The Mechanism of Complex Formation Reactions of Diethylenetriaminepalladium(II) with Nucleosides: A Case of Anation, Aquation, and Manipulation

Ernst L. J. Breet,† and Rudi van Eldik*

Institute for Physical Chemistry, University of Frankfurt, Niederurseler Hang, 6000 Frankfurt/Main, Federal Republic of Germany

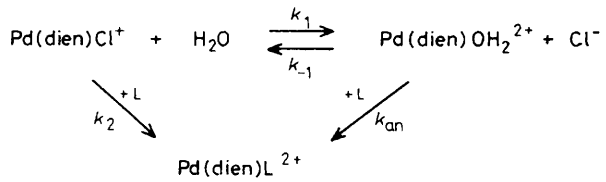
A kinetic study of the complex formation reactions of Pd(dien)Cl^+ and Pd(dien)OH_2^{2+} (dien = diethylenetriamine) with nucleosides indicated that the nucleic acid entities enter the co-ordination sphere according to three different mechanisms, which are distinguished on the basis of having as rate-determining step the anation of Pd(dien)OH_2^{2+} by L (L = nucleoside) either singly or in combination with the aquation of either Pd(dien)Cl^+ or Pd(dien)L^{2+}.

The substitution reactions at the square-planar Pd(dien)Cl^+ and Pd(dien)OH_2^{2+} (dien = diethylenetriamine) centres generally proceed according to the mechanism in Scheme 1, in which the rate-determining aquation step (k_1) is followed by a fast anation step (k_{an}) such that $k_{obs} = k_1 + k_2[L]$ for L = strong nucleophile and $k_{obs} = k_1$ for L = weak nucleophile or the dien ligand being sterically hindered through methyl or ethyl substituents.[1,2]

We measured k_{obs} for L = nucleosides as a function of [L] and $[Cl]_T$ at neutral pH, a fixed [complex] and ionic strength and various temperatures and pressures using stopped-flow spectrophotometry (λ 340 nm) to contribute to the understanding of the substitution behaviour of related antitumour complexes.[3,4] The major results are reported in this communication, a fully detailed description being given in a later paper[5] covering this investigation and its extension to the corresponding nucleic free bases and 5′-monophosphate nucleotides.

The most surprising aspect of the investigated reactions is that, contrary to normal square-planar substitution, the rate-determining step is not the aquation of Pd(dien)Cl^+, but rather the subsequent anation of Pd(dien)OH_2^{2+}. This is clearly illustrated by the rate constants k_{obs} in Table 1, which predict values of the aquation rate constant k_1 (intercept of k_{obs} *vs.* [L] for $[Cl]_T = 1 \times 10^{-3}$) totally different from the known value[1] of $k_1 \sim 40\ s^{-1}$ but fit kinetic expressions yielding values of k_{an} (last column) almost identical to the directly determined (slope of k_{obs} *vs.* [L] for $[Cl]_T = 0$) anation rate

† On leave from the Research Unit for Chemical Kinetics, Potchefstroom University for C.H.E., 2520 Potchefstroom, Republic of South Africa.



Scheme 1. Equations (1) and (2).

constants k_{an} (penultimate column) under all conditions ($0 < [Cl]_T < 5 \times 10^{-3}$ mol dm^{-3}). The fast anation step following the rate-determining aquation step in normal substitution behaviour is slowed down to such an extent by the nucleosides that it becomes rate-determining in all cases.

The kinetic expressions referred to above are associated with the various mechanisms according to which the complexation occurs. A distinction amongst *three* possible mechanisms can be made depending on the complexation capability and concentration of the nucleoside concerned. The term $k_{an}[L]$ is determined by the complexation capability and its magnitude relative to that of k_1 and $k_{-1}[Cl^-]$ therefore governs the condition for a given mechanism to operate as illustrated below.

The spontaneous aquation preceding the rate-determining anation can under conditions where $k_{an}[L] < k_1, k_{-1}[Cl^-]$ be treated as a fast pre-equilibration and equation (3) applies, with $K_1 = k_1/k_{-1} = 1 \times 10^{-3}$ mol dm^{-3}.[6] Figure 1(a) presents a plot of k_{obs} *vs.* $K_1/(K_1 + [Cl^-])$ for the complexation with adenosine as a representative example, the average of the resulting values of k_{an} being included in Table 1.

