Complex-formation Reactions of Dichloro(L-methioninato)-palladium(II) with Inosine and Inosine 5'-Monophosphate. Labilization induced by the S-Donor Chelate‡

Frans F. Prinsloo,† Jacobus J. Pienaar† and Rudi van Eldik*
Institute for Inorganic Chemistry, University of Erlangen-Nürnberg, Egerlandstrasse 1, 91058 Erlangen, Germany

The kinetics and mechanism of the complex-formation reactions of $[Pd(met)Cl_2]^-$ (met = L-methionine anion) with inosine and inosine 5'-monophosphate were studied in detail as a function of the chloride and nucleophile concentrations, temperature and pressure in weakly acidic aqueous solutions. Two consecutive reaction steps which both depend on the nucleophile concentration were observed. A comparison with rate data for the corresponding ethylenediamine and substituted ethylenediamine complexes reveals the significant lability induced by the S-donor chelate in $[Pd(met)Cl_2]^-$. The reported activation parameters underline the operation of an associative ligand-substitution mechanism under all conditions.

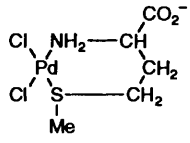
Complex-formation and ligand-substitution reactions of model *cis*-bis(amine)palladium(II) complexes with nucleobases, nucleosides and nucleotides have been studied in much detail in recent years.[1-4] The goal of such studies was to contribute toward a mechanistic understanding of the interaction of the related anticancer drug *cis*-platin, *cis*-$[Pt(NH_3)_2Cl_2]$, with DNA and its constituents.[5] These investigations have revealed the versatile complex-formation kinetics observed for such reactions as well as the steric and nucleophilic control over such processes.[3,4]

A number of reports have dealt with the interaction of *cis*-platin with L-methionine (Hmet) to produce S,N-chelated platinum(II) complexes of the type $[Pt(NH_3)_2(met\text{-}S,N)]$ and $[Pt(met\text{-}S,N)_2]$.[6-8] The latter complex is one of the few characterized metabolites of *cis*-platin and has been isolated from urine.[9] Recently we extended our earlier work on model *cis*-bis(amine)palladium(II) complexes[1-4] to a study of the steric control over the complex-formation and chelation kinetics with L-methionine and *S*-methyl-L-cysteine.[10] Once such ligands are present in the co-ordination sphere of platinum(II) and palladium(II) complexes they may significantly affect the subsequent substitution behaviour, for instance lead to the loss of ammonia and control the interaction with DNA constituents.[6,10]

We have now performed a detailed investigation of the complex-formation kinetics of $[Pd(met)Cl_2]^-$ with inosine and inosine 5'-monophosphate as a function of chloride and nucleophile concentration, temperature and pressure. A comparison with corresponding data for the reactions with complexes of the type $[Pd(R_2NCH_2CH_2NR_2)Cl_2]$ (R = H, Me or Et) enables us to comment on the labilization induced by the S,N-chelate.

† Work performed in part at the Institute for Inorganic Chemistry, University of Witten/Herdecke, Witten, Germany. On leave from the Department of Chemistry, Potchefstroom University for CHE, Potchefstroom, South Africa.

‡ *Supplementary data available* (No. SUP 57103, 17 pp.): dependences of k_{obs} on temperature, pressure and concentration. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1995, Issue 1, pp. xxv–xxx.



Experimental

Materials.—The complex $[Pd(Hmet)Cl_2]$ was synthesized and characterized according to literature procedures for the synthesis of palladium and platinum complexes of methionine and its derivatives,[7,11-13] and a modified method adopted before,[14] to eliminate the formation of mixed species. The carboxylate group is protonated in acidic aqueous media; deprotonation occurs above pH 2.5 to form $[Pd(met)Cl_2]^-$. Chemical analysis (Beller Mikroanalytisches Laboratorium, Göttingen) confirmed the purity of the isolated complex. It was converted in solution into the diaqua complex by treating it with 2 equivalents of $AgClO_4$ as described.[15] Inosine and inosine 5'-monophosphate were obtained from Sigma and used without further purification. The pH of the test solutions was adjusted with $HClO_4$ and NaOH, and measured before and after the reactions. The reference electrode of the pH meter was filled with NaCl instead of KCl to prevent precipitation of $KClO_4$, since $NaClO_4$ was used to adjust the ionic strength of all test solutions to 0.5 mol dm^{-3} in the final reaction mixture.

Measurements.—The UV/VIS spectra were recorded on a Hewlett-Packard 8452A diode-array spectrophotometer and a Bio Sequential SX-17MV (Applied Photophysics) stopped-flow spectrofluorimeter. In the latter case time-dependent spectra were generated from individual absorbance measurements at different wavelengths. Infrared spectra were recorded on a Bruker IFS 113 FT-IR instrument. The pH titrations were performed on an automatic titrator (Metrohm SM-Titrino 702) coupled to a Metrohm electrode and calibrated according to the Gran method.[16a] The titrator was equipped with a reactor in which well controlled pH and temperature conditions were possible. All titrations were performed under an argon

