MOLECULAR STRUCTURE AND BONDING IN PLATINUM–PICOLINE ANTICANCER COMPLEX: DENSITY FUNCTIONAL STUDY

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Danuta Michalska dedicates this paper to Professor Rudolf Zahradník on the occasion of his 75th birthday, with deep gratefulness for his help and support.

Density functional study has been performed for a new anticancer agent, *cis*-[$PtCl_2(NH_3)$(2-picoline)] (**1**), AMD473, now clinically tested. The molecular structure, natural charges, orbital occupancies, vibrational frequencies and metal–ligand stretching force constants were calculated using the modified Perdew–Wang functional (mPW1PW) with the combined D95V(d,p) and LANL2DZ basis set. For comparison, analogous calculations were performed for: *cis*-[$PtCl_2(NH_3)$(3-picoline)] (**2**), *cis*-[$PtCl_2(NH_3)$(pyridine)] (**3**) and cisplatin. The interesting structural feature of **1** is almost perpendicular orientation of the 2-picoline ligand with respect to the molecular plane. In the remaining complexes, **2** and **3**, the tilt of the pyridine ring is smaller. The position of the methyl group in **1** introduces steric hindrance to an axial approach of the Pt metal. The natural bond analysis (NBO) has provided detailed insight into the electronic donor–acceptor interactions within the platinum coordination sphere. The results clearly indicate that the Pt–N(py) bond is stronger than Pt–NH_3 bond, and the Pt–Cl bond *trans* to 2-picoline is weaker than the *cis* Pt–Cl bond. Thus, both the trans effect of the 2-picoline ligand and a steric hindrance of Pt in **1** can be of key importance in the different mode of binding of this drug to DNA, in comparison with cisplatin.

Keywords: Platinum anticancer agents; *cis*-[$PtCl_2(NH_3)$(2-picoline)]; Cisplatin; AMD473; Trans effect; Structure–reactivity relationship; DFT calculations; *Ab initio* calculations.

The discovery of the antitumor activity of cisplatin (*cis*-diamminedichloroplatinum(II), *cis*-[$PtCl_2(NH_3)_2$]) by Rosenberg[1] has initiated very intensive search for new platinum-centered chemotherapeutic agents with lower toxicity and better activity. Recently, efforts have been undertaken to rationally design new Pt complexes, on the basis of an improved understanding of the mechanism of Pt drug resistance[2–5]. One approach to overcome cisplatin resistance is the preparation of drugs that bind to DNA in a

structurally different way compared to cisplatin[6]. It is known already that this requirement can be reached by using non-ammonia ligands. As the results of these efforts, the new sterically hindered anticancer complex containing 2-picoline (2-methylpyridine) ligand has been discovered: *cis*-[$PtCl_2(NH_3)$(2-picoline)], AMD473 (also called JM473 or ZD473)[2,7–11]. Now, this compound undergoes clinical tests. It has been shown that AMD473 possesses remarkable activity against Pt-resistant cell lines. Recently, it has been discovered that AMD473 possesses an additional desirable property of being orally active against clinical tumor models[2]. Furthermore, AMD473 is less reactive than cisplatin towards the sulfur-containing substances, including glutathione[9]. In reaction with DNA, it has a slower rate of reaction than cisplatin, though it eventually platinates DNA to the same extent as cisplatin. It is interesting that the DNA-binding properties of AMD473 differ from those of cisplatin and several unique DNA-AMD473 adducts have been observed[10]. Sadler and coworkers[11] reported the X-ray crystal structures of *cis*-[$PtCl_2(NH_3)$(2-picoline)] and its 3-picoline (3-methylpyridine) analogue, and determined the hydrolysis rates for chloride ligands in these complexes.

