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Origin of the Regioselective Reduction of Chlorins

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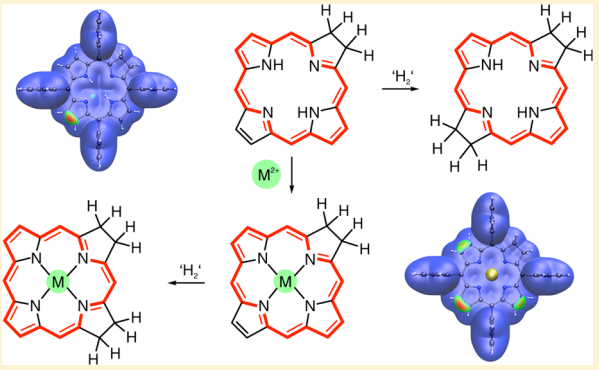
Supporting Information

ABSTRACT: The reduction of a free-base chlorin generally forms a bacteriochlorin (BC), while the reduction of the corresponding metallochlorin forms a metalloisobacteriochlorin (M-iBC). This regioselectivity has been long known but was never fully rationalized. In the free-base case, this regioselectivity can be explained using resonance arguments, but the explanations for the regioselectivity in the metallochlorin reactions requires a more sophisticated approach. A combination of DFT-calculated average local ionization energies (ALIEs), thermodynamics of the products, and the transition-state trajectories of reduction reactions of *meso*-tetraaryl- and *β*-octaethylchlorins, as their free bases and zinc complexes, now fully delineate the theoretical basis of the reduction regioselectivity. The reactions are kinetically controlled. Steric effects originating in the conformational flexibility of the chlorin macrocycle direct the reactions toward the formation of iBCs. Only when electronic effects are strong enough to override the steric effects are BCs formed. Depending on the substituents present on the chlorin, this regioselectivity may change, but ALIE calculations provide reliable guidelines to predict this. The practical value of this work lies in the presentation of a simple predictive method toward synthetic tetrahydroporphyrins by reduction of chlorins.



INTRODUCTION

Hydroporphyrins are key members of the pigments of life (Figure 1).[1−5] The parent porphyrin macrocycle is present in the ubiquitous prosthetic group heme *b*, an iron complex of protoporphyrin IX (**1**).[6] Algae and higher plants use chlorophylls, a group of variously substituted chlorin (7,8-dihydroporphyrin) Mg^{2+} complexes, such as chlorophyll *a* (**2Mg**), as their primary light-harvesting dyes.[7,8] Some bacterial oxidases or catalases contain heme *d*, an iron complex of a chlorin.[9] Other naturally occurring nonphotosynthetic chlorins include bonellin[10] and the tunichlorins.[11,12] Bacteriochlorin (7,8,17,18-tetrahydroporphyrins) Mg^{2+} complexes, such as bacteriochlorophyll *a* (**3Mg**), are the light-harvesting chromophores of phototrophic purple bacteria, heliobacteria, or green sulfur bacteria.[7,13] The natural role of other bacteriochlorins is unknown, but they possess intriguing medicinal properties.[14−17] The iron complex of the isomeric isobacteriochlorin (7,8,12,13-tetrahydroporphyrin), siroheme (**4Fe**), is the prosthetic group in sulfite and nitrite reductases.[18,19]

Bacteriochlorins (BCs) possess near-IR absorbance and emission or singlet oxygen sensitization properties that make them attractive targets for synthetic chromophores to be utilized in tumor imaging,[21] photomedicine,[22−27] or as artificial light harvesting pigments.[28−30] Isobacteriochlorins (iBCs) possess optical properties that are more chlorin-like.[3,31] Generally much less investigated than their isomers,[3,32,33] iBCs have recently stirred interest because of their relatively high 2-photon cross sections,[34−37] and the Ni(I) complex of an iBC was recognized as a "supernucleophile".[38]

A number of methodologies are known that generate synthetic tetrahydroporphyrins,[1−5,32] among them semisynthetic[8,22,33,39] and total synthesis approaches.[40−43] The most common method is the conversion of porphyrins or chlorins.[32] Raney nickel-catalyzed reductions convert chlorins to tetrahydroporphyrins,[44] but the most common and specific reductant is diimide (HN═NH), generated in situ.[25,45−48] However, since many tetrahydroporphyrins tend to oxidize back to the chlorin or porphyrin oxidation state, reactions that irreversibly remove the *β*,*β*′-double bonds from conjugation were developed.[32,49] Most of these reactions are electrophilic attacks on the double bonds by reagents such as OsO_4,[50−58] ozone,[59] or dienes[60−62] or 1,3-dipoles such as azomethine ylides, nitrones, or nitrile oxides.[32,35−37,63−67] Biosynthetically, many hydroporphyrins are generated by enzymatic reduction reactions from porphyrins and chlorins.[68]

An intriguing regioselectivity, first explicitly described in 1969,[45] is generally observed in the majority of abiological tetrahydroporphyrin syntheses by reduction of a chlorin (Scheme 1):[44,52,69−71] The conversion of a free-base chlorin leads to the formation of a BC, while the conversion of a metallochlorin leads to the formation of a metalloisobacteriochlorin (M-iBC). With rare exceptions,[36,37,56] the regioselec-

