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Cisplatin interaction with cysteine and methionine, a theoretical DFT study

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Abstract

Interactions of hydrated cisplatin complexes with sulphur-containing amino acids cysteine and methionine were explored. The square-planar *cis*-$[Pt(NH_3)_2(H_2O)X]^+$ complexes (where $X = Cl^-$ and OH^-) were chosen as mono- and dihydrated reactants. Calculations using density functional theory (DFT) techniques with B3LYP functional were performed. The isolated molecules and the supermolecular approaches were employed for the determination of the reaction energies. Bond dissociation energies (BDE) were estimated in the model of isolated molecules and supermolecules were used for the determination of the association energies between the two interacting parts. Formation of monodentate complexes by replacing the aqua-ligand with the S, N, and O-sites of both amino acids represents an exothermic process. The highest BDE was found in cysteine structures for the Pt–S coordination. The bonding energy is about 114 kcal/mol, which is comparable with cisplatin–guanine adducts. Analogous BDE for methionine complexes is smaller by about 40 kcal/mol. This correlates well with the known fact that cysteine forms irreversible cisplatin adducts while similar adducts in the methionine case are reversible. The formation of chelate structures is an exothermic reaction only for the hydroxo-form of reactants in the supermolecular approach where additional association interactions between the released water and chelate molecules sufficiently stabilize the final product.

Keywords: Cisplatin; Cysteine; Methionine; Theoretical calculations

1. Introduction

Despite very intensive research, cisplatin is still one of the most commonly used anticancer drug [1–7]. It is known that the mechanism responsible for its activity is based on a platinum bridge formation between two adjacent guanine DNA bases [8–11]. Before such a bridge can be created, cisplatin must pass from the cellular membrane to the nucleus membrane. During this period cisplatin can interact with many active sites, e.g., RNAs/DNAs, proteins, peptides, and other molecular structures. All these interactions are facilitated by at least partial cisplatin activation [12–18], when a chloro-ligand is replaced by a molecule of water. The main cisplatin targets, before nucleus is reached, are peptides like glutathione or amino acid side-chains on the surface of proteins [19,20]. A lot of effort was devoted to the investigation of these interactions. Among other, sulphur-containing amino acids like methionine and cysteine were considered [21–23]. Some attention was also paid to interactions of cisplatin with the N-side chains of amino acids like histidine [24–27], arginine, or amides of aspartic [28] and glutamic acids [29], as well as other amino acids [30,31].

In the cases of cysteine and methionine amino acids, a formation of the strong dative bonds between the Pt and S atoms can be expected according to HSAB (Hard–Soft-Acid–Base) principle [32,33], since both the sulphur or platinum atom (as well as most of the transition metals) belong to the so-called soft atoms with a relatively

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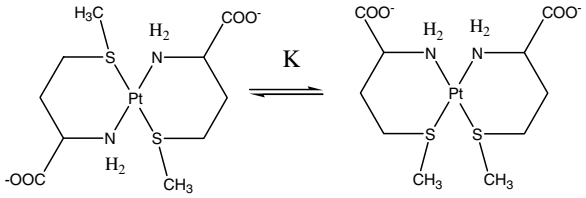
high polarizability. Interactions between such atoms are generally considered to be strong. Therefore, it can be expected that cysteine and methionine will play an important role in the cisplatin metabolism. This assumption was confirmed when the $Pt(L–Met–S,N)_2$ complex was recognized in the patient's urine after cisplatin administration [34]. Such complexes were studied also using the NMR technique by Norman et al. [35], who found both *cis*- and *trans*-chelate conformers, the *cis*-form was preferred ($K = 7.0$).



trans-[Pt(L-Met-S,N)$_2$] cis-[Pt(L-Met-S,N)$_2$]

The most important differences when comparing the cysteine and methionine interactions with Pt-complexes are the following two basic features. First, the Pt–S bond in a cysteine complex is stronger than the Pt–S bond in a methionine complex. Moreover, Pt-cysteine adducts are usually irreversible while methionine complexes undergo reversible splitting. The irreversible Pt-cysteine binding can be assumed as a reason for very high cisplatin nephrotoxicity [36]. The accumulation of platinum complexes in kidneys leads to the saturation of cysteine side-chains by platinum, which blocks the proper activity of proteins [37]. The second difference can be found in the fact that thioethers like methionine react faster with ammine–platinum complexes than thiols [38,39]. As an interesting consequence selective replacement of the methionine side-chain ligands by 5′-GMP in water solution of the cisplatin adduct with methionine was observed [40,41]. Similarly, the tripeptide glutathione (where cysteine is present) can interact with a monofunctional cisplatin–guanine adduct. However, once the bifunctional cross-link between platinum and two guanine bases is formed, the interaction with glutathione does not occur [42].

As for the computational approach to these interactions, some model systems were studied by Deubel [43,44], who examined competition between nitrogen and sulphur sites for the coordination of dicationic cisplatin derivatives. His calculations gave a general insight but for an accurate description, the exploration of the individual molecules of amino acids is necessary. Recently, Yang et al. [45] have published a DFT study on the vibrational spectra of the Pd(II) and Pt(II) complexes with methionine and histidine. But unlike in our investigations, they examined neutral dihalogeno-complexes instead of diammine-complexes.

As for cisplatin interaction with DNA bases, a great deal of effort is remarkable from published both computational and experimental studies. From the recent theoretical calculations we find as most relevant the studies of Eriksson et al. [46], Baik et al. [47,48], Costa et al. [49,50], Sponer et al. [51], Zhang et al. [52], Carloni et al. [53] and many others [54–57]. Experimental studies are substantially more abundant. Among the leading groups let us mention at least Lippard and co-workers [11,58–60], Marzilli et al. [59,61,62], Lippert and co-workers [63,64], Brabec et al. [65,66], and or Reedijk and co-workers [19,67,68].

This work can be considered as an extension of our previous studies on platinum activation [17,18,69,70] and platinum interaction with DNA bases and base pairs [71–75].

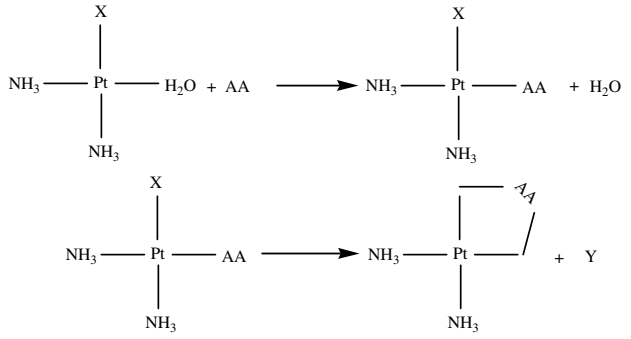
2. Computational details

First, the *cis*-$[Pt(NH_3)_2(H_2S)(OH)]^+$ complex was used for a comparison of various ab initio (MP2, MP4, CCSD) and DFT methods in order to choose an appropriate computational tool. The following functionals were explored: one of the most successful Becke functionals – B3LYP [76,77], MPW1PW91 from the Barone group [78,79], HCTC407 from the Handy's family of functionals with gradient-corrected correlation [80], and PBE1PBE from the Perdew group [81,82]. The bond dissociation energy (BDE) of the Pt–S bond was computed with the 6-31++G(d,p) basis set; the single point calculations were performed on the structure optimized at the B3LYP/6-31+G(d) level.

