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ARTICLE

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Which One among the Pt-Containing Anticancer Drugs More Easily Forms Monoadducts with G and A DNA Bases? A Comparative Study among Oxaliplatin, Nedaplatin, and Carboplatin

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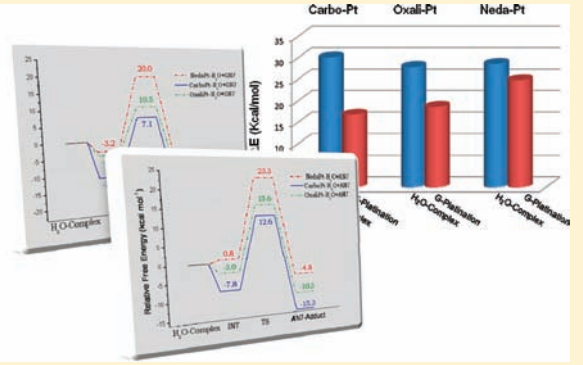
Supporting Information

ABSTRACT: The platination processes of DNA bases with second- and third-generation Pt(II) anticancer drugs have been investigated using density functional theory (DFT) combined with the conductor-like dielectric continuum model (CPCM) approach, in order to describe their binding mechanisms and to obtain detailed data on the reaction energy profiles. Although there is no doubt that a Pt−N7 bond forms during initial attack, the energetic profiles for the formation of the monofunctional adducts are not known. Herein, a direct comparison between the rate of formation of the monofunctional adducts of the second- and third-generation anticancer drugs with guanine (G) and adenine (A) DNA bases has been made in order to spotlight possible common or different behavior. The guanine as target for platination process is confirmed to be preferred over adenine for all the investigated compounds and for both the hydrolyzed forms considered in our investigation. The preference for G purine base is dominated by electronic factors and promoted by a more favorable hydrogen-bonds pattern, confirming the important role played by H-bonds in determining both structural and kinetic control on the purine platination process.



INTRODUCTION

The antineoplastic activity of cisplatin, the first platinum-based drug to enter clinical use, was unexpectedly discovered in the late 1960s.[1,2] Despite the wide spectrum of anticancer activity showed by this Pt compound (primarily administered for testicular tumors[3] but also for ovarian, cervical, head and neck, esophageal, and non-small-cell lung cancers[3−5]), its therapeutic efficacy is somewhat compromised by the occurrence of serious side effects, such as nausea/vomiting; nephro-, oto-, and neurotoxicity;[3,6,7] and development of resistance.[8]

Much progress has been made in elucidating its mode of action, and many details of the mechanism by which platinum-based drugs kill cancer cells are now well-established. It is generally accepted that these compounds induce apoptosis in tumor cells, first being nonenzymatically converted to active derivatives by hydrolysis and then binding to nuclear DNA.

Hydrolysis of Pt(II) drugs is expected to play an important role in the activation of these compounds before they reach DNA. The formation of charged active species is essential for the subsequent interaction with cellular nucleophiles. Previous to binding to genomic or mitochondrial DNA, the formation of aquo species is hence required.

Although a variety of binding sites are available to heavy metals on DNA, the pyridine-like and imidazole-like nitrogen atoms have a greater affinity for the polarizable Pt(II) atom. Under neutral conditions, platinum can bind to the N7 atom of guanine, the N7 and N1 atoms of adenine, and the N3 atom of cytosine. In DNA, atoms involved in base pairing, i.e., N1 of adenine and N3 of cytosine, are less available for metal binding than the more exposed N7 of the GMP site in the groove. N7 of guanine, located in the major groove of the double helix, is very accessible to metal binding and is the most reactive nucleophilic site for platination.[9−12] The so generated monofunctional adducts subsequently close by coordination to the N7 position of an adjacent purine (mainly another G or A base) to afford an intrastrand cross-link [namely 1,2-d(GpG) and 1,2-d(ApG)]. The resultant structural distortions are key for the antitumor activity of cisplatin, suppressing DNA transcription efficiently and ultimately leading to cell death.[13]

