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Molecular Mechanics Modelling of Pt(II) Complexes with Antitumor Activity. Influence of the Type and the Positions of the Ring Substituents on the Conformational Energies and Thermodynamic Stabilities

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Summary. The influence of the type and the positions of the ring substituents on the conformational energies and thermodynamic stabilities of a series of Pt(II) complexes of the general formula [1,2-*bis*(hydroxyphenyl)ethylenediamine]PtL_2($L_2 = 2Cl^-$, $2I^-$, SO_4^{2-}) has been studied by molecular mechanics. The calculations were carried out for the ligand conformations (*R,S/S,R*)-λ, (*R,S/S,R*)-δ, (*R,R*)-δ, and (*S,S*)-λ. The obtained energies and thermodynamic stabilities are in agreement with experimental data on the reactivity and antitumor activity of the compounds.

Keywords. Platinum complexes; Estrogen activity; Molecular mechanics.

Molecular Modelling von Pt(II)-Komplexen mit Antitumoraktivität. Einfluß von Art und Position von Substituenten auf Konformationsenergien und thermodynamische Stabilitäten

Zusammenfassung. Die konformationellen Energien und thermodynamischen Stabilitäten einer Reihe von Pt(II)-Komplexen mit der allgemeinen Formel [1,2-*bis*(Hydroxyphenyl) ethylendiamin] PtL_2($L_2 = 2Cl^-$, $2I^-$, SO_4^{2-}) wurden mittels molekularmechanischer Methoden in Abhängigkeit von Art und Stellung der Substituenten an den Phenylringen untersucht. Die Berechnungen wurden für die Ligandenkonformationen (*R,S/S,R*)-λ, (*R,S/S,R*)-δ, (*R,R*)-δ und (*S,S*)-λ durchgeführt. Die erhaltenen Energien und Stabilitäten stimmen mit experimentellen Daten über Reaktivität und Antitumoraktivität der Verbindungen überein.

Introduction

Cis-$Pt(NH_3)_2Cl_2$ (cisplatin) was the first platinum compound tested on a wide scale for cytostatic effects [1–4]. This compound, however, is toxic and, in some cases, not selective enough [5]. Compounds in which the NH_3 groups are replaced by ethylenediamine and its derivatives also show a cytostatic effect and have been tested against human breast cancer cell line [1, 2].

A new class of Pt(II) compounds, designed by combination of the cytotoxic $PtCl_2$ group (the active moiety in cisplatin) with an estrogen receptor affinic diamine ligand, has been described by *Gust et al.* [6–9]. These new complexes retain the estrogen properties of the ligand which binds to the estrogen receptor (specific for the tumor cell); thus, the complexes attack selectively critic areas of the *DNA* [9–21]. Such compounds are more selective and less toxic [6].

Recently, we have shown that the thermodynamic stability correlates with the rate of hydrolysis of (*R,S/S,R*)- and (*R,R/S,S*)-[1,2-*bis*(2-hydroxyphenyl)ethylenediamine]dichloroplatinum(II) (*3-PtCl*$_2$) [22]. Among the studied conformers, the (*S,S*)-λ isomer shows a higher rate of hydrolysis (and higher antitumor activity) as compared with both (*R,S/S,R*) conformers. In order to explain this behaviour, we focused on molecular and electronic structures and tried to find correlations between geometry and thermodynamic stability on one side and antitumor activity on the other. The results from molecular modelling calculations showed that in the case of *3-PtCl*$_2$ (OH in positions 2 and 6) the (*S,S*)-λ conformer has a significantly lower energy than both (*R,S/S,R*) conformers ($\Delta \sim 3\,\text{kcal}\cdot\text{mol}^{-1}$) [22]. Insignificant energy differences between (*R,S/S,R*) and (*S,S*)-λ conformers were found for compounds with and without OH in positions 3 and 4. Obviously, the OH groups in positions 2 and 6 of the phenyl ring stabilize the (*S,S*)-λ conformer of *3-PtCl*$_2$. Structural data in the solid state give evidence for N-H$\cdots$O hydrogen bonds (two in the case of (*S,S*)-λ and one in the case of (*R,S/S,R*)) with OH in positions 2 and 6 [21]. The higher thermodynamic stability of the (*S,S*)-λ conformer of *3-PtCl*$_2$ probably increases its transport properties; the compound reaches the cell unchanged and hydrolyses upon entering it. As a result, the (*S,S*)-λ conformer has a higher antitumor activity as compared with (*R,S/S,R*) conformers. This is in agreement with the suggestion made previously that different positions of the OH substituents cause different properties which affect the antitumor efficacy [11, 13, 20–24]. It was found further that the presence of other substituents as Cl or F in different positions of the phenyl rings and their combination with OH increases the estrogen activity of the studied complexes [5, 7–10, 14–19]. The activity of the diastereomeric [1,2-*bis*(2,6-dihalo-4-hydroxyphenyl)ethylenediamine]$PtCl_2$ (Cl, F) on the hormon sensitive MXT-M3.2 mammary carcinoma of the mouse is strongly dependent on the type of the halogen atoms and on their positions in the aromatic rings [7]. Thus, we decided to study the influence of the type and the positions of different substituents in the phenyl rings on the conformational energies and thermodynamic stabilities of the title compounds. The stability of Pt(II) compounds used as antitumor agents is important during the transport of the complex to the cell. The more stable complex will reach the tumor cell in higher concentration, and thus its activity is expected to be higher [23].