Then the cisplatin–hydrogen sulphide interactions were studied. The computational model for all the cisplatin ligand replacements by H_2S originated from the +1 charged supermolecule formed by *cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$ and neutral sulphide.

Analogously, the platinum–amino acid interactions were explored. In this case not only the monohydrated *cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$ complex but also dihydrated *cis*-$[Pt(NH_3)_2(H_2O)(OH)]^+$ complex were chosen for interactions with methionine and cysteine. In the first reaction step, the aqua-ligand of the cisplatin cation was replaced by the given amino acid. All three possible active sites of the amino acid (S, N, and O atoms) were considered for the formation of a dative bond with platinum. In the second step, one of the two remaining free active sites further replaced the second Pt-ligand (either chloride or hydroxyl group) forming three possible combinations of chelate rings (Pt(AA–N,O), Pt(AA–S,O) and Pt(AA–S,N)) (see Scheme 1):

The geometry optimizations were performed with the hybrid density functional B3LYP and 6-31+G(d) basis set. It is worth stressing the importance of diffuse functions for a proper description of the hydroxyl groups in



Scheme 1.

the above-mentioned complexes. Since a heavy metal element is present in the calculations, quasi-relativistic pseudopotentials from Stuttgart–Dresden laboratory were employed for the platinum atom (MWB-60) [83], as well as for the second row elements chloride and sulphur (MWB-10) [84]. The original pseudoorbitals were augmented by the appropriate diffuse and polarization functions ($\alpha_f(\mathrm{Pt}) = 0.998$, $\alpha_d(\mathrm{Cl}) = 0.618$, $\alpha_d(\mathrm{S}) = 0.499$), as it was shown in the study [69]. The ground-state of the complexes was always a closed-shell singlet.

The single-point energy analyses were done with the same functional and 6-31++G(d,p) basis. The stabilization energy of the supermolecules was defined according to the formula

$$\Delta E^{\mathrm{Stab}} = -(E_{\mathrm{supermolecule}} - \Sigma E_{\mathrm{monomer}}) - \Sigma E^{\mathrm{deform}}. \quad (1)$$

The association energy between both supermolecule components was determined by the same Eq. (1). Both the energies were calculated using the counterpoise corrections [85] including the basis set superposition error (BSSE) together with the deformation energy contributions. The BDE of the Pt–L bonds was computed for the isolated complexes, re-optimized omitting the remote molecule from the equation

$$\mathrm{BDE} = (E_{\mathrm{complex}} - \Sigma E_{\mathrm{part}}), \quad (2)$$

where the E_{part} is the BSSE corrected energy of the given part of the Pt–AA complex calculated with ghost AO functions on the complementary part of the whole complex. In some cases, the "dissociated" amino acid does not correspond to the most stable conformer. Nevertheless, no corrections were applied since the higher lying conformer is enforced by better stabilization of the whole complex, and thus this energy should be considered as a part of the BDE, too.

The vibrational frequencies were estimated at the same level of theory as geometry optimizations, i.e., B3LYP/6-31+G(d). The natural population analysis (NPA) was computed using the program Natural Bond Orbitals – NBO v. 5.0 [86,87] at the more accurate B3LYP/6-31++G(d,p) level. In addition, partial charges distributions, based on the fit of the electrostatic potential using the Merz–Singh–Kollmann [88,89] and CHelpG [90] schemes, were determined.

3. Results and discussion

In the calculations of the *cis*-$[Pt(NH_3)_2(OH)(H_2S)]^+$ complex, the BDE for the Pt–S dative bond was determined by several methods. Table 1 summarizes BDEs for the wave-function based methods (HF, MPx, CC), as well as the electron density methods with several recent functionals. The CCSD(T) level was chosen as a reference method with the best accessible accuracy. It was found that the perturbation approach to the second order (MP2) exaggerates the strength of the Pt–S bond by about 10 kcal/mol due to the overestimated value of the sulphur polarizability. It can be noticed that already the third order of perturbation theory improves the MP2 discrepancy. Comparing the CC methods with and without the inclusion of triple-excitations, it can be seen that the corrections on these excitations still represents about 1 kcal/mol in the total BDE.

An interesting conclusion follows from the comparison of the individual functionals used in DFT calculations. The Becke3LYP functional gives the closest BDE to the reference energy. However, it is surprising that two of the recent functionals (PBE1PBE and MPW1PW91) display a relatively large deviation from the CCSD(T) value (similar to MP2), and also Handy's HCTC is not closer than B3LYP (at least in this particular case). Therefore, the B3LYP functional was chosen for calculations in this study.

3.1. Model substitutions with H_2S in the cis-$[Pt(NH_3)_2Cl(H_2O)]^+$ model complex

The reaction of the *cis*-diammine-chloro-aqua-platinum cation with hydrogen sulphide was studied in order to reveal a possible general preference for the replacement of the individual ligands by a thio-group. Three substitution reactions without proton transfer and two reactions with proton transfer (obtaining an NH_4^+ cation and HCl molecule) were performed. From the data in Table 2, it follows that out of these five there are two

Table 1
Bond dissociation energies of the Pt–S dative bond in the *cis*-$[Pt(NH_3)_2(OH)(H_2S)]$ complex at selected levels of calculations (in kcal/mol)

Method	BDE	Method	BDE
HF	−35.2	MP2	−52.1
B3LYP	−45.6	MP3	−43.1
MPW1PW91	−50.5	MP4(SDQ)	−45.1
HCTH407	−42.6	CCSD	−43.4
PBE1PBE	−51.6	CCSD(T)	−44.3

Table 2
Reaction energies for the ligand replacement of monohydrated cisplatin by H_2S at the B3LYP/6-31+G(d) level (in kcal/mol)