These early steps of triggering cell death by platinum(II) compounds were extensively investigated from both experimental and theoretical points of view.[12,14−24,53]

For over 3 decades, significant efforts have been devoted to design new platinum antitumor agents in an attempt to overcome cisplatin resistance or enhance its antitumor activity. Nevertheless only three of them are currently registered for clinical use, namely, oxaliplatin,[25,26] carboplatin,[27,28] and nedaplatin.[29]

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Due to the introduction of the kinetically less labile cyclobutane dicarboxylate, oxalate, and glycolate and to the presence of a large group in the NH_3 position in the case of oxaliplatin (DACH), the cisplatin-like compounds show a reduced rate of replacement of the O,O ligands.[30−33] The reduced toxicity displayed from these second- and third-generation anticancer drugs in comparison with cisplatin is usually correlated to the slower hydrolysis processes. The hydration mechanisms were previously studied in order to have a correct understanding of all steps preceding the DNA binding and to provide insights on the active species that probably will react with the purine bases.[34−37]

On the other hand, differences between the steric and chemical properties of DNA lesions formed by cisplatin and those formed by its analogues are thought to underlie the differences in the biological activity. Nevertheless, a significant biological difference in the spectrum of activity and in the ability to circumvent some cisplatin resistance mechanisms was observed only for oxaliplatin.[38,39] The better safety profile and the lack of cross-resistance phenomenon are thought to result from the chemical and steric characteristics of the DACH−platinum−DNA adducts and from the absolute configuration of the DACH ligand.[38,39]

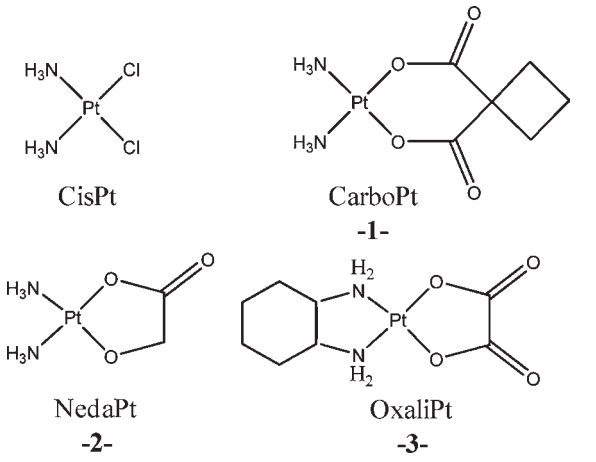
A good understanding of the interaction of the second- and third-generation Pt-anticancer drugs with models of binding sites present in DNA is of fundamental importance to unravel the mode of action of this class of compounds. Although there is no doubt that a Pt−N7 bond forms during initial attack, the energetic profiles for the formation of the monofunctional adducts are not known.

In the present work the reactions of platinum monoaqua complexes with guanine (G) and adenine (A) were explored by means of the DFT/CPCM approach, under both neutral and acidic conditions. The goal is to contribute to the elucidation of the whole mechanism employed by these compounds to reach the biological target.

COMPUTATIONAL DETAILS

All calculations were performed with the Gaussian 03[40] code at density functional theory level, using the hybrid B3LYP functional, composed of Becke's[41] three-parameter hybrid exchange functional (B3) and the correlation functional of Lee, Yang, and Parr (LYP).[42] Geometry optimizations without symmetry constraints were carried out with a 6-31G(d) basis set for all atoms except the platinum atom, which was described by the quasi-relativistic Stuttgart−Dresden pseudopotentials[43] with the pseudo-orbital basis set augmented by a set of diffuse functions, α_s = 0.0075, α_p= 0.013, and α_d = 0.025, and polarization functions, α_f = 0.98.[44] In order to confirm proper convergence to equilibrium and transition state geometries, vibrational frequency analysis was done on the basis of analytical second derivatives of the Hamiltonian at this level of theory. Intrinsic reaction coordinate (IRC) calculations have been performed to confirm that the transition states properly connect reactants and products.[45,46] Solvent effects (ε = 80) were included a posteriori by single-point calculations with the larger basis set 6-31++G(2df,2pd) by means of the CPCM method[47] and using Klamt radii to construct the solute cavity.[48] Natural bond orbital (NBO) analysis[49] has been carried out to determine net charges and electronic properties. The energetic profiles of each reaction reported in this work have been estimated as the energy difference between the total free energy in solution of the complex and the separated reactants.[18]

