DALTON
FULL PAPER

Kinetics and mechanisms of the ligand substitution reactions of bis(amine)(cyclobutane-1,1-dicarboxylato)palladium(II) †

Azza Shoukry, Tobias Rau, Mohamed Shoukry and Rudi van Eldik *

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

Received 2nd June 1998, Accepted 13th July 1998

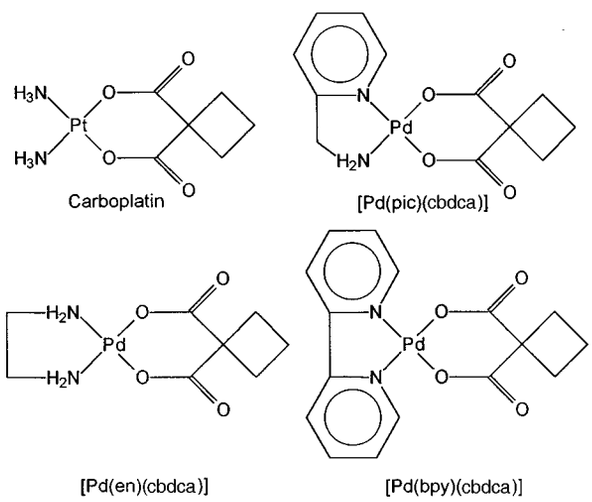
Kinetic and mechanistic investigations have been made on the displacement of the bidentate cyclobutane-1,1-dicarboxylate ligand (cbdca) from the complexes [Pd(en)(cbdca)] (en = ethane-1,2-diamine) and [Pd(bpy)(cbdca)] (bpy = 2,2′-bipyridine). Two consecutive reaction steps were observed for the substitution of cbdca with thiourea (tu), tetramethylthiourea (tmtu), inosine 5′-monophosphate (5′-IMP) and iodide, as well as for the acid-catalysed hydrolysis reaction. After displacement of cbdca by tu and tmtu the strong *trans* influence of the Pd-bound sulfur-containing nucleophiles resulted in displacement of the en ligand from [Pd(en)(cbdca)], whereas no such reaction was found to occur for [Pd(bpy)(cbdca)]. All rate and activation parameters are consistent with associative substitution mechanisms.

Introduction

The clinical application of the second generation drug carboplatin {*cis*-diammine(cyclobutane-1,1-dicarboxylato)-platinum(II), $[Pt(NH_3)_2(cbdca)]$} allowed a significant decrease of toxic side effects encountered in the treatment of cancer with cisplatin {*cis*-diamminedichloroplatinum(II), *cis*-$[Pt(NH_3)_2Cl_2]$}. It does not exhibit any neurotoxicity and significantly less nephrotoxicity than cisplatin,[1] which was attributed to the greater pharmacokinetic stability of the cbdca ligand.[2] Recent work on the reaction mode of carboplatin focused on the interaction with DNA building blocks[3] and sulfur-containing amino acids.[4] It was concluded that the reaction with carboplatin proceeds *via* a direct substitution mechanism, since the reaction with chloride was too slow to account for an aqua or chloro complex as the reactive species.[3–6]

For kinetic and mechanistic investigations of the mechanism of action of platinum(II) anticancer drugs their palladium(II) analogues are suitable model compounds since they exhibit *ca.* 10^4–10^5 times higher reactivities, whereas their structural and equilibrium behavior is similar.[7] Work in our laboratories has concentrated on reactions of *cis*-bis(amine)palladium(II) complexes with DNA building blocks,[8–11] sulfur containing amino acids,[12] the cbdca ligand[13] and simple nucleophiles such as chloride.[14] A decrease in reactivity was induced by increasing the steric hindrance on the amine ligands, and attributed to the axial sites becoming blocked for the incoming ligands. The introduction of palladium–sulfur[15] or platinum–carbon[16,17] bonds resulted in a significant labilization of the *trans* position, which led to increased reaction rates.

With the investigation of the substitution behavior and associated kinetics of [Pd(en)(cbdca)], where en = ethane-1,2-diamine, and [Pd(bpy)(cbdca)], where bpy = 2,2′-bipyridine, we extend our previous work on [Pd(pic)(cbdca)],[13] where pic = 2-pyridylmethylamine, to palladium(II) complexes of solely aliphatic or aromatic amine ligands, as shown below.



Experimental

Chemicals

Palladium(II) chloride was donated from Degussa, and ethane-1,2-diamine and 2,2′-bipyridine were obtained from Sigma and cyclobutane-1,1-dicarboxylic acid (H_2cbdca) from Aldrich. Inosine 5′-monophosphate (5′-IMP) and $NaClO_4$ were from Fluka, thiourea (tu) and sodium iodide from Merck, and tetramethylthiourea (tmtu) from Janssen. All substances were used without further purification. The complexes $[Pd(en)Cl_2]$[18] and $[Pd(bpy)Cl_2]$[19] were prepared according to literature procedures. For kinetic studies $[Pd(en)Cl_2]$ and $[Pd(bpy)Cl_2]$ were converted into the diaqua complexes by treating them with 2 equivalents of $AgNO_3$ as described before for $[Pd(en)Cl_2]$.[20] Ultra pure water was used to prepare all solutions.

Syntheses

[Pd(en)(cbdca)]. The complex $[Pd(en)Cl_2]$ (500 mg, 2.1 mmol) was stirred with $AgNO_3$ (700 mg, 4.12 mmol) in water (10 cm^3), 20 °C overnight in the dark. After filtering off the white AgCl precipitate, H_2cbdca (288 mg, 2.0 mmol) was added to the yellow filtrate. The pH was adjusted to 5 with NaOH and yellow crystals were isolated by vacuum filtration and washed three times with water, ethanol and diethyl ether. Drying in vacuum gave 520 mg (1.68 mmol; 80%) of fine yellow needles (Found: C, 31.25; H, 4.62; N, 9.07. Calc. for $C_8H_{14}N_2O_4Pd$: C, 31.13; H, 4.57; N, 9.07%).

[Pd(bpy)(cbdca)]. The complex $[Pd(bpy)Cl_2]$ (500 mg, 1.5 mmol) was stirred with $AgNO_3$ (424 mg, 2.5 mmol) in water (10 cm^3) for 2 h at 60 °C. After filtering off the white AgCl precipi-

† Dedicated to Professor Dr. Bernt Krebs on the occasion of his 60th birthday.

tate, H_2cbdca (216 mg, 1.5 mmol) was added to the yellow filtrate. Adjusting the pH to 5 gave yellow crystals which were isolated by vacuum filtration and washed three times with water, ethanol and diethyl ether. Drying in vacuum, gave 566 mg (1.4 mmol, 93%) (Found: C, 47.58; N, 6.99; H, 3.34. Calc. for $C_{16}H_{14}N_2O_4Pd$: C, 47.48; N, 6.92; H, 3.48%).

