Kinetics and Mechanism for Reduction of *trans*-Dichlorotetracyanoplatinate(IV) by Thioglycolic Acid, L-Cysteine, DL-Penicillamine, and Glutathione in Aqueous Solution

Tiesheng Shi, Johan Berglund, and Lars I. Elding*

Inorganic Chemistry 1, Chemical Center, Lund University, P.O. Box 124, S-221 00, Lund, Sweden

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Reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ (as a model compound for antitumor-active platinum(IV) complexes) by thiols, RSH (thioglycolic acid, L-cysteine, DL-penicillamine, and glutathione), has been studied in a 1.00 M aqueous perchlorate medium by use of stopped-flow spectrophotometry at 25 °C in the interval $7.08 \times 10^{-6} \leq [H^+] \leq 1.00$ M. Time-resolved spectra show that redox takes place directly without initial substitution at Pt(IV). The stoichiometry is [RSH]:[Pt(IV)] = 2:1. Reduction is first-order with respect to [Pt(IV)] and the total concentration of thiol $[RSH]_{tot}$. The bromide complex *trans*-$[Pt(CN)_4Br_2]^{2-}$ is reduced 47 times faster than *trans*-$[Pt(CN)_4Cl_2]^{2-}$ by cysteine. The $[H^+]$-dependence of the observed kinetics can be rationalized by a reaction mechanism in which the platinum(IV) complex is reduced in parallel reactions by the various protolytic species present in rapid equilibria with each other, via halide-bridged electron transfer. Second-order rate constants for a particular reductant derived from the pH-dependence of the overall kinetics increase several orders of magnitude when the molecular forms of the reductants are deprotonated. For instance, no reduction of platinum(IV) by the fully protonated cation of glutathione can be observed, whereas the various deprotonated forms reduce the complex with second-order rate constants of 23.4 ± 0.3, 655 ± 4, and $(1.10 \pm 0.01) \times 10^8$ M^{-1} s^{-1}, respectively. Thiolate anions reduce the platinum(IV) complex $(1.7-19) \times 10^5$ times faster than the corresponding vicinal thiol forms. The second-order rate constants k_{RS^-} for reaction of thiolate anions RS^- with $[Pt(CN)_4Cl_2]^{2-}$ are described by the Brønsted correlation $\log k_{RS^-} = (0.82 \pm 0.08)pK_{RSH} + (1.1 \pm 0.7)$. The slope of 0.82 indicates that the basicity of RS^- is a predominant factor in determining the reactivity toward the Pt(IV) complex. Reduction of Pt(IV) antitumor drugs by thiol-containing molecules before interaction between Pt(II) and DNA may take place via similar reaction mechanisms.

Introduction

Many biological functions of thiol-containing compounds are governed by their easy oxidation.[1,2] Glutathione, a tripeptide with the sequence γ - glutamylcysteinylglycine, is frequently the most prevalent intracellular thiol with concentrations up to 8 mM.[3,4] Its important functions include the maintenance of the intracellular thiol redox balance (RSH/RSSR).[3,4] Oxidation of thiols, in particular L-cysteine, D-penicillamine, and glutathione, by metal ions[5−14] and nonmetallic oxidants[15−21] proceeds by a variety of mechanisms. For instance, with dichromate, the overall mechanism involves formation of a long-lived RS−Cr(VI) thioester intermediate, followed by two parallel intra- and intermolecular redox reactions.[5] In the reduction of $[Fe(H_2O)_6]^{3+}$ and $[Fe(H_2O)_5OH]^{2+}$, complex formation usually precedes the redox process.[6] Among the nonmetallic oxidants used, there are a number of disulfides. Brønsted correlations have been observed for these processes,[19,20] usually referred to as thiol−disulfide interchange reactions.[19−21]

