The Preparation and Characterisation of Some Aminesulfoxidedichloroplatinum(II) Complexes†

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A series of compounds designed to bind to GpA sequences of DNA has been prepared and characterised. Procedures have been developed for the syntheses of $[Pt\{MeS(O)CH_2CH_2NH_2\}Cl_2]$ **1** and (2*S*,*SR*)- and (2*S*,*SS*)-$[Pt\{MeS(O)CH_2CH_2CH(CO_2Me)NH_2\}Cl_2]$ **2a**, **2b**. The crystal structures of **1** and of the two diastereomers, **2a** and **2b**, have been determined. Crystals of **1** are orthorhombic, space group *Pcab*, $a = 9.405(1)$, $b = 10.847(1)$, $c = 16.170(1)$ Å, $Z = 8$, $R = 0.30$ for 1410 reflections. Crystals of **2a** are orthorhombic, space group $P2_12_12_1$, $a = 9.738(1)$, $b = 10.588(1)$, $c = 11.090(1)$ Å, $Z = 4$, $R = 0.021$ for 1382 reflections. Crystals of **2b** are orthorhombic, space group $P2_12_12_1$, $a = 10.977(3)$, $b = 13.738(9)$, $c = 25.24(1)$ Å, $Z = 12$, $R = 0.078$ for 1482 reflections. Energy minimisation calculations have been used to develop a force field for a series of dichloroplatinum(II) sulfoxide complexes.

Since the discovery of the anticancer action of cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$, in 1969[1] there have been numerous studies directed at determining its mechanism of action.[2] It is now generally accepted that the intracellular target is DNA[2] and a number of cisplatin–DNA adducts have been characterised.[3–5] The major adducts are shown in Fig. 1. Which of these adducts is responsible for the anticancer action has not been established unequivocally but, three of them (**a**, **b** and **c**) have received the most attention.[6] The interstrand GG adduct **c** is conceptually attractive because it links the two strands of the DNA and this would undoubtedly interfere with DNA replication. However, it accounts for only about 1% of the cisplatin bound to DNA.[3–5] Most of the cisplatin bound to DNA is bound intrastrand to GpG (65%) and ApG sequences (25%).[3–5] In order to shed further light on which of the adducts is responsible for anticancer activity, we have been using computer-aided molecular design to investigate each of these three adducts and to design probes to test their roles.[7]

A number of groups have noted that while cisplatin binds readily to GpG and ApG sequences, it does not bind to GpA sequences.[3–5] This sequence specificity indicates that secondary interactions probably play a role in the binding of cisplatin to DNA. Therefore, as a first step in determining the factors that mediate cisplatin–DNA interactions we undertook a detailed analysis of this curious dichotomy.[8–10] Using molecular modelling techniques we produced models of the cisplatin–ApG adduct (Fig. 2) and the cisplatin–GpA 'non-adduct' (Fig. 3).[8–10] The only significant difference between these models lies in the nature of the interaction between one of the NH_3 ligands and the exocyclic group of the nucleobase on the 3′ side of the adduct. In the case of the ApG adduct this interaction is a hydrogen bond, between the NH_3 ligand and the exocyclic O atom of the guanine. In the GpA adduct, the equivalent interaction is a repulsive one between the NH_3 ligand and the exocyclic NH_2 group of the adenine. Thus, binding to ApG sequences will be promoted by the formation of the hydrogen bond and formation of the GpA adduct will be mitigated against by the repulsive interaction between the NH_3 and NH_2 groups. We have proposed that this difference is sufficient to account for the formation of the ApG adduct and the non-formation of the GpA adduct.[8–10]

