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Kinetics and mechanism of the reaction of chelated Pd(II) complexes with thiols in acidic aqueous solution. Synthesis and crystal structure of [Pd(bpma)Cl]Cl·H_2O (bpma = bis(2-pyridylmethyl)amine) †

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The kinetics of the complex-formation reactions between monofunctional palladium(II) complexes $[Pd(N–N–N)H_2O]^{2+}$, where N–N–N is 2,2′:6′,2″-terpyridine (terpy), diethylenetriamine (dien) or bis(2-pyridylmethyl)amine (bpma), with L-cysteine, DL-penicillamine and glutathione, have been studied in an aqueous 0.10 M perchloric acid medium using variable-temperature and -pressure stopped-flow spectrophotometry. Second-order rate constants, k_1^{298}, varied between 2.8×10^2 and 4.4×10^4 M^{-1} s^{-1}. The highest reactivity was observed for the $[Pd(terpy)H_2O]^{2+}$ complex, whereas glutathione is the strongest nucleophile. Activation volumes for these reactions varied between -5.6 ± 0.3 and -10.7 ± 1.0 cm^3 mol^{-1}. 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 [Pd(bpma)Cl]Cl·H_2O has been determined by X-ray diffraction at 190 K. Crystals are triclinic with space group $P\bar{1}$ and consist of distorted square-planar $[Pd(bpma)Cl]^+$ cations. The Pd–N distances are all equal to 2.005(7) Å. The Pd–Cl distance is 2.305(3) Å.

Introduction

Notwithstanding the fact that substitution reactions of square-planar complexes in general and of Pt(II) and Pd(II) in particular have received much attention from various investigators over the past two decades, the interest in this field continues uninterruptedly as demonstrated by the high number of papers appearing annually. This interest mainly focuses on the ability to use steric and electronic effects to tune the solubility, acidity and reactivity of such complexes for their application as antitumor drugs[1,2] and as catalysts for C–H activation.[3] In these studies a careful distinction between and variation of σ-donor and π-acceptor effects plays an important role in controlling the reactivity of the complexes.[4,5] For mechanistic studies on the action of Pt(II) anticancer drugs, their Pd(II) analogues are usually good model compounds since they exhibit a 10^4 to 10^5 fold higher reactivity, whereas their structural and equilibrium behaviour is rather similar.

Interactions between Pt(II) and Pd(II) complexes with sulfur-containing biomolecules are very important from a biological and medical point of view. For instance, *cis*-$[PtCl_2(NH_3)_2]$ is routinely used in chemotherapy and has been particularly successful in the treatment of testicular and ovarian cancer.[1,2] Although the platinum interactions with DNA are held responsible for their antitumor activity, there are many other potential biomolecules that can react with these Pt(II) complexes. For instance, sulfur-donor ligands in proteins would rapidly bind and generate very stable bonds. Traditionally, interactions of platinum with sulfur-containing biomolecules have only been associated with negative phenomena such as resistance and toxicity in the antitumor treatment.[2] The tripeptide glutathione (GSH or $glutH_5$) provides a model compound for the study of these interactions. Glutathione, a cysteine-containing tripeptide with the sequence γ-glutamylcysteinylglycine, is frequently the most prevalent intracellular thiol with concentrations up to 8 mM.[6] The nephrotoxicity of antitumor platinum drugs has been ascribed to their reactions with thiol groups of proteins. In other words, nephrotoxicity is supposed to be the result of inactivation of certain enzymes due to the binding of cisplatin to the thiol groups of cysteine residues.[7,8]

The non-antitumor active monofunctional coordination compounds of Pd(II) with the tridentate ligands diethylenetriamine (dien), bis(2-pyridylmethyl)amine (bpma) and 2,2′:6′,2″-terpyridine (terpy), $[Pd(N–N–N)H_2O]^{2+}$, shown below, provide useful substrates for kinetic studies on substitution reactions of square-planar complexes. It is well known that relatively small structural modifications in a multidentate ligand can produce significant changes in the reactivity of the complexes.[4,5,9–12]

We report here kinetic studies on the complex-formation reactions of the three $[Pd(N–N–N)H_2O]^{2+}$ complexes with thiols, such as L-cysteine, DL-penicillamine and glutathione. In addition, we report the crystal structure of [Pd(bpma)Cl]Cl·H_2O.

