Hypothesis

Are *syn*-ligated (bacterio)chlorophyll dimers energetic traps in light-harvesting systems?

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Abstract A recent study of the stereochemical details of chlorophyll ligation in photosystem I [Balaban et al., Biochim. Biophys. Acta 1556 (2002) 197–207] has revealed that only 14 chlorophylls out of the total 96 are ligated from the same side (*syn*) as the 17-propionic acid residue which is esterified with phytol. The *syn* chlorophylls are carefully surrounding the reaction center forming the inner core antenna system and their ligands have been strongly conserved in several species during evolution. We hypothesize here that the two dimers of closely spaced *syn* chlorophylls which are encountered within roughly 2 nm of P700 are the ultimate energetic traps of this light-harvesting system. Structurally very similar bacteriochlorophyll *a* dimers are encountered within the Fenna–Matthews–Olson protein complex and within the B850 ring of the LH2 complex of purple bacteria. The non-random disposal of these dimers lends support to our hypothesis that the *syn* ligation coupled with a strong excitonic interaction leads to the most red-shifted pigments in light-harvesting systems. We would like to encourage both theoretical and experimental studies to either prove or disprove this intriguing structure–function conjecture in view of designing efficient artificial light-harvesting systems.
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Key words: Hypothesis; Photosynthesis; Light-harvesting; Chirality; Nomenclature

1. Introduction

Higher life on Earth depends upon chlorophyll-based photosynthesis, which starts by light-harvesting within specialized antenna complexes. Rapid excitation energy transfer (EET) occurs towards an energetic trap that usually absorbs light at longer wavelengths, i.e. which is more red-shifted than the bulk antenna chromophores. From the energetic trap, the reaction center (RC) is photoexcited within a special pair of (bacterio)chlorophylls [(B)Chls] where charge separation occurs, thus setting the stage for a cascade of successive electron transfer (eT) steps. Charge recombination is cleverly retarded in contrast to the forward eT, which finally leads to separation of the hole and the electron on the opposite sides of the photosynthetic membrane. This allows photosynthetic organisms to transform light energy into a chemical potential used to transport protons, which in turn drive the adenosine triphosphate (ATP)-synthase to transform adenosine diphosphate (ADP) into the energy-rich ATP. Concomitantly, the reductant nicotinamide adenine dinucleotide phosphate is formed, where a proton and two electrons are bound for 'active' hydrogen storage (actually a hydride ion equivalent). ATP represents the energy currency of living cells, which use it to drive uphill endergonic biochemical transformations. The overall process has been extremely well optimized during evolution and it occurs with stunning efficiency.

Artificial photosynthesis, a topic of acute interest that includes nanoscience and nanotechnological applications, tries to mimic this natural process and produce with reasonable quantum yields and efficiencies transformation of light energy into electrical current (as in photovoltaic devices or solar cells) or into chemical energy. That this is not just a myth has been eloquently demonstrated by Devens Gust together with Thomas and Anna Moore and their coworkers, who have synthesized artificial RCs and have incorporated these into synthetic membranes (liposomes) together with a reconstituted ATP-synthase which was fully operational. Upon illumination, ADP to ATP conversion could be demonstrated [1]. More recently, transport of Ca^{2+} against a chemical potential could be surmounted by using artificial RCs incorporated into liposomes [2]. For reviews see [3,4].

In view of non-biochemical applications, photochemical ATP production is not a goal per se. Rather, by using the principles of natural antenna systems combined with efficient artificial RCs or photovoltaic devices, higher efficiencies and lower production costs combined with environmentally more friendly ingredients could be used to fabricate better devices than the present state-of-the-art silicon-based solar cells.

