

THE PORPHYRINS

Volume II

Structure and Synthesis, Part B

Edited by

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Synthesis and Stereochemistry of Hydroporphyrins

HUGO SCHEER

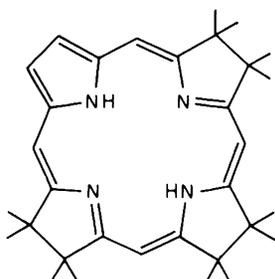
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I. INTRODUCTION

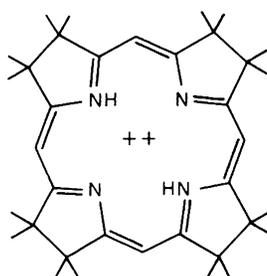
The fully unsaturated porphyrin macrocycle (**1**) (see Scheme 1, structures **1–13**) contains 11 conjugated double bonds. Strictly speaking, the term “porphyrin” applies only to this system, but a variety of compounds are known in which the macrocyclic porphyrin skeleton is retained, while one or more of the double bonds are removed. These compounds are formally derived from porphyrins by hydrogenation, and are, therefore, commonly termed hydroporphyrins. Reduction is probably the most common pathway to hydroporphyrins, and the known redox reactions and isomerizations of true hydroporphyrins are summarized in the reaction scheme (Scheme 1). However, compounds that contain the chromophore of hydroporphyrins are accessible, too, by oxidation of porphyrins yielding the oxy and oxo analogues of the hydroporphyrins (see Chapter 2).

Some of the hydroporphyrins are of central biological importance. Most chlorophylls are Mg complexes of chlorins (**4**) or bacteriochlorins (**13**), in which one or two of the peripheral double bonds are reduced, the sirohemes found in nitrate and sulfate reductases^{1a} contain the "cis" bacteriochlorin chromophore (**12**),^{1b} porphyrinogens (**16**) and porphomethenes (**10**)^{1c} are intermediates in porphyrin biosynthesis (Volume VI, Chapters 1 and 2), and oxophlorins (**18**) are discussed as first intermediates in the degradation of porphyrins into bile pigments (Volume VI, Chapter 5). In addition to these naturally occurring hydroporphyrins, a variety of synthetic systems has been characterized in the past, which yielded a detailed insight into the reactivity and electronic structure of the porphyrin macrocycle.

The hydroporphyrins can be arbitrarily divided into two classes, depending on whether or not the macrocyclic conjugation is retained. In chlorins (**4**), bacteriochlorins (**12**, **13**), dihydrobacteriochlorins (**14**),¹ and corphin dications (**15**),² one or more of the macrocyclic peripheral double bonds are reduced

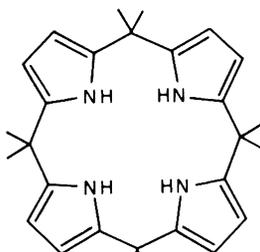


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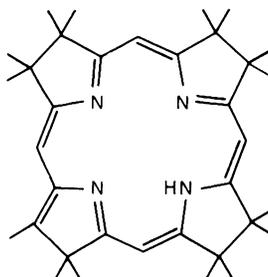


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without loss of the macrocyclic conjugation as evidenced, for example, by the aromatic (**4**, **12**, **13**, **14**) and antiaromatic (**15**) ring-current effects, respectively, in their nuclear magnetic resonance (nmr) spectra.³ In the nonaromatic hydroporphyrins, the cyclic conjugation is usually interrupted at one or more of the bridging methine positions, leaving one to four conjugated pyrrole



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subunits (structures **5**, **6**, **9**, **10**, **16**). In the corphins (**17**),^{4,5} the cyclic conjugation is interrupted in an essentially different manner at one α -pyrrolic carbon atom and one N atom. Some related structures in which the conjugation is interrupted by other means are discussed elsewhere. In most cases, the respective carbon atoms become sp^3 hybridized by either hydrogenation of or addition of new C-C bonds. However, exocyclic oxohydroporphyrins with exocyclic C=O bonds are widely investigated due to their greater stability toward oxidation (see Chapter 2).

II. SYNTHESIS OF HYDROPORPHYRINS

A. Chemical Reduction

1. CHEMICAL REDUCTION TO CHLORINS

To date no synthetic method has been devised in which the chlorin, and almost any other hydroporphyrin macrocycle,^{2,6} is built in the rational step-by-step fashion now commonly employed in porphyrin synthesis. Chlorins are usually found as the undesired by-products in *meso*-tetraarylporphyrins,^{7,8} and a wide variety of chlorins is accessible by suitable modification of chlorophylls.^{9-12a} The recent progress in the chemical modification of chlorophyll derivatives is summarized in the appendix to this chapter. The general synthetic approach to chlorins, however, involves first the synthesis of the respective porphyrin and then its subsequent reduction to chlorin. (It is noteworthy that the same approach is used in the biosynthesis of chlorophylls, too.¹³)

There are 26 isomeric neutral dihydroporphyrin structures possible¹⁴ for symmetric porphyrins that are chemically reasonable. Most of these structures are still theoretical, and, indeed, only three of them have been prepared as defined compounds and characterized in detail: the chlorins (**4**), the phlorins (**5**), and the porphodimethenes (**6**). Nonetheless, the synthetic problem is complicated by the possibility of stereoisomers, and, when unsymmetrically substituted porphyrins are to be reduced, of structural isomers. The selective reduction of porphyrins is then a major problem, and, for example, the regio- and stereoselective reduction of the 7,8-double bond was one of the key reactions in Woodward's chlorophyll synthesis.¹⁵ In spite of the straightforward reactions now available to prepare the common model chlorins like H₂(OEC) and H₂(TPC), there is still no generally applicable set of conditions to obtain chlorins with sensitive substituents.

The best approach to the etio-type chlorins is the treatment of porphyrins with reagents typical for the hydrogenation of isolated double bonds. Reactions of this type support an electronic structure of the porphyrin macrocycle in which at least two of the peripheral double bonds do not fully

participate with the 18π aromatic conjugation system. Catalytic hydrogenation^{15a-17} or reduction with diimide^{18,19} yields exclusively the *cis*-chlorins. Borohydration yields a 5:1 mixture of the *cis* and *trans* isomers,^{17,20} possibly due to two competing pathways in which *trans*-OEC is formed via a phlorin intermediate, rather than by a direct attack of B_2H_6 on the peripheral double bond. *trans*-OEC is best prepared by reduction of Fe(III)(OEP)Cl with sodium in amyl alcohol, and subsequent demetalation of the formed Fe(OEC).^{19,21-22c} The Sn(IV) and Mn(III) complexes of OEP can be reduced in comparable yield to the metallochlorin,²¹⁻²⁴ but demetalation is less satisfactory in this case for preparative purposes.²⁴

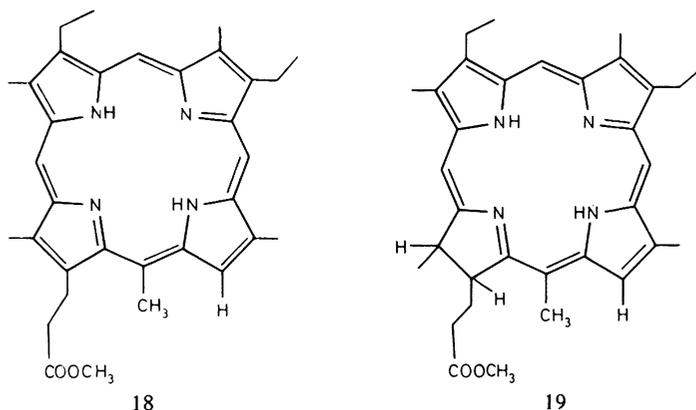
Considerable attention has been given to the influence of the central metal on the reduction of metalloporphyrins. Central metals generally reduce the possibility of side reactions. Phlorin formation is precluded at low pH and in neutral solutions,²⁵ although at higher pH phlorin (= porphodimethene) anions (3) can be formed.²⁶⁻²⁹ The preferential reduction of metalloporphyrins with highly charged central metals can be rationalized in first order by an electrostatic model, which was introduced to explain their one-electron redox potentials.³⁰ The latter ones are primarily determined by the electron density at the periphery, which, in turn, can be controlled by the electronegativity of the central metal. Thus, Fe(III), Mn(III), and Sn(IV) porphyrins are easily reduced both chemically^{21-22c} and photochemically.^{23,24} On the other hand, Mg and Zn porphyrins are more difficult to reduce. However, Zn is exceptional in stabilizing chlorins and/or in promoting the rearrangement of *meso*-hydrogenated by-products into chlorins.^{26,28,31-31b} Such subtle influences of the central metal have found some attention, but they cannot yet be rationalized. Finally, the demetalation properties of the formed metallochlorins are an important synthetic aspect. Fe(III), Mn(III), and Sn(IV) complexes can be demetalated only under harsh conditions not suitable for chlorins that are easily oxidized,^{17,20} or which bear delicate substituents, while metals of intermediate stability like Zn seem to be again the best choice.

The synthesis of *meso*-tetraarylporphyrins from pyrroles and benzaldehydes^{32,33} is always accompanied by the formation of hydroporphyrins, especially chlorins.^{7,8} These are usually undesired contaminants of the porphyrins, and methods have been devised for their removal by selective oxidation to porphyrins.³³ If the chlorins are the desired products, they can be separated by fractionated crystallization (which leaves the chlorins enriched in the mother liquor), by fractionated acid extraction (in which the lower basicity³⁴ of the chlorins is used^{9,19}), and, only with difficulty and only if small amounts have to be separated, by chromatography. The mechanism of hydroporphyrin formation during the synthesis of TPP has been studied by several groups.^{7,8,35,36} It could be shown that the initially formed

TPP-porphinogen is oxidized in an acid-catalyzed reaction to the porphyrin via a porphodimethene³⁷ intermediate.⁸ The chlorin is then formed by the subsequent re-reduction of the porphyrin.⁸ The best synthetic approach to TPC is the diimide reduction method of Whitlock *et al.*,¹⁹ which yields about 50% of the crude product.