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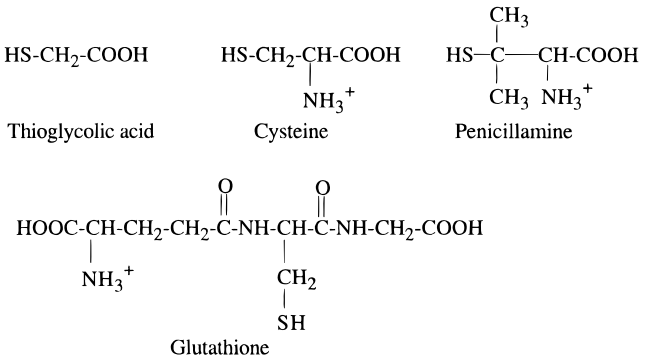
There is a current interest in the antitumor activity of Pt(IV) diamine complexes such as tetrachloro(DL-*trans*-1,2-diaminocyclohexane)platinum(IV),[22,23] *cis*,*cis*,*trans*-$[Pt(i\text{-}PrNH_2)_2Cl_2(OH)_2]$,[24−26] and *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(OH)_2]$.[26,27] These are potential second-generation platinum antitumor drugs. However, platinum(IV) complexes undergo ligand substitution reactions much more slowly than their platinum(II) analogs, usually requiring assistance by an excess of ligand or platinum(II).[28] Therefore, biotransformation of platinum(IV) complexes is generally assumed to involve reduction to platinum(II) prior to reaction with DNA.[23,24,26,29,30] Thiol-containing biomolecules and ascorbic acid seem to be the major cellular components responsible for that reduction. The reaction mechanism for this redox process is poorly understood, although some preliminary kinetics data have been published.[23d,24]

We here report kinetics studies of reduction of *trans*-dichlorotetracyanoplatinate(IV) by thioglycolic acid, L-cysteine, DL-penicillamine, and glutathione in a wide range of pH. Chart 1 gives the structures of the protonated forms of the reductants used. The use of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ as the model substrate complex has the advantage over platinum(IV) diamine complexes that the reaction product $[Pt(CN)_4]^{2-}$ is so robust that no subsequent reactions will interfere with the redox process. Moreover, *trans*-$[Pt(CN)_4Cl_2]^{2-}$ does not hydrolyze in the pH range studied, enabling an unambiguous evaluation of each specific rate constant for the various protolytic forms of the reductants without disturbance of a proton ambiguity.

Chart 1



Experimental Section

Chemicals and Solutions. $K_2[Pt(CN)_4Cl_2]$ was synthesized by oxidation of $K_2[Pt(CN)_4]\cdot 3H_2O$ with chlorine as described previously.[31] The UV−vis spectrum agreed with that reported earlier for $[Pt(CN)_4Cl_2]^{2-}$.[28b] $K_2[Pt(CN)_4Br_2]$ was prepared according to the literature.[32] Stock solutions of 5.0 mM $K_2[Pt(CN)_4Cl_2]$ in 10 mM $HClO_4$, 10 mM NaCl, and 0.98 M $NaClO_4$ ionic medium were stable for several months. Thioglycolic acid (Janssen pa), L-cysteine (Merck, pa, ≥99%), DL-penicillamine (Janssen, pa, ≥99%), glutathione (Merck, pa, ≥99%), and 5,5′-dithiobis(2′-nitrobenzoic acid) (Ellman's reagent, ICN Biomedicals Inc.) were used as received. For the kinetic measurements, 5−50 mM stock solutions of the reductants were prepared fresh daily by dissolving the samples either in 1.00 M $NaClO_4$ or in acetic acid/acetate buffer solutions. Stock solutions (1.000 M) of $HClO_4$, $NaClO_4$, and NaCl were prepared from concentrated $HClO_4$ (Merck, pa, 70−72%), anhydrous sodium perchlorate (Janssen, pa), and sodium chloride (Merck, pa), respectively. Acetic acid/acetate buffer solutions (0.20 M) were prepared from acetic acid (Janssen, >99%) and anhydrous sodium acetate (Janssen, >99%). The ionic strength was kept constant at 1.00 M, and all experiments were run at sufficiently high chloride concentrations to suppress hydrolysis of $[Pt(CN)_4Cl_2]^{2-}$. The hydrogen ion concentrations were adjusted with 1.000 M $HClO_4$ for $[H^+] \geq 1.0 \times 10^{-3}$ M and with acetic acid/acetate buffer solutions for $[H^+] \leq 5.25 \times 10^{-4}$ M. Water was doubly distilled from quartz.