Instrumentation

Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. Kinetic measurements were carried out on an Applied Photophysics SX.18MV stopped-flow instrument coupled to an online data acquisition system. At least eight kinetic runs were recorded under all conditions, and the reported rate constants represent the mean values. The pH of the solutions, which was measured with a Mettler-Toledo electrode on a Mettler Delta 340 pH meter, was adjusted with $HClO_4$ or NaOH, and no buffers were added. Kinetic measurements were carried out at a complex concentration of 1.0 mM for [Pd(en)(cbdca)] and 0.1 mM for [Pd(bpy)(cbdca)], due to its low solubility, using a 0.10 M ionic strength which was adjusted with $NaClO_4$. All kinetic measurements were performed under pseudo-first-order conditions; *i.e.* at least a 10-fold excess of nucleophile was used. Except for the hydrolysis reactions and, if not otherwise stated, the pH of the solutions was in the range 6–7.

Spectroscopy

Proton NMR spectra were recorded in 5 mm tubes at 25 °C on a Bruker Avance DPX 300 spectrometer at 300.1 MHz using D_2O as solvent and referenced with respect to sodium 3-trimethylsilylpropionate as internal standard. Solutions of DNO_3 and NaOD were used to adjust the pH* that was not corrected for the deuterium isotope effect.

Results and discussion

^{1}H NMR spectra

The ^{1}H NMR spectra of the complexes [Pd(en)(cbdca)] and [Pd(bpy)(cbdca)], recorded under neutral conditions, exhibit triplets at δ 2.95 and 2.92, respectively for the H(β) protons, which indicate bidentate co-ordination of the cbdca ligand. They are shifted to lower field by *ca.* 0.6 ppm with respect to the signal of free cbdca, which exhibits peaks at δ 2.34 (pH* 7.00).[3] The quintets of the H(γ) resonances are observed at δ 1.93 and 1.91 for both complexes, respectively, shifted only slightly to lower field by *ca.* 0.1 ppm in comparison to that of free cbdca (at pH* 7.00, δ 1.82).[3] On addition of DNO_3 to the solutions to reach a pH* of *ca.* 1.0 the complexes are hydrolysed to give free H_2cbdca and the corresponding diaqua complexes $[Pd(en)(H_2O)_2]^{2+}$ and $[Pd(bpy)(H_2O)_2]^{2+}$. The resonances for the free fully protonated H_2cbdca are observed at δ 2.55 and 1.99 for H(β) and H(γ), respectively. The chemical shifts of the en and bpy ligands differ only slightly when comparing the cbdca with the diaqua complexes. The en ligand of [Pd(en)(cbdca)] gives a singlet at δ 2.67 for the CH_2 groups, whereas for the diaqua complex the signal is observed at δ 2.64. For both, [Pd(bpy)(cbdca)] and the corresponding diaqua complex, the ^{1}H resonances of the bpy ligand appear at δ 8.30 and 7.72. These small shift differences of the amine ligands can be explained in terms of small changes occurring in the first co-ordination sphere, since an oxygen donor ligand (carboxylate) is replaced by an oxygen donor ligand (water).

Kinetic investigations

Reaction of [Pd(en)(cbdca)] with acid. At a concentration of 1 mM the complex [Pd(en)(cbdca)] remains stable in solution in a pH range 3.5 to 7.0. At pH values lower than 3.5 the dicarboxylato ligand becomes protonated and this is consequently followed by dechelation. At pH ≤ 1 the cbdca ligand is removed quantitatively from the metal center. The UV/VIS spectra of the complex [Pd(en)(cbdca)] dissolved in water recorded as a function of pH clearly show a shift in the absorbance maximum from 320 to 360 nm on decreasing the pH from 6.0 to 1.0, which is characteristic for the aquation of [Pd(en)(cbdca)] to give $[Pd(en)(H_2O)_2]^{2+}$ and H_2cbdca. A typical plot of the absorbance at 360 nm as a function of pH is presented in Fig. 1, from which it follows that the overall aquation reaction [reactions (1)

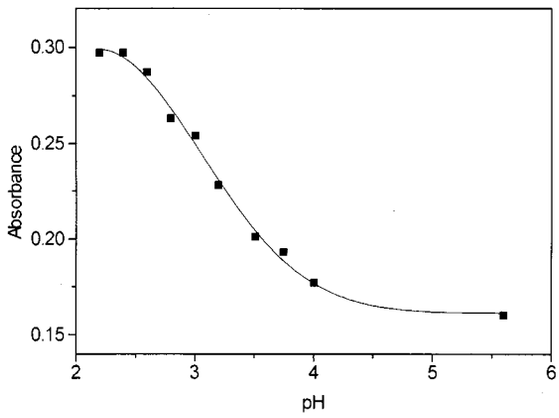


Fig. 1 Typical plot of the absorbance of [Pd(en)(cbdca)] as a function of pH. Experimental conditions: [Pd(en)(cbdca)] = 1.0 mM, I = 0.10 M, λ = 360 nm, T = 25 °C.

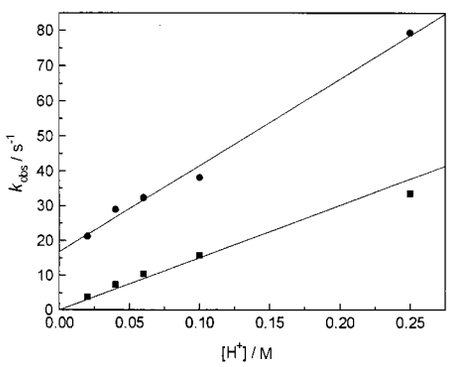


Fig. 2 Plot of k_{obs} *versus* [H^+] for the aquation of [Pd(en)(cbdca)]. Experimental conditions: [Pd^{II}] = 1.0 mM, I = 0.50 M, λ = 360 nm, T = 25 °C. ●, Fast step (1); ■, slow step (2).

$$[Pd(en)(cbdca\text{-}O,O')] + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Pd(en)(Hcbdca\text{-}O)(H_2O)]^+ \quad (1)$$

and (2)] is characterized by an apparent protonation constant (pK) of 3.2 ± 0.1.

$$[Pd(en)(Hcbdca\text{-}O)(H_2O)]^+ + H_3O^+ \xrightarrow{k_2} [Pd(en)(H_2O)_2]^{2+} + H_2cbdca \quad (2)$$

In order to study the hydrolysis reaction, [Pd(en)(cbdca)] was dissolved in water at pH 6 and treated with an excess of $HClO_4$. The reaction was monitored at 360 nm. At a proton concentration between 0.05 and 0.25 M two exponential functions, which both depend on the proton concentration, can be fitted to the resulting absorbance *vs.* time traces. A plot of k_{obs} *versus* [H^+] for both reaction steps (Fig. 2) shows linear dependencies on the proton concentration with a significant intercept for the fast and an insignificant intercept for the slow reaction step. The latter trend indicates that aquation of the ring-opened complex is irreversible. The ring opening itself is a reversible process, since deprotonation of the ring-opened intermediate will consequently result in ring closure. No significant contribution to the observed intercept for the fast reaction is expected to

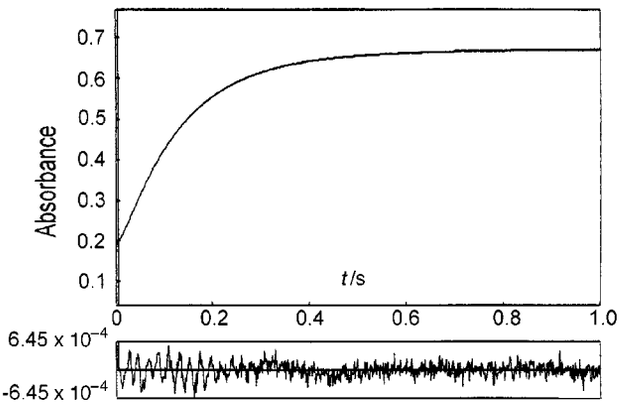


Fig. 3 Typical absorbance *vs.* time trace, fitted with three exponentials, for the reaction of [Pd(en)(cbdca)] with tu. Experimental conditions: $[Pd^{II}] = 1.0$ mM, $I = 0.10$ M, $\lambda = 340$ nm, pH ≈ 6, $T = 25$ °C. The deviation between the experimental and fitted curve is given below.