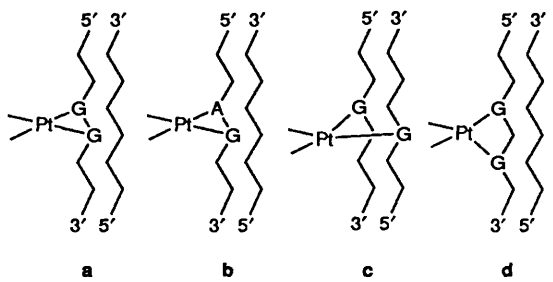


Fig. 1 Schematic representation of the major bifunctional cisplatin DNA adducts

In order to test this hypothesis we have designed a number of compounds in which one of the NH_3 ligands is replaced by a group able to hydrogen bond to the exocyclic NH_2 group of the adenine. One such group is the sulfoxide moiety and two compounds that we have designed which incorporate it are shown in Fig. 4. A schematic view of the anticipated interaction between these compounds and the GpA sequence is shown in Fig. 5. Bidentate ligands were used to avoid potential *cis–trans* isomerisation problems and the ligand of **2** was based on a chiral amino acid in order that the diastereomers with different chiralities at the sulfoxide group might be readily separated. The methyl ester forms of the amino-acid ligands were used to preclude isomerisation to carboxylate co-ordinated forms of the complex and so that the complexes were neutral. Neutral platinum complexes are generally substantially more active than charged complexes. Each of the diastereomers would be expected to interact differently with DNA [Fig. 5(*b*) and (*c*)].

The present paper describes the preparation of the ligands, their dichloroplatinum(II) complexes **1**, **2a** and **2b**, and the separation of the diastereomers, **2a** and **2b**. The crystal structures of the three complexes are also described. These compounds were subjected to analysis by molecular mechanics in order to develop a force field for the modelling of their interaction with DNA and the results of this study are also described.

Experimental

Syntheses.—*2-Aminoethyl methyl sulfide.* Phthalic anhydride (296 g) was purified and added slowly to freshly distilled

† *Supplementary data available* (No. SUP 56971, 3 pp.): Force field parameters. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.

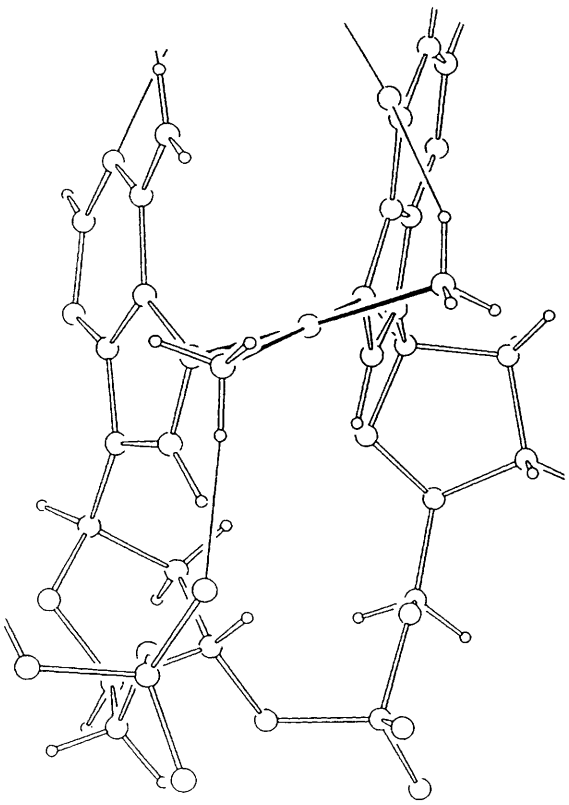


Fig. 2 Model of the cisplatin–ApG adduct

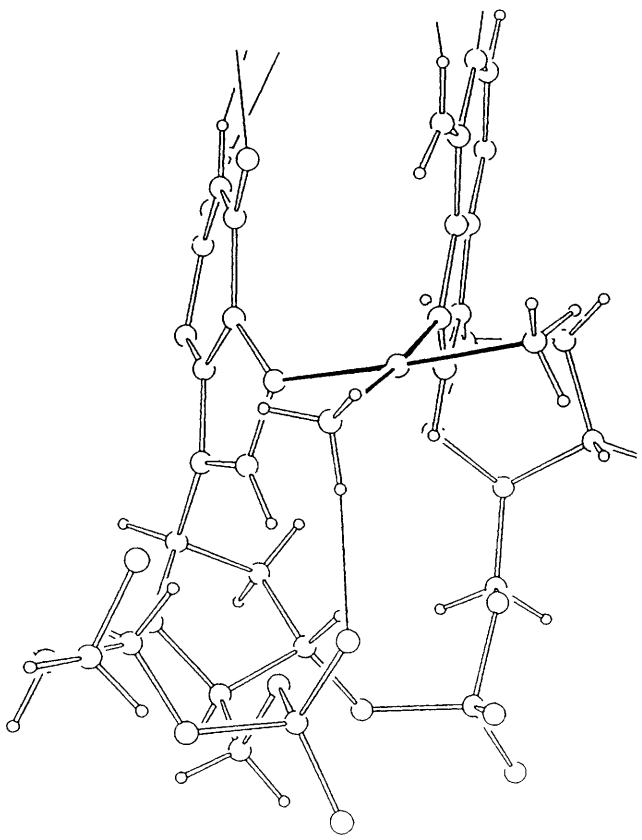
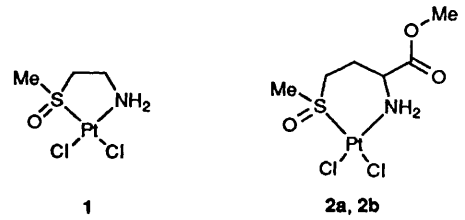


