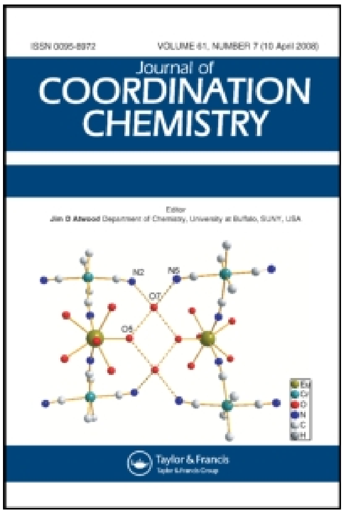

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BARRIERS TO INTERNAL ROTATION AND CONFORMATIONAL BEHAVIOUR OF THE *MESO* AND *D,L* ISOMERS OF Pt(II) COMPLEXES WITH ANTITUMOUR ACTIVITY

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The conformational behaviour of a series of ring substituted (*ortho*-Cl, F and *meta* or *para* OH) Pt(II) complexes of general formula [(1,2-hydroxyphenyl)ethylenediamine]PtL_2 [L = Cl, I] has been studied by molecular mechanics (MM) methods. Preferred orientations of the phenyl rings, which are important for the complexes' biological activity, were obtained by calculations of rotational energies about C_{sp3}–C_{ar} bonds for all theoretically possible isomers and conformers, *meso*-λ (*R,S/S,R*-λ), *meso*-δ (*R,S/S,R*-δ), *d,l*-λ (*S,S/R,R*-λ) and *d,l*-δ (*S,S/R, R*-δ). The influence of the ring substituents and the conformation type on the positions of the energy minima and barriers to rotations about C_{sp3}–C_{ar} and C_{ar}–O(H) bonds were investigated in detail. Theoretical predictions were compared with the experimental results where appropriate.

Keywords: Pt(II) complexes; molecular mechanics; rotational barriers

INTRODUCTION

Cis-$Pt(NH_3)_2Cl_2$ (cisplatin) was the first Pt(II) compound successfully tested on a large scale in tumour models.[1–4] Recently, analogues of cisplatin, designed by combination of the cytotoxic $PtCl_2$ group (the active moiety in cisplatin) with an estrogen-receptor-affinic diamine ligand have been investigated by Gust *et al.*[5–7] The biological activity of the Pt(II) complexes was

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[*] Corresponding author.

mainly determined by the structure of the diamine ligand, *i.e.*, ring substitution pattern, configuration and the type of conformation.[8–15]

In a previous study, we have shown[16,17] that the thermodynamic stability of (*R*,*S*)- and (*S*,*S*)-[1,2-bis(2-hydroxyphenyl)ethylenediamine]dichloroplatinum(II) (*meso*- and *d*,*l*-3-$PtCl_2$) correlates with the rates of their hydrolysis. Among the studied conformers, the lowest energy conformer, (*S*,*S*-λ), showed the highest rate of hydrolysis and highest antitumour activity.[16]

In another study we have shown that the type and the positions of the ring substituents as well as the ligand conformations alter the calculated conformational energies (thermodynamic stabilities) of the studied compounds in agreement with their antitumour activities.[18,19] It was shown that some of the tested compounds increased their activity significantly by exchange of the substituent positions or by replacing Cl with F.[8] Since no explanation of these effects was given, we decided to investigate further all combinations of substituents used as well as their possible positions in the phenyl rings. Previously, we presented only results for the conformers with OH in *ortho* positions and in *para* positions but in combination with Cl and F substituents. Meanwhile, new results on the biological activity of the complexes studied were reported indicating that the positions of the OH groups are very important for the biological activity of the complexes studied.[20] Thus, we decided to investigate all positions of the OH substituents in the phenyl rings as well as all theoretically possible combinations with other substituents in the phenyl rings. Further, rotational energies of the C_{sp3}–C_{ar} and C_{ar}–O(H) bonds of a series of Pt(II) complexes of the general formula [(1,2-hydroxyphenyl)ethylenediamine]PtL_2 [L = Cl, I] were investigated to obtain the most stable conformations for the studied compounds. The rotational energies of the C_{sp3}–C_{ar} and C_{ar}–O(H) bonds were calculated as a function of the dihedral angles H–C_{sp3}–C_{ar}–C_{ar} and C_{ar}–C_{ar}–O–H, respectively, from 0° to 360°, with 10° increments.

