Specific Chelate Tuning of the Substitution Kinetics of Platinum(II) Complexes in Aqueous Solution

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Both reaction steps observed for the substitution of water by thiourea in the complexes $[Pt(en)(OH_2)_2]^{2+}$ and $[Pt(phen)(OH_2)_2]^{2+}$ (en = ethylenediamine, phen = 1,10-phenanthroline) were investigated under pseudo-first-order conditions using the stopped-flow technique. The substitution of the second water molecule in each complex was also studied under high pressure. The observed pseudo-first-order rate constants k_{obs} (s^{-1}) obeyed the equation $k^{1,2}_{obs} = k^{1,2}[tu]$ (tu = thiourea), where "1" and "2" refer to the first and the second substitution reactions, respectively. Kinetic parameters associated with the substitution process are: k^1_{en} (25.0°C, pH = 3.0, I = 0.1 M) = 25.6 $M^{-1}\ s^{-1}$, $\Delta H^{\#}$ = 51 kJ mol^{-1}, $\Delta S^{\#}$ = −48 J K^{-1} mol^{-1}; k^2_{en} (same conditions) = 12.1 $M^{-1}\ s^{-1}$, $\Delta H^{\#}$ = 30 kJ mol^{-1}, $\Delta S^{\#}$ = −124 J K^{-1} mol^{-1}, $\Delta V^{\#}$ = −7 cm^3 mol^{-1}; k^1_{phen} (25.0°C, pH = 1.0, I = 0.1 M) = 2900 $M^{-1}\ s^{-1}$, $\Delta H^{\#}$ = 41 kJ mol^{-1}, $\Delta S^{\#}$ = −41 J K^{-1} mol^{-1}; k^2_{phen} (same conditions) = 1170 $M^{-1}\ s^{-1}$, $\Delta H^{\#}$ = 37 kJ mol^{-1}, $\Delta S^{\#}$ = −61 J K^{-1} mol^{-1}, $\Delta V^{\#}$ = −5 cm^3 mol^{-1}. The temperature and pressure dependence of all the processes studied suggest an associative substitution mechanism. The hydroxo-bridged dinuclear complex $[\{Pt(phen)(\mu\text{-}OH)\}_2]^{2+}$ is formed from $[Pt(phen)(OH_2)_2]^{2+}$ in aqueous solution unless the solution is very dilute and highly acidic. The X-ray structure of $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2 \cdot 2\ H_2O$ was determined. It belongs to the triclinic space group $P\bar{1}$ and has one formula unit in the unit cell. The unit cell dimensions are a = 7.126(5), b = 9.665(5), c = 12.774(7) Å; α = 71.85(5) , β = 85.52(5), γ = 73.12(5) deg; V = 799.9(8) $Å^3$. The structure was solved with the Patterson method and refined to R = 0.061. A square planar coordination of the platinum centers is observed, with no deviations from planarity but distortions due to the small bite angle of phen and the four-membered ring. No significant lengthening of the Pt−O bond [mean value: 2.03(1) Å] is observed in comparison with $[\{Pt(NH_3)_2(\mu\text{-}OH)\}_2]^{2+}$.

Introduction

The substitution kinetics of d^8 transition metal complexes are both of fundamental[1][2][3][4][5] and practical importance, the latter stemming from applications in catalysis[6][7] and cancer chemotherapy[8][9][10][11][12]. In particular the influence of spectator ligands has found considerable attention. For example, a recent study showed that the rate of DMSO-exchange on *cis*-$[Pt('N_2')(CH_3)(DMSO)]^+$ ('N_2' = *N,N*-chelating ligand) can vary by ten orders of magnitude depending on the nature of the non-leaving 'N_2' spectator group[13]. The more labile complexes of platinum and palladium often contain electron-withdrawing groups such as phenanthroline, bipyridine or terpyridine[13][14][15][16][17].

We are mainly interested in complexes which offer two labile substitution sites and two non-leaving N-donors in the *cis*-position, since similar systems are used in tumor therapy. Complexes of the structure *cis*-$[Pt^{II}am_2x_2]$ (am = am(m)ine, x = leaving group) have been investigated systematically since the discovery by Rosenberg, that *cis*-$[Pt(NH_3)_2Cl_2]$ (Cisplatin) exhibits anti-tumor activity[18]. Since then, Cisplatin has been very succesfully used against testicular cancer and with good results against ovarian tumors, cancer of the head, neck, and bladder. Unfortunately, the anti-tumor activity of Cisplatin and structurally related compounds does not extend to the most common tumors like lung tumors or adenotumors of the gastrointestinal tract[10]. Promising results were recently obtained with platinum complexes containing α-diimine ligands instead of amine ligands[19][20][21][22]. This prompted us to investigate the substitution behaviour of complexes with two *cis*-bound labile ligands and an electron-withdrawing non-leaving α-diimine group in aqueous solution.

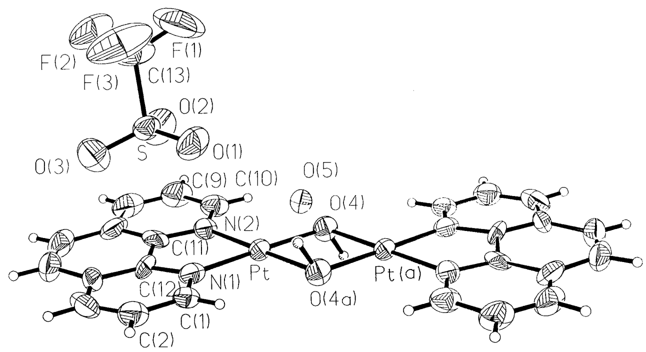
In the present study we have chosen to investigate the substitution of water by thiourea, a strong nucleophile, in $[Pt(phen)(OH_2)_2]^{2+}$. For comparison, we have investigated the corresponding reactions with $[Pt(en)(OH_2)_2]^{2+}$. The complex $[Pt(phen)(OH_2)_2]^{2+}$ was generated by cleaving the hydroxo-bridged dimer $[\{Pt(phen)(\mu\text{-}OH)\}_2]^{2+}$ with perchloric acid. X-ray structural data for the dimer were obtained.

