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Evaluation of Intermolecular Potentials for Carboplatin and Oxaliplatin in Aqueous Solution.

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Abstract: Platinum complexes are widely studied due to their anticancer activity. The first step of mechanism of action is the hydrolysis reaction, which takes places in water environment. Aiming to study cisplatin hydrolysis in first place, two different intermolecular parameters sets were developed by Lopes[1,2]. Transferability for carboxylate analogous as Carboplatin and Oxaliplatin, however, were not tested at that time and are presented in this work. First of all, both molecules were optimized using 6-31g(d,p) basis set for the light atoms, while for Pt the LANL2DZ basis set were used. The atomic charge was calculated by ChelpG method. Geometries and charges were also evaluated in solution by means of IEFPCM. All quantum mechanical calculations were performed using Gaussian09 software and for Monte Carlo simulations, DICE[3] software was used. In MC simulations two LJ parameters were settled[1,2], so as two different charges (gas, IEFPCM), resulting in 4 combinations. A system was defined as a cubic box and filled with 1.10^3 molecules of solvent. The system was equilibrated in a 5.10^5steps on first stage and then followed by a simulation stage of 1.10^6 steps, both in a NPT ensemble. The **Fig. 1** shows snapshots of MC simulation with first LJ parameters developed for cisplatin[1].

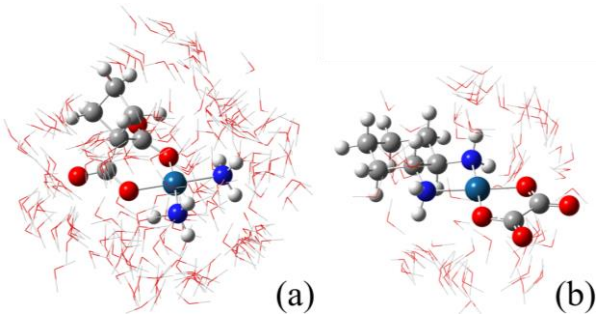

Figure 1 – MC Simulations snapshots for one uncorrelated configuration first solvation shell of Carboplatin**(a)** and Oxaliplatin**(b)**.

Water distribution around the Carboplatin is described by RDF of center of masses interactions in **Fig. 2**. **Fig. 3** shows the same data respective to Oxaliplatin.

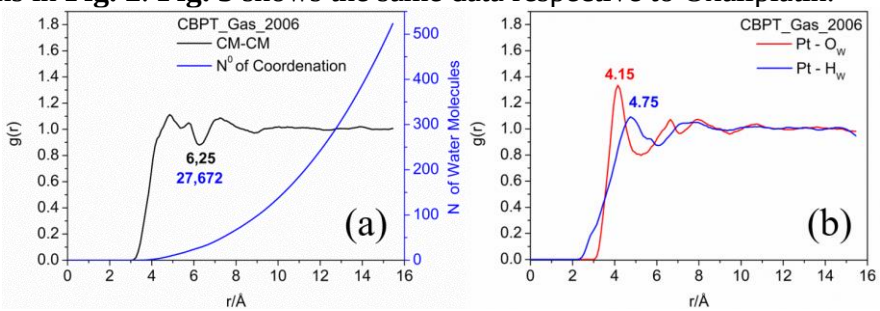

Figure 2 – RDFs of MC simulation of Carboplatin. **(a)** Center of mass pair correlation function. **(b)** RDFs Pt···O_w and Pt···H_w.

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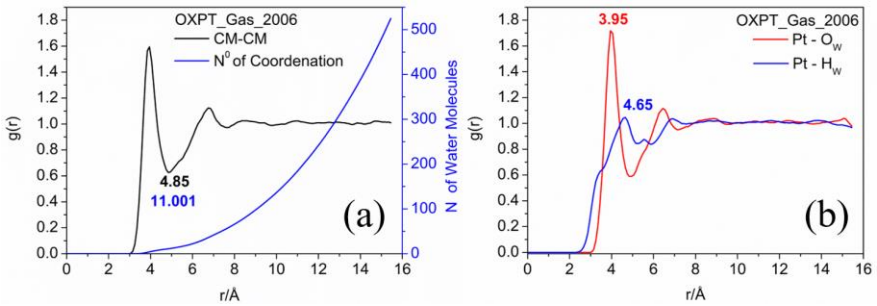

Figure 3 – RDFs of MC simulation of Oxaliplatin. **(a)** Center of mass pair correlation function. **(b)** RDFs Pt···O_w and Pt···H_w

Analysis g(r) solute-solvent center of masses (CM), **Fig. 2(a)**, one can see the solvation shell finishing at 6.2 Å, the coordination number (NC) calculated for this shell were 28 water molecules. To Oxaliplatin, **Fig. 3(a)**, was verified the first shell finishing at 4.85 Å and NC for the first shell were 11 water molecules which indicates that carboplatin is more stable in aqueous solution. The g(r) Pt···O_w and Pt···H_w pair correlation functions, to Carboplatin, **Fig. 2(b)**, two peaks centered at 4.15 and 4.75 Å, to Oxaliplatin, **Fig. 3(b),** two peaks centered at 3.95 and 4.65 Å, so the O_w in average stay closer than H_w, however, H_w shows closer distance to Pt atom, indicating a stronger interaction with it. To execute QM calculation, as reference to parametrization process, the structure of complex with one water interaction was extracted of the simulations. With the correlation processes 100 configurations was selected to Carboplatin in water and 140 configurations to Oxaliplatin. These configurations were used as base for Scan calculations. In **Fig. 4** shows one configuration of Scan calculations for carboplatin and the classical curve with the two parameters of literature[1,2] with different atomic charges. Classical curve has a significant difference, indicating that a new and specific set of parameters is necessary to Carboplatin. To make the parametrization all the 100 different Potential Energy curves will be used on a specific program, for fitting these values with the adjust a new set of LJ parameters will be defined. Carboplatin scan calculations are already finished; Oxaliplatin scan calculations are still running.

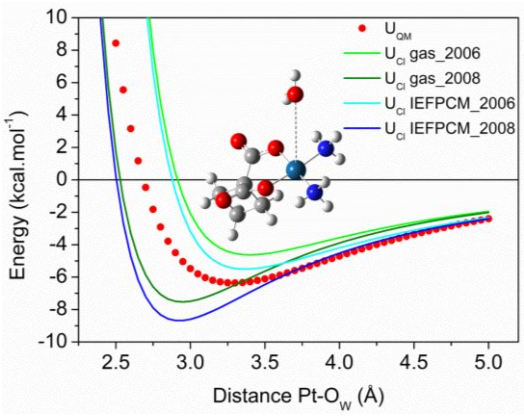

Figure 4 – QM and classical potential energy curves calculated for the Carboplatin-water interaction.

Key-words: Platinum compounds, Monte Carlo simulation, Parametrization.
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References:

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