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Neutral and Acidic Hydrolysis Reactions of the Third Generation Anticancer Drug Oxaliplatin

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The hydrolysis of oxaliplatin, a third generation anticancer drug, is expected to play an important role in the activation of this compound before it reaches DNA. The first and second hydrolysis corresponding to the addition of the first water molecule concomitant with the ring-opening, followed by addition of a second water and loss of the monodentate oxalato ligand, respectively, were studied combining density functional theory (DFT) with the conductor-like dielectric continuum model (CPCM) approach. The reaction was studied in neutral and acidic conditions, and all stationary points have been identified. The computed potential energy surfaces show that, for the neutral hydrolysis, the ring-opening reaction is the rate-limiting process, with an activation barrier of about 28 kcal/mol. For the acid degradation in water, according to experimental data, the reaction is expected to proceed in a faster biphasic process, and the rate-limiting process is the ligand detachment that occurs with a barriers of about 22 kcal/mol. According to the calculated results, we expect that the reaction is favored in acidic conditions and that the monoaquated complex should be the species reacting with DNA.

Introduction

In 1965, Rosenberg unexpectedly found that *cis*-diamminedichloroplatinum, commonly known as cisplatin, was able to inhibit cell division.[1] This discovery led to the investigation on the antitumor properties of platinum compounds.[2] Cisplatin-based chemotherapy has become a fundamental treatment in some types of tumors that were essentially fatal before the introduction of this drug. Cisplatin exhibits high efficiency in the treatment of ovarian, bladder, head, and neck as well as non-small lung and cervical cancers.[3] However, in spite of the impressive antitumor activity, this drug presents several limitations. Side effects such as nausea/vomiting, nephrotoxicity, and ototoxicity have been registered for cisplatin. In addition, it has poor activity (intrinsic resistance) against some of the most common types of cancer, such as colorectal and pancreatic. Acquired resistance has also been observed with the inability to confer lasting remissions. These limitations have promoted the search for new drugs that are able to circumvent cisplatin's resistance and reduce its toxicity.

Carboplatin (*cis*-diamminecyclobutane-1,1-dicarboxylateplatinum) was the first drug to follow cisplatin in cancer treatment; however, in spite of the reduction of some side effects, when compared to cisplatin, this drug still exhibits limitations.[4]

Through the years many platinum-based compounds have been synthesized and investigated. Compounds containing 1,2-diaminocyclohexane (DACH) carrier ligands were identified in the early 1970s as non-cross-resistant with cisplatin, and for this reason they have received special attention.[5,6] These DACH compounds were considered promising given their reduced nephrotoxic activity toward acquired cisplatin resistance and appeared to be clinically effective in intrinsically resistant tumor cells.

Oxaliplatin (1,2-diaminocyclohexaneoxalateplatinum) developed by Kidani et al.,[7] in 1980, while testing several new platinum compounds, was accepted as a third generation platinum drug.[8] Oxaliplatin was initially approved in France in 1998, followed by the rest of Europe and finally, in 2002, in the United States. It is active against some tumors that are primarily resistant to cisplatin and carboplatin being the first antineoplastic agent to exhibit activity against metastatic colorectal cancer.[9−11] It is normally used in combination with 5-fluorocil and leucovorin[12,13] in the treatment of this type of tumor which is the second leading cause of cancer death in developed countries. It has also been reported that oxaliplatin is active in platinum-pretreated advanced ovarian cancer.[14,15]

Much research has been done in this area, and platinum compounds are expected to interact with DNA following several steps: aquation of the platinum complex, preassociation with the DNA, monofunctional adduct formation, closure of the bifunctional adduct, distortion of the DNA, and recognition of this distortion.[16,17]

A large amount of experimental evidence shows that the success of platinum complexes, in killing tumor cells, mainly results from their ability to form various types of adducts with DNA.[18] Oxaliplatin acts as an alkylating agent on DNA, forming essentially three types of cross-link adducts: intrastrand, interstrand, and DNA−protein. In spite of the different binding modes, it has been suggested that only the kinetically preferred binding modes are important in biological systems.[19] The most common adduct is the intrastrand that bridges two adjacent purine bases (1,2-GG or AG) at the N7 position.[20,21] Guanine N7 is the most easily oxidized site on DNA, and the major adducts of platinum drugs with DNA are 1,2-GpG and 1,2 ApG intrastrand cross-links. The properties of these adducts have been extensively characterized.[5,22,23]

Comparison of the crystal structure of oxaliplatin adduct of a DNA duplex reveals that it is identical to the cisplatin

