results for the atomic charge distribution (Figure 1b) based on the multipole refinement are in good agreement with the following observations:[17,18] the H, C, and S atoms are positive, and the O and N atoms are negative. This is in accordance with what was proposed for $(H_2N)_2C^+$ with the positive charge mainly on H atoms and for SO_2^- with the electron density mainly polarized toward the oxygen atoms, leaving the S and C atoms slightly positive, which enables the nucleophilic attack.[17] The κ value of the H atom seems to be highly correlated with its net charge. The result here is from the fixed κ value of 1.4. This gives the least correlation between dipole terms of H and those of the N atom. The bond lengths (Figure 1a) at low temperature are longer than those of at room temperature, as expected for the thermal motion differences.[19,20] However, the C-S length, on the contrary, is shortened somewhat. A similar phenomenon has been observed in other related sulfur bond lengths.[16] The S-O distance is longer than a localized double bond,[15] and the C-N distance is comparable to a partially double bond. The C-S bond is slightly longer than the single bond. Thus, the geometry of the structure itself reveals the charge polarization of the form proposed previously.[1,3]

The experimental deformation density distribution of thiourea *S,S*-dioxide in the plane of thiourea appears to be quite similar to that of thiourea,[6] and the density accumulation along the C-S bond is slightly polarized toward the C atom indicating S→C. Although both atoms are positive, the carbon atom is less positive than the sulfur atom. The density accumulation along the N-H and C-N bonds is as expected. The loss of density near the sulfur nucleus has been found in other sulfur-containing compounds.[15,16,21] This also agrees well with the atomic net charges obtained from the multipole refinement. The density accumulation along the S-O bonds is less apparent or more diffuse than that of other experimental results.[15] This may be due to the fact that each oxygen atom accepts two intermolecular hydrogen bonds in the crystal. It is interesting to notice that, in the dynamic multipole deformation density map of Figure 2b, the density along the S-O bond is less diffuse and polarized more toward the oxygen atoms (thus yielding a relatively large negative charge for the oxygen atom) than that of the experimental one (Figure 2a). Nevertheless, the H-bonds are still clearly observed in the multipole deformation density map, in spite that the multipole model is a better representation near the nucleus and in the intramolecular bonded atom region. The influence of the intermolecular H-bonding on the electron distribution has been noticed and studied recently.[22] Similarly, the lone-pair density at the sulfur atom is better represented in the multipole deformation density map (Figure 3b) than in the experimental one (Figure 3a) and is comparable to that of the theoretically calculated one (Figure 3d). The pseudo static deformation density distribution (Figures 2c and 3c) gives the deformation density distribution without the thermal smearing effect at the same resolution level. The resemblance between the dynamic and static deformation density distributions indicates little correlation between thermal motion and the deformation density.

In order to see the effect of each multipole term on the deformation density distribution, a multipole density map was produced at each step of expanding the multipole terms on all the atoms. It was obvious that, at least, all terms up to the quadrupole terms are needed for building up the density between the bonded atoms. Adding octapole terms certainly improved the density accumulation significantly. Additional hexadecapole terms on the C, N, and O atoms improved the density accumulation only slightly; however, this term was important for the sulfur atom.

The net atomic charges from the EHMO calculation given in Figure 1b are in agreement with the ones obtained by the multipole refinement. The deformation density based on the EHMO calculation only provides a qualitative comparison. The small basis set calculations such as those with EHMO often underestimate the deformation density in the bonding regions but overestimate it in the lone-pair regions. A more sophisticated ab initio calculation of the title compound is underway.

Conclusion

Deformation density studies of thiourea dioxide, both by direct inspection of an experimental deformation density map and by construction of it according to a multipole model, lead to a better understanding of the atomic net charge distribution of the molecule. The need of up to octapole terms for building up the density in the bonds is confirmed. The extra hexadecapole term is important for the sulfur atom, which implies the angular complexity of the electronic distribution of sulfur atom in the molecule. The intermolecular H-bonding effect is observable in both the experimental and model deformation density maps. Simple EHMO calculations can provide a qualitative comparison.

