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DEPURINATION OF (dien)Pt(II) COMPLEXES OF PURINE DEOXYRIBONUCLEOSIDES. COMPARISON WITH THE EFFECTS OF (dien)Pd(II) ION COMPLEXING

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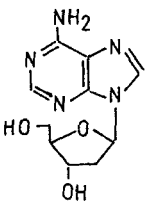
First-order rate constants for the hydrolytic depurination of 2′-deoxyinosine and its various (dien)Pt(II) ion complexes were measured over the acidic pH range. The rate profiles obtained indicate that the uncomplexed nucleoside and its N^1-(dien)Pt(II) complex are depurinated via mono- and di-protonated species, whereas the N^7-(dien)Pt(II) and N^1, N^7-di(dien)Pt(II) complexes exhibit significant spontaneous hydrolysis, which competes with a markedly retarded acid-catalysed reaction. Rate constants for the various partial reactions were calculated and the results were employed to explain the effects that (dien)Pd(II) ion exerted on depurination rates of the same compounds. Similar measurements were carried out with the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyadenosine in order to further the understanding of the previously reported rate-enhancing effect of (dien)Pd(II) ion on the depurination of 2′-deoxyadenosine.

INTRODUCTION

Pd(II) ion is known to form exceptionally stable complexes with nucleic acid bases and their derivatives.[1] Interestingly, complexing with this metal ion exerts specific influences on the hydrolytic stability of purine nucleosides. It has been shown, for example, that adenine residues are hydrolysed from DNA much faster than guanine residues in the presence of $K_2[PdCl_4]$, whereas in the absence of this salt both of these purine nucleosides are depurinated at comparable rates.[2] More recently, the influence of Pd^{2+} coordination on the acid-catalysed hydrolysis of 2′-deoxyadenosine (**1**) and 2′-deoxyguanosine (**2**) was studied in detail at the monomeric level, using monofunctional (dien)Pd(II) ion as a complexing agent.[3] In the presence of this metal ion the hydrolysis of 2′-deoxyguanosine was retarded by a factor of 65, whereas only a minor effect on the hydrolysis of 2′-deoxyadenosine was observed, viz. a rate retardation at pH < 2 and a rate accelaration at pH > 3. Comparative kinetic studies with substitution inert (dien)Pt(II) complexes of these nucleosides indicated that binding of a metal ion to N-7 of 2′-deoxyguanosine markedly retards acidic depurination, as suggested earlier by Johnson *et al.*[4] In contrast, coordination to either N-1 or N-7 sites of 2′-deoxyadenosine was observed to have only a small effect on hydrolytic stability. No data on the hydrolysis of the N^1-(dien)Pt(II) complex of 2′-deoxyguanosine or N^1, N^7-di(dien)Pt(II) complexes of 2′-deoxyadenosine or 2′-deoxyguanosine were presented. The rate-accelerating effect that a (dien)Pd(II) ion had on the depurination of 2′-deoxyadenosine under mildly acidic conditions was tentatively attributed to N-3 coordination.

This paper is intended to give a more detailed picture of the effects that binding of (dien)Pd(II) or (dien)Pt(II) ion to various coordinations sites has on the hydrolytic stability of purine nucleosides. For this purpose, pH–rate profiles for the hydrolysis of 2′-deoxyinosine (**3**) and its substitution inert N^1-(dien)Pt(II) (**4**), N^7-(dien)Pt(II) (**5**) and N^1, N^7-di(dien)Pt(II) complexes (**6**) were determined. In addition, the effect of the substitution labile (dien)Pd(II) ion on the depurination of these compounds at different hydronium ion concentrations was



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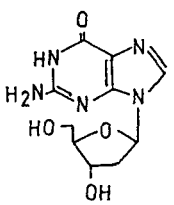

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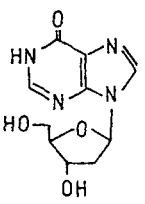

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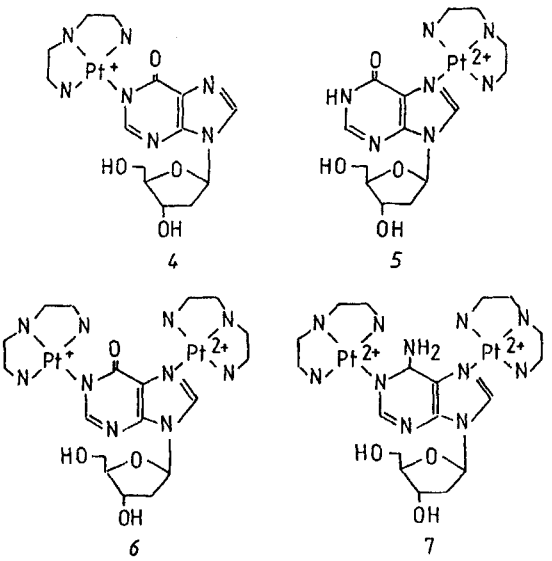


