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Reduction of *trans*-dichloro- and *trans*-dibromo-tetracyanoplatinate(IV) by L-methionine†

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Reduction of *trans*-$[Pt(CN)_4X_2]^{2-}$ (X = Cl or Br) [as model compounds for antitumour-active platinum(IV) pro-drugs] to $[Pt(CN)_4]^{2-}$ by L-methionine, MeSR, has been studied at 25 °C in the range 0 < pH < 12 (X = Cl) and 0 < pH < 6 (X = Br) by use of stopped-flow spectrophotometry. The stoichiometry is $[Pt^{IV}]:[MeSR] \approx 1:1$; the reaction products are methionine *S*-oxide and $[Pt(CN)_4]^{2-}$ as identified by NMR and UV spectroscopies, respectively. The kinetics is first order with respect to the platinum(IV) and methionine concentrations and the second-order rate constants have a small pH dependence. In analogy with reduction of platinum(IV) complexes by thioglycolic acid, cysteine, penicillamine and glutathione, a mechanism is postulated in which $[Pt(CN)_4X_2]^{2-}$ is reduced by the various protolytic species of methionine in parallel reactions. In the transition state the thioether group of methionine is assumed to interact with co-ordinated halide, mediating the electron transfer to the platinum(IV) centre. The transition states for previously studied reactions between $[Pt(CN)_4X_2]^{2-}$ and thiols are discussed in view of these results. It is concluded that methionine-containing biomolecules may compete with thiol compounds for reduction of platinum(IV) pro-drugs under acidic conditions, and also in neutral solutions with low concentrations of thiol-containing biomolecules.

Antitumour-active platinum(IV) drugs are assumed to be reduced to their platinum(II) analogues within the cell prior to interaction with DNA.[1–9] Potential intracellular reducing agents are ascorbate and thiol-containing biomolecules, in particular glutathione (γ-glutamylcysteinylglycine) which is frequently present in high concentrations.[10,11] We have recently reported on the kinetics and mechanism for the reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ to $[Pt(CN)_4]^{2-}$ with the thiols thioglycolic acid, L-cysteine, DL-penicillamine (3-sulfanyl-D-valine) and glutathione.[12] The platinum complex was chosen as a convenient model compound for the study of reactions of various platinum(IV) pro-drugs, since the redox process is not disturbed by subsequent substitution processes in the platinum(II) product formed, $[Pt(CN)_4]^{2-}$. The reaction kinetics can be interpreted in terms of a mechanism involving chloride-mediated electron transfer from the different protolytic species of the reductant to the platinum centre.‡ A Brønsted correlation of the type $\log k_{RS^-} = 0.82\ pK_{RSH} + 1.1$ between the rate constants for oxidation of the four thiolate anions, RS^-, and the pK_{RSH} of the thiol was observed, indicating that the basicity of the reductant is a predominant factor in determining the reactivity towards the platinum(IV) complex. Interestingly, the same type of correlation is also found for the different species within each single protolytic thiol system as shown in Fig. 1. Unfortunately, it was not possible to determine the rates under conditions where the amino groups are deprotonated because the reactions become too fast to be monitored by the conventional stopped-flow technique already at pH *ca.* 5.

Methionine, $MeS(CH_2)_2CH(NH_3^+)CO_2H$, as part of some intracellular proteins, is also a potential reductant for platinum(IV) pro-drugs. Thus, it is interesting to compare the reactivity of this thioether-containing amino acid with the thiol-containing biomolecules studied previously. Thioethers are less reactive than thiols and we were, therefore, able to study the reduction of the complexes *trans*-$[Pt(CN)_4X_2]^{2-}$ (X = Cl or Br) with methionine in a much broader pH range than with the thiol compounds. Contrary to the large variations in rate with pH observed in the thiol systems, with methionine there is only a minor change of reduction rate in the range 0 < pH < 12.

