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Effects of peripheral substituents on diastereoselectivity of the fifth ligand-binding to chlorophylls, and nomenclature of the asymmetric axial coordination sites

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Abstract—A preference for one of the two axial ligand-binding sites on the central metal atom of chlorophylls (Chls) and bacteriochlorophylls (BChls) was confirmed. In recently reported crystallographic data on PS2 and LHC2 complexes, there are 42 Chl molecules whose fifth ligands were identified; 33 of 42 molecules bound the fifth ligand at the axial position where the $C13^2$-methoxycarbonyl group protrudes (denoting as the 'back'-type isomer). Among 151 (B)Chl *a*/*b* molecules found in eight types of (B)Chl proteins including PS2 and LHC2, 124 molecules (82%) are the 'back'-type isomers. Such a statistical selection was observed not only for Chl *a* but also for Chl *b* and BChls *a*/*b*, indicating that the C3-, C7-, and C8-substituents as well as the macrocyclic π-conjugates would have little influence on the ligand-binding site. Computational examinations revealed that the energetic gap between the 'back' and its opposite 'face' complexes was inherent to (B)Chls and that the $C13^2$-methoxycarbonyl moiety contributed relatively greatly to the diastereomeric preference in the ligand binding. Nomenclature of the two distinguishable sides on chlorophyllous macrocycles, as well as the two asymmetric ligand-binding sites, is also discussed.

1. Introduction

Chlorophylls (Chls) and bacteriochlorophylls (BChls) are abundant, natural tetrapyrroles (Fig. 1). The central metal atoms of these compounds (Mg or Zn) take the five-coordinated states in all photosynthetic proteins resolved so far as well as in most solvents. Since (B)Chls *a*/*b* are asymmetric molecules, the fifth ligand can coordinate to the central metal atom either from the chlorin macrocycle side where the $C13^2$-methoxycarbonyl moiety protrudes (denoting as the 'back' side) or from the other side (the 'face' side): the 'back'- and 'face'-type ligand–(B)Chl complexes are a pair of epimers. Possible difference between the two asymmetric ligand-binding sites had not been noticed. We investigated, for the first time, which side of the macrocycle is favored for the ligand coordination, by survey of the highly resolved crystal structures of various photosynthetic (B)Chl-containing proteins:[1] photosystem 1 (PS1) core complex, peridinin-Chl protein, purple bacterial reaction centers (RCs), BChl-containing light-harvesting complexes 2 and 3 (LH2 and LH3), and FMO protein. It was found that Chl *a* as well as BChls *a*/*b* in these proteins mostly bind their ligands on the 'back' sides (back/face = 81/14 in Chl *a* and 10/4 in BChls). The finding was confirmed by the theoretical calculations for imidazole complexes of methyl chlorophyllide *a* (MeChlid *a*, Fig. 1) and methyl bacteriochlorophyllide *a* (MeBChlid *a*): the 'back'-type complex was ca. 1 kcal/mol more stable than the 'face' one. These results were supported by Balaban and his colleagues.[2,3]

The coordination chemistry of (B)Chls is a basis for an understanding of how these pigments are fixed at the specific sites in the photosynthetic proteins in the folding processes. For development of the study, there are the following four issues that should be addressed. For the first subject, although we have surveyed six types of (B)Chl proteins whose precise structures had been obtained, it should be verified whether the 'back'-type stereoisomer is also abundant in newly resolved (B)Chl

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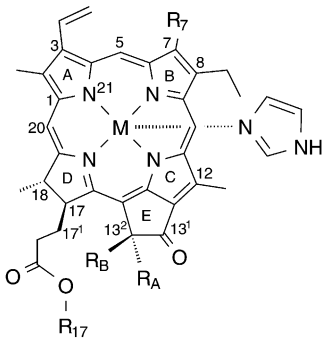