Computational Procedure

Molecular mechanics has successfully been applied to many Pt(II) compounds to study their conformational behaviour.[21–31] In this paper we have used the standard MMX (an enhanced version of MMP2) procedure.[32] To improve the MM force field, available X-ray data for Pt–N, Pt–Cl bond lengths and Cl–Pt–Cl, N–Pt–N bond angles were used during the optimisation procedure. All other geometry parameters, obtained from the X-ray analysis, were in agreement with those included in the MM database.

The calculated MM energies were used to access the relative stability of the studied conformers as suggested elsewhere.[33]

RESULTS AND DISCUSSION

The studied Pt(II) complexes are given in Figures 1 and 2: (i) four *meso* isomers (*S*,*R*/*R*,*S*-λ) and (*S*,*R*/*R*,*S*-δ), Figure 1a and b; (ii) four *d*,*l* isomers (*R*,*R*/*S*,*S*-λ) and (*R*,*R*/*S*,*S*-δ), Figure 2a and b. Since the dimeric structure of the studied compounds hinders biaxial orientation of the phenyl rings (Figure 2b) the *d*,*l*-δ conformers were never observed experimentally.[34] These conformers are not discussed in this study. In order to obtain the preferred orientations of the phenyl rings and of the H atoms in the OH groups (Figure 3) the rotational energies, E_{rot}, about C_{sp3}–C_{ar} and C_{ar}–O(H) bonds were calculated for all complexes, starting always from the optimised geometry ($E_{rot} = 0.0$ kcal mol^{-1}).[†] The calculated MM energies of the conformers studied are given in Table I.

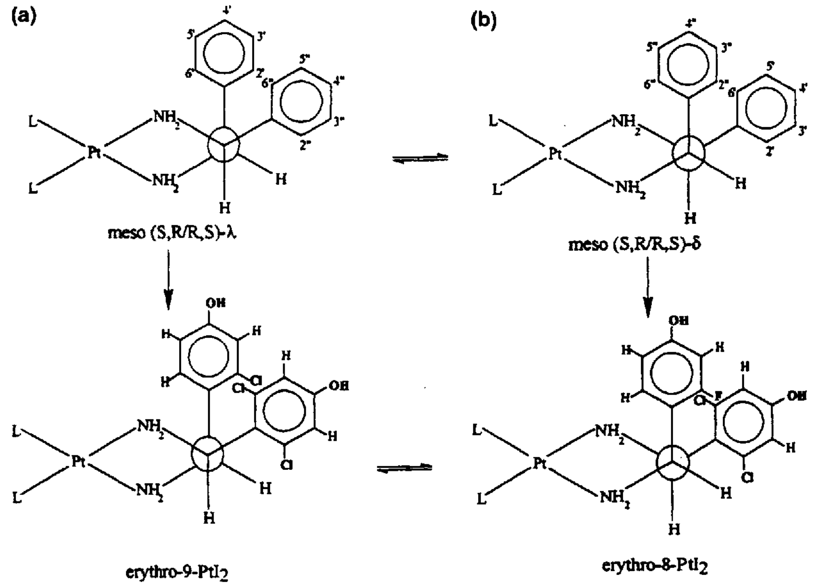

FIGURE 1 *Meso* (*S*,*R*/*R*,*S*) conformations (λ and δ) for the studied compounds with numbering of the substituent positions in the phenyl rings.

[†] 1 cal = 4.184 J.

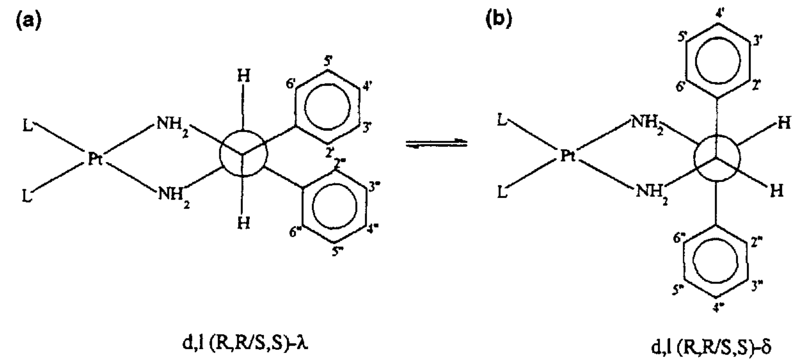

FIGURE 2 The *d,l* conformations (λ and δ) for the studied compounds with numbering of the substituent positions in the phenyl rings.

