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FULL PAPER

Kinetics and mechanism of the reactions of $[Pt(terpy)H_2O]^{2+}$ with thiols in acidic aqueous solution. Synthesis and crystal structure of $[Pt(terpy)(tu)](ClO_4)_2$ (tu = thiourea)†

Živadin D. Bugarčič,[a,b] Günter Liehr[b] and Rudi van Eldik *[b]

[a] *Department of Chemistry, University of Kragujevac, 34000 Kragujevac, Yugoslavia*
[b] *Institute for Inorganic Chemistry, University of Erlangen-Nürnberg, Egerlandstrasse 1, 91058 Erlangen, Germany*

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The kinetics of the complex-formation reactions between $[Pt(terpy)H_2O]^{2+}$, where terpy is 2,2′:6′,2″-terpyridine, with L-cysteine, DL-penicillamine, glutathione and thiourea (tu) were studied in an aqueous 0.10 M perchloric acid medium using variable-temperature and -pressure stopped-flow spectrophotometry. Thiourea is the best nucleophile with a second order rate constant, k_1^{298}, of 1.72×10^5 M^{-1} s^{-1}, whereas glutathione is the strongest nucleophile of the studied thiols, for which k_1^{298} varied between 38 and 583 M^{-1} s^{-1}. Activation volumes for the reactions with thiourea, L-cysteine, glutathione and DL-penicillamine, are -6.0 ± 0.3, -9.3 ± 0.4, -12.4 ± 0.6 and -20.6 ± 1.0 cm^3 mol^{-1}, respectively. The negative entropies and volumes of activation support a strong contribution from bond making in the transition state of the substitution process. The crystal structure of $[Pt(terpy)(tu)](ClO_4)_2$ was determined by X-ray diffraction. Crystals are monoclinic with the space group $P21/c$ and consist of the distorted square-planar $[Pt(terpy)(tu)]^{2+}$ complex. The Pt–N (central) bond distance, 1.971(14), is shorter than the other two Pt–N distances, 2.078(15) and 2.046(15) Å. The Pt–S distance is 2.301(5) Å.

Introduction

The chemistry of transition metal complexes containing metal–sulfur bonds has become of considerable biological importance. Furthermore, Pt complexes such as cisplatin and carboplatin are well known antitumor agents,[1] although of the thousands of Pt complexes evaluated as antitumor agents, only a very small fraction has shown sufficient promise during preclinical evaluation.[2] The interaction of Pt with DNA is thought to be responsible for the antitumor activity, but there are many other potential biomolecules which can react with the platinum complexes.[1–3] Sulfur containing molecules play a significant role in the metabolism of platinum-based antitumor complexes. In fact already in the blood, where the Pt drug is administered by injection or infusion, several S-donor ligands are available for kinetic and thermodynamic competition.[4,5] Binding of *cis*-diamminedichloroplatinum(II), (cisplatin, *cis*-DDP), to intracellular thiol groups is known to be the reason for its renal toxicity and other side effects.[3] Reaction with SH groups of protein side chains (*e.g.*, in metallothioneins and glutathione, GSH) is thought to trap and deactivate the drug before it reaches its cellular target, DNA, to form the 1,2 intra-strand cross-link of the guanine bases, the likely cytotoxic adduct.[6] The interactions of Pt species with sulfur-containing biomolecules have been associated with negative phenomena, such as nephrotoxicity, gastrointestinal toxicity, ototoxicity and neurotoxicity.[7]

Molecules containing sulfur are currently under study as chemoprotectants in platinum-based chemotherapy. However, Pt-sulfur (thioether) adducts could perhaps serve as a drug reservoir for platination at DNA.[4] In particular, thiocarbonyl and thiol donors have shown promising properties for chemical use in modulating cisplatin nephrotoxicity.[7] A result suggesting a decrease of cisplatin or carboplatin nephrotoxicity has been observed in combined therapy with thiols.[7,8] However, methionine and its derivatives can form stable ring-opened complexes with carboplatin and its analogues. Since carboplatin reacts with nucleobases very slowly, it is conceivable that a methionine-containing peptide or protein may play an important role in the transport or activation of carboplatin.[9] For cisplatin and a few related species, binding at two neighbouring guanines results in intrastrand chelation and specific distortion of the DNA, changing its interactions with the proteins.[10] Competitive binding of platinum(II) antitumor complexes to DNA constituents (mainly guanine-N7 and adenine-N7) and protein-bound sulfur (cysteine and methionine residues) is critical to the metabolism and to the stability of the cytotoxic lesions of the drugs. In recent years, competition studies for Pt-amine compounds with S-donor ligands and nucleobases have shown that easy transfer from a thioether S ligand occurs only to a guanine-N7 site, and not from thiolates or to the adenine-N7 site.[4,8] Model studies under physiologically relevant conditions have conclusively shown that the kinetic preference of Pt(II) is for biorelevant thiols (cysteine, GSH) rather than (5′-GMP).[11]

