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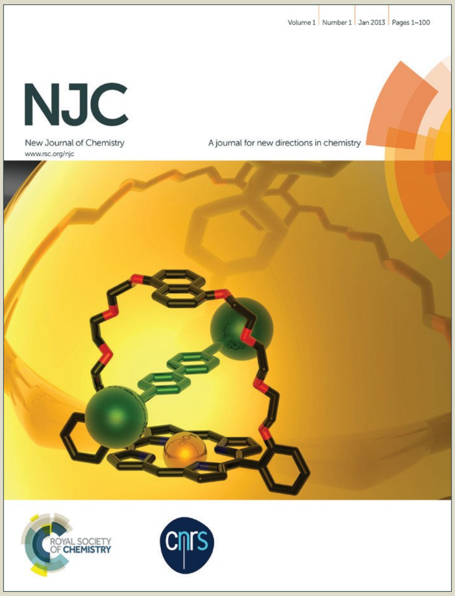

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Interactions of copper (II) and zinc (II) with chlorophyll: insights from Density Functional Theory Studies.

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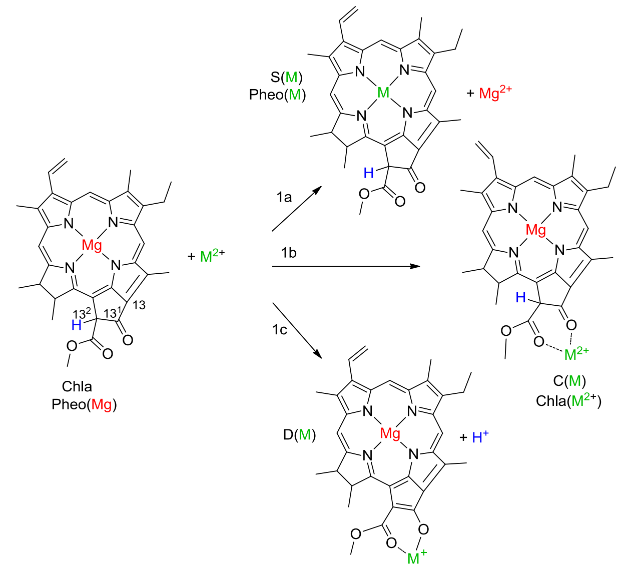
Reaction of chlorophyll (a) with Cu^{2+} or Zn^{2+} in presence of acetonitrile has been studied on a slightly simplified model using DFT computations of three potential processes: substitution of the central Mg^{2+} cation, chelation of the peripherial keto-ester, associated or not to deprotonation. Mg-substitution is found to be highly favored in the case of copper, whereas chelation without deprotonation is proposed to occur for zinc. It is proposed that chelation associated to deprotonation could become competitive if water is present in the reaction medium. The resulting compounds are shown to have interesting electronic properties as metal→ ligand spin transfer is observed in the case of Cu^{2+}.

Introduction

Characterization of chlorophyll properties in reaction conditions and mechanisms at stake during photosynthesis has made considerable progress in the past four decades,[1] down to the isolated molecule level.[2] Among them, computational approaches proved valuable in understanding the energetic[3,4,5] and electronic[6,7,8] properties as well as the reactivity[9,10,11] of these systems. In parallel, mastering the potential modulation of its properties to develop new bio-inspired tools for health[12] or energy conversion[13] remains a major challenge to chemists.[14] In particular, formation of bimetallic complexes proved an interesting direction.[15] Numerous experimental approaches were developed, either through total synthesis or through functionalization of the natural materials. Among them, modulation of its reactivity upon direct reaction with metal cation is of great interest as it would shed light on both the toxicity mechanisms of these metal cations and the potential properties of these systems. Despite these motivations, the experimental data remain scattered[16,17] and computational approaches to their properties are mostly non-existing,[18] which makes the rationalization challenging. The majority of the experiments are concerning Cu or Zn interaction with chlorophyll or with simpler models. In particular, when it comes to the point of how Cu^{2+} or Zn^{2+} can interact with chlorophyll, three different coordination processes are proposed (Scheme 1).



Scheme 1: Three possibilities for reaction of M^{2+} = Cu^{2+} or Zn^{2+} with Chla: substitution (process 1a), chelation (process 1b) and deprotonation (process 1c).