It is well known that a large variety of light-harvesting systems have been developed by photosynthetic organisms. Thus, green photosynthetic bacteria, which are able to capture sunlight even deeper than 10 m under the water surface, have a different antenna system than bacteria living near the water surface, which, in turn, have evolved different light-harvesting apparata than algae or higher plants. This leads us to conclude that there are many possibilities to orchestrate an efficient EET process. In stark contrast to this, there is only one common ancestor for the natural RC, in both bacterial and plant photosynthesis, as can be concluded from the recently disclosed crystal structures of photosystems (PS) II [5] and I [6]. Organisms with other eT chains than one the presently

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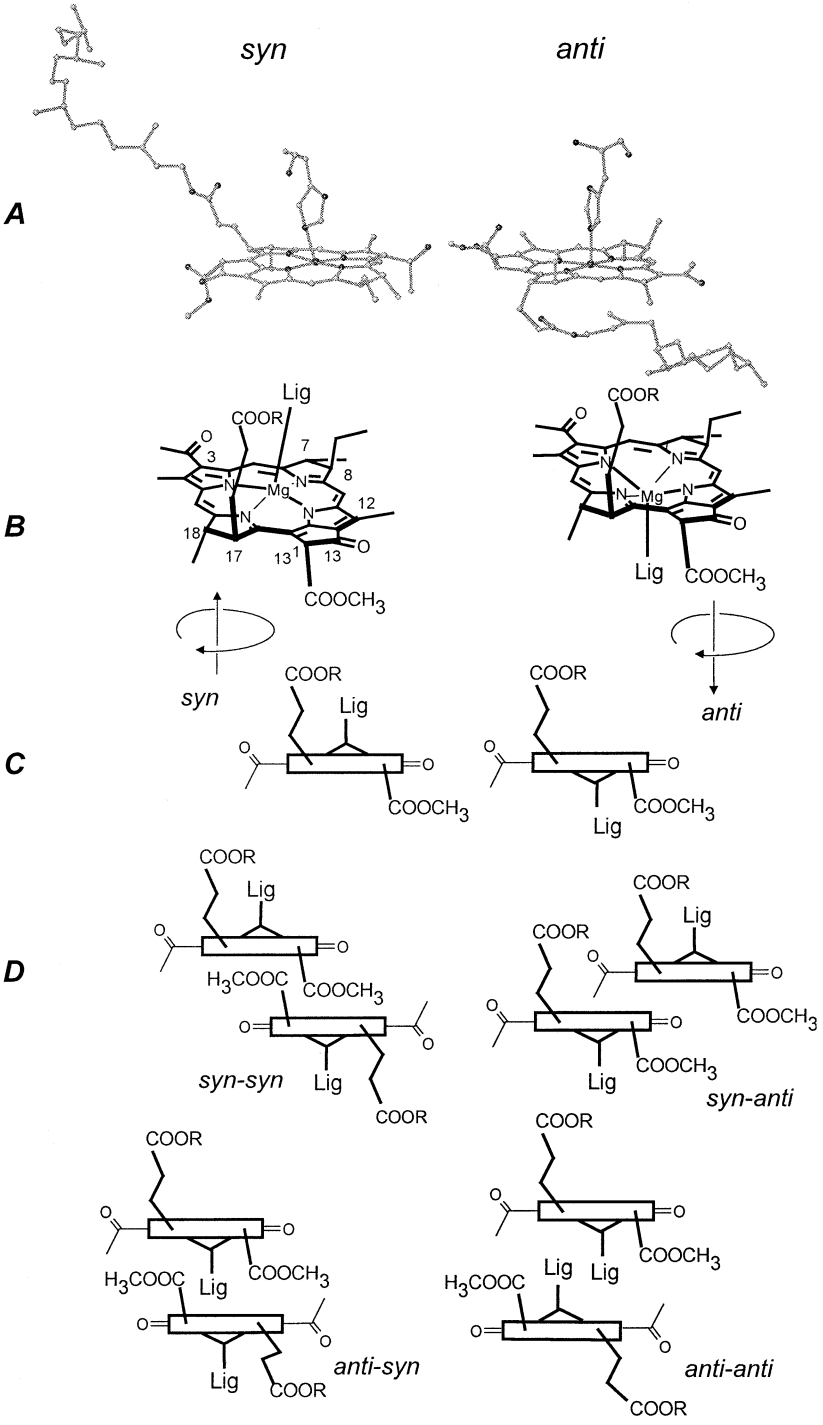

