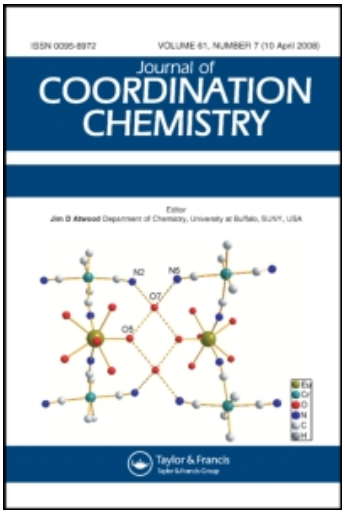

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FORCE FIELD CALCULATIONS OF ANTITUMOR PLATINUM(II) COMPLEX SYSTEMS

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FORCE FIELD CALCULATIONS OF ANTITUMOR PLATINUM(II) COMPLEX SYSTEMS

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Strain-energy minimization calculations of adducts of platinum(II) complexes containing 1,2-diaminocyclohexane (DACH) with the sequence d(pCpGpAp)·d(pGpCpTp) of a synthetic B-DNA were carried out by using a modification of the MM2 program. (C, G, A, T, and p denote cytidine, guanosine, adenosine, thymidine, and phosphate, respectively). In result, the more antitumor-active *trans*-DACH complex adducts are about 37 kJ/mol more stable than the *cis* complex in total energy.

Platinum-complex adducts of 2-(aminomethyl)cyclohexylamine abbreviated as AMCHA were also estimated. In calculations, the *trans*-AMCHA-complex adducts are about 6 to 14 kJ/mol more stable than the *cis* ones. The differences are less than between the DACH complexes. In addition, this relaxation of strain occurred in the six-membered ring.

KEYWORDS: calculations, Pt(II), antitumor, platinum drugs

INTRODUCTION

The antitumor activity of *cis*-DDP (*cis*-diamminedichloro-platinum(II); cisplatin) was first reported by Rosenberg, *et al.* in 1969.[1] In order to obtain platinum compounds with reduced toxicity and better efficacy than cisplatin, a large number of new platinum complexes have been synthesized and their antitumor activities have been tested.

The platinum complexes containing 1,2-diaminocyclohexane abbreviated as DACH (DACH has three isomeric structures, 1*R*, 2*R*(*l-trans*); 1*R*, 2*S* and/or 1*S*, 2*R*(*cis*); 1*S*, 2*S*(*d-trans*) as the non-leaving group have lower citotoxicity and lack cross-resistance[2–4] in comparison with *cis*-DDP. Interestingly, *trans* isomers are more efficacious than the corresponding *cis* isomer. Examination of molecular models shows that the cyclohexane ring of the *cis*-DACH complex is almost perpendicular to the chelate ring, while in the *trans*-DACH complexes, both rings are coplanar and adjacent to one another. From the structural point of view, if these

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complexes are linked to a DNA fragment, the *cis*-DACH complex will be more hindered sterically than the *trans* analogues.

In the present report, we carried out strain-energy minimization calculations of adducts of these isomeric-ligand complexes with the sequence d(pCp*G*pAp)d(pG-pCpTp) of a synthetic B-DNA[5] by using a modification of the MM2 program, and discuss the relationship between antitumor activity and the strain energies of the DNA adducts.

Similarly to the DACH-platinum DNA-adducts, those of 2-(amino-methyl)-cyclohexylamine AMCHA were also estimated (AMCHA has four isomeric structures, 1*R*, 2*R*(*l-cis*), 1*R*, 2*S*(*l-trans*), 1*S*, 2*R*(*d-trans*), and 1*S*, 2*S*(*d-cis*)).

It was reported that the efficacy difference between *cis*- and *tans*-AMCHA complexes is less than that between the DACH ones.[6-8] These experimental findings are explained in the present strain-energy calculations. The AMCHA complexes have a six-membered chelate ring and would less hinder interactions with a DNA fragment than DACH compounds, since the six-membered chelate ring may be more flexible than the latter five-membered one.

From an energetic point of view it is reasonable to assume that the more stable systems are more antitumor-active than the corresponding less stable ones. The correspondence between the computational and experimental findings are carefully checked.