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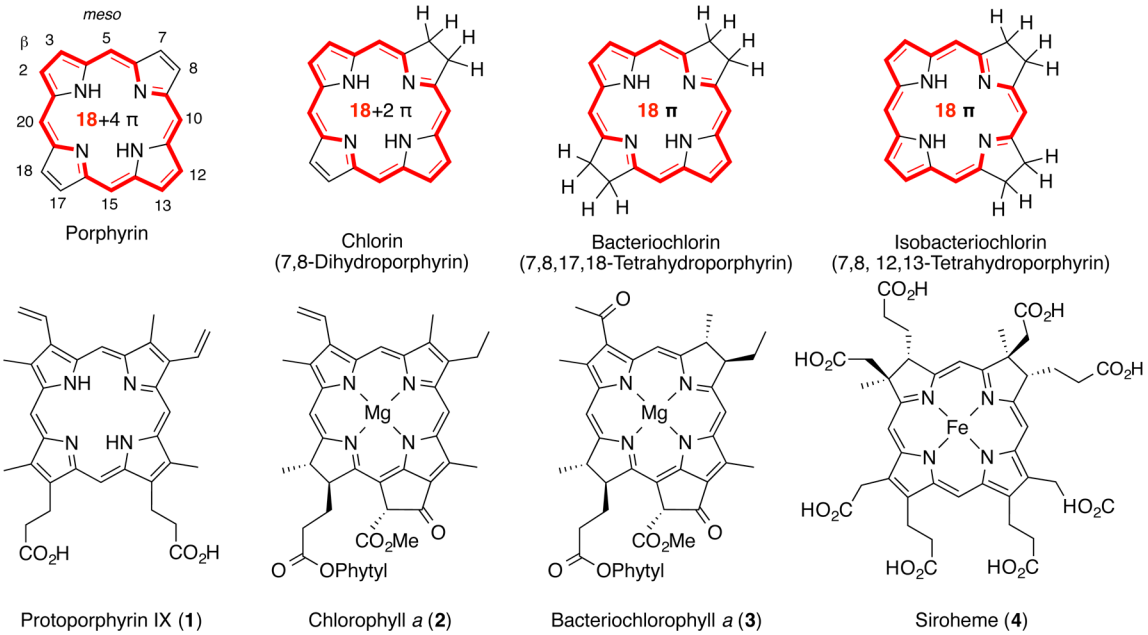
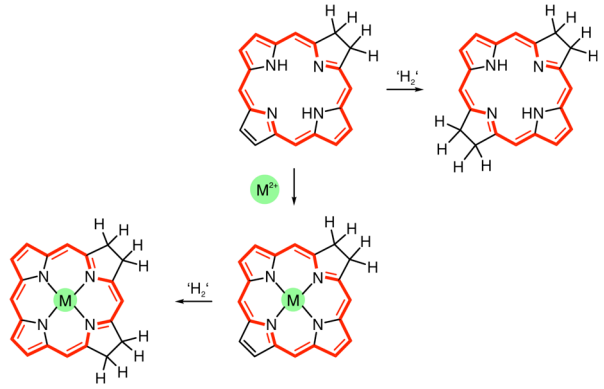


Figure 1. Examples of a naturally occurring porphyrin, chlorin, bacteriochlorin, and isobacteriochlorin and the framework structures and π-systems that characterize their parent chromophore. The IUPAC-recommended numbering system of the porphyrinoid framework is also indicated, as are the β- and *meso*-positions.[20]

Scheme 1. Experimentally Observed Regioselectivity of the Reduction of Chlorins and Metallochlorins



tivity of these reactions is frequently high enough to be practically absolute. Some of the exceptions were attributed to the electronic or steric influences of (electron-withdrawing) substituents in nonsymmetric porphyrins/chlorins,[56] but other examples are less readily explained.[36,37,72]

The formation of a free-base BC from a free-base chlorin can be predicted using simple resonance arguments (elaborated below), but the formation of a M-iBC from a metallochlorin requires more sophisticated explanations. In case of the reduction of symmetric β-octaethyl- or *meso*-tetraarylmetallochlorins, steric effects are not apparent that could direct the reaction one way or the other. Nonetheless, substituent influences were cited as a possible source of the regioselectivity of the dihydroxylation of octaethyloxochlorin and its M^{2+} complexes, but they were not further elaborated.[52] The authors also acknowledged examples in which this metal-induced switching of the regioselectivity was observed but for which substituent effects are unlikely playing a role.[45] Early Hückel calculations could not illuminate the situation.[73,74]

A 2008 DFT study by Jiménez-Osés et al. on the site selectivity of successive 1,3-cycloadditions of free-base *meso*-tetraarylporphyrins with azomethine ylide (forming preferentially iBCs as a mixtures of regio- and stereoisomers) and *N*-methylnitrone (forming preferentially BCs as a mixtures of stereoisomers) provided the best attempt to date to rationalize a related nucleophile-dependent regioselectivity.[72] Neither thermodynamic nor frontier molecular orbital effects could explain the experimental findings, and complete reaction pathway calculations were needed to tease out some nucleophile- and solvent-dependent effects of these complex reactions. However, this investigation did not address the influence of the central metal on the outcome of the reduction of a chlorin.