Fig. 1. A: Two BChl *a* molecules from the *Chlorobium tepidum* FMO crystal structure [22], both ligated by histidine residues. The *syn* ligation (BChl #3, at left) has the Mg ligand on the same side of the chlorin plane as the 17-propionic acid residue which is esterified by phytol. In the *anti* configuration (exemplified with BChl #1) the histidine ligand and the phytyl chain are on opposite sides. Note in the latter case the curling of the hydrophobic chain under the chlorin plane, which favors binding of the Mg atom by polar residues only from the other side. B: Molecular formulae for *syn* and *anti* BChls *a* which are coordinated by an arbitrary ligand (Lig) with the IUPAC atom numbering. As the numbering is in a clockwise direction, one can define as *syn* the position of the ligand given by a 'left-hand rule', i.e. by the direction of the thumb if the fingers of the left hand point clockwise. For easy memorization, *syn* can be thought to be derived (which is actually not the case) from the Latin *sinister* meaning left. Alternatively, the *syn* ligation can be described by the direction of movement of a left-handed screw when turned in the sense given by the IUPAC nomenclature. The corresponding *anti* diastereoisomer can then be described by a 'right-hand rule' or the direction of movement of a right-handed screw turned nomenclature-wise. C: Cartoon representations of the above formulae. D: Some of the possible diastereomeric face-to-face dimers. Note that rotations around the metal–ligand bond are possible so that different pyrrolic rings in the macrocycles may π-stack in an off-set geometry. Interconversion between these dimers can occur only by cleavage of the metal–ligand bond followed by a 'flip' of the (B)Chl ring and re-ligation from the opposite side. Although feasible in solution, this interconversion is entropically disfavored within a protein matrix. For a *syn–syn* dimer, for example, the ligands may both point outward (as depicted), both inward, or one outward and one inward.

known apparently have not survived the evolutionary pressure.

In the present Hypothesis article we draw attention to a common feature of the light-harvesting protein complexes encountered in several phylogenetically distant organisms. This feature is related to the occurrence of similar (B)Chl dimers or oligomers, which, being red-shifted, we believe to be ultimately the energetic traps of the respective complexes from which EET is passed on either to neighboring complexes or directly to the special pair of (B)Chls within the RC. We hope to stimulate both theoreticians and experimentalists to take into consideration the stereochemical details of how (B)Chls are ligated by the protein matrix, a fact which may considerably influence the photophysical properties of these pigments.

2. Diastereotopicity of the magnesium ligation of (B)Chls: *syn* and *anti* complexes

We were the first to note that the fifth ligand of the magnesium atom in BChl *c* can occupy two non-equivalent positions if the chemical exchange process (i.e. ligand dissociation followed by ligation with the alternative stereochemistry) is slower than the observation method employed [7]. In that study, by using circular dichroism, we could show that due to the other chiral centers which exist in BChl *c*, the dimers, oligomers and higher self-assembled species are diastereomeric with respect to the magnesium ligation. We have denoted as *syn* the configuration where the fifth magnesium atom is on the same side of the chlorin macrocycle as the 17-propionic acid residue which in naturally occurring (B)Chls is usually esterified by a long chain fatty alcohol. The other diastereomer, with the Mg ligand on the opposite side, was accordingly denoted as *anti* (Fig. 1, where R is a long chain, e.g. phytyl). In self-assembled BChls *c*, *d* and *e*, which are also encountered within the chlorosomal antenna system of green photosynthetic bacteria [8], the isomerization between *syn* and *anti* complexes is a slow process at room temperature, being both entropically and enthalpically disfavored. Even greater kinetical stability must be encountered within protein complexes where the dissociation of the magnesium atom from a (proteic) ligand followed by re-ligation from the other side by the same ligand is highly improbable.