They are based on two important sites of chlorophyll a. The the Mg^{2+} cation bonded in the center of the tetrapyrrole macrocycle called pheophytin (Pheo) is the first reactive group. The ß-ketoester site at the periphery (13^1,13^2 position according to IUPAC labelling)[19] is the second one. Chla will also be named Pheo(Mg) in this work, since it can be viewed as a Mg^{2+} complex of the Pheo ligand. In the first reaction process, denoted later as substitution, the central Mg^{2+} cation is replaced by Cu^{2+} or Zn^{2+} (eq. 1a), yielding the substitution complex S(M) (M = Cu or Zn), which can be also considered as a Pheo(M) complex. This is the most commonly proposed process, and appears to be preferred for Cu^{2+}.[16b] In the second one, considered as chelation, the incoming cation binds to the

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Electronic Supplementary Information (ESI) available: Cartesian coordinates and thermodynamic data for all optimized geometries, TD-DFT simulation and tests for UV-visible spectra. See DOI: 10.1039/x0xx00000x

ß-ketoester system at the periphery of the chlorin ring (eq. 1b). This yields the chelation complex C(M), which can be viewed as a complex of M^{2+} with the Chla as ligand, also called Chla(M). This is claimed to be one of the major product for Zn^{2+} interaction with chlorphylls.[17i] In the third one, named later deprotonation, the coordination of the incoming cation to the ß-ketoester system is associated to the deprotonation of the sp^3 carbon in position 13^2(eq. 1c) to form complex D(M). This process was proposed in the 70's to take place in presence of excess Mg^{2+} and allowed interpreting bands evolution in IR data.[20] It was later proposed in the case of Zn^{2+}.[16d] No computational evaluations of these processes has ever been done to our knowledge. The sole theoretical studies involving zinc or copper are dealing with UV visible data on zinc porphyrins[18b] or zinc pheophytin[18a]. We hereafter present computational evaluation of these processes.

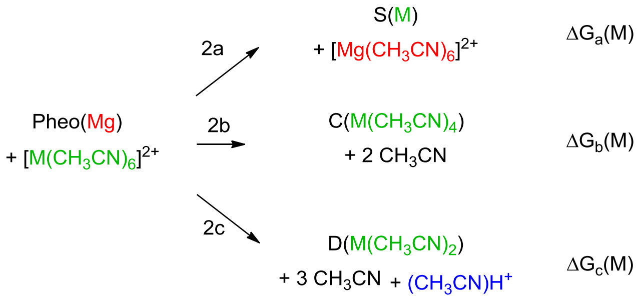
Results and Discussion

Solvation considerations.

The processes introduced in Scheme 1 are formal equations as they don't take into account the species really at stake in solution. In particular, solvent or additives coordination to the metal cation is not included. These are especially important to include as they play a major role in the theoretical evaluation of the energetic of the three processes. Indeed, they imply modifications of the charge of the system and of the coordination number at the metal cation. Considering the reaction takes place in coordinating solvent and involves coordinating Lewis acids, an adequate modelling requires introduction of explicit binding molecules.[11e] Acetonitrile CH_3CN was used as a model of binding additive, as it has been used experimentally as solvent for spectroscopy[21,] and for studies of chlorophyll-cation interaction[17e]. In addition, it has been proposed as a model of biological substrate[22]. The number of CH_3CN molecules added to the various complexes is justified in the computational section and defines the modelling scheme. The equations modelling the processes in Scheme 1 resulting from these choices are given in Scheme 2. When acetonitrile is bonded to the metal centers in the C(M) or D(M) species, it is mentioned in the parenthesis together with the metal M. Since the number of molecules on the product side depends strongly on the process at stake, the entropic contributions will be strongly different in the three processes so that the Gibbs free energy must be used for evaluation of the potential reactivity. They will be reported, for the three processes 2a, 2b and 2c, together with electronic and geometrical data, in the following.

Substitution Process (2a).

We will first examine the thermodynamic of the substitution process, that is the exchange of the central Mg by either Cu or Zn. The main geometrical, electronic and energetic date for compounds S(M) are reported in Table 1. At first glance, it can be seen that the metal cation, either native (Mg) or substituted (Cu or Zn), is located in the plane of the chlorin ring, the out-of-plane distortions being in all cases negligible.



Scheme 2. Equations chosen to model the processes proposed in Scheme 1

Table 1: geometric (distances in Å) and energetic (in kcal mol 1) parameters for S(M) complexes as a function of M.