Scheme 1



RESULTS AND DISCUSSION

Substitution reactions in square planar compounds have been studied intensively on a number of different complexes, including different metal ions and ligands. These reactions proceed via a collision between the reactant with a nucleophilic species attacking the metal center to release the leaving group, employing the second-order nucleophilic substitution mechanism.[50] In such a process, the overall geometry of the transition state is a pentacoordinated trigonal bipyramid, consistent with a classical associative mechanism that is the rule for square-planar platinum(II) complexes.

Previous investigations on the hydrolysis mechanisms of these drugs[30−37] give some insights concerning the nature of the aquated complexes that act as the active species for the monofunctional adduct formation. In this work, we evaluated the water substitution by the DNA nucleobases guanine and adenine, for the compounds carboplatin, oxaliplatin, and nedaplatin (Scheme 1), identifying mechanistic details as well as differences in their kinetic activities.

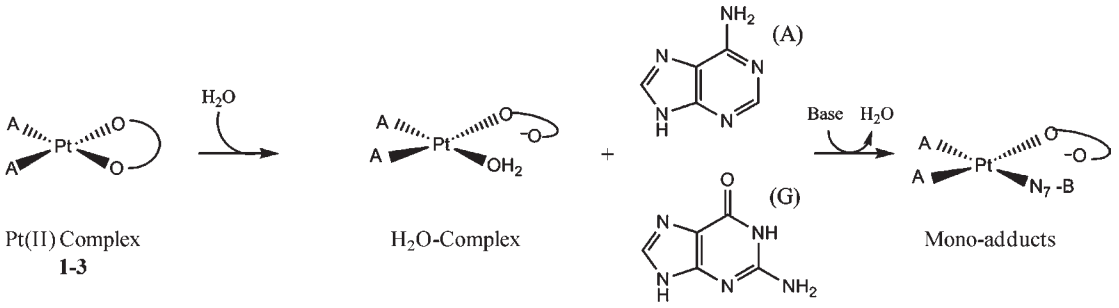
The early steps of triggering cell death by platinum(II) compounds, involving the activation of the drugs by hydrolysis and the consequent monofunctional binding to DNA bases G and A, are reported in Scheme 2.

It should be noted that two monoaqua complexes can be obtained in the hydrolysis process for NedaPt, due to the asymmetric nature of the glycolate ligand. Actually, as reported in our previous study,[35] the detachment of the ligand can occur in two different ways, by rupture of the bond that involves the oxygen α to the carbonyl group or by breaking the other Pt−O bond forming two different H_2O complexes. As a consequence, the reactions with G and A purine bases have been investigated by considering both hydrolyzed forms of nedaplatin. A significant difference in the energetic profiles has been obtained by using the two possible reactants, and only the most favorable paths, concerning the mentioned reactions, are reported in this work.

The free energy profiles for the binding of monohydrated CarboPt, NedaPt, and OxaliPt compounds to guanine and adenine bases in neutral conditions are reported in Figure 1. The optimized structures of the stationary points located along the paths and key geometrical parameters are reported in the Supporting Information (SI).

