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Reaction of Cyanide with Pt-Nucleobase Complexes: Preparative, Spectroscopic, and Structural Studies. Unexpected Stability of Pt-Thymine and Pt-Uracil Complexes

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The behavior of a series of model nucleobase complexes of composition *cis*-$(NH_3)_2PtLX$, *trans*-$(NH_3)_2PtLX$, $(NH_3)_3PtL$, *trans*-$L_2Pt(NH_3)X$, *cis*-$[(NH_3)_2PtL]_2^{2+}$ (L = 1-methylcytosine (C), 9-ethylguanine (G), 9-methyladenine (A), deprotonated 1-methyluracil (U), deprotonated 1-methylthymine (T), or deprotonated 1-methylcytosine (C-H) and X = Cl^-, OH^-, H_2O, or another nucleobase) toward CN^- has been studied in aqueous solution by spectroscopic (^1H NMR, IR), preparative, and X-ray crystallographic methods. ^1H NMR studies were performed with samples containing Pt at a concentration of 0.025 M and CN^- of 0.5 M at pD 8.2 ± 0.1 and 30 °C. Monodentate bound G(N7), A(N7), and C(N3) bases were substituted rather quickly by CN^- ($t_{1/2}$ between minutes and 25 h), except from mixed-nucleobase complexes containing one U or T bound through N3. There, replacement of the bases was very slow (G,U) or no reaction occurred at all (C,U). Neither *cis*-$(NH_3)_2PtU_2$ nor *cis*-$(NH_3)_2PtT_2$ showed reaction with CN^-. Rather slow reaction was also observed with the dinuclear complex *cis*-$[(NH_3)_2PtL]_2^{2+}$ with L = deprotonated 1-methylcytosine in head-tail orientation. These results are interpreted in terms of a kinetic stability of U-, T-, and (C-H)-containing complexes as a consequence of steric shielding of Pt by the exocyclic oxygens ortho to the Pt coordination site. Reactions of selected nucleobase complexes with CN^-, performed on a preparative scale, indicated that the first substitution of a ligand in the nucleobase complexes by CN^- leads to a strong labilization of both cis and trans ligands and subsequently to formation of $[Pt(CN)_4]^{2-}$. If a large excess of CN^- is avoided, and in certain cases of low solubility, it is possible to isolate complexes of composition *cis*-$[(NH_3)_2PtLX]_n[Pt(CN)_4]$ (n = 1 or 2, depending on charge of X) and *cis*-$(NH_3)_2LPt(NC)Pt(CN)_3$ with ionic and bridging $[Pt(CN)_4]^{2-}$, respectively. The behavior of Pt-nucleobase complexes toward CN^- is compared with that of simple Pt-ammine complexes, and reaction of thiourea with two selected nucleobase complexes is reported. The relevance of these findings with respect to substitution reactions of Pt-nucleobase complexes and the nature of the tightly DNA-bound Pt, which cannot be removed by excess KCN, is discussed.

Introduction

The antitumor agent *cis*-diamminedichloroplatinum(II), *cis*-$(NH_3)_2PtCl_2$, reacts with DNA in various ways: monofunctionally with binding to a single nucleobase and bifunctionally with formation of cross-links between two bases at the same strand (intrastrand),[2] between two bases of opposite strands (interstrand),[2] or between a nucleobase and a histone protein residue.[3] The possibility of chelate formation with guanine (via N7 and O^6) has also been suggested.[4] There is strong evidence from enzymatic studies with small DNA molecules and from ^1H NMR spectroscopic studies with short oligonucleotides ($10 \geq n \geq 3$) that intrastrand cross-linking of two guanine bases in d(GpG)[5] and/or in d(GpXpG) sequences (X = cytosine, thymine, adenine, guanine)[5b,6] are major products, the formation of which appears to be kinetically favored. On the other hand, there is an increasing awareness of the fact that the tertiary structures of DNA and the local environment (base sequence) may substantially affect the site of platinum coordinate. Findings that binding patterns of *cis*-$(NH_3)_2Pt^{II}$ are altered in the presence of other DNA-binding molecules such as the intercalators ethidium[7] or bleomycin[5a] support this idea. The ultimate question whether there is a specific cross-link responsible for the antitumor activity of *cis*-$(NH_3)_2Pt^{II}$ has not been settled yet. The answer to this question appears to be of particular relevance also with regard to the observed loss of Pt from DNA of living cells, which has been attributed to a DNA repair process,[8] and the possibility of a selective rescue from Pt toxicity through administration of strong nucleophiles such as diethyldithiocarbamate,[9] thiourea,[10,11] thiouracil,[10] methionine,[10] or thiosulfate.[12]

In the course of related studies on the possible reversal of DNA cross-links caused by *cis*-$(NH_3)_2Pt^{II}$, it has been found that it is not possible to fully remove Pt from platinated DNA with cyanide,[13] unless platinum binding occurs in the presence of ethidium bromide.[14] It is suspected that EtdBr prevents bifunctional binding of *cis*-$(NH_3)_2Pt^{II}$ and therefore permits a greatly enhanced recovery of Pt upon CN^- reversal. The fact that up to 10% of the DNA-bound platinum is not removed by a large excess of CN^- is surprising since cyanide exercises a strong trans effect, leading to the very stable $[Pt(CN)_4]^{2-}$ anion (stability constant $\log \beta_4 \sim 65$-75)[15] from almost any Pt^{II} species containing N or O donors. It is only these donor atoms that are believed to be relevant for *cis*-$(NH_3)_2Pt^{II}$ interactions with DNA.

At least two possible explanations for this phenomenon can be seen: (1) The Pt-nucleobase bond resistant to CN^- is very thermodynamically stable. It is felt that only a Pt-sulfur or Pt-carbon bond to a nucleobase could accomplish this. While

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metal–carbon bonds in nucleic acid derivatives are documented for Hg,[16] Ru,[17] and Pd,[18] no similar findings have been reported thus far for Pt. (2) There may be kinetic reasons for this stability. Either the DNA tertiary structure, that is the neighboring bases, prevents easy access of CN^- or the cross-link is of inherent kinetic stability due to favorable shielding of the metal center by exocyclic groups of the platinated base.

It has been the purpose of the present study to improve the understanding of the nature of the strongly bound cisplatin on DNA by studying the reactivity of a large number of complexes of *cis*-$(NH_3)_2Pt^{II}$ with the model nucleobases 9-ethylguanine (G), 9-methyladenine (A), 1-methylcytosine (C), 1-methylthymine (T), and 1-methyluracil (U) toward a large excess of cyanide. Without a C-bound nucleobase–Pt complex available, this study cannot give an answer to the question of thermodynamic stability. With isolated model nucleobases, an answer to the question of stability due to local structural effects cannot be expected either. However, as will be shown, there is the possibility of inherent kinetic stability of Pt–nucleobase complexes toward cyanide if Pt coordinates to the N3 sites of thymine or uracil. A preliminary report on this finding has appeared.[19]

