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ABSTRACT

The effects of the incorporation of oxygen, sulfur, selenium, and tellurium into the porphyrin core over nitrogen have been explored using density functional theory (DFT) and its time-dependent and quadratic response implementations (TDDFT and QR-TDDFT). The aim was to investigate how substitution affects the photophysical properties of these dyes and how such modifications could make them more suitable to be proposed as heavy-atom-free agents in photodynamic therapy (PDT). The photophysical properties assessed in our investigation, relevant for the PDT mechanism, allow us to establish that chalcogens trigger beneficial bathochromic shifts enabling the achievement of more bio-compatible wavelengths while enhancing spin-orbit coupling and kinetic constants for intersystem crossings. Considering the higher safety profile of sulfur in biological systems and the numerous studies highlighting the role of Se-containing materials in inducing apoptosis in cancer cells with minimal side effects on normal cells, we believe that the results presented here on both the S- and Se-heterosubstitution strategies could be highly promising.

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INTRODUCTION

Due to their widespread use in many modern technological domains,^{1–3} porphyrin-based systems have been the subject of intense research for several decades, from both theoretical and experimental points of view. Their outstanding photophysical properties made them, since the beginning, highly effective in light-based medical protocols such as photodynamic therapy (PDT).^{4–12}

The latter is a well-known non-invasive and highly selective approach that exploits a photosensitizer (PS) and a biocompatible light-source to cause vascular injury leading to necrosis or apoptosis of tumor cells, mainly through the generation of the cytotoxic singlet oxygen species (¹O₂). The photodynamic process triggered by light requires the PS to populate the excited triplet states by

intersystem crossing, from which two types of reactions can possibly occur, namely, the energy-transfer mechanism to molecular oxygen, producing the singlet excited species ¹O₂ (type II), or electron-transfer reactions to biological substrates, forming radical anions or cations and reactive oxygen species (ROS) (type I).^{4–6} Type I and type II reactions may occur concurrently, with the relative proportions of these processes influenced by the specific PS employed, as well as the concentrations of substrate and oxygen present. The higher reactivity of singlet oxygen, coupled with the ability to localize its production, made type II the most likely mechanism implicated in the apoptosis or necrosis of malignant cells.

The distinctive strong absorption of light in the visible regions of porphyrin-based systems, particularly around 400–700 nm corresponding to their characteristic Soret and Q bands, is the reason

why they have become broadly adopted and studied in the field. Anyway, they suffer from several limitations, among which are no optimal absorption at longer wavelengths and poor light penetration within tumors. Therefore, to further advance the search for more effective photosensitizers overcoming porphyrins' limitations, several novel potential drugs have been recently proposed that defy the established porphyrin-as-PS paradigm, among which are several promising metal-based photosensitizers.^{13–21} Nevertheless, despite the significant efforts made, the currently approved PS for PDT are still based on tetrapyrrolic rings.²² Therefore, the need to properly tune the photophysical properties of porphyrin-related systems through structural modifications is still a very active research field, with the most widely used strategy being the incorporation of metals or other heavy atoms into the cavity or its periphery, particularly exploiting the carbon meso-position.²³

A highly promising strategy to improve the physicochemical properties of porphyrins is their core-modification by substituting the pyrrole nitrogen atom with heteroatoms (O, S, Se, Te, Si, P, and C).^{24–27} The introduction of S, Se, and Te chalcogen atoms has been previously ascertained to cause a bathochromic shift in the absorption band and to enhance the spin–orbit coupling constants in some other kinds of photosensitizers, both of which are essential properties for their application in photodynamic therapy (PDT).^{28–34} Therefore, they can be particularly useful to induce the heavy atom effect without resorting to metals. Indeed, stable structures between selenoderivatives and RNA,³⁵ DNA duplex,^{36,37} and G-quadruplex³⁷ were previously identified, with enhanced photophysical properties with respect to thio-analogs. Moreover, numerous studies highlight the role of Se-compounds in inducing apoptosis in cancer cells with minimal side effects on normal cells, and many efforts are in progress to design and develop newer organic Se molecules for cancer therapy.^{38,39}