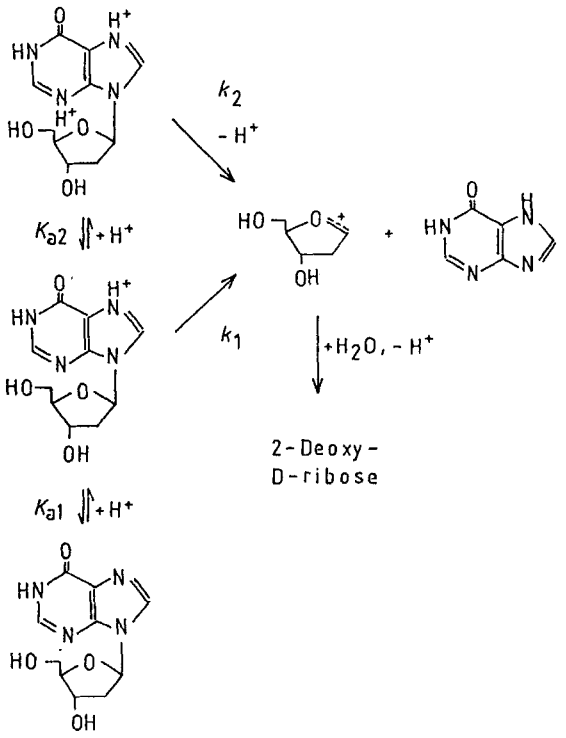
examined. Previous data[3] on the hydrolysis of 2′-deoxyadenosine were completed by carrying out analogous measurements with its N^1, N^7-di(dien)Pt(II) complex (7). 2′-Deoxyinosine was chosen as a model compound instead of 2′-deoxyguanosine, since (i) the N^1-(dien)Pt(II) and N^1, N^7-di(dien)Pt(II) complexes of 2′-deoxyinosine are easier to prepare than those of 2′-deoxyguanosine and (ii) N-3 coordination, which was assumed to play an important role in the (dien)Pd(II) acceleration, is sterically less hindered with 2′-deoxyinosine than with 2′-deoxyguanosine.

RESULTS AND DISCUSSION

Hydrolysis of 2′-deoxyinosine (3)

2′-Deoxyadenosine[5] and 2′-deoxyguanosine[6] have been shown to hydrolyse under acidic conditions by a mechanism involving a rapid initial protonation of the base moiety, giving either a mono- or di-cation, and a subsequent rate-limiting heterolysis to the free base and a resonance-stabilized 2-deoxyribofuranosyl carbonium ion. The same mechanism can probably also be applied to the hydrolysis of 2′-deoxyinosine (Scheme 1). The first protonation takes place at N-7 and the second probably at N-3, the pK_a values being of the order of 1 and −4, respectively.[1] The observed pseudo-first-order rate constant, k(obs.), may therefore be expressed by the equation

$$k(\text{obs.}) = \frac{\frac{k_1}{K_{a1}}[H^+] + \frac{k_2}{K_{a1}K_{a2}}[H^+]^2}{1 + \frac{[H^+]}{K_{a1}} + \frac{[H^+]^2}{K_{a1}K_{a2}}} \qquad (1)$$



Scheme 1

where the partial rate and equilibrium constants are those indicated in Scheme 1. At pH ≫ pK_{a2}, the concentration term of the dicationic species, $[H^+]^2/(K_{a1}K_{a2})$, may be neglected in the denominator of the right-hand side, and equation (1) is hence reduced to

$$k(\text{obs.}) = \frac{k_1[H^+] + \frac{k_2}{K_{a2}}[H^+]^2}{K_{a1} + [H^+]} \qquad (2)$$

Figure 1 shows the pH–rate profile for the hydrolysis of 2′-deoxyinosine. The profile is non-linear, passing through an inflection point at pH ≈ pK_{a1}, in striking contrast to the normal behaviour of purine nucleosides. Usually the rate profiles are linear, which means that k_1/K_{a1} and k_2/K_{a2} are of the same magnitude.[4] The values obtained by least-squares fitting[7] for 2′-deoxyinosine are listed in Table 1. As can be seen, k_1/K_{a1} is almost 30 times larger then k_2/K_{a2}, indicating that hydrolysis via the diprotonated substrate is abnormally slow. Comparison with the data reported by Zoltewicz *et al.*[6] for 2′-deoxyguanosine reveals that 2′-deoxyinosine and 2′-deoxyguanosine are hydrolysed via the substrate monocation (k_1/K_{a1}) approximately as readily, whereas the reaction via substrate dication (k_2/K_{a2}) is one order of magnitude slower with

