Kinetics and Mechanism of the Substitution Reactions of *cis*-Diamminebis(1-methyluracilato)platinum(II) in Aqueous Solution

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The substitution behavior of *cis*-$Pt(NH_3)_2(1\text{-}MeU)_2$, *cis*-$Pt(NH_3)_2(1\text{-}MeU)Cl$ and *cis*-$[Pt(NH_3)_2(1\text{-}MeU)H_2O]^+$ (1-MeU = 1-methyluracil anion, $C_5H_5N_2O_2^-$) was studied in detail as a function of entering nucleophile concentration, pH, temperature, and pressure. The reactivity of these species is controlled by the lability of the aqua complex. Protonation of the exocyclic O(4) atom of the 1-methyluracil ligand is essential in order to increase the lability of the bis(methyluracilato) complex. Solvolysis is the rate-determining step for substitution reactions of the latter complex, for which $k = (2.40 \pm 0.06) \times 10^{-5}$ s^{-1} at 60 °C and pH = 3, $\Delta H^{\ddagger} = 79 \pm 1$ kJ mol^{-1}, $\Delta S^{\ddagger} = -98 \pm 11$ JK^{-1} mol^{-1}, and $\Delta V^{\ddagger} = -5.6 \pm 0.6$ cm^3 mol^{-1}. All the reported rate and activation parameters support the operation of an associative substitution mechanism. The results are discussed in reference to data reported in the literature for related systems.

Introduction

Substitution reactions of Pt(II) and Pd(II) complexes that are of relevance to the antitumor activity of *cis*-Pt(II) complexes have been studied by various groups.[2,3] These include a systematic variation of steric hindrance on the nonparticipating ligands and the nature of the entering nucleophile, viz. nucleobase, nucleoside or nucleotide. In general such substitution reactions all follow an associative reaction mechanism that is characterized by a second-order rate law and significantly negative entropies and volumes of activation.[3] Steric hindrance on the nonparticipating ligands can decrease the substitution rate by up to 6 orders of magnitude, and can also affect the nucleophilicity scale usually reported for such processes.[4] However, steric hindrance could up to now not cause a changeover from associative to dissociative in the nature of the substitution mechanism.[3,5] Such a mechanistic changeover can probably only be achieved electronically as recently reported for complexes of the type $PtR_2(Et_2S)_2$ (R = Me, Ph), i.e. species that contain two Pt–C bonds.[6,7] The reason for the changeover in mechanism is a combination of ground-state labilization by the trans-effect of the Pt–C bonds and the increased electron density at the metal center that inhibits the nucleophilic attack of incoming ligands.[7] The introduction of a single Pt–C bond in the orthoplatinated derivative of *N,N*-dimethylbenzylamine causes an increase in the substitution rate constant of 4 orders of magnitude, but no changeover in mechanism.[8,9] The question remains whether other combinations of steric and electronic effects can cause a changeover in the substitution mechanism of Pt(II) complexes that could be of importance to their antitumor activity.

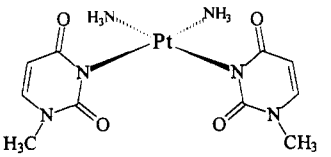

Figure 1. Schematic presentation of *cis*-$Pt(NH_3)_2(1\text{-}MeU)_2$.

Recently Lippert and co-workers[10] reported a series of studies on complexes of the type *cis*-PtA_2B_2, A = amine and B = nucleobase, in an effort to resolve the apparent inertness of a fraction of the DNA-bound *cis*-$(NH_3)_2Pt^{II}$.[11] Remarkable protective effects of the exocyclic oxygens of N(3)-bound thymine and uracil (Figure 1) were noted, which might explain why an associative attack by CN^- is very difficult.[10,12] A possible changeover in mechanism was also considered.[10] In order to shed more light on the influence of exocyclic oxygen atoms on the substitution behavior of Pt(II) complexes, we have now performed a detailed kinetic analysis of the substitution reactions of *cis*-

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$Pt(NH_3)_2(1\text{-}MeU)_2$, where 1-MeU = 1-methyluracil anion. The results demonstrate a remarkably deceleration of the substitution reaction as observed before, but clearly indicate no changeover in mechanism.

