Metal-Modified Nucleobase Pairs and Triplets as Cytosine Receptors**

Marc Sven Lüth,[a] Eva Freisinger,[b] and Bernhard Lippert*[a]

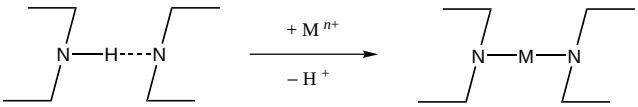
Dedicated to Prof. Dr. Ernst-Gottfried Jäger, Friedrich-Schiller-Universität Jena, on the occasion of his 65th birthday

Abstract: A preorganized cationic receptor **2** for cytosine (C) is described which is composed of *trans*-a_2Pt^{II} (a = NH_3 or CH_3NH_2) cross-linked modules with adenine (A), guanine (G), and uracil (U) or thymine (T) model nucleobases. The functions of these three modules are as follows: i) Adenine orientates the two other bases at right angles, thus producing the L-shape of the receptor. ii) Guanine is the primary receptor. iii) Uracil or thymine act as coreceptors. Compared with the normal Watson–Crick pair between G and C, the association constant between **2** and C increases by a factor of 3 (in DMSO). As deduced from ^{1}H NMR spectroscopy and confirmed by the X-ray crystal structure of the C adduct **4b**, cytosine is fixed through five hydrogen bonds to the receptor, one of which involves the aromatic H(5) of C. A comparison of C binding is made with a structurally related linkage isomer receptor as well as the precursor molecule *trans*-$[a_2PtAG]^{2+}$. The potential of modular, cationic receptors is illustrated.

Keywords: hydrogen bonds · nucleobases · platinum · receptors · solid-state structures

Introduction

The simple concept of replacement of a weakly acidic proton of a hydrogen bond between nucleobases by a metal entity of suitable geometry (linear, *trans*-square-planar, *trans*-octahedral) yields "metal-modified base pairs" or larger aggregates.[1, 2] The metal complexes obtained in this way may be considered models of temporary or permanent interstrand cross-links of metal ions with nucleic acids.[3] If extended to metalated oligonucleotides, targeting single-stranded or double-stranded nucleic acids is relevant to antisense and antigene approaches for gene silencing.[4] Finally, regular metal cross-linking of duplex DNA (*M*–DNA) can lead to a situation in which DNA behaves as a molecular wire.[5]



In the course of our studies on metal-modified base pairs and triplets of model nucleobases, it occurred to us that the ability of metalated nucleobases to act as hydrogen-bonding partners for suitable molecules,[1a, 1h] together with the structural variations possible in such systems,[1d, 1f] might make them interesting as receptors. The design of artificial receptors for biomolecules is an area of active research,[6] examples being hosts for biologically interesting guests such as barbituric acid derivatives,[7] creatinine,[8] or purine nucleobases,[9] among others. The multitopic receptor molecules frequently utilize donor–acceptor hydrogen-bonding interactions between NH, OH, or NH_2 groups and N- or O-sites, sometimes combined with π stacking, and only these scenarios will be considered here. Metal ions have been included only rarely in these studies, but from available data it is clear, that the role of the metal ion can be manifold. i) If positioned at the periphery of the (organic) receptor,[10, 11] the metal may just modulate the receptor properties. However, if located close to the recognition surface, the metal may ii) either facilitate recognition (e.g., through coordinative bond formation[12]) or iii) effectively prevent docking of the guest molecule through allosteric inhibition[13] and general steric blockage (e.g., by other ligands of the metal). The 90° angular building block provided by the purine base adenine (A), when metalated simultaneously at *N1* and *N7*,[1f, 14] and the possi-

[a] Prof. Dr. B. Lippert, Dr. M. S. Lüth
Fachbereich Chemie der Universität Dortmund
Otto-Hahn-Strasse 8, 44221 Dortmund (Germany)
Fax: (+49) 231-755-3797
E-mail: lippert@pop.uni-dortmund.de

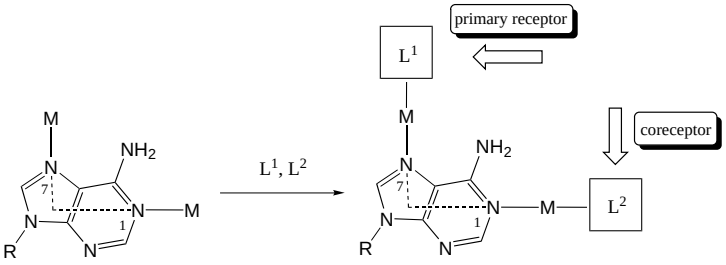
[b] Present address:
Dr. E. Freisinger
Department of Pharmacological Sciences
State University of New York at Stony Brook
Stony Brook, NY 11794 (USA)

[**] **Abbreviations**: 9-EtA, 9-ethyladenine; 9-MeA, 9-methyladenine; 9-RA, 9-alkyladenine; 1-MeC, 1-methylcytosine; 9-EtGH, 9-ethylguanine; 9-MeGH, 9-methylguanine; 9-MeHxH, 9-methylhypoxanthine; 1-MeT, 1-methylthymine anion; 1-MeU, 1-methyluracil anion; A, adenine; C, cytosine; G, guanine; T, thymine; U, uracil; Br^5U, 5-bromouracil; a, am(m)ine; pu, purine base; pym, pyrimidine base

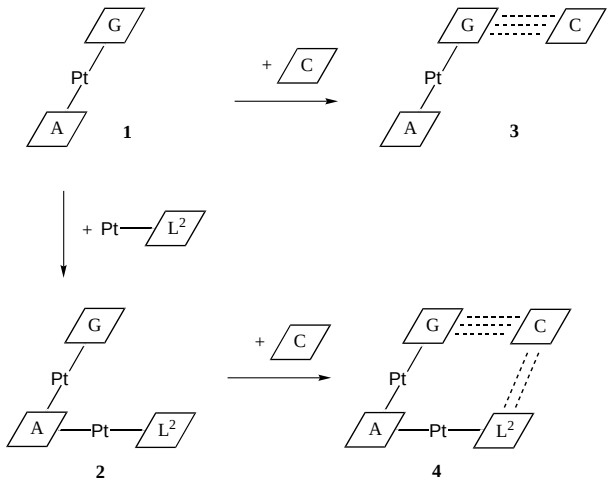
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

  0947-6539/01/0710-2104 $ 17.50+.50/0

bility of varying the ligands L^1 and L^2 and hence their hydrogen-bonding properties, proved a good starting point for this study.



Here we study in more detail the hydrogen-bonding interactions between a *N7* platinated guanine (G) model nucleobase (L^1) and its complementary nucleobase 1-methylcytosine (1-MeC). We have previously demonstrated that Pt^{II} coordination to the *N7* position of guanine strengthens the Watson–Crick pair,[15] a finding originally put forward by theoreticians,[16] and therefore we decided to investigate in more detail the role of the ancillary ligand L^2 as a potential coreceptor. Specifically, a comparison between the mixed nucleobase complex *trans*-$[(NH_3)_2Pt(9\text{-EtA-}N7)(9\text{-MeGH-}N7)]^{2+}$ (**1**) (9-EtA = 9-ethyladenine; 9-MeGH = 9-methylguanine) and the diplatinated base triplet complex *trans,trans*-$[(9\text{-MeGH-}N7)Pt(NH_3)_2(N7\text{-}\mu\text{-9-RA-}N1)Pt(a)_2(L^2)]^{3+}$ (**2**) (a = ammine or methylamine; 9-RA = 9-alkyladenine; L^2 = 1-methyluracilate or 1-methylthyminate) with regard to their affinities for 1-MeC was made (Scheme 1).

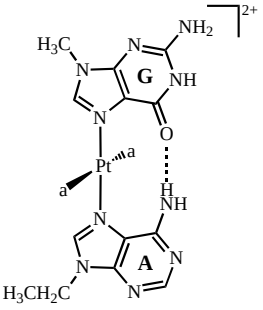


Scheme 1. Schematic representation of cytosine receptors consisting of Pt-modified base pair **1** and Pt_2-modified base triplets **2**.

Results and Discussion

Platinated base pair *trans*-$[(NH_3)_2Pt(9\text{-EtA-}N7)(9\text{-MeGH-}N7)](ClO_4)_2\cdot H_2O$ (1): The mixed adenine, guanine complex **1** was prepared by exchanging the nitrate ion in the corresponding complex *trans*-$[(NH_3)_2Pt(9\text{-EtA-}N7)(9\text{-MeGH-}N7)](NO_3)_2\cdot 1.4\,H_2O$ with perchlorate. The latter complex has recently been described by us.[1f] Our special interest in this platinated base pair was the relative orientation of the cations in the solid state and whether these (partially) self-complementary cations might dimerize by means of hydrogen-bond formation.[1d] However, the solid state structure of the nitrate compound revealed that formation of a diplatinated nucleobase quartet is prevented by hydrogen bonding between a nitrate oxygen atom and N(1)H of guanine.[1f] Therefore, we decided to prepare complex **1** with perchlorate as counter ion, in particular, with the corresponding 9-methylhypoxanthine (9-MeHxH) compound *trans*-$[(NH_3)_2Pt(9\text{-MeA-}N7)(9\text{-MeHxH-}N7)](ClO_4)_2$ the proposed self-association to a quartet indeed takes place in the solid state.[17] Unfortunately crystals of **1** suitable for X-ray analysis could not be obtained.