Chlorins obtained by the above procedures are always accompanied by bacteriochlorins, which can be enriched and isolated if the reaction conditions are carefully controlled. Both isomers, namely, the true bacteriochlorins (**13**) and the isobacteriochlorins (**12**), are formed, the latter ones usually in higher yield. True bacteriochlorins are obtained in highest yield under the conditions of the Wolff-Kishner reduction,^{20,38} and there seems to be a tendency that central metals stabilize the isobacteriochlorins.^{19,20,22a,22b,25,38,39} If chlorins are the desired reaction products, the yield can be increased by selective reoxidation of the bacteriochlorin by-products to the chlorin level.^{19,40,41}

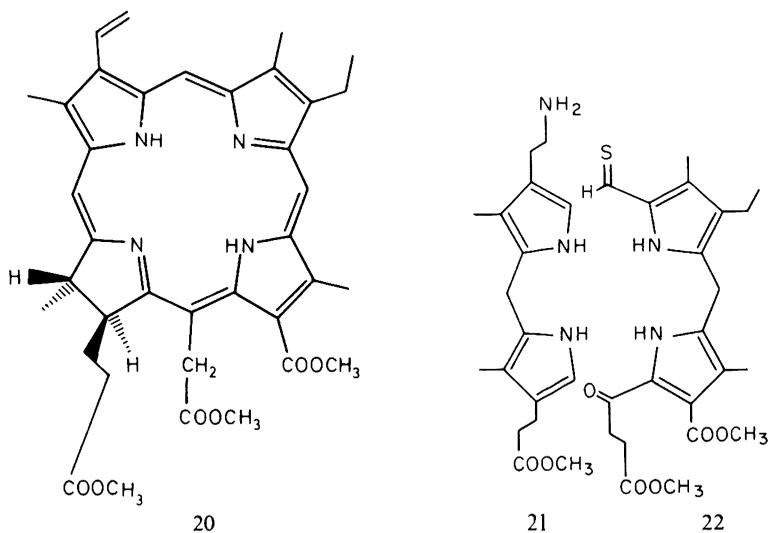
In summary, chlorins derived from the highly symmetric model porphyrins like OEP and TPP can be prepared in high yields by chemical reduction, but less symmetric chlorins like the ones related to chlorophylls are not accessible in this way. Surprisingly, the formation of a mono-*meso*-substituted chlorin more closely related to the chlorophylls was reported as early as 1929.⁴² Treatment of the phylloporphyrin **18** with sodium ethoxide at 185°C produced in good yield (20%) a chlorin to which structure **19** was assigned on the basis



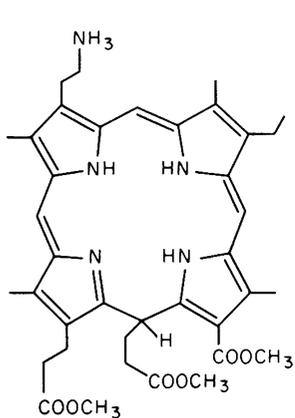
of its uv-vis spectrum. This structure was proved correct 40 years later by X-ray crystallography.⁴³ Although the mechanism of its formation is not known, the driving force seems to be the same steric hindrance between the peripheral substituents on which Woodward's approach¹⁵ to chlorophyll *a* (Chl *a*) was based. The outline and the details of this synthesis are reviewed earlier.^{15,44} Here we want to discuss briefly only the final and crucial conversion steps leading to the 7,8-*trans*-chlorin **27**. The principal concept of the

selective reduction at C-7 and C-8 was based on the hypothesis of the "overcrowded periphery." In porphyrins possessing neighboring *meso*- and β -pyrrole substituents, there exists considerable steric hindrance between these coplanar groups. This interaction provides a driving force for the selective sp^3 hybridization of either one of the substituent sites in the "overcrowded" region, by which the respective substituent(s) are positioned out of plane, and, thus, the steric hindrance is relieved. There are now numerous examples of regio- and stereoselective reductions of porphyrins to support this principle (see also Section III), which will here be exemplified by the respective reactions in the original work, the last steps of the Chl *a* synthesis leading to chlorin-*e*₆ trimethyl ester (**20**).

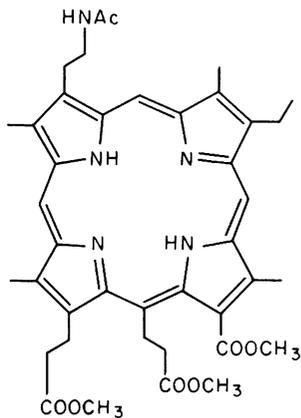
Double condensation of the two dipyrromethanes **21** and **22** (via a Schiff base intermediate) with 12 *N* HCl in MeOH leads not to a porphyrin, but to



the phlorin **23** instead. Compound **23** was the first example of this class of compounds, and its formation is obviously favored (as compared to the porphyrin formation) by the steric relief due to the out-of-plane positioning of the γ -substituent. Compound **23** can be oxidized, e.g., with iodine, to the corresponding γ -substituted porphyrin **24**. The latter is not only easily re-reduced back to the phlorin **23**, but also undergoes a remarkable acid-catalyzed isomerization to the phlorin **25**. Thus, the steric hindrance due to the γ -substituent in **24** must be large enough to overcome the resonance stabilization of the cyclic conjugated system, and, in acetic acid, an equilibrium is established with about equal amounts of **24** and the γ -allylphlorin **25**. No similar equilibrium of **24** was found with the desired chlorin, but this goal

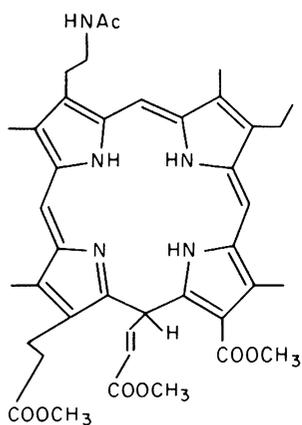


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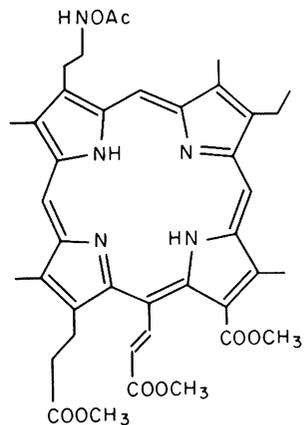


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was achieved by an additional oxidation of **25** to the γ -allylporphyrin **26**. The latter compound is no more capable of undergoing a similar isomerization (**24** \rightarrow **25**) due to the double bond in the γ -substituent. Instead, in this case, the steric strain is relieved by isomerization of the porphyrin **26** into the



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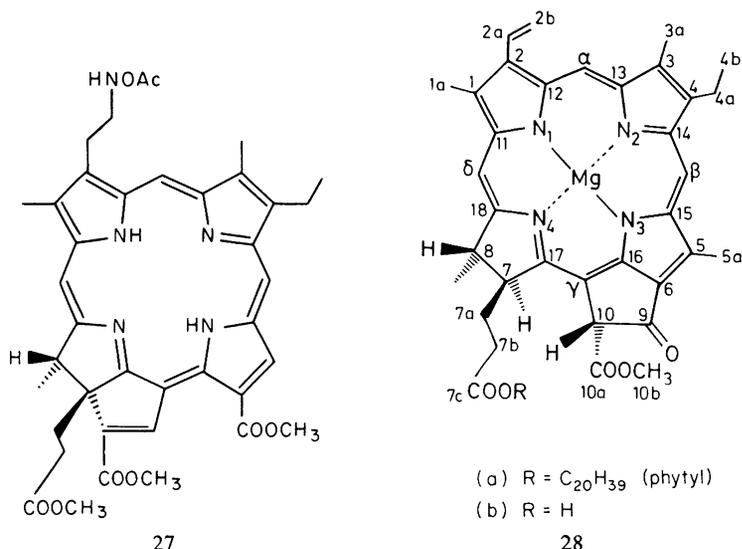


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chlorin (= purpurin) **27**.^{*} This step is both stereo- and regioselective. Not only is the desired 7,8-chlorin preferentially formed, due to the larger steric hindrance of the 6-COOCH₃ versus the 7-propionic side chain, but also the right stereochemistry at ring IV is obtained by the transoid arrangement of

^{*} Recently, the need for an electrophilic β -pyrrole substituent for this isomerization has been invoked from model studies [L. Witte and J.-H. Fuhrhop, *Angew. Chem.* **87**, 387 (1975)].

the substituents with the largest effective volume, namely, the 7-propionester and the 8-CH₃ group. By this means, the essential 7,8-*trans*-chlorin structure has been formed in high yields in a rational approach. The subsequent conversions of **27** and resolution of the racemate then lead to chlorin-e₆ trimethyl ester (**20**) and finally to chlorophyll *a* (**28a**) by methods devised



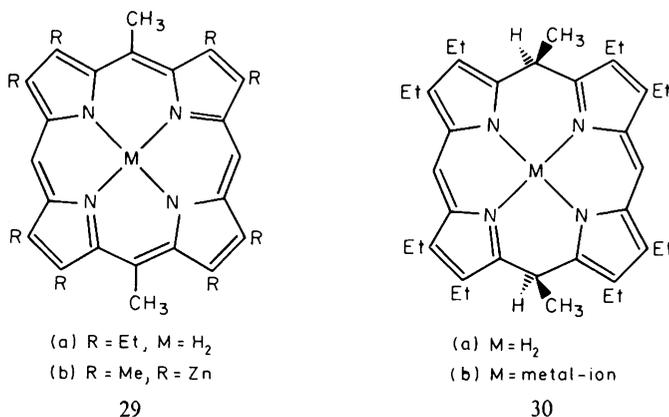
already by the groups of Willstätter and Stoll, and of Fischer.^{9,45} The functionalization of the 3-methyl group of **20** leading to the chlorophyll *b* series has been described by Inhoffen *et al.*^{45a} (Chapter 2).

2. CHEMICAL REDUCTION TO INTERRUPTED SYSTEMS

The most widely investigated chemical reduction that leads to interrupted systems is the treatment of porphyrins (**1**) with alkali metals,⁴⁶⁻⁵⁰ or, better, with aromatic radical anions^{26,28} to yield the porphyrin dianions, and the subsequent addition of protic solvent (reductive protonation) or alkylating reagents like alkyl iodides (reductive alkylation). The reaction of metalloporphyrins with aromatic radical anions was first investigated by Closs and Closs.²⁶ Two subsequent^{50,51} one-electron reductions yielding the dianion can be followed by uv-vis and esr spectroscopy.^{26,47} Addition of 1 mole of methanol to the dianion yields the anion of type **3**, which can be considered as the conjugated base of either a phlorin or a porphodimethene. Addition of a second mole of methanol then results (with Zn as central metal) in an isomerization of the porphodimethene (**6**) into a chlorin (**4**).^{26,28} The reductive protonation was studied in the OEP series for a variety of central metals by

Buchler *et al.*^{28,52,53} and can be summarized as follows: (a) the reduction step leads normally to the dianion, although with some transition metals (Co, Cu, Ni, Cr) only the monoanion is accessible; (b) upon protonation, four reaction products are generally observed: the metal complexes of the porphodimethene (**6**), the chlorin (**7**), the isobacteriochlorin (**12**), as well as the metal-free porphyrin. The chlorin yield (isomerization of **6** into **7**) is best for the Zn complexes; (c) there are two yet to be identified types of porphodimethenes (?) with absorptions at about 455 and 520 nm, respectively; (d) the protonation is accompanied by disproportionation reactions, as evidenced by the formation of the porphodimethene from monoanions, as well as by the formation of isobacteriochlorins from the dianions.

