Substitution Reactions of Platinum(II)−Nucleobase Complexes by Associative Mechanism Involving Pseudorotation of the Five-Coordinate Intermediate

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Substitution reactions of N7-platinated guanosine and adenosine complexes {$[Pt(dien)(Guo\text{-}N7)]^{2+}$ (**1**), $[Pt(dien)(Ado\text{-}N7)]^{2+}$ (**2**), dien = diethylenetriamine} by thiourea (tu) and I^- have been studied in aqueous solution in the pH range 1.4−8.3 at different temperatures. Reactions of both complexes with I^- follow the usual associative two-path mechanism throughout the pH range studied, as do reactions with thiourea under neutral conditions (pH 6.5). With both nucleophiles (Y), the observed rate constant linearly increases with increasing [Y] up to 1000-fold excess of Y. Plots of $k_{1,obs}$ vs [Y] were employed to calculate the rate parameters k_S for the solvent path and k_Y for the nucleophile-dependent path by the equation $k_{1,obs} = k_S + k_Y[Y]$ at different temperatures. The following activation parameters were obtained at 298.2 K for the reaction of thiourea with **1**, $\Delta H^{\ddagger} = (72 \pm 1)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-79 \pm 4)$ J K^{-1} mol^{-1}, and with **2**, $\Delta H^{\ddagger} = (72.8 \pm 0.3)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-86 \pm 1)$ J K^{-1} mol^{-1}. The corresponding data for I^- with **1** are $\Delta H^{\ddagger} = (83 \pm 3)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-49 \pm 8)$ J K^{-1} mol^{-1}, and with **2**, $\Delta H^{\ddagger} = (78 \pm 3)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-67 \pm 10)$ J K^{-1} mol^{-1}. Activation parameters for the solvent path are $\Delta H^{\ddagger} = (85 \pm 1)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-105 \pm 2)$ J K^{-1} mol^{-1} for **1**, and $\Delta H^{\ddagger} = (87 \pm 7)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-98 \pm 22)$ J K^{-1} mol^{-1} for **2**, on the basis of the data found for reactions with thiourea. Rate parameters for the formation and solvolytic decomposition gave log *K* values of 7.5 ± 0.1 and 6.1 ± 0.2 for the equilibrium constants of **1** and **2**, respectively, in aqueous 0.1 M $NaClO_4$ solution at 298.2 K. Ring opening of the tridentate dien group in acidic solution provides a competing route for the overall substitution by thiourea. All experimental data found are consistent with an associative mechanism involving pseudorotation of the five-coordinate intermediate formed by the attack of thiourea, including activation parameters (298.2 K) $\Delta H^{\ddagger} = (69.2 \pm 0.3)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-81 \pm 1)$ J K^{-1} mol^{-1} for **1**, and $\Delta H^{\ddagger} = (70.9 \pm 0.7)$ kJ mol^{-1} and $\Delta S^{\ddagger} = (-79 \pm 2)$ J K^{-1} mol^{-1} for **2**. According to kinetic analysis, about 60% of **1** and 70% of **2** yield free nucleoside via the ring-opening step, whereas the remainder give free nucleoside by direct replacement with thiourea. The ratio of these routes is practically independent of thiourea concentration and temperature. The ^1H, ^{13}C, and ^{195}Pt NMR spectroscopic data for the isolated ring-opened species **3**(**1**) and **3**(**2**) (from **1** and **2**, respectively) are consistent with a four-coordinate species $[Pt(dienH)(L\text{-}N7)(tu)]^{3+}$, in which the dien group acts a bidentate ligand and one of the dien amino groups is trapped by protonation. Although both **3**(**1**) and **3**(**2**) are stable in cold acidic solution, they decompose predominantly back to the starting material when the pH of the solution is increased. According to HPLC analysis, the former gives **1** and guanosine in a 12:1 ratio, and the latter yields **2** and adenosine in a 10:1 ratio. The ability of the dien-NH_2 group to displace coordinated thiourea from Pt(II) contradicts the trans effect S > N and exemplifies the nucleophilic power of the NH_2 group of a partially chelated amine.

Introduction

The ability of Pt(II) to form covalent adducts with the base residues in DNA is crucial for the biological activity of various anticancer Pt drugs.[1,2] Several lines of evidence suggest that the N7 sites of guanine and adenine residues are the most preferred binding targets of Pt(II).[1] Once formed, the Pt−nucleobase complexes are quite stable owing to the inertness and high thermodynamic stability of the Pt−N bond.[3] For example, a half-life of about 23 years has been estimated for the direct NH_3 exchange in $[Pt(NH_3)_4]^{2+}$ at 25 °C in aqueous NH_3 solution.[4] With deprotonated uridine, *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ forms a N3-bound 1:1 complex, for which a logarithmic stability constant of ca. 9.6 has been estimated.[5] However, in a few cases, relatively easy migration of coordinated Pt(II) from one nucleobase to another has been reported in both single-stranded[1,6] and double-stranded oligonucleotides,[6,7] with a half-life as short as ca. 6 h at 37 °C.[8] Unfortunately, the exact mechanism of the migration reactions is largely unknown.[6]

The displacement of nucleobases from Pt can be facilitated

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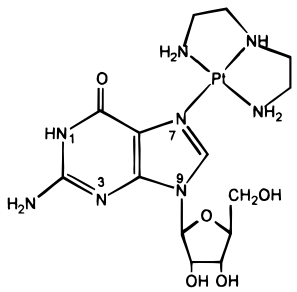
by the attack of strong nucleophiles, e.g., CN^- and sulfur ligands.[5] In particular, various sulfur-containing (bio)molecules have received considerable interest owing to their important roles in the biological processing of anticancer platinum drugs. Thiols (sodium thiosulfate) or thioethers (sodium diethyldithiocarbamate) may reduce the nephrotoxic side effects of *cis*-$[PtCl_2(NH_3)_2]$, and small peptides such as glutathione or metallothionine may prevent Pt binding to DNA.[9] In addition, sulfur-containing molecules (e.g., thiourea) are used as trapping agents in studying platinum binding to nucleic acid fragments.[1]