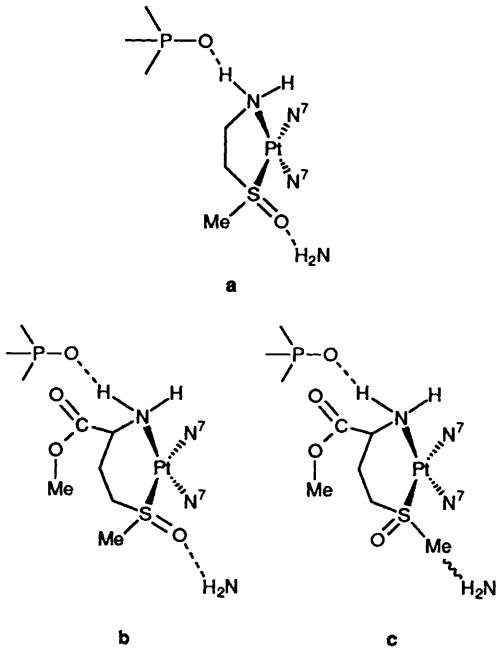
Fig. 3 Model of the cisplatin–GpA adduct

ethanolamine (244 g) in a 2 dm^3 round-bottom flask. The mixture was heated on a steam-bath for 2 h and allowed to cool. The crude product was recrystallised from water (*ca.* 1 dm^3) and



1 **2a, 2b**

Fig. 4 Schematic representation of complexes **1**, **2a** and **2b**



a **b** **c**

Fig. 5 Schematic representation of (*a*) **1**, (*b*) **2a** and (*c*) **2b** interacting with DNA

dried over phosphorus pentaoxide to yield white crystals of *N*-(2-hydroxyethyl)phthalimide (310 g, 81%). The phthalimide (171 g) was dissolved in freshly distilled pyridine (400 cm^3) and the solution cooled. To this was added toluene-*p*-sulfonyl chloride (200 g). Following the development of a yellow colour, precipitation occurred and the mixture was stirred overnight at room temperature. A solution (1.5 dm^3) of methanol, water and concentrated (10 mol dm^{-3}) HCl (1 : 2 : 1 respectively) was added with cooling and the precipitate was filtered off and washed with water and dried over phosphorus pentaoxide to yield a white solid (284 g, 92%). *N*-[2-Toluene-*p*-sulfonylethyl]-phthalimide (123 g) was placed in a 1 dm^3 round-bottom flask to which was added absolute alcohol (*ca.* 300 cm^3) and sodium thiomethoxide (25 g). The mixture was refluxed overnight and the ethanol removed. The phthalimide group was cleaved by refluxing the residue for 20 h in 20% HCl. The resulting white solid (a mixture of phthalic and toluene-*p*-sulfonic acids) was filtered off and discarded. The filtrate contained the crude 2-aminoethyl methyl sulfide in ionic form. The product was isolated by basification with 40% NaOH solution (**CAUTION**: cooling required) and extraction into diethyl ether (5 × 50 cm^3). The ether fractions were combined and dried over calcium chloride, the ether removed and the product distilled as a pale yellow oil at reduced pressure.

2-Aminoethyl methyl sulfoxide hydrochloride. The sulfide ligand was oxidised using a modification of the procedure detailed by Allain *et al.*[11] Glacial acetic acid (40 cm^3) was slowly added to 2-aminoethyl methyl sulfide (1.80 g) with intermittent cooling. Hydrogen peroxide (27.5%, 2.33 cm^3) was added dropwise to this mixture and the resulting solution was stirred for approximately 5 h. The bulk of the acetic acid (*ca.* 30 cm^3) was first removed by distillation under reduced pressure. After acidifying the residue (pH 1) by the addition of hydrochloric

acid (1 mol dm^{-3}), the remaining solvent was removed by evaporation under vacuum. The sulfoxide as the hydrochloride salt was obtained as a pale brown liquid in quantitative yield.