Experimental

Synthesis of complexes

[Pd(bpma)Cl]Cl·H_2O was prepared by dissolving 0.0752 g $PdCl_2$ under reflux in a mixture of 10 mL H_2O and 3 mL concentrated HCl. The clear solution was filtered, and a solution of bis(2-pyridylmethyl)amine (0.0844 g in 10 mL methanol) was added dropwise to the warm solution of $[PdCl_4]^{2-}$. The pH of the solution was carefully adjusted to 5.0–5.5 by addition of NaOH. The clear, bright yellow solution was filtered and

† Electronic supplementary information (ESI) available: kinetic data for the concentration-, temperature- and pressure-dependence of the observed pseudo-first-order rate constants, k_{obsd}. See http://www.rsc.org/suppdata/dt/b1/b106038b/

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allowed to stand at room temperature until crystals precipitated. The bright yellow complex was filtered off, washed with cold water and diethyl ether, dried in air, and recrystallized from a minimum amount of 0.1 M HCl at 40–50 °C. The bright yellow needles were collected by filtration, washed with water and diethyl ether, and dried in air. Yield: 0.1517 g (90%) (Found: N, 10.58; C, 36.54; H, 3.78. Calc.: N, 10.65; C, 36.52; H, 3.29%).

The complexes [Pd(dien)Cl]Cl and [Pd(terpy)Cl]Cl·$3H_2O$ were prepared according to literature methods.[13–15] The chemical analysis and UV–Vis spectral data were in good agreement with those obtained in previous preparations.

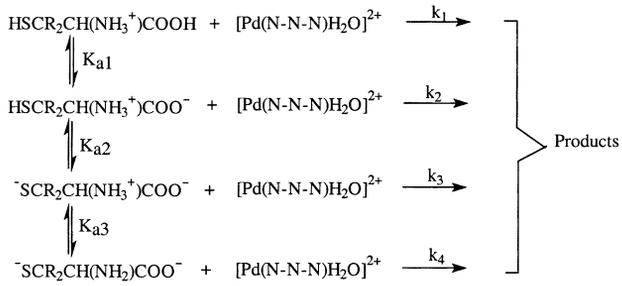
Chemicals and solutions

The chloro complexes were converted into the aqua analogues 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 solutions were free of Ag^+ ions and that the chloro complexes had been converted completely into the aqua species. Since perchlorate ion does not coordinate to Pt(II) and Pd(II) in aqueous solution,[16] the kinetics of the complex-formation reactions were studied in perchlorate medium. 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%) and glutathione (Fluka, assay >99%) in 0.1 M $HClO_4$ as supporting electrolyte. Under these experimental conditions, pH = 1.0, the $[Pd(N–N–N)H_2O]^{2+}$ complexes were stable and hydrolysis of the complexes was negligible.[17,18] Millipore water was used in the preparation of all solutions.

Acid dissociation constants

Acid dissociation constants are defined in Scheme 1 below. At 25 °C and μ = 1.0 M, their values are: for cysteine[19a] pK_{a1} = 1.9, pK_{a2} = 8.10 and pK_{a3} = 10.1; for penicillamine[19b] 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.[20] Under the selected experimental conditions, $[H]^+ \gg K_a$, all nucleophiles are fully protonated, such that the reaction pathways described by k_2, k_3 and 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.