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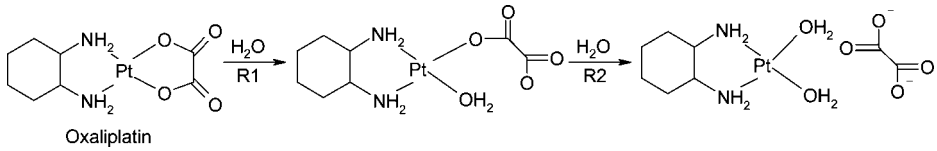
SCHEME 1: Investigated Reaction Path for Oxaliplatin Ring-Opening (R1) and the Loss of the Ligand (R2) in Neutral Conditions



adduct.[24−27] However, important differences are observed between cisplatin and carboplatin adducts when compared with oxaliplatin DNA adducts. The presence of the cyclohexane ring in oxaliplatin induces a strong nonpolar region in the DNA, leading to differences in cellular recognition. The DACH−platinum DNA adducts resulting from oxaliplatin are more bulky and hydrophobic than the ones formed from cisplatin and carboplatin. As a consequence, these adducts are more effective in inhibiting DNA synthesis and usually more cytotoxic than *cis*-diamineplatinum adducts.[28]

Structure−activity relationships for platinum compounds have been formulated, and most drugs reported possess two amines in the cis position.[29,30] For the antitumor activity of platinum compounds it is significant that they possess two labile groups in cis geometry. Chloride found in cisplatin is a good leaving group, but the kinetically less labile carboxylate, glycolate or oxalate, present in second and third generations drugs such as carboplatin, nedaplatin, and oxaliplatin are expected to be responsible for the reduced side effects observed on patients treated with these drugs in comparison with cisplatin.

The higher lipophilicity observed in oxaliplatin should be responsible for the more efficient removal from the blood through enhanced tissue penetration. For this reason, substitutions at the nonleaving group should influence the tumor inhibiting activity of oxaliplatin.[31]

The proposed hydration process for cisplatin is consistent with the fact that water is a better leaving group than the chloro ligand,[32] and several theoretical studies exposing the most likely path for cisplatin hydrolysis prior to DNA binding can be found in the literature.[33−38] A correct understanding of the hydration mechanism of these drugs is essential. It is expected that the difference between cisplatin and oxaliplatin results from the resistance mechanisms rather than from any fundamental difference in their modes of action.[39,40] However, it is still essential to have a correct understanding on all steps preceding the DNA binding.

The rapid development of computational chemistry has allowed the theoretical modeling of a large variety of chemical reactions. DFT methods have been successfully applied in the study of reactions such as oxidative/reductive eliminations, nucleophilic additions, and substitutions involving transition metals as well as catalytic processes.[41−43] Many platinum anticancer drugs have been subject of theoretical study,[44−48] and in this work we present the first computational approach to the hydrolysis mechanisms of oxaliplatin in water and acid conditions. According to experimental results, oxaliplatin degradation in water should take place in two consecutive steps: first, water addition with ring-opening followed by loss of the ligand with the reaction of the second water molecule.[49,50]

Computational Details

All structures were optimized using density functional theory (DFT) with the B3LYP functional which includes the Becke's hybrid[51] exchange and correlation functional of Lee, Yang, and Parr[52] as implemented in the Gaussian 03 quantum chemical program package.[53] For all structure optimizations, we have used the 6-31G(d) basis set for all atoms except the platinum atom, which was described by the quasi-relativistic Stuttgart−Dresden pseudopotentials[54] with pseudo-orbital basis set augmented by a set of diffuse functions—$\alpha_s = 0.0075$, $\alpha_p = 0.013$, and $\alpha_d = 0.025$—and polarization functions—$\alpha_f = 0.98$.[37] In order to confirm proper convergence to equilibrium and transition state geometries, vibrational frequency analysis were done based on analytical second derivatives of Hamiltonian at this level of theory.

Geometry optimizations were then redone in water environment performing a PCM calculation using the CPCM[55] polarizable conductor calculation model. In these methods, dominating electrostatic interaction with a continuum is provided by polarization charges appearing on the boundary surface of studied molecule.[56] In here, this solvent-accessible surface was constructed using Klamt's radii[57] with explicit hydrogens.

On the optimized structures, single-point (SP) energy calculations were also carried out with the larger basis set 6-31++G-(2df,2pd). Similarly, platinum valence basis set was augmented with diffuse ($\alpha_f = 0.46$) and polarization ($\alpha_g = 1.21$) functions.[37] Potential energy profiles were estimated from total electronic energies at the 6-31++G(2df,2pd) level adding zero point energy (ZPE) and enthalpy corrections at room temperature (298.15 K).

Results

1. Oxaliplatin Hydrolysis in Neutral Conditions. As previously exposed, oxaliplatin is expected to undergo water degradation in a biphasic process: addition of the first water molecule connected to the ring-opening process followed by the release of the oxalato ligand upon reaction with a second water molecule.

The first reaction studied was the degradation of oxaliplatin in water. The proposed hydrolysis mechanism, in neutral conditions, is presented in Scheme 1.