Results and Discussion

Structure of $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2 \cdot 2\ H_2O$

An ORTEP view of the molecular structure of $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2 \cdot 2\ H_2O$ together with the atom numbering scheme of the most important unique atoms is shown in Figure 1, whereas the crystallographic data are summarized in Table 1 and the relevant intramolecular distances and angles in Table 2. Some intermolecular distances and angles are also shown in Table 2, which suggest that the structure is stabilized by the water molecule of crystallization. The latter apparently forms hydrogen bonds to both the oxygen atoms of the $F_3CSO_3^-$ ion and the hydrogen atom of the μ-hydroxo groups. There is a crystallographic center of inversion between the two platinum atoms. The $N_2PtO_2PtN_2$ moiety is planar, and deviations from the best plane calculated through the eight atoms are within the error limits. The mean deviation from the best plane is smaller than 0.01 Å. The phen ligand is nearly planar, but slightly twisted. A torsion of 7.2° N(1)−C(12)−C(11)−N(2) is found. The chelate ligand forces a bite angle N(1)−Pt−N(2) of 81.3(4)°. The geometric features of the phen ligand are in good agreement with values reported in the literature for other phen containing complexes of platinum or palladium[23][24][25]. Pt−O distances of 2.02(1) and 2.03(1) Å are found together with Pt−N distances of 1.99(1) and 2.01(1) Å. It is noteworthy, that the Pt−O distances are within the experimental error limits the same as found in the cations[26][27][28] $[\{Pt(NH_3)_2(\mu\text{-}OH)\}_2]^{2+}$ and $[\{Pt(N,N\text{-dimethylethylenediamine})(\mu\text{-}OH)\}_2]^{2+}$. Since the phen ligand causes an increase (with respect to the amine derivative) in the rate of substitution of the *trans* ligands by a factor of 10^2 (see below), it is quite remarkable, that this enhanced reactivity is not mirrored in the Pt−O bond distance of the dimer. A strong kinetic *trans*-effect without a corresponding static *trans*-influence is an effect caused by π-acceptor ligands[29]. This clearly shows that the increase in lability in this case does not result from bond weakening to the leaving group. Therefore, the structural data support the interpretation of the kinetic data in terms of an associatively activated substitution mechanism (see below).

Figure 1. View of $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2\cdot 2\ H_2O$ showing the atomic numbering scheme. For clarity's sake only one counterion and water molecule are shown. The thermal ellipsoids are 50% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter.



Reaction of $[Pt(en)(OH_2)_2]^{2+}$ with Thiourea

The reaction of $[Pt(en)(OH_2)_2]^{2+}$ with thiourea (tu) was studied at a pH of 3.0 in order to prevent formation of hydroxo-bridged oligomers (see above). Preliminary studies were performed by ^{1}H-NMR. A 0.1 M solution of $[Pt(en)(OD_2)_2]^{2+}$ (300 μl) was prepared and reacted in an NMR tube with 200 μl of 0.4 M tu. DNO_3 was used to preadjust the pH* to 3.00. Before mixing, the signal of $[Pt(en)(OD_2)_2]^{2+}$ (singlett at $\delta = 2.51$ with satellites, $^3J_{H\text{-}Pt} = 24$ Hz) was observed, while after mixing a signal due to $[Pt(en)tu_2]^{2+}$ $\delta = 2.83$ ($^3J_{H\text{-}Pt} = 24$ Hz) was seen. After 48 h a product indicative of a very slow reaction was observed: the appearence of a signal due to uncoordinated en ($\delta = 3.06$, no satellites) was accompanied by an increase in pH* to 8.1. These observations point to a substitution of en by tu, which is thought to be due to the strong *trans*-effect of the already coordinated tu. The initial substitution of water by tu, however, was too fast to be measured by NMR and was therefore followed by UV-Vis spectroscopy. Two reactions were observed in accord with reactions (1) and (2).

A clear separation of two reaction rates which differ only by a small factor (approximately 2 in the present case, as

Table 1. Crystallographic data[62] for $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2\cdot 2\ H_2O$

formula	$C_{26}H_{18}N_4O_8F_6S_2Pt_2\cdot 2\ H_2O$
fw	1118.0
cryst. dimensions [mm]	0.6 × 0.18 × 0.05
cryst. system	triclinic
space group	$P\bar{1}$
a [Å]	7.126(5)
b [Å]	9.665(7)
c [Å]	12.774(5)
α [deg]	71.85(5)
β [deg]	85.52(5)
γ [deg]	73.12(5)
V [Å^3]	799.9(8)
Z	1
T [K]	293(2)
d_{calc} [g cm^{-3}]	2.321
μ [mm^{-1}]	8.95
Index ranges	$-8 \le h \le 8$, $-11 \le k \le 11$, $-14 \le l \le 14$
F(000)	508.0
θ range [deg]	$2.99 \le \theta \le 23.97$
radiation (Mo-K_α) [Å]	0.71069 (graphite monochromator)
R_1[a] (all data)	0.061
wR_2[b] (all data)	0.141
GooF[c]	1.356

[a] $R_1 = \Sigma(\|F_0| - |F_c\|)/\Sigma(|F_0|)$. – [b] $wR_2 = [\Sigma w(F_0^2 - F_c^2)^2/\Sigma(wF_0^2)^2]^{1/2}$; $w = 1/[\sigma^2(F_0^2) + (aP)^2 + bP]$; $P = (\max(F_0^2) + 2F_c^2)/3$; – [c] GooF $= [\Sigma[w(F_0^2 - F_c^2)^2]/(n - p)]^{1/2}$; n = number of reflexes measured; p = number of parameters used.

