Bis(purine) Complexes of *trans*-a_2Pt^{II}: Preparation and X-ray Structures of Bis(9-methyladenine) and Mixed 9-Methyladenine, 9-Methylguanine Complexes and Chemistry Relevant to Metal-Modified Nucleobase Triples and Quartets

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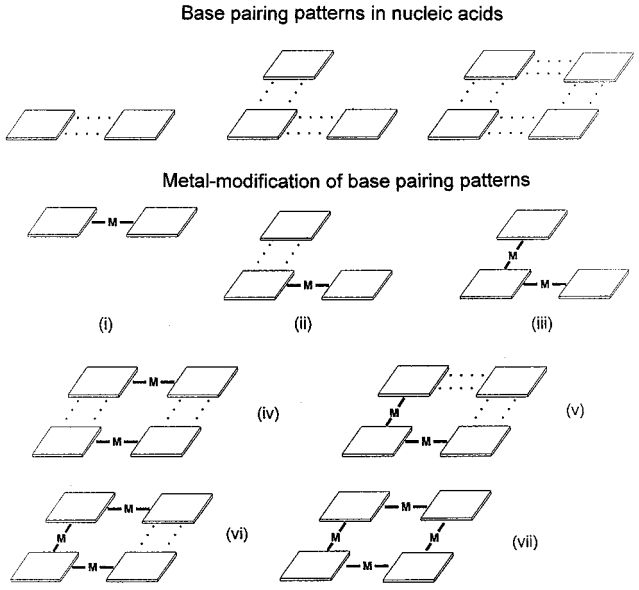
Abstract: Mononuclear bis(purine) complexes of *trans*-a_2Pt^{II}, *trans*-$[(NH_3)_2Pt(9\text{-MeA-}N7)(9\text{-MeGH-}N7)](NO_3)_2\cdot H_2O$ (**1b**) and *trans*-$[(NH_3)_2Pt(9\text{-MeA-}N7)_2](ClO_4)_2\cdot H_2O$ (**3c**), have been prepared and their structures determined by X-ray crystallography. **1b**: Space group $P1$, $a = 7.245$ (5) Å, $b = 7.715(6)$ Å, $c = 10.907(8)$ Å, $\alpha = 82.36(6)°$, $\beta = 86.62(6)°$, $\gamma = 70.15(6)°$, $V = 568.3(7)$ Å^3, $Z = 1$. **3c**: Space group $P2_1/c$, $a = 8.312(2)$ Å, $b = 15.386(3)$ Å, $c = 12.365(2)$ Å, $\beta = 94.83(3)°$, $V = 1575.72(55)$ Å, $Z = 2$. The cation of **3c** is centrosymmetric. In the cation of **1b**, the two purines adopt a *head*−*head* orientation with an intramolecular H bond of 2.94(3) Å between the exocyclic amino group of 9-MeA and the exocyclic carbonyl group of 9-MeGH. Di- and trinuclear derivatives of **1b** and **3c** have been synthesized and/or studied in solution. They include compounds of types Cl•*N1*-A-*N7*•GH (**2a**), T•*N1*-A-*N7*•GH (**2b**), GH•*N1*-A-*N7*•T (**2c**), and GH•*N7*-A-*N1*•*N1*-A-*N7*•GH (**2d**) as well as X•*N1*-A-*N7*•*N7*-A-*N1*•X (X = Cl (**4**), GH (**5a**), T (**5b**)) with • representing *trans*-a_2Pt^{II} entities (a = NH_3 or CH_3NH_2). The fact that Pt−(A-*N1*) and Pt−(A-*N7*) vectors are at right angles and the nucleobases essentially coplanar in many cases leads to intramolecular H bonding involving $NH_2(6)$ of 9-MeA and exocyclic groups of the other nucleobases. The chemical shifts of the NH_2 protons of 9-MeA in DMSO-d_6 or DMF-d_7 permit a differentiation between the various possibilities (no H bonding, single H bond, 2 H bonds, 1 Pt or 2 Pt coordinated to 9-MeA). As far as intermolecular H bonding is concerned, the neutral 9-MeGH ligand in **1b** forms a Watson−Crick pair with 1-MeC but a 9-MeGH ≡ 9-MeG pair at pH 8. The potential usefulness of the complexes prepared with regard to the formation of two-dimensional sheet structures and molecular squares built up of purine nucleobase and *trans*-a_2Pt^{II} entities is briefly discussed, as are aspects of the stabilization of triplex nucleic acid structures by metal ions.

Introduction

Base-pairing patterns commonly observed in nucleic acids involve two, three, or four nucleobases, examples being Watson−Crick, Hoogsteen and wobble pairs or other mismatches, triples, and quartets, as schematically depicted in Chart 1.[1] The heterocyclic nucleobase may be neutral, protonated,[2] or deprotonated[3] in principle, but pairing patterns between neutral entities clearly dominate. The replacement of hydrogen bonds, in part or fully, by metal ions adopting linear or close-to-linear coordination geometries[4] yields aggregates in which the nucleobases are essentially still coplanar but much more strongly bonded. Such "metal-modified nucleobase pairs" may be biologically relevant (metal-induced mutagenicity, irreversible cross-links) and useful in antisense and antigene strategies.

We have previously prepared and structurally studied three

Chart 1



[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

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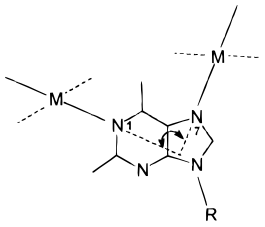
(4) Under special circumstances, even tetrahedral metal coordination can allow a coplanar arrangement of two nucleobases; cf.: Fusch, E. C.; Lippert, B. *J. Am. Chem. Soc.* **1994**, *116*, 7204.

S0002-7863(95)03595-5 CCC: $12.00

Chart 2



types of metal-modified nucleobase pairs and triples (Chart 1, (i)−(iii)). Both identical nucleobases,[5] complementary bases (in Watson−Crick and Hoogsteen manner),[6,7] and noncomplementary bases[8,9] have been applied.[10] From work with base triples containing a central purine base (Chart 1, (iii)), two aspects emerged, namely the importance of intramolecular H bonding and the possibility to extend the triples to planar quartets for purines.[11] The latter is a consequence of the fact that in *N1,N7*-dimetalated purine complexes (Chart 2) the M−N1 and M−N7 vectors always form angles close to 90°.[11,12]

In continuation of this work, we have now prepared two bis(purine) complexes of *trans*-$(NH_3)_2Pt^{II}$, *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot H_2O$ (**1b**) and *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)$_2$]$(ClO_4)_2\cdot 2H_2O$ (**3c**), in order to study their ability to form platinated triples or quartets in solution and in the solid state (Chart 1, (iv)−(vii)).[13]

Experimental Section

Starting Compounds. 9-MeA[14] and deuterated 9-MeA[15] (ND_2, C(8)D) were prepared as previously described. 9-MeGH, 9-EtGH, and 1-EtTH were purchased from Chemogen, Konstanz, Germany, and used without further purification. *trans*-$Pt(NH_3)_2Cl_2$ was prepared according to the method of Kauffman and Cowan,[16] and *trans*-$Pt(NH_2CH_3)_2Cl_2$[17] was prepared as described in the literature. The preparation and isolation of 1-MeTH,[18] *trans*-$Pt(NH_3)_2$(1-MeT-*N3*)Cl,[6] and *trans*-[$Pt(NH_3)_2$(9-MeGH-*N7*)Cl]Cl[19] were performed according to published methods. *trans*-$Pt(NH_3)_2$(1-EtT-*N3*)Cl and *trans*-[$Pt(NH_3)_2$(1-EtT-*N3*)(9-MeA-*N7*)]NO_3 were prepared in analogy to the corresponding 1-MeT compounds[6] and identified by ^{1}H NMR spectroscopy.

In the following, only those compounds are described that have been synthesized *and* isolated. Additional compounds, prepared but *not* isolated, are dealt with under Results.

***trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot H_2O$ (1b).** *trans*-[$Pt(NH_3)_2$(9-MeGH-*N7*)Cl]Cl (1488 mg, 3.2 mmol) was suspended in water (120 mL), and the pH was adjusted to 1.4 by means of 1 N HNO_3. A solution of 9-MeA (521.7 mg, 3.5 mmol) in water (40 mL) was likewise brought to pH 1.4 and added to the suspension, and $AgNO_3$ (1085 mg, 6.4 mmol) dissolved in H_2O (40 mL) was slowly added over a 4-h period. The mixture was stirred for 6 days at 40 °C in the dark and cooled to 4 °C, and the precipitated AgCl was removed by filtration. Slow evaporation of the clear yellowish solution gave crystalline **1b**, which was washed with MeOH and then water and dried in air (yield 32%). Anal. Calcd (found) for $C_{12}H_{22}N_{14}PtO_8$: C, 21.0 (21.1); H, 3.2 (3.2); N, 28.6 (28.5).