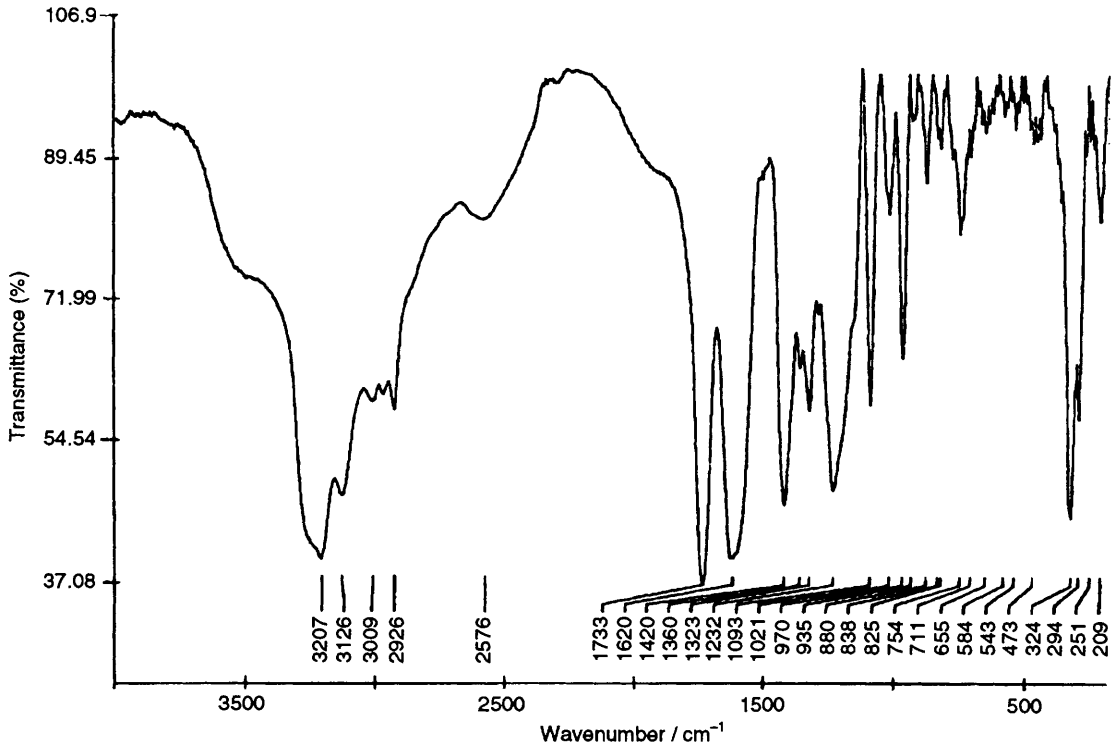


Fig. 1 Infrared spectrum of the palladium(II) complex of methionine

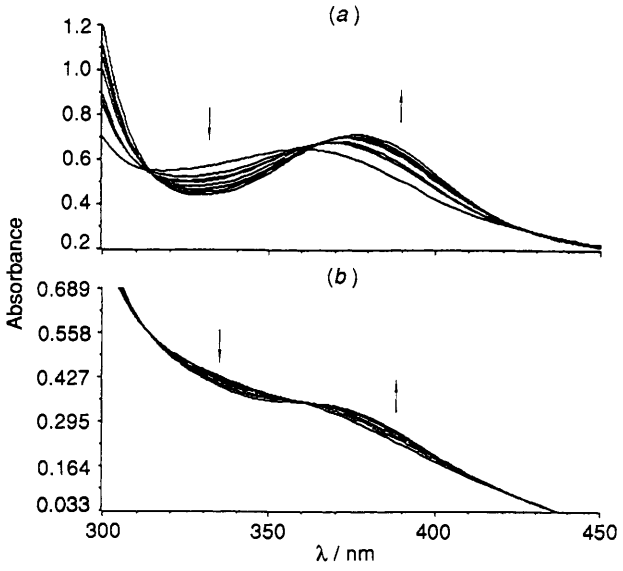


Fig. 2 Spectrophotometric determination of the stability constants in equations (1)–(3). Experimental conditions: $[Pd^{II}]_T$ = 1 mmol dm^{-3}; optical path = 1.0 cm; pH 4; I = 0.1 mol dm^{-3}. Spectrophotometric titration of (*a*) $[Pd(met)Cl(H_2O)]$ with Cl^- {$[Pd(met)Cl(H_2O)]$, λ_{max} = 355–365 nm; $[Pd(met)Cl_2]^-$, λ_{max} = 370–380 nm}, (*b*) $[Pd(met)(H_2O)_2]^+$ with Cl^-

atmosphere. The data from the titrations were fitted with a PSEQUAD program[16b] to obtain the different equilibrium constants. Kinetic measurements at ambient pressure were performed on a Durrum D 110 stopped-flow spectrophotometer which was run on-line with an IBM compatible personal computer, and data fitting was performed with the OLIS KINFIT set of programs.[16c] Experiments at elevated pressure were performed on a laboratory-made high-pressure stopped-flow unit.[17] All kinetic measurements were performed under pseudo-first-order conditions, *i.e.* an excess of ligand was employed. The reported pseudo-first-order rate constants are the averages from at least 10 kinetic runs. All instruments were thermostatted at ± 0.1 °C.

Results and Discussion

Equilibrium Studies.—Infrared analysis on $[Pd(Hmet)Cl_2]$ (Fig. 1) confirms literature findings that platinum(II) and palladium(II) are chelated by methionine and other related amino acids through the nitrogen and sulfur atom.[18–21] The sharp $\delta(NH_2)$ peak at 1620 cm^{-1} and doublet in the range 324–294 cm^{-1} are indicative of chelation *via* the nitrogen and sulfur atoms, respectively. The S–M stretching vibrations have been observed in the ranges 385–378 and 320–305 cm^{-1} for DL-methionine and S-methyl-L-cysteine complexes of palladium(II)[18] and for *cis*-$[PtX_2(SMe_2)_2]$ (X = Cl or Br).[22] The $\nu_{asym}(CO_2)$ mode occurs at 1733 cm^{-1}. This high frequency denotes that the carboxylic group is neither co-ordinated to the metal nor hydrogen bonded, since saturated monobasic aliphatic acids, which do not carry electron-attracting substituents, display a strong band in the range 1725–1705 cm^{-1}.[18] Co-ordinated methionine has a pK_a = 2.5.[21] Thus apart from the normal spontaneous solvolysis when $[Pd(Hmet)Cl_2]$ is dissolved in acidic aqueous media, deprotonation of the carboxylic acid group also occurs. The solvolysis products are $[Pd(met)Cl(H_2O)]$ and $[Pd(met)(H_2O)_2]^+$. The UV/VIS spectrum of such a solution exhibits an absorption maximum at 360 nm. Addition of an excess of Cl^- causes a shift to 376 nm (ε = 739 dm^3 mol^{-1} cm^{-1}) [Fig. 2(*a*)]. The $[Pd(met)(H_2O)_2]^+$ species exhibits a shoulder at 360 nm, which gradually shifts to 370 nm on addition of small amounts of Cl^- and, upon addition of an excess of Cl^-, to 380 nm [Fig. 2(*b*)] according to the complex-formation reactions outlined in equations (1)–(3).

$$[Pd(Hmet)(H_2O)_2]^{2+} \overset{K_a}{\rightleftharpoons} [Pd(met)(H_2O)_2]^+ + H^+ \quad (1)$$

$$[Pd(met)(H_2O)_2]^+ + Cl^- \overset{K_1}{\rightleftharpoons} [Pd(met)Cl(H_2O)] + H_2O \quad (2)$$

$$[Pd(met)Cl(H_2O)] + Cl^- \overset{K_2}{\rightleftharpoons} [Pd(met)Cl_2]^- + H_2O \quad (3)$$

Values for K_1 were determined spectrophotometrically by recording spectra of 1 mmol dm^{-3} $[Pd(met)(H_2O)_2]^+$ (ε = 507 dm^3 mol^{-1} cm^{-1}) in the presence of between 0.08 and 1.6 mmol dm^{-3} Cl^- [Fig. 2(*b*)]. Analysis of the spectra at 370 nm resulted in a K_1 value of 1125 ± 115 dm^3 mol^{-1}. Similarly by recording spectra of $[Pd(met)Cl_2]^-$ (ε = 303 dm^3 mol^{-1} cm^{-1}) in the presence of between 3 and 50 mmol dm^{-3} Cl^- [Fig. 2(*a*)] a value for K_2 = 171 ± 13 dm^3 mol^{-1} was determined.

The diaqua complex can be titrated with base in order to determine its acid-dissociation constant. A series of titrations at 0.1 mol dm^{-3} ionic strength and 25 °C gave pK_3 = 5.2. The direct formation of hydroxo-bridged dimeric species was also evident from the titration curves, equations (4) and (5).

$$[Pd(met)(H_2O)_2]^+ \overset{K_3}{\rightleftharpoons} [Pd(met)(H_2O)(OH)] + H^+ \quad (4)$$

$$2[Pd(met)(H_2O)(OH)] \longrightarrow [(met)Pd(\mu\text{-}OH)_2Pd(met)] + 2H_2O \quad (5)$$

The pK_a value of the $[Pd(met)Cl(H_2O)]$ complex was determined by titrating a solution of $[Pd(met)Cl_2]^-$ in 0.1 mol dm^{-3} NaCl with base in a similar way as outlined before.[14] The titration curves gave pK_a = 7.9 ± 0.1. Surprisingly, the acid-dissociation constants in equations (4) and (6), *i.e.* pK_3 =

$$[Pd(met)Cl(H_2O)] \overset{K_4}{\rightleftharpoons} [Pd(met)(OH)Cl]^- + H^+ \quad (6)$$

5.2 ± 0.1 and pK_4 = 7.9 ± 0.1, are very similar to those reported for similar equilibria in the $[Pd(en)Cl_2]$ system (en = ethane-1,2-diamine), *viz.* pK_3 = 5.6 and pK_4 = 7.3,[14] which implies that they represent the acidity of the H_2O molecule *trans* to a N donor.

