Using DFT and Semi-Empirical Methods as Alternative to QM/MM Approach to Study Biological Systems: Interaction between Metal Complexes Containing Phenanthroline Derivatives and DNA Duplex and G-quadruplexes.

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DFT and semi-empirical methods were used to study the interaction of two isomers of the [Mo($\eta^3$$C_3H_5$)Br$(CO)_2$(phen)] metal complex with DNA to gain insight on the comprehension and rationalization of its experimentally observed cytotoxicity [1]. Regular duplex chains of DNA and G-quadruplexes were considered to analyze several modes of interaction for the [Mo($\eta^3$$C_3H_5$)Br$(CO)_2$(phen)] metal complex. From a methodological point of view, the DFT treatment of the whole systems, ~500 atoms for the regular duplex DNA and ~1000 atoms for the G-quadruplex, including van der Waals contributions at the LMKLL/DZ2P level with the SIESTA software [2] gives excellent results at a reasonable computing time. PM6-DH2 [3,4] and PM7 [5] semi-empirical methods including also dispersion perform quite well for the geometries but the energetics of the system are not correctly described. From a biophysical point of view the [Mo($\eta^3$$C_3H_5$)Br$(CO)_2$(phen)] metal complex prefers the intercalation rather than the groove binding in the case of the regular DNA duplex, whereas for the G-quadruplex a system in which the [Mo($\eta^3$$C_3H_5$)Br$(CO)_2$(phen)] is totally inside the G-quadruplex is the most stable. Energy Decomposition Analysis and topological studies were also carried out to know the nature of the interaction and our results confirm the importance of the role of weak interactions. The cytotoxicity of [Mo($\eta^3$$C_3H_5$)Br$(CO)_2$(phen)] seem to be related to a subtle balance between the stabilizing weak interactions and the destabilizing steric contribution. The entropic factor associated to the solvation effects results also of great importance.

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