In order to evaluate the effect of one pyrrole nitrogen substitution by chalcogen atoms, we herein present a DFT/TDDFT/QR-TDDFT exploration of the photophysical properties of monosubstituted porphyrins (N_3X), in which N represents *meso*-phenyl substituted porphyrin and X the tested heteroatom (O,

S, Se, and Te), at density functional theory (DFT) and its time-dependent and quadratic response implementations (TDDFT and QR-TDDFT). The examined derivatives are illustrated in Fig. 1.

To assess the possibility of inducing a type II reaction, we have characterized the absorption spectra, the singlet–triplet energy gap (ΔE_{S-T}), and the spin–orbit coupling (SOC) matrix elements, and we have also computed the non-radiative constant for the intersystem crossing rate (k_{nr}). It is noteworthy that, despite the extensive literature on porphyrins, studies that incorporate the computation of k_{nr} are notably scarce due to the challenges in acquiring it both experimentally and theoretically, so that providing these data represents a step forward compared to the usual description of the photophysical properties of new porphyrin derivatives.

In addition, we have also computed the vertical ionization potentials (VIPs) and vertical electron affinities (VEAs) to determine the viability of type I processes.

COMPUTATIONAL METHODS AND DETAILS

Ground and excited states geometry optimizations, excitation energies, and singlet–triplet energy gaps have been performed by means of DFT and TDDFT levels of theory as implemented in the Gaussian 16 code (G16).⁴⁰ All the structures have been optimized without any constraint by using the B3LYP hybrid functional^{41,42} along with the 6-31+G(d,p) basis sets for all atoms, except for the tellurium one, which was described through the quasi-relativistic Stuttgart–Dresden pseudopotential.⁴³ The B3LYP functional was extended with the Becke–Johnson D3BJ version of Grimme's dispersion correction.⁴⁴ To mimic the experimental environments, the calculations have been performed in toluene ($\epsilon = 2.3741$) by means of the integral equation formalism polarizable continuum model (IEF-PCM),⁴⁵ which corresponds to a linear response in non-equilibrium solvation. The vibrational analysis has been performed to verify if the obtained structures were minima in the potential energy surface. TDDFT calculations have been carried out on the ground state (S_0) equilibrium structures using the same basis set as for the optimizations and evaluating both B3LYP and the range-corrected cam-B3LYP XC-functionals. The vertical triplet energies (E_T), the vertical ionization potentials, and the electron affinities of the low-lying singlet (VIP, VEA) and triplet states [$VIP(T_1)$, $VEA(T_1)$] have been obtained over the S_0 electronic structures.

Spin–orbit matrix elements between S_1 and the lowest two triplet states (T_1 and T_2) have been computed by using the DALTON⁴⁶ code, adopting the atomic-mean field approximation⁴⁷ for O, S, and Se compounds and the spin–orbit coupling operators for effective core potentials with the effective nuclear charge for tellurium-containing species. DALTON implements quadratic response (QR-TDDFT) to compute SOC matrix elements between singlet and triplet excited states. The B3LYP functional has been selected for SOC calculations, combined with the cc-pVDZ basis set for all atoms and SDD for Te.

The SOC's have been defined based on the following formula:

$$SOC_{ij} = \sqrt{|\psi_{S_i}|\hat{H}_{SO}|\psi_{T_j,n}|^2} \quad n = x, y, z, \quad (1)$$

where $\hat{H}_{SO}$ is the spin–orbit Hamiltonian.