Results and Discussion

The studied complexes are given in Fig. 1. The following conformers have been investigated: (*i*) two (*R,S/S,R*) conformers (one aromatic ring is in axial and one in equatorial position; *meso*) among them one (*R,S/S,R*)-δ (Fig. 1a) and one (*R,S/S,R*)-λ conformer (Fig. 1b), (*ii*) one (*R,R*)-δ conformer (both aromatic rings are in axial

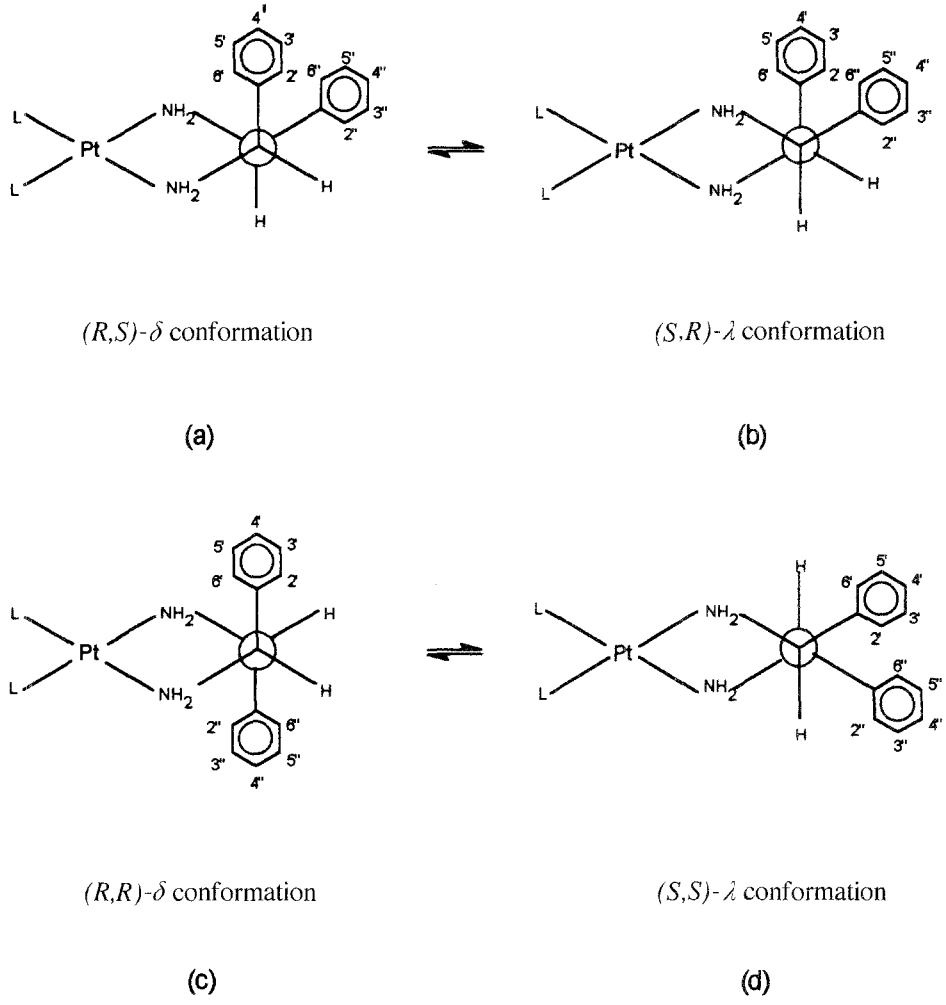

Fig. 1. (*R,S/S,R*) and (*R,R/S,S*) conformations for the studied compounds with numbering of the substituent position in the aromatic rings

positions, Fig. 1c), and (*iii*) one (*S,S*)-λ conformer (both aromatic rings are in equatorial positions, Fig. 1d).

We shall now examine the influence of the type of the ring substituents (Cl, F, and OH) and their positions in the phenyl rings (2, 3, 4, 5, and 6) on the conformational energies and thermodynamic stabilities of the studied compounds.