In this work, we have performed a thorough density functional study on *cis*-[$PtCl_2(NH_3)$(2-picoline)], which is illustrated in Fig. 1. For comparison, calculations were also performed for similar complexes containing 3-picoline and pyridine ligands, and cisplatin, using the density functional theory (DFT) with the modified Perdew–Wang functional, mPW1PW [12,13]. It has been reported that this DFT protocol yields very good results for covalent and long-range noncovalent interactions in molecules[12]. In our earlier work on cisplatin and carboplatin we have shown that the mPW1PW func-

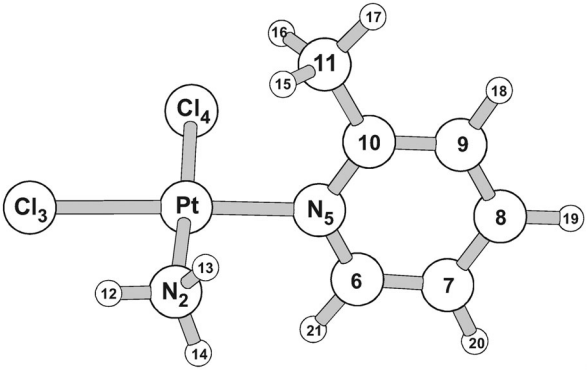

FIG. 1
The calculated molecular structure and atom numbering in *cis*-[$PtCl_2(NH_3)$(2-picoline)] (**1**)

tional is clearly superior to other density functional methods (including B3LYP) in a simultaneous prediction of both the geometry and vibrational frequencies of platinum(II) complexes[14]. Calculations performed for the isolated molecules, at the same level of theory, can provide a detailed insight into the intrinsic differences in the structure and bonding in the investigated Pt(II) complexes.

THEORETICAL METHODS

Full geometry optimization and frequency calculations have been performed for the complexes **1**–**3** and cisplatin, using the DFT(mPW1PW) method[12]. This is the Becke-style one parameter functional coupled with the modified Perdew–Wang exchange and correlation functionals[13]. The computations were performed using the D95V(d,p) basis set for N and H atoms[15]. This basis set yielded good results in our previous calculations of the nitrogen heterocyclic compounds[16,17]. To account for the relativistic effects in Pt, the *ab initio* effective core potential, LANL2DZ of Hay and Wadt[18] was applied. The normal coordinate analyses (NCA) were carried out, according to the procedure described in our previous studies[17]. From NCA the potential energy distributions (PEDs) and internal force constants were obtained. The calculated PED provided a clear-cut assignment of the platinum–ligand frequencies (the complete results from vibrational analyses of complexes **1**–**3** will be published elsewhere). The atomic charges and the nature of electronic interactions in these complexes were studied by natural bond orbital (NBO) analysis[19]. All calculations have been performed with the Gaussian 98 package[20].

RESULTS AND DISCUSSION

Molecular Structures

Figure 1 shows the optimized structure and the numbering of atoms of *cis*-[$PtCl_2(NH_3)$(2-picoline)] (**1**). Table I compares the theoretical geometrical parameters of **1** with those of *cis*-[$PtCl_2(NH_3)$(3-picoline)] (**2**), *cis*-[$PtCl_2(NH_3)$(pyridine)] (**3**) and cisplatin, calculated at the same level of theory.

According to calculations, the two chlorine atoms and two nitrogen atoms are in a square-planar configuration around platinum in **1**, **2**, **3** and cisplatin. As follows from Table I, the Pt–N2 (ammonia) bond length is approximately the same in all the investigated complexes. However, the

TABLE I
Comparison of atom distances (in Å) and bond angles (in °) in *cis*-[$PtCl_2(NH_3)Am$] complexes, where Am = 2-picoline (**1**), 3-picoline (**2**), pyridine (**3**), and in cisplatin