Based on the application of Fermi's golden rule expression, by assuming that both singlet and triplet electronic states are harmonic,

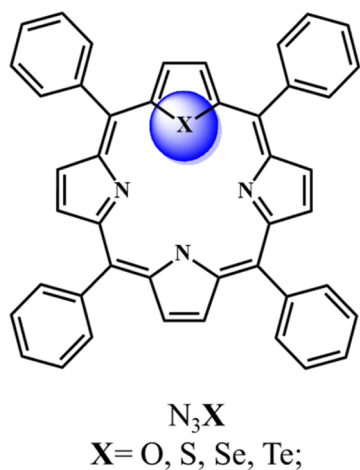
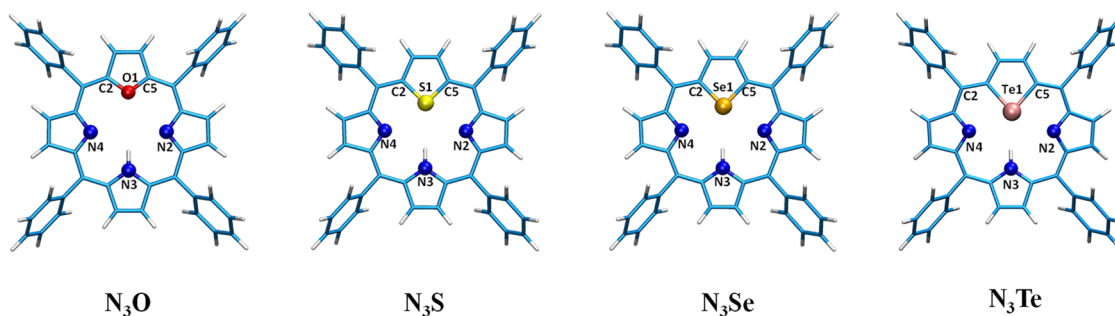


FIG. 1. Chemical structures of the investigated N_3X substituted porphyrins.

FIG. 2. Optimized structures of the herein investigated N_3X porphyrins.

the rate constant of the non-radiative transition (k_{nr}) from any of the lowest singlet excited states (S_1) to any triplet excited state (T_j) is expressed as⁴⁸

$$k_{nr}(S_1 \rightarrow T_j) = \frac{2\pi}{\hbar} \frac{\langle S_1 | H_{SOC} | T_j \rangle^2}{(4\pi\lambda_s k_B T)^{1/2}} x \sum_{n_M} \frac{S_M^{n_M}}{n_M!} \exp(-S_M) x \times \exp\left(\frac{\Delta E - n_M \hbar \omega_M - \lambda_s}{4\lambda_s k_B T}\right)^2. \quad (2)$$

This expression can be applied when $\hbar \omega_M \gg k_B T$ and the solvent orientational and vibrational motions are treated classically. ω_M are the high-frequency (hf) vibrational modes ($\hbar \omega_M > 1000 \text{ cm}^{-1}$), typically corresponding to the aromatic C=C and C=N(X) stretching modes ($\hbar \omega_M$ 1200–1800 cm^{-1}) and N–H stretching modes ($\hbar \omega_M > 3000 \text{ cm}^{-1}$). ΔE is given by

$$\Delta E = E_{00} - \lambda_{lf}, \quad (3a)$$

in which ΔE is the zero-point energy difference between the S_1 and T_j states and λ_{lf} is the reorganization energy contributed by the low-frequency (lf) modes (i.e., $\hbar \omega_M < 1000 \text{ cm}^{-1}$). Assuming that all the normal modes are harmonic oscillators,

$$\lambda_{lf} = \sum_{j \in lf} S_j \hbar \omega_j, \quad (3b)$$

$$S_j = \frac{1}{2} \left(\frac{m_j \omega_j}{\hbar} \right) \Delta Q_j^2. \quad (3c)$$

