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Mixed-Ligand Cis and Trans Complexes of Platinum(II) with Cytosine and Adenine Nucleobases: Crystal Structures and Solution Studies of Cis and Trans Isomers of (9-Methyladenine-N^7)(1-methylcytosine-N^3)diammineplatinum(II) Perchlorate. Different Selectivities of Aquadiammine(1-methylcytosine)platinum(II) Isomers for N1 and N7 Donor Atoms of Adenine

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A series of mixed 9-methyladenine (9-MeA) and 1-methylcytosine (1-MeC) complexes of *cis*- and *trans*-$(NH_3)_2Pt^{2+}$ have been studied: *cis*-[$(NH_3)_2$Pt(9-MeA-N^7)(1-MeC-N^3)]$^{2+}$ (**1**), *cis*-[$(NH_3)_2$Pt(9-MeA-N^1)(1-MeC-N^3)]$^{2+}$ (**2**), *cis*-[$(NH_3)_2$(1-MeC-N^3)Pt(9-MeA-N^1,N^7)Pt(1-MeC-N^3)$(NH_3)_2$]$^{4+}$ (**3**), *cis*-[$(NH_3)_2$Pt(1-MeC-N^3)(9-MeAH-N^7)]$^{3+}$ (**4**), *trans*-[$(NH_3)_2$Pt(1-MeC-N^3)(9-MeA-N^7)]$^{2+}$ (**5**), *trans*-[$(NH_3)_2$Pt(1-MeC-N^3)(9-MeA-N^1)]$^{2+}$ (**6**), and *trans*-[$(NH_3)_2$(1-MeC-N^3)Pt(9-MeA-N^1,N^7)Pt(1-MeC-N^3)$(NH_3)_2$]$^{4+}$ (**7**). (**1**)(perchlorate, monohydrate), (**4**)(perchlorate, dihydrate), and (**5**)(perchlorate) were isolated in crystalline form, and the crystal structures of **1** and **5** were determined. **1** crystallizes in the monoclinic system, space group $C2/c$, with a = 30.526 (5) Å, b = 8.380 (2) Å, c = 20.925 (4) Å, β = 121.92 (1)°, and Z = 8. **5** crystallizes in the monoclinic form as well, space group $P2_1/n$, with a = 13.234 (2) Å, b = 11.406 (2) Å, c = 14.620 (4) Å, β = 93.78 (2)°, and Z = 4. The X-ray data were collected with Mo Kα radiation by using Syntex $P2_1$ (**1**) and Nicolet P3 (**5**) diffractometers and the structures solved by heavy-atom methods. On the basis of 4512 and 4784 reflections, respectively, the structures were refined to R_1 = 0.059 (**1**), 0.068 (**5**) and R_2 = 0.074 (**1**), 0.064 (**5**). The cation of **1** has the two nucleobase planes approximately at right angles relative to the Pt coordination plane, with a moderately strong hydrogen bond between the exocyclic keto group of 1-MeC and the exocyclic amino group of 9-MeA, leading to a 91.6° angle between the two base planes. In the trans isomer **5**, the two nucleobases are almost coplanar (dihedral angle 2.4°) but again are perpendicular to the Pt coordination plane. While the *cis*-$(NH_3)_2$Pt(1-MeC) moiety reacts preferentially with the N7 position of 9-MeA, the *trans*-$(NH_3)_2$Pt(1-MeC) moiety prefers N1 over N7. Possible reasons for these differences in selectivity are discussed. ^{1}H NMR spectra of the various complexes are compared and interpreted in terms of differences of diamagnetic anisotropies caused by ring-current effects. Relevant acid–base equilibria for N7- and N1-platinated 9-MeA are reported and discussed briefly with regard to alternations in the base-pairing properties toward thymine.

Introduction[2]

There is good reason to attribute the alteration of physicochemical properties of DNA on reaction with bifunctional Pt(II) coordination compounds to a structural modification of the DNA as a consequence of the heavy-metal interaction with nucleobases.[3,4] The interest in details of these interactions and factors causing the macroscopic changes arises from the fact that *cis*-$(NH_3)_2Pt^{II}$ derivatives represent successful antitumor agents[5,6] and has lead to numerous crystallographic studies on this subject.[7] As a result, the importance of the dihedral base/base angles in bis(nucleobase) complexes of Pt(II) on the expected distortion of double-helical DNA has been recognized; for example, the base/base dihedral angles observed in bis(cytosine), mixed cytosine, guanine, and bis(guanine) cis complexes of Pt^{II} decreases in the order CC > GC > GG, suggesting that a bis(cytosine) product might cause the largest local denaturation of duplex DNA of the three combinations.[8a] However, recent work by Lippard[8b] has suggested that if hydrogen-bonding patterns are changed, even the GG–Pt system can be accommodated in a double helix with minimum distortion, so the approach based solely on dihedral angles may be too simplistic.

In order to get additional structural data for other model nucleobase complexes, we have extended our previous studies on complexes of cis Pt^{II} complexes containing 9-EtG and 1-MeC[9,10] to the corresponding trans isomers[11] and to other model bases such as 1-MeT, 1-MeU, and 9-MeA.[12,13] As part of these studies we have also prepared mixed cis and trans 1-methylcytosine and 9-methyladenine complexes of Pt^{II} and determined the crystal structures of two of these, with platinum bound to the 9-MeA ligand via N7 and 1-MeC via N3.

The biological relevance of platinum–adenine complex formation is not clear. Although a preferential binding of cis Pt^{II} complexes to DNAs rich in guanine and cytosine is established,[14]

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(2) Abbreviations used: 1-MeC = 1-methylcytosine; 9-MeA = 9-methyladenine; 9-MeAH = 9-methyladenium cation; 9-EtG = 9-ethylguanine; 1-MeT = 1-methylthyminate anion; 1-MeU = 1-methyluracilate anion; 9-MeA-N^7 = 9-methyladenine platinated at N7 etc. Occasionally A C, and G are used for adenine, cytosine, and guanine, respectively.
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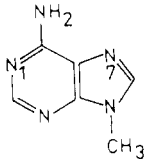
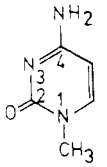
and in particular binding to adjacent guanines is favored,[15] the nucleophilicity of 5'-AMP toward cis Pt^{II} complexes has been found to be closest to that of 5'-GMP.[16] With GAG trinucleotides, cis-Pt^{II} complexes form both GG and AG cross-links,[17] though the GG product is favored.

Evidence on the preferred site of platinum binding to adenine residues is ambiguous; for example, solution studies on the reaction of Pt(II) with adenine bases have shown that metal binding can occur at N1, at N7, or at both sites simultaneously[18] but also that minor products of yet unknown composition may be formed.[19] The reaction of ApA and ApC dinucleoside monophosphates with the diaquo species of cisplatin gives a complicated mixture of products, and only the N7,N7-coordinated compound has been characterized.[20] Similarly, with the GpA dinucleotide only products containing Pt(II) bound to the N7 sites of the two purines have been well characterized, although there are several other minor species.[21] In an early study,[22] the involvement of the exocyclic amino group at the 6-position in ApA in Pt(II) binding has been proposed.

Crystallographically the following metal binding sites have been established for N9-substituted adenines: N7 for Cu,[23] Ni,[24] Co,[25] Pt,[26] and Cd,[27] N1 for Zn[28] and Hg,[29] and both N1 and N7 for Ag,[30] Co,[31] Zn,[32] and Pt.[33] In addition, a complex has been reported with two Hg centers bridged through N1 and the deprotonated amino group at the 6-position,[34] which bears a close resemblance to similar complexes of 1-methylcytosine with two Pt[35] or two Hg[36] atoms coordinated at N3 and N6. With unsubstituted adenine, the variety of structurally characterized metal binding sites is even higher, although with one exception (N7 binding[37]) not biologically relevant, e.g. N9,[38] N3,N9,[39] N7,N9,[40] and N3,N7,N9.[41]



9-MeA



1-MeC

Metal binding sites of N1-substituted cytosines have been reviewed.[42,43] With cis Pt^{II} complexes in the majority of cases N3 binding has been observed.[7,35]

Apart from steric aspects of possible cross-linking models of *cis*- and *trans*-$(NH_3)_2Pt^{II}$ with nucleobases, which motivated us to determine the crystal structures of both geometrical isomers of (9-methyladenine-N^7)(1-methylcytosine-N^3)diammineplatinum(II) perchlorate, we were also interested in electronic changes in the adenine ring as a consequence of Pt binding, which might be relevant to hydrogen-bonding and stacking interactions with other nucleobases.