The monofunctional $[Pt(terpy)Cl]^+$ complex (terpy = 2,2′:6′,2″-terpyridine), shown below, is a very useful model for studying the binding of platinum compounds to different nucleophiles. This and related complexes of the general type $[Pt(terpy)X]^{n+}$ have been the subject of active research in recent years. The kinetics of the substitution reactions involving several different X ligands have been investigated.[12–16] However, it has been known for more than 25 years that 2-hydroxyethanethiolato-2,2′:6′,2″-terpyridineplatinum(II) nitrate intercalates into DNA with a binding constant of 0.83×10^5 M^{-1}.[17] Moreover, it has also been shown that 4-picoline-2,2′:6′,2″-

† Electronic supplementary information (ESI) available: tables of observed pseudo-first-order rate constants and the pressure dependence of reaction (1) with different thiols. See http://www.rsc.org/suppdata/dt/b2/b201930m/

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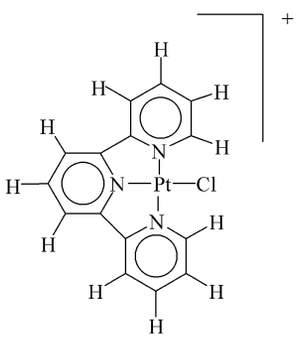
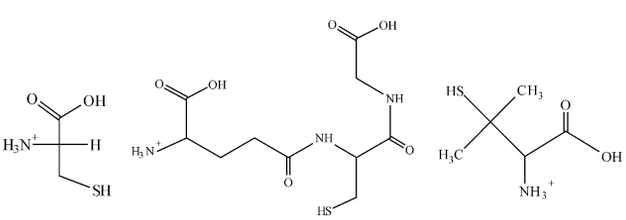
terpyridineplatinum(II)bis(tetrafluoroborate) is a more potent intercalator of DNA ($K = 2 \times 10^7$ M^{-1}), and this has been ascribed to the retention of the double positive charge on platinum. This complex platinates guanosine residues at N7 in double-stranded DNA.[18] Very recently, (2,2′:6′,2″-terpyridine)-platinum(II) complexes were demonstrated to be cytotoxic to human ovarian cancer and that bis[(2,2′:6′,2″-terpyridine)-platinum(II)] complexes with short and rigid linkers are particularly effective.[19–21] This study was extended to the (2,2′:6′,2″-terpyridine)platinum(II) thiolate complexes.[22]



We recently reported the kinetics of the complex-formation reactions between $[Pt(NNN)H_2O]^{2+}$ (NNN is tridentate nitrogen-bonding ligands, including terpy) with different nucleophiles.[12] However, we also studied the kinetics of the complex-formation reactions between $[Pd(NNN)H_2O]^{2+}$ and thiols, such as L-cysteine, DL-penicillamine and glutathione, in an acidic aqueous solution.[23] With the aim to extend our earlier work, we investigated the $[Pt(terpy)H_2O]^{2+}$ complex and report here a detailed kinetic study on the complex-formation reactions with thiols (*viz*. L-cysteine, DL-penicillamine and glutathione) and thiourea (tu) in acidic aqueous solution, eqn. (1).

$$[Pt(terpy)H_2O]^{2+} + L \rightleftarrows [Pt(terpy)L]^{2+} + H_2O \; k_1, k_{-1} \quad (1)$$

L = L-cysteine, DL-penicillamine, glutathione and thiourea.