S_j , m_j , and ΔQ_j are the Huang–Rhys factor, the reduced mass, and the equilibrium displacement of the j -th normal mode ω_j , respectively; and S_M and n_M are the Huang–Rhys factor and the number of quanta of the effective high frequency $\hbar \omega_M$ mode (corrected to the nearest integer), respectively,

$$S_M = \sum_{j \in hf} S_j, \quad (4)$$

$$n_M = \frac{\Delta E - \lambda_s}{\hbar \omega_M}. \quad (5)$$

The Huang–Rhys factor S_j [using Eq. (3c)] for the normal mode ω_j was obtained by performing a Franck–Condon calculation. Geometry optimizations and frequency calculations of the singlet excited state S_1 and the two lowest triplet excited states, T_1 and T_2 ,

were, respectively, carried out using a restricted procedure without symmetry constraints. The high-frequency normal modes ($\hbar \omega_M$ 1200–1800 cm^{-1}) can be characterized by a mean frequency ω_M and an effective electron–phonon coupling strength (or Huang–Rhys factor) S_M ,

$$\hbar \omega_M = \frac{\lambda_M}{S_M}, \quad (6a)$$

$$\lambda_M = \sum_{j \in m} S_j \hbar \omega_j, \quad (7b)$$

$$S_M = \sum_{j \in m} S_j. \quad (8c)$$

The solvent reorganization energy (λ_s) [Eq. (2)], computed on the specific-state (SS) approach, estimates the triplet excited state energy difference calculated with non-equilibrium solvation [$E_{NEq}^{T_j}(Q_0^{S_1})$] and with equilibrium solvation [$E_{Eq}^{T_j}(Q_0^{T_j})$] at the optimized excited state geometry ($Q_0^{S_1}$) (Fig. 2),

$$\lambda_s = E_{NEq}^{T_j}(Q_0^{S_1}) - E_{Eq}^{T_j}(Q_0^{T_j}). \quad (9)$$

Similarly, the intramolecular reorganization energy (λ_v^{SS}) is given by

$$\lambda_v^{SS} = E_{Eq}^{T_j}(Q_0^{S_1}) - E_{Eq}^{T_j}(Q_0^{T_j}), \quad (10a)$$

where $E_{Eq}^{T_j}(Q_0^{S_1})$ is the energy of the triplet excited state computed with equilibrium solvation at the optimized ground state geometry $Q_0^{T_j}$. Under the harmonic oscillator approximation, the intramolecular reorganization energy, λ_v^{FC} , could be estimated as

$$\lambda_v^{FC} = \sum_j S_j \hbar \omega_j, \quad (10b)$$

where the summation runs over all the normal modes, ω_j . Calculations performed based on vibrationally resolved electronic spectra implemented in the G16 package.⁴⁰

RESULTS AND DISCUSSION

The optimized ground-state mono-substituted structures of N_3O , N_3S , N_3Se , and N_3Te are reported in Fig. 2. The replacement of the native porphyrin (N_4) nitrogen with heteroatoms

TABLE I. Main vertical singlet–singlet electronic transitions energies (ΔE , nm) and oscillating strengths (f) in the B and Q regions for N_4^{33} and N_3X ($X = O, S, Se, Te$) porphyrins in toluene at the B3LYP-6-31+G(d,p) level of theory, along with experimental values (Exp, given in bold italic), in nm. For the lowest energy transitions (Q bands), ΔE is reported even in eV. NTOs relative to S_1 states are reported in Fig. 3, while those for S_2 can be found in the [supplementary material](#) (Fig. S5).

