Steric Control over the Complex-formation and Chelation Kinetics of *cis*-Bis(amine)palladium(II) Complexes with Methionine and *S*-Methylcysteine in Weakly Acidic Aqueous Solution

Surapong Suvachittanont and Rudi van Eldik*

Institute for Inorganic Chemistry, University of Erlangen-Nürnberg, Egerlandstrasse 1, 91058 Erlangen, Germany

A detailed kinetic study was undertaken of the complex-formation reactions of *cis*-[Pd($R_2NCH_2CH_2NR_2$)Cl_2] (R = H, Me or Et) with L-methionine (Hmet) and *S*-methyl-L-cysteine (mcys) as a function of nucleophile and chloride concentrations. Two consecutive reaction steps were observed for nearly all cases studied. All complex-formation reactions proceed *via* the formation of a reactive intermediate of the type [Pd($R_2NCH_2CH_2NR_2$)Cl(H_2O)]$^+$. The kinetic data for the reaction with Hmet for R = H at low concentration are equally in accord with pre-equilibrium and steady-state rate laws, which is also the case for R = Et. In addition, a direct methionine path with [Pd(en)Cl_2] (en = $H_2NCH_2CH_2NH_2$) was observed at higher methionine concentrations. This is followed by a slower ring-closure reaction. The kinetic data for the first reaction steps for R = H and with mcys are only consistent with the pre-equilibrium model. This is followed by slower nucleophilic attack by a second mcys molecule to give the 1:2 complex for R = H in competition with either a solvolysis or a ring-closure reaction. The results are compared to available data for the complex-formation reactions with inosine and inosine 5′-monophosphate and allow a detailed discussion of the steric control over the kinetics and the nucleophilicity of such reactions.

In recent years we have undertaken a systematic study of the effect of steric hindrance and nucleophilicity on the complex-formation kinetics of model *cis*-bis(amine)palladium(II) complexes with a variety of nucleobases, nucleosides and nucleotides.[1-6] These studies have revealed a richness of mechanistic versatility in terms of rate-controlling steps for ligand displacement and complex-formation reactions in these systems, which could be of fundamental importance to the understanding of the antitumour activity of related platinum complexes.[7] In general such ligand-substitution reactions are characterized by various kinetic rate laws depending on the reactivity ratio of the various reaction steps involved in such interactions with DNA constituents.[4-6,8-10]

Appleton and co-workers[11] studied the reactions of *cis*-[$Pt(NH_3)_2(H_2O)_2$]$^{2+}$ with methionine and *S*-methylcysteine using multinuclear NMR techniques to distinguish between S,O and S,N chelation. They reported evidence for the formation of two slowly interconverting diastereomers in weakly acidic solution, as well as the conversion from S,O into S,N chelation in strongly acidic solution during complex formation by *S*-methylcysteine. Similar results were also reported for the reaction with methionine. Up to now we have not studied the effect of S-donor ligands on the substitution behaviour of the model *cis*-bis(amine)palladium(II) complexes, an aspect which could be of relevance in terms of the interaction of such species with sulfur-containing amino acids. There is presently an increasing interest in the role of S-donor ligands in such systems.[12,13] We have therefore undertaken a detailed kinetic study of the complex-formation reactions of *cis*-[Pd($R_2NCH_2CH_2NR_2$)Cl_2] with L-methionine (Hmet) and *S*-methyl-L-cysteine (mcys) for R = H, Me or Et in order to analyse the effect of steric hindrance on the non-participating ligand. In addition we have systematically varied the chloride concentration in order to detect the reactivity of the corresponding aqua complexes, *viz.* *cis*-[Pd($R_2NCH_2CH_2NR_2$)Cl(H_2O)]$^+$.