OH substituents

First we shall consider only one substituent in each phenyl ring of [1,2-*bis*(hydroxyphenyl)ethylenediamine]dichloroplatinum(II). The results are shown in Table 1. For all combinations of OH positions in the phenyl rings, the (*R,R*)-δ conformer has the lowest energy. The lower energies obtained for this conformer could be explained by lower Ph-Ph repulsion as compared with the Ph-Ph repulsion in the (*S,S*)-λ and both (*R,S/S,R*) (λ and δ) conformers. The (*R,R*)-δ conformer (with phenyl rings oriented bisaxially) was never observed experimentally since

Table 1. MMX energies (kcal·mol^{-1}) of (*R,S/S,R*)-λ, (*R,S/S,R*)-δ (*S,S*)-λ, and (*R,R*)-δ conformers of [1,2-*bis*(hydroxyphenyl)ethylenediamine]PtL_2 (L = Cl, I) with different positions of OH substituents in the phenyl rings (2, 3, 4, 5, and 6)

Substituents and positions		Compound	(*R,S/S,R*)-λ (*meso*)	(*R,S/S,R*)-δ (*meso*)	(*S,S*)-λ (−)	(*R,R*)-δ (+)
axial ring (′)	equatorial ring (″)					
			Leaving group Cl			
OH (2′)	OH (2″)		47.7	48.6	48.9	43.2
OH (2′)	OH (6″)	*meso-3-PtCl$_2$*	49.1*	49.2	49.0	44.3
OH (6′)	OH (2″)	*meso-3-PtCl$_2$*	51.4[a]	51.9[a]	49.3[a,**]	49.5[a]
			46.7[b]	46.9[b]	49.6[b]	42.4[b]
OH (6′)	OH (6″)	*meso-3-PtCl$_2$*	52.3[a,**]	52.0[a]	48.6[a,*]	48.4[a]
			47.6[b]	47.7[b]	50.0[b]	44.3[b]
OH (3′)	OH (3″)		52.6	51.8	51.0	47.5
OH (3′)	OH (5″)		52.5	51.9	50.8	47.5
OH (5′)	OH (3″)		52.4	51.6	50.9	47.3
OH (5′)	OH (5″)		52.4	51.7	50.9	47.6
OH (4′)	OH (4″)		52.5	52.1	51.5	48.3
			Leaving group I			
OH (2′)	OH (2″)		83.6	82.7	83.9	82.3
OH (2′)	OH (6″)		84.6	83.5	83.3	85.1
OH (6′)	OH (2″)		86.7	85.5	84.2	88.2
			82.0	80.5	84.2	79.9
OH (6′)	OH (6″)		87.6	86.8	84.6	83.5
			83.2	81.6	83.1	79.7
OH (3′)	OH (3″)		86.2	87.0	86.2	84.5
OH (3′)	OH (5″)		86.4	87.2	86.1	84.3
OH (5′)	OH (3″)		86.3	86.9	86.2	84.5
OH (5′)	OH (5″)		86.4	87.0	86.2	84.4
OH (4′)	OH (4″)		87.3	87.7	86.8	84.9

* Structures found in the solid state [21]; ** structures found in solution [21]; [a] the hydrogen atom from the OH group in position 6′ is oriented away from the N-Pt-N plane; [b] the hydrogen atom from the OH group in position 6′ is oriented towards the N-Pt-N plane

the dimeric structure of the studied compounds hinders bisaxial orientation of the phenyl rings [21]. The other three conformers ((*R,S/S,R*)-λ, (*R,S/S,R*)-δ, and (*S,S*)-λ) could be obtained, and structural data for some of them (marked by asterisks in Table 1) are available [21] indicating dimeric structures in which either both phenyl rings adopt bisequatorial positions (*S,S*)-λ or one phenyl ring is oriented axially and the second one equatorially (*R,S/S,R*)-λ and (*R,S/S,R*-δ). We shall consider further only these three conformers. In general, both (*R,S/S,R*) conformers have higher energies than the (*S,S*)-λ conformer due to higher ring repulsion. A survey of the results in Table 1 shows that in two cases (substituents in 2′,2″ and 2′,6″; see also Fig. 1) the three conformers have comparable energies. For they (*R,S/S,R*) conformers, the primed positions are always in the axial ring, whereas the double-primed ones refer to the equatorial ring. For the (*S,S*)-λ

conformer, both rings are equatorially oriented; in this case, the primary only indicates the different phenyl rings.

Among all studied combinations, the most interesting ones are those in which one OH substituent is in 6′-position (close to the N-Pt-N plane), namely 6′,2″ and 6′, 6″. These are the structures observed in solution: 6′,2″ for the (*S*,*S*)-λ conformer and 6′,6″ for the (*R*,*S*/*S*,*R*)-λ conformer [21]. As can be seen from the results in Table 1 the (*R*,*S*/*S*,*R*) conformer has higher energy (52.3 kcal·mol^{-1}) than the (*S*,*S*)-λ conformer (49.3 kcal·mol^{-1}). This energy difference correlates with the different rate of hydrolysis and antitumor activity obtained for this two conformers: the lower energy conformer (the more stable one) has better antitumor activity [21].