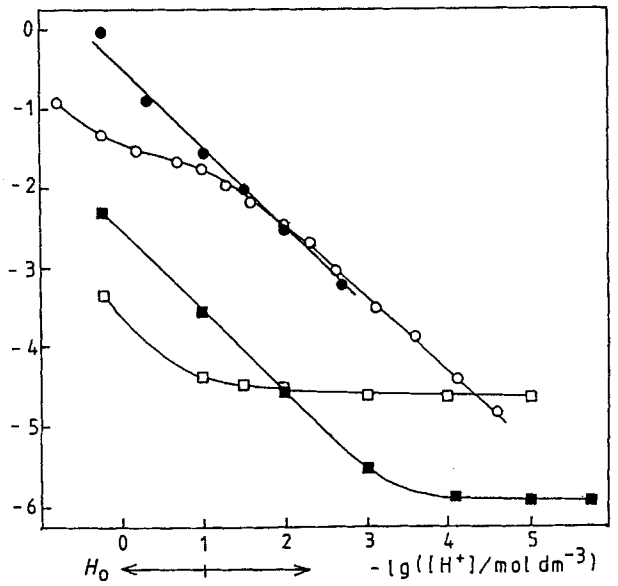


Figure 1. pH-rate profiles for depurination of 2′-deoxyinosine (**3**, open circles) and its N^1-(dien)Pt(II) (**4**, filled circles), N^7-(dien)Pt(II) (**5**, open squares) and N^1, N^7-di(dien)Pt(II) complex (**6**, filled squares) at 333·2 K ($I = 0{\cdot}1$ mol dm^{-3})

2′-deoxyinosine than with 2′-deoxyguanosine. This difference in behaviour may tentatively be attributed to impeded formation of the 2′-deoxyinosine dication, i.e. protonation of N-3. The pK_{a1} and pK_{a2} values for hypoxanthine, for example, differ by 5·6 units,[8,9] whereas the corresponding difference with guanine is only 4·4 units.[9,10]

Hydrolysis of the N^1-(dien)Pt(II) complex of 2′-deoxyinosine (4)

The pH–rate profile for hydrolysis of the N^1-(dien)Pt(II) complex of 2′-deoxyinosine remains linear on passing the pK_{a1} value (Figure 1), reported[11] to be 2·3 at 298·2 K ($I = 0{\cdot}1$ mol dm^{-3}), i.e. 1 unit higher than that of the free nucleoside. The values obtained by equation (2) for the partial rate constants (Table 1) indicate that platination of N-1 has virtually no effect on depurination via the monoprotonated substrate (k_1/K_{a1}); the pre-equilibrium concentration of protonated substrate is increased, but the heterolysis step is simultaneously retarded owing to increased electron density of the purine ring. In contrast, hydrolysis via the diprotonated substrate (k_2/K_{a2}) is one order of magnitude faster than with the uncomplexed 2′-deoxyinosine. Accordingly, replacement of the N-1 proton with a (dien)Pt(II) ion appears to facilitate N-3 protonation to a larger extent than to retard heterolysis of the diprotonated substrate. For comparison, the pK_a value of the N^1, N^7-di(NH$_3$)$_3$Pt(II) complex of 9-ethylguanine is known to be more than 1·5 units higher than that of the N^1-H, N^7-(NH$_3$)$_3$Pt(II) complex.[12]

Hydrolysis of the N^7-(dien)Pt(II) complex of 2′-deoxyinosine (5)

The pH–rate profile for hydrolysis of the N^7-(dien)Pt(II) complex of 2′-deoxyinosine (Figure 1) differs markedly from those obtained with uncomplexed 2′-deoxyinosine and its N^1-(dien)Pt(II) complex. As with 7-alkylated guanosines,[6,13] the depurination rate becomes independent of pH at pH > 2, indicating that N-7 platination results in a spontaneous rupture of the *N*-glycosidic bond. The pH dependence of the observed first-order rate constants may thus be expressed by the equation

$$k(\text{obs.}) = \frac{k_0 + \dfrac{k_1}{K_{a1}}[H^+]}{1 + \dfrac{[H^+]}{K_{a1}}} \qquad (3)$$

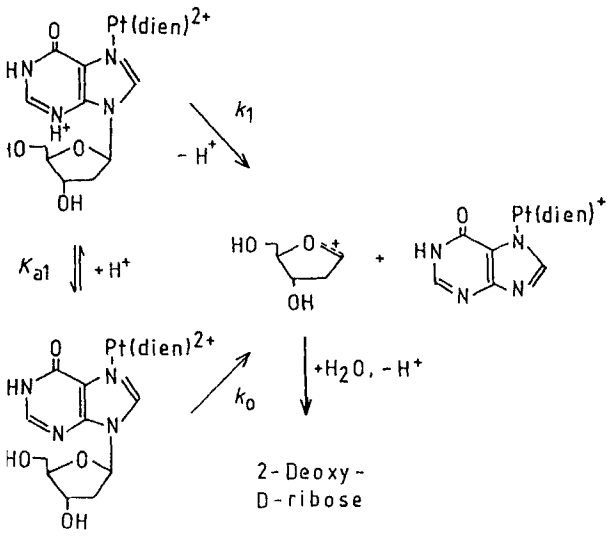
where the partial rate and equilibrium constants are those indicated in Scheme 2.