Experimental

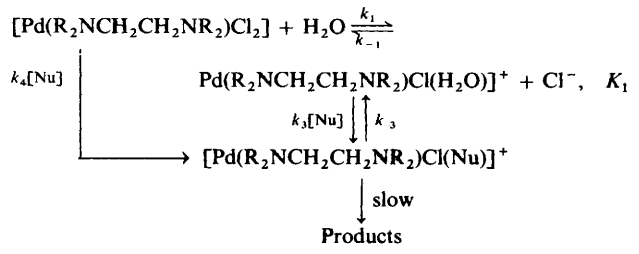
Materials.—The [Pd(en)Cl_2], [Pd(tmen)Cl_2] and [Pd(teen)Cl_2] complexes (tmen = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, teen = *N*,*N*,*N*′,*N*′-tetraethylethylenediamine) were prepared and characterized as described before.[2] L-Methionine and *S*-methyl-L-cysteine were obtained from Fluka and 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 the precipitation of $KClO_4$, since $NaClO_4$ was used to adjust the ionic strength of all test solutions to 0.10 mol dm^{-3}. Millipore water was used in the preparation of all solutions.

Measurements.—The UV/VIS spectra were recorded on Shimadzu UV 250 and Hewlett-Packard 8452A diode-array spectrophotometers. Kinetic measurements were performed on a Durrum D110 stopped-flow unit attached to an on-line data-acquisition system with which the kinetic traces were evaluated, using the KINFIT set of programs.[14] Pseudo-first-order conditions were employed throughout.

Results and Discussion

Our earlier studies on related systems have shown that the rate of substitution reactions of complexes of the type *cis*-[Pd($R_2NCH_2CH_2NR_2$)Cl_2] is strongly affected by the free chloride-ion concentration in solution since this controls the overall palladium(II) speciation.[1,4-6] Equilibrium data for the aquation reactions (1) and (2) suggest that under the

$$[Pd(R_2NCH_2CH_2NR_2)Cl_2] + H_2O \overset{K_1}{\rightleftharpoons} [Pd(R_2NCH_2CH_2NR_2)Cl(H_2O)]^+ + Cl^- \quad (1)$$



Scheme 1 Nu = Nucleophile

$$[Pd(R_2NCH_2CH_2NR_2)Cl(H_2O)]^+ + H_2O \overset{K_2}{\rightleftharpoons} [Pd(R_2NCH_2CH_2NR_2)(H_2O)_2]^{2+} + Cl^- \quad (2)$$

experimental conditions selected in this study, *i.e.* pH and chloride concentration range, it will mainly be reaction (1) that will contribute to the observed kinetic behaviour. Thus the dichloro and monochloroaqua complexes will be the main species in solution.[1] It is well known that the latter species is orders of magnitude more substitution labile than the dichloro complex, with the result that the chloroaqua complex will be the main reactive species in solution.[4–6,8,9]

Our recent work[4–6] has shown that ligand-substitution reactions of such complexes under the conditions mentioned above can be described by the general Scheme 1. The kinetic traces for such reactions usually show two exponential functions of which the faster step is assigned to the formation of the 1:1 complex and the slow step to the subsequent formation of the 1:2 complex, or a ring-closed species as in the present case.[4–6,11] The fast reaction can follow two rate laws depending on the relative size of k_1, $k_{-1}[Cl^-]$ and $k_3[Nu]$ (the parallel $k_4[Nu]$ path will not contribute significantly under normal conditions), *i.e.* whether a pre-equilibrium or a steady-state situation is applicable.[4–6] This results in the rate equations (3) and (4), respectively, and a variation in steric hindrance on

$$k_{obs} = k_{-3} + \frac{K_1 k_3[Nu]}{K_1 + [Cl^-]} \quad (3)$$

$$k_{obs} = k_{-3} + \frac{k_1 k_3[Nu]}{k_3[Nu] + k_{-1}[Cl^-]} \quad (4)$$

$R_2NCH_2CH_2NR_2$ or in the nucleophilicity of the entering nucleophile can easily cause a changeover in the observed kinetic behaviour.[4–6]

