

# Hydrogen bonding patterns of N(7) platinated guanine: Watson–Crick and different self-pairing motifs in a tris(9-methylguanine) complex of Pt<sup>II</sup>†

Eva Freisinger, Susanne Meier and Bernhard Lippert\*

Fachbereich Chemie, Universität Dortmund, 44221 Dortmund, Germany

Received 22nd June 2000, Accepted 26th July 2000

First published as an Advance Article on the web 5th September 2000

The tris(nucleobase) complex [Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)]<sub>3</sub><sup>2+</sup> **1** (Hmgua = 9-methylguanine) has been synthesised and crystallised as the nitrate (**1a**) and a mixed perchlorate, chloride salt (**1b**). In the cation of **1a** the three bases are oriented *head–tail–head*, as in one of the two crystallographically different cations of **1b**. The second cation of **1b** displays a *head–head–tail* arrangement of the three bases. Of special interest is the H bonding pattern of the *head–tail–head* rotamer of **1b** in that pairs of the two *trans*-oriented guanine bases associate to a novel guanine quartet structure. If **1b** is co-crystallised with an excess of 1-methylcytosine (mcyt) from weakly acidic aqueous solution, a supramolecular ensemble **2** of ten nucleobases is obtained which consists of four Watson–Crick base pairs arranged as two base quartets as well as a Hmgua/mgua self-pair.

The question if and how metal co-ordination to the heterocyclic part of a nucleobase can affect its base pairing pattern is of general interest, relevant to aspects such as DNA condensation,<sup>1</sup> stabilisation of unusual nucleic acid structure motifs,<sup>2</sup> or heavy metal toxicity and mutagenicity,<sup>3</sup> to name these only. In a broader sense the topic also relates to the subject of molecular architecture developed from metal ions and heterocyclic ligands by taking advantage of a combination of metal co-ordination and H bonding.<sup>4–6</sup> We have applied both alkali metal ions and kinetically inert Pt<sup>II</sup> species<sup>7</sup> to model relevant scenarios. Among these, N(7) platinated guanine has been found to be particularly versatile as far as H-bonding patterns are concerned. Thus, in addition to Watson–Crick pairing with cytosine,<sup>8–11</sup> self-pairing following hemi-deprotonation<sup>12,13</sup> or complete deprotonation,<sup>14</sup> also pairing between deprotonated, platinated guanine and neutral, unplatinated guanine has been observed.<sup>14</sup> In the course of these studies we also noticed that the combination of a platinated guanine and a properly spaced second nucleobase gives rise to novel H-bonding interactions of the guanine ligand. For example, *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(mcyt-*N*<sup>3</sup>)-(egua-*N*<sup>7</sup>)]<sup>+</sup> (mcyt = 1-methylcytosine; egua = 9-ethylguanine anion) dimerises both in solution<sup>15</sup> and in the solid state<sup>16</sup> to produce a dimetalated base quartet displaying, among others, also two CH...N hydrogen bonds. This observation, hence the ability of the second base to act as a co-acceptor or co-donor in H bond formation with the guanine, prompted us to further pursue this aspect.

Here we report on H-bonding patterns of N(7) platinated 9-methylguanine (Hmgua) and, following deprotonation, of 9-methylguaninate (mgua) model nucleobases in the tris-(nucleobase) complex [Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)]<sub>3</sub><sup>2+</sup> **1**. The coplanar *head–head* orientation of two Pt-cross-linked and *trans*-oriented guanine nucleobases provided a unique opportunity for such a study.

## Experimental

### Starting materials and syntheses

Hmgua was purchased from Chemogen, Konstanz (Germany).

The model base mcyt was prepared according to the literature.<sup>17</sup> NH<sub>4</sub>[Pt(NH<sub>3</sub>)Cl<sub>3</sub>]·H<sub>2</sub>O<sup>18</sup> was synthesised from *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>-Cl<sub>2</sub>]<sup>19</sup> and HCl in a somewhat modified literature procedure and isolated as orange–yellow single crystals.

[Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)]<sub>3</sub>[NO<sub>3</sub>]<sub>2</sub>·6H<sub>2</sub>O **1a**. Hmgua (0.510 g, 3.09 mmol) was suspended in water (50 ml) and NH<sub>4</sub>[Pt(NH<sub>3</sub>)Cl<sub>3</sub>]·H<sub>2</sub>O (0.267 mg, 0.75 mmol) was added. The mixture was stirred for 8 d at 75 °C in a stoppered flask, then brought to room temperature and filtered from unreacted Hmgua. After addition of an excess of NaNO<sub>3</sub> (0.210 g, 2.5 mmol), **1a** precipitated and was filtered off (60% yield). Recrystallisation from hot water gave colourless crystals of **1a** suitable for X-ray crystallography (Found: C, 23.5; H, 3.8; N, 27.4. Calc. for pentahydrate C<sub>18</sub>H<sub>34</sub>N<sub>18</sub>O<sub>14</sub>Pt: C, 23.5; H, 3.7; N, 27.3%. Calc. for hexahydrate C<sub>18</sub>H<sub>36</sub>N<sub>18</sub>O<sub>15</sub>Pt: C, 23.1; H, 3.9; N, 26.9%).

[Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)]<sub>3</sub>[ClO<sub>4</sub>]<sub>1.35</sub>Cl<sub>0.65</sub>·4.1H<sub>2</sub>O **1b**. The compound was prepared in analogy to **1a**, but with NaClO<sub>4</sub> added instead of NaNO<sub>3</sub>, and isolated as colourless crystals (75% yield). It was characterised by <sup>1</sup>H NMR spectroscopy and X-ray analysis. Elemental analysis indicated a higher water content than X-ray analysis (Found: C, 21.9; H, 3.5; N, 22.8. Calc. for hexahydrate C<sub>18</sub>H<sub>36</sub>N<sub>16</sub>O<sub>14.4</sub>Cl<sub>2</sub>Pt: C, 22.2; H, 3.7; N, 23.0%).

{[Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)]<sub>2</sub>(mgua-*N*<sup>7</sup>)}{Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)}-{mcyt}<sub>4</sub>[ClO<sub>4</sub>]<sub>3</sub>·4H<sub>2</sub>O **2**. **1b** (0.078 g, 0.085 mmol) was dissolved in water at 70 °C and mcyt (0.054 g, 0.43 mmol) was added. The solution was allowed to cool to room temperature (pH 5.7). After 3 d, colourless crystals of **2** were harvested (20% yield). The stoichiometry of **2** was established by <sup>1</sup>H NMR spectroscopy, as subsequently confirmed by X-ray analysis.