Computed average local ionization energies (ALIEs) were recently shown to be simple quantitative reactivity predictors of the nucleophilicities of aromatic molecules in cases where steric influences are low.[75] This method provided excellent predictions in cases where more commonly used resonance theory, electrostatic models, Fukui functions, or frontier molecular orbital theories failed to reproduce the experimental findings. In large part, this is because kinetic reactivity cannot be extrapolated from ground-state properties. On the other hand, the ionization energies approximate the electronic energy change accompanying the rate-determining step in the reactions of electrophiles with aromatic molecules. Thus, ignoring steric effects, a plot of the ALIE surfaces allows the direct visualization of the predicted sites of reactivity upon an electrophilic attack. Given the predominantly electrophilic character of the "reduction" reactions that convert chlorins to bacteriochlorins,[32] we were encouraged to also test whether computed ALIE values would allow us to rationalize the regioselective "reductions" of chlorins and metallochlorins.[49]

We describe here the computed ALIEs of free-base and metalated *meso*-tetraphenyl- and ß-octaethylchlorins. These two chlorin classes represent the major synthetic chlorin classes and a simplified model for naturally occurring chlorins, respectively

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(ignoring that many of the naturally occurring chlorins also possess an annulated ring system, cf. to Figure 1). Alas, the ALIE surfaces could only partially reproduce the experimental findings. The relative thermodynamic stabilities of the possible isomeric product pairs also turned out to be an unreliable predictor as to which product will be formed. Therefore, using dihydrogen as a simplified model electrophile with minimal steric bulk, we determined the reaction trajectories of all permutations of the reactions and calculated the activation energy parameters of this reaction, well aware that the direct reaction of hydrogens with chlorins does not take place. However, we rationalized that this hypothetical reaction provides a simplified platform to gain general information about the relative reaction barriers of any reaction with a predominantly electrophilic character. Indeed, this combination of thermodynamic and kinetic considerations provides for the first time a clear description of the origins of the regioselectivity of the reduction of chlorins and metallochlorins.

RESULTS AND DISCUSSION

The Reduction of Free-Base *meso*-Tetraphenylchlorin. The regioselectivity of the reduction of free-base *meso*-tetraphenylchlorin (as well as *β*-octaethylchlorin, discussed below) can be rationalized in a straightforward manner using resonance arguments (Figure 2):[45,52,73] As demonstrated experimentally, the dominant, low-energy chlorin tautomer **5H$_2$-A** carries the inner NH protons at opposite nitrogens.[76,77] This "isolates" the pseudo-olefinic *β*,*β*′-double bond opposite of the pyrroline moiety by virtue of the fact that removal of this bond from conjugation has the least impact on the resonance stabilization energy of the central 18-*π* electron system.[78] Therefore, a reduction of a second *β*,*β*′-double bond in a free-base chlorin preferentially generates a BC over the corresponding iBC. The driving force toward BCs is strong, as examples that override inhibiting steric substituent effects demonstrate.[48]

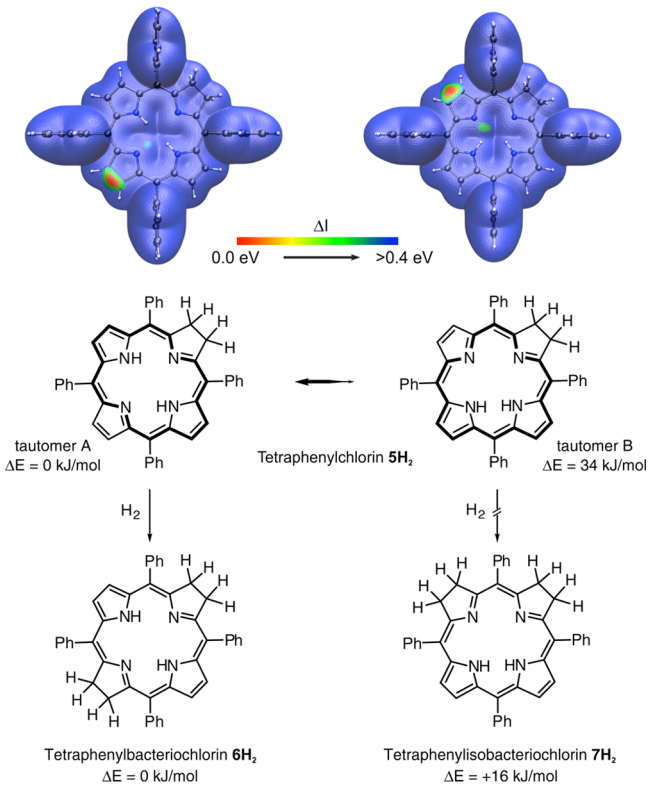

Figure 2. Outcome of the reduction of free-base *meso*-tetraphenylchlorin (**5H$_2$**) in its prevalent tautomer **5H$_2$-A** and its energetically unfavored tautomer **5H$_2$-B**, with the computed ALIE surfaces of both tautomers, highlighting the sites of highest nucleophilicity. The red color in the ALIE surfaces shows the area of lowest ionization energy.