Scheme 2 provides a view of the cation of **1**. In aprotic solvents such as $[D_6]$DMSO and $[D_7]$DMF the two purines adopt a *head,head*-conformation which is stabilized by an intramolecular hydrogen bond between the exocyclic 9-EtA-$N(6)H_2$ and 9-MeGH-C(6)O groups. This arrangement is verified by ^{1}H NMR spectroscopy. The simplicity of the spectrum at ambient temperature (single sets of resonances, also in D_2O) and the characteristic chemical shift of the adenine NH_2 resonance (δ = 8.57, $[D_6]$DMSO, Table 1) are consistent with a single rotamer form (Scheme 2). As we have previously observed,[1d, 1f] the NH_2 resonance is particularly sensitive, and its chemical shift permits insight into the platination/protonation state of the base and into the involvement of NH_2 in intramolecular hydrogen bonding. Table 1 gives an overview of the NH_2 chemical shift data of all the com-



Scheme 2. Solution structure of the platinated base pair **1** as deduced from ^{1}H NMR spectroscopy (a = NH_3).

Abstract in German: *Es wird ein kationischer Rezeptor **2** für Cytosin (C) vorgestellt, der aus drei über zwei trans-a_2Pt^{II}-verknüpften Einheiten, bestehend aus Adenin (A)-, Guanin (G)- und Uracil (U)- oder Thymin (T)-Modellnukleobasen, aufgebaut ist. Diese drei Module besitzen folgende Funktionen: i) Adenin orientiert die beiden anderen Basen (G und U bzw. T) derart, dass ein L-förmiger Rezeptor entsteht. ii) Guanin stellt den Primärrezeptor dar. iii) Uracil bzw. Thymin fungieren als Corezeptoren. Die Assoziationskonstante des o.g. Rezeptors mit C ist im Vergleich zum Watson–Crick G,C-Basenpaar ca. dreimal größer (DMSO). Aus ^{1}H NMR-Untersuchungen geht hervor, dass vom Corezeptor zusätzlich zu den drei "normalen" H-Brücken nach Watson–Crick zwei weitere H-Brücken beigesteuert werden, C also über insgesamt fünf Wasserstoffbrücken gebunden wird. In eine dieser H-Brücken ist das aromatische H(5)-Proton von C involviert. Die Röntgenstrukturanalyse des C-Addukts **4b** bestätigt diesen Sachverhalt. Weiterhin wird die Assoziation von C mit einer Vorstufe des Rezeptors **2** untersucht und ein Vergleich zwischen **4b** und einem isomeren Basenquartett angestellt. Abschließend erfolgt eine Diskussion über potenzielle Anwendungsmöglichkeiten des vorgestellten Konzepts.*

Table 1. Chemical shifts of exocyclic NH_2 resonances and platination state of adenine ligands.[a]

Compound	Solvent	Pt per A	$\delta(NH_2)$
trans-$[(NH_3)_3Pt(9\text{-MeA-}N7)]^{2+}$[1d]	$[D_6]$DMSO	1	8.04
1	$[D_6]$DMSO	1	8.57
$\{[(dien)Pt]_2(\mu\text{-9-MeA-}N1,N7)\}^{4+}$[14]	$[D_7]$DMF	2	9.30
2a	$[D_6]$DMSO	2	9.69
2a	$[D_7]$DMF	2	9.74
2b	$[D_6]$DMSO	2	10.14
2b	$[D_7]$DMF	2	10.30
3	$[D_6]$DMSO	1	8.57
4a	$[D_6]$DMSO	2	9.74

[a] Ambient temperature, in ppm.

pounds prepared and discussed in this study. Neither the NH nor the NH_2 resonances of **1** displayed any concentration dependence in $[D_6]$DMSO, thus measurable association in this solvent was ruled out.

Platinated base triplets *trans,trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$-(*N7*-μ-9-MeA-*N1*)Pt$(NH_3)_2$(1-MeT-*N3*)]$(ClO_4)_3\cdot 5.5H_2O$ (2a) and *trans,trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N7*-μ-9-EtA-*N1*)Pt-$(CH_3NH_2)_2$(1-MeU-*N3*)]$(ClO_4)_3\cdot 5H_2O$ (2b): Reaction of the nitrate salt of **1** (or the corresponding 9-MeA analogue in the case of **2a**) with the 1:1 complexes *trans*-$[(NH_3)_2Pt$(1-MeT-*N3*)Cl][1c] and *trans*-$[(CH_3NH_2)_2Pt$(1-MeU-*N3*)Cl][1h] in the presence of $AgNO_3$ and excess $NaClO_4$ leads to the L-shaped, diplatinated base triplets **2a** and **2b**, respectively. The 1-MeT compound **2a** has been studied by X-ray diffraction (see Table 4). Compound **2a** contains two crystallographically independent cations, one of which is depicted in Figure 1.

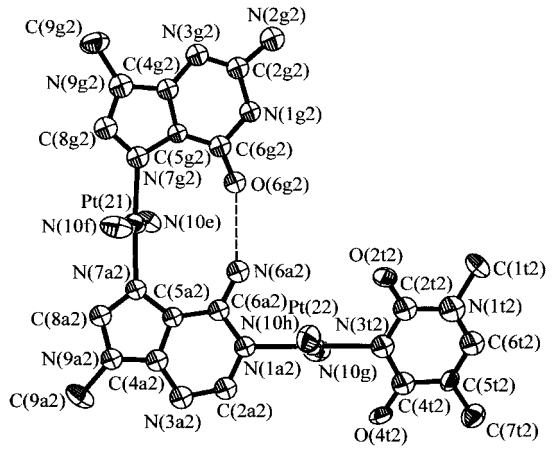


Figure 1. View of one of the two crystallographically independent cations of the metal-modified triplet *trans,trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N7*-μ-9-MeA-*N1*)Pt$(NH_3)_2$(1-MeT-*N3*)]$(ClO_4)_3\cdot 5.5H_2O$ (**2a**).

Both cations are structurally similar. They adopt a L-shape, and the thymine entity is opposite the *N1* position of 9-MeA. The orientation of the 1-MeT ligand with its pseudo C_2 axis through *N3* and C(6) is based on crystallographic arguments. Both rotamers have been tested during refinement and neither showed significantly better *R* values. The rotamer forms presented here (see also Supporting Information) are those that displayed the most reasonable isotropic (*N*(1t1) and *N*(1t2)) and anisotropic (C(5t1) and C(5t2)) displacement factors. The *head,head*-orientation of the two purine bases and the intramolecular hydrogen bond as seen in the starting compound[1f] is maintained in the metalated nucleobase triplet **2a**. The overall geometry of the two crystallographically independent cations, as measured by the distances between the exocyclic C atoms of the three bases (C(9g)$\cdots$C(9a), 10.60(2) and 10.63(1) Å; C(9a)$\cdots$C(1t) or C(7t), 11.87(2) and 11.90(2) Å), is identical within standard deviations. Minor differences between the two cations of **2a** are the length of the intramolecular hydrogen bond between the two purines (2.81(1) and 2.86(1) Å, respectively, see also crystallographic data). The two Pt–*N* vectors at the adenine nucleobase in **2a** are close to perpendicular, that is, 86.0(5)° and 89.4(4)°. Thus the diplatinated adenine again provides the desired 90° angular building block. In both cations the three nucleobases are not coplanar (angles between G/A, 24.3(2)° and 26.7(4)°; between A/T, 25.1(4)° and 24.1(6)°), a feature also seen in related compounds.[1f, 1h] These angles appear to be, at least in part, caused by intercationic base stacking interactions (Figure 2) between terminal thymine bases about a center of inversion as well as terminal guanine bases of crystallographically independent cations.

In the context of right angles generated by the two Pt–adenine vectors, it is interesting to compare **2a** with a linkage isomer, in which the adenine sites are inverted, hence A-*N1* is opposite to G-*N7* and A-*N7* is opposite to T-*N3*.[18] In this case, a marked deviation from 90° is observed (83.0(3)°). It appears that a major determining factor for this feature is the difference in intramolecular hydrogen-bonding capacities, that is, one hydrogen bond for **2a**, and two hydrogen bonds in the linkage isomer. This conclusion is fully supported by a large body of structural data of nucleobase complexes of M = *trans*-a_2Pt^{II} ($a = NH_3$ or CH_3NH_2)[1] and proves that intramolecular hydrogen bonding between nucleobases is possible, in principle, for any of the following combinations: (pu-*N1*)M(pu′-*N7*), (pu-*N7*)M(pu′-*N7*), and (pu-*N7*)M(pym-*N3*), but not for (pu-*N1*)M(pym-*N3*), (pu-*N1*)M(pu′-*N1*) or (pym-*N3*)M(pym′-*N3*) or compounds containing two identical bases ($(pu\text{-}N1)_2M$; $(pu\text{-}N7)_2M$; $(pym\text{-}N3)_2M$), unless the 180° angle about the metal M is substantially reduced. A rare example of this situation is observed in *trans*-$[(CH_3NH_2)_2Pt$(1-MeC-*N3*)(1-MeU-*N3*)]$NO_3\cdot 2H_2O$ with a Pt angle of 169.7(2)° and an intramolecular hydrogen bond between C–NH_2 and U–O(2) of 3.352(7) Å.[19] Thus, in **2a** only a single intramolecular hydrogen bond can be formed ((pu-*N7*)M(pu′-*N7*)) and consequently, deviation from 90° is minimal.