EXPERIMENTAL

The initial coordinates of DNA bonded to a platinum complex were adopted from the X-ray structural data of a DDP adduct with the sequence d(CGC*G*AATTC*G*CG)·d(GCGCTTAA*G*CGC) determined by Wing, *et al.*,[5] where the *cis*-DDP complexes were monofunctionally linked to N7 of the guanosine sites (*G*). For simplicity of calculations, a characteristic six-base fragment (d(pCp*G*pAp)·d(pGpCpTp)) was selected.

Platinum(II) complexes have a planar structure. In the present study, however, we assume them to be *pseudo*-octahedral containing a non-bonded *d*-orbital (d_{z^2}) as the other two axial coordination sites for their ease and a mathematical validity[9] of treatment of the torsional terms including a platinum atom inside. This assumption of a *psuedo*-octahedral structure for a Pt(II) complex is also reasonable used in order to keep the planar structures.

Although cisplatin is not aquated in blood (the concentration of Cl^- ion (0.1 M) is higher than that in cell membrane (0.004 M)), it exists as an aquated species in cell membrane. From both physiological and structural data, it is assumed that a Pt(II) complex is aquated and mono-functional in an adduct with a DNA fragment.[10]

In the present calculations, van der Waals interactions of longer distances than 10 Å were omitted in order to increase the efficiency of calculations.

Total strain energies (E_{tot}) were calculated according to the following expression:

$$E_{tot} = E_{com} + E_{ben} + E_{out} + E_{tor} + E_{nob} + E_{ele}$$

E_{com}; compression energy
E_{ben}; bending energy
E_{out}; out of plane energy
E_{tor}; torsional energy

E_{nob}; non-bonding energy (van der Waals energy)
E_{ele}; electrostatic interaction with energy.

At present, the precision of the absolute energy values obtained from the empirical force-field calculation is not high. But the results by these methods are considered to be significant for obtaining the molecular structures and their relative energies (for example, especially the energy difference between the isomeric structures can be reliably discussed).

Therefore we discuss only the relative energies throughout the present paper. Force-field parameters in DNA were mainly adopted from those reported by Weiner, *et al.*[11]

Parameters for platinum complexes were referred to the values reported by Hambley.[12,13] A few reasonable values were assumed in the present study. Others were adopted from those of the MM2 or MMP2 program.

Charges of individual atoms of DNA bases and sugar sites were previously calculated from the bond dipole moments.[14] Charge parameters in platinum-complex sites were referred to those reported by Hambley, *et al.*[15–17] Only for charges of an electron in the axial *d*-orbital were a value assumed *i.e.*, about half of that for a usual lone pair, −0.1 e.[18]

RESULTS AND DISCUSSION

DACH Complexes

Prior to the minimization calculations of the DNA adducts, those of $[Pt(H_2O)_2$(*cis*-DACH)$]^{2+}$ and $[Pt(H_2O)_2$(*trans*-DACH)$]^{2+}$ were carried out. Figure 1 shows their ORTEP drawings. As expected from molecular-model considerations, the cyclohexane ring of the *cis*-DACH complex is perpendicular to the chelate ring, but that of *trans*-DACH is not. The *trans* form is more stable by 8 kJ/mol than the *cis* one in total energy. Table 1 shows the energy values. The main energy difference results from the torsional energy related to the chelate ring and the cyclohexane ring.

As a result of calculations on the DNA adducts, the total energies of the *d-trans* and *l-trans* systems are −437 and −440 kJ/mol, respectively, and that of the *cis* form is −402 kJ/mol (Table 2). The differences between the *cis* and *trans* forms are 36 to 38 kJ/mol in total energy. These differences are 27 to 30 kJ/mol larger than for the diaqua platinum complexes without DNA. These findings show that the *trans*-ligand-complex adducts are more stable than the *cis* ones, and may consequently have higher antitumor activity. Figure 2 shows the stereoviews. The energy differences in the *cis* and *trans* forms are found around their platinum planes, while there is little structural difference in comparison with those of the diaqua

Table 1 Strain energy of the diaqua DACH platinum complexes (kJ/mol)

	trans-DACH	*cis*-DACH
Bond stretching energy	2.09	2.43
Angle bending energy	9.29	9.92
van der Waals	5.65	7.03
Torsional energy	5.82	11.59
Total energy	22.85	30.97