2-Aminoethyl methyl sulfoxide. The free base was generated by the addition of sodium hydroxide solution (1 mol dm^{-3}) to the liquid sulfoxide as the hydrochloride until the pH was approximately 12. Following removal of the water by evaporation, the product was isolated by extraction into chloroform, and the combined organic phases were dried over anhydrous calcium chloride. After filtering and removal of the solvent, 2-aminoethyl methyl sulfoxide was obtained as a dark brown viscous paste in approximately quantitative yield.

L-Methionine methyl ester sulfoxide. The hydrochloride salt of L-methionine methyl ester (Sigma) was oxidised to the corresponding sulfoxide ligand using a method analogous to that described for 2-aminoethyl methyl sulfide. The ligand was isolated as the hydrochloride salt in near quantitative yield.

(2-Aminoethyl methyl sulfoxide)dichloroplatinum(II) **1**. An aqueous solution (3 cm^3) of 2-aminoethyl methyl sulfoxide (0.32 g) was added dropwise with stirring to potassium tetrachloroplatinate(II) (1.23 g) dissolved in water (10 cm^3). The pink complex which immediately precipitated was heated in acidified water (*ca.* 0.05 cm^3, 1 mol dm^{-3} HCl per 5 cm^3 H_2O) to form two products in low yield; prism shaped crystals of (2-ammonioethyl methyl sulfoxide)trichloroplatinum(II) and a pale yellow powder (2-aminoethyl methyl sulfoxide)dichloroplatinum(II). Although the ratio of the products was 20:80, subsequent experiments have indicated that this is pH dependent. Numerous attempts at crystallisation were necessary before a sample suitable for X-ray diffraction analysis was obtained.

(2S,SR)- and (2S,SS)-Dichloro[methyl L-2-amino-4-(methylsulfinyl)butanoate]platinum(II) **2a**, **2b**. An aqueous solution of methyl L-2-amino-4-(methylsulfinyl)butanoate hydrochloride was added dropwise with stirring to a stoichiometric quantity of potassium tetrachloroplatinate(II) dissolved in water, and the resulting mixture left to stand overnight at 4 °C. Dull yellow globules formed and were isolated by filtration. After heating the orange filtrate gently with evaporation for approximately 30 min, pale yellow needle shaped crystals precipitated. The two products are diastereomers and were recrystallised independently from acidified water (0.05 cm^3, 1 mol dm^{-3} HCl in 5 cm^3 H_2O), the first being the (2*S*,S*S*) isomer, **2b** (yield 17%) and the latter being the (2*S*,S*R*) isomer, **2a** (yield 46%).

Crystallography.—Crystal data. $C_3H_9Cl_2NOPtS$ **1**, M = 373.16, orthorhombic, space group *Pcab*, a = 9.405(1), b = 10.847(1), c = 16.170(1) Å; U = 1649.7(1) Å^3, $D_c(Z = 8)$ = 3.005 g cm^{-3}, μ(Mo-Kα) = 179.44 cm^{-1}, λ = 0.7107 Å, $F(000)$ = 1360 electrons. Specimen: pale yellow prism, 0.11 × 0.11 × 0.24, $A^*_{max,min}$ = 8.40, 1.67, N = 2177, N_o = 1410, *hkl* 0–12, 0–14, 0–20, $R(=\Sigma||F_o| - |F_c||/\Sigma|F_o|)$ = 0.030, $R'[=\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2)^{\frac{1}{2}}]$ = 0.032, $w = 1.44/[\sigma^2(F_o) + 0.0005F_o^2]$.

$C_6H_{13}Cl_2NO_3PtS$ **2a**, M = 445.23, orthorhombic, space group $P2_12_12_1$, a = 9.738(1), b = 10.588(1), c = 11.090(1) Å; U = 1143.4(1) Å^3, $D_c(Z = 4)$ = 2.586 g cm^{-3}, μ(Mo-Kα) = 129.68 cm^{-1}, λ = 0.7107 Å, $F(000)$ = 832 electrons. Specimen: pale yellow needles, 0.065 × 0.055 × 0.30, $A^*_{max,min}$ = 2.98, 1.89, N = 1537, n_o = 1382, *hkl* 0–12, 0–13, 0–14, R = 0.021, R' = 0.023, $w = 0.99/[\sigma^2(F_o) + 0.000\,25F_o^2]$.