Despite their importance, surprisingly little is known about the factors affecting substitution reactions of Pt−nucleobase complexes and those by thiourea in particular. The rate of displacement of guanosine from *cis*-$[Pt(NH_3)_2(Guo\text{-}N7)_2]^{2+}$ by thiourea and other sulfur-containing nucleophiles has been studied by ^{13}C NMR spectroscopy.[10] Substitution reactions of the 1:1 and 1:2 complexes of *cis*-$Pt^{II}(NH_3)$ with 1-methyluracilato anion have shown that the bis(methyluracilato) complex is inert to substitution by thiourea and I^-, unless the exocyclic O4 atom is protonated.[11] On the other hand, the reactivity of the 1:1 complexes bearing Cl^- or H_2O as the fourth ligand is controlled by the lability of the aqua ligand, which dramatically decreases with increasing pH. The inertness of the bis(methyluracilato) complex parallels the behavior of N3-platinated thymine and uracil complexes in the presence of CN^-, which has been attributed to the remarkable protective effect of the exocyclic oxygens.[12,13]

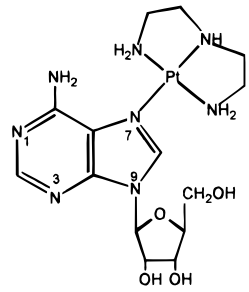
In all these cases, the substitution reactions follow an associative mechanism that is the overwhelming mechanism in substitution reactions of square-planar Pt(II) compounds.[3] It has been proposed that steric retardations do not cause a changeover from associative to dissociative mechanism, even though they may slow the substitution rate by several orders of magnitude.[11] Instead, electronic effects may result in a changeover into dissociative mechanism in complexes containing two Pt−C bonds.[14] It has been suggested that ground-state destabilization and increase of electron density at the metal due to Pt−C bonds favor the dissociative pathway by preventing the approach of nucleophiles.[14c] However, a single Pt−C bond appears not to cause a changeover in mechanism.[15] Also, very rarely, electrophilic catalysis has been proposed to effect the dissociation of some simple Pt(II) compounds in nonaqueous medium via an associative mechanism.[16]

In this work, we have studied substitution reactions of Pt−nucleobase complexes by the nucleophiles I^- and thiourea. The N7-bound Pt^{II}(dien) complexes of adenosine and guanosine (Chart 1) were chosen as model compounds because they represent the major binding modes of Pt(II) in DNA. The displacement of the coordinated nucleobase by I^- follows the usual associative mechanism in both neutral and acidic aqueous solution, as do reactions with thiourea in neutral solution. By contrast, in slightly acidic solution, reactions of both complexes with thiourea were accompanied by a changeover in mechanism due to ring opening of the tridentate dien ligand. All experimental data found are consistent with an associative mechanism involving pseudorotation of the five-coordinate intermediate formed by the attack of thiourea, which results in two parallel reaction pathways for the overall process.

Chart 1



$[Pt(dien)(Guo\text{-}N7)]^{2+}$ (**1**)



$[Pt(dien)(Ado\text{-}N7)]^{2+}$ (**2**)

Experimental Section

Materials and Solutions.[17] The nucleobase derivatives were commercial products from Sigma, and they were used as received. Thiourea (99+%, Aldrich) was recrystallized from methanol. All other chemicals were of the highest purity available, and they were used as received. [Pt(dien)]I and its aqua derivative,[18] $[PtI(dien)(tu)]^{2+}$,[19] $[Pt(tu)_4]Cl_2$,[20] $[Pt(dien)(Guo\text{-}N7)](ClO_4)_2$ (**1a**),[21] and $[Pt(dien)(Ado\text{-}N7)](ClO_4)_2$ (**2a**)[22] were prepared by literature methods. Solutions of $[Pt(dienH)(Guo\text{-}N7)(tu)]^{3+}$ [**3**(**1**)] and $[Pt(dienH)(Ado\text{-}N7)(tu)]^{3+}$ [**3**(**2**)] were obtained by treating the corresponding Pt−nucleoside complexes with thiourea under acidic conditions, followed by LC fractionation of the reaction mixtures as previously described,[23] except that the mixture[24] containing **3**(**2**) was directly chromatographed after 6 h reaction at 45 °C without ethanol extraction.

Kinetic Measurements. Kinetics for the dissociation of Pt(II)−nucleobase complexes were studied in aqueous solution (pH =1.4−8.3) at different temperatures and monitored using HPLC. The measurements in the pH range of 1.4−3.5 were carried out in unbuffered solution, and the pH was adjusted with 1.0 M $HClO_4$. In the pH range of 3.5−8.3, buffered solutions were employed to maintain the pH in kinetic runs.[25] In each measurement, the pH of the reaction mixture remained practically constant (within 0.2 log units). Kinetics for the formation of **1** and **2** were studied in excess of Pt(II) as previously described.[18] Peak areas at 260 nm were used as the measure of the concentration by employing 1,3-dimethyluracil as an internal standard. Reactions were started by adding the desired Pt(II) species into a prethermostated reaction mixture, the ionic strength of which was adjusted to 0.1 M with $NaClO_4$. Samples were withdrawn from the reaction mixture at suitable time intervals and diluted with ice-cold water or 0.01 M $HClO_4$ (1:1); they were stored in ice prior to chromatographic analysis.

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(17) Abbreviations used: dien = diethylenetriamine, Ado = adenosine, Guo = guanosine, tu = thiourea.
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(24) Reaction mixture: 78 mg of **2** (0.1 mmol), 0.12 mmol of $HClO_4$, and 0.06 mmol of tu.
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Table 1. Selected Chemical Shifts (^{1}H, ^{13}C, and ^{195}Pt) in ppm for **1** and **2** and Their Dien Ring-Opened Species **3**(**1**) and **3**(**2**)[a]

		δ_H			
compound	δ_{Pt}	H8	H2	H1′	δ_C, C=S
1[b]	−2855	8.398		5.933 (d)	
3(**1**)[b]	−3060	∼8.46[c]		5.955 (d)	177.8
2[d]	−2875[c,e]	8.901 (br)	8.383	6.156 (d)	
3(**2**)	−3030	∼8.93[c]	∼8.43[c]	6.211 (d)[f]	176.76[g]

[a] Spectra recorded at ambient temperature in D_2O or H_2O/D_2O. [b] From ref 23. [c] Two or more signals which merge at higher temperatures. [d] From ref 22. [e] The value for the major signal. [f] Two doublets in concentrated sample. [g] Two signals of equal intensity, $\delta_C = 176.56$ ppm for the other.