The solution structures of the metal-modified triplets **2a** and **2b** have been explored by ^1H NMR spectroscopy. From the spectra of both species in the protic solvent D_2O it is evident that two rotamer forms are present at ambient temperature. Figure 3 shows the aromatic region of the proton NMR spectra (25 °C, D_2O, 0.02 M) of **2a** (top) and **2b** (middle). The A–H(2) resonances (assignment of the signals by $^1H,^1H$ NOESY experiments) are split into two equally intense singlets, and suggest hindered rotation of the 1-MeT/U ligands about the T/U-*N3*–Pt–*N1*-A bonds, as illustrated in Figure 3 (bottom). A likely explanation for this finding is

0947-6539/01/0710-2106 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

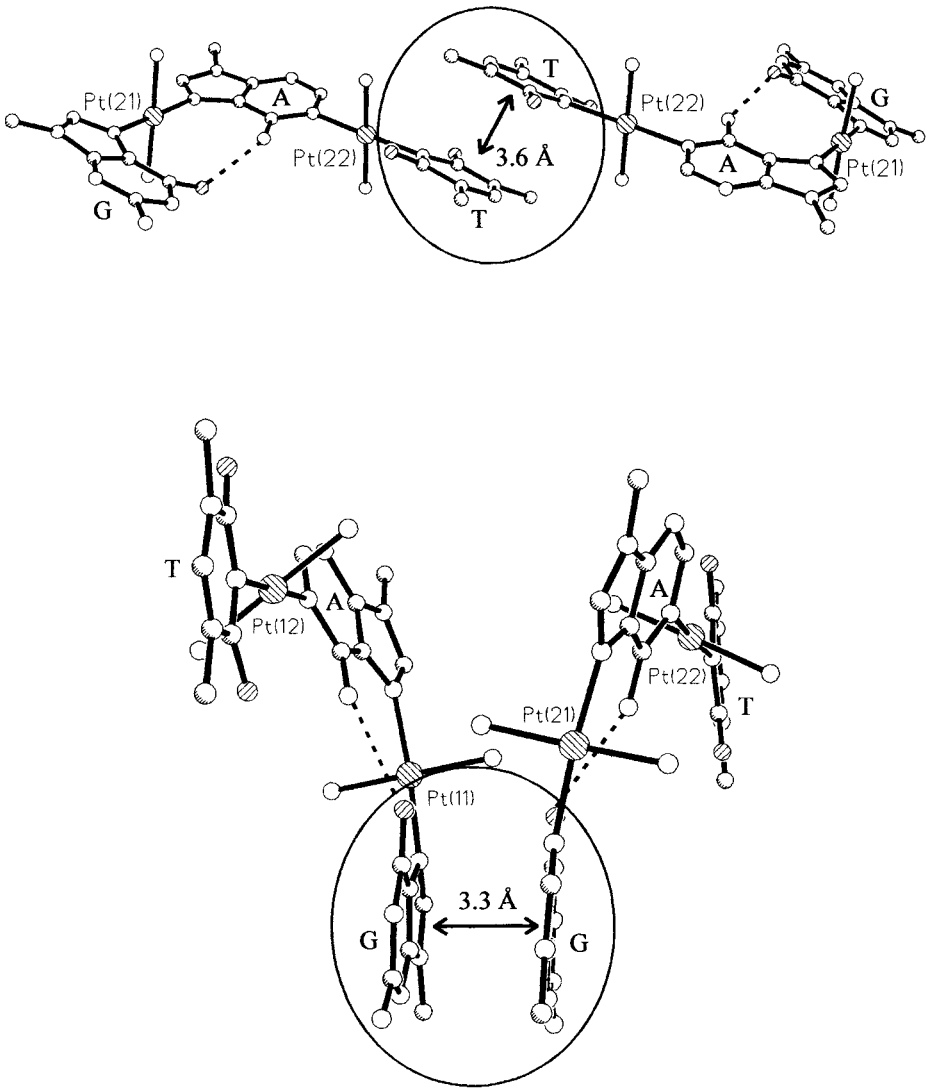


Figure 2. Top: view of the intermolecular stacking interactions of the terminal coordinated 1-MeT ligands between two crystallographically equivalent cations of **2a**; bottom: intermolecular π stacks of the 9-MeGH ligands of two independent cations.

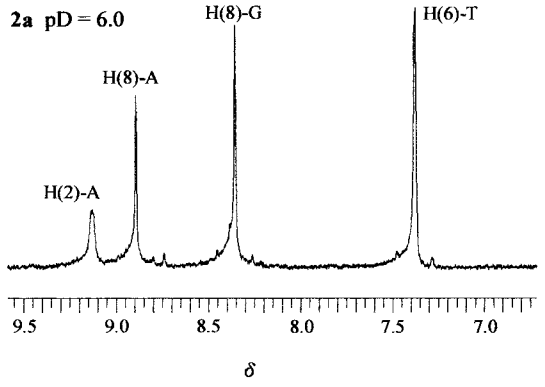
that intermolecular hydrogen bonds with solvent molecules slow down nucleobase rotation about these bonds. Indeed, the solid-state X-ray structure of *trans*-$[(CH_3NH_2)_2Pt(1\text{-MeT-}N3)(9\text{-MeA-}N1)]ClO_4 \cdot 3.25\,H_2O$[1c] reveals the presence of a water molecule between the exocyclic O(4) group of 1-MeT and the exocyclic N(6)H_2 group of 9-MeA. In the aprotic solvents [D_6]DMSO and [D_7]DMF, the ^{1}H NMR spectra of **2a** and **2b** are very simple, and show only single sets of resonances without any signal splitting. A similar solvent dependence has previously been observed with metal-modified base pairs.[1e, 18] The downfield shifts of the exocyclic A-N(6)H_2 groups of **2a** and **2b** in these solvents strongly suggest that the *head,head*-conformation of the two purines, as known from the solid-state structure of **2a** (Figure 1), is maintained in solution (Table 1). The fact that the A-N(6)H_2 resonance is not split is consistent with rapid rotation of the NH_2 group and signal averaging.

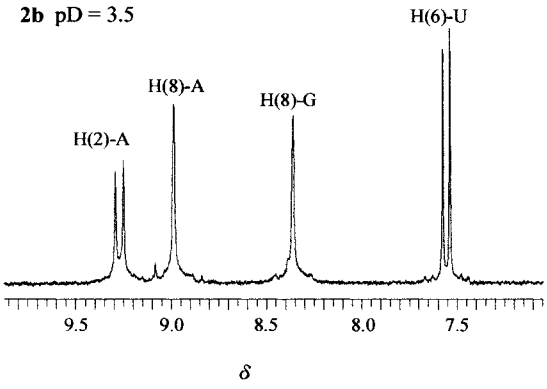
Cytosine adduct of 1: ***trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeGH-*N7*)≡1-MeC]$(ClO_4)_2 \cdot 3H_2O$ (3)**: We have recently shown that *N7* platinated guanine model nucleobases not only undergo Watson–Crick hydrogen bonding with 1-MeC in DMSO solution, but also that Pt^{II} coordination stabilizes this association.[15] Consequently, the isolation and crystallization of Watson–Crick adducts between platinated guanine and free cytosine was desirable, because the number of available examples is still rather limited and anything but uniform.[1a, 1h, 15b, 20] Therefore, the metal-modified base pair **1** has been cocrystallized with an excess of 1-MeC from D_2O, and leads to the platinated triplet **3**, as verified by X-ray crystallography. Figure 4 gives a view of the cation of **3**.

Selected structural details are listed in Table 2 (see also crystallographic data). The pyrimidine base 1-MeC is bound in a Watson–Crick manner to the *N7* platinated 9-MeGH ligand by three hydrogen bonds with distances of 2.772(5) Å [N(2g)···O(2c)], 2.958(4) Å [N(1g)···N(3c)], and 3.021(5) Å [O(6g)···N(4c)]. The two bases are almost coplanar (dihedral angle 2.3(2)°). The guanine and adenine bases are likewise close to coplanar (dihedral angle 4.9(2)°) and are fixed in a *head*, *head*-arrangement through an

Table 2. Comparison of selected bond lengths [Å], hydrogen bonds [Å], and angles between different nucleobase/nucleobase planes [°] in the two cytosine adducts **3** and **4b**.

	3	**4b**
Pt(1)-*N*(*7a*)	2.004(3)	1.983(8)
Pt(1)-*N*(*7g*)	1.999(3)	2.020(8)
Pt(2)-*N*(*1a*)	–	2.027(8)
Pt(2)-*N*(*3u*)	–	2.036(9)
N(2g)···O(2c)	2.772(5)	2.87(1)
N(1g)···N(3c)	2.958(4)	2.91(1)
O(6g)···N(4c)	3.021(5)	2.88(1)
N(6a)···O(6g)	3.003(5)	2.93(1)
N(4c)···O(2w) or O(2u)	2.931(6)	2.98(1)
N(6a)···O(2w)	3.037(6)	–
C(5c)···O(2u)	–	3.51(1)
A/G	4.9(2)	28.0(2)
G/C	2.3(2)	1.8(4)
A/U	–	26.4(3)
U/C	–	15.4(5)





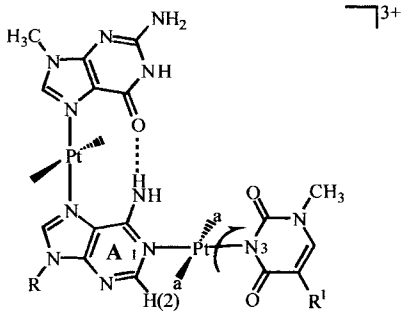


Figure 3. Top: aromatic region of the ^{1}H NMR spectrum of **2a** in D_2O (pD 6.0) at ambient temperature with the assignment of the signals; middle: aromatic region of the ^{1}H NMR spectrum of **2b** in D_2O (pD 3.5) at ambient temperature, the existence of two rotameric forms is observed; bottom: proposed structure of **2** in D_2O solution with the terminal pyrimidine base rotating about the A-*N1*-Pt-*N3*-L^2 bonds (R and $R^1 = CH_3$ for **2a**, $R = CH_2CH_3$ and $R^1 = H$ for **2b**).

