Intramolecular Migration of Coordinated Platinum(II) from the N7 Site to the Exocyclic Amino Group in 9-Methyladenine

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The N7 sites of the guanine and adenine nucleobases are the major targets for anticancer Pt drugs and related compounds in DNA.[1−4] Because of the general inertness of Pt(II) and the high thermodynamic stability of the Pt−N bond, substitution of the nucleobases in the relevant Pt adducts is very difficult, even in the presence of strong nucleophiles (e.g., thiourea and CN^-).[5] In this respect, findings on relatively easy rearrangements of various Pt(II) bisadducts at the oligonucleotide level are of interest.[2,6,7] For example, rearrangement of *trans*-[$Pt(NH_3)_2${d(G*XG*)}] intrastrand adducts [X = A, T, C; the asterisk (*) denotes the platination site] into interstrand cross-links appears as soon as the platinated oligonucleotides are hybridized with their complementary ribonucleotide or deoxyribonucleotide strands.[6] Unfortunately, the exact mechanism of this type of rearrangement is not known, which makes model studies in this field highly desirable. Very recently, we have shown that Pt(II) migration from the endocyclic N1 site to the exocyclic NH_2 group occurs (with concomitant proton displacement) in 9-methyladenine in alkaline aqueous solution.[8] Although the exact migration mechanism has not yet been unequivocally determined, the platinum N1 → N6 migration in adenine proceeds without any detectable redox reaction thus differentiating it from the Pt migration from the ring nitrogen to the exocyclic amino group in platinated pyrimidine complexes, which involve Pt(IV) as an intermediate.[9−11] The readiness of the reaction (3 h, 65 °C) is a striking feature of the N1 → N6 migration, and we now report that the platinum N7 → N6 migration in adenine proceeds under basic conditions almost as easily as the N1 → N6 migration.

The employment of *trans*-[$Pt(OH)_2(NH_3)_2$]·$2H_2O$[12,13] as the platination agent offers a convenient way to prepare the N7-bound biscomplex of 9-methyladenine[14] (9-made). The reaction in acidic aqueous solution (to prevent N1 platination) yielded *trans*-[$Pt(NH_3)_2$(9-madeH-N7)$_2$](ClO_4)$_4$·$2H_2O$ (**1**) as colorless prisms in 75% yield after 10 days.[15,16] Treatment of **1** under basic conditions resulted in the migration of the coordinated Pt(II) from the endocyclic N7 site to the exocyclic NH_2 group, with a concomitant proton displacement, in one of the 9-made ligands to yield *trans*-[$Pt(NH_3)_2$(9-made-N6)(9-made-N7)](NO_3)$_2$·$2H_2O$ (**2**) as colorless plates.[19,20]

A thermal ellipsoid diagram for the dication of **2** is shown in Figure 1. The platinum atom has an almost idealized square-planar geometry, typical for these types of complexes. The Pt−N bond lengths in **2** are comparable, and indeed very similar, to those in **1** except that the Pt−N(6a) bond in **2** is significantly shorter than the Pt−NH_3 distances [excluding the Pt−N(10) bond in **2**]. Hydrogen bonding involving primarily the NH hydrogens with the nitrate and water oxygens stabilizes the packing of **2**. Most notable, though, is the intramolecular H-bond N(6b)···N(7a) 3.08(1) Å, which aids the coplanarity of the 9-made ligands [the dihedral angle between the base moieties is 13.8(3)°]. The packing is further stabilized by the stacking of the six-membered rings of the adjacent adenine bases in a head-to-tail fashion with a distance of ca. 3.5 Å between the centers of the rings. In **2**, the N6-platinated adenine bears a proton at N1, found from the electron density map. Thus, this neutral 9-made ligand exists in the rare imino form, analogous to the earlier reported Hg(II) complex also bearing the metal ion at the exocyclic N6 group.[22]

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(15) For the preparation of **1**, about 150 mg of 9-methyladenine (1 mmol) was dissolved in 20 mL of 0.15 M $HClO_4$ (3 mmol), followed by the addition of 150 mg of *trans*-[$Pt(OH)_2(NH_3)_2$]·$2H_2O$ (0.5 mmol). The reaction mixture was kept at ambient temperature for 10 days to yield **1** as colorless prisms. The crystals were filtered off, washed with cold water, and air-dried; yield 340 mg (75% from Pt). ^{1}H NMR (D_2O, 400 MHz): δ 8.954 (s, H8), 8.432 (s, H2), 3.985 (s, CH_3).
(16) The crystal structure analysis confirmed both the platination site and stoichiometry in **1**.[17,18]
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(19) For the preparation of **2**, about 100 mg of **1** (0.1 mmol) was suspended in 10 mL of 0.1 M NaOH in a stoppered tube. The mixture was kept in a boiling water bath for 2 h, after which the solution was neutralized with 1 M $HClO_4$ to pH 6 and then concentrated to ca. 5 mL. The solid material (55 mg) that precipitated overnight at 4 °C was filtered off and then dissolved in 0.25 mL of 0.5 M HNO_3; any undissolved material remaining was removed by centrifugation. The addition of 0.3 mL of DMF to the supernatant afforded crystals of **2** when left for 2 weeks at 4 °C. Finally, **2** was recrystallized from water. ^{1}H NMR (D_2O, 500 MHz, platination site in italics, minor species with an intensity of 10−20% of the major one in brackets): δ 8.999 [9.041] (s, H8, *N7*), 8.593 [8.611] (s, H2, *N7*), 8.220 [8.315] (s, H2, *N6*), 8.055 [8.302] (s, H8, *N6*), 4.023 [4.050] (s, CH_3, *N7*), 3.861 [3.878] (s, CH_3, *N6*). ^{195}Pt NMR (H_2O/D_2O, 107 MHz, relative intensity in parentheses): −2463 (0.8), −2517 (0.2).
(20) Crystal data for **2**: triclinic, $P\bar{1}$, a = 12.113(5) Å, b = 12.579(6) Å, c = 8.238(3) Å, α = 90.09(4)°, β = 96.93(3)°, γ = 110.60(3)°, V = 1165.2(9) Å^3, Z = 2, D_{calc} = 1.960 g/cm^3, T = 294 K, Rigaku AFC5S diffractometer, Mo Kα radiation (λ = 0.710 69 Å), 2 θ_{max} = 50°. Full-matrix least-squares refinement on F^2 based on 4108 reflections and 334 parameters gave $R1$ = 0.0817 and wR2 = 0.0812, GOF(F^2) = 1.029; computer program:[21] SHELXL 97.