Table 2. Selected distances [Å] and angles [deg] for $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2\cdot 2\ H_2O$

Pt−N(1)	1.986(10)	O(5)−O(1)	2.87(1)
Pt−N(2)	2.007(10)	O(5)−O(4a)[a]	2.66(1)
Pt−O(4)	2.024(9)	O(4)−Pt−O(4a)[a]	81.0(4)
Pt−O(4a)[a]	2.032(8)	N(1)−Pt−N(2)	81.3(4)
Pt−Pt(a)[a]	3.0837(14)	Pt−O(4)−Pt(a)[a]	99.0(4)
N(1)−C(1)	1.329(14)	O(1)−O(5)−O(3*)[b]	118(1)
N(1)−C(12)	1.364(14)	Pt−O(4)−H(11)	103(1)
N(2)−C(10)	1.32(2)	Pt−N(1)−C(12)	114.2(7)
N(2)−C(11)	1.34(2)	Pt−N(2)−C(11)	112.8(8)
C(11)−C(12)	1.43 (2)	N(1)−C(12)−C(11)	113(1)
O(5)−O(3*)[b]	2.86(1)	(2)−C(11)−C(12)	118(1)

[a] Coordinates for atoms labelled 'a': $1 - x$, $1 - y$, $1 - z$. – [b] Coordinates of O(3*) are obtained from the coordinates of O(3) by the symmetry operations: $2 - x$, $-y$, $1 - z$.

$$[Pt(en)(OH_2)_2]^{2+} + tu \xrightarrow{k_1} [Pt(en)tu(OH_2)]^{2+} + H_2O \quad (1)$$

$$[Pt(en)tu(OH_2)]^{2+} + tu \xrightarrow{k_2} [Pt(en)(tu)_2]^{2+} + H_2O \quad (2)$$

will be shown below) by UV-Vis spectroscopy depends on the changes in absorbance associated with the two reactions. A favourable situation is the case where the absorbance change for the first reaction is much smaller than the absorbance change for the second reaction. This enables the observation of a typical induction curve, from which both rates can be obtained with a rather low error. A series of measurements at different wavelengths demonstrated that the reaction can be followed at 276 nm, where this condition is best fulfilled. It can be seen from the spectra shown in Figure 2, that the absorbance change for the second substitution step at 276 nm is more than five times larger than the absorbance change for the first substitution step. Under these conditions an induction behaviour is observed (Figure 3). The observed time trace was fitted to a two exponential model. The fitted curve is shown in the lower part of Figure 3, whereas the deviation from the fit (residuals) is indicated in the upper part of Figure 3. The two exponential model is confirmed by the fact that the residuals are statistically scattered. A linear dependence of the observed rate constants on the tu concentration was found (Figure 4). The absence of an intercept suggests that both steps are irreversible in nature.

The two observed reactions were assigned to the substitution steps (1) and (2) by pre-mixing the complex solution with sub-stoichiometric amounts of thiourea. The absorbance change associated with the fast reaction decreases to a much larger extent than the absorbance change associated with the slower reaction with increasing amount of pre-added thiourea, which provides evidence that the first reaction is the faster one. The temperature dependence results in the activation parameters quoted in Table 3.

The effect of high pressure on the reaction could not be followed at 276 nm due to the absorption properties of the pressure medium employed (*n*-heptane). Therefore the absorbance change at 330 nm was used, which, however, did not allow the evaluation of the first substitution step, since the absorbance changes for the two steps are too similar (see Figure 2) to allow separation. Following the arguments outlined for the very similar spectral situation of the Pt(phen) system below, the second (slower) reaction can be followed at 330 nm. For this step (Figure 5) the dependence of ln(*k*) on the applied pressure was linear within the experimental error limits. From this dependence an activation volume of -7.1 ± 0.9 cm^{3}mol^{-1} was obtained. These activation parameters are in accord with those generally observed for associative substitution reactions of d^8 complexes[4][30]. The more negative entropy of activation for the second step might be due to the steric hindrance caused by the thiourea ligand already coordinated during the first step. The $\Delta H^{\#}$ values are discussed below.

Figure 2. UV-Vis spectra of the reactants, intermediate and product for the two-step substitution reaction obtained using a 0.88 cm tandem cuvette. Conditions: [Complex] = 0.1 mM, pH = 3.0, I = 0.1 M, T = 25°C. The spectrum of $[Pt(en)(OH_2)tu]^{2+}$ was obtained from an equilibrated solution containing a fourfold platinum excess over thiourea and was corrected for the excess platinum background. The spectrum of an equimolar amount of uncoordinated tu was then added arithmetically in order to show the overall absorbance change observed for the formation of the 1:1 complex.

