of the two MoL_4 (or $MoL_2L'_2$) units to the sign of the CD band. This is summarized in Figure 3. The sector rule predicts that $Mo_2Cl_4(S,S\text{-dppb})_2$ should have either the Λ configuration[4] with a twist angle of between 0 and 45° or the Δ configuration with a twist angle between 45 and 90°. Since the conformational preference of the $Mo_2P_2C_2$ rings (dictated by the *S* configuration of the methyl groups) is expected to impose the Λ configuration on the complex, the sector rule predicts that the twist angle of the two MoP_2Cl_2 units should be less than 45°. This has been confirmed by crystallography:[5] $Mo_2Cl_4(S,S\text{-dppb})_2$ has the Λ configuration and a twist angle of 23°. The Cotton effect shown by the $\delta \rightarrow \delta^*$ transition of $\beta\text{-}Mo_2Cl_4(R\text{-dppp})_2$ implies (given the Δ configuration dictated by the *R* conformation of the methyl group) that this complex also has a twist angle of less than 45°. The CD spectrum of the $\delta \rightarrow \delta^*$ transition of $[Mo_2(R\text{-pn})_4]^{4+}$ has the sign opposite to that found for $\beta\text{-}Mo_2Cl_4(R\text{-dppp})_2$. Since the *R* conformation of the methyl groups will impose the same (Δ) configuration on both complexes, we conclude that the twist between the two MoN_4 units of $[Mo_2(R\text{-pn})_4]^{4+}$ is between 45 and 90°, in contrast to that for the diphosphine complexes. The CD spectrum of $[Mo_2(S,S,\text{-bn})_4]^4$+ has, as expected, a magnitude similar and sign opposite to that of the *R*-pn complex, implying once again a twist of greater than 45°.

Acknowledgment. We thank the U.K. Science and Engineering Research Council for a studentship (I.F.F.)

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(3) Agaskar, P. A.; Cotton, F. A.; Fraser, I. F.; Peacock, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 1851–1853.

(4) The absolute configuration is given by the twist of the two MoL_4 or $MoL_2L'_2$ units about the Mo–Mo bond. If, as one looks down the Mo–Mo bond, the rear MoL_4 unit is rotated counterclockwise, the complex has the Λ configuration and vice versa.

(5) Agaskar, P. A.; Cotton, F. A.; Fraser, I. F.; Manojlovic-Muir, Lj.; Muir, K.; Peacock, R. D., paper in preparation.

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Chemistry of Mono(guanine) Complexes of Cisplatin and Its Relevance to the N7,O6 Chelate Hypothesis

Sir:

Of all the theories put forward to explain the antitumor activity of *cis*-$(NH_3)_2PtCl_2$ (cisplatin) and the inactivity of the *trans* isomer, the so-called N7,O6 chelate hypothesis has evoked the biggest controversy.[1] In brief, this hypothesis assumes the formation of a specific cross-link of *cis*-$(NH_3)_2Pt^{II}$ with the nucleobase guanine through N7 and O6, which would then affect the normal hydrogen-bonding pattern of guanine and lead to base-substitution mutations and eventually to cell death.[2] *trans*-$(NH_3)_2Pt^{II}$ is not capable of forming such a chelate.

Our approach to the question of chelate formation of *cis*-$(NH_3)_2Pt^{II}$ with guanine was as follows: By replacement of the chloro ligand in *cis*-$[(NH_3)_2Pt(G\text{-}N^7)Cl]^+$ (G = 9-ethylguanine, platinated at N7),[3] with the aqua ligand (Figure 1), the behavior of the aqua diammine 9-ethylguanine complex **1** was studied.[4] It was assumed that if chelate formation were to take place, it should occur from precursor **1**.

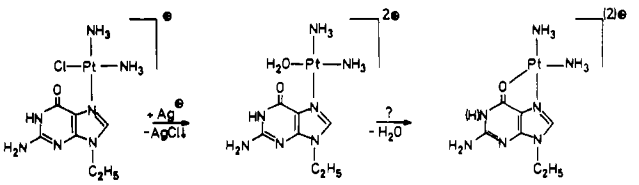

Figure 1. Formation of *cis*-$[(NH_3)_2Pt(G)H_2O]^{2+}$ (**1**).