Apparatus. Spectra were recorded by use of a Milton Roy 3000 diode array spectrophotometer and 1.00 cm quartz Suprasil cells. Time-resolved spectra and kinetic traces were collected using an Applied Photophysics Bio Sequential SX-17 MX, stopped-flow ASVD spectrofluorimeter. Rate constants were evaluated by the Applied Photophysics software package.[33] Hydrogen ion concentrations were calculated according to $-\log [H^+] = pH - 0.20$, based on a mean activity coefficient of 0.630 for 1.00 *m* $NaClO_4$.[34]

Protolysis Constants. Protolysis constants are defined in Schemes 1−3 below. At 25 °C and $\mu = 1.0$ M, their values are as follows: for thioglycolic acid,[20c,35a] $pK_{a1} = 3.53$ and $pK_{a2} = 10.05$; for cysteine,[35b] $pK_{a1} = 1.9$, $pK_{a2} = 8.10$, and $pK_{a3} = 10.1$; and for penicillamine,[35c] $pK_{a1} = 1.9$, $pK_{a2} = 7.92$, and $pK_{a3} = 10.5$. Protolysis constants for glutathione at 25 °C and 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 $pK_{a4} = 9.49$.[36]

Results

Spectra. Time-resolved spectra for reaction between $[Pt(CN)_4Cl_2]^{2-}$ and glutathione display an absorbance peak

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Table 1. Stoichiometry for Reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ by Thiols[a]

reductant	$[RSH]_0$/mM[b]	$[Pt(IV)]_0$/mM[b]	$\Delta[RSH]/\Delta[Pt(IV)]$[c,d]
thioglycolic acid	1.160	0.066−0.220	2.0 ± 0.1
cysteine	1.082	0.066−0.220	2.0 ± 0.1
penicillamine	1.020	0.066−0.220	1.8 ± 0.1
glutathione	1.056	0.066−0.220	1.7 ± 0.1

[a] $[Cl^-] = 0.10$ M, $[H^+] = 0.01$ M, ionic strength 1.00 M, and room temperature. [b] $[RSH]_0$ and $[Pt(IV)]_0$ denote initial concentrations. [c] $\Delta[RSH]$ and $\Delta[Pt(IV)]$ denote concentrations consumed in reaction 1. [d] Average value of three determinations with varying $[Pt(IV)]_0$.

Table 2. Chloride Dependence of the Observed Rate Constants for Reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ by Thioglycolic Acid and L-Cysteine at 25 °C and Ionic Strength 1.00 M

reductant	$[H^+]$/M	$[Cl^-]$/mM	k_{obsd}/s^{-1}
thioglycolic acid[a]	3.0×10^{-2}	1.0−400	0.041 ± 0.002[c]
L-cysteine[b]	2.09×10^{-4}	0.50−475	4.2 ± 0.2[d]

[a] $C_{Pt(IV)} = 5.0 \times 10^{-5}$ M, [thioglycolic acid] = 3.20 mM. [b] $C_{Pt(IV)} = 2.48 \times 10^{-5}$ M, [cysteine] = 1.06 mM. [c] Mean value of eight determinations at different $[Cl^-]$. [d] Mean value of four determinations at different $[Cl^-]$.

appearing at 255 nm, characteristic of the reaction product $[Pt(CN)_4]^{2-}$. Well-defined isosbestic points at 243 and 286 nm indicate that there is no accumulation of any long-lived intermediates during the reaction. This is true also for the other three reductants as shown by similar spectral data. Typical spectra are given in Supporting Information Figure S1.

Stoichiometry. The stoichiometry of the redox process was determined under conditions similar to those used for the kinetic measurements, *i.e.* excess of reductant over platinum(IV) complex. Solutions of platinum(IV) complex and thiol were aged for 10−30 min. Unreacted thiol was determined spectrophotometrically as described in the literature[37] by use of Ellman's reagent at pH 7.4 in 0.020 M NaH_2PO_4/0.080 M Na_2HPO_4 buffer solutions containing 1 mM EDTA. Results given in Table 1 indicate that 2 mol of thiol/mol of Pt(IV) is consumed in the predominant reaction:

$$Pt(CN)_4Cl_2^{2-} + 2RSH \rightarrow Pt(CN)_4^{2-} + RSSR + 2Cl^- + 2H^+ \quad (1)$$

Slight deviations from the 2:1 stoichiometry for penicillamine and glutathione are probably due to subsequent processes.