Experimental Section

Preparation of Compounds. The following compounds were prepared as described elsewhere: *cis*-$(NH_3)_2PtCl_2$,[20] *trans*-$(NH_3)_2PtCl_2$,[21] $[(NH_3)_3PtCl]Cl$,[22] $[(NH_3)_4Pt]Cl_2$,[23] $K_2[Pt(CN)_4]$,[24] *cis*-$(NH_3)_2PtT_2$,[25] *cis*-$(NH_3)_2PtU_2$,[26] *cis*-$[(NH_3)_2PtT]_2(NO_3)_2$ (head–head),[27] *cis*-$[(NH_3)_2PtUC](NO_3)$,[28] *cis*-$[(NH_3)_2PtUG](ClO_4)$,[29] *cis*-$[(NH_3)_2PtU(H_2O)](NO_3)$,[30] *cis*-$[(NH_3)_2PtC_2](NO_3)_2$,[31] *cis*-$[(NH_3)_2PtC(H_2O)](NO_3)_2$,[32] *cis*-$[(NH_3)_2Pt(C-H)]_2(NO_3)_2$ (head–tail),[33] *cis*-$[(NH_3)_2PtG_2]Cl_2$,[34] *cis*-$[(NH_3)_2PtG(Cl)]Cl$,[35] $[(NH_3)_3PtG]Cl_2$, *cis*-$[(NH_3)_2PtGC](ClO_4)2$,[36] *trans*-$[(NH_3)_2PtG(Cl)]Cl$,[35] *trans*-$[(NH_3)_2PtGC](ClO_4)_2$,[37] *trans*-$[(NH_3)PtG_2C](ClO_4)_2$,[38] and *trans*-$[(NH_3)_2PtAC](ClO_4)_2$.[39]

cis-$[(NH_3)_2PtC(Cl)]_2[Pt(CN)_4]$ (**1**) was prepared as follows: *cis*-$[(NH_3)_2PtC(Cl)]Cl\cdot H_2O$[32] (0.22 mmol) was dissolved in 2 mL of H_2O, and KCN (0.22 mmol) was added. The solution (pH 10.7) was brought to pH 9 by means of 1 mL of 0.1 N HCl and the solution kept in a stoppered flask for 2 days at 22 °C and then for 3 days at 3 °C. Colorless to slightly yellowish cubes that appeared as early as 20 h after start of the reaction were then collected on a filter and briefly dried in air; field 40 mg. With an excess of KCN, e.g. 3 equiv per Pt, the yield of **1** decreased to 15 mg. Anal. Calcd for $C_{14}H_{26}N_{14}O_2Cl_2Pt_3$: N, 18.18. Found: N, 18.39. The identity of **1** was confirmed by a crystal structure analysis.[40]

***cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]\cdot 2H_2O$ (2).** *cis*-$[(NH_3)_2PtC_2]Cl_2$[31] (0.125 mmol) was dissolved in 2.5 mL of H_2O, and KCN (2.5 mmol) was added. The strongly alkaline solution was then brought to pH 8.3 by means of 2 N HCl and the solution kept for 24 h at 30 °C in a stoppered flask. Then, 25 mg of crystalline **2** was collected and dried in air. Anal. Calcd for $C_{14}H_{24}N_{12}O_4Pt_2$: C, 20.64; H, 2.98; N, 20.64; Pt, 47.89. Found: C, 20.76; H, 3.04; N, 20.49; Pt, 47.5. The identity of **2** was confirmed by a crystal structure analysis.[40]

***cis*-$[(NH_3)_2PtG_2][Pt(CN)_4]\cdot 3H_2O$ (3).** *cis*-$[(NH_3)_2PtG_2](NO_3)_2\cdot 2H_2O$[41] (0.1 mmol) was dissolved in 3 mL of H_2O, and KCN (0.4 mmol) was added. The solution (pH 9.6) was kept for 1 day at 22 °C and then for 3 days at 3 °C, then centrifuged from some unidentified precipitate (2 mg), and finally brought to pH 4.5 with 1 N HNO_3. The precipitate that formed slowly was filtered off after 24 h at 3 °C (10 mg). From the resulting clear solution was isolated 10 mg of colorless cubes of **3** after another 24 h at 3 °C. The compound obtained was, according to its IR spectrum, identical with that obtained by precipitation of *cis*-$[(NH_3)_2PtG_2]X_2$ (X = Cl^-, NO_3^-) with $K_2Pt(CN)_4$. The elemental analysis and crystal structure of **3** will be reported elsewhere.[41]

***cis*-$[(NH_3)_2PtC(OH)]_2[Pt(CN)_4]$ (4).** *cis*-$[(NH_3)_2PtC(OH)](NO_3)\cdot 2H_2O$[32] (0.12 mmol) was dissolved in 0.5 mL of H_2O (pH 9.6), and $K_2Pt(CN)_4\cdot 3H_2O$ (0.06 mmol) was added. The clear solution was kept in ice for 24 h and then filtered from 35 mg of colorless, shiny crystal plates. In air, the crystals loose transparency. Anal. Calcd for $C_{14}H_{28}N_{14}O_4Pt_3$ (air-dried sample): C, 16.14; H, 2.71; N, 18.83; Pt, 56.18. Found: C, 16.27; H, 2.79; N, 18.87; Pt, 57.9. A product that according to the IR spectrum, was identical with **4** was obtained if *cis*-$[(NH_3)_2PtC(H_2O)](NO_3)_2\cdot H_2O$[32] was treated with KCN (2 equiv per Pt) in aqueous solution (pH 9.4) and the solution concentrated to a small volume. IR: $\nu(Pt(CN)_4^{2-})$ 2120 vs, 2080 w cm^{-1}; $\nu(OH^-)$ 3500 vs cm^{-1}.

***cis*-$[(NH_3)_2CPt(NC)Pt(CN)_3]\cdot 3H_2O$ (5).** *cis*-$[(NH_3)_2PtC(H_2O)](NO_3)_2\cdot H_2O$[32] (0.5 mmol) was dissolved in 7 mL of H_2O (pH 2.4), and $K_2Pt(CN)_4\cdot 3H_2O$ (0.5 mmol) was added. After 1 h a pale yellow precipitate was filtered off, washed with 1 mL of cold water, and dried in air (glassy material, 170 mg). Anal. Calcd for $C_9H_{19}N_9O_4Pt_2$: C, 15.28; H, 2.71; N, 17.82; Pt, 55.14. Found: C, 15.42; H, 2.76; N, 18.43; Pt, 55.4. IR: ν(CN) 2200 s, 2150 sh, 2130 vs cm^{-1}.

***cis*-$[(NH_3)_2Pt(C-H)]_2[Pt(CN)_4]\cdot 2H_2O$ (head–tail) (6).** *cis*-$[(NH_3)_2Pt(C-H)]_2(NO_3)_2$[33] (0.05 mmol) was dissolved in 1.5 mL of H_2O, and KCN (0.3 mmol) was added. The solution (pH 11.2) was then heated to 90 °C for 10 min and then kept at 50 °C for 5 h and 15 h at 22 °C. A 20-mg portion of **6** was centrifuged, washed with 1 mL of H_2O, and dried in air. Alternatively, **6** was prepared by precipitating *cis*-$[(NH_3)_2Pt(C-H)]_2^{2+}$ (nitrate salt) with 1 equiv of $[Pt(CN)_4]^{2-}$ (potassium salt); yield 90%. Anal. Calcd for $C_{14}H_{24}N_{14}O_2Pt_3$: C, 16.14; H, 2.71; N, 18.83; Pt, 56.18. Found: C, 16.46; H, 2.71; N, 18.20; Pt, 55.3. IR: $\nu(Pt(CN)_4^{2-})$ 2130 vs, 2075 w, sh cm^{-1}; no NO_3^- modes; cation vibrations virtually identical with those of starting compound.