### Crystallography

Intensity data for all crystal structures presented were collected on an Enraf-Nonius-KappaCCD (Mo-Kα = 0.71069 Å, graphite monochromator). Data processing was performed using DENZO and SCALEPACK.<sup>20</sup> The structures were solved by standard patterson methods<sup>21</sup> and refined by full-matrix least squares based on *F*<sup>2</sup> using the SHELXTL-PLUS<sup>22</sup> and SHELXL-93 programs.<sup>23</sup> Because of the poor parameter to observed reflections ratio in all three compounds, only the

† Electronic supplementary information (ESI): packing of pairs of **1a**. See <http://www.rsc.org/suppdata/dt/b0/b004993j/>

**Table 1** Crystallographic data for compounds **1a**, **1b** and **2**

	<b>1a</b>	<b>1b</b>	<b>2</b>
Chemical formula	C <sub>18</sub> H <sub>36</sub> N <sub>18</sub> O <sub>15</sub> Pt	C <sub>36</sub> H <sub>64.4</sub> N <sub>32</sub> O <sub>25</sub> Cl <sub>4</sub> Pt <sub>2</sub>	C <sub>28</sub> H <sub>41.5</sub> N <sub>22</sub> O <sub>13</sub> Cl <sub>1.5</sub> Pt
<i>M</i> /g mol <sup>−1</sup>	936.74	1877.58	1142.60
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	<i>P</i> 2 <sub>1</sub> / <i>c</i>	<i>P</i> 1̄	<i>P</i> 1̄
<i>a</i> /Å	12.669(3)	10.944(2)	10.236(2)
<i>b</i> /Å	19.594(4)	14.955(3)	15.115(3)
<i>c</i> /Å	14.038(3)	21.437(4)	15.132(3)
<i>α</i> /°		73.67(3)	68.99(3)
<i>β</i> /°	103.55(3)	76.98(3)	87.16(3)
<i>γ</i> /°		82.08(3)	73.72(3)
<i>V</i> /Å <sup>3</sup>	3387.7(13)	3270.0(11)	2094.5(7)
<i>T</i> /K	293(2)	293(2)	293(2)
<i>Z</i>	4	2	2
<i>μ</i> (Mo-Kα)/mm <sup>−1</sup>	4.235	4.539	3.535
2θ Range/°	9.7–51.6	6.3–47.1	6.3–41.6
No. reflections collected	6436	9188	4156
No. independent reflections [ <i>I</i> > 2σ( <i>I</i> )]	6436	9188	4156
<i>T</i> <sub>max</sub> / <i>T</i> <sub>min</sub>	0.6768/0.8161	0.3849/0.5899	0.4719/0.6565
<i>R</i> <sub>int</sub>	0.165	0.085	0.781
<i>R</i> 1 (obs. data) <sup>a</sup>	0.0732	0.0509	0.0546
<i>wR</i> 2 (obs. data) <sup>a</sup>	0.1370	0.0962	0.0925

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

heavy atoms and a part of the exocyclic atoms of the nucleobases were refined anisotropically. The occupancy factors of the perchlorate (70%) and the chloride (30%) ion in **1b** were determined by applying similar temperature factors for both chlorine atoms and refining the occupancy thus reaching a minimum in the *wR*2 value. The 8.2 water molecules in **1b** are strongly disordered and spread over 18 positions. Crystal data and data collection parameters are summarised in Table 1.

CCDC reference number 186/2111.

See <http://www.rsc.org/suppdata/dt/b0/b004993j/> for crystallographic files in cif format.

### Spectroscopic measurements

Proton NMR spectra were recorded on Bruker AC200 and DRX400 FT spectrometers in D<sub>2</sub>O and Me<sub>2</sub>SO-*d*<sub>6</sub> solutions using sodium 3,3,3-trimethylpropanesulfonate and tetramethylsilane as internal references. Values of pD (D<sub>2</sub>O solutions) were determined by use of a glass electrode and addition of 0.4 units to the pH meter reading.<sup>24</sup> D<sub>2</sub>O solutions of NaOD were applied to adjust pD values.

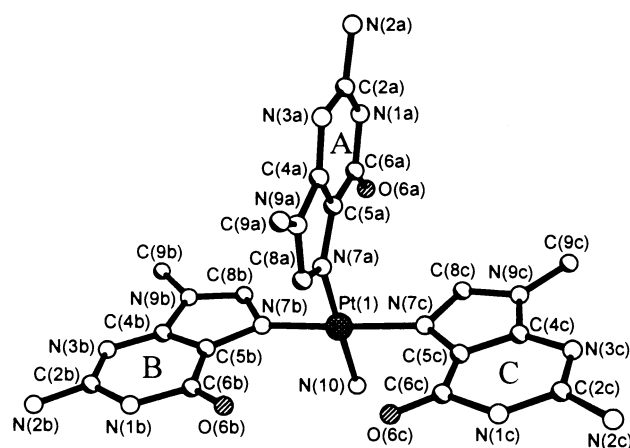
## Results and discussion

### Tris(guanine) complexes **1a** and **1b**

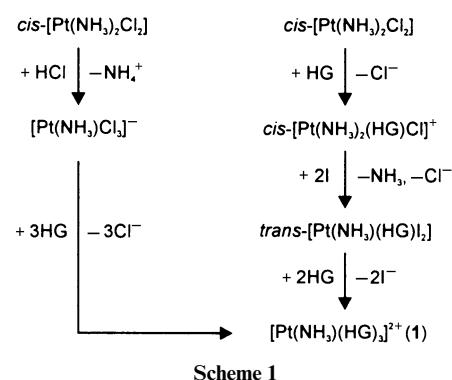
Complexes of composition [Pt(NH<sub>3</sub>)(HG-*N*<sup>7</sup>)<sub>3</sub>]<sup>2+</sup> **1** with HG = 9-methylguanine, Hmgua or 9-ethylguanine, Hegua, are obtained either by reaction of [Pt(NH<sub>3</sub>)Cl<sub>3</sub>]<sup>−</sup> with an excess of HG or, alternatively, from *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>(HG)Cl]Cl via *trans*-[Pt(NH<sub>3</sub>)(HG)I<sub>2</sub>] and subsequent displacement of the two iodo ligands by HG (Scheme 1).<sup>25</sup>

[Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)<sub>3</sub>][NO<sub>3</sub>]<sub>2</sub>·6H<sub>2</sub>O **1a** and [Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)<sub>3</sub>][ClO<sub>4</sub>]<sub>1.35</sub>[Cl]<sub>0.65</sub>·4.1H<sub>2</sub>O **1b** were now obtained via the first route.

In the cation of **1a** the three bases are oriented *head–tail–head*, implying that the two *trans*-oriented bases are *head–head* (Fig. 1 and Table 2). It is noted that this arrangement is also realised in the majority of other tris(nucleobase) complexes known to date, e.g. in [M(NH<sub>3</sub>)(mcyt-*N*<sup>3</sup>)<sub>3</sub>]<sup>2+</sup> (M = Pt<sup>II</sup>,<sup>26</sup> Pd<sup>II</sup>,<sup>27</sup>), [Pt(mcyt-*N*<sup>3</sup>)<sub>3</sub>Cl]<sub>2</sub>,<sup>28</sup> and *trans*-[Pt(NH<sub>3</sub>)(mcyt-*N*<sup>3</sup>)<sub>2</sub>(Hmgua-*N*<sup>7</sup>)]<sup>2+</sup>.<sup>25</sup> In the latter case the *head–tail–head* description refers to the orientation of the exocyclic oxygen atoms of the three bases with respect to the metal coordination plane, which are *up,down,up* or +,−,+.<sup>29</sup> There are presently only two



**Fig. 1** View of cation of [Pt(NH<sub>3</sub>)(Hmgua-*N*<sup>7</sup>)<sub>3</sub>][NO<sub>3</sub>]<sub>2</sub>·6H<sub>2</sub>O **1a** with atom numbering scheme. The arrangement of the three nucleobases is *head–tail–head*.