Kinetics. The reduction of $[Pt(CN)_4Cl_2]^{2-}$ was followed under pseudo-first-order conditions with reductants in at least 10-fold excess over platinum complex by monitoring the increase of absorbance at the 255 nm $Pt(CN)_4^{2-}$ peak. Single-exponential traces were obtained in all cases. Reported rate constants represent average values of five to seven independent runs. The chloride dependence of the observed rate constants was studied for the reactions of thioglycolic acid and cysteine, with pH and the concentrations of thioglycolic acid and cysteine kept constant. As can be seen from the data in Table 2, variation of chloride concentration has no influence on the observed rate constants. The role of the excess chloride is thus only to suppress hydrolysis of $[Pt(CN)_4Cl_2]^{2-}$.

Experiments were carried out in the presence of varying total concentrations of reductants and hydrogen ion. Plots of k_{obsd} versus excess $[RSH]_{tot}$ at different proton concentrations (using data given in Tables S1−S4 in the Supporting Information) are linear, displaying negligible intercepts, indicating a simple rate law according to eq 2, where k' denotes the overall pH-dependent second-order rate constant and $[RSH]_{tot}$ represents the total concentration of reductant. The values of k' calculated by a linear least-squares routine at different hydrogen ion concentrations for the four reductants are given in Figure 1 and in Supporting Information Table S5.

$$d[Pt(CN)_4^{2-}]/dt = k_{obsd}[Pt(CN)_4Cl_2^{2-}] = k'[RSH]_{tot}[Pt(CN)_4Cl_2^{2-}] \quad (2)$$

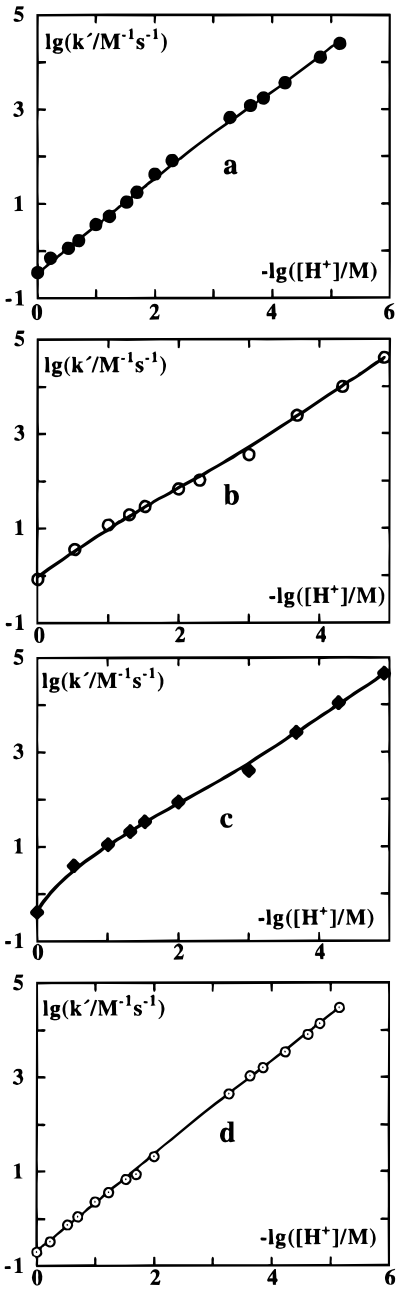

Figure 1. Second-order rate constants, k', defined by eq 2 as a function of $[H^+]$ at 25 °C for reactions of $[Pt(CN)_4Cl_2]^{2-}$ with thiols: (a) thioglycolic acid; (b) cysteine; (c) penicillamine; (d) glutathione. The solid lines represent the best fit of eqs 6 (curves a−c) and 7 (curve d) to the experimental data.