***cis*-$[(NH_3)_2GPt(NC)Pt(CN)_3]\cdot 2H_2O$ (7).** *cis*-$[(NH_3)_2PtG(Cl)]Cl\cdot H_2O$[35] (0.25 mmol) was treated with $AgNO_3$ (0.5 mmol) in 3 mL of H_2O at 22 °C for 12 h, then AgCl was centrifuged, and $K_2Pt(CN)_4\cdot 3H_2O$ (0.25 mmol) was added with stirring to the solution (pH 2.1). The precipitate formed was filtered, washed with 2 mL of H_2O and then acetone and ether, and finally dried in air; yield 50 mg. Anal. Calcd for $C_{11}H_{19}N_{11}O_3Pt_2$: C, 17.77; H, 2.58; N, 20.73; Pt, 52.47. Found: C, 17.85; H, 2.63; N, 20.78; Pt, 52.4. IR: ν(CN) 2200 s, 2140 vs cm^{-1}.

***cis*-$[(NH_3)_2UPt(NC)Pt(CN)_2(CN)PtU(NH_3)_2]\cdot 6H_2O$ (8).** It was prepared in analogy to **5** from *cis*-$[(NH_3)_2PtU(H_2O)](NO_3)$[30] (0.25 mmol) and $K_2Pt(CN)_4\cdot 3H_2O$ (0.125 mmol) at pH 3. The first precipitate that had formed within 15 min was discarded, and the pale yellow filtrate was evaporated under N_2 at 22 °C to dryness. Brief treatment of the glassy residue with 1 mL of H_2O and filtration left 30 mg of a

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Table I. Displacement of Nucleobases from Pt–Nucleobase Complexes by Excess Cyanide[a]

fast $t_{1/2}$[b] ≤ 3 h	moderate 3–25 h	slow 50–300 h	no reaction
cis-$[a_2PtC(H_2O)]^{2+}$	$[a_3PtG]^{2+}$	*cis*-$[a_2PtU(H_2O)]^{+}$	*cis*-a_2PtT_2
cis-$[a_2PtG(Cl)]^{+}$	*cis*-$[a_2PtG_2]^{2+}$	*cis*-$[a_2PtUG]^{+}$	*cis*-a_2PtU_2
trans-$[a_2PtAC]^{2+}$	*cis*-$[a_2PtC_2]^{2+}$	*cis*-$[a_2Pt(C-H)]_2^{2+}$	*cis*-$[a_2PtUC]^{+}$
trans-$[a_2PtG(Cl)]^{+}$	*cis*-$[a_2PtGC]^{2+}$		
trans-$[a_2PtGC]^{2+}$	*trans*-$[aPtG_2C]^{2+}$		

[a] Concentrations: 0.025 M Pt; 0.5 M CN^-. pD 8.2 ± 0.1. [b] Time necessary to displace 50% of the nucleobase(s).

slightly beige, shiny material. Anal. Calcd for $C_{14}H_{34}N_{12}O_{10}Pt_3$: C, 15.07; H, 3.08; Pt, 52.50. Found: C, 14.52; H, 2.84; Pt, 52.5. IR: ν(CN) 2200 s, 2140 s cm^{-1}; no NO_3^- modes.

Treatment of *trans*-$[(NH_3)_2PtG(Cl)]Cl$ with KCN. *trans*-$[(NH_3)_2PtG(Cl)]Cl$[35] (0.14 mmol) was suspended in 1.5 mL of H_2O, and KCN (0.28 and 0.56 mmol, respectively) was added. The slurry (pH 11) was stirred at 22 °C for 40 and 70 min, respectively; the precipitate was filtered, washed with H_2O, air-dried, and studied by IR spectroscopy. It consisted of a mixture of neutral G and *trans*-$(NH_3)_2Pt(CN)_2$. Treatment of the precipitate with Me_2SO removed most of the G and left the cyano complex behind.

***trans*-$(NH_3)_2Pt(CN)_2$.** *trans*-$(NH_3)_2PtCl_2$ (0.2 mmol) was suspended in 2 mL of H_2O, KCN (0.8 mmol) was added, and the mixture was stirred in a stoppered flask at 22 °C. Within several minutes, the yellow sample became white. After 20 min the mixture was cooled to 3 °C; the precipitate was collected and washed with 0.3 mL of ice cold water; yield 30 mg. Anal. Calcd for $C_2H_6N_4Pt$: C, 8.54; H, 2.15; N, 19.93; Pt, 69.38. Found: C, 8.48; H, 2.10; N, 20.42; Pt, 69.7. The yield decreased to ca. 2–3 mg when the mixture was kept at 45 °C for 1 h. From the filtrate was isolated $K_2Pt(CH)_4 \cdot 3H_2O$ on evaporation.

trans-$(NH_3)_2Pt(CN)_2$ was obtained in a similar way from $[(NH_3)_3PtCl]Cl$ (0.125 mmol in 0.5 mL of H_2O) after addition of KCN (0.25 mmol); white precipitate, 30 mg. IR (<1400 cm^{-1}): 1330 vs, 870 w, b, 535 w, 498 s, 467 s, 412 vs cm^{-1}.

$[(NH_3)_4Pt][Pt(CN)_4]$. $[(NH_3)_4Pt]Cl_2$ (0.5 mmol) was dissolved in 4 mL of H_2O (pH 7.4), and KCN (4 mmol) was added. The solution (pH 11.8) was kept at 3 °C for 24 h; then, the white precipitate was filtered, washed twice with 2 mL of H_2O, acetone, and ether, and finally dried in air. Anal. Calcd for $C_4H_{12}N_8Pt_2$: C, 8.54; H, 2.15; N, 19.93; Pt, 69.38. Found: C, 8.52; H, 2.22; N, 19.62; Pt, 68.7. If the solution is heated to 70 °C for a few minutes, only $K_2Pt(CN)_4 \cdot 3H_2O$ is obtained as colorless needles on concentration of the solution.

In an alternative way, $[(NH_3)_4Pt][Pt(CN)_4]$ was obtained by mixing $[(NH_3)_4Pt]Cl_2$ and $K_2Pt(CN)_4 \cdot 3H_2O$ in 1:1 ratio and filtering the precipitate after 5 min. IR (<1400 cm^{-1}): 1350, 1340 vs, 870, 830 vs, 502 s, 474 m, 425 sh, 420 vs cm^{-1}.

***cis*-$[(NH_3)_2Pt(NC)_2Pt(CN)_2] \cdot 2H_2O$.** *cis*-$(NH_3)_2PtCl_2$ (0.5 mmol) was reacted with $AgNO_3$ (1 mmol) in 4 mL of H_2O for 12 h; then, the AgCl was filtered and $K_2Pt(CN)_4 \cdot 3H_2O$ (0.5 mmol) was added to the solution (pH 2.1). The mixture became rapidly cloudy, and a yellow precipitate formed. It was filtered, washed with H_2O, and dried in air; yield 160 mg. Anal. Calcd for $C_4H_{10}N_6O_2Pt_2$: C, 8.51; H, 1.79; N, 14.89; Pt, 69.13. Found: C, 8.28; H, 1.74; N, 14.80; Pt, 70.0. Thermogravimetry indicated loss of 2 molecules of water, beginning at 65 °C, with most of the water removed at 110 °C, and constant weight above 200 °C until decomposition above 250 °C. The IR spectrum of the fully dehydrated compound shows some differences as compared to the hydrated sample, which may indicate that some of the material isolated from water actually is *cis*-$[(NH_3)_2(H_2O)Pt(NC)Pt(CN)_3] \cdot H_2O$ (cf. text).