The disappearance of the starting material and the formation of the free nucleoside were employed to calculate the observed rate constants, $k_{1,obs}$, for the attack of the nucleophiles on **1** and **2** by eq 1. Here $[ML]_0$

$$\ln[ML]_t = -k_{1,obs} + \ln[ML]_0 \quad (1)$$

is the initial concentration of the complex and $[ML]_t$ is the concentration at time t.[26] For thiourea-assisted dissociation in acidic solution, the time-dependent concentration of the species $[Pt(dienH)L(tu)]_t^{3+}$ gave the rate constants $k_{2,obs}$ and $k_{4,obs}$ by eq 2. In kinetic runs, the concentration

$$[Pt(dienH)L(tu)]_t = [ML]_0 \frac{k_{2,obs}}{k_{1,obs} - k_{4,obs}} (e^{-k_{1,obs}t} - e^{-k_{4,obs}t}) \quad (2)$$

of $[Pt(dienH)L(tu)]_t^{3+}$ was calculated by converting a known solution of this species back to the starting material under basic conditions.

NMR Studies. The NMR measurements were carried out in D_2O (^{1}H) or in H_2O/D_2O (^{13}C and ^{195}Pt) at different temperatures ranging from +8.5 °C to +60 °C (D_2O or H_2O/D_2O), as previously described.[22,23] The ^{1}H and ^{13}C spectra were referenced internally to DSS, assigned as 0.015 ppm for proton and 0 ppm for carbon, and the ^{195}Pt spectra were referenced externally to $[PtCl_4]^{2-}$ (δ_{Pt} −1625 ppm from $[PtCl_6]^{2-}$). After treatment of **3**(**2**) with aqueous alkali, the sample was acidified prior to ^{1}H NMR measurement to avoid deuteration of H8. Selected chemical shifts are summarized in Table 1. The complete spectral data for **1**, **2**, and their dien ring-opened species **3**(**1**) and **3**(**2**) are given in Table S1 for ^{1}H chemical shifts and in Table S2 for ^{13}C and ^{195}Pt chemical shifts (Supporting Information).

Results and Discussion

Substitution by I^- Ion. According to chromatographic analysis, the action of I^- ion on both Pt(II)−nucleobase complexes resulted in the formation of free nucleoside and $[PtI(dien)]^+$. However, in kinetic runs, the quantification of the latter was uncertain by UV-detected HPLC due to its low molar absorptivity at 260 nm. In both complexes, the ring nitrogen N1 may affect the overall dissociation by losing (**1**) or accepting (**2**) a proton. To find out the effect of possible side reactions on the overall reaction due to (de)protonation of the complexes, their dissociation was studied in 0.1 M NaI solution as a function of the pH at 338.2 K. As seen in Figure 1, the observed rate constants remain practically constant in the pH range of 3.5−6 in both cases.[27] Below pH 3.5, the rate constant of **2** begins to increase, whereas that of **1** remains unaffected down to pH 1. This may be attributed to the protonation of the N1 site of **2**, which increases the electrostatic interactions between I^- and the cationic complex and makes protonated adenosine a better leaving group. By contrast, competition of the proton and Pt(II) for the N7 site, which should be more significant in **1** due to the higher basicity of the guanosine N7 atom, appears to be unimportant. On the other hand, unknown side reactions may also affect the rate enhancement of **2**, because below pH 2.5, the reaction mixtures slowly darkened and HPLC analysis showed small signals at the final stage of the reaction which were not detected at higher pH. Above pH 6, the rate constant of **1** decreases, whereas that of **2** remains constant, suggesting that deprotonation of N1H in **1** renders guanosine a poorer leaving group. Electrostatic interactions between the reactants seem not to be so important because the susceptibility of deprotonated **1** toward both nucleophiles is diminished in a similar manner above pH 6.5.

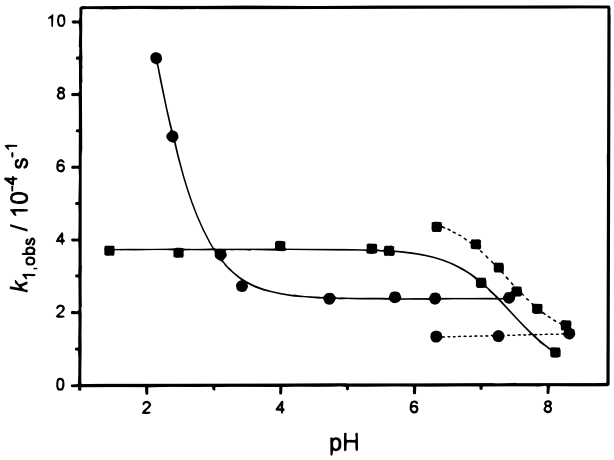

Figure 1. Observed rate constant for the substitution reactions of **1** (■) and **2** (●) in aqueous 0.1 M NaI solution (solid line) and in 0.1 M thiourea solution (dotted line) as a function of the pH at 338.2 K.

In excess of I^-, the disappearance of the complex and the formation of free nucleoside obeyed the first-order rate law in both **1** and **2**.[28] With **2**, the plots of ln[ML] vs t were strictly linear over three half-lives, whereas in the case of **1**, a slight upward curvature was observed at low $[I^-]$ values after two half-lives. Most probably, this deviation from linearity results from reverse reaction, as it became more significant at higher initial concentrations of **1**. It was also found that addition of free guanosine to a solution of $[PtI(dien)]^+$ in 1 mM NaI slowly gave **1**. In all cases, the observed rate constant linearly increased with increasing $[I^-]$ concentration up to 1000-fold excess of the nucleophile (Figure 2; observed rate data are given in Table S3, Supporting Information). At each temperature, strictly linear plots of $k_{1,obs}$ vs $[I^-]$ exhibited a positive, though small, intercept. Accordingly, the usual two-path mechanism (solvent path and nucleophile-dependent path) completely describes the dissociation of both Pt(II) complexes under these conditions.[3] The observed rate constant may be expressed by eq 3, where k_S is

$$k_{1,obs} = k_S + k_Y[Y] \quad (3)$$

the first-order rate constant for the solvent path, k_Y denotes the second-order rate constant for the nucleophile-dependent path, and Y stands for the nucleophile. The k_S and k_Y values, obtained as the intercept and slope, respectively, from the plots of $k_{1,obs}$ vs [Y] at different temperatures, are listed in Table 2.