With the exception of corrins, the fact that the central metal atom, within a tetrapyrrolic macrocycle, is an additional ste-

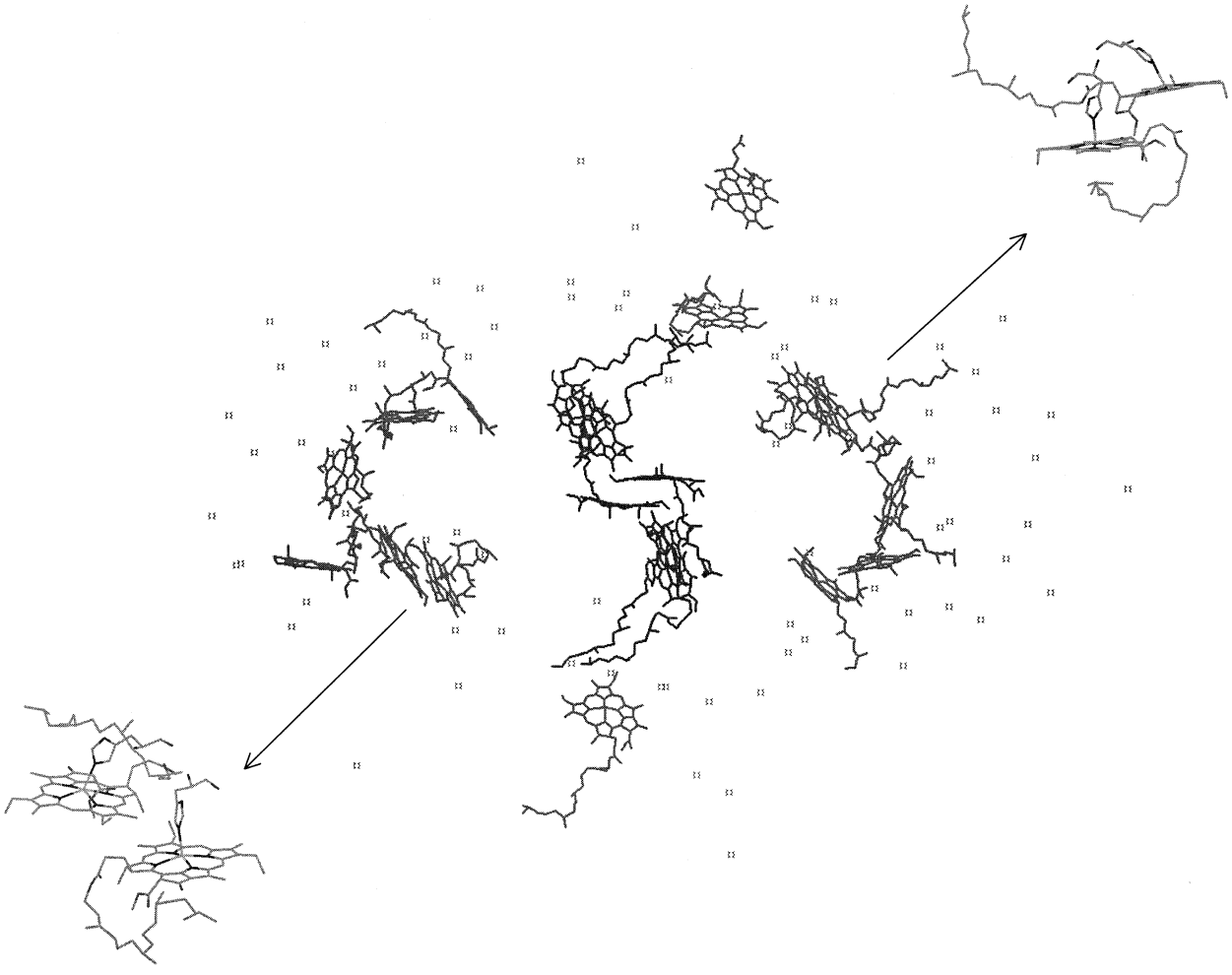

Fig. 2. Disposition of the PSI antenna Chls around the special pair P700 of the eT chain shown as blue line formulae. All other *anti*-ligated Chls (except the blue ones) are represented only by their Mg atoms (shown as incomplete circles with four dashes), while the *syn*-ligated Chls are drawn as red-line formulae. The two *syn–syn* dimers are detailed as colored insets indicated by arrows (nitrogen atoms are blue, oxygen atoms are red and carbon atoms are cyan). Note that both these dimers are of one type only, having a histidine ligand pointing outward while the other histidine ligand is pointing inward. The figure was produced with the HyperChem® program package [38] using the Protein Data Bank coordinates (PDB access code 1JBO).

