Interaction of metallodrugs with DNA, QM/MM MD study

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Biologically relevant interactions of piano-stool ruthenium(II) complexes with ds-DNA are studied in this paper by hybrid QM/MM computational technique. The whole reaction mechanism is divided into three phases: i) hydration of the $[Ru^{II}(\eta^6\text{-benzene})(en)Cl]^+$ complex, followed by ii) monoadduct formation between the resulting aqua-Ru(II) complex and N7 position of one of the guanines in the ds-DNA oligomer model and the final phase – iii) formation of the intra-strand Ru(II) bridge (cross-link) between two adjacent guanines. Free energy profiles of all the reactions are explored by QM/MM MD umbrella sampling approach where the Ru(II) complex and two guanines represent a quantum kernel, which is described by DFT methods. The combined QM/MM scheme is realized by our own software (QMS v. 1.4), which was developed to couple several quantum chemical programs (in this study Gaussian 09) and Amber 11 program. Calculated free energy barriers of the both ruthenium hydration and Ru(II)-N7(G) DNA binding process are in good agreement with experimentally measured rate constants. Then this method was used to study a possibility of cross-link formation. One feasible pathway leading to Ru(II) guanine-guanine cross-link with synchronous releasing of benzene ligand is predicted. The cross-linking is exergonic process with energy barrier lower than for monoadduct reaction of Ru(II) complex with ds-DNA.