***trans*-{[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)] ≡ [(9-MeG-*N7*)(9-MeA-*N7*)Pt$(NH_3)_2$]} $(NO_3)_3\cdot 6H_2O$ (1b·1c).** **1b** (200 mg, 0.3 mmol) was dissolved in water (25 mL) at 45 °C, and 0.1 N NaOH was added until the pH was 8. A gel formed immediately which could not be filtered off. Therefore the sample was brought to dryness and then suspended in MeOH. After 5−10 min of stirring, a powder was filtered off and kept under vacuum to remove MeOH. The yield was 30%. Anal. Calcd (found) for $C_{24}H_{51}N_{27}O_{17}Pt_2$: C, 20.9 (20.5); H, 3.7 (3.4); N, 27.4 (27.5).

***trans,trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N7*-9-MeA-*N1*)Pt$(NH_3)_2$Cl]-$(ClO_4)_3\cdot H_2O$ (2a).** **1b** (20 mg, 0.03 mmol) was dissolved in 600 μL of D_2O and stirred with an excess of *trans*-$(NH_3)_2PtCl_2$ (15 mg, 0.05 mmol) for 4 d at 45 °C. Then the mixture was cooled to 4 °C, and the unreacted *trans*-$(NH_3)_2PtCl_2$ was removed. Solid $NaClO_4$ (3.7 mg, 0.03 mmol) was added to the clear solution. **2a** precipitated as a white powder, which was filtered off, washed with ice water, and dried at 40 °C (yield 70%, 23.6 mg). Anal. Calcd (found) for $C_{12}H_{28}N_{14}Pt_2O_{14}Cl_4$: C, 12.8 (12.8); H, 2.5 (2.7); N, 17.4 (17.5); Cl, 12.6 (12.9). IR (cm^{-1}): 353 (ν(Pt−Cl)). ^{195}Pt NMR (D_2O, δ, ppm): −2413, −2472.

***trans,trans,trans*-{$(NH_3)_2$Pt(*N1*-9-MeA-*N7*)$_2$[$(NH_3)_2$Pt(9-MeGH-*N7*]$_2$}$(ClO_4)_4$ $(NO_3)_2\cdot 7H_2O$ (2d).** *trans*-$(NH_3)_2PtCl_2$ (45 mg, 0.15 mmol) was suspended in H_2O (10 mL) and stirred with $AgNO_3$ (50 mg, 0.295 mmol) for 2 h at 70 °C with daylight excluded. After the solution was cooled to room temperature, AgCl was filtered off and **1b** (200 mg, 0.3 mmol), dissolved in water (20 mL), was added. The mixture (pH 5) was kept at 40 °C for 4 d and filtered from some unidentified dark precipitate, and the filtrate was concentrated to a 15 mL volume. Then an excess of $NaClO_4$ (122 mg, 1 mmol) was added, and the precipitate that formed was filtered off, briefly washed with water, and dried at 40 °C overnight. The compound was isolated in 42% yield. Anal. Calcd (found) for $C_{24}H_{60}N_{28}O_{31}Pt_3Cl_4$: C, 14.7 (14.5); H, 3.1 (3.0); N, 20.0 (20.0); Cl, 7.2 (7.3). Thermogravimetry was consistent with the presence of 7 molecules of water of crystallization. IR (cm^{-1}), 1356 ($\nu_1(NO_3^-)$); 1087 ($\nu_3(ClO_4^-)$).

***trans*-[a_2Pt(9-MeAH-*N7*)$_2$]$(ClO_4)_4\cdot 2H_2O$ (a = NH_3 (3a), CH_3NH_2 (3d)).** To a suspension of *trans*-a_2PtCl_2 (a = NH_3 or CH_3NH_2) (300 and 328 mg, 1 mmol) in water (50 mL) was added $AgClO_4$ (415 mg, 2 mmol), and the mixture was stirred in the dark for 90 min at 80 °C. After cooling of the mixture to room temperature, the precipitated AgCl was filtered off and the pH of the filtrate was adjusted to 1.2 by means of 0.1 N $HClO_4$. An acidic solution (pH 1.2) of 9-MeA (596 mg, 4 mmol) was added, and the reactants were stirred for 2 d at 45 °C. The precipitated white product was isolated, washed with water and acetone, and redissolved in dilute $HClO_4$. Slow evaporation of the solvent gave colorless cubes of **3a** and a white powder for **3d** at a later stage (yields: **3a**, 40%; **3d**, 12%). Anal. Calcd (found) for $C_{12}H_{26}N_{12}PtO_{18}Cl_4$ (**3a**): C, 15.0 (15.3); H, 2.7 (2.8); N, 17.4 (17.1). Calcd (found) for $C_{14}H_{30}N_{12}PtO_{18}Cl_4$ (**3d**): C, 17.0 (16.8); H, 3.1 (3.0); N, 17.0 (16.9). A colorless crystal isolated from a solution of **3a** soon after redissolving in $HClO_4$ proved to be *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)]$_2(ClO_4)_2\cdot H_2O$ (**3c**) according to X-ray analysis. **3c** was also prepared in situ from **3a** by treatment with 2 equiv of base.

***trans,trans,trans*-{Pt$(NH_3)_2$(*N7*-9-MeA-*N1*)$_2$[Pt$(NH_2CH_3)_2$Cl]$_2$}-$(ClO_4)_4$ (4a) and *trans,trans,trans*-{Pt$(NH_3)_2$(*N7*-9-MeA-*N1*)$_2$[Pt-**

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(10) Proposals on the replacement of H bonds by metal ions of linear geometry have been made before, especially for Hg^{II}. See, e.g.: (a) Yamane, T.; Davidson, N. *J. Am. Chem. Soc.* **1961**, *83*, 2599. (b) Katz, S. *Biochim. Biophys. Acta* **1963**, *68*, 240. (c) Kosturko, L. S.; Folzer, C.; Stewart, R. F. *Biochemistry* **1974**, *13*, 3949. (d) Buncel, E.; Boone, C.; Joly, H. *Inorg. Chim. Acta* **1986**, *125*, 167.

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(12) Frommer, G.; Schöllhorn, H.; Thewalt, U.; Lippert, B. *Inorg. Chem.* **1990**, *29*, 1417.

(13) Abbreviations used: 9-MeA = 9-methyladenine, 9-MeGH = 9-methylguanine, 9-EtGH = 9-ethylguanine, 1-MeTH = 1-methylthymine, 1-EtTH = 1-ethylthymine, 9-MeAH = 9-methyladeninium cation, 1-MeT = 1-methylthymine anion, etc. Occasionally, A, G, T are used for the nucleobases adenine, guanine, and thymine. Coordination sites are indicated, e.g. 9-MeA-*N7*. In cases with Pt's binding both to N1 and N7, e.g. X_2Pt(*N7*-9-MeA-*N1*)$_2$[PtY_2L]$_2$, donor sites are indicated in a sequential manner; *viz.* X_2Pt is bound to two N7 sites, and two PtY_2L entities are bound to two N1 sites.

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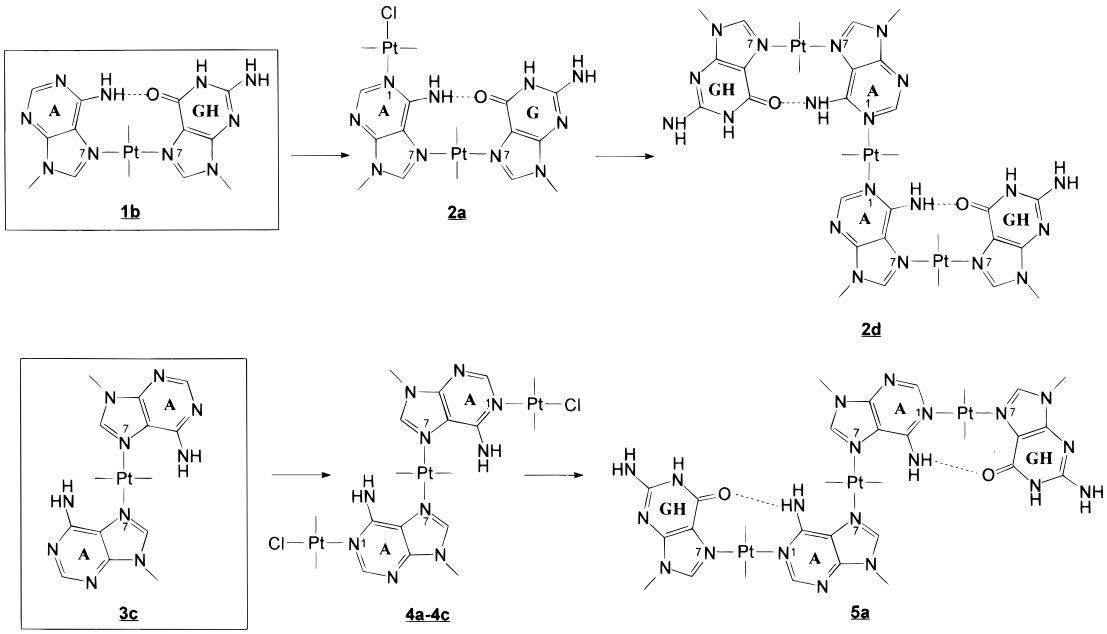

Figure 1. Schematic drawings of isolated compounds derived from **1b** and **3c**. Charges are omitted, and NH_3/amine ligands are not indicated.