Fig. 3. The seven BChl *a* molecules within the monomeric unit of the *Chlorobium tepidum* FMO crystal structure [22] together with their ligands. The *syn–syn* dimer (formed from BChls #3 and #7) is highlighted by thicker lines than the *anti*-ligated BChls. The ligand of BChl #2 (lowest position) is a water molecule, in the *anti* configuration. The figure was produced with the HyperChem® program package [38] using the Protein Data Bank coordinates (PDB access code 1KSA).

reogenic center in the case when it has a fifth axial ligand [i.e. is five coordinated (5c)], has been largely ignored in the (bio)-chemical literature. Due to the early X-ray structure of vitamin B_{12} [9,10], it became clear that stereoisomerism may be generated via the axial cobalt ligand(s) and considerable synthetic effort coupled with structural investigations has been dedicated to metallocorrins since then [11]. However, for asymmetric chlorins (among which chlorophylls must be counted) or bacteriochlorins, due to lack of crystal structures, the metal ligand was usually ignored. Even current textbooks present (B)Chl formulae with a tetracoordinated Mg atom. This is erroneous, as all known structures show a 5c Mg atom, even if only a water molecule acts as the fifth ligand [12,13]. In spite of using harsh drying conditions [14], a water molecule remains tightly bound and/or oligomerization of Chls occurs, a fact which preserves the energetically favored 5c-Mg atom. So far, to our knowledge, there is no experimental evidence for a 4c-Mg atom within cyclic tetrapyrroles such as (bacterio)chlorins or porphyrins.

Evidence for the occurrence of this isomerism on the nuclear magnetic resonance (NMR) time scale was presented for the first time by Abraham and Smith, who observed in the thallium complex of octaethylporphyrin non-equivalence of the ethyl groups [15]. However, although the authors have considered that the thallium atom could be displaced from the porphyrin plane, thus generating two non-equivalent porphyrin faces, they have attributed the non-equivalence of the ethyl groups to their restricted rotation. Today, we can accurately estimate rotation barriers and thus state that, at room temperature, the ethyl groups should have appeared as equivalent, as actually was the case for the metal-free (base) octaethylporphyrin. The fifth ligand on the 5c-thallium atom, namely a water molecule, was actually responsible for the observed desymmetrization of the complex. Very recently, dynamic NMR evidence has been presented for *N*-methylimidazole–Chl *a* complexes [16], which also show splitting of signals attributable to the *syn*, respectively *anti*, diastereomeric complexes.

We have analyzed this stereochemical feature of the ligation of magnesium atoms in Chl *a* within the crystal structure of

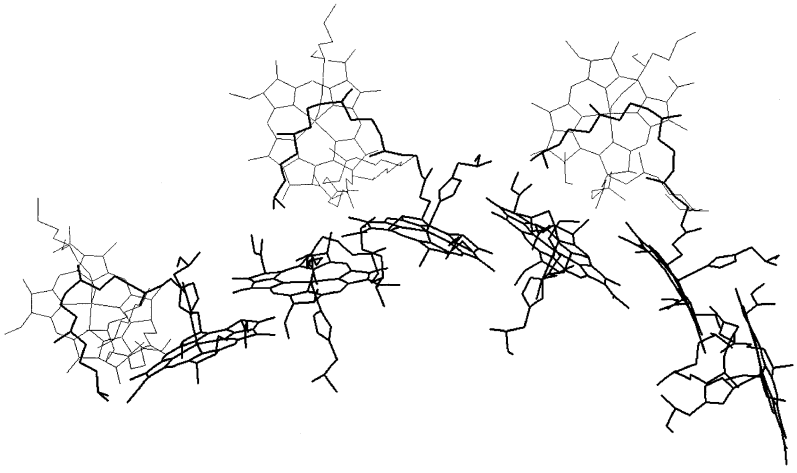

Fig. 4. One-third of the two B800 and B850 rings of the *Rps. acidophila* crystal structure [24]. The *syn* BChls *a*, ligated by histidine residues, and which form the B850 ring are highlighted by thicker lines. The B800 BChls *a* shown in the back have an *N*-formylmethionine ligand in the *anti* configuration. The figure was produced with the HyperChem® program package [38] using the Protein Data Bank coordinates (PDB access code 1KZU).