Thermogravimetry. The thermogravimetric study was performed with a Perkin-Elmer TGS-2 system at a rate of 10 °C min^{-1}.

IR Spectra. They were taken on a Perkin-Elmer 580 grating spectrometer as KBr pellets and Nujol mulls (CsI windows).

^1H NMR Spectra. Samples of the Pt–nucleobase complexes were dissolved in D_2O to give solutions of c_{Pt} 0.05 M. These solutions were then mixed in 1:1 ratio (by volume) with CN^--containing solutions of c_{CN} ≃1.0 M, thus giving final concentrations of c_{Pt} 0.025 M and c_{CN} ≃0.5 M. Cyanide stock solutions were made freshly by dissolving solid KCN in D_2O and adjusting the pD to ca. 8.2 ± 0.1 by means of 2 N HCl. This procedure was performed in a hood. On prolonged standing (several days) at 22 °C in a stoppered flask, the CN^--containing stock solutions became brownish and eventually viscous.

The NMR samples were kept at 30 °C throughout the reaction time, and ^1H NMR spectra (JEOL JNM-FX 60 Fourier transform spectrometer, $N(CH_3)_4^+$ internal standard) were recorded at intervals. The resonances of the librated nucleobases were identified by comparison with the spectra of the free bases in D_2O at pD 8. Occasionally, stacking interactions between two bases, e.g. C and A, were observed which caused upfield shifts of the CH resonances as compared to the individual components. pD values (pH meter reading plus 0.4) were measured immediately after mixing solutions of the Pt complex and the cyanide and after each spectrum recorded. No major changes in pD were observed as reactions proceeded. With N7-platinated G, no significant isotopic exchange of the proton at C8 was observed.

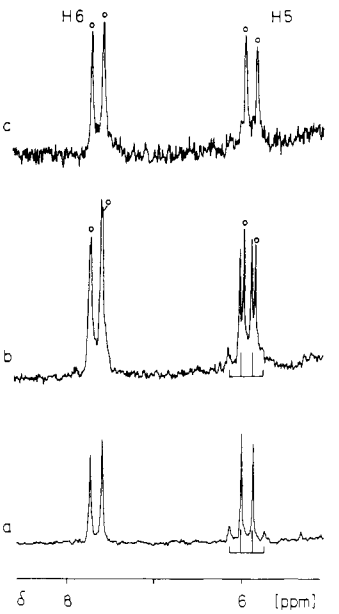

Figure 1. ^1H NMR spectra (H5, H6 resonances only) of *cis*-$[(NH_3)_2PtC_2]Cl_2$ (0.025 M): (a) immediately after addition of CN^- (0.5 M, D_2O, pD 8.3); (b) after 12 h at 30 °C (Approximately 50% of the bound C is replaced. The spectrum consists of signals due to starting compound and free C (circles)); (c) after 50 h at 30 °C (At that stage, the solution contains some precipitate of *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]$ (cf. text)).

Results and Discussion

^1H NMR Studies. In Table I the Pt–nucleobase complexes are listed that were reacted with cyanide on an NMR scale. They are divided into four categories on a qualitative basis which refers to the relative rates of nucleobase displacement after addition of CN^- under identical reaction conditions (Pt:CN^- = 1:20; 30 °C; pD ≃8). No attempts were made to measure the exact kinetics of the reactions for a variety of reasons. For example, occasionally reactions were too fast to be followed by FT NMR methods, and only the complete time of the reactions were established. In other cases, e.g. with *cis*- and *trans*-$[(NH_3)_2PtG(Cl)]Cl$, addition of CN^- resulted in an immediate formation of a precipitate, which gradually redissolved as reaction proceeded or, as with *cis*-$[(NH_3)_2PtC_2](NO_3)_2$, the reaction came to a stop due to precipitation of insoluble *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]$ (vide infra). Finally, there was some indication (cf. Experimental Section) that the CN^--containing solutions were not stable at pH 8, possibly due to polymerization reactions of HCN. In Figure 1, spectra of a representative example, *cis*-$[(NH_3)_2PtC_2]^{2+}$, obtained after different time periods following addition of excess cyanide, are given.

There are several aspects of the reactions studied that are noteworthy: (1) With one exception (*trans*-$[(NH_3)_2PtG(Cl)]Cl$, cf. Preparative Studies), intermediates between the starting

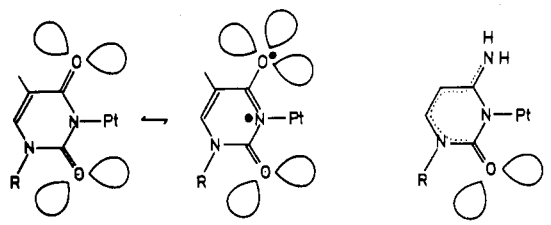

Figure 2. Different degrees of Pt shielding in N3-platinated U(T) and C.

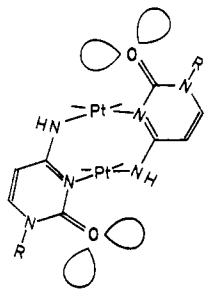

Figure 3. Shielding of Pt in the head–tail dimer containing deprotonated 1-methylcytosine bridges.

complexes and the final product ($K_2Pt(CN)_4$) were not observed. This means that once the first ligand (NH_3 or nucleobase) is displaced by CN^-, all other three original ligands are lost quickly with no (by the ^1H NMR technique) intermediates detectable. This finding is in agreement with results from preparative studies (vide infra) that showed that it is not possible to isolate mixed cyanide–nucleobase complexes by treating mixed ammine–nucleobase complexes with 1 or 2 equiv of KCN. (2) There appears to be a trend toward faster ligand substitution in complexes containing a single base (C or G) as compared to complexes containing two nucleobases. The present data do not, however, permit any statement concerning differences in the rates of ligand substitutions in complexes of cis and trans Pt^{II}. (3) Complexes containing N3-bound U or T react very slowly with CN^- or not at all. We attribute this finding to the effective shielding of the Pt through the lone electron pairs at the exocyclic oxygens adjacent to the Pt binding site which prevent easy access of the cyanide nucleophile from the axial positions of Pt (Figure 2). A single exocyclic oxygen in ortho position to the Pt binding site such as in complexes of cytosine apparently is not sufficient to prevent coordination of CN^-; an exocyclic amino group, as in C, has no effect either, possibly because the formal lone electron pair at N4 is delocalized into the ring π system. This interpretation is supported by the observation that steric crowding about the Pt, as in the tris(nucleobase) complex *trans*-$[(NH_3)PtG_2C]^{2+}$, has no great effect in slowing down the reaction with CN^-. One might speculate that with *cis*-$[(NH_3)_2PtC_2]^{2+}$ only the rotamer with head–head-arranged C ligands is reacting with CN^-, yet not the head–tail rotamer. In the head–tail arrangement of the two bases, as found in the solid state for both the NO_3^- salt[31,42] and the $Pt(CN)_4^{2-}$ salt,[40] the oxygens of each cytosine should have a similar shielding effect as a single U or T ligand. (4) The slow reaction of the dinuclear complex containing two head–tail-arranged 1-methylcytosinato ligands coordinated to Pt through N3 and N4 might be explained in similar terms (Figure 3): The exocyclic oxygens above the Pt atoms, combined with the rigidity of the complex and the strength of the Pt–N(cytosine) bonds, could prevent easy access of CN^- and formation of a trigonal-bipyramidal transition state. (5) The behavior of uracilato- and thyminato-bridged head–tail dimers differs substantially from that of the cytosinato-bridged dimer mentioned above: with U and T head–tail dimers an equilibrium exists with the mononuclear *cis*-$[(NH_3)_2PtL(H_2O)]^+$,[30] and both nucleophiles such as chloride[43]