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Supplementary Material Available: Tables SI-SIII, listing complete crystal data, atomic thermal parameters from various refinements, and coefficients of atomic multipole terms up to the hexadecapole level for non-hydrogen atoms and to the dipole level for hydrogen atoms (3 pages); Table SIV, listing calculated and observed structure factors (11 pages). Ordering information is given on any current masthead page.

(19) Busing, W. R.; Levy, H. A. *Acta Crystallogr.* **1964**, *17*, 142.
(20) Wang, Y.; Blessing, R. H.; Ross, F.; Coppens, P. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 572.
(21) Wang, Y.; Liao, J. H. *Acta Crystallogr., Sect. B: Struct. Sci.* **1989**, *B45*, 65.
(22) Kring, M. P. C. M.; Graafsma, H.; Feil, D. *Acta Crystallogr., Sect. B: Struct. Sci.* **1988**, *B44*, 609.

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Head-Tail Oriented Nucleobases (B = Guanine, Cytosine) in *cis*-A_2PtB_2 Resisting Cyanide Substitution. Implications for the Nature of Strongly DNA-Bound Cisplatin

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The adducts formed by the antitumor agent *cis*-diamminedichloroplatinum(II), *cis*-DDP (Cisplatin), with DNA cannot be completely removed even with excess cyanide.[1] Model nucleobase complexes of *cis*-DDP exhibit quite substantial differences in substitution rates when treated with CN^-. These observations have led us to speculate that cross-links other than those between two guanines on one DNA strand (intrastrand G,G adduct) might account for this phenomenon.[2] Specifically, the protective effect of the exocyclic oxygens of N3-bound thymine (and likewise uracil) ligands has been noted. It was suggested that the electron lone pairs of the carbonyl oxygens at either side of the Pt coordination plane in uracil and thymine complexes were responsible for this phenomenon. These oxygens are positioned such as to make an associative substitution mechanism difficult. In contrast, the two 9-ethylguanine (9-EtGH) ligands in *cis*-$[(NH_3)_2Pt(9\text{-EtGH-}N^7)_2]^{2+}$, which, in the solid state, are arranged head-head[3] very

(1) (a) Stone, P. J.; Kelman, A. D.; Sinex, F. M. *Nature* **1974**, *251*, 736. (b) Munchhausen, L. L.; Rahn, R. O. *Biochim. Biophys. Acta* **1975**, *414*, 242. (c) Lippard, S. J.; Hoeschele, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 6091. (d) Tullius, T. D.; Lippard, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 4620. (e) Ushay, H. M.; Tullius, T. D.; Lippard, S. J. *Biochemistry* **1981**, *20*, 3744. (f) Bauer, W.; Gonias, S. L.; Kam, S. K.; Wu, K. C.; Lippard, S. J. *Biochemistry* **1978**, *17*, 1060. (g) Leng, M. Personal communication.
(2) Raudaschl-Sieber, G.; Lippert, B. *Inorg. Chem.* **1985**, *24*, 2426.
(3) (a) Lippert, B.; Raudaschl, G.; Lock, C. J. L.; Pilon, P. *Inorg. Chim. Acta* **1984**, *93*, 43. (b) Schöllhorn, H.; Raudaschl-Sieber, G.; Müller, G.; Thewalt, U.; Lippert, B. *J. Am. Chem. Soc.* **1985**, *107*, 5932.

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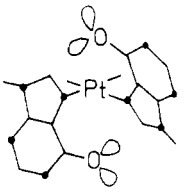
much as in the corresponding d(pGpG) adduct,[4] are displaced reasonably rapidly by excess CN^- at pH 8 according to

$$cis\text{-}[(NH_3)_2Pt(9\text{-}EtGH\text{-}N^7)_2]^{2+} + 4CN^- \rightarrow 2NH_3 + [Pt(CN)_4]^{2-} + 2(9\text{-}EtGH)$$

A recent discussion[18] on the phenomenon of incomplete removal of *cis*-DDP from single-stranded DNA prompted us to extend our earlier studies. We postulated that Pt displacement by CN^- might also be slow if two nucleobases having *a single* exocyclic oxygen each (O6 of 9-methylguanine and O2 of 1-methylcytosine) were trapped in a head-tail arrangement without the possibility of rotating about the Pt-N(nucleobase) bond. It is well established[5-8] that bulky substituents at the amine ligands in A_2PtBX entities can successfully prevent nucleobase (B) rotation. We thus reasoned that compounds with a fixed head-tail orientation of two bases having a single exocyclic oxygen (e.g. two guanines, structure I) might represent adequate species to test this hypothesis. Cramer



