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Registry No. I, 137944-52-6; $(NH_4)_2[\{V(O)_2(\eta^2\text{-}O,O''\text{-ehba-}\mu\text{-}O')\}_2]$, 138124-70-6; $(NH_4)[V(O)(ehbaH)(ehba)]$, 137944-53-7.

Supplementary Material Available: Tables of positional parameters, thermal parameters, torsional angles, bond lengths, and bond angles (3 pages); a listing of observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

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Articles

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Kinetics and Mechanism of the Complex Formation Reactions of Diaqua(ethylenediamine)- and Diaqua(tetraethylethylenediamine)palladium(II) with the Purine Nucleosides Adenosine and Inosine

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The kinetics of the complex formation reactions of $Pd(R_4en)(H_2O)_2^{2+}$ (R = H, Et; en = ethylenediamine) with adenosine and inosine have been studied as a function of nucleoside concentration, temperature, and pressure in a weakly acidic aqueous solution. All systems exhibited two consecutive reaction steps, which each depended on the nucleoside concentration according to the rate law $k_{obs} = k_a + k_b[Nu]$. In the case of adenosine, both k_a and k_b increase significantly with increasing pH, which is ascribed to pronounced participation of the N(1) coordination site. However the produced complex appears to be less stable than the corresponding inosine complex, presumably due to the interference by the exocyclic amine group. The effect of steric hindrance on the en ligand appeas to be more pronounced on the second complex formation reaction, i.e. where one nucleoside molecule is already coordinated to the metal center. The reported activation parameters (especially ΔV^*) underline the operation of an associative ligand substitution mechanism. A detailed comparison with related systems reported in the literature is made.

Introduction

There is presently a significant interest in the interaction of *cis*-Pt^{II}(diamine) and *cis*-Pd^{II}(diamine) with DNA and its constitutents in an effort to improve our understanding of the antitumor activity of such complexes and their use in chemotherapy.[2,3] Many of the quoted studies[3] involve the structural identification of reaction products using NMR and X-ray techniques, such that a good understanding of the bonding modes has been achieved. This is to a lesser degree the case for the reactivity, i.e. kinetics, of the produced species. In our earlier work we have focused on the substitution behavior of diethylenetriamine (dien) and substituted diethylenetriamine complexes of Pd(II) as labile model complexes for the corresponding, more inert Pt(II) complexes.[4] In this work we also investigated the complex formation of $Pd(dien)Cl^+$ and $Pd(dien)H_2O^{2+}$ with typical nucleic bases, nucleosides, and 5'-nucleotides.[4g,h] We have now extended this work to the ethylenediamine(en) and N-substituted tetraethylethylenediamine (Et_4en) dichloro complexes of Pd(II). The Pd(en)Cl_2 complex exhibits aquation and subsequent acid dissociation equilibrium constants very similar to those *cis*-$Pt(NH_3)_2Cl_2$ species,[5,6] although the ligand substitution rate constants (aquation and reverse anation steps) are 5 orders of magnitude larger for

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the Pd(II) complex. It follows that the equilibria are established rapidly in the case of the Pd(II) complexes, which in general simplifies kinetic and thermodynamic investigations of such systems. Furthermore, the aquation products of such complexes, viz. $Pd(en)(Cl)H_2O^+$ and $Pd(en)(H_2O)_2^{2+}$, closely resemble the active species suggested to bind to DNA in the case of *cis*-$Pt(NH_3)_2Cl_2$. For this reason we have selected the $Pd(en)(H_2O)_2^{2+}$ and $Pd(Et_4en)(H_2O)_2^{2+}$ complexes and studied their complex formation reactions with two purine nucleosides, viz. adenosine (ado) and inosine (ino), in the present investigation. The interpretation of our kinetic results is based on our experience with the corresponding reactions with chloride[5,8] and iodide.[7] In addition some kinetic and structural data are available from the literature for the reaction of (ethylenediamine)Pd^{II} with adenosine and inosine.[9,10] In this way the effect of bulky substituents on the ethylenediamine ligand on such complex formation reactions will be revealed.

Experimental Section

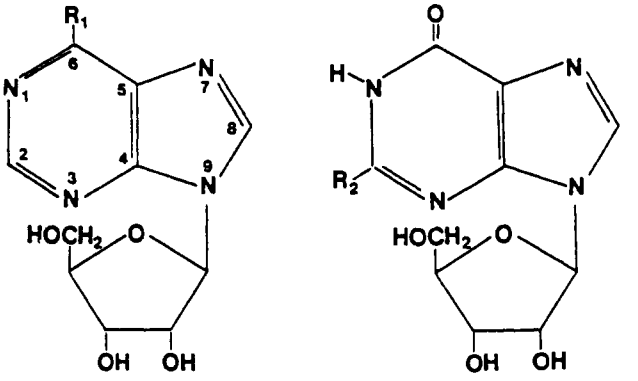
Materials. $Pd(en)Cl_2$ and $Pd(Et_4en)Cl_2$ were prepared according to the general procedure published before.[5] In the case of the ethyl-substituted complex, *N,N,N',N'*-tetraethylethylenediamine (Alfa) was used as ligand. Chemical analyses[11] indicated that the isolated complexes were pure substances. The dichloro complexes were converted in solution to the diaqua complexes by treating them with $AgClO_4$ as described before.[5] The nucleoside solutions were prepared from inosine (Sigma) and adenosine as the hemisulfate salt (Sigma), without further purification. The ionic strength of all test solutions was adjusted to 0.1 M by the addition of $NaClO_4$. Millipore water was used in the preparation of all solutions.