	Mg^{2+}	Cu^{2+}	Zn^{2+}
<M-NNN>	0.004	0.012	0.009
M-N(I)	2.031	1.972	1.981
M-N(II)	2.149	2.105	2.181
M-N(III)	2.017	1.950	1.975
M-N(IV)	2.074	2.010	2.053
<M-N>	2.068	2.009	2.047
Δ(M-N) [a]	0.132	0.155	0.206
E_{bind}[b]	-721.6	-827.1	-791.8
ΔG_a	-	-44.1	-19.2
ΔG_{CH3CN}	-2.4	5.3	1.6
NPA charge	1.413	1.116 (0.676)[c]	1.287
Valence pop NPA	3s(0.26) 3p(0.32)	3d(9.14) 4s(0.41) 4p(0.33)	3d(9.91) 4s(0.44) 4p(0.37)

[a] Δ(Mg-N) is the difference between the longer and the shorter M-N bond; [b] E_{bind}=E (S(M)) - (E (M^{2+}) + E (Pheo)).; [c] in parenthesis, difference between α and β valence population of Cu, which can be interpreted as spin at the Cu center.

The value obtained for Mg is in good accordance with experimental X-ray results in protein,[23] or with previous theoretical studies[6,9a,24]. A closer look at the M-N distances reveals that M does not exactly lies at the N barycenter and a dissymmetry in the M-N distances, according the following trend: M-NII > M-NIV > M-NI > M-NIII. Substitution of metal cation Mg by Cu and Zn divalent ions retains the order of M-N bond distances. The average of the M-N distances <M-N> is smaller in the substitution complexes S(Zn) (2.047 Å) and S(Cu) (2.009 Å) than in the chlorophyll model Pheo(Mg) (2.068 Å). In the case of copper, the smaller M-N distance is associated to a larger binding energy. The dissymmetry of the M-N bonding scheme has been evaluated using Δ(M-N), which is the difference between the longer and the shorter M-N distances. It is found to be larger in the substitution complexes, especially in the case of zinc.

The Gibbs free energy of process 2a ΔG_a is reported in Table 1. The substitution process is found to be exergonic for both copper (-44.1 kcal mol-1) and zinc (-19.2 kcal mol-1). The substitution of Mg by Cu is the most favorable process. These results are consistent with experimental findings.[16a,16b,17h] This preference can be associated with a stronger binding of copper to the Pheo ligand compared to the other cations, a preference which is not offset by solvation of the free cations, or by inclusion of additional implicit solvation (see E.S.I).

Better understanding of this preference is found in the population analysis of the Chla model and of the two substitution compounds S(Cu) and S(Zn). The charge on the central atom is smaller in the S(M) compounds, compared to chlorophyll, even though the central atom formally bears in all cases a +2 charge. All the cations have a computed charge significantly smaller to +2, as expected from the strong charge transfer from the Pheo macrocycle to the central cation. The charge transfer nevertheless remains significantly smaller than 1 e, evidencing a rather ionic Pheo-M binding. A population analysis of the valence shell allows decomposing this charge transfer. The population of the p orbitals is similar for the three cations, but that an increase of the population of the s shell (from 0.26 to 0.42 in averages) is responsible for the difference between the native metal (Mg) and its substituted. The difference between Cu and Zn comes from the behavior of the d shell, which is slightly depleted in the case of Zn (9.91 instead of an expected value of 10) whereas it is slightly overpopulation for Cu (9.16 instead of 9). Let us also notice that, for copper, the spin is majorly located on copper, proving the small amplitude of the $Cu^{2+} \rightarrow$ Pheo spin transfer.

The Pheo → M^{2+} charge transfer, which can be computed from the difference between +2 and the cation charge (0.587 for Mg, 0,713 for Zn and 0,884 for Cu), is found to correlate with : i) the binding energy of the central cation to the Pheo macrocycle (which becomes more negative for larger charge transfer : -721.6, -791.8 and -827.1 kcal mol^{-1} respectively) ; ii) the average M-N bond length (which becomes shorter for larger charge transfer : 2.068, 2.047 and 2.009 Å respectively).