The pK_{a1} value of the N^7-(NH$_3$)$_3$Pt(II) complex of 9-ethylguanine has been reported to be of the order of zero,[12] which suggests the pK_{a1} value of **5** to be of the order of −1 (the hypoxanthine ring is known to be one

Table 1. Partial rate constants for the hydrolysis of 2′-deoxyinosine, its [Pt(dien)]$^{2+}$ complexes and the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyadenosine at 333·2 K[a]

Compound	k_0 (10^{-5} s^{-1})	k_1 (10^{-3} s^{-1})	K_{a1} (mol dm^{-3})	k_1/K_{a1} (dm^3 mol^{-1} s^{-1})	k_2/K_{a2} (dm^3 mol^{-1} s^{-1})
3		21	0·048	0·44	0·016
4		2·1	0·0079[b]	0·27	0·37
5	2·6			0·00025	
6	0·12			0·0027	
7	8·7			0·00062	

[a] Ionic strength adjusted to 0·1 mol dm^{-3} at [H$^+$] < 0·1 mol dm^{-3}. For the definition of rate constants, see Schemes 1 and 2.
[b] From Ref. 11.



Scheme 2

order of magnitude less basic than the guanine ring[1]). The experimental data thus refer to conditions where the denominator of the right-hand side of equation (3) does not significantly deviate from unity ($[H^+] \ll K_{a1}$). Consequently, the equation

$$k(\text{obs.}) = k_0 + \frac{k_1}{K_{a1}}[H^+] \qquad (4)$$

may be used to fit the data. The value of $2{\cdot}5 \times 10^{-5}$ s^{-1} obtained for k_0 at 333·2 K indicates that N-7 platination destabilizes the *N*-glycosidic bond, but to a markedly lesser extent that N-7 alkylation. The first-order rate constant for the pH-independent depurination of 2′-deoxy-7-methylguanosine may be estimated to be $1{\cdot}4 \times 10^{-3}$ s^{-1} at this temperature.[6]

2′-Deoxy-7-methylinosine probably reacts even faster since 7-methylhypoxanthine is more acidic than 7-methylguanine,[1] and is hence a better leaving group. The pH-independent depurination of 2′-deoxy-7-methylinosine is thus at least two orders of magnitude faster than that of the N^7-(dien)Pt(II) complex. The pathway through the monopronated substrate (k_1/K_{a1}) is, in turn, three orders of magnitude slower than with 2′-deoxyinosine or its N^1-(dien)Pt(II) complex, owing to the fact that protonation of N-7 is prevented by the platinum ion (Table 1). Accordingly, N-7 platination retards the depurination of 2′-deoxyinosine at pH < 4, whereas at higher pH an acceleration is observed.

Hydrolysis of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyinosine (6)

Hydrolysis of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyinosine also becomes independent of pH at low hydronium ion concentrations (Figure 1). The observed first-order rate constant may thus be expressed by equation (4). The rate of the spontaneous depurination (k_0) is about 5% of that of the N-7 complex (5), whereas the acid-catalysed reaction (k_1/K_{a1}) is one order of magnitude faster than with 5 (Table 1). As stated above, replacing the N-1 proton with a (dien)Pt(II) ion increases the electron density of the purine ring, the pyrimidine ring probably being affected more than the imidazole ring. Accordingly, rate-limiting rupture of the *N*-glycosidic bond is retarded, but enhanced protonation of N-3 overcompensates this rate deceleration, resulting in a rate acceleration at pH < 2.

In summary, binding of (dien)Pt(II) ion at the N-7 site retards the acidic depurination of 2′-deoxyinosine by preventing N-7 protonation, but accelerates the spontaneous rupture of the *N*-glycosidic bond. Replacing the N-1 proton with a (dien)Pt(II) ion does not markedly affect the rate of the partial reaction via the N-7-monoprotonated substrate, owing to opposite effects on protonation and heterolysis, but the reaction via the N-3, N-7-diprotonated species is moderately enhanced. N-1 platination of the N^7-(dien)Pt(II) complex of 2′-deoxyinosine retards, in turn, the spontaneous depurination and accelerates the acid-catalysed reaction.

Effect of (dien)Pd(II) ion on hydrolysis of 2′-deoxyinosine and its (dien)Pt(II) complexes

Figure 2 shows the effects that an increasing concentration of (dien)Pd(II) ion has on the hydrolysis rate of 2′-deoxyinosine at hydrogen ion concentrations of 0·1 and 0·001 mol dm^{-3}. The reaction rate decreases

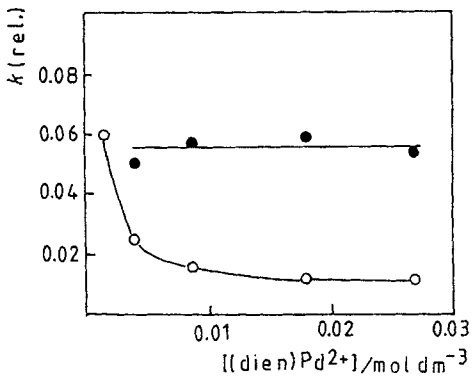


Figure 2. Effect of (dien)Pd(II) ion on depurination of 2′-deoxyinosine (3). The data at $[H^+] = 0{\cdot}1$ mol dm^{-3} (open circles) refer to $T = 333{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}19$ mol dm^{-3} and those at $[H^+] = 0{\cdot}001$ mol dm^{-3} (filled circles) to $T = 353{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}1$ mol dm^{-3}