PS I [17]. Astonishingly, out of the 96 Chls only 14 are *syn*-ligated, a fact which by a crude Boltzmann distribution would indicate a greater stability for the *anti* ligation. This was supported by computational results, where the *anti* ligation was found to be about 1 kcal/mol more stable. Of course, within a protein matrix, thermodynamic stability cannot be invoked for a preferential conformation, or a certain protein folding around cofactors, as kinetic effects often play the dominant role [18]. Moreover, the *syn* Chls are all part of the inner core PS I antenna system, carefully engulfing the RC. All Chl ligands have been strictly conserved during evolution within different species, a fact which emphasizes that incorporation of the Chl pigments within the protein matrix is a highly stereospecific process which occurs in a non-random manner. Tamiaki and Oba have independently counted the number of *syn* versus *anti* Chls and have come to the same numbers as we did [19,20]. They denoted as 'face-' and 'back-' side ligation the *syn* and *anti* configurations, respectively, which in our opinion is somewhat ambiguous as they used the 13^2-carbomethoxy group of Chl *a* as a reference. This group can also have opposite orientation (in the epimeric Chl *a*′) or is even absent in pyrrochlorophylides, such as BChls *c*, *d,* or *e*[1].

Semiempirical ZINDO-S calculations indicate that face-to-face dimers are red-shifted by about 20–40 nm in comparison with histidine-coordinated Chl monomers [17]. Within PSI there are two such *syn–syn* dimers, situated on two neighboring histidines positioned centrosymmetrically with respect to the special pair at about 2.5 nm (2.9 nm Mg–Mg separation). Fig. 2 shows these two dimers highlighted by thick lines as well as colored insets (in a different orientation than in the crystal structure) so that the face-to-face disposition (ca. 5.3–5.5 Å interplanar separation) which is responsible for the excitonic interaction can be visualized.

Fig. 3 presents the BChl *a* pigments of a monomer within the Fenna–Matthews–Olson (FMO) complex, the first chlorophyll–protein complex to be structurally characterized with excellent resolution [21,22]. Again a *syn–syn* dimer formed by BChl *a* molecules coordinated by two proximate histidines is encountered within a special position. One of these two molecules is situated centrally, having the minimal sum of distances to all other BChls (Mg–Mg distances are considered). It is thus ideally placed to receive the EET from the other BChls within the complex. At the same time the other dimer half, which spectroscopically must be indistinguishable as being part of the same red-shifted unit, is well positioned to transmit the EET to the RC, or alternatively, between the monomers of the trimeric FMO complex [23].

In both PS I and the FMO complexes the *anti* (B)Chls outnumber the *syn* ones. Semiempirical computations of the heats of formation indeed indicate a more stable *anti* configuration [19,20]. An interesting reversed situation is encountered within the B850 complex of the LH2 of purple photosynthetic bacteria such as *Rhodopseudomonas acidophila* [24] or *Rhodospirillum molischianum* [25]. Here all the 18 (or 16, respectively) BChls *a* are grouped into *syn–syn* dimers within a protomer [26], although the inter-dimer separation (between adjacent protomers) is actually smaller (0.90 nm Mg–Mg distance) than the intra-dimer separation (0.94 nm). This leads to an extension of the dimeric units, which lose their identity, to a strongly coupled chromophoric system in an *all-syn* configuration. A fully delocalized excitonic state over the whole ring is thus staged [27–29]. All the more loosely coupled B800 BChls are in the normal *anti* ligation, accounting for the rest of nine (or eight, respectively) BChls of the LH2 complexes. Fig. 4 presents one-third of the B800 and B850 rings[2]of the *acidophila* crystal structure with the *syn*-ligated BChls highlighted. Again it is evident that the role of the *syn* BChls (B850 ring) is to act as the red-shifted trap for the EET from the B800 *anti* BChls, as put into evidence by femtosecond pump-probe spectroscopy [30]. Due to the favorable Förster orientation factor[3], EET within the *anti*-ligated B800 BChls, which are 2.1 nm apart (Mg–Mg distance), occurs within 400 fs, while EET from the B800 to the B850 BChls occurs somewhat slower (700 fs), although the Mg–Mg distance is smaller (1.8 nm) due to a less favorable Förster orientation factor. Once the *syn* BChls have been excited, due to the extensive π–π overlap, a Dexter-type EET mechanism[3] operates that is ideal to delocalize and to store the energy among all the *syn* B850 BChls. These then transfer the EET to the larger LH I complex (within 3–5 ps [32]) which engulfs the RC [33,34] and which finally receives the energy by a slower excitation transfer on a 35 ps time scale [32].