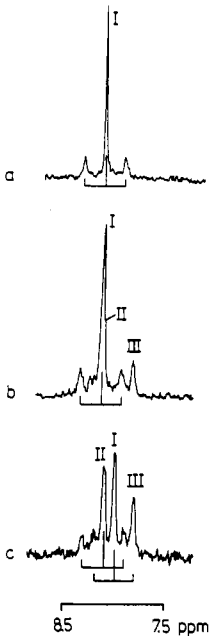

Figure 4. ^1H NMR spectra (H8 resonances): (a) *cis*-$[(NH_3)_2PtG_2](NO_3)_2$ (I) (0.05 M Pt) in D_2O, pD 7; (b) spectrum 40 h after addition of thiourea, tu (0.2 M), with sample kept at 22 °C [Signal III is due to G]; (c) spectrum (b) after 6 h at 55 °C, pD now 9.0 [The intensity of the G signal III in (c) does not reflect its actual concentration, since G partially has precipitated. The signal I is shifted upfield due to partial deprotonation of the G ligands in I. Signal II is tentatively assigned to *trans*-$[(tu)_2Pt(NH_3)G]^{2+}$.]

and electrophiles such as Ag^+[44] shift the equilibrium toward the mono(nucleobase) complex. Reaction with CN^-, which is very slow, thus proceeds from the mononuclear complex rather than the dimer. With the head–head dimers *cis*-$[(NH_3)_2PtL]_2^{2+}$, Cl^- has been shown to cleave the Pt–O4 bond with formation of the bis(nucleobase) complex and *cis*-$(NH_3)_2PtCl_2$.[43] If CN^- is used instead of Cl^-, instantaneously the following reaction (L = U or T) takes place:

$$cis\text{-}[(NH_3)_2PtL]_2^{2+} + 4CN^- \rightarrow cis\text{-}(NH_3)_2PtL_2 + Pt(CN)_4^{2-} + 2NH_3$$

Due to the inertness of *cis*-$(NH_3)_2PtL_2$, reaction stops at this stage, and there is no further displacement of L.

Comparison with Thiourea. Thiourea has been demonstrated to restore the biological activity of platinated DNA through reversal of cross-links induced by cis and trans Pt^{II}.[11] While this fact by itself does not prove that all Pt is actually removed—monofunctionally bound (dien)Pt^{II} has little or no effect on the replication of DNA[45] —we were interested in finding out how thiourea compares with CN^- in its reactivity toward two selected nucleobase complexes, *cis*-$(NH_3)_2PtU_2$ and *cis*-$[(NH_3)_2PtG_2]^{2+}$. Mixing *cis*-$(NH_3)_2PtU_2$ (0.05 M Pt) and thiourea (0.2 M) in D_2O and keeping the solution (pH 7.7) at 55 °C, we found that within 48 h only 5% of the bound uracil had been replaced by thiourea. No reaction was observed if the sample was kept at 22 °C, not even after 16 days. On the other hand, *cis*-$[(NH_3)_2PtG_2]^{2+}$, under comparable conditions (concentration, temperature), reacted with thiourea as evident from the increase in pD (from 6.6 to 9 after 6 h at 55 °C) due to loss of NH_3 from the complex, from formation of a yellow color ($[Pt(tu)_4]^{2+}$), and from the appearance of signals due to free 9-ethylguanine in the ^1H NMR spectrum (Figure 4). After 3 h at 55 °C and 40 h at 22 °C, approximately 40% of the bound G had been substituted by thiourea. Unlike with CN^-, with thiourea an intermediate, which is tentatively assigned to *trans*-$[(tu)_2Pt(NH_3)G]^{2+}$, can be detected in the ^1H NMR spectrum.[46]

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(43) Neugebauer, D.; Lippert, B. *Inorg. Chim. Acta* **1982**, *67*, 151.
(44) Thewalt, U.; Neugebauer, D.; Lippert, B. *Inorg. Chem.* **1984**, *23*, 1713.
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Preparative Studies. Parallel to the ^1H NMR solution studies, selected model nucleobase complexes such as *cis*-$[(NH_3)_2PtCX]^{n+}$ (X = Cl^-, H_2O, C), *cis*-$[(NH_3)_2PtG_2]^{2+}$, *cis*-$(NH_3)_2PtU_2$, and *cis*-$[(NH_3)_2Pt(C-H)]_2^{2+}$ (head–tail) were treated with stoichiometric amounts of KCN (2–4 equiv per Pt) without pH adjustment, and the reaction products were characterized. It was the intention to isolate, if possible, intermediates with the original ligands partially replaced by CN^- in order to get some insight in the sequence of ligand-substitution reactions in these nucleobase complexes. In short, these attempts failed with one exception (vide infra). Our findings can be summarized as follows: (1) There is no substitution of 1-methyluracil or 1-methylthymine from the respective bis(nucleobase) complex of cis Pt^{II}. For example, in the presence of a fourfold excess of KCN over Pt, neither at 22 °C (H_2O, pH 11.5, 20 days) nor at 90 °C (4 h) is there any sign of displacement of U or T. (2) *trans*-$[(NH_3)_2PtG(Cl)]Cl$ reacted, when treated with 2 equiv of KCN, according to

$$trans\text{-}[(NH_3)_2PtG(Cl)]^+ + 2CN^- \rightarrow trans\text{-}(NH_3)_2Pt(CN)_2 + G + Cl^-$$