In addition, in this two cases two different orientations of the 6′-OH hydrogen were calculated for the (*R*,*S*/*S*,*R*) conformers: towards the N-Pt-N plane and away from it. In order to obtain the preferred orientation of the OH hydrogens, the rotational energies about the C_{ar}-O bond were calculated as a function of the dihedral angel C_{ar}-C_{ar}-O-H. The obtained rotational barriers are above 100 kcal·mol^{-1}, excluding free rotation. When both hydrogen atoms are oriented away from the N-Pt-N plane (the structure found in solution), the (*R*,*S*/*S*,*R*)-λ conformer has a higher energy (52.3 kcal·mol^{-1} compared to the case when the H(6′) is oriented towards the N-Pt-N plane (47.6 kcal·mol^{-1}). The same trend was found for the (*R*,*S*/*S*,*R*)-δ conformer. Thus, the energies of both (*R*,*S*/*S*,*R*) conformers are lowered by $\sim$ 4 kcal·mol^{-1} when the OH(6′) hydrogen is oriented towards the N-Pt-N plane, and they become even lower when compared with the energy of the (*S*,*S*)-λ conformer. This orientation of the hydrogen atoms, however, was not observed for the studied conformers in solution; in this case, only the highest energy conformer ((*R*,*S*/*S*,*R*)-λ, 52.3 kcal·mol^{-1}, H atom away from the N-Pt-N plane) could be detected.

The experimental data have also shown that in the (*S*,*S*)-λ conformer in solution OH groups in positions 6′,2″, both OH residues point towards the N-Pt-N plane, and the hydrogens are oriented away from it [21]. The structure of the (*S*,*S*)-λ conformer is stabilized by two N-H$\cdots$O hydrogen bonds. Our calculations showed that the orientations of the OH hydrogens for (*S*,*S*)-λ are of minor importance when they are in positions 6′ and 2″ (the obtained energies are almost equal: 49.3 and 49.6 kcal·mol^{-1}). As can be seen from Table 1, conformers the tested experimentally for antitumor activity ((*R*,*S*/*S*,*R*)-λ and (*S*,*S*)-λ) show different energies and stabilities. Probably, the obtained energy difference between (*R*,*S*/*S*,*R*) and (*S*,*S*)-λ conformers ($\sim$ 3 kcal·mol^{-1}) is one of the reasons for the different reactivities and antitumor activities of these two conformers. The results thus obtained are also in agreement with the previously made suggestion that mainly steric effects of the 1,2-diphenylethylenediamine ligands determine the reaction rates, and that electronic effects are of only subordinate importance for the substitution reaction [21].

X-ray data have shown different solid state structures for (*R*,*S*/*S*,*R*) and (*S*,*S*)-λ conformers: the OH groups are in positions 2′,6″ for the (*R*,*S*/*S*,*R*) conformers and in 6′,6″ for the (*S*,*S*)-λ conformer. The energies of both (*R*,*S*/*S*,*R*) conformers (49.1 and 49.2 kcal·mol^{-1}), however, are only slightly higher than that of (*S*,*S*)-λ (48.6 kcal·mol^{-1}). Different orientations of the hydrogen atoms (away and towards the N-Pt-N plane) were also modelled, but they do not alter the calculated energies.

Thus, the calculated conformational energies show that the different reactivities and antitumor activities could be explained by comparison of the structures obtained in solution rather than in the solid state.

As seen from Table 1, all combinations for positions 3, 4 and 5 of the OH groups do not alter significantly the energies of the studied conformers, and the energy differences between (*R,S/S,R*) and (*S,S*)-λ are smaller (up to 1 kcal·mol^{-1}). Different 6′-OH hydrogen orientations were considered also for all other cases (OH in positions 3, 4, and 5), but an energy lowering analogous to the case of 6′,2″ and 6′,6″ was not observed.

The same trends were obtained with I as leaving groups. The results are listed in Table 1; they show that the type of the leaving group does not alter the obtained energy orders. There are no experimental results for this group of compounds therefore, comparison is not possible.

OH, Cl and F substituents

In order to increase the lipophilic character of the studied compounds, Cl and F substituents were introduced into positions 2 and 6 of the phenyl rings, and the OH groups were shifted positions 3 or 4. Such compounds have been prepared, and they show estrogen affinity and activity [5, 7–10, 14–19]. First, we shall consider the OH groups in position 4 and Cl and/or F in positions 2 and 6 of the phenyl rings. We shall examine all possible combinations and where possible comparison with experimental data will be made.

The calculated MMX energies for the studied conformers with $L = I$ are shown in Table 2. The following trends were observed:

1. One Cl

For all conformers, the highest energies were obtained in the case when Cl is in position 6′. Obviously, the repulsion by the atoms in the N-Pt-N plane is strong. For (*S,S*)-λ positions 2′ and 6″ are slightly preferred (within $\sim$ 1 kcal·mol^{-1}).

2. Two Cl (erythro-5-PtI$_2$)

The lowest energies were found when both Cl atoms are located in one phenyl ring (*erythro-5-PtI$_2$*). For (*R,S/S,R*), the equatorial ring is preferred (2″6″; 77.6 and 77.8 kcal·mol^{-1}; Table 2) to the axial one (2′,6′; 78.8 and 79.6 kcal·mol^{-1}). Cases where every phenyl ring bears one Cl atom and the two atoms are in position 6′,6″ (83.1, 83.0 kcal·mol^{-1}) or 6′,2″ (81.9, 81.8 kcal·mol^{-1}) are unfavorable. For the (*S,S*)-λ conformer, the lowest energies were also obtained for *erythro-5-PtCl$_2$* (both Cl are in one phenyl ring, and – as expected due to the equivalent orientation of the phenyl rings – the obtained energies do not differ significantly (76.1, 76.3 kcal·mol^{-1}). These energies are lower as compared with those mentioned previously for the (*R,S/S,R*) conformers (77.6, 77.8 kcal·mol^{-1}). The same trends were obtained for conformers with two F substituents.

