

Dissociation of Platinum(II) Nucleobase Complexes—Evidence for a Three-path Mechanism *via* a Five-coordinate Intermediate

Marjaana Mikola, Jouko Vihanto and Jorma Arpalahti*

Department of Chemistry, University of Turku, FIN-20500 Turku, Finland

In thiourea assisted dissociation of $[\text{Pt}(\text{dien})(\text{Guo-N7})]^{2+}$ (Guo = guanosine, dien = diethylenetriamine) in aqueous solution (pH = ca. 3) the nucleophile dependent reaction follows a three-path mechanism, in which the initial binding of the nucleophile to the complex and the ring-opening step of the terdentate dien ligand are reversible.

Aqueous solution substitution reactions of platinum(II) complexes are generally explained by a two-path mechanism, in which both paths involve a five-coordinate intermediate.¹ In the solvent path the rate-limiting step is the attack of a solvent molecule to the complex followed by loss of the leaving group and rapid substitution of a coordinated solvent molecule by the nucleophile, while the nucleophile dependent path involves direct substitution of the leaving group by the incoming nucleophile. In non-aqueous medium an electrophilic catalysis has been proposed to affect the dissociation of some platinum(II) complexes *via* an associative mechanism,² while a few cases report a dissociative mechanism for the overall reaction.³ In connection with our studies on Pt^{II} -nucleobase interactions we found that the thiourea assisted dissociation of $[\text{Pt}(\text{dien})(\text{Guo-N7})]^{2+}$ follows neither the usual two-path mechanism nor the more rare electrophilic catalysis or dissociative mechanism in slightly acidic aqueous solution. Instead, our kinetic data suggests that the nucleophile dependent reaction obeys a three-path mechanism *via* a five-coordinate intermediate, in which the initial binding of the nucleophile to the complex and the ring-opening step of the terdentate dien ligand are reversible. The proposed reaction mechanism is depicted in Scheme 1.

Dissociation of $[\text{Pt}(\text{dien})(\text{Guo-N7})]^{2+}$ **1** in the presence of various amounts of thiourea was studied in slightly acidic aqueous solution (pH = ca. 3) at 338.2 K by using HPLC.† In a typical kinetic run the disappearance of **1** was accompanied by the formation of species **3**, **4**, **5** and **L**, of which **5** and **L** were clearly end-products (Fig. 1). In each case **L** began to accumulate earlier than **5**, but their final amounts were equal which was verified by authentic compounds. By contrast, **3** is first formed and then consumed during the overall reaction indicative for a species capable of reacting further with thiourea. The same holds also for **4**, the assignment of which was supported by co-elution of **4** and added $[\text{Pt}(\text{dien})(\text{tu})]^{2+}$ (tu = thiourea), although its signal was only poorly resolved from free thiourea.

The fact that **3** could be detected by HPLC prompted its isolation in a preparative scale. For this purpose $[\text{Pt}(\text{dien})(\text{Guo-N7})](\text{ClO}_4)_2$ (0.08 mmol) was suspended into 500 μl of 0.1 mol dm^{-3} HClO_4 , 0.04 mmol of thiourea was added, and the mixture was stirred for 2 h at 338 K. After evaporation to dryness the residue was extracted with 2 ml of ethanol. The procedure was repeated by adding 0.04 mmol of thiourea into the remaining solid. The combined ethanol solutions were acidified to pH 2, evaporated to dryness and the residue dissolved in 1 ml of water was fractionated on a preparative RP-

18 column (40 μm , 30 \times 200 mm) by using 0.1 mol dm^{-3} NaClO_4 and 1 mmol dm^{-3} HClO_4 in 5% methanol as eluent. Excess electrolyte from the combined fractions of **3** was removed by refractionating with 5% methanol in 1 mmol dm^{-3} HClO_4 . Spectroscopic data‡ for isolated **3** 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 signal at -3060 ppm is typical for a PtN_3S chromophore,^{6,7} while the ^{13}C NMR and ^1H NMR spectra reveal the presence of the guanosine, thiourea and dien ligands.§ The asymmetry of the coordinated dien strongly suggest 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 also earlier in platinum(II) complexes.^{6,8} Even though **3** is reasonably stable in acidic aqueous solution, it converts into **1** and **L** in a 12 : 1 ratio based on HPLC studies. The rate of the reaction is directly proportional to the pH of the solution (the slope of the plot of $\log k_{-2,\text{obs}}$ vs. pH is 1.01 at 338.2 K). The conversion of **3** predominantly into **1** was confirmed by ^1H NMR by treating **3** with aqueous alkali and acidifying the sample prior to the NMR measurements to avoid deuteration of H-8.

