Pt^{II} Binding to N1 of Cytosine: Strengthening the Watson–Crick Pair with Guanine and yet Confining Its pH Existence Range**

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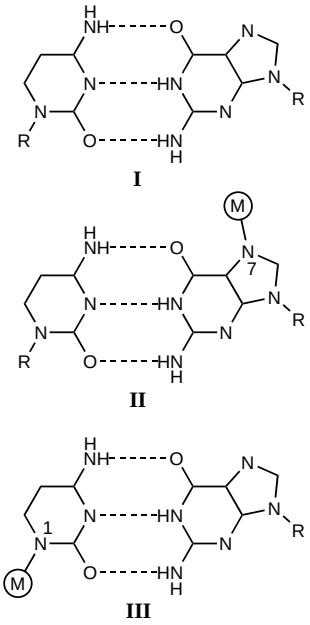
Metal coordination to a nucleobase donor atom remote from its hydrogen bonding sites neither prevents base-pair formation for steric reasons nor diminishes their strength. On the contrary, it enhances it. This effect, which was originally proposed by theoretical chemists and attributed to polarization effects of the metal ion as well as electrostatic attraction,[1] has recently been found to be also true for solutions of guanine nucleobases carrying a Pt^{II} entity at N7.[2] X-ray crystallographic results are consistent with this view.[2a, 3]

As will be shown here, the previously demonstrated case of Watson–Crick pairing between N7-platinated guanine and cytosine can be inverted by coordination of the metal to the cytosine N1 position and hydrogen bonding it with a non-metalated guanine (Scheme 1). The order of stability in



Scheme 1. The Watson–Crick base pairs C/G, C/G-Pt, and Pt-C/G.

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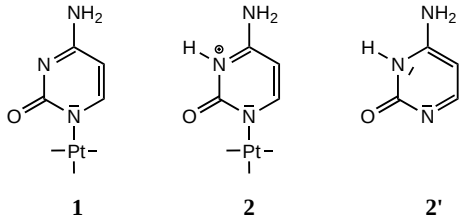
DMSO solution is **II** ≈ **III** > **I**; thus, the artificial (platinated) base pairs are more stable than the natural ones.

We have recently prepared and characterized (X-ray crystallography, NMR spectroscopy) two complexes of composition *trans*-$[(CH_3NH_2)_2Pt(C\text{-}N1)_2]$ (**1**) and *trans*-$[(CH_3NH_2)_2Pt(HC\text{-}N1)_2]^{2+}$ (**2**) (C = cytosine anion, HC = neutral cytosine) (Scheme 2).[4] The cytosine ligand in **2**



Scheme 2.

represents a platinated form of a rare cytosine tautomer **2′**. Cocrystallization of the neutral complex **1** with 9-ethylguanine (9-EtGH) yielded crystals of *trans*-$[(CH_3NH_2)_2Pt(C\text{-}N1)_2]\cdot 2[9\text{-EtGH}]\cdot 8H_2O$ (**3**) (Figure 1).[5] The two cytosi-

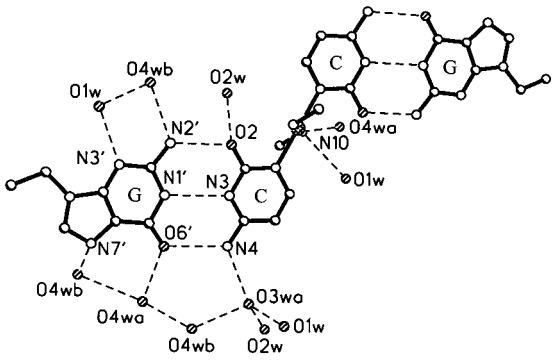


Figure 1. Structure of *trans*-$[(CH_3NH_2)_2Pt(C\text{-}N1)_2]\cdot 2[9\text{-EtGH}]\cdot 8H_2O$ (**3**) in the crystal.

nate ligands adopt a head–tail orientation and form large (70.6(2)°) dihedral angles with the Pt coordination plane, which is a normal arrangement. There are no unusual features of the cytosine ligands compared to those in **1**.[4] The two cytosine bases in **3** are involved in Watson–Crick pairing with the 9-EtGH nucleobases. The complementary bases are almost coplanar (2.9(2)°). Hydrogen bonds within the base pairs are 2.882(5) (N4···O6′), 2.930(4) (N3···N1′), and 2.833(4) Å (O2···N2′), thus paralleling the trend in the nonmetalated Watson–Crick pair[6] but deviating somewhat from distances in base pairs containing N7-platinated guanine bases.[3e,f] The solid-state structure of **3** (Figure 1) is dominated by extensive base stacking interactions along the *x* axis: Thus the Watson–Crick pairs form stacked dimers (3.4 Å), which themselves are stacked (3.5 Å) in such a way that a layer structure with repeating units of four bases (Pt-C, 9-EtGH, 9-EtGH, Pt-C) is formed.