Measurements. UV–vis spectra were recorded on Shimadzu UV 2100 and Zeiss DMR 10 spectrophotometers. Repetitive scan spectra for slow reactions were recorded in the thermostated (±0.1 °C) cell compartments of these instruments. pH measurements were performed with an Ingold micro-electrode and a Metrohm E520 pH meter. Samples used in these measurements were rejected in order to prevent chloride contamination of the test solutions. The reference electrode was filled with NaCl instead of KCl in order to prevent the precipitation of $KClO_4$. The pH of the test solutions was adjusted with $HClO_4$ or NaOH and measured before and after the reactions. Kinetic measurements at ambient pressure were performed on a Durrum D110 stopped-flow instrument attached to an on-line data acquisition system[12] with which the kinetic traces could be evaluated. Experiments at elevated pressure (up to 100 MPa) were performed on a homemade high-pressure stopped-flow unit.[13] All kinetic measurements were performed under pseudo-first-order conditions, i.e. an excess of the nucleoside was employed. Absorbance-time traces were analyzed using the OLIS KINFIT (Jefferson, GA) set of programs. More details on the data-fitting procedures are given in the following section.

Results and Discussion

General Considerations. Complexes of the type $Pd(R_4en)(H_2O)_2^{2+}$ closely resemble the coordination geometry of *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ and do not undergo any cis–trans isomerization. The introduction of N-substituents on the ethylenediamine ligand enables a gradual increase in steric hindrance and control over the lability of the coordinated solvent molecules.[4] These complexes exhibit characteristic acid dissociation constants[5,8] for which the first pK_a values are 5.6 and 5.9 at 25 °C and 0.1 M ionic strength for the en and Et_4en complexes, respectively. It follows from these values that a significant concentration of the aquahydroxo species will be present at pH > 5, which can undergo subsequent deprotonation and/or dimerization to produce hydroxy-bridged species. Such hydroxo species are inert and will cause a significant decrease in the substitution rate constants at pH > 5. For this reason all measurements in this study were performed at pH ≤ 4.7, i.e. where less than 10% of the hydroxo species will be present in the diaqua solution.

The selected nucleosides ado and ino offer a variety of potential binding sites for metal ions and complexes. A survey of the



purine nucleosides at neutral pH

$R_1 = NH_2$: adenosine (ado)
$R_2 = NH_2$: guanosine (guo)
$R_2 = H$: inosine (ino)

available literature[2-4,9,10] revealed that ado and ino preferably bind through N7 and N1, whereas binding through N3 or the exocyclic groups in position 2 and 6 of the purine ring can in general be neglected under the selected experimental conditions. This trend is also partially due to Pd(II) being a soft metal that prefers binding to a N- instead of an O-donor ligand. The N7 site is significantly more acidic than the N1 site; $pK_a(N7) = -1.6$ and 1.2, and $pK_a(N1) = 3.9$ and 9.1 for ado and ino, respectively.[10,14,15] It follows that the N7 site is available for coordination under all the selected conditions whereas the availability of N1 will depend on the selected pH. For this reason N1 coordination was only detected in neutral or basic solutions of ino. Thus under the selected conditions of pH ≤ 4.7, coordination at N1 and N7 in ado and N7 in ino is expected. Although it would have been logical to include guanosine (guo) in the series of nucleosides, this species is too insoluble to reach a workable concentration range for the kinetic measurements. In this respect inosine represents a suitable alternative since their chemical compositions, except for the 2-amine group, are identical, and the pK_a values are very similar ($pK_a(N7) = 1.6$ and $pK_a(N1) = 9.2$ for guanosine[10,14,15]).

All attempts to isolate the pure species produced during the complex formation reactions, via slow evaporation of product solutions, etc., were unsuccessful. X-ray diffraction analysis is a powerful method to resolve structural aspects,[2,3] but is unfortunately restricted to the isolation of crystalline products, which may not necessarily represent the major product species in solution. For this reason significant progress has been made with the application of NMR techniques in the study of such systems in solution.[2,3] Häring and Martin[10] reported a detailed NMR study of the complex formation of $(en)Pd^{2+}$ with ado, ino, and guo, as well as their monophosphates. They find predominantly N7 coordination for ino at pH < 5 and the formation of 1:1 and 1:2 metal-to-ligand complexes at equimolar solutions in the presence of an excess of ino, respectively. In the case of ado the authors report evidence for the formation of $Pd(en)(ado\text{-}N1)_2$ and the production of several types of polymers involving N1 as well as N7 coordination. The tendency for $(en)Pd^{2+}$ to produce polymers is also illustrated by the formation of a cyclic adduct with guanine(gua) $[Pd(en)(gua)]_4$, which involves N1 and N7 coordination of gua to different Pd atoms.[3p]

Complex Formation Reactions. The reactions of $Pd(R_4en)(H_2O)_2^{2+}$ with ado and ino exhibit uncharacteristic spectral changes as demonstrated by the examples in Figures 1 and 2. Suitable wavelengths can be selected from these figures for a kinetic investigation. Multistep reactions were observed in all cases, and a detailed study of their dependence on the nucleoside

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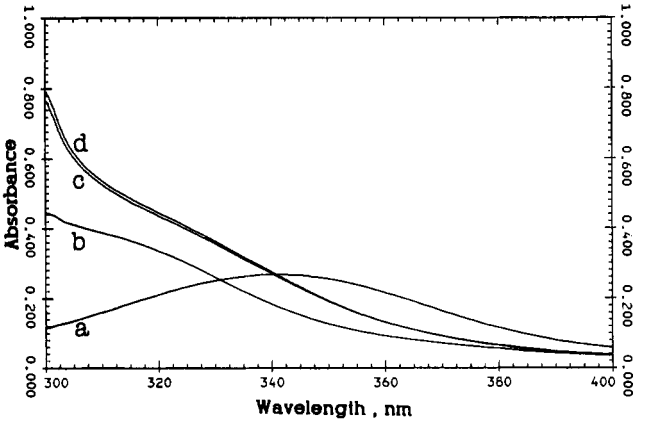

Figure 1. UV–vis spectra of mixtures of $Pd(en)(H_2O)_2^{2+}$ and adenosine and inosine: (a) $Pd(en)(H_2O)_2^{2+}$ at pH 2.9–4.4; (b) $Pd(en)(H_2O)_2^{2+}$ with 0.01 M ino at pH = 4.4; (c) $Pd(en)(H_2O)_2^{2+}$ with 0.01 M ado at pH = 4.3; (d) $Pd(en)(H_2O)_2^{2+}$ with 0.01 M ado at pH = 2.9. Conditions: [Pd(II)] = 1.0×10^{-3} M; optical pathlength = 1.0 cm.

