Invited feature article

A quantum chemical investigation of the solvatochromism of a phthalocyanine within a lipid bilayer: Comparison between *continuum* and atomistic models

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A B S T R A C T

The excitation properties of a charged phthalocyanine dye within a phospholipidic membrane have been investigated using hybrid polarizable quantum/classical models. Two different approaches for the description of the membrane environment were compared, based on *continuum* and atomistic representations, respectively. In the latter case, a two-step scheme was adopted: quantum mechanics calculations of the electronic transitions in a polarizable medium are combined with a classical molecular dynamics simulation of the dye in the membrane to account for thermal fluctuations. The results indicate that the two models reproduce a qualitatively similar red-shift of the lowest bright transitions. However, the thermal effects on the internal geometry of the dye which are included only in the two-step scheme are shown to be fundamental to properly describe the solvatochromism within the membrane.

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1. Introduction

In photodynamic therapy (PDT), light-sensitive photosensitizers are excited in order to generate reactive oxygen species through energy transfers to surrounding molecular oxygen, and consequently damage the target cell. Since the concentration of oxygen is larger in the cellular membrane, photosensitizers are also rated according to their penetration. It is therefore important to investigate the excitation process of the dyes commonly used as photosensitizers in PDT when placed in a membrane environment, as this analysis can help to predict their potential efficiency [1–3]. Classical molecular dynamics (MD) is one of the most suitable computational methods to model the interaction between dyes and phospholipid membranes, and it has been largely applied in studies aimed at improving PDTs [4–8]. This methodology can describe well the interfacial region, as well as the interactions of the dye with the environment. However, electronic processes are not directly accessible from the classical MD simulations. It is therefore necessary to resort to quantum mechanical (QM) methods, but these are computationally expensive and not feasible when treating large and complex systems. A possible solution is the use of hybrid quantum/classical models, where the dye is treated at QM level while the environment is classical. Among these, the *continuum* models, such as the polarizable continuum model (PCM) [9], resort to a description of the environment as a structureless dielectric medium. An alternative approach consists in representing the environment atoms as classical particles and modeling their interaction with the QM subsystem through the use of atomic charges. Mutual polarization effects between the quantum and the classical parts can also be included by complementing the atomic charges with induced dipoles [10]. The resulting polarizable embedding (MMPol) is generally more computationally expensive than a *continuum* model, since a large number of different configurations of the system are required for a proper description.

In this work we compare the efficiency of both *continuum* and atomistic models in describing the effects of a membrane on the electronic transitions of a dye belonging to the family of phthalocyanines (Pc) which are largely used as photosensitizers to PDT [11–17].

In a recent computational study, Cordeiro et al. [4] have shown that the porphyrin substituted with cationic groups in *cis*

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configuration penetrates further within the membrane than the *trans* substituted porphyrin, thus having access to the oxygen-rich region in the membrane. Following such a suggestion, we have considered the cationic amino-substituted metal-free phthalocyanine (NPc), shown in Fig. 1. First, a *continuum* model was employed to describe the effect of the membrane on the two lowest singlet excitations (Q bands) of the dye (see Fig. 1). To account for the heterogeneity of the membrane, an extended formulation of the model was used, in which the dielectric constant of the environment can change along membrane bilayer [18,19]. Secondly, an atomistic description of the environment was tested using a two-step strategy: a classical MD of the dye in the anionic 1-palmitoyl-2-oleoyl-*sn-glycero*-3-phosphatidylglycerol (POPG) bilayer was run to simulate the "natural" environment of the dye when within the cell membrane [20,21]; then, QM/MMPol calculations were performed on several different configurations extracted from the MD trajectories.
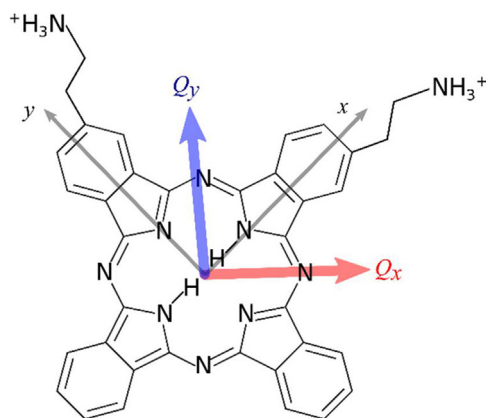
2. Computational details