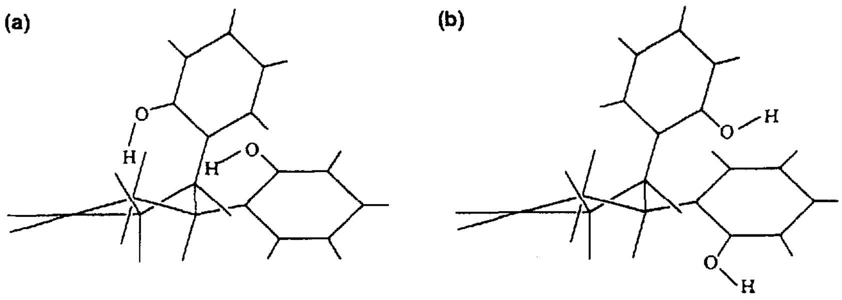

FIGURE 3 Possible orientations of the hydrogen atoms in the OH groups for the *meso* (*S,R*) conformers: (a) H atoms are directed to the N–Pt–N plane; (b) H atoms are turned away from the N–Pt–N plane.

OH Substituents in the Phenyl Rings

OH Substituents in Ortho *Positions of the Phenyl Rings*

For the studied *meso*-λ conformers, the rotations about C_{sp3}–C_{ar} bonds of the axial (OH in 2′) and the equatorial ring (OH in 2″) show second higher energy minima at ~ 180°, Figures 4b and 5b. These correlations refer to the case when H is away from the N–Pt–N plane (Figure 3b). The second minimum corresponds to the higher energy conformers with OH in 6′ and 6″ positions. Obviously, the 6 position, both in axial and equatorial rings, is less favourable, in *meso* conformers 1, 2 in Table I. The rotation about C_{sp3}–C_{ar} bonds of the *ortho* OH substituted phenyl rings is unfavourable

TABLE I Calculated MM energies (kcal mol^{-1}) of some *meso*-λ and *d,l*-λ conformers[1]