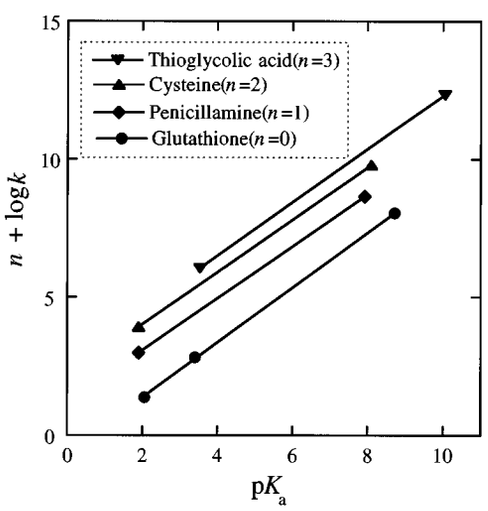


Fig. 1 Correlations between log *k* for reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ and pK_a for the various species within thiol protolytic systems (glutathione, cysteine, penicillamine and thioglycolic acid) based on data from ref. 12 (*n* is an arbitrary constant added to separate the lines for clarity)

Experimental

Chemicals and solutions

The salt $K_2[Pt(CN)_4Cl_2]$ was synthesized by oxidation of $K_2[Pt(CN)_4]\cdot 3H_2O$ with chlorine as described previously.[13] The UV/VIS spectrum of the sample solution agreed with that reported earlier for $[Pt(CN)_4Cl_2]^{2-}$.[14] The salt $K_2[Pt(CN)_4Br_2]$ was prepared according to the literature.[15] Stock solutions of 5.0 mmol dm^{-3} $K_2[Pt(CN)_4X_2]$ in 10 mmol dm^{-3} $HClO_4$, 10

† *Supplementary data available* (No. SUP 57246, 6 pp.): pseudo-first-order and second-order rate constants. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1.

‡ The thiols contain two to four protolytic groups, glutathione $[HO_2CCH(NH_3^+)CH_2CH_2CONHCH(CH_2SH)CONHCH_2CO_2H]$ for example contains two carboxylic, one thiol, and one amine group. The structures of the other three thiols are given in ref. 12.

mmol dm^{-3} NaX and 0.98 mol dm^{-3} $NaClO_4$ ionic medium were stable for several months. Deuterium oxide (Janssen, 99.5%), L-methionine (Merck, pa, ≥99%) and DL-methionine *S*-oxide (Acros Organics, ≥99%) were used as received. Stock solutions of methionine were prepared fresh daily. Acetate (0.2 mol dm^{-3}), phosphate (0.05–0.10 mol dm^{-3}), borate (0.05 mol dm^{-3}) and carbonate (0.10 mol dm^{-3}) buffers were used in the range 3.5 < pH < 12 and perchloric acid was used to adjust the pH in the range pH < 2.4. The ionic strength, *I*, was adjusted to 1.00 mol dm^{-3} with sodium perchlorate, and all experiments were run at sufficiently high halide concentrations (usually 0.10 mol dm^{-3}) to suppress hydrolysis of $[Pt(CN)_4X_2]^{2-}$. Water was doubly distilled from quartz.

Apparatus and measurements

The UV/VIS spectra were recorded by use of a Milton Roy 3000 diode-array spectrophotometer and 1.00 cm quartz Suprasil cells and proton NMR spectra on a Varian UNITY 300 MHz spectrometer working at room temperature. Proton NMR chemical shifts were measured in ppm relative to the residual solvent peak calibrated by $SiMe_4$. Kinetic traces were collected using an Applied Photophysics Bio Sequential SX-17 MX stopped-flow ASVD spectrofluorimeter, and rate constants (reported as average values from five to seven independent runs) were evaluated with the Applied Photophysics software package.[16] Hydrogen-ion concentrations were calculated from equation (1) which is based on a mean activity coefficient of 0.630 for 1.00 mol kg^{-1} $NaClO_4$.[17]