L-cysteine glutathione DL-penicillamine

In addition, we report the crystal structure of [Pt(terpy)-(tu)]$(ClO_4)_2$. It was envisaged that this study could throw more light on the mechanism of the nephrotoxicity of active platinum antitumor complexes.

Experimental

Synthesis of complexes

The complex $[Pt(terpy)Cl]Cl\cdot H_2O$ was prepared according to a literature method.[24] Chemical analysis, UV-VIS and ^1H NMR spectral data were in good agreement with those obtained in previous preparations.

$[Pt(terpy)(tu)](ClO_4)_2$ was prepared from [Pt(terpy)Cl]Cl which was dissolved (0.04271 g) in 20 mL aqueous methanol (MeOH : H_2O = 95 : 5 (v/v)). The chloro complex was converted to the aqua complex, by precipitating chloride by adding an equivalent of $AgClO_4$ (0.03308 g), heating to 40 °C for 1 h, and removing the AgCl by filtration. To a stirred solution, a solution of thiourea (0.0062 g) in 10 cm^3 of methanol was added dropwise. The clear green–yellow solution was filtered and allowed to stand at room temperature until crystals precipitated. The green–yellow needles, $[Pt(terpy)(tu)](ClO_4)_2$, were filtered off, washed with water and diethyl ether, and dried an air. Yield: 0.05034 g (90%); found: N 9.87, C 27.33, H 2.47, S 4.45%; calc.: N 9.95, C 27.29, H 2.13, S 4.54%.

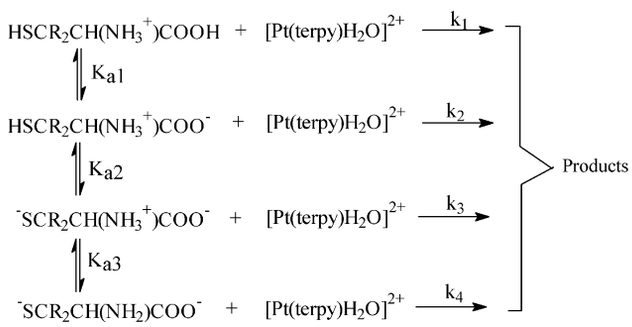
Chemicals and solutions

The chloro complex was converted into the aqua analogue in solution by adding an equivalent of $AgClO_4$, heating to 40 °C for 1 h, and removing the AgCl precipitate by filtration through a 0.1 μm pore membrane filter. Great care was taken to ensure that the resulting solution was free of Ag^+ ions and that the chloro complex had been converted completely into the aqua species. Since the perchlorate ion does not coordinate to Pt(II) and Pd(II) in aqueous solution,[25] the kinetics of the complex-formation reactions were studied in perchlorate media. The ionic strength of the solutions was adjusted to 0.1 M with $HClO_4$ (Merck, p.a.).

Ligand stock solutions were prepared without further purification shortly before use by dissolving the chemicals L-cysteine (Fluka, Assay > 99.5%), DL-penicillamine (Fluka, Assay > 99%), glutathione (Fluka, Assay > 99%) and thiourea (Merck, p.a.) in 0.1 M $HClO_4$ as supporting electrolyte. Under these experimental conditions, pH = 1.0, the $[Pt(terpy)H_2O]^{2+}$ complex was stable and deprotonation of the complex was negligible.[14,16] Millipore water was used in the preparation of all solutions.

Acid dissociation constants

Acid dissociation constants are defined in Scheme 1 below. At



Scheme 1 Cysteine, R = H; penicillamine, R = Me.

25 °C and μ = 1.0 M, their values are: for cysteine[26a] pK_{a1} = 1.9, pK_{a2} = 8.10 and pK_{a3} = 10.1; for penicillamine[26b] pK_{a1} = 1.9, pK_{a2} = 7.92 and pK_{a3} = 10.5. Such constants for glutathione at 25 °C and an ionic strength of 0.2–0.55 M have been reported as pK_{a1} = 2.05, pK_{a2} = 3.40, pK_{a3} = 8.72 and pK_{a4} = 9.49.[27] Under the selected experimental conditions, $[H^+] \gg K_a$ and all nucleophiles are fully protonated, such that the reaction pathways described by k_2, k_3, k_4 in Scheme 1 can be neglected at pH = 1.0 where all rate and activation parameters were determined. At this pH, the reactions with rate constants k_2, k_3 and k_4 contribute less than 5% to the overall kinetics, which is within the error limits of the kinetic measurements and determined activation parameters.