**Scheme 1**

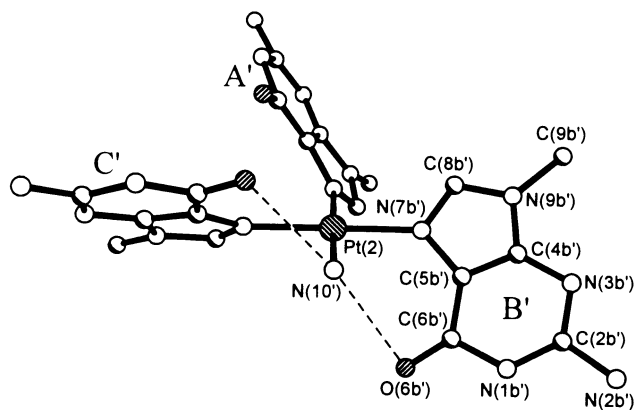
exceptions to this “rule”, namely in one of the two crystallographically different cations of **1b** (type II, see below) and in *trans*-[Pt(NH<sub>3</sub>)(mcyt-*N*<sup>3</sup>)(Hmgua-*N*<sup>7</sup>)<sub>2</sub>Na(H<sub>2</sub>O)<sub>2</sub>]<sup>3+</sup>.<sup>30</sup> In the latter case all exocyclic oxygen atoms are *up* (or +) as a consequence of binding of the alkali metal ion to the three oxygen donors.

There are two crystallographically independent cations in the asymmetric unit of **1b**. In one of the cations (cation I) the *head–tail–head* arrangement of the three nucleobases as seen in **1a** is adopted, while in the second one (cation II) the orientation is

**Table 2** Selected distances (Å) and angles (°) for [Pt(NH<sub>3</sub>)-(Hmgua)<sub>3</sub>]<sub>2</sub>X<sub>2</sub> (**1a** and **1b**)<sup>a</sup>

	<b>1a</b>	<b>1b</b> (cation I)	<b>1b</b> (cation II) <sup>b</sup>
Pt–N(10)	2.07(1)	2.036(9)	2.039(8)
Pt–N(7a)	1.99(1)	2.022(10)	2.033(9)
Pt–N(7b)	1.87(1)	2.004(9)	2.004(10)
Pt–N(7c)	2.01(1)	2.004(9)	2.034(10)
N(10)–Pt–N(7a)	177.9(5)	179.0(5)	178.0(4)
N(10)–Pt–N(7b)	89.9(4)	88.5(4)	88.0(4)
N(10)–Pt–N(7c)	90.2(5)	91.1(4)	91.6(4)
N(7a)–Pt–N(7b)	91.3(4)	91.4(4)	90.8(4)
N(7a)–Pt–N(7c)	88.8(5)	89.0(4)	89.6(4)
N(7b)–Pt–N(7c)	177.3(5)	178.5(4)	179.6(4)
N(10)···O(6b)	2.917(8) <sup>1</sup>	3.17(1)	3.03(1)
N(10)···O(6c)	2.792(9) <sup>1</sup>	2.92(1)	2.86(1)
N(1b)···O(6b)		2.89(1) <sup>2</sup>	
N(2b)···O(6c)		2.79(1) <sup>2</sup>	

<sup>a</sup> Symmetry operations: <sup>1</sup>  $-x + 1, -y + 1, -z + 1$ ; <sup>2</sup>  $-x + 2, -y + 1, -z + 1$ . <sup>b</sup> Atom numbering with '.

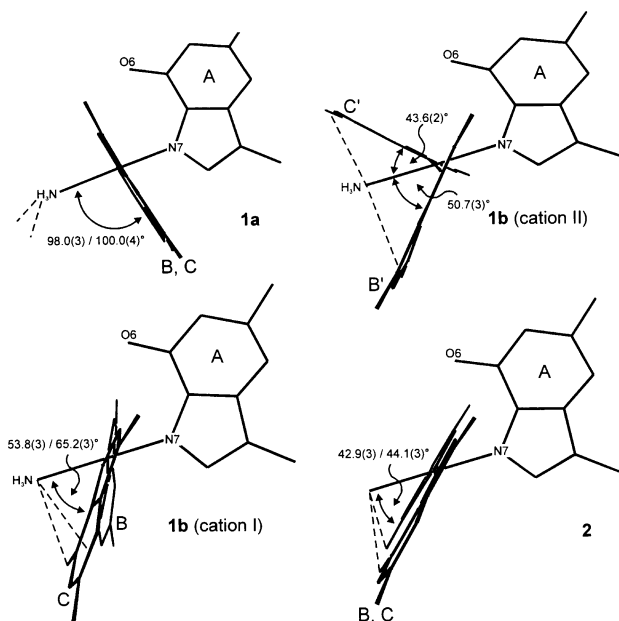


**Fig. 2** View of cation (type II) of **1b** with head-head-tail arrangement of the three guanine bases.

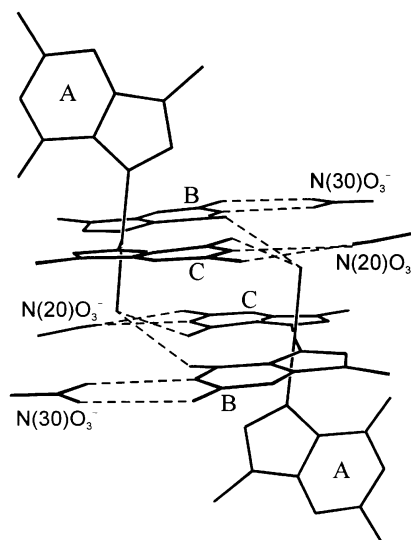
head-head-tail (Fig. 2). Salient structural features are listed in Table 2.

The similarities between the cation of **1a** and the type I cation of **1b** refer to the orientation of the three bases. There are differences as far as the angles between the *trans*-arranged guanine bases [close to coplanar in **1a**, angle 4.1(2)°; markedly propeller-twisted in type I cation of **1b**, angle 18.1(4)°], the angle between the Pt–N(7) vector of base A and the two other bases, and the packing patterns are concerned. In **1a**, the Pt–N(7) vector is almost perpendicular to the bases B and C [angles 100.0(4)° and 98.0(3)°], whereas the angles are only 65.2(3) and 53.8(3)°, respectively, in the case of type I cation in **1b** (Fig. 3). As a consequence only in the second case is there intramolecular H-bonding between the NH<sub>3</sub> ligand *trans* to N(7a) and the O(6) sites of bases B [3.17(1) Å] and C [2.92(1) Å]. In **1a** pairs of cations are associated *via* four intermolecular H-bonds involving the two NH<sub>3</sub> groups and the four O(6) oxygen atoms of the B and C bases. This arrangement is further stabilised by base stacking (3.4 Å) of the *trans*-oriented guanine bases of adjacent cations, and completed by H-bonding between the NO<sub>3</sub><sup>−</sup> anions and bases B and C (Fig. 4). This packing pattern appears to be quite common also for complexes of composition *trans*-[a<sub>2</sub>PtL(L')]<sup>2+</sup> (a = NH<sub>3</sub> or MeNH<sub>2</sub>; L, L' = nucleobase), except that the presence of an additional am(m)ine ligand permits further H-bonding between individual pairs, thus leading to an array of H-bonded cation pairs.<sup>31,32</sup> Each of the three bases in **1a** is involved in additional base stacking in the crystal lattice (ESI†).