Under the experimental conditions employed the disappearance of **1** obeys first-order rate law only when the concentration of thiourea exceeds 0.05 mol dm^{-3} , whereas below that value a clear upfield curvature is observed. Most probably this results from the reversal of the ring-opening step of the dien group. The plot $k_{1,\text{obs}}$ vs. $[\text{tu}]$ gives $k_1 = (8.80 \pm 0.03) \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. A rate equation for two consecutive reactions in which the first step consists of two parallel reactions was applied to compute the rate parameters for the formation and disappearance of **3**. In each case $k_{2,\text{obs}}$ was about 60% of $k_{1,\text{obs}}$ indicating that the forward reactions of **2** yield **3** and **L** in a ratio of 1.5 : 1. In the presence of an excess of thiourea isolated **3** gave **L** and **5** in a ratio of 1 : 1 with a second-order rate constant comparable to that found for the disappearance of **3** in the overall reaction, *viz.* $k_4 = (2.6 \pm 0.1) \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.

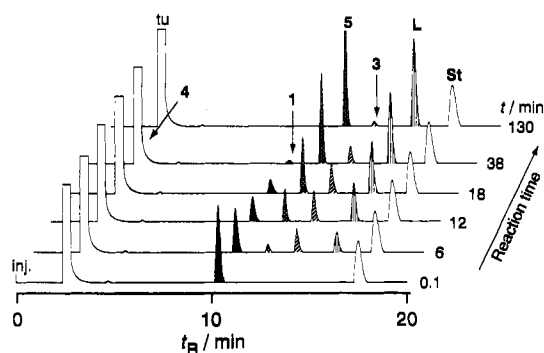
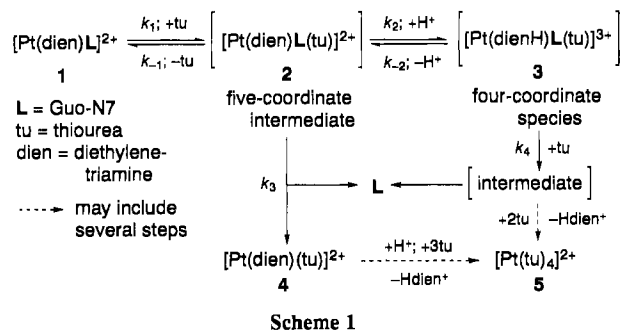


Fig. 1 HPLC traces of the mixture of $[\text{Pt}(\text{dien})(\text{Guo-N7})]^{2+}$ (**1**, 8×10^{-5} mol dm^{-3}) and thiourea (tu, 0.1 mol dm^{-3}) at 338.2 K (pH 3) at selected time intervals. St denotes 1,3-dimethyluracil (5×10^{-5} mol dm^{-3}) employed as an internal standard. An RP-18 column (endcapped, 5 μm , E. Merck AG) using water-methanol in 0.05 mol dm^{-3} NaClO_4 (pH 3) as an eluent (0 \rightarrow 12% methanol/3 \rightarrow 12 min, 1 ml min^{-1}).

These findings are in agreement with the proposed reaction mechanism and manifest the importance of the five-coordinate intermediate in the overall reaction, although this species could not be detected by HPLC due to its immeasurably fast reactions under these conditions. Usually a trigonal-bipyramidal structure is proposed for the intermediate, in which the incoming nucleophile and the leaving group adopt apical positions.¹ The unexpected inertness of the N-7 bound guanosine suggests that it prefers an equatorial position in the intermediate rather than the apical site expected from the *trans*-effect $\text{NH} > \text{N}-7$, which can be attributed to the rigidity of the terdentate dien ligand. However, the concomitant formation of **3** and **L** from **1** as well as the decomposition of **3** into **1** and **L** reveal also an apical site for **L**, which may result from the rearrangement of the intermediate either directly or *via* reversible reaction steps. The most striking feature in this system is the ability of the NH_2 group to displace coordinated thiourea from Pt^{II} , which contrasts the *trans* effect $\text{S} > \text{N}$ and suggests that the NH_2 group of a partially chelated amine is a powerful nucleophile to Pt^{II} .[¶] It is worth noting that in neutral solution **1** converts into **4** and **L** without detectable formation of **3** and **5**. This change in the reaction pattern at higher pH may be attributed to the reversibility of the step $2 \rightarrow 3$, which efficiently prevents forward reactions of **3**.