$(NH_3)_2Cl]_2\}(ClO_4)_3(NO_3)$(4b) and *trans,trans,trans*-{Pt$(NH_2CH_3)_2$-(*N7*-9-MeA-*N1*)$_2$[Pt$(NH_2CH_3)_2Cl]_2\}(ClO_4)_4$ (4c) were synthesized by treating *trans*-[Pta$_2$(9-MeA-*N7*)$_2$]X_2 (0.5 mmol) (X = ClO_4^-, NO_3^-, a = NH_3 or NH_2CH_3) in aqueous solution (pH 7) with *trans*-Pta$_2Cl_2$ (2 mmol) for 24 h at 45 °C. Unreacted *trans*-Pta$_2Cl_2$ was then removed, and solid $NaClO_4$ was added in excess. The pure products (**4a**−**c**) were obtained as white powders. Isolated yields were ca. 15% (**4a**), 20% (**4b**), and 18% (**4c**). Anal. Calcd (found) for $C_{16}H_{40}N_{16}Pt_3O_{16}Cl_6$ (**4a**): C, 12.7 (12.4); H, 2.7 (2.7); N, 14.8 (14.7). Calcd (found) for $C_{12}H_{32}N_{17}Pt_3O_{15}Cl_5$ (**4b**): C, 10.2 (10.1); H, 2.3 (2.7); N, 16.8 (16.8). Calcd (found) for $C_{18}H_{44}N_{16}Pt_3O_{16}Cl_6$ (**4c**): C, 14.1 (14.1); H, 2.9 (3.0); N, 14.6 (14.6).

***trans,trans,trans*-{(NH$_3$)$_2$Pt(*N7*-9-MeA-*N1*)$_2$[(CH$_3$NH$_2$)$_2$Pt(9-EtGH-*N7*)]$_2$}(ClO$_4$)$_5$(NO$_3$)·1.5H$_2$O (5a).** *trans,trans,trans*-{Pt$(NH_3)_2$(9-MeA-*N7,N1*)$_2$[Pt$(NH_2CH_3)_2$ $Cl]_2\}(ClO_4)_4$ (**4a**) (45 mg, 0.03 mmol) and $AgNO_3$ (10 mg, 0.06 mmol) were stirred in water (24 h, 22 °C), and 9-EtGH (11 mg, 0.06 mmol) was added. After 4 d at 40 °C the mixture was cooled and then filtered from AgCl. After addition of $NaClO_4$ (22 mg, 0.18 mmol) the product **4a** precipitated as a slightly yellowish powder. Recrystallization from MeOH/H_2O (4:1) gave thin needles of **5** (yield 30%). Anal. Calcd (found) for $C_{30}H_{61}N_{27}Pt_3O_{26.5}Cl_5$: C, 18.1 (18.3); H, 3.1 (3.4); N 19.0 (18.8).

Schematic representations of the isolated starting compounds are given in Figure 1.

Instrumentation. ^{1}H NMR spectra were recorded on a Bruker AC 200 FT NMR spectrometer using D_2O (with TSP as internal reference), DMSO-d_6, and DMF-d_7 (with TMS as internal standard) as solvents. For aqueous solutions, pD values were determined by use of a glass electrode and addition of 0.4 to the pH meter reading. Uncorrected values (pH*) were used for the determination of pK_a values. Variable-temperature spectra were also run on the Bruker AC 200 instrument equipped with a VT-1000 E variable-temperature unit. The VT unit was calibrated with samples of methanol or ethylene glycol. The 43.02-MHz ^{195}Pt-NMR and 2D ^{1}H−^{195}Pt HMQC spectra were also recorded on the AC 200 spectrometer with Na_2PtCl_6 being the external reference. Elemental analyses were performed with a Carlo Erba Model 1106 Strumentazione Element-Analyzer.

Crystallography. Crystal data for compound **1b** were taken at room temperature on a Nicolet R3m/V single-crystal diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Unit cell parameters were obtained from a least-squares fit with 10 reflections in the range $15.03 \le 2\theta \le 23.3°$. Intensity data were collected at variable scan speed in the range $3.76 \le 2\theta \le 50.10°$ using an $\omega/2\theta$-scan technique. Crystal data of compound **3c** were recorded on a Siemens R3m/V single-crystal diffractometer using ω-scans (room temperature, Mo Kα radiation). The unit cell parameters were obtained from 17 reflections ($10.07 \le 2\theta \le 26.73°$). For both compounds an empirical absorption correction via ψ-scans was applied. Crystal data and experimental details for **1b** and **3c** are listed in Table 1 and the Supporting Information, respectively.

Table 1. Crystal Data and Experimental Details of the X-ray Studies

	1b	**3c**
compd	$C_{12}H_{22}N_{14}O_8Pt$	$C_{12}H_{22}Cl_2N_{12}O_9Pt$
formula wt	685.53	744.377
cryst size, mm	0.32 × 0.32 × 0.32	0.2 × 0.3 × 0.2
space group	$P\bar{1}$	$P2_1/c$
a, Å	7.245(5)	8.312(2)
b, Å	7.715(6)	15.386(3)
c, Å	10.907(8)	12.365(2)
α, deg	82.35(6)	
β, deg	86.62(6)	94.83(3)
γ, deg	70.15(6)	
V, Å^3	568.3(7)	1575.72(55)
Z	1	2
temp, K	293	293
ρ_{calcd}, g cm^{-3}	2.003	1.569
λ(Mo Kα), Å	0.710 73	0.710 73
max 2θ deg, reflcns collcd	50.1	50
h,k,l	$0 \le h \le 8$, $-8 \le k \le 9$, $-12 \le l \le 12$	$0 \le h \le 9$, $0 \le k \le 18$, $-14 \le l \le 14$
no. of indepdt reflcns	2012	2769
no. of obsd reflcns	1041 ($F > 4\sigma(F)$)	1622 ($F > 4\sigma(F)$)
final *R*, w*R*	R_1 = 6.9%;[a] wR_2 = 14.9%[b]	R_1 = 7.66%;[a] w*R* = 7.53%[c]
final diff map		
highest peak, e Å^{-3}	1.68	2.83
deepest valley, e Å^{-3}	−2.40	−2.17

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = (\sum w(|F_o^2| - |F_c|^2)^2/\sum w|F_o|^2)^2)^{0.5}$; $w^{-1} = \sigma^2(F_o^2) + (0.0833P)^2$; $P = (F_o^2 + F_c^2)/3$. [c] $wR = \sum w||F_o| - |F_c||)/\sum w|F_o|$; $w^{-1} = \sigma^2(F) + 0.0001F^2$.

The structures were solved by Patterson and Fourier methods and refined by full-matrix least squares using the SHELXTL PLUS and SHELX-93 systems of crystallographic computer programs.[20] Fractional atomic coordinates and equivalent isotropic displacement parameters for **1b** and **3c** are given in the Supporting Information, and selected interatomic distances and angles are listed in Tables 2 and 3. The purine entities of **1b** were determined using constraints of bond lengths and angles; the N−O bonds of the nitrate anion in **1b** were constrained to 1.255 ± 0.03 Å. No attempt was made to locate the

(20) (a) Sheldrick, G. M. SHELXTL-PLUS (Release 3.4) for Nicolet R3m/V Crystallographic System, University of Göttingen, FRG, 1987. (b) Sheldrick, G. M. SHELX-93, University of Göttingen, FRG, 1993.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **1b**

	Distances		
Pt(1)−N(7)	2.05(1)	Pt(1)−N(10)	2.11(2)
N(7)−C(5′)	1.38(2)	N(7)−C(5)	1.37(2)
C(4′)−C(4)	1.31(2)	C(4′)−C(5′)	1.37(2)
C(4′)−N(3′)	1.41(2)	C(5′)−C(6′)	1.37(2)
C(6′)−O(6′)	1.26(3)	C(6′)−N(1′)	1.40(2)
N(1′)−C(2′)	1.33(2)	C(2′)−N(3′)	1.31(2)
C(2′)−N(2′)	1.33(3)	C(5)−C(6)	1.37(2)
C(5)−C(4)	1.38(2)	C(4)−N(3)	1.41(2)
C(2)−N(3)	1.34(2)	C(2)−N(1)	1.36(2)
N(1)−C(6)	1.37(2)	C(6)−N(6)	1.33(3)
	Angles		
N(7)−Pt(1)−N(10)	89.4(6)	C(5)−N(7)−C(5′)	108.4(14)
C(5)−N(7)−Pt(1)	126.6(11)	C(5′)−N(7)−Pt(1)	124.9(11)
C(4)−C(4′)−C(5′)	110.0(14)	C(5′)−C(4′)−N(3′)	123.0(13)
C(4′)−C(5′)−C(6′)	122(2)	C(4′)−C(5′)−N(7)	106.4(14)
C(6′)−C(5′)−N(7)	130(2)	N(3′)−C(2′)−N(1′)	125(2)
O(6′)−C(6′)−C(5′)	131(2)	O(6′)−C(6′)−N(1′)	116(2)
C(5′)−C(6′)−N(1′)	112(2)	C(2′)−N(1′)−C(6′)	124(2)
N(2′)−C(2′)−N(1′)	121(2)	C(2′)−N(3′)−C(4′)	113(2)
N(7)−C(5)−C(4)	106.2(14)	C(2)−N(3)−C(4)	116(2)
C(6)−C(5)−C(4)	117.2(14)	C(4′)−C(4)−C(5)	109.0(14)
C(4′)−C(4)−N(3)	127(2)	C(5)−C(4)−N(3)	123.6(13)
N(3)−C(2)−N(1)	121(2)	C(2)−N(1)−C(6)	122(2)
N(6)−C(6)−N(1)	115(2)	N(6)−C(6)−C(5)	126(2)
N(1)−C(6)−C(5)	119(2)		