Type I cations of **1b** interact in a completely different manner, namely through base pairing (Fig. 5). As a result, a



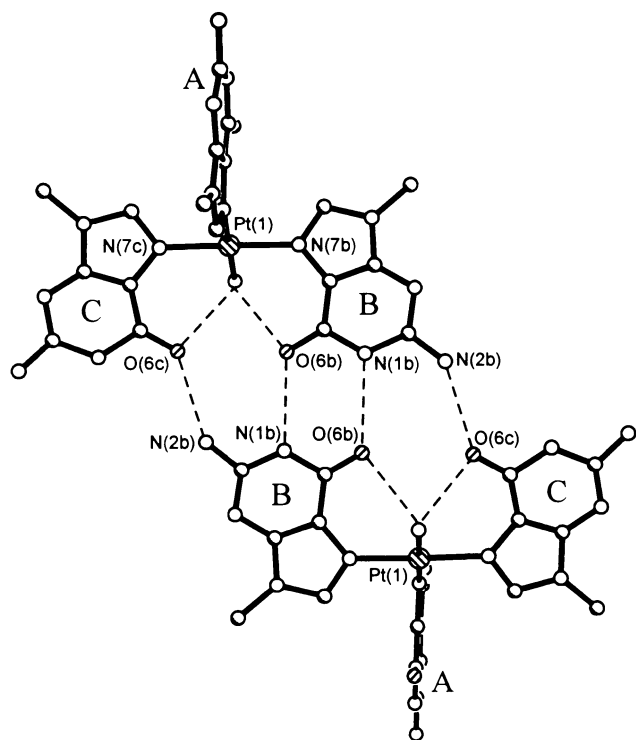
**Fig. 3** Relationship between angles built between PtN<sub>4</sub> plane and Hmgua planes and H-bonding properties of NH<sub>3</sub> ligands in **1a**, **1b** and **2**.



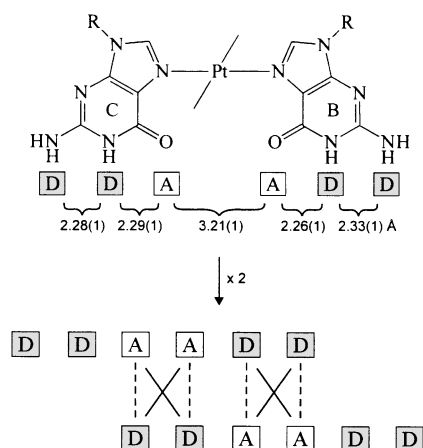
**Fig. 4** Packing diagram of pairs of cations of **1a**.

two-fold platinated nucleobase quartet structure is formed with intermolecular H-bonds of 2.79(1) Å [N(2b)···O(6c)] and 2.89(1) Å [N(1b)···O(6b)]. As can be seen (Fig. 6, top), the two *trans*-positioned guanine bases B and C provide an array of six sites capable of acting as H-bond donors (D) and acceptors (A), giving a sequence DDAADD. Clearly, only if the two sequences slide past each other is there a possibility for H-bonding interactions (Fig. 6, bottom).

Consequently, out of the 12 potential H-bonding sites only 8 are utilised. Formally within the four intermolecular H-bonds four attractive and two repulsive secondary electrostatic interactions<sup>4a,33</sup> exist. We do not wish to overemphasize this aspect considering the fact that separations between acceptor and donor sites are uneven (*cf.* Fig. 6, top) and that repulsive secondary interactions not necessarily allow prediction of the overall stability. For example, the homo guanine pair with a pair of H-bonds between N(1)H and O(6), which has two repulsive secondary electrostatic interactions, is the most stable homo pair of all nucleobases in the gas phase and almost as stable as the Watson–Crick pair between G and C.<sup>34</sup>



**Fig. 5** Association of pairs of type I cations of **1b** (*head-tail-head*) to a twofold platinated nucleobase quartet. The guanine ligands A do not participate in base pair formation.



**Fig. 6** Sequence of D and A sites at *head-head* oriented guanines (top) and sliding motion to give an H-bonding pattern observed between type I cations of **1b**. Attractive secondary electrostatic interactions in the center of the array are indicated by a cross.

In the type II cation of **1b**, the two *trans*-positioned bases are no longer *head-head* but rather *head-tail*, *viz.* these two bases have their O(6) oxygen atoms at different sides of the PtN<sub>4</sub> co-ordination plane. The interconversion **1a** → **1b** requires essentially only three steps: loss of one of the two intramolecular H bonds between NH<sub>3</sub> and O(6) of guanine, rotation of *ca.* 70° of this guanine past the NH<sub>3</sub> ligand, and reformation of the intramolecular H bond from the other Pt side. Depending on which of the two bases (B or C) is rotating, the two enantiomers present in the solid state are formed. Bases B' and C' are almost perpendicular to each other [86.6(2)°] in the type II cation of **1b**. There is also a tilting of base A' with respect to the PtN<sub>4</sub> co-ordination plane, but this represents no major principal difference to **1a**.

#### <sup>1</sup>H NMR spectra of **1**

The <sup>1</sup>H NMR spectra of **1a** and **1b** in D<sub>2</sub>O, pD 5 are identical

and consist of singlets in a 2:1 ratio at δ 8.14 [H(8), Hmgua's *trans* to each other] and 8.13 [H(8), Hmgua *trans* to NH<sub>3</sub>] as well as 3.72 (CH<sub>3</sub>, Hmgua's *trans* to each other) and 3.66 (CH<sub>3</sub>, Hmgua *trans* to NH<sub>3</sub>). These values compare with δ 7.75 and 3.64 for the free nucleobase and are consistent with expectations. There is no indication for the presence of different rotamers stable on the NMR time scale at ambient temperature. The <sup>1</sup>H NMR spectrum of **1b** in Me<sub>2</sub>SO-*d*<sub>6</sub> likewise is consistent with the presence of a single species. The two types of Hmgua bases are readily differentiated on the basis of their relative intensities. Chemical shifts are somewhat different from those in the solvent D<sub>2</sub>O, *viz.* δ 3.56 (CH<sub>3</sub>, ring A), 3.60 (CH<sub>3</sub>, rings B,C) and 8.20 [H(8), ring A], 8.13 [H(8), rings B,C], N(2)H<sub>2</sub> at δ 6.86 (ring A) and 6.92 (rings B,C) and the NH<sub>3</sub> group resonates at δ 4.69. Spectra recorded at different concentrations do not reveal significant differences of N(1)H and N(2)H<sub>2</sub> resonances in chemical shifts, therefore excluding any measurable association of cations of **1b** as seen in the solid state in this solvent.

The existence of two different rotamers in the solid state structure of **1b** (*head-tail-head* and *head-head-tail*) and the simplicity of the <sup>1</sup>H NMR spectrum of **1b** strongly suggest that the two rotamers interconvert quickly on the NMR time scale. As to the mechanism of this interconversion, we have pointed out (see above) that a relatively minor movement of one of the two *trans*-oriented guanine bases, namely a swing of the O(6) past the NH<sub>3</sub> ligand from one side of the Pt co-ordination plane to the other, is sufficient to accomplish the switch from *head-tail-head* to *head-head-tail*. Of course, the other *trans*-positioned guanine is capable of undergoing the identical movement. In summary, there appears to be no need for the guanine bases B or C to do an almost 300° rotation past the third guanine (A), which might lead to some steric interference between O(6) of B and C with the π system of base A.