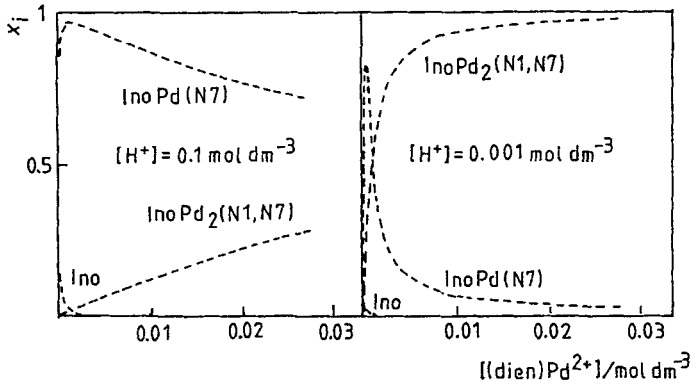


Figure 3. Distribution of (dien)Pd(II) complexes of inosine at $[H^+] = 0{\cdot}1$ and $0{\cdot}001$ mol dm^{-3} ($T = 307$ K, $I = 0{\cdot}5$ mol dm^{-3}). Based on the data of Kim and Martin[14]

considerably on increasing the metal ion concentration from 0 to $0{\cdot}005$ mol dm^{-3}, and remains fairly constant thereafter. The plateau value at pH 1 is 1·3%, and at pH 3 it is 6·7% of the rate constant observed in the absence of (dien)Pd(II) ion. Kim and Martin[14] have shown by ^{1}H NMR measurements that the N^7-(dien)Pd(II) complex of inosine predominates at pH 1 and the N^1, N^7-di(dien)Pd(II) complex at pH 3, when the concentration of (dien)Pd(II) ion falls in the range used in the kinetic measurements ($0{\cdot}005$–$0{\cdot}03$ mol dm^{-3}) (Figure 3). It is worth noting that coordination to N-3 is of minor importance. Accordingly, the rate retardations observed at pH 1 and 3 may be attributed to the formation of the N^7-(dien)Pd(II) and N^1, N^7-di(dien)Pd(II) complex, respectively. Comparison with the rate profiles in Figure 1 reveals that both of these complexes are depurinated faster than the corresponding (dien)Pt(II) complexes, the hydrolysis rates of **5** and **6** being 0·25% (at pH 1) and 0·7% (at pH 3) of that of 2′-deoxyinosine, respectively.

The effect of (dien)Pd(II) ion on hydrolysis of the N^1-(dien)Pt(II) complex of 2′-deoxyinosine (**4**) is similar to that observed for 2′-deoxyinosine itself (Figure 4). The large rate retardation may be attributed to binding of (dien)Pd(II) ion at N-7. The data of Kim and Martin[14] on the stability of the N^1, N^7-di(dien)Pd(II) complex of inosine suggest that **4** is almost completely present as its N^7-(dien)Pd(II) complex under the conditions used to study the influence of the (dien)Pd(II) ion. Comparison of the data in Figures 1 and 4 indicates that attachment of (dien)Pd(II) ion to N-7 of **4** retards acidic depurination slightly less than attachment of (dien)Pt(II) ion: (dien)Pd(II) by a factor of 20–50 and (dien)Pt(II) by a factor of 100.

As can be seen from Figure 5, (dien)Pd(II) ion does not markedly affect the depurination rate of the N^7-

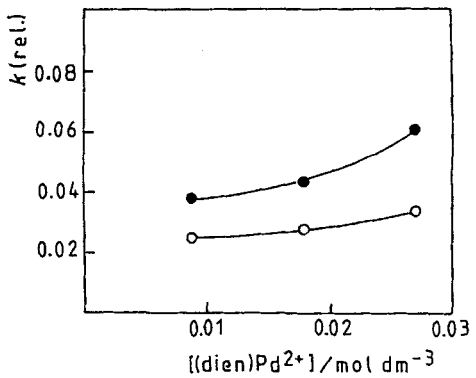


Figure 4. Effect of (dien)Pd(II) ion on depurination of the N^1-(dien)Pt(II) complex of 2′-deoxyinosine (**4**). The data at $[H^+] = 0{\cdot}1$ mol dm^{-3} (open circles) refer to $T = 333{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}19$ mol dm^{-3} and those at $[H^+] = 0{\cdot}001$ mol dm^{-3} (filled circles) to $T = 353{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}1$ mol dm^{-3}

(dien)Pt(II) complex of 2′-deoxyinosine (**5**). Figure 6 shows distribution diagrams constructed for the N^1-(dien)Pd(II) complex of **5** by assuming that the influence of an N-7-bound (dien)Pt(II) ion on deprotonation and metal ion binding at N-1 is similar to that of the N^7-(dien)Pd(II) ion.[14] At pH 1 the (dien)Pd(II) ion is unable to displace the N-1 proton. In contrast, at pH 3 this displacement takes place, and the N^1-(dien)Pd(II) complex prevails at $[(dien)Pd^{2+}] > 0{\cdot}01$ mol dm^{-3}. However, even under these conditions the influence of (dien)Pd(II) ion on the depurination rate remains small. The slight acceleration observed may possibly be attributed to N-3 coordination, as discussed below in the context of hydrolysis of the N^1, N^7-di(dien)Pt(II) complex.