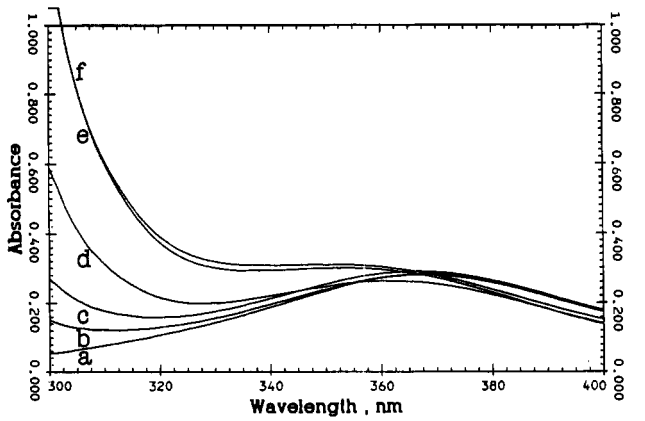

Figure 2. UV–vis spectra of mixtures of $Pd(Et_4en)(H_2O)_2^{2+}$ and adenosine: (a) [ado] = 0; (b) [ado] = 5×10^{-4} M; (c) [ado] = 1.0×10^{-3} M; (d) [ado] = 5.0×10^{-3} M; (e) [ado] = 1.5×10^{-2} M; (f) [ado] = 2.5×10^{-2} M. Conditions: [Pd(II)] = 5×10^{-4} M; pH = 4.7; optical pathlength = 0.88 cm.

concentration, temperature, and pressure was undertaken. The latter variables enable an estimation of the activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta V^{\ddagger}$) for the complex formation reactions and the assignment of the underlying reaction mechanism.[4] The fitting of a typical absorbance–time trace for the reaction of $Pd(en)(H_2O)_2^{2+}$ with ino is demonstrated in Figure 3. A single exponential fit of the trace up to 0.2 s results in a rate constant of 91 s^{-1}, and the theoretically predicted curve deviates significantly from the experimental one (Figure 3a). When the time window is decreased to 0.04 s, the single exponential fit improves significantly and results in a rate constant of 140 s^{-1} (Figure 3b). This clearly demonstrates that we are dealing with two consecutive reaction steps, and the corresponding two-exponential fit (Figure 3c) results in the rate constants 154 and 25 s^{-1}, respectively. These observations are interpreted in terms of a rapid formation of the 1:1 substitution product followed by the slower formation of the 1:2 species. When the reaction is repeated by starting with a 1:1 mixture and reacting it with an excess ino, then only the second, slower reaction is observed.

The reactions with ado can either be followed as an absorbance increase at 300 nm or an absorbance decrease at 360–370 nm. A pH jump of ca. −0.2 units was observed on mixing the reagents in the stopped-flow instruments, which can be ascribed to the release of a proton during complex formation with N1 and/or to a decrease in the pK_a(N1) value during complex formation with N7.[30] No buffers could be employed in the complex formation studies, since such species react rapidly with the labile diaqua complexes. Typical absorbance–time traces at 360 nm clearly indicated the participation of two consecutive steps, which both

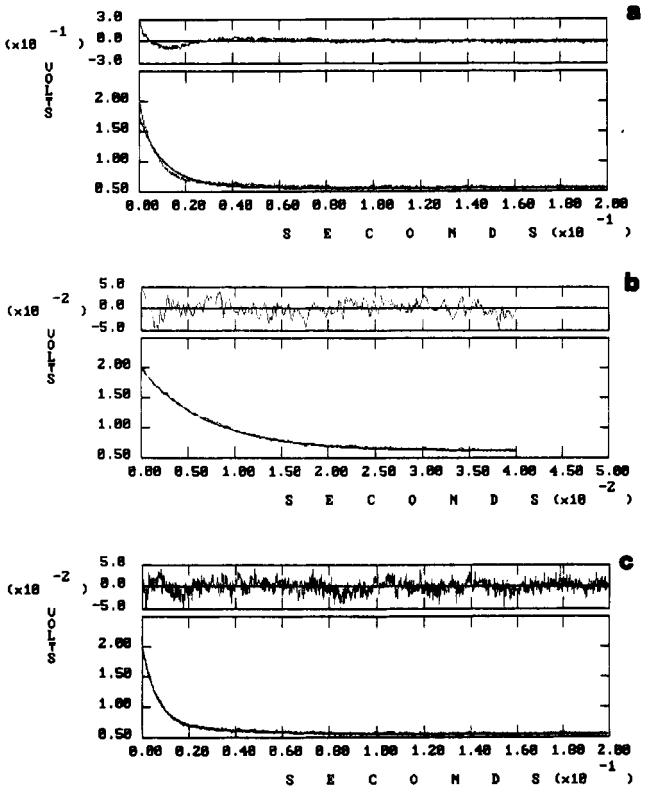

Figure 3. Typical absorbance time plots at 360 nm to demonstrate the kinetic analysis for two consecutive reactions. See Discussion.