Compound	M	R_7	R_A	R_B	R_{17}
Chl *a*	Mg	Me	COOMe	H	phytyl
Chl *b*	Mg	CHO	COOMe	H	phytyl
MeChlid *a*	Mg	Me	COOMe	H	Me
Zn-MeChlid *a* (**1aR**)	Zn	Me	COOMe	H	Me
Zn-MeChlid *a*'(**1aS**)	Zn	Me	H	COOMe	Me

Figure 1. Molecular structures of chlorophylls with partial numbering according to the IUPAC system. An imidazole molecule coordinates to the central M from the 'back' side.

proteins. Ben-Shem et al.[4] and Krauß et al.[5] reported structures of super-complexes of PS1 core and LHC1 with >4 Å resolutions. Stroebel et al.[6] and Kurisu et al.[7] found one Chl *a* molecule in cytochrome b_6f complex (at 3.0–3.1 Å resolutions), but regretfully its ligand, probably a water, was not fully resolved. The ligand-bound sides of Chls in LHC1 and cytochrome b_6f still remain unclear. On the other hand, X-ray crystallography of photosystem 2 (PS2) has been extensively studied.[8–12] Kamiya and Shen,[10] Ferreira et al.,[11] and Biesiadka et al.[12] have recently reported the structures of PS2 core complexes at 3.70, 3.50, and 3.20 Å resolutions, respectively. These crystals involved the core D1 and D2 subunits and CP43 and CP47 core antennas that bound about 36 Chl *a* molecules as a whole. Although ligands of some Chl molecules are yet unclear, the reported data allow us to study coordination chemistry of the Chls and pigment–protein interactions. Külbrandt et al. had first reported the crystal structure of light-harvesting complex 2 (LHC2) at resolution of 3.4 Å,[13] and more precise one was reported recently by Liu et al. at the 2.72 Å resolution.[14] The latter is sufficient for the analysis of the ligand-binding macrocycle side of Chls *a* and *b*.

The second issue is the origin of the small energy differences (ca. 1 kcal/mol) between the 'back' and the 'face' ligand–(B)Chl stereoisomers obtained from the theoretical (PM3) calculations.[1] The results predicted the influence of the $C13^2$-stereochemistry on the choice of the macrocycle side for the ligand coordination:[1] it is suggested that correlation between the ligand binding and the peripheral substituents may be a key to examine whether the preference of one of the two axial ligand-binding sites is the inherent property of (B)Chls.

The third subject, detection of the small difference between the 'back' and 'face' stereoisomers for real Chl molecules, is, of course, quite important. We are now approaching to this subject by organic chemistry. Synthesis and analysis of the model compounds will be presented elsewhere.

The fourth is a nomenclature. Natural corrins and porphyrins, for example, vitamin B_{12} and protoheme, have asymmetric molecular structures. Their macrocycle faces are distinguished and named by IUPAC recommendations. Although (B)Chls are also abundant, natural tetrapyrroles, the nomenclature for the macrocycle faces of chlorophylls and their related compounds has not yet been defined. For future discussion on structure–function relationships of (B)Chls and fully synthetic chlorins, it is required to name the faces unambiguously.

Here, we address and discuss on the above issues 1, 2, and 4.[15] We examined the numbers of the 'back'- and 'face'-type ligand–Chl complexes in crystal structures of PS2 core complex and LHC2. Among 42 Chl molecules in the two proteins, whose fifth ligands were identified, 33 molecules are the 'back'-type ligand–Chl complexes. Of 151 (B)Chls *a*/*b* in eight types of (B)Chl-containing proteins we surveyed, 124 molecules are the 'back'-type complexes (82%). Comparing the stabilities of a variety of in silico ligand–chlorin complexes revealed that the energy gap between the 'back' and the 'face' complexes is inherent to (B)Chls that possess the $C13^2$-methoxycarbonyl moiety. These results confirmed the diastereomeric preference in the ligand binding at the central metal atom of (B)Chl. Nomenclature of the macrocycle sides of (B)Chls is also discussed.