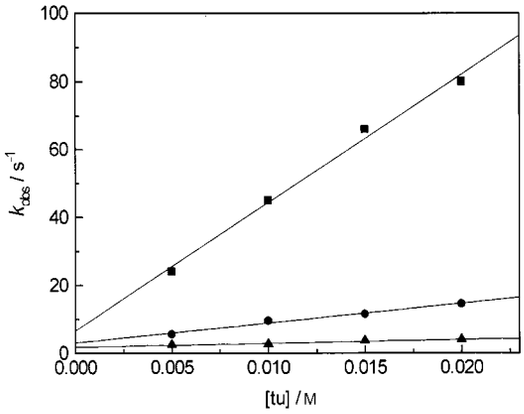


Fig. 4 Concentration dependence for the reaction of [Pd(en)(cbdca)] with tu. Experimental conditions as in Fig. 3. ■, Fast step (5); ●, slow step (6); ▲, slowest step (7).

come from the spontaneous reaction, since the complex is known to be stable at pH ⩾ 4. These data can be accounted for in terms of eqns. (1) and (2) in which the first reaction includes protonation and ring opening.

For the acid-catalysed reversible ring-opening reaction the rate equation $k_{1obs} = k_{-1} + k_1[H^+]$ is valid, whereas the subsequent aquation reaction proceeds *via* $k_{2obs} = k_2[H^+]$, since this step is not reversible, as indicated by a non-significant intercept of the concentration dependence in Fig. 2. Under such acidic conditions no k_{-2} reaction will occur, since free H_2cbdca is fully protonated. From the concentration dependence of the first reaction it follows that $k_{1app} = 247 \pm 13$ M^{-1} s^{-1} and $k_{-1app} = 17 \pm 2$ s^{-1} at 25 °C, and the slope for the second reaction k_{2app} has the value 151 ± 6 M^{-1} s^{-1}.

Since the apparent rate constants k_{app} for both steps are of the same order of magnitude, this simplified treatment is not fully correct in terms of biphasic consecutive reactions. In such a case a complete analysis method has to be applied, and eqns. (3) and (4) are derived.[21] From the slope of a plot of $k_{1obs} +$

$$k_{1obs} + k_{2obs} = (k_1 + k_2)[H^+] + k_{-1} \quad (3)$$

$$k_{1obs}k_{2obs} = k_1[H^+](k_2[H^+] + k_{-1}) \quad (4)$$

k_{2obs} *versus* $[H^+]$ the sum of $k_1 + k_2$ is obtained, whereas the intercept gives k_{-1}. A value of 373 ± 12 M^{-1} s^{-1} was calculated for $k_1 + k_2$, and a value of 19 ± 2 s^{-1} for k_{-1}. The slope of a plot of $k_{1obs}k_{2obs}/[H^+]$ *versus* $[H^+]$ gives a value of $(2.7 \pm 0.2) \times 10^4$ M^{-2} s^{-2} for the product k_1k_2. Combining the sum and the product of k_1 and k_2 yields values of 275 M^{-1} s^{-1} for k_1 and 98 M^{-1} s^{-1} for k_2. These correct values of k_1, k_{-1} and k_2 differ from those for k_{app}, but are of very similar magnitude.

The determined rate constants are in reasonable correspondence to earlier data for the [Pd(pic)(cbdca)] system.[13] For the acid-catalysed ring-opening reaction a somewhat larger value of 431 ± 9 M^{-1} s^{-1} with an intercept of >30 s^{-1} was found. Both values are somewhat larger for the pic system, which can be explained based on the enhanced electrophilicity of the metal center resulting from the aromatic pic ligand. For the second reaction step a rate constant of 101 ± 1 M^{-1} s^{-1} with no intercept was reported,[13] which is nearly identical to k_2 found for [Pd(en)(cbdca)] in Fig. 2.

Reaction of [Pd(en)(cbdca)] with thiourea and tetramethylthiourea

The reaction of [Pd(en)(cbdca)] with thiourea (tu) at pH ≈ 6, which is characterized by a shift in the absorbance maximum from 320 nm for [Pd(en)(cbdca)] to 340 nm for the corresponding thiourea complex, was followed by UV/VIS spectroscopy. Kinetic measurements were carried out at 340 nm where a significant absorbance change was observed, and absorbance *vs.* time traces could only be fitted by three exponentials as shown in Fig. 3. Various other kinetic models were tested without leading to satisfying fits of the kinetic traces. The concentration dependence of the three exponentials is presented in Fig. 4. The first step, outlined in reaction (5), shows a linear

$$[Pd(en)(cbdca\text{-}O,O')] + tu \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Pd(en)(cbdca\text{-}O)(tu)] \quad (5)$$

$$[Pd(en)(cbdca\text{-}O)(tu)] + tu \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} [Pd(en)(tu)_2]^{2+} + cbdca^{2-} \quad (6)$$

$$[Pd(en\text{-}N,N')(tu)_2]^{2+} + tu \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} [Pd(en\text{-}N)(tu)_3]^{2+} \quad (7)$$

$$k_{5a} \searrow +H_2O \qquad -H_2O \nearrow +tu \quad k_{5b}$$

$$[Pd(en\text{-}N)(tu)_2(H_2O)]^{2+}$$

$$[Pd(en\text{-}N)(tu)_3]^{2+} + tu \xrightarrow{fast} [Pd(tu)_4]^{2+} + en \quad (8)$$

concentration dependence with $k_3 = 3800 \pm 120$ M^{-1} s^{-1} at 25 °C with an insignificant intercept. This step is very fast and is suggested to involve formation of the ring-opened intermediate. The second step is slower ($k_4 = 580 \pm 50$ M^{-1} s^{-1}) and is assigned to the second nucleophilic substitution reaction (6). The intercepts associated with reactions (5) and (6), although not significant, are assumed to result from the corresponding back reactions rather than from the parallel solvolysis reactions, since no hydrolysis of [Pd(en)(cbdca)] was observed under neutral conditions. The third step is plausibly due to a further reaction with thiourea, which displaces the en ligand as a result of the *trans* influence of co-ordinated thiourea, as outlined in reaction (7).[4a,22] Free H_2en^{2+} can easily be detected in the ^{1}H NMR spectra. The amine labilization process has frequently been observed for reactions of such complexes with sulfur-containing amino acids.[23] For this reaction either a direct substitution [reaction (7), k_5] by the incoming nucleophile or substitution with prior displacement by a solvent molecule [reaction (7), k_{5a}/k_{5b}] is expected. This step is slow with respect to the substitution of cbdca and was found to depend on [tu] with a k_5 value of 110 ± 22 M^{-1} s^{-1}. It follows that the reaction, due to the [tu] dependence, proceeds *via* a direct substitution mechanism. An intercept of 1.8 ± 0.3 s^{-1} is attributed to contributions from the reverse reaction (k_{-5}) that includes ring closure of the ring-opened en and contributions from the solvolytic pathway k_{5a}. The displacement of the ring-opened en [reac-