Concentration-dependent ^1H NMR spectra of **3** recorded in $[D_6]$DMSO are consistent with intermolecular hydrogen bond formation between platinated cytosine and 9-EtGH; the

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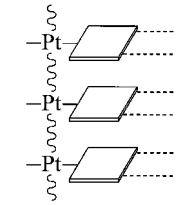
signal of the N1H proton of 9-EtGH undergoes an upfield shift of about 1 ppm in a dilution range of 0.18 M to 0.0056 M, whereas, shifts of the signals of the exocyclic NH_2 groups of both the cytosine and guanine nucleobases are expectedly smaller (ca. 0.5 ppm). These shifts are consistent with Watson–Crick pairing, since in each case only one of the two amino protons is hydrogen-bonded; however, an averaged signal of the two protons in an amino group is recorded. Stacking interactions between complexes can be ruled out since the chemical shifts of the aromatic protons of the two bases are virtually unaffected by changes in concentration. Under the assumption that the two cytosine ligands in **3** behave independently as far as hydrogen bonding with 9-EtGH is concerned, the stability of the base pair has been calculated to be $K = 10.0 \pm 1.7\,\text{M}^{-1}$ (3σ). This value is higher than for the nonplatinated base pair 9-EtGH/1-MeC (1-MeC = 1-methylcytosine) in the same solvent ($K = 6.9 \pm 1.3\,\text{M}^{-1}$) and is in the same range as found for various pairs of [Pt(9-EtGH-*N7*)] complexes with 1-MeC.[2]

As with thymine/adenine pairs, it is not possible to quantify Hoogsteen pairing of the CH ligands in **2** with 9-EtGH in DMSO due to the presence of two hydrogen bonds only. However, the formation of hydrogen bonds between the CH ligands in **2** and free 1-MeC is evident from concentration-dependent ^{1}H NMR spectroscopy. The base pair formed is a metalated analogue of the well known hemiprotonated cytosinium/cytosine pair and reveals an association constant of $K = 24 \pm 8\,\text{M}^{-1}$.

Apart from base pair stability, the question of the pH range in which a pair exists, is of importance. For guanine/cytosine pairing, to a first approximation the pK_a values of guanine define the boundaries for existence in aqueous solution.[7] Thus, Watson–Crick pairing becomes obsolete when guanine is an anion ($\text{pH} > \text{p}K_a \approx 9$) or alternatively when cytosine is protonated at N3 ($\text{pH} < \text{p}K_a \approx 4$). However, protonated cytosine can still pair with neutral guanine in the Hoogsteen fashion down to a pH value at which guanine becomes protonated at N7 (pK_a(guaninium) ≈ 3). Base pairing between guanine and cytosine (**I**) therefore covers roughly the pH range 3–9 (Figure 2a). The same pH range is also valid for the guanine/cytosine base pair **III** with a pyrimidine ligand platinated at N1, but as a consequence of the pK_a of about 7 for [Pt(CH-*N1*)],[4] the stability range of the Watson–Crick pair becomes much narrower (pH 7–9) at the expense of the Hoogsteen range, which extends now from about pH 3–7 (Figure 2b). Using similar arguments, it can be concluded that N7-platinated guanine and cytosine have a range of pH 4–9 for Watson–Crick pairing (**II**), with Hoogsteen pairing prevented (Figure 2c) owing to the position of the platination. Finally it can be concluded that [Pt(CH-*N1*)] is able to form hydrogen bonds with a free cytosine base over a wider pH range (pH 4–7, Figure 2e)) than two hemiprotonated free cytosine bases (Figure 2d).[7]