	ΔE
Processes without proton transfer	
cis-$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2S$	−9.6
→ *cis*-$[Pt(NH_3)_2Cl(H_2S)]^+ + H_2O$	
cis-$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2S$	7.2
→ *cis*-$[PtNH_3Cl(H_2O)(H_2S)]^+ + NH_3$	
cis-$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2S$	19.2
→ *cis*-$[Pt(NH_3)_2(H_2O)(H_2S)]^{2+} + Cl^-$	
Processes with proton transfer	
cis-$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2S$	−8.9
→ *cis*-$[PtNH_3Cl(H_2O)(SH)] + NH_4^+$	
cis-$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2S$	9.0
→ *cis*-$[Pt(NH_3)_2(H_2O)(SH)]^+$+HCl	

exothermic reactions releasing the water molecule and/or the NH_4^+ cation. In correspondence with the HSAB principle [33], the affinity of the sulphur atom to the metal is higher than the affinity of oxygen, which can be demonstrated by the energetical preference for the replacement of the aqua-ligand by about 10 kcal/mol. The dechlorination process remains endothermic. Comparing the two dechlorination reactions, with and without proton transfer (lines three and five in Table 2), an interesting feature can be noticed. The reaction on the third line of Table 2, where the 2+ Pt-complex is present as product, is about 10 kcal/mol more endothermic. The reason is the worse stabilization of the platinum complexes with the higher total charge. The Pt(II) atom is connected with a smaller number of dative bonds from negatively charged ligands where the dative bond is accompanied with an electrostatic contribution, like in the case of the Pt^{2+}–Cl^- bond. A similar situation occurs for the ammine-replacement in lines 2 and 4 of Table 2, where the NH_4^+ cation is split off forming a neutral complex. This process leads to an even larger release of energy. However, the above-mentioned electrostatic enhancement is not the only reaction driving force and therefore it must not be generally overemphasized. For the sake of simplicity, the effects of slightly different basicity of both proton acceptors (Cl^- and NH_3), as well as small differences in weak interactions stabilizing the individual supermolecules are not regarded in the considerations above.

3.2. Structures of the Pt(II) complexes with amino acids

First, the isolated amino acid molecules and chloro-aqua (monohydrated) and hydroxo-aqua (dihydrated) platinum complexes were explored. The obtained structural parameters are in good accord with studies devoted to computations of the cysteine and methionine amino acids [91–97] and other studies on Pt(II) complexes at high level ab initio calculations [69]. Since the gas-phase model was accepted, the formation of zwitterionic arrangement of the amino acids was not observed and the structures with COOH–NH_2 groups were obtained as the global minima of non-coordinated amino acids [98,99]. In our study, all three possibilities for the replacement of the aqua-ligand in platinum complex were considered. The amino acids can bind with the carboxyl or amino group or coordinate through an S-atom of the side chain. In the cysteine monodentate products, a proton transfer from the S or O atoms to amino group occurred creating more stable dative bonds enhanced by additional electrostatic contributions as mentioned in the previous part. For a better insight into the most stable optimized structures in the first reaction step, see Figs. 1 and 2. The Pt–X bond distances are collected in Table 3. From the Table it follows that the Pt–S distance is about 2.34 Å in all the monodentate adducts where Pt–S occurs, which is in good agreement with other computational studies [43,44]. As for the Pt–N distances, the longest Pt–N bonds are in cysteine adducts (more than 2.10 Å). In the methionine case, the Pt–N distance is slightly shorter – 2.08 Å. Pt–O distances are about 2.04 Å. These distances are fairly illustrative, since for, e.g., hydrated cisplatin complexes (using the same method and basis set) [18] the opposite relation between the Pt–N (2.04 Å) and Pt–O (2.10 Å) bonds can be noticed. Shorter Pt–O distances in the

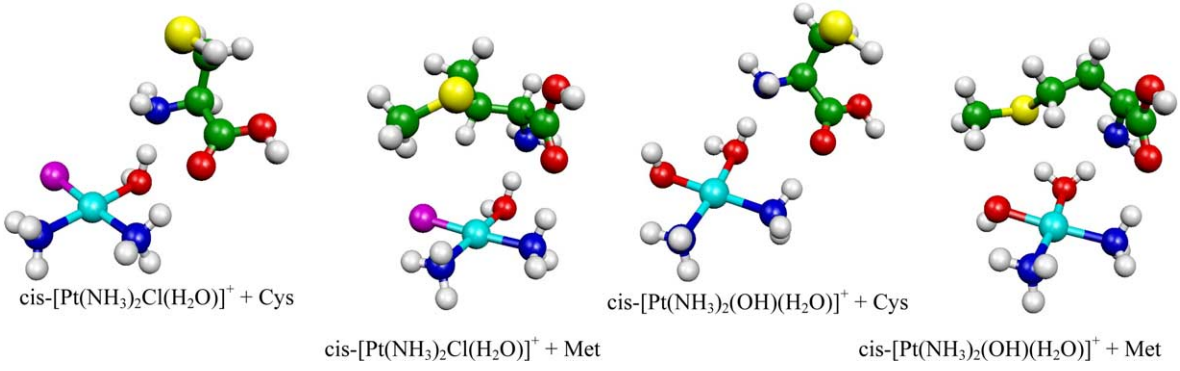


Fig. 1. Structures of the reactants in the supermolecular approach.