Experimental Section

Materials. *cis*-Diamminebis(1-methyluracilato)platinum(II) was prepared as described in the literature.[13] X-ray structure data for this complex and its monoprotonated form are reported elsewhere.[13,14] *cis*-Diammine(1-methyluracilato)chloroplatinum(II) was prepared from the bis(1-methyluracilato) complex on treatment with HCl as described in the literature.[15,16] Both complexes were characterized by the upfield shift of the H(5) and H(6) protons of the coordinated nucleobase in comparison to those in the neutral ligand. In addition, elemental analyses[17] were in good agreement with the theoretically expected values. All other chemicals used were of analytical reagent (Merck) quality, and Millipore water was used in the preparation of all solutions.

Measurements. UV–vis spectra were recorded in the thermostated (±0.1 °C) cell compartment of Varian Cary 1 and Zeiss DMR 10 spectrophotometers. These instruments were also used to measure slow kinetic traces, whereas faster reactions were followed in a Dionex D 110 stopped-flow instrument. Kinetic measurements at elevated pressure were performed in a high pressure cell[18] built into a modified double beam Zeiss M4Q II spectrophotometer. pH measurements were performed with an Ingold microelectrode and a Metrohm E 520 pH meter. The reference electrode was filled with NaCl instead of KCl in order to prevent the precipitation of $KClO_4$. The pH of the solutions was adjusted with $HClO_4$ or NaOH and measured before the reaction. All kinetic measurements were performed under pseudo-first-order conditions, i.e. at least a 10-fold excess of the nucleophile was employed. The observed first-order rate constant, k_{obs}, was calculated in the usual way from the slope of a plot of $\ln(A_\infty - A_t)$ versus t. Solutions of the *cis*-$[Pt(NH_3)_2(1\text{-}MeU)H_2O]^+$ species were prepared via aquation of *cis*-$Pt(NH_3)_2(1\text{-}MeU)_2$ and *cis*-$Pt(NH_3)_2(1\text{-}MeU)Cl$ at pH = 3 and room temperature for 13 and 4 days, respectively.

Results and Discussion

General Observations. The 1-methyluracilato complexes prepared in this study undergo slow acid-catalyzed and spontaneous aquation reactions in weakly acidic medium (pH ca. 3) according to eqs 1 and 2, to produce the same aqua complex. Further

$$cis\text{-}Pt(NH_3)_2(1\text{-}MeU)_2 + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} cis\text{-}Pt(NH_3)_2(1\text{-}MeU)H_2O^+ + 1\text{-}MeUH \quad (1)$$

$$cis\text{-}Pt(NH_3)_2(1\text{-}MeU)Cl + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} cis\text{-}Pt(NH_3)_2(1\text{-}MeU)H_2O^+ + Cl^- \quad (2)$$

aquation of *cis*-$[Pt(NH_3)_2(1\text{-}MeU)H_2O]^+$ to produce the diaqua species is very slow and does not interfere under the selected experimental conditions. It was possible to measure K_2 (= k_2/k_{-2}) for reaction 2 by following the released Cl^- concentration with the aid of a chloride selective electrode. A 2×10^{-3} M solution of *cis*-$Pt(NH_3)_2(1\text{-}MeU)Cl$ at pH 3, 40 °C, and 0.1 M ionic strength ($NaClO_4$), showed after 24 h no further spectral changes, and contained 1.46×10^{-3} M chloride. This resulted in $K_2 = 3.9 \times 10^{-3}$ M at 40 °C.