In summary, the presented results show that a strengthening of the G/C Watson–Crick base pair can be accomplished by either metalation of N7 of the guanine or of N1 of the cytosine base. Similarly, the strength of the pair between Pt-CH and 1-MeC exceeds that of the regular G/C pair, even though it does not reach the record value recently observed for the hemideprotonated pair of N7-platinated guanine.[8]

Our findings have led us to pursue the idea of creating artificial oligonucleotide analogues that consist of a backbone of metal ions and bridging ligands, with nucleobases attached either through N1 (unsubstituted pyrimidine bases), through N9 (unsubstituted purine bases), or through N7 (N9-substituted purine bases) to the metal centers. These coordination polymers might be considered relatives of purely organic neutral[9] and cationic[10] oligonucleotide analogues. Indeed, X-ray crystal structure studies on metal-containing oligo- or polymeric compounds of this kind have been described[11] although the reported ones represent kinetically labile entities. The use of Pt^{II} might be advantageous in that it not only is expected to lead to kinetically more robust species, but that additionally the bases, regardless of their binding site (as long as endocyclic sites are involved), are forced in a more or less parallel fashion (Scheme 3). As outlined here, hydrogen bonding properties of nucleobases attached to Pt and the pH range available for hydrogen bonding make them attractive synthesis goals.



Scheme 3. Simplified representation of nucleobases linked through Pt^{II}.

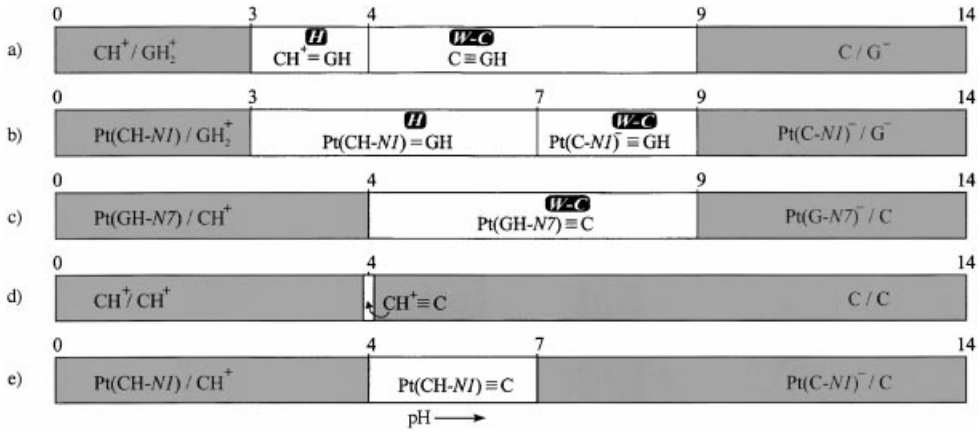


Figure 2. Approximate existence ranges of Hoogsteen (H) (=) and Watson–Crick (W–C) base pairs (≡) considering various protonation states of free and platinated cytosine (C) and 9-ethylguanine (G) nucleobases (see also text).

Experimental Section

Compounds **1** and **2** were synthesized as described in reference [4], 9-EtGH was purchased from Chemogen (Konstanz, Germany).

9-EtGH (20 mg, 116 μmol) was added to a solution of **1** (30 mg, 58 μmol) in water (10 mL). The mixture was briefly warmed to 70 °C and then allowed to cool and slowly evaporate at 4 °C. Colorless crystals of **3** were isolated in 55 % yield. Elemental analysis (%) calcd for $C_{24}H_{52}N_{18}O_{12}Pt$ (979.8634): C 29.4, H 5.3, N 25.7; found: C 29.2, H 5.4, N 25.7.

NMR data: Concentration-dependent ^{1}H NMR measurements were performed on a Bruker AC200 instrument at 20 °C in [D_6]DMSO using TMS as internal standard. For calculation of *K* values, the two

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bound cytosine nucleobases were considered independent binding sites for the partners; association constants were determined in analogy to the method described in reference [2a]. For **3** $K = 10.0 \pm 1.7\,\text{M}^{-1}$ (3σ) corresponds to the weighted mean of the individually calculated association constants of the NH_2 ($K = 10.14 \pm 2.37\,\text{M}^{-1}$, $\delta_0 = 6.472 \pm 0.023$, $\delta_\infty = 7.432 \pm 0.055$; the index 0 denotes a high dilution, the index ∞ denotes a high concentration) and N1H ($K = 9.89 \pm 2.51\,\text{M}^{-1}$, $\delta_0 = 10.576 \pm 0.051$, $\delta_\infty = 12.541 \pm 0.125$) protons of 9-EtGH. Since NH_2 of cytosine could not be detected at higher concentrations, only a rough estimate of K could be obtained; however, this value was, within the given error limits, in agreement with that for the guanine protons.