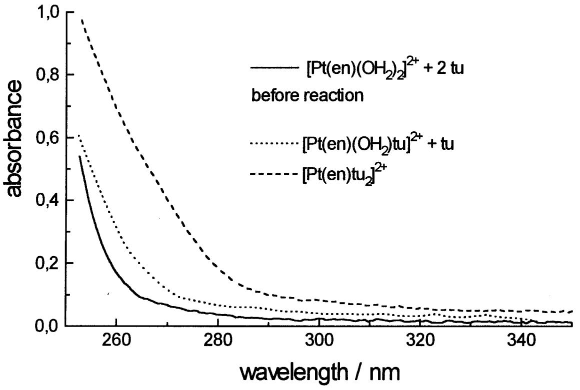
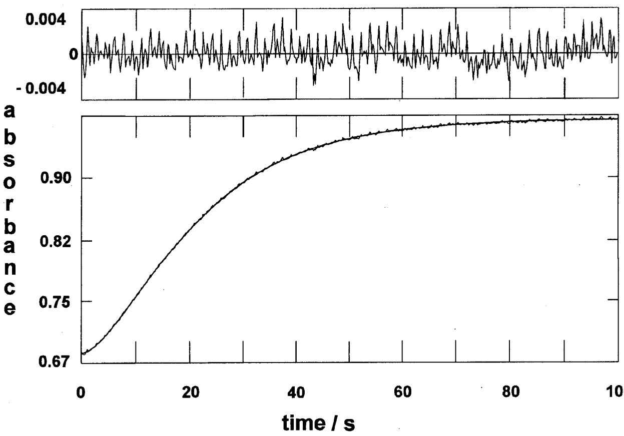


Figure 3. Fit of two exponentials and residuals (upper part) for the reaction of $[Pt(en)(OH_2)_2]^{2+}$ (0.1 mM) with thiourea (5 mM) followed at 276 nm. pH = 3.0, I = 0.1 M ($NaClO_4$), T = 25.0°C.



The Equilibrium Between $[Pt(phen)(OH_2)_2]^{2+}$ and $[\{Pt(phen)(\mu\text{-}OH)\}_2]^{2+}$

During the investigation of the hydrolysis behaviour of Cisplatin the property of complexes of the type $[Pt('N_2')(OH_2)_2]^{2+}$ ('N_2' = am(m)ine$_2$ or bidentate amine) to form dimeric[26][27][28][31], trimeric[32][33][34] and (rarely) tetrameric[35] species of the general formula $[\{Pt('N_2')(\mu\text{-}OH)\}_n]^{n+}$ was discovered. In dilute solutions the higher oligomers are not formed, but dimeric species must be taken into account in the appropriate pH range. Preparation of the monomeric diaqua complexes is possible at a pH of 2 or 3. Attempts to synthesize the diaqua complex in the case where 'N_2' is an aromatic α-diimine, the central atom being platinum or palladium, has led to studies[36][37][38][39] that were criticized later by Wimmer and Castan[31][40], who showed that under the selected conditions reported for synthesis and reaction, the dimeric species is the main species present in solution. In the present study attempts were made to apply the synthetic route for the preparation of

Figure 4. Reaction of $[Pt(en)(OH_2)_2]^{2+}$ (0.1 mM) with thiourea; k_{obs} as a function of thiourea concentration, followed at 276 nm. pH = 3.0, I = 0.1 M $(NaClO_4)$, T = 25.0°C.

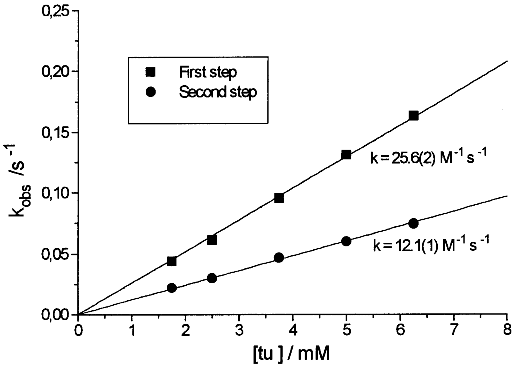
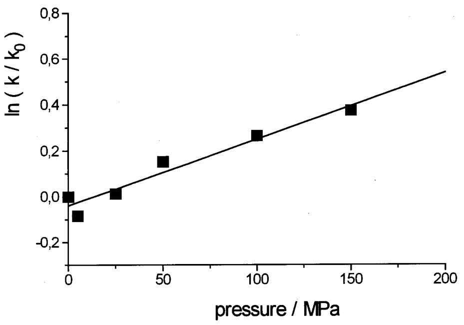


Table 3. Temperature dependence and activation parameters for the first (k_1) and second (k_2) step in the irreversible substitution of water by thiourea (6.25 mM) in $[Pt(en)(OH_2)_2]^{2+}$ (0.1 mM) at pH = 3.0, I = 0.1 M, reaction followed at λ = 276 nm

T /°C	k_1 / M^{-1} s^{-1}	k_2 / M^{-1} s^{-1}
10.0	10.1 ± 0.5	6.0 ± 0.1
15.0	12.2 ± 1.3	7.7 ± 0.6
20.0	19.8 ± 1.6	9.1 ± 0.5
25.0	26.1 ± 1.6	11.8 ± 0.2
30.0	38.2 ± 3.2	14.8 ± 0.2
35.0	62.2 ± 4.3	18.2 ± 0.5
activation parameter	1st step	2nd step
$\Delta H^{\#}$ / kJ mol^{-1}	50.6 ± 3.5	29.9 ± 0.9
$\Delta S^{\#}$ / J K^{-1} mol^{-1}	−48 ± 12	−124 ± 3

Figure 5. Determination of the volume of activation for the substitution of the remaining water molecule in $[Pt(en)(OH_2)tu]^{2+}$ by thiourea. This is done by plotting the logarithm of the ratio k/k_0 (where k and k_0 denote the rate constant for elevated and ambient pressure, respectively) according to: $\delta(\ln k)/\delta p = -\Delta V^{\#}/RT$. The measured values are shown together with the linear regression results; $\Delta V^{\#}$ = −7.1 ± 0.9 cm^3 mol^{-1}. Experimental conditions: [Pt] = 0.8 mM, [tu] = 25 mM, pH = 3.0, I = 0.1 M, T = 25.0°C, reaction followed at 330 nm.