$$-\log [H^+] = p[H^+] = pH - 0.20 \quad (1)$$

Results and Discussion

Stoichiometry

Ten solutions with $[Pt(CN)_4Cl_2^{2-}] = 1.0 \times 10^{-4}$ mol dm^{-3}, $[HClO_4] = 0.10$ mol dm^{-3}, $[Cl^-] = 0.10$ mol dm^{-3}, $I = 1.00$ mol dm^{-3} and $0 \leqslant [MeSR]_{tot} \leqslant 2.0 \times 10^{-4}$ mol dm^{-3} were aged for *ca.* 18 h and their absorbances at the typical 255 nm maximum of $[Pt(CN)_4]^{2-}$ were recorded. The stoichiometry was determined as $[Pt^{IV}]:[MeSR]_{tot} = 1:0.93$ from the plot in Fig. 2. In order to check the reaction products further, ^1H NMR spectra of a solution of *ca.* 1.0×10^{-2} mol dm^{-3} methionine, 1.0×10^{-2} mol dm^{-3} $[Pt(CN)_4Br_2]^{2-}$ in D_2O and standard samples of DL-methionine *S*-oxide and L-methionine in D_2O were recorded. Comparison of those spectra shows that methionine is consumed almost completely when reduced by platinum(IV) as indicated by the decrease of the signal at δ(CH_3S) 1.98. The appearance of a sharp signal at δ[$CH_3S(O)$] 2.62 indicates that methionine *S*-oxide is the oxidation product. From the UV/VIS and NMR measurements we conclude that the stoichiometry can be expressed by equation (2). No subsequent reaction

$$[Pt(CN)_4X_2]^{2-} + MeSR + H_2O \longrightarrow [Pt(CN)_4]^{2-} + MeS(O)R + 2X^- + 2H^+ \quad (2)$$

between methionine *S*-oxide and $[Pt(CN)_4Cl_2]^{2-}$ could be detected under similar conditions during 18 h.

Kinetics

Reduction of $[Pt(CN)_4X_2]^{2-}$ was studied under pseudo-first-order conditions with methionine in at least a 10-fold excess. It was monitored by following the increase of absorbance at the 255 nm maximum of $[Pt(CN)_4]^{2-}$ or the decrease of the 240 nm peak of $[Pt(CN)_4Br_2]^{2-}$, respectively. Single-exponential kinetics traces were obtained in both cases and the concentration of the excess of halide had no influence on the rate of reaction. Time-resolved spectra for the reaction with $[Pt(CN)_4Cl_2]^{2-}$ are shown in Fig. 3, indicating that there is no accumulation of

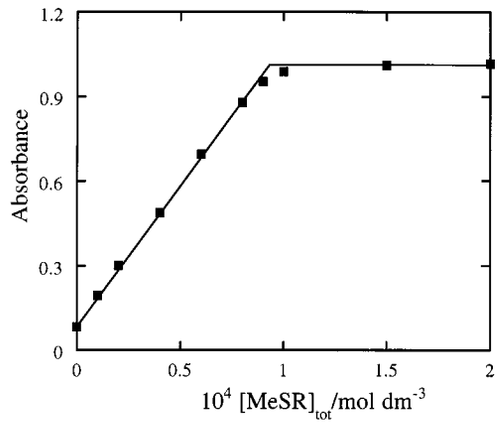


Fig. 2 Absorbance at 255 nm for solutions with constant $[Pt^{IV}]$ and increasing $[MeSR]_{tot}$. Conditions: $[Pt(CN)_4Cl_2^{2-}] = 1.0 \times 10^{-4}$ mol dm^{-3}, $[Cl^-] = 0.10$ mol dm^{-3}, $[H^+] = 0.10$ mol dm^{-3}, $I = 1.00$ mol dm^{-3} and room temperature