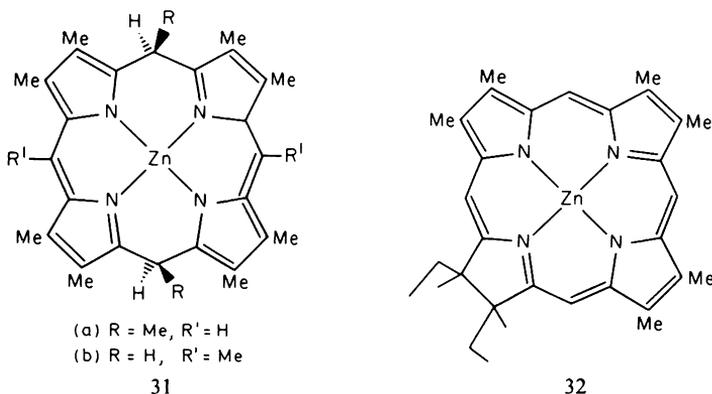
In an alternative reaction, the dianion can be treated with alkylating electrophilic agents instead of methanol. This reductive alkylation allows an insight into the reaction mechanism and the electron density of the dianion, even in cases in which the ultimately isolated reaction product is the re-oxidized porphyrin. With CH₃I as methylation reagent, and subsequent oxidation, the α,γ -methylated OEP **29a** was obtained from the dianion of



OEP in 60% yield, thus confirming a high electron density of the dianion at opposite methine positions.⁵³

The uv-vis spectra of the dimethylporphyrins **29** show considerable bathochromic shifts (as compared to the educt porphyrins), which are characteristic for oligopyrrole pigments that are twisted due to steric hindrance (Brunings-Corwin effect^{17,31-31b}; for a critical study see ref. 55). In analogy with Woodward's considerations concerning the effects of an overcrowded porphyrin periphery,¹⁵ one would expect the α,γ -dimethylporphyrins to be destabilized, while the reduced dimethylporphodimethenes should be stabilized. In agreement with this concept, the free porphomethene **30a** and a series of its metal complexes could be isolated.^{28,52,53} It is further

proved by the direct comparison of the two isomeric porphodimethenes obtained by photoreduction of the α,γ -dimethylporphyrin **29b**.⁵⁶ One of them, the α,γ -dimethyl- β,δ -porphodimethene **31a**, is again stabilized for steric reasons. The other product is spectroscopically very similar, but is rapidly oxidized to the educt. Therefore, the isomeric structure **31b** was proposed,



which is not sterically stabilized against rearomatization. In an interesting variant of the reductive alkylation, the diethylchlorin **32** was recently obtained by alkylation of the OMP-dianion.⁵⁷ In this reaction, two ethyl groups have seemingly migrated from methine to β -pyrrole positions.

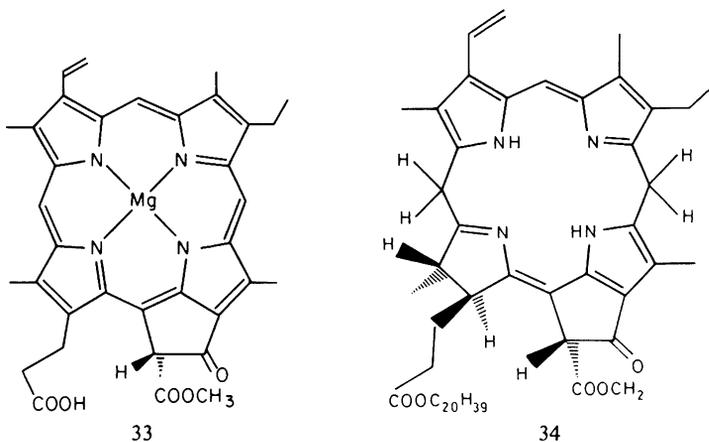
B. Photochemical Reduction

Life on earth depends on photosynthesis, and the conversion step of light into chemical energy involves chlorophylls in all known photosynthetic organisms. Photoreactions of chlorophylls, which are usually either chlorins or bacteriochlorins,⁵⁸ as well as photoreactions of porphyrins in general are, therefore, extensively studied.⁵⁹ At least two* photochemical conversions of chlorophylls *in vivo*^{59a} are well characterized: the photoreduction of protochlorophyllide *a* (**33**) to chlorophyllide *a* (**28b**) as one of the last steps of Chl *a* biosynthesis in higher plants and some algae,¹³ and the reversible oxidation of reaction center chlorophyll as the primary reaction of photosystem I (for leading references, see refs. 60; Volume IV, Chapter 3; and Volume V, Chapter 9). Comparably little is known about a third one, the primary reaction of photosystem II, except that chlorophyll *a* is involved as well.^{61,62}

Although chlorophyll was used as the red photosensitizer for photographic emulsions as early as the beginning of this century,^{63,64} the first defined

* For the photochemistry of chenopodium chlorophyll protein, c.f. T. Oku and G. Tomita, *Plant Cell Physiol.* **16**, 1009 (1975); and *Photochem. Photobiol.* **25**, 199 (1977).

reversible *in vitro* photoreaction of chlorophyll was not described before 1948 by Krasnovskii.⁶⁵ In this reaction, chlorophyll *a* in pyridine is reversibly reduced by ascorbic acid. First, a transient yellow product ($\lambda_{\max} = 470, 340$ nm) can be observed, followed by a fairly stable pink product ($\lambda_{\max} = 515$ nm). The latter pink Krasnovskii product was recently characterized as the α,γ -porphodimethene **34**.⁶⁶ During the Krasnovskii reaction reductive



capacity is generated, therefore, the reaction was extensively studied as a possible model for the photosynthetic conversion of light into chemical energy. It could be shown that the reaction is quite general for porphyrins,⁶⁷⁻⁷⁰ and that various reductants can be used, including hydrazines, sulfhydryl compounds, hydroquinones, and stannous chloride. With ascorbic acid as the reducing agent, the presence of a base is always required, and the reaction occurs via electron transfer from the ascorbate anion, and subsequent proton transfer from the protonated base⁷⁰ present in the ion pair. On the other hand, reduction with SnCl_2 is quantitative in strongly acidic solutions.^{23,71} Several investigations are focused on the influence of pH^{71,72,72a} and solvent system^{25,31-31b,72b,72c,73} on the reaction.

The original work of Krasnovskii deals with the reduction of chlorophyll *a* (**28**), and, due to its potential implications for photosynthesis, a large amount of work has been focused on this molecule, a metallochlorin. Most of the recent studies are concerned with other porphyrin type compounds, however, be it for use of model systems or for the interest as such in these structures. Although some details of the Krasnovskii reductions are still to be clarified, the general scope of the reaction does strongly resemble the scheme outlined for the chemical reduction in Section II, A, 2. It can be summarized as follows. (a) Metalloporphyrins (**2**) are reduced subsequently

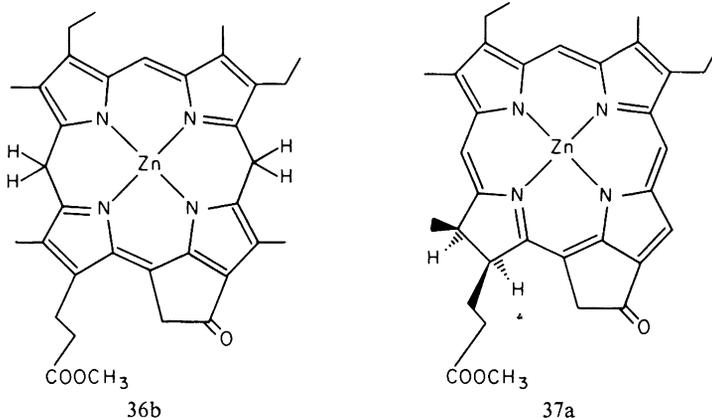
to metalloporphodimethenes (**6**), metalloisobacteriochlorins (**11**), and metallohypobacteriochlorins (**14**). (b) Porphyrins (**1**) are reduced subsequently to phlorins (**5**) and porphomethenes (**10**). (c) The reduction of chlorins yields the corresponding structures with one peripheral double bond removed, namely, chlorinphlorins (**9**) are obtained from chlorins (**4**), and metallochlorinporphodimethenes (**11**) are obtained from metallochlorins (**7**). Structures of chlorin reduction products beyond the dihydrochlorin level are yet to be characterized. (d) Phlorins (**5**) can isomerize to chlorins (**4**) (see Section II, B), or they can be metalated to metalloporphodimethenes (**6**).⁷⁴ (e) Metalloporphodimethenes (**6**) can isomerize to metallochlorins (**7**). They can be demetalated to porphodimethenes, and certain results indicate that they can be demetalated to phlorins as well. (f) Chlorinphlorins can probably isomerize to porphomethenes.

The chromophore in some of the products with retained macrocyclic conjugation (chlorins, bacteriochlorins) is relatively safely identifiable by means of uv-vis spectroscopy. However, reduced forms with interrupted cyclic conjugation, but conjugation of more than one pyrrolic subunit, usually have absorptions close to 500 nm. Early additional techniques involved acid-base and redox titrations for the characterization of these types of compounds¹⁴; in addition, the usefulness of infrared spectroscopy (ir) and especially nmr has been demonstrated recently.^{3,31b,56,66,71,75-79} Thus, at least four different compounds with an absorption at $\lambda_{\max} = 500$ nm have been characterized as reduction products: porphomethenes (**10**),^{14,79} chlorinphlorins (**9**),^{78,80} chlorinporphodimethenes (**11**),⁶⁶ and porphodimethenes (**6**).^{31b,56} All these products contain the common dypyrromethene chromophore, which gives rise to the observed absorption.⁸¹

1. METALLOPORPHYRINS TO METALLOCHLORINS

The photoreduction of protochlorophyllide *a* (**33**) to chlorophyllide *a* (**28b**) is, in higher plants and some algae, one of the last steps in the biosynthesis of chlorophyll *a*.¹³ This step is both regio- and stereospecific *in vivo*: only the 7,8-double bond in (**33**) is reduced, and the "extra" hydrogens are transoid to each other. The thermodynamic stability of this structure as compared to other isomers was first discussed by Woodward and proved by the approach of the Harvard group¹⁵ to the synthesis of chlorophyll *a* (see Section II, A, 1).

In spite of the thermodynamic stability of chlorophyll *a*, however, attempts to stimulate the photoreduction of protochlorophyll *a* and related Zn complexes *in vitro* have been only partially successful. The reduction yields the 7,8-*cis* rather than the *trans* isomers,^{31-31b,82-83a} and there are indications that the reaction proceeds via a porphodimethene intermediate, which subsequently isomerizes to the chlorin.^{31-31b,82}



reduced to the pink Krasnovskii product⁶⁵ (chlorin porphodimethene,⁶⁶ $\lambda_{\max} = 515 \text{ nm}$). Although the above discussed kinetics seem to disfavor this interpretation, at least for the photoreduction of **35**, the question remains open as long as the structure of the intermediates is not determined in a more direct approach (namely, by *in situ* ^1H nmr.^{66,80}). Formation of two isomeric porphodimethenes (**36a,b**), or another type of "isomerism" (namely, ionic versus neutral) is conceivable, which is suggested by the similar spectroscopic properties of the porphodimethene isomers obtained by reductive alkylation of symmetric porphyrins.²⁸

To stress the similarity between the chemical and photochemical reduction once more, Sn(IV)(OEC) was obtained in excellent yield from Sn(IV)(OEP) by photoreduction with tetramethylethylenediamine.²⁴ Chemical reduction of Sn(IV) complexes is well known and has been interpreted by an electrostatic model with increased macrocycle electron density.²⁹ As a preparative method, the reduction became attractive after a method had been developed to demetallate the Sn(IV) chlorins.²⁴ Unfortunately, only porphyrins without functional groups like C=O are accessible by this method.