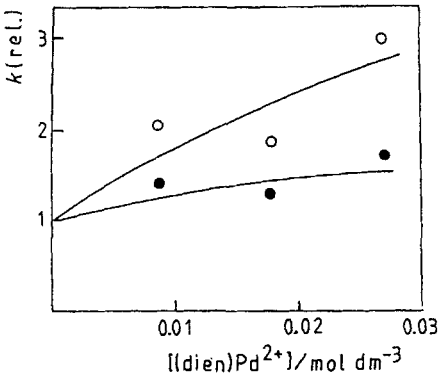


Figure 5. Effect of (dien)Pd(II) ion on depurination of the N^7-(dien)Pt(II) complex of 2′-deoxyinosine (**5**). The data at $[H^+] = 0{\cdot}1$ mol dm^{-3} (open circles) refer to $T = 333{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}19$ mol dm^{-3} and those at $[H^+] = 0{\cdot}001$ mol dm^{-3} (filled circles) to $T = 353{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}1$ mol dm^{-3}

Depurination of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyinosine (**6**) is accelerated by (dien)Pd(II) ion, the rate enhancement increasing with decreasing hydronium ion concentration (Figure 7). Since N-3 is the only available binding site in this molecule, it appears reasonable to assume that attachment of (dien)Pd(II) ion to this atom is responsible for the metal ion catalysis observed. In other words, the depurination reaction may be depicted by Scheme 3, and the observed first-order rate constant expressed by the equation

$$k(\text{obs.}) = \frac{\frac{k_1}{K_{a1}}[H^+] + k_0 + k_M K_M[(\text{dien})Pd^{2+}]}{\frac{[H^+]}{K_{a1}} + 1 + K_M[(\text{dien})Pd^{2+}]} \quad (5)$$

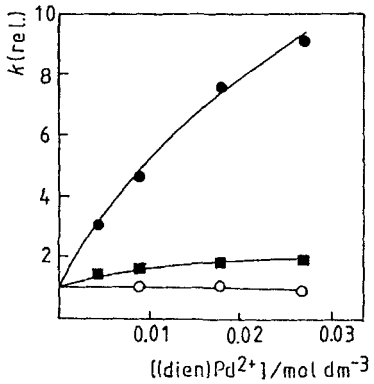


Figure 7. Effect of (dien)Pd(II) ion on depurination of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyinosine (**6**). The data at $[H^+] = 0{\cdot}1$ mol cm^{-3} (open circles) refer to $T = 333{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}19$ mol cm^{-3}, those at $[H^+] = 0{\cdot}01$ mol dm^{-3} to $T = 333{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}1$ mol dm^{-3} and those at $[H^+] = 0{\cdot}001$ mol dm^{-3} (filled circles) to $T = 353{\cdot}2$ K and $I(NaClO_4) = 0{\cdot}1$ mol dm^{-3}

Under the conditions used in the kinetic measurements $[H^+]$ is small compared with K_{a1}, and hence the term $[H^+]/K_{a1}$ may be neglected in the denominator of the right-hand side of equation (5). For comparison, the pK_{a1} value for the N^1, N^7-di$(NH_3)_3$Pt(II) complex of 9-ethylguanine is of the order of 1,[12] and probably **6** is at least one unit less basic. Accordingly, equation (5) may be approximated by the equation

$$k(\text{obs.}) = \frac{\frac{k_1}{K_{a1}}[H^+] + k_0 + k_M K_M[(\text{dien})Pd^{2+}]}{1 + K_M[(\text{dien})Pd^{2+}]} \quad (6)$$

where the sum $(k_1/K_{a1})[H^+] + k_0$ represents the first-order rate constant obtained in the absence of (dien)Pd(II) ion.

