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Hydrolysis of new Pt(II) complexes with ligands of natural origin: a DFT study

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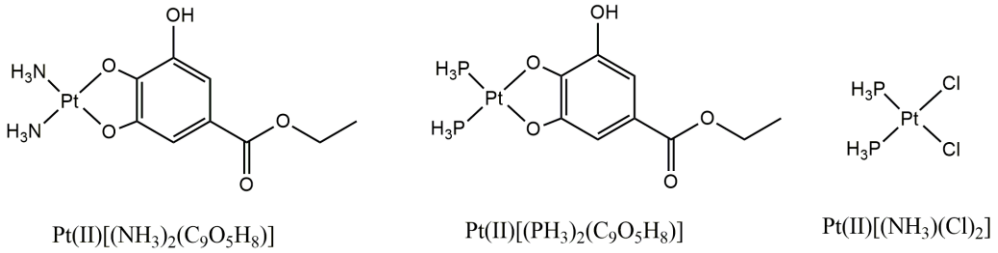
Since the discovery of the first complex which exhibited anti-tumor properties(cis-diamminedichloro-Pt(II), cisplatin) [1] numerous Pt(II) complexes have been used as anti-cancer drugs, but only few have been approved for clinical use. The accepted mechanism of action of cisplatin consist in two stages: intracellular activation by the hydrolysis of a ligand (for example Cl^- in cisplatin) and formation of intra-strand cross-links in DNA which produces a bending that causes the generation of defective proteins and ultimately the cell death [2].Unfortunately, its therapeutic efficacy is somewhat compromised by occurrence of serious side effects [3]. In order to overcome these limitations, many studies have been done to find other platinum drugs with an equivalent or improved range of activity but with less toxic side effects [4]. Hydrolysis reactions are the rate determining step of the whole process and therefore many experimental and theoretical studies [5] have been carried out to obtain structure-reactivity relationships.

In this work we report the theoretical study of the hydrolysis reaction processes of $Pt(II)[(NH_3)_2(C_9O_5H_8)]$ (A), $Pt(II)[(PH_3)_2(C_9O_5H_8)]$ (B) and $Pt(II)[(PH_3)_2(Cl)_2]$ (C) shown in figure 1. The complexes A and B once hydrolyzed within the cell, release ethylene gallate($C_9O_5H_8$), compound which has anti-oxidantandanti-inflammatory and antiproliferative properties[6]. Complex C has been studied for comparison.



$Pt(II)[(NH_3)_2(C_9O_5H_8)]$ $Pt(II)[(PH_3)_2(C_9O_5H_8)]$ $Pt(II)[(NH_3)(Cl)_2]$

Figure 1: complexesbased on platinumstudied in this work.

These complexes have been studied using density functional theory (DFT) in order to obtain detailed data on its mechanism of action. DFT calculations were performed with the Gaussian 09 program, using the mPW1PW91 functional. Geometry Optimizations were carried out in vacuum and PCM with a 6-31+G(d) basis set for all atoms except the platinum atom, which was described by the quasi-relativistic Struttgart-Dresden pseudopotential (SDD). Solvent effect have been introduced by the PCM approach. The results were compared with those present in the literature for several anti-cancer drugs [5,7-8].

The computed potential energy surface shows that the lower activation energy is found for $[Pt(II)[(PH_3)_2(Cl)_2]$. For complex $Pt(II)[(PH_3)_2(C_9O_5H_8)]$ it can be observed that activation energy is comparable to cisplatin. $Pt(II)[(NH_3)_2(C_9O_5H_8)]$, instead, shows the highest energy barrier, this indicates that the hydrolysis reaction is disfavored in this complex.

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