On the Hydrolysis Mechanism of the Second Generation Anticancer Drugs Carboplatin and Oxaliplatin

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Abstract: The hydrolysis reaction mechanisms of carboplatin and oxaliplatin, second generation drugs, have been explored combining Density Functional Theory (DFT) with the conductor-like dielectric continuum model approach (CPCM) approach. The decomposition of both drugs is expected to take place through a biphasic mechanism with a ring-opening process followed by the loss of the ligand. We have investigated these reactions in water and acidic conditions and established that the number of protons present in the malonato and oxalato ligands have a direct effect on the energetics of these systems. In addition, we were able to observe that the introduction of an explicit water molecule in the carboplatin system has a stabilizing effect on the transition states.

From the computed potential energy surfaces, the water hydrolysis of oxaliplatin takes place with an activation barrier of 24 kcal.mol$^{-1}$. Carboplatin must overcome a 30 kcal.mol$^{-1}$ barrier, confirming the very slow reaction observed experimentally. The decomposition of carboplatin upon acidification was also investigated and we find 21 kcal.mol$^{-1}$ to be overcome (experimental value 23 kcal.mol$^{-1}$) while oxaliplatin requires only 17 kcal.mol-1. Activation barriers for oxaliplatin appear to be about 3 kcal.mol$^{-1}$ underestimated with respect to experimental counterpart. However, we were able to determine the reason for the lower activation barriers calculated. We have examined all structures and observed a direct correlation between the charge separation observed in going from the reactants to the transition state structures.

From our studies, it was established that the rate limiting process for carboplatin is the first hydration process. In addition, we have ascertained the importance of a water molecule in the vicinity of the amine groups in lowering the activation barriers for the ring-opening processes. For oxaliplatin we have observed that the neutral hydrolysis will take place with the ring-opening as the rate limiting process. However, in acidic conditions the slowest process is expected to be the ligand detachment, which is consistent with experimental results.

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