Table 1 Temperature dependence and activation parameters for the substitution reactions of [Pd(en)(cbdca)] (1.0 mM) with tmtu, I^- and 5′-IMP, $I = 0.10$ M

Nu	T/°C	k_3/M^{-1} s^{-1}	k_{-3}/s^{-1}	k_4/M^{-1} s^{-1}	k_{-4}/s^{-1}	k_5/s^{-1}
tmtu	15.0	100 ± 4	0.18 ± 0.05	7.6 ± 0.60	0.181 ± 0.001	0.18 ± 0.01
	20.0	132 ± 8	0.21 ± 0.10	15.1 ± 0.7	0.21 ± 0.01	0.25 ± 0.01
	25.0	157 ± 2	0.45 ± 0.02	14.4 ± 2.0	0.39 ± 0.02	0.40 ± 0.02
	30.0	189 ± 8	0.62 ± 0.11	17.4 ± 1.5	0.64 ± 0.02	0.63 ± 0.03
	35.0	208 ± 3	1.40 ± 0.04	33 ± 3	0.78 ± 0.03	0.93 ± 0.05
	$\Delta H^{\ddagger}$/kJ mol^{-1}	23 ± 1	65 ± 6	50 ± 2	59 ± 6	60 ± 2
	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	−126 ± 4	−33 ± 20	−53 ± 6	−55 ± 19	−52 ± 8
I^-	15.0	158 ± 4	0.7 ± 0.3	14 ± 3.6	0.02 ± 0.01	
	20.0	186 ± 3	1.12 ± 0.04	16 ± 2	0.025 ± 0.002	
	25.0	206 ± 13	2.6 ± 0.2	20 ± 2	0.05 ± 0.03	
	30.0	300 ± 32	2.8 ± 0.4	28 ± 5	0.09 ± 0.03	
	35.0	400 ± 50	5.4 ± 0.7	31 ± 3	0.14 ± 0.03	
	$\Delta H^{\ddagger}$/kJ mol^{-1}	32 ± 2	66 ± 5	28 ± 0.8	72 ± 4	
	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	−92 ± 8	−17 ± 16	−126 ± 3	−29 ± 13	
5′-IMP	25.0	35 ± 3	0.0 ± 0.3	0.98 ± 0.05	0.010 ± 0.001	
	30.0	41.2 ± 0.7	0.03 ± 0.01	1.3 ± 0.2	0.023 ± 0.001	
	35.0	52 ± 5	0.04 ± 0.07	1.4 ± 0.2	0.041 ± 0.003	
	40.0	61.5 ± 0.7	0.083 ± 0.001	1.73 ± 0.01	0.060 ± 0.001	
	45.0	71.8 ± 0.5	0.131 ± 0.001	2.0 ± 0.6	0.120 ± 0.001	
	$\Delta H^{\ddagger}$/kJ mol^{-1}	26.2 ± 0.9	72 ± 2	27 ± 1	73 ± 2	
	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	−128 ± 3	−37 ± 7	−154 ± 4	−35 ± 7	

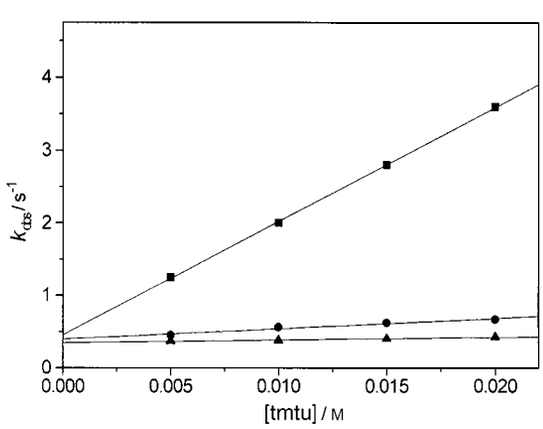


Fig. 5 Concentration dependence for the three reaction steps of [Pd(en)(cbdca)] with tmtu. Experimental conditions: [Pd^{II}] = 1.0 mM, $I = 0.10$ M, $\lambda = 350$ nm, pH ≈ 7, $T = 25$ °C. ■, Fast step (5); ●, slow step (6); ▲, slowest step (7).

tion (8)] is thought to be fast with respect to the ring-opening reaction. The overall substitution process is summarized in eqns. (5)–(8).

The choice of nucleophiles was extended from thiourea to tetramethylthiourea, since the reaction with thiourea was too fast to be monitored at a temperature higher than 25 °C. Tetramethylthiourea reacts much slower due to the steric effect of the bulky methyl groups. This reaction again exhibits three steps, as found for unsubstituted thiourea, and the nucleophile concentration dependence of the three rate constants is presented in Fig. 5. The corresponding rate constants are summarized in Table 1. It is observed that the rate constants of the three steps are significantly smaller than those for thiourea. This can be explained on the basis of steric effects caused by the methyl groups on tetramethylthiourea. The first and second substitution reactions, corresponding to reactions (5) and (6), depend on [tmtu] and exhibit significant intercepts. However, the third reaction step in Fig. 5 is nearly independent of [tmtu] and can be attributed to a first-order process, which contrasts the behavior of tu. It is believed that tmtu, due to the bulky methyl groups, prefers to react *via* a solvolysis path, where the rate constant is mainly determined by the *trans* influence of the co-ordinated ligands. This pathway is described in reaction (7) by the rate constants k_{5a} and k_{5b}.

The effect of temperature on the reactions of tetramethylthiourea with [Pd(en)(cbdca)], similar to those outlined in reactions (5) to (8), was studied in the range from 15 to 35 °C, and the results along with the thermal activation parameters are summarized in Table 1. The enthalpies of activation ($\Delta H^{\ddagger}$) of 23 ± 1, 50 ± 2 and 60 ± 2 kJ mol^{-1} for the three steps, respectively, are in fair agreement with those found for related palladium(II) complexes with substituted amine ligands.[24] The first reaction step exhibits the smallest activation enthalpy and is consequently more favored than the others. The third step shows the largest activation barrier and is consequently the least favored. This can be explained in terms of the displacement of a much stronger chelate in the case of en than in the case of cbdca. The activation entropies ($\Delta S^{\ddagger}$) for all reaction steps with tetramethylthiourea have significantly negative values, which is in line with associative substitution mechanisms. The large negative $\Delta S^{\ddagger}$ values for k_3 and k_4 can be ascribed to the dechelation of cbdca and the co-ordination of tetramethylthiourea. Ring opening and release of cbdca will be accompanied by a large increase in electrostriction due to charge creation. The dechelation of en in reaction (7) is characterized by a significantly negative $\Delta S^{\ddagger}$ value, suggesting that the solvolysis reaction path has an associative character.

