Trans-influence of nitrogen- and sulfur-containing ligands in *trans*-platinum complexes: a density functional theory study

2009 J. Phys.: Condens. Matter 21 064210

(http://iopscience.iop.org/0953-8984/21/6/064210)

J. Phys.: Condens. Matter **21** (2009) 064210 (6pp) doi:10.1088/0953-8984/21/6/064210

Trans-influence of nitrogen- and sulfur-containing ligands in *trans*-platinum complexes: a density functional theory study

William W Manalastas Jr[1], Eben S Dy[2], Nikko P Quevada[1] and Hideaki Kasai

Department of Precision Science and Technology and Applied Physics, Osaka University, Suita, Osaka, 565-0871, Japan

E-mail: dy@dyn.ap.eng.osaka-u.ac.jp

Received 29 June 2008, in final form 4 August 2008
Published 20 January 2009
Online at stacks.iop.org/JPhysCM/21/064210

Abstract

Transplatin complexes with N- or S-containing ligands were modeled *in silico*. We performed density functional theory calculations using the B3LYP exchange–correlation functional as incorporated in the Gaussian03 software package. The 6-311+$G(d, p)$ basis set was used for first-row elements, and the LanL2DZ with effective core potential (ECP) basis set was used for platinum. The various neutral N- or S-containing ligands do not give rise to considerable variations in the *trans*-bond lengths and strengths. The reactions leading to complex formation also yield close net energy values. Nevertheless, Pt complexes with anionic thiolate (CH_3S^-) ligand are significantly more energetically stable by at least ∼5 eV (∼115 kcal mol^{-1} or ∼484 kJ mol^{-1}) compared to transplatin complexes with other ligands. An examination of the net energetic stabilities and dipole moments of transplatin complexes with N- and S-ligands led us to hypothesize adenine to be the most suitable candidate among naturally occurring organic ligands (X) for the development of *trans*-Pt(NR)(NR′)Cl(X) anticancer agent.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

The *trans*-influence in platinum (Pt) complexes refers to the effect of a ligand on another that is coordinated opposite to it (figure 1). It is a significant determinant of structure in square planar platinum-coordinate complexes and is quantifiable in terms of bond lengths, force constants and vibrational frequencies of the opposite ligand [1]. This *trans*-influence is a ground-state thermodynamic phenomenon [1, 2]. Structural properties of square planar *trans*-Pt complexes are important for catalysis [3], for understanding their structural–activity relationship (SAR) behavior as drugs [4], and for achieving some degree of control over their geometric parameters and stability [1, 3].

In anticancer applications, Pt accumulates in the cell and binds to intracellular DNA (usually through guanine) to stop cellular mitosis [4–6]. If the cell fails to repair the damage, apoptosis or cell death occurs [5, 6]. Traditionally, cancer researchers believed that only neutral *cis*-isomers (as opposed to *trans*-isomers) of Pt complexes have pharmacological action [6]. In fact, generations of *cis*-Pt drugs, such as cisplatin, carboplatin, nedaplatin and oxaliplatin, have been synthesized in an effort to improve cytotoxicity and delivery, while decreasing cell resistance, nephrotoxicity and neurotoxicity [6]. However, a Pt drug with superb selectivity and efficacy and with low side-effects remains to be discovered.

[1] On leave from: Chemistry Department, CENSER, De La Salle University-Manila, 2401 Taft Avenue, Manila 1004, Philippines.

[2] Author to whom any correspondence should be addressed.