In general the co-ordinated water molecule *trans* to the S donor atom is expected to be significantly more substitution labile, accompanied by a significantly higher pK_a value, *i.e.* closer to that of unco-ordinated water. The reported thermodynamic and equilibrium constants for equations (1)–(4) and (6) can be used to construct distribution curves for the different species present as function of pH and $[Cl^-]$. The molar fraction of the species was calculated from the mass-balance equations. The distribution curves are reported in Fig. 3(*a*) and (*b*). The data in Fig. 3(*b*) clearly demonstrate the importance of hydroxo species at physiological pH (≈7), which are only present at very low levels at pH 3. A comparison of the plots in Fig. 3 with those reported for the en[14] and $Me_2NCH_2CH_2NMe_2$ (tmen)[23] systems clearly demonstrates that a smaller fraction of chloroaqua species is produced in the met system. Such distribution curves also demonstrate the important influence of the free $[Cl^-]$ especially in terms of the large variation in $[Cl^-]$ under physiological conditions. The data in Fig. 3(*b*) were used to determine a condition under which no significant variation in the rate constants as a function of pH is expected. Therefore, pH 4 was selected for all the kinetic experiments outlined in the following section. At this pH the deprotonation of the aqua complexes produced in equations (1)–(6) is ruled out in view of the values of K_3 and K_4.

Kinetic Measurements.—At pH 4 only the N^7 position (pK_a = 1.2)[24] of inosine (Ino) and inosine 5′-monophosphate (IMP) will bind to the central metal atom, since at this pH the N^1 position (pK_a 8.88)[24] is protonated. Binding through the N^7 position at neutral pH has been verified by many investigations.[25–34] It is also expected that at this pH the 5′-monophosphate residue of the nucleotide ($pK_a \approx 6$) will not bind to the central metal atom, which can lead to additional complications in the mechanism of complex formation at higher pH.[35] According to reasons outlined before,[36] all experiments in this study involving reactions with Ino and IMP were always performed in an excess of chloride where the speciation could be well predicted and no significant change in chloride concentration would occur during the substitution process. Reactions with the $[Pd(met)(H_2O)_2]^+$ species were not performed.

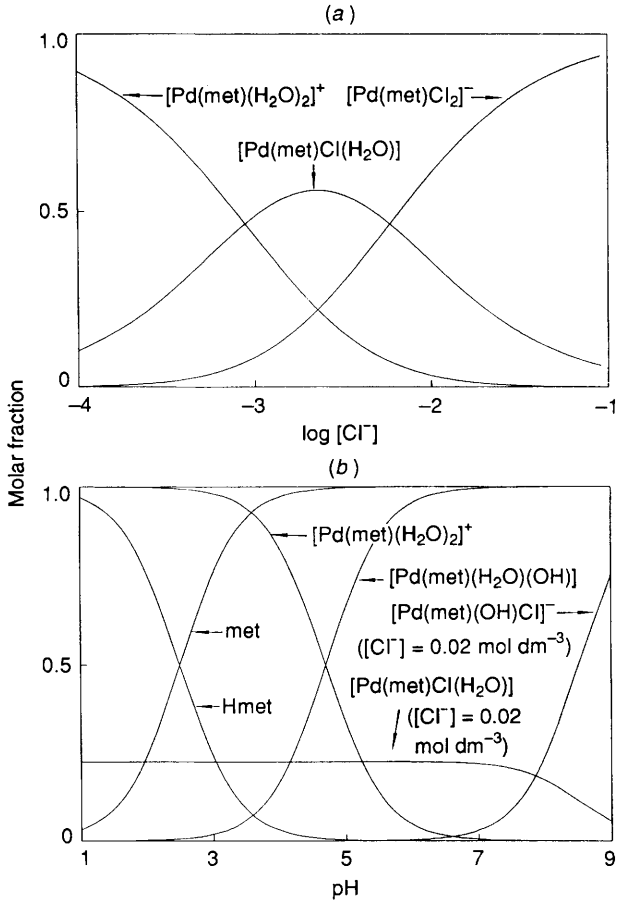


Fig. 3 Distribution curves of various palladium(II) complexes. Conditions: 25 °C; I = 0.5 mol dm^{-3}; $[Pd^{II}]_T = 5 \times 10^{-4}$ mol dm^{-3}. (*a*) Molar fraction as function of $[Cl^-]$, pH 4. (*b*) Molar fraction as function of pH for the $[Pd(met)Cl_2]^-$ and $[Pd(met)(H_2O)_2]^+$ systems

On treating the dichloro system with Ino and IMP two steps were evident from the repetitive scan spectra and absorbance *vs.* time traces recorded under such conditions (Figs. 4 and 5). In a typical experiment repetitive scan spectra were constructed from absorbance *vs.* time traces recorded at constant-wavelength intervals (typically $\Delta\lambda$ = 5 nm). In this way multiple-wavelength kinetic data are generated which are arranged in matrix form with the spectra occupying the rows and the kinetic profiles occupying the columns. Each row vector contains a spectrum, each column vector a kinetic trace. A typical data set may comprise absorbance measurements taken at several hundred time points and several hundred wavelengths. From the repetitive-scan spectra and absorbance *vs.* time traces it is clear that the first step is much faster than the second, such that in most cases it was possible to fit both steps separately to a first-order decay.

The dependence of k_{obs} on the nucleophile concentration for the first (Fig. 6) and second reaction step (Fig. 7) exhibits very similar kinetic behaviour to those reported for ethylenediamine and substituted ethylenediamine systems.[1–4] From Figs. 6 and

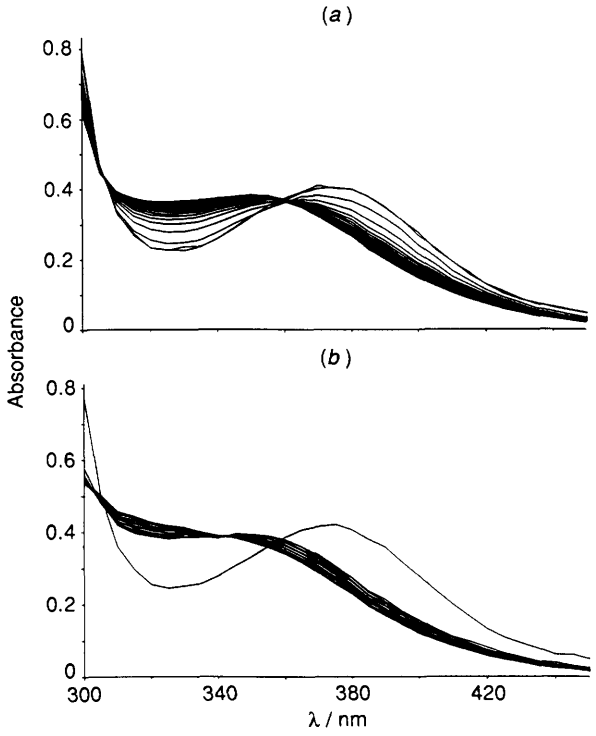


Fig. 4 Rapid-scan spectra recorded for the reaction of [Pd(met)-$Cl(H_2O)$] with Ino. Conditions: 5 °C; I = 0.5 mol dm^{-3}; pH 4; $[Pd^{II}]_T = 5 \times 10^{-4}$ mol dm^{-3}; [Ino] = 1×10^{-2} mol dm^{-3}. (*a*) $[Pd(met)Cl(H_2O)] + Ino \longrightarrow [Pd(met)Cl(Ino)] + H_2O$, Δt = 0.005 s; (*b*) $[Pd(met)(Ino)(H_2O)]^+ + Ino \longrightarrow [Pd(met)(Ino)_2]^+ + H_2O$, Δt = 0.05 s