intramolecular hydrogen bond (3.003(5) Å) between O(6) of guanine and $N(6)H_2$ of adenine. An unexpected feature of **3** is the presence of a water molecule, which is hydrogen bonded to $N(4)H_2$ of 1-MeC (2.931(6) Å) and $N(6)H_2$ of 9-EtA (3.037(6) Å). Although hydration of nucleobases in DNA is not uncommon,[21] it is rare in cases of metal containing nucleobase associates.[1c] Water molecules often link exocyclic groups of nucleobases present in two adjacent steps of DNA base pairs, and there are also examples with H_2O bridging two exocyclic groups in Watson–Crick base pairs, for example, A-$N(6)H_2$ and O(4) of Br^{5}U in a double stranded octamer,[22]

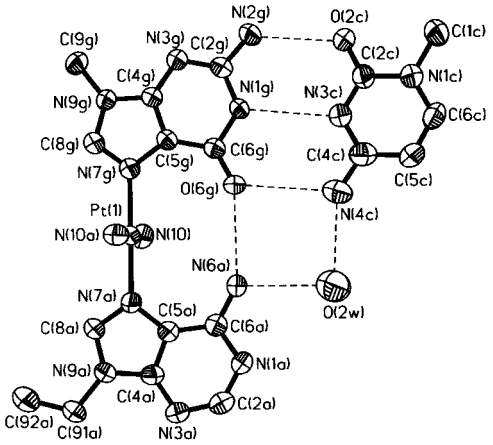


Figure 4. X-Ray structure of the cation of *trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)-(9-MeGH-*N7*)≡1-MeC]$(ClO_4)_2 \cdot 3H_2O$ (**3**). The water molecule O(2w) involved in the base pairing pattern is also shown.

in various wobble base pairs of A-DNA duplexes,[21] as well as in mismatches.[23] Very recently, we have come across another case of water hydrogen bonding to two cytosine bases which are involved in the formation of a flat $[GC]_2$ nucleobase quartet with the two guanines cross-linked by Pt^{II}.[20]

The geometry of the Watson–Crick pair in **3** (Table 2) contrasts some of the other cases we have studied,[1a, h, 15b, 20] where a trend to a longer central hydrogen bond (G-N(1)H ··· N(3)-C) is observed. It appears that in **3** the divergence is caused by the O(2w) water molecule that forms the two additional hydrogen bonds with the exocyclic amino groups of 9-EtA and 1-MeC. Apart from various intermolecular cation–anion interactions, the crystal packing of **3** also reveals some significant base stacking of the metalated adenines (ca. 3.2 Å) as well as the 1-MeC≡9-MeGH entities (ca. 3.9 Å) of different cations.

Recently, we applied a method for the quantitative determination of the association constant of Watson–Crick GC adducts in DMSO solution by the use of concentration-dependent ^{1}H NMR measurements.[15] A 1:1 mixture of 1-MeC and complex **1** in [D_6]DMSO (20 °C) was successively diluted (here 73.5–11.8 mM) and spectra were taken at each concentration. The concentration-dependent change in chemical shifts of the NH protons which are involved in hydrogen bonding could be fitted with a non-linear least-squares curve-fit after Newton–Gauss.[15] For **3** the exocyclic NH_2 and N(1)H of the guanine moiety, as well as the exocyclic NH_2 of 1-MeC all show a downfield shift with increasing concentration, as expected for Watson–Crick pairing (Figure 4). The change of the chemical shifts of the NH protons is depicted in Figure 5 as a stackplot of the aromatic part of the ^{1}H NMR spectra at different concentrations. Since the shifts of CH protons, for example, H(8) and H(2) of 9-EtA, H(8) of 9-MeGH and H(6) of 1-MeC, are not significantly affected by the change in concentration of the 1:1 mixture, other interactions such as stacking can be excluded as they would cause upfield shifts of the CH protons with an increase in concentrations.[24] For calculation of the stability constant of the adduct **3**, the chemical shifts of the three mentioned NH protons were evaluated and fitted as described previously.[15b]

0947-6539/01/0710-2108 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

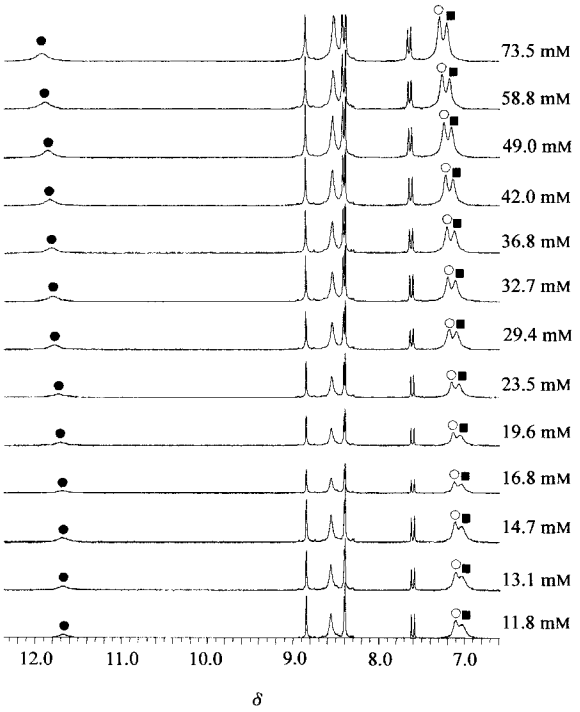


Figure 5. Stackplot of the aromatic region of the ^{1}H NMR spectra in [D_6]DMSO for a 1:1 mixture of **1** and 1-MeC at the depicted concentrations. 9-MeGH-N(1)H (●), 9-MeGH-NH_2 (○), and 1-MeC-NH_2 (■) show a downfield shift with increasing concentration.

The results for three independent experiments were $K^*(1) = 20.86 \pm 5.03\,\text{M}^{-1}$, $K^*(2) = 10.30 \pm 3.11\,\text{M}^{-1}$ and $K^*(3) = 9.83 \pm 2.04\,\text{M}^{-1}$, and they correspond to the weighted mean of the values obtained from the fit of the individual protons in each experiment, with an error of one standard deviation. The final stability constant was calculated with the weighted mean of the K^* values to give $K(\mathbf{3}) = 11.1 \pm 3.2\,\text{M}^{-1}$ (2σ). This result is in excellent agreement with values obtained for similar adducts such as [(dien)Pt(9-EtGH-*N7*)≡1-MeC]$^{2+}$ ($K = 13.0 \pm 2.0\,\text{M}^{-1}$)[15b] and appears to be larger than the value for the association of unplatinated 9-EtGH≡1-MeC ($K = 6.9 \pm 1.3\,\text{M}^{-1}$).[15] The fit of the experimental data with the final value of $K(\mathbf{3})$ is given in the Supporting Information. In Table 3 the calculated chemical shifts of the monomeric (δ_0) and dimeric species (δ_∞) as well as the $\Delta\delta$ values from the differences between δ_0 and δ_∞ are given. Usually, the change of the chemical shift ($\Delta\delta$) for N(1)H of the guanine bases is about twice as large as that for the exocyclic NH_2 groups.[15b, 25]

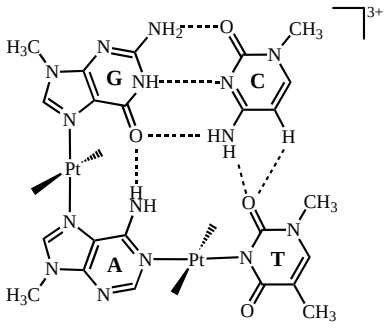
Table 3. Calculated chemical shifts of the NH protons involved in the formation of the metal-modified base triplet **3**.[a]

Proton	δ_0	δ_∞	$\Delta\delta$
9-MeGH-NH_2	6.993 ± 0.007	7.778 ± 0.051	0.785 ± 0.10
9-MeGH-N(1)H	11.522 ± 0.008	12.574 ± 0.081	1.052 ± 0.16
1-MeC-NH_2	6.968 ± 0.005	8.065 ± 0.093	1.097 ± 0.19

[a] The chemical shifts listed are the weighted means of those obtained in the individual experiments. δ_0 corresponds to the chemical shift of the monomeric and δ_∞ of the associated species. $\Delta\delta = \delta_\infty - \delta_0$ is given with an error which corresponds to at least two times the standard deviation. All other error limits correspond to one standard deviation.

This can be explained by the fact that of the NH_2 protons only one is involved in hydrogen bonding (in Watson–Crick pairing) and, because of rapid rotation about the C–NH_2 bond, only an averaged signal for the two protons is observed. In the case of the cytosine adduct **3** the values of $\Delta\delta$ for 9-MeGH-N(1)H and 1-MeC-NH_2 are almost identical (column 4 of Table 3). This observation indicates that the arrangement of the metal-modified triplet with the additional water molecule seen in the solid-state structure (Figure 4) is maintained in [D_6]DMSO solution. In contrast, no significant shift of the 9-EtA-NH_2 resonance is observed (Figure 5) which, on the other hand, points against a strictly identical structure in solution and in the solid state.