$[Pt('N_2')(OH_2)_2]^{2+}$ to the phen complex. Even at pH 2, the formation of a precipitate was observed, which was yellow or orange red, depending on whether silver trifluormethanesulfonate or silver perchlorate was used. UV-Vis spectroscopy, IR spectroscopy and elemental analysis showed this to be identical with the dimer reported in the literature[31][40]. During our investigations we found that the dimer does react with strong nucleophiles, which is in accord with the well known reactivity of analogous halo-bridged dimers[41][42][43]. Its reaction with thiourea is currently being investigated in more detail. In contrast to the behaviour observed for terminal hydroxo ligands bound to platinum or palladium[44][45][46], which cannot easily be substituted, bridging hydroxo-groups are relatively labile, which could be responsible for the high and unspecific toxicity[47][48][49] of these compounds. Preliminary studies on the reactivity of $[\{Pt(phen)(\mu\text{-}OH)\}_2]^{2+}$ with thiourea, however, have shown that the dimeric complex reacts ca. 100 times slower than the monomeric one. This allowed us to distinguish between the reactions of the dimer and the monomer species and conditions suitable for complete cleavage of the dimer were found (see next section).

Reaction of $[Pt(phen)(OH_2)_2]^{2+}$ with Thiourea

The cleavage of the hydroxo-bridged dimer to give the monomeric diaquacomplex is complete following hydrolyses of a 0.05 mM (with respect to platinum) solution of the dimer in 0.1 M perchloric acid for 40 min at 100°C. The reaction of $[Pt(phen)(OH_2)_2]^{2+}$ with thiourea had to be studied at very low thiourea concentrations, since the separation of both substitution steps was only possible at a wavelength of 260 nm, where the reactant and the intermediate (1:1 complex) have almost identical absorptivities which lead to the favourable observation of an induction curve. The observation at 260 nm is made impossible by the absorption of thiourea itself (broad and intense band with a maximum at 238 nm), if a concentration higher than 0.5 mM is used. First the reaction of 2.5×10^{-5} M $[Pt(phen)(OH_2)_2]^{2+}$ with 0.5 mM thiourea was followed over a spectral range from 250 to 370 nm for 10 s and a Global Analysis evaluation was performed. This revealed that two first-order reactions occurred and gave preliminary k_{obs} values of 1.3 s^{-1} and 0.6 s^{-1}. The residuals of the fit were smaller than 2% of the absorbance change and statistically scattered. The spectra of $[Pt(phen)(OH_2)_2]^{2+}$, $[Pt(phen)(OH_2)tu]^{2+}$ (calculated using the Global Analysis software) and $[Pt(phen)(tu)_2]^{2+}$ are shown in Figure 6. The spectral changes do not show very characteristic features, since the bands observed are due to intraligand π-π* transitions of the phen ligand. These are known to show a relatively weak dependence on the nature of the coordination sphere of the metal centre[31][40][50]. The aim of the Global Analysis treatment was to confirm the two-step mechanism and to provide a spectrum of the intermediate 1:1-complex. For the determination of the exact rate constants the kinetics were followed at a single wavelength, 260 nm, using complex concentrations of 2.5×10^{-5} and 1.0×10^{-5} M for the temperature and concentration dependence, respectively. Each k_{obs} value reported is the mean value of at least five measurements. From the concentration dependence (Figure 7) bimolecular rate constants of 2900±40 M^{-1} s^{-1} and 1170±10 M^{-1} s^{-1} were obtained. The assignment of the two reactions was done by pre-mixing (see above), showing that also in this case the first reaction step is the faster one. Activation parameters are derived from the temperature dependence and summarized in Table 4. In the case of the $[Pt(phen)(OH_2)_2]^{2+}$ complex the $\Delta H^{\#}$ values for the first and the second substitution step do not differ significantly. The fact that the second reaction is slower seems to be completely due to the more negative entropy of activation, resulting from steric hindrance due to the thiourea molecule already coordinated. This contrasts with the observations for the $[Pt(en)(OH_2)_2]^{2+}$ complex, where an even more negative $\Delta S^{\#}$ for the second step in comparison to the first one is accompanied by a decrease in $\Delta H^{\#}$ by 20 kJ mol^{-1} (Table 3). We believe that this anomaly of the en complex is caused by hydrogen bonding of the amine protons to thiourea in the transition state. It could be argued, that the fact that we observe the second step to be slower by a factor of roughly two (at room temperature) for the en- as well as for the phen-system is due to a statistical factor in the sense that the first entering tu can substitute two water positions, whereas the second one only one. This probability consideration would be valid for a dissociative mechanism, where the probability of dissociation is proportional to the number of coordinated water molecules. It would not be valid for the case of a limiting associative mechanism, where the bond to the leaving group is not weakened during formation of a five-coordinate intermediate. The nucleophilic attack governs the rate and will not be influenced by the number of possible leaving groups. For an interchange mechanism, where bond-making and bond-breaking take place simultaneously, certainly a statistical factor will contribute, which however will be difficult to estimate. In the present system all observations point to a mechanism which is associative in nature: thus either a limiting associative (A) or an associative interchange (I_a) mechanism.