3. Three Cl (or F)

The conformers with three Cl atoms (*erythro-9-PtCl$_2$*, (*R,S/S,R*)-λ conformer) in the phenyl rings have lower energies than the conformers with one and two Cl atoms. The conformers with three Cl atoms (for leaving group I) have been studied in detail and their structures and antitumor activities are known [18]. The (*R,S/*

S,R)-λ conformer (*erythro-9-PtCl*$_2$) was one of the compounds with significant estrogen activity [18]. Our calculations show that the most preferred case for this conformer is when two Cl atoms are located in the equatorial ring and the third one in the axial ring in position 2′ (away from the N-Pt-N plane, 71.8 kcal·mol^{-1}). All other combinations have higher energies and are thus unfavourable. This is in full agreement with the experimental data about the structures and antitumor activities of this compound: above-mentioned low energy (*R,S/S,R*)-λ conformer (*erythro-9-PtI*$_2$, 71.8 kcal·mol^{-1}) has antitumor properties [18]. The obtained (*S,S*)-λ energies were of the same order (71.8, 71.8 kcal·mol^{-1}) only in the case when the third Cl atom is far from the phenyl ring with two Cl atoms (in position 6′ or 2″). The same trends were obtained for the conformers with three F substituents.

4. Four Cl (meso-1-PtCl$_2$*, (R,S/S,R)-λ)*
The obtained energies are the lowest in the studied series of compounds (67.6 and 68.4 kcal·mol^{-1} for the (*R,S/S,R*) conformers and 65.9 kcal·mol^{-1} for the (*S,S*)-λ conformer, Table 2). The lowest energy (*R,S/S,R*)-λ conformer with four Cl atoms in positions 2 and 6 (*meso-1-PtI*$_2$, 67.6 kcal·mol^{-1}) exhibits the best antitumor activity [18]. The same trends were obtained for the conformers with four F substituents.

5. Two Cl and one F (erythro-8-PtL$_2$*, (R,S/S,R)-δ)*:
As in the case with three Cl atoms, conformers which have two Cl atoms in one phenyl ring (the equatorial one for (*R,S/S,R*)) and F in the axial ring in position 6′(75.66 kcal·mol^{-1}) and in position 2′ (75.6 and 74.4 kcal·mol^{-1}) are preferred. In this group of compounds, the most interesting conformer is *erythro-8-PtL*$_2$*, ((R,S/S,R)-δ*, 74.4 kcal·mol^{-1}; two Cl atoms in the equatorial and one F in the axial ring, position 2′ $L = I$)). The other combinations in this case (2Cl and 1F) do not bring about significant differences in the conformational energies; they vary only slightly (within ∼ 1 kcal·mol^{-1}).

As can be seen from Table 2, variations of the substituent positions in the case of *three Cl and one F and two Cl and two F atoms*, do not alter significantly the calculated energies; they vary within ∼ 1 kcal·mol^{-1}. The (*S,S*)-λ conformers are slightly preferred.

The same trends were observed for Cl and SO_4^{2-} as leaving groups. The results for Cl are given in Table 3. A survey of Table 3 shows that the type of the leaving group does not influence the trends in the calculated conformational energy and the thermodynamic stabilities of the complexes as studied by molecular mechanics. Unfortunately, there are not experimental structural data, and a comparison with real structures is not possible.

There are some experimental results, however, about the antitumor activity of compounds with leaving group SO_4^{2-}. When the OH group of *meso-1-PtSO*$_4$ was shifted from position 4 to 3, the antitumor activity of the (*R,S/S,R*) conformer was decreased [5]. However, by additionally exchanging the Cl atoms in positions 2 and 6 by F, the parent compound [*meso*-1,2-*bis*(2,6-dichloro-4-hydroxyphenyl)ethylenediamine]sulfatoplatinum(II) (*meso-1-PtSO*$_4$) was transformed into the very potent complex [*meso*-1,2-*bis*(2,6-difluoro-3-hydroxyphenyl)ethylenediamine]sulfatoplatinum(II) (*meso-4-PtSO*$_4$) [5]. The calculated energies for this series of conformers are given in Table 4. Our calculations showed that after shifting the OH

Table 2. MMX energies (kcal·mol^{-1}) of (*R,S/S,R*)-λ, (*R,S/S,R*)-δ (*S,S*)-λ, and (*R,R*)-δ conformers of [1,2-*bis*(2,6-dihalo-4-hydroxyphenyl)ethylenediamine]PtL_2 (L = I) with different positions of the halo substituents in the phenyl rings (2 and 6); halo = Cl and F; for the meaning of asterisks, cf. Table 1