The reactions of $[Pd(R_2NCH_2CH_2NR_2)Cl_2]$ with L-methionine are characterized by large spectral changes below 350 nm and clearly show two consecutive reactions. These can be separated in terms of a rapid increase and a slow decrease in absorbance at 300 nm as shown in Fig. 1. The rate constants for the fast reaction in general increase with increasing nucleophile concentration and decrease with increasing chloride concentration in agreement with what is expected on the basis of equations (3) and (4). The data are in agreement with rate equation (3) for R = Me and Et, and over a limited concentration range of Hmet for R = H, as shown by the plots of k_{obs} *versus* $[Hmet]/(K_1 + [Cl^-])$ in Fig. 2(*a*)–2(*c*). The data for R = Et are also in agreement with equation (4) for $k_{-3} \approx 0$ as shown by the plot of k_{obs}^{-1} *versus* $[Cl^-]/[Hmet]$ in Fig. 2(*d*). At higher Hmet concentrations the data for R = H show an exceptional behaviour [see Fig. 3(*a*)] in that k_{obs} becomes independent of $[Cl^-]$ and increases with increasing [Hmet]. Under such conditions the direct attack of Hmet on the dichloro complex must be taken into consideration. This step (k_4) only seems to play a role for the less sterically hindered (R = H) complex, and is most probably suppressed by steric hindrance in the other cases (R = Me or Et). The rate equation

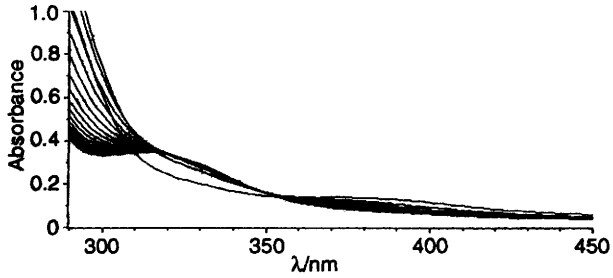


Fig. 1 Repetitive-scan spectra recorded for the overall reaction $[Pd(teen)Cl_2]$ + Hmet ⟶ $[Pd(teen)(met\text{-}S,N)]^+ + 2Cl^- + H^+$. Experimental conditions: $[Pd^{II}] = 2.5 \times 10^{-4}$, [Hmet] = 0.01, $[Cl^-] = 0.025$ mol dm^{-3}; pH 4.0; ionic strength, $I = 0.1$ mol dm^{-3}; $T = 25$°C; $\Delta t = 10$ s

based on steady-state kinetics is given by (5). At high [Hmet]

$$k_{obs} = \frac{k_1 k_3[Hmet]}{k_{-1}[Cl^-] + k_3[Hmet]} + k_4[Hmet] \quad (5)$$

this simplifies to $k_{obs} = k_1 + k_4[Hmet]$, which accounts for the $[Cl^-]$ independence of the data under such conditions [Fig. 3(*a*)]. Furthermore, the extrapolated intercept of *ca.* 9.5 s^{-1} is indeed very close to that reported[1] for the aquation of $[Pd(en)Cl_2]$. For the data at lower Hmet concentration in Fig. 3(*a*), equation (5) can be rewritten in the form (6), from which it

$$(k_{obs} - k_4[Hmet])^{-1} = k_{-1}[Cl^-]/k_1 k_3[Hmet] + k_1^{-1} \quad (6)$$

follows that a plot of the left-hand side *versus* $[Cl^-]/[Hmet]$ should be linear. This is indeed the case as shown in Fig. 3(*b*). The intercept results in a k_1 value of 20 ± 4 s^{-1} which is close to a range of values between 11.4 and 19.7 s^{-1} reported recently.[6] The results in Figs. 2 and 3 can be used to estimate some of the rate constants in Scheme 1, and these are summarized in Table 1.

The data for the subsequent slower reaction with Hmet are reported in Table 2. In general these data are subjected to large error limits since in many cases the observed rate constant for the slower reaction only differs by a factor of 2–4 from that of the fast reaction step. More accurate data could be obtained for the teen system, where this factor is between 6 and 10, such that k_{obs} for the slower reaction is more reliable. The results in Table 2 demonstrate that in some cases there is an effect of the $[Cl^-]$ or [Hmet] on the observed rate constant, but it is really small. Within the experimental error range of ± 7%, the data in Table 2 do not exhibit any specific $[Cl^-]$ or [Hmet] dependence, which is in line with our suggestion of a rate-determining ring-closure reaction under such conditions as shown in equation (7).