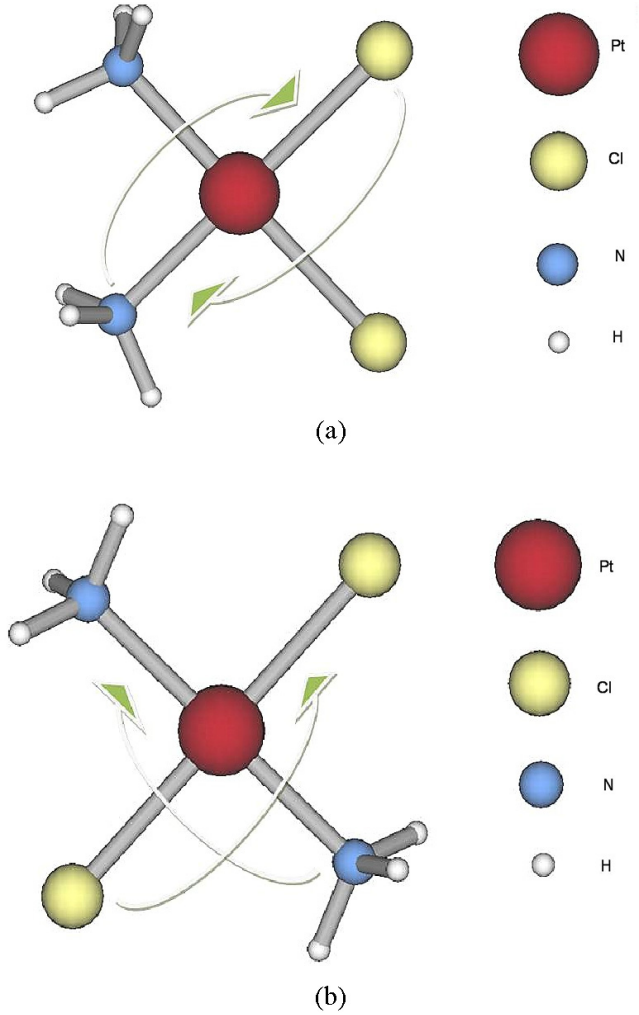

Figure 1. (a) Cisplatin (*cis*-diamminedichloroplatinum(II)). The *trans* influence is exerted by NH_3 on the Cl atom (see the direction of the arrow) and vice versa. (b) Transplatin (*trans*-diamminedichloroplatinum(II)). The *trans* influence is exerted by Cl on the opposite Cl atom (see the direction of the arrow) while that of NH_3 is exerted on the opposite NH_3.

Trans-$Pt(NH_3)_2Cl_2$, on the other hand, is experimentally known to be more unstable than its *cis*-isomer [7]. It reacts readily with non-target proteins (especially S-containing metallothionein and glutathione), and its impotency has been partly attributed to this phenomenon [5, 8, 9]. It has been proposed that antitumour properties of *trans*-complexes can be increased by using sterically hindering carrier ligands to reduce the rate of chloro-ligand replacement and restrict axial access to the Pt atom [10]. Furthermore, recent experimental findings have shown that certain *trans*-Pt complexes [6, 11–13] and UVA-photoactivated (400–315 nm) transplatin [14] yield improved cytotoxicities (lower IC_{50} values) against cisplatin-resistant cancer cell lines, and that certain modified *trans*-Pt complexes target and destroy specific S–Zn–S viral structures crucial in the HIV reproductive cycle [15]. Although there is no trans-Pt compound medically prescribed yet, intensive research for new *trans*-Pt medicinal concepts is ongoing. Of note, *trans*-$Pt(II)Cl_2$ complexes with aliphatic amine, iminoether, planar amine, carboxylate, piperidine, phosphine or pyridine-like carrier ligands are some modification examples that make transplatin anticancer-active [10–13].

Kapoor and Kakkar modeled different inorganic ligand elements in the complex $[PtClX(dms)_2]$ (dms = dimethylsulfide), where X is H_2O, NH_3, F^-, Cl^-, Br^-, I^-, H_2S, CH_3S^-, $C_6H_5^-$, H^-, SiH_3^-, AsH_3 and PH_3, and found correlations between the Pt–Cl(*trans* to X) bond length and ligand hardness, partial charge densities on the Pt and Cl atoms and their orbital populations [1]. Furthermore, the study suggests that geometry and the *trans*-influence are factors in determining kinetic lability [1, 16].

In this study, we inspect several structural and energetic trends of *trans*-platinum complexes having nitrogen- and sulfur-containing organic ligands to simulate the effects of biological ligands on square planar *trans*-Pt(II) complexes.

2. Calculations

We performed density functional theory calculations using the B3LYP exchange–correlation functional [17] as incorporated in the Gaussian03 software package [18]. The 6-311+$G(d, p)$ basis set was used for first-row elements, and the LanL2DZ [19–21] with effective core potential (ECP) basis set was used for platinum. B3LYP can reproduce thermodynamic trends computed at a higher level of theory (MP2) [3].

The structures of transplatin (figure 1(b)) and various Pt^{2+} complexes of the form $[Pt(NH_3)_2ClX]^{m+}$, where X is Cl^-, H_2O, NH_3, CH_3NH_2, CH_3NHCH_3, imidazole, guanine, adenine, H_2S, CH_3S^-, CH_3SH, and CH_3SCH_3, were optimized (see figures 2(a) and (b)). Here, m is 0 for $X = CH_3S^-$, and m is +1 for the other ligands. Next, we determined the optimized geometries for $[Pt(NH_3)_2(H_2O)X]^{n+}$ where $n = +1$ for X = CH_3S^- and $n = +2$ for the other ligands (see figures 2(a) and (c)). Note that in our complexes the two NH_3 ligands are positioned *trans* to each other.

Reaction energy, E_{rxn}, for the nucleophilic substitutions of the chlorine and H_2O by various X, and Pt–X bond dissociation energies (BDE; see figure 3) were determined for all the transplatin complexes. We used tight convergence criteria exclusively.

