SAR analysis of phthalocyanines, porphyrins and chlorins using properties obtained with density functional calculations

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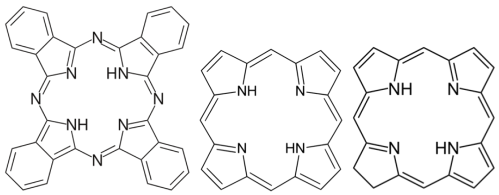
INTRODUCTION

We have carried out computational studies for some phthalocyanines (Ph), porphyrins (Pc) and chlorins (Ch), Fig. 1. These dyes have a conjugated π-electron system that gives them catalytic, spectrophotometric, magnetic and electrochemical applications. They are vastly used in photodynamic therapy (PDT), a therapy for several types of cancer. [1] The dyes studied here have different substituents (including amine, alcohol, piridine, methyls, etheres, esters, ketones and carboxilic acids), are free or complexed with Al^{+3}, Zn^{+2} and Si^{+4}. We have included in this study three dyes approved for PDT: Foscan®, used to treat head and neck cancers; Levulan®, employed in dermatological treatments and urinary bladder cancers; and Visudyne®, used against ocular vascular disorders.



(a) (b) (c)

Figure 1. Structures of free (a) phthalocyanine, (b) porphyrin and (c) chlorin.

METHODS

We have studied 37 molecules derived from phthalocyanines, porphyrins and chlorins, including 3 approved drugs: Levulan®, Foscan® and Visudyne®. Structures were optimized at B3LYP/LanL2DZ level and electronic properties were obtained with TD-DFT/OLYP/6-31g(d). The solvent effects were added by IEFPCM solvation model. Aiming to better correlate all properties with the differences in those molecules, hierarchical cluster analysis (HCA) and principal components analysis (PCA) were performed.

RESULTS AND DISCUSSION

PDT occurs by the administration of a dye followed by light irradiation. The dye transfers the absorbed energy to molecular oxygen (or other reactive species of oxygen) that may cause irreversible damage to the cell. So, we have studied properties that can influence the interaction with the environment and with the molecular oxygen, such as the absorption wavelength in water (λ) of the Q band, oscillator strength, energies of HOMO and LUMO (Δ_{H-L}), solvation free energy (ΔG_{solv}) in different solvents (to simulate the interaction with lipid bilayer), molecular area and volume, dipole moment.

Using HCA and PCA analyses, we considered the division of the studied molecules in two groups, each of them containing at least one approved drug: (i) the group of Visudyne® is composed by free Ph, charged Ph (with pyridine and amine), Ph substituted with ether, carboxylic acid and methyl; and (ii) the group of Levulan® and Foscan®, containing the complexed and substituted phenyl Ph, free Pc and free Ch. The main variables that characterize the Visudyne® group were oscillator force, molecular volume and dipole moment. For the other group, ΔG_{solv} and LUMO energy play an important role.

CONCLUSIONS

Electronic and structural properties were used to evaluate different dyes to PDT. PCA and HCA analyses allowed grouping structurally different molecules with approved drugs, indicating that the molecules can be used for the same applications.

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