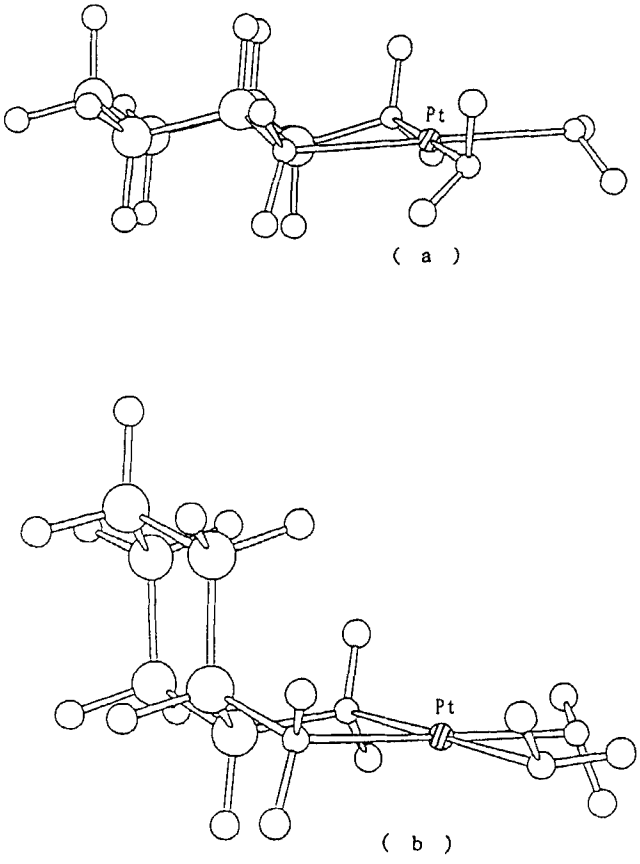

Figure 1 Energy-minimized structures (ORTEP) of (a) $[Pt(H_2O)_2-(l\text{-}trans\text{-}DACH)]^{2+}$ and (b) $[Pt(H_2O)_2(cis\text{-}DACH)]^{2+}$.

complexes. (The chair form of cyclohexyl ring is retained in both the DNA adducts.) However, there are differences in the structures of both the nucleotide sites. For example, especially in the *cis* system, the guanine base attached to the platinum complex is displaced from inside to outside of the helix, and the hydrogen bonds

Table 2 Strain energy of the DACH platinum complexes (kJ/mol)

	l-trans-DACH	*d-trans*-DACH	*cis*-DACH
Bond stretching energy	56.36	58.53	56.86
Angle bending energy	208.91	214.35	214.47
van der Waals	33.26	34.35	47.40
Torsional energy	294.68	288.95	304.60
Electrostatic energy	-1032.82	-1033.28	-1024.91
Total energy	-439.61	-437.10	-401.58