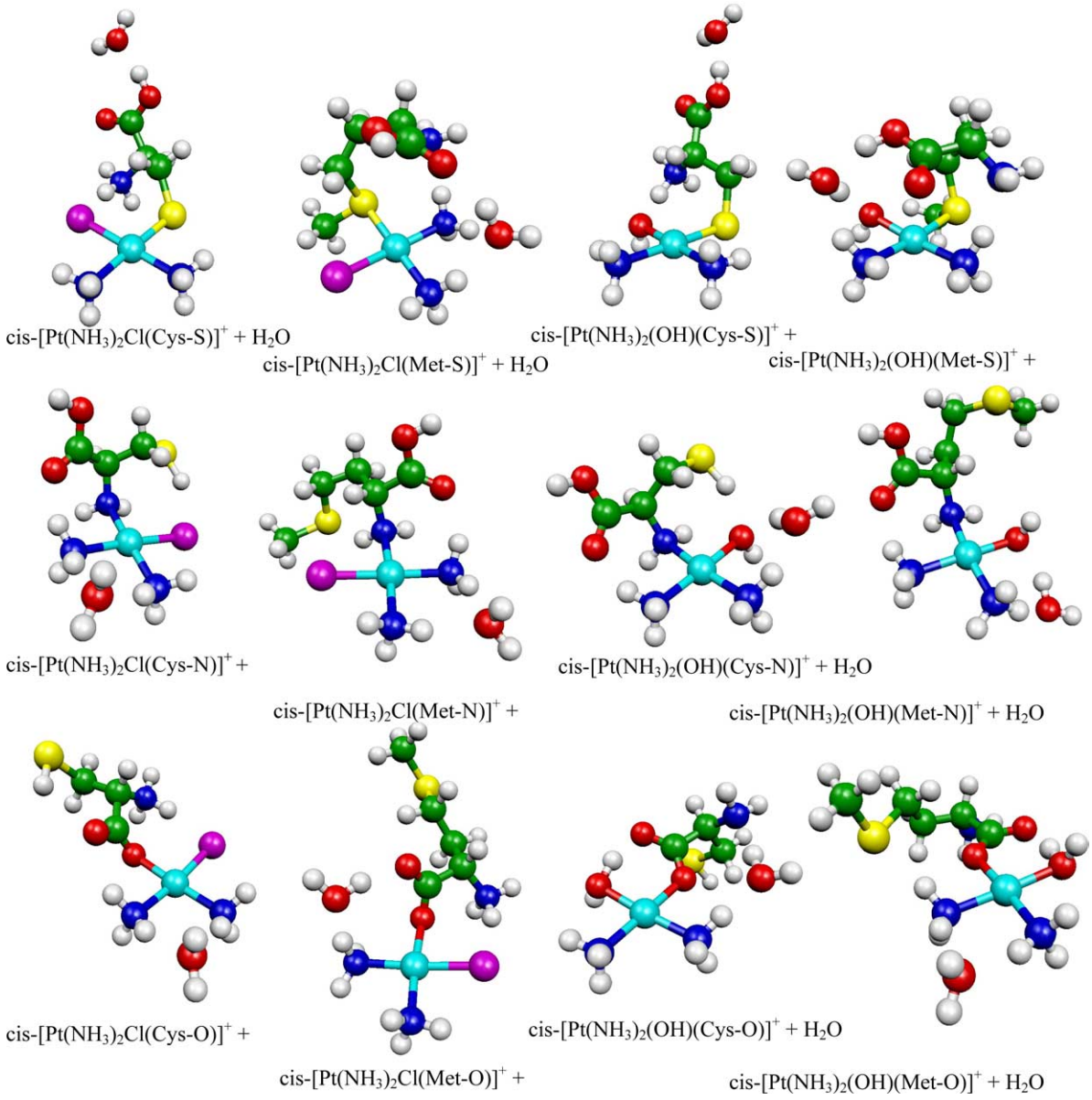


Fig. 2. Products of the substitution reaction (first interaction step) in the supermolecular model. The Pt–S monodentate products are displayed in the first row, the Pt–N complexes are in the second row, and the Pt–O complexes are in the third row.

studied complexes clearly demonstrate higher electrostatic contributions in comparison with ligated water; the Pt–O bonds of hydroxo-ligands are still a little bit shorter (about 2.01 Å).

In the second reaction step, the formation of κ^2-chelate structures was explored. Such an arrangement was found experimentally [18] as a final product in reactions where sulphur-containing amino acids were involved. In the used models, a proton was passed from the amino acid to the negatively charged leaving ligand (Cl^- or OH^-) terminating in HCl or H_2O molecule. However, the HCl is formed only in cysteine chelates. In the case of methionine, the release of a Cl^- anion is thermodynamically preferred in the supermolecular approach. The formation of the HCl molecules was found energetically more convenient for both cysteine and methionine cases in the model of isolated molecules. Here, the release of the Cl^- anion is connected with an additional electrostatic work, which causes that the reaction is much more demanding. The Pt–X distances (where X is an amino acid donor atom) are usually shortened in the course of chelate formation. Low influence of chelation on the length of Pt-bonds can be observed only in the case of two methionine structures containing the Pt–S bonds. The shortening of Pt–X distances is accompanied by the elongation of Pt–N (ammine) bonds in trans positions. The Pt-ligand distances are occasionally non-negligibly influenced by the released particle in the

Table 3
Pt–X bond distances between platinum and its ligands (in Å) in the model of isolated complexes; *t* means *trans* and *c* means *cis* position to aqua-ligand or amino acid, X = Cl or OH

Complex	Pt–S(AA)	Pt–O(AA)	Pt–N(AA)	Pt–X	Pt–$(NH_3)_t$	Pt–$(NH_3)_c$
cis-$[Pt(NH_3)_2Cl(H_2O)]^+$		2.11[a]		2.30	2.04	2.12
cis-$[Pt(NH_3)_2(OH)(H_2O)]^+$		2.11[a]		1.97	2.04	2.13
cis-$[Pt(NH_3)_2Cl(Cys\text{-}S)]^+$	2.34			2.36	2.15	2.09
cis-$[Pt(NH_3)_2(OH)(Cys\text{-}S)]^+$	2.33			2.04	2.15	2.09
cis-$[Pt(NH_3)_2Cl(Cys\text{-}N)]^+$			2.13	2.33	2.09	2.12
cis-$[Pt(NH_3)_2(OH)(Cys\text{-}N)]^+$			2.10	1.99	2.07	2.11
cis-$[Pt(NH_3)_2Cl(Cys\text{-}O)]^+$		2.04		2.34	2.06	2.09
cis-$[Pt(NH_3)_2(OH)(Cys\text{-}O)]^+$		2.04		2.01	2.06	2.09
cis-$[Pt(NH_3)_2(Cys\text{-}N,O)]^+$		1.98	2.07		2.09	2.12
cis-$[Pt(NH_3)_2(Cys\text{-}S,O)]^+$	2.31	2.05			2.18	2.06
cis-$[Pt(NH_3)_2(Cys\text{-}S,N)]^+$	2.30		2.08		2.20	2.09
cis-$[Pt(NH_3)_2Cl(Met\text{-}S)]^+$	2.34			2.33	2.10	2.10
cis-$[Pt(NH_3)_2(OH)(Met\text{-}S)]^+$	2.34			2.00	2.09	2.12
cis-$[Pt(NH_3)_2Cl(Met\text{-}N)]^+$			2.08	2.32	2.09	2.11
cis-$[Pt(NH_3)_2(OH)(Met\text{-}N)]^+$			2.08	1.99	2.08	2.12
cis-$[Pt(NH_3)_2Cl(Met\text{-}O)]^+$		2.04		2.35	2.07	2.09
cis-$[Pt(NH_3)_2(OH)(Met\text{-}O)]^+$		2.04		2.02	2.06	2.09
cis-$[Pt(NH_3)_2(Met\text{-}N,O)]^+$		1.98	2.07		2.09	2.12
cis-$[Pt(NH_3)_2(Met\text{-}S,O)]^+$	2.34	2.01			2.10	2.10
cis-$[Pt(NH_3)_2(Met\text{-}S,N)]^+$	2.33		2.01		2.11	2.18

[a] Means Pt–O in aquacomplex of the cisplatin reactants.

supermolecular model (not shown in Table 3). The most stable conformers in the course of the reaction are depicted in Figs. 1–3.