Experimental Section

Preparations. 9-MeA and deuterated 9-MeA (ND_2, C(8)D)[12] were prepared as previously described. *cis*-$Pt(NH_3)_2Cl_2$[44] was purified from DMF,[45] *trans*-$Pt(NH_3)_2Cl_2$ was prepared according to the method of Kauffman and Cowan.[46]

***cis*-[Pt$(NH_3)_2$(9-MeA-N^7)(1-MeC)]$(ClO_4)_2\cdot H_2O$ (1)** was prepared through the reaction of *cis*-[Pt$(NH_3)_2$(1-MeC)H_2O]$(ClO_4)_2$, obtained in situ from *cis*-[Pt$(NH_3)_2$(1-MeC)Cl]$Cl\cdot H_2O$ and $AgClO_4$ in water,[47] with 1 equiv of 9-MeA (c_{Pt} = 0.03 M; 48 h at 40 °C, pH 5–5.5) after filtration of AgCl and slow evaporation of 22 °C. **1** was obtained as colorless cubes, recrystallized from water; yield 67%. Anal. Calcd for [Pt$(NH_3)_3(C_6H_7N_5)(C_5H_7N_3O)$]$(ClO_4)_2\cdot H_2O$: C, 18.22; H, 3.09; N, 19.42; O, 22.24; Pt, 27.12. Found: C, 18.25; H, 3.16; N, 19.18; O, 22.13; Pt, 27.0. The glassy residue obtained after filtration of **1** and evaporation to dryness consisted of a mixture of **1** (additional 15–20%), *cis*-[Pt$(NH_3)_2$(1-MeC)(9-MeA-N^1)]$(ClO_4)_2$ (**2**) (2–5%), the dimer *cis*-[$(NH_3)_2$Pt(1-MeC)(9-MeA-N^1, N^7)Pt(1-MeC)$(NH_3)_2$]$(ClO_4)_4$ (**3**) (<5%), and unreacted 9-MeA (2–5%), **2** and **3** were identified by ^1H NMR spectroscopy. Although a partial separation of the products was achieved by using Sephadex chromatography (sequence of elution: **3**, **2**, **1**), the products obtained were not analytically pure, mainly because of contamination with free 9-MeA.

***cis*-[Pt$(NH_3)_2$(1-MeC)(9-MeAH)]$(ClO_4)_3\cdot 2H_2O$ (4)** was isolated in 70% yield from an aqueous solution of **1**, to which 1 equiv of 0.4 N HNO_3 and $NaClO_4$ had been added, on slow evaporation as colorless crystals. Anal. Calcd for [Pt$(NH_3)_2(C_5H_7N_3O)(C_6H_8N_5)$]$(ClO_4)_3\cdot 2H_2O$: C, 15.75; H, 3.01; N, 16.69; Cl, 12.68. Found: C, 15.54; H, 3.09; N, 16.66; Cl, 12.20.

***trans*-[Pt$(NH_3)_2$(9-MeA-N^7)(1-MeC)]$(ClO_4)_2$ (5)** was prepared by analogy to the preparation of **1** from *trans*-[Pt$(NH_3)_2$(1-MeC)Cl]Cl.[48]

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Table I. Crystal Data

	cis-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-MeA})](ClO_4)_2\cdot H_2O$	*trans*-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-MeA})](ClO_4)_2$
mol formula	$C_{11}H_{22}Cl_2N_{10}O_{10}Pt$	$C_{11}H_{20}Cl_2N_{10}O_9Pt$
fw	720.4	702.3
cryst shape	cylinder	right parallelpiped
cryst size, mm	$r = 0.075$, $l = 0.30$	$0.32 \times 0.26 \times 0.45$
syst absences	hkl, $(h + k = 2n + 1)$; $h0l$ $(l = 2n + 1)$	$h0l$, $(h + l = 2n + 1)$; $0k0$ $(k = 2n + 1)$
space group	$C2/c$	$P2_1/n$
unit cell params		
a, Å	30.526 (5)	13.234 (2)
b, Å	8.380 (2)	11.406 (2)
c, Å	20.925 (4)	14.620 (4)
β, deg	121.92 (1)	93.78 (2)
V, Å^3	4543 (1)	2202.1 (8)
Z	8	4
ρ_{calcd}, g cm^{-3}	2.149	2.118
ρ_{obsd}, g cm^{-3}	2.07 (2)	2.09 (2)
linear abs coeff, cm^{-1}	68.1	70.2
abs corr factor, Å	2.29–2.33	
mas 2θ, deg; reflcns collcd	55; $h,k,\pm l$	55; $h,k,\pm l$
std reflcns (esd, %)	4,2,–4 (1.1); 314 (1.2)	–4,–3,–1 (1.4); 404 (1.8)
temp, °C	22	22
no. of indep reflcns.	4515	5095
no. of reflcns with $I > 0$ (used)	4512	4784
final R_1[a], R_2[a]	0.059, 0.074	0.068, 0.064
final shift/error max (av)	0.154 (0.007)	0.195 (0.005)
secondary extinction (x)	0.00011	0.00023
weighting	$(\sigma_F^2 + 0.001906F_o^2)^{-1}$	$(\sigma_F^2 + 0.00040F_o^2)^{-1}$
error in an abservn of unit wt	1.911	1.806
final difference map		
highest peak, e Å^{-3}	1.74	2.26
lowest valley, e Å^{-3}	–1.11	–1.41

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$; $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$.

On slow evaporation of the reaction mixture at 22 °C, compound **5** crystallized first. Colorless crystals of **5** suitable for X-ray analysis were obtained on recrystallization from water. Anal. Calcd for $[Pt(NH_3)_2(C_6H_7N_5)(C_5H_7N_3O)](ClO_4))_2$: C, 18.81; H, 2.88; N, 19.90. Found: C, 18.42; H, 2.86; N, 20.11. Further concentration of the reaction mixture gave several crops consisting of **5**, *trans*-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-MeA-}N^1)](ClO_4)_2$ (**6**), the dimer *trans*-$[(NH_3)_2Pt(1\text{-meC})(9\text{-MeA-}N^1,N^7)Pt(1\text{-MeC})(NH_3)_2](ClO_4)_4$ (**7**), and unreacted 9-MeA. Attempts to isolate **6** and **7** in analytically pure form by fractional crystallization or Sephadex chromatography were not fully successful. The relative yields of **5**:**6**:**7**:**9**-MeA were ca. 30:40:10:20.

Spectra. ^{1}H NMR spectra were recorded on a JEOL JNM-FX 60 Fourier transform spectrometer at 30 °C. Experimental details have been reported before.[12] pD values were measured with a glass electrode and were obtained by adding 0.4 units to the meter reading. pD variations were made by means of aqueous solutions of NaOD and CF_3CO-OD, respectively.

Collection of X-ray Data. A crystal of **1** was cut to a needle and ground to a cylinder. A right-parallelpiped-shaped crystal of **5** was used as obtained. Precession photographs revealed the symmetry of the crystals, and unit cell parameters were obtained from a least-squares fit of χ, ϕ, and 2θ for 15 reflections for each compound in the range $13.2 < 2\theta < 25.4°$ (**1**) or $11.2° < 2\theta < 23.5°$ (**5**) recorded on a Syntex $P2_1$ (**1**) or a Nicolet P3 (**5**) diffractometer with use of Mo Kα radiation ($\lambda = 0.709\,26$ Å). Crystal data and other numbers related to data collection are summarized in Table I. Densities were obtained by suspension in a diiodomethane–carbon tetrachloride mixture. Intensities were measured on the same diffractometers used for cell determination with a coupled θ(crystal)–2θ(counter) scan. The methods of selection of scan rate and initial data treatment have been described.[49,50] Corrections were made for Lorentz–polarization and absorption.

