On Camptothecin Aggregation in DMSO and Aqueous Solutions

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The lactone form of quinolone alkaloid camptothecin (CPT), (S)-4-ethyl-4-hydroxy-1h-pyrano[3‘,4‘:6,7]-indolizino-[1,2-b]-quinoline-3,14-(4h,12h)-dione, is a potent anticancer drug (Fig. 1). The shifts of its two strong peaks in a critical 300-400 nm region of UV-Vis absorption spectra in neutral DMSO and aqueous solutions of various CPT concentrations may be explained by the formation of J-aggregates with bathochromic shift in absorption bands. These are formed by the stacking interaction between quinoline rings of CPT chromophores with the inverse position of the nitrogen atoms [1, 2]. Dvoranova *et al.* [2] investigated UV–Vis absorption spectrum of 50 μM CPT in various solutions. They performed B97D/cc-pVDZ geometry optimizations of the CPT lactone monomer and of its head-to-tail π-dimer in six solvents treated within Integral Equation Formalism Polarizable Continuum Model (IEFPCM). Unfortunately, the difference between the TD-B3LYP calculated electron transitions (1 – 5 nm) was very small in comparison with the difference between experimental bands (6 – 17 nm) in all the solvents under study. In the next study [3] the structures of CPT lactone head-to-tail π-aggregates in the *anti* conformation up to tetramers were optimized in DMSO and aqueous solutions using various DFT functionals with cc-pVDZ basis sets. Solvent effects were estimated using IEFPCM treatment. Only B3LYP with D2 dispersion correction of Grimme and ωB97XD functionals were able to produce reliable results on their geometries and TD-B3LYP electron transitions..
This study deals with the geometry optimization of CPT lactone head-to-tail π-aggregates in the *syn* conformation up to tetramers in DMSO and aqueous solutions using B3LYP with D2 dispersion correction of Grimme and ωB97XD functionals, cc-pVDZ basis sets and the IEFPCM approximation of solvent effects. Our results indicate that the *syn* conformation is more stable than the *anti* one but the agreement of its TD-B3LYP electron transitions with experimental spectra is worse.

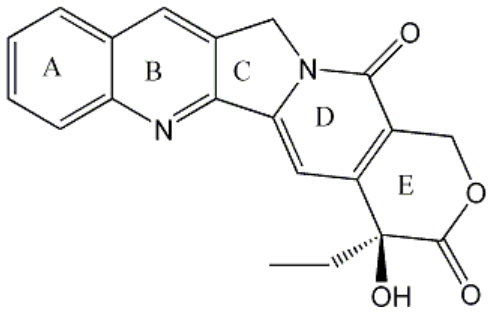

Figure 1: Molecular structure of CPT in the lactone form with standard ring notation.

References

1. I. Nabiev *et al.*, *Biochem. Pharmacol.* **55** (1998) 1163.
2. D. Dvoranova *et al.*, *Chem. Phys. Let.* **580** (2013) 141.
3. M. Breza, *Comput. Theor. Chem.* **1143** (2018) 1.