Concerning the guanine platination processes, no significant differences were found in the geometries of the stationary points

Scheme 2



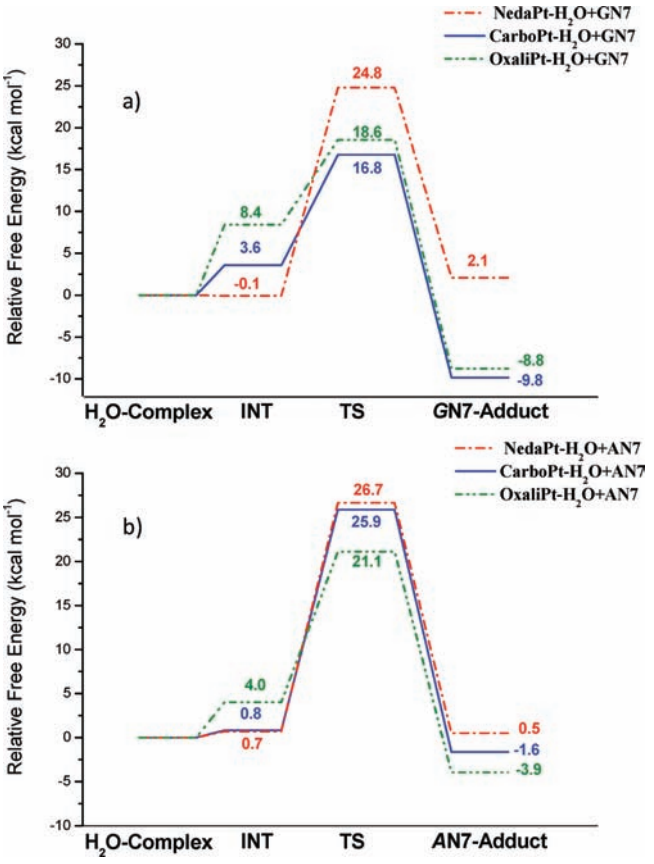


Figure 1. Overposition of the computed relative free energy profiles (at 298.15 K), for the reactions of monohydrated NedaPt, OxaliPt, and CarboPt with (a) N7-guanine and (b) N7-adenine purine bases, under neutral conditions.

considering the three Pt(II) complexes. According to previous findings,[35−37] all the monoaqua complexes show a proton transfer from the entered water molecule to the close oxygen of the ligand (O_L). Actually, the hydroxo complexes are accessible at physiological pH and temperature, even if in the vicinity of macromolecules the local pH could be influenced, reflecting its effect on the hydrolysis rates.[51,52] In the intermediate structures, for all the compounds, the guanine ring is oriented such as to allow the ammine ligand to act as a hydrogen-bond donor to the oxo group at the C6 position and with the N7 atom of the ring interacting with the hydroxo ligand. The overall geometry of the transition states for the reaction with the purine bases is, in agreement with previous results for this type of associative substitution reactions, a trigonal bipyramid.[34−37,50,53,54] A proton transfer between the O ligand and the hydroxo group is observed in each transition state geometry, allowing the release of the water molecule, a better leaving group than the hydroxo one. In the penta-coordinated transition states, the Pt−N7 bond has started to form at distances of 2.592, 2.606, and 2.527 Å and the Pt−OH_2 bond is half-broken at a distance of 2.370, 2.322, and 2.398 Å, for NedaPt, OxaliPt, and CarboPt, respectively. All the TS structures are largely characterized by a hydrogen bond between the ammine ligands and the C6-oxo groups, as well as by interactions between the leaving water molecules and the carboxylate groups of the Pt-coordinated O ligands. Nevertheless, it is possible to observe that such interactions are stronger in the CarboPt transition state, as is indicated by the shorter distances between the G-C6 oxo group and the ammine as well as between the leaving water molecule and the O ligand (see the SI and Figure 2). Therefore, the lower activation barrier found for the G-platination process by CarboPt (Figure 1a) is a direct consequence of the more favorable network of hydrogen bonds that takes place in the transition state geometry. The intermolecular forces are then implicated to impose a kinetic control on the platination processes. The Pt−nucleobase adducts, crucial for the biological activity of such drugs, are then obtained with the complete loss of the water molecule and with the Pt(II) forming covalent adducts with the DNA base. The coordinated guanine still interacts by its C6-oxo group with the ammine ligand.