Solution of the Structures. The platinum atoms were found from three-dimensional Patterson maps, and subsequent full-matrix least-squares refinement and electron density difference syntheses revealed all the non-hydrogen atoms. Further refinement with use of anisotropic temperature factors for Pt and Cl (**1**) or Pt, Cl, and N bound to Pt and

Table II. Atomic Positional Parameters ($\times 10^4$) and Temperature Factors ($\times 10^3$ Å^2) for *cis*-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-MeA})](ClO_4)_2\cdot H_2O$ (**1**)

atom[a]	x	y	z	U_{iso} or U_{eq}
Pt	5960.4 (1)	5366.8 (4)	4552.5 (2)	22.1 (2)[b]
Cl(1)	–828 (1)	201 (3)	3073 (1)	36 (1)[b]
O(11)	–469 (5)	–456 (15)	3782 (8)	106 (4)
O(12)	–586 (5)	1442 (17)	2889 (7)	106 (4)
O(13)	–1243 (5)	828 (15)	3114 (7)	93 (3)
O(14)	–995 (6)	–919 (22)	2547 (10)	136 (5)
Cl(2)	3155 (1)	1342 (4)	–429 (2)	45 (2)[b]
O(21)	2855 (6)	–15 (17)	–797 (8)	110 (4)
O(22)	3066 (8)	1657 (23)	168 (10)	162 (7)
O(23)[a]	2979 (8)	2669 (27)	–800 (11)	113 (6)
O(23′)[b]	3333 (10)	1963 (30)	–912 (14)	59 (6)
O(24)[c]	3689 (8)	767 (25)	–30 (11)	119 (6)
O(24′)[d]	3492 (13)	1858 (40)	362 (17)	64 (8)
N(11)	5669 (3)	3873 (11)	5000 (4)	38 (2)
N(12)	5504 (3)	4404 (10)	3504 (5)	43 (2)
N(1)	5665 (4)	9703 (10)	5887 (5)	38 (2)
C(2)	6078 (4)	10051 (12)	6569 (5)	38 (2)
N(3)	6545 (3)	9353 (10)	6924 (5)	37 (2)
C(4)	6568 (3)	8209 (11)	6509 (5)	30 (2)
C(5)	6180 (3)	7697 (10)	5800 (5)	27 (2)
C(6)	5702 (3)	8494 (11)	5476 (5)	30 (2)
N(7)	6365 (3)	6465 (9)	5558 (4)	28 (2)
C(8)	6836 (4)	6205 (13)	6117 (6)	39 (2)
N(9)	6978 (3)	7209 (9)	6697 (4)	32 (2)
N(6)	5267 (3)	8114 (10)	4804 (4)	38 (2)
C(9)	7494 (5)	7301 (15)	7415 (6)	55 (3)
N(1′)	6227 (3)	9170 (11)	3472 (5)	42 (2)
C(2′)	6017 (4)	8168 (12)	3751 (5)	37 (2)
N(3′)	6283 (3)	6826 (9)	4125 (4)	32 (2)
C(4′)	6736 (4)	6456 (12)	4196 (6)	39 (2)
C(5′)	6954 (4)	7523 (14)	3912 (6)	49 (3)
C(6′)	6698 (4)	8875 (15)	3571 (6)	52 (3)
C(1′)	5968 (6)	10682 (18)	3139 (8)	72 (4)
O(2′)	5595 (3)	8454 (9)	3672 (4)	50 (2)
N(4′)	6972 (4)	5108 (13)	4533 (6)	55 (2)
O	5153 (3)	1350 (11)	3741 (5)	62 (2)

[a] Atoms a–d were given occupancies of (a) 0.657, (b) 0.343, (c) 0.714, and (d) 0.286, respectively. [b] $U_{eq} = {}^1/_3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$.

(48) *trans*-$[Pt(NH_3)_2(1\text{-MeC})Cl]Cl$ was prepared from *trans*-$Pt(NH_3)_2Cl_2$ and 1-MeC. The crystal structure and details of the preparation will be published.

(49) Hughes, R. P.; Krishnamachari, N.; Lock, C. J. L.; Powell, J.; Turner, G. *Inorg. Chem.* **1977**, *16*, 314–319.
(50) Lippert, B.; Lock, C. J. L.; Rosenberg, B.; Zvagulis, M. *Inorg. Chem.* **1977**, *16*, 1525–1529.

Table III. Atomic Positional Parameters ($\times 10^4$) and Temperature Factors ($\times 10^3$ Å^2) for *trans*-[Pt(NH_3)$_2$(1-MeC)(9-MeA)](ClO_4)$_2$ (**5**)

atom	x	y	z	U_{eq}[a] or U
Pt	812.3 (2)	2034.1 (3)	6355.6 (2)	22.2 (2)*
N(11)	894 (6)	1829 (7)	7764 (6)	44 (4)*
N(12)	753 (6)	2280 (7)	4957 (6)	41 (5)*
N(1)	3553 (6)	−893 (7)	6114 (5)	45 (2)
C(2)	4481 (8)	−424 (9)	6098 (7)	48 (3)
N(3)	4745 (6)	704 (7)	6183 (5)	28 (2)
C(4)	3932 (7)	1374 (8)	6261 (6)	32 (2)
C(5)	2928 (6)	1033 (7)	6252 (5)	29 (2)
C(6)	2747 (7)	−185 (8)	6174 (6)	35 (2)
N(7)	2330 (5)	1993 (6)	6372 (5)	31 (4)*
C(8)	2964 (8)	2924 (8)	6476 (6)	41 (2)
N(9)	3931 (6)	2564 (7)	6411 (5)	41 (2)
N(6)	1803 (6)	−669 (7)	6177 (5)	42 (2)
C(9)	4842 (9)	3347 (10)	6526 (8)	55 (3)
N(1′)	−2143 (5)	686 (6)	6254 (5)	33 (2)
C(2′)	−1100 (6)	817 (7)	6239 (6)	30 (2)
N(3′)	−723 (5)	1943 (6)	6313 (5)	29 (4)*
C(4′)	−1332 (7)	2882 (8)	6389 (6)	35 (2)
C(5′)	−2403 (8)	2732 (9)	6368 (7)	46 (2)
C(6′)	−2786 (8)	1637 (9)	6301 (7)	44 (2)
C(1′)	−2585 (8)	−503 (9)	6271 (7)	43 (2)
O(2′)	−553 (5)	−40 (6)	6157 (4)	38 (1)
N(4′)	−909 (6)	3938 (8)	6505 (6)	46 (2)
Cl(1)	3633 (2)	820 (2)	8832 (2)	46.9 (1)*
Cl(2)	3293 (2)	3831 (2)	3915 (2)	55.0 (1)*
O(11)	3452 (14)	1818 (9)	9344 (11)	150 (10)*
O(12)	2773 (9)	591 (10)	8287 (9)	122 (8)*
O(13)	3883 (8)	−119 (10)	9431 (8)	110 (8)*
O(14)	4446 (10)	1137 (19)	8314 (9)	170 (10)*
O(21)	3541 (12)	4641 (13)	4678 (11)	160 (20)*
O(22)	2250 (8)	3798 (13)	3604 (11)	150 (10)*
O(23)	3746 (11)	4498 (12)	3264 (10)	140 (10)*
O(24)	3776 (11)	2792 (11)	3827 (16)	230 (20)*

[a] $U_{eq} = {}^1/_3(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$. Starred values are U_{eq}.

O(perchlorate) (**5**) minimized $\sum w(|F_o| - |F_c|)^2$ and was terminated when the maximum shift/error fell below 0.2. No attempt was made to locate hydrogen atoms. Corrections were made for secondary extinction by the SHELX method.[51] Scattering curves were from ref[52], as were the anomalous dispersion corrections applied to the scattering curves for Cl and Pt.[53] The atom parameters are listed in Table II (**1**) and III (**5**).[54]

Results and Discussion

Formation of Products and ^{1}H NMR Spectra. Reaction of *cis*-[Pt(NH_3)$_2$(1-MeC)H_2O]$^{2+}$ with 9-MeA in water (1:1 ratio, pH 5–5.5, 40 °C) gives three products: *cis*-[Pt(NH_3)$_2$(1-MeC)(9-MeA-N^7)]$^{2+}$ (**1**) (ca. 85% based on adenine), *cis*-[Pt(NH_3)$_2$(1-MeC)(9-MeA-N^1)]$^{2+}$ (**2**) (less than 5%), and *cis*-[(NH_3)$_2$(1-MeC)Pt(9-MeA-N^1,N^7)Pt(1-MeC)(NH_3)$_2$]$^{4+}$ (**3**) (ca. 2–5%). Similarly, with *trans*-[Pt(NH_3)$_2$(1-MeC)H_2O]$^{2+}$ three products are formed under comparable reaction conditions, but the distribution of species is distinctly different, with *trans*-[Pt(NH_3)$_2$(1-MeC)(9-MeA-N^1)]$^{2+}$ (**6**) being the major product (40% based on adenine), followed by *trans*-[Pt(NH_3)$_2$(1-≤MeC)(9-MeA-N^7)]$^{2+}$ (**5**) (30%), the dinuclear complex *trans*-[(NH_3)$_2$(1-MeC)Pt(9-MeA-N^1,N^7)-*trans*-Pt(1-MeC)(NH_3)$_2$]$^{4+}$ (**7**) (10%), and unreacted 9-MeA.