It is generally accepted that the determination of the volume of activation can elucidate the nature of the intimate mechanism. If no charge is neutralized or created during the reaction, a significantly negative volume of activation points to an associative (A) or associatve interchange (I_a) mechanism. For the system under investigation, the pressure dependence of the reaction could not be followed at 260 nm because of the absorption of the pressure medium (*n*-heptane). This made the simultaneous observation of both steps under high pressure impossible. However, the observation of the second step was possible due to the spectral properties of the species involved and the ratio of the reaction rates. This effect is described in the literature[51]. For a biphasic first-order process, the absorption changes in the following way as function of time (R, I, and P denoting reactant, intermediate and product, respectively):

$$\begin{aligned} Abs = d[R]_0\{ & e^{-k_1 t}\left(\varepsilon_R + \frac{e^{-k_1 t}}{e^{-k_2 t}-e^{-k_1 t}}\varepsilon_I - \frac{e^{-k_2 t}}{e^{-k_2 t}-e^{-k_1 t}}\varepsilon_P\right) \\ & +\varepsilon_P + e^{-k_2 t}\left(-\frac{e^{-k_1 t}}{e^{-k_2 t}-e^{-k_1 t}}\varepsilon_I + \frac{e^{-k_1 t}}{e^{-k_2 t}-e^{-k_1 t}}\varepsilon_P\right)\} \end{aligned} \tag{3}$$

For the system under investigation, it was found experimentally that $k_1 \approx 5/2\ k_2$. Insertion of $k_1 \approx 5/2\ k_2$ into equation (3) leads to a monophasic time-dependence of the absorbance $Abs_{(t)}$, if $\varepsilon_I - \varepsilon_R \approx 2/3\ (\varepsilon_P - \varepsilon_I)$.

This condition is fulfilled at 350 nm (compare Figure 6), such that the second reaction step can be followed at this wavelength under the assumption that the ratio k_1/k_2 remains approximately constant. This assumption was confirmed by the fact that even under high pressure, single exponential kinetics were always observed at this wavelength. From the pressure dependence of the rate constants (Figure 8) a volume of activation of -5.0 ± 0.8 cm^3/mol was calculated. This confirms the assignment of an associative or associative interchange mechanism. The activation volumes found in the present study compare well with available data on the substitution of water by uncharged sulfur donor nucleophiles in related complexes (Table 5).

Figure 6. UV-Vis spectra of reactant, intermediate (calculated using Global Analysis) and product. pH = 1.0, $I = 0.1$ M, $T = 25.0$°C, [Pt] = 0.025 mM. Background absorption of thiourea (0.5 mM) was subtracted.

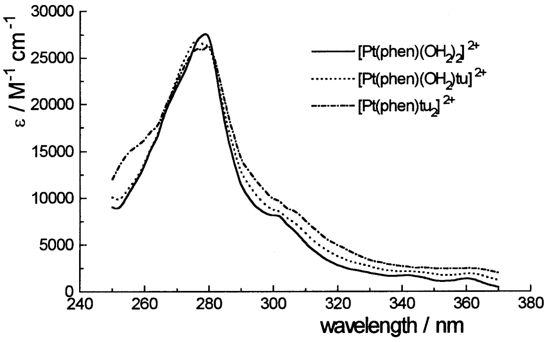


Figure 7. Reaction of $[Pt(phen)(OH_2)_2]^{2+}$ (0.01 mM) with thiourea; k_{obs} as a function of thiourea concentration . pH = 1.0, $I = 0.1$ M, $T = 25.0$°C. The reaction was followed at 260 nm.

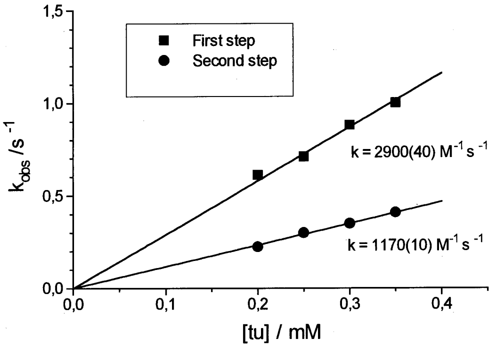


Table 4. Temperature dependence for the first (k_1) and second (k_2) step in the irreversible substitution of water by thiourea (0.5 mM) in $[Pt(phen)(OH_2)_2]^{2+}$ (0.025 mM) at pH = 1.0, $I = 0.1$ M. The reaction was followed at 260 nm (isosbestic for the first step)

T /°C	k_1 / M^{-1} s^{-1}	k_2 / M^{-1} s^{-1}
15.0	1500 ± 40	686 ± 10
25.0	2560 ± 160	1240 ± 20
35.0	4540 ± 80	2040 ± 20
45.0	8400 ± 200	3300 ± 40
activation parameter	1st step	2nd step
$\Delta H^{\#}$ / kJ mol^{-1}	41 ± 2	37.3 ± 0.7
$\Delta S^{\#}$ / J K^{-1} mol^{-1}	−41 ± 6	−61 ± 2

Figure 8. Determination of the volume of activation for the substitution of the remaining water molecule in $[Pt(phen)(OH_2)tu]^{2+}$ by thiourea (compare Figure 5). $\Delta V^{\#} = -5.0 \pm 0.8$ cm^{3}mol^{-1}). Experimental conditions: [Pt] = 0.1 mM, [tu] = 2.0 mM, pH = 1.0, I = 0.1 M, T = 25.0°C, reaction followed at 350 nm.