3. Results and discussion

All our systems were found to be singlet in the spin ground states. Our calculated geometric parameters and frequencies for transplatin (figure 1(b)) agree very well with experimental data collected in solvent-free solid phase, as shown in table 1.

We calculated the reaction energy, E_{rxn}, for the nucleophilic substitution of the Cl^- or H_2O by various X. E_{rxn} was computed by subtracting the total electronic energy of the reactants from those of the products ($\Delta E_{rxn} = \Sigma E_{products} - \Sigma E_{reactants}$) for the following reactions: replacement of Cl^- in transplatin by X to yield $Pt(NH_3)_2ClX$ (equation (1)), replacement of H_2O in monoaquated transplatin by X to yield $Pt(NH_3)_2ClX$ (equation (2)), replacement of Cl^- in monoaquated transplatin by X to yield $Pt(NH_3)_2(H_2O)X$

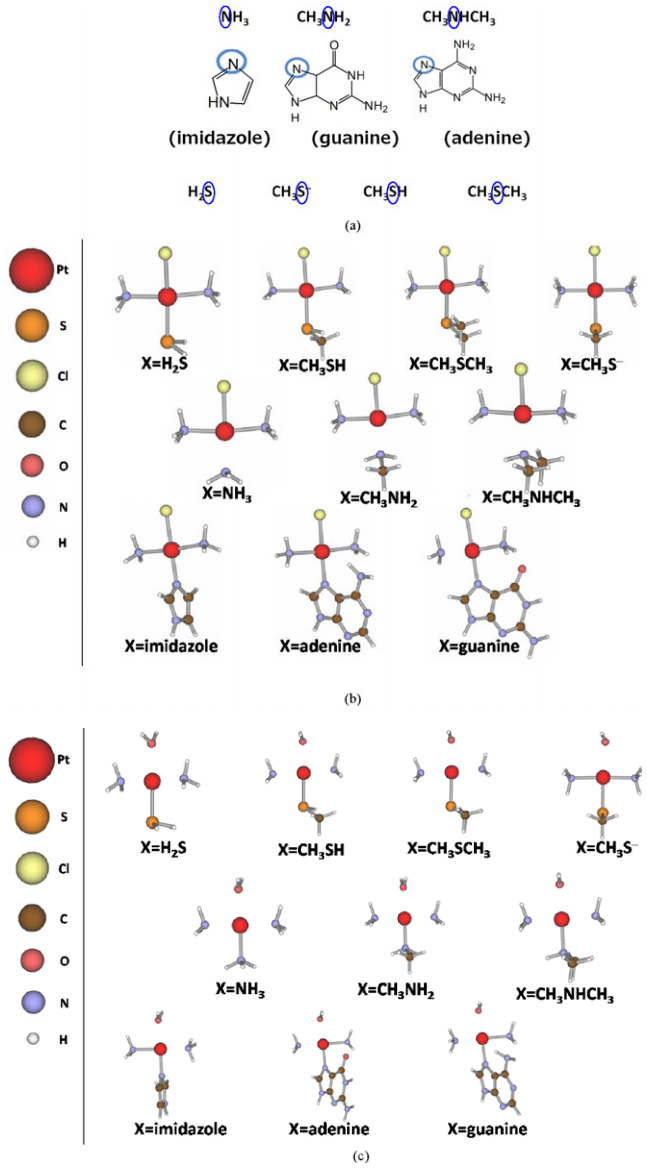

Figure 2. (a) The different ligands X in our study. The circles indicate the sites of Pt binding. (b) Optimized geometries for $Pt(NH_3)_2ClX]^{m+}$ complexes. (c) Optimized geometries for $[Pt(NH_3)_2(H_2O)X]^{n+}$ complexes.

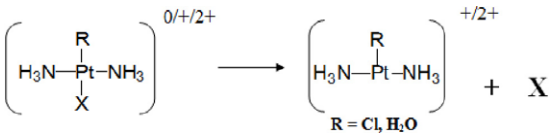

Figure 3. Reaction equation for bond dissociation energy (BDE). X stands for one of the ligands: NH_3, CH_3NH_2, CH_3NHCH_3, imidazole, guanine, adenine, H_2S, CH_3S^-, CH_3SH, or CH_3SCH_3. Bond dissociation energy is estimated by $E_{BD} = E_R + E_X - E_{RX}$, where R stands for $[Pt(NH_3)_2(Cl)]^+$ or $[Pt(NH_3)_2(H_2O)]^{2+}$.