The potential energy profile for reaction R1 (Scheme 1) and the optimized structures for the stationary points along R1 are

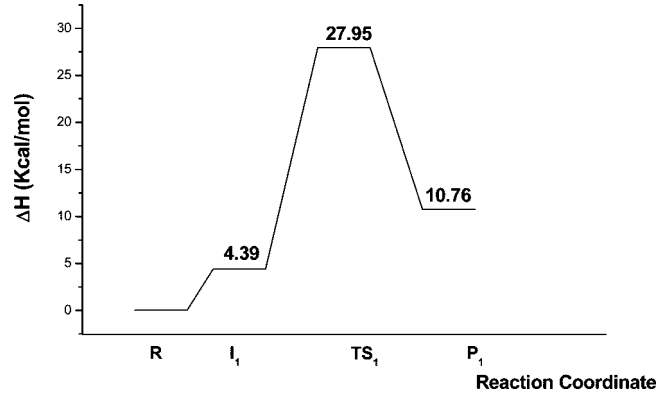


Figure 1. Activation enthalpy (at 298.15 K) and reaction heat for the addition of the first water molecule to oxaliplatin (R1), in neutral conditions, in water phase.

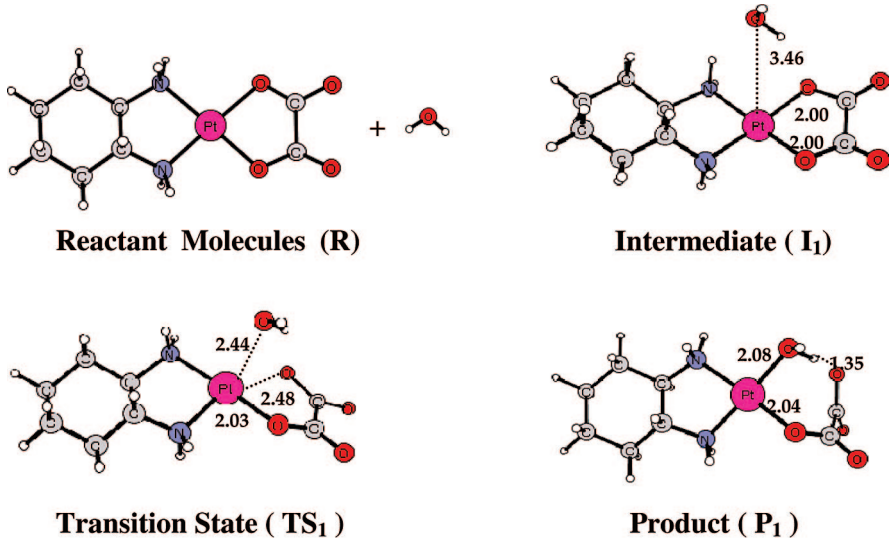


Figure 2. Optimized structures and selected structural parameters for the addition of the first water molecule to oxaliplatin (R1), in neutral conditions, in water phase. The distances reported are in angstroms.

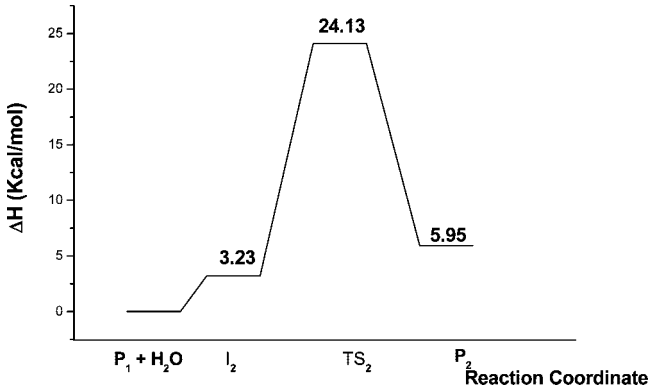


Figure 3. Activation enthalpy (at 298.15 K) and reaction heat for the addition of the second water molecule to oxaliplatin in the opposite plane of the exiting ligand (R2), in neutral conditions, in water phase.

displayed in Figures 1 and 2. The reacting water molecule lies at 3.46 Å away from the platinum atom. The distances between the oxygen atoms in the oxalato ligand and the platinum atom are always essentially 2.0 Å in the reactants as well as the products. As the water molecule approaches the Pt center, the platinum−oxygen (of the ligand) bond distance starts to increase until the transition state geometry is reached. The distances of the bonds being broken and formed in the transition state (TS_1) geometry do not change significantly upon optimization of the structures in gas phase or including solvent effects (2.45 and 2.48 Å, respectively). The platinum−oxygen bond distance between the entering water molecule (Pt−OW) in gas phase is 2.34 Å while in solvent it is 2.44 Å. The imaginary frequency observed in the transition state is about 200i cm^{-1} in gas phase and 183i cm^{-1} in solvent, and the analysis of this vibrational mode clearly indicates the rupture of the Pt−OL bond and the simultaneous formation of the Pt−OW bond. The activation barrier is 27.95 kcal/mol in solvent. The reaction is endothermic by 10.76 kcal/mol in water. The final product of this reaction in gas phase displays a proton transfer from the water molecule bonded to platinum to the carboxylate group of the ligand. On the contrary in solvent, the final product does not exhibit proton transfer.