Bonds and angles	**1**	**2**	**3**	**Cisplatin**
Pt–N2	2.083	2.082	2.083	2.079
Pt–Cl3	2.390	2.392	2.391	2.385
Pt–Cl4	2.380	2.376	2.376	2.385
Pt–N5	2.039	2.031	2.031	
N5–C10	1.354	1.348	1.347	
N5–C6	1.347	1.344	1.346	
C6–C7	1.386	1.389	1.389	
C7–C8	1.395	1.393	1.395	
C8–C9	1.391	1.399	1.393	
C9–C10	1.399	1.395	1.391	
$C–CH_3$[a]	1.495	1.503		
C11–H15	1.094	1.092		
C11–H16	1.095	1.092		
C11–H17	1.092	1.094		
N2–H12	1.025	1.025	1.026	1.027
N2–H13[b]	1.017	1.017	1.017	1.017
N–Pt–N	95.8	95.6	95.7	98.8
Cl–Pt–Cl	94.6	94.2	94.2	96.0
Cl3–Pt–N2	82.9	82.7	82.7	82.5
C10–N5–C6	119.9	119.0	118.9	
N5–C6–C7	122.8	121.8	122.4	
C6–C7–C8	118.3	119.1	118.9	
C7–C8–C9	118.7	119.6	118.5	
C8–C9–C10	120.6	117.5	119.4	
C9–C10–N5	119.8	123.0	121.9	
C10–N5–Pt–N2	104.4	126.8	126.6	
C6–N5–Pt–N2	–80.2	–55.5	–55.9	
Pt···H15–C11	89.8			

[a] The methyl group at carbon C10 in **1** (or at carbon C9 in **2**). [b] The same for N2–H14 bond.

Pt–Cl3 bond (*trans* to the coordinated pyridine ring) becomes consistently longer (by 0.01–0.016 Å) than the *cis* Pt–Cl4 bond in **1**, **2** and **3**. This indicates that the picoline (and pyridine) ligand coordinated to platinum elongates the Pt–Cl bond *trans* to the ring and simultaneously shortens the *cis* Pt–Cl bond. We have obtained similar results in calculations at the MP2 level of theory[21]; however, the MP2-calculated bond lengths are longer than those obtained by the mPW1PW method, and longer than experimental[11].

The calculated Pt–N5(py) bond length in complexes **1**, **2** and **3** is shorter (by about 0.04–0.06 Å) than the Pt–NH_3 bond. These results are supported by the X-ray data. It should be noted, however, that strong intermolecular hydrogen bonding in crystal can obscure the intrinsic differences in the bond lengths of two Pt–N (or Pt–Cl) bonds. For example, according to the X-ray crystal structure of **1**, the Pt–Cl3 bond is shorter (by about 0.02 Å) than Pt–Cl4 bond, which is just opposite to the theoretical results. This discrepancy is probably caused by the different strength of N2–H···Cl4′ and N2–H···Cl3′ hydrogen bonds between the neighboring molecules in crystal, as indicated by the different N2–H···Cl interatomic distances ranging from 2.55 to 2.74 Å [11].

The interesting structural feature of **1** is almost perpendicular orientation of the 2-picoline ligand with respect to the molecular plane. According to calculations, the C10–N5–Pt–N2 dihedral angle is equal to 104.4°. This is in very good agreement with the experimentally determined angle between the pyridine ring and the Pt square plane, 102.7° [11]. In the remaining complexes, **2** and **3**, the tilt of the pyridine ring is smaller, as indicated by the C6–N5–Pt–N2 angle of about –56°. This value is also supported by the experiment (the angle of 48.9° between the pyridine and $PtCl_2N_2$ planes in **2**)[11].

Of particular importance is the fact that the 2-methyl group in **1** is placed over the square coordination plane: the Pt···C11 distance is equal 3.18 Å, while the Pt···H15 distance is 2.99 Å. This introduces steric hindrance to an axial approach of the Pt metal from above and it may have an important impact on the biological activity of **1**.

A weak electrostatic interaction is noted between the H12 atom of the ammonia ligand and the neighboring Cl3 chlorine atom. As is shown in Table I, the N2–H12 bond (lying in the molecular plane and pointing towards Cl3) is slightly longer than the out-of-plane N–H bonds, by about 0.008–0.01 Å, in all the Pt complexes.