Cpd	B bands (nm)			Q Bands			
	ΔE	f	Exp. (nm)	f	ΔE	Exp. (nm)	
	(nm)			eV	(nm)		
N_4^{33}	415,409	1.497, 1.740	417	$S_1(Q_x)$ 0.045 2.13 (579)	647		
				$S_2(Q_y)$ 0.068 2.26 (546)	548		
N_3O	418,411	1.251, 1.710	419	$S_1(Q_x)$ 0.046 2.08 (595)	671		
				$S_2(Q_y)$ 0.034 2.28 (544)	539		
N_3S	427,424	1.256, 1.638	429	$S_1(Q_x)$ 0.067 2.03 (609)	675		
				$S_2(Q_y)$ 0.080 2.23 (556)	547		
N_3Se	431,424	0.902, 1.510	451	$S_1(Q_x)$ 0.065 2.05 (604)	666		
				$S_2(Q_y)$ 0.051 2.24 (552)	578		
N_3Te	447,442	1.321, 0.930	/	$S_1(Q_x)$ 0.097 2.01 (631)	/		
				$S_2(Q_y)$ 0.043 2.10 (590)	/		

induces conformational changes that slightly distort the geometries, modulating the electronic properties.

In agreement with previous indications on the diheterosubstituted porphyrins,²⁶ the introduction of chalcogen atoms allows the central core of the heterocyclic ring to undergo thinning and elongation of N_3-X_1 and N_2-N_4 distances, respectively (see Table S1 of the [supplementary material](#)). Such an effect is due to the size of the chalcogen atoms that increases along the 16th group of the periodic table, and it is also connected with their lower electronegativity. While distances and angles remain largely unchanged between N_4 and N_3O compounds (see Table S1 of the [supplementary material](#)), the introduction of a sulfur atom still impacts the structure, elongating the C_2-S_1 bond at 1.76 Å and the N_2-N_4 distance at 4.46 Å while reducing the $C_2-X_1-C_5$ angle at 91.9° and the S_1-N_3 distance at 3.56 Å (vs 1.37 Å, 110.7° , 4.07 Å, and 4.21 Å of the N_4 compound, respectively).

The impact of the substitution is even greater going from the Se to the Te heteroatom, where the N_2-N_4 distance is elongated enough to allow X_1-N_3 to be closer (4.55 and 4.69 Å for N_2-N_4 distances; 3.38 and 3.25 Å for X_1-N_3 ones, respectively). So, the N_2-N_4 distance increases proportionally with the size of the heteroatom, while the X_1-N_3 decreases. The phenyl groups on *meso* carbons are about normal with respect to the almost planar porphyrin ring plane, and their dihedral angles remain quite constant along the series, even in the S_1 excited state (see Figs. S1 and S2 and Table S1 of the [supplementary material](#)).

Concerning the photophysical behaviors, the main singlet–singlet vertical electronic energies along with the corresponding oscillating strengths are reported in Table I for the N_3O , N_3S , N_3Se , and N_3Te structures, together with the available experimental data in toluene.²⁴ The four Goutermann MOs plots and HOMO–LUMO gaps are reported in Figs. S3 and S4 of the

