Formation of $Pt^{II}(DACH)Cl_2$ from $Pt^{IV}(DACH)Cl_4$ in the presence of dGMP. DFT study

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Platinum (II) complexes are some of the most used anticancer drugs. Nevertheless there is an effort to discover new compounds which have smaller side effects and are simultaneously active in the treatment of recently resistant tumors. Pt(IV) complexes represent such a class of drugs. However they must be initially reduced to Pt(II) analogues in an organism to reach their anticancer activity [1], but the reduction mechanisms are still not well-known.

In this study we focus on the reduction mechanism of $Pt^{IV}(DACH)Cl_4$ (DACH= diaminocyclohexane) in the presence of 5'-dGMP (2'-deoxyguanosine-5'-monophosphate) and 3'-dGMP, which was suggested by experimenters (shown at Fig. 1). [2] At first a chloride ligand in the complex is substituted by dGMP which leads to a formation of Pt-N7 bond. The reaction continues with nucleophilic attack of the phosphate or hydroxyl group at C5' end to the C8 position. Consequently the complex is reduced to $Pt^{II}(DACH)Cl_2$. The last step represents a hydrolysis of C8-O bond leading to a formation of 8-oxo-dGMP.

We studied geometry parameters of all species involved in this quite complex mechanism and changes in the electron density distribution. Explored structures were optimized at the DFT level with B3LYP functional in 6-31G(d) basis set and CPCM/Klamt solvation model. The energy parameters for the whole reaction were determined using the single-point calculations at the DFT level B3LYP-GD3BJ/6-311++G(2df,2pd) with IEFPCM/scaled-UAKS solvation model developed in our laboratory recently [3].

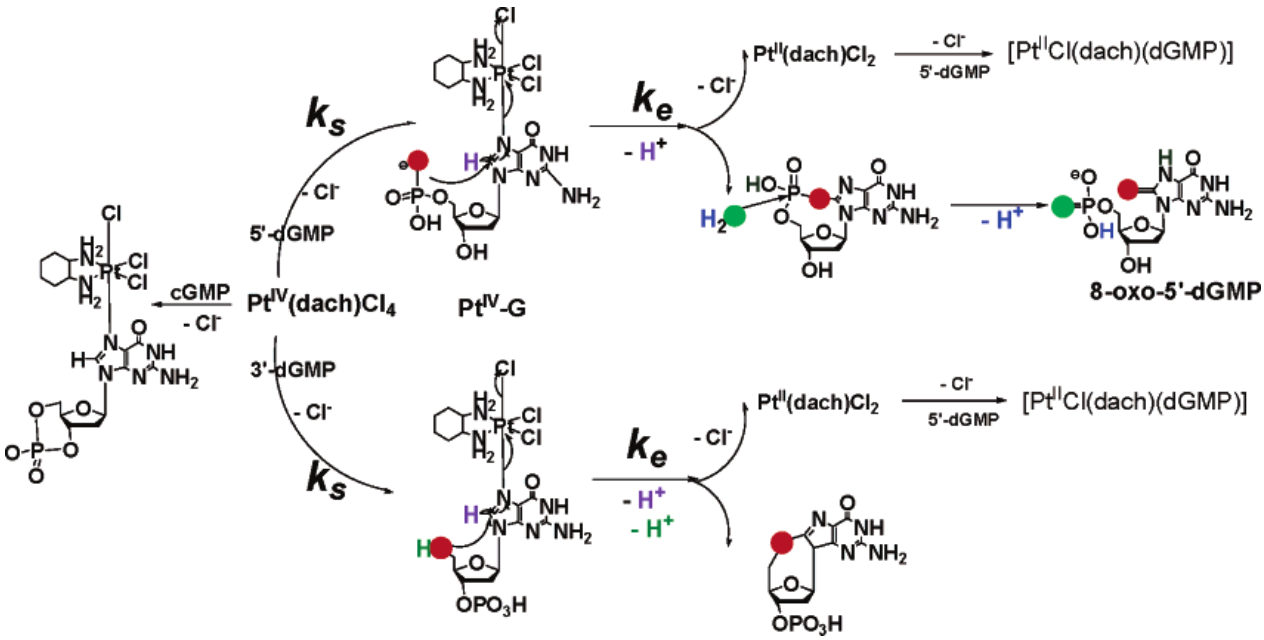

Fig. 1: Scheme of the explored reaction (taken over from [2])

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