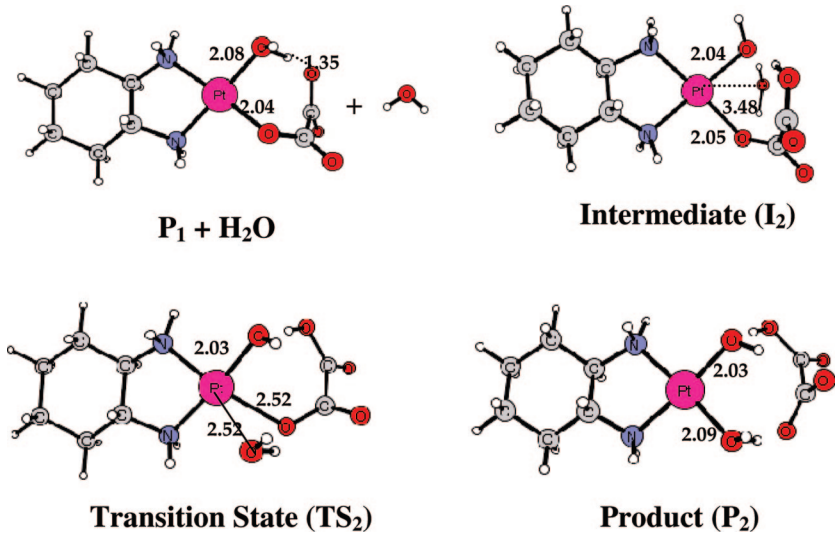
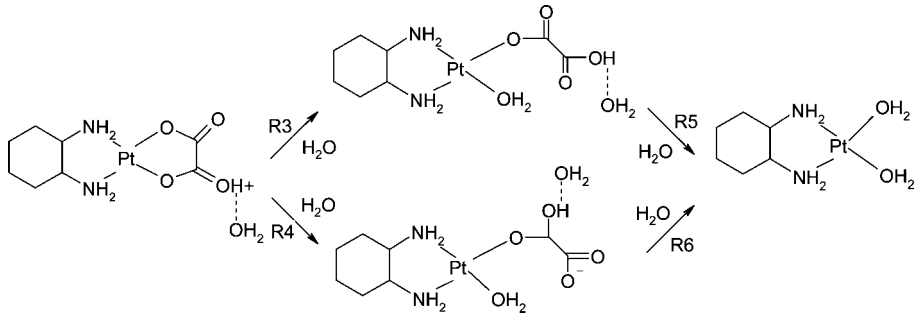


Figure 4. Optimized structures and selected structural parameters for the addition of the second water molecule to oxaliplatin (R2), in neutral conditions, in water phase. The distances reported are in angstroms.

SCHEME 2: Investigated Reaction Path for Oxaliplatin Ring-Opening (R3, R4) in Acid Conditions as Well as the Loss of the Ligand (R5, R6)[a]



[a] The protonated ligand has the extra proton in a cis position relative to the entering water molecule in reactions R3 and R5 and in a trans position in reactions R4 and R6.

In the next step of the reaction, leading to the loss of the oxalate ligand (R2), the addition of the second water molecule can occur in two different ways. In the first, we consider addition on the same plane of the monodentate ligand while in the second one the addition occurs on the opposite plane. This last water attack result to be the lowest energy path, and the results are shown in Figures 3 and 4. In the intermediate structure the water molecule approaches the platinum center with a distance of 3.48 Å which becomes 2.52 Å in the TS and 2.09 Å in the product. Similar results are obtained in the gas phase. The imaginary frequencies for the transition state corresponding to the Pt−OL and Pt−OW bonds being broken and formed, respectively, are 190i cm^{-1} in solvent. The activation barrier is found to be 24.13 kcal/mol, and the reaction endothermicity is 5.95 kcal/mol.

It is interesting to notice that although the final product of reaction R1 is different, depending on the medium it has been optimized, the reactants for this step are identical. In fact, starting from the reactant containing or not a proton transferred to the oxalate monodentate ligand, the obtained structure of the intermediate is identical.

From Figures 1 and 3 it is evident that, in neutral solution, the rate-limiting process is the ring-opening. The computed activation barriers (27.95 kcal/mol) agree with that extracted from the experimental reaction rate (26.50 kcal/mol).[50]

2. Oxaliplatin Hydrolysis in Acid Conditions. Oxaliplatin degradation in acid conditions has also been investigated. We have initiated the study by introducing a H_3O^+ molecule to the system and observed a proton transfer to oxaliplatin. Once the proton is transferred, the water molecule remains hydrogen bonded to this proton throughout the hydrolysis process. The addition of the first water molecule with consequent ring-opening has been explored following two possibilities: Pt−OL cleavage with proton in the neighboring carboxylate oxygen or in the trans position considering the Pt−OL bond. In Scheme 2 both situations are illustrated as well as the proposed reaction path for acid degradation of oxaliplatin water.