A number of acid–base equilibria also exist in solution. First of all, the 1-methyluracil ligand can be protonated in acidic solution. The H(5) and H(6) resonances showed a low-field shift for both complexes on lowering the pH, which was ascribed to the protonation of the exocyclic O(4) site. The results suggested pK_a values smaller than 3, which are in agreement with the values of ca. 1.5[14,19] for the bis(methyluracilato) complex and 0.9[14] for the mono(methyluracilato)aqua complex reported in the literature. Secondly, the aqua complex produced in reactions 1 and 2 can deprotonate to produce the corresponding hydroxo complex. A pH titration of this product in 0.1 M $NaClO_4$ resulted in a pK_a of 7.2 at 25 °C.[20] The latter value is in close agreement with that reported for related aqua complexes of Pt(II) and Pd(II).[3]

Kinetic Measurements. The aquation of *cis*-$Pt(NH_3)_2(1\text{-}MeU)_2$ in weakly acidic medium (pH ca. 3) and 60 °C was accompanied by spectral changes too small to be measured directly. However, an indirect method was used by allowing a solution of this complex to aquate at 25 °C and pH = 3 and then treating samples of this solution with iodide as a function of time. The rate of the reaction with iodide depends linearly on the fraction of the aqua complex in solution and could be used to monitor the aquation rate constant k_1, which turned out to have a value of $(7.8 \pm 0.1) \times 10^{-7}$ s^{-1} under these conditions. The spontaneous aquation of *cis*-$Pt(NH_3)_2(1\text{-}MeU)Cl$ could be measured in a buffered solution at 40 °C and pH = 7.8 using a 10-cm optical pathlength cuvette. This resulted in $k_2 = (3.92 \pm 0.06) \times 10^{-4}$ s^{-1} under these conditions, which is close to the value of 3×10^{-4} s^{-1} reported for the aquation of the $Pt(en)Cl_2$ complex at 40 °C.[21] This experiment could not be repeated at pH = 3.0 due to significantly smaller spectral changes. At pH = 7.8 the produced aqua complex is largely present as the hydroxo species in solution, which results in larger spectral changes than at lower pH. Any μ-OH dimerization was considered negligible at the concentrations applied.

Both complexes aquate to the same product as suggested in reactions 1 and 2. This could easily be proven by reacting aquated solutions with iodide, which gave identical results for both cases. This reaction is accompanied by significant spectral changes as shown in Figure 2, and 320 nm was selected for the kinetic measurements at ambient and 325 nm at elevated pressure. Rate data for reaction 3 are summarized in Tables 1 and 2 for Nu =

$$cis\text{-}Pt(NH_3)_2(1\text{-}MeU)H_2O^+ + Nu \overset{k_3}{\rightarrow} cis\text{-}Pt(NH_3)_2(1\text{-}MeU)Nu^+ + H_2O \quad (3)$$

I^- and $SC(NH_2)_2$, respectively. A plot of k_{obs} versus $[I^-]$ is a straight line with no intercept, from which it follows that $k_3 = (6.01 \pm 0.04) \times 10^{-2}$ M^{-1} s^{-1} at 25 °C. When the aqua complex prepared via aquation of the bis(methyluracilato) complex (reaction 1), instead of the chloro complex (reaction 2), was used, a value of $(6.42 \pm 0.05) \times 10^{-2}$ M^{-1} s^{-1} was obtained. The temperature and pressure dependence of the reaction with I^- resulted in the activation parameters summarized in Table 1. The plot of ln k_3 versus pressure gave an excellent straight line from which ΔV^* (slope = $-\Delta V^*/RT$) was estimated (see Figure 3). Similar results are reported in Table 2 for the reaction with thiourea. Unfortunately, the pressure dependence of this reaction could not be studied using a high-pressure stopped-flow system[22]