Interestingly, the value of the charge on the central atom can be correlated to the Gibbs Free Energies of binding for CH_3CN to the central atom which becomes less favorable (-2.9, +0.8 and +5.2 kcal mol^{-1} for Mg, Zn and Cu) as the charge decreases (1.41, 1.29 and 1.12 respectively). A similar binding trend is also obtained when coordination of tetrahydrofuran (resp. -6.2, -1.5 and +3.8 kcal/mol) or pyridine (resp. -6.1, -3.4 and 4.6 kcal/mol) to the central metal are examined.

We next tried to evaluate the UV-visible properties of these substitution compounds. Considering the difficulties associated to a precise reproduction of the position of the bands,[6] we only focused on their displacement upon the three processes (2a, 2b or 2c). The Q-band of chlorophyll can be quite easily reproduced computationally as it is made of a single strong transition at 579,6 nm (Q_y, whereas Q_x participation to the band maximum remains negligible). As this is not the case for the B-band (B_1-transition at 391.6 nm and B_2 at 373.1 nm, see ESI), we focused only on the Q one. As coordination of one acetonitrile molecule to Mg cation should occur in Chla, explicit solvation by coordination of one acetonitrile molecule was also examined. The change on the Q_y state is negligible (+ 2 nm). In contrast, substituting the central Mg^{2+} cation by Cu^{2+} (572.4 nm (intensity : 0.2471)) or Zn^{2+} (571.9 nm (intensity : 0.2386) slightly increases the Q_y transition energy, with a lowering of the transition wave length by 7 to 8 nm.

As a conclusion, substitution is found to be possible for both Cu^{2+} and Zn^{2+} and is associated to a slight shift of the Q-band for both cations without significant change of the band height.

Chelation Process (2b).

The second process proposed in the literature is the chelation of the Cu^{2+} or Zn^{2+} on the periphery of the chlorophyll without departure of the central Mg^{2+} cation. The obtained complex bears a +2 charge. This process should be favored kinetically, as it does not imply Mg-N bond breaking. The chelation products are obtained by coordinating Cu^{2+} and Zn^{2} at the β-keto-ester site and by completing the coordination sphere of the cation by four CH_3CN molecules (see Computational Details), thus ensuring a pseudo-octahedral coordination of the incoming cation. Two acetonitrile molecules are thuis released in this process. The major geometric and energetic parameters of the obtained complex are given in Table 2. The coordination of the magnesium in the central pocket is very similar to that in the non-chelated chlorophyll. The average Mg-N distance is modified by only 0.003 Å and the dissymmetry in the Mg-N bond Δ(Mg-N) is decreased by no more than 0.011 Å. Consistently, the charge (NPA) at the Mg cation is not significantly altered by upon chelation at the periphery. Considering the chelated cation itself, copper exhibits slightly shorter M-O distances than zinc, as already observed for the Cu-N and Zn-N distances in the substitution compound S(M). The charge at the metal follows the same trend: it is smaller for Cu (1.065) than for Zn (1.154), in line with stronger ligand-metal interaction for the former. These charges are slightly smaller than those for the substitution compound, which can be proposed as the result of equilibrium between two opposite effects: chelation compounds $C(M(CH_3CN)_4)$ exhibit a larger coordination number (6 with respect to 4 in S(M)) at the metal (increasing the number of ligand → metal interactions) whereas in S(M) the ligand formally bears a -2 charge (instead of 0 in $C(M(CH_3CN)_4)$, and should thus be considered as more electron donating).

The Gibbs free energy for the chelation process 2b is given in Table 2. Both chelation of copper and zinc is found to be exergonic, but this value is found to be highly sensitive to the inclusion of implicit solvation (see E.S.I.). This induces a strong sensitivity of the process to reaction environment. As for substitution, chelation of the copper is found to be preferred over that for zinc. But the difference between the two cations is much smaller than in the case of substitution. To put these results in perspective with experimental data, it should be taken into account that the ester chain can be included in various intermolecular arrangements, such as water molecule chains[3b] or dimers[4a]. Using the evaluations of these processes published elsewhere,[3b,4a] the chelation process is found to be twice more favourable than both hydration or dimerization, which are both found to be exergonic by around 10 kcal mol^{-1} per chlorophyll molecule or less. As a consequence, chelation processes for Cu and Zn should be possible, but is most probably highly sensitive to the nature of the solvent and to temperature. In the case of copper, considering the strong rearrangement necessary to substitute Mg by Cu,[25] it can be proposed that the chelation product $C(Cu(CH_3CN)_4)$ should be considered as a kinetic product whereas the substitution one S(Cu) should be considered as the thermodynamic one.