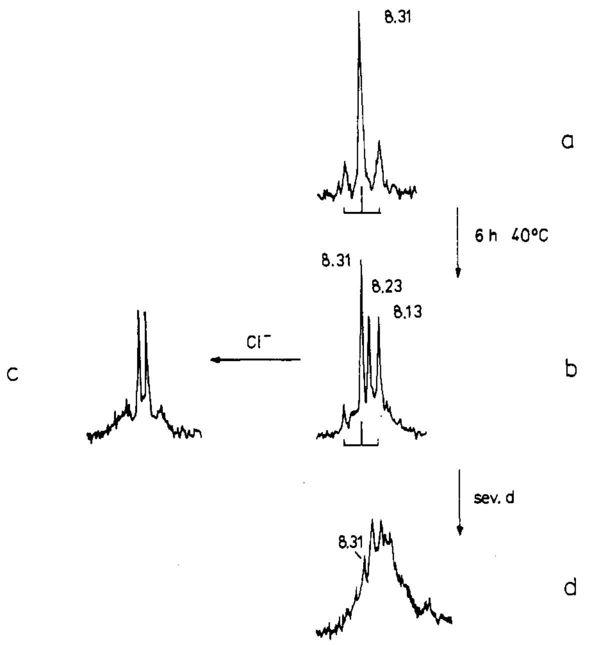

Figure 2. ^1H NMR spectra (H8 resonances only, D_2O, 0.1 M Pt) of *cis*-$[(NH_3)_2Pt(G)D_2O]^{2+}$ (**1**) prepared as described in ref 4: (a) at pD 2.5; (b) at pD 1.8, 6 h at 40 °C after spectrum a; (c) after addition of 30 mg of NaCl and centrifugation of precipitated *cis*-$[(NH_3)_2Pt(G)Cl]Cl$ (**1′**); (d) without addition of NaCl, 4 days at 22 °C after spectrum b at pD 1.6. Internal reference in all cases was $[NMe_4]^+$.

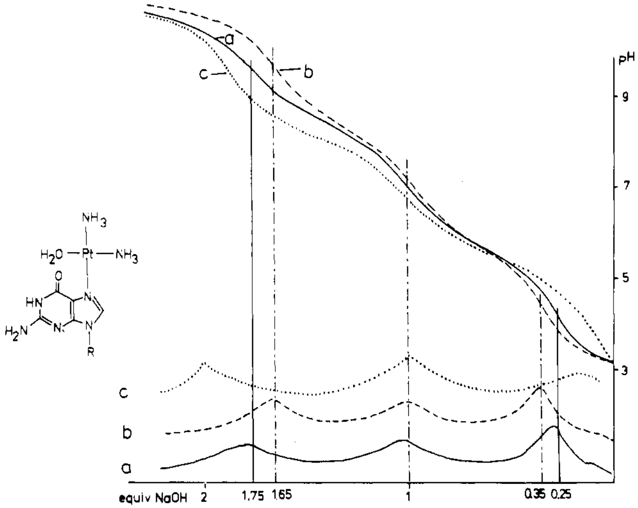

Figure 3. Titration curves (top) and derivatives (bottom): (a) of aged *cis*-$[(NH_3)_2Pt(G)H_2O]^{2+}$ (1 h at 22 °C after preparation according to ref 4 and then diluted as described in ref 6); (b) of aged *cis*-$[(NH_3)_2Pt(G)H_2O]^{2+}$ (20 min at 80 °C and 2 h at 22 °C); (c) under the assumption that **1** remains unchanged.

Figure 2 gives the ^1H NMR spectroscopic changes of **1** with time. As can be seen, the spectrum changes rapidly, and in an early stage of the reaction, two new sets of resonances in exactly 1:1 ratio are formed. The reaction can be stopped at this point by adding an excess of NaCl,[5] which precipitates unreacted **1** as

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(1) For a critical evaluation see, e.g.: (a) Chu, G. Y. H.; Mansy, S.; Duncan, R. E.; Tobias, R. S. *J. Am. Chem. Soc.* **1978**, *100*, 593. (b) Martin, R. B.; Mariam Y. H. *Met. Ions Biol. Syst.* **1979**, *8*, 55.