Kinetic data presented in this study show that ring-opening of the terdentate dien ligand and displacement of the nucleobase compete upon attack of thiourea into $[\text{Pt}(\text{dien})(\text{Guo-N7})]^{2+}$ under acidic conditions. With increasing pH the former reaction becomes less significant due to the reversibility of the ring-opening mode and is not detected in neutral solution. Also the initial binding of the nucleophile to the complex is strongly reversible. The relative rate constants of the different steps reveal that the five-coordinate intermediate yields free ligand, ring-opened species and starting material in a ratio of 1:1.5:12.

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Footnotes

† The compounds $[\text{Pt}(\text{dien})(\text{Guo-N7})(\text{ClO}_4)_2]^{4+}$ and $[\text{Pt}(\text{tu})_4]\text{Cl}_2^{5+}$ were prepared by the literature methods. Guanosine was purchased from Sigma

and contained 1.75 mol of crystal water (TG-analysis). A solution of $[\text{Pt}(\text{dien})(\text{tu})]^{2+}$ was obtained by mixing $[\text{Pt}(\text{dien})(\text{H}_2\text{O})]^{2+}$ and thiourea in a 1:1 ratio.⁶ Samples withdrawn from the reaction mixture at suitable time intervals were diluted with cold $0.01 \text{ mol dm}^{-3} \text{ HClO}_4$ (1:1), and they were stored on ice prior to LC analysis. Peak areas at 260 nm were used as a measure of concentration by employing 1,3-dimethyluracil as internal standard.

‡ *Spectroscopic data for 3*: $^1\text{H NMR}$ (D_2O , 500 MHz) δ 2.8–3.6 (m, 8 H), 3.80–3.94 (m, 2 H), 4.21–4.24 (q, 1 H), 4.35–4.37 (m, 1 H), 4.63–4.66 (q, 1 H), 5.240 (s, br, 1 H), 5.359 (s, br, 1 H), 5.955 (d, 1 H, $J = 4 \text{ Hz}$), 6.755 (s, br, 1 H), 8.457 and 8.461 (2s, 1 H). $^{13}\text{C NMR}$ (D_2O , 125.65 MHz) δ 39.12, 47.35, 52.01, 52.06, 58.61, 63.49, 63.51, 72.41 (72,34), 76.66, 76.70, 87.84, 91.64, 117.27, 142.75, 153.14, 157.12, 159.85 and 177.78. $^{195}\text{Pt NMR}$ (D_2O , 107.17 MHz) δ –3060. For **1**: $^1\text{H NMR}$ (D_2O , 500 MHz) δ 2.86–3.28 (m, 8 H), 3.827 (dd, 1 H, $J = 4.0, 12.9 \text{ Hz}$), 3.905 (dd, 1 H, $J = 2.8, 12.9 \text{ Hz}$), 4.230 (q, 1 H), 4.374 (t, 1 H, $J = 5.0 \text{ Hz}$), 4.675 (t, 1 H, $J = 5.0 \text{ Hz}$) 5.933 (d, 1 H, $J = 5.0 \text{ Hz}$), and 8.398 (s, 1 H). $^{13}\text{C NMR}$ (D_2O , 125.65 MHz) δ 52.98, 56.65, 63.64, 72.61, 76.52, 88.09, 91.42, 117.58, 142.50, 153.24, 157.10 and 159.98.

§ Some of the resonances in the ^{13}C and $^1\text{H NMR}$ spectra of **3** show additional splitting that is absent in the spectra of **1**: H-8 (2 Hz), H-2' (5 Hz), H-3' (2 Hz), C-2' (5.5 Hz), C-5' (2.6 Hz), and one carbon of the dien group (6.4 Hz). At this stage the reason for this splitting remains unclear.

¶ *Note added at proof*: In a few cases the guanosine N7 atom has been shown to displace S-bound ligands on Pt^{II} .^{9,10}

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