Cysteine, R = H; penicillamine, R = Me

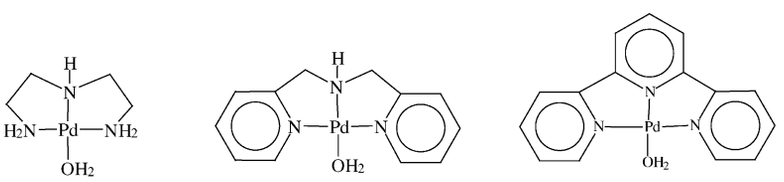
Scheme 1

Instrumentation

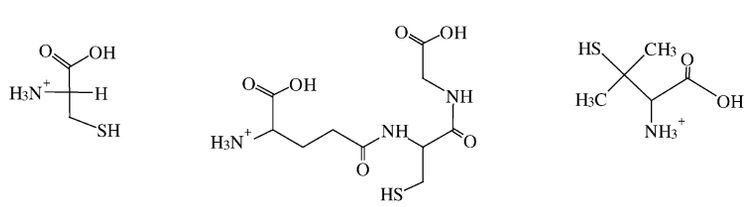
Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. UV–Vis spectra were recorded on Shimadzu UV 250 and Hewlett-Packard 8452A diode-array spectrophotometers with thermostated 1.00 cm quartz Suprasil cells. Kinetic measurements were carried out on an Applied Photophysics SX.18MV stopped-flow instrument coupled to an on-line data acquisition system. Kinetic measurements at ambient pressure were performed on Applied Photophysics SX.18MV and Durrum D110 stopped-flow instruments attached to on-line data acquisition systems[21] with which the kinetic traces could be evaluated, using the OLIS KINFIT (Bogart, GA) set of programs. Experiments at elevated pressure (up to 130 MPa) were performed on a homemade high-pressure stopped-flow unit.[22] 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 each nucleophile was used.

Kinetic measurements

Spectral changes resulting from mixing complex and ligand solutions were recorded over the wavelength range 220–450 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 of absorbance at 262, 267 or 320 nm under pseudo-first-order conditions, with thiol in at least a 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 the average of five to eight independent kinetic runs. The temperature dependence of k_{obsd} was studied over the range 10–35 °C. Data are reported as ESI † in Tables SI–SIX and are summarized in Fig. 1.



