Trying to Understand the Modulation in the Activity of the DNA Intercalating Anticancer Drugs: The Importance of CH/π Interactions

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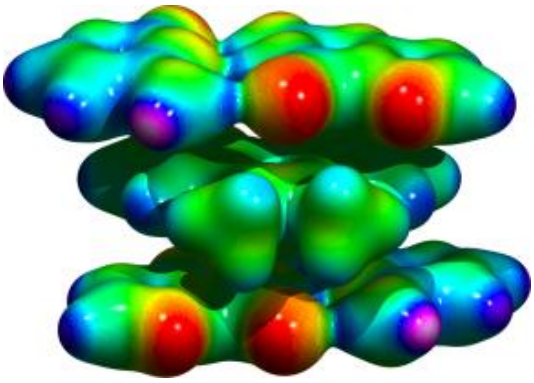

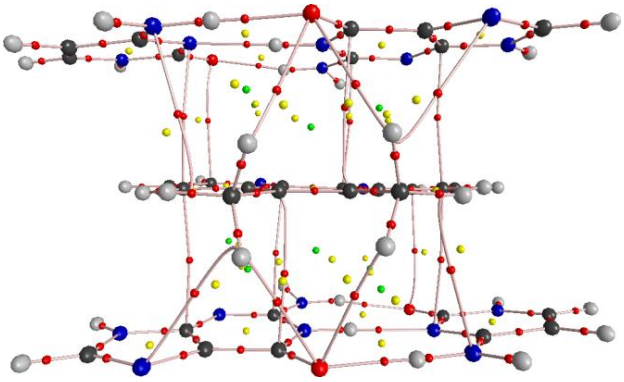

Several flat ligands, alone or in coordination complexes (CCs), are active against tumor cells and can be used in chemotherapy.[1] Such activity is related to their mode of interaction with DNA and intercalation is a binding mode associated to cytotoxicity towards tumor cells.[1,2] Phenanthroline (phen) proved to be effective against different tumor cell lines,[3] and methylated phen derivatives also exhibited cytotoxicity, which was found to be deeply connected to the number and position of $-CH_3$ groups.[2] Several works addressing the intercalation of small molecules in DNA have appeared recently in the literature [4,5] and there is still some debate about the intercalation/deintercalation process [4-7] and the mechanism that could explain the tuning of cytotoxicity. We tried to rationalize the intrinsic forces and substitution patterns ruling the intercalation to get some insight on the relation with cytotoxicity by means of DFT methods including dispersion, models consisting on the intercalator and four DNA bases, Energy Decomposition Analysis (EDA) and Atoms in Molecules (AIM) analysis. The results given by the AIM analysis confirm the existence of CH/π interactions and the Energy Decomposition Analysis shows a perfect direct correlation between the increasing number of CH/π interactions found in the studied systems and the stabilization of ΔE_{int}. This finding is fundamental to understand the connection between substitution in number and position and cytotoxicity. Moreover, despite the important role of dispersion energy in the systems with more methyl groups, dispersion cannot yet compensate the Pauli repulsion term, ΔE_{Pauli}. The role of attractive contributions, namely the orbital contribution, ΔE_{orb}, and the electrostatic contribution, ΔE_{elstat}, become crucial for the stabilization of the structures in the intercalation process.

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