(equation (3)) and replacement of H_2O in diaquated transplatin by X to yield $Pt(NH_3)_2(H_2O)X$ (equation (4)):

$$Pt(NH_3)_2Cl_2 + X \rightarrow Pt(NH_3)_2ClX + Cl^- \quad (1)$$

$$Pt(NH_3)_2Cl(H_2O) + X \rightarrow Pt(NH_3)_2ClX + H_2O \quad (2)$$

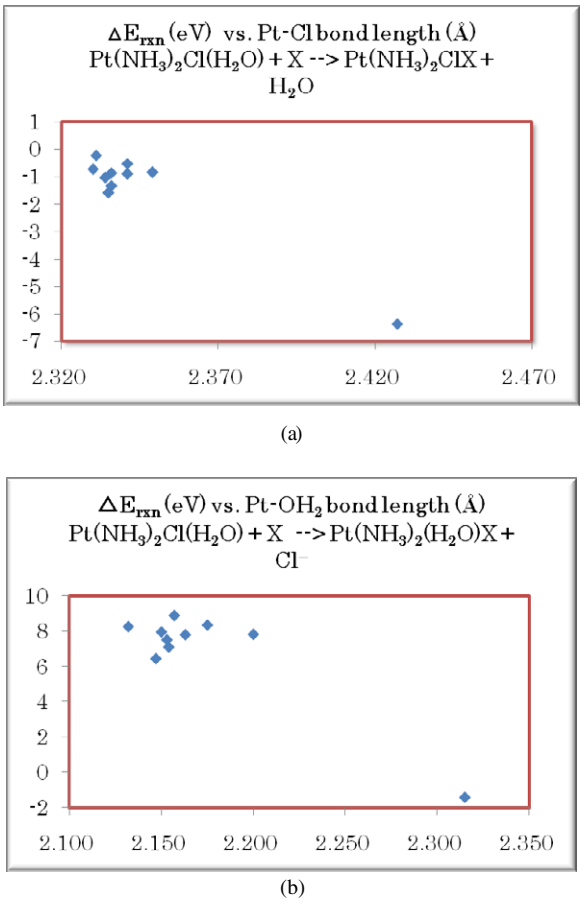

Figure 4. Ligands with similar *trans*-influences have similar ΔE_{rxn}.

$$Pt(NH_3)_2Cl(H_2O) + X \rightarrow Pt(NH_3)_2(H_2O)X + Cl^- \quad (3)$$

$$Pt(NH_3)_2(H_2O)_2 + X \rightarrow Pt(NH_3)_2(H_2O)X + H_2O. \quad (4)$$

As shown in tables 2 and 3, transplatin reaction with CH_3S^- is energetically most favored by at least ~5 eV (~115 kcal mol^{-1} or 484 kJ mol^{-1}) compared to our other ligands. This is a considerable net exoenergetic difference, which we attribute primarily to the greater covalent bond character, and thus greater energy release from bond formation, of the CH_3S–Pt bond. This probably explains the experimental observation that CH_3S^- is unlikely to be removed once bound to Pt even if other ligands become kinetically competitive [22–25].

The optimized *trans*-Pt complexes with CH_3S^- exhibit the smallest X–Pt–NH_3 angles (see table 4). Furthermore, we attempted transition state searches for reaction equations (1)–(4) (with entering/leaving ligands Cl^-, H_2O or CH_3S^- in axial and equatorial positions to achieve pentacoordination) via the synchronous transit-guided quasi-Newton method (STQN) as implemented in Gaussian03 [18], but were unable to successfully isolate one. These facts seem to suggest that for *trans*-$Pt(NH_3)_2(CH_3S)Cl$ or *trans*-$Pt(NH_3)_2(CH_3S)(H_2O)$ reactions a dissociative (S_N1) rather than an associative (S_N2) mechanism is preferred. In support of this, we examined the bond dissociation energies (BDEs; figure 3) for our complexes and found that Pt–Cl (table 5) and Pt–O (table 6) bonds *trans* to CH_3S–Pt were significantly lower (~3 eV; 0.98 eV) than others

Table 1. Comparison of transplatin geometry and frequency parameters with experimental solvent-free crystal x-ray results. Values are given in angstroms, degrees and cm^{-1}.

Transplatin geometry	Pt–N distance (Å)	Pt–Cl distance (Å)	N–Pt–Cl angle (deg.)	Pt–N vibrational freqs (cm^{-1})	Pt–Cl vibrational freqs (cm^{-1})
Current study (DFT, in vacuum)	2.074	2.378	89.37, 90.63	504	316
Experimental in solvent-free solid phase	2.05 ± 0.04 [a]	2.32 ± 0.01 [a]	89, 91	507[d] (509)[c]	(322)[b], 330[b], 331[c]
% Diff. with current method	1.12%	2.46%	0.41%, 0.40%	∼0.4%	∼1.8%

[a] Reference [28].
[b] Parentheses are used for shoulders. Reference [29].
[c] Reported as weak signals. Reference [30].
[d] Reported as very weak signal. Reference [31].