No.	*Substituents*		*meso* (*S*,*R*)-λ[2]	*d,l* (*R*,*R*)-λ[2]
1	2′-OH (H-away)[3]	2″-OH (H-away)	47.7	48.0
2	6′-OH (H-away)	2″-OH (H-away)	51.4-1(H) bond	48.5-1(H) bond (solid state)
3	2′-OH (H-away)	6′-OH (H-away)	47.8-1(H) bond	48.3-1(H) bond
4	2′-OH (H-away)	6″-OH (H-to)[4]	49.0-1(H) bond (solid state)	48.1-1(H) bond
5	6′-OH (H-away)	6″-OH (H-to)	52.3-2(H) bonds (solution)	48.2-2(H) bonds (solution)
6	6′-OH (H-away)	6″-OH (H-away)	52.2-2(H) bonds	48.3-2(H) bonds
7	6′-OH (H-to)	6″-OH (H-to)	48.4-1(H) bond	48.8-2(H) bonds
8	3′-OH (H-away)	3″-OH (H-away)	50.1	50.8
9	5′-OH (H-away)	5″-OH (H-away)	51.1	51.0
10	5′-OH (H-to)	5″-OH (H-away)	50.6	50.8
11	4″-OH	4′-OH	51.9	51.5
	1 Cl			
12	5′-OH (H-to)	2″-Cl, 5′-OH	82.8	82.7
13	6′-Cl, 5′-OH (H-away)	5″-OH (H-to)	90.7	87.0
14	6′-Cl, 5′-OH (H-to)	5″-OH (H-to)	89.4	86.1
15	2′-Cl, 5′-OH (H-away)	3″-OH (H-to)	83.1	82.7
16	2′-Cl, 3′-OH (H-to)	5″-OH (H-to)	85.1	84.9
17	6′-Cl, 3′-OH (H-away)	5″-OH	86.5	83.9
18	2′-Cl, 4′-OH	4″-OH	82.3	82.2
19	6′-Cl, 4′-OH	4″-OH	86.7	84.5
20	4′-OH	2″-Cl, 4″-OH	82.6	82.2
21	4′-OH	6″-Cl, 4″-OH	84.1	83.4
	2 Cl			
22	2′-Cl, 5′-OH	2″-Cl, 5″-OH	78.8	78.9
23	6′-Cl, 3′-OH	6″-Cl, 3″-OH	84.1	82.1
24	2′-Cl, 3′-OH	2″-Cl, 3″-OH	83.9	83.9
25	6′-Cl, 5′-OH	6″-Cl, 5″-OH	88.3	86.2
26	2′-Cl, 6′-Cl, 5′-OH	5″-OH	82.1	79.6
27	5′-OH	2″-Cl, 6″-Cl, 5″-OH	80.1	79.7
28	2′-Cl, 4′-OH	2″-Cl, 4″-OH	78.0	77.7
29	6′-Cl, 4′-OH	6″-Cl, 4″-OH	82.2	80.6
30	2′-Cl, 6′-Cl, 4′-OH	4″-OH	78.1	76.3
31	4′-OH	2″-Cl, 6″-Cl, 4″-OH	76.7	76.1
	3 Cl			
32	6′-Cl, 5′-OH	2″-Cl, 6″-Cl, 3″-OH	82.2	79.8
33	2′-Cl, 5′-OH	2″-Cl, 6″-Cl, 3″-OH	75.4	75.9
34	2′-Cl, 4′-OH	2″-Cl, 6″-Cl, 3″-OH	71.8 (solid state)	71.8
35	6′-Cl, 4′-OH	2″-Cl, 6″-Cl, 4″-OH	76.1	73.3
36	2′-Cl, 6′-Cl, 4′-OH	2″-Cl, 4″-OH	74.9	71.8
37	2′-Cl, 6′-Cl, 4′-OH	6″-Cl, 4″-OH	75.1	73.4
	4 Cl			
38	2′-Cl, 6′-Cl, 5′-OH	2″-Cl, 6″-Cl, 3″-OH	74.0	73.1
39	2′-Cl, 6′-Cl, 4′-OH	2″-Cl, 6″-Cl, 4″-OH	67.6	65.9

[1] Only results for *meso* (*S*,*R*)-λ (Figure 1a) and *d,l* (*R*,*R*)-λ (Figure 2a) are presented in the table. The notations ′ and ″ correspond to the notations given in Figures 1 and 2. [2] The results obtained for *meso* (*R*,*S*)-λ and *meso* (*S*,*R*/*R*,*S*)-δ showed the same trends as *meso* (*S*,*R*)-λ and they are not presented in the table; *d,l*-δ conformers were not considered in this study since these conformations were not experimentally obtained (see text). [3] H(O) atom is turned away from the N–Pt–N plane. [4] H(O) atom is directed to the N–Pt–N plane.

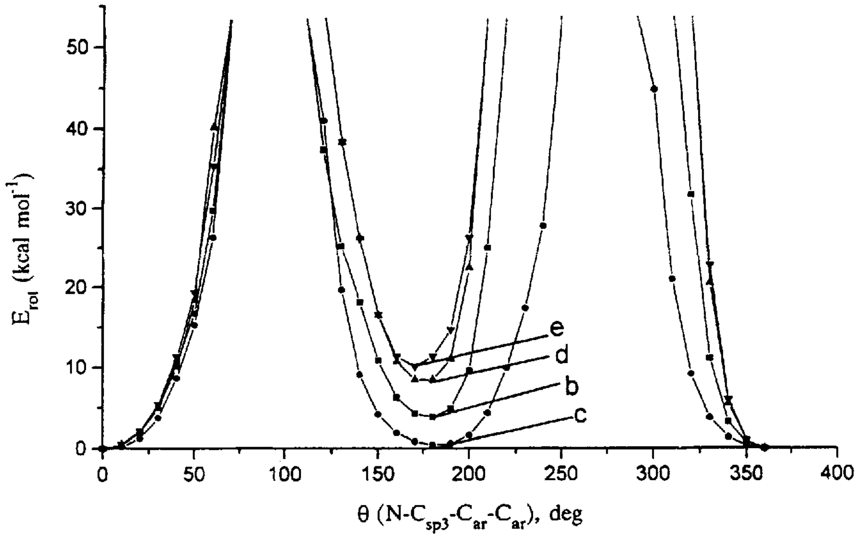

FIGURE 4 Calculated rotational energies (kcal mol^{-1}) by rotation about C_{sp3}–C_{ar} bonds of the axial ring for *meso* (*S*,*R*)-λ conformers: b – OH in the 6′ position (H is away); c – OH in the 5′ position (H is away); d – OH in the 4′ position, Cl in the 6′ position; e – OH in the 5′ position, Cl in the 6′ position.