exhibit a dependence on the nucleoside concentration. These observations can best be interpreted in terms of two consecutive complex formation steps, as indicated in a general way in eq 1.

$$Pd(R_4en)(H_2O)_2^{2+} + Nu \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Pd(R_4en)(Nu)H_2O^{2+} + H_2O$$

$$Pd(R_4en)(Nu)H_2O^{2+} + Nu \underset{k_4}{\overset{k_3}{\rightleftharpoons}} Pd(R_4en)(Nu)_2^{2+} + H_2O \quad (1)$$

The observed rate constants measured at different wavelengths and as a function of all rate variables are summarized in Table I. Absorbance–time traces recorded at 300 nm mainly exhibit the first reaction step and cannot be resolved to estimate the rate constant of the second step. The observed rate constants follow the expression given in (2), for which k_a and k_b were calculated

$$k_{obs} = k_a + k_b[Nu] \quad (2)$$

from a plot of k_{obs} versus [Nu] and are included in Table I. This notation is employed throughout this report, such that k_a and k_b are the experimentally observed first- and second-order rate constants, respectively, and must be assigned to various reaction steps depending on the selected conditions. The rate constants for the two reaction steps differ by less than a factor of 5 at pH 4.1, which complicates the analysis of the data. The pressure dependence of only the first reaction step could be resolved under these conditions.

According to the general information outlined in the previous section, both positions N1 and N7 on ado can coordinate at pH 4.1. Measurements at pH 2.9, where practically only N7 can coordinate due to the protonation of N1, were performed in order to distinguish between the reactivity of these coordination sites. Under these conditions the observed rate constants for the two steps become very close and can only be separated by following the reactions at different wavelengths as indicated in Table I (see also Figure 4). Temperature and pressure dependence studies were also performed under these conditions. In addition, similar measurements were performed for the reaction of ado with the Et_4en complex, for which the data are also included in Table I. Here it was not possible to obtain accurate data for the second reaction step since this reaction is accompanied by a very small absorbance change. Some preliminary data resulted in a forward

Table I. Kinetic Data for the Reactions of $Pd(R_4en)(H_2O)_2^{2+}$ with Adenosine

Pd compd[a]	pH	λ, nm	P, MPa	T, °C	[L], M	first step			second step		
						k_{obs},[b] s^{-1}	k_a, s^{-1}	k_b, M^{-1} s^{-1}	k_{obs},[b] s^{-1}	k_a, s^{-1}	k_b, M^{-1} s^{-1}
R = H	4.1	360	0.1	10.5	0.006	3.4 ± 0.4	1.8 ± 0.3	260 ± 22	0.9 ± 0.2	0.41 ± 0.18	99 ± 12
					0.012	4.8 ± 0.6			2.0 ± 0.4		
					0.020	7.0 ± 0.6			2.3 ± 0.1		
				25.0	0.006	15.6 ± 2.0	9.3 ± 0.8	1124 ± 60	3.9 ± 0.5	1.5 ± 1.0	368 ± 75
					0.012	23.4 ± 0.5			5.6 ± 1.5		
					0.020	31.4 ± 2.2			9.0 ± 2.2		
				32.1	0.006	27 ± 2	15.8 ± 0.3	1926 ± 176	8.5 ± 0.7	3.2 ± 0.7	886 ± 48
					0.012	39 ± 3			14.0 ± 1.0		
					0.020	55 ± 4			21.0 ± 1.2		
	2.9	360	0.1	14.3	0.006		[c]		2.1 ± 0.1	0.34 ● 0.15	273 ± 9
					0.012				3.5 ± 0.2		
					0.020				5.8 ± 0.3		
					0.025				7.2 ± 0.5		
				25.0	0.006				4.2 ± 0.1	1.54 ± 0.24	411 ± 14
					0.012				6.3 ± 0.2		
					0.020				9.8 ± 0.4		
					0.025				12.0 ± 0.5		
				34.9	0.006				7.1 ± 0.3	3.13 ± 0.17	645 ± 10
					0.012				11.0 ± 0.8		
					0.020				16.0 ± 0.7		
					0.025				19.3 ± 0.7		
	4.1	300	0.1	25.0	0.006	12.1 ± 0.3	5.5 ± 0.5	1111 ± 41		[c]	
					0.012	18.9 ± 1.0					
					0.020	27.7 ± 1.5					
			5		0.010	16.6 ± 1.3					
			25			17.6 ± 1.9					
			50			18.7 ± 1.0	$(\Delta V^{\ddagger}_{(0.01)} = -7.1 \pm 0.3)$[f]				
			75			20.4 ± 1.5					
			100			21.7 ± 1.4					
			5		0.012	20.7 ± 0.9					
			25			22.9 ± 0.9					
			50			25.0 ± 1.7	$(\Delta V^{\ddagger}_{(0.012)} = -9.6 \pm 0.9)$				
			75			28.6 ± 2.0					
			100			29.5 ± 2.4					
			5		0.015	23.6 ± 1.6					
			25			25.2 ± 2.4					
			50			27.0 ± 1.0	$(\Delta V^{\ddagger}_{(0.015)} = -7.9 \pm 0.3)$				
			75			29.2 ± 2.4					
			100			32.1 ± 1.0					
	2.9	300	0.1	25	0.006	5.0 ± 0.1	≈0	934 ± 8		[c]	
					0.012	10.8 ± 0.3					
					0.020	18.3 ± 0.1					
	2.9	300	0.1	11.8	0.01	6.1 ± 0.4[d]					
				17.6		7.7 ± 0.5					
				25.0		9.2 ± 0.3					
				34.0		14.6 ± 0.4					
			5	25	0.01	8.3 ± 0.5[d]					
			25			9.1 ± 1.5					
			50			9.4 ± 1.0	$(\Delta V^{\ddagger}_{(0.01)} = -6.7 \pm 0.6)$				
			75			10.3 ± 1.0					
			100			10.7 ± 2					
R = Et	4.7	310	0.1	14.1	0.00192	0.0091 ± 0.002	0.005 ± 0.002	2.4 ± 0.2			
					0.0075	0.025 ± 0.001					
					0.015	0.040 ± 0.005					
			0.1	25.0	0.00188	0.023 ± 0.0001	0.013 ± 0.002	6.3 ± 0.1			
					0.0075	0.062 ± 0.003					
					0.015	0.106 ± 0.003					
					0.030	0.200 ± 0.004					
			4.8		0.001875	0.022 ± 0.001	0.013 ± 0.002	6.3 ± 0.1			
					0.0075	0.0620 ± 0.0005					
					0.015	0.106 ± 0.005					
					0.030	0.198 ± 0.005					
			50		0.001875	0.027 ± 0.001	0.013 ± 0.022	7.8 ± 0.2			
					0.0075	0.074 ± 0.002					
					0.015	0.129 ± 0.003					
			100		0.001875	0.031 ± 0.001	0.016 ± 0.006	9.4 ± 0.6			
					0.0075	0.092 ± 0.001					
					0.015	0.155 ± 0.001					
				35.6	0.00096	0.034 ± 0.002	0.0195 ± 0.0003	10.6 ± 0.4			
					0.00192	0.041 ± 0.004					
					0.0050	0.069 ± 0.001					
					0.0075	0.095 ± 0.012					
					0.015	0.182 ± 0.011					