$[Pd(dien)H_2O]^{2+}$ **$[Pd(bpma)H_2O]^{2+}$** **$[Pd(terpy)H_2O]^{2+}$**



L-cysteine **glutathione** **DL-penicillamine**

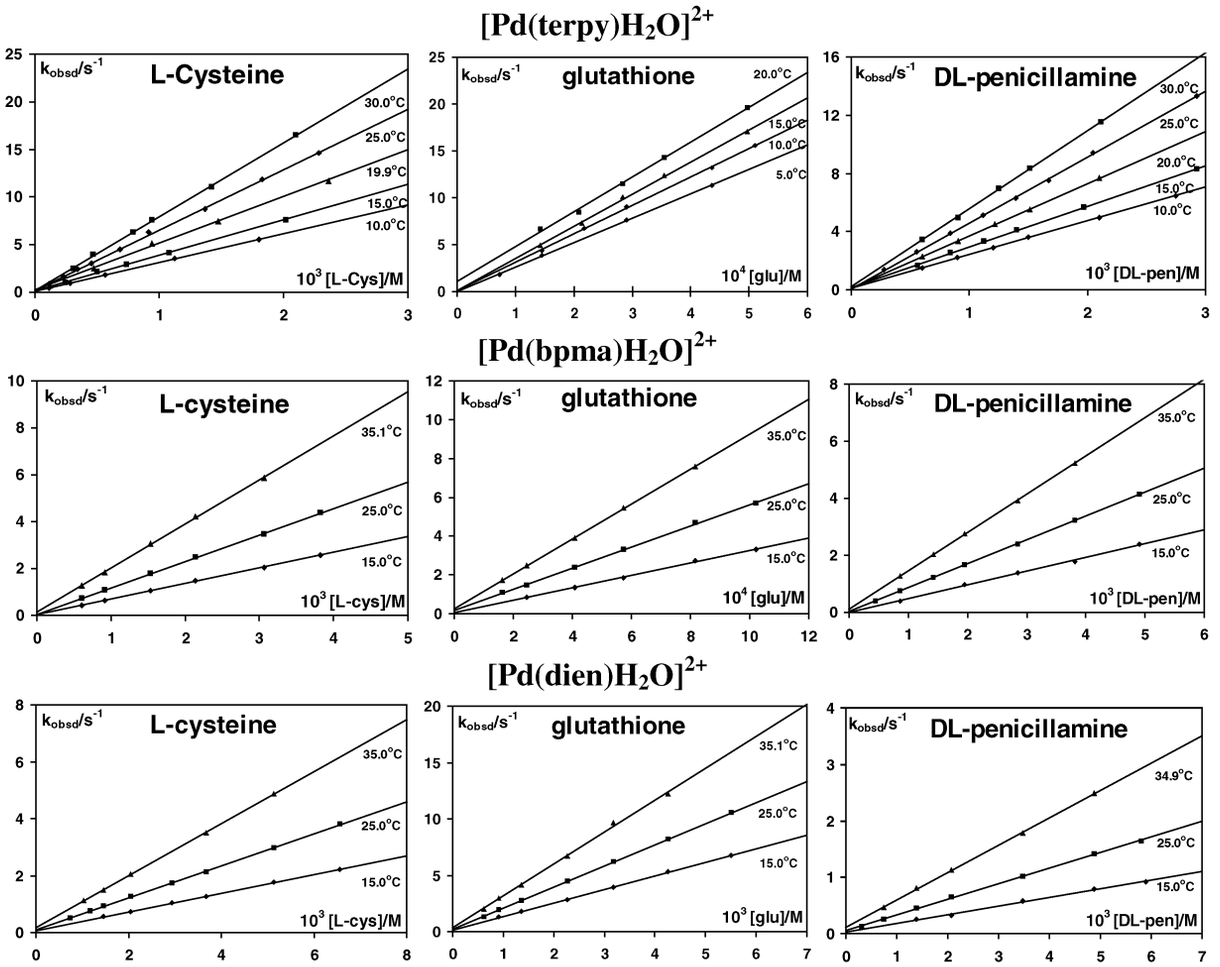


Fig. 1 Observed pseudo-first-order rate constants, k_{obsd}, as a function of thiol concentration and temperature.

The pressure dependencies of the observed rate constants were studied at 25 and at 10 °C for glutathione, in the interval 0.1–130 MPa. These reactions were also followed under pseudo-first-order conditions with thiol in excess. The observed pseudo-first-order rate constants, k_{obsd}, at elevated pressure were calculated as the average values from three to five independent runs. High pressure kinetic data are given as ESI † in Tables SX–SXVIII and are summarized in Fig. 2.

Crystal structure determination

X-Ray intensities were collected at low temperature (190 K) on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.70930 Å) with the ω–2θ scan technique. A total of 6110 reflections was measured of which 2854 are independent, and of these 2043 were considered observed. Crystal data and details of the data collection are given in Table 1. For solution and refinement of the structure, the program SHELXL-97[23a] was used, and for computing molecular graphics and publication material, the program package PLATON[23b] was used.

CCDC reference number 173337.