2.1. Quantum-mechanical calculations

All quantum chemical calculations were performed using Density Functional Theory (DFT) and its extension to excitation processes (namely Time Dependent DFT, TDDFT). The functional OLYP [23,24,35,36] was used in combination with the 6–31G(d) basis set, as proposed by Bettanin et al. [37] for this class of dyes. Accordingly to the model used to account for the environment effects, different ground state geometries of the dye have been considered:

- For the *continuum* model (QM/PCM) we used the geometry of NPc optimized at the DFT level of theory using B3LYP 88 hybrid functional [22–24] and the 6–31G(d) basis set [25–34]. As no significant differences were found in the ground state geometries when optimized in gas-phase or in the PCM water, the gas-phase geometry was used in the different environments (water and membrane).
- For the atomistic model (QM/MMPol), different configurations were extracted from MD trajectory of the dye in water and in the lipid membrane, as detailed below.

All quantum chemical calculations have been performed with a locally modified version of the Gaussian G09 computational package [38].

2.1.1. QM/PCM calculations

The common formulation of the PCM refers to homogeneous solvents; however, an extension has been devised within the Integral Equation Formalism (IEF) [39] to allow for a description of interfaces [18], using a dielectric function continuously varying in space along one axis. In this work, we made use of such an extension in order to represent the membrane environment. The profile of the dielectric function along the direction normal to the membrane surface (z), is assumed to be:

$$\varepsilon(z) = \frac{1}{2}\left[\varepsilon_1 + \varepsilon_2 + (\varepsilon_1 - \varepsilon_2)\tanh\left(\frac{z - z_{12}}{D_{12}}\right) - (\varepsilon_2 - \varepsilon_3)\tanh\left(\frac{z - z_{23}}{D_{23}}\right)\right]$$

$$(1)$$

where $\varepsilon_1 = 80$ (i.e. the bulk water), $\varepsilon_2 = 7$ (the center of the phospholipid layer) and $\varepsilon_3 = 2$ (the bilayer center); the parameters z_{12} and z_{23} define the position of the interfaces along z, while D_{12} e D_{23} determine the interface widths. Both D parameters have been set to 1.16 Å. In Fig. 2, the value of the dielectric function along the z axis is reported as a black line.
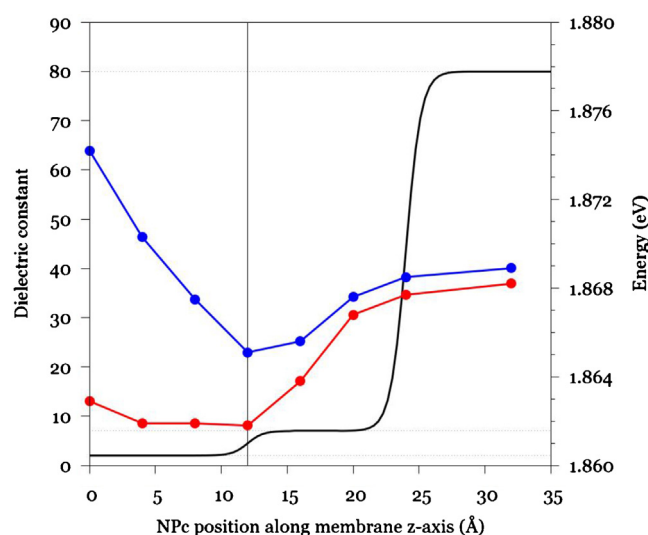
Fig. 2. Calculated Q transition energies of NPc when crossing the membrane. The membrane environment is simulated with PCM using the permittivity profile reported in Eq. (1) and here shown by the black line. Vertical line represents the equilibrium position of NPc as obtained from the MD simulation. In all calculations the geometry of the dye is kept frozen in the gas-phase optimized structure.

Fig. 1. Left: Structure of the dye studied. Gray arrows indicate the *x, y* molecular axis, as in the phthalocyanine nomenclature; the red and blue arrows indicate the direction of the Q_x and Q_y electric transition dipole moments. Note that the presence of the two protonated amino groups determines a rotation of $-45°$ ($+51°$) for the Q_x (Q_y) transitions with respect the molecular axes. Right: Optimized structure of NPc.