Instrumentation

Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. UV-VIS spectra were recorded on Shimadzu UV 250 and Hewlett-Packard 8452A spectrophotometers with thermostatted 1.00 cm quartz Suprasil cells. Kinetic measurements were carried out on an Applied Photophysics SX.18MV stopped-flow instrument coupled to an online data acquisition system. Experiments at elevated pressure (up to 130 MPa) were

Table 1 Crystallographic data for $[Pt(terpy)(tu)](ClO_4)_2$

Formula	$C_{16}H_{15}N_5PtS$, $2(ClO_4)$
FW	703.3
Crystal size/mm	0.05 × 0.13 × 0.38
Crystal system	Monoclinic
Space group	$P21/c$ (no. 14)
a/Å	12.811(4)
b/Å	17.855(4)
c/Å	19.277(5)
β/°	150.888(10)
V/Å^3	2145.3(10)
Z	4
T/K	293
μ(Mo-Kα)/mm^{-1}	6.9
F(000)	1352
μ(Mo-Kα)/Å	0.70930 (graphite monochromator)
Total, unique data	3357, 3357
Observed data [$I > 2\sigma(I)$]	2438
R, wR, S	0.0726, 0.2049, 1.368

performed on a homemade high-pressure stopped-flow unit[28] attached to an online data acquisition system[29] with which the kinetic traces could be evaluated, using the OLIS KINFIT (Bogart, GA) set of programs. The temperature was controlled throughout all kinetic experiments to ±0.1 °C. All kinetic measurements were performed under pseudo-first-order conditions, *i.e.*, at least a 10-fold excess of the nucleophile was used.

Kinetics measurements

The spectral changes resulting from mixing of complex and ligand solutions were recorded over the wavelength range 220 to 450 nm to establish a suitable wavelength at which kinetic measurements could be performed. Reactions were initiated by mixing equal volumes of the complex and thiol solutions directly in the stopped-flow instruments and were followed for at least eight half-lives. Complex formation was monitored as an increase in absorbance at 260, 267 or 340 nm under pseudo-first order conditions, with thiol in at least 10-fold excess. All kinetic runs could be fitted by single exponentials, and no subsequent reactions were observed. The observed pseudo-first-order rate constants, k_{obsd}, were calculated as average values from five to eight independent runs. The temperature dependence of k_{obsd} was studied in the range 15 to 35 °C. Experimental data are reported in Tables SI to SIII (ESI) and are summarized in Fig. 1.

The pressure dependence of the observed rate constants was studied at 25 °C, in the range 0.1 to 130 MPa. These reactions were also followed under pseudo-first-order conditions with thiol in excess. High-pressure kinetic data are reported in Tables SIV to SVI (ESI) and are summarized in Fig. 2.

Crystal structure determination

X-Ray intensities were collected at room temperature on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.70930 Å) with the ω–2θ scan technique. All reflections with $I > 2\sigma(I)$ were considered observed and used in the analysis. A total of 3357 reflections were measured of which 2438 were considered observed. Due to decay of the crystal, it was necessary to stop the data collection, and it was not possible to add another asymmetric unit to the data set. Crystal data and details of the data collection are given in Table 1. For solution and refinement of the structure, the program SHELXL-97, and for computing molecular graphics and publication material, the program package PLATON were used.[30]

CCDC reference number 180738.

See http://www.rsc.org/suppdata/dt/b2/b201930m/ for crystallographic data in CIF or other electronic format.