A series of kinetics measurements were also conducted for the reaction between *trans*-$[Pt(CN)_4Br_2]^{2-}$ and cysteine under the following conditions: $[Pt(CN)_4Br_2^{2-}] = 9.5 \times 10^{-6}$ M, $6.25 \times 10^{-5} \leq$ [cysteine] $\leq 3.0 \times 10^{-3}$ M, $[H^+] = 0.030$ M, $[Br^-]$

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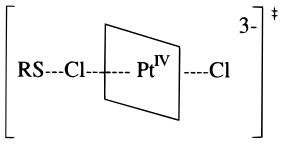
= 0.100 M, 25 °C, and 1.00 M ionic strength. The reaction is first-order in both Pt(IV) and cysteine, with a second-order overall rate constant $k' = (1.37 \pm 0.01) \times 10^3\ M^{-1}\ s^{-1}$ (data in Table S2 in the Supporting Information). This value is 47 times larger than that for reaction between $[Pt(CN)_4Cl_2]^{2-}$ and cysteine (28.9 $M^{-1}\ s^{-1}$) at the same pH.

Influence of Autoxidation. It has been known for a long time that molecules containing thiol groups are sensitive to autoxidation catalyzed by metal ions such as Cu(II) and Fe(III).[38−40] The rate of autoxidation increases with pH. In order to check whether autoxidation influences the present kinetic measurements, control experiments with glutathione in the absence of oxygen were conducted. In these experiments, both the Pt(IV) and glutathione solutions contained 0.5 mM EDTA in order to eliminate the possible catalytic effect of any traces of metal ions.[39,41] Before the reactions were initiated in the stopped-flow instrument, both the Pt(IV) and glutathione solutions were flushed with nitrogen for at least 30 min. No significant discrepancy between these experiments and those performed in air-saturated solutions was observed (data in Table S4 in the Supporting Information).

Discussion

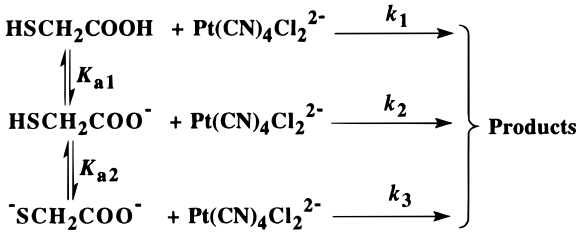
Reaction Mechanism. It is obvious from the experimental data in Figure 1 that the rate of reduction of $[Pt(CN)_4Cl_2]^{2-}$ increases several orders of magnitude with increasing pH, indicating that the deprotonated protolytic species are much more reactive than the protonated ones. Initial complex formation between platinum(IV) and reductant can be excluded because of the substitution inertness of platinum(IV), the single-exponential build-up of $[Pt(CN)_4]^{2-}$, the chloride-independent kinetics, and the well-defined time-resolved spectra with two isosbestic points. A plausible stoichometric mechanism for the redox process involves parallel reactions between platinum(IV) and the various protolytic species of each reductant, as depicted in the schemes.

Reductive elimination reactions of platinum(IV) halide complexes[28,31,32,42−47] have been interpreted in terms of halide-bridged electron transfer. The transition state in the case of the present systems (with S attacking) might be formulated as follows:

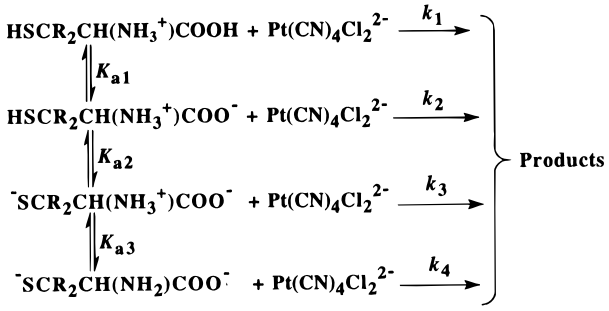


This is formally equivalent to a Cl^+ transfer from the Pt(IV) center to the incoming thiolate nucleophile.[44−47] When the thiolate approaches a chloride ligand in $[Pt(CN)_4Cl_2]^{2-}$ (or a bromide ligand in $[Pt(CN)_4Br_2]^{2-}$), the electron density of the Pt−halide bond is displaced toward the platinum center, making the halide ligand more prone to accept electrons from the incoming nucleophile. This reaction might be visualized as a nucleophilic substitution on the halogen with the platinum moiety as the leaving group. As already pointed out by Taube,[48] there is no sharp distinction between a two-electron redox change involving atom transfer and such a nucleophilic substitution.