At present a continuation of these calculations is running within the COSMO polarizable continuum model. Up to now it can be stated that besides preferential zwitterionic structure, which was expected (by 10.2 kcal/mol lower than neutral in the cysteine case, by 11 kcal/mol in the case of methionine), some additional conformational changes occurred in several cases. Especially in the case of hydroxo-complexes the proton transfer from the amino acid lead to the formation of the aqua-ligand. Also in monodentate complexes, the amino acid always takes zwitterionic conformation, and in the case of Pt–N coordinated compounds the nitrogen atom keeps NH_2 form.

3.3. Reaction energies of the cisplatin interactions with cysteine and methionine

An energetical description of the formation of platinum–amino acid complexes is summarized in Table 4. Two types of possible reactants were considered, chloro-complex: *cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$ and hydroxo-complex: *cis*-$[Pt(NH_3)_2(OH)(H_2O)]^+$, in order to distinguish between incomplete and complete cisplatin hydration products [18]. These two complexes represent different activation stages of cisplatin in the cellular environment. The first two columns of Table 4 contain reaction energies in the model of isolated molecules, the following columns contain results for the supermolecules. In this approach not only ΔE, but also $\Delta H(0)$ and $\Delta G(298)$ are presented. In the latter model, weak interactions between both molecules in reactant {cisplatin + amino acid} or product supermolecule {adduct complex + water} are included in the total energies of the supercomplexes. In this way, a better estimation of the reaction energies is obtained. Table 4 demonstrates a varying affinity of the Pt(II) cation for coordination to the different atoms (O, N, and S). The largest energy release in the formation of a monodentate complex occurs for the replacement of the aqua-ligand when the amino acid binds to Pt with the sulphur atom, followed by nitrogen, and the least efficient coordination is by carboxyl oxygen. The creation of a monodentate complex is most exothermic when cysteine coordinates to the Pt atom in the hydroxo-complex (about 22 kcal/mol in the supermolecular model). An important exception from the above coordination preferences occurs in the methionine interaction with the chloro-complex where the largest energy release (ΔG) is connected with the formation of the Pt–N bond (about 16 kcal/mol). This points to a reduced activity of the sulphur atom in the case of methionine and generally to a reduced activity for thioether compounds in comparison with thiols. (For an explanation see Section 3.4.1.) It is interesting that while in the cysteine case all the substitution reactions are more exothermic for the hydroxo-complex, in the methionine case the reactions of the chloro-complex are more exothermic with the exception of the Pt–O adduct.

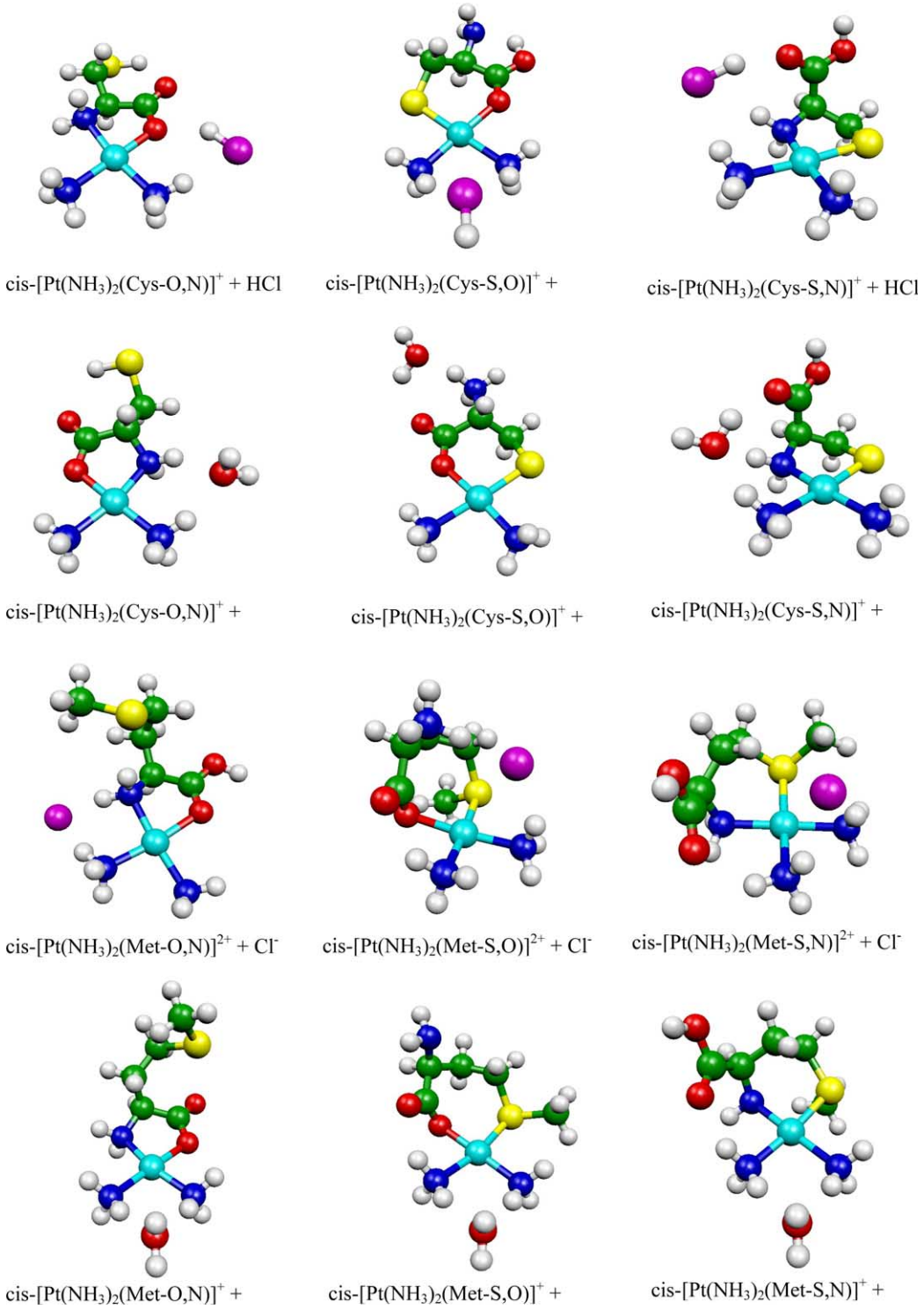


Fig. 3. Products of the chelation reaction (second step) in the supermolecular approach. The Pt(AA–O,N) chelates are in the first column, Pt(AA–S,O) chelates are in the second column, and Pt(AA–S,N) chelates are in the third column.