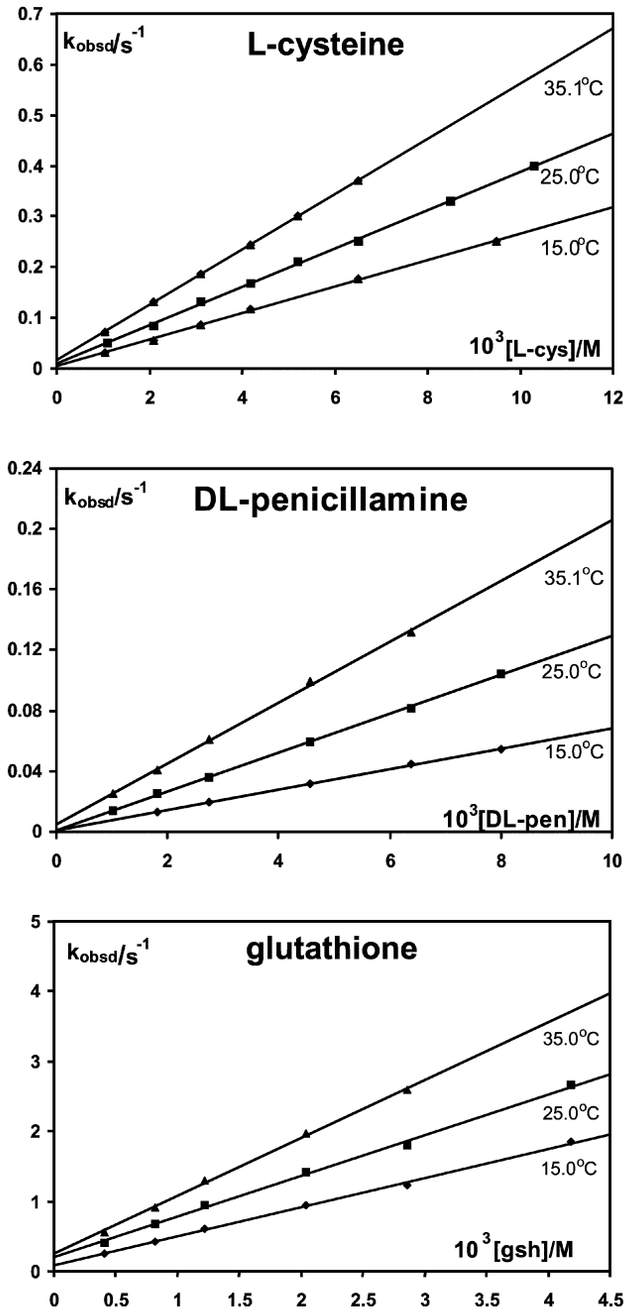


Fig. 1 Observed pseudo-first order rate constants, k_{obsd}, as a function of thiol concentration and temperature.

Results and discussion

The observed pseudo-first-order rate constants, k_{obsd}, as a function of the total concentration of thiols is described by eqn. (2).

$$k_{obsd} = k_{-1} + k_1[\text{thiol}] \quad (2)$$

A least-squares fit of the experimental data according to eqn. (2), resulted in values for the forward complex-formation rate constant, k_1, and the reverse aquation rate constant, k_{-1}. In all cases the substitution reactions are characterized by small values for k_{-1} since the observed intercepts (see Fig. 1) are in most cases negligible, illustrating that the solvent cannot effectively displace the coordinated thiols. Thus, the complex-formation reaction goes almost to completion. The second-order rate constants k_1 were obtained directly from the plot of k_{obsd} *vs.* thiol concentration. The temperature dependencies of these rate constants allowed for the calculation of the enthalpies and entropies of activation by use of the Eyring

Table 2 Rate constants and activation parameters for the reaction of $[Pt(terpy)H_2O]^{2+}$ with thiols and thiourea [a]

L	k_1^{298}/M^{-1} s^{-1}	$\Delta H^{\neq}$/kJ mol^{-1}	$\Delta S^{\neq}$/J K^{-1} mol^{-1}	$\Delta V^{\neq}$/cm^3 mol^{-1}
L-Cysteine	37.8 ± 0.1	25 ± 0.5	−132 ± 2	−9.3 ± 0.4
L-Glutathione	(5.8 ± 0.1) × 10^2	23 ± 1	−116 ± 3	−12.4 ± 0.6
DL-Penicillamine	12.8 ± 0.1	38 ± 1	−98 ± 3	−20.6 ± 1.0
Thiourea	(1.72 ± 0.02) × 10^5	22 ± 1 [b]	−73 ± 1 [b]	−6.0 ± 0.3 [b]

[a] All values refer to 0.10 M $HClO_4$. [b] Data from ref. 12.