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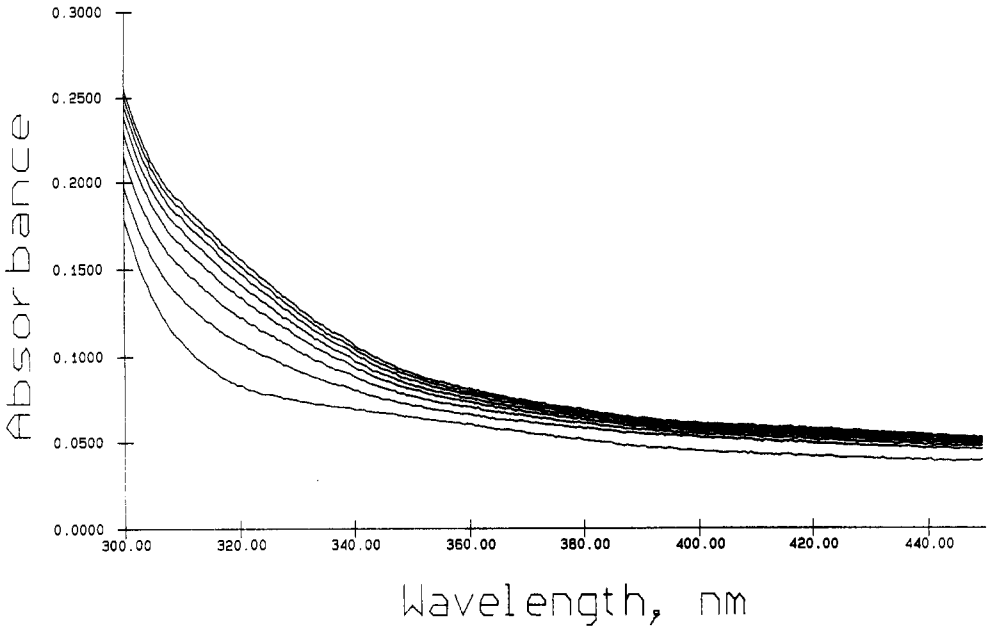

Figure 2. UV–vis spectra recorded for the reaction *cis*-$[Pt(NH_3)_2(1\text{-MeU})H_2O]^+ + I^- \rightarrow$ *cis*-$Pt(NH_3)_2(1\text{-MeU})I + H_2O$. Experimental conditions: [Pt(II)] = 5×10^{-4} M; [I^-] = 0.10 M; pH = 3.0; ionic strength = 0.10 M; T = 25 °C; Δt = 90 s; optical pathlength = 0.88 mm.

Table 1. Effect of Nucleophile Concentration, Temperature, and Pressure on the Reaction[a]

cis-$[Pt(NH_3)_2(1\text{-MeU})H_2O]^+ + I^- \xrightarrow{k_3}$ *cis*-$Pt(NH_3)_2(1\text{-MeU})I + H_2O$

T, °C	P, MPa	[I^-], M	$k_{obs} \times 10^3$, s^{-1} [b]	$k_3 \times 10^2$, M^{-1} s^{-1}
25.0	0.1	0.010	0.65 ± 0.01	6.01 ± 0.04
		0.020	1.22 ± 0.06	
		0.030	1.79 ± 0.07	
		0.040	2.41 ± 0.01	
		0.050	3.03 ± 0.02	
		0.10	6.04 ± 0.04	
15.0	0.1	0.040	0.86 ± 0.02	2.14 ± 0.05
25.0			2.41 ± 0.01	6.01 ± 0.03
35.0			5.61 ± 0.10	14.0 ± 0.3
45.0			13.5 ± 0.4	33.8 ± 0.9
15.0	5	0.020	0.41 ± 0.02	2.07 ± 0.09
	25		0.45 ± 0.02	2.20 ± 0.10
	50		0.48 ± 0.01	2.39 ± 0.06
	75		0.52 ± 0.01	2.60 ± 0.06
	100		0.56 ± 0.03	2.80 ± 0.10
	$\Delta H^{\ddagger}$, kJ mol^{-1}			67 ± 1
	$\Delta S^{\ddagger}$, J K^{-1} mol^{-1}			−44 ± 4
	$\Delta V^{\ddagger}$, cm^3 mol^{-1}			−7.7 ± 0.1

[a] Experimental conditions: [Pt(II)] = 5×10^{-4} M; pH = 3.0; ionic strength = 0.10 M; wavelength = 320 nm at ambient and 325 nm for elevated pressure. [b] Mean value of at least five kinetic runs at ambient pressure and three kinetic runs at elevated pressure.

due to a shorter optical pathlength, small spectral changes, and solubility limitations.