Table 2: geometric (distances in Å) and energetic (in kcal mol^{-1}) parameter for Chelation (C) and Deprotonation (D) complexes as a function of M.

	$C(M(CH_3CN)_4)^+$		$D(M(CH_3CN)_2)$	
M	Cu^{2+}	Zn^{2+}	Cu^{2+}	Zn^{2+}
Mg-N(I)	2.022	2.022	2.024	2.024
Mg-N(II)	2.143	2.144	2.174	2.156
Mg-N(III)	2.029	2.028	2.016	2.010
Mg-N(IV)	2.065	2.066	2.074	2.078
<Mg-N>	2.065	2.065	2.067	2.065
Δ(Mg-N) [a]	0.121	0.122	0.146	0.122
Mg charge	1.423	1.422	1.431	1.413
M-OCOMe	2.005	2.144	2.031	1.892
M-O(V)	1.923	2.010	1.979	1.879
M charge	1.065	1.154	0.767	1.258
Valence pop	3d(9.11) 4s(0.34) 4p(0.47)	3d(9.94) 4s(0.37) 4p(0.53)	3d(9.46) 4s(0.28) 4p(0.48)	3d(9.90) 4s(0.35) 4p(0.48)
ΔG_b or ΔG_c	-27.7	-22.5	-15.6	1.5

[a] Δ(Mg-N) is the difference between the longer and the shorter M-N bond

An evaluation of the UV-visible transition associated to the chelation compounds was carried out to determine the effect of chelation on the Q-band. A 570.5 nm transition is found for Cu (intensity: 0.3521) and a 568.8 nm one for Zn (intensity: 0.3208), which can both be considered as Q_y transition. They are thus associated to a slight blue shift and an increase in intensity with respect to a single molecule of chlorophyll. These values are strongly similar to those obtained for the substitution compounds 572.4 nm and 571.9 nm for Cu and Zn respectively). It is thus possible to conclude that the chelation process is computed to be exergonic but highly sensitive to environment and cannot be distinguished through UV-visible spectroscopy.

Deprotonation Process (2c).

Finally, the products resulting from deprotonation of position 13^2 in order to form $D(M(MeCN)_2)$ have been envisioned, the formation being considered as resulting from process 2c. Deprotonation of the β-keto-ester is proposed to yield a change on the M binding scheme, as it goes from pseudo-octahedral in the case of simple chelation (2b) to pseudo-tetrahedral in the case of chelation-deprotonation (2c). Data concerning this process are given in Table 2. Most surprisingly, copper and zinc coordination exhibit very different features in these compounds. For zinc, deprotonation does not change the coordination at Mg, and results in a shortening of the Zn-O bounds. The associated population analysis of the Zn center yields an increase of the Zn charge: incorporation of an anionic ligand in the Zn coordination sphere is not sufficient to counter-balance the loss of two CH_3CN molecules. A totally different picture is obtained for Cu. In this case, dissymmetry is increased with a significant lengthening of the Mg-N(II) distance. In addition, a lengthening of the Cu-O bonds is observed, in contrast to the Zn behavior. The population analysis shows that, whereas the charge at Mg is unchanged, deprotonation leads to a strong decrease of the charge at copper, which becomes significantly smaller than one (0.767). This is associated to a shift of the spin density on the system. Whereas the difference between the α and β electron population at the Cu is close to 0.6e for the chelation compound C(M), it drops to 0.1e when deprotonation occurs (compounds D(M)). The spin is transferred to the deprotonated carbon. As a consequence, it can be proposed that the deprotonation process in the case of Cu is associated to an electron transfer and reduction of Cu(II) to a Cu(I) center. This electronic process is associated to a major change in the electronic transition (see E.S.I. for simulations of the spectrum). The Q-band decreases and widens as the two states found in the 550-600nm region (at 583.7 and 562.3 nm) have low intensities (0.0686 and 0.0421 respectively). In addition, a new transition appears between the Q and the B bands (468.6 nm, intensity 0.2452). In contrast, a minor red-shift is computed for Zn (585.5 nm with intensity 0.2083). From an energetic point of view, process 2c is exergonic for copper (-15.6 kcal mol^{-1}) but not for zinc (+1.5 kcal mol^{-1}). Both values are significantly smaller than those found for processes 2a and 2b, a phenomenon increased by inclusion of implicit solvation (see E.S.I). Comparison to experimental data requires to discuss the model taken for the H^+ acceptor. Indeed, considering approximate pK_A values, a simple change of the H^+ acceptor from acetonitrile ($pK_A \sim 25$) to water ($pK_A = 14$) could lead to a lowering of the reaction energy by more than 15 kcal/mol. As a consequence, it can be proposed that changing the reaction medium from a moderately to a strongly basic solvent could change the preference between processes 2b and 2c. In conclusion, process 2c can be made possible if a sufficiently strong proton acceptor is present. It could be easily identified by UV visible spectroscopy in the case of copper only, as no cleat cut effect is obtained for zinc.