$$[Pd(R_2NCH_2CH_2NR_2)Cl(Hmet)]^+ \xrightarrow{k_5} [Pd(R_2NCH_2CH_2NR_2)(met\text{-}S,N)]^+ + Cl^- + H^+ \quad (7)$$

The substitution reactions with *S*-methylcysteine (mcys) were studied in detail for the en and tmen complexes. Two steps were observed for the en complex, only one for the tmen complex. The first reaction step fits the pre-equilibrium model [equation (3)] and plots of k_{obs} *versus* $[mcys]/(K_1 + [Cl^-])$ (see Fig. 4) are linear for both systems. The subsequent slower reaction exhibits a significant increase in k_{obs} with increasing [mcys], but no significant dependence on $[Cl^-]$ in the range 10–25 mmol dm^{-3}, as illustrated by the data in Fig. 5. The latter data suggest the rate-determining attack of a second mcys molecule on the 1:1 complex in competition with either a solvolysis or ring-

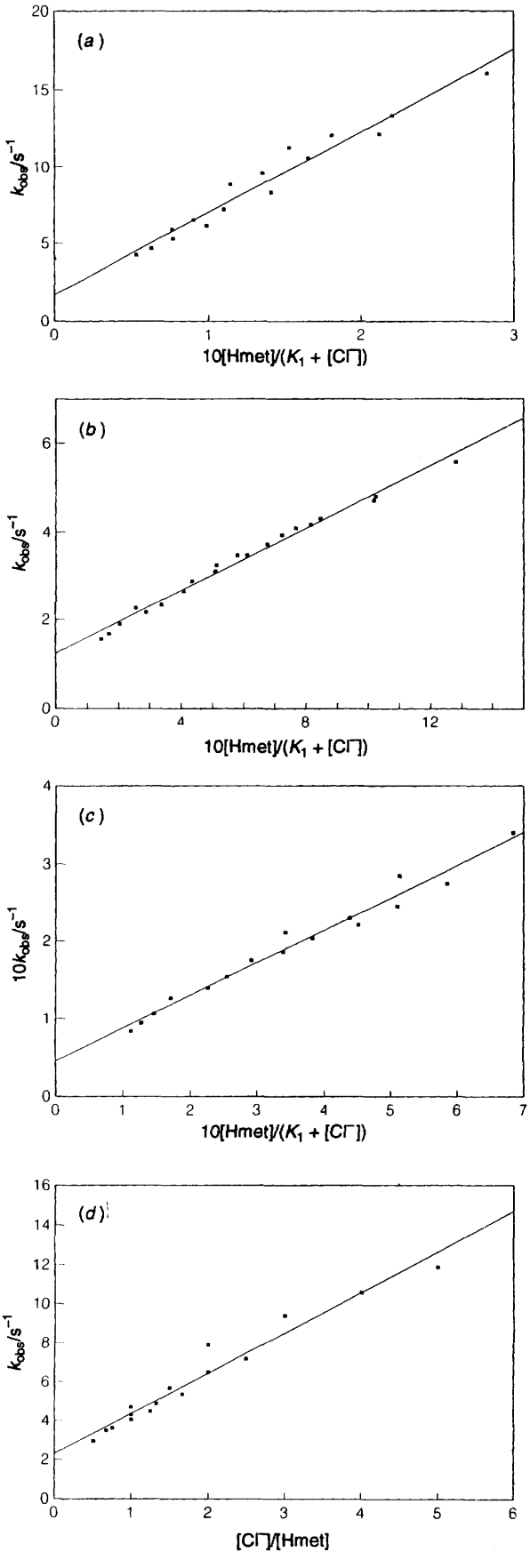


Fig. 2 Plots of k_{obs} *versus* [Hmet]/(K_1 + [Cl^-]) for the reaction $[Pd(R_2NCH_2CH_2NR_2)Cl_2]$ + Hmet ⟶ $[Pd(R_2NCH_2CH_2NR_2)Cl(Hmet)]^+$ + Cl^-. Experimental conditions: see Table 1. R = H (*a*), Me (*b*) or Et (*c*). A plot of k_{obs}^{-1} *versus* [Cl^-]/[Hmet] is given in (*d*)