I

and Dahlstrom[5a] had suggested that the Pt complex with the bulky *N,N,N',N'*-tetramethylethylenediamine (tmeda) ligand, on reaction with guanosine, gave two diastereomers with head-tail orientation of the two bases only. No head-head isomer was observed. Orbell et al.[9] demonstrated that 9-MeGH and 9-EtGH also form head-tail complexes when reacted with $[(tmeda)Pt(H_2O)_2]^{2+}$.

We have prepared $[(tmeda)Pt(D_2O)_2](NO_3)_2$ (**1**)[10] and $[(tmeda)Pt(9\text{-}MeGH\text{-}N^7)_2](ClO_4)_2\cdot 3H_2O$ (**2**)[11] according to published methods. $[(tmeda)Pt(1\text{-}MeC\text{-}N^3)_2](ClO_4)_2\cdot H_2O$ (**3**)[12] and $[(tmeda)Pt(py)_2)](ClO_4)_2\cdot 2H_2O$ (**4**)[13] were prepared in an analogous manner. The compounds were treated with a 20-fold excess of CN^- in D_2O at pD ~ 8 and 30 °C, as previously described,[2] and the reaction was followed by ^1H NMR spectroscopy.[14] The previously studied reaction of $cis\text{-}[(NH_3)_2Pt(9\text{-}EtGH\text{-}N^7)_2]^{2+}$ with CN^- was repeated as a control.

The following observations were made: (1) CN^- quickly displaces all ligands in **1** and **4**, half-lives being less than 15 min each. (2) In the case of **2**, it takes between 150 and 200 h to displace 50% of the guanine ligands. This time is to be compared with ca. 12-15 h for $cis\text{-}[(NH_3)_2Pt(9\text{-}EtGH\text{-}N^7)_2]^{2+}$. Although 9-MeGH precipitates in part from solution, the intensities of the signals of the intact complex confirm our previous observations that CN^- displaces *all* ligands, including tmeda, from **2**. (3) The bis(1-methylcytosine) complex **3** proves to be the one that resists CN^- treatment most effectively. After 120 h, less than 10% of 1-MeC was substituted.

Although we have not characterized **3** by X-ray crystallography as yet, we propose a head-tail orientation of the two nucleobases as in the case of $cis\text{-}[(NH_3)_2Pt(1\text{-}MeC)_2]^{2+}$.[7a,15] The observation that **3** exhibits the greatest inertness toward CN^- among the compounds described here could be due either to the additional shielding effect of the NH_2 group at the 4-position[16] or—more likely—to the greater barrier of rotation about the Pt-N bond as compared to purine-N^7 compounds.[7a]

Our findings unambiguously demonstrate that a single exocyclic oxygen on either side of the Pt coordination plane in bis(nucleobase) complexes makes an associative substitution mechanism by CN^- very difficult and causes a remarkable kinetic stability. The steric bulk of the amine substituents is, at least in the compounds studied (cf. behavior of **1** and **4**), not primarily responsible for this effect. With respect to the nature of DNA-bound *cis*-DDP that resists CN^- treatment, the previously suggested possibilities[2] need to be extended: Apart from thymine-N^3-containing adducts which, in every possible combination with a second nucleobase give inert complexes, any of the following combinations is expected to behave similarly, *provided the DNA structure fixes the respective nucleobase orientation*: (C-N^3),(C-N^3) (*head-tail*), (C-N^3),(GH-N^7) (*head-head*), (C-N^3),(G-N^1) (*head-head*), (G-N^1),(G-N^1) (*head-tail*), (GH-N^7),(GH-N^7) (*head-tail*). It thus appears likely that involvement of donor sites that normally are in the interior of the duplex (T-N^3, C-N^3, G-N^1) can lead to an inert cross-link. As far as guanine-N^7 binding is concerned, a binding pattern generally believed to be kinetically favored, a *head-tail* geometry as proposed for the interstrand (GH-N^7),(GH-N^7) adduct of *cis* DDP,[17] probably makes this cross-link CN^- resistant. In contrast, the major adduct of *cis*-DDP in double-stranded DNA, the intrastrand guanine,guanine (*head-head*) complex, reacts relatively fast with CN^-.