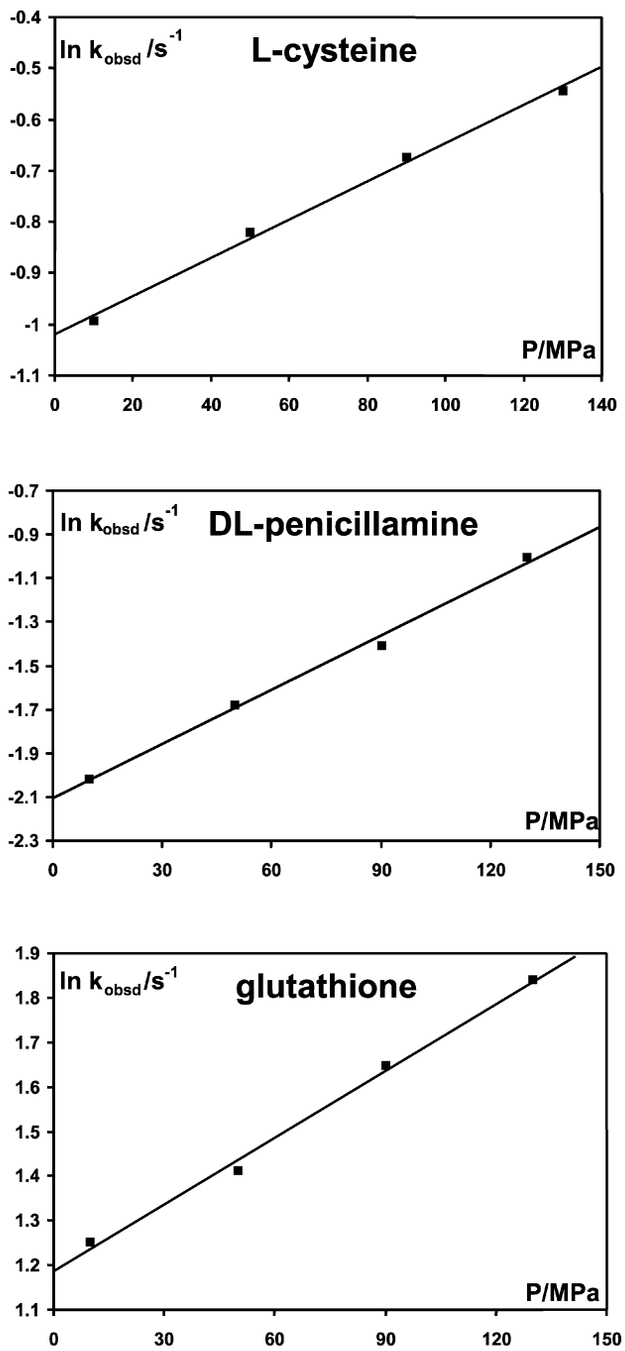


Fig. 2 Observed pseudo-first-order rate constants, ln k_{obsd}, as a function of pressure.

equation. Rate constants and activation parameters derived from these experiments are summarized in Table 2.

From Table 2 it can be seen that although the thiol ligands are good entering groups for the Pt(II) complex, thiourea is the best nucleophile. From a comparison of the thiols used, it can be concluded that the variation in size, bulkiness and solvation of the entering thiols reflect in their properties as nucleophiles. The difference in nucleophilicity of the selected thiols is obvious, and their reactivity follows the order DL-penicillamine < L-cysteine < glutathione < thiourea. The sensitivity of the reaction rate towards the σ-donor properties of the entering ligands is in line with that expected for an associative mode of activation. In addition, steric effects are very important as well. For example, DL-penicillamine has the lowest reactivity of the thiols used, which can be ascribed to steric effects involving the two methyl groups on carbon near the sulfur atom. At the same time, glutathione is considerably more reactive than expected. This anomaly seems to suggest an appreciable anchimeric effect capable of reducing the activation energy of the substitution reaction, arising from hydrogen bonding interactions between the acidic group located in a suitable position of the nucleophile. The anchimeric effect has been reported for other reactions at Pt(II) complexes and is well known for organic reactions.[31] This clearly demonstrates that the versatile kinetic behaviour is controlled by steric hindrance on the tridentate ligand and the nucleophilicity of the entering nucleophiles. Increasing steric hindrance is expected to slow down the ligand substitution reactions, whereas increasing nucleophilicity is expected to speed up this process in terms of an associative mechanism. All available activation parameters (see further discussion) support the operation of an associative substitution mechanism.

