

Tuning Excited State Properties of Photosensitizers by Rational Functionalization

Juan José Nogueira, Markus Oppel, Leticia Gonzalez
University of Vienna

Photosensitizers are usually employed as anticancer drugs by inducing DNA damage into cancer cells in photodynamic therapy. Methylene blue is a type II photosensitizer, which has shown promising results for tumor treatment [1]. The mode of action of type II photosensitizers is related to the generation of triplet excited states by intersystem crossing, and further energy transfer to the molecular oxygen present in the environment. Thus, rationalizing the factors that influence intersystem crossing in biological environment is crucial to improve the efficacy of photodynamic therapy. Laser flash spectroscopic experiments have shown that the triplet generation quantum yield of methylene blue drastically decreases upon addition of different amounts of DNA [2]. This was explained by the quenching of the bright state of the dye by electron transfer from the guanine and adenine residues. Although electron transfer reactions between the photosensitizer and DNA can be considered as DNA damage by themselves, the degradation of the photosensitizer by electron transfer avoids further excitation of oxygen by energy transfer from the triplet state of the dye, lowering the efficacy of the photodynamic treatment. Electron transfer from the nucleobases to methylene blue can be suppressed by a suitable functionalization of the dye with electron donors groups, as was suggested recently by us [3]. The insertion of electron donor substituents on the aromatic system of methylene blue red-shifts the electronic states involved in intersystem crossing. This way, the charge transfer state, which inhibits the triplet state generation, is not energetically accessible and does not participate in the deactivation mechanism of the drug. Here, we show how a rational functionalization of methylene blue was carried out based on QM(CASPT2 and TD-DFT)/MM(Amber) calculations and simple molecular orbital theory concepts, and how the charge-transfer excited state can be easily identified by calculating the charge transfer numbers [4] from the one electron transition density matrix.

References

- [1] A. E. O'Connor, W. M. Gallagher, A. T. Byrne, *Photochem. Photobiol.* 2009, 85, 1053.
- [2] J. M. Kelly, W. J. van der Putten, D. J. McConnell, *Photochem. Photobiol.* 1987, 45, 167.
- [3] J. J. Nogueira, M. Oppel, L. González, *Angew. Chem. Int. Ed.* 2015, 54, 4375.
- [4] F. Plasser and H. Lischka. *J. Chem. Theory Comput.* 2012, 8, 2777.