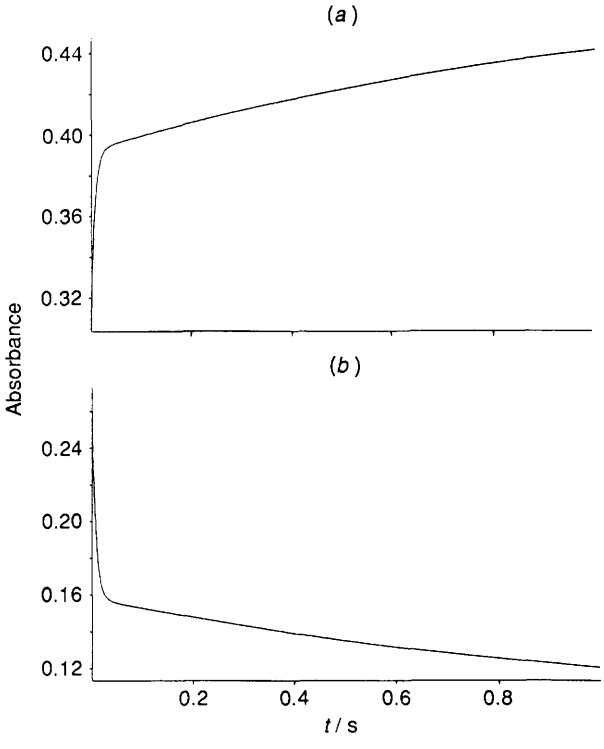


Fig. 5 Two-exponential fit to the absorbance *vs.* time traces taken from Fig. 4(*b*): λ = 315(*a*) 400 nm (*b*)

7 it is clear that k_{obs}, for the first step at $[Cl^-] < 0.1$ mol dm^{-3} and for the second step at $[Cl^-] < 0.02$ mol dm^{-3}, for both nucleophiles, exhibits a non-linear dependence on the nucleophile concentration. Such plots for the first step show

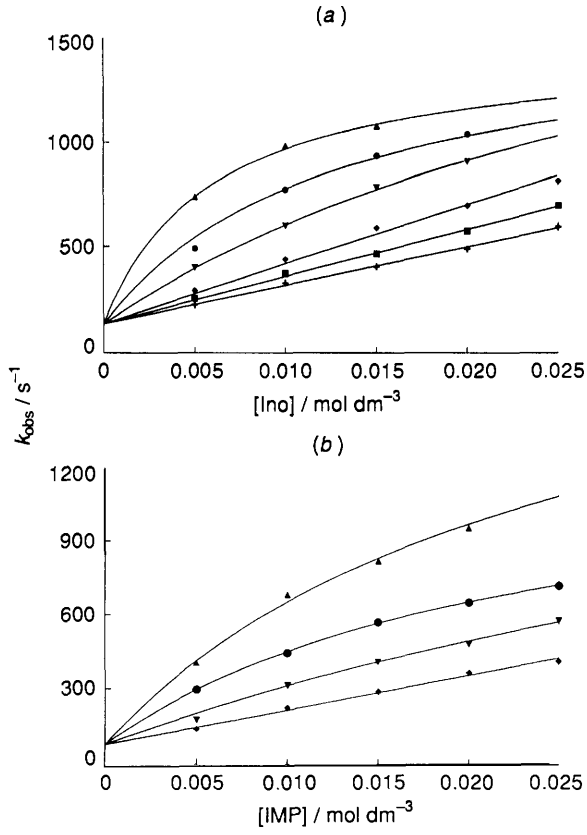


Fig. 6 Plots of k_{obs} *versus* $[L]_T$ as function of $[Cl^-]$ for the overall reaction in equations (7) and (8). Conditions: I = 0.5 mol dm^{-3}; 25 °C; pH 4; $[Pd^{II}]_T = 5 \times 10^{-4}$ mol dm^{-3}. L = Ino (*a*) or IMP (*b*). $[Cl^-]$: (*a*) 0.02 (▲), 0.05 (●), 0.1 (▼), 0.15 (◆), 0.2 (■), 0.3 (+); (*b*) 0.02 (▲), 0.05 (●), 0.1 (▼) and 0.2 mol dm^{-3} (◆)

distinct intercepts which can be interpreted in terms of the reverse aquation reaction. These trends are in agreement with the mechanisms outlined in equations (7), (8) and (9), (10) under

$$[Pd(met)Cl_2]^- + H_2O \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} [Pd(met)Cl(H_2O)] + Cl^- \quad (7)$$

$$[Pd(met)Cl(H_2O)] + Nu \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} [Pd(met)Cl(Nu)] + H_2O \quad (8)$$

$$[Pd(met)Cl(Nu)] + H_2O \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} [Pd(met)(Nu)(H_2O)]^+ + Cl^- \quad (9)$$

$$[Pd(met)(Nu)(H_2O)]^+ + Nu \xrightarrow{k_8} [Pd(met)(Nu)_2]^+ + H_2O \quad (10)$$

the condition that the steady-state approximation applies to the aquachloro or the aquanucleophile complex species, respectively. The corresponding rate equations are given in (11a) and (12a) which can be rewritten in the linearized forms (11b) and (12b), respectively. The experimental data in Figs. 6

$$k_{obs} = (k_5k_6[Nu] + k_{-5}k_{-6}[Cl^-])/(k_{-5}[Cl^-] + k_6[Nu]) \quad (11a)$$

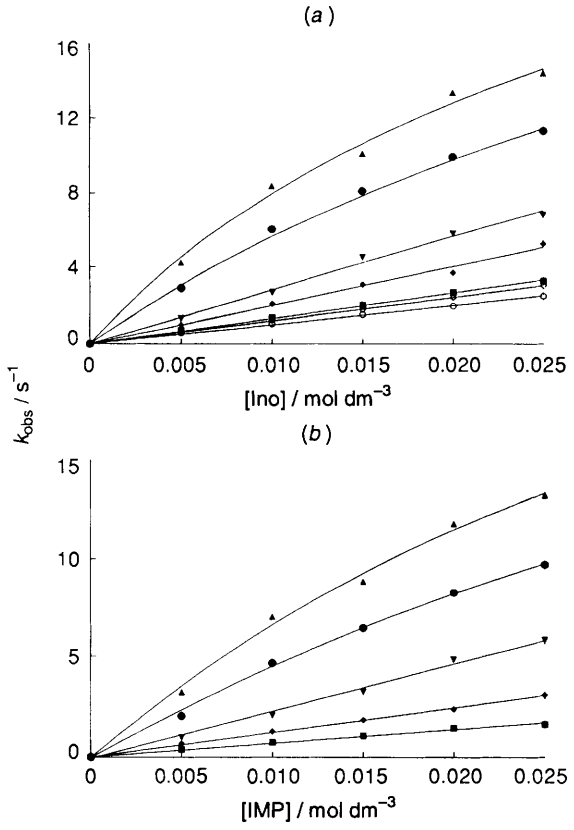


Fig. 7 Plots of k_{obs} *versus* $[L]_T$ as function of $[Cl^-]$ for the overall reaction in equations (9) and (10). Conditions: as in Fig. 6. L = Ino (*a*) or IMP (*b*). $[Cl^-]$: (*a*) 0.01 (▲), 0.02 (●), 0.05 (▼), 0.1 (◆), 0.15 (■), 0.2 (◇), 0.3 (○); (*b*) 0.01 (▲), 0.02 (●), 0.05 (▼), 0.1 (◆) and 0.2 mol dm^{-3} (■)