The data for a more reactive nucleoside like inosine cannot be presented in the same way as in Figure 1(a) since the values of k_{obs} in Table 1 measured for the direct anation of $Pd(dien)OH_2^{2+}$ do not fit those measured under the remaining conditions ($1 \times 10^{-3} < [Cl]_T < 5 \times 10^{-3}$ mol dm^{-3}) on applying equation (3). The rate of anation is such that $k_{an}[L] \sim k_1, k_{-1}[Cl^-]$, implying that the preceding aquation can no longer be regarded as a fast pre-equilibration but rather as a steady-state controlling step requiring the utilization of the steady-state approximation to fit the data. The corresponding rate-law [equation (4)] offers in its inverse form the possibility to fit the data by plotting $1/k_{obs}$ *vs.* $[Cl^-]/[L]$. This is done for inosine in Figure 1(b) and realistic values of k_1 and k_{an} are obtained.

$$k_{obs} = k_{an}K_1[L]/(K_1 + [Cl^-]) \quad (3)$$

$$k_{obs} = k_{an}k_1[L]/(k_{-1}[Cl^-] + k_{an}[L]) \quad (4)$$

$$k_{obs} = k_{aq} + k_{an}[L] \quad (5)$$

A third mechanistic case is presented by nucleosides with poor complexation capability. The slope and intercept of the k_{obs} *vs.* [L] plots ($0 < [Cl]_T < 5 \times 10^{-3}$ mol dm^{-3}) in Figure 1(c) for uridine as a representative example were shown to be equal to the rate constants k_{an} and k_{aq} of the forward anation and reverse aquation reactions respectively. This was done experimentally by acidifying $Pd(dien)L^{2+}$ to effect the reverse aquation reaction and checking that the same intercept is obtained as when the forward anation reaction with $Pd(dien)OH_2^{2+}$ is performed, as shown by the dashed and solid line for $[Cl]_T = 0$ in Figure 1(c) respectively. The rate law is thus given by equation (5), with both right side terms showing a $[Cl^-]$ dependence such that the pre-equilibrium treatment is applicable to the forward anation reaction to obtain values of k_{an} for inclusion in Table 1 and a competitive reaction that

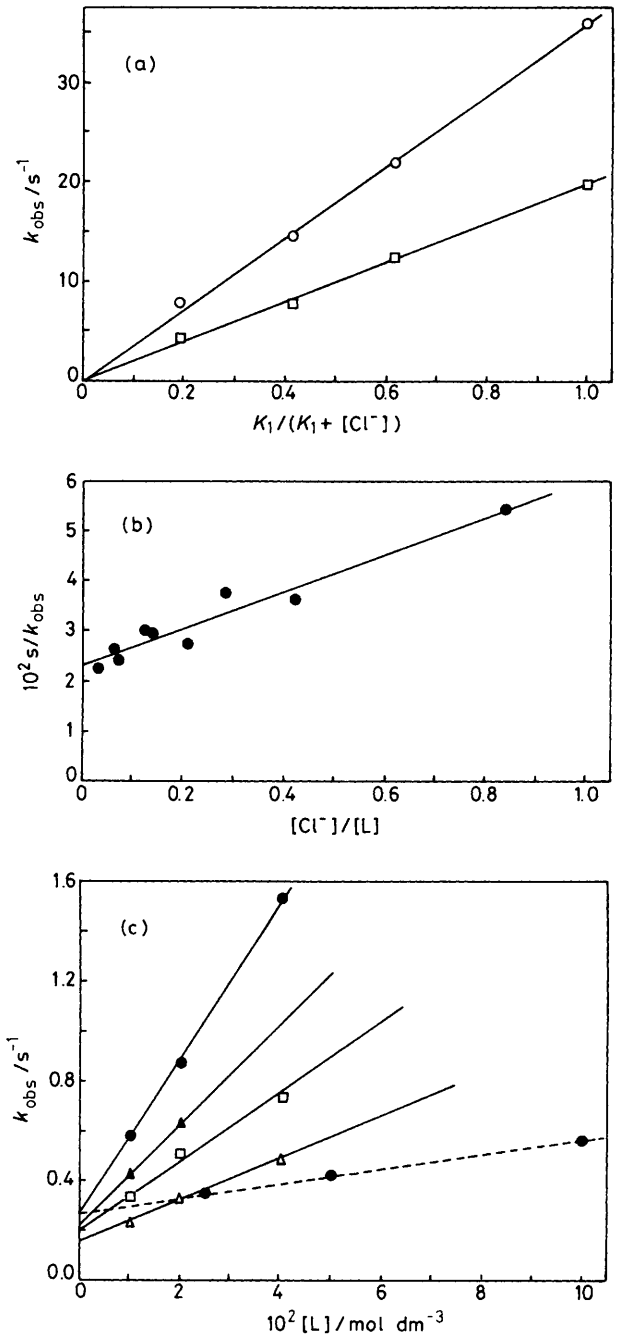


Figure 1. Graphical representation of rate laws [equations (3)—(5)] for various mechanisms of complexation of $Pd(dien)Cl^+$ with nucleosides L. (a), Pre-equilibrium model, equation (3), L = adenosine, [L] = 2×10^{-2} (○) and 1×10^{-2} (□) mol dm^{-3}; $k_{an} = (17.9 \pm 0.2) \times 10^2$ (○) and $(19.9 \pm 0.3) \times 10^2$ (□) dm^3 mol^{-1} s^{-1}. (b) Steady-state model, equation (4), L = inosine, $k_1 = 43.2 \pm 2.3$ s^{-1}; $k_{an} = (269 \pm 27) \times 10^2$ dm^3 mol^{-1} s^{-1}. (c) Reverse aquation model, equation (5), L = uridine, $[Cl]_T = 0$ (●), 1×10^{-3} (▲), 2×10^{-3} (□), and 5×10^{-3} (△) mol dm^{-3}.

probably involves ion-pairing is imaginable for the reverse aquation reaction in the presence of chloride ion. The rate constants are such that $k_{an}[L] \sim k_{aq}$, indicating that the reverse aquation reaction becomes sufficiently significant to contribute to the overall observed rate constant.