Conclusions

We have studied and compared the Mg-substitution process to formation of various bimetallic complexes in a chlorophyll model, using Cu^{2+} and Zn^{2+} as additional cations. Substitution processes exhibit very similar geometric and electronic properties as those of chlorophyll. The substitution complex does not permit coordination of apical ligand to the central metal, thus prohibiting substrate binding or dimerization. Dimerization is also forbidden for both chelation products as the keto-ester group is no more available for coordination to Mg. This can justify the loss of activity of chlorophyll in presence of these cations. The sole chelation of a cation on the β-keto-ester site on the periphery of the chlorophyll is energetically favored and leads to compounds with very similar electronic and geometric properties as those of chlorophyll. In addition, when sufficiently basic additives are used, we have shown the possibility to form chelation-deprotonation compounds. These compounds can be proposed as excellent candidates to build bimetallic compounds allowing electron transfer between the two metal centers, as we have already pointed out the reduction potential of the obtained system toward Cu^{2+}. Theoretical data highlight the promising potential of the reaction products of transition metal dications with chlorophyll in order to design bioinspired and biologically derived molecular systems for photovoltaics.

Computational details

Computations have been carried using the Gaussian 03[26] program within the framework of the density functional theory at the B3LYP/6-31G* level[27], (using unrestricted formalism UB3LYP for copper containing systems). Empirical corrections for dispersion were not included since they are expected to play a minor role in the substitution or chelation processes. has Calculations were based on a Chla model containing 73 atoms reported in Scheme 1 which was proposed in our previous work.[3b,5a,5b] This model retains the structure of Chla except for the phytyl ester side chain which was replaced by a methyl group to reduce the number of atoms for computation. The geometries were fully optimized in the gas phase and vibrational frequencies were computed in the harmonic approximation to confirm structural assignment to energy minima and contributions to Gibbs free energies. Solvation was carried out using addition of explicit solvent (CH_3CN) molecules. Considering the presence of Lewis acid site on the cations and of H-bonding one on the macrocycle,[3a-b] and taking into account the occurrence of open shell structures, we decided not to add implicit solvation, as it can be shown to be associated to various computational artefacts for that kind of systems.[28] Single points computations using a mixed explicit / implicit solvation have been carried out and are given in the E.S.I.

Chla and its substitution products, which can all be considered as HPheo(M) complexes, can accommodate additional solvent molecules on the central cation, in addition to the tetracoordination of the HPheo ligand. Nevertheless, the Gibbs free binding energy of the first acetonitrile ligand varies from slightly exothermic for Mg^{2+} (-2.4 kcal mol^{-1}) to slightly endothermic for Zn^{2+} and Cu^{2+} (+1.6 and +5.3 kcal mol^{-1} respectively). Corrections for dispersion and basis set superposition error effects don't change significantly the results (+4.3 and +5.1 kcal mol^{-1} respectively). As such, Chla should be considered as monosolvated, whereas HPheo(Zn) and HPheo(Cu) should be considered as non-solvated. Nevertheless, this difference in solvation does not yield significant variations in the reaction free energies (only a 2.4 kcal mol^{-1} difference). As a consequence, for the sake of homogeneity, no solvation will of HPheo(M), whatever the nature of M for the thermodynamic part.