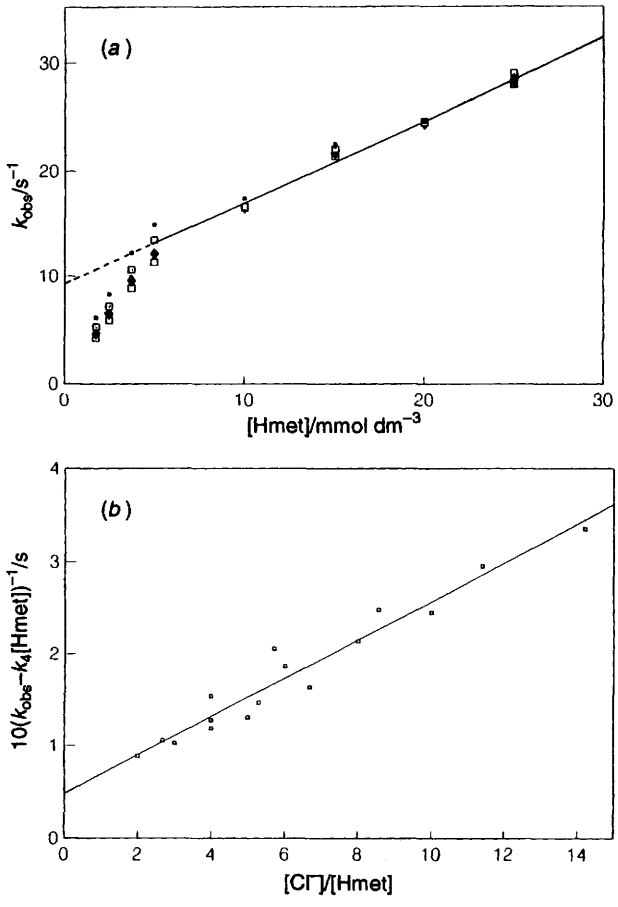


Fig. 3 Treatment of kinetic data for the reaction of $[Pd(en)Cl_2]$ (en = $H_2NCH_2CH_2NH_2$) with Hmet at higher nucleophile concentrations (*a*) and at low nucleophile concentrations (*b*). Experimental conditions: see Table 1. (*a*) Plot of k_{obs} *versus* [Hmet], where [Cl^-] = 10 (■), 15 (⊡), 20 (◆) or 25 mmol dm^{-3} (□). (*b*) Plot of $(k_{obs} - k_4[Hmet])^{-1}$ *versus* [Cl^-]/[Hmet]

closure reaction path of $[Pd(en)Cl(mcys)]^+$ which will account for the observed intercept in Fig. 5. The treatment of the data in Figs. 4 and 5 enables the estimation of rate and equilibrium constants for the reactions with mcys, summarized in Table 1 and compared to related data in Table 3.

We now turn to a comparative discussion of the data in Tables 1 and 3. The complex-formation reaction of $[Pd(R_2NCH_2CH_2NR_2)Cl(H_2O)]^+$ with Hmet exhibits some remarkable kinetic behaviour as a function of steric hindrance on the ethylenediamine ligand. For the less sterically hindered case (R = H), the kinetic data at low [Hmet] equally well fit the pre-equilibrium and steady-state rate equations (3) and (4). However, at higher [Hmet] evidence for the direct reaction with $[Pd(en)Cl_2]$ (k_4) was found [see Fig. 3(*a*)]. This reaction path is *ca.* 10 times slower than the reaction with the aquachloro complex (compare k_3 and k_4 in Table 1), which is in agreement with the general reactivity order observed for such complexes. The k_4 reaction path was not observed for any other systems studied in this investigation, nor those studied before.[1-6] On increasing steric hindrance on $R_2NCH_2CH_2NR_2$, k_3 decreases significantly for both Hmet and mcys, in line with the associative nature of the ligand-substitution mechanism. In the case of the most sterically hindered complex (R = Et), the kinetic data for the reaction with Hmet can once again be fitted with both rate equations (3) and (4), see Fig. 2(*c*) and 2(*d*). The reaction with mcys is characterized by kinetic data very similar to those for the reaction with Hmet, which is probably not surprising on the basis of their rather similar structure. The ring-closure reaction of the $[Pd(R_2NCH_2CH_2NR_2)Cl-$