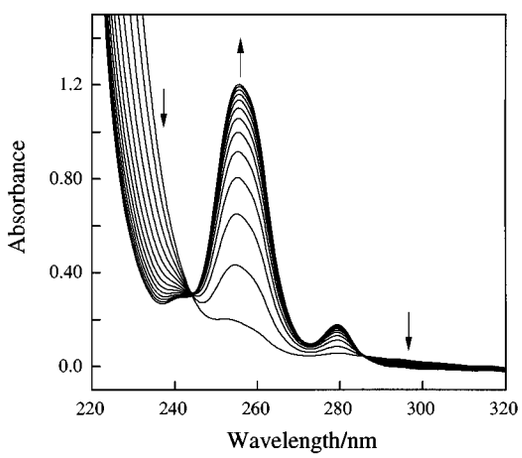


Fig. 3 Time-resolved spectra for reduction of $[Pt(CN)_4Cl_2]^{2-}$ by methionine. Conditions: $[Pt^{IV}]_{tot} = 1.25 \times 10^{-4}$ mol dm^{-3}, $[MeSR]_{tot} = 2.0$ mmol dm^{-3}, $[HClO_4] = 0.10$ mol dm^{-3}, $[Cl^-] = 0.10$ mol dm^{-3}, 25 °C and $I = 1.00$ mol dm^{-3}; 1.00 mol dm^{-3} sodium perchlorate was used as reference. Time interval between scans 50 s; first scan obtained *ca.* 10 s after mixing

intermediates during reduction to $[Pt(CN)_4]^{2-}$.§ Slight systematic deviations from the isosbestic points at 285 and, in particular, 246 nm are due to the absorbance contribution from the methionine *S*-oxide product. The observed rate constants, k_{obs}, are proportional to the excess concentration of methionine in the whole pH region studied (*cf.* Fig. 4), giving overall second-order kinetics according to equation (3), where k' denotes the

$$-d[Pt(CN)_4X_2^{2-}]/dt = d[Pt(CN)_4^{2-}]/dt = k'[MeSR]_{tot}[Pt(CN)_4X_2^{2-}] \quad (3a)$$

$$k_{obs} = k'[MeSR]_{tot} \quad (3b)$$

pH-dependent second-order rate constants. Values of k', calculated by the use of equation (3b) from the data summarised in SUP 57246 are shown as a function of $p[H^+]$ in Fig. 5.¶ Values of k_{obs} and k' are summarised in SUP 57246.

Stoichiometric reaction mechanism

Platinum(IV) complexes are substitution inert and initial complex formation prior to electron transfer does not normally take

§ This has been shown to be true also when thiols[12] and sulfite[13] are used as reductants.

¶ Reduction of $[Pt(CN)_4Br_2]^{2-}$ was only studied in the interval 0 < pH < 6 since this complex is not stable at pH > 7 (see ref. 15).

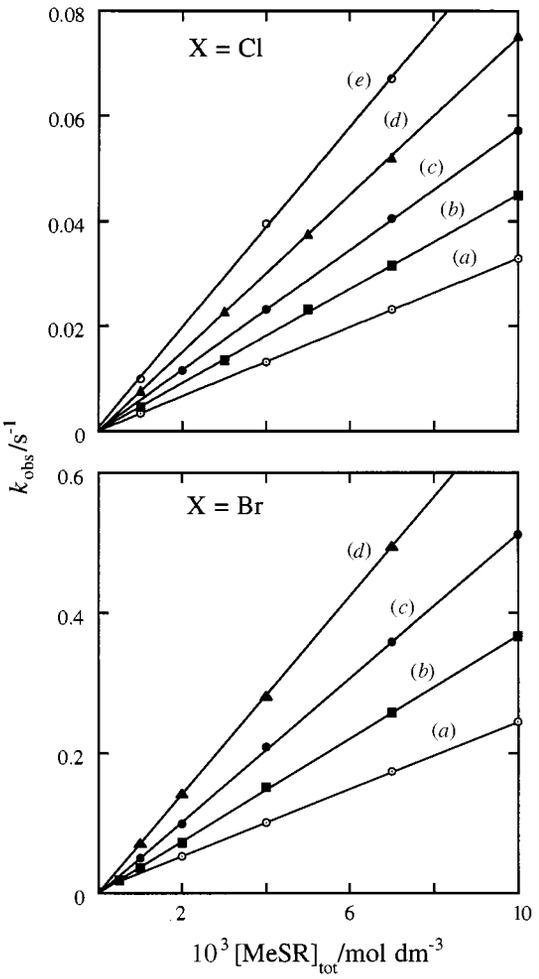


Fig. 4 Plots of k_{obs} as a function of $[MeSR]_{tot}$ and temperature for reduction of $[Pt(CN)_4X_2]^{2-}$ (X = Cl or Br). Conditions: p[H$^+$] = 4.22, 0.20 mol dm^{-3} acetic acid–acetate buffer, [X$^-$] = 0.10 mol dm^{-3}. Temperatures are 20.0 (*a*), 25.0 (*b*), 30.0 (*c*), 35.0 (*d*) and 40.1 °C (*e*)

