



# Rotational isomerization of 3-substituents in synthetic chlorophyll derivatives



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## ABSTRACT

Methyl pyropheophorbides-*a* possessing a (pseudo)planar substituent at the 3-position were prepared from naturally occurring chlorophyll-*a*. Some of the semisynthetic  $\pi$ -conjugates with the chlorin skeleton took two atropisomeric conformations for the sterically demanding 3-substituents, CONMe<sub>2</sub>, NHCOMe, C[CH=C(CN)<sub>2</sub>]=C(CN)<sub>2</sub>, and Ph(2,3,4,5-Ph<sub>4</sub>). Their rotational isomerization in a solution was analyzed by <sup>1</sup>H NMR and HPLC. Zinc complex of the 3-aryl-chlorin gave a large energy barrier for the rotation of the C3–C3<sup>1</sup> single bond (estimated  $\Delta G^\ddagger=108$  kJ mol<sup>-1</sup> at 20 °C) and the atropisomerically pure conformers were separated at room temperature.

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## 1. Introduction

A variety of  $\pi$ – $\pi$  conjugates covalently linked with a single bond are available for functional molecules. In the molecules, planar structures are useful for stabilization of  $\pi$ -extended conformations and steric repulsion rotates the connected single bond from such coplanar conformers to a perpendicular direction. Typically, *meso*-arylporphyrins have the single bond(s) between the *meso*-carbon and its connecting carbon in the *meso*-aryl group, and their conformations were analyzed by crystallographic analyses. The *meso*-phenyl group in tetraphenylporphyrin (top of Fig. 1) was rotated by 61–3° from the porphyrinic core  $\pi$ -plane due to the steric interaction of the *ortho*-protons of the *meso*-phenyl group (X=H) with its closest two  $\beta$ -protons (Y=H).<sup>1</sup> This situation is comparable to the reported torsional angles of biphenyl (44°) in the gas phase<sup>2</sup> and 9-phenylanthracene (73°) in the crystal state.<sup>3</sup> In tetramesitylporphyrin (middle of Fig. 1), the average dihedral angles between the mesityl group and porphyrin core plane increased to be 84°,<sup>4</sup> which was ascribable to larger steric repulsion of the *o*-Me (X=Me) with  $\beta$ -H (Y=H). Similarly, the intramolecular interaction of *o*-H (X=H) with  $\beta$ -Me (Y=Me) induced almost orthogonal conformation (85°) in *meso*-diphenyl- $\beta$ -octaalkylporphyrin (bottom of

Fig. 1).<sup>5</sup> Such lower  $\pi$ -conjugation blue-shifted visible absorption bands in a solution.<sup>6</sup>

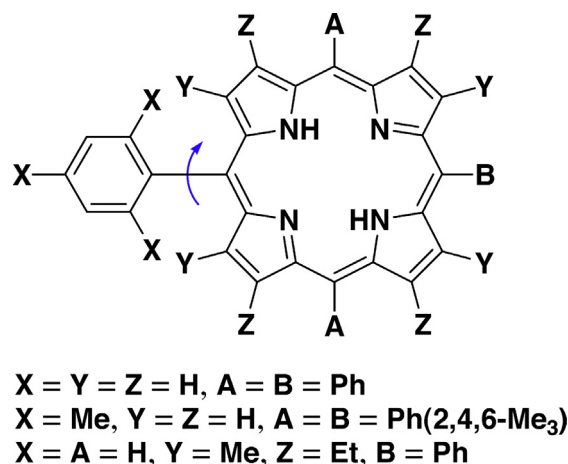


Fig. 1. Molecular structures of *meso*-arylporphyrins and the rotation of the single bond between the *meso*-carbon and aryl groups.