See http://www.rsc.org/suppdata/dt/b1/b106038b/ for crystallographic data in CIF or other electronic format

Results and discussion

Spectra and kinetics

In all cases the spectrum of the reaction mixture evolves with time in a first-order fashion and with well defined isosbestic points, from that of the aqua complex $[Pd(N–N–N)H_2O]^{2+}$ to that of an authentic sample of the substitution products $[Pd(N–N–N)(HSR)]^{2+}$ measured under the same experimental conditions.[24] This clearly indicates that the process studied is the displacement of the coordinated water molecule by thiol. The kinetics traces follow single exponentials, suggesting that only 1:1 complexes are formed according to eqn. (1).

$$[Pd(N–N–N)H_2O]^{2+} + L \rightleftharpoons [Pd(N–N–N)L]^{2+} + H_2O \qquad k_1, k_{-1} \quad (1)$$

L = L-cysteine, DL-penicillamine and glutathione

The observed rate constant, k_{obsd}, as a function of the total concentration of thiol is described by eqn. (2).

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

A least-squares fit of the data according to eqn. (2), resulted in values for the forward anation rate constant, k_1, and the reverse aquation rate constant, k_{-1}. In most cases the substitution reactions are characterized by almost zero values for k_{-1} (see Fig. 1), illustrating that the solvent cannot effectively displace the coordinated thiols. The temperature dependencies of these rate constants allowed for the calculation of the enthalpies and entropies of activation by use of the Eyring equation. Rate constants and activation parameters derived from these experiments are summarised in Table 2.

Reactivity

From a comparison of the data for the three complexes in Table 2, it can be seen that $[Pd(terpy)H_2O]^{2+}$, in which the tridentate ligand involves three aromatic pyridine rings in the coordination plane, is the most reactive complex in accordance with the stronger π-acceptor effect, as already reported in kinetic studies

Table 1 Crystallographic data for [Pd(bpma)Cl]Cl·H_2O

Parameter	
Formula	$C_{12}H_{13}N_3Cl_2Pd·H_2O$
M	394.31
Crystal dimensions/mm	0.06 × 0.08 × 0.43
Crystal system	Triclinic
Space group	$P\bar{1}$ (no. 2)
a/Å	7.039(5)
b/Å	8.534(5)
c/Å	12.831(5)
α/°	106.52(2)
β/°	102.56(2)
γ/°	91.46(2)
V/Å^3	718.1(7)
Z	2
T/K	190
D_c/g cm^{-3}	1.81
D_{obsd}	Not determined
μ(Mo-Kα)/mm^{-1}	1.6
F(000)	386
θ Range/°	2.5–26
λ(Mo-Kα)/Å	0.70930 (graphite monochromator)
Min., max. residual electron density/e Å^{-3}	−0.92, 0.85
Measured reflections	6110
Independent reflections	2854
Observed reflections	2043 [$I > 2\sigma(I)$]
R_{int}	0.101
R_1 (for all observed reflections)	0.086
R_2 (for all observed reflections)	0.146