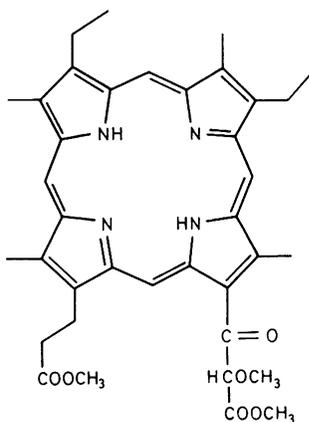
Spectral differences between the chlorins produced by photoreduction of Zn pheophorphyrins, and the corresponding chlorins delivered from natural sources, were first observed in 1970 by Krasnovskii⁸⁶ and by Scheer.⁸² As demonstrated independently by two groups,^{31-31b,82-83a} these differences are due to the *cisoid* configuration of the extra hydrogen atoms in the synthetic photoproducts, as compared to the *transoid* configuration in their natural counterparts (see Section III, C).

The above discussed results, namely, the formation of chlorins via isomerization of primary photoreduction products (e.g., **36**) and the "wrong" stereochemistry of the chlorins at C-7 and C-8, present two problems: They

render the *in vitro* reaction only to be a limping model of the biosynthetic reduction step of protochlorophyllide *a* **33** → **22b**, and they present an interesting problem, as this reaction sequence produces identical structures (with respect to the 7,8-stereochemistry) under various conditions.*^{31-31b,83,83a}

2. METALLOPORPHYRINS TO PORPHODIMETHENES

Metalloporphodimethenes (**6**) are generally the first long-lived intermediates in the photoreduction of metalloporphyrins (**2**). Although a dipyrromethene chromophore was concluded earlier for these products, direct proof was not obtained until recently.⁵⁶ Photoreduction of the α,γ -dimethylporphyrin **29b** yielded two spectroscopically similar isomers (**31a**, **b**). One of them (**31b**) is easily reoxidized to the starting material, while the other isomer could be isolated and identified by ¹H nmr as the β,γ -porphodimethene **31a**. It is suggested that both the α,γ - (**31b**) and the β,δ -isomer (**31a**) were formed, but that only the latter one is stabilized for steric reasons.⁵⁶ The formation of two isomeric porphodimethenes from Zn phylloerythrin methyl ester (**35**) as well is suggested from ¹H/²H exchange experiments and from the careful analysis of the reoxidation products.^{31b} In the β,δ -porphodimethene, the isocyclic ring is considerably stressed. This is manifested by the isolation of the rhodochlorin **37b** among the products in about 5% yield, which results from rupture of the C- γ to C-10 bond instead of a C-H bond.



37b

The photoreduction of Zn-etio has been investigated at low temperature.²⁷ At first a phlorin anion (= porphodimethene anion **3**) is formed, which upon

* Nothing is known as yet on the stereochemistry of the products obtained by reduction of Sn(IV) (OEP).^{23,24}

warming is protonated to the porphodimethene. Although the products are only characterized by their uv-vis spectra, the characteristic absorptions of the products and the striking analogy to the reductive protonation^{26,28} make these assignments of the structure tempting. The most interesting finding is the light-induced deprotonation of the porphodimethene back to the anion, which is again thermally reprotonated. This process stabilizes the anion in the light, allowing it to thus react separately from the dimethene.

3. METALLOCHLORINS TO METALLOCHLORINPORPHODIMETHENES

The photoreduction of metallochlorins is principally very similar to that of metalloporphyrins. The hydrogenation of the 7,8-double bond is, with respect to the photochemistry, probably only a minor perturbation. In its original work,⁶⁵ Krasnovskii reports the formation of a pink product ($\lambda_{\max} = 523, 411$ nm) upon illumination of a pyridine solution of Chl *a* in the presence of ascorbic acid. The assignment of both absorption bands to one product is probable from recent ¹H nmr experiments, which showed formation of a single product only ($\geq 90\%$).⁶⁶ This product is probably formed by the following sequence.^{69,87}

(a) Electron transfer from the ascorbate anion⁷⁰ and formation of a short-lived ($< 10^{-2}$ sec) Chl-radical anion* with $\lambda_{\max} = 475$ and 745 nm.^{73,93-97}

(b) Proton transfer from the protonated base⁷⁰ and formation of a monohydrochlorophyll with $\lambda_{\max} = 480$ nm. †^{93,98,98a,99}

(c) Repetition of processes (a) and (b)¹⁰⁰ to form the pink product. This latter process is favored by kinetic data,¹⁰⁰ but there are indications of a disproportionation step of the monohydrochlorophyll⁹⁴ similar to the one observed with phlorins.¹⁰¹ Even in the absence of oxygen, this reduction is reversible in the dark, and the latter product could not yet be isolated from the reaction product in pure form. The proposed β,δ -dihydrochlorophyll structure⁸⁸ (**34** = 7,8-chlorin- α,γ -porphodimethene) was proved, however, by carrying out the reduction directly with H₂S in the nmr tube.⁶⁶

(d) The reduction requires water or other proton donors.^{72c,73,102}

(e) Due to the lability of magnesium in the dihydroproduct, pheophytinization is a frequent side reaction,¹⁰²⁻¹⁰⁴ and, in fact, photopheophytinization is believed to always involve intermediate photoreduction.^{87,105}

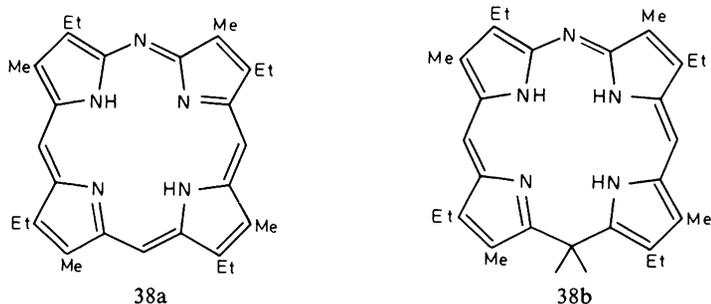
* A direct observation of the anion radical of the pigments⁸⁸ during the photoreduction was not yet possible, while signals of the reducing agents, ascorbic acid,⁸⁹ and hydroquinone⁹⁰ are well studied.^{91,92}

† In analogy to the intermediates observed during the reductions with aromatic radical anions,^{26,28} and the photochemical reduction of porphyrins,²⁷ a phlorin-anion structure **3** is probable for the intermediate with $\lambda_{\max} = 475$ and 745 nm in the Krasnovskii reduction as well.

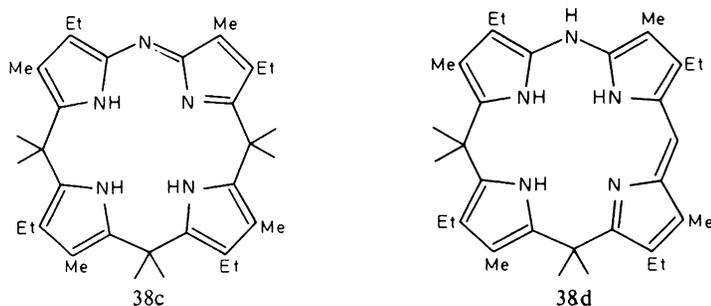
4. PORPHYRINS TO PHLORINS AND PORPHOMETHENES

The reduction sequence porphyrin (**1**) \rightarrow phlorin (**5**) \rightarrow porphomethene (**10**) has been observed under various reaction conditions and over a wide pH range from neutral¹⁴ to highly acidic.^{71,106} The reaction gives usually high spectroscopic yields, and the only major side reaction is formation of iso-bacteriochlorins.¹⁰⁶ Porphomethenes can be isolated in pure form and were studied directly.⁷¹

The phlorin structure for the first long-lived intermediate in the photo-reduction of porphyrin-free bases was first established by Mauzerall.¹⁴ This conclusion was drawn from redox titrations, and from the characteristic¹⁰⁷ pH-dependent spectral changes of the formed dihydro product. Recent ¹H/²H exchange experiments^{75,76} were interpreted on the same basis, involving an intermediate formation of a phlorin. For the primary reduction product of the monoazaporphyrin **38a**,¹⁰⁸ the γ -phlorin structure **38b** has been



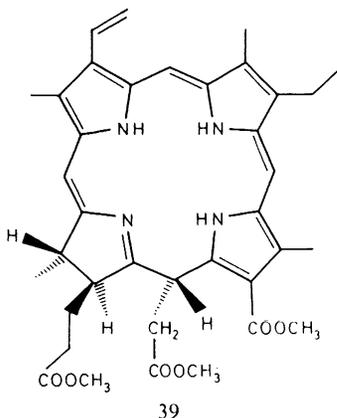
proposed.⁷⁶ By kinetic analysis, it has been demonstrated recently^{108a} that the phlorin radical formed as the initial product of TPP photoreduction undergoes a light-dependent dimerization. The dimer is suggested as the immediate precursor of TPC (and TPP), which is obtained in the TPP series instead of the phlorin. The preparation and chemistry of phlorins is discussed in detail in Chapters 3 and 4.



Upon longer reaction, porphyrin-free bases are reduced beyond the phlorin stage to porphomethenes. The structure was again established first by a combination of redox and acid-base titrations,¹⁴ and recently supported by isotope exchange experiments^{75,76} and by direct ¹H nmr and ir measurements.⁷¹ The reduction of the monoazaporphyrin **38a** yields two isomeric porphomethenes¹⁰⁸ for which the α -methene (**38c**, $\lambda_{\max} = 545$ nm) and the β -methene structure (**38d**, $\lambda_{\max} = 510$ nm), respectively, have been proposed on the basis of ¹H/²H exchange studies.⁷⁶

5. PHOTOREDUCTION OF CHLORINS

The photoreduction of chlorin-free bases gives rise to two principal products. In a comparative study of various chlorins, these primary products, as well as some of their reaction products, were characterized by their absorption spectra.¹⁰⁹ Chlorins without an additional isocyclic five-membered ring yield one product only. It shows an absorption at 525 nm in neutral solution and at about 610 nm in acidic medium. Upon admission of air, products with bacteriochlorin-type absorptions are obtained. The product obtained from chlorin-e₆ trimethyl ester **20** could recently be isolated and characterized by ¹H nmr as the 7,8-chlorin- γ -phlorin **39**.⁷⁸ This isomer is



probably again stabilized against oxidation for the same steric reasons discussed for the porphodimethenes. It is noteworthy, however, that electrochemical reduction of the same chlorin **20** yields solely an isomer of **39**, which is reduced at the β -position (see Sections II, C and III) and which was shown to be stabilized for steric reasons, too.¹¹⁰ In the case of pheophorbides (namely, chlorins containing an isocyclic five-membered ring), the chlorin-phlorin is no longer stabilized and could only be observed spectroscopically. In addition to it, a second, yet uncharacterized, product is formed with a

broad absorption peaking at 580–600 nm.¹⁰⁹ The reduction of chlorins in acidic media was studied spectrophotometrically for a variety of educts.^{72a,74} Among other structures, the formation of isomeric chlorin porphodimethene dications (chlorinphlorin dications) was discussed. The isomerization of reduced chlorins to porphomethenes (**9** → **10**) leads to porphyrins in the reoxidized reaction mixture.¹⁴

6. FORMATION OF BACTERIOCHLORINS

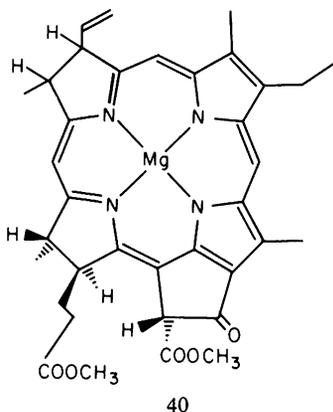
Besides the chlorins, bacteriochlorins are the second major group of naturally occurring hydrophorphyrins. The last steps in bacteriochlorophyll biosynthesis are not yet well understood, but there is no evidence that light-induced reactions are involved. Bacteriochlorin type pigments are observed, however, as by-products in many *in vitro* photoreductions, and in at least one case, the main product belongs to this class of compounds.