Such a result can also be rationalized from an electronic point of view. NBO analysis shows that the energy of the lone pair at the N7 position of the guanine ring is significantly lower in the carboplatin−guanine transition state compared with those shown in the transition states with nedaplatin and oxaliplatin. Similarly, also the NBO charge on the same nucleophilic nitrogen atom is more negative in the transition state involving carboplatin complex than those involving the other Pt(II) drugs. These data suggest that a stronger donor−acceptor interaction between guanine and the carboplatin complex could contribute to the stabilization of such stationary point. Further details are given in the SI.

Common mechanistic details were found by studying the reactions of the Pt(II) complexes with adenine base (see the SI). Actually, given the similarity of the N7 binding site in both bases,

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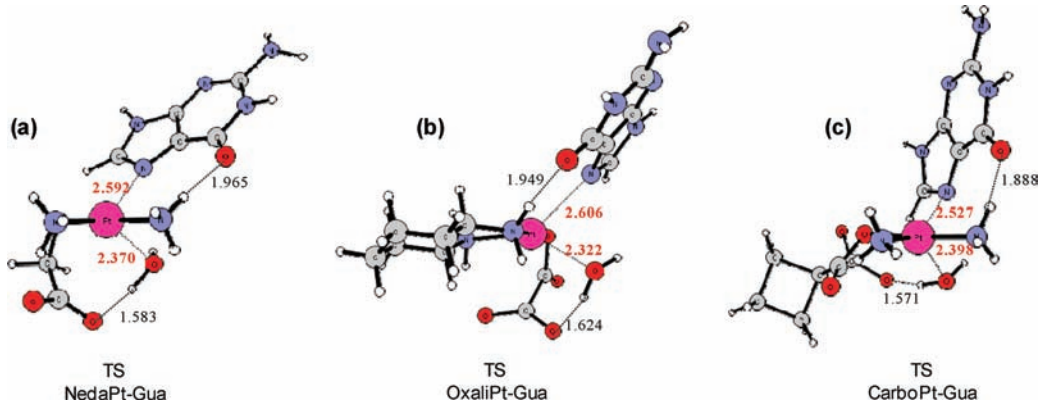

Figure 2. Transition state structures for the guanine platination process using monoaqua complexes. The reported distances are in angstroms.

it is difficult to imagine a fundamentally different Pt-binding mechanism. The platination of adenine proceeds through the formation of the classical pentacoordinated transition state, in which the entering purine base and the leaving water molecule show, from the metal center, similar distances found in the case of the G-platination process. Only slight differences in the intermolecular forces governing the interactions between the Pt moiety and the nucleobases were observed. The weaker interactions have been previously suggested to be the reason for the observed preference of guanine over adenine as a target for platination.[53] Actually, in the case of adenine, due to the weaker hydrogen-bond-acceptor nature of the amino group at the C6 position of the adenine ring compared to the C6-oxo group of guanine, we found that the interactions with the ammine ligand are significantly weaker, as reflected in the pronounced longer distances between them (see the SI). Nevertheless, a concurrent H-bond between the amino group at the C6 position and the water molecule is observed in these structures. The NH_2 group of the adenine has then the possibility to act also as a weak hydrogen-bond donor, as already suggested.[53]

The observed preference for guanine in a competitive reaction with the adenine site is attributable also to electronic factors. The energy of the molecular orbital whose dominating component is the lone pair located on the N7 atom of the guanine reactants is lower than that obtained for adenine (−8.47 and −7.62 eV, respectively). As a consequence, in a reaction with the empty Pt $d_{x^2-y^2}$ orbital, a stronger donor−acceptor interaction should be observable in the case of guanine moiety. Moreover, the energy of the occupied N7 lone pair of guanine is lower considering all the transition states found for the reaction between the Pt(II) drugs and the two purine bases (see the SI). Nevertheless, a significant difference in the activation energy barriers between G- and A-platination processes takes place only in the case of CarboPt, while for the other compounds the reaction with adenine is also feasible.