Substituents and positions				Substituents (Compound)	(*R,S/SR*)-λ (*meso*)	(*R,S/SR*)-δ (*meso*)	(*S,S*)-λ (–)
in the axial ring		in the equatorial ring					
2′	6′	2″	6″				
Cl				1 Cl	82.7	82.3	82.2
		Cl			82.8	82.7	83.4
	Cl				86.5	86.2	84.5
			Cl		84.8	84.2	82.2
		Cl	Cl	2 Cl (*erthro-5-PtI$_2$*)	77.6	77.8	76.1
Cl	Cl				78.8	79.6	76.3
Cl		Cl			78.7	78.4	79.5
Cl			Cl		79.1	79.3	77.9
	Cl	Cl			81.9	81.9	80.6
	Cl		Cl		83.1	83.0	80.6
Cl		Cl	Cl	3 Cl (*erythro-9-PtI$_2$*)	71.8*	72.4	71.8
Cl	Cl		Cl		74.9	76.2	71.8
Cl	Cl	Cl			75.1	76.9	73.4
	Cl	Cl	Cl		76.1	77.5	73.3
Cl	Cl	Cl	Cl	4 Cl (*meso-1-PtI$_2$*)	67.6*	68.4	65.9
Cl	F	Cl		2 Cl, 1 F (*erythro-8-PtI$_2$*)	75.7	75.7	75.6
F		Cl	Cl		75.6	74.4*	76.1
F	Cl	Cl			76.4	76.2	76.4
Cl	F		Cl		76.5	76.8	74.2
F	Cl		Cl		77.0	77.0	75.0
Cl	Cl		F		78.2	78.1	76.1
Cl	Cl	F			78.9	79.5	76.8
	F	Cl	Cl		78.8	77.9	77.1
Cl	F	Cl	Cl	3 Cl, 1 F	63.1	64.0	61.2
Cl	Cl	Cl	F		63.8	64.4	62.0
F	Cl	Cl	Cl		63.7	64.4	62.0
Cl	Cl	F	Cl		64.2	64.8	61.2
Cl	F	F	Cl	2 Cl, 2 F	60.0	60.2	57.0
Cl	F	Cl	F		59.1	59.4	57.8
F	Cl	Cl	F		59.8	60.4	58.5
F	F	Cl	Cl		60.1	60.3	58.1
F	Cl	F	Cl		60.6	61.0	57.7
Cl	Cl	F	F		61.1	61.0	58.0

Table 3. MMX energies (kcal·mol^{-1}) of (*R,S/S,R*)-λ, (*R,S/S,R*)-δ, (*S,*S)-λ and (*R,R*)-δ conformers of [1,2-*bis*(2,6-dihalo-4-hydroxyphenyl)ethylenediamine]PtL_2 (L = Cl) with different positions of the halo substituents in the phenyl rings (2 and 6); halo = Cl and F

Substituents and positions				Substituents (Compound)	(*R,S/SR*)-λ (*meso*)	(*R,S/SR*)-δ (*meso*)	(*S,S*)-λ (−)
in the axial ring		in the equatorial ring					
2′	6′	2″	6″				
Cl				1 Cl	47.6	47.6	47.2
		Cl			48.0	47.9	48.4
	Cl				51.2	50.9	48.6
			Cl		49.1	49.1	47.1
		Cl	Cl	2 Cl (*erthro-5-PtIC$_2$*)	41.9	41.9	40.9
Cl	Cl				43.8	43.4	41.0
Cl		Cl			43.1	43.4	44.1
Cl			Cl		43.8	44.1	42.5
	Cl	Cl			47.0	46.7	45.6
	Cl		Cl		47.8	47.4	44.2
Cl		Cl	Cl	3 Cl (*erythro-9-PtCl$_2$*)	36.3	36.5	36.3
Cl	Cl		Cl		39.5	39.3	36.4
Cl	Cl	Cl			39.6	39.3	38.2
	Cl	Cl	Cl		40.2	40.1	38.3
Cl	Cl	Cl	Cl	4 Cl (*meso-1-PtCl$_2$*)	32.4	32.2	31.8
Cl	F	Cl		2 Cl, 1 F (*erythro-8-PtI$_2$*)	39.6	38.1	38.1
F		Cl	Cl		39.6	39.2	38.5
F	Cl	Cl			40.3	40.9	39.0
Cl	F		Cl		40.6	40.9	36.4
F	Cl		Cl		40.9	41.6	37.2
Cl	Cl		F		42.0	43.1	38.5
Cl	Cl	F			42.2	42.9	39.4
	F	Cl	Cl		42.6	42.4	39.5
Cl	F	Cl	Cl	3 Cl, 1 F	28.2	28.0	26.2
Cl	Cl	Cl	F		29.3	28.2	27.0
F	Cl	Cl	Cl		28.9	28.4	27.1
Cl	Cl	F	Cl		28.3	28.7	26.3
Cl	F	F	Cl	2 Cl, 2 F	24.6	24.6	22.0
Cl	F	Cl	F		24.2	24.0	22.7
F	Cl	Cl	F		25.1	24.2	23.7
F	F	Cl	Cl		24.8	24.8	23.0
F	Cl	F	Cl		25.4	25.0	23.0
Cl	Cl	F	F		25.6	25.0	23.2