Table 1. Rate data for reaction of $Pd(dien)OH_2^{2+}$ ($[Cl]_T = 0$) and $Pd(dien)Cl^+$ ($1 \times 10^{-3} < [Cl]_T < 5 \times 10^{-3}$ mol dm^{-3}) with nucleosides. [complex] = 1×10^{-3} mol dm^{-3}; ionic strength = 0.1 mol dm^{-3}; T = 25 °C; λ = 340 nm.

Nucleoside L	[L]/mol dm^{-3}	k_{obs}/s^{-1}				k_{an}/10^2 dm^3 mol^{-1} s^{-1}	
		$[Cl]_T = 0$	$[Cl]_T = 1 \times 10^{-3}$	$[Cl]_T = 2 \times 10^{-3}$	$[Cl]_T = 5 \times 10^{-3}$	From $[Cl]_T$ = 0 results	From eq. (3), (4), or (5)
Adenosine	1×10^{-2}	19.9 ± 0.4	12.4 ± 0.2	7.8 ± 0.1	4.3 ± 0.2	18.2 ± 0.7	18.9 ± 1.4
	2×10^{-2}	36.0 ± 2.2	21.9 ± 0.8	14.5 ± 0.3	7.7 ± 0.1		
Inosine	5×10^{-3}	132 ± 2	33.1 ± 0.8	26.6 ± 0.0	18.3 ± 0.1	263 ± 1	269 ± 27
	1×10^{-2}	263 ± 10	37.3 ± 0.6	34.0 ± 0.4	27.5 ± 0.9		
	2×10^{-2}		43.6 ± 1.2	41.3 ± 1.2	37.0 ± 0.2		
Uridine	1×10^{-2}	0.58 ± 0.01	0.43 ± 0.01	0.34 ± 0.01	0.23 ± 0.00	0.31 ± 0.01	0.31 ± 0.03
	2×10^{-2}	0.87 ± 0.01	0.63 ± 0.01	0.52 ± 0.01	0.33 ± 0.00		
	4×10^{-2}	1.53 ± 0.03		0.74 ± 0.01	0.49 ± 0.02		

The temperature and pressure dependencies of the rate constants k_{obs} in Table 1 ($[Cl]_T = 0$) were also studied. Despite a small variation in the values of $\Delta H^{\ddagger}$ amongst the various nucleosides, an activation enthalpy order that neatly corresponds with the anation rate constant order in Table 1 could be deduced. The values of $\Delta V^{\ddagger}$ show that there is practically no pressure dependence. This means that during the associative bond formation suggested by the negative values of $\Delta S^{\ddagger}$ the overlap of radii hardly occurs, explaining the relatively poor complexation capabilities of the nucleosides.

To summarize, the complex formation reactions of the palladium(II) dien species with nucleosides have different rate-determining steps, *viz.* anation [of $Pd(dien)OH_2^{2+}$] or a combination of anation and aquation [of $Pd(dien)Cl^+$ or $Pd(dien)L^{2+}$], 'manipulated' by the nature and concentration of the nucleoside under consideration.

The authors gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. E. L. J. B. thanks the Alexander von Humboldt-Stiftung for a fellowship and the South African Council for Scientific and Industrial Research and the Potchefstroom University for Christian Higher Education for sabbatical leave bursaries.

Received, 25th June 1986; Com. 881

References

1 R. van Eldik, E. L. J. Breet, M. Kotowski, D. A. Palmer, and H. Kelm, *Ber. Bunsenges. Phys. Chem.*, 1983, **87**, 904.
2 E. L. J. Breet and R. van Eldik, *Inorg. Chem.*, 1984, **23**, 1865.
3 'Platinum, Gold and Other Metal Chemotherapeutic Agents,' ed. S. J. Lippard, ACS Symp. Ser. 209, Washington, 1983.
4 'Platinum Coordination Complexes in Cancer Chemotherapy,' eds. M. P. Hacker, E. B. Douple, and I. H. Krakoff, Martinus Nijhoff, Boston, 1984.
5 E. L. J. Breet and R. van Eldik, to be published.
6 M. Kotowski and R. van Eldik, *Inorg. Chem.*, 1984, **23**, 3310.