Unravelling the Mechanisms of Cytotoxicity for Phenanthroline Derivatives: Interaction with DNA

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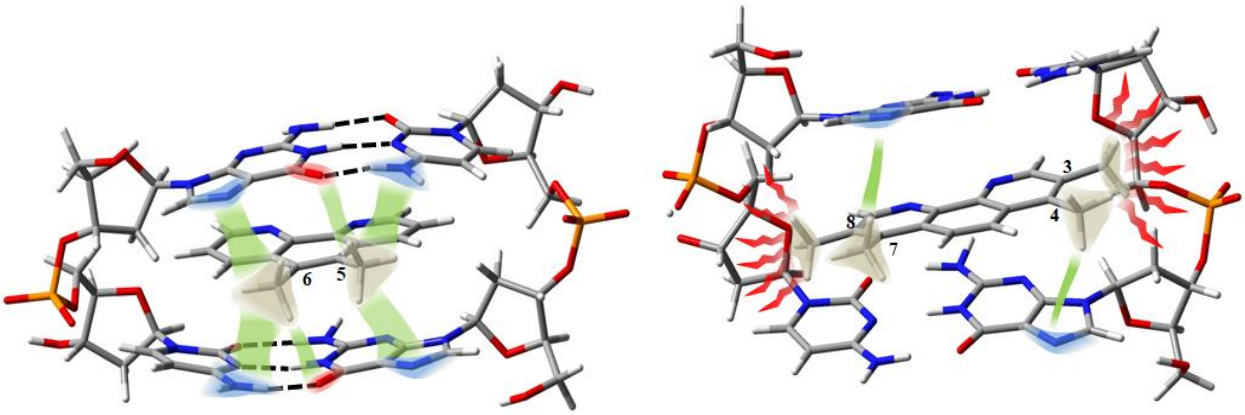

Flat ligands, alone or within metal complexes, are active against tumor cells and may be used in chemotherapy.[1] The activity of these drugs is related to their mode of interaction with DNA being the intercalation mode identified as the cytotoxic mode against tumor cells.[1,2] 1,10-phenanthroline (phen) was demonstrated to be effective towards several tumor cell lines,[3] and their derivatives also showed cytotoxicity. Moreover, it was observed that this cytotoxicity was deeply connected to the number and position of the functional groups incorporated in phen.[3] Different studies on the intercalation of small molecules in DNA have appeared in the bibliography during the last years [4,5] and some debate still remains about the intercalation/deintercalation process [4-7] and the mechanism that could explain the modulation of the cytotoxicity. In our work, we try to rationalize the role of weak interactions with the stability of the interaction and we extrapolate our results to the cytotoxic effects. The systems were mainly optimized by using semiempirical methods including dispersion effects. We also carried out DFT calculations including dispersion effects for the Energy Decomposition Analysis (EDA) and to perform the Quantum Theory of Atoms in Molecules (QTAIM) and the Non-Covalent Interaction (NCI) analyses to obtain topological pictures of the weak interactions that rules the intercalation process. Solvent effects were also taken into account by continuum approaches. Our results confirm the importance of weak interactions and we extrapolate the link with the cytotoxicity by means of a subtle balance between the stabilizing weak interactions and the destabilizing steric contribution. The role of desolvation energy is also crucial when looking at the stability of the studied systems.

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