Table 4. MMX energies (kcal·mol^{-1}) of (*R,S/S,R*)-λ, (*R,S/S,R*)-δ and (*S,S*)-λ of [1,2-*bis*(2,6-dihalo-3-hydroxyphenyl)ethylenediamine]PtL_2 ($L_1 = SO_4^{2-}, L_2 = H_2O$) with different positions of the halo substituents in the phenyl rings (2 and 6); halo = Cl and F

Substituents and positions				Compound OH position	(*R,S/S,R*)-λ (*meso*)	(*R,S/S,R*)-δ (*meso*)	(*S,S*)-λ (–)
in the axial ring		in the equatorial ring					
2′	6′	2″	6″				
Cl	Cl	Cl	Cl	*meso-1-PtSO$_4$* 4	32.1	32.3	30.7
Cl	Cl	Cl	Cl	*meso-1-PtSO$_4$* 3, 5	39.9	39.5	38.0
Cl	F	F	Cl	*meso-2-PtSO$_4$*	31.3	30.8	29.2
F	Cl	Cl	F	*meso-3-PtSO$_4$* 3, 5	31.9	31.4	31.2
F	F	F	F	*meso-4-PtSO$_4$* 3, 5	24.0	23.7	23.2

group from position 4 to 3 the calculated energies for the three conformers of *meso-1-PtSO$_4$* increased by 7 kcal·mol^{-1} (*i.e.*, the compound has decreased antitumor activity). However, the substitution of two Cl atoms with two F atoms lowers the calculated energies by 8 kcal·mol^{-1} (this compound has significant antitumor activity). Further substitution of all Cl atoms with F atoms lowers the obtained energy by 6 kcal·mol^{-1}. Thus, among all the studied substituent combinations, the (*R,S/S,R*) conformers of *meso-4-PtSO$_4$* (four F atoms in positions 2 and 6 and OH in positions 3 and 5 exhibit the lowest energy (24.0 and 23.2 kcal·mol^{-1}), and they have significant antitumor activity. The (*S,S*)-λ conformer has also low energy, but antitumor activity for this conformer was not observed. This has been explained previously in terms of two factors: (*a*) the spacial location of the two N atoms, which is different from that in the (*R,S/S,R*) conformers, and (*b*) the lack of flexibility in the five-membered chelate ring which hinders the approach of the two Ph rings as in the (*R,S/S,R*) series [7]. This fact, however, cannot be explained in terms of the calculated energies.

Conclusions

The type and the positions of the ring substituents alter the calculated conformational energies (thermodynamic stabilities) of the studied compounds in agreement with their antitumor activity. In general, the substitution of hydrogen atoms in the aromatic rings with Cl or F leads to a lowering of the conformational energies and an increase of the antitumor activity.

For the (*S,S*)-λ conformers where both rings are oriented equatorially, the substituent positions are of minor importance for the calculated energies and structures of the complexes. In general, Cl (F) substituents in positions 2 and 6 and OH groups in position 4 of the phenyl rings are preferred.

For both (*R,S/S,R*) conformers, the substituents in the equatorially oriented aromatic ring are also of minor importance for the structure and conformational energies. Conversely, the substituents in the axial aromatic ring of the (*R,S/S,R*) conformers alter the calculated energies. The 6′-position (in the axial ring) is not preferred for the OH group (when other substituents are absent); the obtained energies are higher as compared with the case when the OH is directed away from the N-Pt-N plane (in position 2′). When Cl (F) substituents are also present, the calculated conformational energies depend on the number and the positions of the Cl or F atoms.

(*R,S/S,R*) and (*S,S*)-λ differ significantly in energy ($\sim 2\,\text{kcal} \cdot \text{mol}^{-1}$) when there is a substituent in the axial ring in position 6′. When position 6′ is not substituted, (*R,S/S,R*) and (*S,S*)-λ conformers do not differ in energy.

The obtained energies compare well with experimental data for structure, reactivity, and antitumor activity of the studied compounds. The obtained energy orders explain the different antitumor activity observed for *meso-1-PtL*$_2$, *meso-2-PtL*$_2$, *meso-3-PtL*$_2$, *meso-4-PtL*$_2$, *erythro-9-PtL*$_2$, and *erythro-8-PtL*$_2$. The substituent variations which decrease the MM energy of the compounds increase their antitumor activity.

Materials and Methods

Molecular mechanics is now a well-established technique in the field of inorganic chemistry, and it has successfully been applied to many coordination compounds to predict and rationalize the conformational behaviour of different metal complexes [25–34] as well as for modelling of a number of Pt(II) compounds used as anticancer drugs [35].