Table 2. Reaction energies for equation (1) ($Pt(NH_3)_2Cl_2 + X \rightarrow Pt(NH_3)_2ClX + Cl^-$) and equations (2) ($Pt(NH_3)_2Cl(H_2O) + X \rightarrow Pt(NH_3)_2ClX + H_2O$).

		$\Delta E_{rxn} = \Sigma E_{products} - \Sigma E_{reactants}$ in eV (kJ mol^{-1})	
Ligand (X)	Charge of complex	Equation (1) reaction treatment	Equation (2) reaction treatment
NH_3	1	4.691 (454.2)	−0.729 (−70.6)
CH_3NH_2	1	4.558 (441.4)	−0.862 (−83.4)
CH_3NHCH_3	1	4.521 (437.8)	−0.899 (−87.0)
Imidazole	1	4.089 (396.1)	−1.330 (−128.8)
Guanine	1	3.832 (371.0)	−1.588 (−153.8)
Adenine	1	4.377 (423.8)	−1.043 (−101.2)
H_2S	1	5.190 (502.6)	−0.230 (−22.2)
CH_3SH	1	4.894 (474.0)	−0.526 (−51.0)
CH_3SCH_3	1	4.569 (442.5)	−0.851 (−82.3)
CH_3S^-	0	−0.946 (−91.6)	−6.365 (−616.4)
H_2O	2	5.420 (524.9)	N/A

Table 3. Reaction energies for equation (3) ($Pt(NH_3)_2Cl(H_2O) + X \rightarrow Pt(NH_3)_2(H_2O)X + Cl^-$) and equation (4) ($Pt(NH_3)_2(H_2O)_2 + X \rightarrow Pt(NH_3)_2(H_2O)X + H_2O$).

		$\Delta E_{rxn} = \Sigma E_{products} - \Sigma E_{reactants}$ in eV (kJ mol^{-1})	
Ligand (X)	Charge of complex	Equation (3) reaction treatment	Equation (4) reaction treatment
NH_3	2	8.258 (799.4)	−1.126 (−109.0)
CH_3NH_2	2	7.951 (756.0)	−1.430 (−138.5)
CH_3NHCH_3	2	7.800 (755.3)	−1.582 (−153.2)
Imidazole	2	7.094 (686.9)	−2.288 (−221.6)
Guanine	2	6.440 (623.7)	−2.941 (−284.8)
Adenine	2	7.508 (727.1)	−1.873 (−181.4)
H_2S	2	8.882 (860.2)	−0.499 (−48.3)
CH_3SH	2	8.345 (808.1)	−1.037 (−100.4)
CH_3SCH_3	2	7.821 (757.4)	−1.561 (−151.1)
CH_3S^-	1	−1.415 (−137.1)	−10.797 (−1045.5)
H_2O	2	9.381 (908.5)	N/A

(∼10 eV; ∼2 eV) in the group (1.000 eV = 96.82 kJ mol^{-1}). Their vibration frequencies also have the same trend.

Overall, although neutral sulfur ligands exert slightly greater *trans*-influence than neutral nitrogen ligands, it appears that the differences are generally small (with a maximum of 0.02 Å for the Pt–Cl *trans* bond), while the Pt–OH_2 *trans* bond varies by as much as 0.07 Å (figure 4). The *trans*-influence is more pronounced in CH_3S–Pt complexes, with a Pt–Cl bond length ∼0.09 Å longer than those of other complexes (table 3) and a Pt–OH_2 bond length ∼0.15 Å longer than those of other complexes (table 4). Further, the values of transplatin ΔE_{rxn} (net resulting stability of final products) for neutral ligands, as with their *trans*-influences, do not vary as much compared to those of the anionic thiolate (CH_3S^-).

Solubility in polar solvents increases with dipole moment. The converse is true for non-polar environments. For platinum anticancer drugs, it is important to be able to cross non-polar cell membranes to reach biological targets (DNA). However, in medical practice, a practical level of solubility is required to be able to deliver drugs through blood plasma, which is mostly water. In light of the facts that instability in the presence of non-target proteins is one major factor causing transplatin inefficacy and that a drug must get to its target and react with it fast, the development of a *trans*-Pt(NR)(NR′)(Cl)(adenine) compound class is proposed.

There are two reasons behind this. First, for our model, $Pt(NH_3)_2(Cl)$ (adenine), the net total electronic energy stability achieved is higher than for most neutral nitrogen- or sulfur-containing ligands. However, it is lower than for guanine, our biological target. If we attach NR, NR′, and adenine (where NR and NR′ are bulky groups such as planar amines, iminoethers, etc *trans* to each other) [6] as ligands to Pt, binding to Pt by metallothionein or glutathione thiolate (CH_3S^-) in plasma medium would be more hindered. As such, adenine would be a possible chemoprotectant for Pt against sulfur ligands in solution.