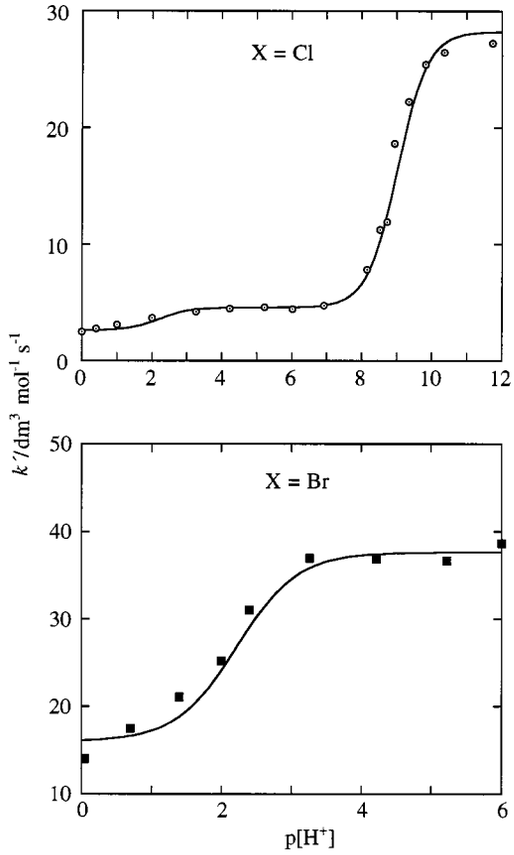


Fig. 5 Second-order rate constants k' defined by equation (3), as a function of p[H$^+$] at 25.0 °C for reduction of $[Pt(CN)_4X_2]^{2-}$ (X = Cl or Br) with methionine. The solid lines represent the best fits of equations (4) and (5), respectively, to the experimental data by use of a weighted least-squares regression analysis

place in reductive-elimination reactions.[13–15,18–24] The simple and well defined monophasic kinetics observed for reduction of $[Pt(CN)_4Cl_2]^{2-}$ is consistent with that general behaviour. In analogy with the previously studied thiol systems,[12] we propose a mechanism (Scheme 1) where all protolytic species of methionine reduce $[Pt(CN)_4X_2]^{2-}$ in parallel reactions, giving MeS(X)R as short-lived intermediates; in a subsequent rapid step, MeS(X)R will hydrolyse to give MeS(O)R as the final oxidation product. Similar short-lived intermediates were also suggested previously for reduction of gold(III) complexes by dimethyl sulfide.[25,26] The second-order rate constants k' defined in equation (3) can be derived as in (4). A weighted non-linear

$$k' = \frac{k_1[H^+]^2 + k_2K_1[H^+] + k_3K_1K_2}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (4)$$

least-squares fit of equation (4) to the experimental data for the chloride complex with the rate and protolysis constants as adjustable parameters gave pK_1 = 1.7 ± 0.2 and pK_2 = 8.9 ± 0.1, and the values of the rate constants listed in Table 1, *cf.* Fig. 5. The protolysis constants derived from the curve fit are in reasonably good agreement with those reported in the literature (pK_{a1} = 2.22 ± 0.04 and pK_{a2} = 9.02 ± 0.02),[27] if the difference in ionic medium used is taken into account.