$C_6H_{13}Cl_2NO_3PtS$ **2b**, M = 445.23, orthorhombic, space group $P2_12_12_1$, a = 10.977(3), b = 13.738(9), c = 25.24(1) Å; U = 3806(2) Å^3, $D_c(Z = 12)$ = 2.331 g cm^{-3}, μ(Mo-Kα) = 116.91 cm^{-1}, λ = 0.7107 Å, $F(000)$ = 2496 electrons. Specimen: pale yellow needles, 0.050 × 0.032 × 0.38, $A^*_{max,min}$ = 1.87, 1.44, N = 2485, N_o = 1482, *hkl* 0–11, 0–14, 0–26, R = 0.078, R' = 0.082, $w = 1.92/[\sigma^2(F_o) + 0.0037F_o^2]$.

Structure determination. For diffractometry crystals were mounted on glass fibres with cyanoacrylate resin. Lattice parameters at 21 °C were determined by least-squares fits to the setting parameters of 25 independent reflections, measured and refined on an Enraf-Nonius CAD4F four-circle diffractometer employing graphite-monochromated Mo-Kα radiation. Intensity data for **1** and **2a** were collected in the range $1 < \theta < 27.5°$ and for **2b** in the range $1 < \theta < 22.5°$. Data reduction and application of Lorentz, polarisation, absorption and decomposition corrections were carried out using the Enraf-Nonius Structure Determination Package.[12]

Structure solution. The structures of **1** and **2a** were solved by heavy-atom methods using SHELX 76[13] and that of **2b** was solved by direct methods using SHELXS 86[14] and the solutions were extended by Fourier difference methods. Hydrogen atoms were included at calculated sites with group isotropic thermal parameters. All other atoms in structures **1** and **2a** were refined anisotropically. In **2b** only Pt, S and Cl atoms were refined anisotropically. The crystals of **2b** were of very poor quality and many of the atoms exhibited very high thermal parameters. These factors severely limit the quality of the data for structure **2b**.

Full-matrix least-squares methods were used to refine an overall scale factor, positional and thermal parameters. Scattering factors and anomalous dispersion terms for Pt were taken from ref. 15 and for all other atoms the terms supplied in SHELX 76 were used. All calculations were carried out using SHELX 76 and plots were drawn using ORTEP.[16]

The atom numbering schemes are given in Figs. 6–8. Final atomic coordinates are listed in Tables 1–3.