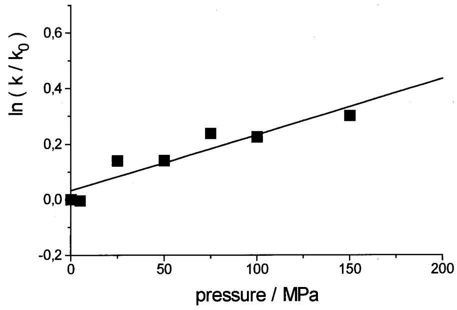


Table 5. Summary of rate constants (298.1 K) and $\Delta V^{\#}$ data for the substitution of H_2O by uncharged sulfur donor nucleophiles in Pt^{II} and Pd^{II} complexes

complex	nucleophile	k / M^{-1} s^{-1}	$\Delta V^{\#}$/ cm^3 mol^{-1}	ref.
$[Pd(Me_5dien)(OH_2)]^{2+}$	$SC(NH_2)_2$	1583 ± 46	−9.4 ± 0.4	[a]
	$SC(NHMe)_2$	718 ± 28	−9.1 ± 0.6	[a]
	$SC(NMe_2)_2$	195 ± 5	−13.4 ± 0.7	[a]
$[Pd(Et_5dien)(OH_2)]^{2+}$	$SC(NH_2)_2$	1.12 ± 0.04	−8.4 ± 0.3	[a]
	$SC(NHMe)_2$	0.54 ± 0.01	−10.2 ± 0.6	[a]
	$SC(NMe_2)_2$	0.117 ± 0.002	−12.7 ± 0.6	[a]
$[Pt(OH_2)_4]^{2+}$	$SC(NH_2)_2$	13.9		[b]
	Me_2S	0.90 ± 0.02	−15.3 ± 0.4	[b]
	Et_2S	0.48 ± 0.02	−17.0 ±0.3	[b]
$[Pt(en)(OH_2)_2]^{2+}$	$SC(NH_2)_2$	25.6 ± 0.2		[c]
$[Pt(en)(OH_2)tu]^{2+}$	$SC(NH_2)_2$	12.1 ± 0.1	−7.1 ± 0.9	[c]
$[Pt(phen)(OH_2)_2]^{2+}$	$SC(NH_2)_2$	2900 ± 40		[c]
$[Pt(phen)(OH_2)tu]^{2+}$	$SC(NH_2)_2$	1170 ± 10	−5.0 ± 0.8	[c]

[a] Ref.[57] – [b] Ref.[58] – [c] This work.

Conclusion

We conclude that the results of this study have shown that the use of phenanthroline instead of ethylenediamine increases the substitution rates of diaqua complexes by a factor of 10^2, during which the associative way of substitution is retained. This effect was investigated in aqueous media for a platinum complex exhibiting two labile positions. As far as we know, we are the first to have generated the complex $[Pt(phen)(OH_2)_2]^{2+}$ (and not the dimer) in solution and have investigated its reactivity. The observations are in good agreement with earlier studies on monophasic substitution reactions by sulfur-containing nucleophiles performed in non-aqueous media on complexes of Pt or Pd bearing aliphatic amines and aromatic imines by way of comparison. A factor of approximately 10^2 (the factors range between 41 and 64) was found in the latter studies[14][16]. The factor of 2 × 10^4 reported by Romeo et al.[13] for DMSO exchange on the complexes $[Pt(phen)Me(DMSO)]^+$ and $[Pt(en)Me(DMSO)]^+$, obviously calls for a further explanation beyond the electron-withdrawing effect of phen alone. The electronic effects of the *cis* Pt−C bond and of the *trans* phen ligand seem to act cooperatively.

As far as possible anti-tumor activity is concerned, it seems a reasonable assumption, that platinum complexes of α-diimines exhibiting two labile positions can bind to DNA in a fashion similar to the well-established binding mode of Cisplatin[52][53], using both substitution sites for the covalent binding of purine bases. The enhanced reactivity for both substitution steps is a feature which adds to the unique properties of such ligands as DNA intercalators[54][55][56].

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Experimental Section

Materials: All chemicals were used as received. $[Pt(phen)Cl_2]$ and AgF_3CSO_3 were purchased from Aldrich in the highest quality available. Thiourea and $HClO_4$ were p.a. quality from Merck. $NaClO_4$ was p.a. quality from Fluka. Non-aqueous solvents were purchased from Roth in p.a. quality (ROTIPURAN®). Ultra pure water was used for the kinetic measurements.

Syntheses

$[Pt(en)Cl_2]$ and $[Pt(en)(OH_2)_2]^{2+}$: The $[Pt(en)Cl_2]$ complex was prepared in 76% yield using a procedure from the literature[59]. Calc. for $[Pt(en)Cl_2]$: C 7.37, H 2.47, N 8.59%; found: C 7.19, H 2.41, N 8.37%. The IR spectrum was in excellent agreement with that reported in the literature[60]. A stock solution of the diaqua complex was prepared according to literature methods[61] by treating the dichloro complex with $AgNO_3$ in acidic solution, followed by filtration of the AgCl precipitate. A MILLIPORE filter (0.2 μm) was used for this purpose.