A trigonal bipyramidal transition state for reaction (1), is probably stabilized by hydrogen bonding between the entering thiol and the leaving water ligand as already proposed for the reaction of $[Pd(H_2O)_4]^{2+}$ with monodentate acetate, propionate, glycolate, and carboxylic acids,[32,33] and of $[Pt(H_2O)_4]^{2+}$ with thioglycolic acid.[34] These findings indicate that bond-making with the entering thiol is important in the activation process and that water is still tightly bound to the metal centre in the transition state.

The ratios $k_{1(Pd)}/k_{1(Pt)}$, for the second order rate constants for the complex-formation reactions of $[Pd(terpy)H_2O]^{2+}$ [23] and $[Pt(terpy)H_2O]^{2+}$ with these thiols, vary from only 80 for glutathione to 350 for DL-penicillamine. This small difference in the reactivity of these two complexes can be accounted for in terms of the extraordinary high lability of the $[Pt(terpy)H_2O]^{2+}$ complex, which has been suggested to arise from the efficient electronic communication between the Pt(II) centre and the terpyridine chelate.[12] Along these lines, Pt(II) is a softer metal centre and more sensitive to electronic communication with the aromatic rings than Pd(II). On the other hand, $[Pt(terpy)H_2O]^{2+}$ is 10^4–10^5 times more reactive than the $[Pt(dien)H_2O]^{2+}$ complex with the same thiols,[35,36] which is in agreement with the difference in lability of these two complexes.[12] The aromatic terpy ligand increases the lability of the $[Pt(terpy)H_2O]^{2+}$ complex due to the chelate ring aromaticity and the electron withdrawing effect through π-back bonding, thus making the metal centre a more attractive target for the entering nucleophiles.[12]

In conclusion, the results presented here show that these thiols have a high affinity for the $[Pt(terpy)H_2O]^{2+}$ complex, which may have important biological implications because it supports the hypothesis of a drug reservoir mechanism [37–40] in which the platinum-sulfur (thioether) adduct is an intermediate for platinum binding to DNA. It should be noted, however, that ligand substitution reactions of platinum complexes are not limited to DNA but can be expected to occur with nucleophilic functional groups of proteins like thiols or selenols.[4] Potential

positive effects of the platinum–sulfur interaction, such as the possible prevention of side effects and optimal transport of the compounds, have been discussed recently.[4] However, very recently it was shown that the (2,2′:6′,2″-terpyridine)-platinum(II) thiolate complexes inactivate hTrxR in almost stoichiometric quantities and inactivation seems to be irreversible under *in vivo* conditions.[22] This very high specificity of the complex is due to the high affinity of thiols for platinum(II).

Activation parameters

The second-order rate constants, k_1, were studied as a function of temperature and pressure. Plots of $\ln(k_1)$ *versus* pressure are linear (see Fig. 2 and ESI) and the volumes of activation were calculated by application of eqn. (3).

$$\ln k_1 = \ln k_1^0 - \Delta V_1^{\neq} P/RT \qquad (3)$$

The derived values of $\Delta V_1^{\neq}$ are listed along with the thermal activation parameters $\Delta H_1^{\neq}$ and $\Delta S_1^{\neq}$ in Table 2. The significantly negative activation entropies and activation volumes for the forward reactions (k_1) suggest that the activation process in the present systems seems to be strongly dominated by bond making. This is in agreement with a net decrease in partial molar volume in the activation process, as expected for an associative mechanism involving a five-coordinate transition state. The results are in excellent agreement with data reported for Pd(II) complexes with the same thiols.[23] However, the values of $\Delta V_1^{\neq}$ are significantly more negative in the case of the Pt(II) complex. Since structural studies show that Pd(II) and Pt(II) terpy complexes have very similar bond lengths,[41–43] and as a result also molar volumes, the differences observed in the values of $\Delta V_1^{\neq}$ must be related to properties of the transition states. Less extensive orbital overlap in the five-coordinate transition state of Pd(II) should result in weaker and longer metal–ligand bonds, and a less compact structure, compared to those of isostructural Pt(II) complexes. The volume of activation for the reactions with DL-penicillamine is significantly more negative than for the other thiols. This could be accounted for in terms of the bulkiness of this particular thiol that causes a larger overlap of the van der Walls radii in the transition state as compared to the ground state.