Cytosine adducts of 2a and 2b: ***trans*,*trans*-[(1-MeT-*N3*)$Pt(NH_3)_2$(*N1*-*μ*-9-MeA-*N7*)$Pt(NH_3)_2$(9-MeGH-*N7*)≡1-MeC]$^{3+}$ (4a) and *trans*,*trans*-[(1-MeU-*N3*)$Pt(CH_3NH_2)_2$(*N1*-*μ*-9-EtA-*N7*)$Pt(NH_3)_2$(9-MeGH-*N7*)≡1-MeC]$(ClO_4)_3 \cdot 5H_2O$ (4b)**: As mentioned in the introduction, one aim of this study was to investigate the influence of the covalently attached pyrimidine bases 1-MeT or 1-MeU (L^2 in Scheme 1) on the formation of the Watson–Crick pair between the *N7* platinated guanine and 1-MeC. Therefore, we performed analogous concentration-dependent ^{1}H NMR measurements as shown before for **3** with a 1:1 mixture of **2a** and 1-MeC in [D_6]DMSO (20 °C; 62.0–9.9 mM), in order to determine the association constant of **4a**. The changes in chemical shifts of 9-MeGH-N(1)H, 9-MeGH-NH_2 and 1-MeC-NH_2 are consistent with the Watson–Crick Scheme (see above). In addition, we found that the C(5)H resonance of 1-MeC undergoes a significant downfield shift (0.13 ppm in the concentration range studied) with an increase in concentration. Hence, the 1-MeC-C(5)H proton must be involved in intermolecular H-bonding with the coreceptor 1-MeT (Scheme 3). The



Scheme 3. Solution structure of the cytosine adduct of **2a** as determined by ^{1}H NMR spectroscopy in the aprotic solvent [D_6]DMSO, to form the metal-modified quartet **4a** in which 1-MeC is fixed to the receptor unit by five hydrogen bonds, including 1-MeC–C(5)H.

association constant of **4a**, as determined independently from the shifts of all four mentioned protons, amounts to $K(\mathbf{4a}) = 24.2 \pm 12.4\,\text{M}^{-1}$. On the one hand the large error (2σ of the arithmetic mean of three independent experiments) is due to the broad resonances of 9-MeGH-N(1)H, 9-MeGH-NH_2, and 1-MeC-NH_2 protons in the concentration range applied, which makes an accurate determination of the chemical shifts

rather difficult (see Supporting Information). Furthermore, the singlet of the 1-MeT-C(6)H proton overlaps with the resonances of the NH_2 protons. On the other hand even trace amounts of water still present in DMSO have a marked influence on the stability of the Watson–Crick pair, because the water molecules will compete for hydrogen-bonding sites at the nucleobases at the expense of base association.[15b] Nevertheless, the association constant of **4a** reveals a higher stability than that between 9-EtGH and 1-MeC in the same solvent (see above) and it is probably larger than the value determined for the corresponding linkage isomer *trans,trans*-[(1-MeT-*N3*)Pt$(NH_3)_2$(*N7*-μ-9-MeA-*N1*)Pt$(CH_3NH_2)_2$(9-EtGH-*N7*)≡1-MeC]$^{3+}$ ($K = 16.4 \pm 4.0\,M^{-1}$).[15b] Because of the large error of K(**4a**), no meaningful comparison with the latter result is possible, but the observed tendency indicates an enhanced association of 1-MeC in the metal-modified quartet **4a**. Attempts to determine the stability of the analogous quartet **4b** derived from the triplet **2b** and 1-MeC failed because of rapid and as yet unexplained decomposition of **2b** in DMSO following addition of 1-MeC. While **2a** likewise decomposed in DMSO in the presence of 1-MeC, the reaction was sufficiently slow (12 h at room temperature) to permit determination of the association constant.

Repeated attempts to obtain single crystals of the base quartet **4a** suitable for X-ray diffraction from aqueous solution were not successful. However, it was clear from ^{1}H NMR spectroscopy, that no decomposition of **2a** took place in the presence of 1-MeC, hence the mentioned difficulties were DMSO-specific. Eventually, suitable crystals were obtained of the base quartet **4b** upon cocrystallization of the 1-MeU containing triplet **2b** with 1-MeC in D_2O. X-ray analysis of **4b** (Figure 6) reveals that 1-MeC is involved in

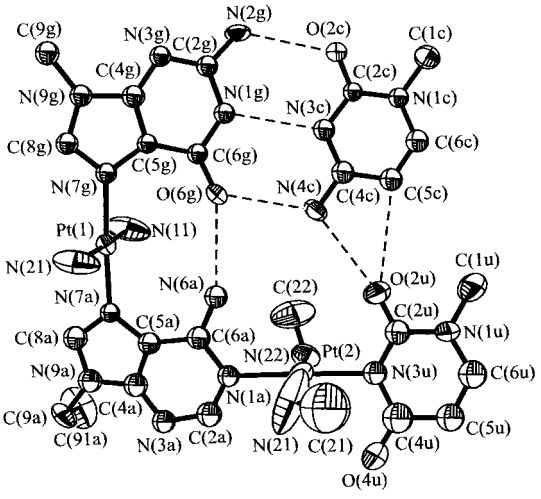


Figure 6. Cation of the solid-state structure for the nucleobase quartet **4b** with atom-numbering scheme.

hydrogen bonding with the receptor unit 9-MeGH through three hydrogen bonds in the normal Watson–Crick fashion (Table 2) and in addition a bifurcated hydrogen bond extends from O(2) of 1-MeU and involves the second amino proton of 1-MeC as well as H(5) of 1-MeC. Distances are 2.98(1) Å for O(2u)···N(4c) and 3.51(1) Å for O(2u)···C(5c) (Table 2). Furthermore, the H(5c)···O(2u) distance is 2.92(1) Å, and the angle at the H(5c) is 123(1)°. The length of the CH···O hydrogen bond, although larger than in typical NH···O systems, is normal, especially if the influence of the dominating H-bonds of the N(4c) group is considered.[26] The other well known features of these complexes, such as orthogonality of the Pt-*N1*- and Pt-*N7*-vectors [angle between Pt(2)-*N*(*1a*)/Pt(1)-*N*(7a) 87.9(3)°] and stabilization of the *head,head*-conformation of the two purine bases by the intramolecular H-bond between the exocyclic 9-MeA-N(6)H_2 and 9-MeGH-C(6)O groups [distance N(6a)···O(6g) 2.93(1) Å], are also realized in **4b**. The coordination geometry of the two Pt^{II} centers is square-planar and no unusual bond lengths or angles can be found (see crystallographic data). Finally, intermolecular base stacking interactions of the platinated 9-MeGH≡1-MeC parts of different cations (distance ca. 3.2 Å) of **4b** are responsible for the distinct deviations of the nucleobases from coplanarity (Table 2, Figure 7).

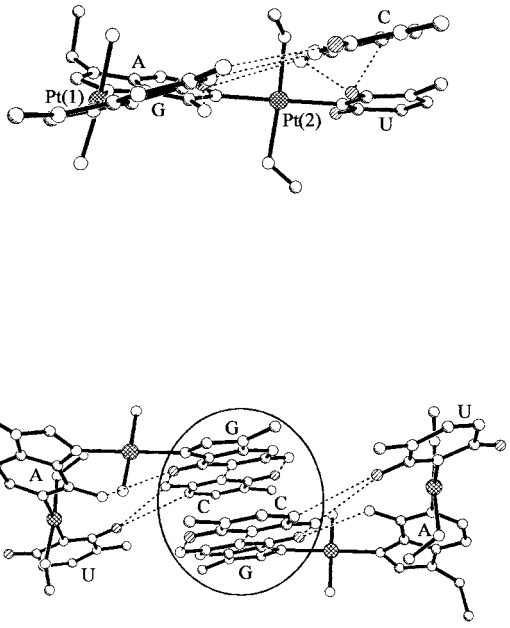
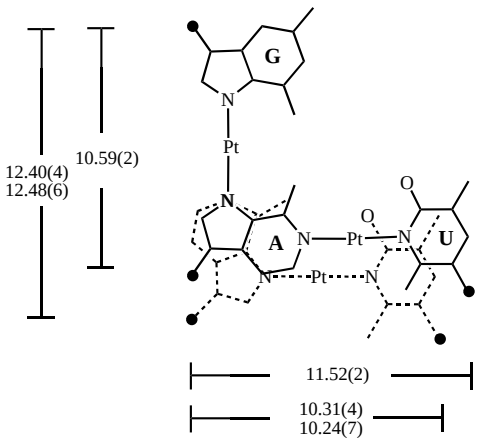


Figure 7. Top: side view of the cation of **4b**; bottom: intermolecular π-stacking interactions of the 9-MeGH≡1-MeC parts of different cations of the metal-modified quartet **4b** (distance ca. 3.2 Å).