$[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2 \cdot 2\ H_2O$: The title complex was prepared in the following way: 335 mg of $[Pt(phen)Cl_2]$ (0.75 mmol) was stirred together with 580 mg of AgF_3CSO_3 (2.25 mmol) in 50 ml of EtOH/H_2O (9:1) at 75°C in the dark for 4 h. The fine bright yellow precipitate, which formed was filtered off with a MILLIPORE-filter (0.2 μm). The product was extracted from the wet precipitate by stirring in 100 ml of an acetone/H_2O mixture (1:1) at 50°C. AgCl was removed from this suspension by filtering the yellow solution with a MILLIPORE-filter (0.2 μm). On cooling to room temperature, yellow crystals (ca. 0.5 mm in diameter) formed within 24 h. These were washed with H_2O, EtOH, and Et_2O and dried under vacuum for 2 h. Yield: 200 mg (48%). The experimental analysis was in excellent agreement with the theoretically expected values for the dihydrate. Calc. for $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2 \cdot 2\ H_2O$: C 27.91, H 1.98, N 5.01%; found: C 28.05, H 1.88, N 4.94%. – ^{1}H-NMR ([D$_7$]DMF, 300.13 MHz, assignment based on coupling pattern and constants): δ = 9.05 [d, 4 H, $^3J_{H\text{-}H}$ = 8.1 Hz, aromat. CH *para* to N]; 9.00 [d, 4 H, $^3J_{H\text{-}H}$ = 5.3 Hz, aromat. CH *ortho* to N]; 8.27 [dd, 4 H, $^3J_{H\text{-}H}$ = 8.1, 5.3, aromat. CH *meta* to N]; 8.16 [s, 4 H, aromat. CH, middle ring of phen]. ^{13}C-NMR ([D$_6$]acetone/D_2O (1:1), 100.62 MHz, tentative assignment according to similar complexes): δ = 151.4 [*ortho* to N]; 147.4 [*ipso, ortho* to N]; 142.0 [*para* to N]; 131.6; 129.9; 127.9.

$[Pt(phen)(OH_2)_2](ClO_4)_2$: The diaqua complex was prepared as a 0.05 mM solution by cleavage of the hydroxo-bridged dimer according to the following procedure: 5 ml of a 0.5 mM stock solution of $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2$ in water was diluted to 80 ml. This solution was then heated to boiling. To this solution 0.01 mol $HClO_4$ in the form of a 60% solution was added. An orange coloured precipitate of $[\{Pt(phen)(\mu\text{-}OH)\}_2](ClO_4)_2$ appeared and

dissolved after some minutes. After boiling for 40 min. the volume was adjusted to 100 ml. This solution was prepared freshly for each measurement.

Instrumentation: UV-Vis spectra were recorded on a Shimadzu UV-2101-PC spectrophotometer. − IR spectra were recorded on a Mattson Polaris FT-IR-spectrophotometer using KBr pellets. − NMR spectra were measured on an Avance DPX 300 (Bruker) with TSP as internal standard. − The pH values measured in D_2O are referred to as "pH*" and reported without any correction for the isotope effect. − Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. − Kinetic measurements on the en complexes were performed on a Biologic SFM-3/S (Claix, France) stopped-flow instrument coupled to an on-line data aquisition system. The syringe control device MPS-51 and the BIOKINE-Software V3.0 from the same supplier were used. The kinetic traces were converted into olis-format with BIOKOLIS (1990) and evaluated using the OLIS KINFIT (Bogart, GA) program. Measurements on the phen complexes were performed using SX-18MV hardware and software from APPLIED PHOTOPHYSICS. The Global Analysis evaluation of the data was done with the Pro-Kineticist software, which is part of the SX-18MV software. Rapid scan spectra were recorded with a J&M-Tidas 16-416 diode-array detector connected to the SX-18MV stopped-flow apparatus. Measurements under high pressure were performed on a home-made high-pressure stopped-flow instrument[62]. Kinetic measurements, unless otherwise stated, were performed at a temperature of 25.0±0.1 °C and an ionic stength of 0.1 M, which was adjusted with $NaClO_4$ if necessary. The pH of the solution was 1.0 and 3.0 for the phen and the en complexes, respectively. All kinetic measurements were performed under pseudo-first-order conditions and a pseudo-first-order behaviour was found.

X-ray Crystallography: Crystals of $[\{Pt(phen)(\mu\text{-}OH)\}_2](F_3CSO_3)_2 \cdot 2\,H_2O$ suitable for X-ray crystallography were obtained by slow evaporation of the solvent from a saturated solution of the complex in acetone/H_2O (20:1). The scattering data were collected using a CAD-4 (Enraf-Nonius) diffractometer. All reflections with $I > 2\sigma(I)$ were used in the analysis. Details on data collection and the crystal data are given in Table 1[63]. Standard software and literature was used[64][65][66][67]. The structure was solved using the Patterson method and refined anisotropically (non-hydrogens) by the full-matrix least-squares method. The hydrogen atom of the hydroxo-bridge was found in the Fourier map. As a refinement of the O(4)−H(11) distance was not possible, this distance was fixed using the option DFIX of the SHELX software (distance = 0.99 Å, σ = 0.03) and the orientation refined.

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[63] Tables giving further information about the crystal structure (23 pages, including structure factor tables) can be obtained from the authors on request. Details on the crystal structure determination (excluding structure factors) can also be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen (e-mail: crysdata@fiz-karlsruhe.de) on quoting the CSD number 406492.

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