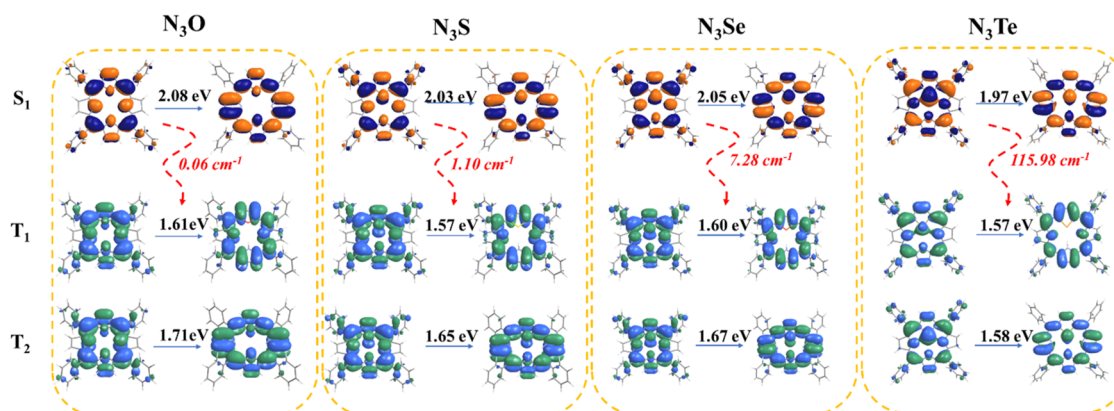


FIG. 3. Natural transition orbitals (NTOs) for the S_1 , T_1 , and T_2 states, along with the corresponding excitation energy (eV) reported on the solid horizontal arrows; spin–orbit couplings (SOCs, cm^{-1}) between S_1 and T_1 states are reported on the curved red arrows connecting the two involved states.

supplementary material, while the NTOs associated with the main transitions in the Q-region are depicted in Figs. 3 and S5.

The computed B bands of all compounds are in good agreement with the experimental Soret band, with a maximum deviation from the available data of 27 nm obtained for the selenium containing system. In addition, our data reproduce accurately the bathochromic shift registered upon the substitution of the N atom with O, S, and Se. The same effect is detected for N₃Te, whose predicted B-bands appear redshifted, despite the lack of available experimental data for comparison. As previously observed for other similar systems,³³ the computed values quite well replicate the H → L + 1 excitation associated with S₂ states (Qy bands), while a greater deviation from the experimental data is obtained for the Qx bands (H → L). Despite this, computations allow us to correctly reproduce the redshifted Q bands of hetero-substituted porphyrins compared with N₄, as well as the almost negligible effect observed when sulfur is replaced with selenium. Both induce a similar effect on the absorption properties of porphyrins in the highest region of the spectrum, due to the smaller size difference between them and a consequent similar H–L gap (see Fig. S3 of the supplementary material). The cam-B3LYP was also tested to compute the UV–Vis spectra (see the supplementary material). Nevertheless, consistent with the absence in the porphyrin structures of crucial donor–acceptor substituents able to induce a significant charge-transfer character to the main transitions, the results obtained with the range separated functional do not lead to a better comparison with experimental data.

Inspection of the Franck–Condon region allows us to identify two triplet states lying below S₁, whose energy is compatible with an energy transfer mechanism toward oxygen, being both triplet states higher than 0.98 eV, i.e., the experimental energy required to promote the oxygen ³Σ_g → ¹Δ_g transition (see Fig. 3). Inspection of the NTOs associated with the triplet states, as reported in Fig. 3, provides evidence that T₁ exhibits an increasing n–π* character, which correlates with the growing contribution of the heteroatom in the donor orbital as its atomic number increases. As a consequence, an enhancement of spin–orbit coupling (SOC) values is expected for the S₁ → T₁ deactivation channel, in agreement with El-Sayed's rule.⁴⁹ Despite this, the obtained SOC's for S₁ → T₁ intersystem crossing (ISC), reported in Table III, are quite small for N₄ and N₃O systems, even lower than those computed for the clinically approved

drug 5,10,15,20-tetrakis-(*m*-hydroxyphenyl) chlorin (Foscan) (2.4 × 10^{−1} cm^{−1}).⁵⁰ On the contrary, the presence of a heavier atom in the molecular structure increases the SOC's values, which become 1.10, 7.28, and 115.98 cm^{−1} for N₃S, N₃Se, and N₃Te cm^{−1}, respectively, as also reported in Fig. 3.

Accordingly, the higher values of SOC obtained as the atomic number of the substituent increases could indicate higher triplet formation quantum yields, provided that competing deactivation processes remain unchanged. Nevertheless, due to the higher biocompatibility of sulfur and, to a lesser extent, of selenium compared with tellurium, the indications coming from the sulfur and selenium substituents to induce the heavy atom effect in metal-free porphyrins are particularly relevant. For the S₁ → T₁ channel, we also determined the kinetic constants (*k*_{nr}) (see Table II and Fig. 3) by means of the procedure reported in the computational details section [Eq. (2)].