In Figure 5 the potential energy profile for reaction R3 (Scheme 2) and the relative optimized structures for the stationary points along this reaction liquid phase are depicted in Figure 6. Also in this case, for both the considered media, the optimized structures of the species located along the path are very similar (e.g., for the transition state the Pt−OW distance is 2.47 Å in gas phase and 2.50 Å in water). The final product for this reaction displays cleavage of the Pt−OL bond and the formation of the monodentate ligand. On the contrary to what took place in neutral conditions, no proton transfer is observed. Imaginary frequencies for the transition state corresponds to the Pt−OL and Pt−OW bonds being broken and formed are about

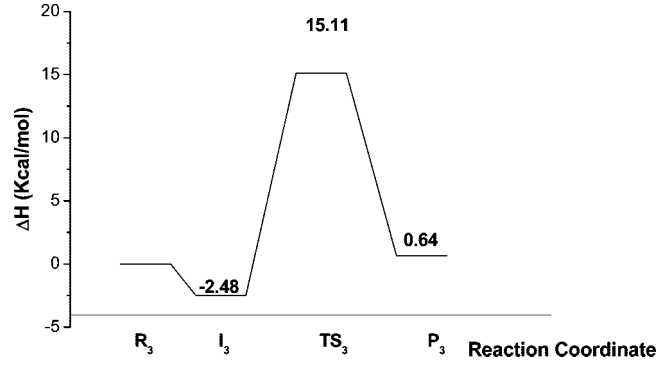


Figure 5. Activation enthalpy (at 298.15 K) and reaction heat for the addition of the first water molecule to oxaliplatin in acidic conditions (R3), in water phase.

150i cm^{-1} in gas phase and solvent. The reaction presents a similar potential energy profile in gas and in solution with an activation barrier of 15.11 kcal/mol (optimizations in water) and is essentially thermoneutral.

In addition to the protonated system on the carboxylate group in the vicinity of the Pt−OL breaking bond, we have investigated the acidic hydrolysis of oxaliplatin with an extra proton in a trans position (R4) relatively to the bond that is being broken. Also in this case, the activation energy is not significantly affected by the inclusion of solvent effects on the calculations. In fact, in the identical reaction R3 (addition of the water molecule in a cis position to the proton), the activation barrier is essentially the same in both mediums. In this case, however, the energy to be surmounted is higher, 18.26 kcal/mol opposed to 15.11 kcal/mol. The distance separating the water molecule from the Pt center is about 0.10 Å shorter than in the R3 reaction, and also the TS critical distances are slightly smaller. As in the R3 reaction, two products are expected depending on the conditions of the optimizations. For gas phase the product is formed by simultaneous Pt−OL cleavage and proton transfer from the water molecule to the neighboring carboxylate group. When solvent effects are included, this proton shift does not take place, and the final product contains a water molecule bonded to the Pt atom. The reaction is endothermic in both mediums with a calculated energy gain of 3.15 kcal/mol in water. Imaginary frequencies are somewhat larger than in R3 with about 170i cm^{-1} instead of 150i cm^{-1}.

The reaction should then proceed with the addition of a second water molecule (R5). Like in the case of the neutral solution, in acid conditions we must consider the possibility of addition of the second attacking water molecule in the same plane of the exiting ligand or on the opposite plane. Reaction

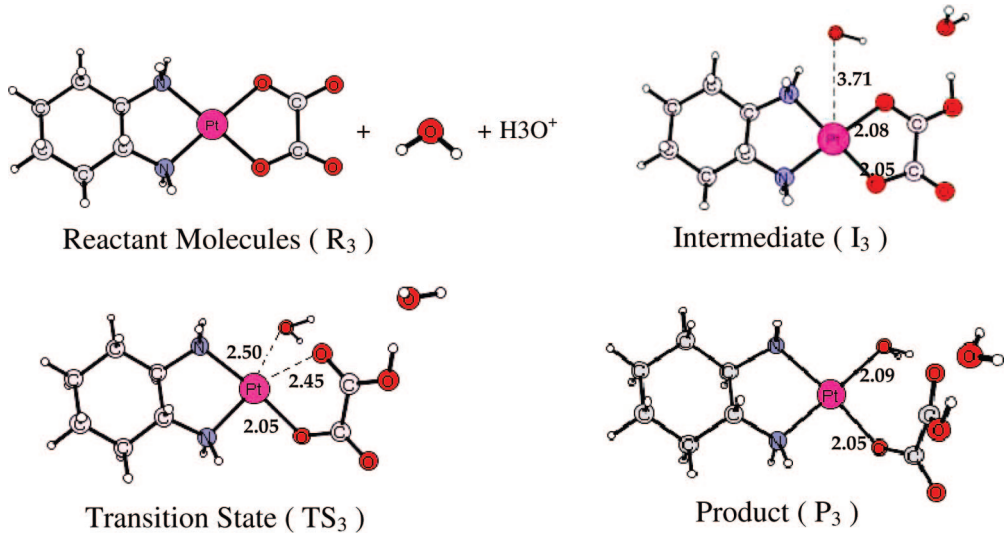


Figure 6. Optimized structures and selected structural parameters for the addition of the first water molecule to oxaliplatin in acidic conditions (R3), in water phase. The distances reported are in angstroms.