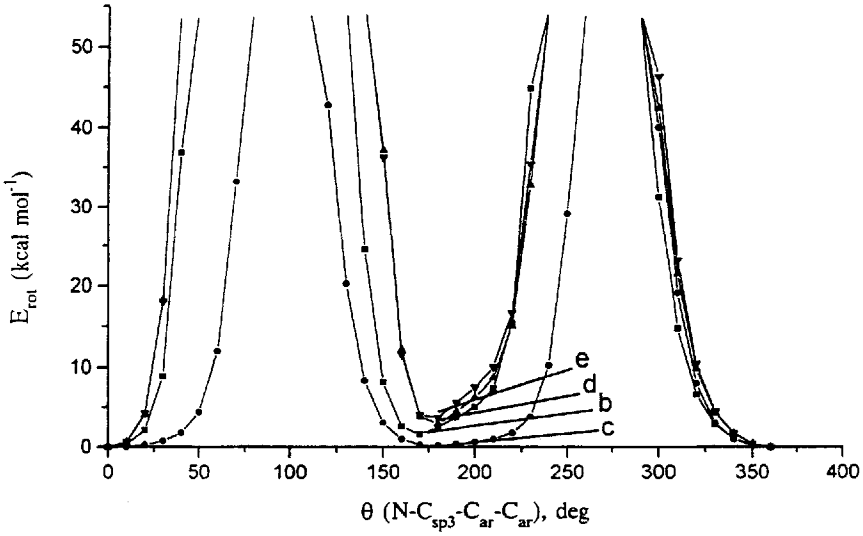

FIGURE 5 Calculated rotational energies (kcal mol^{-1}) by rotation about C_{sp3}–C_{ar} bonds of the equatorial ring for *meso* (*S*,*R*)-λ conformers: b – OH in the 6″ position (H is away); c – OH in the 5″ position (H is away); d – OH in the 4″ position, Cl in the 6″ position; e – OH in the 5″ position, Cl in the 6″ position.

since the calculated rotational barriers are very high (> 100 kcal mol^{-1}). As seen from Table I, among all *ortho* positions of the OH, the combination 2′ and 2″ (*meso* conformer 1) is with the lowest MM energy, 47.7 kcal mol^{-1}. From the other side, our MM calculations showed that when OH groups are in 6′ or 6″ positions intramolecular hydrogen bonds from the amino proton to the phenolic oxygen (N)H ··· O(H) are possible and these bonds stabilise the obtained structures (*meso* conformer 3, Table I). X-ray diffraction data confirmed the presence of one hydrogen bond ((N)H ··· O(H)-6″) for *meso*-3-$PtCl_2$ (OH in 2′ and 6″ positions), but the orientation of the H atom was not assigned.[34] According to our calculations, the H atom is directed to the N–Pt–N plane since the calculated N ··· O distance in the equatorial ring, 2.812 Å, is in agreement with the experimental value, 2.813 Å (*meso* conformer 4, Table I). In solution, two hydrogen bonds were detected experimentally for *meso*-3-$PtCl_2$.[34] This is the conformer with OH in 6′ (H is turned away from the N–Pt–N plane) and 6″ (H is directed to the N–Pt–N plane), (*meso* conformer 5, Table I).