Effect of pH on the release of cbdca and the reaction with tetramethylthiourea

The reaction of [Pd(en)(cbdca)] with tetramethylthiourea was investigated in the pH range 2.0–7.5 and the values of k_{obs} for the three reaction steps are plotted as a function of pH in Fig. 6. The k_{obs} values for the first two steps were found to increase with a decrease in pH. This may be explained on the basis that increasing the acidity of the solution will result in an increased contribution from dechelation of cbdca by acid hydrolysis (see Fig. 1) followed by the rapid reaction with tmtu. For the third reaction step the k_{obs} values were not significantly affected by a change in pH. This is probably due to the amine labilization mainly resulting from the *trans* influence of co-ordinated tmtu and that bond making, assumed to involve co-ordination of a solvent molecule, is the crucial step before ring opening can occur.

Table 2 Rate and equilibrium constants calculated from the effect of pH on the substitution of [Pd(en)(cbdca)] by tmtu according to reaction (9)

Parameter	First step	Second step
$k_7/M^{-1}\,s^{-1}$	202 ± 7	64 ± 5
$k_8/M^{-1}\,s^{-1}$	583 ± 11	142 ± 5
K_6/M	$(1.3 \pm 0.3) \times 10^{-4}$	$(3 \pm 1) \times 10^{-5}$
pK_6	3.9 ± 0.1	4.5 ± 0.2

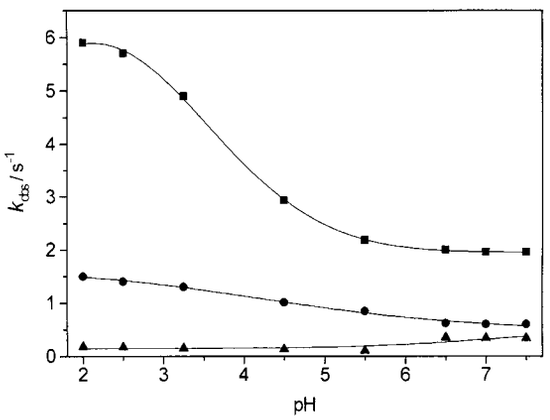


Fig. 6 pH Dependence for the three reaction steps of [Pd(en)(cbdca)] with tmtu. Experimental conditions: [Pd^{II}] = 1.0 mM, [tmtu] = 0.01 M, I = 0.10 M, T = 25 °C. ■, Fast step (5); ●, slow step (6); ▲, slowest step (7).

The pH dependence of the first and the second reaction steps (5) and (6) can be accounted for in terms of a protonation pre-equilibrium, in which co-ordinated cbdca is protonated, as indicated in the set of reactions (9a)–(9c) for reaction (5). A

$$[Pd(en)(Hcbdca\text{-}O,O')]^+ \overset{K_6}{\rightleftharpoons} [Pd(en)(cbdca\text{-}O,O')] + H^+ \quad (9a)$$

$$[Pd(en)(cbdca\text{-}O,O')] + tmtu \xrightarrow{k_7} [Pd(en)(cbdca\text{-}O)(tmtu)] \quad (9b)$$

$$[Pd(en)(Hcbdca\text{-}O,O')]^+ + tmtu \xrightarrow{k_8} [Pd(en)(Hcbdca\text{-}O)(tmtu)]^+ \quad (9c)$$

similar scheme can be written for the second substitution reaction (6). The rate equation for such an acid-catalysed process is given by (10) from which it follows that $k_{obs} = k_7$[tmtu] and $k_{obs} =$

$$k_{obs} = \frac{k_7K_6 + k_8[H^+]}{K_6 + [H^+]}[tmtu] \quad (10)$$

k_8[tmtu] at low and high [H$^+$], respectively. A fit of the data according to eqn. (10) resulted in the k_7, k_8 and K_6 values summarized in Table 2. The results clearly demonstrate the catalytic effect of H$^+$ on both substitution processes. It is noteworthy that the deprotonation constant (pK_6) values of co-ordinated cbdca for the two steps discussed above are lower[13] than the deprotonation constant of free Hcbdca$^-$ (5.46). The lowering of pK_6 is due to the acidification of cbdca as a result of complex formation. A similar behaviour was found in earlier investigations.[25,26]

Reaction of [Pd(en)(cbdca)] with iodide

On mixing [Pd(en)(cbdca)] and I$^-$ in the stopped-flow instrument two subsequent reactions can be observed at 380 nm, which correspond to (5) and (6) undergone with tu and tmtu. No subsequent release of en was observed in the reaction with I$^-$, which demonstrates that only the sulfur donor ligands are capable of labilizing en. The rate constants for these reactions (see Fig. 7) differ significantly, and they can easily be separated. The first reaction step shows a linear dependence of k_{obs} on the iodide concentration with a non-zero intercept. This can be expressed by the two-term rate eqn. (11),[14] where k_3 represents

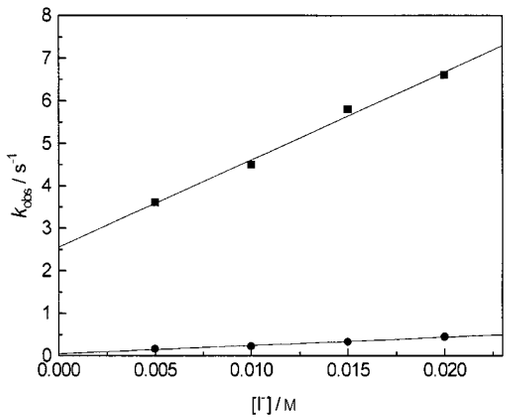


Fig. 7 Concentration dependence for the two reaction steps of [Pd(en)(cbdca)] with iodide. Experimental conditions: [Pd(en)(cbdca)] = 1.0 mM, I = 0.10 M, λ = 385 nm, pH ≈ 6, T = 25 °C. ■, Fast step; ●, slow step.

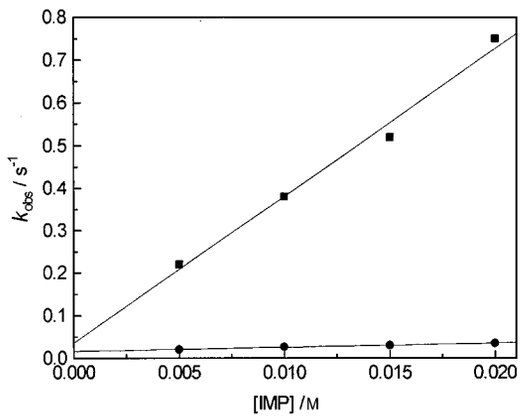


Fig. 8 Concentration dependence for the two reaction steps of [Pd(en)(cbdca)] with 5′-IMP. Experimental conditions: [Pd^{II}] = 1.0 mM, I = 0.10 M, λ = 320 nm, pH ≈ 7, T = 25 °C. ■, Fast step; ●, slow step.

$$k_{obs} = k_{-3} + k_3[I^-] \quad (11)$$

the concentration dependent reaction rate constant. The concentration independent term (k_{-3}) represents contributions from the back reaction, which is possibly due to the ring-closure reaction. The linear dependence of k_{obs} on the iodide concentration for the second step shows a nearly zero intercept. This is due to the absence of any significant chance for a backward reaction when cbdca is completely replaced by iodide, as observed for tu and tmtu. The values of k_3, k_{-3}, k_4 and k_{-4} are included in Table 1.