Thiourea as a Nucleophile. Preliminary experiments showed that dissociation of both **1** and **2** in 0.1 M thiourea solution

(26) For the formation of the free ligand, the term $([L]_\infty - [L]_t)$ stands for $[ML]_t$ and $[L]_\infty$ for $[ML]_0$ in eq 1. In eqs 1 and 2 charges are omitted for clarity. For the formation of **1** and **2**, the terms $[ML]_t$ and $[ML]_0$ in eq 1 should be replaced by $[L]_t$ and $[L]_0$, respectively.

(27) Pseudo-first-order rate constants obtained from the disappearance of the starting material and from the formation of the free nucleoside were compatible in both cases.

(28) In unbuffered solution, pH 4−5.

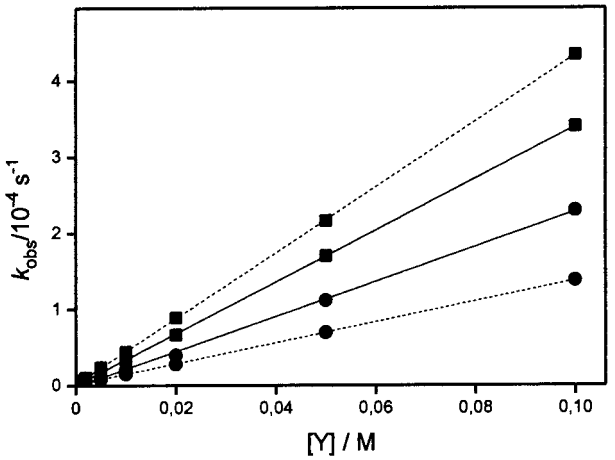

Figure 2. Observed rate constant for the substitution reactions of **1** (■) and **2** (●) by I^- (solid line) and thiourea (dotted line) at 338.2 K (pH ≈ 6.5, [ML] = 1×10^{-4} M).

Table 2. Rate Constants k_S and k_Y for the Dissociation of **1** and **2** According to eq 3 in the Presence of the Nucleophiles (I^- and tu) in Aqueous Solution at Different Temperatures[a]

	k_S (10^{-7} s^{-1})		k_Y 10^{-4} M^{-1} s^{-1})	
T (K)	**1**	**2**	**1**	**2**
318.2	2.1 ± 0.7	2.3 ± 0.2	8.25 ± 0.07	2.45 ± 0.02
	2.1 ± 0.3	2.3 ± *0.4*	*4.80 ± 0.03*	*3.18 ± 0.04*
328.2	5.7 ± 0.8	7.4 ± 0.9	18.8 ± 0.2	5.87 ± 0.09
	6.0 ± 0.6	*7.2 ± 0.2*	*12.2 ± 0.1*	*8.54 ± 0.01*
338.2	15 ± 5	17 ± 3	43.4 ± 0.5	13.2 ± 0.1
	12 ± 2	*14 ± 1*	*32.4 ± 0.1*	*19.2 ± 0.1*

[a] I = 0.1 M ($NaClO_4$). The values in italics refer to data found for I^-.

proceeds differently in neutral than in slightly acidic solution and that the disappearance of the starting material is faster at low pH. According to HPLC analysis, both complexes converted under neutral conditions into free nucleoside and a species that is tentatively assigned as $[Pt(dien)tu]^{2+}$. However, in acidic solution, two additional products were detected in both cases, indicating that the dissociation mechanism is pH-dependent.

Substitution at pH 6.5. To minimize the effect of N1H deprotonation on the dissociation of **1**, triethanolamine−HNO_3 buffer was employed to maintain the pH at about 6.5 in the reaction mixtures. Under these conditions, the thiourea-assisted dissociation of both complexes is similar to that found for the I^- ion, i.e., the usual two-path mechanism is obeyed. The observed rate constants obtained from the slopes of strictly linear plots of ln[ML] vs t are given in Table S4 (Supporting Information).[27] In these cases, increasing the initial concentration of the complex affected neither the linearity of the plot nor the magnitude of the slope, showing that the attack of thiourea on both complexes is irreversible under these conditions. As with I^-, the observed rate constant linearly increases with increasing thiourea concentration up to 1000-fold excess of the nucleophile (Figure 2). The rate data obtained gives the rate parameters k_S and k_Y for the thiourea-assisted dissociation as the intercept and slope from the plots of $k_{1,obs}$ vs [tu], which are included in Table 2.

The data in Table 2 reveal that the k_Y values for thiourea and I^- are surprisingly similar for both complexes. This is in contrast to the usual reactivity order tu > I^- predicted by n^o_{Pt} values (nucleophilic reactivity constants) assigned to these nucleophiles.[3,16] It should be noted, however, that the standard n^o_{Pt} values refer to reactions of *trans*-$[PtCl_2py_2]$ with various nucleophiles in methanol. In aqueous solution, the reactivity difference between thiourea and I^- has been found to decrease, particularly with charged platinum substrates.[29] In the case of certain dicationic Pt(II) species $\{[Pt(dien)L]^{2+}$, L = H_2O or DMSO,[29c] and $[Pt(L)(en)(H_2O)]^{2+}$, L = dimethyl sulfide[29b]$\}$, the reactivity order of thiourea and I^- is even reversed. On the other hand, with *cis*-$[Pt(NH_3)_2(1\text{-MeU})(H_2O)]^{2+}$, the reactivity of thiourea is slightly higher than that of I^-.[11] In addition to electrostatic interactions that may promote the reactivity of I^- with cationic Pt compounds, an increase in the charge on the metal may also cause an opposite effect by reducing the reactivity of thiourea.[29c] As a biphilic nucleophile, thiourea is able to utilize π back-donation from the metal to stabilize the transition state, and with increasing charge on the metal, the contribution of this π back-donation is reduced.[29b,d] Thus, a reactivity order of I^- ≈ thiourea may be anticipated with dicationic **1** and **2**. However, the data in Table 2 show that the coordinated nucleoside has a small, but significant, influence on this reactivity order.