Table IV. ^{1}H NMR Shifts of Resonances of Respective Cis and Trans Isomers with N7-Platinated 9-MeA, N1-Platinated 9-MeA, and Bridging 9-MeA in D_2O[a]

	9-MeA			1-MeC		
	H8	H2	CH_3	H6[b]	H5[b,c]	CH_3
1	8.543[d]	8.327	3.865	7.558	6.007	3.350
5	8.638[e]	8.388	3.951	7.690	6.155	3.489
2	8.094	8.682[f]	3.796	7.553	5.984	3.416
6	8.184	8.854[g]	3.861	7.690	6.155	3.489
3	8.682[h]	8.801[h]	3.861	7.563	5.996	3.338
	8.658[h]	8.850[h]		7.518	5.976	3.367
7	8.944[i]	9.177[i]	4.012	7.690[j]	6.155[j]	3.489
		9.099[i]				

[a] pD 6, 0.07 M Pt. All shifts in ppm. [b] ^3J(H5–H6) = 7.6 Hz. [c] ^4J(^{195}Pt–H5) = 15.6 Hz. [d] ^3J(^{195}Pt–H8) = 24.2 Hz. [e] ^3J(^{195}Pt–H8) = 24.9 Hz. [f] ^3J(^{195}Pt–H2) = 22.9 Hz. [g] ^3J(^{195}Pt–H2) = 22.6 Hz. [h] ^3J(^{195}Pt–^{1}H) = 20.0 Hz. [i] ^3J(^{195}Pt–^{1}H) = 23.4 Hz. [j] Two sets not well resolved.

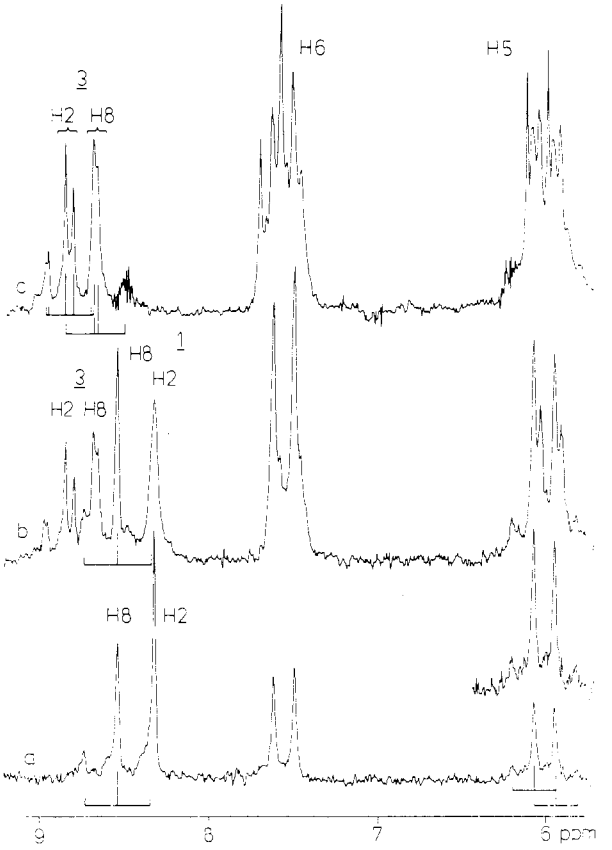

Figure 1. Low-field portions of ^{1}H NMR spectra (D_2O). (a) Spectrum of **1** (pD 7.5, identical spectrum at pD 4, c_{Pt} = 0.07 M). Only single sets of H2 and H8 resonances are observed, indicating that rotation about the Pt-(1-MeC) and/or the Pt-(9-MeA) bond is either prevented or fast on the NMR time scale. (b) Spectrum after addition of 0.5 equiv of *cis*-[Pt(NH_3)$_2$(1-MeC)D_2O]$^{2+}$ to **1** (pD 3.8 after 2.5 h at 40 °C and 48 h at 22 °C). The new signals due to **3** appear in pairs, indicating the formation of two rotamers. (c) Spectrum after addition of 2 equiv of *cis*-[Pt(NH_3)$_2$(1-MeC)D_2O]$^{2+}$ to **1** (pD 2.1 after 1.5 h at 40 °C and 48 h at 22 °C). Only signals of **3** are left in the region of the 9-MeA resonances.

^{1}H NMR chemical shifts of compounds **1–3** and **5–7** at pD 6 are given in Table IV. The various complexes were either isolated in crystalline form and the structure determined by X-ray methods (**1** and **5**), identified by alternative preparations (**3** and **7**), or assigned on the basis of the pH dependence of their ^{1}H resonances. The differentiation between H2 and H8 resonances of the 9-MeA ligands was achieved by utilization of 9-MeA selectively deuterated at the 8-position[12] and by taking advantage of the ^{195}Pt coupling with H2 and H8, respectively, depending on the site of coordination. 1-MeC resonances were assigned by comparison with

(51) Sheldrick, G. M. "SHELX: A Program for Crystal Structure Solution"; Cambridge University: Cambridge, England, 1976.
(52) Cromer, D. T.; Waber, J. T. "International Tables for X-ray Crystallography"; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2B.
(53) Cromer, D. T.; "International Tables for X-ray Crystallography"; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1, pp 149–150.
(54) All computations were carried out on CYBER 170/730 and 170/815 computers. Programs used for initial data treatment were from the XRAY76 package (Stewart, J. M. Technical Report TR-446; University of Maryland: College Park, MD, 1976). The structures were solved with use of SHELX.[51] Planes were calculated with NRC-22 (Ahmed, F. R.; Pippy, M. E. "NRC-22"; National Research Council of Canada: Ottawa, Canada, 1978). Diagrams were prepared from ORTEPII (Johnson, C. K. Report ORNL-5138; Oak Ridge National Laboratory, Oak Ridge, TN, 1976).

Table V. Differences in Chemical Shifts of ^{1}H NMR Resonances of Cis and Trans Isomers[a]

	9-MeA		1-MeC	
	H8	H2	H6	H5
9-MeA-N^7	0.10	0.06	0.13	0.16
9-MeA-N^1	0.09	0.17	0.14	0.15
9-MeA-N^7,N^1	0.26	0.38 (0.30)[b]	0.13	0.16
	0.28	0.25 (0.33)[b]	0.17	0.18

[a] In ppm. [b] Assignment of two rotamer signals reversed.

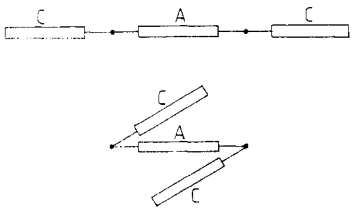

Figure 2. Different arrangement of nucleobases in adenine-bridged dinuclear complexes without (top) and with strong base overlap (bottom).

related complexes.[10a,12] Resonances of the respective trans isomers occur downfield from those of the cis isomers, reflecting the effects of the ring currents of the cis-arranged heterocycles,[54] as is shown for isomers **1** and **5** (N7-platinated 9-MeA) and **2** and **6** (N1-platinated 9-MeA) in Table IV. It can be seen that H8 is affected more than H2 in the case of N7 platinum binding, while the opposite is true if Pt coordinates through N1.

Dinuclear μ-(9-MeA-N^1,N^7) Complexes. Formation of the diplatinated 9-MeA complexes **3** and **7** in the reaction of the mononuclear complex $[Pt(NH_3)_2(1\text{-MeC})(9\text{-MeA-}N^7)]^{2+}$ and excess $[Pt(NH_3)_2(1\text{-MeC})D_2O]^{2+}$ was followed by use of NMR spectroscopy (cf. Figure 1 for the cis isomers **1**). Unlike related dinuclear complexes with *cis*-$(NH_3)_2Pt^{II}$ or (dien)Pt^{II} at N1 and N7,[18a,d,e] complex **3**, *cis*-$[(NH_3)_2(1\text{-MeC})Pt(9\text{-MeA-}N^1,N^7)Pt(1\text{-MeC})(NH_3)_3]^{4+}$, exists in two rotamer forms. While two sets of 1-MeC resonances can be expected because of the inequivalence of N1- and N7-bound $(NH_3)_2Pt(1\text{-MeC})$, splitting of H2 and H8 resonances of the 9-MeA bridge indicates the existence of rotamers of **3** in solution. On the basis of our NMR data it is not possible to decide whether it is rotation of 1-MeC about the Pt–(1-MeC) bond or rotation of the Pt(1-MeC) moieties about the Pt–(9-MeA) bonds that is slow enough to lead to individual rotamers. Likewise, the dinuclear complex **7**, derived from a trans Pt^{II} complex, occurs in two rotamer forms in solution (ratio ca. 2:1), but only the adenine H2 resonances are well resolved whereas the two H8 resonances are not. We note that, unlike dinuclear Pt complexes of adenosine of 5′-AMP where H8 is downfield from H2,[18] in the 9-methyladenine-bridged complexes discussed here these positions are reversed, as is also the case with the respective free bases in the absence of Pt.[12]

Expectedly, and in contrast to those of **1** and **2** (vide infra), the ^{1}H resonances of **3** and **7** are rather insensitive to pH. Only under very acidic conditions (pD < 1) is there a slight downfield shift of H8, indicating the beginning of protonation of 9-MeA, presumably at N3.