At pH < 6, where the reduction of $[Pt(CN)_4Br_2]^{2-}$ was studied, the data indicate that the pH is sufficiently far from the pK_2 value of methionine to assure that the concentration of fully deprotonated methionine can be neglected; equation (4) can then be simplified to (5). A weighted non-linear least-squares fit of equation (5) to the data for the bromide complex gave

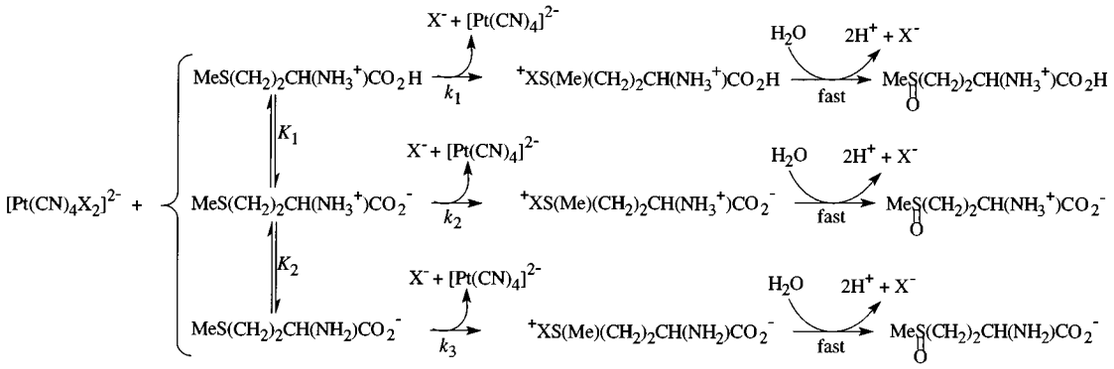
$$k' = (k_1[H^+] + k_2K_1)/(K_1 + [H^+]) \qquad (5)$$

pK_1 = 1.85 ± 0.11 and the values of k_1 and k_2 listed in Table 1 (Fig. 5). In the interval 4 < p[H$^+$] < 7, $MeSCH_2CH_2CH(NH_3^+)CO_2^-$ is the only contributing reductant. Activation enthalpies and entropies for the reduction of $[Pt(CN)_4X_2]^{2-}$ by this protolyte were calculated by fitting the Eyring equation to the variable-temperature data for k_2 at p[H$^+$] = 4.22, *cf.* Table 2.

Transition states for reactions with methionine and thiols

Halide-mediated reductive-elimination reactions of platinum(IV) complexes involving various reductants have been suggested to take place *via* an attack by the reductant on coordinated halide.[12–15,22–24] In the present case the transition state may be formulated as in **I**. The reductive elimination might be visualized as a classical S_N2 attack of the reductant on coordinated halide with the platinum moiety as the leaving group.[12] The increase in rate with increasing pH as shown in Fig. 5 could easily be accounted for by the observed decrease in redox potential of methionine as the pH is increased.[28] Thus, it is likely that it is the thioether group of the various protolytic species of methionine that interacts with the platinum complex in all cases, as indicated above. Reduction of the bromide complex with methionine is faster than reduction of the chloride complex, consistent with bromide being a better bridging ligand than chloride.‖ In addition, the negative activation entro-

‖ The k^{Br}:k^{Cl} ratios of 6–8:1 observed in the present study are significantly smaller than those of about 400:1 observed previously for reduction of $[Pt(CN)_4X_2]^{2-}$ with SCN^-, I^-, CN^- and SO_3^{2-}.[23]



Scheme 1

Table 1 Second-order rate constants, k_n (n = 1–3), for reduction of *trans*-$[Pt(CN)_4X_2]^{2-}$ (X = Cl or Br) by the different protolytic species of methionine at 25 °C and 1.00 mol dm^{-3} ionic strength

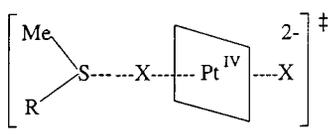
Reductant	k_n^{Cl}/dm^3 mol^{-1} s^{-1}	k_n^{Br}/dm^3 mol^{-1} s^{-1}	k_n^{Br} : k_n^{Cl}
$MeSCH_2CH_2CH(NH_3^+)CO_2H$	2.54 ± 0.01	14.8 ± 0.2	5.8 : 1
$MeSCH_2CH_2CH(NH_3^+)CO_2^-$	4.47 ± 0.01	36.9 ± 0.2	8.3 : 1
$MeSCH_2CH_2CH(NH_2)CO_2^-$	27.5 ± 0.1		