The calculated rotational energies of the C_{ar}–O bond for the *meso* conformers showed the following trends. When the OH groups are in 2′ or 2″ positions, the H(O) atoms prefer to be oriented away from the N–Pt–N plane, Figure 3b. The energy of the second higher minimum at 180° is low ~ 1.6 kcal mol^{-1}. In the case, when OH is located in the 6″ position in the equatorial ring, the H(O) atom prefers again an orientation away from the N–Pt–N plane but the energy of the second minimum, obtained at ~ 180°, is higher, 3.2 kcal mol^{-1}. These are the *meso* conformers 3 and 4 in Table I. The most interesting case is when the OH group occupies the 6′ position in the axial ring. In this position, the H(O) atom prefers an orientation to the N–Pt–N plane, Figure 3a, and *meso* conformer 7 in Table I. The second minimum is the highest in this series, ~ 5 kcal mol^{-1}, Figure 6c. The orientation of the H(O) atom away from the N–Pt–N plane, when OH takes the 6′ position, increases the calculated MM energy by ~ 4 kcal mol^{-1}, *meso* conformers 7 and 5 in Table I. Our calculations show that when the H atom is directed to the N–Pt–N plane, the hydrogen bond, (N)H ··· O(H)-6′ is impossible due to the increased distance between the (H)O and $H(NH_2)$. In general, the obtained barriers of rotation about C_{ar}–O(H) bonds are much lower (5–10 kcal mol^{-1}) compared with those by rotation about C_{sp3}–C_{ar} bonds. Thus, free rotation about the C_{ar}–O(H) bond could be possible.

For *d,l*-λ conformers the rotations about C_{sp3}–C_{ar} and C_{ar}–O(H) bonds of both equatorial rings of the conformers showed also second minima at ~ 180° with low energies ~ 1–1.5 kcal mol^{-1} and the results are similar to those obtained for the equatorial ring of the *meso* conformers (Figure 5b).

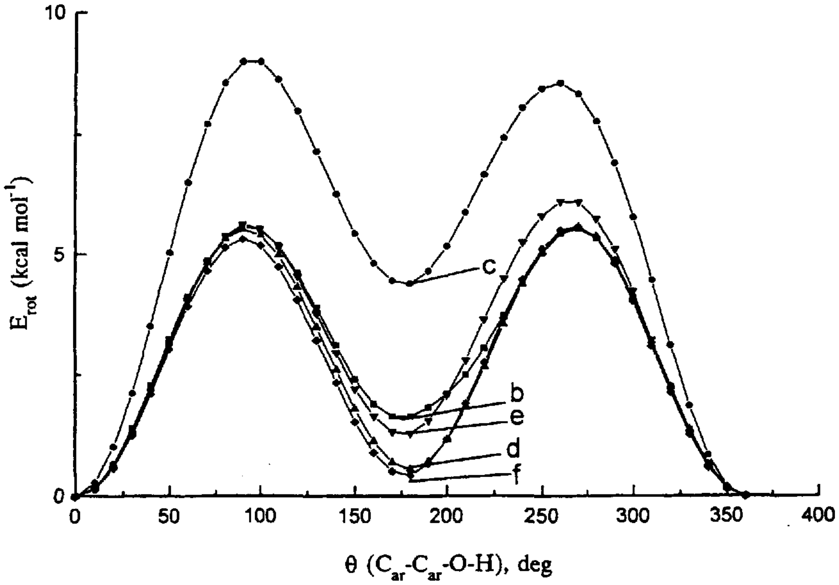

FIGURE 6 Calculated rotational energies (kcal mol^{-1}) by rotation about C_{ar}–O(H) bonds for *meso* (*S*,*R*)-λ conformers: b – OH in the 2′ position, H is directed to the N–Pt–N plane; c – OH in the 6′ position, H is turned away from the N–Pt–N plane; d – OH in the 5′ position, H is turned away from the N–Pt–N plane; e – OH in the 5′ position, Cl in the 6′ position, H is away from Cl; f – OH in the 3′ position, Cl in the 2′ position, H is away from Cl.

The calculated MM energies of the studied *d,l* conformers vary slightly (*d,l* conformers 1–7, Table I). The 2 and 6 positions of the equatorial rings of the *d,l*-λ conformers are not equivalent (Figure 2a). When OH groups are in 2′ and 2″ positions, the *d,l*-λ conformer has the lowest MM energy among all the *d,l* conformers (48.0 kcal mol^{-1}). Although the 6′ and 6″ positions are less favourable, the corresponding conformers showed approximately the same MM energy, 48.2 kcal mol^{-1}. In this case, additional stabilisation of the *d,l* conformers is possible by two N–H···O hydrogen bonds, which were obtained for these structures in solution.[34] In the solid state, two (N)H···O(H) hydrogen bonds were detected for the *d,l*-λ conformer (6′, 2″-OH).[34] Our MM calculations showed only one, with OH in the 6′ position, *d,l* conformer 2 in Table I. The other H-bond was obtained only by rotation of the second ring (with OH in the 2″ position) about the C_{sp3}–C_{ar} bond. However, the conformer thus obtained is not a minimum structure.