2. Results and discussion

2.1. 'Back'/'face'-type (B)Chl complexes in photosynthetic proteins

We examined coordination chemistry of Chls in PS2 (Ferreira et al., PDB code 1S5L)[11] and LHC2 (Liu et al., PDB code 1RWT).[14] The resolved PS2 complex contains the core D1 and D2 proteins, the core antenna CP43 and CP47 proteins, cytochrome *b559*, and some small proteins. In the D1/D2 proteins (Table 1a), the special pair Chl *a* (P680, CL13/14) and two additional Chl *a* (Chl_Z, CL19/110) are coordinated by N^{ε} atoms of His residues from the 'back'-side of the macrocycle. The axial ligands of the 'accessory' Chl *a* (CL15/16) were not resolved. Among the 30 Chl *a* in CP43/47 (Table 1b), ligands of 24 Chls are identified (His, 23; Asn, 1), of which 18 Chls have the ligands at the 'back' side. The same analysis revealed that another PS2 crystal (1W5C, Ref. 12) has 22 'back'-type and 5 'face'-type ligand–Chl *a* complexes (Chls with unidentified ligand, 8; total Chl molecules, 35). Although we should bear a word of caution for over-interpretation in the 3.2–3.8 Å structures in mind,[12] it can be safely said that the 'back'-type is the major form in PS2.

Table 1. Axial fifth coordination of (bacterio)chlorophylls *a*/*b* in photosynthetic proteins: name on the PDB data/axial ligand/coordination site are depicted from the left to right at each line of a–c

(a) D1/D2 proteins in PS2 (6 Chl a)					
CL13	(P680	His	Back		
CL14	(P680)	His	Back		
CL15	(accessory)	Unknown	Unknown		
CL16	(accessory)	Unknown	Unknown		
CL19	(Chl_Z)	His	Back		
CL110	(Chl_Z)	His	Back		
(b) CP43/47 proteins in PS2 (30 Chl a)					
CL111	His	Back	CL126	Unknown	Unknown
CL112	Unknown	Unknown	CL127	His	Back
CL113	His	Face	CL128	His	Back
CL114	His	Back	CL129	His	Back
CL115	His	Face	CL130	His	Back
CL116	His	Back	CL131	His	Back
CL117	His	Back	CL132	His	Back
CL118	His	Back	CL133	His	Back
CL119	His	Face	CL134	His	Face
CL120	His	Back	CL135	His	Back
CL121	His	Back	CL136	Unknown	Unknown
CL122	Unknown	Unknown	CL137	His	Back
CL123	His	Back	CL144	Asn	Back
CL124	His	Face	CL146	Unknown	Unknown
CL125	His	Face	CL147	Unknown	Unknown
(c) LHC2 (8 Chl a, 6 Chl b)					
Chl *b* 601	Tyr	Face	Chl *b* 608	Water	Back
Chl *a* 602	Glu	Back	Chl *b* 609	Glu	Back
Chl *a* 603	His	Face	Chl *a* 610	Glu	Back
Chl *a* 604	Water	Back	Chl *a* 611	Phosphodiester—P=O	Back
Chl *b* 605	Val–C=O	Back	Chl *a* 612	Asn	Face
Chl *b* 606	Water	Back	Chl *a* 613	Gln	Back
Chl *b* 607	Water	Back	Chl *a* 614	His	Back

(d) Summary				
Protein	'Back'	'Face'	Total	
Purple bacterial reaction center	4	0	4	Ref. 1
LH2 and LH3 (purple bacteria)	1	2	3	Ref. 1
FMO protein	5	2	7	Ref. 1
Peridinin-Chl protein	2	0	2	Ref. 1
PS1 core complex	79	14	93[a]	Ref. 1
PS2 core complex	22	6	28[a]	This work
LHC2	11	3	14	This work
Total	124	27	151	

[a] The numbers of Chls whose ligands were identified.

Each LHC2 monomer[14] possesses eight Chl *a* and six Chl *b* molecules (Table 1c). A variety of ligands including phosphodiester P=O and valinyl C=O groups, coordinate to the 14 Chl molecules. It is intriguing that water is the most abundant ligand in this protein (water, 4; Glu, 3; His, 2). The numbers of 'back'- and 'face'-type Chl *a* complexes were six and two, respectively, per one LHC2 monomer, while those of the 'back'- and 'face'-type Chl *b* were five and one, respectively. All the four monohydrated Chls (one Chl *a* and three Chl *b*) bind the ligand from the 'back' side.