Natural Charges and NBO Occupancies

The NBO analyses of the investigated platinum(II) complexes have provided interesting details on the electronic interactions within the coordination sphere. Table II lists the natural atomic charges obtained from NBO analysis of the investigated Pt(II) complexes. Recently, we have shown for aniline (structurally similar to pyridine ligands) that the natural charges are consistent with chemical properties of this molecule (*ortho*- and *para*-directing power of the NH_2 group in electrophilic substitutions), whereas Mulliken charges are not reliable[22]. Therefore, in this study only the natural charges have been considered.

As follows from Table II, the polarity of the Pt–N2 (ammonia) bond in the investigated complexes is very similar. However, the N5(py) atom in complexes **1**–**3** has a smaller negative charge (–0.5 e) than the N2 (ammo-

TABLE II
Natural charges (in e) in *cis*-[$PtCl_2(NH_3)$Am] complexes, where Am = 2-picoline (**1**), 3-picoline (**2**), pyridine (**3**), and in cisplatin

Atom	**1**	**2**	**3**	**Cisplatin**
Pt	0.605	0.619	0.618	0.591
N2	–1.067	–1.070	–1.070	–1.078
Cl3	–0.530	–0.529	–0.526	–0.516
Cl4	–0.513	–0.509	–0.507	–0.516
N5	–0.542	–0.521	–0.528	
C6	0.097	0.073	0.082	
C7	–0.254	–0.239	–0.247	
C8	–0.153	–0.169	–0.162	
C9	–0.249	–0.029	–0.240	
C10	0.311	0.091	0.101	
C11	–0.682	–0.652		
H12	0.442	0.443	0.443	0.444
H13	0.426	0.427	0.428	0.428
H14	0.425	0.423	0.423	0.428
H15	0.241	0.233		
H16	0.277	0.234		
H17	0.227	0.230		

nia) nitrogen atom (–1.07 e). Furthermore, it is evident that the Pt–Cl3 bond (*trans* to the Pt–N5(py) bond) is slightly more polarized than Pt–Cl4 bond (*cis*).

As revealed by NBO analysis, the occupancy in the Pt–Cl3 σ antibonding orbital (σ^*_{PtCl3}) is higher, by 0.023 e than occupancy in the σ^*_{PtCl4} orbital. It should be noted that increase in electron density (occupancy) in the antibonding acceptor orbital can be directly correlated with a weakening of the bond associated with this orbital[19]. On the basis of these results it can be concluded that the Pt–Cl3 bond is weaker than Pt–Cl4 bond.

In picoline and pyridine complexes, the dominant donor–acceptor interaction within the coordination sphere is the electron donation from the N5 nitrogen lone pair orbital, LP_{N5}, to the antibonding acceptor σ^*_{PtCl3} orbital, $LP_{N5} \rightarrow \sigma^*_{PtCl3}$. The LP_{N5} orbital has 77% p-character and is occupied by 1.67 electrons (which is consistent with significant delocalization of electron density from this orbital). It should be noted that in each complex, *trans* donor–acceptor interaction energy (estimated by the second order perturbation theory[19]) is larger for $LP_{N5} \rightarrow \sigma^*_{PtCl3}$ than for $LP_{N2} \rightarrow \sigma^*_{PtCl4}$. This indicates stronger *trans* interaction for pyridine nitrogen atom, relative to ammonia nitrogen.

We have noted quite a short distance (2.75 Å) between the chlorine Cl4 atom and the H16 atom from the methyl group, which suggests the presence of a weak electrostatic Cl4···H16 interaction in **1**. This conclusion is supported by a slight increase in occupancy in the antibonding σ^*_{C11H16} (to 0.013 e), as the result of a very weak $LP_{Cl4} \rightarrow \sigma^*_{C11H16}$ electron donation. This effect corresponds to a weakening of the C11–H16 bond.