The higher basicity of Guo-N7 as compared to Ado-N7 suggests that the inherent lability of **2** is higher than that of **1**, which is supported by the behavior of **1** upon deprotonation of N(1)H (Figure 1). Yet, **1** is more susceptible to attack of both nucleophiles than is **2**. Because of the overall structural similarities between **1** and **2**, it is reasonable to assume that the reactivity differences observed are due to the active role of the substituent at C6, either directly or through the solvation sphere, though quantification of the latter is difficult. In the crystalline state, the dihedral angle between the PtN_4 coordination plane and the purine base plane is 62.7° (**1**)[21] and 71.9° (**2**).[22] Thus, the substituent at C6 may sterically hinder the nucleophilic attack on its side of the PtN_4 coordination sphere, provided that rotation about the Pt−N7 bond is restricted. Most probably, this is not the case with **1**,[30] as evidenced by the sharp signals in the ^{1}H NMR spectra. Instead, **2** exhibits slow rotation about the Pt−N7 and C6−NH_2 bonds on the NMR time scale, indicated by two ^{195}Pt resonances and a broad signal for H8 at ambient temperature.[22] In addition, the minimum distance between the NH_2 hydrogen and Pt(II) is 2.79 Å in **2**, assuming coplanarity for the C6−NH_2 group and the base moiety,[22] and this distance is well within the range of 2.2−3.25 Å given in the literature for a hydrogen bond type of interaction of N−H···Pt.[31] These findings suggest that the C6−NH_2 group of **2** may prevent the nucleophilic attack on Pt(II) more efficiently than the oxo group of **1**, resulting in higher reactivity for the latter. Further difference in reactivities may be due to hydrogen bonding interactions between the nucleophiles and the C6 substituent. With **1**, the oxo group is expected to favor the approach of thiourea over that of I^-, whereas in **2**, the NH_2 group may have an opposite effect.

Substitution at pH 3. In slightly acidic solution, the similar dissociation of **1** and **2** in the presence of excess of thiourea occurs by a different mechanism from that at pH 6.5. According to chromatographic analysis, the disappearance of the complexes

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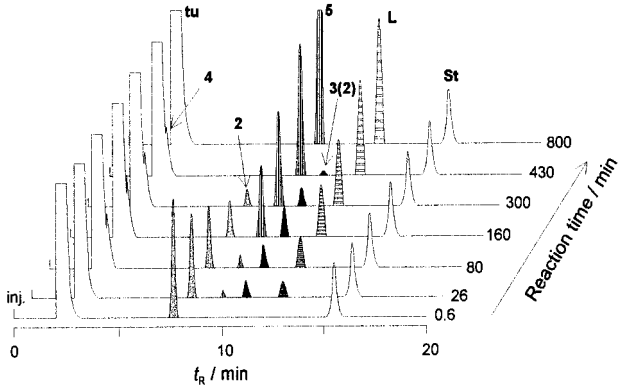

Figure 3. HPLC traces of the mixture of $[Pt(dien)(Ado\text{-}N7)]^{2+}$ (**2**, 1×10^{-4} M) and thiourea (tu, 0.1 M) at 318.2 K (pH 2.8) at selected time intervals. **L** denotes free adenosine and **St** is 1,3-dimethyluracil (8×10^{-5} M) employed as an internal standard. For the notation of other signals, see Scheme 1.

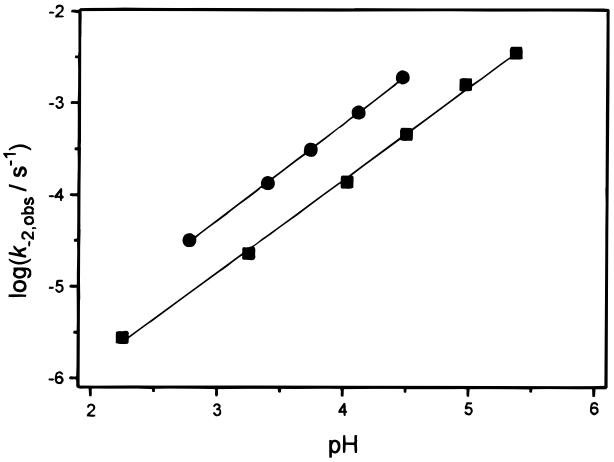

Figure 4. Observed first-order rate constant, $k_{-2,obs}$, for the decomposition of **3**(**1**) [■] and **3**(**2**) [●] at 338.2 K ($I = 0.1$ M) as a function of pH.

in kinetic runs was accompanied by the formation of a total of four detectable species. Both gave free nucleoside (**L**) and two different platinum−thiourea compounds, viz., $[Pt(dien)(tu)]^{2+}$ (**4**) and $[Pt(tu)_4]^{2+}$ (**5**), of which **5** and **L** are clearly end products (Figure 3). In each run, **L** began to accumulate earlier than **5**, but their final amounts were equal, as verified by authentic compounds. By contrast, the fourth product, denoted as **3**(**1**) and **3**(**2**) for **1** and **2**, respectively, is first formed and then consumed during the overall reaction, indicative for a species capable of reacting further with thiourea. Under these conditions, the same also holds true for **4**, although its signal was only poorly resolved from free thiourea. Coelution of **4** and added $[Pt(dien)tu]^{2+}$ further supports the assignment of **4**. It is worth noting that in acidic solution, the independently prepared **4** was converted into **5** in the presence of excess of thiourea, a reaction which was not observed at pH 6.5.[32]

Under the experimental conditions employed, the disappearance of **1** and **2** in kinetic runs obeys the first-order rate law only when the concentration of thiourea exceeds 0.05 M, whereas below this concentration, plots of ln[ML] vs *t* showed slight upward curvature. Although isolated **3**(**1**) and **3**(**2**) are both stable in cold acidic solution, they slowly decompose predominantly into starting material at higher temperatures, and the decomposition rate constant linearly increases with increasing pH (Figure 4).[33] However, both ring-opened species also yielded free nucleoside as a minor product. According to HPLC analysis, **3**(**1**) decomposes into **1** and guanosine in a ratio of 12:1, whereas **3**(**2**) gives **2** and adenosine in a ratio of 10:1 throughout the pH range studied. Unfortunately, reliable detection of the other expected decomposition products, i.e., thiourea and $[Pt(dien)tu]^{2+}$, was not possible, although HPLC traces did reveal very small signals at the retention times characteristic for these species. Evidently, this decomposition of **3**(**1**) and **3**(**2**) predominantly back to the starting material, verified also by ^{1}H NMR spectroscopy (Table S1),[34] explains the nonlinear disappearance of **1** and **2** at low thiourea concentration. This is strongly supported by the fact that steps k_{-2} and k_4 become comparable when [tu] < 0.02 M (cf. Table 3 and Figure 4, T = 338.2 K). By contrast, when [tu] > 0.05 M, isolated **3**(**1**) and **3**(**2**) gave **5** and free nucleoside in a 1:1 ratio in acidic solution without any detectable formation of **4** or the starting material.