This bond activation of the double bond opposite the pyrroline moiety toward an electrophilic attack can also be visualized using ALIE surfaces (Figure 2). In tautomer **5H$_2$-A**, the *β*,*β*′-double bond opposite of the pyrroline moiety is by ∼0.5 eV more readily oxidized than either of the two adjacent *β*,*β*′-double bonds. Electronic (kinetic) arguments therefore also correctly predict that a BC is the only product of an electrophilic attack. Interestingly, the ALIE surface for the high energy tautomer **5H$_2$-B** (+34 kJ/mol, and thus not present in the equilibrium mixure) predicts that an iBC will be formed.

Thermodynamically, the BC product is also preferred by ∼16 kJ/mol over the isomeric iBC. This large thermodynamic bias can primarily be attributed to the increased steric interaction of the inner NH protons that are forced in an iBC to be located on adjacent nitrogens. Hence, resonance, thermodynamic, and electronic arguments are all in accordance with the experiment. As will be shown below, other scenarios considered here are not as clear cut.

Reduction of *β*-Octaethylchlorins. Equivalent resonance arguments brought forward for the reduction of *meso*-tetraphenylchlorin (**5H$_2$**) also hold for the outcome of the reduction of *β*-octaethylchlorin (**8H$_2$**). Thus, the ALIE surfaces for **8H$_2$** show that the *β*,*β*′-double bond opposite the pyrroline moiety is activated toward ionization (Figure 3).

However, the presence of ethyl groups at the *β*-positions introduces a systematic complication. Each ethyl side chain can assume one of two principle conformations: either pointing above or below the plane defined by the chlorin. We assume fast rotation of the ethyl groups and rapid equilibration between all conformers. The rear side (the hemisphere both ethyl groups point away from) is the one that is sterically more accessible for any incoming electrophile. Importantly, the ALIE values of a pyrrole *β*,*β*′-double bond are also dependent upon whether the front or rear side is considered, with the rear side possessing a lower ionization potential of 0.47 eV because of a stabilizing hyperconjugation effect with the ethyl chain. ALIE computations further revealed that the conformation of all other *β*-ethyl side groups have negligible effects on the ionization potential of the *β*,*β*′-double bond to be reduced. This allows a reduction of the computational efforts by considering only one conformer, namely the one shown presenting all ethyl substituents on one hemisphere (for the ALIE surfaces of other conformers, see the Supporting Information).

All of the reduction/addition reactions considered here possess *cis*-selectivity. Hence, a *cis*-reduction of *β*-octaethylchlorin (**8H$_2$**) can form a *trans*- (**9H$_2$-*trans***) and a *cis*-BC (**9H$_2$-*cis***), depending on whether the chlorin-to-BC reduction takes place from the opposite or the same side as the initial porphyrin-to-chlorin conversion. The experimental ratio of the *trans*- and *cis*-isomers resulting from, e.g., the diimide reduction of octaethylporphyrin **8H$_2$** is not known,[45] but the computations predict only a small to negligible thermodynamic preference for the *cis*-isomer (by 1.8 kJ/mol). It was experimentally determined that the OsO_4-mediated dihydroxylation reaction of *meso*-tetraaryl-7,8-dihydroxychlorins appear

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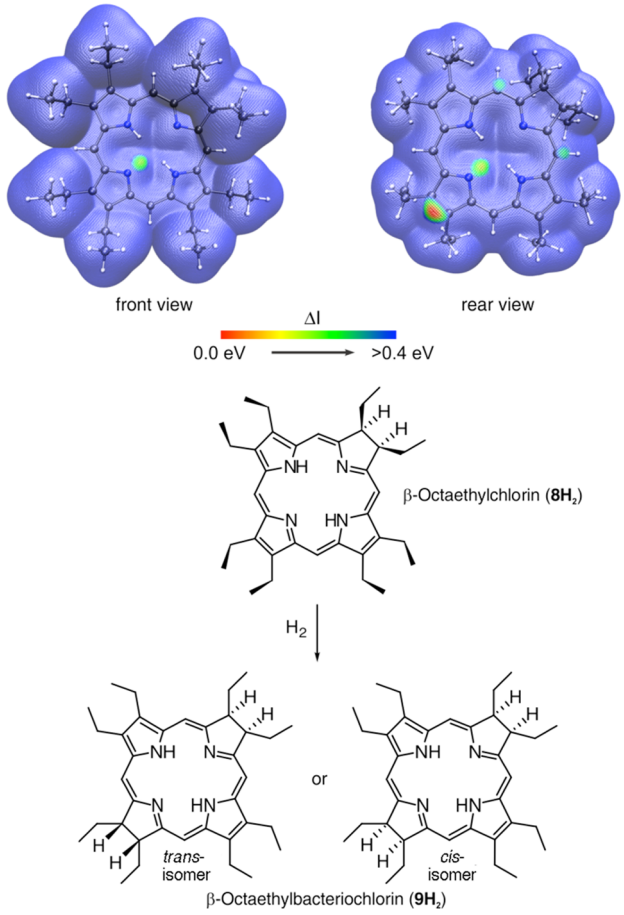

