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Sparsely substituted chlorins as core constructs in chlorophyll analogue chemistry. Part 1: Synthesis

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Abstract—Five routes to stable chlorins bearing 0 or 1 meso substituents have been investigated, among which reaction of a 9-bromo-1-formyldipyrromethane and 2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin proved most effective. Application of this route afforded metallochlorins [Cu(II), Zn(II), and Pd(II)] including the chlorin lacking any β-pyrrole and meso substituents.

1. Introduction

The dihydroporphyrin, known as a chlorin constitutes the chromophore of plant chlorophylls. In comparison with porphyrins, chlorins absorb more strongly in the red region of the spectrum.[1] The prototypical chlorins are chlorophyll *a* and chlorophyll *b*, whose structure and absorption spectra are shown in Figure 1. The spectra differ owing to the presence of the methyl group or the formyl group at the 7-position. Thus, chlorin spectra can be significantly altered upon modification of even a single substituent. To gain a deep understanding of the effects of substituents on the spectral properties of chlorins requires the ability to prepare chlorins bearing diverse patterns of substituents. To tailor chlorins for use in diverse applications also requires a fundamental understanding of how substituents alter reactivity. A comprehensive treatment of the effects of substituents requires access to chlorins bearing a systematic progression of substituents, beginning with no substituents and proceeding to one, two, or more groups at designated locations. An ultimate objective of this work is to be able to design and synthesize chlorins that exhibit desired spectral and photophysical properties for diverse applications ranging from artificial photosynthesis to photomedicine.

Surprisingly few systematic studies are available concerning the effects of substituents on chlorin properties. The dearth stems largely from synthetic limitations. Two simple routes

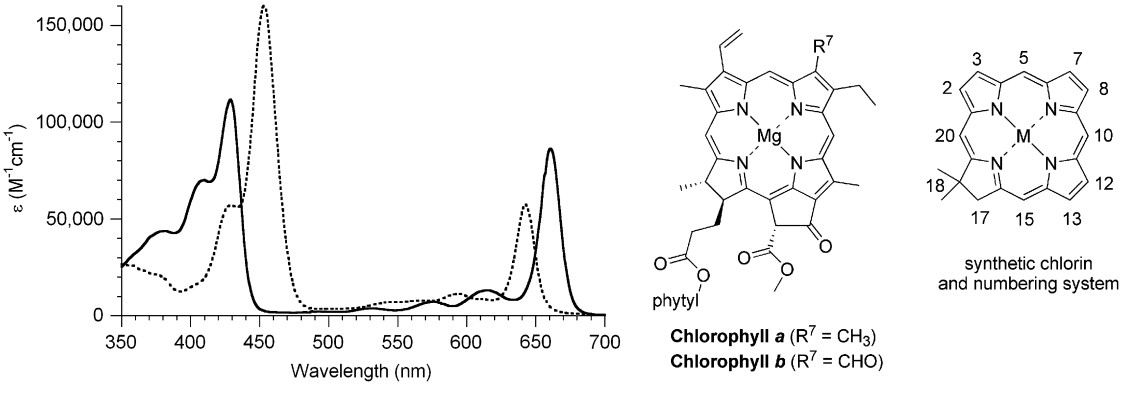

Figure 1. Absorption spectra of chlorophyll *a* (solid line) and chlorophyll *b* (dashed line) in diethyl ether at room temperature.[2] The chlorin numbering system is shown at right.

Keywords: Chlorin; Hydroporphyrin; Hydrodipyrrin; Dipyrromethane.
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to chlorins entail (1) derivatization of naturally occurring chlorins,[3] and (2) reduction/derivatization of synthetic porphyrins.[4] The former route is constrained by the numerous substituents present in the naturally occurring macrocycles. The lack of regioselectivity of the latter route typically limits the scope to the reduction of porphyrins having substitution patterns (giving 4-fold or 2-fold symmetry) wherein regioisomers cannot form. Benchmark chlorins of the latter type include *meso*-tetraphenylchlorin (**H_2TPC**)[5] and octaethylchlorin (**H_2OEC**),[6] which are commercially available, and 5,15-diphenylchlorin.[7] Analogues such as *meso*-tetrakis(3-hydroxyphenyl)chlorin,[8] 2,3-dihydroxy-*meso*-tetraphenylchlorin,[9] and diverse 5,15-diarylchlorins[10] have been prepared for studies of photodynamic therapy.