For the Cu^{2+} and Zn^{2+} containing complexes [M] with a lower coordination number, the number of solvent molecules n to be added was chosen as the smallest n value for which the Gibbs free energy ΔG(n) for equation 2 is positive :

Eq (2) : $[M](CH_3CN)_n + CH_3CN \rightarrow [M](CH_3CN)_{n+1}$ ΔG(n)

Table 3: Gibbs Free energies (ΔG(n) in kcal mol^{-1}, ΔH(n) in kcal mol^{-1} is given in parenthesis) for the coordination of an additional acetonitrile molecule to the $[M(MeCN)_n]^{2+}$ complex

	Mg^{2+}	Cu^{2+}	Zn^{2+}
n = 3	-39.9 (-49.1)	-37.5 (-50.2)	-39.5 (-49.2)
n = 4	-19.2 (-27.2)	-16.3 (-26.2)	-10.8 (-18.9)
n = 5	-11.4 (-26.4)	-4.6 (-10.8)	-6.1 (-15.0)
n = 6	10.6 (-0.7)	Not obtained	10.1 (-0.5)

The results for the isolated cations Mg^{2+}, Cu^{2+} and Zn^{2+} are gathered in Table 3. Gibbs free energies for coordination of an additional solvent molecule to $[M(MeCN)_6]^{2+}$ complexes is strongly positive (> 10 kcal mol^{-1}) and optimization is even impossible in the case of Cu as decoordination of the MeCN molecule occurs during the course of the optimization. As a consequence, six-solvated cations will be used to model the structure of free cations in solution. Considering the proton H^+ released in process 1c (Scheme 1), no more than one CH_3CN molecule could be added to the proton, so that our computational model for solvated H^+ is $H(CH_3CN)^+$.

Finally, the coordination of solvent molecules to the peripheric M^{2+} cation in the chelation (formation of $[(M)HPheo(Mg)]^{2+}$ complex) and in the deprotonation (formation of $[(M)Pheo(Mg)]^+$ complex) products should be examined. For $[(Cu)HPheo(Mg)]^{2+}$, binding of the third acetonitrile molecule is hardly exergonic (-0.9 kcal mol^{-1}) whereas the fourth is hardly disfavoured (+1.1 kcal mol^{-1}). In contrast, binding of the third and fourth acetonitrile molecules to zinc in $[(Zn)HPheo(Mg)]^{2+}$ leads to negative Gibbs free energy values, the latest being only -3.0 kcal mol^{-1}). As a consequence, tetrasolvation of Cu^{2+} and Zn^{2+} will be used for both $[(Cu)HPheo(Mg)]^{2+}$ and $[(Zn)HPheo(Mg)]^{2+}$ complexes, this difference in solvation yielding a variation in the Gibbs free energies evaluated of 4 kcal mol^{-1}. For both $[(Cu)Pheo(Mg)]^+$ and $[(Zn)Pheo(Mg)]^+$, the coordination of two acetonitrile molecules to Cu or Zn is found to be favourable, whereas the Gibbs free energy for binding of the third acetonitrile molecule is evaluated to +4.1 and +1.6 for Cu and Zn respectively. Disolvation by acetonitrile will thus be used for these two structures.

We next envisioned the possibility to correct the Gibbs free energies values by inclusion of implicit solvation to the explicitly solvated models.[28b] Complete results are given in E.S.I. Comparison to previous PCM implementations included in Gaussian is also given for process 2a,[29] and shows that the two implementations give totally opposite results for this Scheme. We thus examined the origin of the difference. Surprisingly, the major effects of the corrections to the free energies could be associated to effects on the $[M(MeCN)_6]^{2+}$ (correction by -135.8 kcal mol^{-1} for Mg^{2+}, -129.1 kcal mol^{-1} for Zn^{2+} and -119.7 kcal mol^{-1} for Cu^{2+}). Considering that solvation of small cations remains an essential challenge for solvation models,[28b] these data were thus considered with extreme caution and not to include them directly in the text. Nevertheless, considering that a better representation of these atomic cations should also include coordination of counter ions, we chose to consider that the sensitivity to implicit solvation should be consider as an indicator to a great sensitivity to reaction conditions. They are thus included in E.S.I. and discussed when necessary.

Modelling of the UV-visible spectra was carried out using the TD-DFT implementation30 at the same computational level as geometry optimization, as resorting to other computational levels only leads to global shift of the spectrum (see Sup. Info for more details). All the same, no inclusion of implicit solvation was included, as it also leads to a global shift. NPA population analyses were carried out using the NBO version implemented in Gaussian.

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The most favored reaction of chlorophyll is computed to be substitution for Cu^{2+} and peripheral chelation for Zn^{2+}.