Figure 3. Outcome of the reduction of free-base *β*-octaethylchlorin ($\mathbf{8H_2}$) in its prevalent tautomer; conformer with all ethyl substituents on the same side of the porphyrin plane, top and bottom views, the corresponding computed ALIE surfaces and the two possible stereoisomeric BC products. The red color in the ALIE surfaces shows the area of lowest ionization energy.

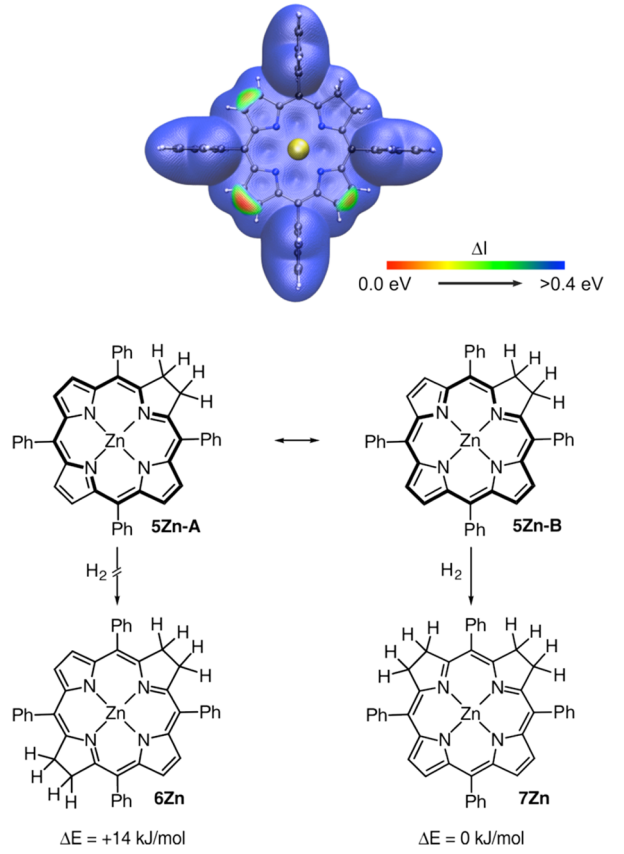

Figure 4. Outcome of the reduction of metalated *meso*-tetraphenylchlorin (**5Zn**) in its two limiting resonance structures, **5Zn-A** and **5Zn-B**, and its computed ALIE surface. The red color in the ALIE surface shows the area of lowest ionization energy.

to slightly prefer the formation of the bacteriochlorin tetraol *cis*-isomers.[58]

The switch from *meso*-substituents to *β*-substituents does not change the relative thermodynamic stability of the two possible regioisomeric tetrahydroporphyrins. Thus, the thermodynamic stability of free-base iBCs $\mathbf{10H_2}$, in both their *cis*- and *trans*-forms, are energetically by about 12 kJ/mol less stable than the corresponding BCs $\mathbf{9H_2}$. However, since the experimental reduction of octaethylchlorin $\mathbf{8H_2}$ leading to the formation of BCs ($\mathbf{9H_2}$)[45] is not reversible, kinetic effects should direct the regioselectivity of the reaction.

We also note that the ALIE surfaces also predict enhanced reactivity of the *meso*-positions adjacent to the pyrroline toward electrophiles when compared to the reactivity of the distant *meso*-positions. While this reactivity rationalizes the synthetically important ability to introduce *meso*-substituents to a chlorin moiety in a regioselective fashion,[79] we will not discuss this *meso*-reactivity of chorins any further, except to say that ALIE surface plots appear to be a valuable tool in the prediction of the regioselectivity of these reactions.

Reduction of [*meso*-Tetraphenylchlorinato]zinc(II) Complexes. The replacement of the two inner hydrogens in chlorin $\mathbf{5H_2}$ by a zinc atom in **5Zn** renders any tautomer arguments to explain the regioselectivity of a reduction reaction obsolete, and the relative stability of the two limiting resonance structures **5Zn-A** and **5Zn-B**, cannot be readily discerned (Figure 4). The ALIE surface computed for metallochlorin **5Zn** identifies all of the three possible *β*,*β*′-double bonds as possible reaction sites, but the two different site types (adjacent and opposite of the pyrroline) possess dissimilar ionization energies. The *β*,*β*′-double bond opposite the pyrroline has the lowest ionization energy, with the adjacent pyrrole double bonds requiring a 0.09 eV higher energy for ionization. Using purely electronic arguments, the reduction of metallochlorin **5Zn** is expected to form a ∼3:1 mixture of metallobacteriochlorin (M-BC) **6Zn** and M-iBC **7Zn**, a prediction not matched by the experimentally observed complete regioselectivity toward the M-iBC.[45] Thermodynamically, M-iBC **7Zn** is ∼14 kJ/mol more stable than the corresponding isomer M-BC **6Zn**. In a purely thermodynamically controlled (equilibrium) reduction reaction, therefore, the M-iBC product **7Zn** would indeed be the sole (>99.9%) product. However, given the assumed irreversibility of the reduction reactions (and the indications listed above), the reaction is unlikely thermodynamically controlled.