Considering six other (B)Chl-containing proteins we have examined (purple bacterial reaction center, LH2, LH3, FMO protein, peridinin-Chl protein, and PS1)[1] together, 124 (B)Chl complexes are the 'back'-types (82%, Table 1d) among 151 molecules in the eight structurally resolved proteins; for Chl *a*, 109 of 131 molecules are the 'back'-type (83%). The side of the macrocycle that bears a small ligand, water, indirectly (non-covalently) fixed by protein scaffolds, can be a measure to clarify the favorable side for the ligand coordination: 23 of 24 hydrated (B)Chls are the 'back'-type (96%). It is clear that the 'back'-side ligated complexes are the major epimers, confirming that the 'back'-type ligand–(B)Chl complexes are more stable than the other ones. The content of the 'back'-type epimers (82%) is consistent with the value assuming an equilibrium between the two types of epimers in a matrix.[1] It is noted that, not only for Chl *a* but also for Chl *b* and BChls *a*/*b*, the 'back'-type complexes are major over the 'face' ones. This shows that the peripheral substituents at the C3, C7, and C8 positions as well as the macrocyclic π-conjugates would give little influence on binding sites of the ligand, which is consistent with the fact that some Chl *a* in the photosystems of cyanobacteria can be replaced

with Chl *b*.[16–18] It is also suggested that the 'back'-type is also the major isomer for Chl *d* in *Acaryochloris marina*[19] and BChl *g* in *Heriobacteria*,[20] respectively, because they are the C3/8-derivatives of (B)Chl *a*.

2.2. Origin of the difference between the 'back' and 'face' complexes

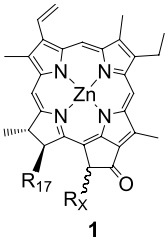
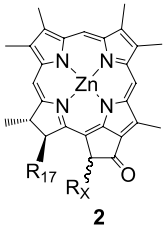
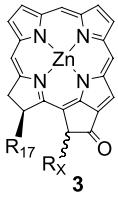
In the previous report,[1] we presented a small energy difference ($\Delta\Delta H_f$ = 0.7 kcal/mol) between the 'back' and 'face' isomers of methyl chlorophyllide *a* (MeChlid *a*, Fig. 1) possessing an imidazole molecule as an axial ligand, by theoretical (PM3) calculations. Exploration for origin of the small energy gap will give an additional evidence to confirm preferential ligand binding to one of the two axial coordination sites. We also found that the energy gap depended on the stereochemistry at the $C13^2$-position: the optimized 'back'-type imidazole—zinc methyl chlorophyllide *a* (Zn-MeChlid *a* [$C13^2$-(*R*)-COOMe], **1aR**, Fig. 1) complex was 2.0 kcal/mol more stable than the optimized 'face'-type complex, while the 'back' isomer of its $C13^2$-epimer (Zn-MeChlid *a*′ [$C13^2$-(*S*)-COOMe], **1aS**) was 4.0 kcal/mol less stable than the 'face' one (Table 2).[1] This finding suggests that stereochemical effects of such peripheral substituents can lead to the origin of the energy gaps. We build a series of simple, virtual zinc chlorin molecules in silico to examine influence of each substituent on $\Delta\Delta H_f$ (Table 2). The model compounds examined in this study were zinc chlorins for the following four reasons. (1) Zn-chlorins are similar to Mg-chlorins in their properties and functions in a photosynthetic organism (*Acidiphilium rubrum*).[21] (2) Zn-chlorins have been employed in various model systems[22–25] that can provide experimental supports. (3) The PM3 parameters for Zn atom seem to be better than those of Mg atom.[26] (4) Essentially, similar tendency in $\Delta\Delta H_f$ was obtained for Zn- and Mg-chlorins.[1]