OH Substituents in Meta *or* Para *Position of the Phenyl Rings*

When both OH substituents are in *meta* (3 or 5) positions, their orientations do not influence significantly the calculated MM energies since the substituents are relatively far from the N–Pt–N plane and the NH_2 groups (*meso* and *d,l* conformers 8, 9, 10 in Table I). As seen from Figures 4, 5 and 6, by rotation about C_{sp3}–C_{ar} and C_{ar}–O bonds the calculated rotational minima have relatively low energies, 0.1–0.5 kcal mol^{-1} for C_{sp3}–C_{ar} (Figures 4c and 5c) and 0.04–1 kcal mol^{-1} for C_{ar}–O (Figure 6d). The orientation of the H(O) atom, when both OH groups are in *para* (4) positions, does not alter the calculated energies of the studied conformers. However, both *meta* and *para* positions for the OH substituents are very important for biological activity when halo substituents are introduced in *ortho* positions of the phenyl rings. These complexes will be considered in the next section.

OH and Halo Substituents in the Phenyl Rings

The conformational behaviour of the complexes was studied for Pt(II) complexes with leaving group I. X-ray data are available for two conformers, *erythro*-8-PtI_2 and *erythro*-9-PtI_2 in the studied series of compounds. Our previous study has shown that the type of the leaving group (Cl^-, I^- or SO_4^{2-}) is of minor importance for the calculated order of conformational energies.[18] Thus, the obtained correlations could be transferred for the complexes with different leaving groups.

OH Substituents in Meta *or* Para *Position and One Cl in* Ortho *Position*

The most interesting features were obtained for the studied *meso* conformers by rotation of the axial ring. Conformers with Cl in the 2′ position (*meso* conformers 15, 16 and 18) of the axial ring are with lower energies as compared with the conformers with Cl in the 6′ position (*meso* conformers 17, 14 and 19). The higher energy conformers (those with Cl in the 6′ position) were obtained by rotation about the C_{sp3}–C_{ar} bond and they correspond to the second higher minimum of E_{rot} shown in Figure 4e (OH in *meta* positions) and 4d (OH in *para* positions), 10 and 8.5 kcal mol^{-1}. Obviously, the 6′ position for Cl is less favourable. The preferred position for the Cl atom in the equatorial ring is 2″. The rotation of the equatorial ring of *meso* conformers shows also a second minimum but it is of lower energy, 3.8 kcal mol^{-1} (OH in *meta* positions, Figure 5e) and 3 kcal mol^{-1} (OH in *para* positions, Figure 5d). Similar trends were obtained by rotation of both equatorial rings of the *d,l* conformers. When the OH substituents are in *meta* positions and thus close to the *ortho* Cl substituents, the obtained MM energies are higher in comparison with the conformers in which Cl and OH are far from each other, *meso* and *d,l* conformers 13 and 17, 15 and 16. The orientation of the H atom alters the calculated MM energies only when Cl and OH substituents are neighbours. In this case the H atom prefers to be directed to the Cl atom. This influence is stronger when the Cl and OH substituents are in 6′ and 5′ positions in the axial ring, *meso* conformers 13 and 14.

OH Substituents in Meta *or* Para *Position and Two* Ortho *Cl Substituents*

Some new trends were obtained for this group of compounds. When both *ortho* Cl substituents are in one phenyl ring, the calculated MM energies are lower in comparison with the cases when they are in different rings (*meso* and *d,l* conformers 26, 27 compared with 23, 24, 25; also, 30, 31 compared with 28, 29). In all cases, when both *ortho* Cl substituents are in the equatorial ring (2″,6″), the conformers have lower MM energies in comparison with the conformers with two Cl substituents in the axial phenyl ring (2′,6′), (*meso* conformers 27 and 26, 31 and 30). As we mentioned above, the 6″ position is unfavourable for the Cl atom. However, when both Cl atoms are in the equatorial ring (2″,6″) and OH in the 4″ position, the calculated energy of the *meso* conformer is lower, 76.7 kcal mol^{-1}, as compared even with the conformer with the most preferred positions of the phenyl rings (2′,2″), 78.0 kcal mol^{-1}. The same trends were observed for the axial ring. When both Cl atoms are in *ortho* positions (2′,6′) and OH in the 4′ position of the axial ring, the conformer energy is close to the energy of the conformer with the most preferred positions for Cl atoms (2′,2″), 78.1 and 78.0 kcal mol^{-1}. As seen from Table I the conformers with both *ortho* Cl substituents in one phenyl ring and OH in a *para* position have lower MM energies in comparison with the same conformers with OH in the *meta* position (*meso* and *d,l* conformers 30, 31, and 26, 27).