(2) Rosenberg, B. *Biochimie* **1978**, *60*, 859 and references cited therein.

(3) Raudaschl, G.; Lippert, B. *Inorg. Chim. Acta* **1983**, *80*, L 49.

(4) Preparation of **1**: A 0.1-mmol sample of *cis*-$[(NH_3)_2Pt(G)Cl]Cl\cdot 0.5H_2O$ is suspended in 1 mL of D_2O, and 0.2 mmol of $AgNO_3$ is added. The slurry is stirred at 0–3 °C for 6 h and then centrifuged from AgCl: colorless solution, pD 2.5.

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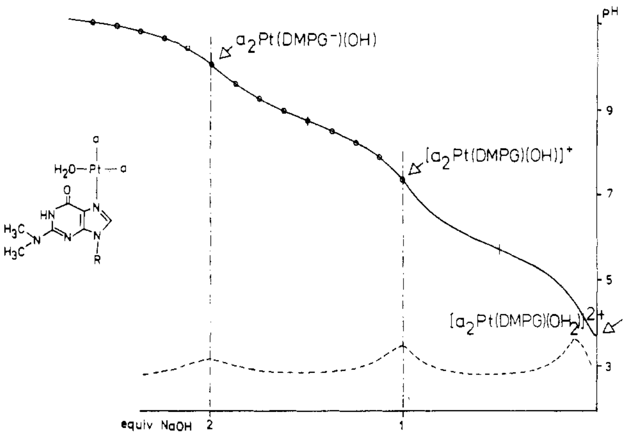

Figure 4. Titration curve (top) and derivative (bottom) of *cis*-$[(NH_3)_2Pt(DMPG)H_2O]^{2+}$ 20 h after preparation (22 °C, 0.02 M Pt). The curves do not change with time.

the insoluble *cis*-$[(NH_3)_2Pt(G\text{-}N^7)Cl]Cl$ (**1′**) and leaves signals due to the new species **2**. Without added NaCl, the reaction, which is accompanied by a drop in pH, proceeds and leads to a series of additional resonances after several days.

Parallel to the ^1H NMR experiments, potentiometric titrations of **1** after different reaction times were performed (Figure 3).[6] The titration curves obtained showed that instead of the two end points expected for the stepwise titration of the H_2O ligand (estimated pK_a 5.5) and the G ligand (estimated pK_a of N(1)H 8.2)[7] after exactly 1 and 2 equiv of NaOH, three end points are reached and that the complete titration uses up less NaOH than expected for unaltered **1**.

Clearly, the reduction in NaOH consumption is due to a condensation reaction with H_2O ligands removed from the Pt coordination sphere and no longer titratable. Of the three possible condensation reactions—chelate formation, OH bridging, G bridging—the first two can be excluded under our reaction conditions for the following reasons: (1) The trans complex, *trans*-$[(NH_3)_2Pt(G\text{-}N^7)H_2O]^{2+}$,[3] which by virtue of its geometry cannot form a chelate, shows the same behavior as the cis isomer.[8] (2) A chelate cannot account for the formation of *two* new sets of ^1H NMR signals in a 1:1 ratio. If formed, it should give just *one* new set. (3) Modification of the guanine ligand at the exocyclic amino group prevents **1** from undergoing changes with time. *cis*-$[(NH_3)_2Pt(DMPG\text{-}N^7)H_2O]^{2+}$ (DMPG = *N,N*-dimethyl-9-propylguanine coordinated to Pt through N7)[9] shows the expected titration curve (Figure 4) and no changes in the ^1H NMR spectrum with time.

There is no good reason to assume that modifying the NH_2 group should prevent chelate or OH-bridge formation, unless these two processes do not take place at all. On the other hand, it is known that methylation of the amino group effectively blocks the N1 site and prevents metal coordination there.[10]

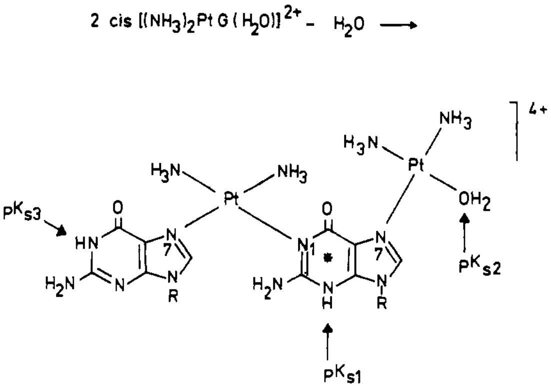

Figure 5. Proposed structure of the dinuclear complex **2**, formed in the early stage of the condensation reaction of *cis*-$[(NH_3)_2Pt(G)H_2O]^{2+}$ (**1**). The sequence of acidic protons to be titrated by NaOH is indicated.