$$(k_{obs} - k_{-6})/[Nu] = (-k_{obs}k_6/k_{-5}[Cl^-]) + (k_5k_6/k_{-5}[Cl^-]) \quad (11b)$$

$$k_{obs} = k_7k_8[Nu]/(k_{-7}[Cl^-] + k_8[Nu]) \quad (12a)$$

$$1/k_{obs} = ([Cl^-]/k_8K_7[Nu]) + (1/k_7) \quad (12b)$$

($[Cl^-] < 0.1$ mol dm^{-3}) and 7 ($[Cl^-] \leqslant 0.02$ mol dm^{-3}) nicely conform to this requirement. This was verified by plotting $(k_{obs} - k_{-6})/[Ino]$ *versus* $-k_{obs}/[Cl^-]$ (first step) and $1/k_{obs}$ *versus* $[Cl^-]/[Nu]$ (second step). The values of k_5, k_6, k_7 and k_8, were determined from the slope and intercepts of such plots. It follows that $k_5 = (1.9 \pm 0.5) \times 10^3$ (Ino) and $(1.7 \pm 0.4) \times 10^3$ s^{-1} (IMP), $k_{-5} = (2.5 \pm 0.3) \times 10^5$ (Ino) and $(3.0 \pm 0.7) \times 10^5$ dm^3 mol^{-1} s^{-1} (IMP), $k_6 = (9.0 \pm 1.3) \times 10^5$ (Ino) and $(4.4 \pm 1.0) \times 10^5$ dm^3 mol^{-1} s^{-1} (IMP), $k_{-6} = 136$ (Ino) and 80 s^{-1} (IMP), $k_7 = 28 \pm 14$ (Ino) and 47 ± 61 s^{-1} (IMP), $k_{-7} = (5.2 \pm 0.7) \times 10^2$ (Ino) and $(1.9 \pm 0.1) \times 10^2$ dm^3 mol^{-1} s^{-1} (IMP), and $k_8 = 120 \pm 9$ (Ino) and 81 ± 6 dm^3 mol^{-1} s^{-1} (IMP). In the last-mentioned calculations the values of the equilibrium constants (K_5 and K_7) were obtained from spectrophotometric titrations (see *Equilibrium Studies*) or kinetic measurements (see discussion below). The value for K_7 from the kinetic data for Ino was used to obtain the value of k_8 for IMP.

Depending on the $[Cl^-]$, the first ($[Cl^-] > 0.1$ mol dm^{-3}) and second ($[Cl^-] > 0.02$ mol dm^{-3}) steps exhibit a linear dependence on the nucleophile concentration. For this case the reaction schemes outlined in (7), (8) and (9), (10) where a rapid pre-equilibration precedes the rate-determining substitution step as a result of the higher $[Cl^-]$, could in principle be valid. Under these conditions $k_{-5}[Cl^-] \gg k_6[Nu]$ and $k_{-7}[Cl^-] \gg k_8[Nu]$ and equation (11) and (12) simplify to (13) and (14). The kinetic data can now be treated by plotting k_{obs} *versus* [Nu] for both steps at each $[Cl^-]$. According to equations (13) and (14), the slope obtained in this manner *versus* $1/[Cl^-]$

$$k_{obs} = k_{-6} + (K_5k_6[Nu]/[Cl^-]) \quad (13)$$

$$k_{obs} = k_8K_7[Nu]/[Cl^-] \quad (14)$$

should result in a linear relationship if stationary conditions are valid. This was the case for the first but not for the second reaction step. For the first step it is thus possible to obtain k_6 from the slope of plots of k_{obs} *versus* $K_5[Nu]/[Cl^-]$ at $[Cl^-] > 0.1$ mol dm^{-3} (Table 1).

It is more appropriate to use the rate equation (15) for the

$$k_{obs} = k_8K_7Nu/([Cl^-] + K_7) \quad (15)$$

second reaction scheme. According to this plots of k_{obs} *versus* [Nu] should be linear with slope equal to $k_8K_7/(K_7 + [Cl^-])$. From the $[Cl^-]$ dependence of the slope it is possible to estimate K_7 and k_8 by plotting 1/slope *versus* $[Cl^-]$. It follows that $K_7 = 0.11 \pm 0.02$ mol dm^{-3} and $k_8 = 370 \pm 100$ dm^3 mol^{-1} s^{-1} for the reaction with inosine.

The temperature and pressure dependence of k_{obs} for the second step has also been studied (SUP 57103). It is expected that the value of K_7 will depend on pressure and temperature.[36] Consequently, the values of the stoichiometric and equilibrium constants as a function of temperature and pressure were determined by fitting the experimental data by equations (12a) and (15) using non-linear least-squares routines and the resulting values for k_7, k_{-7}, K_7 and k_8 together with the values of k_5, k_{-5} K_5 and k_6 are summarized in Table 1. It should be noted that these values were obtained from only a limited number of k_{obs} values. To eliminate the uncertainty that may arise, a three-dimensional view at various values for the microscopic rate constants and the equilibrium and thermodynamic constants assisted in finding a global minimum of the overall function.

Values for the activation and thermodynamic parameters for the reaction of $[Pd(met)Cl_2]^-$ with both nucleophiles for the second step are summarized in Table 2. The rate data can be measured more accurately for the second step since the reactions are significantly slower than the first step. The $\Delta S^\ddagger$ values for k_8 are negative for both nucleophiles and in agreement with the $\Delta V^\ddagger$ data. The values of $\Delta V^\ddagger(k_8)$ and $\Delta S^\ddagger(k_8)$ support the assignment of associative complex formation, in agreement with that published for substitution reactions of square-planar complexes.[1,2,23,36-41] The activation parameters for the reverse step, k_{-7}, are also in line with the assignment of an associative complex-formation mechanism. This is supported by the values for $\Delta V^\ddagger(k_8)$, which are significantly negative and underline the associative nature of the substitution process. Keeping the error limits of the data fits in mind, it can also be concluded that the overall reaction volume for the solvolysis reaction, $\Delta V = \Delta V^\ddagger(k_7) - \Delta V^\ddagger(k_{-7})$, is small negative or positive, due to the binding of a chloride ion and the release of a water molecule; $\Delta V^\ddagger(k_7)$ involves bond formation with a water molecule and is in good agreement with data reported for related reactions.[36,42,43] There is no apparent dependence on the nature of the ligand, which demonstrates the similarity in the substitution process in all cases.