Table I (Continued)

Pd compd[a]	pH	λ, nm	P, MPa	T, °C	[L], M	first step k_{obs},[b] s^{-1}	first step k_a, s^{-1}	first step k_b, M^{-1} s^{-1}	second step k_{obs},[b] s^{-1}	second step k_a, s^{-1}	second step k_b, M^{-1} s^{-1}
R = Et	4.7	310	0.1	25	0.0024				0.00006	≈0[c]	0.047 ± 0.018
					0.0045				0.00029		
					0.0090				0.00053		
					0.012				0.00064		
					0.015				0.00072		

[a] [Pd] varies but was adjusted according to pseudo-first-order requirements: i.e. at least a 10-fold excess of ligand concentration. [b] Mean values of at least five kinetic runs. [c] Reactions are not observed under mentioned experimental conditions. [d] $[Pd(en)(H_2O)_2]^{2+}$ = 0.001 M. [e] Low absorbance changes and large scattering in kinetic data. [f] Units for $\Delta V^{\ddagger}$ are cm^3 mol^{-1}.

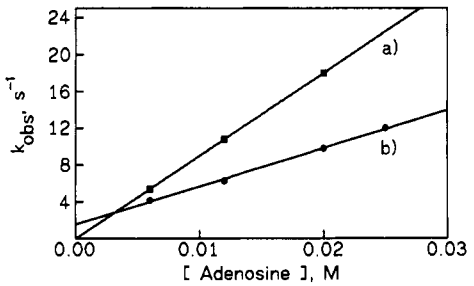

Figure 4. Typical kinetic data for the reaction of $Pd(en)(H_2O)_2^{2+}$ with adenosine: (a) rate data for the first step of the reaction recorded at 280 nm, k_b = 934 M^{-1} s^{-1}; (b) rate data for the second step of the reaction recorded at 360 nm, k_b = 411 M^{-1} s^{-1}. Conditions: [Pd(II)] = 6×10^{-4} M; pH = 2.9.

rate constant (k_3) of 4.7×10^{-2} M^{-1} s^{-1} at 25 °C. The first reaction exhibits no significant pH dependence in the range 4.1–5.2 in the case of the Et_4en complex.

The general kinetic behavior observed for the complex formation of ado with $Pd(R_4en)(H_2O)_2^{2+}$ as expressed by eq 2 and the data in Table I indicates that the process involves a nucleoside-dependent path (k_b) and an independent path (k_a), which could arise from a parallel or a reverse reaction step. Since the first observed complex formation step starts from the diaqua complex, a parallel (solvolysis) pathway is not possible and k_a must represent the contribution from the reverse aquation step, i.e. k_2 in (1). In the case of the second step, a parallel and/or a reverse reaction step can in principle account for the nucleoside-independent path. A comparison of the data for the first complex formation step of the en complex at pH 2.9 and 4.1 reveals that there is a significant increase in both k_a and k_b with increasing pH. Whereas it is safe to conclude that the data at pH 2.9 represent the reaction with ado-*N7*, this increased reactivity must be due to the partial deprotonation of N1 and a reaction with ado-*N1* as indicated in (3).

$$Pd(en)(H_2O)_2^{2+} \xrightarrow[k_5]{+\text{ado-}N7} Pd(en)(H_2O)(\text{ado-}N7) + H_2O \qquad (3)$$
$$\xrightarrow[k_6]{+\text{ado-}N1} Pd(en)(H_2O)(\text{ado-}N1) + H_2O$$

The participation of the parallel reaction steps will be controlled by the pK_a(N1) = 3.9. An analysis of k_b as a function of pH suggests that k_5 = 903 and k_6 = 1245 M^{-1} s^{-1} and so accounts for the increase in k_b with increasing pH. In addition, the Pd(en)(H_2O)(ado-*N1*) species is less stable due to interference by the exocyclic 6-NH_2 group, as found for the *cis*-Pt(II) analogue,[2h,3g,3n] and therefore aquates more easily. This accounts for the increase in k_a observed with increasing pH and indicates that an equilibrium is reached in the coordination of ado-*N1*, for which the formation constant is k_6/k_a = 134 M^{-1}, where k_6 and k_a represent k_1 and k_2 in the general reaction scheme outlined in (1), respectively. The kinetic data for the second complex formation step are within the experimental error limits independent of pH and indicate the occurrence of a reversible process for which the equilibrium constant is $k_3/k_4 \approx 260 \pm 20$ M^{-1}. The values of k_b for the second step are significantly smaller than those for the first step and account for the occurrence of two consecutive reactions. The pH independence suggests that the final product is most probably Pd(en)(ado-*N7*)$_2$.