In the second reaction step, it was found that the structure of the S,N-chelate is the most stable in the cysteine case. The S,O-chelate is by about 10 kcal/mol and the N,O-structure by about 20 kcal/mol less stable. Similarly for methionine, the most stable chelate ring involves S,N-sites preserving also the order of the three chelates. However, the differences in chelation energies are much smaller (by about 3 kcal/mol in the isolated molecules model and up to 8 kcal/mol in the supermolecules model). This relative order is approximately

Table 4
ΔE, $\Delta H(0)$, and $\Delta G(298)$ reaction energies for the formation of monodentate and chelate complexes (in kcal/mol)

Reactant	Model product	Isolated molecules		Supermolecules					
		Cys	Met	Cys			Met		
				ΔE	ΔH	ΔG	ΔE	ΔH	ΔG
Pt(Cl) + AA	Pt(Cl)(AA-S)	−32.1	−29.0	−16.8	−15.6	−16.1	−17.1	−16.7	−14.1
	Pt(Cl)(AA-N)	−23.5	−31.2	−8.5	−8.0	−7.4	−17.2	−16.7	−15.9
	Pt(Cl)(AA-O)	−13.5	−16.9	3.4	2.0	2.4	−2.8	−2.5	−2.3
Pt(OH) + AA	Pt(OH)(AA-S)	−37.1	−26.8	−23.1	−22.1	−22.0	−15.0	−14.7	−12.9
	Pt(OH)(AA-N)	−24.8	−25.8	−10.9	−10.3	−9.3	−10.4	−10.4	−11.6
	Pt(OH)(AA-O)	−18.2	−21.4	−7.6	−8.1	−7.4	−5.5	−7.0	−8.1
Pt(Cl)(AA-S)	Pt(AA-S,O)	25.6	36.9	20.5	16.8	15.6	14.4	14.9	17.0
	Pt(AA-S,N)	17.9	31.3	10.8	8.3	8.3	13.8	14.8	16.5
Pt(OH)(AA-S)	Pt(AA-S,O)	8.7	12.9	−2.8	−2.8	−3.5	−1.7	−2.3	−2.5
	Pt(AA-S,N)	1.1	7.2	−14.6	−13.9	−13.5	−5.7	−6.5	−6.5
Pt(Cl)(AA-N)	Pt(AA-N,O)	32.1	41.2	25.1	21.9	20.7	23.9	22.7	22.8
	Pt(AA-S,N)	9.4	33.5	2.3	1.2	0.7	16.0	16.4	18.6
Pt(OH)(AA-N)	Pt(AA-N,O)	11.5	13.8	−3.6	−4.5	−5.8	−0.8	−1.3	−2.0
	Pt(AA-S,N)	−11.2	6.2	−26.8	−25.3	−25.6	−6.8	−8.0	−6.9
Pt(Cl)(AA-O)	Pt(AA-S,O)	7.0	24.9	2.0	0.0	−1.3	2.3	2.5	6.2
	Pt(AA-N,O)	22.1	26.8	15.0	12.2	11.4	9.5	8.7	9.9
Pt(OH)(AA-O)	Pt(AA-S,O)	−10.1	7.5	−21.7	−18.9	−19.0	−7.0	−6.7	−6.4
	Pt(AA-N,O)	4.9	9.5	−10.2	−9.2	−9.2	−5.1	−4.1	−5.5

AA means amino acid.

preserved regardless of the chosen form of cisplatin reactants (chloro- or hydroxo-complexes). In any computational model, the chelate formation is energetically less demanding for the hydroxo-complexes. Their reaction energies differ from the corresponding energies of chloro-complexes by more than 20 kcal/mol for cysteine and 10 kcal/mol for methionine in the supermolecular model. Notice that the weak interactions play an interesting role in the thermodynamic description of the chelation step because qualitatively different reaction energies are obtained for the hydroxo-complexes. In the supermolecular approach, all these chelate reactions are exothermic in contrast with the model of isolated molecules due to the additional relatively strong association energies of the {chelate···water} complex.

The effect of the higher activation for the dihydrated cisplatin is visible in both parts of Table 4. Despite the fact that the hydroxo-form is less active than the corresponding diaqua-form (the hydroxo-form was chosen for allow to comparison with chloro-complexes, keeping the unique total charge +1), a more exothermic or less endothermic course for the amino acid substitution was usually obtained in comparison with the chloro-complexes. This difference is up to 10 kcal/mol in the first reaction step (due to an only indirect polarization influence), but up to 30 kcal/mol in the case of the chelation reaction.

The first reaction step is still an exothermic reaction including the solvent effects, but in absolute value ΔG decreases (at most by 10 kcal/mol in the case of the isolated model where all the energies are higher, cf. Table 4). In the second reaction step, only small a decrease of ΔG usually takes place. Presence of a solvent moreover facilitates the release of a Cl^- ion in the second reaction step (especially in the model of isolated molecules due to the higher permittivity of water).

3.4. Analysis of the BDEs and association energies

The reaction energies represent the resulting numbers, which do not allow a detailed insight into the various contributions. Therefore, additional energy descriptors were chosen. The BDE usually enables an important insight into the bond strength between the both interacting parts: in our case metal complex – amino acid. From a closer inspection of Table 5, it can be seen that BDEs do not follow the trend of the reaction energies at all. As for the BDE values of monodentate complexes with a single Pt–X(AA) bond, the highest energy was obtained for the Pt–S(Cys) bond, about 114 kcal/mol. In the case of methionine, the analogous BDE is smaller by about 40 kcal/mol. This difference is larger than it should follow from the reaction energies discussed in the previous part. The explanation lies in the fact that monodentate cysteine adducts with the Pt–S coordination take the NH_3^+–COOH–S^- amino acid conformation, which become more stable after coordination to the metal by about 10 kcal/mol for the

Table 5
Bond dissociation energies of cisplatin–amino acid adducts in the model of isolated molecules (in kcal/mol)

	Cys			Met		
	Pt-AA	Pt–NH3c	Pt–NH3t	Pt-AA	Pt–NH3c	Pt–NH3t
Pt(Cl)		−52.3	−71.0		−52.3	−71.0
Pt(OH)		−51.5	−67.0		−51.5	−67.0
Pt(Cl)(AA-S)	−108.4	−48.1	−40.8	−80.6	−49.9	−49.7
Pt(OH)(AA-S)	−114.3	−52.8	−38.1	−74.1	−55.1	−47.7
Pt(Cl)(AA-N)	−70.9	−53.2	−57.4	−78.6	*−52.1*	*−54.5*
Pt(OH)(AA-N)	−67.4	−53.3	−55.2	−68.4	−50.9	−54.2
Pt(Cl)(AA-O)	−82.8	−55.9	−60.3	−86.0	*−55.4*	*−59.5*
Pt(OH)(AA-O)	−71.6	−56.8	−60.1	−77.6	−60.9	−58.1
Pt(AA-O,N)	−346.4	−59.4	−51.5	−355.4	*−58.9*	*−49.6*
Pt(AA-O,S)	−365.9	−38.4	−59.0	−348.2	−53.5	−52.3
Pt(AA-N,S)	−378.1	−56.2	−35.8	−404.5	*−37.9*	*−50.3*

chloro-complex and by about 17 kcal/mol for the hydroxo-complex (the stabilization energy of ca. 4–8 kcal/mol was determined for a similar zwitterionic structure of Pt(II)–glycine complexes – J.V. Burda, M. Orozco, F.J. Luque, in preparation). Moreover, the deformation energy of this (NH_3^+–COOH–S^-) conformer is also non-negligible (about 10 kcal/mol). Methionine conformation in the Pt–S complexes has the NH_2–COOH arrangement, which corresponds to the global minimum of the isolated amino acid. Its deformation energy is also smaller – by about 7 kcal/mol.