Table 1 Summary of rate and equilibrium constants obtained for the fast reaction step observed during the reaction of $[Pd(R_2NCH_2CH_2NR_2)Cl_2]$ with Hmet and mcys according to the mechanism outlined in Scheme 1[a]

R	Nucleophile	K_1[b]/mol dm^{-3}	k_1/s^{-1}	k_3/dm^3 mol^{-1} s^{-1}	k_{-3}/s^{-1}	k_4/dm^3 mol^{-1} s^{-1}	k_5[c]/s^{-1}	Source
H		$(7.7 \pm 0.8) \times 10^{-3}$						
	Hmet			$(6.9 \pm 1.1) \times 10^3$	1.69 ± 0.04		8.9 ± 0.7	Fig. 2(*a*)
						756 ± 30		Fig. 3(*a*)
			20 ± 4	$(4.5 \pm 0.3) \times 10^3$				Fig. 3(*b*)
	mcys			$(2.57 \pm 0.06) \times 10^3$	6.8 ± 0.3			Fig. 4(*a*)
Me		$(9.5 \pm 1.2) \times 10^{-3}$						
	Hmet			$(3.73 \pm 0.10) \times 10^2$	1.24 ± 0.06		0.75 ± 0.10	Fig. 2(*b*)
	mcys			$(3.07 \pm 0.06) \times 10^2$	0.20 ± 0.03			Fig. 4(*b*)
Et		$(1.9 \pm 0.3) \times 10^{-2}$						
	Hmet			22 ± 1	0.046 ± 0.007		0.018 ± 0.002	Fig. 2(*c*)
			0.43 ± 0.05	25 ± 1				Fig. 2(*d*)

[a] Experimental conditions: $[Pd^{II}] = 2.5 \times 10^{-4}$ mol dm^{-3}, [Hmet] = [mcys] = 2–25 mmol dm^{-3}, $[Cl^-]$ = 10–25 mmol dm^{-3}; pH ≈ 4; I = 0.1 mol dm^{-3}; T = 25.1 °C. [b] Data taken from ref. 1. [c] Mean value from Table 2, for which $k_{obs} = k_5$ (see Discussion).

Table 2 Observed rate constant k_{obs} as a function of [Hmet] and $[Cl^-]$ for the slower reaction step observed during the reaction of $[Pd(R_2NCH_2CH_2NR_2)Cl_2]$ with Hmet[a]

		k_{obs}[b]/s^{-1}			
R	[Hmet]/mmol dm^{-3}	$[Cl^-]$ = 0.010	0.015	0.020	0.025 mol dm^{-3}
H	5	—	—	—	—
Me		0.700	0.638	0.613	0.595
Et		0.0185	0.0176	0.0153	0.0133
H	10	9.28	9.40	8.37	7.94
Me		0.774	0.675	0.664	0.621
Et		0.0196	0.0193	0.0185	0.0177
H	15	8.18	7.98	8.12	8.05
Me		0.792	0.762	0.734	0.691
Et		0.0139	0.0197	0.0190	0.0186
H	20	9.25	9.37	9.73	9.40
Me		0.847	0.841	0.790	0.764
Et		0.0139	0.0197	0.0192	0.0194
H	25	9.48	9.72	9.51	9.16
Me		0.939	0.876	0.856	0.789
Et		—	—	—	—

[a] Experimental conditions: see Table 1. [b] Mean value from at least five kinetic runs with an average standard deviation of 7%.