The S₁ → T₁ intersystem crossing (ISC) rate increases proportionally with the atomic number of the chalcogen substituents and follows the trend observed in spin–orbit coupling (SOC) values. This indicates that SOC values can serve as reliable predictors for ISC efficiency. The smaller ISC rates for the S₁ → T₂ transition, computed only for O-, S-, and Se-substituted porphyrins (see Table S2 of the supplementary material), indicate a less favorable deactivation pathway, as expected.

As previously mentioned, the populated triplet state can follow other deactivation pathways, which generally originate from autoionization processes leading to the formation of a radical PS through reactions (a) and/or (b) and subsequent electron transfer to oxygen through reaction (c), with the generation of superoxide. Collectively, these reactions are known as type I photoreactions. The superoxide could even be generated by a direct electron transfer following the last reactions (d) and (e) involving the singlet or triplet state of the PS, which are, however, generally less feasible,

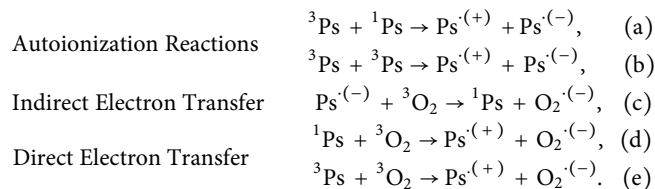


TABLE II. Effective Huang–Rhys factors (*S*_M) for the high-frequency mode, intramolecular (*λ*_v) and solvent (*λ*_s) reorganization energies (in cm^{−1}), dipole moments of the S₁ and T₁ excited states (Debye), squared SOC's (in cm^{−1}), Franck–Condon factors (cm^{−1}), and non-radiative decay rate constants (s^{−1}) for the N₃X.

	<i>S</i> _M ^a	<i>λ</i> _v		<i>λ</i> _s	<i>μ</i> ^{S₁}	<i>μ</i> ^{T₁}	<i>⟨S₁ H_{SOC} T₁⟩</i> ²	<i>k</i> _{nr} (S ₁ → T ₁)
		SS	FC					
N ₃ X								
N ₄ ³³	1.1	1523	1588	1950	0.000	0.000	8.91 × 10 ^{−3}	8.94 × 10 ⁸
N ₃ O	2.70	3774	3902	2005	0.938	1.059	3.87 × 10 ^{−3}	2.44 × 10 ⁷
N ₃ S	2.58	3577	3686	2010	0.421	0.300	1.2	4.64 × 10 ¹⁰
N ₃ Se	2.40	3270	3355	1935	1.016	0.879	52.99	2.61 × 10 ¹²
N ₃ Te	2.86	3972	6452	3423	2.728	2.142	13 451	7.65 × 10 ¹³

^a*S*_M corresponds to the effective Huang–Rhys factor of the high frequency modes 1000 (ω_j) 1800 cm^{−1}.

TABLE III. Vertical electron affinity (VEA) and vertical ionization potential (VIP) of N_3X porphyrins in water. $VEA(T_1) = VEA - E_{T_1}$, $VIP(T_1) = VIP - E_{T_1}$; $VEA = E_{an\ rad} - E_p$, $VIP = E_{cat\ rad} - E_p$; and $VEA(^3O_2) = -3.69$ eV in water.

Cpds	VEA (S_0)	VIP (S_0)	VEA (T_1)	VIP (T_1)
N_4	-1.92	5.36	-3.30	3.98
N_3S	-1.98	5.42	-3.32	4.08
N_3O	-2.02	5.43	-3.36	4.09
N_3Se	-2.04	5.47	-3.39	4.12
N_3Te	-2.08	5.46	-3.40	4.14