Thus, cyanide replaces Cl^- and G in trans position to ech other, yet not NH_3. It is suspected that the low solubility of *trans*-$(NH_3)_2Pt(CN)_2$ is the reason why this intermediate, unlike in the examples mentioned in (3), can be isolated. (3) With a low CN^-:Pt ratio (2:1) applied, in several cases crystalline compounds of composition *cis*-$[(NH_3)_2PtL_1L_2]_n[Pt(CN)_4]$ (with L_1 = nucleobase, L_2 = nucleobase or Cl^- or OH^-, n = 1 or 2) have been isolated: *cis*-$[(NH_3)_2PtC(Cl)]_2[Pt(CN)_4]$ (**1**), *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]$ (**2**), *cis*-$[(NH_3)_2PtG_2][Pt(CN)_4]$ (**3**), *cis*-$[(NH_3)_2PtC(OH)]_2[Pt(CN)_4]$ (**4**), and *cis*-$[(NH_3)_2Pt(C-H)]_2[Pt(CN)_4]$ (h–t) (**6**). The identity of these complexes has been established by elemental analysis, IR spectroscopy, and X-ray analysis, as well as alternative preparation through crystallization of the respective *cis*-$[(NH_3)_2PtL_1L_2]^{n+}$ species with the $[Pt(CN)_4]^{2-}$ anion. The formation of these complexes can be rationalized if one assumes that substitution of the first ligand of $[(NH_3)_2PtL_1L_2]^{n+}$ by CN^- leads to a very strong labilization of both ligands trans and cis to cyanide with subsequent substitution of all the original ligands. Rather than forming mixed cyanide–nucleobase–ammine complexes, cyanide substitutes for all four ligands to give $[Pt(CN)_4]^{2-}$ until all CN^- is used up. Then, reaction stops and unreacted nucleobase complex precipitates as the tetracyanoplatinate salt:

$$[(NH_3)_2PtL_1L_2]^{2+} + 2CN^- \rightarrow 0.5[Pt(CN)_4]^{2-} + NH_3 + 0.5L_1 + 0.5L_2 + 0.5[(NH_3)_2PtL_1L_2]^{2+}$$

$$0.5[(NH_3)_2PtL_1L_2]^{2+} + 0.5[Pt(CN)_4]^{2-} \rightarrow [(NH_3)_2PtL_1L_2][Pt(CN)_4]$$

Occasionally we found that tetracyanoplatinate salts of complexes could be isolated even in the presence of a large excess of KCN, if the solubility of the complex formed was sufficiently low (e.g., *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]$). (4) With nucleobases containing an aqua ligand in the first coordination sphere of Pt, $[(NH_3)_2PtL(H_2O)]^{n+}$, the possibility exists that the cyano group in $[Pt(CN)_4]^{2-}$ acts as a bridge via its N atom to the Pt of the nucleobase complex. As in other systems containing bridging cyano ligands,[47] the presence of CN^- bridges may be deduced from IR spectroscopy. A comparison of the CN stretching frequencies of $K_2Pt(CN)_4 \cdot 3H_2O$ and the crystallographically characterized complexes **1–3**, as well as those of products obtained from direct reaction of $[(NH_3)_2PtL(H_2O)]^{n+}$ with KCN or via precipitation with $[Pt(CN)_4]^{2-}$, strongly suggests that this indeed is the case (Figure 5). With L = G, the stretching mode of the bridging cyano group is shifted to higher energy by 70 cm^{-1} as compared to the terminal CN^- group. With L = U, the two bands are

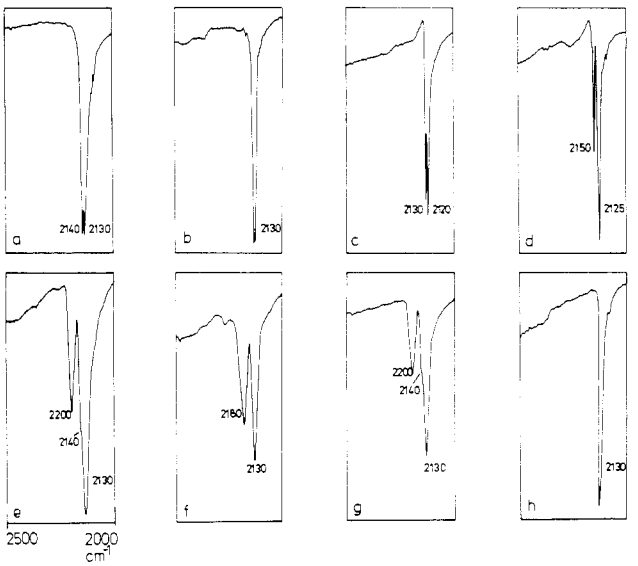

Figure 5. ν(CN) modes in the IR spectra (KBr): (a) $K_2Pt(CN)_4 \cdot 3H_2O$; (b) *cis*-$[(NH_3)_2PtG_2][Pt(CN)_4]$ (**3**); (c) *cis*-$[(NH_3)_2PtC(Cl)]_2[Pt(CN)_4]$ (**1**); (d) *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]$ (**2**); (e) *cis*-$(NH_3)_2GPt(NC)Pt(CN)_3$ (**7**); (f) *cis*-$[(NH_3)_2PtU]_2[(NC)Pt(CN)_3]$ (**8**); (g) *cis*-$(NH_3)_2CPt(NC)Pt(CN)_3$ (**5**); (h) *cis*-$[(NH_3)_2PtC(OH)]_2[Pt(CN)_4]$ (**4**).

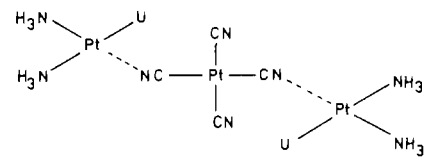

Figure 6. Proposed structure of *cis*-$[(NH_3)_2PtU]_2[(NC)Pt(CN)_3]$ (**8**).

separated by 50 cm^{-1} (Figure 6). It should be noted, however, that splitting of the ν(CN) of nonbridging $[Pt(CN)_4]^{2-}$, as a consequence of a lowering of the D_{4h} symmetry within the crystal, may be as large as 25 cm^{-1}, as found in the case of *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4]$. Bridge formation is prevented if the aqua ligand in $[(NH_3)_2PtL(H_2O)]^{2+}$ is replaced by a hydroxo group. *cis*-$[(NH_3)_2PtC(OH)]^+$ crystallizes with $[Pt(CN)_4]^{2-}$ as counterion, as evident from the single ν(CN) mode at 2120 cm^{-1} and the sharp ν(OH) band at 3500 cm^{-1}.

Structural Studies. In order to unambiguously confirm the reaction sequence of Pt–nucleobase complexes with low concentrations of KCN, crystal structures of three products have been performed: *cis*-$[(NH_3)_2PtC(Cl)]_2[Pt(CN)_4]$ (**1**), *cis*-$[(NH_3)_2PtC_2][Pt(CN)_4] \cdot 2H_2O$ (**2**), and *cis*-$[(NH_3)_2PtG_2][Pt(CN)_4] \cdot 3H_2O$ (**3**). Details of the structures will be reported elsewhere.[40,41] At this point it should only be noted that the crystal data[40] of **1** and **2** do not reveal any significant differences from those of two modifications of *cis*-$[(NH_3)_2PtC(Cl)](NO_3)$[48] and of *cis*-$[(NH_3)_2PtC_2](NO_3)_2 \cdot C$,[31,42] except that **2** does not contain the extra C ligand in the lattice. The structure of the bis(9-ethylguanine) complex **3** is quite interesting in the sense that it has the two purines in a head–head arrangement which makes this compound, like the previously reported chloride salt,[34] a "real" model for an intrastrand cross-link of cis Pt^{II} with two adjacent guanines.[41]

Comparison with Simple Platinum–Ammine Complexes. Reactions of CN^- with simple Pt(II) ammines such as $[Pt(NH_3)_4]^{2+}$ and *cis*- and *trans*-$(NH_3)_2PtCl_2$ are reported in the literature.[49] In order to compare these results with our findings on the reactions

(46) The assignment is based on (a) the fact that G is still coordinated (^{195}Pt–^1H coupling) and (b) the established behavior of thiourea in the Kurnakov reaction to replace the ligand trans to itself.