Comparison of 4b with linkage isomer: The nucleobase quartet **4b** represents a linkage isomer of the reported platinated base quartet *trans,trans*-[(1-MeU-*N3*)Pt$(NH_3)_2$-(*N7*-μ-9-EtA-*N1*)Pt$(CH_3NH_2)_2$(9-EtGH-*N7*)≡(1-MeC)]$^{3+}$.[1h] An idealized superposition (differences in angles at A not considered) of the two metalated parent base triplets in the two quartet structures (Scheme 4) reveals differences in the geometries of the L-shaped cations in the lengths of the bars of the L. Addition of cytosine to the two receptors (not shown) further indicates that thymine and uracil bases act as coreceptors for cytosine N(4)H_2 through an exocyclic oxygen atom in both cases, but that only in **4b** this keto oxygen is close enough to H(5) of cytosine to allow additional hydrogen-bond formation. Hydrogen-bond lengths of the Watson–Crick

0947-6539/01/0710-2110 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10



Scheme 4. Superposition (idealized) and dimensions [Å] of the two linkage isomers **4b** (solid lines) and *trans*,*trans*-[(1-MeU-*N3*)Pt$(NH_3)_2$-(*N7*-μ-9-EtA-*N1*)Pt$(CH_3NH_2)_2$(9-EtGH-*N7*)≡(1-MeC)]$^{3+}$ (dashed structure; data are given for two crystallographically independent cations). 1-MeC nucleobases are omitted for clarity.

pairs in the two compounds do not differ significantly, despite rather substantial differences in angles between G and C bases (1.8(4)° in **4b**; 14.7(9) and 14.0(6)° in two crystallographically different species (I, II) of the linkage isomer).[1h] For the interaction between 1-MeC and the coreceptor base 1-MeU in the two compounds, the following similarities and differences exist: Two relatively long hydrogen-bonding contacts (2.98(1) and 3.51(1) Å) and a moderate dihedral angle of 15.4(5)° between the two pyrimidine nucleobases in **4b** contrast with one short H-bond (2.82(4) Å) and a small dihedral angle between the bases (5.9(9)°) in one of the two crystallographically independent cations (I) of the previously reported compound and a long (3.15(2) Å) hydrogen bond and a large dihedral angle (26.1(7)°) in the second independent cation (II). It appears that the marked out-of-plane motion of 1-MeC in **4b** (Figure 7) is, at least in part, caused by the bulk of the methyl group of 1-MeU, very much as in II of the linkage isomer quartet. As in the latter, a rotation of the 1-MeU base about the Pt(2)–*N*(*3u*) bond would avoid any steric clash of the methyl group of 1-MeU while maintaining the bifurcated H-bond extending from O(4u). It is surprising to find that this possibility is not realized in **4b**, even though it is in species I of the related complex.

Comparison of 3 with 4: Superficially, the oxygen atom of the water molecule O(2w) in **3** has a function comparable with that of the carbonyl oxygen O(2u) in **4b**, namely to act as a H-bond acceptor for the exocyclic amino group of 1-MeC. A major difference lies in the separation of this oxygen atom from the exocyclic amino group of the adenine base. It is longer by about 1 Å in the case of **4b**. Still, it is obvious that the 1-MeC guest is "following" the movement of this oxygen atom as evidenced by the incline of 1-MeC with respect to the guanine base. Thus, the angle formed between the three Watson–Crick hydrogen bonds (e.g., N(3c)···N(1g)) and the Pt(1)–*N*(*7g*) vector diminishes from 84.6(1)° in **3** to 80.6(3)° in **4b**.

The propensity of the Watson–Crick GC pair to have the second amino proton of cytosine also involved in hydrogen bonding,[1h, 20] is confirmed both in **3** and **4b**. The situation is in a sense reminiscent of that seen in nucleobase quartets generated by dimerization of two Watson–Crick pairs.[21a, 27]

As already pointed out, a unique feature of **4b** is the involvement of H(5) of 1-MeC in hydrogen-bond formation with the coreceptor 1-MeU. Hydrogen bond formation of aromatic nucleobase protons is indeed rare,[28, 29] but the fact that 1-MeC is fixed through five hydrogen bonds utilized by four different sites is, to the best of our knowledge, unprecedented. In addition to the receptor properties, the assemblies of **2a** and **2b** with 1-MeC represent metal-modified quartets which combine the four different model nucleobases of DNA (**4a**) or RNA (**4b**) in a single compound.

Conclusion

The ability of nucleobases to form hydrogen bonds is retained in their Pt^{II} complexes as long as the metal does not impede hydrogen bonding by steric hindrance. We have previously shown[17, 18, 29, 30] several examples of partial or complete self-complementary metal–nucleobase complexes that enable dimerization by hydrogen bonds and production of metalated base quartets or sextets. Here we demonstrate that guanine containing metal-modified base pairs and triplets interact with the complementary cytosine and that through use of a suitably spaced coreceptor, the number of the usual three hydrogen bonds of the Watson–Crick pair can be increased to five. Consequently, the thermodynamic stability of the associate is enhanced.

It is obvious that the concept presented here can be extended to modular receptors in general, and, moreover, can be applied to target molecules other than nucleobases. There are at least the following three points to be considered. i) In principle, *all* available donor/acceptor sites in metal-modified base pairs and triplets may be utilized for recognition of a guest. ii) The positive charge of the here described compounds makes these hosts particularly suitable for anionic species, including nucleotides. iii) Attachment of a reporter group[31] to the receptor unit is feasible, and eventually a sensor could be produced.

Compounds **3** and **4** reported here are also of interest in another context, that is, the potential application of *trans*-a_2Pt^{II} modified oligonucleotides as antigene agents. Thus, the structure of **3** indicates that a *trans*-$a_2Pt^{II}Cl$ entity bound to *N7* of an adenine base within a suitable antigene oligonucleotide might form a stable cross-link with *N7* of guanine within a DNA duplex and be supported by a hydrogen bond from A-N(6)H_2 to G-O(6). Similarly, from compounds **4** it may be possible to prepare an antigene oligonucleotide which recognizes a *GC pair* rather than an *individual G* base. If a suitably positioned adenine is introduced into the oligonucleotide with a *trans*-$a_2Pt^{II}Cl$ unit at *N7* for cross-linking with G-*N7* and simultaneously a *trans*-a_2PtL^2 unit (L^2 = 1-methyluracilate) for hydrogen-bond formation with C, such a situation may be envisaged. We wish to emphasize that the use of *trans*-a_2Pt^{II} modified oligonucleotides as antigene agents, originally derived from a model compound,[1a] has indeed been demonstrated.[32]

Experimental Section

Materials: 1-MeC,[33] *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot H_2O$,[1d] *trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot 1.4\,H_2O$,[1f] *trans*-[$(NH_3)_2$Pt(1-MeT-*N3*)Cl][1c] and *trans*-[$(CH_3NH_2)_2$Pt(1-MeU-*N3*)Cl][1h] were synthesized according to literature methods. For the synthesis of the other complexes see below. All other chemicals used (pro analysi) were purchased from Merck, Darmstadt (Germany). All aqueous solutions were prepared with deionized water.

Instrumentation: All ^{1}H and ^{195}Pt NMR spectra were recorded on a Bruker AC 200 (200.13 MHz) spectrometer at 25 °C or 20 °C in D_2O or [D_6]DMSO and [D_7]DMF, respectively. D_2O, [D_6]DMSO, and [D_7]DMF were from Deutero (Kastellaun, Germany) and Cambridge Isotope Laboratories (Andover, USA). Sodium-3-(trimethylsilyl)propane sulfonate was used as internal (^{1}H, D_2O) and Na_2PtCl_6 as external (^{195}Pt) reference. [D_6]DMSO was dried over 4 Å molecular sieves for at least one week before use and the resonance of [D_5]DMSO ($\delta = 2.5025$ relative to TMS) was taken as internal reference. pD values were obtained by adding 0.4 to the pH meter reading (Metrohm 632).[34] Elemental analyses were carried out on a LECO Elemental Analyzer CHNS-932 and a Carlo Strumentazione 1106 instrument. The IR spectra were recorded on a Bruker FT-IR IFS 28 (32 scans in the region between 4000 and 250 cm^{-1}, KBr) and evaluated with the program Opus, version 2.0 (Bruker).

Determination of association constants: The association constants of the guanine–cytosine pairs in [D_6]DMSO solution were determined according to the recently published method.[15]

X-ray diffraction studies: Intensity data of **2a**, **3** and **4b** were collected on an Enraf-Nonius KappaCCD[35] ($Mo_{K\alpha}$, $\lambda = 0.71069$ Å, graphite monochromator). Sample-to-detector distances were 28.7 (**2a**), and 29.2 mm (**3**, **4b**), respectively. They covered the whole sphere of reciprocal space by measurement of 360 frames rotating about ω in steps of 1°. Exposure times were 50 (**2a**, **4b**), and 60 s (**3**) per frame. Preliminary orientation matrices and unit cell parameters were obtained from the peaks of the first ten frames and refined using the whole data set. Frames were integrated and corrected for Lorentz and polarization effects using DENZO.[36] The scaling as well as the global refinement of crystal parameters were performed by SCALEPACK.[36] Reflections, which were partly measured on previous and following frames, were used to scale these frames on to each other. Merging of redundant reflections eliminates in part absorption effects, and also a crystal decay if present is considered.

All structures were solved by standard Patterson methods[37] and refined by full-matrix least-squares based on F^2 using the SHELXTL-PLUS[38] and SHELXL-93 programs.[39] The scattering factors for the atoms were those given in the SHELXTL-PLUS program. Transmission factors were calculated with SHELXL-97.[40] Hydrogen atoms were included in calculated positions and refined with isotropic displacement parameters according to the riding model. A part of the nonhydrogen atoms in the structures **2a** and **4b** were only refined isotropically in order to save parameter because of the poor observed reflections to parameter ratios present.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151703–151705. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table 4. Crystal data and details of structure refinement for **2a**, **3** and **4b**.