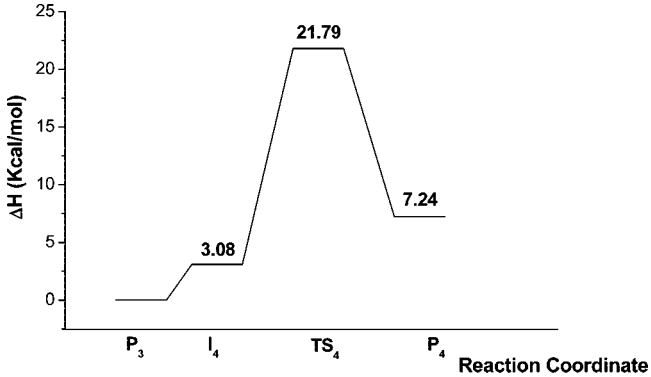


Figure 7. Activation enthalpy (at 298.15 K) and reaction heat for the addition of the second water molecule to oxaliplatin (R5), in the same plane of the ligand, in acid conditions, in water phase.

on the same plane of the ligand for the system with an extra proton on the cis position (following reaction R3) lies at lower energy than on the opposite plane. The potential energy profile for this reaction is depicted in Figure 7 while the corresponding optimized structures are reported in Figure 8. In gas phase, the reacting water molecule in the intermediate lies 3.55 Å away from the platinum center. This water molecule then approaches the metal, and the transition state geometry is reached with a Pt−OW distance of 2.39 Å in gas phase and the Pt−OL distance is 2.36 Å. When solvent effects are included, the distances are somewhat longer with 2.49 Å for the Pt−OW and 2.42 Å for the Pt−OL bond. The final product for this reaction consists of a double aqua complex for the water optimization and a proton transfer from the water molecule to the oxalate ligand in gas phase.

According to the results here obtained, reaction on the same plane requires an activation barrier of 21.79 kcal/mol. The imaginary frequencies for the transition state are 180i cm^{-1} in gas and 170i cm^{-1} in solvent.

Considering the addition of the second water molecule in the system with an extra proton on the trans position (following reaction R4), we must analyze, just as in R5, the possibility of

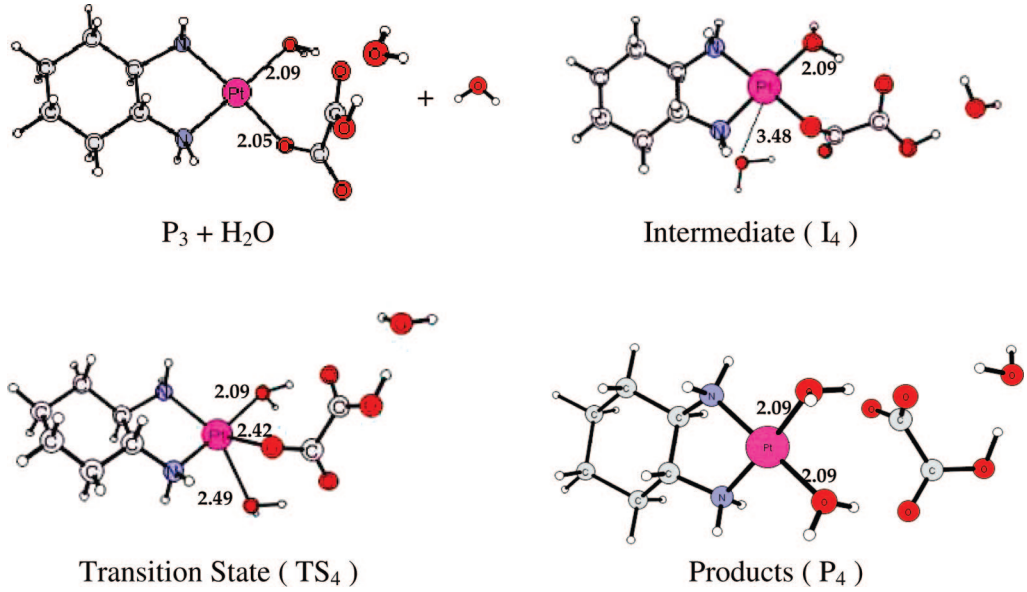


Figure 8. Optimized structures and selected structural parameters for the addition of the second water molecule to oxaliplatin (R5), in the same plane of the ligand, in acidic conditions, in water phase. The distances reported are in angstroms.