A comparison of the chemical shifts of the aromatic protons of 9-MeA and 1-MeC in the dinuclear complexes **3** and **7** reveals similar differences among the mononuclear complexes, with the trans complex having its resonances at lower field than the cis complex (Table IV). Again, this is consistent with a diamagnetic anisotropy caused by ring-current effects in the cis isomer. There is, however, a remarkable difference in the magnitude of shift variation between mono- and dinuclear complexes derived from cis and trans Pt^{II} complexes, respectively (Table V), which suggests that the adenine protons H2 and H8 are affected by ring currents from either side of the base plane. A possible arrangement of the bases that could account for this finding is given in Figure 2.

Basicity of 9-MeA Ligands in 1 and 2. Addition of acid to an aqueous solution of **1** leads to protonation of the 9-MeA ligand at the N1 position, as evidenced by downfield shifts of all adenine

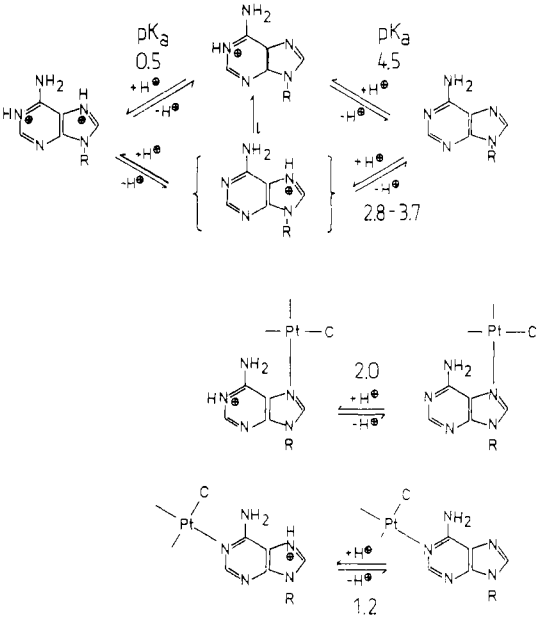

Figure 3. Relevant acid–base equilibria of free 9-MeA and 9-MeA when platinated at N7 and N1, respectively.

resonances. The 1-MeC resonances are almost unaffected. The pK_a of the protonated, N7-platinated 9-MeA in **1** is 2.0 in D_2O, corresponding to a value of 1.6 in H_2O (cf. supplementary material). This value, which is in good agreement with data reported by other groups,[18e,19] compares with a value of 4.5 (D_2O) for the unplatinated ligand, which agrees well with the literature data.[55] The observed increase in acidity of the N1 proton of 9-MeAH$^+$ on N7 platinum binding is not unexpected and parallels a similar increase in acidity of the N1 proton of neutral 9-ethylguanine platinated at N7.[9]

If the N1 position is blocked by Pt, as in **2**, protonation to give the adeninium ligand occurs at N7 as shown by the large effect on the H8 resonance (cf. supplementary material). The pK_a determined in D_2O is 1.2, corresponding to 0.8 in H_2O. It is consistent with a similar value reported for $[Pt(dien)(9\text{-MeA-}N^1)]^{2+}$.[18e] While this pK_a indicates a gross reduction in ligand basicity (cf. 4.5 (D_2O) for unplatinated 9-MeA), the effect of N1 Pt binding on the basicity of N7 is more difficult to assess. Comparison with the pK_a of the second protonation of 9-MeA to give 9-MeAH_2^{2+} (ca. 0.5 in D_2O) seems to indicate an increase in basicity of N7 in the Pt complex, yet such a comparison is valid only if a bound proton and a Pt electrophile (both at N1) had an identical effect on the ring. This undoubtedly is not the case. If one assumes that Pt bound to N1 acidifies a proton at N7 to approximately the same extent as Pt and N7 does a proton at N1 (1.6[9]–2.5 log units), one comes up with a pK_a of about 2.8–3.7 for an N7-protonated 9-MeA.[55] In Figure 3 the relevant acid–base equilibria are shown.

With regard to the effects of the electronic changes within neutral adenine caused by platination at N7 or N1 on the hydrogen-bonding behavior, the reduction in basicity will reduce the ability to accept a proton in a hydrogen bond. On the other hand, since Pt coordination, in particular through N1,[18e] should increase the acidity of the exocyclic amino group in the 6-position, the hydrogen donor properties of adenine are improved on Pt coordination. It is hard to say which of the two opposed effects is larger or if they cancel each other. However, the electronic complementarity between adenine and its complementary base thymine is drastically perturbed, and one might, therefore, expect changes (geometry and/or association constant) in a T–(A–Pt) base pair as compared to the normal TA pair, irrespective of whether base pairing occurs according to the Watson–Crick scheme (Pt at N7 of adenine) or in a Hoogsteen or reversed-Hoogsteen fashion (Pt

(55) Izatt, R. M.; Christensen, J. J.; Rytting, J. H. *Chem. Rev.* **1971**, *71*, 439–481.

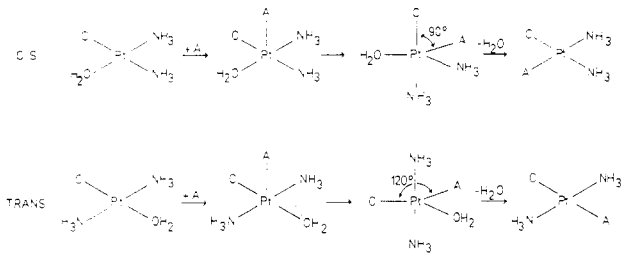

Figure 4. Differences in relative orientation of 1-MeC and 9-MeA in the five-coordinate transition state derived from *cis*- and *trans*-$(NH_3)_2$(1-MeC)Pt^{II}.

at N1). An experimental verification of an altered hydrogen bonding behavior of platinated adenine with use of ^1H NMR spectroscopy is hampered by the same difficulties as that in the absence of Pt, namely the problem of finding appropriate solvents.[56] It should be noted that with guanine an alteration of the hydrogen-bonding pattern has been demonstrated when platinum is bound to N7.[57]

Decomposition of *cis*-[$Pt(NH_3)_2$(1-MeC-N^3)(9-MeAH-N^7)]$^{3+}$ (4). The protonated form of **1**, *cis*-[$(NH_3)_2$(1-MeC)(9-MeAH-N^7)]$^{3+}$ (**4**), has been isolated as a perchlorate in crystalline form and analyzed (cf. Experimental Section). Heating of **4** in water (90 °C, several hours) results in a partial decomposition with formation of 1-$MeCH^+$ and 9-$MeAH^+$. A different behavior is observed in Me_2SO: besides 1-MeC, the formation of NH_4^+ (triplet of 1:1:1-intensity in the ^1H NMR spectrum at 6.30, 7.15, and 8.00 ppm) is observed, but the reaction is less complete than in the case of the mixed 1-MeT, 9-MeAH complex.[12] As with the thymine-containing complex, Me_2SO replaces the pyrimidine nucleobase and subsequently labilizes NH_3 (probably trans to Me_2SO). Protonation of the liberated NH_3 by the strong acid $Pt(9\text{-MeAH})^+$ prevents the reverse reaction from occurring.[58]

N7 vs. N1 Platinum Binding. As mentioned above, *cis*-$[(NH_3)_2Pt(1\text{-MeC})H_2O]^{2+}$ exhibits a pronounced preference for N7 of 9-MeA, whereas the trans isomer has a slight preference for N1 binding over N7 binding. Factors influencing metal binding sites in nucleobases in general, and at adenine in particular, have been discussed elsewhere, e.g. differences in intrinsic basicities, pH of reaction, attractive hydrogen bonding, and nonbonding respulsion interactions.[59-61] Our results suggest that the preference of the cis isomer for N7 of 9-MeA does not correlate with proton binding (first at N1) nor can it be related to pH and the fact that the N1 site becomes less available under acidic conditions because of protonation. There is no increase in the yield of the N1-coordinated product **2** when going from pH 4 to pH 8, even though the reaction is slower at higher pH. From models of **1** and **2** no convincing steric argument can be deduced as to why N7 is favored by the *cis*-isomer: with N1 binding, a similar favorable hydrogen bond between O2 of 1-MeC and NH_2 of 9-MeA can be expected to be formed. On the other hand, the separation between these two sites can be estimated to be about 4 Å in the case of *trans*-[$(NH_3)_2Pt$(1-MeC)(9-MeA-N^1)]$^{2+}$, certainly much too long to attribute the preference of the trans isomer for N1 to a favorable interligand hydrogen-bonding interaction.