Bacteriochlorins, strictly speaking, have two peripheral double bonds reduced at opposite pyrrole rings (**13**). The parent compounds of this class are the bacteriochlorophylls *a*¹¹¹ and *b*.⁴¹ The isomeric isobacteriochlorins ("cis"-bacteriochlorins, **12**) are often encountered as synthetic products, and recently this chromophore has been found in the sirohemes,^{1b} which are present in sulfate and nitrate reductases.^{1a} The identification of bacteriochlorins in complex reaction mixtures is facilitated by their characteristic long wavelength absorption, while isobacteriochlorin pigments ($\lambda_{\max} \approx 620$ nm) are likely to be obscured by other bands.

Reduction products with absorption spectra of true bacteriochlorins were first observed by Byteva *et al.*¹¹² and by Krasnovskii and Voinovskaya.¹¹³ Similar by-products of photoreductions were occasionally observed by other investigators,⁷⁹ but to our knowledge none of them has been analyzed for their molecular structure. The formation of bacteriochlorin pigments from several Mg-containing chlorophyll derivatives was studied in some detail.¹¹⁴ Photoreduction in the presence of air leads to the subsequent formation of two pigments of this type. The results indicate that both of the pigments are formed indirectly by reoxidation of colorless intermediates at a lower oxidation level.

The formation of isobacteriochlorins seems to be favored considerably with respect to the isomeric bacteriochlorins. Products of this type have been consistently reported for the photoreduction of porphyrins^{1, 23, 25, 115–117} (for the spectral properties, see Seely and Inhoffen *et al.*^{115,117}).

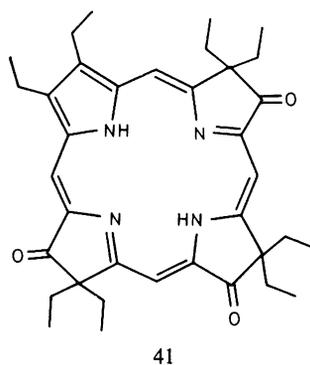
The most carefully investigated reduction to isobacteriochlorins is the formation of hypochlorophyll *a* (**40**) from chlorophyll *a* **24**.¹¹⁵ The reduction proceeds in high yield, and the structure **40** for hypochlorophyll was suggested mainly on the basis of absorption spectra and redox titrations. However,



proof of the structure by more detailed methods like ^1H nmr is desirable. Of special interest would be the stereochemistry of the additional hydrogens at ring A, as 7,8-*cis*-chlorins are formed under similar conditions from metalloporphyrins.^{31a,82} Chlorophylls without the 2-vinyl group do not undergo the hypochlorophyll reduction, and attempts to obtain the free base hypochlorin by demetalation were unsuccessful.¹¹⁵

7. FORMATION OF HYPOBACTERIOCHLORINS

The formation of hexahydro compounds with the hypobacteriochlorin chromophore (**14**) was suggested by Seely and Calvin.¹ In the reduction of Zn-TPP with photoactivated benzoin, formation of a product with a chlorin-type absorption ($\lambda_{\text{max}} = 642, 425 \text{ nm}$) was observed. It forms upon prolonged irradiation of the isobacteriochlorin (**12**), and can be reoxidized in high yield to the latter. The structure proposed was based on the absorption spectrum,



and this assignment is supported by the chlorin-type spectra observed for geminiporphin triketones, namely, **41**.¹¹⁸ Similar products are encountered in other studies on the photoreduction of metalloporphyrins, but their instability has precluded thus far a more detailed investigation.

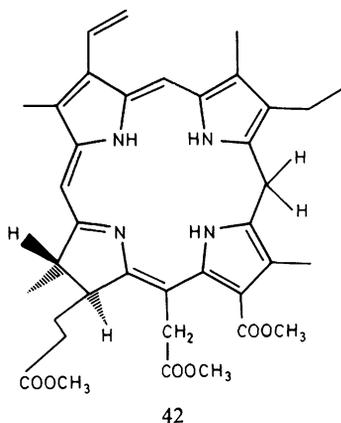
C. Electrochemical Reduction

In the polarographic reduction of porphyrins, three distinct steps have been well established, and there is possibly a fourth one close to the dissociation voltage of the solvent. The first step yields, in a one-electron reduction in aprotic solvents, the radical anion.^{29,48,49,119,120,121} In protic solvents, this electron transfer is thought to be followed rapidly by a proton transfer, thus yielding a neutral radical.^{48,49} This hypothetical intermediate is unstable, however, and the first detectable reduction product is a phlorin.* Thus, the first polarographic step in protic solvents is a two-electron reduction.¹²²⁻¹²⁴ It has been shown that porphyrin-free radicals generated photochemically disproportionate rapidly into porphyrin and phlorin.¹⁰¹ A similar disproportion close to the electrode would account for the polarographic result. A subsequent polarographic step has been characterized in protic solvents,¹²⁴ but the structure of the product is not known. The anion radicals of chlorophylls and pheophytins have been obtained by electrochemical reduction of the parent pigments.^{88,120,121}

Phlorins can be produced electrochemically in good yield by reduction at a controlled potential.^{48,49} They are easily reoxidized to the parent porphyrins, but their structure has been established^{48,49} from their characteristic^{10,14} uv-vis absorption spectrum, from coulometric studies, and from ¹H/²H exchange experiments. In a similar reaction, chlorinphlorins are produced from chlorins. The required potential is about 100 mV less negative† for the chlorin ($E_{1/2} \approx -0.5$ V) than for the porphyrins ($E_{1/2} \approx \leq 0.6$ V for etio-type porphyrins), but it varies considerably with the peripheral substitution.¹¹⁰ Stability and structure of the chlorinphlorins show large variations, too, depending on the structure of the chlorin educt.¹¹⁰ Sterically nonhindered chlorins without an isocyclic ring form a mixture of isomeric chlorinphlorins with a half-life on the order of minutes to hours, while sterically hindered chlorins like chlorin-*e*₆ trimethyl ester (**20**) form exclusively 7,8-chlorin- β -phlorins (namely, **42**), which are stable for days. Selectivity and stability in the latter case can be rationalized by the model of the overcrowded periphery.^{14,107} However, 7,8-chlorin- γ -phlorins are produced photochemically with a similar degree of selectivity, and their similar high stability has been accounted for by the same model.⁷⁸ The choice between the two attacks leading to products of comparable

* For the reactivity of phlorins, as studied by electrochemical methods, see Chapter 2.

† Polarographic half-wave potentials in methanolic HCl buffered with aniline.



stability, namely, at C- β and C- γ , are probably governed by the electronic structure of the anion radical. In the electrochemical reduction, this primary product is formed in the ground state, in the photoreduction it is produced in the excited state. In the chlorins, the relative electron densities vary considerably between the ground¹²⁵⁻¹²⁸ and first excited singlet and triplet states,^{127,128} but no comparable calculations have been made for the anion.

Very short-lived chlorin phlorins are produced from pheophorbides,¹¹⁰ namely, chlorins with an isocyclic ring between C-6 and C- γ . ¹H/²H exchange experiments indicate the reduction at the position corresponding to the middle methine ¹H nmr signal,¹¹⁰ i.e., the α -position.^{129,129a}

III. STEREOCHEMISTRY

To a large extent, stereochemistry of hydroporphyrins has been the stereochemistry of chlorophylls and related structures (see also Chapter 9). The majority of stereochemical information has been drawn from degradation experiments (Chapter 9) and spectroscopic studies, especially from nmr³ and ORD/CD¹³⁰ spectroscopy. Compared to the well over 100 X-ray analyses of true porphyrins (for recent reviews, see Hoard¹³¹ and Fleischer,¹³² and Volume III, Chapters 10 and 11), only few crystal data are available for the (less readily crystallizing) chlorins.^{43,133-136} The stereochemistry of porphodimethenes has been studied by Buchler *et al.*,^{28,137} and some attention has been focused on chlorinphlorins.^{78,110} Conformation studies of β -pyrrolic substituents in solution have been reviewed recently.³ For crystal structural studies, the reader is referred to Volume III, Chapters 10 and 11 and Hoppe *et al.*,⁴³ Hoard,¹³¹ Fleischer,¹³² Fisher,^{133,134} Strouse,¹³⁵ and Kratky and Dunitz.^{135a}

A. The Macrocycle

The macrocycle in the fully unsaturated porphyrins has been shown to be rather flexible. Planar structures are an exception, and the macrocycle shows generally regular deviations from planarity which are described, for example, as domed, or ruffled, and by which any steric strain is evenly distributed over the entire macrocycle.^{28,131,132} The flexibility of the macrocycle is further supported by markedly different structures for a single compound in different crystal forms,^{138,139} by large thermal out-of-plane motions of the atoms of the ring system^{132,139} and by pronounced distortions upon local steric perturbations (for leading references, see Scheer and Katz,³ and Strouse¹³⁵). In contrast to the rather flexible macrocycle as a whole, however, the individual pyrrolic subunits in all porphyrins are nearly planar, thus underlining Woodward's concept of the aromatic subunits (see below).^{15,107} Even in porphyrins with an "overcrowded periphery,"^{15,107} the pyrrolic subunits remain essentially planar in spite of considerable local distortions.¹⁴⁰ This concept was the key in understanding the selective formation of 7,8-chlorins and γ -phlorins in the course of Woodward's chlorophyll synthesis (see Section II, A, 1).¹⁵ In the former ones, the β -pyrrole positions C-7 and C-8 are sp^3 hybridized, in the latter ones the bridging C- γ . In either case, the substituents come out of plane, and the quaternized carbon atom becomes more flexible, thus relieving the steric strain. Recent examples to underline the same principle include the stabilization of *meso*-substituted porphodimethenes^{28,52,56} and chlorinphlorins.^{78,110}

In the chlorins, the macrocycle is perturbed by the hydrogenation of one of the peripheral double bonds. By this means, ring D is no longer an aromatic subunit. Thus, pronounced deviations from planarity are observed in this region, not only for the substituents, but also for ring D itself. Thus far, the main interest in chlorin stereochemistry has focused on chlorins closely related to chlorophylls. A series of related metal-free chlorins^{43,133,134} and more recently on their Mg complexes¹³⁵ have been investigated by X-ray analysis.