Scheme 1



Scheme 2



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

Despite the larger driving force for reduction of $[Pt(CN)_4Cl_2]^{2-}$ compared to $[Pt(CN)_4Br_2]^{2-}$, it was observed that cysteine reduces the latter ca. 47 times faster than the former ($[Pt(CN)_4Cl_2]^{2-}/[Pt(CN)_4]^{2-}$ = 0.926 V,[49] $[Pt(CN)_4Br_2]^{2-}/[Pt(CN)_4]^{2-}$ = 0.75 V[50]). This observation provides further evidence in favor of a bridged electron transfer mechanism operating in the present system with RSCl and (in the case of $[Pt(CN)_4Br_2]^{2-}$) RSBr as the initial reaction products. RSCl will hydrolyze in a fast subsequent step according to reaction 3, and the RSOH formed will be trapped by RSH and RS^- according to reactions 4 and 5, respectively.[51]

$$RSCl + H_2O \rightarrow RSOH + Cl^- + H^+ \quad (3)$$

$$RSOH + RSH \rightarrow RSSR + H_2O \quad (4)$$

$$RSOH + RS^- \rightarrow RSSR + OH^- \quad (5)$$

Thioglycolic Acid. On the basis of the reaction mechanism in Scheme 1, the second-order overall rate constants, k', defined by eq 2, can be derived as eq 6. This equation was fitted by a

$$k' = \frac{k_1[H^+]^2 + k_2K_{a1}[H^+] + k_3K_{a1}K_{a2}}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}} \quad (6)$$

weighted nonlinear least-squares routine to the experimental data in Figure 1a and in Table S5 in the Supporting Information

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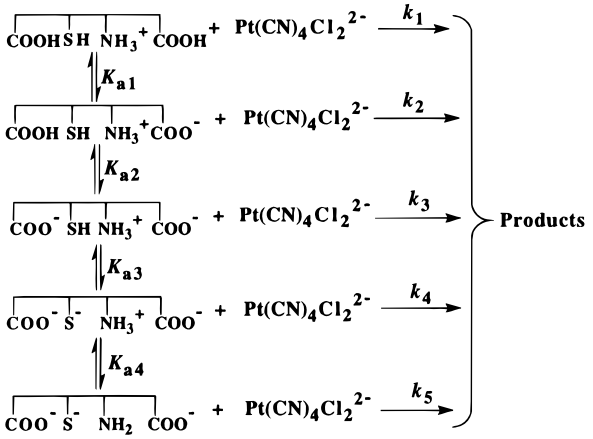
Scheme 3



with k_1, k_2, and k_3 as adjustable parameters. The curve fit displayed in Figure 1a gives $k_1 = -0.01 \pm 0.01$, $k_2 = 1147 \pm 4$, and $k_3 = (2.23 \pm 0.01) \times 10^9$ M^{-1} s^{-1}, respectively. Excluding the pathway described by k_1 in Scheme 1 gives the values $k_2 = 1143 \pm 3$ and $k_3 = (2.23 \pm 0.01) \times 10^9$ M^{-1} s^{-1}. Thus, even in the region of $0.1 \le [H^+] \le 1.0$ M, the contribution of the k_1-term in eq 6 is too small to allow evaluation from the present data. It is obvious that the thioglycolic acid molecule is much less reactive than the anion $HSCH_2COO^-$ and that the thiolate anion $^-SCH_2COO^-$ is about 6 orders of magnitude more reactive than the thiol $HSCH_2COO^-$; *i.e.*, $k(HSCH_2COOH) \ll k(HSCH_2COO^-) \ll k(^-SCH_2COO^-)$.