Attempts to explain the different selectivities of *cis*- and *trans*-$[(NH_3)_2Pt(1\text{-MeC})H_2O]^{2+}$ unambiguously on the basis of attractive or repulsive interligand interactions in the five-coordinate transition state of the substitution reaction are also unsuccessful. Although the differing arrangements of the two nucleobases in the transition state (Figure 4) can be seen, a rationale can only be found for the preference of the trans isomer for N1; it appears that, in the case of the trigonal bipyramid derived from the trans complex, there may be less steric crowding and less interference of the adenine NH_2 group with the other ligands if coordination is through N1. No explanation for the preference of the cis isomer of N7 can be found on the basis of similar considerations.

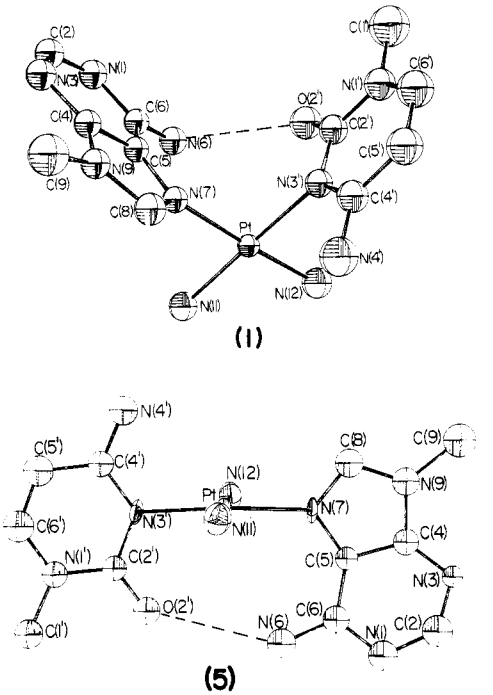

Figure 5. Structures of the cations of *cis*- and *trans*-[$(NH_3)_2Pt$(1-MeC)(9-MeA-N^7)]$(ClO_4)_2$ (**1**) and (**5**).

We suggest that besides the factors influencing the site of metal binding at the adenine mentioned above, the effect of the ligand trans to the entering adenine may be of importance. While the significance of the trans effect in Pt chemistry is widely recognized, there appears to have been no attempts to apply it to the question of the N1 vs. N7 dichotomy in adenine. In all cases with preferential Pt binding to N7 the ligand trans to N7 is either NH_3 or NHR_2 (in dien),[18d,62] regardless of whether the ligand in the cis position is another nucleobase (e.g. 1-methyluracil anion, 1-methylthymine anion, 9-ethylguanine),[63] NH_3, or Cl^-. However, with *trans*-$[(NH_3)_2Pt(1\text{-MeT})H_2O]^+$, as with *trans*-$[(NH_3)_2Pt(1\text{-MeC})H_2O]^{2+}$ where the result is another base trans to adenine, the N1 site is preferred over N7.[63] Despite the limitation of the present data, it seems worthwhile to pay more attention to the aspect of the nature of the ligand trans to the adenine as being important for the discrimination between two potential binding sites.

Crystal Structures of 1 and 5. The molecular cations of *cis*-$[(NH_3)_2Pt(1\text{-MeC})(9\text{-MeA-N}^7)](ClO_4)_2\cdot H_2O$ (**1**) and its anhydrous trans isomer **5** are illustrated to Figure 5, and selected interatomic distances and angles are listed in Table VI. Both cations contain a $(NH_3)_2Pt^{II}$ moiety bound to 1-methylcytosine through N3 and to 9-methyladenine through N7. In **1** the nucleobases are roughly at right angles to the square plane about platinum (1-MeC = 96 (1)°; 9-MeA = 84.7 (8)°) and to each other (89 (1)°). The ligand atoms square plane is not quite planar, and the platinum atom is displaced from the plane as shown by the inequivalent N(11)–Pt–N(3′) (177.7 (3)°) and N(12)–Pt–N(7) (175.1 (3)°) angles. In **5**, while the bases are at right angles to the ligand atom square plane (1-MeC = 87.5 (8)°; 9-MeA = 89.5 (8)°), they are essentially coplanar (dihedral angle 2.4 (8)°),

(56) The N7-protonated species is a tautomer of the N1-protonated species, which is the more stable one, as evident from its higgher pK_a value.
(57) (a) Shoup, R. R.; Miles, H. T.; Becker, E. D. *Biochem. Biophys. Res. Commun.* **1966**, *23*, 194–201. (b) Katz, L.; Penman, S. *J. Mol. Biol.* **1966**, *15*, 220–231.
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(63) Beyerle-Pfnur, R.; Lippert, B., submitted for publication.

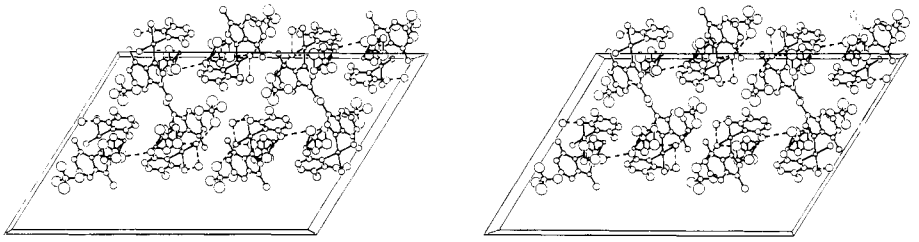

Figure 6. Packing diagram of **1**. *a* and *c** are parallel to the bottom and sides of the page, respectively, and the view is down *b*.

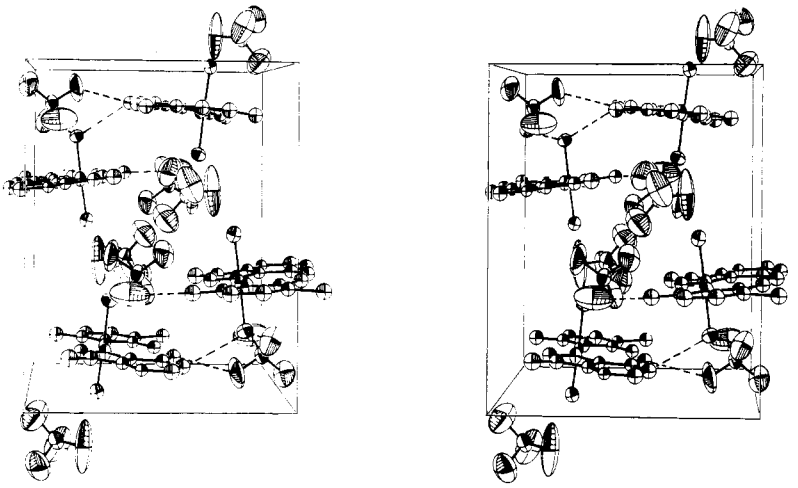

Figure 7. Packing diagram of **5**. *b* and *c* are parallel to the bottom and sides of the page respectively and the view is down *a**.

probably assisted in part by the weak N(6)···O(2′) hydrogen bond. The square plane also shows a significant distortion caused by this hydrogen bond. There is a tetrahedral distortion such that N(7) and N(3′) lie significantly out of the best plane (0.080 (7) Å). This is shown best by comparing the N(11)–Pt–N(12)(178.5 (3)°) and N(7)–Pt–N(3′) (175.6 (3)°) angles, where the latter angle is clearly much more distorted from 180° so as to shorten the N(6)···O(2′) distance. A similar weak intramolecular hydrogen bond and consequent distortion was seen in the *trans*-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-EtG})]^{2+}$ cation.[11b] Thus the trans cation reported here, like *trans*-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-EtG})]$,$^{2+}$ can be considered as a Hoogsteen pair in which the proton is replaced by the platinum atom.