Table 3. Selected Bond Distances (Å) and Angles (deg) for **3c**

	Distances		
Pt(1)−N(7)	2.00(2)	Pt(1)−N(10)	2.09(2)
N(7)−C(8)	1.36(3)	N(1)−C(2)	1.38(3)
N(3)−C(2)	1.31(3)	N(3)−C(4)	1.33(3)
N(9)−C(8)	1.41(3)	N(9)−C(4)	1.30(3)
N(9)−C(9)	1.44(3)	C(5)−C(4)	1.45(3)
C(5)−C(6)	1.41(3)	C(5)−N(7)	1.37(3)
C(6)−N(1)	1.36(3)	C(6)−N(6)	1.34(3)
	Angles		
N(7)−Pt(1)−N(10)	90.2(7)	Pt(1)−N(7)−C(8)	123.6(14)
C(5)−N(7)−Pt(1)	129.2(13)	N(7)−C(5)−C(4)	108.4(16)
N(1)−C(6)−N(6)	118.7(18)	N(3)−C(2)−N(1)	125.0(19)
N(3)−C(4)−N(9)	130.2(19)	N(9)−C(8)−N(7)	107.9(17)
C(2)−N(1)−C(6)	115.8(18)	C(4)−C(5)−C(6)	117.4(17)
C(4)−N(9)−C(9)	128.2(20)	C(5)−C(6)−N(6)	124.8(18)
C(5)−C(6)−N(1)	116.5(18)	C(5)−N(7)−C(8)	107.3(16)
C(5)−C(4)−N(9)	105.8(17)	C(5)−C(4)−N(3)	124.0(18)
C(6)−C(5)−N(7)	134.1(18)	C(6)−N(1)−C(2)	121.2(17)
C(8)−N(9)−C(9)	120.9(18)	C(8)−N(9)−C(4)	110.6(18)

hydrogen atoms. Because of the special kind of disorder in compound **1b** all atoms of the imidazole ring of the purine bases (with the exception of N(7)) were treated as carbons. The adenine C(9) carbon and the guanine N(3) nitrogen were treated as a single atom. In the disordered guanine, adenine complex the coordinates of guanine N(3) are occupied by 50% N(3) and 50% C(9′).

Results

Formation and Solid-State Structure of *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot H_2O$ (1b). Reaction of *trans*-[$(NH_3)_2$Pt(9-MeGH-*N7*)Cl]Cl with 9-MeA in weakly acidic or neutral solution yields a complex mixture of species (*N7*, *N1*, *N7/N1* linkage isomers). Likewise, when the guanine, aqua complex *trans*-[$NH_3)_2$Pt(9-MeGH-*N7*)$(H_2O)]^{2+}$ is prepared (via $AgNO_3$) prior to addition of 9-MeA, a number of products are formed, with self-condensation of the guanine species playing a major role.[5b] However, at pH 1.3−1.5 (with 9-MeA protonated), the *N*7 linkage isomer is formed preferentially and **1b** is isolated.

In Figure 2, the cation of **1b** with the atom-numbering scheme is shown. The solution of the structure was hampered by a severe disorder of the cations which could be solved satisfactorily with the assumption that two *head*−*head* oriented cations (having the intramolecular H bond) are present in a 1:1 ratio (Figure 3). Other models, e.g. rotation of a single base about Pt−N(7) (*head*−*head/head*−*tail* equilibrium) or simultaneous rotation of both bases along the N(7)−Pt−N(7) vector, must be excluded since they violate the crystallographic inversion center at the Pt. Consistent with the crystallographic results would be a model with a *head*−*tail* arrangement of the two bases and a superposition of two different (1:1) orientations of such a cation. The main difference with our favored model would be the absence of an intramolecular H bond between the two bases. We consider this possibility less likely in view of findings in related complexes[6−8] which, without exception, show the nucleobases in a relative orientation that permits intramolecular H bonding whenever possible. With the NH_3 ligands being almost at a right angle to the nucleobase planes, the two positions of these groups are not well-defined. The refinement of the structure gave only one position (with an occupancy factor of 1) with relatively large thermal ellipsoids for the two NH_3 ligands.

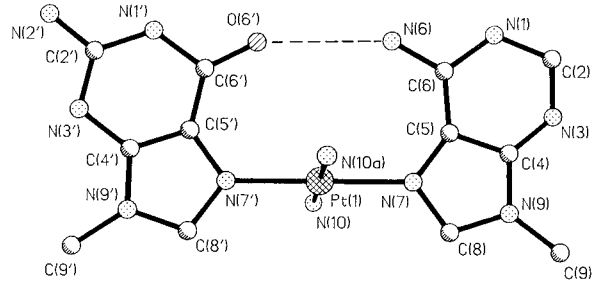

Figure 2. Idealized structure of the cation of *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot H_2O$ (**1b**) with H bond (2.94(3) Å) between exocyclic groups of the nucleobases.

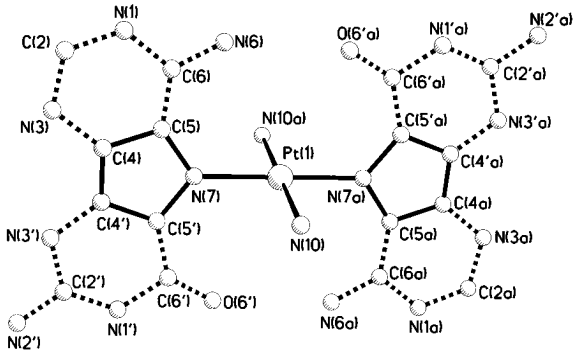

Figure 3. Disordered structure of the cation of **1b** with atom-numbering scheme. The following positions have 50% occupancies each: C(4), C(4) of 9-MeA and N(9) of 9-MeGH; C(5), C(5) of 9-MeA and C(8) of 9-MeGH; C(4′), C(4) of 9-MeGH and N(9) of 9-MeA; C(5′), C(5) of 9-MeGH and C(8) of 9-MeA; N(3′), N(3) of 9-MeGH and C(9) of 9-MeA.

The coordination geometry of Pt is square planar, and the Pt−N bond lengths are in the normal range (Pt(1)−N(7) = 2.04-(2) Å, Pt(1)−N(10) = 2.09(2) Å). The torsion angles N(10)−Pt(1)−N(7)−C(5) and N(10)−Pt(1)−N(7)−C(5′) are 101.8(16)° and −82.6(15)°, respectively. Guanine and adenine are almost coplanar, and the best weighted planes through the nucleobases form an angle of 1.6(13)°. This orientation is stabilized by an intramolecular hydrogen bond of 2.94(3) Å between N(6) of adenine and O(6′) of guanine.

The packing of the molecules in the crystal is given in the Supporting Information. The cations form layers with a Pt−Pt distance of 7.72 (1) Å. The cations are connected through hydrogen bonds between the amine nitrogen N(10) and the guanine oxygen (O6′) at $-x + 1$, $-y$, $-z$ (3.04(3) Å) and between the amine nitrogen and the adenine nitrogen N(1) at

Table 4. ^{1}H NMR Chemical Shifts (D_2O, 30 °C)

	9-MeA	other base	other base	pD
1b	H2 H8 CH_3 8.417 8.772 3.977	9-MeGH H8 CH_3 8.379 3.906	---	3.9
2a	 8.975 8.886 3.990	9-MeGH H8 CH_3 8.353 3.790	---	5.4
2b	 9.132 8.902 4.004 9.113	9-MeGH H8 CH_3 8.393 3.796	1-EtT H6 C(5)CH_3 CH_2 CH_3 7.426 1.906 n.o.[a] 1.282 1.847	5.1
2c	 8.966 8.856 4.001	9-MeGH H8 CH_3 8.384 3.796	1-EtT H6 C(5)CH_3 CH_2 CH_3 7.452 1.902 n.o.[a] 1.287	5.5
3c	8.424 8.954 3.978	---	---	7.8
3d	8.516 9.270 4.036	---	---	5.6
4a	9.172 9.218 4.051	---	---	7.0
4b	9.044 9.185 4.041	---	---	6.3
4c	9.212 9.433 4.082	---	---	5.7
5a	 9.098 9.296 4.120	9-EtGH H8 CH_2 CH_3 8.591 4.279 1.538	---	6.9
5b	 8.806 9.129 3.986	1-MeT H6 C(5)CH_3 NCH_3 7.380 1.930 3.431 1.897 3.397	---	4.2

[a] Quartet of CH_2 (1-EtT) is covered by intense CH_3 resonance of 9-MeGH.