Even when structural freedom and electronic conjugation of Zn-MeChlid *a* and *a*′ (**1aR** and **1aS**) were reduced by replacing both C3-vinyl and C8-ethyl moieties with methyl groups, substantial energy gaps were still kept between the 'back' and 'face' isomers of the methylated compounds **2aR** and **2aS** (−2.0 → −1.3 and +4.0 → +3.5 kcal/mol). Further substitution of all the six methyl groups with hydrogen atoms, in going from **2aR/S** to **3aR/S**, hardly changed $\Delta\Delta H_f$ (−1.3 → −1.1 and +3.5 → +3.5 kcal/mol). Removal of $C13^2$-COOMe (**1/2/3a** → **1/2/3b**) reduced the amplitudes of $\Delta\Delta H_f$ values considerably. When both the $C13^2$- and C17-moieties were removed as in **1/2/3c**, the enthalpy differences ($\Delta\Delta H_f$) were nearly disappeared. The $\Delta\Delta H_f$ values of **2aR** and **3aR** [$C13^2$-(*R*)-COOMe/C17-$(CH_2)_2$-COOMe] nearly matched to those of **2dR** and **3dR** [$C13^2$-(*R*)-COOMe/C17-H], respectively. More than a half part of the $\Delta\Delta H_f$ value of **1aR** was attributable to the $C13^2$-moiety alone, as suggested by $\Delta\Delta H_f$ of **1dR**. The $\Delta\Delta H_f$ values of **1/2/3aS**, ca. 3.0 kcal/mol greater than expected by **1/2/3b** and **1/2/3dS** (Table 2), were rationalized by steric repulsion between the bulky $C13^2$- and C17-moieties.[22,27,28] It is noted that **3dR**-type derivatives singly substituted at the $C13^2$-position varied amplitudes and signs of their $\Delta\Delta H_f$ values depending on type of the $C13^2$-substituent and on absolute configuration at the $C13^2$-position. Electron-withdrawing substituents gave negative $\Delta\Delta H_f$ values lower than −1.0 kcal/mol (–CHO, −1.5; –COOMe, −1.1; –CN, −1.0), while methoxy and methyl groups gave positive values (+0.1 and +0.5 kcal/mol, respectively). The $C13^2$-COOMe compounds **3dR** and **3dS** have $\Delta\Delta H_f$ values of the same absolute amplitudes and different signs depending on the absolute configuration at the $C13^2$-position, respectively (Table 2).[29] These indicate that the energy gap between the 'back' and the 'face' ligand–(B)Chl complexes, or a preference for one of the two axial ligand-binding sites of the central metal atom, is an inherent property of (B)Chls, and that the gap is affected by electronic and steric effects of the $C13^2$-moiety on the chlorin macrocycle.[30]

2.3. Nomenclature of macrocycle faces of chlorophylls and related compounds

The nomenclature to distinguish the two asymmetric macrocycle faces as well as the ligand-binding sites on

Table 2. Energetic difference $\Delta\Delta H_f$ (kcal/mol) between the 'back' and 'face' complexes of zinc chlorins **1**–**3** with imidazole as an axial ligand: $\Delta\Delta H_f = \Delta H_f$ ('back'-type) − ΔH_f ('face'-type)

	C17 R_{17}	$C13^2$ R_X	 **1**	 **2**	 **3**
aR	$(CH_2)_2$COOMe	(*R*)-COOMe	−2.0 (**1aR**)	−1.3 (**2aR**)	−1.1 (**3aR**)
aS	$(CH_2)_2$COOMe	(*S*)-COOMe	+4.0 (**1aS**)	+3.5 (**2aS**)	+3.5 (**3aS**)
b	$(CH_2)_2$COOMe	H	0.0 (**1b**)	−0.2 (**2b**)	−0.3 (**3b**)
c	H	H	−0.1 (**1c**)	−0.1 (**2c**)	0.0 (**3c**)
dR	H	(*R*)-COOMe	−1.1 (**1dR**)	−1.2 (**2dR**)	−1.1 (**3dR**)
dS	H	(*S*)-COOMe	+1.0 (**1ds**)	+0.9 (**2dS**)	+1.1 (**3dS**)