Distances and angles within the respective nucleobases of the two complexes do not differ significantly. As compared to the free 1-MeC values,[10a,64] the expected minor changes in internal ring angles are seen.[10a] Comparison of the molecular dimensions of the platinated 9-MeA with those of both neutral and protonated[65] residues shows that bond angles and lengths are closer to those of the neutral molecule, and the use of the discriminant function suggested by Taylor and Kennard[66] confirms this view.

The nucleobases are nearly planar. Nevertheless, the dihedral angle between the six-and five-membered ring of the purine in **5** (3.7 (8)°) is quite large and larger than the 0.8 (8)° angle in **1**. Exocyclic atoms are significantly displaced from the ring planes, but not excessively.

The packing of **1** in the unit cell is shown in Figure 6. The cations, which resemble an open oyster with the disordered perchlorate (Cl(2)) as the pearl, are arranged in layers parallel to the *ab* face at $z = 0, {}^1/_2$. These layers are separated by the $Cl(1)O_4^-$ ions and any cation–cation interactions are van der Waals interactions and involve the $C(9)H_3$ or H atoms on the rings. Within the cation layers there is an extensive, but weak, hydrogen-bond lattice (shown by dotted lines in Figure 7) involving the water molecule, the ammine ligands, and the perchlorate ions in the *a* direction and N(6)···N(1) hydrogen bonds in the *b* direction.

The packing of **5** in the unit cell is shown in Figure 7. The structure consists of pleated layers of cations parallel to the *ab* plane. The bases in each cation are also roughly parallel to the *ab* plane and the "pleating" is caused by N(11)···N(1)[9] hydrogen bonds between adjacent cations in the *b* direction. The cation layers are separated by elliptical double chains of perchlorate anions along the *a* direction. The chain at $y = {}^1/_2$, $z = {}^1/_2$ has the major elliptical axis along [0,-1,0], and at $y = 0$, $z = 0$ the major elliptical axis is along [010]. The cation layers are bound to the anion chains by weak ammonia–perchlorate and amine–hydrogen bonds (N(11)···O(12), N(12)···O(13)[g], N(6)···O(11)[g], N(4′)···O(14)[I], O(22)[j]) as well as the ionic interactions.

Possible Relevance of Cytosine and Adenine Cross-Links. The complexes *cis*- and *trans*-$[Pt(NH_3)_2(1\text{-MeC})(9\text{-MeA})]^{2+}$ discussed here represent models of hypothetical cross-links of the two $(NH_3)_2Pt^{II}$ isomers between N3 sites of cytosine and N1 or N7 sites of adenine and can be considered as models for core–core and core–periphery cross-linking, respectively.[8] As to the possible significance of these cross-links in the course of DNA platination, it is clear that they are theoretically feasible in a completely denatured DNA since the donor sites discussed are not protonated at physiological pH and therefore in principle are available for metal binding. More relevant, however, is the question as to whether a duplex is still possible with a cross-link between cytosine and adenine and what the degree of disruption of DNA helix continuity may be.

In all the cases considered below the Watson–Crick hydrogen-bonding pattern will have to be disrupted in order to free the N1 and N3 sites for bonding, and this will affect the ease and nature of any distortion, although not in an easily predictable manner.

Inspection of the location of the respective donor atoms in intact B-DNA (Figure 8), with cytosine and adenine separated by one thread in the DNA helix, suggests the following possibilities.

An intrastrand cross-link through N3 of cytosine and N7 of adenine by cis Pt(II) complexes is possible if both bases rotate about the glycosidic bonds by approximately 135 and 45° (each in the same direction). The two bases are then roughly perpendicular to each other with the donor atoms separated by ca. 2.8 Å in order to accomplish Pt binding (Figure 9). A rotation of

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Table VI. Selected Interatomic Distances (Å) and Angles (deg) for **1** and **5**[a]

dist	1	5	dist	1	5
Pt–N(11)	2.030 (8)	2.069 (8)	Pt–N(12)	2.044 (8)	2.061 (8)
Pt–N(7)	2.012 (7)	2.007 (6)	Pt–N(3′)	2.049 (10)	2.031 (6)
N(1)–C(2)	1.35 (1)	1.34 (1)	C(2)–N(3)	1.35 (1)	1.34 (1)
N(3)–C(4)	1.32 (1)	1.33 (1)	C(4)–C(5)	1.39 (1)	1.38 (1)
C(5)–C(6)	1.41 (1)	1.41 (1)	C(6)–N(1)	1.37 (1)	1.35 (1)
C(5)–N(7)	1.40 (1)	1.37 (1)	N(7)–C(8)	1.30 (1)	1.36 (1)
C(8)–N(9)	1.35 (1)	1.35 (1)	N(9)–C(4)	1.38 (1)	1.38 (1)
C(6)–N(6)	1.37 (1)	1.37 (1)	N(9)–C(9)	1.50 (1)	1.50 (1)
N(1′)–C(2′)	1.36 (2)	1.40 (1)	C(2′)–N(3′)	1.37 (1)	1.38 (1)
N(3′)–C(4′)	1.35 (2)	1.35 (1)	C(4′)–C(5′)	1.42 (2)	1.43 (1)
C(5′)–C(6′)	1.35 (2)	1.35 (2)	C(6′)–N(1′)	1.36 (2)	1.38 (1)
C(1′)–N(1′)	1.46 (2)	1.48 (1)	O(2′)–C(2′)	1.23 (2)	1.23 (1)
C(4′)–N(4′)	1.33 (1)	1.33 (1)			
		Contact Distances in **1**			
N(11)···O(11)[a]	3.08 (1)	N(11)···O(23′)[b]	3.06 (3)	N(11)···O	3.08 (1)
N(12)···O	2.92 (1)	N(6)···N(1)[d]	3.03 (1)	N(6)···O(2′)	3.03 (2)
N(4′)···O(21)[e]	3.12 (3)	N(4′)···O(22)[b]	2.97 (2)	N(4′)···O(24′)[b]	3.13 (4)
O···O(24)[b]	3.15 (2)	O···O(2′)[f]	2.82 (1)	O···N(1)[c]	3.11 (2)
		Contact Distances in **5**			
N(11)···O(12)	2.92 (1)	N(11)···N(1)[g]	3.13 (1)	N(12)···O(13)[i]	3.13 (1)
N(12)···O(2′)[h]	3.03 (1)	N(6)···O(11)[g]	2.98 (1)	N(6)···O(2′)	3.29 (1)
N(4′)···O(14)[i]	3.17 (2)	N(4′)···O(22)[j]	3.13 (2)		
angle	1	5	angle	1	5
N(11)–Pt–N(12)	92.1 (4)	178.5 (3)	N(11)–Pt–N(7)	88.6 (3)	89.9 (3)
N(11)–Pt–N(3′)	177.7 (3)	90.6 (3)	N(12)–Pt–N(7)	175.1 (3)	89.3 (3)
N(12)–Pt–N(3′)	88.8 (4)	90.2 (3)	N(3′)–Pt–N(7)	90.7 (3)	175.6 (3)
Pt–N(7)–C(5)	125.1 (5)	117.0 (6)	Pt–N(7)–C(8)	129.6 (8)	125.5 (6)
Pt–N(3′)–C(2′)	117.7 (8)	114.0 (5)	Pt–N(3′)–C(4′)	121.1 (7)	124.0 (6)
C(6)–N(1)–C(2)	119.0 (9)	119.6 (9)	N(1)–C(2)–N(3)	128 (1)	128 (1)
C(2)–N(3)–C(4)	111.2 (7)	110.7 (8)	N(3)–C(4)—C(5)	128.0 (9)	128.2 (8)
C(4)–C(5)–C(6)	116.7 (9)	115.8 (8)	C(5)–C(6)–N(1)	117.1 (7)	117.6 (8)
N(9)–C(4)–C(5)	104.5 (8)	105.6 (8)	C(4)C(5)–N(7)	109.6 (7)	109.7 (7)
C(5)–N(7)–C(8)	105.2 (8)	106.3 (7)	N(7)–C(8)–N(9)	112 (1)	109.7 (8)
C(8)–N(9)–C(4)	108.1 (7)	108.8 (8)	N(3)–C(4)–N(9)	127.5 (7)	126.1 (8)
C(6)–C(5)–N(7)	133.7 (7)	134.4 (8)	C(5)–C(6)–N(6)	125.4 (9)	123.2 (8)
N(6)–C(6)–N(1)	117.5 (8)	119.2 (8)	C(8)–N(9)–C(9)	127 (1)	124.6 (9)
C(9)–N(9)–C(4)	124.7 (9)	126.6 (8)	C(6′)–N(1′)–C(2′)	121.4 (9)	122.0 (8)
N(1′)–C(2′)–N(3′)	119 (1)	117.0 (7)	C(2′)–N(3′)–C(4′)	121 (1)	148.9 (6)
N(3′)–C(4′)–C(5′)	119.3 (9)	120.1 (8)	C(4′)–C(5′)–C(6′)	119 (1)	118.8 (9)
C(5′)–C(6′)–N(1′)	120 (1)	120.0 (9)	C(6′)–N(1′)–C(1′)	119 (1)	118.3 (8)
C(1′)–N(1′)–C(2′)	119 (1)	119.6 (7)	N(1′)–C(2′)–O(2′)	121.3 (9)	120.6 (8)
O(2′)–C(2′)–N(3′)	120 (1)	122.4 (8)	N(3′)–C(4′)–N(4′)	120 (1)	118.6 (8)
N(4′)–C(4′)–C(5′)	121 (1)	121.3 (9)			