$-x$, $-y-1$, $-z$ (2.99(4) Å). Other short contacts are found between the nitrate oxygens and the nitrogen of the amine ligands or of the purine rings. The shortest contact is formed between O(210) and N(1′) at $x-1$, y, z (2.71(4) Å). The disordered water molecules are also involved in hydrogen bonding (N(10)−O(1W) = 2.83(5) Å; symmetry operation $-x+1$, $-y$, $-z$).

Solution Behavior of 1b. The assignment of the aromatic proton resonances in the ^{1}H NMR spectrum of **1b** was accomplished by use of 9-MeA deuterated at the 8-position[15] and by following the formation of **1** in the NMR. The simplicity of the spectrum (D_2O, DMSO-d_6, DMF-d_7) at ambient temperature with single sets of resonances for 9-MeGH and 9-MeA (Tables 4 and 5) is consistent with either fast rotation of the nucleobases about the Pt−N(7) bonds or, more likely, a single rotamer form stabilized by an intramolecular H bond between guanine O(6) and adenine NH_2(6), as also observed in the solid state. The chemical shift of the adenine NH_2 resonance (δ, 8.55 ppm, DMSO-d_6, ca. 8.65 ppm, DMF-d_7) certainly supports H bond formation, considering NH_2 shifts in systems having no possibilities for H bond formation, e.g. in *trans*-$[(NH_3)_2$Pt(9-MeA-*N7*)$_2]^{2+}$ (8.02 ppm) or in $[(NH_3)_3$Pt(9-MeA-*N7*)$]^{2+}$ (8.04 ppm).[21] Low-temperature spectra (in DMF-d_7; Supporting Information) reveal that rotation of the NH_2 group of the 9-MeA ligand is frozen below 280 K (two separate signals) whereas two resonances for the NH_2 protons of the 9-MeGH ligand appear below 245 K only. A concentration dependence of resonances of **1b** was not observed in any of the solvents applied. We were interested in this aspect since from model building molecular recognition and self-assembly of two cations of **1b** seemed possible on the basis of H bonding (Figure 4a). If realized, this adduct could be considered a metalated form of a base quartet containing noncomplementary bases, related to quartet structures proposed between pairs of complementary AT and GC pairs.[22] We consider our NMR data not necessarily

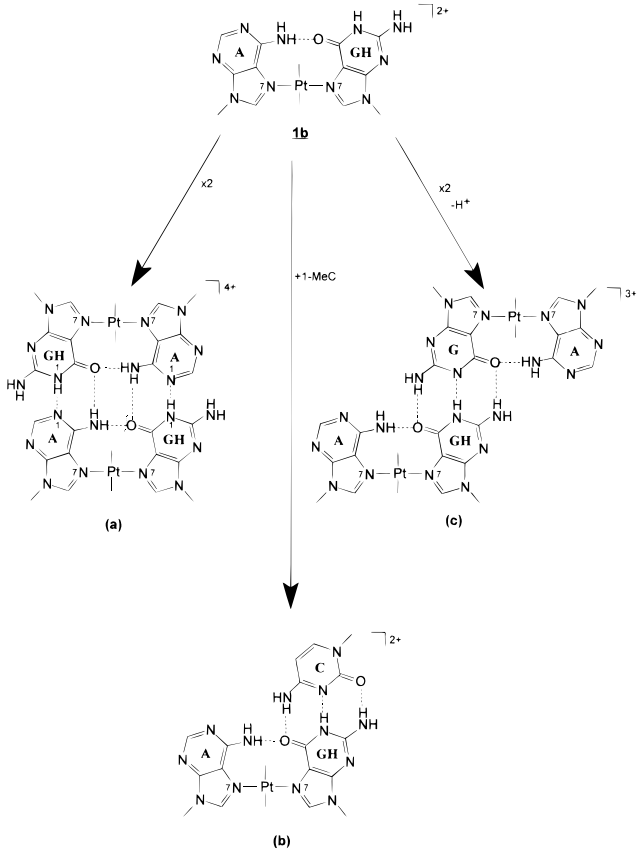

Figure 4. H-bonding interactions of **1b**: (a) Feasible dimerization (experimentally not detected); (b) Watson−Crick pair between platinated guanine in **1b** and free cytosine; (c) interguanine pair between neutral and anionic guanine ligands of **1b** occurring at pH = 8.

contradictory of such a possibility, in view of the general difficulty to detect pairs of H bonds (as opposed to triply H-bonded adducts) in solvents of good H donor/acceptor properties. After all, base pairing between A and T is likewise not to be observed in DMSO-d_6 and DMF-d_7,[23] and the intermolecular H bonding interaction between platinated 9-MeA and 9-MeGH would correspond to that observed in one of four possible types of A,G mispairs as verified by crystal structure analysis in a dA(*anti*) = dG(*anti*) mismatch in DNA.[24] H-bonding between the metalated guanine base in **1b** and the complementary base 1-MeC according to Watson−Crick is still possible, as previously demonstrated for related systems in solution[25] and in the solid state.[7] ^{1}H NMR spectra of mixtures containing **1b** and increasing amounts of 1-MeC in DMSO-d_6 display smooth downfield shifts for the guanine N(1)H and NH_2 resonances. As expected for this pattern (Figure 4b),[23,25] the effect on the N(1)H signal is approximately twice that of the guanine amino group of **1b** in any mixture. For example, at c(**1b**) = 0.015 mol L^{-1} and c(1-MeC) = 0.08 mol L^{-1}, downfield shifts are 0.52 and 0.28 ppm for these two resonances. The NH_2 resonance of 1-MeC is likewise shifted downfield (by 0.06 ppm at the above conditions), but the shift is smaller due to averaging between free and H-bonded 1-MeC.

pK_a values for the equlibria

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Table 5. Chemical Shifts of NH_2 Resonances of 9-MeA and 9-MeA Ligands[a]

compd	solvent	Pt per 9-MeA	H bonds[b]	$\delta(NH_2)$	ref
9-MeA	DMSO-d_6			7.19	*c*
$[Pt(NH_3)_3$(9-MeA-*N7*)$]^{2+}$	DMSO-d_6	1		8.04	23
3c	DMSO-d_6	1		8.02	*c*
3c	DMF-d_7	1		8.35	*c*
1b	DMSO-d_6	1	1	8.55	*c*
1b	DMF-d_7	1	1	8.65	*c*
trans-$[(NH_3)_2$Pt(9-MeA-*N7*)(1-MeT)$]^+$	DMSO-d_6	1	1	8.65	6
trans-$\{[a_2ClPt]_2$(9-MeA-*N1,N7*)$\}^{2+}$	DMF-d_7	2		9.3	11
$\{[Pt(dien)]_2$(9-MeA-*N1,N7*)$\}^{4+}$	DMF-d_7	2		9.3	11
2a	DMSO-d_6	2	1	9.39	*c*
2a	DMF-d_7	2	1	9.75	*c*
5a	DMF-d_7	2	1	9.82	*c*
trans-$\{[a_2$Pt(9-EtGH-*N7*)$]_2$(9-MeA-*N1,N7*)$\}^{4+}$	DMF-d_7	2	2	10.8	11

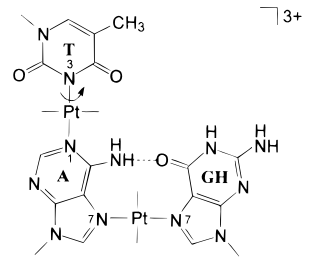
[a] In ppm; ambient temperature. [b] Number of possible intramolecular H bonds. [c] This work.

$$\textit{trans}\text{-}[a_2Pt(AH)(GH)]^{3+} \overset{pK_{a1}}{\rightleftharpoons} \textit{trans}\text{-}[a_2PtA(GH)]^{2+} \overset{pK_{a2}}{\rightleftharpoons} \textit{trans}\text{-}[a_2PtAG]^{+}$$
1a **1b** **1c**

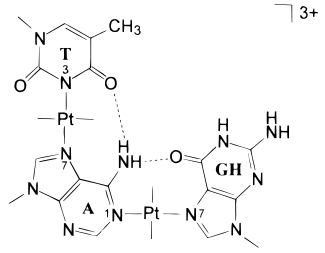
were found to be *ca.* 1.5 (pK_{a1}) and *ca.* 8 (pK_{a2}), applying pH-dependent ^{1}H NMR spectroscopy in D_2O. **1c** was not isolated since it forms a poorly soluble 1:1 adduct with **1b** at a pH corresponding to pK_{a2} ($\approx$8). ^{1}H NMR spectroscopy in DMSO-d_6 confirms that the adduct **1b·1c** formed contains a H-bonded GH $\equiv$ G entity as previously observed in related compounds (Figure 4c).[3a,b,26,27] Intermolecular H bond formation was followed by mixing **1b** and **1b·1c** at defined ratios of GH and G ligands and following ^{1}H NMR chemical shifts (DMSO-d_6) of (averaged) guanine N(1)H and guanine N(2)H_2 resonances (cf. Supporting Information). While the N(1)H resonance is not observed for **1b·1c**, addition of increasing amounts of this adduct to pure **1b** results in large downfield shifts of this resonance and a concomitant broadening. The effect on the guanine N(2)H_2 resonance (downfield shift) is less dramatic as a consequence of two opposing effects, H bonding (downfield shift) and guanine deprotonation (upfield shift), as well as due to the fact that only one of the NH_2 protons is involved in H bonding and rotation about the C$-$$NH_2$ bond is still fast on the NMR time scale. All other resonances, including NH_2 of 9-MeA are either hardly affected or not at all.