The pH dependence of the reaction with iodide was studied and a typical series of data is reported in Figure 4. There is a substantial decrease in k_{obs} with increasing pH, which must be due to the deprotonation of the aqua ligand to produce the hydroxo complex. Measurements at pH > 8.5 were not possible due to too small spectral changes under such conditions. The data in Figure 4 are in agreement with a pK_a value of 7.1 as indicated by the solid line calculated on this basis. Furthermore, the results clearly demonstrate that the hydroxo complex is inert to substitution, such that substitution reactions that are studied at higher pH will be prevented in case aquation (accompanied by deprotonation) is involved as the rate-determining step.

Table 2. Effect of Nucleophile Concentration and Temperature on the Reaction[a]

cis-$[Pt(NH_3)_2(1\text{-MeU})H_2O]^+ + SC(NH_2)_2 \xrightarrow{k_3}$ *cis*-$[Pt(NH_3)_2(1\text{-MeU})SC(NH_2)_2]^+ + H_2O$

T, °C	[$SC(NH_2)_2$], M	$k_{obs} \times 10^2$, s^{-1} [b]	k_3, M^{-1} s^{-1}
25.0	0.050	1.74 ± 0.09	0.37 ± 0.02
	0.075	2.83 ± 0.06	
	0.10	3.79 ± 0.14	
	0.125	4.71 ± 0.09	
	0.15	5.45 ± 0.10	
15.0	0.15	2.93 ± 0.03	1.95 ± 0.02
20.0		3.78 ± 0.06	2.52 ± 0.04
25.0		5.57 ± 0.17	3.71 ± 0.12
30.0		7.13 ± 0.19	4.75 ± 0.13
35.0		8.71 ± 0.25	5.81 ± 0.17
	$\Delta H^{\ddagger}$, kJ mol^{-1}		39 ± 2
	$\Delta S^{\ddagger}$, J K^{-1} mol^{-1}		−122 ± 8

[a] Experimental conditions: [Pt(II)] = 1×10^{-3} M; pH = 3.0; ionic strength = 0.10 M; wavelength = 320 nm. [b] Mean value of at least five kinetic runs.

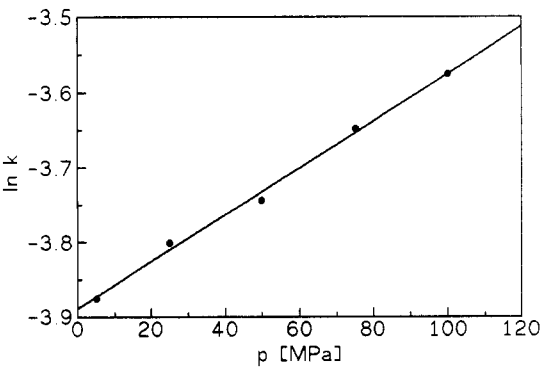

Figure 3. Plot of ln k versus pressure for reaction 3 with Nu = I^-. For experimental conditions see Table 1.

The substitution of the bis(methyluracilato) complex by iodide was studied at higher temperatures at pH 3.0. The reactions are extremely slow and were therefore monitored in the high pressure cell in order to avoid the formation of gas bubbles and slow

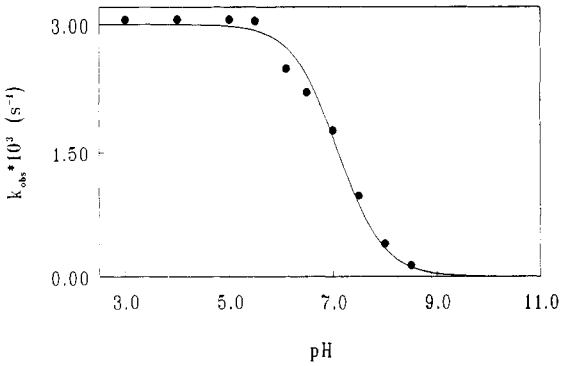

Figure 4. pH dependence of k_{obs} for the reaction cis-$Pt(NH_3)_2(1\text{-}MeU)H_2O^+ + I^- \rightarrow$ *cis*-$Pt(NH_3)_2(1\text{-}MeU)I + H_2O$. Experimental conditions: [Pt(II)] = 5×10^{-4} M; [I^-] = 0.050 M; ionic strength = 0.10 M; T = 25 °C.