An increase in steric hindrance on the en ligand in going to Et_4en results in k_a and k_b values for the first complex formation reaction that are at least 2 orders of magnitude smaller than for the reaction of the en complex with ado. The overall equilibrium constant for the first step is 500 ± 50 M^{-1} and is of the same order as found for the en complex. The preliminary data for the formation of the final product also indicate a rate constant that is almost 4 orders of magnitude slower than for the en complex, viz. 4.7×10^{-2} compared to 368 M^{-1} s^{-1} at 25 °C. This trend clearly demonstrates the significant effect of steric hindrance on, in particular, the entrance of a second nucleoside moiety into the coordination sphere of the Et_4en complex.

Kinetic data for the reaction with ino are summarized in Table II. On the basis of the information given before, it is safe to assume that ino-*N7* will be the only observed coordination possibility. The absorbance time traces recorded at 355 nm for the en complex clearly exhibit two consecutive reaction steps that both depend on the ino concentration. In this system the first step exhibits no significant intercept (k_a), whereas the second step does. The forward rate constant for the first step, k_b = 13 600 ± 220 M^{-1} s^{-1} at 25 °C, is in close agreement with the value of 12 000 M^{-1} s^{-1} reported in the literature.[9] The second step is more than 10 times slower, k_b = 933 ± 63 M^{-1} s^{-1}, and exhibits a significant intercept. If the latter is interpreted in terms of the back-reaction, then the second formation constant k_3/k_4 = 108 ± 20 M^{-1} and is of the same order of magnitude as found for ado. Similar observations were made for the Et_4en complex, with the difference that the second step does not exhibit a k_a path (intercept in the concentration dependence of k_{obs}), in agreement with the data reported for the reaction with ado. Comparison of the k_b values indicates that the second step is ca. 20 times slower than the first at 25 °C. The increase in steric hindrance from en to Et_4en decreases k_b from 13 600 to 245 M^{-1} s^{-1} for the first step, and from 933 to 12.4 M^{-1} s^{-1} for the second step with ino at 25 °C, i.e. a decrease of almost 2 orders of magnitude.

Rate and Activation Parameters. We now turn to a discussion of the rate and activation parameters for the investigated reactions summarized in Table III. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for k_1 and k_3 for the reactions of ado with $Pd(en)H_2O)_2^{2+}$ strongly vary with pH. This is ascribed to the influence of the temperature dependence of the protonation constant of ado, which is expected to have negative ΔH° and ΔS° values. This difference does not show up in the rate constant and the values for $\Delta V^{\ddagger}$, which means that ΔV is close to zero for the protonation step. The corresponding reactions for ino are accompanied by similar activation parameters. The reverse steps k_2 and k_4 exhibit, where available, activation parameters that are subjected to larger error limits due to the difficulties involved to obtain accurate values for these constants. The corresponding complex formation reactions of the Et_4en complex exhibit $\Delta G^{\ddagger}$ values that are on the average between 10 and 20 kJ mol^{-1} higher, which can be ascribed to the effect of steric hindrance in terms of an associative substitution mechanism.[4a-e,p-r] The $\Delta S^{\ddagger}$ values are throughout the systems negative and in agreement with the $\Delta V^{\ddagger}$ data. The rate data (and therefore the corresponding activation parameters) can be measured more accurately for the Et_4en complex than for the en complex, since the reactions are significantly slower. The overall complex formation constants are not largely affected by the introduction of steric hindrance on the en ligand, in agreement with earlier findings for the related diethylenetriamine complexes.[4d] All in all the

Table II. Kinetic Data for the Reactions of $Pd(R_4en)(H_2O)_2^{2+}$ with Inosine