The effect of temperature on these reactions was studied at five different temperatures in the range from 15 to 35 ° C, and the activation parameters are shown in Table 1. The $\Delta H^‡$ values correspond well with those found for reactions of related palladium(II) complexes with similar amine ligands.[14] The $\Delta S^‡$ values are significantly negative, indicating associative mechanisms for these reactions.

Reaction of [Pd(en)(cbdca)] with inosine 5′-monophosphate

The reaction of [Pd(en)(cbdca)] with 5′-IMP, taken as a representative example of DNA constituents, was investigated on the stopped-flow instrument at 315 nm, where an increase in absorbance due to product formation was observed. From the

kinetic time traces two exponential functions could be resolved (Fig. 8), as summarized in Table 1. The faster step was attributed to the ring-opening process and co-ordination of the first 5′-IMP molecule, whereas the slower reaction was assigned to the displacement of the ring-opened cbdca. For both reaction steps linear dependencies of k_{obs} on the 5′-IMP concentration with nearly zero intercepts were found, revealing the absence of any significant backward reaction. This may be explained on the basis of strong coulombic forces operating between the negatively charged 5′-IMP anion and the palladium(II) complex. The formation of hydrogen bonds between the phosphates and the NH groups of the en ligand is also assumed to account for the less efficient back reactions,[27] since this will favor the forward reaction and consequently the reaction will be irreversible. However, at high temperatures the concentration dependence plots for both reaction steps show significant intercepts, which reveal the presence of the back reactions under such conditions. The reaction steps are similar to those in (5) and (6).

$$[Pd(en)(cbdca\text{-}O,O')] + 5'\text{-}IMP^{2-} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Pd(en)(cbdca\text{-}O)(IMP)]^{2-} \quad (5)$$

$$[Pd(en)(cbdca\text{-}O)(IMP)]^{2-} + 5'\text{-}IMP^{2-} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} [Pd(en)(IMP)_2]^{2-} + cbdca^{2-} \quad (6)$$

Experiments were also performed in the presence of an excess of cbdca in order to check the reversibility of the substitution process. Both reaction steps exhibited a linear dependence on the cbdca concentration at a fixed 5′-IMP concentration due to the competition between co-ordination of cbdca and 5′-IMP. The dependence of reaction (5) on [cbdca] is thought to result from the attack of a second cbdca molecule on the ring-opened species to form [Pd(en)(Hcbdca-*O*)$_2$]. Thus cbdca can compete efficiently with DNA moieties such as 5′-IMP in binding to Pd^{II}.

A pressure dependence study was performed in order to evaluate $\Delta V^{\ddagger}$. Unfortunately, it was not possible to determine meaningful values since only poor absorbance *vs.* time traces could be resolved under pressure. The thermal activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are summarized in Table 1 and correspond to an associative mechanism.

Reaction of [Pd(en)Cl$_2$] with thiourea

By way of comparison for the [Pd(en)(cbdca)] complex we also studied the substitution behavior of the corresponding dichloro complex. The reaction of [Pd(en)Cl$_2$] with thiourea was followed by UV/VIS stopped-flow spectroscopy. Kinetic measurements were carried out at 340 nm, where the largest change in absorbance was observed. Preliminary experiments with [Pd(en)Cl$_2$] indicated that three exponential functions could be fitted to the absorbance *vs.* time traces. Owing to aquation of the dichloro complex, it is more difficult to obtain rate constants for the [Pd(en)Cl$_2$] complex, since the hydrolysed species will react much faster. The equilibria involved in such a reaction system are outlined in eqns. (12a) and (12b). In the

$$[Pd(en)Cl_2] + H_2O \rightleftharpoons [Pd(en)(H_2O)Cl]^+ + Cl^- \quad (12a)$$

$$[Pd(en)(H_2O)Cl]^+ + H_2O \rightleftharpoons [Pd(en)(H_2O)_2]^{2+} + Cl^- \quad (12b)$$

absence of added Cl^- the monoaqua species will predominate in solution.

For this reason the reactions of thiourea with [Pd(en)Cl$_2$] were investigated in media of increasing chloride concentration in the range 0.00–0.05 M. The results, presented in Fig. 9, show a significant decrease in k_{obs} on increasing the [Cl^-], reaching limiting conditions at a Cl^- concentration of *ca.* 0.04 M. This is accounted for on the basis that the concentration of the more

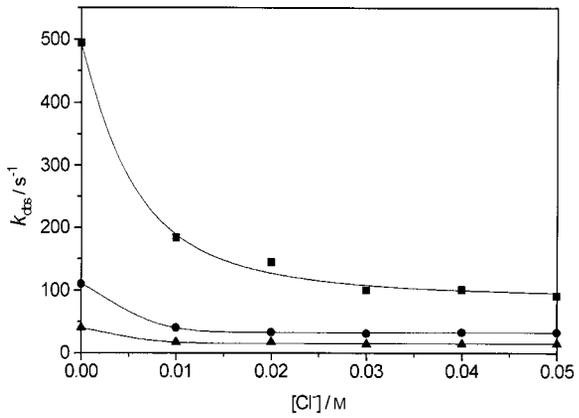


Fig. 9 Typical plot of k_{obs} *versus* [Cl^-] for the reaction of [Pd(en)Cl$_2$] with tu. Experimental conditions: [Pd^{II}] = 1.0 mM, [tu] = 10 mM, I = 0.1 M, λ = 340 nm, pH ≈ 6, T = 25 °C. ■, Fast step (5); ●, slow step (6); ▲, slowest step (7).

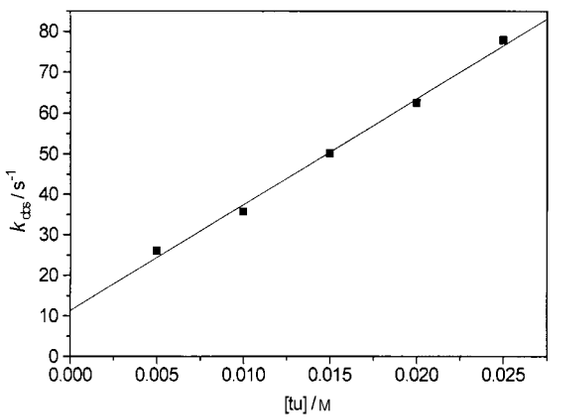


Fig. 10 Concentration dependence for the reaction of [Pd(en)Cl$_2$] with tu. Experimental conditions: [Pd^{II}] = 1.0 mM, [Cl^-] = 0.1 M, I = 0.10 M, pH ≈ 6, T = 25 °C.

reactive species, the mono- and di-aqua complexes, decrease on increasing [Cl^-], and this in turn will result in a decrease in k_{obs} for the various reaction steps. However, at [Cl^-] > 0.05 M only one step, assigned to that of the dichloro complex, could be resolved from the absorbance *vs.* time traces. The reaction of [Pd(en)Cl$_2$] with thiourea was therefore investigated at a high chloride ion concentration (0.10 M) where only one exponential function is observed, which corresponds again to k_3 and k_{-3} of the cbdca complex, as shown in reaction (13).

$$[Pd(en)Cl_2] + tu \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Pd(en)Cl(tu)]^+ + Cl^- \quad (13)$$

The [tu] dependence of k_{obs} (see Fig. 10) can be explained on the basis that under such a high chloride ion concentration only the first substitution reaction is accomplished. The second reaction step, leading to the formation of $[Pd(en)(tu)_2]^{2+}$, is obviously hindered as a result of the high chloride ion concentration. The concentration dependence of k_{obs} with thiourea is linear with an intercept, representing either the parallel solvolysis or the back reaction. The latter may be explained on the basis that the presence of a high chloride ion concentration will enhance the back reaction. The resulting rate constant for this reaction (from Fig. 10; [Cl^-] = 0.10 M) k_3 has a value of 2600 ± 110 M^{-1} s^{-1} and for the back reaction k_{-3}[Cl^-] has a value of 11 ± 2 s^{-1}. Rate constant k_3 is slightly smaller than that found for [Pd(en)(cbdca)], which allows us to conclude that [Pd(en)(cbdca)] exhibits a rather similar reactivity to that of the dichloro complex, if for the latter the solvolysis path is excluded and only the direct substitution path is taken into account.