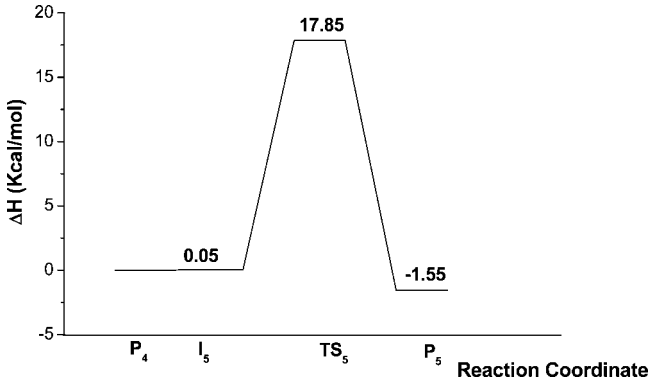


Figure 9. Activation enthalpy (at 298.15 K) and reaction heat for the addition of the second water molecule to oxaliplatin with an extra proton on the trans position, in the opposite plane of the ligand, in acid conditions, in water phase.

addition in the same or opposite plane of the exiting ligand (R6). Results show that addition on the opposite plane exhibits a lower energy path which is reported in Figure 9. The optimized structures are shown in Figure 10. The reacting water molecule is 3.84 Å away from the platinum atom in the intermediate system. The critical distances in the transition state are identical in water and gas phase, with a Pt−OW distance of about 2.50 Å and the Pt−OL distance about 2.45 Å in both phases. Concerning the addition of the second water molecule in the opposite plane of the ligand, and in spite of the fact that the product from the previous step shifted a proton from the water molecule to the ligand (in gas phase), we have observed that the optimization of the reactant for next step (extra water molecule) retrieves the proton back to the water ligand. However, in the remaining stationary points (TS and products in gas phase) the proton is located on the exiting ligand. In case of reaction proceeding in solvent, the proton always stays with the attacking water molecule during the whole reaction. The calculated activation energy in water phase is 17.85 kcal/mol, and the process is slightly exothermic (−1.55 kcal/mol). As previously observed, also here, the final product is different depending on the medium. The final product is a double aqua complex for the system optimized with solvent effects included one water molecule, while in gas phase we observed a proton transfer from the water molecule to the oxalate ligand. The transition states have an imaginary frequencies of about 200i cm^{-1}.

Discussion

From the results obtained we can see that the relative position of the proton on the oxalate ligand has an important influence on the energetics of the system. A cis position leads to a faster reaction with an activation barrier of 15.11 kcal/mol (R3) opposed to 18.26 observed for the trans configuration (R4). We have also established that the most favorable position for the second entering water molecule is in the case of neutral conditions, in the same plane of the exiting ligand, while in the acidic conditions the entering water molecule prefers the opposite side.

In acid conditions according to our calculations this reaction should overcome a 21.79 kcal/mol activation barrier corresponding to the second water attack.

As previously reported, oxaliplatin has proven to been an important drug in cancer treatment. It is active in some cisplatin intrinsic and acquired resistant tumors, and a correct description of the aqueous degradation products is essential. Just as its predecessor, cisplatin, we can expect that in solution oxaliplatin should degrade according to a biphasic process. Cisplatin can undergo two hydrolysis reactions; however, the second process is much slower, and for this reason, it has been suggested that cisplatin should bind to DNA monohydrated.[38] Oxaliplatin exhibits a different behavior depending on the medium. In neutral conditions, the rate-limiting process is the ring-opening reaction with the ligand release occurring quickly, and for this reason oxaliplatin is more likely to bind to DNA in its completely hydrolyzed form. In acid conditions, the first step is faster than the second, and the activation barriers for the first and second hydrolysis are R3 = 15.11 kcal/mol and R5 = 21.79 kcal/mol. In addition, the presence of the large monodentate oxalate group can promote stereochemical hindrance in reaction with DNA.

Comparison of the neutral hydrolysis barriers (Table 1), between oxaliplatin, carboplatin, and cisplatin, reveals that