Reduction of [*β*-Octaethylchlorinato]zinc(II) Complexes. Considering the ALIE surface of the zinc complex of octaethylchlorin **8Zn** (Figure 5), both types of *β*-double bonds are activated toward an electrophilic attack, with the position opposite of the pyrroline also slightly more active (by 0.09 eV). And again, solely based on the ionization energy differences, a 3:1 ratio in favor of the M-BC **9Zn** would therefore be expected (as a mixture of *cis*- and *trans*-stereoisomers). In contrast, the thermodynamic product is M-iBC **10Zn**, with an advantage of ∼15 kJ/mol over the M-BC isomer **9Zn**, with a negligible

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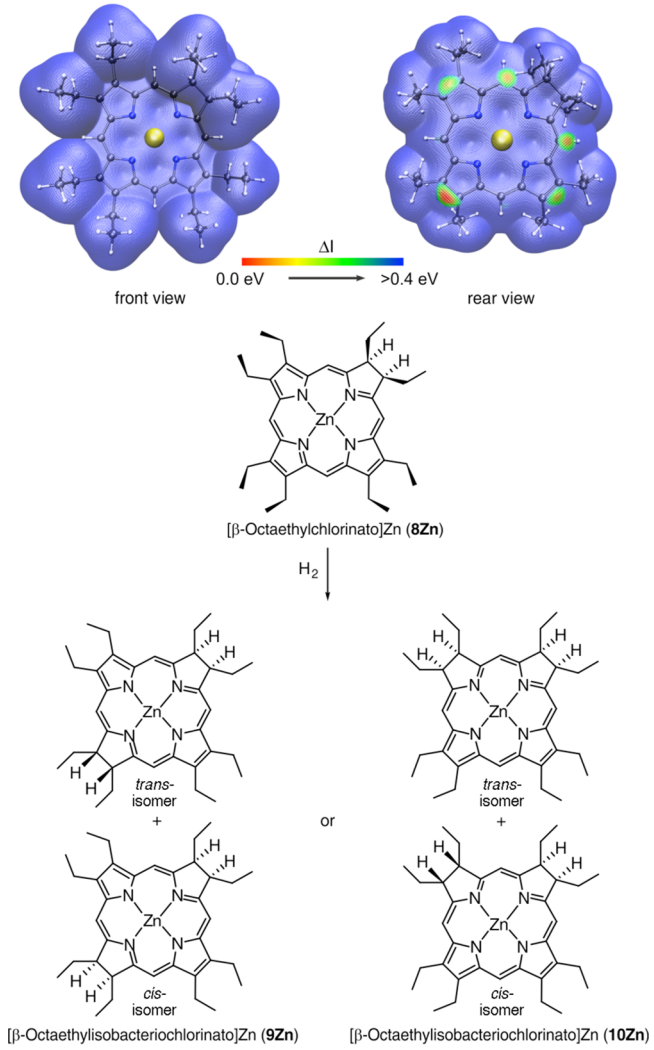

Figure 5. Computed ALIEs of the *β*-octaethylchlorin zinc complex (**8Zn**); conformer with all ethyl substituents on the same side of the porphyrin plane, top and bottom views, and the two possible stereoisomeric iBC products that are predicted to form. The red color in the ALIE surfaces shows the area of lowest ionization energy.

difference between the energy of the *trans*- and *cis*-products (0.56 kJ/mol, i.e., less than the typical error of the method used).

Reduction-Step Transition-State Calculations. Taken together, neither the ALIEs nor the relative thermodynamic stabilities of the isomeric product pairs are good predictors for the regiochemical outcome of the chlorin reductions. Seemingly, the controlling factors change with the presence of *meso*- or *β*-substituents and with the metalation of the chlorin. To shed light on the mechanism of these reductions, we performed transition-state (TS) calculations, at the B3LYP-D3/def2-SVP level, on the reduction of *meso*-tetraphenylchlorin **5** and *β*-octaethylchlorin **8** in their free-base (**5H$_2$**, **8H$_2$**) and zinc(II) complex forms (**5Zn**, **8Zn**) using dihydrogen as a model electrophile with minimal bulk. We determined two trajectories for each chlorin, one leading to the corresponding BC/M-BCs and resulting in TS$^{\#1}$ and a second leading to the corresponding iBCs/M-iBCs, delivering TS$^{\#2}$.