A Dimetalated Base Pair Derived from 1b: *trans,trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N7*-9-MeA-*N1*)Pt$(NH_3)_2$Cl](ClO$_4$)$_3$ (2a). A dinuclear complex **2a** is formed when **1b** and *trans*-$(NH_3)_2PtCl_2$ are reacted. The reaction is conveniently followed by ^{1}H NMR spectroscopy. Blocking of the adenine N(1) by Pt site is evident from pH-dependent ^{1}H NMR spectroscopy (no downfield shift of H(2) at pD $\leq$ 2). The simplicity of the ^{1}H NMR spectrum (D_2O, pD 5.4, ambient temperature) of **2a**$-$a single set of 9-MeA resonances with three singlets at 8.975, 8.886, and 8.353 ppm for H2(A), H8(A), and H8(GH), as well as two resonances at 3.990 and 3.790 ppm for CH_3(A) and CH_3-(GH)$-$suggests a single, fixed structure for **2a** with a *head*$-$*head* orientation of the two nucleobases. This arrangement permits (as observed for **1b**) H bonding between adjacent bases. It is supported by the chemical shifts of the adenine N(6)H2 resonances in DMF-d_7 and DMSO-d_6 (Table 5). As expected, two equally intense ^{195}Pt signals are observed, at $-$2413 and $-$2472 ppm (D_2O). We note that the difference in chemical shifts between the two Pt's is rather small considering the general sensitivity of ^{195}Pt NMR shifts to changes of donor atoms in the coordination sphere.[28]

Chart 3



2b



2c

The assignment of the aromatic nucleobase protons is straightforward on the basis of an HMQC experiment since H8-(GH) and H8(A) couple to the same Pt nucleus. Unfortunately the two Pt resonances could not be assigned, since the cross-peak with H2(A) was not detected, probably due to insufficient concentration.

Dimetalated Triples Containing Three Different Nucleobases (T, A, GH). Two linkage isomers of a diplatinum(II) nucleobase triple containing the three different nucleobases 1-EtT, 9-MeA, and 9-MeGH have been prepared in solution (Chart 3): *trans,trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N1*-9-MeA-*N7*)-Pt$(NH_3)_2$(1-EtT-*N3*)$]^{3+}$ (**2b**) is formed upon reaction of **1b** with *trans*-$(NH_3)_2$Pt(1-EtT-*N3*)Cl whereas the linkage isomer *trans,-trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N1*-9-MeA-*N7*)Pt$(NH_3)_2$ (1-EtT-*N3*)$]^{3+}$ (**2c**) forms from *trans*-$[(NH_3)_2$Pt(1-EtT-*N3*)(9-MeA-*N7*)$]^+$ and *trans*-$[(NH_3)_2$Pt(9-MeGH-*N7*)Cl$]^+$.

The ^{1}H NMR spectra of **2b**,**c** show the H(2) resonance of 9-MeA shifted downfield (0.7 ppm in **2b**; 0.6 ppm in **2c**) relative to the corresponding precursors **1b** and *trans*-$[(NH_3)_2$Pt(1-EtT-*N3*)(9-MeA-*N7*)$]^+$, respectively (Table 4 and Supporting Infor-

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(28) (a) Pregosin, P. S. *Annu. Rep. NMR Spectrosc.* **1986**, *17*, 285. (b) Ismail, I. M.; Sadler, P. *Platinum, Gold and Other Metal Chemotherapeutic Agents*; Lippard, S. J., Ed.; American Chemical Society: Washington, DC, 1983; ACS Symp. Ser. No. 209, pp 171$-$190. (c) Appleton, T. G.; Bailey, A. J.; Barnham, K. J.; Hall, J. R. *Inorg. Chem.* **1992**, *31*, 3077.

mation). This indicates additional platination at N(1) of 9-MeA. For **2b** a splitting of the adenine H(2) and the thymine C(5)-CH_3 signals into two resonances is observed which is caused by a slow or hindered rotation of the thymine ligand about the Pt−N(1, adenine) bond, whereas the N(7)-bound guanine ligand is kept in a *head−head* arrangement by an intramolecular hydrogen bond between its carbonyl O(6) group and the exocyclic-NH_2(6) of 9-MeA. The spectrum of **2c** does not display any doubling of resonances, strongly suggesting that there the two bases guanine and thymine are fixed by an intramolecular H bond. Similar differences have previously been observed by us for HG•A•GH, T•A•T, and C•A•C triples[11] and for the two linkage isomers of (T)Pt(A).[6] In all cases free rotation of the pyrimidine base bound across the N(1) site of adenine and a fixed arrangement for the N(7)-bound pyrimidine ligand is observed. In contrast, guanine rotation, irrespective of the Pt binding site at adenine, is prevented because of intramolecular H bonding.

"Open" Metalated Nucleobase Quartet Derived from 1b: *trans,trans,trans*-{$(NH_3)_2$Pt(*N1*-9-MeA-*N7*)$_2$[$(NH_3)_2$Pt(9-MeGH-*N7*)]$_2$}$(ClO_4)_4(NO_3)_2\cdot 7H_2O$ (2d). Compound **2d** was prepared by reaction of *trans*-$[(NH_3)_2Pt(H_2O)_2]^{2+}$ with 2 equiv of **1b** at pH 4−5. The ^{1}H NMR spectrum (D_2O) is consistent with 2-fold Pt binding at N7 and N1 (H2,H8 shifted downfield by 0.8 and 0.2 ppm as compared to **1b**) and indicates the presence of two species (several resonances split), most likely of rotamers. While the poor quality of high-temperature spectra was not conclusive in this point, the room-temperature ^{195}Pt NMR spectrum of **2d** supports this view: There are three resonances at −2457, −2572, and −2593 ppm with relative intensities of 2:0.3:0.7 (Supporting Information). We propose that the major resonance is due to the two Pt atoms coordinated by guanine N7 and adenine N7, while the two minor resonances arise from the Pt atom bound to two adenine N1 sites. Rotation about the Pt−(9-MeA-*N1*) bonds therefore is feasible, whereas rotation about the Pt−(9-MeA-*N7*) bond probably is impaired as a consequence of H bonding with the guanine nucleobase.

***trans*-[$(NH_3)_2$Pt(9-MeAH-*N7*)$_2$]$(ClO_4)_4\cdot 2H_2O$ (3a) and *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)$_2$]$(ClO_4)_2\cdot 2H_2O$ (3c).** These compounds were obtained by reaction of *trans*-a_2PtCl_2 (with a = NH_3 (**3a**) or CH_3NH_2 (**3d**)) with 2 equiv of 9-MeA in strongly acidic medium in order to force coordination of cationic 9-MeAH$^+$ to Pt(II) via N(7) by protonating the N(1) site (pK_a(N(1)), 4.5).[29]

pH-dependent ^{1}H NMR spectra ($0 \le pH^* \le 6$) are consistent with protonation of **3c** (deprotonation of **3a**) according to

$$\underset{\mathbf{3c}}{trans\text{-}[a_2PtA_2]^{2+}} \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} \underset{\mathbf{3b}}{trans\text{-}[a_2Pt(AH)A]^{3+}} \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} \underset{\mathbf{3a}}{trans\text{-}[a_2Pt(AH)_2]^{4+}}$$

The experimentally determined p$K_a \cong 1.3$ for protonated **3c** (Supporting Information) is to be considered the mean value for the two successive protonation steps, which overlap. We conclude this from the downfield shifts of 9-MeA protons (ΔH(8) *ca.* 0.5 ppm; ΔH(2) *ca.* 0.25 ppm), which are considerably larger than found in Pt^{II} complexes containing a single 9-MeA-*N7* ligand. There, pK_a values for protonation are also higher, typically between 2 and 2.6.[6,8,21]

The X-ray structure analysis of **3c** confirms N(7) coordination of Pt^{II} to two 9-MeA bases (Figure 5). The cation is centrosymmetric, with Pt being in the inversion center. Consequently, the two bases are in a *head−tail* orientation. Bond lengths and angles are in the normal range (Table 3). The adenines are approximately perpendicular to the Pt coordination plane (dihedral angle 88.7°).

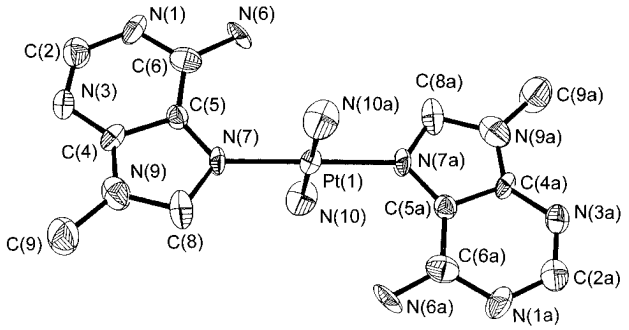

Figure 5. Cation of *trans*-$[(NH_3)_2Pt(9\text{-MeA-}N7)_2](ClO_4)_2\cdot 2H_2O$ with atom-numbering scheme.