[a] Atoms are related to those in Tables II and III by the following symmetry transformations: (a) $^1/_2 - x, ^1/_2 - y, 1 - z$; (b) $1 - x, y, ^1/_2 - z$; (c) $1 - x, 1 - y, 1 - z$; (d) $1 - x, 2 - y, 1 - z$; (e) $^1/_2 - x, ^1/_2 + y, ^1/_2 - z$; (f) $x, y - 1, z$; (g) $^1/_2 - x, y - ^1/_2, 1^1/_2 - z$; (h) $-x, -y, 1 - z$; (i) $^1/_2 - x, ^1/_2 + y, 1^1/_2 - z$; (j) $-x, 1 - y, 1 - z$.

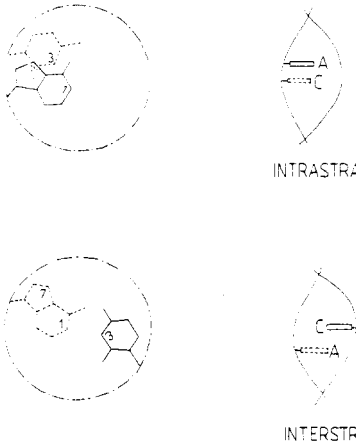

Figure 8. Relative orientations of cytosine and adenine nucleobases separated by one tread in double-helical B-DNA. The view is down the helix axis from the 5′-end (left) and perpendicular to this axis (5′-end at the top), respectively. The base drawn in dotted lines is situated below the other nucleobase.

135° corresponds to an incomplete conformational change of the base from the usual anti into the unusual syn orientation. There is evidence that nucleobases, and in particular purines, undergo this change in conformation in the presence of DNA-binding species.[20,66] For obvious reasons, a drastic local distortion of DNA is expected to result from this type of cross-link.

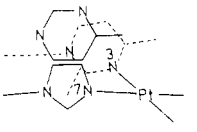

Figure 9. Schematic drawing of a cis cross-link of Pt(II) between N3 of cytosine and N7 of adenine with adenine in a *syn* orientation relative to the sugar.

cis Pt(II) complex intrastrand cross-linking through N3 or cytosine and N1 of adenine could occur relatively easily if both bases are rotated about the respective glycosidic bond by 90 and 45°.

Interstrand cross-linking of cytosine and adenine through trans Pt(II) complexes appears to be possible in two ways: between N3 of cytosine and N1 of adenine with the two bases in their normal anti conformation or between N3 of cytosine and N7 of adenine with the purine in its syn conformation. In the former case, the two bases probably are not coplanar because of steric repulsion between the exocyclic amino groups. Steric distortion of DNA by this cross-link can be expected to be substantial, since

not only base stacking and hydrogen bonding will be affected by the necessity of making N3 of cytosine and N1 of adenine colinear with Pt will also affect the backbone of DNA. In the latter case coplanarity of the bases may be possible. In addition, distortion may be much less because when platinum replaces the proton, the sugar–sugar distance of 8.65 Å in a Hoogsteen pair[67] is increased to 10.4 Å, which is close to the Watson–Crick distance of 10.8 Å.

A comparison of the model compounds **1** and **5** with the cross-links discussed here suggests that **1** and **5** do not represent "real" models in the sense that the two bases do not adopt a head–head orientation as they do in DNA. Rather, one of the two bases is rotated about the Pt–N bond in order to make a favorable intramolecular hydrogen bond between O2 of cytosine and NH_2 of adenine and to avoid repulsion between the amino groups of both bases.

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Supplementary Material Available: Tables of anisotropic temperature factors, perchlorate bond lengths and angles, best planes and dihedral angles, and moduli of F_o and F_c and a figure depicting the chemical shifts as a function of pD (51 pages). Ordering information is given on any current masthead page.

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EPR Spectra of Low-Symmetry Tetrahedral High-Spin Cobalt(II) in a Cinchoninium Tetrachlorocobaltate(II) Dihydrate Single Crystal

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EPR spectra of a cinchoninium tetrachlorocobaltate(II) dihydrate [cin$(CoCl_4)\cdot 2H_2O$] single crystal were recorded at 4.2 K. The principal effective g' factors were determined to be $g'_z = 2.13$, $g'_y = 5.57$, and $g'_x = 3.83$ and related to the $\pm^1/_2$ ground state level of the high-spin cobalt(II) in a low-symmetry $CoCl_4^{2-}$ tetrahedron. The true spin-Hamiltonian parameters are $g_\parallel = 2.23$, $g_\perp = 2.38$, and $\lambda = E/D = 0.125$. The relations between g' factors and λ values for several Co(II) tetrahedral complexes are discussed.

Introduction

High-spin tetrahedral Co(II) complexes with different chromophores have been studied by EPR in several crystal lattices.[4-13] EPR results have been described in terms of effective g' factors, which have been interpreted by using the spin-Hamiltonian[11] or/and angular-overlap formalism.[9,13] Hyperfine splitting of ^{59}Co ($I = {}^7/_2$) tends to be relatively small in tetrahedral complexes, is easily smeared out by dipolar and exchange interactions, and thus has been observed only in a few cobalt(II) salts or in magnetically diluted crystals.[4,8]

In regular T_d symmetry the orbital singlet $^4A_2$ is the ground state. When the symmetry is lowered, the spin degeneracy is lifted and either the $\pm^1/_2$ state or the $\pm^3/_2$ state can be lower in energy. The $\pm^1/_2$ state is lower in a flattened tetrahedron, and the $\pm^3/_2$ state is lower in an elongated tetrahedron of D_{2d} symmetry.[9] In most cases, the $\pm^1/_2$ state has been postulated or proved to be the lowest level. The true g-factor values are expected to lie in a range of 2.2–2.7 with $g_\parallel = 2.2$–2.4 in tetrahedral Co(II) complexes.[14] The zero-field splitting $2D$ between $\pm^1/_2$ and $\pm^3/_2$ states in such complexes is found to be rather large, usually of the order of few reciprocal centimeters. For this reason the lowest level is a Kramers doublet and the EPR spectrum can be described in terms of a fictitious spin $S' = {}^1/_2$ using effective g' factors. the g' values are very sensitive to low-symmetry components of the crystal field and thus differ strongly from the true g factors of the Co(II) ions.

In the present paper EPR single-crystal measurements of a low-symmetry $CoCl_4^{2-}$ complex in cin$(CoCl_4)\cdot 2H_2O$ are presented (cin = cinchoninium). The detailed structure of the crystal is not known, but the crystal data of isomorphous cin$(CdCl_4)\cdot 2H_2O$ are available.[15] The stick-bond diagram of the cinchonine molecule is presented in Figure 1. The X-ray data indicate that a series of cinchonine hydrochloride complexes with Cd, Co, Zn, and Hg are isomorphous. The crystals are orthorhombic, with space group $P2_12_12_1$ and $Z = 4$. Tetrahedral $CdCl_4^{2-}$ anions are involved in hydrogen bonds with cinchonine molecules and have essentially C_1 symmetry with Cd–Cl distances in the range 2.42–2.49 Å and bond angles 97.9–117°.

Experimental Section

Preparation of cin$(CoCl_4)\cdot 2H_2O$. The compound was prepared by Dyrek's method.[16] A solution of 10 g of cinchonine ($C_{19}H_{22}N_2O$) in 60

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