The comparison between the kinetic barriers for the platination of both the purine bases obtained in this work and those previously found concerning the formation of the monoaquated carboplatin, oxaliplatin, and nedaplatin complexes[35−37] allows us to provide insight into the kinetics governing the whole process employed by these Pt(II) drugs to reach their final target.

From our data emerges that the coordination processes of both G and A purine bases proceed faster than the hydrolysis reactions, under neutral condition. This finding confirms the general trend observed for other platinum-containing anticancer drugs, for which the formation of the aqua complex was found to be the rate-limiting step of the process[18,30,54] (Figure 3).

The chemical behavior of the second- and third-generation Pt(II) drugs is then similar to that observed for the parent cisPt, for which the hydrolysis of the first chloride ion via association of solvent water was suggested to be the rate-determining step for the initial binding to DNA.[55] For cisplatin, values for the Gibbs free energy of activation determined for the first aquation range between 19.5 and 21.5 kcal/mol,[20,56,57] while the monofunctional DNA platination was suggested to be ≈23 kcal/mol.[53] Nevertheless, the latter value was not unequivocally attributed to the reaction of the monoaqua cisplatin with the DNA, being the same value obtained for the hydrolysis of the first chloride ion in the same solution[55] and very similar to the first-order rate constant for the hydrolysis of cisPt reported in a previous work.[58] For this reason and due to the large amount of data concerning cisplatin's reactions, making a direct comparison with it would be a difficult job. Nevertheless it should be stressed that all cisplatin-like compounds show slower hydrolysis rates compared to cisplatin, due to the introduction of the kinetically less labile carboxylate, oxalate, and glycolate and to the presence of a large group in the NH_3 position in the case of oxaliplatin. A slower hydration could be the reason for the lower side effects displayed from the second- and third-generation anticancer drugs, as already suggested in a number of works.[59,60]

It is interesting to note that, according to our results reported in Figure 3, Carbo-Pt shows the slowest hydrolysis rate among the cisplatin-like compounds,[35−37] but at the same time, the formation of the CarboPt−guanine adduct proceeds significantly faster than the other adducts. This chemical behavior could explain the high activity of the carboplatin compound. A too fast drug degradation to reactive charged species by hydrolysis, is actually believed to be one of the main reasons for the inactivity and toxicity of metal-based drugs. On the other hand, a slow reaction with the biological target could allow competitive reactions with other biomolecules to take place with the consequent lack of activity.[10,18,61]

The monofunctional binding to guanine and adenine by monohydrated complexes in acid solution was also investigated in this work. In such a condition, the cyclobutane dicarboxylate, oxalate, and glycolate groups become protonated. Our previous results concerning the hydrolysis processes showed that acidification of the solution increases the rate of the reactions.[34−37] In analogy to those findings, also G and A platination processes were found to proceed faster at lower pH. From the geometric

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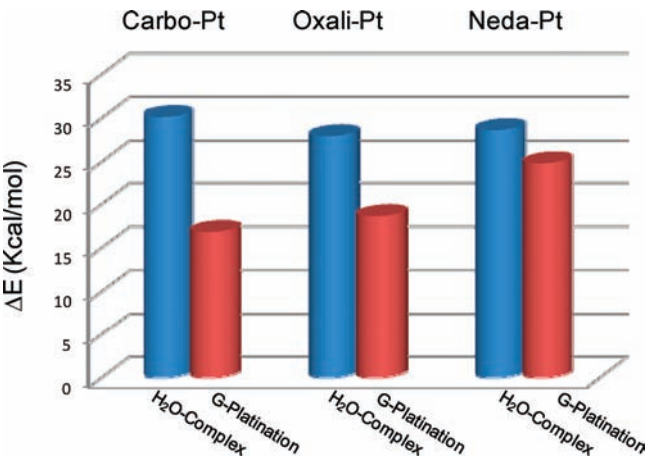

Figure 3. Comparison between calculated activation energies for hydrolysis and G-platination processes of carboplatin, oxaliplatin, and nedaplatin under neutral condition.