In the Fischer notation (cf. compound **28**) the chlorophylls are reduced at C-7 and C-8 (C-17 and C-18), but they also have an additional substituent at C- γ (C-15) (IUPAC notation in brackets). In all these compounds, the steric interaction of the γ -substituent with the β -pyrrole substituents at the neighboring C-6 and C-7 is, therefore, an additional strong perturbation, which impedes inferences on the steric consequences of the reduced double bond. Substitution at C- γ leads to a pronounced dissymmetry in the region of the γ -7a bond. The γ -substituent is forced out of plane to one side, the 7-carbon to the opposite side of the macrocycle (Fig. 1). As all natural chlorins are chiral, the twist of the γ -7a double bond is chiral, too. Due to the

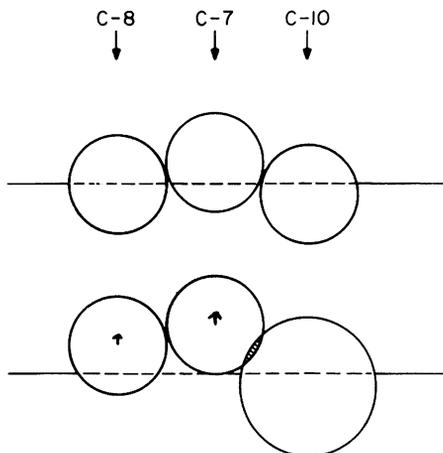


Fig. 1. Steric hindrance of a bulky substituent at C- γ with ring D substituents in chlorins. Schematic drawing of a chlorophyllide (cf. 37), and of a strongly hindered chlorin like the peripheral metal complex 43. For numbering see formula 28.

bulky propion ester side chain situated “above” the plane (7*S* configuration),¹⁴¹⁻¹⁴³ C-7 is pushed “up,” too, while C- γ comes below the plane.¹³³ The twist of the 7 α - γ bond and of the adjacent bonds render the macrocycle inherently dissymmetric (Fig. 2). This is indicated from the chiroptic properties of pheophorbides,¹³⁰ and reflected in the X-ray analysis.^{43,133-135} The basic features of the ORD/CD spectra are determined by the chirality of C-7, while substituents and chirality of the asymmetric C-8, 9, and 10 yield incremental contributions superimposed on the spectrum of the inherently dissymmetric chromophore.¹³⁰

The increased flexibility of the reduced ring D was first demonstrated by ¹H nmr studies of δ -substituted chlorins.^{129a,143a,144} Introduction of a bulky substituent into this position in pheophorbides leads to pronounced incremental chemical shifts of proton resonances arising from ring D substituents,

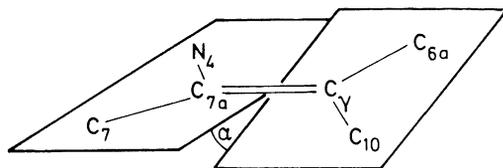
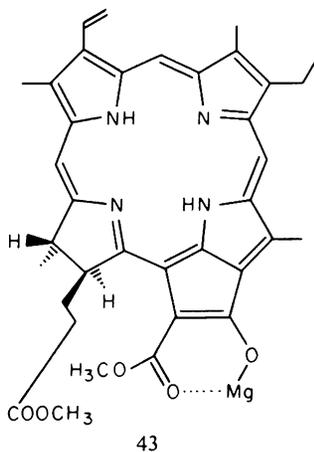
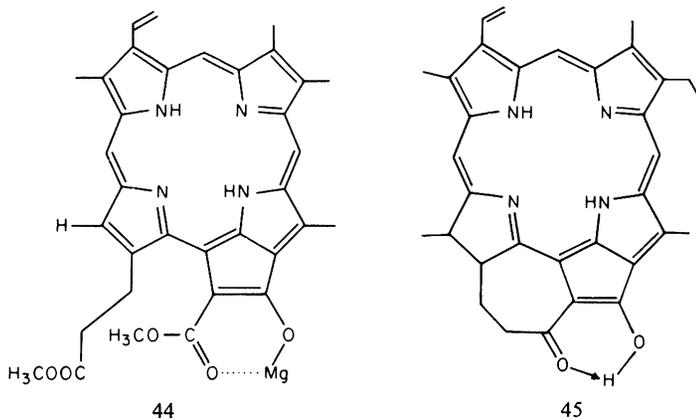


Fig. 2. Twist of the C- γ , C-17 double bond due to the steric hindrance of the “substituents” C-10 and C-7. Schematic drawing of a partial structure; for numbering see formula 28.

which have been interpreted as arising from a conformational change of ring D. Similar induced conformational changes have recently been observed as the result of increased steric interaction with the γ -substituents in peripheral metal complexes of porphyrins.¹⁴⁵ Stability differences in these enolic structures seem to be mainly due to a varying degree of steric hindrance. The complex **43** of methylpheophorbide *a* is stable in the absence of strongly



competing ligands for magnesium.¹⁴⁵ Under the conditions where equilibrium amounts of the free ligand methylpheophorbide *a* are below 2%, the strongly hindered pheoporphyrin complex **44** exists only in a 1:4 equilibrium with the free ligand.¹²⁴ On the other hand, the *s-cis* β -diketone **45** is enolized even in the absence of chelating metal ions.¹⁸⁸ Spectroscopic differences observed between the natural 7,8-*transoid* chlorins and their *cisoid* isomers are a further



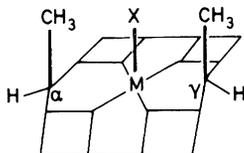


Fig. 3. Stereochemistry of α,γ -dimethyloctaethyl- β,δ -porphodimethenes and their metal complexes. Schematic drawing according to Buchler *et al.*¹³⁷

indication of the enhanced flexibility of ring D.^{31a,130} ^1H nmr signals originating from protons in ring D may show pronounced differences, while other signals are shifted uniformly and to a lesser degree.^{31a} All available X-ray data support this interpretation of a more flexible ring D. They show pronounced deviations from planarity in ring D, allowing a local relief of steric strain.^{43,133-135} In contrast, ring D is planar in the corresponding pheophorphyrins, and the steric strain is dissipated over the entire macrocyclic system.¹⁴⁶

The stereochemistry of dimethylporphodimethenes has been investigated in some detail by Buchler *et al.*^{28,52,147} α,γ -Dimethyl- β,δ -porphodimethenes are stabilized against reoxidation (rearomatization) by steric interaction of the *meso*-methyl groups with the β -pyrrole substituents in the parent porphyrins. This is yet another example of Woodward's thesis of the "overcrowded periphery,"¹⁵ which was invoked from ^1H nmr data,^{28,52} from a comparative study between two isomeric dimethylporphodimethenes,⁵⁶ and which has recently been proved by X-ray analysis.¹³⁶ The macrocycle of the two porphodimethenes of type **30b** ($\text{M} = \text{Ni}, \text{TiO}$, respectively) is folded like a gabled roof along the two reduced bridging C atoms. The two methyl groups are cisoid to each other and in "chimney"¹³⁷ (*exo*) positions, and the central metal with the fifth ligand occupies a chimney position as well.¹³⁶ The details of this structure are then mainly determined by the size and preferential coordination of the central metal²⁸ (Fig. 3).

Some aspects of the stereochemistry of chlorin phlorins were inferred from the selective formation of chlorin- β -phlorins (namely, **41**) during electrolytic reduction of chlorin- e_6 and related structures. Space-filling models show that, by this means, the steric relief at the periphery is probably even larger than by sp^3 hybridization of C- γ .¹¹⁰ However, a respective γ -phlorin (**39**) has been obtained with a similar degree of selectivity by a photochemical reduction.⁷⁸ The steric concept is supported by the formation of isomeric chlorinphlorin mixtures upon reduction of chlorins lacking the 6- or γ -substituent.

B. Metallochlorins

Insertion of a metal into porphyrins gives rise to two additional stereochemical aspects; the metal ion can be out of the plane of the macrocycle,

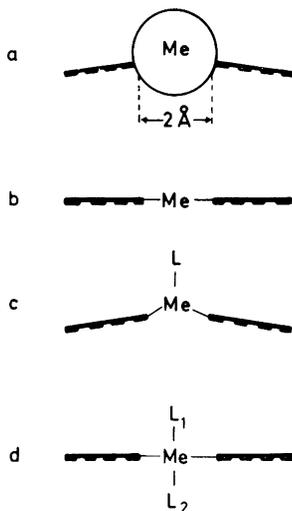


Fig. 4. Stereochemistry of metallochlorins. Metal ions with a diameter considerably larger than 2.01 Å, which do not fit into the central 4-N cavity (a), metal ions with a diameter ≤ 2.01 Å and a coordination number of four (b), five (c), and six (d). In porphyrins without σ_h plane (cf. in all chlorophylls), isomers are possible in the cases a and c, and in case d with different axial ligands, depending on the orientation of the metal with respect to the two faces of the macrocycle.

and it can be ligated in various distinct ways. In chlorins (and other hydrophorphyrins), the possible nonequivalency of the two sides of the macrocycle gives rise to a third problem (see Fig. 4). If the metal is out of plane, or if it is ligated with two different extra ligands, isomeric structures will be formed depending upon their orientation with respect to the two nonequivalent sides of the macrocycle. In the crystal structure of both chlorophyll *a* and *b*, the central Mg is five coordinate and displaced “below” the macrocycle if written in the normal way (i.e., on the same side as the 7-H, the 8-CH₃ and the 10-COOCH₃ groups).¹³⁵ No example of this kind of isomerism is known as yet in solution, although it may play a key role in chlorophyll aggregation¹⁴⁸ (see Volume V, Chapter 9).

Metals with an ionic radius not significantly larger than 2.01 Å fit principally without distortions into the central cavity of the porphyrin macrocycle.¹³¹ All metals commonly encountered in chlorins, especially Mg being present in all chlorophylls, belong to this class. In this case, the type of ligation essentially determines whether the metal is in plane or out of plane (Fig. 4). In a symmetric ligand field (no or two similar extra ligands), the metal is in plane. With only one extra ligand, or with two different ligands, the metal is usually positioned out of plane. For five coordinate Mg chlorins with

pyridine as the axial ligand, a displacement of 0.7–0.8 Å from the mean plane of the macrocycle has been estimated by ^1H nmr.¹⁴⁹ X-Ray analysis of methylchlorophyllides *a* and *b* yield similar structures that have the Mg about 0.45 Å out of the mean plane.¹³⁵ In addition, they show a regular, bowl-shaped deformation of the macrocycle, with the four nonbonding N orbitals directed toward the metal. This type of macrocyclic distortion (Fig. 4) is commonly encountered in metalloporphyrins with the metal situated out of plane.