As planar functional moieties at the 3-position of natural (bacterio)chlorophylls [(B)Chls] and their synthetic derivatives (see Fig. 2) increase in size, their molecular conformations are distorted

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in the  $\pi$ -conjugates and/or the 3-substituents ( $R^3$ ) are rotated around the C3–C3<sup>1</sup> single bond from the coplanar conformation with the (bacterio)chlorin  $\pi$ -systems. This is attributable to the steric repulsion of the large 3-substituent with the 2-methyl group and 5-hydrogen atom in a molecule. Additionally, relatively small 3-substituents of (B)Chls were frequently rotated in photosynthetic apparatuses due to their interaction with peptidyl environments.<sup>7</sup> Crystallographic analysis of some (B)Chl–protein complexes<sup>8</sup> showed that the 3-vinyl group of Chl-*a*<sup>9,10</sup> and 3-acetyl group of BChl-*a*<sup>11–13</sup> (left drawing of Fig. 2) took several rotational conformations. Such rotation induces deconjugation of the functional groups with core  $\pi$ -skeletons to blue-shift the redmost (Qy) absorption band and enhance the intrinsic singlet excited (site) energy.<sup>7,14–16</sup> These observations were confirmed by semisynthetic chlorophyll models bearing alkenyl<sup>17–19</sup> and acyl groups<sup>20,21</sup> at the 3-position (right drawing of Fig. 2).

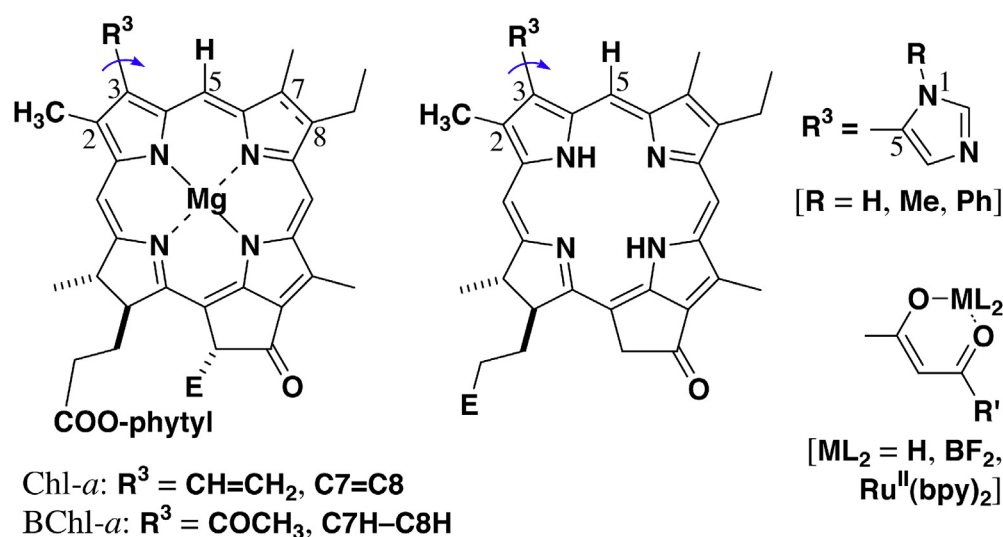


Fig. 2. Molecular structures of natural (B)Chls-*a* (left) and synthetic Chl-*a* derivatives, methyl 3-substituted pyropheophorbides-*a* (right): E=COOMe.

Sterically demanding moieties at the 3-position of some Chl-*a* derivatives restricted the rotation around the C3–C3<sup>1</sup> bond to give atropisomers in a solution. A large  $\beta$ -octaalkylporphyrinyl group (see Fig. 1) was directly connected with a chlorin  $\pi$ -system at the 3-position and the synthetic molecule, methyl 3-substituted pyropheophorbide-*a* (see right drawing of Fig. 2), was an atropisomeric mixture from the <sup>1</sup>H NMR spectral analysis.<sup>22</sup> Although methyl 3-(1-unsubstituted 5-pyrazolyl)pyropheophorbide-*a* (R=H in right drawing of Fig. 2) afforded free rotation of the C3–C3<sup>1</sup> single bond, the 1-methylation and phenylation (R=Me, Ph) of the pyrazolyl group enhanced the steric crowdedness at around the 3-position to be two atropisomers (1:1) in CDCl<sub>3</sub> at room temperature.<sup>23</sup> A similar situation was observed in the complexation of ruthenium bis(bipyridine) with the diketonate group [ML<sub>2</sub>=Ru<sup>II</sup>(bpy)<sub>2</sub> in right drawing of Fig. 2] at the 3-position to give a 1:1 rotameric mixture,<sup>24</sup> while no isomers were visible in small ML<sub>2</sub>(=H or BF<sub>2</sub>).<sup>25,26</sup>