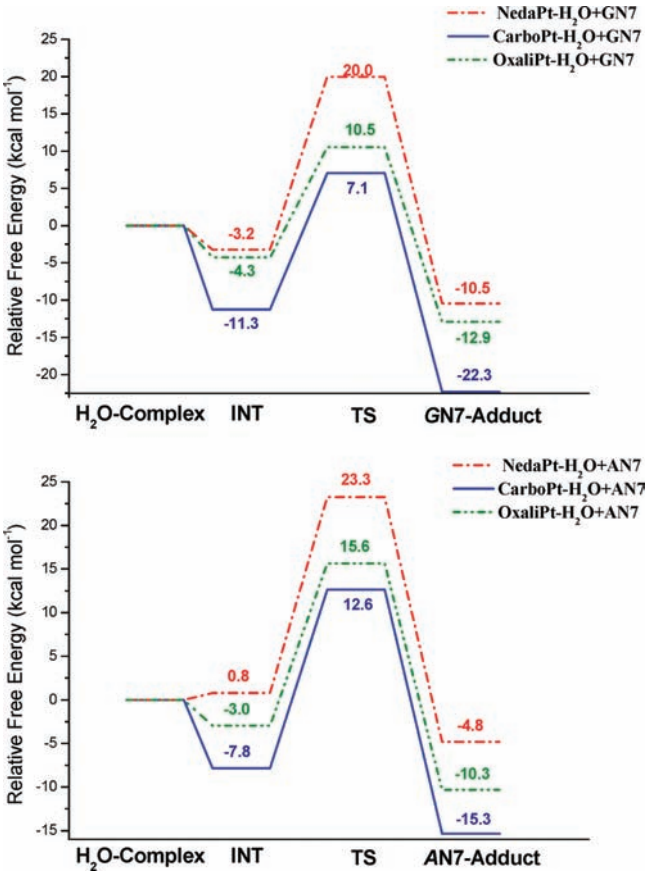

Figure 4. Overposition of the computed relative free energies profiles (at 298.15 K), for the reactions of monohydrated NedaPt, OxaliPt, and CarboPt with (a) N7-guanine and (b) N7-adenine purine bases, under acid conditions.

point of view (see the SI), under acid condition we observe a stronger network of H-bonds between the Pt moiety and the purine bases, which is probably responsible for the lower activation barriers (Figure 4). The dominating preference for the G purine base is also observable under such conditions, and again it seems to arise from electronic and geometric factors. The rate

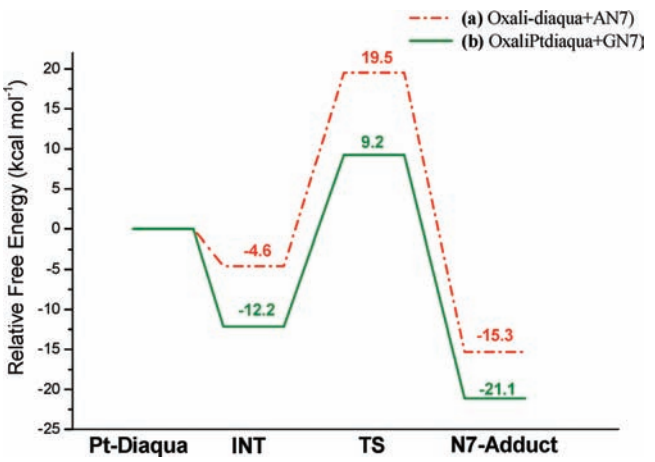

Figure 5. Overposition of the computed relative free energies profiles (at 298.15 K), for the reactions of fully hydrated OxaliPt with (a) N7-guanine and (b) N7-adenine purine bases.

of the guanine-platination process is confirmed to be improved in the case of Carbo-Pt.