L-Cysteine and DL-Penicillamine. For these reductants, the mechanism depicted in Scheme 2 gives expression 7 for the second-order overall rate constant defined by eq 2. Because

$$k' = \frac{k_1[H^+]^3 + k_2K_{a1}[H^+]^2 + k_3K_{a1}K_{a2}[H^+] + k_4K_{a1}K_{a2}K_{a3}}{[H^+]^3 + K_{a1}[H^+]^2 + K_{a1}K_{a2}[H^+] + K_{a1}K_{a2}K_{a3}} \quad (7)$$

the k_4-term in eq 7 gives a negligible contribution to the overall kinetics in the pH region studied (*vide infra*), eq 7 can be simplified to eq 6 since $[H^+] \gg K_{a3}$. The fits of eq 6 to the experimental data are shown in Figure 1b,c, resulting in $k_2 = 80.7 \pm 0.3$ and 94.5 ± 0.5 M^{-1} s^{-1} and $k_3 = (6.09 \pm 0.02) \times 10^7$ and $(4.45 \pm 0.04) \times 10^7$ M^{-1} s^{-1} for cysteine and penicillamine, respectively. As in the case of thioglycolic acid, the values of k_1 are too small to be observed.

If the k_1-pathway is neglected and a large value for k_4, *e.g.* 10^{10} M^{-1} s^{-1} (corresponding to diffusion-controlled reaction), is used in fitting eq 7 to the experimental data, the same result as calculated from eq 6 is obtained. Therefore, it can be concluded that the k_4-pathway does not contribute significantly to the overall kinetics for $[H^+] \le 10^{-5}$ M.

Glutathione. The second-order overall rate constants k' of eq 2 can be derived as eq 8 for the mechanism depicted in Scheme 3. Since the contribution of the k_5-term in eq 8 is negligible in the pH region studied, eq 8 is reduced to eq 7 for $[H^+] \gg K_{a4}$. Equation 7 was fitted to the experimental data given in Figure 1d and in Table S5 in the Supporting Information. The fit, shown in Figure 1d, gives $k_1 = -0.01 \pm 0.01$, $k_2 = 23.4 \pm 0.3$, $k_3 = 655 \pm 4$, and $k_4 = (1.10 \pm 0.01) \times 10^8$ M^{-1} s^{-1}. The same result within experimental errors is obtained if the k_1-pathway is neglected and $k_5 = 10^{10}$ M^{-1} s^{-1} is used in eq 8. It follows that the k_5-term in eq 10 does not influence the evaluation of the rate constants for $[H^+] < 10^{-6}$ M.

$$k' = \{k_1[H^+]^4 + k_2K_{a1}[H^+]^3 + k_3K_{a1}K_{a2}[H^+]^2 + k_4K_{a1}K_{a2}K_{a3}[H^+] + k_5K_{a1}K_{a2}K_{a3}K_{a4}\}/\{[H^+]^4 + K_{a1}[H^+]^3 + K_{a1}K_{a2}[H^+]^2 + K_{a1}K_{a2}K_{a3}[H^+] + K_{a1}K_{a2}K_{a3}K_{a4}\} \quad (8)$$

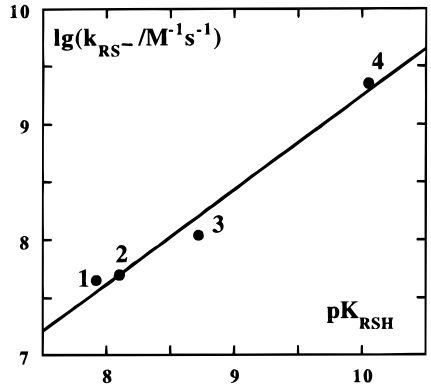


Figure 2. Brønsted plot for reactions of thiolate anions with $[Pt(CN)_4Cl_2]^{2-}$: (1) $^-SC(CH_3)_2CH(NH_3^+)COO^-$; (2) $^-SCH_2CH(NH_3^+)COO^-$; (3) $^-OOCCH_2NHCOCH(CH_2S^-)NHCO(CH_2)_2CH(NH_3^+)COO^-$; (4) $^-SCH_2COO^-$. The line represents the best fit of eq 9 to the data using a linear least-squares regression analysis.

