In silico modelling insight into assessing NSAIDS excited states deactivation mechanisms

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Drugs' light exposure, either in the visible (Vis) or ultraviolet (UV) range, along the pharmaceutical chain is inevitable. Thus, it is crucial to investigate the photophysics and the photoreactive paths that can be activated upon photon absorption [1]. The International Council of Harmonization (ICH) S10 guidance (and the associated ICH M3 guidance) suggests the characterization of the UV-Vis absorption spectrum as the initial assessment because it can obviate any further photosafety evaluation.

Thus, we have computed the absorption spectra of a set of eleven NSAIDs (piroxicam, carprofen, indomethacin, benoxaprofen, naproxen, diclofenac, suprofen, tiaprofenic acid, ketoprofen, ibuprofen and aspirin) in gas phase as well as in solution. Multistate second order perturbation theory on state average complete active space self-consistent field wavefunctions MS-CASPT2//SA-CASSCF (for aspirin and ibuprofen) and time dependent density functional theory (TD-DFT) (for all the NSAIDs set) were the computational protocols used for this purpose [2,3,4].

Besides, we have also considered the presence of triplet states close in energy to the singlet spectroscopic states at the Franck-Condon (FC) region. In fact, triplet excited states might be involved in the diversion of the excited population to pathways different from the return of the population back to the original ground state. Understanding the complexity of the deactivation mechanism, however, requires the in-detail mapping of the potential energy landscape for the ground and excited states. The accessibility of lower lying singlet electronic states and the coupling to the triplet excited states are key to explain the photostability or photoreactivity of these systems. Calculations exploring the topography of the potential energy surfaces of singlet and triplet multiplicity for the NSAIDs ibuprofen and aspirin are in course.

In a next stage, within the mechanistic scenario provided by the static calculations, the most probable photophysical deactivation mechanism of the excited molecules will be determined with the help of semi-classical dynamics simulations, performed with the surface-hopping algorithm incorporating spin orbit coupling, recently developed by Granucci et al. in Pisa [5]. These results are expected to shed light on the lifetime of the excited state. Our final aim is to generate a model phototoxicity alert that will improve the assessment of the photophysical properties of drugs.

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References

[1] H.H. Tønnesen et al., *Photostability of Drugs and Drug Formulations*, (CRC Press, New York 2004).
[2] B. O. Roos et al., *in Ab initio Methods in Quantum Chemistry II*, (Wiley, Chichester, 1987).
[3] K. Andersson et al., *J. Chem. Phys*. **96**, 1218 (1992)
[4] J. Finley, et al., *Chem. Phys. Lett*. **288**, 299 (1998).
[5] G. Granucci, et al., *J. Chem. Phys.* **137**, 22A501 (2012).