Table 3. Effect of pH on the Reaction[a]

cis-$Pt(NH_3)_2(1\text{-}MeU)_2 + I^- \xrightarrow{H^+}$ *cis*-$Pt(NH_3)_2(1\text{-}MeU)I$ + 1-MeUH

pH	[H^+], M	$k_{obs} \times 10^5$, s^{-1} [b]
7.0	1×10^{-7}	no reaction
6.0	1×10^{-6}	no reaction
5.0	1×10^{-5}	no reaction
4.0	1×10^{-4}	no reaction
3.0	1×10^{-3}	2.40 ± 0.06
2.7	2×10^{-3}	4.7 ± 0.1
2.3	5×10^{-3}	11.0 ± 0.2
2.0	1×10^{-2}	23.0 ± 0.2

[a] Experimental conditions: [Pt(II)] = 5×10^{-4} M; [I^-] = 5×10^{-3} M; T = 60 °C; p = 10 MPa; ionic strength = 0.10 M; wavelength = 325 nm. [b] Mean value of at least three kinetic runs.

evaporation of the solution over long reaction times. Reaction 4 was found to be independent of the I^- concentration over the

cis-$Pt(NH_3)_2(1\text{-}MeU)_2 + I^- \xrightarrow{H^+}$ *cis*-$Pt(NH_3)_2(1\text{-}MeU)I$ + 1-MeUH (4)

range 0.005–0.02 M, which indicates that the acid-catalyzed solvolysis reaction 1 is the rate-determining step. A systematic [H^+] dependence of this reaction (see Table 3) demonstrated that the solvolysis rate constant depends linearly on [H^+] in the range $2.0 \leq pH \leq 3.0$. This is in agreement with the protonation of the 1-methyluracil ligand under the conditions mentioned above, and the absence of a significant solvolysis reaction at higher pH. The temperature and pressure dependence of k_{obs} for this reaction are summarized in Table 4. From the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for reaction 4, it is possible to calculate the rate constant for the solvolysis reaction 1 at 25 °C. It results in a value of $k_1 = 7.3 \times 10^{-7}$ s^{-1}, which is in close agreement with the value of 7.8×10^{-7} s^{-1} obtained from the indirect determination reported above.

Efforts were also made to study the reaction of this complex with cyanide at pH 11, where HCN will be deprotonated and have its highest nucleophilicity as CN^-. No significant reaction could be observed for hours at 60 °C. Similar results were also reported for this reaction at lower pH (ca. 8) where CN^- will be present in the less reactive protonated form.[10] However, the *cis*-$[Pt(NH_3)_2(1\text{-}MeU)H_2O]^+$ species did show a reaction with cyanide under such conditions.[10] Other experiments were performed at pH 4, 5, 6, and 7, but no spectral changes could be observed over a period of 3 days when a solution of this complex was reacted with an excess of iodide.

Mechanistic Interpretation. The results of this investigation confirm earlier findings that the bis(1-methyluracilato) complex

Table 4. Effect of Temperature and Pressure on the Reaction[a]

cis-$Pt(NH_3)_2(1\text{-}MeU)_2 + I^- \xrightarrow{H^+}$ *cis*-$Pt(NH_3)_2(1\text{-}MeU)I$ + 1-MeUH

T, °C	P, MPa	$k_{obs} \times 10^5$, s^{-1} [b]
50.0	10	0.88 ± 0.04
55.0		1.60 ± 0.07
60.0		2.40 ± 0.06
65.0		3.50 ± 0.10
70.0		5.40 ± 0.17
60.0	10	2.40 ± 0.06
	25	2.55 ± 0.04
	50	2.65 ± 0.05
	75	2.80 ± 0.09
	100	2.90 ± 0.08
$\Delta H^{\ddagger}$, kJ mol^{-1}		79 ± 4
$\Delta S^{\ddagger}$, J K^{-1} mol^{-1}		−98 ± 11
$\Delta V^{\ddagger}$, cm^3 mol^{-1}		−5.6 ± 0.6