NMR spectroscopic data for isolated **3**(**1**) and **3**(**2**) are consistent with a four-coordinate Pt(II) species in which the protonated dien ligand acts as a bidentate group and the remaining two coordination sites of Pt(II) are occupied by guanosine and thiourea ligands. In particular, the ^{195}Pt NMR signals at −3060 ppm for **3**(**1**) and −3030 ppm for **3**(**2**) are typical for a PtN_3S coordination sphere,[19,35] whereas ^{13}C NMR and ^{1}H NMR spectra reveal the presence of guanosine, thiourea, and dien ligands (Tables 1, S1, and S2). The asymmetry of the coordinated dien, as evidenced by ^{1}H and ^{13}C spectra, strongly suggests that one NH_2 group is dissociated from Pt(II). In fact, this kind of ring-opening mode of the dien group has been reported earlier in Pt(II) complexes.[36] In addition, very fast ring opening of the dien group ($t_{1/2} = 5$ min) has been reported in the reaction of [PtCl(dien)]Cl with diethyldithiocarbamate at pH 7.[19]

Table 3 records the observed rate constants for the reactions of **1** and **2** with thiourea at different temperatures at pH 3. The rate constants $k_{2,obs}$ and $k_{4,obs}$ for the formation and disappearance of the ring-opened species **3**(**1**) and **3**(**2**) were obtained by eq 2 from the time-dependent concentration of $[Pt(dienH)L(tu)]_t^{3+}$ by employing the $k_{1,obs}$ values found from the disappearance of the starting material by eq 1. Kinetic analysis revealed that in both cases the free ligand is formed via two routes (Figure 5) and that the ratio of these routes (shown by the term $r = k_{2,obs}/k_{1,obs}$ in Table 3) is practically independent of thiourea concentration and temperature ([tu] = 0.05−0.4 M). This clearly indicates that both pathways follow an associative mechanism, as the rate-limiting step in the dissociative mechanism should be independent of the concentration of the nucleophile.[3b] Moreover, the fact that I^- caused no alteration in the substitution reactions down to pH 1 strongly argues against the dissociative mechanism. If formed, the analogous ring-opened species having I^- as the fourth ligand should be stable enough to be detected during kinetic runs, because even the more weakly coordinating Cl^- forms an isolable ring-opened complex, $[Pt(dienH)Cl_2]^+$ (which is relatively stable in acidic solution).[36] Without the

(32) Both reactions were followed for 24 h at 338.2 K ([tu] = 0.02 M).
(33) The slopes of the plots $k_{-2,obs}$ vs pH are 1.01 for **1** ($R = 0.9992$) and 1.05 for **2** ($R = 0.9998$) at 338.2 K.
(34) With base-treated **3**(**2**), the ^{1}H NMR spectra revealed the formation of both the starting material and free adenosine.

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Table 3. Observed Rate Constants, $k_{i,obs}$ (10^{-6} s^{-1}), for the Dissociation of **1** and **2** in the Presence of Various Amounts of Thiourea (tu) in Acidic Solution (pH 3) at Different Temperatures[a]

		$k_{1,obs}$		$k_{4,obs}$		r[b]	
[tu]	T (K)	**1**	**2**	**1**	**2**	**1**	**2**
0.05	328.2	2.00 ± 0.02	1.31 ± 0.01	0.7 ± 0.1	0.87 ± 0.02	0.59	0.71
	338.2	4.36 ± 0.02	2.75 ± 0.05	1.7 ± 0.1	2.37 ± 0.02	0.61	0.75
0.1	318.2	1.86 ± 0.01	1.16 ± 0.01	0.50 ± 0.01	0.78 ± 0.03	0.56	0.71
	328.2	4.05 ± 0.02	2.67 ± 0.01	1.3 ± 0.1	1.80 ± 0.04	0.59	0.73
	338.2	8.85 ± 0.03	5.71 ± 0.02	3.1 ± 0.1	4.38 ± 0.03	0.59	0.75
0.2	318.2	3.58 ± 0.03	2.22 ± 0.01	1.0 ± 0.1	1.59 ± 0.04	0.60	0.72
	328.2	8.09 ± 0.07	5.35 ± 0.08	2.3 ± 0.1	3.30 ± 0.04	0.57	0.68
	338.2	17.6 ± 0.1	11.4 ± 0.1	5.5 ± 0.1	8.08 ± 0.05	0.59	0.71
0.4	318.2	7.09 ± 0.04	4.49 ± 0.03	2.0 ± 0.1	3.61 ± 0.07	0.57	0.76
	328.2	16.1 ± 0.1	10.6 ± 0.1	4.2 ± 0.1	6.49 ± 0.09	0.53	0.72
	338.2	34.8 ± 0.5	22.8 ± 0.3	9.9 ± 0.2	15.6 ± 0.2	0.58	0.71

[a] $I = 0.1$ M. [b] The ratio of $k_{2,obs}/k_{1,obs}$.

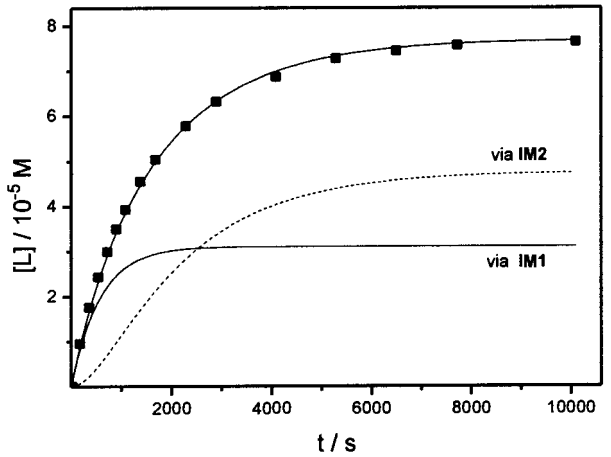

Figure 5. Time-dependent concentration of free guanosine formed in the reaction of **1** (7.7×10^{-5} M) with thiourea (0.2 M) at 338.2 K (pH 3.3). The lines represent computer simulations by using the rate parameters obtained for different steps; see Scheme 1.