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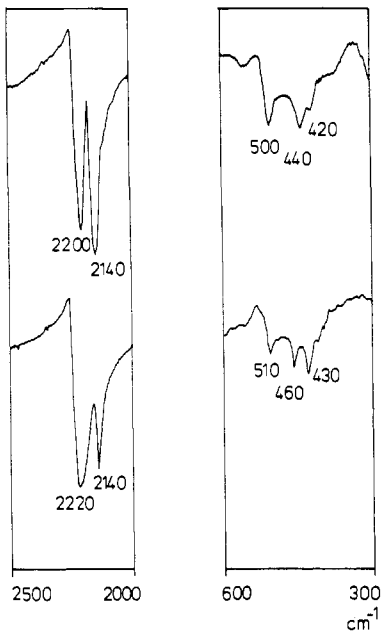

Figure 7. Sections of the IR spectra of "*cis*-$(NH_3)_2Pt(CN)_2Pt(CN)_2 \cdot 2H_2O$" (top) and after complete removal of H_2O at 200 °C (bottom).

of CN^- with nucleobase complexes, we repeated some of this earlier work. Contrary to a literature report,[49a] we were not able to isolate *cis*-$(NH_3)_2Pt(CN)_2$ through reaction of *cis*-$(NH_3)_2PtCl_2$ and KCN. Instead, we observed formation of $K_2Pt(CN)_4 \cdot 3H_2O$ only, with yields depending on the Pt:CN^- ratio applied, e.g. 50% with $r = 0.5$ and 100% with $r \leq 0.25$. $K_2Pt(CN)_4 \cdot 3H_2O$ was unambiguously identified by its IR spectrum.[50]

Depending on the temperature, *trans*-$(NH_3)_2Pt(CN)_2$ (20 °C, 20 min) or $K_2Pt(CN)_4 \cdot 3H_2O$ (45 °C, 2 h) was obtained from solutions containing *trans*-$(NH_3)_2PtCl_2$ and KCN in a 1:4 ratio. *trans*-$(NH_3)_2Pt(CN)_2$ was identified by elemental analysis and its IR spectrum.[49d]

$[(NH_3)_3PtCl]Cl$ reacted with 2 equiv of KCN to give *trans*-$(NH_3)_2Pt(CN)_2$ or, with an excess of KCN, to give $K_2Pt(CN)_4$.

Depending on the temperature, $[(NH_3)_4Pt]Cl_2$ gave two different products with KCN (8 equiv): After 24 h at 3 °C, $[(NH_3)_4Pt][Pt(CN)_4]$ was isolated, whereas after 5 min at 70 °C only $K_2Pt(CN)_4 \cdot 3H_2O$ was recovered. The identity of $[(NH_3)_4Pt][Pt(CN)_4]$ was established by elemental analysis, IR spectroscopy, and alternative reaction of $[(NH_3)_4Pt]Cl_2$ and $K_2Pt(CN)_4$.

Reaction of *cis*-$[(NH_3)_2Pt(H_2O)_2](NO_3)_2$ with 2 equiv of KCN has been reported to give NH_3 and an amorphous, yellow material as byproducts.[49a] We believe that the yellow product might be "*cis*-$(NH_3)_2Pt(CN)_2Pt(CN)_2$" with bridging cyano groups. We obtain such a product (dihydrate) analytically pure on reaction of the diaqua species of cisplatin with an equimolar amount of $K_2Pt(CN)_4$. The IR spectrum clearly indicates CN^- bridges (2200 s, 2140 s, 500 s, 440 s cm^{-1}), which undergo some changes after all water is removed (Figure 7). This may be indicative of a rearrangement process in which still coordinated aqua ligands are replaced by bridging cyano groups:

$$(NH_3)_2(OH_2)Pt\cdot\cdot(NC)Pt(CN)_3\cdot\cdot \xrightarrow{-H_2O} (NH_3)_2Pt\begin{matrix}\cdot\cdot(NC)Pt(CN)_3\cdot\cdot\\ \cdot\cdot(NC)Pt(CN)_3\cdot\cdot\end{matrix}$$

The behavior of simple Pt–ammine complexes toward CN^- thus is similar to that of Pt–nucleobase complexes. Specifically, the "all-or-nothing" reactivity pattern of $[(NH_3)_4Pt]^{2+}$ resembles that of *cis*-$[(NH_3)_2PtL_1L_2]^{n+}$ complexes. The behavior of $[(NH_3)_3PtCl]^+$ indicates that the first ligand to be displaced by CN^- is Cl^-, followed by substitution of the NH_3 ligand trans to the entered CN^-. A similar pattern probably accounts for the formation of *trans*-$(NH_3)_2Pt(CN)_2$ from *trans*-$[(NH_3)_2PtG(Cl)]^+$.

Possible Relevance and Conclusions. The inertness of *cis*-$(NH_3)_2PtL_2$ (L = U, T) and the rather slow rate of reaction of *cis*-$[(NH_3)_2PtL(H_2O)]^+$ with CN^- in alkaline medium are contrasted by the facile replacement of U and T ligands in acidic medium. There, protonation of U (T) at the exocyclic O4 site leads to a strong labilization of the Pt–N3(U, T) bond and subsequent removal of the neutral UH (TH) from the complex. At the moment of displacement, UH (TH) is present in its unusual iminol tautomeric structure.[51] The slow reaction of *cis*-$[(NH_3)_2PtL(H_2O)]^+$ with CN^- is also in contrast to its reasonably fast reaction with other nucleophiles, e.g. the nucleobases G, C, and A, to give mixed-nucleobase complexes (reactions almost complete within 24 h at 40 °C)[28,52] and its condensation reaction to the head–tail dimer.[30,44]

From our present data, it is probably fair to conclude that the relative nucleophilicity order of incoming groups, established for *trans*-$Pt(py)_2Cl_2$ as a standard,[53] is not applicable to Pt complexes containing U or T bases. As outlined above, the steric hindrance exercised by the two exocyclic oxygens adjacent to the Pt coordination site may account for the kinetic stability of complexes containing these nucleobases. While steric effects have long been known to influence the rate of substitution, and in cases with the sterically demanding ligand bound to the Pt may lead to a dissociative mechanism,[54] examples have been limited to systems with alkyl groups being responsible for steric hindrance. Our findings that the hydrophilic oxygens may have a similar effect appear not to have been observed before.

As to the incomplete recovery of Pt from platinated DNA by means of excess KCN, it is possible that steric reasons are responsible for this finding. As has been demonstrated in this work, monofunctional binding of Pt to a thymine base in DNA, mixed thymine–nucleobase complex formation, or bis(thymine) complex formation could account for an incomplete deplatination of DNA. Although thymine generally is not considered a likely binding site of cisplatin, hydroxo-bridged hydrolysis species of composition *cis*-$[(NH_3)_2Pt(OH)]_n^{n+}$ ($n = 2, 3$)[55] readily react with T and U. Once formed, a Pt–N3(T, U) complex should be thermodynamically quite stable.

Moreover, two other bases containing a single exocyclic oxygen (C and G), which are linked by Pt and locked in a head–tail orientation within the DNA helix, e.g. C(N3),C(N3), C(N3),G(N1), G(N1),G(N1), or the discussed cytosinato-bridged dimer, could possibly resist CN^- treatment.