At this point it is of interest to compare our findings with those of related studies. A summary of the available kinetic, equilibrium and thermodynamic data for the complex-formation reactions of $[Pd(L)Cl_2]$ [L = en, tmen, $Et_2NCH_2CH_2NEt_2$ (teen) or met] according to the general reactions in Scheme 1 is given in Table 3. First of all, the values of K_1, K_2, K_3 and K_4 compare favourably with those of the related

Table 1 Rate and equilibrium data for the reaction of $[Pd(met)Cl_2]^-$ with Ino and IMP in the presence of an excess of Cl

Nucleophile	$[Cl^-]$/ mol dm^{-3}	T/°C	p/MPa	Step	$10^{3}\,k_5$/s^{-1}	$10^{-5}\,k_5$/ dm^3 mol^{-1} s^{-1}	$10^{3}\,K_5$/ mol dm^{-3}	$10^{-5}\,k_6$/ dm^3 mol^{-1} s^{-1}	k_7/s^{-1}	$10^{2}\,k_7$/ dm^3 mol^{-1} s^{-1}	$10\,K_7$/ mol dm^{-3}	$10^{2}\,k_8$/ dm^3 mol^{-1}
Ino	0.01	25	atm	2					33 ± 6	4.66 ± 0.14	0.75 ± 0.16	1.50 ± 0.42
	0.02	25	atm	1	1.48 ± 0.32	2.54 ± 0.35	5.83 ± 0.05	8.22 ± 0.16				
				2					49 ± 8	5.70 ± 0.01	0.85 ± 0.02	2.07 ± 0.28
			25						40 ± 8	5.16 ± 0.09	0.78 ± 0.18	1.63 ± 0.44
			50						51 ± 10	5.70 ± 0.09	0.89 ± 0.20	1.71 ± 0.45
			75						51 ± 10	5.29 ± 0.09	0.97 ± 0.20	1.82 ± 0.45
			100						48 ± 6	5.45 ± 0.07	0.89 ± 0.12	2.29 ± 0.39
			125						44 ± 6	5.37 ± 0.11	0.83 ± 0.13	2.96 ± 0.63
		30	atm						62 ± 18	6.24 ± 0.15	0.99 ± 0.31	2.07 ± 0.79
		35							60 ± 3	6.92 ± 0.04	0.87 ± 0.05	3.29 ± 0.24
		40							76 ± 5	8.96 ± 0.08	0.85 ± 0.07	4.19 ± 0.42
	0.05	25	atm	1	1.63 ± 0.27	2.79 ± 0.24	5.8 ± 1.5	10.4 ± 1.2				
				2							2.00 ± 0.21	3.52 ± 0.07
	0.1	20	atm	2							1.00 ± 0.04	2.88 ± 0.06
		25		1	1.32 ± 0.22	2.25 ± 0.20	5.9 ± 1.5	8.38 ± 0.10				
				2							0.90 ± 0.05	4.26 ± 0.11
		30		2							0.95 ± 0.05	4.85 ± 0.13
		35		2							1.20 ± 0.07	5.30 ± 0.15
		40		2							1.70 ± 0.07	5.90 ± 0.01
	0.1	25	25	2							0.90 ± 0.03	4.19 ± 0.09
			50	2							1.00 ± 0.04	4.59 ± 0.10
			75	2							1.10 ± 0.07	4.70 ± 0.15
			100	2							1.20 ± 0.06	4.90 ± 0.01
			125	2							1.20 ± 0.08	5.32 ± 0.07
	0.15		atm	1				7.20 ± 0.16				
											0.70 ± 0.01	4.20 ± 0.01
	0.2			1				7.57 ± 0.08				
				2							0.85 ± 0.01	4.08 ± 0.00
	0.3			1				9.23 ± 0.11				
				2							0.90 ± 0.02	4.38 ± 0.01
IMP	0.01	25	atm	2					42 ± 11	1.92 ± 0.05	2.20 ± 0.62	0.36 ± 0.12
	0.02	20	atm	2					42 ± 18	2.20 ± 0.04	1.92 ± 0.85	0.40 ± 0.20
	0.02	25	atm	1	2.06 ± 0.68	3.52 ± 0.90	5.85 ± 3.43	2.88 ± 0.01				
				2					46 ± 13	2.50 ± 0.04	1.82 ± 0.53	0.55 ± 0.19
		30	atm						46 ± 12	2.35 ± 0.04	1.98 ± 0.57	0.67 ± 0.23
		35							70 ± 16	3.58 ± 0.05	1.95 ± 0.48	0.82 ± 0.24
		40							59 ± 24	3.65 ± 0.13	1.62 ± 0.71	1.26 ± 0.68
	0.05	25	atm	1	1.32 ± 0.16	2.25 ± 0.10	5.89 ± 0.98	4.85 ± 0.04				
				2							1.70 ± 0.18	2.98 ± 0.07
	0.1	20	atm	2							1.60 ± 0.05	1.47 ± 0.01
		25		1	1.86 ± 0.57	3.17 ± 0.73	5.87 ± 3.15	4.85 ± 0.01				
				2							1.20 ± 0.05	2.30 ± 0.04
		30		2							1.01 ± 0.03	2.80 ± 0.04
		35		2							1.75 ± 0.02	2.89 ± 0.10
		40		2							1.95 ± 0.02	3.65 ± 0.10
	0.1	25	25	2							2.80 ± 0.15	1.93 ± 0.07
			50	2							2.90 ± 0.15	2.10 ± 0.03
			75	2							3.10 ± 0.02	2.20 ± 0.04
			100	2							2.38 ± 0.08	2.56 ± 0.03
			125	2							1.82 ± 0.02	2.92 ± 0.03
	0.2		atm	1				4.57 ± 0.09				
				2							1.44 ± 0.07	1.66 ± 0.05

Experimental conditions: $[Pd^{II}]_T = 5 \times 10^{-4}$ mol dm^{-3}; 25 °C; $I = 0.5$ mol dm^{-3}; pH 4; λ = 400 (atmospheric pressure, atm); 320 nm (elevated pressures).

Table 2 Summary of activation parameters for the second reaction step[a]

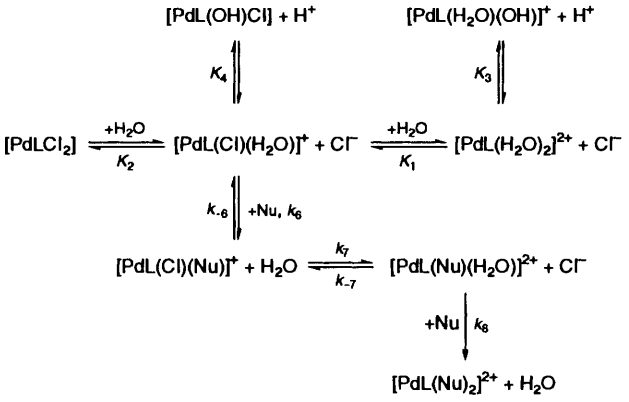
L	$[Cl^-]$/ mol dm^{-3}	$\Delta H^{\ddagger}(k_7)$/ kJ mol^{-1}	$\Delta S^{\ddagger}(k_7)$/ J K^{-1} mol^{-1}	$\Delta H^{\ddagger}(k_{-7})$/ kJ mol^{-1}	$\Delta S^{\ddagger}(k_{-7})$/ J K^{-1} mol^{-1}	$\Delta H^{\ddagger}(k_8)$/ kJ mol^{-1}	$\Delta S^{\ddagger}(k_8)$/ J K^{-1} mol^{-1}	$\Delta V^{\ddagger}(k_8)$/ cm^3 mol^{-1}	$\Delta H(K_8)$/ kJ mol^{-1}	$\Delta S(K_8)$/ J K^{-1} mol^{-1}	$\Delta V(K_8)$/ cm^{3}mol^{-1}
Ino	0.02[b]	18 ± 6	−153 ± 19	20 ± 5	−125 ± 15	37 ± 10	−76 ± 32	−15 ± 3	18 ± 8	−205 ± 27	−1 ± 3
Ino	0.1					23 ± 5	−119 ± 16	−5.4 ± 0.6	18 ± 8	−205 ± 27	−7 ± 1
IMP	0.02	11 ± 2	−177 ± 7	−17 ± 1	−232 ± 2	10 ± 2	−155 ± 7		28 ± 2	−55 ± 6	
IMP	0.1					10 ± 7	−163 ± 22		38 ± 7	−103 ± 23	−9 ± 2

[a] For experimental conditions see Table 1. [b] $\Delta V^{\ddagger}(k_7) = -1 \pm 4$ cm^3 mol^{-1}, $\Delta V^{\ddagger}(k_{-7}) = 1 \pm 2$ cm^3 mol^{-1}.