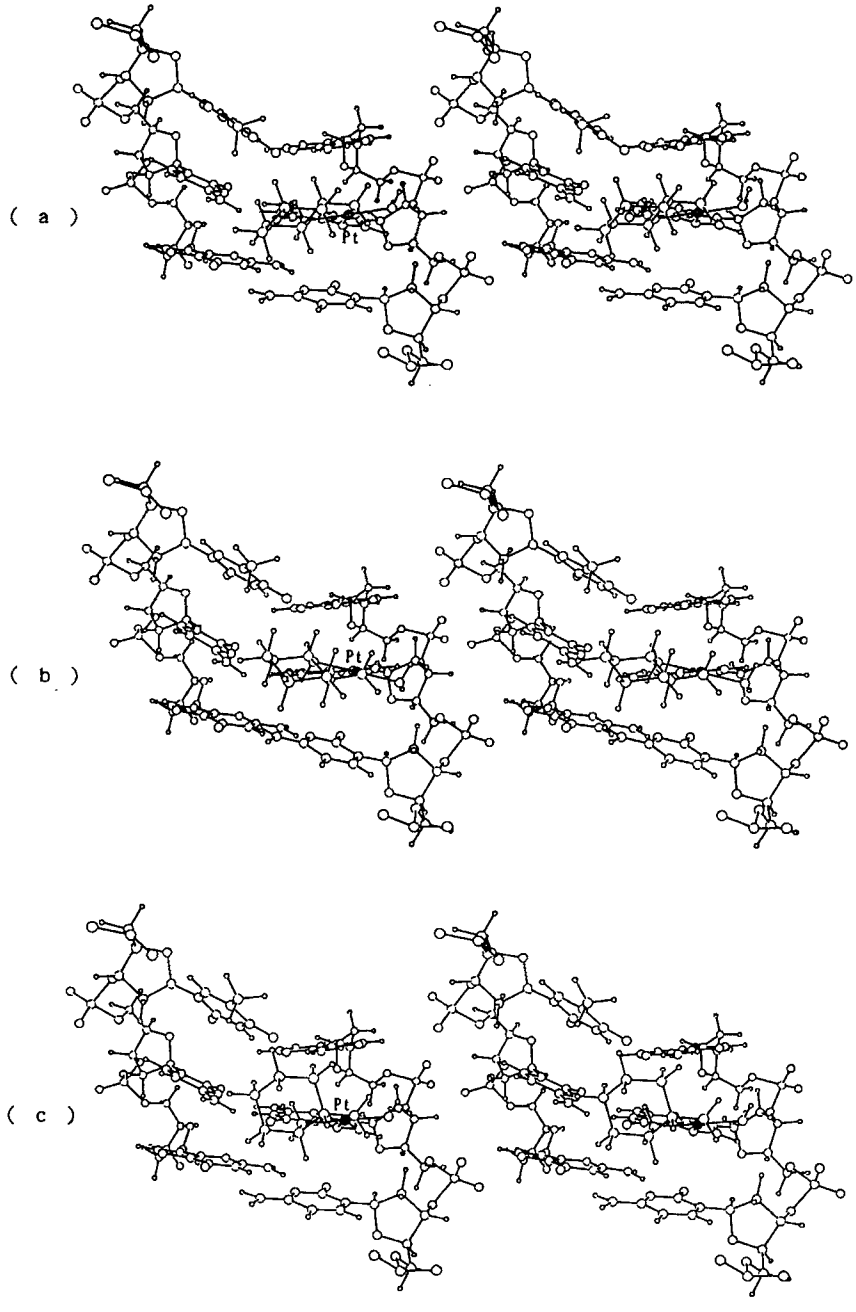

Figure 2 Energy-minimized structures (ORTEP stereoviews) of the DNA adducrts with (a) $[Pt(H_2O)(l\text{-}trans\text{-}DACH)]^{2+}$, (b) $[Pt(H_2O)(d\text{-}trans\text{-}DACH)]^{2+}$, and (c) $[Pt(H_2O)(cis\text{-}DACH)]^{2+}$. (Each solid circle shows a Pt ion.)

between cytosine (under guanine) and another guanine (in the opposite side of cytosine) tend to be cleaved. This may be attributed to more bulkiness of the cyclohexyl ring of the *cis* form.

AMCHA Complexes

Similarly to the DACH compounds, the strain energies of $[Pt(H_2O)_2$ (*d-cis*-AMCHA)$]^{2+}$ and $[Pt(H_2O)_2$(*d-trans*-AMCHA)$]^{2+}$ were independently minimized and their ORTEP drawings are shown in Figure 3. Here again, the cyclohexane ring of the *cis*-AMCHA complex is perpendicular to the chelate ring, but not for the *trans* complex. The energy difference between the *d-cis* and *d-trans* forms is 6 kJ/mol in total energy (Table 3). The energy difference comes mainly from torsional energies related to the chelate and cyclohexyl rings. In general, the larger the number of atoms, the greater the total energy in MM2 calculations should be; the inverse is