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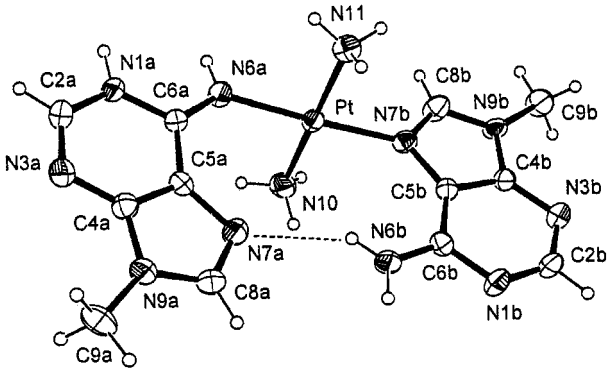

Figure 1. ORTEP[36] plot of the cation of *trans*-[Pt(NH$_3$)$_2$(9-made-*N*6)(9-made-*N*7)](NO$_3$)$_2$·2H$_2$O showing 30% probability ellipsoids. Selected interatomic distances (Å) and angles (deg): Pt−N(6a) 2.003(7), Pt−N(7b) 2.021(7), Pt−N(10) 2.035(7), Pt−N(11) 2.057(7), C(6a)−N(6a) 1.303(9), C(6b)−N(6b) 1.312(9), N(6a)−Pt−N(7b) 177.0(3), N(10)−Pt−N(11) 178.1(3), N(6a)−Pt−N(10) 91.3, N(6a)−Pt−N(11) 89.6(3), N(7b)−Pt−N(10) 90.5(3), N(7b)−Pt−N(11) 88.6(3), C(6a)−N(6a)−Pt 128.2(6).

Mechanistically, the formation of **2** is very interesting. The readiness of the reaction without additional 9-made is strongly suggestive of an intramolecular N7 → N6 substitution, since the route via hydrolysis of the Pt−N7 bond and formation of the Pt−N6 bond is highly unlikely for the following reasons. First, the hydrolysis of the Pt(II)−nucleobase bond is known to be extremely slow.[5,23] Second, at high pH the incoming aqua ligand[24] in the hydrolysis step would be immediately converted to the OH group, which can be considered substitution inert.[25] And finally, only traces of free 9-made were detected by HPLC during the N7 → N6 conversion, which effectively rules out an intermolecular reaction. Although the exocyclic NH$_2$ group of the adenine base is a poor coordination site for metal ions, a few examples of this binding mode are known.[8,22,26−30] In all cases the metal ion has displaced a proton in the NH$_2$ group, the pK_a of which is ca. 17 in uncomplexed nucleobase.[1] However, the attachment of electrophilic Pt(II) to any of the endocyclic ring nitrogens increases the acidity of the NH$_2$ group by ca. 4 log units.[1] This, together with the N6···Pt proximity of about 3.4 Å, leads to the suggestion that the N6 group in **1** can act as a powerful nucleophile for Pt(II) under basic conditions. The attack of NH$^-$ on platinum results in a five-coordinate intermediate, whereby cleavage of the presumably weaker Pt−N7 bond furnishes the N7 → N6 migration of Pt.

The novel Pt−N bond rearrangement found in this study lends strong support to a similar mechanistic explanation for the N1 → N6 migration, since in N1 platinated adenine derivatives the distance between N6 and Pt is shorter[8,31] and the influence of Pt(II) on the NH$_2$ acidity may even be stronger than in N7 bound species.[1] Importantly, though, the intramolecular N7 → N6 migration demonstrates the nucleophilic power of a nitrogen atom close to the metal center, which may therefore have important implications regarding the Pt−DNA rearrangements mentioned above. In fact, a few examples have shown that a nitrogen atom may even displace sulfur bound ligands from the Pt coordination sphere, despite the trans effect S > N.[5,32−35]

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Supporting Information Available: Crystallographic data for **2** including positional parameters, thermal parameters, interatomic distances and angles, torsion angles, hydrogen atom parameters, and possible hydrogen bonds; one X-ray crystallographic file, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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