The computation of the vertical electron affinity (VEA) and vertical ionization potential (VIP), reported in Table III, allow us to evaluate the feasibility of the above-described reaction by computing the thermodynamics of each reaction. Data lead to excluding the possibility that the investigated porphyrins could be reduced by autoionizations, due to the endothermicity of both reactions (1) and (2). The indirect electron transfer reaction (c) from the reduced PS to O_2 is evidently favorable for all species due to the significantly higher electron affinity of oxygen (-3.69 eV)³³ compared with that obtained for all the tested porphyrins. It appears clear that such a process could occur, provided that the porphyrins could be reduced by other biological agents. On the other hand, the direct electron transfer from the singlet state (i.e., in the dark) and even from the populated triplet state of the PS is not feasible, suggesting that those systems are not able to efficiently promote type I photoreactions, as already suggested for the dihetero-substituted analogs.³³

CONCLUSIONS

The introduction of oxygen, sulfur, selenium and even tellurium over nitrogen as substituents in the core of porphyrin photosensitizers has been tested, and the consequent influence on the photophysical properties connected with their possible use in PDT has been explored.

The outcomes of our investigation validate the effectiveness of this strategy to access a more clinically relevant region of the spectrum, thereby contributing to the development of more appropriate heavy-atom-free PDT agents.

The study demonstrates that the incorporation of chalcogen, starting from sulfur, allows us to reach more biocompatible wavelengths and significantly influence the intersystem crossing process, leading to an enhancement of k_{nr} as the substituent's atomic number increases. The most plausible deactivation channel to populate the triplet state is suggested to be S_1-T_1 , which shows the highest SOC values and the highest k_{nr} . On the contrary, the incorporation of oxygen over nitrogen does not significantly affect the photophysical behavior.

The VEA and VIP values obtained, along with the thermodynamics of type I reactions, suggest that autoionization reactions and direct electron transfer to oxygen to form superoxide are not feasible processes. Consequently, none of the compounds studied are capable of initiating electron transfer reactions on their own, unless they can be reduced by other biological substrates to facilitate the indirect electron transfer from the reduced photosensitizer (PS) to O_2 , which results in what is instead an exothermic reaction.

In conclusion, considering the greater safety biological profile of the sulfur substituent and the promising properties of seleno-compounds to induce apoptosis in cancer cells recently proposed,³⁸ the indications coming from their incorporation in metal-free porphyrins to induce the heavy atom effect are particularly relevant among the tested ones and could be used to pave the way to achieve a more suitable heavy atom effect on metal-free PDT agents.

SUPPLEMENTARY MATERIAL

The supplementary material includes the following: Selected geometrical parameters and superposition of the optimized geometries of S_0 and excited S_1 , T_1 , and T_2 states of N_4 and N_3X substituted porphyrins ($X = O, S, Se, Te$); graphical representation of the computed HOMO, HOMO-1, LUMO, and LUMO+1 for N_3X porphyrins and their relative energies; natural transition orbitals (NTOs) for the Q and B bands for N_3X porphyrins; main vertical singlet-singlet electronic transition energies (ΔE) in the B and Q regions for N_4 and N_3X ($X = O, S, Se, Te$) porphyrins in toluene at the cam-B3LYP-6-31+G(d,p) level of theory along with experimental values; and effective Huang-Rhys factors for the high-frequency mode, intramolecular and solvent reorganization energies (in cm^{-1}), dipole moments of the S_1 and T_1 excited states (Debye), squared SOCs (in cm^{-1}), Franck-Condon factors (cm^{-1}), and non-radiative decay rate constants (s^{-1}) for the N_3X .

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Wichien Sang-aroon and Alessandra Gilda Ritacca contributed equally to this work and share first authorship.

Wichien Sang-aroon: Investigation (equal). **Alessandra Gilda Ritacca:** Data curation (equal); Investigation (equal). **Marirosa Toscano:** Conceptualization (equal); Writing - review & editing (equal). **Marta Erminia Alberto:** Conceptualization (lead); Supervision (lead); Writing - review & editing (lead). **Nino Russo:** Funding acquisition (equal); Project administration (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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