Since we were only interested in the differences between pairs of TS, and not their absolute values, we determined $\Delta\Delta G = \Delta G(\mathrm{TS}^{\#1}) - \Delta G(\mathrm{TS}^{\#2})$, whereby the transition state TS$^{\#1}$ ΔG value was arbitrarily set as a reference point (at 0 kJ/mol). It follows that a positive $\Delta\Delta G$ value corresponds to a lower TS for the reaction leading to the formation of a BC, while a negative value corresponds to a preference for the formation of an iBC. We further assumed ideal Curtin−Hammett-type behavior to allow the calculation of the product ratios from the $\Delta\Delta G$ values derived. The results are tabulated in Table 1.

We further dissected the differential activation energy parameters to gain a more detailed insight into the electronic and steric influences factors controlling the regioselectivity of the reductions. Given the premise that the differences of the ALIE values (ΔI) along the two different pathways approximate the electronic barrier toward electrophilic attack onto the double bond,[75] we can estimate the energy value attributed to steric effect ($\Delta E_{\mathrm{steric}}$) by subtracting the "electronic" factor ΔI from the overall barrier difference $\Delta\Delta H$ (Table 1).

The $\Delta E_{\mathrm{steric}}$ values suggest that in all cases TS$^{\#2}$ (leading to the formation of an iBC) is the sterically less demanding TS, with the steric demands being ∼25 kJ/mol higher for the free-base derivatives. At first glance, this is a counterintuitive finding since one would expect a smaller steric influence farther away from the already established pyrroline than closer by. However, ring strains explain the findings: In the TS, the reacting pyrrole is slightly bent out of plane to avoid a perfectly eclipsed arrangement of the pyrroline hydrogens, affecting also the conformation of the remainder of the macrocycle. Evidently, the trajectory leading toward the formation of iBCs is better able to accommodate this strain than the corresponding alternative trajectory leading to the formation of BCs (see the Supporting Information for further information). Ring strain also explains the smaller steric differences for the metalated chlorins as the whole macrocycle is less flexible, and thus, any steric differences get smaller.[80,81]

Because of the comparable steric preferences within each class of chlorins, the TS calculations isolate electronic factors (ionization potential ΔI values) as being the decisive controlling factor of the reduction regioselectivity. Only in

Table 1. Differential Gibbs Energies ($\Delta\Delta G$), Enthalpies ($\Delta\Delta H$), Entropies ($\Delta\Delta S$), Average Local Ionization Energies (ΔI), and Approximated Steric Energies ($\Delta E_{\mathrm{steric}}$) of TS$^{\#2}$ (chlorin → iBC) Relative to TS$^{\#1}$ (Chlorin → BC)[a]

compd being reduced	$\Delta\Delta G$	favored product	$\Delta\Delta H$	$\Delta\Delta S$	ΔI (from ALIE)	$\Delta E_{\mathrm{steric}} = \Delta\Delta H - \Delta I$
meso-tetraphenylchlorin						
free-base **5H$_2$**	23.3	BC	4.9	−18.4	52.1	−47.2
zinc complex **5Zn**	−35.4	M-iBC	−18.1	17.3	8.7	−26.8
β-octaethylchlorin						
free-base **8H$_2$**	12.6	BC	10.5	−2.1	53.0	−42.5
zinc complex **8Zn**	−52.0	M-iBC	−9.0	14.2	8.7	−17.7

[a]All energies are given in kJ/mol and were derived from B3LYP-D3/def2-SVP calculations (at 298 K).

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the presence of large, favorable ΔI values will the steric propensity to form isobacteriochlorins be overridden, leading to the formation of BCs. Otherwise, the intrinsic macrocycle steric strains dominate and the iBC is formed. In case of free-base chlorins, the ionization potential (ΔI) value has to be above 50 kJ/mol (~0.5 eV); for the metaled derivatives a lower ΔI value of 0.3 eV is sufficient. It therefore follows that the metal is not acting as an electronic directing group but that instead it has a direct steric influence. The prediction of the site of reduction of chlorophyllide *a* illustrates these points.

Reduction of Chlorophyllide *a*. A key step in the biosynthesis of the BC bacteriochlorophyll *a* is the chlorophyllide *a* reductase-mediated reduction of the chlorin magnesium complex, chlorophyllide *a* (**11**) (Figure 6). The regioselectivity of this reduction is surprising since, as delineated above, the natural propensity of a metallochlorin is to form a M-iBC. Furthermore, bacteriochlorophyll *a* is not the thermodynamically preferred product (5 kJ/mol higher than the minimum 2,3,17,18-reduced isobacteriochlorin).