The LH3 complex from *Rps. acidophila* strain 7050, which is formed under low-light illumination conditions, has a high homology to the LH2 complex and a similar B800 absorbance, but instead of the B850 BChls it has a B820 band, i.e. a more blue-shifted second absorption band. The crystal structure of this complex, at 3 Å resolution [35], is very similar to the LH2 complex and shows that the B820 ring is also formed from 18 *syn* histidine-coordinated BChls *a* with very similar Mg–Mg distances and orientations of the transition dipole moments as encountered in the B850 ring(s). In this case, the blue shift which leads to more efficient light harvesting under dim light, is accounted for by a change in the conformation of the 3-acetyl group out of the macrocycle plane, which becomes thus less conjugated. Single-molecule fluores-

[1] A referee suggested that a unified nomenclature, which should be unambiguous, should be devised, maybe in a similar manner as the Cahn–Ingold–Prelog (CIP) rules for defining the stereochemistry around stereogenic centers. A first attempt in this direction is exemplified in the caption of Fig. 1. While the convention proposed herein is applicable to chlorins, chlorophylls, bacteriochlorophylls, corrins, etc., where strict rules for numbering the macrocycle exist, it will fail for porphyrins. In corrinoid chemistry the two non-identical faces of the macrocycle are usually referred to as the α- and β-sides, the α-side being the side from which the nucleotide base coordinates the central Co atom. For the more symmetric porphyrins the clockwise/counterclockwise numbering sense may be reversed due to the alphabetical order of the substituents [e.g. acetyl (or 1-ethanone-1-yl) prevails over formyl] and due to the fact that the smallest numbers for the substituents must be chosen (e.g. 3,7-diformyl- is correct although 2,18-diformyl- denotes the same di-substituted isomer). In this case the order of the first three substituents, according to the CIP ranking, could be used to define unambiguously the numbering sense of the macrocycle's numbering, which, however, may contradict nomenclature rules currently in use. Once a numbering scheme is established, we propose that the *syn* coordination denotes the configuration given by the left-hand-rule as explained in the caption of Fig. 1, while the *anti* coordination is the alternate one.

[2] B stands for bulk BChl and 800, 850 or 820 are the wavelengths (in nm) at which the respective absorption bands are encountered.

[3] For a discussion of the Förster (dipolar or Coulomb-type) and Dexter (electron exchange-type) EET in natural and artificial systems see [31]

cence microscopy has recently been performed [36] and confirms that the spectral shift from 850 to 820 nm is not due to changes in the interaction energy but rather in the site energies of the BChls. Thus the *syn* ligation is maintained, which speaks for a very stereospecific incorporation of the pigments within the homologous apoproteins. Subtle conformational changes are then used to fine-tune the absorption characteristics of the complex.

3. Conclusion

We have presented three examples from known crystal structures of natural (B)Chl–protein complexes and here raise the question whether the functional implication of the diastereotopic ligation of the Mg atoms in (B)Chls within the protein matrix is to provide pigments with a more red-shifted absorption. In the case of *syn–syn* dimers, or *syn* oligomers, these would then represent the ultimate energy trap of the respective light-harvesting complex. Our previously presented ZINDO-S calculations [17] are a crude indication towards this assumption. Presently, high-level ab initio calculations appear feasible for histidine-complexed monomers but not for any dimeric Chl assemblies [37]. Accordingly, we would like to stimulate both theoreticians and experimentalists to prove or disprove this intriguing structure–function conjecture. This might help design fully synthetic light-harvesting systems with tunable properties, in view of the still distant goal of artificial photosynthesis.

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