the central metal atom of chlorophylls and their related compounds has not yet been defined. For future studies on structure–function relationships of (B)Chls, including the folding processes of the (B)Chl proteins, these faces and sites should be named unambiguously. The nomenclature should be absolute and simple, and should also be convenient when comparing with other natural tetrapyrroles such as vitamin B_{12}, protoheme (iron(III) protoporphyrin IX) and their derivatives. Senge et al. distinguished the epimers of Fe(III)Cl methyl phytochlorin as 'α-chloro form' and β-chloro form' (corresponding to our 'back' and 'face', respectively).[31] Kosaka and Tamiaki proposed to distinguish the (bacterio)chlorin macrocycle faces by '*re*-face' and '*si*-face' (corresponding to our 'back' and 'face', respectively), referring to the 13-carbonyl face.[32] Balaban et al. named these faces as '*syn*- and *anti*-faces'[2,33] (corresponding to our 'face' and 'back', respectively).

Vitamin B_{12} (cyanocobalamin, Fig. 2a) has a six-coordinated cobalt atom in the corrin macrocycle. One of the axial coordination positions where a benzimidazole moiety linking to the C17-position of the corrin macrocycle is bound, is defined as the cobalt-α position and the other position coordinated with cyanide is β position (IUPAC recommendation for corrinoids).[34] In case that the position number of the carbon atoms in the corrin macrocycle increases in a clockwise manner when viewing the plane from above, the axial ligands above and below the plane are designated by the use of β and α, respectively (these α/β correspond to our 'back'/'face', respectively). Two axial ligands of protoheme (L_1 and L_2, Fig. 2b) are also called as β- and α-ligands. The positions of the α- and β-ligands, relative to the porphyrin macrocycle plane, are the same as those of vitamin B_{12} (IUPAC rule TP-8.1 and 8.2):[35] in the case that the porphyrin macrocycle is oriented with the clockwise numbering from above, the axial ligands above (L_1) and below (L_2) the plane are then designated by β and α, respectively.

It is noted that, for some important tetrapyrroles such as protoheme, the assignment of the α/β ligands has to change when the systematic numbering rule (IUPAC rule TP-1.7) is employed instead of the trivial one (IUPAC rule TP-2, TP-4, and -Appendix),[35] because the α/β assignment depends on the direction of numbering of the substituents (Fig. 3).[36] In inorganic chemistry,

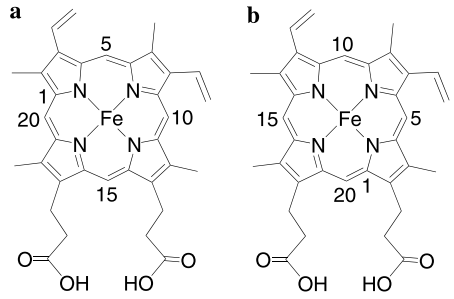


Figure 3. Numbering systems for protoheme: trivial numbering (a, Ref. TP-2.1) and systematic numbering (b, Ref. TP-1.7).

absolute stereochemistry in coordination compounds other than tetrahedral complexes is specified by the symbols *C* (clockwise) and *A* (anticlockwise).[37,38] For square pyramidal five-coordinated complexes, the symbol *C* is used in case that the priority numbers of the ligating atoms in the base plane increase in a clockwise manner when viewing the plane from the ligating atom at the top. This *C*/*A* notation could be used for tetrapyrroles in the five-coordinated state, if the priority numbers of the four pyrrole nitrogen atoms can have easily be assigned: this rule depends again on whether one employs trivial or systematic numbering. The relativity is, thus, inevitable for nomenclature of the macrocycle faces of tetrapyrroles.