Table 2 Rate constants, k_2, as a function of temperature and activation parameters for the reduction of *trans*-$[Pt(CN)_4X_2]^{2-}$ by $MeSCH_2CH_2CH(NH_3^+)CO_2^-$ at 1.00 mol dm^{-3} ionic strength

$[Pt(CN)_4X_2]^{2-}$	T/ °C	k_2/dm^3 mol^{-1} s^{-1}
X = Cl	20.0	3.28 ± 0.01
	25.0	4.47 ± 0.01
	30.0	5.71 ± 0.04
	35.0	7.49 ± 0.05
	40.1	9.5 ± 0.2
$\Delta H^‡$ 37.7 ± 0.7 kJ mol^{-1}, $\Delta S^‡$ −106 ± 2 J K^{-1} mol^{-1}		
X = Br	20.0	24.1 ± 0.1
	25.0	36.9 ± 0.2
	30.0	51.4 ± 0.4
	35.0	70.6 ± 0.2
$\Delta H^‡$ 51 ± 2 kJ mol^{-1}, $\Delta S^‡$ −44 ± 7 J K^{-1} mol^{-1}		

pies derived for reductions with $MeSCH_2CH_2CH(NH_3^+)CO_2^-$ given in Table 2 are very similar to those calculated previously for reduction of gold(III) complexes by dimethyl sulfide,[26] also supporting a transition state of the type suggested above.

The kinetics for reduction with thiols studied previously[12] is very different from the present findings. The Brønsted correlation observed between the rate of reduction of $[Pt(CN)_4Cl_2]^{2-}$ and the protolysis constants of the thiol groups in thioglycolic acid, L-cysteine, DL-penicillamine, and glutathione indicates that the basicity of the reductant is a crucial parameter in determining the reactivity towards the platinum complex.[12] Within each protolytic thiol system, there are carboxylate, thiol and amine groups which may act as nucleophiles towards co-ordinated chloride, depending on the pH. The similar Brønsted correlations observed for the four different thiolate anions are also observed within all four protolytic thiol systems (log k = α pK_a + β with 0.93 < α < 1.0 and small intercepts, β), *cf.* Fig. 1. Eventually, these correlations might indicate that the protolytic group with the highest basicity interacts with the platinum(IV) complex in the rate-limiting step. Thus, at low pH, where the thiol groups are protonated, the carboxylate groups should be able to attack $[Pt(CN)_4Cl_2]^{2-}$ forming a bridged intermediate in which electron transfer from the thiol group to the platinum(IV) centre could take place rapidly. This mechanistic interpretation



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would imply that the rate of oxidation should continue to increase in alkaline solutions, where the amine groups are deprotonated. We were not able to verify if this is the case, since the reactions become too fast to be followed by the stopped-flow technique at pH *ca.* 5.

At the moment, it is not possible to conclude with certainty whether the carboxylate and amine groups in the previously studied thiols in fact do attack $[Pt(CN)_4X_2]^{2-}$. It may be possible that only the thiol group is interacting with the complex, as seems to be the case with the methionine thioether moiety, and that the strong Brønsted correlations and large variations in rates observed for the thiol protolytic systems have alternative explanations. For example, in the transition state formed between $[Pt(CN)_4Cl_2]^{2-}$ and the cysteine protolyte $HSCH_2CH(NH_3^+)CO_2^-$, the carboxylate group might form an intramolecular hydrogen bond with the thiol (SH),[29] resulting in an increased electron density on the sulfur atom, facilitating electron transfer. Similar intramolecular interactions within the other polyfunctional protolytic thiol systems might change the electronic properties of the thiol moieties and the redox rates.

Implications for platinum(IV) antitumour drugs

Reduction of the platinum(IV) model complex by methionine is considerably slower than reduction by cysteine, penicillamine and glutathione in neutral solutions, but the rates are comparable under acidic conditions. The conclusion must be, then, that in neutral solutions, methionine-containing biomolecules can compete for reduction of platinum(IV) pro-drugs only under conditions of relatively low concentrations of thiols; under acidic conditions, however, methionine-containing biomolecules may be as competitive as thiols for reduction of platinum(IV) pro-drugs to antitumor-active platinum(II) complexes.

Acknowledgements

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