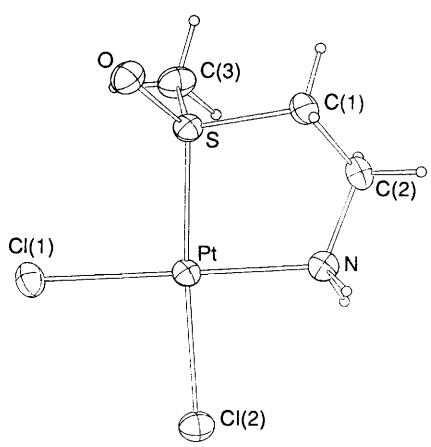


Fig. 6 ORTEP (30% probability) plot of complex **1** giving atom numbering

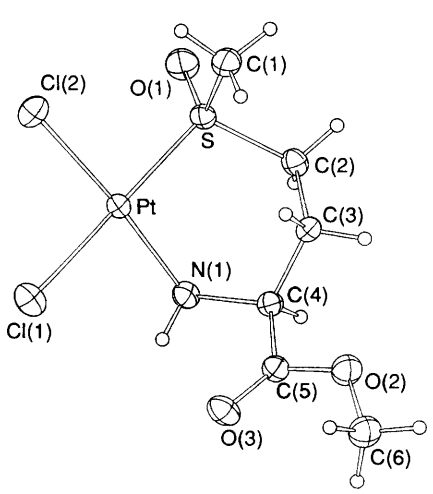


Fig. 7 ORTEP (30% probability) plot of complex **2a** giving atom numbering

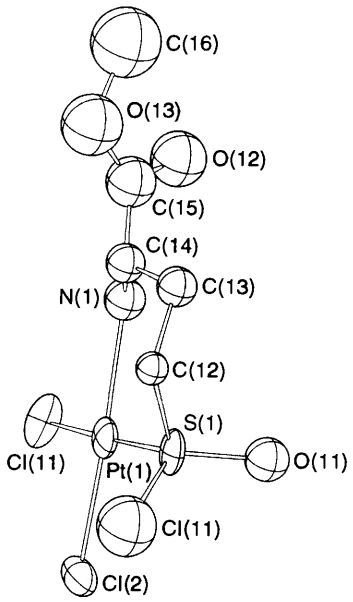


Fig. 8 ORTEP (30% probability) plot of complex **2b** giving atom numbering

Table 1 Positional parameters (× 10^4) for complex **1**

Atom	*x*	*y*	*z*
Pt	424(1)	1136(1)	734(1)
S	1037(2)	160(2)	1860(1)
Cl(1)	−1910(2)	1374(2)	1162(1)
Cl(2)	30(2)	2332(2)	−439(1)
N	2457(7)	814(5)	325(4)
O	125(6)	−719(5)	2278(3)
C(1)	2679(8)	−538(7)	1534(5)
C(2)	3438(8)	328(7)	983(5)
C(3)	1594(11)	1276(7)	2599(5)

Table 2 Positional parameters (× 10^4) for complex **2a**

Atom	*x*	*y*	*z*
Pt	5 561(1)	11 144(1)	4 301(4)
S	5 275(2)	12 638(2)	2 953(2)
N	3 563(7)	11 210(7)	4 882(6)
O(1)	5 958(7)	13 858(6)	3 181(6)
O(2)	888(7)	9 704(6)	3 199(6)
O(3)	2 085(7)	9 086(6)	4 802(5)
C(1)	5 767(9)	12 056(10)	1 528(8)
C(2)	3 472(8)	12 885(8)	2 735(8)
C(3)	2 725(8)	11 611(7)	2 766(7)
C(4)	2 375(8)	11 186(8)	4 034(7)
C(5)	1 781(8)	9 841(7)	4 073(7)
C(6)	140(10)	8 532(9)	3 152(9)
Cl(1)	5 863(3)	9 532(2)	5 659(2)
Cl(2)	7 851(2)	11 052(2)	3 816(2)

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and remaining bond lengths and angles.

Molecular Mechanics.—Strain energies were calculated according to the formalism $U_{tot} = E_b + E_\theta + E_\varphi + E_\delta + E_{nb}$ where E_b represents bond deformation energy, E_θ the valence angle deformation energy, E_φ the torsion angle deformation energy, E_δ the out-of-plane deformation energy and E_{nb} the non-bonded interaction energy.

Starting values for the force field parameters were taken from the force fields described previously for platinum complexes[17] and methionine–cobalt(III) complexes.[18] The only new parameters needed were those for the sulfoxide group and its interactions with Pt and C. Four sulfoxide complexes; dichloro[(2*S*,S*R*)-*S*-methylcysteine sulfoxide]platinum(II), the (2*S*,S*R*) and (2*S*,S*S*) isomers of dichloro(methionine sulfoxide)-platinum(II) and (2-aminoethyl methyl sulfoxide)dichloro-platinum(II), were modelled and sets of initial coordinates were obtained from crystal structures of the complexes described above or related complexes.[19] Strain energies were minimised using the program MOMEC-87,[20] which employs a modified version of the Newton Raphson scheme developed by Boyd.[21] Convergence was defined as the point where shifts for the atomic coordinates were less than or equal to 0.001 Å. Constraints were applied using the method of Lagrangian multipliers.[22]

The criterion used to test the force field was its ability to reproduce the bond lengths and angles determined from X-ray structure analyses. In some cases, trends of poor correspondence were observed and values for these input parameters were altered until correlation was optimal. Where adjustment was necessary the criterion for an acceptable parameter was the ability of a single parameter to reproduce the structures of a number of complexes. The values for the force field parameters are listed in SUP 56971.

Results and Discussion

Syntheses.—There have been previous reports of the preparation of 2-aminoethyl methyl sulfoxide. The approach taken previously has been to start with 2-aminoethanethiol and treat it with methylating reagents such as methyl iodide.[23] In our hands such approaches were unsuccessful or gave poor yields. Therefore we developed an alternative approach starting with ethanolamine. The amine group of ethanolamine was protected by reaction with phthalic anhydride, the hydroxyl group was activated by tosylation and this compound was treated with sodium thiomethoxide and then deprotected to give the desired product in high yield.

Difficulties were encountered when attempting to develop synthetic routes to the platinum complex using the protonated form of 2-aminoethyl methyl sulfoxide. (2-ammonioethyl methyl sulfoxide)trichloroplatinum(II), in which the protonated ligand is co-ordinated to the metal centre in a monodentate fashion, is stable and formed preferentially under acidic conditions (pH 3) whilst under less acidic conditions(> pH 5) the predominant product was **1**. As cisplatin derivatives tend to form hydroxo polymers under neutral conditions, the pH dependency becomes an important factor in the synthesis and governs the product distribution.