We have used the standard MMX (an enhanced version of MMP2) procedure with the parameters collected in its 1988 version [36]. The calculated MM energies are used to access the relative stability of the studied conformers as suggested elsewhere [37]. Repeated calculations with the same geometry but with different bond lengths and angles gave reproducible results from which one might guess that the MM energies are correct to $\pm 0.1\,\text{kcal} \cdot \text{mol}^{-1}$ within errors in the bond lengths of ± 0.01 Å and valence angles of $\pm 1°$.

In some cases, namely for cisplatin and its substituted ethylenediamine derivative, MM calculations, which ignore explicity the electronic factors, gave lower energies for the tetrahedral structures than for the planar ones [22]. To calculate the geometry of the higher energy square-planar structures by the MM method in such cases, we fixed the ligand donor atoms in a plane [22]. This fixing implicitly takes into account the electronic factor.

The geometry of *erythro-8-PtI*$_2$ and *erythro-9-PtI*$_2$ was optimized starting with available X-ray diffraction data for Pt-N, Pt-I bond lengths and I-Pt-I, N-Pt-N bond angles (Table 5) [18]. The other geometry parameters do not differ significantly from those included in the MM database. In those cases where X-ray data are not available, Pt-L bond lengths and L-Pt-L and N-Pt-N bond angles close to those of *erythro-9-PtI*$_2$ were used in the geometry optimization. This assumption seems to be reasonable since the selection of X-ray diffraction data shows that these parameters vary only slightly for the studied complexes. Furthermore, we compare the calculated energies for different conformers of one compound with different substituents in the phenyl rings. The complexes were modelled by restraining Pt in the plane of the ligand donor atoms. For *erythro-8-PtI*$_2$ and *erythro-9-PtI*$_2$, the calculated bond lengths and bond angles are compared with the experimental values in Table 5. Within the constraints used in the calculations, the experimental bond lengths and bond angles were reproduced quite well by MM calculations (Table 5).

Table 5. MMX energies (kcal·mol^{-1}) and selected structural parameters (calculated and experimental for *(−)-3-PtCl$_2$*, *meso-3-PtCl$_2$*, *erythro-8-PtI$_2$*, and *erythro-9-PtI$_2$*

	erythro-8-PtI$_2$ (*R,S/S,R*)-*δ*)		*erythro-9-PtI$_2$* (*R,S/S,R*)-*λ*)		(−)-3-PtCl$_2$. (*S,S*)-*λ*)		*meso-3-PtCl$_2$* (*R,S/S,R*)-*δ*)	
	Calc. (this work)	Exp. [21]	Calc. (this work)	Exp. [21]	Calc. (this work)	Exp. [16]	Calc. (this work)	Exp. [16]
MMXE	74.4		71.8		48.6		49.1	
r(Pt-L_1) (Å)	2.566	2.566	2.584	2.583	2.313	2.34[1] 2.29[2]	2.314	2.295
r(Pt-L_2) (Å)	2.579	2.574	2.586	2.586	2.314	2.32[1] 2.28[2]	2.317	2.316
r(Pt-N_1) (Å)	2.078	2.09	2.123	2.05	2.136	2.00[1] 2.09[2]	2.18	2.13
r(Pt-N_2) (Å)	2.115	1.95	2.167	2.08	2.12	1.99[1] 2.07[2]	2.09	2.01
L_1PtL_2(°)	94.64	94.15	94.39	94.59	89.73	89.29[1] 94.82[2]	90.71	92.43
N_1PtN_2 (°)	82.73	82.1	81.50	82.1	80.64	86.46[1] 83.04[2]	82.69	81.24
L_1PtN_1 (°)	93.04	93.70	93.14	91.9	91.87	92.14[1] 92.06[2]	96.42	93.25
L_2PtN_2 (°)	89.58	90.0	90.97	90.2	97.48	92.04[1] 90.08[2]	90.05	93.29
L_1PtN_2 (°)	175.73	175.5	174.51	175.1	176.55	–	176.35	–
L_2PtN_1 (°)	172.24	171.8	172.47	173.1	171.14	–	172.53	–
$N_1C_1C_2N_2$ (°)	54.35	51.90	−50.53	−51.50	46.09	58.0[1] 54.0[2]	53.10	49.0
$N_2PtN_1C_1$ (°)	19.46	17.79	−24.57	−12.45	17.62	10.0[1] 3.0[2]	31.77	20.0
$N_1PtN_2C_2$ (°)	10.01	12.35	12.21	16.37	−7.94	–	−4.76	–
$N_1C_1C_{11}C_{12}$ (°)	−146.62	−141.70	145.19	150.04	135.47	70.0[1] 57.0[2]	−156.43	139.0
$N_2C_2C_{21}C_{22}$ (°)	149.67	151.68	37.51	41.81	−44.98	−93.0[1] −111.0[2]	24.57	50.0
r(O-O) (Å)	8.40	8.10	8.27	7.80	3.68	3.77[1] 3.58[2]	3.66	4.01

[1,2] There are two molecules with different structures in the dimer (21); $**L$ = Cl for (−)-3-PtCl$_2$ and *meso-3-PtCl$_2$*, L = I for *erythro-8-PtI$_2$* and *erythro-9-PtI$_2$*

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