Table 3 Summary of rate, equilibrium and thermodynamic data for the reaction of $[PdLCl_2]$ with Ino, IMP and Cl^- according to the general reaction Scheme 1 in the presence of an excess of Cl^-

L	Nu	$10^4 K_1$	$10^3 K_2$/ dm^3 mol^{-1}	k_2/ dm^3 mol^{-1} s^{-1}	$10^3 k_2$/ s^{-1}	$10^6 K_3$/ mol dm^{-3}	$10^8 K_4$/ mol dm^{-3}	$10^5 k_6$/ dm^3 mol^{-1} s^{-1}	k_{-6}/ s^{-1}	$10^2 K_7$/ mol dm^{-3}	k_7/s^{-1}	$10^2 k_{-7}$/ dm^3 mol^{-1} s^{-1}	k_8/ dm^3 mol^{-1} s^{-1}
en[a]	Cl^-	2.50 ± 0.10	7.69 × 1.16	9.7	1.34 ± 0.02	2.51	5.01 ± 0.14						
				14.7 ± 0.5	1.29 ± 0.04								
	Ino			15.6 ± 0.2	1.34 ± 0.02	0.002		0.017 ± 0.00[b]					
	IMP			10.6 ± 1.2	1.34 ± 0.02	0.013		0.13 ± 0.02[b]					
tmen[c]	Cl^-	3.12 ± 0.49	9.52 ± 1.27		0.29 ± 0.00	3.98	0.1		4.3				
	Ino			3.45 ± 0.78	0.29 ± 0.01	0.0004		0.004 ± 0.001, 0.006 ± 0.000			2.80 ± 0.40		
	IMP			2.83 ± 0.04	0.29 ± 0.01	0.0003		0.031 ± 0.003, 0.006 ± 0.000					37.3 ± 0.4, 2.6 × 10^2
teen[d]	Cl^-	3.55 ± 0.21	19.2 ± 3.32		0.013 ± 0.00	1.58	1.99						
	Ino			0.29 ± 0.03	0.13 ± 0.05	0.0001		0.000 86 ± 0.000 06		0.5 ± 0.1			4.0 ± 0.6, 12.4
	IMP			0.28 ± 0.02	0.13 ± 0.05	0.000 13		0.001 3 ± 0.000 2		1.4 ± 0.1			2.8 ± 0.2 9.7
met[e]	Cl^-	8.89 ± 0.91	5.85 ± 0.44			6.31	1.26						
	Ino		5.84 ± 0.02	1860 ± 530	318 ± 91			9.0 ± 1.3	136	11 ± 2[f]	41 ± 11[f]	5.2 ± 0.7	120 ± 9[g] 370 ± 100[h]
	IMP		5.87 ± 0.02	1750 ± 380	298 ± 66			4.4 ± 1.0	80	17 ± 4[f]	44 ± 3[f]	1.9 ± 0.1	81 ± 6

[a] Data taken from refs. 4, 14 and 41. [b] Average from data taken from ref. 4. [c] Data taken from refs. 4, 36 and 41. [d] Data taken from refs. 2, 4 and 41. [e] This study. [f] Average from Table 1 (25 °C). [g] According to equation (12). [h] According to equation (15).



Scheme 1

$[Pd(en)Cl_2]$ (and substituted derivatives) and *cis*-$[Pt(NH_3)_2Cl_2]$ complexes[44] since they all involve the H_2O molecule *trans* to a nitrogen donor. This suggests that in general the equilibrium situation for chelated complexes of Pd^{II} and Pt^{II} is similar, and supports the feasibility of using chelated palladium(II) complexes as model antitumour complexes. This similarity has also been pointed out previously.[23] The anation rate constants, k_6 and k_8, are much larger than those for $[Pd(en)Cl_2]$ and substituted derivatives thereof. This marked increase in reactivity can only be ascribed to the *trans* influence of the sulfur donor of the methionine ligand. This is also seen in a comparison of the anation and aquation constants, k_2 and k_{-2}, which are two orders of magnitude larger than those for the related en system and three orders of magnitude larger than those for the related tmen and teen systems. Also the anation and aquation rate constants, k_6 and k_{-6}, determined for the two nucleophiles in this study are approximately one order of magnitude larger than those reported for the highly substitution-labile iodide ion in the en system.[45] The substitution behaviour of the methionine complex of palladium(II) does not differ much from those of other square-planar complexes in the sense that for the relatively unreactive Ino and IMP nucleophiles the aqua complexes are the reactive entities and complicated kinetics with a changeover in rate-determining step upon increasing or decreasing the $[Cl^-]$ is observed.

Contrary to investigations with $[Pd(en)Cl_2]$ and $[Pd(dien)Cl]^+$ (dien = diethylenetriamine) and sterically hindered derivatives thereof, Ino is more reactive than IMP in the investigated reactions. In the present case this can only be attributed to the larger steric hindrance when IMP acts as a nucleophile. Furthermore the pH at which antitumour complexes bind to DNA is significantly higher than that used in this study. It is expected that at neutral pH the phosphate residue on the nucleotide will also bind to the central metal atom as a result of deprotonation.[35] We have also investigated complex formation of $[Pd(met)Cl_2]^-$, $[Pd(en)Cl_2]$ and $[Pd(dien)Cl]^+$ with Ino and IMP over a wide pH range and will report our findings in due course. The formation of $[Pt(met)_2]$ *in vivo* is related to the toxicity of *cis*-platin *in vivo*. Macquet *et al.*[46] have attributed the greater reactivity of the *cis* configuration of $[Pt(NH_3)_2Cl_2]$ in comparison to the *trans* to the possible binding of *cis*-platin to amino acids *in vivo* which could cause a *trans*-labilizing effect. Such a labilization has clearly been illustrated by the results of the present study in comparison with those for the related $[Pd(en)Cl_2]$ system. The $[Cl^-]$-dependence data demonstrated that a changeover in mechanism is observed upon changing the $[Cl^-]$, and even at very high $[Cl^-]$ it is the aqua entities that are kinetically reactive towards substitution. It can thus be concluded that it will be the chloroaqua complex which will bind to the nucleic bases especially at the chloride concentration level of 4 mmol dm^{-3} in the cell.