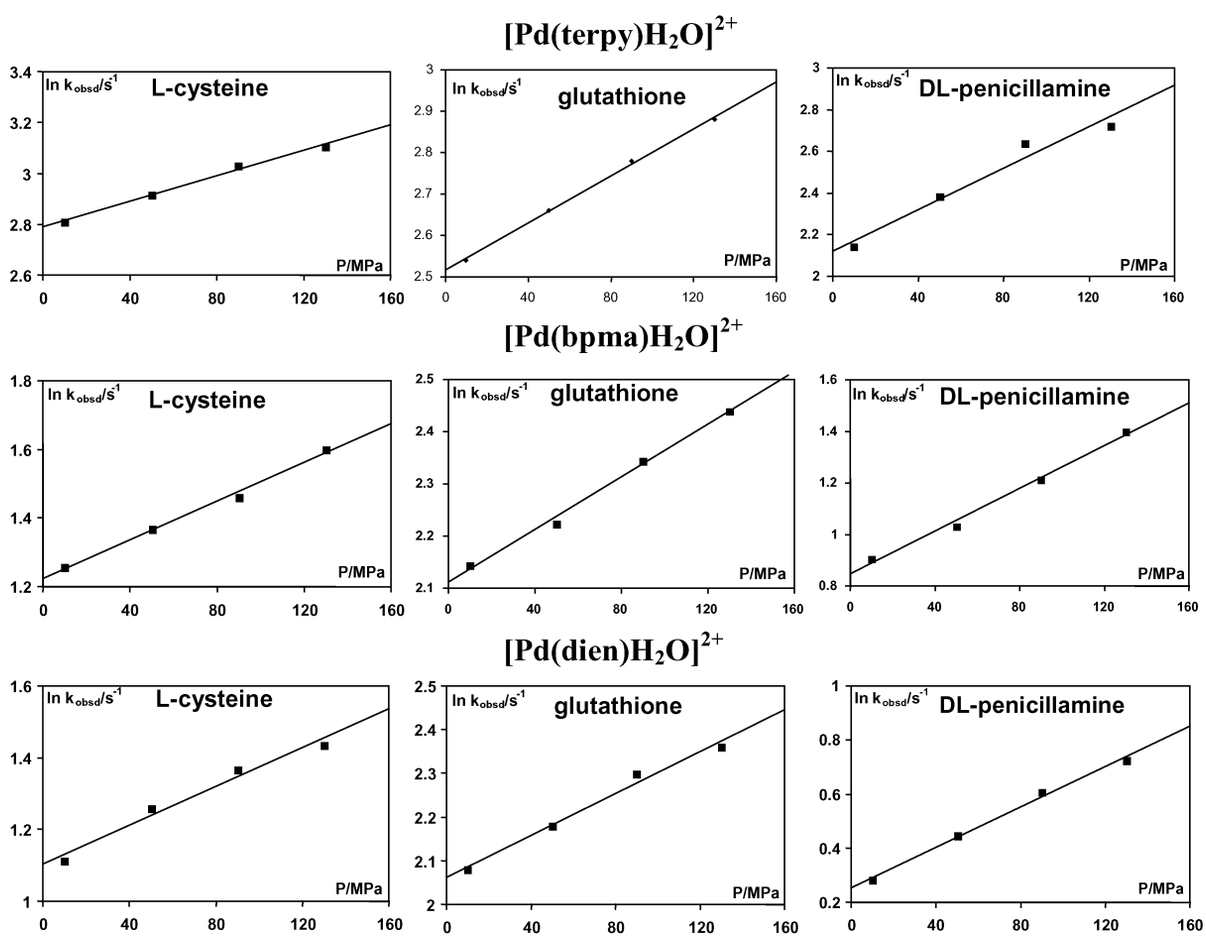


Fig. 2 Observed pseudo-first-order rate constants, ln k_{obsd}, as a function of pressure.

on the $[Pd(terpy)Cl]^+$ [25] and $[Pt(terpy)Cl]^+$ complexes.[24,26,27] This effect can be ascribed to the coordination geometry of the aromatic pyridine rings, leading to a relative increase in the electrophilicity of the metal centre, as a consequence of delocalization of electron density.[5] A comparison between the $[Pd(bpma)H_2O]^{2+}$ and $[Pd(dien)H_2O]^{2+}$ complexes reveals a much smaller acceleration for the bpma complex than for the terpy complex, but the observed effect must again be due to the presence of two pyridine aromatic rings that can accept electron density and make the metal center more electrophilic. The reactivity order of the three complexes is therefore $[Pd(terpy)H_2O]^{2+}$ > $[Pd(bmpa)H_2O]^{2+}$ > $[Pd(dien)H_2O]^{2+}$. It

Table 2 Rate constants and activation parameters for the reaction between $[Pd(N–N–N)H_2O]^{2+}$ and thiols[a]