presence of certain acidic compounds (e.g., CH_3COOH, H_3BO_3, HNO_2),[16] the contribution of the rare electrophilic catalysis can be ruled out in this study, and furthermore, the different behavior of the nucleophiles under identical experimental conditions argues against this explanation. Accordingly, an associative mechanism most likely operates in the substitution reactions of **1** and **2** by thiourea in acidic solution; the very similar activation parameters for substitution of **1** and **2** by thiourea in neutral and acidic solution support this (Table 4). The observation that I^- does not cause ring opening of the tridentate dien ligand in acidic aqueous solution indicates that either the trans influence or the π-accepting ability (or both) of I^- is weaker than that of thiourea. Comparison of the activation parameters in Table 4 shows that the $\Delta S^{\ddagger}$ values (at pH 6.5) are significantly less negative for the reaction of both complexes with I^- as compared to those with thiourea. Thus, in the reactions with I^-, the favorable $\Delta S^{\ddagger}$ term compensates the less favorable $\Delta H^{\ddagger}$ and results in a comparable kinetic trans effect for I^- and thiourea. An analogous situation has been reported earlier for the reactions of *cis*-$[Pt(NH_3)_2(1\text{-MeU})(H_2O)]^{2+}$ with these nucleophiles, where the less negative $\Delta S^{\ddagger}$ for I^- was attributed to a decrease in electrostriction in the transitition state due to partial charge neutralization.[11]

In the reactions of **1** or **2** with thiourea, two different five-coordinate intermediates are feasible in which the nucleobase adopts either an equatorial (**IM1**) or an apical (**IM2**) position (Chart 2). The former should be more favorable because of the trans effect $R_2NH > RNH_2$, as evidenced by the aquation rate constants for $[Pt(dien)Cl]^+$ ($k_{aq} = 1.0 \times 10^{-4}$ s^{-1})[3] and $[Pt(en)Cl(H_2O)]^+$ ($k_{aq} = 4.4 \times 10^{-5}$ s^{-1})[37] at 298.2 K, for example. The forward reaction of **IM1** leads to the formation of the free nucleobase and $[Pt(dien)tu]^{2+}$. By contrast, **IM2** gives ring opening of the tridentate dien ligand, and the four-coordinate species thus formed may be trapped upon protonation of the dissociated dien-NH_2 group, i.e., as $[Pt(dienH)(L)tu]^{3+}$. This dien-NH_2 group may intramolecularly attack Pt(II), resulting again in the intermediate **IM2**, which gives the starting material upon dissociation of thiourea.

The observation that both **3**(**1**) and **3**(**2**) spontaneously also give, in addition to the starting material, free ligand as a minor product is of significance. Dissociation of **L** in the reverse reactions of **3**(**1**) and **3**(**2**) would require the formation of such an intermediate, where the equatorial sites are occupied by dien-NH, **L**, and the incoming dien-NH_2 group. However, this is highly unlikely for geometric reasons, because one HN−Pt−NH_2 angle would be about 90° and the other should be about 120°. In fact, theoretical studies predict that the angle between the entering and leaving ligands in the five-coordinate intermediate is quite small (70−85°) and the trans-directing group is away from the entering and leaving groups by an angle larger than 135°.[38] Moreover, this configuration requires the repositioning of the thiourea ligand trans to the dien-NH group (initially trans to the dien-NH_2) upon dissociation of **L**. Alternatively, the ligand **L** may directly dissociate from the apical site in **IM2**. This is also highly unlikely, because it contrasts the generally accepted mechanism in Pt(II) substitution reactions and would require a similar repositioning of the thiourea ligand as above. Thus, it seems to us that the only acceptable mechanism for the formation of both the starting material and free ligand in the backward reactions of **3**(**1**) and **3**(**2**) involves an equilibrium between the intermediates **IM1** and **IM2**, i.e., pseudorotation of the five-coordinate intermediates. Quite interestingly, the data in Table 3 show that even if the formation of the ring-opened species is slightly more favorable with **2** than with **1**, the step **IM1** → **L** is significant in both cases. In fact, changes in the pH of the reaction mixture seem not to affect the contribution of this step to the overall disappearance of the starting material.

These findings are fully consistent with the mechanism depicted in Scheme 1 for the thiourea-assisted dissociation of **1** and **2** in acidic solution. Here, [I.A] denotes the initial, presumably square-pyramidal adduct formed between the complexes and thiourea.[3,39] Although interconversion of apical and

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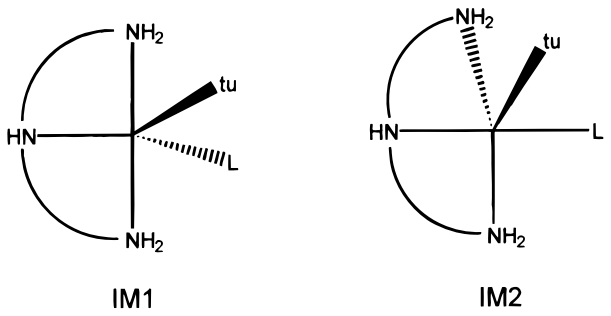
Table 4. Activation Parameters for the Reactions of Pt^{II}(dien) Species with Different Nucleophiles in Aqueous Solution at 298.2 K[a]

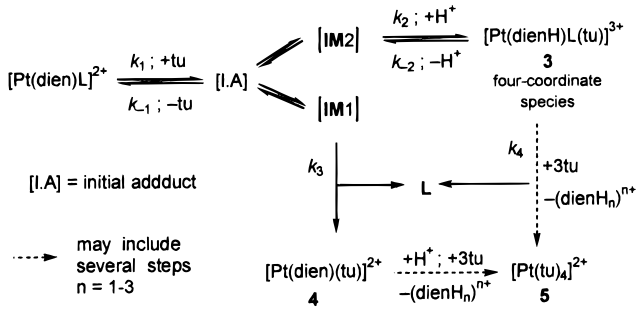
complex	nucleophile	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
1	H_2O	85 ± 1 (76 ± 8)[b]	−105 ± 2 (−135 ± 24)[b]
	I^-	83 ± 3	−49 ± 8
	tu	72 ± 1 [69.2 ± 0.3][c]	−79 ± 4 [−81 ± 1][c]
3(**1**)	tu	66 ± 5	−100 ± 15
2	H_2O	87 ± 7 (78 ± 11)[b]	−98 ± 22 (−125 ± 33)[b]
	I^-	78 ± 3	−67 ± 10
	tu	72.8 ± 0.3 [70.9 ± 0.7][c]	−86 ± 1 [−79 ± 2][c]
3(**2**)	tu	62 ± 8	−108 ± 25
$[Pt(dien)(H_2O)]^{2+}$	Guo-N7	54.0 ± 0.3	−66 ± 1
$[Pt(dien)(H_2O)]^{2+}$	Ado-N7	54.5 ± 0.1	−90.6 ± 0.1

[a] I = 0.1 M. [b] The data in parentheses refer to the I^- system. [c] The data in brackets refer to pH 3.