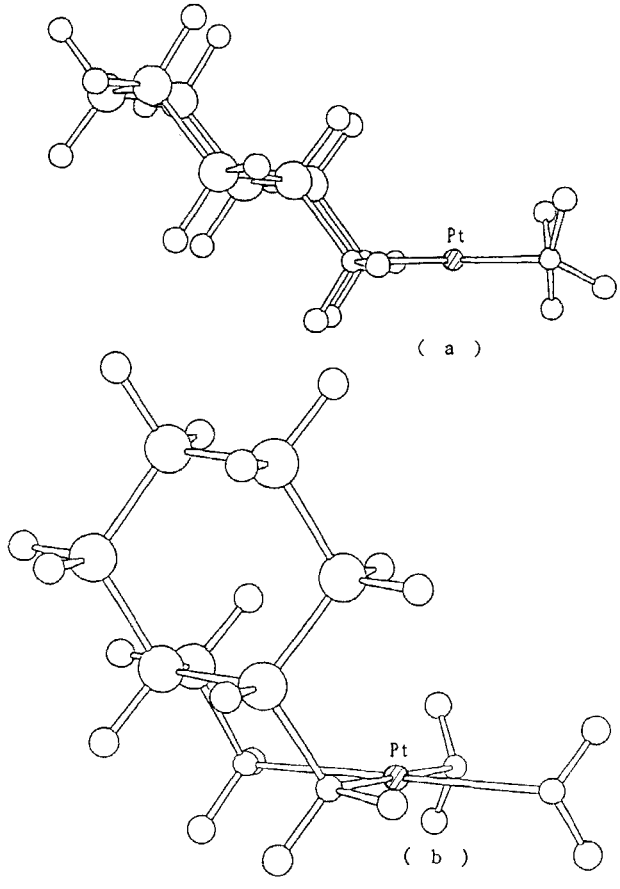

Figure 3 Energy-minimized structures (ORTEP) of (a) $[Pt(H_2O)_2$-(*d-trans*-AMCHA)$]^{2+}$ and (b) $[Pt(H_2O)_2$(*cis*-AMCHA)$^{2+}$.

Table 3 Strain energy of diaqua AMCHA platinum complexes (kJ/mol)

	trans-AMCHA	*cis*-AMCHA
Bond stretching energy	2.89	3.05
Angle bending energy	8.58	11.46
van der Waals	7.87	7.91
Torsional energy	12.34	15.36
Total energy	31.68	37.78

found in the present systems. DACH compounds show greater difference than AMCHA complexes. (The strain energy difference between the AMCHA complexes is by 2 kJ/mol less than that between the DACH ones.) This is because the six-membered chelate ring can relax the torsional strain better than the five-membered one.

The total energies of the DNA adducts of the *d-trans* and *d-cis* forms are −480 and −466 kJ/mol, respectively (Table 4). Similar to the DACH compounds, the energy difference between them is larger than the difference between the corresponding diaqua platinum complexes. This also shows that adducts with the *trans* forms are more stable and therefore more active than *cis* ones for antitumor activity. Figure 4 shows their stereoviews. There are differences in strain energy around the platinum plane in both systems of DACH- and AMCHA-complex DNA-adducts, but these energy differences between the latter adducts are larger than those of the DACH ones. Both the cyclohexyl and six-membered chelate rings of platinum complexes were chair forms in the starting structures. After minimization, the chair forms were retained in the cyclohexyl rings of both the *d-cis*- and *dl-trans*-AMCHA complexes, but the chelate ring of the *d-trans* complex changed to a distorted chair form. The larger strain-energy difference around the platinum plane in these systems is responsible. Interestingly there is no structural difference between nucleotides with *d-cis* and *d-trans* forms.

On the other hand, the total energy difference between the adducts of *d-cis*- and *d-trans*-AMCHA complexes (14 kJ/mol) is less than that among the DACH adducts (36 or 38 kJ/mol), thus relaxation of strain in DNA complexes was more effectively made by the six-membered ring. This is consistent with the finding that there is considerable difference in antitumor activity between DACH-platinum complexes with isomeric ligands, while the differences among isomeric-AMCHA complexes are less than the DACH ones. The calculations for *l-trans*- and *l-cis*-AMCHA-complex DNA-adducts were also carried out, but the difference between them (23 kJ/mol) is more than that of the *d-trans* and *dl-cis* complexes, ('*l-trans*' and '*l-cis*' are −424 and −448 kJ/mol, respectively).