Table 3 Comparison of rate data for the reaction*

$$[Pd(R_2NCH_2CH_2NR_2)Cl(H_2O)]^+ + Nu \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Pd(R_2NCH_2CH_2NR_2)Cl(Nu)]^+ + H_2O$$

R	Nucleophile	k_3/dm^3 mol^{-1} s^{-1}	k_{-3}/s^{-1}	Source
H	Hmet	$(6.9 \pm 1.1) \times 10^3$	1.69 ± 0.04	Fig. 2(*a*)
	mcys	$(2.57 \pm 0.06) \times 10^3$	6.8 ± 0.3	Fig. 4(*a*)
	Ino	$(1.9 \pm 0.2) \times 10^3$		Ref. 6
	IMP	$(1.3 \pm 0.1) \times 10^4$		Ref. 6
Me	Hmet	$(3.7 \pm 0.1) \times 10^2$	1.24 ± 0.06	Fig. 2(*b*)
	mcys	$(3.07 \pm 0.06) \times 10^2$	0.20 ± 0.03	Fig. 4(*b*)
	Ino	$(4.0 \pm 0.6) \times 10^2$		Ref. 6
	IMP	$(3.1 \pm 0.3) \times 10^3$		Ref. 6
Et	Hmet	22 ± 1	0.046 ± 0.007	Fig. 2(*c*)
	Ino	11 ± 1		Ref. 6
	IMP	126 ± 19		Ref. 6

* At 25 °C and I = 0.1 mol dm^{-3}.

$(Hmet)]^+$ complexes (k_5 in Table 1) once again slows down significantly on increasing the steric hindrance R = H > Me > Et.

The data in Table 3 clearly demonstrate that Hmet and mcys behave very similarly to inosine (Ino) but significantly slower than inosine 5′-monophosphate (IMP). The first complex-formation step under the selected conditions involves S-donor co-ordination, followed by ring closure in the case of Hmet to produce the N,S-chelate.[11] Such a ring-closure reaction was not observed for mcys, but rather the attack of a second mcys molecule (see Fig. 5). This is in line with the general observation that for ligands that do not contain double bonds, those that

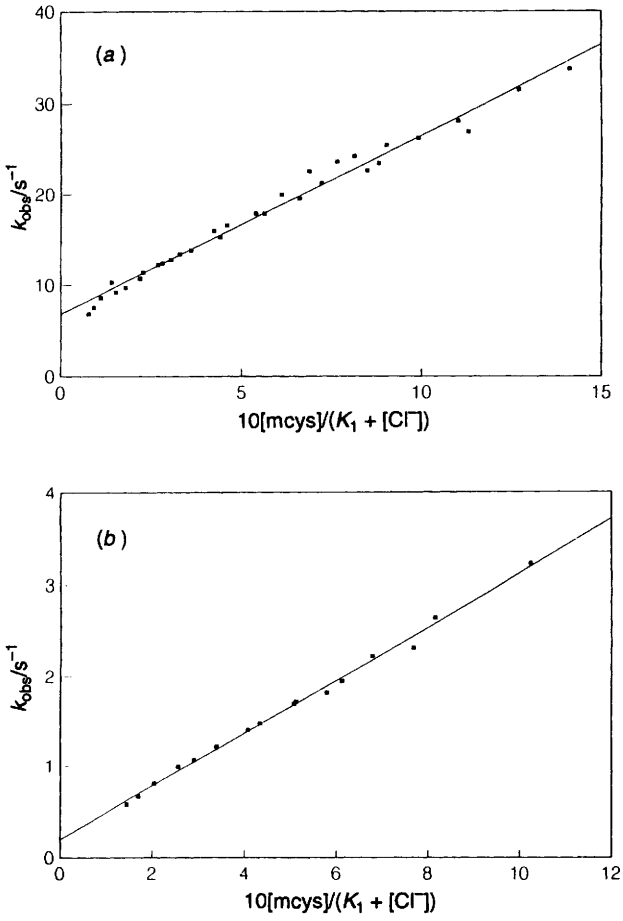


Fig. 4 Plots of k_{obs} *versus* [mcys]/(K_1 + [Cl^-]) for the reaction $[Pd(R_2NCH_2CH_2NR_2)Cl_2]$ + mcys ⟶ $[Pd(R_2NCH_2CH_2NR_2)Cl(mcys)]^+$ + Cl^-. Experimental conditions: see Table 1. R = H (*a*) or Me (*b*)

form six-membered chelates give the more stable products. The trend that the S-donor nucleophiles are less reactive than inosine 5′-monophosphate is also important, since this could affect the antitumour activity of the corresponding platinum(II) complexes.[11] Once such ligands are present in the co-ordination sphere of Pt^{II} and Pd^{II} they may significantly affect the subsequent substitution reactions, as well as the reactions with DNA constituents.[11,13,15,16] S-Donor ligands, especially, are expected to cause a significant labilization effect.[11] This aspect is presently under investigation in our laboratories.