The coordination type of Mg chlorins was first investigated by Miller and Dorough¹⁵⁰ and in some detail by Fried and Sancier.¹⁵¹ The equilibrium between five and six coordination is temperature dependent.¹⁵¹ Katz *et al.*¹⁵² derived from ^1H nmr data equilibrium constants for the formation of the monosolvate of chlorophyll *a* with alcohols, which are about 100 times larger than for the disolvate. The preferential five coordination of chlorophylls is also manifested in chlorophyll aggregates, which arise from ligation of the central Mg of one molecule, preferentially with the peripheral 9-carbonyl group in another molecule^{3,148} (for details, see Volume V, Chapter 9). Recently, a shift of the orange band in the uv-vis spectrum of bacteriochlorophyll *a* from 580 to 610 nm could be related to the change from coordination number five to six,¹⁵³ and related spectral shifts have been observed as well for chlorophylls *a* and *b*.¹⁵³

C. Asymmetric Centers

In many cases, the formation of hydroporphyrins is accompanied by the formation of asymmetric C atoms. Research in this field was focused again predominantly on chlorophylls, which can have asymmetric C atoms at C-2a, C-3, C-4, C-7, C-8, and C-10* (Fig. 5). In addition, a variety of modified

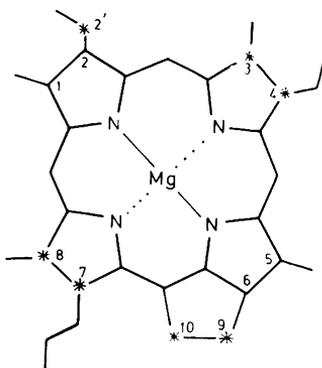


Fig. 5. Location of asymmetric C-atoms (*) studied in chlorophylls and their derivatives.

* Phytol has two additional asymmetric centers at C-P7 and C-P11.¹⁵⁴

or synthetic chlorins with nonnatural configurations or additional asymmetric C atoms have been investigated in the past decade.^{3,130}

C-7, C-8. Chlorophylls of the chlorin series (chlorophylls *a*, *b*, and *d*) contain two asymmetric centers at C-7 and C-8, and usually* a third one at C-10. All natural chlorins, as well as those obtained under equilibrating conditions, have the thermodynamically favored^{15,19,157,158} 7,8-*trans* configuration.† The (relative) *trans* configuration of C-7 and C-8 was first suggested from racemization experiment.^{157,158} It was supported by the outcome of the synthesis of Chl *a*, in which the natural isomer (as racemic mixture) was formed under equilibrating conditions,¹⁵ by the small ¹H nmr coupling constant of the "extra" hydrogens at C-7 and C-8,¹⁵⁹ and by the induced conformational changes of ring D upon substitution introduction of bulky γ -¹⁴⁵ or δ -substituents.^{143,143a} The chemical proof of the 7,8-*transoid* configuration was achieved by chromic acid degradation¹⁴¹ to *trans*-disubstituted succinic acid derivatives. The absolute configuration at C-7 and C-8 has been determined by the same oxidative degradation method. By correlation with hematinic acid derived from (–)- α -santonine,¹⁴² and with hydrocarbons of known absolute configuration,¹⁴³ the chlorin C atoms were shown to be 7*S*, 8*S* configured. Recently, the same conclusion has been drawn¹⁶⁰ by applying a modification of Horeau's¹⁶¹ method on 9-hydroxypheophorbides of the *a* series.^{162,163}

7,8-*cis*-Chlorins are obtained from the corresponding (metallo) porphyrins by chemical reduction with typical *cis*-reducing agents as well as by photochemical hydrogenation (Section II, B, 1). *cis*-Chlorins are thermodynamically less stable than the corresponding *trans* isomers. This is due to steric hindrance of the *cisoid* substituents and is manifested by a bathochromic shift of the uv-vis spectrum,^{17,19,20,31–31b} a more pronounced dehydrogenation in the mass spectrometer,^{20,31–31b} and by a more ready oxidation with quinones.^{17,20} The ¹H nmr spectra of *cis*-chlorins show generally a slight reduction of the aromatic ring current as compared to the *trans* isomers, but the spectral differences are mostly dominated by neighboring group effects in the vicinity of the reduced pyrroline ring.^{31a} The ORD/CD spectra of pheophorbides are comparably insensitive to the relative configuration of C-7 and C-8, but the sign of the major π - π^* transitions is determined by the absolute configuration at C-7. This striking feature has been interpreted in terms of an inherently dissymmetric chromophore¹³⁰ (see above).

* The bacteriochlorophylls *c*, *d*, and *e* have an asymmetric C-2a instead.^{155,156}

† In the following the shorter but less precise terms "cis" and "trans" are used instead of "cisoid" and "transoid," respectively.

C-9, C-10. The *trans* configuration of *C-7* and *C-10* was deduced from a combined ^1H nmr and ORD/CD investigation of *C-10* mono- and disubstituted methylpheophorbides.^{164,165} From systematic variations of the *C-10* substituents in pheophorbides of the *a*¹⁶⁴ and *b* series,¹⁶⁵ characteristic increments of the neighboring proton chemical shifts and the ORD/CD amplitudes have been derived. Both methods can be used independently and were recently reviewed.^{3,130}

The same methods that have been used to link the stereochemistry at *C-10* with that at *C-7* and *C-8* can be used to link the stereochemistry of *C-9* with that at *C-10*. In the chlorophylls, *C-9* is *sp*² hybridized and, thus, achiral. Reduction of the 9-CO group to a CHOH group yields *C-9* stereoisomers, however, which have been studied in some detail.^{160,162,163} The increments of the 9-OH group to the ORD/CD spectra is much less pronounced than that of *C-10* substituents, but the configuration at *C-9* can be deduced by ^1H nmr and ir spectroscopy.^{162,163} In all the *C-9* alcohols, H-bonds are observed between the 9-OH and the *C-10* carbomethoxy, the *C-10* alkoxy, or the *C-7c* propionester group, respectively (Fig. 6). Identification of the bridge-head substituents can then be used as additional aid for the configuration assignment, besides the chemical shift argument.

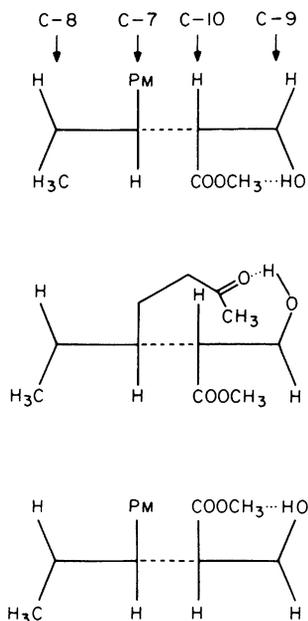


Fig. 6. Hydrogen bonds between substituents at *C-7*, *C-9*, and *C-10* in 9-desoxo-9-hydroxypheophorbides. Schematic drawing of the periphery, viewed parallel to the macrocyclic plane, and parallel to the axis through *C- α* and *C- γ* .

D. Configurational Stability

The formulation of possible chlorophyll structures containing asymmetric C atoms¹⁶⁶ focused some interest on their optical activity. In the first study, Stoll and Wiedemann¹⁶⁷ did demonstrate chlorophylls to be optically active, but they also noticed an extremely easy racemization of their samples. The subsequent investigations of Fischer and Stern¹⁶⁸ did support the optical activity, but they found it to persist over extended times and during extensive transformations of the molecule. From the compounds studied, it became clear that the optical activity was due to C-7 and C-8 and that their configuration was stable against refluxing in mineral acidic solutions (transesterification of the propionic acid), heat (pyrolysis to pyropheophorbides), and (in some cases) reduction to porphingens. However, epimerization is possible under alkaline conditions. In strongly basic solutions, all benzylic protons are exchangeable,^{12a} which leads in the case of the "chlorin hydrogens" to configuration equilibration.¹⁵⁷ Only *trans*-chlorins are formed under these equilibration conditions. The loosening of the benzylic "chlorin hydrogens" with strong bases is further demonstrated by the chlorin to phlorin isomerization at high pH.¹⁶⁹

The fate of the asymmetric C-7 and C-8 upon reduction to the porphingens, and their subsequent reoxidation, is still not completely understood. Most leuco compounds investigated by Fischer¹⁶⁸ were found to be inactive, although optical activity was clearly demonstrated in at least one case (leucomesopurpurin-7-trimethyl ester). With the early analytical equipment, no decision could be made as to whether the optical activity was retained in the mesopheophorbides obtained by catalytic hydrogenation and subsequent reoxidation of pheophorbides.¹⁷⁰ Recently, the configurational stability of C-7 and C-8 has been demonstrated for mesopheophorbides obtained by this procedure (as well as for pheophorbides isolated as by-products from the HI-isomerization).^{31a,31b,82} The results obviously prove the presence of "chlorinogens" with asymmetric C-7 and C-8 as intermediates. It is not clear, however, if they convert to porphingens, and both are oxidized separately to the respective chlorins and porphyrins, or whether a common "chlorinogen" is oxidized to a different degree. The results also indicate that re-reduction of the porphyrin during reoxidation is not important in this system. Reactions of this type have been demonstrated⁸ to account for the formation of tetraphenylchlorin during the Rothmund reaction.³²

C-10. When chlorophyll *a* is chromatographed, it is always accompanied by a minor band of a pigment that has very similar spectral properties and which was, therefore, termed Chl *a'*.¹⁷¹ Both Chl *a* and *a'* are rapidly inter-

convertible to an equilibrium mixture of about 7:1, and they have been identified by ^1H nmr as the 10(*S*) and 10(*R*) epimers,^{172*} respectively. Similar configurationally labile epimers have been found for other chlorophylls and pheophorbides containing an enolizable β -ketoester system, and even in cases where a chromatographic separation is not possible, satellite lines in the nmr spectra indicate the presence of prime pigments.^{165,172} In most chlorophylls (except for the bacteriochlorophylls *c*, *d*, and *e*^{155,156}) C-10 is asymmetric and part of an enolizable β -ketoester system. In neutral solutions, the equilibrium is almost entirely on the side of the diketo form. Even under these conditions, however, C-10 epimerizes at room temperature within hours, and the equilibration has been followed by ^1H nmr.¹⁷² The epimerization is greatly enhanced in the presence of base, by which means the equilibrium concentrations can be changed as well. In view of the easy epimerization it is surprising, however, that the C-10 epimers of chlorophylls can be separated by chromatography on powdered sugar, and the reepimerization followed by ^1H nmr. The isolation of an optically active protochlorophyll *a* (**33**) has been reported by Sauer *et al.*¹⁷⁵ In **33**, C-10 is the only asymmetric center, thus the racemization must be slow under the workup conditions. This indicates a considerably enhanced stability of C-10 in **33** (a porphyrin) as compared to **28** (a chlorin), which is probably due to the steric destabilization of the enol intermediate. This conclusion is supported by a similar destabilization of the peripheral complexes of protopheophytin *a* (**44**)¹⁷⁴ (see above).