Previously, a sterically bulky trisubstituted methyl group [R<sup>3</sup>=C(CF<sub>3</sub>)<sub>2</sub>OH in right drawing of Fig. 2] at the 3-position of methyl pyropheophorbide-*a* and its zinc complex was found to provide rotational isomers in a solution at room temperature and their isomerization has been analyzed by NMR spectroscopy.<sup>27</sup> Here we report preparation of Chl-*a* derivatives possessing the other sterically demanding substituents at the 3-position and investigate the atropisomerization around the C3–C3<sup>1</sup> rotation of the

synthetic chlorin conjugates with amides, alkenes, and arene by <sup>1</sup>H NMR spectroscopic analysis in deuterated solvents.

## 2. Results and discussion

### 2.1. Rotamers of synthetic 3-carbamoyl-pyropheophorbides-*a*

Methyl 3-carboxy-3-devinyl-pyropheophorbide-*a* (**5**) was prepared by modifying naturally occurring Chl-*a* according to reported procedures (see Scheme 1).<sup>28</sup> The obtained carboxylic acid **5** was reacted with methylamine and dimethylamine by action of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) as a condensating reagent in the presence of 1-hydroxybenzotriazole (HOBT) to give the corresponding *N*-methylamide **1a** and *N,N*-dimethylamide **1b**, respectively, in the same 59% yields [step (i) of Scheme 1]. The coupling reaction was supe-

rior to the amidation of **5** with CH<sub>3</sub>NH<sub>2</sub> by a water-soluble carbodiimide (EDC) with 4-(dimethylamino)pyridine (DMAP) affording **1a** in a 24% yield.

The synthetic amides **1a/b** were readily dissolved in chloroform and their <sup>1</sup>H NMR spectra were measured in deuterated chloroform. At room temperature, *N*-methylamide **1a** gave one set of sharp signals, while *N,N*-dimethylamide **1b** afforded two sets of proton resonances (1:1). The observation indicated that **1a** was a single species in the solution and **1b** was an isomeric mixture at room temperature. To reveal the isomeric structures, NOESY spectra of **1b** were measured. Since NOE correlation in **1b** was complex at room temperature, its 2D <sup>1</sup>H NMR spectrum was obtained at –20 °C. One of the isomers showed the NOE correlation between the two *N*-methyl groups and also that between 2-methyl group and one of the *N*-methyl groups (Fig. 3, left). In the other isomer, NOE correlations were observed for *N*-C<sup>α</sup>H<sub>3</sub>/*N*-C<sup>β</sup>H<sub>3</sub> and *N*-C<sup>α</sup>H<sub>3</sub>/5-H (Fig. 3, right). The correlations demonstrated that two rotational isomers around the C3–C3<sup>1</sup> bond were found in the solution of **1b**. The rotation around the single bond was partially restricted due to the steric interaction of the *N,N*-dimethylcarbamoyl group with the 2-methyl group and 5-hydrogen atom. The less sterically demanding *N*-methylcarbamoyl group could be freely rotated around the C3–C3<sup>1</sup> bond of **1a** at room temperature to give no atropisomers in the solution. The steric effect was consistent with the reported data for 13-carbamoyl-chlorins.<sup>29–33</sup>

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