Chart 2



Scheme 1



equatorial groups through a square-pyramidal structure is well-known as Berry's pseudorotation[40] in pentavalent main-group element compounds, similar processes in Pt(II) chemistry are rare. In a few cases, isomerization of Pt(II) complexes has been proposed to occur via a pseudorotation mechanism, rather than the usual consecutive displacement mechanism involving ion-pair formation.[39] It should be noted that the products in the reactions of **1** and **2** with thiourea cannot be explained in terms of a consecutive displacement mechanism, because **1** and **2** have no convenient ionic leaving groups. The major argument against a pseudorotation mechanism is that a geometrical change of the intermediate would violate the highly stereospecific nature of substitution reactions of square-planar complexes.[39] However, this is just the case found in this study. Evidently, the comparable trans effect of all donor atoms in **1** and **2** combined with the rigidness of the dien ligand favor the pseudorotation mechanism in these cases.

Formation of 1 and 2. Second-order rate constants for the formation of **1** and **2** at different temperatures are given in Table S6 (Supporting Information). The rate data were obtained by HPLC from the diminution of the signal of the uncomplexed nucleoside in Pt excess. With guanosine, the values directly refer to the formation of **1**. However, in the case of adenosine, both N1 and N7 complexes are formed at about pH 4. According to HPLC measurements, the initial ratio of formation of N7:N1 was approximately 1.5 at all temperatures,[22] consistent with findings reported earlier for various aquated *cis*-Pt^{II} diamines.[41] The activation parameters for the formation of **1** and **2** are included in Table 4.

The knowledge of the rate parameters k_f and k_S for the formation and solvent-assisted dissociation[42] of **1** and **2**, respectively, can be employed to estimate the equilibrium constants $K = k_f/k_S$ for these complexes according to eq 4. The

$$[Pt(dien)(H_2O)]^{2+} + L \underset{k_S}{\overset{k_f}{\rightleftharpoons}} [Pt(dien)(L\text{-}N7)]^{2+} + H_2O \quad (4)$$

data calculated at 25 °C from the activation parameters listed in Table 4 give log K = 7.5 ± 0.1 for **1** and log K = 6.1 ± 0.2 for **2**. For comparison, a value of log K > 6.6 has been estimated for Pt(II) binding to guanosine on the basis of data found for $[Pd(dien)]^{2+}$.[43] Thus, the thermodynamic stablity of various Pt(II) binding modes follows the order Ado-N7 < Ado-N1 < Guo-N7 < Urd-N3.[44] In an earlier study, almost equal formation constants (log K = 3.6 ± 0.1) were reported for the 1:1 complexes of adenosine, cytidine, and guanosine with aquated *cis*-$Pt^{II}(NH_3)_2$ at pH 6.5,[45] but this lack of thermodynamic selectivity was subsequently questioned.[43]

Conclusions

Substitution reactions of the model compounds [Pt(dien)(Guo-N7)]$^{2+}$ (**1**) and [Pt(dien)(Ado-N7)]$^{2+}$ (**2**) by thiourea and I^- follow an associative mechanism in aqueous solution. Under neutral conditions, the usual two-path system involving the solvent path and the nucleophile-dependent path is obeyed. With both dicationic complexes, the reactivities of I^- and thiourea are comparable, which may be attributed to electrostatic interactions between reactants favoring the attack of I^- and to the diminution of π back-donation from the metal disfavoring the reactivity of thiourea. In addition, the substituent at C6 of the base moiety may slightly affect the reactivity order of these nucleophiles through steric effects, H-bonding interactions, or solvation effects.

In acidic solution, substitution reactions of both complexes by thiourea were accompanied by a changeover in mechanism due to ring opening of the tridentate dien ligand, i.e., they follow an associative mechanism involving pseudorotation of the five-coordinate intermediate. Ring opening of the tridentate dien ligand and subsequent trapping of the dissociated dien-NH_2 group by protonation provides a competing route for the direct

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(42) In 0.1 M $NaClO_4$.
(43) Vestues, P. I.; Martin, R. B. *J. Am. Chem. Soc*. **1981**, *103*, 806−809.
(44) Urd refers to deprotonated uridine.[5] The order Ado-N7 < Ado-N1 is based on isomerization studies.
(45) Scovell, W. M.; O'Connor, T. *J. Am. Chem. Soc*. **1977**, *99*, 120−126.

replacement of the nucleoside by thiourea in the overall reaction. According to kinetic analysis, about 60% of **1** and 70% of **2** are converted into free ligand via the ring-opening step.

Although the ring-opened species **3**(**1**) and **3**(**2**) are stable in cold acidic solution, they decompose predominantly back to the starting material when the pH of the solution is increased. The ability of the dien-NH_2 group to displace coordinated thiourea from Pt(II) contradicts the trans effect S > N and suggests that the NH_2 group of a partially chelated amine is a powerful nucleophile to Pt(II). For example, slow intramolecular S → N migration of Pt(II) has been reported earlier for L-methionine,[46] *S*-guanosyl-L-methionine,[47] and histidylmethionine.[48] In addition, 5′-GMP is able to remove S-bound L-methionine from [Pt(dien)(Met-S)]$^{2+}$.[49] The facile displacement of sulfur-bound thiourea from the Pt(II) coordination sphere found in our study is important, as it demonstrates the nucleophilic power of a group which is spatially in a favorable position.

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Supporting Information Available: Tables S1 and S2 listing the ^{1}H, ^{13}C, and ^{195}Pt chemical shifts for **1**, **2**, **3**(**1**), and **3**(**2**). Observed rate constants for the substitution reactions of **1** and **2** by I^- (Table S3) and thiourea (Table S4). Second-order rate constants for substitution reactions of **1**, **2**, **3**(**1**), and **3**(**2**) by thiourea at pH 3 (Table S5), and observed rate constants (Table S6) for the formation of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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