Pd compd[a]	pH	λ, nm	*P*, MPa	*T*, °C	[L], M	first step k_{obs},[b] s^{-1}	first step k_a, s^{-1}	first step k_b, M^{-1} s^{-1}	second step k_{obs},[b] s^{-1}	second step k_a, s^{-1}	second step k_b, M^{-1} s^{-1}
R = H	4.2	355	0.1	18.6	0.0040	44.3 ± 0.3	≈0[c]	10816 ± 280			
					0.0050	48.9 ± 1.0					
					0.0060	63.4 ± 2.8					
					0.0075	87.9 ± 2.1					
				25.0	0.0050	69.3 ± 1.3	≈0	13600 ± 220			
					0.0060	82.0 ± 1.2					
					0.0075	105 ± 2					
					0.0010	139 ± 4					
					0.012	172 ± 4					
					0.015	209 ± 4					
				32.9	0.0040	55.8 ± 2.3	≈0	16314 ± 394			
					0.0050	76.6 ± 3.2					
					0.0060	105 ± 3					
					0.0075	111 ± 4					
				37.8	0.0030	56.7 ± 4.8	...	18800 ± 300			
			5	25.0	0.0030	35.6 ± 2.5	($\Delta V^{\ddagger}$ = −9.7 ± 1.5[g])				
			25			37.1 ± 3.2					
			50			40.9 ± 1.5					
			75			45.3 ± 2.0					
			100			51.3 ± 2.9					
			0.1[d]	18.2	0.015				11.1 ± 0.4	3.4 ± 1.4	551 ± 61
					0.025				18.3 ± 1.0		
					0.030				20.6 ± 1.7		
				25.0	0.015				22.7 ± 3.3	8.7 ± 2.3	933 ± 63
					0.020				24.2 ± 0.2		
					0.025				30.6 ± 2.2		
					0.030				38.3 ± 4.5		
				31.4	0.015				35.4 ± 1.6	18.7 ± 1.7	1133 ± 76
					0.020				42.3 ± 2.1		
					0.025				46.3 ± 2.4		
					0.030				52.9 ± 4.6		
				37.8	0.020				77.4 ± 4.1	29.6 ± 12.2	2358 ± 475
					0.025				88.2 ± 2.0		
					0.030				101 ± 5		
R = Et	4.7	315, 365	0.1	14.0	0.00192	0.75 ± 0.17	0.66 ± 0.06	62.2 ± 4.8		*e*	5.0 ± 0.1
					0.0050	0.97 ± 0.20			0.025 ± 0.001		
					0.010	1.33 ± 0.21			0.050 ± 0.001		
					0.020	1.88 ± 0.40					
				25.0	0.0020	1.80 ± 0.17	1.29 ± 0.05	245 ± 4		...	12.4 ± 0.04
					0.0040	2.27 ± 0.15			0.049 ± 0.001		
					0.0092	3.71 ± 0.11			0.114 ± 0.002		
					0.020	6.21 ± 0.19			0.252 ± 0.002		
				35.6	0.00182	3.78 ± 0.06	3.0 ± 0.7	458 ± 59	0.039 ± 0.002	...	29.0 ± 1.8
					0.0050	4.69 ± 0.14			0.126 ± 0.001		
					0.010	8.51 ± 0.29			0.29 ± 0.02		
					0.020	11.8 ± 0.8					
			5	25.0	0.00284	1.07 ± 0.13	*f*	287 ± 8			
					0.01137	3.4 ± 0.4					
					0.01894	5.7 ± 0.9					
			50		0.00284	1.18 ± 0.09	...	322 ± 20			
					0.01137	3.7 ± 0.6					
					0.01894	6.4 ± 1.5					
			100		0.00284	1.33 ± 0.11	...	363 ± 21			
					0.01137	4.1 ± 0.6					
					0.01894	7.2 ± 1.2					
			5	25.0	0.01137				0.143 ± 0.006	*e*	12.6 ± 0.5
			25						0.152 ± 0.008		13.4 ● 0.7
			50						0.161 ± 0.011		14.7 ± 1.0
			75						0.163 ± 0.003		14.3 ± 0.3
			100						0.170 ± 0.010		15.0 ± 0.9

[a] See Table I. [b] See Table I. [c] k_{a1} values are almost zero with respect to error limits. [d] Pressure-dependence experiment not possible due to a too small absorbance change for the high-pressure stopped-flow instrument. [e] No significant intercept was observed in plots of k_{obs} vs [Ino]. [f] Intercepts too small to measure. [g] Units for $\Delta V^{\ddagger}$ are cm^3 mol^{-1}.

thermal activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in most cases support the assignment of associative complex formation and aquation reactions. In addition the $\Delta V^{\ddagger}$ data are more convincing. Throughout the investigated reactions, $\Delta V^{\ddagger}$ is significantly negative for both forward and reverse steps and underlines the associative nature of the substitution process. The results are in good agreement with those published before for substitution reactions of square-planar complexes.[4,16,17] From the $\Delta V^{\ddagger}$ data for k_1 and k_2 for the complex formation of $Pd(Et_4en)(H_2O)_2^{2+}$ with ado, the overall reaction volume can be estimated as $\Delta V = \Delta V^{\ddagger}(k_1) - \Delta V^{\ddagger}(k_2) = -4 \pm 2$ cm^3 mol^{-1}. The overall negative reaction volume is due to the binding of a large nucleoside and the release of a small solvent molecule on the basis of their significantly different partial molar volumes.[4p] The $\Delta V^{\ddagger}$ data do not exhibit a particular dependence on steric hindrance or the nature of the nucleoside, which demonstrates the similarity in substitution process in all cases.

Comparison with Related Systems. In this section we will discuss the results of this investigation in terms of their meaning to

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Table III. Rate and Activation Parameters (at 25 °C) for the System

$$[Pd(R_4en)(H_2O)_2]^{2+} + Nu \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [Pd(R_4en)(H_2O)(Nu)]^{2+} + Nu \underset{k_4}{\overset{k_3}{\rightleftharpoons}} [Pd(R_4en)(Nu)_2]^{2+}$$

	R = H, [Pd(en)]					R = Et, [Pd(Et$_4$en)]				
Nu	pH	k_1, M^{-1} s^{-1}	k_2, s^{-1}	k_3, M^{-1} s^{-1}	k_4, s^{-1}	pH	k_1, M^{-1} s^{-1}	k_2, s^{-1}	k_3, M^{-1} s^{-1}	k_4, s^{-1}
adenosine	2.9 (300 nm)	934 ± 8	≈0	411 ± 14	1.5 ± 0.2	4.7	6.26 ± 0.11	0.013 ± 0.002	0.047 ± 0.018	≈0 ± 1
	4.1 (300 nm)	1111 ± 41	5.5 ± 0.5							
	(360 nm)	1124 ± 60	9.3 ± 0.8	368 ± 7	1.5 ± 1.0					
inosine	4.5	13600 ± 220	≈0	933 ± 63	8.6 ± 2.3	4.7	245 ± 4	1.29 ± 0.05	12.40 ± 0.04	≈0