In terms of biological implications the following conclusion can be drawn. The reactivities of [Pd(en)(cbdca)] and [Pd(en)-

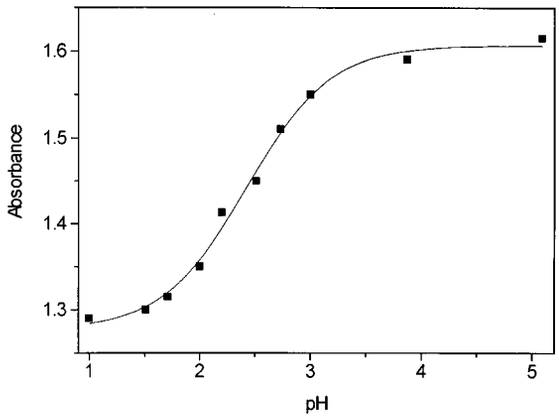


Fig. 11 Typical plot of the absorbance of [Pd(bpy)(cbdca)] *versus* pH. Experimental conditions: [Pd(bpy)(cbdca)] = 0.1 mM, I = 0.10 M, λ = 240 nm, T = 25 °C.

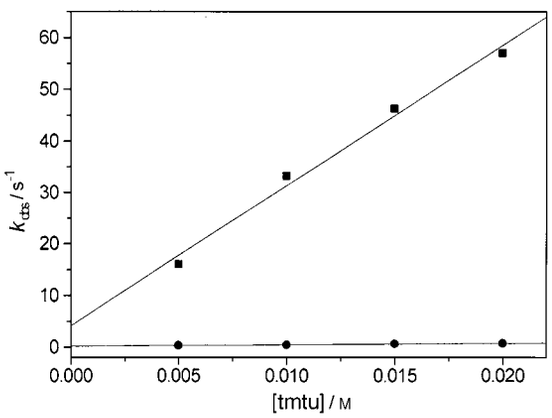


Fig. 12 Concentration dependence for the two reaction steps of the reaction between [Pd(bpy)(cbdca)] and tmtu. Experimental conditions: [Pd^{II}] = 0.1 mM, I = 0.10 M, λ = 380 nm, pH ≈ 5.8, T = 25 °C.

Cl_2] in blood, where [Cl^-] ≈ 0.1 M, are expected to be nearly identical. However, in the cell, where [Cl^-] ≈ 0.004 M, the hydrolysed species of the dichloro complex are expected to lead to a much higher reactivity, whereas the reactivity of [Pd(en)(cbdca)] would remain nearly unchanged, since this complex reacts *via* a direct substitution mechanism.

Reaction of [Pd(bpy)(cbdca)] with acid

The UV/VIS spectrum of [Pd(bpy)(cbdca)] under neutral conditions shows two absorption maxima at 310 and 240 nm, and the effect of pH on the absorbance at 240 nm is presented in Fig. 11. The decrease in absorbance with decreasing pH is due to dechelation of cbdca, which is characterized by a conditional reciprocal pK value of 2.5. This value is significantly lower than that of the corresponding ethane-1,2-diamine complex (pK = 3.2), which can be accounted for in terms of the higher stability of the Pd–O bonds of [Pd(bpy)(cbdca)] due to the π-accepting properties of the pyridine rings. We reported a similar apparent pK value of 2.24 for [Pd($NH_2CH_2C_5H_4N$-2)(cbdca)] before.[13]

A kinetic study of the [Pd(bpy)(cbdca)] hydrolysis reaction could not be performed since the absorbance change at suitable wavelengths was not large enough to be monitored reproducibly.

Reaction of [Pd(bpy)(cbdca)] with tetramethylthiourea

The reaction of [Pd(bpy)(cbdca)] with tmtu is accompanied by a similar spectral change to that reported for the corresponding en system. It consists of an absorbance increase at 380 nm due to product formation. The kinetic traces gave reproducible data when they were fitted with two exponential functions, for which the concentration dependence is shown in Fig. 12. The two

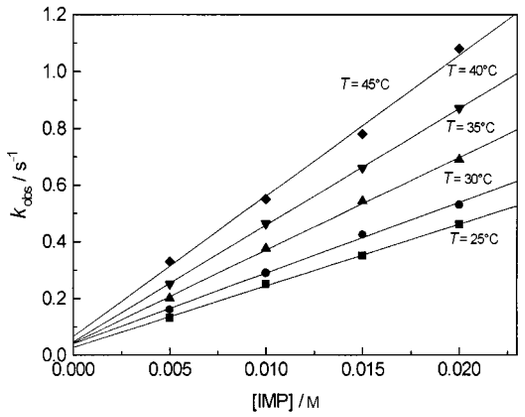


Fig. 13 Concentration dependence for the reaction of [Pd(bpy)(cbdca)] with 5′-IMP at different temperatures. Experimental conditions: [Pd^{II}] = 0.1 mM, I = 0.10 M, T = 25 °C, pH ≈ 6, λ = 320 nm.

steps correspond to the formation of [Pd(bpy)(cbdca-O)(tmtu)] and [Pd(bpy)$(tmtu)_2]^{2+}$. The kinetic data did not show any evidence for a third reaction as a result of *trans* labilization caused by tmtu, as found for the corresponding en system. This may be accounted for in terms of the stronger palladium–amine bond of the bpy complex as compared to that of the en complex. The bpy ligand has successfully been used before for the isolation of platinum(II) complexes of sulfur-containing amino acids.[28]

The effect of temperature on the two reaction steps (5) and (6) was investigated at five different temperatures in the range from 15 to 45 °C, and the activation parameters are given in Table 3. The rate constants for the first reaction step of [Pd(bpy)(cbdca)] with tmtu are *ca.* 17 times faster than those of the corresponding en complex, whereas for the second step the factor is less than two. The $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values are in reasonable agreement with those of the ethane-1,2-diamine system.