	2a	**3**	**4b**
asymmetric unit	$C_{36}H_{86}N_{32}O_{41}Pt_4Cl_6$	$C_{18}H_{35}N_{15}O_{13}PtCl_3$	$C_{25}H_{54}N_{19}O_{21}Pt_2Cl_3$
formula	$C_{18}H_{43}N_{16}O_{20.5}Pt_2Cl_3$	$C_{18}H_{35}N_{15}O_{13}PtCl_3$	$C_{25}H_{54}N_{19}O_{21}Pt_2Cl_3$
M_r	2616.43	935.60	1453.40
crystal system	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a /Å	13.347(3)	8.832(2)	10.556(2)
b /Å	16.568(3)	13.807(3)	12.586(3)
c /Å	20.053(4)	14.161(3)	18.193(3)
α /°	98.71(3)	107.92(3)	78.99(3)
β /°	100.04(3)	97.10(3)	86.60(3)
γ /°	104.59(3)	91.27(3)	85.04(3)
V /Å^3	4135.9(15)	1627.2(6)	2361.4(9)
Z	2	2	2
ρ_{calcd} /g cm^{-3}	2.101	1.910	2.044
μ /mm^{-1}	7.045	4.560	6.184
$F(000)$	2536	928	1424
crystal size /mm	$0.50 \times 0.25 \times 0.23$	$0.40 \times 0.11 \times 0.11$	$0.29 \times 0.14 \times 0.06$
2Θ range for data collection	$5.2 \le 2\theta \le 48.2$	$4.7 \le 2\theta \le 58.4$	$7.2 \le 2\theta \le 50.9$
reflns collected	11350	7601	7558
independent reflns	11350 ($R_{int} = 0.065$)	7601 ($R_{int} = 0.063$)	7558 ($R_{int} = 0.094$)
reflns observed	5976 ($F_o > 4\sigma(F_o)$)	5420 ($F_o > 4\sigma(F_o)$)	3364 ($F_o > 4\sigma(F_o)$)
parameters refined	852	471	481
goodness-of-fit	1.091	1.048	1.028
R_1[a]	0.0532	0.0313	0.0424
wR_2[b]	0.0964	0.0625	0.0665
residuals/eÅ^{-3}	2.009, −1.534	0.920, −0.695	0.883, −0.839

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

***trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeGH-*N7*)]$(ClO_4)_2\cdot H_2O$ (1)**: A threefold excess of $NaClO_4$ (116 mg, 0.954 mmol) was added to an aqueous solution (30 mL, pH 5–6) of *trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot 1.4\,H_2O$ (225 mg, 0.318 mmol). After 12 h at 4 °C under the exclusion of air, **1** (183 mg, 78 %) was filtered off as a white precipitate, and washed with water (10 mL) and dried (1 d, 40 °C). ^{1}H NMR (D_2O, 0.02 M, ambient temperature, pD 7.7): $\delta = 8.82$ (A-H8), 8.37 (A-H2), 8.34 (G-H8), 4.39 (q, A-CH_2), 3.78 (G-CH_3), 1.53 (t, A-CH_3); FT-IR (KBr, cm^{-1}): 1089 (ClO_4^-); elemental analysis (%) calcd for $C_{13}H_{24}N_{12}PtCl_2O_{10}$ (774.4): C 20.2, H 3.1, N 21.7; found: C 20.2, H 3.1, N 21.9.

***trans*,*trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N7*-μ-9-MeA-*N1*)Pt$(NH_3)_2$(1-MeT-*N3*)]$(ClO_4)_3\cdot 5.5\,H_2O$ (2a)**: *trans*-[$(NH_3)_2$Pt(1-MeT-*N3*)Cl] (289 mg, 0.715 mmol) was suspended in a weakly acidic (HNO_3, pH 3.5) aqueous solution (80 mL) of *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(NO_3)_2\cdot H_2O$ (490 mg, 0.715 mmol). A solution of $AgNO_3$ (119 mg, 0.7 mmol) in H_2O (10 mL) was added dropwise over a period of 6 h with daylight excluded and stirred for 6 d at 30 °C. After the mixture was cooled to 4 °C, AgCl was removed by filtration. The faint yellowish filtrate was concentrated to a 25 mL volume and an excess of $NaClO_4$ was added. During further evaporation a tan crystalline solid precipitated, which was filtered off, washed with water, and dried in air. The fraction contained 10 % of unreacted *trans*-[$(NH_3)_2$Pt(9-MeA-*N7*)(9-MeGH-*N7*)]$(ClO_4)_2$ (^{1}H NMR). Recrystallization from H_2O yielded 28 % of pure **2a**. ^{1}H NMR (D_2O, 0.02 M, ambient temperature, pD 7.0): $\delta = 9.15$, 9.13 (A-H2 with relative intensities of 1:1), 8.91 (A-H8), 8.37 (G-H8), 7.39 (T-H6), 4.01 (A-CH_3), 3.81 (G-CH_3), 3.41 (T-NCH_3), 1.91 (T-CCH_3); ^{195}Pt NMR (D_2O, 0.02 M, ambient temperature, pD 7.0): $\delta = -2470$ (A-*N7*-Pt-*N7*-G), −2519 (T-*N3*-Pt-*N1*-A); elemental analysis (%) calcd for $C_{18}H_{43}O_{20.5}N_{16}Pt_2Cl_3$ (1308.1): C 16.5, H 3.3, N 17.1; found: C 16.6, H 3.0, N 17.1.

***trans*,*trans*-[(9-MeGH-*N7*)Pt$(NH_3)_2$(*N7*-μ-9-EtA-*N1*)Pt$(CH_3NH_2)_2$-(1-MeU-*N3*)]$(ClO_4)_3\cdot 5\,H_2O$ (2b)**: The synthesis of **2b** was performed in analogy to that of **2a**, with *trans*-[$(CH_3NH_2)_2$Pt(1-MeU-*N3*)Cl] instead of the thymine complex. The yield of the yellowish solid was 66 %. ^{1}H NMR (D_2O, 0.02 M, ambient temperature, pD 3.5): $\delta = 9.30$, 9.26 (A-H2 with relative intensities of 1:1), 9.00 (A-H8), 8.36 (G-H8), 7.56 (d, U-H6), 5.81 (d, U-H5), 4.46 (q, A-CH_2), 3.80 (G-CH_3), 3.45, 3.44 (U-NCH_3 with relative intensities of 1:1), 2.22 (NH_2CH_3), 1.58 (t, A-CH_3); ^{195}Pt NMR (D_2O, 0.02 M,

0947-6539/01/0710-2112 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

ambient temperature, pD 3.5): $\delta = -2470$ (A-*N7*-Pt-*N7*-G), -2587 (U-*N3*-Pt-*N1*-A); elemental analysis (%) calcd for $C_{20}H_{47}O_{20}N_{16}Pt_2Cl_3$ (1328.2): C 18.1, H 3.6, N 16.9; found: C 18.0, H 3.2, N 16.9.

***trans*-[$(NH_3)_2$Pt(9-EtA-*N7*)(9-MeGH-*N7*)≡1-MeC]$(ClO_4)_2 \cdot 3H_2O$ (3)**: Cocrystallization of **1** (30 mg, 0.04 mmol) with 3 equiv 1-MeC (15 mg, 0.12 mmol) in D_2O (5 mL) at 4 °C gave colorless sticks of **3** within 7 d. Compound **3** was characterized by X-ray crystallography.

***trans*,*trans*-[(1-MeU-*N3*)Pt$(CH_3NH_2)_2$(*N1*-*μ*-9-EtA-*N7*)Pt$(NH_3)_2$-(9-MeGH-*N7*)≡1-MeC]$(ClO_4)_3 \cdot 5H_2O$ (4b)**: Cocrystallization of **2b** (50 mg, 0.04 mmol) with 3 equivalents of 1-MeC (15 mg, 0.12 mmol) in D_2O (5 mL) at 4 °C gave colorless cubes of **4b** within 8 d. Compound **4b** was characterized by X-ray crystallography.

Acknowledgements

This work has been supported by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie (FCI).

[1] a) I. Dieter-Wurm, M. Sabat, B. Lippert, *J. Am. Chem. Soc.* **1992**, *114*, 357; b) S. Menzer, M. Sabat, B. Lippert, *J. Am. Chem. Soc.* **1992**, *114*, 4644; c) O. Krizanovic, M. Sabat, R. Beyerle-Pfnür, B. Lippert, *J. Am. Chem. Soc.* **1993**, *115*, 5538; d) A. Schreiber, M. S. Lüth, A. Erxleben, E. C. Fusch, B. Lippert, *J. Am. Chem. Soc.* **1996**, *118*, 4124 and A. Schreiber, M. S. Lüth, A. Erxleben, E. C. Fusch, B. Lippert, *J. Am. Chem. Soc.* **1999**, *121*, 3248; e) S. Metzger, A. Erxleben, B. Lippert, *J. Biol. Inorg. Chem.* **1997**, *2*, 256; f) M. S. Lüth, E. Freisinger, F. Glahé, J. Müller, B. Lippert, *Inorg. Chem.* **1998**, *37*, 3195; g) M. S. Lüth, E. Freisinger, F. Glahé, B. Lippert, *Inorg. Chem.* **1998**, *37*, 5044; h) R. K. O. Sigel, S. M. Thompson, E. Freisinger, B. Lippert, *Chem. Commun.* **1999**, 19.

[2] B. Lippert, *Coord. Chem. Rev.* **1999**, *182*, 263.

[3] a) B. Andersen, E. Bernal-Méndez, M. Leng, E. Sletten, *Eur. J. Inorg. Chem.* **2000**, 1201; b) Y. A. Shin, G. L. Eichhorn, *Biopolymers* **1980**, *19*, 539.

[4] B. Lippert, M. Leng in *Topics Biol. Inorg. Chem. Vol. 1* (Eds.: M. J. Clarke, P. J. Sadler), Springer, Berlin, **1999**, pp. 117–142.