Furthermore, drug effectivity depends on intracellular drug accumulation [26, 27]. Table 7 shows that adenine has the lowest dipole moment (7 debye) among our complexes (except for CH_3S^-). It should therefore be able to enter non-polar cellular membranes fastest. After this, hydrolysis to Pt(NR)(NR′) (H_2O) (adenine), with a dipole moment of 12 debye, should be able to prevent these molecules from crossing out of the membrane, thus generating an influx and buildup of the compound inside the cell.

Table 4. Angle parameters for Pt(II) complexes of the form $Pt(NH_3)_2Cl(X)$ and $Pt(NH_3)_2(H_2O)(X)$, where X refers to the varying ligands.

	$Pt(NH_3)_2Cl(X)$		$Pt(NH_3)_2(H_2O)(X)$	
X	$H_3N(1)$–Pt–X angle (deg)	$H_3N(2)$–Pt–X angle (deg)	$H_3N(1)$–Pt–X angle (deg)	$H_3N(2)$–Pt–X angle (deg)
NH_3	93.58	93.40	92.08	91.04
CH_3NH_2	93.58	93.58	91.79	91.52
CH_3NHCH_3	94.68	93.00	93.20	91.13
Imidazole	92.61	92.61	90.65	89.75
Guanine	93.30	92.64	91.84	89.56
Adenine	93.89	91.01	92.20	88.62
H_2S	96.53	90.67	95.44	88.59
CH_3SH	97.23	90.07	96.18	87.68
CH_3SCH_3	97.80	89.68	96.94	87.21
CH_3S^-	90.49	90.50	89.22	87.86
H_2O	96.03	88.10	93.59	86.41

Table 5. Bond dissociation energies for $Pt(NH_3)_2Cl(X)$.

	Bond dissociation energy in eV (kJ mol^{-1})			
Complex $[Pt(NH_3)_2XCl]^{m+}$	X + $[Pt(NH_3)_2Cl]^+$	Cl^- + $[Pt(NH_3)_2X]^+$	Pt–X vibrational frequency (cm^{-1}) (in complex)	Pt–Cl vibrational frequency (cm^{-1}) (in complex)
$[Pt(NH_3)_2Cl(H_2O)]^+$	1.338 (129.6)	11.895 (1151.9)	332.308	363.669
$[Pt(NH_3)_2Cl(NH_3)]^+$	2.067 (200.2)	11.160 (1080.7)	407.415	346.820
$[Pt(NH_3)_2Cl(CH_3NH_2)]^+$	2.199 (213.0)	10.833 (1049.1)	422.779	343.071
$[Pt(NH_3)_2Cl(CH_3NHCH_3)]^+$	2.236 (216.5)	10.589 (1025.4)	472.514	339.654
$[Pt(NH_3)_2Cl(imidazole)]^+$	2.668 (258.4)	10.360 (1003.3)	972.166	344.805
$[Pt(NH_3)_2Cl(guanine)]^+$	2.926 (283.4)	9.902 (958.91)	996.453	343.385
$[Pt(NH_3)_2Cl(adenine)]^+$	2.381 (230.6)	10.446 (1011.6)	997.812	347.858
$[Pt(NH_3)_2Cl(H_2S)]^+$	1.567 (151.7)	11.104 (1075.3)	254.982	341.537
$[Pt(NH_3)_2Cl(CH_3SH)]^+$	1.863 (180.4)	10.701 (1036.3)	276.940	336.830
$[Pt(NH_3)_2Cl(CH_3SCH_3)]^+$	2.188 (211.9)	10.369 (1004.1)	299.432	332.091
$[Pt(NH_3)_2Cl(CH_3S)]$	4.978 (482.1)	3.117 (301.85)	331.824	282.447

Table 6. Bond dissociation energies for $Pt(NH_3)_2(H_2O)(X)$.