The chlorin lacking any substituents, 2,3-dihydroporphine (known as 'chlorin' itself, is termed here as **H_2Chlorin**; Chart 1), has been the subject of theoretical calculations[11] and numerous spectroscopic studies.[12–69] The latter include fundamental studies to probe chlorin features, as well as spectral hole-burning experiments to probe the utility of chlorins in optical information storage applications. However, such a potentially valuable benchmark has not been employed for studies of reactivity (other than dehydrogenation[70]), presumably owing to the limited quantities of available material. The only reported synthesis of **H_2Chlorin** entails Grignard-mediated cyclization of 2-(*N,N*-dimethylaminomethyl)pyrrole.[71,72] Photoreduction of zinc porphine affords the corresponding **ZnChlorin**[73] but no preparative procedure has been reported. Regardless, all of the hydroporphyrins shown in Chart 1 are susceptible to adventitious dehydrogenation to give the porphyrin in an aerobic environment, and thus have limited stability toward routine handling in the laboratory.

The naturally occurring chlorins bonellin (a non-photosynthetic pigment) and Faktor I (a biosynthetic intermediate) each contain a geminal dialkyl group in the pyrroline ring, which stabilizes the chlorin to dehydrogenation (Chart 2). Total syntheses of these '*C*-methylated chlorins' and other naturally occurring chlorins have been developed; however, such syntheses are necessarily elaborate owing to the challenges of installing the multiple β-pyrrolic and pyrrolinic substituents.[74]

The methodology developed for preparing bonellin and Faktor I has been extended to gain access to synthetic chlorins bearing more simple substituent patterns (while retaining the geminal dimethyl group).[75–78] Two routes that we developed in this regard include (I) reaction of a 9-bromodipyrromethane-1-carbinol (Eastern half) and a 1,3,3-trimethyltetrahydrodipyrrin (Western half),[76] and (II) reaction of a 9-bromodipyrromethane-1-carboxaldehyde (Eastern half) and the same 1,3,3-trimethyltetrahydrodipyrrin (Western half). The two routes are shown in Scheme 1. The Western half incorporates a geminal dimethyl group that ensures

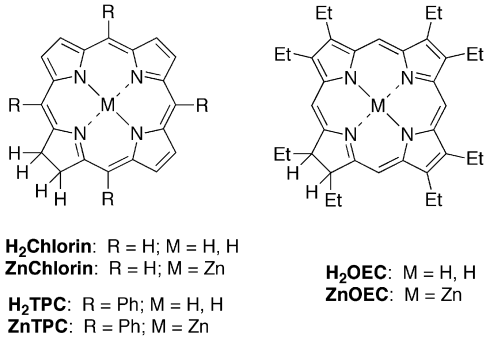


Chart 1.

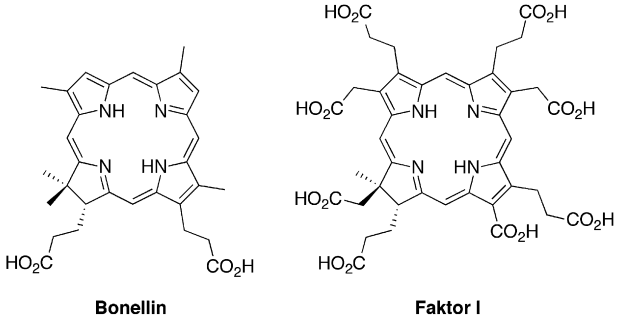
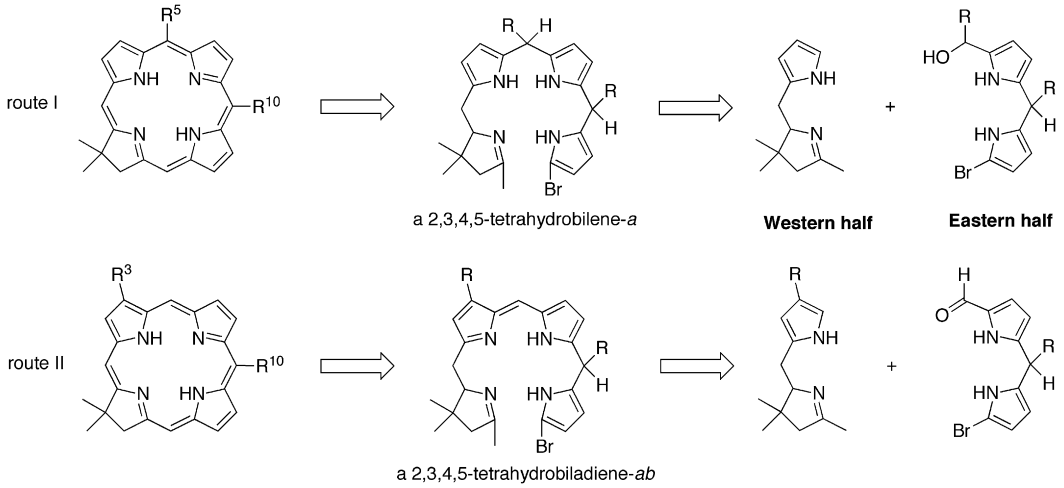


Chart 2.



Scheme 1.