The results of this study have clearly demonstrated the significant lability induced by the S-donor chelate in $[Pd(met)Cl_2]^-$. A similar behaviour is predicted for the corresponding platinum(II) complex. It follows that by changing the donor atom in the chelate ring the reactivity of square-planar complexes can be systematically tuned. The general substitution behaviour of the $[Pd(met)Cl_2]^-$ complex is very similar to that reported for related palladium(II) complexes which are chelated through nitrogen atoms only. It is merely the substitution reactivity, *i.e.* lability, that is affected to a significant extent.

Acknowledgements

The authors gratefully acknowledge a stipend from Deutscher Akademischer Austauschdienst to F. F. P. which enabled him to participate in this study.

References

1 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chem.*, 1992, **31**, 345.
2 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chem.*, 1992, **31**, 1090.
3 S. Suvachittanont, H. Hohmann, R. van Eldik and J. Reedijk, *Inorg. Chem.*, 1993, **32**, 4544.
4 S. Suvachittanont and R. van Eldik, *Inorg. Chem.*, 1994, **33**, 895.
5 E. L. M. Lempers and J. Reedjik, *Adv. Inorg. Chem.*, 1991, **37**, 175; M. Green, M. Garner and D. M. Orton, *Transition Met. Chem. (Weinheim)*, 1992, **17**, 164; J. Reedijk, *Inorg. Chim. Acta*, 1992, **198–200**, 873; E. Holler, in *Metal Complexes in Cancer Chemotherapy*, ed. B. K. Keppler, VCH, Weinheim; 1993, p. 37; L. R. Kelland, S. J. Clarke and M. J. McKeage, *Platinum Met. Rev.*, 1992, **36**, 178.
6 T. G. Appleton, J. W. Connor and J. R. Hall, *Inorg. Chem.*, 1988, **27**, 130.
7 R. E. Norman, J. D. Ranford and P. J. Sadler, *Inorg. Chem.*, 1992, **31**, 877.
8 P. del S. Murdoch, J. D. Ranford, P. J. Sadler and S. J. Berners-Price, *Inorg. Chem.*, 1993, **32**, 2249.
9 C. M. Riley, L. A. Sternson, A. J. Repta and S. A. Slyter, *Anal. Biochem.*, 1983, **130**, 203.
10 S. Suvachittanont and R. van Eldik, *J. Chem. Soc., Dalton Trans.*, 1995, 2027.
11 H. C. Freeman and M. L. Golomb, *Chem. Commun.*, 1970, 1523.
12 C. A. McAuliffe, *J. Chem. Soc. A*, 1967, 641.
13 V. Theodoro and I. Photaki, *Inorg. Chim. Acta*, 1982, **60**, 1.
14 H. Hohmann and R. van Eldik, *Inorg. Chim. Acta*, 1990, **174**, 87.
15 G. Mahal and R. van Eldik, *Inorg. Chem.*, 1985, **24**, 4165.
16 (*a*) G. Gran, *Acta Chem. Scand.*, 1950, 559; (*b*) PSEQUAD, L. Ze'ka'ny and I. Nagypa'l, in *Computational Methods for the Determination of Formation Constants*, D. J. Legett, Plenum, New York, 1985, p. 291; (*c*) OLIS KINFIT, Olis Inc., Bogart, GA.
17 R. van Eldik, W. Gaede, S. Wieland, J. Kraft, M. Spitzer and D. A. Palmer, *Rev. Sci. Instrum.*, 1993, **64**, 1355.
18 G. Pneumatikakis and N. Hadjiliadis, *J. Inorg. Nucl. Chem.*, 1979, **41**, 429.
19 T. G. Appleton, J. W. Connor and J. R. Hall, 1988, **27**, 130.
20 S. E. Livingstone and J. D. Nolan, *Inorg. Chem.*, 1968, **7**, 1447.
21 N. N. Chernova and I. G. Kurskii, *Zh. Neorg. Khim.*, 1978, **23**, 1014.
22 J. R. Allkins and P. J. Hendra, *J. Chem. Soc. A*, 1967, 1325.
23 E. L. J. Breet, R. van Eldik and H. Kelm, *Inorg. Chim. Acta*, 1984, **85**, 151.
24 R. B. Martin, *Acc. Chem. Res.*, 1985, **18**, 32.
25 J. Arpahlati and P. Lehikoinen, *Inorg. Chem.*, 1990, **29**, 2564.
26 J. Arpahlati and B. Lippert, *Inorg. Chem.*, 1990, **29**, 104.
27 R. N. Bose, R. D. Cornelius and R. E. Viola, *J. Am. Chem. Soc.*, 1986, **108**, 4403.
28 G. M. Clore and A. M. Gronenborn, *J. Am. Chem. Soc.*, 1982, **105**, 1369.
29 J. P. Caradonna and S. J. Lippard, *Inorg. Chem.*, 1988, **27**, 1454.
30 J. H. J. Den Hartog, C. Altona, J. H. van Boom, G. A. van der Marel, C. A. G. Haasnoot and J. Reedijk, *J. Am. Chem. Soc.*, 1984, **106**, 1528.
31 F. J. Dijt, G. W. Canters, J. H. J. Den Hartog, A. T. M. Marcelis and J. Reedijk, *J. Am. Chem. Soc.*, 1984, **106**, 3644.
32 N. Goswani, L. L. Bennett-Slavin and R. N. Bose, *J. Chem. Soc., Chem. Commun.*, 1989, 432.

33 J.-P. Girault, G. Chottard, J.-Y. Lallemand, F. Huguenim and J.-C. Chottard, *J. Am. Chem. Soc.*, 1984, **106**, 7227.
34 A. T. M. Marcelis, J. H. J. Den Hartog and J. Reedijk, *J. Am. Chem. Soc.*, 1982, **104**, 2664.
35 R. Jacobs, F. Prinsloo and E. Breet, *J. Chem. Soc., Chem. Commun.*, 1992, 212.
36 M. Shoukry, H. Hohmann and R. van Eldik, *Inorg. Chim. Acta*, 1992, **198–200**, 187.
37 J. J. Pienaar, M. Kotowski and R. van Eldik, *Inorg. Chem.*, 1989, **28**, 373.
38 R. van Eldik, E. L. J. Breet, M. Kotowski, D. A. Palmer and H. Kelm, *Ber. Bunsenges. Phys. Chem.*, 1983, **87**, 904.
39 E. L. J. Breet and R. van Eldik, *Inorg. Chem.*, 1987, **26**, 2517.
40 E. L. J. Breet and R. van Eldik, *J. Chem. Soc., Chem. Commun.*, 1987, 408.
41 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chim. Acta*, 1991, **188**, 25.
42 J. Berger, M. Kotowski, R. van Eldik, U. Frey, L. Helm and A. E. Merbach, *Inorg. Chem.*, 1989, **28**, 3759.
43 M. Kotowski and R. van Eldik, in *Inorganic High Pressure Chemistry: Kinetics and Mechanisms*, ed. R. van Eldik, Elsevier, Amsterdam, 1986, ch. 4.
44 S. E. Miller and D. A. House, *Inorg. Chim. Acta*, 1989, **161**, 131; **162**, 189.
45 H. Hohmann, S. Suvachittanont and R. van Eldik, *Inorg. Chim. Acta*, 1990, **177**, 51.
46 J. P. Macquet, J. L. Butour and N. P. Johnson, in *Platinum, Gold, and other Metal Chemotherapeutic Agents: Chemistry and Biochemistry*, American Chemical Society, Washington, DC, 1983, pp. 75–100.

Received 29*th March* 1995; *Paper* 5/01993A