Structure of [Pt(terpy)(tu)](ClO$_4$)$_2$

The structure of [Pt(terpy)(tu)](ClO$_4$)$_2$ is shown in Fig. 3 and some selected bond lengths and angles are given in Table 3. The structure consists of a discrete $[Pt(terpy)(tu)]^{2+}$ cation and two perchlorate ions. Terpy is coordinated to platinum as a tridentate ligand and the fourth position is occupied by thiourea. The coordination geometry around the platinum centre is distorted square-planar with N–Pt–N angles of 80.0(6), 80.7(6) and 160.7(6)°, and N–Pt–S angles of 99.6(4), 99.7(5) and 178.5(4)°. The Pt–N(1) distance to the central nitrogen atom of the terpy ligand, 1.971(14) C, is shorter than those to the other two nitrogen atoms of terpy, *viz*. 2.078(15) and 2.045(15) Å. The Pt–S distance of 2.301(5) Å is comparable to the Pt–S distance of 2.303(2) Å in 2-hydroxyethanethiolato(2,2′,2″-terpyridine)platinum(II) nitrate.[42] The pyridine rings were found to be planar within the experimental error limits. Bond distances and angles of terpyridine compare well with those already reported.[16,42,43] Further studies in search of a new class of platinum antitumor compounds could be platinum-sulfur adducts in which the thioether or thiol is already incoporated as the leaving ligand. The distinct differences between the systems Pt(II)-thiols and Pt(II)-thioethers, as well as the possible biological implications of these complexes could be of interest for future studies.

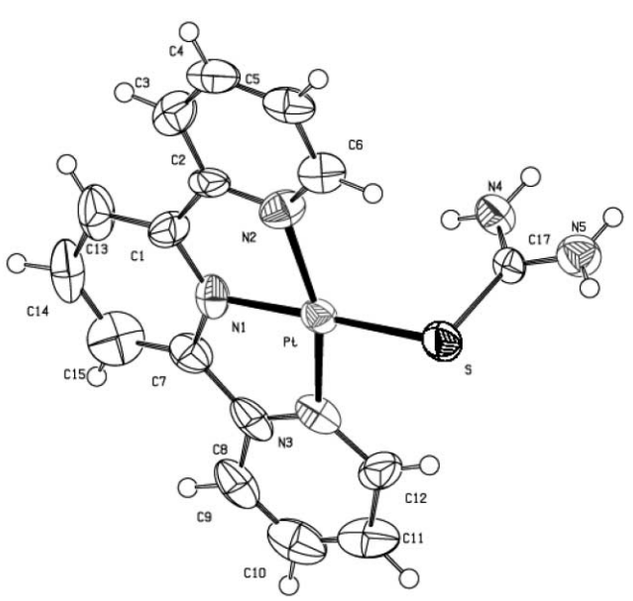


Fig. 3 X-Ray structure of $[Pt(terpy)(tu)]^{2+}$.

Table 3 Selected bond distances (Å) and angles (°) for [Pt(terpy)-(tu)](ClO$_4$)$_2$

Pt–N1	1.971(14)	N2–C2	1.34(2)
Pt–N2	2.078(15)	S–C17	1.705(16)
Pt–N3	2.045(15)	N3–C8	1.31(2)
Pt–S	2.301(5)	C7–C8	1.47(3)
N1–C1	1.35(2)	N4–C17	1.31(2)
N1–C7	1.35(2)	N5–C17	1.33(2)
S–Pt–N1	178.5(4)	Pt–S–C17	106.9(6)
S–Pt–N2	99.6(4)	C1–N1–C7	126.7(16)
S–Pt–N3	99.7(5)	Pt–N1–C1	117.5(12)
N1–Pt–N2	80.7(6)	Pt–N1–C7	115.8(12)
N1–Pt–N3	80.0(6)	Pt–N2–C2	110.9(12)
N2–Pt–N3	160.7(6)	Pt–N3–C8	114.3(14)

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