Both the ^1H NMR spectroscopic results and the titration curves of aged **1** are consistent with formation of a guanine-bridged species **2** as indicated in Figure 5. The bridging guanine ligand in **2**, which formally is present in its unusual tautomer form, is very acidic and is titrated first. In a second step, the terminal H_2O ligand is titrated with NaOH and finally the terminal G ligand. The pK_a values of H_2O and terminal G ligands in **2** are not expected to be markedly different from those of the respective groups in **1**, and therefore these groups are titrated together with those of **1**. After 6 h at 40 °C, approximately 50% of **1** has dimerized (total concentration of Pt 0.1 M).[11] At a later stage of the reaction, condensation exceeds the dimer stage, leading to a more complicated NMR spectrum (cf. Figure 2). It is noteworthy, in this respect, that Reedijk and co-workers[12] reported the formation of a trinuclear complex containing two N7,N1-bridged 9-methylhypoxanthine residues as well as a terminal one and that in dinuclear, N7,N1-bridged Pt complexes of 9-methylhypoxanthine[12] and 9-ethylguanine[13] the bridging ligand is of similar acidity as in the case reported here.

Summary. Our data indicate that, under the conditions employed here, an N7,O6 chelate is not formed. Rather, in slightly to moderately acidic solution (where N1 coordination is less favorable than in basic or neutral solution), bridging through N7 and N1 of 9-ethylguanine occurs.

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Supplementary Material Available: Procedure for the preparation of DMPG, the titration curve of aged *trans*-$[(NH_3)_2Pt(G)H_2O]^{2+}$, and the ^1H NMR spectrum of **2** after addition of excess NaCl (3 pages). Ordering information is given on any current masthead page.

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(5) A 30-mg sample of NaCl was added to an aged solution of **1** (6 h at 40 °C) after preparation according to (4), and the white precipitate of *cis*-$[(NH_3)_2Pt(G)Cl]Cl$ was centrifuged off.

(6) Typically, 6-mL samples, containing 0.02 mmol of **1** (obtained according to (4) and then diluted), were titrated with 0.02 N NaOH on a Metrohm E 536 potentiograph.

(7) Cf. pK_a of N7-platinated G in a mixed cytosine,guanine complex of *cis*-Pt^{II}: Faggiani, R.; Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *Inorg. Chem.* **1982**, *21*, 3216.

(8) ^1H NMR: H8 of G in *trans*-$[(NH_3)_2Pt(G\text{-}N^7)D_2O]^{2+}$ (0.1 M Pt, pD 2.5) at 8.33 ppm (cf. (3)), H8 of new species at 8.43 and 8.22 ppm (1:1). The titration curve (cf. supplementary material) of aged solution shows three end points at approximately pH 4, 7, and 10.

(9) Details of the preparation and characterization of DMPG, a new compound, are given in the supplementary material. The preparation and purification of *cis*-$[(NH_3)_2Pt(DMPG)Cl]Cl$ were analogous to that of the corresponding G complex.[3] Anal. C, H, N, Cl, Pt.

(10) Marzilli, L. G.; de Castro, B.; Solorzano, C. *J. Am. Chem. Soc.* **1982**, *104*, 461.

(11) Distribution: 25% dimer, corresponding to 3 × 0.25 = 0.75 acidic proton; 50% monomer, corresponding to 2 × 0.5 = 1 acidic proton. Total amount of protons to be titrated is 1.75 per Pt.

(12) den Hartog, J. H. J.; Salm, M. L.; Reedijk, J. *Inorg. Chem.* **1984**, *23*, 2001.

(13) Raudaschl-Sieber, G.; Schollhorn, H.; Thewalt, U.; Lippert, B., submitted for publication.

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