In a related system, *trans*-[Pt(NH<sub>3</sub>)(Hmgua)<sub>2</sub>(mcyt)]<sup>2+</sup>, we found evidence from NOE cross-peaks for a similar rotamer equilibrium, even though individual resonances of the rotamers are not detected, even at -55 °C in dimethylformamide.<sup>30</sup>

As expected, chemical shifts of **1a** and **1b** in D<sub>2</sub>O exhibit a pD dependence at neutral to basic medium. The H(8) resonances of both sets of ligands start shifting upfield at pD > 6.5, consistent with the onset of guanine deprotonation at N(1). While the H(8) resonance of the two *trans*-positioned guanine ligands is constant (δ ≈ 7.92) at pD 8.5, the H(8) resonance of the guanine ligand *trans* to NH<sub>3</sub> reaches a maximum upfield shift of δ ≈ 8.00 at pD 8.5 before shifting again downfield (δ ≈ 8.10 at pD ≥ 11). Individual pK<sub>a</sub> values for deprotonation of the three guanine ligands could not be deduced. Moreover, above pD 8 a precipitate forms, which redissolves at pD > 10. It is unclear whether the precipitate consists of a neutral complex *e.g.* [Pt(NH<sub>3</sub>)(mgua)<sub>2</sub>(Hmgua)], or is due to a polymeric species associated *via* mgua...Hmgua triple hydrogen bonds.<sup>12,13</sup> We assume that in strongly basic medium, above pD 10, the soluble species formed is the anionic complex [Pt(NH<sub>3</sub>)(mgua)<sub>3</sub>]<sup>-</sup>.

#### Supramolecular aggregate with 1-methylcytosine in **2**

In an attempt to generate Watson-Crick base pairs between platinated Hmgua in **1b** and the model base mcyt (mcyt = 1-methylcytosine), **1b** was mixed with an excess of mcyt in water and the solution (pH 5.7) allowed to crystallise. The crystals isolated were shown by <sup>1</sup>H NMR spectroscopy to contain guanine and cytosine in a 3:2 ratio. X-Ray crystallography revealed the compound to be [{Pt(NH<sub>3</sub>)(Hmgua)<sub>2</sub>(mgua)}-{Pt(NH<sub>3</sub>)(Hmgua)<sub>3</sub>}{mcyt<sub>4</sub>}] [ClO<sub>4</sub>]<sub>3</sub>·4H<sub>2</sub>O **2**. Crystallisation of a compound containing a N(1) deprotonated 9-methylguanine ligand (mgua) was rather unexpected considering the acidic pH of its formation and the pK<sub>a</sub> values observed for N(7) platinated guanine nucleobases, which are generally around 7.8–8<sup>35</sup> (see also above).

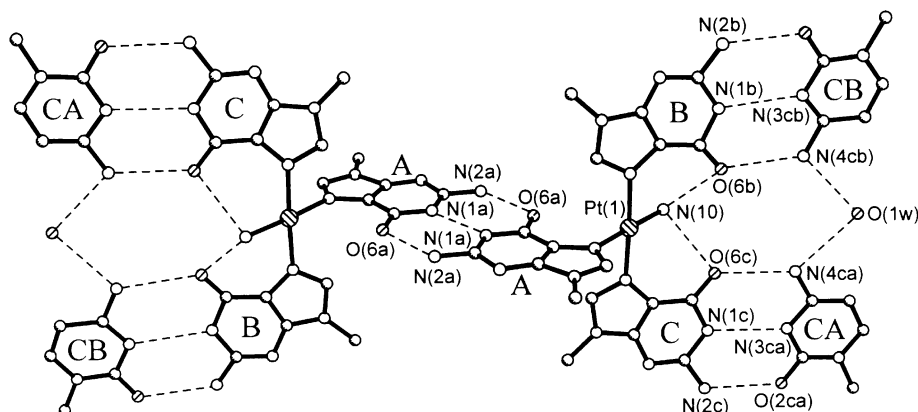


Fig. 7 View of supramolecular cation of **2** consisting of two [guanine, cytosine]<sub>2</sub> quartets and a guanine, guaninate base pair.

Table 3 Selected distances (Å) and angles (°) for **2**<sup>a</sup>

Pt(1)–N(10)	2.023(9)	N(10)···O(6b)	2.91(2)
Pt(1)–N(7a)	2.00(1)	N(10)···O(6c)	2.87(1)
Pt(1)–N(7b)	2.02(1)	N(1a)···N(1a) <sup>1</sup>	2.86(2)
Pt(1)–N(7c)	2.02(1)	N(2a)···O(6a) <sup>1</sup>	2.84(2)
N(10)–Pt(1)–N(7a)	178.3(5)	N(1b)···N(3cb)	2.90(2)
N(10)–Pt(1)–N(7b)	91.3(4)	N(2b)···O(2cb)	2.77(2)
N(10)–Pt(1)–N(7c)	90.4(4)	O(6b)···N(4cb)	2.92(2)
N(7a)–Pt(1)–N(7b)	90.1(4)	N(1c)···N(3ca)	2.89(2)
N(7a)–Pt(1)–N(7c)	88.3(4)	N(2c)···O(2ca)	2.81(2)
N(7b)–Pt(1)–N(7c)	177.3(6)	O(6c)···N(4ca)	2.84(2)
		N(4ca)···O(1w) <sup>2</sup>	2.93(2)
		N(4cb)···O(1w) <sup>2</sup>	2.95(2)

<sup>a</sup> Symmetry operations: <sup>1</sup>  $-x + 1, -y + 1, -z + 1$ ; <sup>2</sup>  $-x + 1, -y + 2, -z + 1$ .

The supramolecular cation **2** is depicted in Fig. 7 and salient structural features are listed in Table 3. The centrosymmetric compound consists of two subunits of tris-(guanine)ammine–platinum(II) species joined by three H-bonds between a neutral Hmgua and an anionic mgua, of four mcyt bases H-bonded to the pairs of *trans*-positioned Hmgua ligands in Watson–Crick manner, and of two water molecules. The arrangement of the three guanine bases in **2** is again *head–tail–head* as in **1a** and type I cation of **1b**. The orientation of the base *trans* to NH<sub>3</sub> is similar to that of **1b**. Specifically the angles between the Pt–N(7a) vector and the approximately coplanar bases B and C are 42.9(3) and 44.1(3)° (*cf.* also Fig. 2). As a consequence, the NH<sub>3</sub> ligand is again within intramolecular H-bonding reach of O(6b) [2.92(2) Å] and O(6c) [2.87(1) Å], respectively.

The two guanine bases (A) that undergo self-pairing are crystallographically identical, meaning that the single proton between the two N(1a) positions of the neutral and the deprotonated guanine ligand has to be disordered over two positions. Details of the hemideprotonated guanine pair in **2** is similar to that seen in *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(tmade)(Hegua)]·[Pt(NH<sub>3</sub>)<sub>2</sub>(tmade)(egua)]·[ClO<sub>4</sub>]<sub>2</sub>·[NO<sub>3</sub>]<sub>2</sub>·1.6H<sub>2</sub>O<sup>13</sup> (tmade = N<sup>6</sup>, N<sup>6</sup>, N<sup>9</sup>-trimethyladenine) as far as coplanarity of the bases and H-bond lengths are concerned, which are 2.84(2) Å for **2** (Table 3). It is noted that in the guanine self-pair found in *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>(mcyt)(Hegua)]·[Pt(NH<sub>3</sub>)<sub>2</sub>(mcyt)(egua)]<sup>3+12</sup> H-bonds between N(1) sites [2.73(1) Å] and N(2) and O(6) positions [2.99(1) Å] differ significantly as a consequence of a rather large propeller twist of 39(1)° between the two guanines. As in the tmade compound<sup>13</sup> the Pt–N(7) and N(1)–N(1) vectors form a characteristic Z shape with angles between the bars of the Z that are virtually identical [80.4(5)° in **2**; 79.4(3)° in tmade compound] [Fig. 8(a)]. The Watson–Crick pairs between the two *trans*-positioned Hmgua ligands and the mcyt bases are not unusual. The two bases deviate only slightly from coplanarity [propeller twist angles 4.6(7)° for bases B and CB and 5.0(8)° for