Table 4 Strain energy of the DNA adducts with the AMCHA platinum complexes (kJ/mol)

	l-trans	*l-cis*	*d-trans*	*d-cis*
Bond stretching energy	57.99	58.41	59.12	60.96
Angle bending energy	215.43	221.54	202.46	219.45
van der Waals	46.28	46.86	30.63	43.56
Torsional energy	301.71	303.55	301.45	300.20
Electrostatic energy	−1069.39	−1054.03	−1073.78	−1090.39
Total energy	−448.00	−423.67	−480.11	−466.22

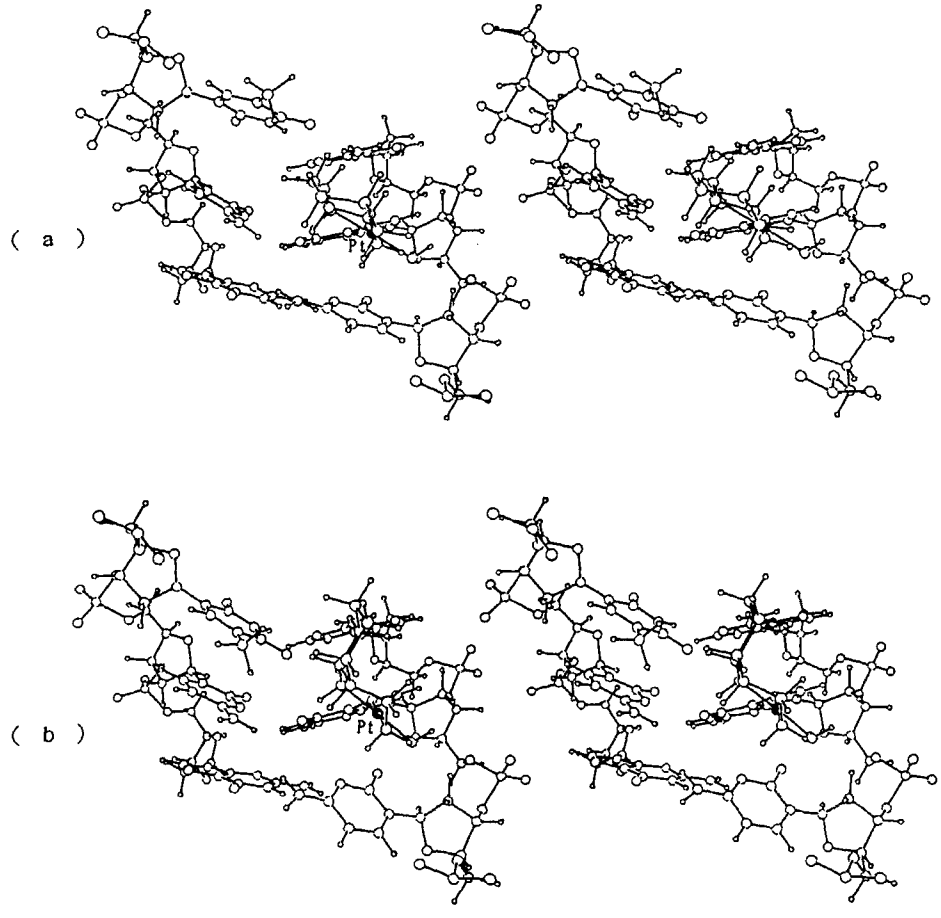

Figure 4 Energy-minimized structures (ORTEP stereoviews) of the DNA adducts with (a) $[Pt(H_2O)(l\text{-}trans\text{-}AMCHA)]^{2+}$, (b) $[Pt(H_2O)(l\text{-}cis\text{-}AMCHA)]^{2+}$. (Each solid circle shows a Pt ion.)

It is generally known that antitumor activity of the *cis*-DDP is due to formation of a coordination bond between platinum complexes and nucleotides. Hence, we consider that the more stable are the adducts of the complexes with the nucleotide, the stronger are their antitumor activities. The experiment, which has been reported in *vivo* (rats), shows that *trans*-ligand complexes are more active than *cis* ones in both DACH- and AMCHA-platinum complexes. In the present calculations, the adducts containing the *trans* complexes are more stable (in the total energies) than the *cis* ones in both DACH and AMCHA systems, and the above hypothesis is satisfied.