We would like to propose that the trivial nomenclature of the asymmetric macrocycle faces as well as the ligand-binding sites of (B)Chls should be the same as those of porphyrins and corrins (α and β), according to the trivial numbering rule. At the same time, we also offer the systematic nomenclature according to the systematic numbering, to distinguish the naming system employed and avoid confusion with 'pyrrole-α and β positions' commonly used in porphyrin chemistry as well as '*meso*-α and β positions' still used in chlorophyll chemistry (=5- and 10-positions, respectively, in IUPAC system). The systematic nomenclature is also advantageous for fully synthetic chlorin compounds. Our recommendations are as follows (Fig. 4).[15]

(1) Trivial nomenclature: in the case that Chl macrocycle is oriented with the *trivial* clockwise numbering from above (IUPAC rule TP-4 and TP-Appendix), the axial ligands above and below the plane are des-

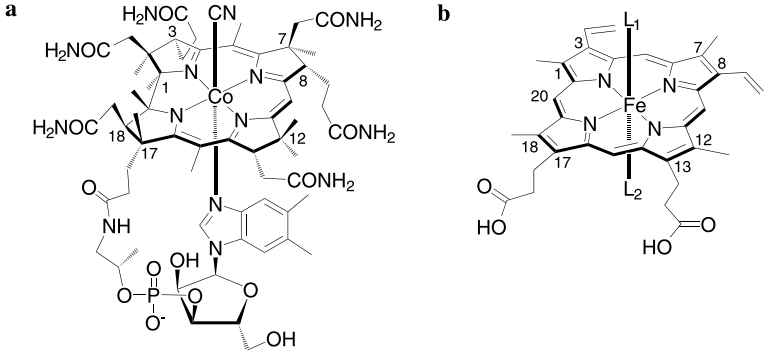


Figure 2. Molecular structures of (a) vitamin B_{12} and (b) protoheme.

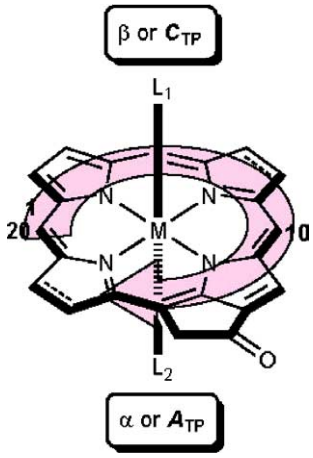


Figure 4. Proposed nomenclatures for the two macrocycle faces and axial ligating positions of (bacterio)chlorophylls.

ignated by β-ligand and α-ligand, respectively (IUPAC rule TP-8.1 and TP-8.2), and the macrocycle faces that bind the β-ligand and the α-ligand are defined as 'β-face' and 'α-face', respectively. These β and α correspond to our 'face' and 'back', respectively.

(2) Systematic nomenclature: in the case that Chl macrocycle is oriented with the *systematic* clockwise numbering from above (IUPAC rule TP-1.7), the upside face and the downside face of the macrocycle plane are defined as C_{TP}-face and A_{TP}-face, respectively, and the ligand bound on the C_{TP}-face and A_{TP}-face are designated by C_{TP}-ligand and A_{TP}-ligand, respectively.[39] For naturally occurring (B)Chls, these C_{TP} and A_{TP} correspond to the above β and α, and to our 'face' and 'back', respectively.[36]

3. Experimental

The crystal structures of PS2 core complexes (PDB codes, 1S5L, and 1W5C)[11,12] and LHC2 (1RWT)[14] were obtained from Protein Data Bank (PDB) at the Brookhaven National Laboratory. Protein structures and molecular modelings were viewed using a program package HyperChem release 5.1 and 7.5 (Hypercube Inc.). The model structures of various imidazole–chlorin complexes were built and optimized by molecular mechanics program MM+ and molecular orbital program PM3, as described previously.[1] Heat of formation (ΔH_f) of each molecule was calculated for the optimized geometry by using PM3, and the values gave relative stability of the 'back' and 'face' isomers ($\Delta\Delta H_f = \Delta H_f$ (back) $- \Delta H_f$ (face)). The potential energy surfaces around the energy-minimized geometries were also explored.

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