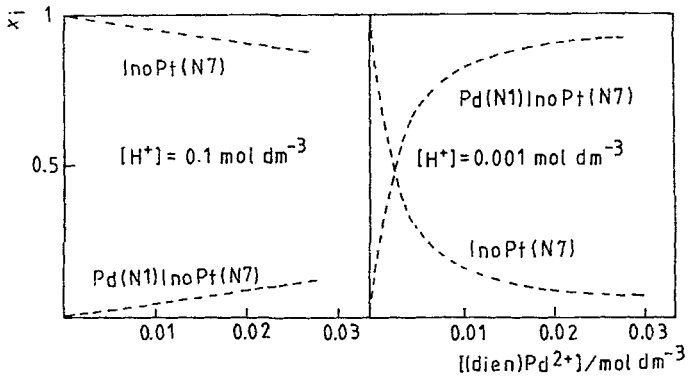
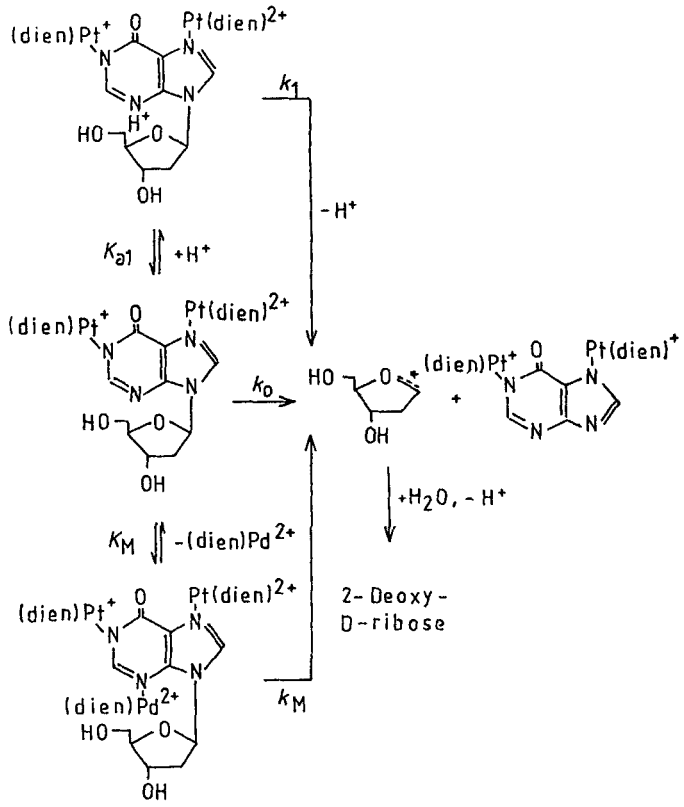


Figure 6. Distribution of (dien)Pd(II) complexes of N^7-(dien)Pt(II)–inosine at $[H^+] = 0{\cdot}1$ and $0{\cdot}001$ mol dm^{-3} ($T = 307$ K, $I = 0{\cdot}5$ mol dm^{-3}). Calculated on the basis of the data of Kim and Martin[14] by assuming that the effect of N^7-(dien)Pt(II) on deprotonation and metal ion binding at N-1 is equal to that of (dien)Pd(II) ion



Scheme 3

The values of k_1/K_{a1} and k_0 in Table 1 show that the hydronium ion catalysed and uncatalysed depurination reactions contribute almost equally to the observed rate constant at pH 3. If it is assumed that binding of the (dien)Pd(II) ion to the N-3 site destabilizes the *N*-glycosidic bond, i.e. $k_M > k_0$, metal ion catalysis may be observed under these conditions. At lower pH the reaction via the N-3 protonated species becomes so rapid that the modest rate-accelerating effect of N-3 metallation cannot be observed. Least-squares fitting of the data obtained at pH 3 gave the values of $9{\cdot}5 \times 10^{-4}\ s^{-1}$ and $28\ dm^3\ mol^{-1}$ for k_M and K_M, respectively. In other words, attachment of (dien)Pd(II) at N-3 of **6** appears to accelerate the spontaneous cleavage of the *N*-glycosidic bond by a factor of 20.

Hydrolysis of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyadenosine (7)

The pH–rate profile for depurination of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyadenosine (Figure 8), resembles those of the N-7-platinated

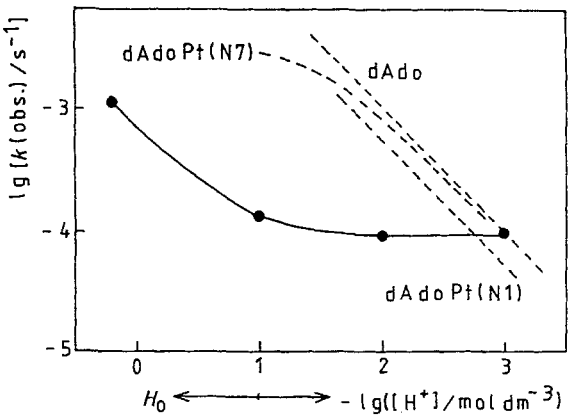


Figure 8. pH–rate profile for depurination of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyadenosine (7) at 333.2 K ($I = 0{\cdot}1$ mol dm^{-3} with $NaClO_4$). The rate profiles reported earlier[3] for 2′-deoxyadenosine (dAdo) and its N^1- and N^7-(dien)Pt(II) complexes [dAdoPt(N1), dAdoPt(N7)] are also included

complexes of 2′-deoxyinosine (**5** and **6**). In other words, the reaction is acid catalysed at low pH and uncatalysed at high pH. The spontaneous reaction is, however, 3–4 times as fast as with **5** and almost two orders of magnitude faster than with **6**, indicating that N-1, N-7-diplatinated adenine is a better leaving group than either N-7-platinated or N-1, N-7-diplatinated hypoxanthine. The N-3 site of **7** appears to be protonated less readily than that of the corresponding 2′-deoxyinosine complex, since the acid-catalysed hydrolysis of **7** is considerably slower than that of **6**.