The configuration at C-10 in pheophorbides can be stabilized by removal of either one of the carbonyl groups, or by substitution of the enolizable proton at C-10.¹³⁰ 10-Alkoxyethylpheophorbides are configurationally stable under most conditions. They were, therefore, investigated in some detail to evaluate the chiroptical and ^1H nmr properties of the pure C-10 epimers.¹⁶³⁻¹⁶⁵ In strongly acidic solution the configuration is unstable, however, and, from isotope labeling experiments, an $\text{S}_{\text{N}}2$ type inversion has been suggested¹⁶³ for the acidic alcoholysis. 10-Alkoxyethylpheophorbides, in which the 10-carbomethoxy group is removed, can be oxidized to porphyrins with retention of the C-10 configuration.^{31a} Epimerization in the presence of base is probable, however, because the 10-protons in pyromethylpheophorbide *a* are easily exchangeable in refluxing pyridine.^{39,176} Upon reduction of the 9-carbonyl group, the configuration at C-10 is stabilized toward bases, but is again unstable in strongly acidic media.^{162,163}

* Recently, an enolic chelate structure was proposed for the primed pigments on the basis of uv-vis spectra.¹⁷³ This structure seems unlikely both on the basis on the nmr evidence for the 10-epimer formulation, and in view of the dramatically different spectra of chlorophyll enolates¹⁰ and peripheral Mg chelates.^{145,174}

The C-9 configuration of 9-hydroxypheophorbides is stable against acid, but labile against base.^{162,163} Under the (basic) reaction conditions of the NaBH₄ reduction of the 9-CO group, epimerization at C-9 of the kinetically to the thermodynamically favored epimers has been observed. During this reduction, pheophorbides of unnatural C-10 configuration are formed from methylpheophorbide *a*. This is a clear chemical indication for the presence of minor amounts of the prime pigment in solution, but it is not clear if the observed 10(*S*):10(*R*) ratio of 1:11 in the reduction product does represent the equilibrium concentrations.

IV. CONCLUSIONS

Reductions are an important aspect of porphyrin chemistry both for hydroporphyrin synthesis and for the understanding of the reactivity of the porphyrin macrocyclic system. Hydroporphyrins derived from the principal model porphyrins OEP and TPP are accessible in moderate to good yields by selective chemical reduction. Selective hydrogenation of less symmetrically substituted or more sensitive porphyrins remains difficult. Photochemical and electrochemical methods have been suitable for this purpose, but the wealth of compounds available through photoreduction is still only partly characterized. A detailed product analysis beyond the chromophoric system (by uv-vis spectroscopy) has been possible recently for some systems by the application of ir and especially of nmr spectroscopy, by which structural and stereoisomers can be distinguished. The importance of stereochemical factors, and to some extent of electronic factors, has been emphasized to account for the products, but these rationalizations are often ambiguous and do not yet permit the prediction of products in a reliable way. Further research is desirable to link the selectivity of, and the relations between, the chemical, photochemical, and electrochemical reductions of porphyrins in a more defined model.

The conformational mobility of the porphyrin, and especially of the hydroporphyrin macrocycle, has evolved as a new stereochemical concept. The macrocyclic conformation is determined on one side by the peripheral substitution pattern, the central metal, and the "extra ligands" at the latter, on the other side by the tendency to distribute strain evenly on the π -system. These effects have been studied both in the crystal and in solution. Probably the most exciting example in the past has been the application to the cooperativity in hemoglobin-oxygen binding, and there is accumulating evidence that stereochemistry plays an equally fundamental role in the primary events of photosynthesis.

V. APPENDIX: RECENT STUDIES IN CHLOROPHYLL CHEMISTRY

The last review on chlorophyll chemistry appeared in 1966,¹⁰ and some more recent results have been incorporated in reviews of porphyrin chemistry.^{11,12} This appendix is a brief summary on the chemistry of chlorophylls of the past decade. Most of the work has been carried out on the more stable, more readily accessible, but from the biochemical point of view less interesting metal-free pheophorbides. However, the chlorophyllides (= Mg complexes) are now accessible from almost any pheophorbide by the metalation procedures described in Chapter 2, Section I, A, 3. For the numbering scheme of chlorophylls, see structure **28**.

Reactions at C-2. The 2-vinyl has been degraded to the 2-formyl group with KMnO_4 .¹⁷⁷ 2-Acetyl chl *a* and related products are obtained by oxidation of Bchl *a* with quinones,⁴⁰ or by acid catalyzed isomerization of Bchl *b*.⁴¹

Functionalization of 3-CH₃ and 4-CH₂CH₃. The 3-CH₃ and 4-CH₂CH₃ groups can be functionalized^{45a} via β -oxophlorins¹¹⁰ by the methods described in Chapter 2, Section II, B, 2. Compounds with 4-CHOH-CH₃ groups, or functional groups derived thereof, are accessible, too, from Bchl *b*.⁴¹

7,8-Stereoisomers. Racemization at C-7,8 occurs under the conditions of the Wolf-Kishner reaction.^{157,158} The 7,8-*cis*-pheophorbides are available via oxidation of *trans*-pheophorbides to the respective porphyrins, and photo-reduction of the Zn-complexes.^{31,31a,82,83}

Oxidation at C-9 and C-10. Oxidation at C-10 of methylpheophorbides of the *a* and *b* series with quinones like chloranil leads to 10-alkoxymethylpheophorbides, which can be pyrolyzed to 10-alkoxypropheophorbides.^{164,165} The latter are available directly from propheophorbides via oxidation with thallium-trifluoroacetate.¹⁷⁸ Prolonged treatment with the latter reagent leads further to 9,10-dioxo derivatives.¹⁷⁸ C-9 alcohols are oxidized with CrO_3 to the 9-CO derivatives.¹⁶³ Oxidation at ring E leading to the allomerization products 10-hydroxyphorbides, δ -lactones, anhydrides and the like have been reinvestigated^{9,10,179} and the products characterized.^{180,181}

Reduction of Carbonyl Groups. Selective reduction of the 3-CHO group in derivatives of the Chl *b* series is possible with NaBH_4 .¹⁸² Prolonged reaction leads to a simultaneous reduction of the 9-carbonyl group.^{160,162,163.}

^{182,184} With LiAlH_4 , both the benzylic 3-OH and 9-OH groups are hydrogenolized to the 3- CH_3 and 9- CH_2 derivatives.^{160,183,184} Under these conditions, the 7d-ester (and other $\text{C}=\text{O}$ groups) are simultaneously reduced to alcohols. Tosylation of the latter, and, subsequently, treatment again with LiAlH_4 leads to a 7-propyl substituent.^{183,184} 3- and 9-Desoxo compounds are also available from the respective alcohols via catalytic hydrogenolysis,^{39,82} or with HI .¹⁸⁵ The stereochemistry of 9-hydroxy derivatives of the *a* series,^{162,163} and of polyols derived from pheophorbides of the *a* and *b* series,^{160,184} has been studied in some detail¹³⁰ (see Sections III, C and D). The aggregation^{3,186} and stereochemistry¹⁸⁷ of 2[α -hydroxy]ethylpheophorbides has been investigated (see Chapter 9).

Peripheral Complexes. Peripheral complexes with Mg or Zn bound to the β -ketoester system of ring E are formed in anhydrous solvents with the anhydrous metal salts.¹⁴⁵ Diketo derivatives like **45** form more stable complexes of the same type.¹⁸⁸ The latter diketones are obtained by intramolecular Dieckmann condensation of the 7-propionic ester with the 10-ester. A Δ -9,10 structure has been suggested, too, for the product obtained by Vilsmeier-Haak formylation of Cu-pyromethylpheophorbide *a*.¹⁸⁹

Dimerization. The dimerizations reported so far^{190,191} involve condensation via the 7-propionic ester side chains. Transesterification with diols (glycols) leads to half-esters, which can then be condensed with a pheophorbide free acid by catalysis with dicyclohexylcarbodiimide,¹⁹⁰ phosgene,¹⁹¹ or the like.

Isotope ($^1\text{H}/^2\text{H}$) Exchange. The methine protons of pheophorbides next to a reduced ring are exchangeable with acid.^{155,192} In chlorophylls, they are already (partially) exchangeable in protic solvents like methanol.¹⁹² The β - and δ -protons are exchangeable via reduction to the Krasnovskii product and reoxidation.⁶⁶ The δ , α , and to considerably lesser extent the β -methine protons in pheophorbides not containing the enolizable β -ketoester system are exchanged^{12a} during metalation with Mg-perchlorate.¹⁹³ All benzylic protons are exchangeable with base in the order^{12a} $10\text{-H}^{192} \gg 5\text{-CH}_3^{11,39} \gg 7,8\text{-H}^{157,158} > 3\text{-CH}_3 > 1\text{-CH}_3 \approx 2\text{-CH}_2 \approx 4\text{-CH}_2$. Exchange of other than $10\text{-H}_{(2)}$ is best carried out in the pyropheophorbides due to loss of the 10-COOCH_3 group under the reaction conditions.¹⁷⁶ The 5-CH_3 protons can be exchanged selectively by first exchanging both the $10\text{-H}_{(2)}$ and 5-CH_3 in refluxing pyridine,^{11,39} and then reexchanging the former^{12a} at the conditions of the Wolff-Kischner reduction.^{157,158} No similarly selective methods have been developed for labeling either one of these positions. The latter reaction also leads to racemization at C-7 and C-8 by proton exchange and also to

reduction of the 2-vinyl group.¹⁵⁸ In addition, base catalysis leads to the exchange of enolic protons, viz., the 7b-protons in 7c-esters,^{12a} or the 2a-protons of 2-acetylchlorins.¹⁷⁸ The facile exchange of the 10-protons even in pyro derivatives¹⁷⁶ is due to the combined effect of enolic and benzylic exchange.

Miscellaneous. Pheophorbides substituted at C-8 (e.g., Cl) are accessible by electrophilic substitution of free base pheophorbides,^{125,129,180,189} while metallopheophorbides seem to be less suitable for this purpose.¹⁸⁹ Mono-, di-, and tri-*N*-methylchlorins have been prepared by methylation with methyl fluorosulfonate and methyl iodide, respectively.¹⁹⁴ The oxidation of pheophorbides to porphyrins, with¹⁸⁰ and without^{31a,164} opening of the isocyclic ring, has been studied by several groups. In the porphyrin series, formation of ring E from 6-(β -dicarbonyl)porphyrins,^{195,196} as well as the inverse reaction,^{31b} have been investigated. Aminolysis of pheophorbides leads to rupture of ring E.¹⁹⁷ The "prime" chlorophylls (e.g., chl *a'*) have been shown to be the C-10 epimers of the respective chlorophylls.¹⁷² Separation of chlorophyll homologues has been achieved by charge-transfer chromatography.¹⁹⁸ For redox reactions of chlorins and bacteriochlorins, see this chapter, and Chapter 2. For the introduction of Mg, see Chapter 2, Section I, A, 3. The nmr spectroscopy of chlorophylls and their derivatives has been reviewed³ (see also Chapter 9 and Volume V, Chapter 9). The chiroptic properties of chlorophylls and pheophorbides have been reviewed.¹³⁰

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