	Bond dissociation energy (BDE) in eV (kJ mol^{-1})			
Complex $[Pt(NH_3)_2(H_2O)X]^{n+}$	X + $[Pt(NH_3)_2H_2O]^+$	H_2O + $[Pt(NH_3)_2X]^+$	Pt–X vibrational frequency (cm^{-1}) (in complex)	Pt–Cl vibrational frequency (cm^{-1}) (in complex)
$[Pt(NH_3)_2(OH_2)_2]^{2+}$	2.514 (243.5)	2.514 (243.5)	431.739	431.739
$[Pt(NH_3)_2(H_2O)(NH_3)]^{2+}$	3.640 (352.5)	2.175 (210.6)	491.608	389.647
$[Pt(NH_3)_2(H_2O)(CH_3NH_2)]^{2+}$	3.944 (381.9)	2.020 (195.6)	500.149	375.339
$[Pt(NH_3)_2(H_2O)(CH_3NHCH_3)]^{2+}$	4.096 (396.7)	1.890 (183.0)	527.387	361.120
$[Pt(NH_3)_2(H_2O)(imidazole)]^{2+}$	4.802 (465.0)	1.936 (187.5)	981.420	381.995
$[Pt(NH_3)_2(H_2O)(guanine)]^{2+}$	5.455 (528.3)	1.873 (181.4)	1190.200	374.713
$[Pt(NH_3)_2(H_2O)(adenine)]^{2+}$	4.387 (424.8)	1.895 (183.5)	1009.607	379.588
$[Pt(NH_3)_2(H_2O)(H_2S)]^{2+}$	3.006 (291.1)	1.985 (192.2)	304.375	368.035
$[Pt(NH_3)_2(H_2O)(CH_3SH)]^{2+}$	3.551 (343.9)	1.831 (177.3)	319.350	353.118
$[Pt(NH_3)_2(H_2O)(CH_3SCH_3)]^{2+}$	4.074 (394.5)	1.698 (164.4)	336.491	329.009
$[Pt(NH_3)_2(H_2O)(CH_3S)]^+$	13.311 (1289.0)	0.892 (86.4)	362.942	260.820

4. Conclusion

In summary, our calculations reveal that transplatin reaction with thiolates (CH_3S^-) results in the most energetically stable complexes among our sulfur- and nitrogen-containing ligands. Furthermore, we observed little variation in the net energetic stabilities, or in the *trans*-influences, corresponding to transplatin bond formation involving different neutral N- or S-containing ligands.

Trans-$Pt(NH_3)_2Cl_2$ is experimentally known to be kinetically more unstable than its *cis*-isomer [7]. It reacts readily with non-target proteins (especially S-containing such as metallothionein and glutathione), and its impotency has been partly attributed to this phenomenon [5, 8, 9]. A possible approach to *trans*-platinum anticancer design may then be to suppress platinum reactivity long enough for the molecule to reach a zone where its target biomolecules and its deactivators can compete evenly. An examination of the net energetic stabilities and dipole moments of transplatin complexes with

Table 7. Dipole moments of complexes.

	Dipole moments	
	In vacuum	In H_2O solvent ($\varepsilon = 80$)
$[Pt(NH_3)_2(H_2O)Cl]^{2+}$	7.35	10.08
$[Pt(NH_3)_2Cl(NH_3)]^{+}$	8.34	11.34
$[Pt(NH_3)_2Cl(CH_3NH_2)]^{+}$	8.06	10.72
$[Pt(NH_3)_2Cl(CH_3NHCH_3)]^{+}$	7.69	9.87
$[Pt(NH_3)_2Cl(imidazole)]^{+}$	9.88	12.65
$[Pt(NH_3)_2Cl(guanine)]^{+}$	11.17	14.29
$[Pt(NH_3)_2Cl(adenine)]^{+}$	**4.88**	**7.00**
$[Pt(NH_3)_2Cl(H_2S)]^{+}$	6.61	9.28
$[Pt(NH_3)_2Cl(CH_3S)]$	2.46	3.34
$[Pt(NH_3)_2Cl(CH_3SH)]^{+}$	7.01	9.41
$[Pt(NH_3)_2Cl(CH_3SCH_3)]^{+}$	7.16	9.08
$[Pt(NH_3)_2(OH_2)_2]^{2+}$	0.00	0.00
$[Pt(NH_3)_2(H_2O)(NH_3)]^{2+}$	0.76	0.79
$[Pt(NH_3)_2(H_2O)(CH_3NH_2)]^{2+}$	0.20	1.32
$[Pt(NH_3)_2(H_2O)(CH_3NHCH_3)]^{2+}$	0.81	2.26
$[Pt(NH_3)_2(H_2O)(imidazole)]^{2+}$	1.29	2.06
$[Pt(NH_3)_2(H_2O)(guanine)]^{2+}$	2.00	4.33
$[Pt(NH_3)_2(H_2O)(adenine)]^{2+}$	**7.72**	**12.54**
$[Pt(NH_3)_2(H_2O)(H_2S)]^{2+}$	1.25	2.12
$[Pt(NH_3)_2(H_2O)(CH_3S)]^{+}$	5.74	8.47
$[Pt(NH_3)_2(H_2O)(CH_3SH)]^{2+}$	1.39	2.67
$[Pt(NH_3)_2(H_2O)(CH_3SCH_3)]^{2+}$	1.39	3.32

N- and S-ligands led us to hypothesize adenine to be the most suitable candidate among naturally occurring organic ligands (X) for the development of *trans*-Pt(NR)(NR′)Cl(X) anticancer agent.

Acknowledgments

This work was partly supported by the Japan Student Services Organization (JASSO) through their Short-Term Students Exchange Promotion Program (Inbound) Scholarship. The calculations presented here were done using the computer facilities of the Cybermedia Center (Osaka University).