The BDEs of Pt–N bonded monodentate complexes are in a good agreement with reaction energies because both amino acids have ''correct'' NH_2–COOH structures and their deformation energies are not high (about 3 kcal/mol). The BDEs of the Pt–O bonded amino acid adducts with the chloro-complexes are affected in a similar way as in the case of Pt–S complexes because amino acids in these complexes adopt the zwitterionic NH_3–COO^- conformation, which is about 19 kcal/mol higher in energy than the NH_2–COOH arrangement. Finally, amino acids in the Pt–O hydroxo-complexes contain the NH_2–COOH conformation but their deformation energies are more than 15 kcal/mol, mainly due to the strong deformation of the carboxyl group in the proximity of a platinum complex.

The higher BDEs of chelate structures in comparison with the BDEs of monodentate complexes are caused by the fact that chelates dissociate to a negatively charged amino acid (−1) and a *cis*-$[Pt(NH_3)_2]^{2+}$ cation, which introduces additional electrostatic work. Further, the explanation of the BDE order of chelates is based on similar principles as used above in the discussion of the monodentate complexes. The high BDE of the Pt(Met–S,N) chelate from Table 5 corresponds to the high-lying methionine conformer with only one proton localized on the amino-group (cf. Fig. 3). Therefore, the BDE of this chelate (405 kcal/mol) is relatively higher than it should be according to the reaction energy. The ''negative'' difference of the BDEs of the Pt(Met–N,O) and Pt(Met–S,O) complexes in comparison with the analogous difference in reaction energies can be explained by the higher electrostatic repulsion in N,O-chelate between the negatively charged N and O interacting sites, which get close to each other. There is no such repulsion in the case of S,O-chelate because the positive partial charge occurs on the S atom in the complex. This explanation cannot be used in analogous cysteine chelates due to the negatively charged sulphur atom (cf. Table 7), and thus a comparable repulsion exists in both N,O- and S,O-chelates. Therefore, the BDE differences in cysteine chelates approximately correlate with corresponding differences in reaction energies.

From this analysis, we can see that usually very descriptive BDE must be treated very carefully in metal complexes with amino acids due to the very high flexibility and variability of the amino acids.

The association interactions between both molecules in a supermolecule were investigated and the results are summarized in Table 6. In the reactant supercomplex, the amino acid and cisplatin are connected with two H-bonds. Regardless of the type of the Pt-complex or amino acid, both H-bonds have the O···N character combining the ammine ligand of the platinum complex with the carbonyl group, and the aqua-ligand with amino group of the acid, cf. Fig. 1. The strength of these two bridges is about 26 kcal/mol, which demonstrates that both bridges are highly polarized. Also, the association interactions of the water molecule in the product supermolecule of the first and second reaction steps are above 10 kcal/mol. The strongest interaction appears in the {*cis*-$[Pt(NH_3)_2(OH)(S\text{-Met})]^+ + H_2O$} complex where the water molecule interacts with oxygen atoms of the hydroxyl groups from cisplatin and the carboxyl group of the acid releasing 16 kcal/mol (22 kcal/mol without deformation corrections), cf. Fig. 2. Such a conformation is not possible in the case of cysteine due to the substantially lower flexibility of its side chain.

Table 6
Association energies between both parts of the supermolecule (in kcal/mol)

Supermolecule	Cys	Met
Pt(Cl) + AA	−27.7	−25.8
Pt(OH) + AA	−25.9	−27.4
Pt(Cl)(AA-S) + w	−13.3	−15.0
Pt(OH)(AA-S) + w	−12.5	−16.1
Pt(Cl)(AA-N) + w	−13.4	−12.8
Pt(OH)(AA-N) + w	−12.4	−13.1
Pt(Cl)(AA-O) + w	−12.9	−12.9
Pt(OH)(AA-O) + w	−15.3	−12.6
Pt(AA-O,N) + cl[a]	−5.9	−177.0
Pt(AA-O,N) + w	−14.4	−13.8
Pt(AA-O,S) + cl[a]	−4.1	−178.5
Pt(AA-O,S) + w	−10.9	−13.8
Pt(AA-N,S) + cl[a]	−6.0	−170.2
Pt(AA-N,S) + w	−14.9	−12.3

[a] cl means Cl^- in methionine and HCl in cysteine cases.

Very high association energies in case of the chloride anion interactions with Pt(Met–X,Y) chelates are caused by the electrostatic work necessary for charge separation. However, this interaction should be substantially reduced as it was shown in the study [18], where polarizable continuum model was used for such a type of interactions. In contrast with methionine, there is one additional proton from the S–H group available in the cysteine case. This proton recombines with the chloride anion resulting in the weakly bonded (ca. 6 kcal/mol) HCl···cysteine-chelate systems, cf. Table 6. In the case of the Pt(Cys–N,O) conformer, the HCl proton originates from O–H of the carboxyl group.

3.4.1. Partial charges analysis

The NBO procedure was utilized for the analysis of the electron density distribution. A comparison of the NPA partial charges with some other techniques (CHelpG [90] and Merz–Kolmann [88] schemes) was done for the studied systems. These methods are based on a fit of electrostatic potential and they require van der Waals radii for the determination of the surface where the potential is evaluated. The recommended value for the Pt atom is 175 pm according to the work of Bondi [100] and Pyykkö [101]. However, the platinum partial charges predicted by both CHelpG and MK techniques are too small using this radius. For several complexes, these two methods give even a negative partial charge of the Pt atom. Therefore only NPA results were chosen as more reliable and will be discussed further. The NPA charges for chosen atoms are displayed in Table 7.

Partial charges on the platinum atom closely correlate with the strength of the individual ligand donations. The relatively weak coordination of aqua or hydroxo-ligands is connected with higher positive charge on the Pt atom (e.g., about 0.75e in the case of the $Pt(NH_3)Cl(H_2O)(OH)$ complex). Similarly, monodentate complexes of *cis*-$[Pt(NH_3)_2(OH)(AA–O)]^+$ exhibit similar high positive charges on the Pt atom, too.