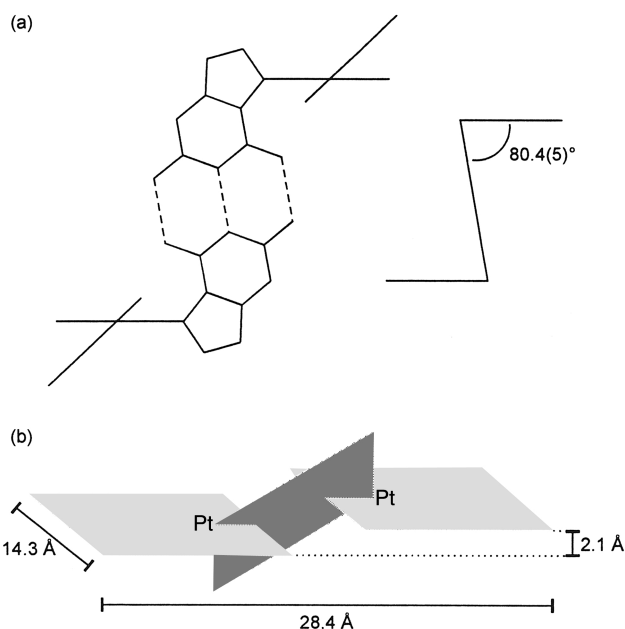
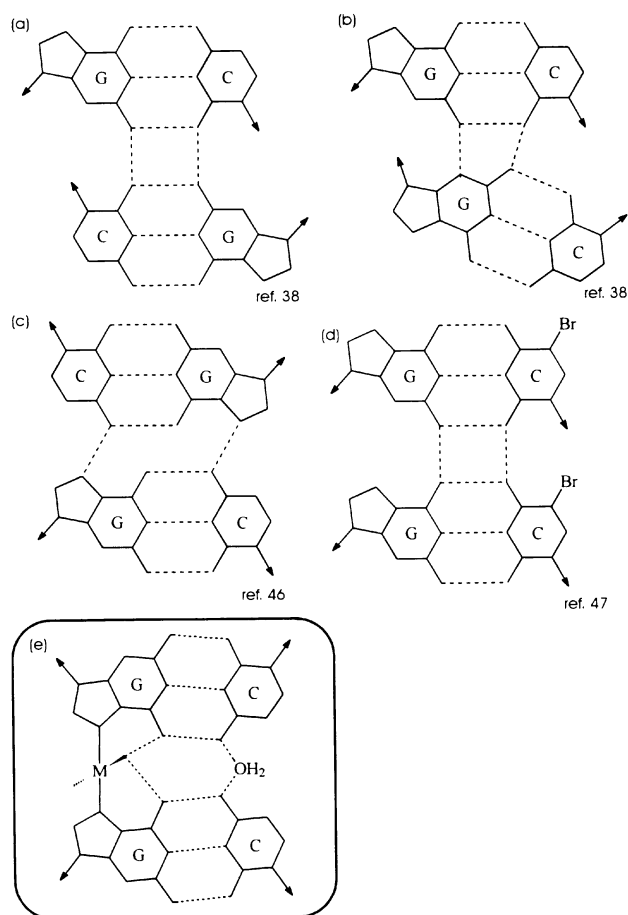


Fig. 8 Details of supramolecular compound **2**: central guanine, guaninate pair (a); staircase arrangement and dimensions of **2** (b).

C and CA] and display H-bond lengths [2.81(2)–2.92(2) Å] that are in the range seen for Watson–Crick pairs between N(7) platinated guanine bases and cytosine such as in *trans*-[Pt(MeNH<sub>2</sub>)<sub>2</sub>(mcyt)(Hegua)]·[mcyt]<sub>2</sub><sup>2+</sup>,<sup>8</sup> in [Pt(en)(Hegua)<sub>2</sub>·[mcyt]<sub>2</sub>]<sup>2+</sup>,<sup>9b</sup> or in a diplatinated base quartet containing a Hegua and a mcyt entity.<sup>10</sup> A comparison with the non-metallated Watson–Crick base pair between G and C in the RNA fragment GpC<sup>36</sup> reveals that there is a trend to shorter H bonding distances in **2**. The near coplanarity of the base quartet formed by *trans*-Pt(Hmgua)<sub>2</sub> and the two mcyt bases is reinforced by the water molecule O(1w) which functions as an acceptor for two amino protons of two cytosine bases [N(4ca)···O(1w) 2.93(2) Å, N(4cb)···O(1w) 2.95(2) Å] (see also below).

The supramolecular cation **2** has dimensions of *ca.* 14.3 × 28.4 Å (between methyl groups of the mcyt bases). The four Watson–Crick pairs in **2** are arranged like two treads of a stair, which are at a distance of *ca.* 2.1 Å. The guanine, guaninate pair is perpendicular to the treads, acting as a central railing of the staircase [Fig. 8(b)].

Geometries of the three different guanine rings are identical within standard deviations. This even refers to the internal ring angles at N(1), which are expected to be larger in the case of neutral guanine ligands as compared to deprotonated ones. However, the disorder of the proton at N(1) of A minimises any difference.



**Fig. 9** Previously established  $[GC]_2$  quartet structures (a),<sup>38</sup> (b),<sup>38</sup> (c),<sup>46</sup> (d)<sup>47</sup> and novel metalated  $[GC]_2$  quartet seen in **2** (e).

The perchlorate counter ions form H-bonds with water molecules and are engaged in contacts with aromatic H(8) and aliphatic N(9)CH<sub>3</sub> protons of guanine bases. None of these are unusually short.

#### An interesting detail: metalated [guanine,cytosine]<sub>2</sub> base quartets in **2**

The feature of guanine,cytosine pairing, as seen in **2**, which results in formation of two nucleobase quartets, deserves some more comments and discussion. Interest in nucleobase quartet structures and four-stranded nucleic acids as well as the question of their potential biological relevance is rapidly increasing.<sup>37</sup> Apart from base quartets formed exclusively through H-bonding, *e.g.* via DNA duplex dimerisation,<sup>38</sup> or formed under the influence of alkali metal ion binding, *e.g.* in guanine,<sup>39</sup> uracil or thymine quartets,<sup>7,40</sup> there exists also the possibility that abiological metal ions are capable of producing or stabilising quartet structures following co-ordinative binding to nucleobase sites. For example, Shin and Eichhorn<sup>41</sup> have demonstrated that Ag<sup>+</sup> ions are capable of producing tetrastranded aggregates of poly(inosine) and a putative model compound has been reported.<sup>42</sup> Applying linear *trans*-a<sub>2</sub>Pt<sup>II</sup> (a = NH<sub>3</sub> or MeNH<sub>2</sub>) units and/or linear Hg<sup>II</sup> ions we have prepared and characterised in recent years a series of metal-modified nucleobase quartets containing two,<sup>9a,10,13,15,16,43</sup> three<sup>44,45</sup> or more<sup>45</sup> metal ions.