[a] Experimental conditions: [Pt(II)] = 5×10^{-4} M; [I^-] = 5×10^{-3} M; pH = 3.0; ionic strength = 0.10 M; wavelength = 325 nm. [b] Mean value of at least three kinetic runs.

is inert to substitution in the neutral pH range.[10] The complex does undergo an acid-catalyzed aquation at $pH \leq 3$, which is also the rate-determining step for the nucleophilic substitution reaction with iodide (data in Table 4). This reaction, although very slow, still exhibits activation parameters, especially the negative $\Delta S^{\ddagger}$ and $\Delta V^{\ddagger}$ values, that support the operation of an associative mechanism.[5,23,24] The apparent inertness of this complex at neutral and higher pH must be related to the blocking effect of the exocyclic oxygen atoms on the uracil ligand (see further Discussion).[10] The observed rate constant at $pH \leq 3$ is a combination of a protonation preequilibrium and a rate-determining solvolysis step. Protonation of *cis*-$Pt(NH_3)_2(1\text{-}MeU)_2$ is not expected to cause any significant volume changes since it does not involve the neutralization of charges. At most protonation can result in dilution of the positive charge that may be accompanied by a small volume increase due to a decrease in electrostriction. It follows that the overall $\Delta V^{\ddagger}$ value measured under these conditions must be largely due to the associative entrance of a solvent molecule into the coordination sphere of the protonated complex.

The mono(methyluracilato)chloro complex undergoes spontaneous aquation at neutral and weakly acidic pH. The resulting mono(methyluracilato)aqua complex undergoes fairly rapid substitution reactions with I^- and $SC(NH_2)_2$ (Tables 1 and 2), and the activation parameters once again confirm the operation of an associative mechanism. The significantly less negative $\Delta S^{\ddagger}$ value found for the reaction with I^- as compared to $SC(NH_2)_2$ can be ascribed to a decrease in electrostriction in the transition state due to partial charge neutralization. The reported $\Delta V^{\ddagger}$ value of −7.7 ± 0.1 cm^3 mol^{-1} is very typical of that found for associative substitution reactions of Pt(II) and Pd(II) complexes.[5,9,23,24] The lability of the aqua complex decreases drastically on going to higher pH (see Figure 4), indicating that the hydroxo complex is an inert species. This is again in good agreement with that reported in general for square planar hydroxo complexes.[23,25]

It follows from the above that the bis(methyluracilato) complex is inert to substitution, unless the exocyclic O(4) atom is protonated in weakly acidic medium. Thus the strong interaction of four exocyclic oxygen atoms with the vacant p_z orbital must prevent

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the associative nucleophilic attack as suggested before.[10] Partial protonation or removal of one methyluracil ligand causes a drastic increase in the substitution reactivity, which underlines the validity of the above statement. The exocyclic oxygen atoms may have a similar effect as coordinated hydroxide, for which it has been suggested[23,25] that a direct interaction of the free electron pairs on the oxygen atom with the p_z orbital in a π bonding way causes a drastic shortening of the metal–oxygen bond and prevents associative nucleophilic attack. It is clear that four exocyclic oxygen atoms may block the p_z orbital completely, whereas only a partial effect will be present in the case of two exocyclic oxygen atoms.

Thus the unique electronic interaction of the exocyclic oxygen atoms with the vacant orbital needed for the associative reaction mode tunes the reactivity of the studied methyluracilato complexes. The reported kinetic data strongly support the operation of an associative reaction mechanism in all cases, and no mechanistic changeover could be observed. Our ability to hinder associative reactions through an increase in steric hindrance on nonparticipating groups and to induce such reactions electronically by introducing metal–carbon bonds as mentioned in the Introduction[3,5,8,9] can now be extented to include electronic hindrance via the interaction with coordinated oxygen atoms. Thus a fine tuning of the substitution lability of such Pt(II) metal centers is indeed possible and may play a fundamental role in the understanding of the antitumor activity of such complexes.

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