L	k_1^{298}/M^{-1} s^{-1}	$\Delta H_1^{\neq}$/kJ mol^{-1}	$\Delta S_1^{\neq}$/J K^{-1} mol^{-1}	$\Delta V_1^{\neq}$/cm^3 mol^{-1}
$[Pd(terpy)H_2O]^{2+}$				
L-Cysteine	$(6.32 \pm 0.02) \times 10^3$	32 ± 1	-67 ± 3	-6.3 ± 0.4
L-Glutathione	$(4.45 \pm 0.02) \times 10^4$	16 ± 1	-102 ± 3	-6.7 ± 0.2
DL-Penicillamine	$(4.52 \pm 0.01) \times 10^3$	28 ± 1	-80 ± 3	-10.7 ± 1.0
$[Pd(bpma)H_2O]^{2+}$				
L-Cysteine	$(1.13 \pm 0.01) \times 10^3$	36 ± 1	-66 ± 3	-6.8 ± 0.2
L-Glutathione	$(5.45 \pm 0.04) \times 10^3$	36 ± 1	-54 ± 3	-6.4 ± 0.2
DL-Penicillamine	$(8.37 \pm 0.02) \times 10^2$	35 ± 2	-70 ± 4	-10.0 ± 0.3
$[Pd(dien)H_2O]^{2+}$				
L-Cysteine	$(5.46 \pm 0.02) \times 10^2$	35 ± 1	-74 ± 2	-5.6 ± 0.3
L-Glutathione	$(1.87 \pm 0.01) \times 10^3$	28 ± 1	-86 ± 1	-5.8 ± 0.5
DL-Penicillamine	$(2.76 \pm 0.02) \times 10^2$	40 ± 1	-64 ± 1	-9.2 ± 0.6

[a] All values refer to 0.10 M $HClO_4$ solutions.

has previously been reported that the $[Pd(terpy)Cl]^+$ complex is about 10^3 times more reactive than the analogous $[Pd(dien)Cl]^+$ complex in reactions with nucleophiles such as I^-, Br^-, NO_2^-, N_3^- and thiourea.[25] In the present case for the reactions with the thiols, the difference is much smaller (*ca.* 10 times), which could be related to steric hindrance due to the bulkiness of these thiols, which makes the reactions less sensitive to the electrophilicity of the metal center. It was recently suggested that the much larger increase in reactivity found for the corresponding Pt(II) terpy complex is due to a direct electronic communication between the adjacent pyridine donor groups that strengthen the π-acceptor effect as a result of an increase in aromaticity.[5] Such a direct communication is not possible in the case of the bpma ligand. The less labile Pt(II) complexes seem to be more sensitive towards this electronic communication phenomenon than found in the present study for the more labile Pd(II) complexes. Thus, tuning the electrophilicity of the metal center plays a more important role in Pt(II) than in Pd(II) complexes. The overall increase in k_1 with increasing electrophilicity of the metal center is direct evidence for an associative attack of the entering nucleophile.

The difference in nucleophilicity of the selected thiols is obvious. 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. On the other hand, the steric effects are very important as well. For example, DL-penicillamine has the lowest reactivity of the thiols used, which can be explained by steric effects involving the two methyl groups on the carbon center near to the sulfur atom. The tridentate (terpy, bmpa or dien) ligand hinders to some extent the configurational changes occurring during the activation process to form a five-coordinate transition state. Moreover, strong steric interactions between the bound tridentate ligand and the entering thiols are responsible for their low nucleophilicity as well. Glutathione is considerably more reactive than expected. This anomaly seems to suggest an appreciable neighbouring group effect capable of reducing the activation barrier of the substitution reaction, arising from hydrogen bonding interactions between the acidic group located in a suitable position of the nucleophile. The anchimeric (neighbouring group) effect has been reported for other reactions at Pt(II) complexes and is well known for organic reactions.[28] 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, carboxylic acids[29,30] and of $[Pt(H_2O)_4]^{2+}$ with thioglycolic acid.[31]

The produced complexes, $[Pd(N–N–N)(HSR)]^{2+}$, are relatively stable. Stability constants derived from the kinetic measurements ($K = k_1/k_{-1}$) vary between 3×10^3 and 9×10^4 M^{-1}. The most stable complexes are formed with glutathione in all cases.