OH Substituents in Meta *or* Para *Position and Three* Ortho *X (X = Cl, F) Substituents in the Phenyl Rings (*Erythro*-9-PtI$_2$ and* Erythro*-8-PtI$_2$)*

The complexes with three Cl atoms and OH substituents in *para* positions have been studied in detail and their structures and antitumour activities are well known.[14] The most favourable positions for Cl substituents, 2″, 6″ in the equatorial ring and 2′ in the axial ring, combined with OH groups in *para* positions, were observed for *erythro*-9-PtI$_2$ (see Figure 1). Our calculations showed that this is the compound with the lowest MM energy

(71.8 kcal mol^{-1}) among all the studied conformers of this group, *meso* conformers 32–37. At the same time, namely *erythro*-9-PtI$_2$ (Figure 1) showed high estrogen activity against breast cancer.[14] Obviously, the lowest energy conformer (the most stable one) has the highest antitumour activity. This correlation was obtained once again when another compound with high estrogen activity (*erythro*-8-PtI$_2$, Figure 1) was theoretically studied. When the Cl atom in the axial ring is substituted with F (*erythro*-8-PtI$_2$) the calculated MM energies are also relatively low.[18,19]

OH Substituents in **Meta** *or* **Para** *Position and Four* **Ortho** *X (X = Cl, F)*

Our calculations have shown that the calculated MM energy correlates with the number of *ortho* Cl substituents in the phenyl rings, the lowest MM energy was obtained for four Cl atoms in the phenyl rings (see Table I). The *meso* conformer with four *ortho* Cl substituents and OH in *para* positions (leaving group I), as well as the *meso* conformer with four *ortho* F and OH in *meta* positions (leaving group SO$_4$) have shown significant antitumour activities.[14] Thus, the lowest energy conformers (the most stable ones) were obtained experimentally and revealed the highest antitumour activity. The *meso*-λ and *d,l*-λ conformers with OH in *para* positions and four Cl substituents showed lower MM energy, 67.6 and 65.9 kcal mol^{-1} in comparison with the same conformers with OH in *meta* positions, 74.0 and 73.1 kcal mol^{-1}.

CONCLUSIONS

By rotation about C$_{sp3}$–C$_{ar}$ and C$_{ar}$–O bonds, all conformers have one minimum at the starting (optimised) geometry and the second one at ~180°. The second minima are of higher energy, 1–12 kcal mol^{-1} and 0.1–5.5, respectively. For the complexes with only OH substituents the lowest energy conformers were obtained when OH are in *ortho* positions. Hydrogen bonds, when possible, decrease the energy of the conformers with substituents in unfavourable positions. The calculated MM energy correlates with the number of the *ortho*-halo (Cl, F) ring substituents, the bigger the number of the halo substituents, the lower calculated MM energies. The 2′ or 2″ positions in the phenyl rings are the most preferred for the *ortho* Cl substituents. The location of both *ortho* Cl substituents in one phenyl ring is preferred. Experimental data for absolute conformations of *erythro*-8-PtI$_2$ and *erythro*-9-PtI$_2$ confirmed the theoretically obtained structures with the lowest energy. The shift of the OH groups from *para* to *meta* positions increased the calculated MM energies by $\sim 1.5-3\,\mathrm{kcal\,mol^{-1}}$. The orientation of H atom of the OH group is important when OH is in the 6′ position in the axial ring. The H(O) atom prefers to be directed to the N–Pt–N plane. Rotation about $C_{sp3}-C_{ar}$ bonds is unfavourable since the rotational barriers are very high ($> 100\,\mathrm{kcal\,mol^{-1}}$). The obtained barriers to rotation about the C_{ar}–O(H) bonds are low, $\sim 5-10\,\mathrm{kcal\,mol^{-1}}$ and thus free rotation about this bond could be supposed.

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