The possibility that the diaqua complex acts as platination agent was also explored in our investigation. Nevertheless, it should be noted that the fully hydrolyzed complexes in the case of NedaPt and CarboPt are equivalent to the diaquated form of cisplatin, previously investigated from both experimental[62] and theoretical points of view.[53] It is evident that for these complexes only the hydrolysis process could be involved to explain the differences in the biological activity, since in their hydrolyzed forms CarboPt, NedaPt, and CisPt complexes give rice to the same active species. On the contrary, in the case of oxaliplatin, the structure of the diaquated complex is different due to the presence of the diaminocyclohexane as carrier ligand in place of the ammonia ones. Actually, oxaliplatin is the only cisplatin analogue showing significant biological difference in the spectrum of activity. This phenomenon could then be a consequence of steric and chemically different properties of DNA lesions. The potential energy profiles for the monofunctional binding to guanine and adenine bases using oxaliPt diaqua complex as reactant are reported in Figure 5. The optimized structures of the stationary points along the paths and key geometrical parameters are reported in the SI. As can be observed from the energetic profiles (Figure 5), the platination of both purine bases is favored in the case of fully hydrated complex, confirming our previous indications on the active species able to reach the DNA target.[35−37] Moreover, according to our calculation, a higher selectivity for the guanine base is observed in such a case, in analogy with previous findings on cisplatin.[35] Actually, a comparison between the energetic profiles reported in Figure 5 reveals that the Guanine coordination process proceeds significantly faster than the adenine binding. In addition, there is also a thermodynamic preference for guanine platination when the diaqua Pt complex is the active agent. Nevertheless, from our data concerning the fully hydrolyzed form of oxaliplatin emerge that the binding to the adenine site, although not preferred over guanine and considerably slower, could also be observable at standard conditions if the diaqua complex is the only active reagent. Therefore, oxaliplatin seems to have a different behavior compared with the $[Pt(NH_3)_2(H_2O)_2]^{2+}$ active species, for which it was found that the adenine binding is highly disfavored.[53]

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From the geometric point of view, the intermolecular forces governing the energetics are not equivalent to those for the monoaqua species. In these cases, there is a preference for the water ligand on Pt to act as the H-bond donor toward both the oxo and amino groups at the C6 position. Moreover, the short distances between the hydrogen-donor and hydrogen-acceptor groups in the molecules indicate strong interactions between them, leading to a greater stabilization of all the stationary points (see Figure S5 in the SI). Other possible hydrogen-bond patterns involving the ammine hydrogen of diaqua complexes and the O═C6 as well as H_2N═C6 moieties of guanine and adenine, respectively, were also considered. In such cases, we found that the transition states lie at higher energy values, confirming previous indications on cisplatin[53] (see the SI).

CONCLUSION

In summary, the binding mechanism of second- and third-generation anticancer drugs with guanine (G) and adenine (A) DNA bases, under both neutral and acidic conditions, has been investigated using density functional theory (DFT) combined with the conductor-like dielectric continuum model (CPCM) approach. This work allowed us to make a direct comparison between the rate of formation of the monofunctional adducts of these compounds and spotlight common or different behavior. The guanine as a target for platination process is confirmed to be preferred over adenine for all the investigated compounds. The dominating preference for G purine seems to be a hydrogen-bond-controlled process, confirming that H-bonds are important in imposing both structural and kinetic control on the purine platination processes. Moreover, the lower energy of the N7 lone-pair MO on guanine ring compared with that observed for adenine permits a more favorable donor−acceptor interaction with the Pt(II) fragment.

In both environments, carboplatin showed the lowest activation barrier for the G-platination process and seems to be a direct consequence of the network of hydrogen bonds that takes place in the transition state geometry. Also in this case, the electronic behavior of the donor orbital located on the nucleophilic N7 atoms on the guanine ring contributes to the stabilization of the transition state.

From our data concerning G- and A-platination by the double-hydrated form of oxaliplatin, we find that the binding to adenine site, although considerably slower, could also be observable under standard conditions, in contrast to previous findings on $[Pt(NH_3)_2(H_2O)_2]^{2+}$ active species.

ASSOCIATED CONTENT

Supporting Information. Optimized structures and selected geometrical parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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