Activation parameters

The second-order rate constants k_1 were studied as a function of temperature and pressure. Plots of ln k_1 *vs.* 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 similar data reported for related systems in the literature.[5] 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 thiol.

Structure of $[Pd(bpma)Cl]Cl·H_2O$

The structure of $[Pd(bpma)Cl]Cl·H_2O$ is shown in Fig. 3 and

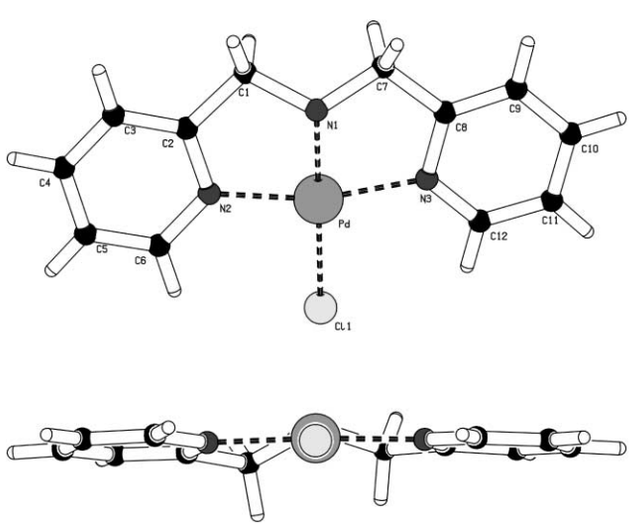


Fig. 3 X-Ray crystal structure of $[Pd(bpma)Cl]Cl·H_2O$.

some selected bond lengths and angles are given in Table 3. The geometry around the palladium is distorted square-planar, with bpma coordinating as a terdentate ligand and the fourth position occupied by the chloride ligand. All Pd–N distances are equal to 2.005(7) Å. The Pd–Cl distance of 2.305(3) Å is perfectly within the range of 2.294–2.422 Å found for Pd–Cl and

Table 3 Selected bond distances (Å) and angles (°) for [Pd(bmpa)Cl]Cl·H_2O

Pd–N1	2.005(7)	Cl1–Pd–N1	174.7(2)
Pd–N2	2.006(6)	Cl1–Pd–N2	96.9(2)
Pd–N3	2.007(6)	Cl1–Pd–N3	96.96(19)
Pd–Cl1	2.305(3)	N1–Pd–N2	82.7(3)
N1–C1	1.491(11)	N1–Pd–N3	83.8(3)
N1–C7	1.478(10)	N2–Pd–N3	165.8(3)
N2–C2	1.348(11)	N1–C1–C2	108.9(6)
C1–C2	1.522(12)	Pd–N2–C2	114.0(5)
N3–C8	1.367(10)	N1–C7–C8	110.5(6)
C7–C8	1.515(10)	Pd–N3–C8	113.1(5)

Pt–Cl distances,[32,33] the lengths being dependent upon the steric nature of the ligands and nature of the *trans*-bond. By comparison with the related crystal structure of chloro-{methyldi-[(6-methyl-2-pyridyl)methyl]amine}palladium(II) chloride,[34] $[Pd(Me_3dmpa)Cl]^+$, it can be seen that the Pd–N distance to the central nitrogen atom of $[Pd(bmpa)Cl]^+$, 2.005(7) Å, is shorter than the Pd–N distances in $[Pd(Me_3dmpa)Cl]^+$, 2.018(8) Å. However, the Pd–Cl distance in $[Pd(bpma)Cl]^+$, 2.305(3) Å, is also shorter than the Pd–Cl, 2.331(3) Å, in $[Pd(Me_3dmpa)Cl]^+$. On the other hand, the central nitrogen Pd–N distance in $[Pd(terpy)Cl]^+$ is shorter,[35] 1.962(9)Å, than in $[Pd(bpma)Cl]^+$, indicating that there is even more strain in the structure of the terpy complex.

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