As far as a dimerisation of two guanine,cytosine Watson–Crick pairs to quartet structures is concerned, four basic arrangements have been observed as a result of crystal packing of oligonucleotides or model nucleobases [Fig. 9(a)–(d)].<sup>38,46,47</sup> In all instances two more intermolecular H bonds are formed between Watson–Crick pairs in addition to the standard 2 × 3 H bonds in the two Watson–Crick pairs. Slight modifications of the motif shown in Fig. 9(c), with Watson–Crick G,C pairs

aligning along the major groove edges, have been observed in several quadruplex solution structures applying sophisticated NMR spectroscopy.<sup>48</sup> In **2** again 8 H bonds exist, but two involve a water molecule [Fig. 9(e)]. In addition, however, there are also two M–N bonds as well as two H bonds from the ancillary NH<sub>3</sub> ligand at the metal to the O(6) acceptor atoms, which make this [guanine,cytosine]<sub>2</sub> quartet energetically more stable than the former ones. Unlike in the situations depicted in Fig. 9(a), (b) and (d), the glycosidic bonds in **2** are pointing outside, very much as in G<sub>4</sub>, U<sub>4</sub> and T<sub>4</sub> quartet structures as well as in the centrosymmetric species depicted in Fig. 9(c). We conclude that the motif seen in **2** might be ideally suited for four-stranded nucleic acid structures. Moreover we propose that any metal ion capable of cross-linking the N(7) positions of two guanine bases in a linear fashion, regardless if two-co-ordinate, *trans*-square-planar, or *trans*-octahedral, could stabilise such an arrangement, in principle. An aqua ligand at the metal ion could easily replace the ammonia ligand(s) present in **2**.

#### Solution structure of **2**

As pointed out above, the integrals of the guanine and cytosine resonances in the <sup>1</sup>H NMR spectrum of **2** are consistent with the stoichiometry of compound **2**. Individual resonances of **2** (DMSO-d<sub>6</sub>, 7.5 mmol l<sup>-1</sup>) are observed at δ 11.63 [N(1)H of guanine], 8.11 [H(8) of Hmgua-B,C], 7.61 [H(6) of mcyt, d, <sup>3</sup>J 7.6 Hz], 7.05 (NH<sub>2</sub> of guanine and mcyt), 5.66 [H(5) of mcyt, d], 4.89 (NH<sub>3</sub>), 3.60 (CH<sub>3</sub> of Hmgua-B,C), 3.57 (CH<sub>3</sub> of guanine-A) and 3.24 (CH<sub>3</sub> of mcyt). It does not however, provide any indication of the protonation state of **2**. In Me<sub>2</sub>SO-d<sub>6</sub>, both the N(1)H resonances of the Hmgua ligands and the N(2)H<sub>2</sub> and N(4)H<sub>2</sub> resonances of Hmgua and mcyt ligands undergo downfield shifts with increasing concentrations. A differentiation of these resonances into the two *trans* positioned Hmgua ligands and the guanine ligand *trans* to NH<sub>3</sub> is not possible. In fact, the N(1)H signal is very broad and the NH<sub>2</sub> resonances of the guanine and cytosine bases overlap over a wide range. Thus, although the concentration dependence is consistent with intermolecular H bonding between guanine and cytosine according to Watson and Crick, no firm conclusions concerning the existence of the interguanine pair can be obtained from the <sup>1</sup>H NMR spectra in Me<sub>2</sub>SO-d<sub>6</sub>. However, we note that we have recently quantified the strength of H-bonding between N(7) platinated guanine and free cytosine on one hand,<sup>9</sup> and of self-pairing of Pt(HG)⋯(G)Pt<sup>49</sup> on the other in systems displaying the one *or* the other H-bonding pattern. It was found that N(7) platination of guanine increases the strength of the Watson–Crick pair by a factor of 2–3<sup>9</sup> and that the hemideprotonated guanine pair has an association constant in Me<sub>2</sub>SO-d<sub>6</sub> which is higher by a factor 80–100 than the Watson–Crick pair.<sup>49</sup> Taken together, these data strongly suggest that the arrangement seen for **2** in the solid state is also relevant in solutions of low dielectric constant.

#### Summary

In continuation of our previous work on metal-modified nucleobase pairs, triplets and larger aggregates,<sup>50</sup> we have studied a Pt<sup>II</sup> complex containing three guanine model nucleobases. The particular alignment of two of its bases (*trans*-arrangement and *head–head* orientation) gives rise to several interesting pairing patterns which lead to larger, H-bonded entities. These include (i) self-association through H-bond formation to give a twofold metalated guanine quartet, (ii) Watson–Crick pairing with cytosine to produce a metalated mixed guanine,cytosine quartet and (iii) additional association through guanine, guanine self-pairing following hemi-deprotonation of the third guanine base.