The second major problem is that in the synthesis detailed in the methods section, a kinetic product, which is believed to be a mixture of the isomers of bis(2-aminoethyl methyl sulfoxide)-platinum(II) tetrachloroplatinate(II), forms and attempts to bypass this pink intermediate have not been successful. As such behaviour is uncharacteristic of platinum sulfoxide compounds, this study has indicated that there is a destabilising interaction in the five-membered 2-aminoethyl methyl sulfoxide chelate ring in **1**.

Description of the Structures.—The structures all consist of neutral square-planar complex molecules, each with two chloro ligands and one bidentate ligand with one amine and one sulfoxide donor group. Each of the H(amine) atoms is involved in one hydrogen bond to a Cl, O(carbonyl) or O(sulfoxide) atom. The high thermal motion and consequent poor quality data for **2b** mean that the structure is too imprecise for detailed description to be useful. Therefore, discussion hereafter is limited to **1** and **2a**. In both structures there are significant (0.10 and 0.05 Å) approximately tetrahedral deviations from the least-squares planes through the Pt atom and the four donor

Table 3 Positional parameters ($\times 10^4$) for complex **2b**

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Pt(1)	1465(2)	1520(2)	1768(1)	C(22)	2994(79)	3451(58)	9876(28)
Cl(11)	1427(18)	780(18)	949(7)	C(23)	3606(60)	4182(51)	9818(25)
Cl(12)	1379(17)	27(14)	2159(10)	C(24)	3080(79)	4861(53)	9369(28)
S(1)	1633(13)	2262(16)	2544(7)	C(25)	3670(95)	5918(6)	9409(52)
N(1)	1554(61)	2927(49)	1307(21)	O(22)	3953(67)	6229(58)	9051(29)
O(11)	2976(53)	2455(40)	2686(19)	O(23)	2929(67)	6198(54)	9865(24)
C(11)	782(7)	1665(84)	2973(40)	C(26)	−1816(8)	−1853(7)	164(77)
C(12)	882(54)	3294(43)	2490(21)	Pt(3)	4812(2)	1120(2)	1451(1)
C(13)	1320(69)	3990(61)	2079(26)	Cl(31)	4812(19)	1003(15)	551(7)
C(14)	1002(71)	3703(54)	1577(26)	Cl(32)	4533(16)	2757(12)	1381(8)
C(15)	1109(8)	4395(84)	1184(44)	S(3)	5085(18)	−442(14)	1502(8)
O(12)	2119(79)	4464(58)	885(28)	N(3)	4757(49)	1228(38)	2379(19)
O(13)	246(90)	5023(68)	1105(35)	O(31)	6360(61)	−850(53)	1447(24)
C(16)	712(6)	5852(4)	776(52)	C(31)	4109(83)	−1070(71)	1091(34)
Pt(2)	3061(2)	3114(3)	8547(1)	C(32)	4678(73)	−823(60)	2140(26)
Cl(21)	2910(18)	3826(22)	7714(8)	C(33)	4995(65)	−341(46)	2617(22)
Cl(22)	2696(16)	1614(19)	8174(8)	C(34)	4553(90)	650(71)	2715(33)
S(2)	3351(16)	2446(18)	9318(8)	C(35)	4947(54)	1067(44)	3213(22)
N(2)	3429(79)	4407(61)	8710(28)	O(32)	5491(96)	1679(75)	3338(33)
O(21)	4525(68)	2160(56)	9426(26)	O(33)	4061(79)	627(66)	3597(32)
C(21)	2348(68)	1380(57)	9453(27)	C(36)	4302(8)	859(96)	4149(39)

Table 4 Metal–ligand bond lengths and angles

Structure	Pt–N	Pt–S	Pt–Cl(*trans*-S)	Pt–Cl(*cis*-S)	Ref.
1	2.053(6)	2.183(2)	2.329(2)	2.317(2)	This work
2a	2.051(7)	2.194(2)	2.295(2)	2.296(2)	This work
2b	2.16	2.188	2.301	2.285	This work
3 [Pt{(2*S*,S*R*)-$H_2NCH(CO_2H)CH_2S(O)Me$}Cl_2]	2.046(12)	2.182(3)	2.292(4)	2.299(4)	19
4 [Pt{(2*S*,S*R*)-$H_2NCH(CO_2H)CH_2CH_2S(O)Me$}$Cl_2$]	2.063(7)	2.198(2)	2.223(2)	2.304(2)	24
5 [Pt{$H_3NCH_2CH_2S(O)Me$}Cl_3]		2.205(1)	2.325(2)	2.298(2)	25
				2.286(2)	