		R = H, [Pd(en)]				R = Et, [Pd(Et$_4$en)]			
	pH	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J K^{-1} mol^{-1}	$\Delta G^{\ddagger}$, kJ mol^{-1}	$\Delta V^{\ddagger}$, cm^3 mol^{-1}	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J K^{-1} mol^{-1}	$\Delta G^{\ddagger}$, kJ mol^{-1}	$\Delta V^{\ddagger}$, cm^3 mol^{-1}
ado k_1	4.1	65 ± 3	+33 ± 9	55.7	−9.6 to −7.1	48 ± 7	−69 ± 22	84.2	−10.6 ± 0.8
	2.9	25 ± 3	−103 ± 11	55.9	−6.74 ± 0.01				
ado k_2	4.1	71 ± 5	+12 ± 18	67.7	*a*	42 ± 7	−139 ± 25	68.8	−6.3 ± 2.5
ado k_3	4.1	68 ± 6	+33 ± 21	58.1	*b*		*d*		
	2.9	28 ± 2	−100 ± 7	58.0					
ado k_4	4.1	64 ± 4	−27 ± 12	71.9	*b*		*d*		
	2.9	86 ± 9	+45 ± 30	72.3					
ino k_1		18.8 ± 1.2	−103 ± 4	49.5	−9.7 ± 1.5	66 ± 12	+21 ± 42	59.9	−6.1 ± 0.1
ino k_2		*c*				49 ± 5	−77 ± 17	72.2	
ino k_3		50 ± 8	−21 ± 28	56.2	*b*	57.8 ± 0.9	−30 ± 3	66.7	−4.3 ± 0.6
ino k_4		81 ± 7	+45 ± 22	67.8	*b*		*c*		

[a] Too small intercept in plots of k_{obs} vs [Nu]. [b] Too small absorbance change to measure all activation parameters. [c] Rate constant of corresponding reaction is close to zero. [d] Too small absorbance change and large scatter in kinetic data.

improve our understanding of the antitumor activity of *cis*-$Pt(NH_3)_2Cl_2$. Throughout our data it is clear that complex formation by ino is ca. 10 times faster than the reaction with ado for the first step in the reaction with the en and Et_4en complexes. In the case of the second complex formation step, this factor reduces to between 2 and 3, presumably partially due to the effect of steric hindrance. Nevertheless, ino seems to be a significantly stronger nucleophile than ado. A similar trend was reported for the reactions of $Pd(dien)H_2O^{2+}$ with ado and ino, which are ca. 2 times faster than for $Pd(en)(H_2O)_2^{2+}$. The latter trend may be related to a higher lability of coordinated water in the dien complex due to the chelation effect. More important, however, is the fact that inosine closely resembles the reactivity of guanosine.[4h] In the case of the dien complex the rate of complex formation of guanosine is slightly higher than of inosine. These results clearly indicate that binding to the nucleic base guanine will be largely favored over the binding to adenine, as generally found for the interaction of *cis*-$Pt(NH_3)_2Cl_2$ with DNA.[2,3] In this respect it should be kept in mind that substitution reactions of *cis*-$Pt(NH_3)_2(H_2O)_2$ are ca. 10^5 times slower than those of $Pd(en)(H_2O)_2$, although the equilibrium situation is almost identical.[5,6] In the presence of Cl^-, less reactive aqua chloro and dichloro complexes will be produced, and it is reasonable to expect the reactivity to decrease in the ratio 1:0.04:0.007 in going from the diaqua to the dichloro complex.[9] At the chloride concentration level in the cell (4 mM), the aqua chloro complex will be the main reactive species in solution.[5,9] The expected interference of chloride in the complex formation reactions with the nucleosides is mainly due to very similar complex formation rate constants reported for these species.[5,9] By way of comparison the reaction of $Pd(en)(H_2O)_2^{2+}$ with inosine exhibits forward rate constants of 13 600 and 933 M^{-1} s^{-1} for the first and second (k_1 and k_3) steps, respectively, whereas the corresponding data for the reaction with chloride are 30 000 and 1300 M^{-1} s^{-1} at 25 °C, respectively.[5] A similar agreement exists for the reverse aquation reactions of the produced complexes. Finally, the pH at which antitumor complexes bind to DNA is significantly higher than the pH used in this study, which will cause deprotonation of the diaqua complex and cause the monoaqua complex to produce less reactive hydroxo and hydroxo-bridged species under those conditions. In general the reactivity of these complexes will decrease significantly at pH > 5.[5] It follows that small differences in pK_a values of various antitumor complexes, as well as small differences in the pH of healthy and tumor cells, may cause a significant difference in the reactivity, i.e. the substitution lability, of the employed complexes.

In some of the investigated systems the observed reaction steps discussed so far were followed by either one or two additional slow steps over very long reaction times. These were in general accompanied by extremely small absorbance changes, which resulted in highly unreproducible kinetic data. Furthermore, such subsequent steps were mainly observed for the Et_4en complex. Some preliminary experiments indicated that these steps may be related to the presence of very low concentrations of Ag^+ ions in solution resulting from the preparation of the diaqua complexes in situ. Evidence for the interaction of Ag^+ with nucleosides and nucleotides has been reported in the literature.[18,19] In other experiments the observed reactions seemed to exhibit a dependence on the entering nucleophile concentration and could be related to a slow hydrolysis process of the employed nucleosides. However, the quality of the data was such that no definite conclusion to the nature of these subsequent reactions could be reached. This observation may be of significance in terms of the interaction of such nucleosides with Pt(II) complexes since these occur orders of magnitude slower than in the case of Pd(II).

The results of this investigation have clearly demonstrated the ability of inosine (and therefore guanosine) to bind via N7 in a stepwise process to diaqua complexes of Pd(II). A similar behavior is predicted for the corresponding Pt(II) complexes. The substitution rate constants agree well with those for chloride and underline the important role of this species under biological conditions. At present this work is being extended to the study of the corresponding 5′-monophosphate nucleotides.

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