References

[1] Kapoor P N and Kakkar R 2004 *J. Mol. Struct. (Theochem.)* **679** 149
[2] Ochiai M, Sueda T, Miyamoto K, Kiprof P and Zhdankin V 2006 *Angew. Chem. Int. Edn* **45** 8203
[3] Harvey J N, Heslop K M, Orpen A G and Pringle P G 2003 *Chem. Commun.* 278
[4] Lau J K and Deubel D V 2005 *Chem. Eur. J.* **11** 2849
[5] Coluccia M and Natile G 2007 *Anti Cancer Agents Med. Chem.* **7** 111
[6] Perez J M, Fuertes M A, Alonso C and Navarro-Ranninger C 2000 *Crit. Rev. Oncol. Hematol.* **35** 109
[7] Knipp M, Karotki A V, Chesnov S, Natile G, Sadler P J, Brabec V and Vasak M 2007 *J. Med. Chem.* **50** 4075
[8] Mikola M and Arpalahti J 1994 *Inorg. Chem.* **33** 4439
[9] Peleg-Shulman T, Najajreh Y and Gibson D 2001 *J. Inorg. Biochem.* **91** 306
[10] Zakovska A, Novakova O, Balcarova Z, Bierbach U, Farrell N and Brabec V 1998 *Eur. J. Biochem.* **254** 547
[11] Kasparkova J, Novakova O, Marini V, Najajreh Y, Gibson D, Perez J-M and Brabec V 2003 *J. Biol. Chem.* **278** 47516
[12] Ramos-Lima F J, Quiroga A G, Serrelde B G, Blanco F, Carnero A and Ranninger C N 2007 *J. Med. Chem.* **50** 2194
[13] Ramos-Lima F J, Vrana O, Quiroga A G, Navarro-Ranninger C, Halamikova A, Rybnickova H, Hejmalova L and Brabec V 2006 *J. Med. Chem.* **49** 2640
[14] Heringova P, Woods J, Mackay F S, Kasparkova J, Sadler P J and Brabec V 2006 *J. Med. Chem.* **49** 7792
[15] Anzellotti A I, Liu Q, Bloemink M J, Scarsdale J N and Farrell N 2006 *Chem. Biol.* **13** 539
[16] Deubel D V 2004 *J. Am. Chem. Soc.* **126** 5999
[17] Becke A D 1993 *J. Chem. Phys.* **98** 5648
[18] Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Montgomery J A Jr, Vreven T, Kudin K N, Burant J C, Millam J M, Iyengar S S, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson G A, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox J E, Hratchian H P, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann R E, Yazyev O, Austin A J, Cammi R, Pomelli C, Ochterski J W, Ayala P Y, Morokuma K, Voth G A, Salvador P, Dannenberg J J, Zakrzewski V G, Dapprich S, Daniels A D, Strain M C, Farkas O, Malick D K, Rabuck A D, Raghavachari K, Foresman J B, Ortiz J V, Cui Q, Baboul A G, Clifford S, Cioslowski J, Stefanov B B, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin R L, Fox D J, Keith T, Al-Laham M A, Peng C Y, Nanayakkara A, Challacombe M, Gill P M W, Johnson B, Chen W, Wong M W, Gonzalez C and Pople J A 2004 *Gaussian 03, Revision C.02* (Wallingford, CT: Gaussian)
[19] Hay P J and Wadt W R 1985 *J. Chem. Phys.* **82** 270
[20] Wadt W R and Hay P J 1985 *J. Chem. Phys.* **82** 284
[21] Hay P J and Wadt W R 1985 *J. Chem. Phys.* **82** 299
[22] Barnham K J, Djuran M I, Murdoch P D-S, Ranford J D and Sadler P J 1995 *J. Chem. Soc. Dalton Trans.* **22** 3721
[23] Teuben J-M and Reeijk J 2000 *J. Biol. Inorg. Chem.* **5** 463
[24] Marchan V, Moreno V, Pedroso E and Grandas A 2001 *Chem. Eur. J.* **7** 808
[25] Hahn M, Kleine M and Sheldrick W S 2001 *J. Biol. Inorg. Chem.* **6** 556
[26] Brabec V and Kasparkova J 2002 *Drug Resist. Updates* **5** 147
[27] Wang D and Lippard S J 2005 *Nat. Rev. Drug Discov.* **4** 307
[28] Milburn G H W and Truter M R 1966 *J. Chem. Soc.* A 1609
[29] Nakamoto K, McCarthy P J, Fujita J, Condrate R A and Behnke G T 1965 *Inorg. Chem.* **4** 36
[30] Adams D M, Chatt J, Gerratt J and Westland A D 1964 *J. Chem. Soc.* A 734
[31] Powell D B 1956 *J. Chem. Soc.* 4495