Results from NBO analysis indicate also some interaction between the Cl3 atom and the in-plane hydrogen atom, H12. In **1**, the calculated occupancy in σ^*_{N2H12} orbital increases to 0.025 e, while occupancies in the remaining σ^*_{N2H} orbitals are only about 0.009 e. The $LP_{Cl3} \rightarrow \sigma^*_{N2H12}$ interaction causes an increase in electron density in the antibonding σ^*_{N2H12} orbital, which leads to slight elongation and weakening of the N2–H12 bond.

Metal–Ligand Stretching Vibrations

Table III lists the theoretical metal–ligand stretching frequencies and the corresponding stretching force constants derived from the normal coordinate analyses. These values can also be used as a measure of the relative strength of the metal–ligand bonds. As follows from comparison of the Pt–N2 stretching force constants, the strength of the Pt–NH_3 bond is almost the same in the investigated complexes. On the other hand, in **1**–**3** com-

plexes, the stretching force constant for Pt–N5(py) bond is higher than that for Pt–N2 (ammonia). It should be noted that the Pt–N5 bond is shorter than Pt–N2 (Table I). The calculated Pt–N5 and Pt–N2 bond lengths show a good correlation with the corresponding force constants (the shorter the bond, the higher the stretching force constant).

These results consistently indicate that the Pt–N(py) bond is stronger than Pt–NH_3. The strong binding of platinum to pyridine nitrogen atom weakens the binding of the Cl3 atom *trans* to the Pt–N(py) bond (trans effect). This is further confirmed by the fact that the ν(Pt–Cl3) stretching frequency is lower than ν(Pt–Cl4) stretching frequency (Table III).

It is interesting that these theoretical results are in good agreement with the experimentally determined hydrolysis rates for each chloride ligand in **1**. The rate of hydrolysis of the Cl^- *trans* to the ring is faster ($k_{1a} = 3.2 \times 10^{-5}$ s^{-1}) than for the Cl^- *cis* to the ring ($k_{1b} = 2.2 \times 10^{-5}$ s^{-1})[11]. However, it should be noted that the kinetic process (hydrolysis) depends also on the other factors (*e.g.*, temperature and ionic strength), as well as activation energy, while the theoretical results describe the intrinsic strength of the bonds in a ground state.

Thus, all the theoretical data consistently indicate that the Pt–Cl bond *trans* to the 2-picoline ligand is weaker than the *cis* Pt–Cl bond in **1**. The

TABLE III

Comparison of theoretical metal–ligand stretching frequencies (ν, cm^{-1}) and the corresponding force constants (*f*, 10^2 N m^{-1}) of *cis*-[$PtCl_2(NH_3)$Am] complexes, where Am = 2-picoline (**1**), 3-picoline (**2**), pyridine (**3**), and in cisplatin

ν/*f*	**1**	**2**	**3**	**Cisplatin**
ν(Pt–N2)	474	473	478/463[a]	475[b]
f(Pt–N2)	2.10	2.10	2.10	2.16
ν(Pt–N5)	232/199[a]	240	239	
f(Pt–N5)	2.28	2.33	2.33	
ν(Pt–Cl3)	333	333	333	340[b]
f(Pt–Cl3)	1.98	1.98	1.97	2.04
ν(Pt–Cl4)	342	344	346	340[b]
f(Pt–Cl4)	2.05	2.08	2.09	2.04

[a] Two normal modes involve Pt–N stretching vibration. [b] The average of the two (symmetric and antisymmetric) stretching frequencies.

trans Pt–Cl bond is slightly longer; it is more polarized; it has a higher occupancy in the antibonding σ*(Pt–Cl) orbital; and it has a slightly lower Pt–Cl stretching frequency, in comparison with the *cis* Pt–Cl bond. It can be concluded that both the trans effect of the 2-picoline ligand and the unique structural features of **1** (sterically hindered Pt atom) can be of key importance in the mechanism of dissociation of this drug, its reduced reactivity toward sulfur-containing nucleophiles, and its different mode of binding to DNA, compared with cisplatin.

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