Note Added in Proof. The X-ray structure of **3** has now been performed. It confirms the head-tail orientation of the two 1-MeC rings. Details will be published elsewhere.[18]

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(4) Sherman, S. E.; Gibson, D.; Wang, A. H.-J.; Lippard, S. J. *Science* **1985**, *230*, 412; *J. Am. Chem. Soc.* **1988**, *110*, 7368.
(5) (a) Cramer, R. E.; Dahlstrom, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3679. (b) *Inorg. Chem.* **1985**, *24*, 3420.
(6) Marcelis, A. T. M.; Erkelens, C.; Reedijk, J. *Inorg. Chim. Acta* **1984**, *91*, 129.
(7) (a) Orbell, J. D.; Kistenmacher, T. J.; Marzilli, L. G. *J. Am. Chem. Soc.* **1981**, *103*, 5126. (b) Reily, M. D.; Wilkowski, K.; Shinozuka, K.; Marzilli, L. G. *Inorg. Chem.* **1985**, *24*, 37. (c) Reily, M. D.; Marzilli, L. G. *J. Am. Chem. Soc.* **1986**, *108*, 6785.
(8) Hambley, T. W. *Inorg. Chem.* **1988**, *27*, 1073.
(9) Orbell, J. D.; Taylor, M. R.; Birch, S. L.; Lawton, S. E.; Vilkins, L. M.; Keefe, L. J. *Inorg. Chim. Acta* **1988**, *152*, 125.
(10) A solution of $[(tmeda)Pt(D_2O)_2](NO_3)_2$ (**1**) was prepared as follows: 0.018 mmol of $(tmeda)PtI_2$ (prepared according to: Dhara, S. G. *Indian J. Chem.* **1970**, *8*, 193) and 0.035 mmol of $AgNO_3$ were stirred for 5 h at 50 °C; then AgI was filtered off.
(11) Anal. Calcd (found) for $C_{18}H_{36}N_{12}O_{13}Cl_2Pt$ (**2**): C, 24.17 (24.5); H, 4.06 (3.7); N, 18.79 (18.5). ^1H NMR [δ (ppm); pD 8]: 9-MeGH, 8.17 (H8, s), 3.65 (CH_3, s); tmeda, 2.65-3.20 (m).
(12) Anal. Calcd (found) for $C_{16}H_{32}N_8O_{11}Cl_2Pt$ (**3**): C, 24.69 (24.8); H, 4.18 (4.0); N, 14.39 (14.0). ^1H NMR [δ (ppm); pD 8]: 1-MeC, 7.61 (H6, d), 6.03 (H5, d), 3.42 (CH_3, s); tmeda, 2.76-3.03 (m).
(13) Anal. Calcd (found) for $C_{16}H_{30}N_4Cl_2O_{10}Pt$ (**4**): C, 27.28 (26.9); H, 4.29 (3.9); N, 7.98 (7.8). ^1H NMR [δ (ppm); pD 8.1]; py 8.96 (H2, H6, d), 8.00 (H4, t), 7.60 (H3, H5, t); tmeda, 3.11 (CH_2, s), 2.79 (CH_3, s).
(14) Bruker AM 300; 300 MHz, TSP as internal standard, 20 °C, c_{Pt} ~ 8.3 mmol/L.
(15) (a) Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1982**, *21*, 3210. (b) Schöllhorn, H.; Thewalt, U.; Raudaschl-Sieber, G.; Lippert, B. *Inorg. Chim. Acta* **1986**, *124*, 207.
(16) Cf. behavior of $cis\text{-}[(NH_3)_2Pt(1\text{-}MeC)_2]^{2+}$ as described in ref 2.
(17) Eastman, A. *Biochemistry* **1985**, *24*, 5027.
(18) Preut, H.; Frommer, G.; Lippert, B. To be submitted to *Acta Crystallogr.*

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Layered Titanate Pillared with Alumina

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Introduction

The pillaring of synthetic clays with large polymeric aluminum-bearing cations has led to the preparation of a whole new family of microporous materials with well-defined pores of di-

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