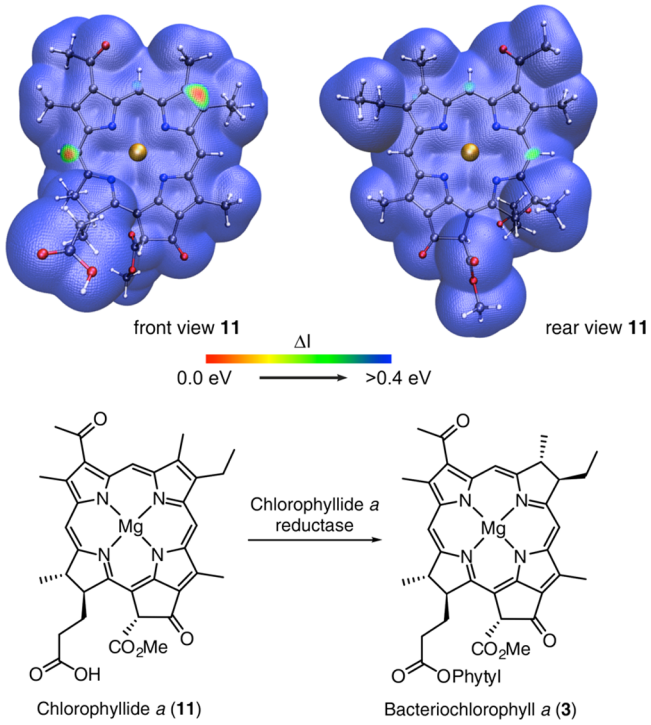

Figure 6. Key chromophore reduction step in the biosynthesis of bacteriochlorophyll *a* (**3**). The red color in the ALIE surfaces shows the area of lowest ionization energy.

Indeed, the ALIE surface of chlorophyllide *a* indicates the lowest ionization potential for the *β*,*β*′-double bond opposite the pyrroline while the other *β*,*β*′-double bonds have (at least) 0.4 eV higher ionization potentials. Thus, the intrinsic reactivity of the metallochlorin is overridden and the metallobacteriochlorin bacteriochlorophyll *a* is the sole expected product (the fact that the reduction takes place in a *trans*-fashion notwithstanding). An equivalent reactivity of related metallochlorins toward OsO_4-mediated dihydroxylations was reported.[56]

CONCLUSIONS

In conclusion, a number of tools were used to investigate the origin of the regioselectivity of the chlorin/metallochlorin reduction reaction (Table 2). Using resonance structures, the regioselectivity could not be rationalized for metallochlorins. The thermodynamic stability of the isomeric BC/iBC products proved to be an altogether unreliable predictor. Unqualified ALIE calculations predict the outcome of the reduction of free base chlorins correctly but provide ambiguous results for the metal complexes. Only the computationally most expensive TS calculations allowed a reliable prediction of the experimental results. Importantly, the detailed TS calculations provided insight into the molecular origin of the regioselectivity: In the absence of any substituent effects, the regioselectivity originates primarily in the intrinsic conformational flexibility of the chlorin macrocycle that steers the reduction—independently of the presence of the metal—toward the formation of iBCs/M-iBCs. On the other hand, the ionization potentials of the bonds to be reduced, as defined by the ALIE calculations, suggest that the formation of the isomeric BCs/M-BCs should be preferred. Only when the difference in the electronic barrier toward electrophilic attack is particularly high (>0.3 eV for metalated compounds and >0.5 eV for free-base chlorins) does it override the conformational barrier and, therefore, determine the outcome of the reaction. This electronic barrier height then defines the boundary conditions for the interpretation of ALIE surfaces, allowing us to rationalize and predict the experimentally observed regioselectivity of the reduction of a second *β*,*β*′-bond of free-base and metalated chlorins. Importantly, the regioselectivity of the reduction is intrinsically independent from the presence of a central metal.

Table 2. Fidelity of the (Computational) Methods Utilized To Predict the Experimentally Determined Outcomes[a]

Reduction of:	(Computational) Method: Tautomeric/-Resonance-Structures	ALIE	Thermodynamics	TS Calculation
meso-Tetraphenylchlorin	●	●	●	●
[*meso*-Tetraphenylchlorinato]Zn	●	◐[b]	●	●
ß-Octaethylchlorin	●	●	●	●
[ß-Octaethylchlorinato]Zn	●	◐[b]	●	●
Chlorophyllide *a*	●	●	●	--

[a]Key: green, correct prediction; red, wrong prediction; red/green, partially correct prediction; black, no prediction possible; −, not determined. [b]With application of the ΔI threshold of 0.3 eV.

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Our findings have obvious implications for the formation of synthetic tetrahydroporphyrins by reduction of chlorins. The ALIE method is recommended as a computationally inexpensive tool to predict the site of reduction of chlorins/metallochlorins with only one limitiation: only reduction reactions that have a dominating electrophilic character can be predicted; radical or dissolved metal-type reductions, for instance, cannot be predicted by the method delineated. In fact, these reductions are also not subject to the regioselectivity described.[32]

COMPUTATIONAL DETAILS

All calculations have been done using Gaussian09[82] using B3LYP-D3/def2-TZVP for the ground-state optimizations and B3LYP-D3/def2-SVP for the transition-state calculations. To verify ground and transition states, frequency computations were performed (no imaginary frequencies for ground states and one imaginary frequency for the transition states). A combination of multiwfn,[83] VMD,[84] and PovRay was used to graph the ALIE surfaces.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates and energies in hartrees of the main compounds as well as animated gifs of the imaginary vibration of the transition states and additional ALIE surfaces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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