The fact that the energy difference among the isomeric-AMCHA platinum complexes is not as large as that of the DACH ones, is in agreement with the above assumption. The energy difference among the adducts containing isomeric ligands is 36 or 38 kJ/mol in the DACH adducts, while it is 14 kJ/mol in the AMCHA

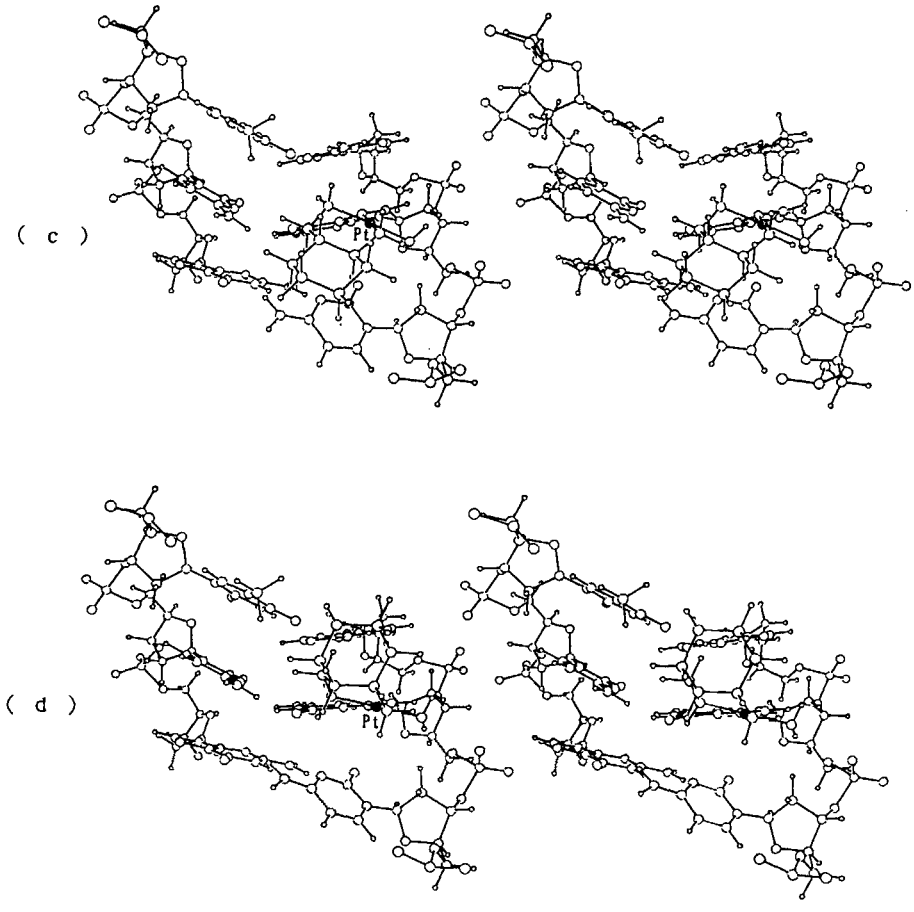

Figure 4 (*Continued*) Energy-minimized structures (ORTEP stereoviews) of the DNA adducts with (c) $[Pt(H^2))(d\text{-}trans\text{-AMCHA})]^{2+}$, and (d) $[Pt(H_2O)(d\text{-}cis\text{-AMCHA})]^{2+}$. (Each solid circle shows a Pt ion.)

adducts. In the *trans*-DACH-complex adducts, the main part of the strain does not exist in the platinum complex containing five-membered chelate and cyclohexyl rings, but is induced in the DNA chain due to the disturbing of stacking of bases in the nucleotide. In the *trans*-AMCHA-complex adducts, however, the strains are mainly present in the complexes. This may show that the six-membered chelate rings in the AMCHA complexes are more flexible than the five-membered rings in the DACH complexes. Thus the six-membered ring may relax the strain of DNA due to the bulky cyclohexyl ring.

The mechanism of antitumour activity, so far, is not clear. The present paper provides a step toward understanding the activity. We assumed a monofunctional model in the present paper, because only monofunctional structures have been

reported in the X-ray analysis.[5] However, after this, we will also take account of bifunctional binding in the DNA adducts.

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