## Acknowledgements

Support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

## References

- 1 V. A. Bloomfield, *Curr. Opin. Struct. Biol.*, 1996, **6**, 334 and references therein; J. G. Duguid and V. A. Bloomfield, *Biophys. J.*, 1995, **69**, 2642.
- 2 V. N. Potaman and V. N. Soyfer, *J. Biomol. Struct. Dyn.*, 1994, **11**, 1035; M. Ortiz-Lombardia, E. Jimenez-Garcia, I. Garcia-Bassets and F. Azorin, *J. Biomol. Struct. Dyn.*, 1998, **16**, 243 and references therein.
- 3 G. Villani, N. Tanguy Le Gac and J.-S. Hoffmann, *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug*, ed. B. Lippert, VCHA Zürich and Wiley-VCH, Weinheim, 1999, p. 135; L. J. N. Bradley, K. J. Yarema, S. J. Lippard and J. M. Essigman, *Biochemistry*, 1993, **32**, 982; D. Burnouf, C. Gauthier, J. C. Chottard and R. P. P. Fuchs, *Proc. Natl. Acad. Sci. USA*, 1990, **87**, 6087.
- 4 (a) A. D. Burrows, C.-W. Chan, M. M. Chowdhry, J. E. McGrady and D. M. P. Mingos, *Chem. Soc. Rev.*, 1995, 329 and references therein; (b) S. L. James, D. M. P. Mingos, X. Xu, A. J. P. White and D. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 1335 and references therein; (c) S. Ulvenlund, A. S. Georgopoulou, D. M. P. Mingos, I. Baxter, S. E. Lawrence, A. J. P. White and D. J. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 1869 and references therein.
- 5 B. Linton and A. D. Hamilton, *Chem. Rev.*, 1997, **97**, 1669 and references therein.
- 6 J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995.
- 7 B. Fischer, H. Preut, B. Lippert, H. Schöllhorn and U. Thewalt, *Polyhedron*, 1990, **9**, 2199; H. Witkowski, E. Freisinger and B. Lippert, *Chem. Commun.*, 1997, 1315.
- 8 I. Dieter-Wurm, M. Sabat and B. Lippert, *J. Am. Chem. Soc.*, 1992, **114**, 357.
- 9 (a) R. K. O. Sigel and B. Lippert, *Chem. Commun.*, 1999, 2167; (b) R. K. O. Sigel, E. Freisinger and B. Lippert, *J. Biol. Inorg. Chem.*, 2000, **5**, 287.
- 10 R. K. O. Sigel, S. M. Thompson, E. Freisinger and B. Lippert, *Chem. Commun.*, 1999, 19.
- 11 M. S. Lüth, E. Freisinger and B. Lippert, *Chem. Eur. J.*, to be submitted.
- 12 R. Faggiani, C. J. L. Lock and B. Lippert, *J. Am. Chem. Soc.*, 1980, **102**, 5418; R. Faggiani, B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem.*, 1982, **21**, 3216.
- 13 C. Meiser, E. Freisinger and B. Lippert, *J. Chem. Soc., Dalton Trans.*, 1998, 2059.
- 14 G. Schröder, B. Lippert, M. Sabat, C. J. L. Lock, R. Faggiani, B. Song and H. Sigel, *J. Chem. Soc., Dalton Trans.*, 1995, 3767.
- 15 S. Metzger and B. Lippert, *J. Am. Chem. Soc.*, 1996, **118**, 12467.
- 16 R. K. O. Sigel, E. Freisinger, S. Metzger and B. Lippert, *J. Am. Chem. Soc.*, 1998, **120**, 12000.
- 17 T. J. Kistenmacher, M. Rossi, J. P. Caradonna and L. G. Marzilli, *Adv. Mol. Relaxation Interact. Processes*, 1979, **15**, 119.
- 18 A. Oksanen and M. Leskelä, *Acta Chem. Scand.*, 1994, **48**, 485.
- 19 G. Raudaschl-Sieber, B. Lippert, J. D. Hoeschele, H. E. Howard-Lock, C. J. L. Lock and P. Pilon, *Inorg. Chim. Acta*, 1985, **106**, 141.
- 20 Z. Otwinowsky and W. Minor, DENZO and SCALEPACK, *Methods Enzymol.*, 1997, **276**, 307.
- 21 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
- 22 G. M. Sheldrick, SHELXTL-PLUS (VMS), Siemens Analytical X-Ray Instruments, Inc. Madison, WI, 1990.
- 23 G. M. Sheldrick, SHELXL 93, Program for Crystal Structure Refinement, University of Göttingen, 1993.
- 24 R. Lumry, E. L. Smith and R. R. Glantz, *J. Am. Chem. Soc.*, 1981, **73**, 4335.
- 25 A. Hegmans, M. Sabat, I. Baxter, E. Freisinger and B. Lippert, *Inorg. Chem.*, 1998, **37**, 4921.
- 26 R. Faggiani, C. J. L. Lock and B. Lippert, *Inorg. Chim. Acta*, 1985, **106**, 75.
- 27 D. Holthénrich, E. Zangrando, F. Pichierri, L. Randaccio and B. Lippert, *Inorg. Chim. Acta*, 1996, **248**, 175.
- 28 A. Hegmans, E. Freisinger, E. Zangrando, A. Ashfar, E. Hübener, T. G. Appleton and B. Lippert, *Inorg. Chim. Acta*, 1998, **279**, 152.
- 29 For a discussion of other stereodescriptors for chiral square planar complexes, see: M. C. Biagini, M. Ferrari, M. Lanfranchi, L. Marchio and M. A. Pellinghelli, *J. Chem. Soc., Dalton Trans.*, 1999, 1575.
- 30 E. Freisinger, A. Schneider, M. Drumm, A. Hegmans, S. Meier and B. Lippert, *J. Chem. Soc., Dalton Trans.*, 2000, 10.1039/b004906i.
- 31 See, e.g.: S. Metzger, A. Erxleben and B. Lippert, *J. Biol. Inorg. Chem.*, 1997, **2**, 256.
- 32 F. Zamora, H. Witkowski, E. Freisinger, J. Müller, B. Thormann, A. Albinati and B. Lippert, *J. Chem. Soc., Dalton Trans.*, 1999, 175.
- 33 W. L. Jorgensen and D. L. Severance, *J. Am. Chem. Soc.*, 1991, **113**, 209; J. Pranata, S. G. Wierschke and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1991, **113**, 2810.
- 34 P. Hobza and C. Sandorfy, *J. Am. Chem. Soc.*, 1987, **109**, 1302.
- 35 B. Song, J. Zhao, R. Griesser, C. Meiser, H. Sigel and B. Lippert, *Chem. Eur. J.*, 1999, **5**, 2374.
- 36 J. M. Rosenberg, N. C. Seeman, R. O. Day and A. Rich, *J. Mol. Biol.*, 1976, **104**, 145.
- 37 See e.g.: D. Kipling, *The Telomere*, Oxford University Press, Oxford, UK, 1995.
- 38 M. C. Wahl and M. Sundaralingam, *Biopolymers*, 1997, **44**, 45 and references therein; G. A. Leonard, S. Zhang, M. R. Peterson, S. J. Harrop, J. R. Helliwell, W. B. T. Cruse, B. Langlois d'Estaintot, O. Kennard, T. Brown and W. N. Hunter, *Structure*, 1995, **3**, 335; P. M. Takahara, C. A. Frederick and S. J. Lippard, *J. Am. Chem. Soc.*, 1996, **118**, 12309.
- 39 C. H. Kang, X. Zhang, R. Ratliff, R. Moyzis and A. Rich, *Nature*, 1992, **356**, 126; G. Laughan, A. I. H. Murchie, D. G. Norman, M. H. Moore, P. C. E. Moody, D. M. J. Lilley and B. Luisi, *Science*, 1994, **256**, 520; N. Spackova, I. Berger and J. Sponer, *J. Am. Chem. Soc.*, 1999, **121**, 5519 and references therein.
- 40 G. Gupta, A. E. Garcia, Q. Guo, M. Lu and N. R. Kallenbach, *Biochemistry*, 1993, **32**, 7098; N. H. Sarma, J. Luo, K. Umamoto, R.-d. Yuan and R. H. Sarma, *J. Biomol. Struct. Dyn.*, 1992, **9**, 1131; C. Cheong and R. B. Moore, *Biochemistry*, 1992, **31**, 8406.
- 41 Y. A. Shin and G. L. Eichhorn, *Biopolymers*, 1980, **19**, 539.
- 42 F. Bélanger-Gariépy and A. L. Beauchamp, *J. Am. Chem. Soc.*, 1980, **102**, 3461.
- 43 I. B. Rother, E. Freisinger, A. Erxleben and B. Lippert, *Inorg. Chim. Acta*, 2000, **300–302**, 339.
- 44 M. S. Lüth, E. Freisinger, F. Glahé, J. Müller and B. Lippert, *Inorg. Chem.*, 1998, **37**, 3195.
- 45 M. S. Lüth, E. Freisinger, F. Glahé and B. Lippert, *Inorg. Chem.*, 1998, **37**, 5044.
- 46 E. J. O'Brien, *Acta Crystallogr.*, 1967, **23**, 92.
- 47 H. M. Sobell, K.-I. Tomita and A. Rich, *Proc. Natl. Acad. Sci. USA*, 1963, **49**, 885.
- 48 A. Kettani, R. A. Kumar and D. J. Patel, *J. Mol. Biol.*, 1995, **254**, 638; S. Bouaziz, A. Kettani and D. J. Patel, *J. Mol. Biol.*, 1998, **282**, 637; A. Kettani, S. Bouaziz, A. Gorin, H. Zhao, R. A. Jones and D. J. Patel, *J. Mol. Biol.*, 1998, **282**, 619.
- 49 R. K. O. Sigel and B. Lippert, unpublished work.
- 50 B. Lippert, *J. Chem. Soc., Dalton Trans.*, 1997, 3971 and references therein.