An equimolar solution of **2** (120 mM) and 1-MeC was stepwise diluted and ^{1}H NMR spectra were recorded. The association constant $K = 24 \pm 8\,\text{M}^{-1}$ corresponds to the weighted mean of the individually calculated association constants of the N3H(C) ($K = 37.8 \pm 14.0\,\text{M}^{-1}$, $\delta_0 = 11.899 \pm 0.035$, $\delta_\infty = 13.127 \pm 0.143$), $N4H_2$(1-MeC) ($K = 16.8 \pm 4.0\,\text{M}^{-1}$, $\delta_0 = 6.925 \pm 0.012$, $\delta_\infty = 7.577 \pm 0.046$), and the $N4H_2$(C) ($K = 29.6 \pm 3.7\,\text{M}^{-1}$, $\delta_0 = 7.184 \pm 0.018$, $\delta_\infty = 8.887 \pm 0.059$) protons. It should be mentioned that the N3H(C) resonance is not observable at high concentrations, and the $N4H_2$ resonance of the Pt-bound cytosine is split into two resonances of which only one is concentration-dependent. Since water of crystallization had not been removed in either case, we consider the reported association constants as lower limits, as the water molecules present in solution will compete for the hydrogen bonding sites.

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[5] Crystal structure data for **3**: $C_{12}H_{27}N_9O_{6.5}Pt_{0.5}$, $M_r = 498.97$, triclinic, space group $P\bar{1}$, $a = 8.949(2)$, $b = 11.177(2)$, $c = 11.889(2)$ Å, $\alpha = 101.06(3)$, $\beta = 103.87(3)$, $\gamma = 113.07(3)^\circ$, $V = 1006.3(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.647$ g cm^{-3}, $Mo_{K\alpha}$ radiation, $\lambda = 0.71069$ Å, $\mu = 3.566$ cm^{-1}, $T = 298$ K. A total of 7013 reflections (3526 unique, $R_{int} = 0.0238$, $\theta < 25.63^\circ$) were collected on a Nonius KappaCCD diffractometer. The structure was solved by patterson synthesis (G. M. Sheldrick, SHELXS-86, **1990**) and refined by full-matrix least-squares on F^2 values of 3476 reflections with $F_o^2 > 2\sigma(F_o^2)$ (G. M. Sheldrick, SHELXL-93, **1993**) to give $wR2 = 0.0621$ and $R1 = 0.0268$ for 286 parameters. Residual electron density max/min 0.508/ − 0.853 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-162162. 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).

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Electrochemical Regeneration of Low-Valent Indium(I) Species as Catalysts for C–C Bond Formations**

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Dedicated to Professor Martin F. Semmelhack on the occasion of his 60th birthday

In recent years the chemistry of indium has become more popular in organic synthesis, partly due to the ability to perform this chemistry in water or aqueous solvent systems. The chemistry of indium metal as well as the chemistry of indium salts for C–C bond formation processes has been reviewed several times.[1] In most cases indium metal is used in stoichiometric amounts and only in a few cases could versions be realized that were catalytic in indium, accompanied with a stoichiometric amount of a reducing agent.[2] In addition, the chemistry of low-valent indium(I) salts has been sparsely investigated, most probably because of the high cost of these species.[3]

Our approach to an electrochemical regeneration process for low-valent indium species was based on the idea of using the cathode as the reducing agent for the spent indium(III) reagent (Scheme 1). We chose the indium-catalyzed allylation of benzaldehyde with allyl bromide as a test reaction. We found, however, that an efficient allylation only took place when sacrifical anodes (preferably aluminum foil anodes)[4] were used in an undivided cell, whereas the reaction proceeded only with low conversions when a divided cell (Pt cathode and Al anode) or a quasi-divided cell (Pt foil cathode and Pt wire anode)[5] were used. We concluded that a major part of the reduction process in an undivided cell must

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