Apart from these steric reasons, there may be even other explanations for the inability of CN^- to fully remove Pt from DNA. For example, Pt binding to rare, S-containing bases in DNA[56] or formation of a Pt–C bond with a nucleic acid constituent could efficiently prevent reaction with CN^-. A recent report by Hollis et al.[57] on the unexpected reaction of Pt with a C atom in vitamin C is interesting in this context.

Finally, we originally considered the possibility that a *rapid* loss of CN^- activity in the biochemical assay due to polymerization of HCN (which is the major species at pH 8) could have occurred. However, our findings did not confirm this idea. Moreover, a recent report by Lippard et al.,[58] which showed that the Pt remaining on DNA after KCN treatment is not recognized by antibodies specific for the *cis*-$(NH_3)_2G_2$ cross-link, seems to rule

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out such a possibility as well and rather points toward some of the other explanations as more likely reasons for tightly bound Pt.

It should be extremely interesting to find out about the role of this firmly bound Pt in the context of the mode of action of Pt antitumor drugs.

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Registry No. **1**, 96617-60-6; **2**, 96617-61-7; **3**, 96617-62-8; **4**, 96617-63-9; **5**, 96617-64-0; **6**, 96648-02-1; **7**, 96617-65-1; **8**, 96617-66-2; *cis*-$[(NH_3)_2PtC(Cl)]Cl$, 75659-46-0; *cis*-$[(NH_3)_2PtC_2]Cl_2$, 76123-94-9; *cis*-$[(NH_3)_2PtG_2](NO_3)_2$, 96617-67-3; *cis*-$[(NH_3)_2PtC(OH)](NO_3)$, 80662-76-6; *cis*-$[(NH_3)_2Pt(C\text{-}H)]_2(NO_3)_2$, 75936-23-1; *cis*-$[(NH_3)_2PtG(Cl)]Cl$, 88080-82-4; *cis*-$[(NH_3)_2PtU(H_2O)](NO_3)$, 85715-80-6; *trans*-$(NH_3)_2Pt(CN)_2$, 14523-27-4; *trans*-$(NH_3)_2PtCl_2$, 14913-33-8; $[(NH_3)_4Pt][Pt(CN)_4]$, 14215-56-6; $[(NH_3)_4Pt]Cl_2$, 13933-32-9; *cis*-$[(NH_3)_2Pt(NC)_2Pt(CN)_2]$, 96633-15-7; *cis*-$[(NH_3)_2PtC(H_2O)]^{2+}$, 80662-70-0; *trans*-$[(NH_3)_2PtAC]^{2+}$, 96617-68-4; *trans*-$[(NH_3)_2PtG(Cl)]^+$, 96617-69-5; *trans*-$[(NH_3)_2PtGC]^{2+}$, 96648-03-2; $[(NH_3)_3PtG]^{2+}$, 96617-70-8; *cis*-$[(NH_3)_2PtGC]^{2+}$, 79301-65-8; *trans*-$[(NH_3)PtG_2C]^{2+}$, 96648-85-0; *cis*-$[(NH_3)_2PtUG]^+$, 88005-67-8; *cis*-$[(NH_3)_2PtUC]^+$, 91003-28-0; *cis*-$(NH_3)_2PtCl_2$, 15663-27-1; KCN^-, 57-12-5; *cis*-$(NH_3)_2PtT_2$, 74539-69-8; *cis*-$(NH_3)_2PtU_2$, 83350-97-4; $[Pt(CN)_4]^{2-}$, 15004-88-3.

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Studies of the Chemical Oxidation of Iron(II) Complexes of *N*-Methylporphyrins To Form the Corresponding Iron(III) Complexes

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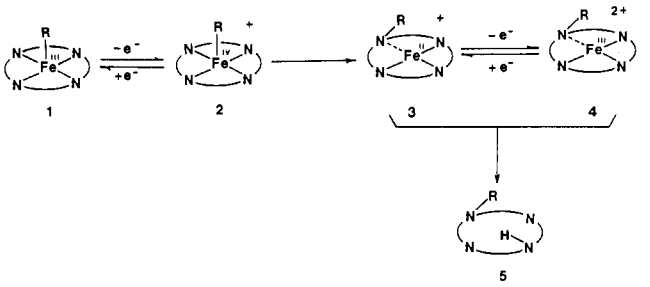
Oxidation of iron(II) *N*-methylporphyrin halide complexes with chlorine, bromine, or iodine in chloroform solution at −50 °C produces the corresponding iron(III) *N*-methylporphyrin halide cations. The oxidations may be reversed by treating the product solutions with zinc. The iron(III) complexes have been characterized by electronic, ^1H and ^2H NMR, and ESR spectroscopy. The NMR results indicate that the C_s symmetry of the iron(II) parent complexes is retained upon oxidation. Characteristic ^1H NMR shifts for these high-spin ($S = {}^5/_2$) species include the very broad *N*-methyl resonance at ca. 270 ppm (observed only by ^2H NMR), three pyrrole resonances in the 130–75 ppm region and one at ca. 2 ppm, pyrrole methylene resonances in the range 80–20 ppm and meso resonances at ca. −70 ppm. The electronic structure of these iron(III) complexes are similar to those of symmetrical high-spin, five-coordinate iron(III) porphyrins except for the local environment of the methylated pyrrole, which suffers from sharply reduced σ-spin transfer as a consequence of the longer Fe–N distance to that ring. On warming, these iron(III) complexes decompose by demetalation (for chloride complexes) or demethylation (for bromide complexes).

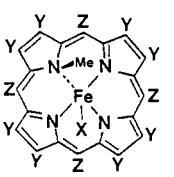
Introduction

The routes to the physiological formation of N-substituted porphyrins have only recently been probed. Substituted hydrazines are known to react with heme proteins to form N-substituted porphyrins,[1,2] and for hemoglobins and myoglobin, there is evidence for the initial formation of (σ-alkyl)- or (σ-aryl)iron(III) porphyrin complexes **1**.[3,4] Studies of model complexes have given insight into the mechanism of transfer of the alkyl or aryl group from iron to the porphyrin. Chemical and electrochemical studies have shown than N-substituted porphyrins **5** are formed from **1** under oxidizing conditions as shown in Scheme I with **2**–**4** as likely intermediates.[4-6]

This paper is concerned with the physical characterization of the iron(III) alkylporphyrin complexes $\mathbf{6^+}$–$\mathbf{10^+}$, formed by chemical oxidation of the air-stable and structurally characterized[7,8] iron(II) halo complexes, **6**–**10**. (i.e. by the second redox step in Scheme I). Particular emphasis is placed on ^1H NMR studies as a source of insight into the electronic structure of these low-symmetry porphyrin species and as a potential means for detecting these complexes in a protein environment. The utility of ^1H NMR studies in the characterization of iron porphyrins has

Scheme I





6, Y = H; Z = C_6H_5; X = Cl [(MeTPP)Fe^{II}Cl]
7, Y = H; Z = C_6H_5; X = Br [(MeTPP)Fe^{II}Br]
8, Y = H; Z = *p*-$C_6H_4CH_3$; X = Cl [(MeTpTP)Fe^{II}Cl]
9, Y = C_2H_5; Z = H; X = Cl [(MeOEP)Fe^{II}Cl]
10, Y = C_2H_5; Z = H; X = Br [(MeOEP)Fe^{II}Br]

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