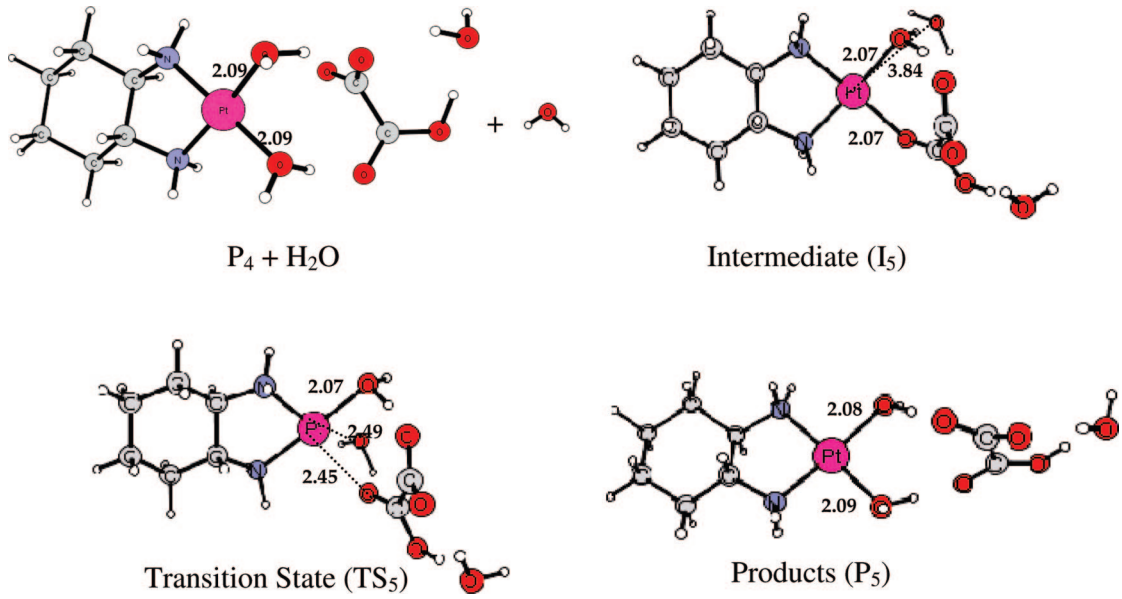


Figure 10. Optimized structures and structural parameters for the addition of the second water molecule to oxaliplatin with an extra proton on the trans position, in the opposite plane of the ligand, in acid conditions, in water phase. The distances reported are in angstroms.

TABLE 1: Comparison between Calculated Activation Energies for Cisplatin, Carboplatin, and Oxaliplatin in Neutral and Acid Conditions

	neutral			acid		
compound	first aquation	second aquation	rate-limiting step	first aquation	second aquation	rate-limiting step
cisplatin[a]	22.9	26.2	second			
carboplatin[b]	30.1	21.3	first	20.9	22.7	second
oxaliplatin[c]	27.9	24.1	first	15.1	21.8	second

[a] From ref 38. [b] From ref 46. [c] From this work.

the oxaliplatin and carboplatin exhibit a common behavior with the rate-liming step in the first aquation process and have values higher than the corresponding barrier in cisplatin. It has been reported that cisplatin-like compounds with one or two large groups in the NH_3 position have slower hydrolysis rates compared to that of cisplatin.[58] Computational studies, in good agreement with experimental data, have confirmed this for drugs such as JM118[59] and carboplatin.[46]

This aspect is important since a slower hydration may allow the drug to reach its cellular targets in its original form, which in turn can be one of the reasons of the lower side effects displayed by oxaliplatin. For oxaliplatin, the second hydrolysis reaction, in neutral conditions, is much faster than the first reaction just as carboplatin. This behavior is dissimilar to cisplatin's where the displacement of the second chloride ion is slower than the first. If we compare carboplatin and oxaliplatin, it is clear that their behaviors are quite different. Carboplatin is very stable in neutral conditions with an activation barrier of 30.1 kcal/mol while oxaliplatin degrades much faster. On the other hand, it is known that these two drugs exhibit lesser side effects when compared to cisplatin. The differences in toxicity can be related to their binding to DNA; however, it can also be a consequence of the different behavior in water and/or dissimilar hydrated forms that react with DNA.

In acid solution both drugs show, again, similar behavior being the second aquation reaction the rate-limiting step.

Conclusions

In this work, we have investigated the hydrolysis reactions of the third generation anticancer drug oxaliplatin by means of density functional theory and employing the CPCM approach in order to take into account the bulk solvent effect. We were able to establish all pertinent stationary points of the aqueous degradation in neutral and acid conditions. In agreement with experimental data, the neutral hydrolysis is much slower than the acid counterpart with a calculated activation barrier of 23.6 kcal/mol opposed to 27.95 kcal/mol. We have also established that for the neutral degradation the limiting process is the first step, the ring-opening reaction, while in acid conditions the slowest process is the ligand detachment. For the reaction in acid conditions, the presence of the extra proton in the carboxylate group has an effect on the activation barriers observed. It is clear that the most favored position is a cis arrangement regarding the bond being broken.

From the results, we can see that oxaliplatin exhibits a different behavior from cisplatin. The degradation in water is slower, and the rate-limiting process is expected to be the first substitution. Cisplatin has been proposed to reach DNA in its monohydrated form, in neutral conditions, while we expect that if oxaliplatin undergoes hydration processes before reacting with DNA, the fully hydrolyzed complex should be the main product.

On the contrary, in acid condition, [Pt(1,2-diaminocyclohexaneoxalateplatinum)(H_2O)(HO)] should reach DNA in its monoaquated forms.

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References and Notes

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