Viewed along the *z*-direction, the crystal lattice is built up of layers perpendicular to each other, thus giving a zigzaglike structure (Supporting Information). The structure is stabilized by a network of hydrogen bonds involving the exocyclic amino groups, the ring nitrogens N(1) and N(3), and the ammine ligands as well as the perchlorate oxygens and water of crystallization. Neighboring stacks are connected via hydrogen bonds formed between the exocyclic amino groups and N(1) at $x, -y-{}^1/_2, z+{}^1/_2$ (2.92(3) Å) as well as through water molecules H bonded to N(3) (3.07(3) Å, $-x+1, y+{}^1/_2, -z+{}^1/_2$) and N(1) (2.73(3) Å, $-x+1, -y, -z$). At the same time the water molecules exhibit short contacts to perchlorate oxygens (O(100)···O(11) 2.79 (4) Å, $-x+1, -y+1, -z$; O(100)···O(21) 2.99(5), $-x+1, y+{}^1/_2, -z+{}^1/_2$). Further possible H bonds are detected between the perchlorate oxygens and the exocyclic amino groups (N(6)···O(14) 3.03 (3) Å, $x-1, -y+{}^1/_2, z-{}^1/_2$; N(6)···O(24) 2.92(3) Å, $-x+1, -y, -z$) and between the perchlorate oxygens and the ammine ligands (N(10)···O(13) 3.05(4) Å, $-x+1, -y+1, -z$; N(10)···O(22) 3.04 (4) Å, $-x+1, -y, -z$).

Trinuclear Complexes Derived from 3c: *trans,trans,trans*-{a_2Pt(*N7*-9-MeA-*N1*)$_2$ [a′$_2$PtX**]$_2$}$^{n+}$.** Bis(adenine) complexes of *trans*-a_2Pt(II), in their unprotonated forms, react with excess *trans*-a′$_2$PtCl$_2$ (with a′ = NH_3 or CH_3NH_2) to give trinuclear species of general composition *trans,trans,trans*-{a_2Pt(*N7*-9-MeA-*N1*)$_2$[a′$_2$PtX]$_2$}Y_n. The following compounds have been isolated: *trans,trans,trans*-{$Pt(NH_3)_2$(*N7*-9-MeA-*N1*)$_2$[$(CH_3NH_2)_2$PtCl]$_2$}$(ClO_4)_4$ (**4a**), *trans,trans,trans*-{$Pt(NH_3)_2$(*N7*-9-MeA-*N1*)$_2$[$(NH_3)_2$PtCl]$_2$}$(ClO_4)_3(NO_3)$ (**4b**), and *trans,trans,trans*-{$Pt(CH_3NH_2)_2$(*N7*-9-MeA-*N1*)$_2$[$(CH_3NH_2)_2$PtCl]$_2$}$(ClO_4)_4$ (**4c**). These compounds are suitable starting materials for the preparation of trinuclear tetrakis(nucleobase) complexes (see below). In all compounds (**4a−c**), two bridging 9-MeA ligands are linked by three Pt(II) centers. As compared to **3c**, additional platination at the N(1) sites of the two 9-MeA nucleobases causes downfield shifts of the adenine resonances in the ^{1}H NMR (D_2O): ΔH(2), *ca.* 0.8 ppm; ΔH(8), *ca.* 0.2−0.3 ppm; ΔCH_3, *ca.* 0.07 ppm (Table 5). Only single sets of 9-MeA resonances are observed.

"Open" Metalated Nucleobase Quartets Derived from 3: *trans,trans,trans*-{$(NH_3)_2$Pt(*N7*-9-MeA-*N1*)$_2$[$(CH_3NH_2)_2$Pt(9-EtGH-*N7*)]$_2$}$(ClO_4)_5(NO_3)\cdot 1.5H_2O$ (5a) and *trans,trans,trans*-{$(NH_3)_2$Pt(*N7*-9-MeA-*N1*)$_2$[$(NH_3)_2$Pt(1-MeT-*N3*)]$_2$}$^{4+}$ (5b). Substitution of the Cl ligands in **4a** can be achieved, e.g. by 9-EtGH, and the metal-modified nucleobase quartet (**5a**) has been prepared and isolated. Ignoring the differences in amine ligands at Pts bound to the guanine nucleobase, **5a** is a linkage isomer of **2d** (Figure 1). As a consequence of Pt(II) coordina-

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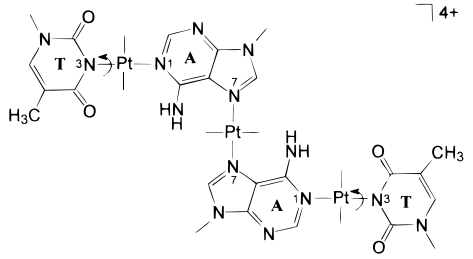
Chart 4



tion via the N(7) of guanine, the guanine H(8) singlet is shifted downfield by *ca.* 0.8 ppm. In contrast, the aromatic adenine resonances are very little affected (Table 4).

The ^{1}H NMR spectrum of **5a** in D_2O at ambient temperature is very simple, with sharp, single resonances observed only. In DMF-d_7 (298 K) the adenine NH_2 resonance occurs at 9.82 ppm (Table 5), indicative of an involvement in H bonding as depicted in Figure 1. This resonance is lost upon cooling (*ca.* 278 K) but starts reappearing (two resonances, at *ca.* 10.2 and 9.5 ppm) below 270 K. As in the case of *trans*-[a$_2$Pt(9-MeA-*N7*)(1-MeT)]$^+$,[6] we interpret this observation in terms of a freezing out of the rotation of the amino group about the C(6)−N(6) axis. From temperature-dependent spectra (DMF-d_7) we have no indication for a rotation around the central Pt−(N7,adenine) bonds.

The 1-MeT analogue of **5a**, *trans,trans,trans*-{(NH$_3$)$_2$Pt(*N7*-9-MeA-*N1*)$_2$[(NH$_3$)$_2$Pt(1-MeT-*N3*)]$_2$}$^{4+}$ (**5b**), was prepared on a ^{1}H NMR scale from **3c** and *trans*-(NH$_3$)$_2$Pt(1-MeT)Cl (Chart 4). The ^{1}H NMR chemical shifts are summarized in Table 4. For this compound a unique proposal for the orientation of the nucleobases cannot be made, but considering the results obtained form metal-modified Watson−Crick analogoues like *trans*-[(NH$_3$)$_2$Pt(9-MeA-*N1*)(1-MeT-*N3*)]$^+$ [6] and metal-modified base triples,[11] free rotation for the 1-MeT-ligands about the Pt−N(3) bond can be anticipated.

Discussion

In continuation of previous work on "metal-modified base pairs",[4−9,11] we have extended this work to mixed guanine, adenine as well as bis(adenine) complexes. Our results confirm essential aspects of these studies and at the same time reveal some novel aspects related to molecular self-assembly[30] and supramolecular chemistry:[31]

(i) Coplanarity of Nucleobases. The presence of two amine ligands in *trans*−a$_2$Pt^{II} bis(nucleobase) complexes forces the two nucleobases in an essentially coplanar orientation. The largest propeller-twist observed as yet in mixed-nucleobase compounds of this type, in a *trans*-[NH$_3$)$_2$Pt(1-MeT-*N3*)(9-MeA-*N7*)]ClO$_4$ complex,[6] is 12°.[32]

(ii) H bonding. Coplanarity of the two bases can be reinforced by intramolecular H-bonding between exocyclic groups of nucleobases. Favorable H-bonding distances (2.9−3.1 Å) can be expected for any of the following combinations (with • = *trans*-a$_2$Pt^{II}):

A-*N7*•*N3*-T	A-*N1*•*N7*-GH
A-*N7*•*N3*-C	GH-*N7*•*N3*-C
A-*N7*•*N7*-GH	
A-*N7*•*N1*-G	

In all cases where X-ray crystal structures are available,[6−8] this feature is confirmed. As shown above (Table 5), the ^{1}H NMR chemical shift of the NH$_2$(6) resonance of 9-MeA is a good qualitative indicator for the involvement of this group in intramolecular H bonding and of the adenine metalation state.[33] As the number of Pt ions bound to 9-MeA and the number of H bonds increases, the NH_2 resonance is shifted to lower field. The record downfield shift, observed with *trans*-{[(CH$_3$NH$_2$)$_2$-Pt(9-EtGH-*N7*)]$_2$(9-MeA-*N1*,*N7*)}$^{4+}$, has been interpreted by us in terms of 2-fold 9-MeA platination *and* involvement of both amino protons in H bonding with O(6) guanine sites.[11] From Table 5 it appears that in DMF downfield shifts are somewhat more pronounced in DMF as compared to DMSO.