[5] a) P. Aich, S. L. Labiuk, L. W. Tari, L. J. T. Delbaere, W. J. Roesler, K. J. Falk, R. P. Steer, J. S. Lee, *J. Mol. Biol.* **1999**, *294*, 477; b) P. Aich, S. L. Labiuk, L. W. Tari, L. J. T. Delbaere, W. J. Roesler, K. J. Falk, R. P. Steer, J. S. Lee, *J. Mol. Biol.* **1999**, *294*, 477.

[6] a) B. Linton, A. D. Hamilton, *Chem. Rev.* **1997**, *97*, 1669 and references therein; b) D. S. Lawrence, T. Jiang, M. Levett, *Chem. Rev.* **1995**, *95*, 2229; c) J. Rebek Jr., *Angew. Chem.* **1990**, *102*, 261; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 245; d) J. M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, Germany, **1995**.

[7] T. Chin, Z. Gao, I. Lelouche, Y.-g. K. Shin, A. Purandare, S. Knapp, S. S. Isied, *J. Am. Chem. Soc.* **1997**, *119*, 12849 and references therein.

[8] T. W. Bell, Z. Hou, Y. Luo, M. G. B. Drew, E. Chapotean, B. P. Czech, A. Kumar, *Science* **1995**, *269*, 671.

[9] a) A. D. Hamilton, N. Pant, *J. Chem. Soc. Chem. Commun.* **1988**, 765; b) S. C. Zimmerman, W. Wu, Z. Zeng, *J. Am. Chem. Soc.* **1991**, *113*, 196; c) C. Seel, F. Vögtle, *Angew. Chem.* **1991**, *104*, 442; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 433; d) H. Furuta, D. Magda, J. L. Sessler, *J. Am. Chem. Soc.* **1991**, *113*, 978; e) V. M. Rotello, E. A. Viani, G. Deslongchamps, B. A. Murray, J. Rebek Jr., *J. Am. Chem. Soc.* **1993**, *115*, 797; f) H.-J. Schneider, T. Blatter, B. Palm, U. Pfingstag, V. Rüdiger, I. Theis, *J. Am. Chem. Soc.* **1992**, *114*, 7704; g) C. S. Wilcox, J. C. Adrian Jr., T. H. Webb, F. J. Zawacki, *J. Am. Chem. Soc.* **1992**, *114*, 10189; h) M. A. Santos, T. Ferreira, M. A. Esteves, M. G. Drew, F. A. Beland, M. M. Marques, *Supramol. Chem.* **1995**, *5*, 243.

[10] B. Lippert, *J. Chem. Soc. Dalton Trans.* **1997**, 3971 and references therein.

[11] a) A. D. Burrows, C. W. Chan, M. M. Chowdry, J. E. McGrady, D. M. P. Mingos, *Chem. Soc. Rev.* **1995**, *24*, 329; b) A. D. Burrows, D. M. P. Mingos, A. J. P. White, D. J. Williams, *J. Chem. Soc. Dalton Trans.* **1996**, 149; c) A. D. Burrows, S. Menzer, D. M. P. Mingos, A. J. P. White, D. J. Williams, *J. Chem. Soc. Dalton Trans.* **1997**, 4237; d) X. Xu, S. L. James, D. M. P. Mingos, A. J. P. White, D. J. Williams, *J. Chem. Soc. Dalton Trans.* **2000**, 3783.

[12] a) E. Kimura, T. Ikeda, S. Aoki, M. Shionoya, *J. Biol. Inorg. Chem.* **1998**, *3*, 259; b) E. Kikuta, N. Katsube, E. Kimura, *J. Biol. Inorg. Chem.* **1999**, *4*, 431; c) E. Kikuta, M. Murata, N. Katsube, T. Koike, E. Kimura, *J. Am. Chem. Soc.* **1999**, *121*, 5426.

[13] M. H. Al-Sayah, N. R. Branda, *Angew. Chem.* **2000**, *112*, 975; *Angew. Chem. Int. Ed.* **2000**, *39*, 945.

[14] A. Schreiber, E. C. Hillgeris, B. Lippert, *Z. Naturforsch. Teil B* **1993**, *48*, 1603.

[15] a) R. K. O. Sigel, B. Lippert, *Chem. Commun.* **1999**, 2167; b) R. K. O. Sigel, E. Freisinger, B. Lippert, *J. Biol. Inorg. Chem.* **2000**, *5*, 287.

[16] a) J. Sponer, J. V. Burda, M. Sabat, J. Leszczynski, P. Hobza, *J. Phys. Chem. A* **1998**, *102*, 5951; b) J. V. Burda, J. Leszczynski, P. Hobza, *J. Phys. Chem. B* **1997**, *101*, 9670; c) E. H. S. Anwander, M. M. Probst, B. M. Rode, *Biopolymers* **1990**, *29*, 757.

[17] I. B. Rother, E. Freisinger, A. Erxleben, B. Lippert, *Inorg. Chim. Acta* **2000**, *300–302*, 339.

[18] R. K. O. Sigel, S. M. Thompson, E. Freisinger, F. Glahé, B. Lippert, *Chem. Eur. J.* **2001**, *7*, 1968.

[19] R. K. O. Sigel, E. Freisinger, B. Lippert, unpublished results.

[20] E. Freisinger, S. Meier, B. Lippert, *J. Chem. Soc. Dalton Trans.* **2000**, 3274.

[21] a) M. C. Wahl, M. Sundaralingam, *Biopolymers* **1997**, *44*, 45 and references therein; b) H. M. Berman, B. Schneider in *Oxford Handbook for Nucleic Acid Structure* (Ed.: S. Neidle), Oxford Science Publications, Oxford, **1999**, pp. 295–312.

[22] O. Kennard, W. B. T. Cruse, J. Nachman, T. Prange, Z. Shakked, D. Rabinovich, *J. Biomol. Struct. Dyn.* **1986**, *3*, 623.

[23] O. Kennard in *Nucleic Acids Mol. Biol.* (Eds.: F. Eckstein, D. M. J. Lilley), Springer, Berlin, **1987**, *1*, 25.

[24] P. R. Mitchell, H. Sigel, *Eur. J. Biochem.* **1978**, *88*, 149.

[25] G. Schröder, M. Sabat, I. Baxter, J. Kozelka, B. Lippert, *Inorg. Chem.* **1997**, *36*, 490.

[26] a) T. Steiner, *J. Chem. Soc. Chem. Commun*. **1994**, 2341; b) G. R. Desiraju, *Acc. Chem. Res.* **1996**, *26*, 441; c) T. Steiner, *Chem. Commun.* **1997**, 727.

[27] a) H. M. Sobell, K.-I. Tomita, A. Rich, *Proc. Natl. Acad. Sci. USA* **1963**, *49*, 885; b) E. J. O'Brien, *Acta Crystallogr.* **1967**, *23*, 92; c) D. J. Patel, S. Bouaziz, A. Kettani, Y. Wang in *Oxford Handbook for Nucleic Acid Structure* (Ed.: S. Neidle), Oxford Science Publications, Oxford, **1999**, pp. 389–453.

[28] a) M. Brandl, K. Lindauer, M. Meyer, J. Sühnel, *Theor. Chem. Acc.* **1999**, *101*, 103 and references therein; b) M. C. Wahl, S. T. Rao, M. Sundaralingam, *Nat. Struct. Biol.* **1996**, *3*, 24.

[29] a) R. K. O. Sigel, E. Freisinger, S. Metzger, B. Lippert, *J. Am. Chem. Soc.* **1998**, *120*, 12000; b) S. Metzger, B. Lippert, *J. Am. Chem. Soc.* **1996**, *118*, 12467.

[30] C. Meiser, E. Freisinger, B. Lippert, *J. Chem. Soc. Dalton Trans.* **1998**, 2059.

[31] See, for example: a) A. S. Georgopoulou, D. M. P. Mingos, A. J. P. White, D. J. Williams, B. R. Horrocks, A. Houlton, *J. Chem. Soc. Dalton Trans.* **2000**, 2969; b) A. Houlton, C. J. Isaac, A. E. Gibson, B. R. Horrocks, W. Clegg, M. R. J. Elsegood, *J. Chem. Soc. Dalton Trans.* **1999**, 3229; c) D. J. Hurley, Y. Tor, *J. Am. Chem. Soc.* **1998**, *120*, 2194; d) C. M. White, M. Fernandez Gonzales, D. A. Bardwell, L. H. Rees, J. C. Jeffrey, M. D. Ward, N. Armaroli, G. Calogero, F. Barigelletti, *J. Chem. Soc. Dalton Trans.* **1997**, 727; e) C. Price, M. Aslanoglu, C. J. Isaac, M. R. J. Elsegood, W. Clegg, B. R. Horrocks, A. Houlton, *J. Chem. Soc. Dalton Trans.* **1996**, 4115.

[32] C. Colombier, B. Lippert, M. Leng, *Nucl. Acids Res.* **1996**, *24*, 4519.

[33] T. J. Kistenmacher, M. Rossi, J. P. Cardonna, L. G. Marzilli, *Adv. Mol. Relax. Interact. Processes* **1979**, *15*, 119.

[34] R. B. Martin, *Science* **1963**, *139*, 1198.

[35] NONIUS BV, KappaCCD package, Röntgenweg 1, P. O. Box 811, 2600 AV Delft, Netherlands, **1997**.

[36] Z. Otwinowsky, W. Minor, *Methods Enzymol.* **1996**, *276*, 307.

[37] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467.

[38] G. M. Sheldrick, SHELXTL-PLUS (VMS), Siemens Analytical X-Ray Instruments, Madison, WI, **1990**.

[39] G. M. Sheldrick, SHELXL-93, Program for crystal structure refinement, University of Göttingen, Germany, **1993**.

[40] G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, **1997**.

Received: November 10, 2000 [F2863]