Table 3. Second-Order Rate Constants for Reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ by Various Reductants at 25 °C and Ionic Strength 1.00 M

reductant	k/M^{-1} s^{-1}
$HSCH_2COOH$	not obsd
$HSCH_2COO^-$	1147 ± 4
$^-SCH_2COO^-$	$(2.23 \pm 0.01) \times 10^9$
$HSCH_2CH(NH_3^+)COOH$	not obsd
$HSCH_2CH(NH_3^+)COO^-$	80.7 ± 0.3
$^-SCH_2CH(NH_3^+)COO^-$	$(6.09 \pm 0.02) \times 10^7$
$HSC(CH_3)_2CH(NH_3^+)COOH$	not obsd
$HSC(CH_3)_2CH(NH_3^+)COO^-$	94.5 ± 0.5
$^-SC(CH_3)_2CH(NH_3^+)COO^-$	$(4.45 \pm 0.04) \times 10^7$
$HSCH_2CHNHCO(CH_2)_2CH(NH_3^+)COOH$ | $CONHCH_2COOH$	not obsd
$HSCH_2CHNHCO(CH_2)_2CH(NH_3^+)COO^-$ | $CONHCH_2COOH$	23.4 ± 0.3
$HSCH_2CHNHCO(CH_2)_2CH(NH_3^+)COO^-$ | $CONHCH_2COO^-$	655 ± 4
$^-SCH_2CHNHCO(CH_2)_2CH(NH_3^+)COO^-$ | $CONHCH_2COO^-$	$(1.10 \pm 0.01) \times 10^8$
HSO_3^-	1.3 ± 0.5[a]
SO_3^{2-}	$(4.5 \pm 0.1) \times 10^5$ [a]

[a] Reference 31.

Trends. Table 3 summarizes the rate constants for reduction of *trans*-$[Pt(CN)_4Cl_2]^{2-}$ by the different reductants. It is obvious from these data (i) that reduction of $[Pt(CN)_4Cl_2]^{2-}$ by the fully protonated thiols is not observed although large driving forces favor reaction and (ii) that there is a strong reactivity−basicity correlation in these systems. For instance, the reactivity of each particular protolytic species of glutathione is almost proportional to its basicity, as expressed by its protolysis constant. Therefore, it is expected that $k_5 > k_4$ for glutathione and that $k_4 > k_3$ for cysteine and penicillamine. This is similar to what was observed previously for reductions with SO_3^{2-} and HSO_3^-;[31] *cf.* Table 3.

The reactivity of the thiolate anions toward $[Pt(CN)_4Cl_2]^{2-}$ can be correlated by a Brønsted relation according to eq 9, as

$$\log k_{RS^-} = (0.82 \pm 0.08)pK_{RSH} + (1.1 \pm 0.7) \quad (9)$$

displayed in Figure 2. The slope of 0.82 again shows that the

basicity of the thiolate is a predominant factor in determining the reactivity toward the Pt(IV) complex. Brønsted correlations have been observed for reactions between thiolates and organic substrates such as *N*-(*p*-2-benzimidazolyl)phenylmaleimide,[52] *p*-nitrophenyl acetate,[53] ethylene oxide,[54] benzene oxide,[55] and several disulfides,[19,20] but eq 9 seems to be the first such relation observed for reactions between thiols and a metal complex.

Implication for Platinum(IV) Antitumor Drugs. Gibbons and co-workers[23d] have measured the second-order rate constants by HPLC for reduction of tetrachloro(DL-*trans*-1,2-diaminocyclohexane)platinum(IV) by cysteine, glutathione, and other reductants at 37 °C and in a 0.15 M NaCl medium. A direct comparison of their rate constants with those derived here is not possible since their pH is not known and their second-order rate constants are pH-dependent. However, the present experiments explicitly demonstrate that the platinum(IV) complex is rapidly reduced and that thiolate anions are the most reactive species at physiological pH, in agreement with previous observations.[23,24,26,29,30] Reductions of Pt(IV) antitumor drugs by thiol-containing biomolecules before interaction with DNA might take place via reaction mechanisms similar to those derived from the present experiments.

Acknowledgment. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

Supporting Information Available: Observed first-order rate constants as a function of hydrogen ion concentration for reactions between *trans*-$[Pt(CN)_4Cl_2]^{2-}$ and thioglycolic acid, L-cysteine, DL-penicillamine, and glutathione and between *trans*-$[Pt(CN)_4Br_2]^{2-}$ and L-cysteine at 25 °C with ionic strength 1.00 M (Tables S1−S4), second-order rate constants k' as a function of hydrogen ion concentration (Table S5), and time-resolved spectra for the reaction between $[Pt(CN)_4Cl_2]^{2-}$ and glutathione (Figure S1) (8 pages). Ordering information is given on any current masthead page.

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