 4-ethylidenechlorins as a key step in the biosynthesis of algal bile pigments. The latter are protein-bound *in vivo* by a thioether linkage in ring A (namely, **36**), which eliminate to give 3-ethylidene-bilins in refluxing methanol.[174]

Synthetic C analogues are accessible by four general types of reactions: (a) the reduction of geminiporphinketones with lithium organic reagents,[170] (b) Woodward's[11] purpurin reaction, (c) the intramolecular cyclization of acetamidoporphyrins,[178] and (d) the addition of ethyl diazoacetate to the



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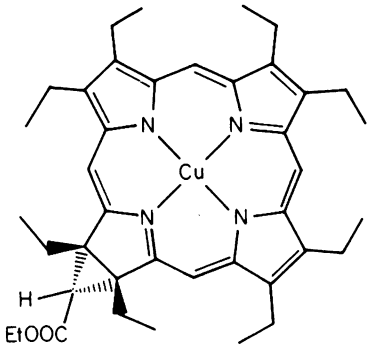
peripheral double bond(s) of porphyrins. The latter reaction has been studied in some detail.[175–177] Starting from TPP, a variety of isomeric cyclopropanochlorins and biscyclopropanobacteriochlorins have been obtained. Due to the conformationally rigid substituents, they are suitable stereochemical models to test, for example, the magnetic anisotropy of the porphyrin macrocycle.[28] Cu(OEP) can react in a similar fashion yielding chlorins which bear four alkyl substituents at the pyrroline ring (**37**). As a by-product, the isomeric ethylidenechlorin **38** is obtained. It is stabilized toward rearrangement of the endocyclic isomer for the lack of a suitable proton.



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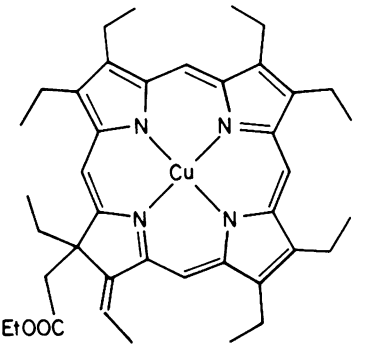

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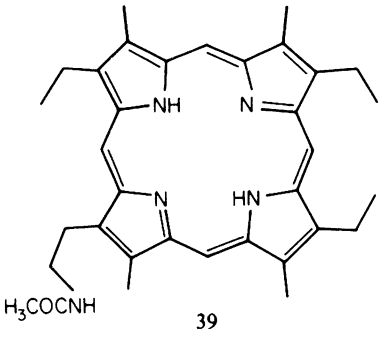
The reaction of etio-type acetamidoethylporphyrins **39**, under the conditions of the Vilsmeier reaction, yields methylene spiropyrrolinochlorins (**40**), which



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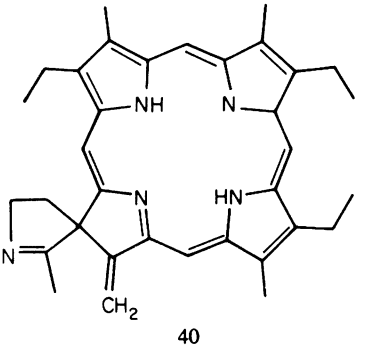

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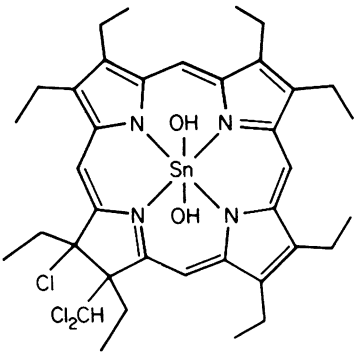
can be reduced to the corresponding methyl-substituted chlorins.[178] The reaction proceeds probably via intramolecular attack at the spiro-C-to-be and prototropic shift of the peripheral to the methylene double bond.

D. Miscellaneous

Only few examples of other hydroporphyrin analogues are known. Fuhrhop *et al.*[179] have reported the formation of the Sn(IV)-chlorodichloromethylchlorin **41** by reaction of $Sn(IV)(OEP)(OH)_2$ with $SnBr_4$ in chloro-



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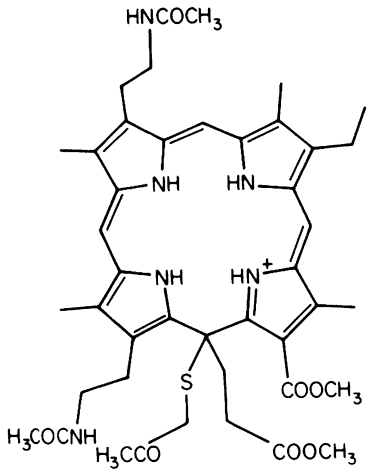
form. The thioacetoxyphlorin **42** is formed by reversible nucleophilic addition of thioacetic acid,[180] a reaction certainly facilitated by the steric hindrance of the parent porphyrin. The thiacyclic chlorin **43** (in rapid exchange equilibrium



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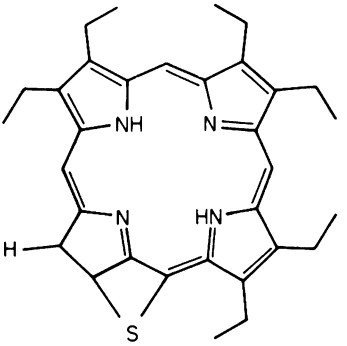

43

with its mirror-image isomer) has been proposed by Clezy and Smythe[181] because of the chlorin-type ^1H nmr spectrum for the product obtained by hydrolysis of a *meso*-thioacetoxyporphyrin.

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