As with the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyinosine, the (dien)Pd(II) ion considerably accelerates the depurination of N-1, N-7-diplatinated 2′-deoxyadenosine under conditions where the spontaneous depurination prevails (Figure 9). In other words, attachment of the (dien)Pd(II) ion at N-3 improves the adenine moiety as a leaving group. Least-squares fitting by equation (6) gave a value of 48 $dm^3 mol^{-1}$ for the stability constant of the 1:1 complex and a value of $6{\cdot}2 \times 10^{-4} s^{-1}$ for the first-order rate constant of its heterolysis. Accordingly, the N-3-coordinated (dien)Pd(II) ion enhances depurination by a factor of 7, less markedly than with the corresponding 2′-deoxyinosine derivative.

The results discussed above also explain why the (dien)Pd(II) ion accelerates the depurination of 2′-deoxyadenosine at pH > 3.[3] Under these conditions, the N^1, N^7-di(dien)Pd(II) complex prevails,[14] and the spontaneous depurination of this species may be expected to be approximately as rapid as acid-catalysed hydrolysis of the uncomplexed nucleoside (compare the rate profiles in Figure 8). At high concentrations of (dien)Pd(II) ion depurination is still enhanced, owing to binding of a third metal ion at N-3.

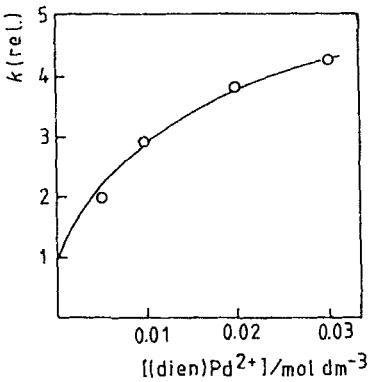


Figure 9. Effect of (dien)Pd(II) ion on depurination of the N^1, N^7-di(dien)Pt(II) complex of 2′-deoxyadenosine (**7**) at $[H^+] = 0{\cdot}01$ mol dm^{-3} ($T = 333{\cdot}2$ K, $I = 0{\cdot}1$ mol dm^{-3} with $NaClO_4$)

CONCLUSIONS

The present data, together with those reported previously,[3] allow the following conclusions. (i) Binding of a (dien)Pt(II) or (dien)Pd(II) ion to N-7 of 6-oxopurine deoxyribonucleosides (2′-deoxyinosine or 2′-deoxyguanosine) retards the acid-catalysed depurination by two orders of magnitude, owing to blocking of the preferential site of protonation. However, the spontaneous cleavage of the *N*-glycosidic bond is simultaneously accelerated. Accordingly, rate retardation is observed at pH < 4 and rate acceleration at pH > 4. With 2′-deoxyadenosine, N-7 metallation results in a significant rate-retardation only at pH < 2, i.e. under conditions where hydrolysis via N-1, N-7-diprotonated species prevails. (ii) Replacement of the N-1 proton of 6-oxopurine deoxyribonucleosides has virtually no effect on the depurination rate at pH > 1, i.e. under conditions where the reaction proceeds by N-7 protonation. In more acidic solutions a moderate rate enhancement is observed. The observed effects may be accounted for by increased electron density in the pyrimidine ring, and to a lesser extent in the imidazole ring. Depurination of 2′-deoxyadenosine is not markedly susceptible to N-1 metallation. (iii) Binding of a metal ion to the N-3 site destabilizes the *N*-glycosidic bond of both 2′-deoxyadenosine and 6-oxopurine nucleosides. Accordingly, a rate acceleration is observed under conditions where the reaction via N-3 protonation is negligible.

EXPERIMENTAL

Materials. The N^1- and N^7-(dien)Pt(II) complexes of 2′-deoxyinosine (**4** and **5**) were prepared as described previously for the corresponding complexes of inosine.[11] The N^1, N^7-(dien)Pt(II) complexes of 2′-deoxyinosine (**6**) and 2′-deoxyadenosine (**7**) were obtained by stirring the free nucleoside in aqueous solution with a double amount of aquated (dien)Pt(II) ion at room temperature. With 2′-deoxyinosine the pH was adjusted to 8 and with 2′-deoxyadenosine to 4. The initially formed 1:1 complexes completely disappeared after 40 h (detected by high-performance liquid chromatography (HPLC)). The reaction mixtures were fractionated by liquid chromatography as described previously.[15] 2′-Deoxyinosine and 2′-deoxyadenosine were obtained from Sigma. [(dien)]PtI]I and [(dien)PdI]I were prepared as described earlier,[16] and converted to the corresponding aquo ions by treating the salts in the dark with 1·95 equiv. of $AgNO_3$.

Kinetic measurements. The rate constants for the depurination reactions were obtained by the HPLC technique described previously.[5,17]

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