(iii) Orthogonality of Pt−*N1* and Pt−*N7* Vectors. The fact, that Pt−*N1* and Pt−*N7* vectors in diplatinated purine nucleobases are virtually at right angles (Chart 2) permits construction of a range of aggregates of different topologies (Figure 6a−e): U forms, S forms, meanders, squares, or rectangles.[34] This holds up in particular for mixed A,G systems. For example, complex **2a**, upon loss of HCl, should be capable of forming either a closed rectangle[11] (e) or an open meander (c), and complex **2c**, after displacement of T and self-condensation, might yield a square[11] (d) or an open meander (c).

Alternatively, *intermolecular* H bonding between metalated purines can lead to larger aggregates as well (Figure 6f−h). In the simplest case, corresponding to Figure 6f, self-assembly of cations of **1b** is feasible (cf. Figure 4a and Results). Another way of generating H-bonded arrays is via guanine N(1) hemideprotonation. We have verified this H-bonding pattern meanwhile twice with mononuclear complexes of 9-ethylguanine, both in the solid state[3a,b,27] and in solution.[25−27] The likely structure of the 1:1 adduct between **1b** and **1c**, which corresponds to the scheme given in Figure 6g, has been depicted in Figure 4c. If a similar H-bonding scheme is applied to **5a**, polymeric strands according to the scheme of Figure 6h should form, with triple H bonds between the trinuclear (pu)•(pu) •(pu) •(pu) building blocks.

As far as donor atoms are concerned, **1b** can be considered a model of the A-*N7*, G-*N7* cross-link of *trans*-a$_2$Pt^{II} which occurs in DNA[35] and has also been detected in the single stranded hexanucleotide d(AGGCCT).[36]

Three of the base triplets studied bear some relevance to metalated triplexes[7,37] (Figure 7). Thus the platinated triplet A•G≡C (**1b**•1-MeC) can be considered a model of platinated DNA triplex, consisting of a normal G≡C pair to which a third strand is covalently attached via an adenine base sitting in the major groove. It is an analogue of a metalated C•G≡C triple recently described by us.[7] The two other compounds, **2b**,**c**, are doubly metalated base triples, consisting of metalated Watson−

(30) See, e.g.: (a) Mathias, J. P.; Seto, C. T.; Simanek, E. E.; Whiteside, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 1725 and references cited. (b) Yang, J.; Fan, E.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314 and references cited.

(31) (a) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304. (b) Lindsey, J. S. *New. J. Chem.* **1991**, *15*, 153. (c) See various articles in: *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; Verlag Chemie: Weinheim, Germany, 1991.

(32) A notable exception has recently been found by us with *trans*-[(CH$_3$-NH$_2$)$_2$Pt(1-MeC-*N3*)$_2$](PF$_6$)$_2$·2H$_2$O (*head*−*head*). The dihedral angle between the two bases is 56°, and the Pt geometry is severely distorted. See: Holthenrich, D.; Sóvágó, I.; Fusch, G.; Erxleben, A.; Fusch, E. C.; Rombeck, I.; Lippert, B. *Z. Naturforsch.* **1995**, *50b*, 1767.

(33) This applies to ambient temperature (DMSO-d_6, DMF-d_7) with single NH_2 resonance due to fast rotation of the NH_2 groups on the NMR time scale. When rotation is slow, the situation becomes more complicated (see, e.g. ref 6 and spectra of **1b** in the Supporting Information). We are aware that the nature of the second ligands and/or the bonding distance is also important and may modify this simple correlation.

(34) For a brief discussion on square-planar and rectangular arrangements of purine metal complexes, see ref 11.

(35) Eastman, A.; Jennerwein, M. M.; Nagel, D. L. *Chem.-Biol. Interact.* **1988**, *67*, 71.

(36) Lepre, C. A.; Strothkamp, K. G.; Lippard, S. J. *Biochemistry* **1987**, *26*, 5651.

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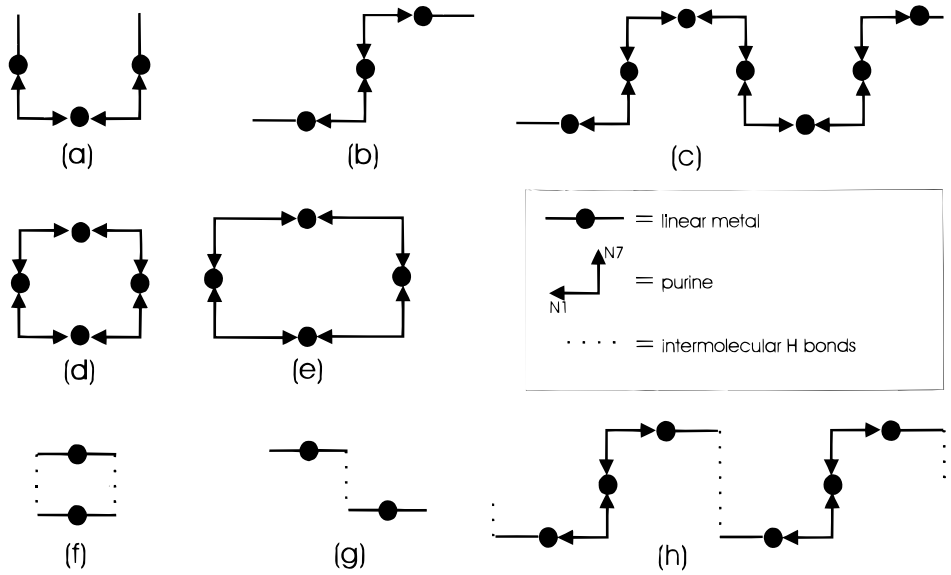

Figure 6. Different topologies of bis(purine) complexes of *trans*-a_2Pt^{II} (or a suitable other metal M) with covalent linkages (a−e) and via intermolecular H bonding (f−h). The square (d) and rectangle (e) differ in donor sites, viz. $[(N1)(N7)]_4$ and $[M(N1)_2]_2[M(N7)_2]_2$, respectively (cf. ref 11).

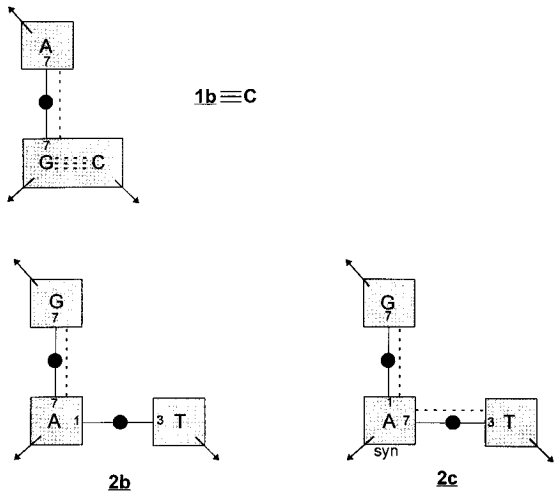

Figure 7. Proposed relevance of adduct **1b**≡C and compounds **2b**,**c** to metalated triplexes. Orientations of the glycosidic bonds, corresponding to *N*-alkyl groups in the model compounds, are indicated by arrows, and interbase H bonds, by dots.

Crick (**2b**) and Hoogsteen (**2c**) analogues,[6] to which a guanine is attached via the second metal ion. Neither binding of a metalated A to a G≡C pair nor binding of a metalated G to a (metalated) AT pair is strictly analogous to situations seen in the two major classes of DNA triplexes (third strand with pyrimidine bases parallel to Watson−Crick purine strand of duplex;[38] purine rich third strand antiparallel to Watson−Crick purine strand of duplex[39]). However, mismatches in these triplets are not uncommon.[40] Specifically, a AH^+═G≡C triplet has been observed, with the AH^+-containing strand parallel to the homopurine strand containing G.[40] But the analogy between AH^+═G≡C and A•G≡C is not strict.[41]

Summary and Outlook

Bis(purine) complexes of *trans*-a_2Pt^{II} combine three properties, namely coplanarity of their heterocyclic rings, orthogonality of Pt−*N1* and Pt−*N7* vectors, and H-bonding properties, that make them relevant to the aspect of metal-modified triplex structures of nucleic acids and at the same time interesting starting materials for the preparation of two-dimensional sheet structures containing nucleobases. Among these, metalated cyclic purine quartets are particularly attractive. Several of the complexes prepared, e.g. **2a**,**c**,**d**, appear to be suitable for this purpose. Work is underway to isolate and characterize such "molecular squares" which would differ drastically from those derived from *cis*-a_2M^{II} (a_2 = diamine, M = Pt or Pd).[42−44] At the same time they would represent attractive analogues of guanine quartets found at the ends of telomeres.[1b,45] The functions of metal ions in stabilizing these latter structures are completely different, however.

Acknowledgment. This work is dedicated to Prof. Herbert Jacobs on the occasion of his 60th birthday. Support by the Deutsche Forschungsgemeinschaft (DFG), the Fonds der Chemischen Industrie (FCI), and Asta Medica is gratefully acknowledged.

Supporting Information Available: Tables of crystal data, atomic coordinates and equivalent isotropic displacement coefficients, and anisotropic displacement coefficients for **1b** and **3** and figures showing packing diagrams of **1b** and **3**, NMR spectra, and the pH* dependence of **3** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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