Table 5 Minimised strain energies

Complex	Diastereomer	Conformer	Strain energy (kJ mol^{-1})
3	2*S*,S*S*		21.62
	2*S*,S*R*		20.19
2	2*S*,S*S*	Chair, axial	27.37
	2*S*,S*R*	Chair, axial	27.69
	2*S*,S*S*	Chair, equatorial	28.85
	2*S*,S*R*	Chair, equatorial	29.64
	2*S*,S*S*	Boat	36.86
	2*S*,S*R*	Boat	37.33
1			16.72

atoms. The Pt–S(sulfoxide) bond lengths are shorter than Pt–S(thioether) bond lengths and are similar to those previously reported for related complexes (Table 4). The Pt–Cl bond lengths are more variable than the Pt–S bond lengths in the present structures and in previously reported structures. However, there is no evidence for the suggestion that the S(sulfoxide) group exerts a *trans* effect.[24] The Pt–N bond lengths are at the long end of the range for Pt–N(amine) bonds.

The structural analyses of **2a** and **2b** confirm that these are diastereomers and show that the configurations at the sulfur atom are *R* and *S* respectively. The six-membered chelate ring in **2a** adopts a skew–boat conformation and that in **2b** a flattened chair conformation in which the ester group is approximately equatorial. In contrast [Pt{(2*S*)-$H_2NCH(CO_2H)CH_2CH_2S(O)$}$Cl_2$], in which the chirality at S is the same as in **2b**, adopts the alternative chair conformation in which the carboxylate is axial.

Molecular Mechanics.—Three complexes were modelled; [Pt{2*S*-$H_3NCH_2CH_2S(O)Me$}Cl_3] **5**, [Pt{(2*S*)-$H_2NCH(CO_2H)CH_2CH_2S(O)Me$}$Cl_2$] **4** and [Pt{2(*S*)-$H_2NCH(CO_2H)CH_2S(O)Me$}$Cl_2$] **3**. The S*S* and S*R* diastereomers of the latter complexes were considered as were chair conformations with equatorial and axial carboxylate groups and the skew-boat conformation observed in the structure of **2a**. Strain energies are collected in Table 5. These show that the strain energies of diastereomeric pairs differ by less than 1.5 kJ mol^{-1}. The strain energies of the two chair conformations of [Pt{(2*S*)-$H_2NCH(CO_2H)CH_2CH_2S(O)Me$}$Cl_2$] differ by 1.5–2 kJ mol^{-1}. The boat conformation is predicted to be nearly 10 kJ mol^{-1} less stable which raises the question why is it observed; if the energies are realistic then one would have to conclude that crystal packing or hydrogen-bonding forces must contribute to the stabilisation of this geometry. The force field generally modelled these complexes well as indicated by its ability to reproduce the bond lengths and angles derived from structural analyses. However, instances of poor correlation were observed, these being the platinum valence angles and the Pt–N–C bond angle and torsion angles about the Pt–N and Pt–S bonds. All of these correspond to the conformation observed in the solid state being flattened when compared to that predicted by the molecular mechanics calculations. It seems feasible that this is a consequence of packing forces; since the complexes are approximately planar then it is possible that the packing would promote still more planar ligand conformations.

Conclusion

To establish whether destabilising contacts lead to the non-formation of the GpA adduct, a series of platinum aminesulfoxide complexes have been designed and we have successfully prepared the ligands and metal complexes. These complexes have been tested for anticancer activity *in vitro* and *in vivo*; they all show modest activity and very low toxicity.[26] It is likely that both the low activity and toxicity are the result of

the increased kinetic liability that the sulfoxide sulfur atom confers. Preliminary results on the binding of these complexes to DNA are consistent with our having achieved the design goal of promoting preferential binding to GA and AA sequences.[27] For example, using T4 polymerase, an enzyme that cuts DNA at or near where Pt is bound, it was shown that **2a** and **2b** bind much more selectively than does cisplatin and that the major binding site on a synthetic 49 base-pair oligonucleotide was at a GAA sequence.[27] The major binding site of cisplatin was at an adjacent GG sequence.

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