Table 7
Natural bond orbitals partial charges in the model of isolated complexes; *t* means *trans* and *c* means *cis* position to aqua-ligand or amino acid, X = Cl or OH, O^x is oxygen from hydroxyl (carboxyl) group, O^n is oxygen from carbonyl group

Complex	Pt	S(AA)	O^n(AA)	O^x(AA)	N(AA)	X	$(NH_3)_t$	$(NH_3)_c$
Cysteine		−0.02	−0.61	−0.71	−0.93			
Methionine		0.21	−0.60	−0.72	−0.94			
cis-$[Pt(NH_3)_2Cl(H_2O)]^+$	0.63					−0.45	−0.99	−1.07
cis-$[Pt(NH_3)_2(OH)(H_2O)]^+$	0.74					−1.01	−1.00	−1.07
cis-$[Pt(NH_3)_2Cl(Cys\text{-}S)]^+$	0.46	−0.22	−0.59	−0.70	−0.81	−0.50	−1.07	−1.04
cis-$[Pt(NH_3)_2(OH)(Cys\text{-}S)]^+$	0.54	−0.21	−0.60	−0.70	−0.82	−1.04	−1.08	−1.03
cis-$[Pt(NH_3)_2Cl(Cys\text{-}N)]^+$	0.59	0.01	−0.65	−0.69	−0.83	−0.49	−1.03	−1.06
cis-$[Pt(NH_3)_2(OH)(Cys\text{-}N)]^+$	0.68	0.00	−0.65	−0.68	−0.84	−1.04	−1.03	−1.06
cis-$[Pt(NH_3)_2Cl(Cys\text{-}O)]^+$	0.67	0.05	−0.64	−0.76	−0.80	−0.51	−1.02	−1.05
cis-$[Pt(NH_3)_2(OH)(Cys\text{-}O)]^+$	0.76	0.01	−0.67	−0.66	−0.91	−1.01	−1.02	−1.04
cis-$[Pt(NH_3)_2(Cys\text{-}N,O)]^+$	0.70	0.03	−0.58	−0.71	−0.83		−1.04	−1.05
cis-$[Pt(NH_3)_2(Cys\text{-}S,O)]^+$	0.56	−0.15	−0.64	−0.65	−0.93		−1.01	−1.09
cis-$[Pt(NH_3)_2(Cys\text{-}S,N)]^+$	0.47	−0.12	−0.61	−0.70	−0.83		−1.10	−1.03
cis-$[Pt(NH_3)_2Cl(Met\text{-}S)]^+$	0.46	0.46	−0.62	−0.71	−0.93	−0.50	−1.05	−1.06
cis-$[Pt(NH_3)_2(OH)(Met\text{-}S)]^+$	0.56	0.45	−0.63	−0.71	−0.93	−1.03	−1.05	−1.07
cis-$[Pt(NH_3)_2Cl(Met\text{-}N)]^+$	0.59	0.22	−0.65	−0.69	−0.84	−0.49	−1.03	−1.06
cis-$[Pt(NH_3)_2(OH)(Met\text{-}N)]^+$	0.68	0.23	−0.65	−0.69	−0.82	−1.03	−1.03	−1.07
cis-$[Pt(NH_3)_2Cl(Met\text{-}O)]^+$	0.67	0.23	−0.64	−0.76	−0.79	−0.51	−1.02	−1.05
cis-$[Pt(NH_3)_2(OH)(Met\text{-}O)]^+$	0.76	0.20	−0.67	−0.68	−0.87	−1.01	−1.02	−1.05
cis-$[Pt(NH_3)_2(Met\text{-}N,O)]^+$	0.70	0.25	−0.57	−0.72	−0.84		−1.04	−1.06
cis-$[Pt(NH_3)_2(Met\text{-}S,O)]^+$	0.59	0.48	−0.65	−0.74	−0.92		−1.04	−1.06
cis-$[Pt(NH_3)_2(Met\text{-}S,N)]^+$	0.48	0.46	−0.66	−0.71	−0.89		−1.07	−1.08

According to increasing electron donation (stronger coordination), the bonding energy increases from the Pt–O (through Pt–N and Pt–Cl) to Pt–S bonds. Therefore, the systems containing the N,S-chelates belong among the most stable complexes ($\delta(Pt) = 0.48e$). The lowest partial charge ($\delta(Pt) = 0.46e$) is observed in the *cis*-$[Pt(NH_3)_2Cl(AA–S)]^+$ structures, which underlines the extent of the dative character in this complex.

The difference between the coordinations of cysteine and methionine clearly follows from the partial charges of the sulphur atom. While the sulphur in the thiol group is practically neutral in the isolated cysteine (or in corresponding complexes not coordinated by sulphur) due to charge compensation by its proton, the partial charge of the S atom in complexes with the Pt–S coordination is not so effectively compensated, which results in a negative electron density on S. In the methionine case, the sulphur atom is slightly positively charged in the isolated amino acid. Under platination, this positive charge is further increased due to the electron-pair donation to the metal atom. It means that while in cysteine complexes at least some electrostatic contributions (enhancement of dative bonds) can be expected, practically purely covalent character occurs in methionine complexes. This clearly points to different bonding mechanisms of the cisplatin complexes with cysteine (and thiols generally) and methionine (and thioethers).

4. Conclusion

The interactions of the hydrated forms of cisplatin with cysteine and methionine were examined using the DFT method with B3LYP functional. Two approaches, the model of isolated molecules and the model of supermolecules, were used for the investigation of the complexes.

Formation of the monodentate complexes with a single Pt–X coordination (X = S, N, and O) has exothermic character for the both amino acids, both types of reactants, and both chosen models. In the cysteine case, preference for the Pt–S coordination over Pt–N and Pt–O bonds was found. Slightly larger preference of the Pt–N coordination in comparison with the Pt–S complex was revealed for interaction of methionine with Pt(II)-chloro-complexes.

Formation of all three chelate types from chloro-complexes is an endothermic process. In the case of hydroxo-complexes, mildly exothermic reactions were predicted in the supermolecular approach. This points to a higher reactivity of the diaqua-form of cisplatin in the anticancer activity discussed already in our previous studies [17,18].

The BDE of Pt–S(Cys) in the monodentate hydroxo-complex (about 114 kcal/mol) is comparable with the platinum coordination to N7-guanine and it is higher than the BDE of Pt–N7 in the cisplatin–adenine adduct. This is in good agreement with the experimentally known fact that Pt–S coordination competes with the formation of Pt–(N7–guanine) complex. The analogous BDE of Pt–S(Met) is smaller by about 40 kcal/mol. Such a conclusion is in good accord with the experimental findings on irreversible cisplatin adducts with cysteine side-chains, while interactions with methionine side-chains exhibit reversible character.

The inclusion of the solvent effect will cause some changes in the thermochemical description of interactions. However, a deeper examination using the PCM model is still necessary for a final analysis of these complexes.

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