Acknowledgements

The authors gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. S. S. kindly acknowledges a fellowship from the Commission of the European Communities through the National Research Council of Thailand, as well as sabbatical leave from the Prince of Songkla University, Songkla, Thailand which enabled him to participate in this work.

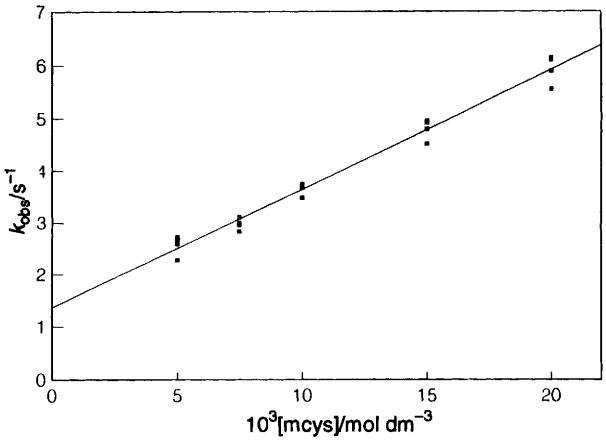


Fig. 5 Plot of k_{obs} *versus* [mcys] for the reaction $[Pd(en)Cl(mcys)]^+$ + mcys ⟶ $[Pd(en)(mcys)_2]^{2+}$ + Cl^-. Experimental conditions: see Table 1

References

1 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chim. Acta*, 1991, **188**, 25.
2 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chem.*, 1992, **31**, 345.
3 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chem.*, 1992, **31**, 1090.
4 M. Shoukry, H. Hohmann and R. van Eldik, *Inorg. Chim. Acta*, 1992, **198–200**, 187.
5 S. Suvachittanont, H. Hohmann, R. van Eldik and J. Reedijk, *Inorg. Chem.*, 1993, **32**, 4544.
6 S. Suvachittanont and R. van Eldik, *Inorg. Chem.*, 1994, **33**, 895.
7 W. I. Sundquist and S. J. Lippard, *Coord. Chem. Rev.*, 1990, **100**, 293; B. K. Keppler, *New J. Chem.*, 1990, **14**, 389; E. L. M. Lempers and J. Reedijk, *Adv. Inorg. Chem.*, 1991, **37**, 175; M. Green, M. Garner and D. M. Orton, *Transition Met. Chem.*, 1992, **17**, 164; J. Reedijk, *Inorg. Chim. Acta.*, 1992, **198–200**, 873.
8 E. L. J. Breet and R. van Eldik, *J. Chem. Soc., Chem. Commun.*, 1987, 408.
9 E. L. J. Breet and R. van Eldik, *Inorg. Chem.*, 1987, **26**, 2517.
10 R. Jacobs, F. Prinsloo and E. Breet, *J. Chem. Soc., Chem. Commun.*, 1992, 212.
11 T. G. Appleton, J. W. Connor and J. R. Hall, *Inorg. Chem.*, 1988, **27**, 130.
12 P. del S. Murdoch, J. D. Ranford, P. J. Sadler and S. J. Berners-Price, *Inorg. Chem.*, 1993, **32**, 2249.
13 P. Espinet, C. Lorenzo, J. A. Miguel, C. Bois and Y. Jeannin, *Inorg. Chem.*, 1994, **33**, 2052.
14 KINFIT, Olis, Bogart, GA, 1993.
15 M. Garner, M. Green, N. Boogard and J. Reedijk, *J. Chem Soc., Chem. Commun.*, 1993, **290**.
16 U. Frey, J. D. Ranford and P. J. Sadler, *Inorg. Chem.*, 1993, **32**, 1333.

Received 1*st February* 1995; *Paper* 5/00595G