Reaction of [Pd(bpy)(cbdca)] with 5′-IMP

The UV/VIS spectra for the reaction of [Pd(bpy)(cbdca)] with 5′-IMP show a maximum increase of absorbance at around 320 nm. The absorbance *vs.* time traces clearly indicate the presence of only one reaction step for which the concentration dependence is shown in Fig. 13. This behavior is different to that found for the corresponding en complex, where two steps with the rate constants k_3 and k_4 of 35 ± 3 and 0.98 ± 0.05 M^{-1} s^{-1}, respectively (see Table 1), were reported. The second-order rate constant for [Pd(bpy)(cbdca)] is 21.7 ± 0.5 M^{-1} s^{-1}. Based on these data and those obtained for the tmtu ligand before, it follows that the reaction observed for the [Pd(bpy)(cbdca)]–5′-IMP system must be due to the second substitution reaction step (6), as shown in Table 3. It is assumed that the first step (5) is too fast to be followed by conventional stopped-flow techniques. The temperature dependence resulted in the activation parameters quoted in Table 3, which are in good agreement with those found for tmtu.

When comparing the reactivities of [Pd(en)(cbdca)] and [Pd(bpy)(cbdca)], it is evident that the lability of the cbdca ligand is strongly influenced by the character of the diamine chelate. In the case of tmtu the reactivity is enhanced by a factor of *ca.* 17 in going from en to bpy. This can be explained based on chelate ring aromaticity[29] and the π-back bonding in case of the bpy ligand, which will increase the positive charge on the metal center making it more electrophilic for the entering nucleophiles. The π-back bonding also results in lower conditional reciprocal formation constants (pK values) of 2.5 and 2.2 for the bpy and pic[13] complexes, respectively, in comparison to 3.2 for the en complex. This also results in stronger Pd–O bonds for the complexes with aromatic ligands.

The effect of strong π-back bonding is also observed for the

Table 3 Temperature dependence and activation parameters for the substitution reactions of [Pd(bpy)(cbdca)] (0.1 mM) with tmtu and 5′-IMP, $I = 0.10$ M

Nu	T/°C	k_3/M^{-1} s^{-1}	k_{-3}/s^{-1}	k_4/M^{-1} s^{-1}	k_{-4}/s^{-1}
tmtu	15.0	1740 ± 200	2 ± 3	13.5 ± 0.6	0.062 ± 0.008
	20.0	2030 ± 140	3 ± 2	21.2 ± 0.7	0.091 ± 0.009
	25.0	2720 ± 200	4 ± 3	28 ± 3	0.16 ± 0.03
	30.0	3050 ± 270	5 ± 4	36 ± 2	0.22 ± 0.02
	40.0	4000 ± 550	7 ± 6	48 ± 7	0.62 ± 0.09
	$\Delta H^{\ddagger}$/kJ mol^{-1}	23 ± 1	34 ± 2	36 ± 3	66 ± 3
	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	−104 ± 4	−120 ± 7	−99 ± 10	−41 ± 9
5′-IMP	25.0			21.7 ± 0.5	0.026 ± 0.001
	30.0			25 ± 1	0.035 ± 0.01
	35.0			33 ± 1	0.042 ± 0.001
	40.0			40 ± 1	0.05 ± 0.01
	45.0			50 ± 3	0.065 ± 0.03
	$\Delta H^{\ddagger}$/kJ mol^{-1}			31 ± 2	32 ± 2
	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}			−115 ± 6	−168 ± 5

displacement reaction of the diamine chelates by tu and tmtu; bpy is bound so strongly to Pd^{II} that no such reaction is observed as it was for the en ligand, which is easily displaced by tmtu.

Conclusion

The pharmacokinetic stability of the cbdca ligand results mainly from its inertness to hydrolysis under neutral conditions and its chelate effect. The complex [Pd(en)(cbdca)] reacts *via* a direct substitution mechanism and is not involved in the formation of reactive aqua complexes as it is observed for $[Pd(en)Cl_2]$. The reactivities of the cbdca and dichloro complexes are comparable, if for $[Pd(en)Cl_2]$ only the dichloro complex and not the corresponding aqua complexes are considered. The aqua complex $[Pd(en)(H_2O)_2]^{2+}$ reacts in the case of iodide *ca.* two orders of magnitude faster than [Pd(en)(cbdca)].[14] The aromatic diamine chelate ligand bpy increases the reactivity of the [Pd(N–N)(cbdca)] complex due to the chelate ring aromaticity and the electron withdrawing effect of the π-back bonding, thus making the metal center a more attractive target for incoming nucleophiles. The cbdca ligand becomes more strongly bound in the case of bpy than en, which is clearly demonstrated by the lower reciprocal conditional formation constant (pK) for the overall aquation reaction of 2.5 and 3.2, respectively. The π-back bonding also leads to the increased stability of the bpy–palladium bonds, since the bpy ligand is not so easily displaced as the en ligand.

The ring-opening reaction of the chelated cbdca ligand is accompanied by a large contribution of the back reaction in the case of iodide. Only strong nucleophiles such as the sulfur-containing ligands or the purine base 5′-IMP decrease the possibility of ring closure of the ring-opened en chelate. This is attributed to the soft character of the sulfur ligands having a high affinity for Pt^{II} or Pd^{II}, or stabilization of the ring-opened intermediate by interaction of the nucleotide phosphate with the NH group. The tu and tmtu ligands lead to displacement of the en, as is observed for cisplatin and carboplatin, which are inactivated by the strong binding to sulfur-containing amino acids and the resulting amine labilization.

Acknowledgements

The authors gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft (DFG), Fonds der Chemischen Industrie, Deutsche Akademische Austauchdienst for a stipend to Azza Shoukry, and DFG for a stipend to Mohamed Shoukry. A. S. and M. S. thank the Department of Chemistry, University of Cairo for leave.

References

1 A. J. Wagstaff, A. Ward, P. Benfield and R. C. Heel, *Drugs*, 1989, **37**, 162.
2 M. E. Heim, *Metal Complexes in Cancer Chemotherapy*, ed. B. K. Keppler, VCH, Weinheim, 1993, p. 9.
3 U. Frey, J. D. Ranford and P. J. Sadler, *Inorg. Chem.*, 1993, **32**, 1333.
4 (*a*) K. J. Barnham, M. I. Djuran, P. del S. Murdoch, J. D. Ranford and P. J. Sadler, *Inorg. Chem.*, 1996, **35**, 1065; (*b*) Z. Guo, T. W. Hambley, P. del S. Murdoch, P. J. Sadler and U. Frey, *J. Chem. Soc.*, *Dalton Trans.*, 1997, 469.
5 M. A. Allsopp, G. J. Sewell, C. G. Rowland, C. M. Riley and R. L. Schowen, *Int. J. Pharm.*, 1991, **69**, 197.
6 L. Canovese, L. Cattalini, G. Chess and M. L. Tobe, *J. Chem. Soc.*, *Dalton Trans.*, 1988, 2135.
7 T. Rau and R. van Eldik, *Metal Ions in Biological Systems*, eds. A. Sigel and H. Sigel, Marcel Dekker, New York, 1996, vol. 32, p. 339.
8 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chem.*, 1992, **31**, 345; 1091.
9 M. Shoukry, H. Hohmann and R. van Eldik, *Inorg. Chim. Acta*, 1992, **198**–**200**, 187.
10 S. Suvachittanont and R. van Eldik, *Inorg. Chem.*, 1994, **33**, 895.
11 S. Suvachittanont, H. Hohmann, R. van Eldik and J. Reedijk, *Inorg. Chem.*, 1993, **32**, 4544.
12 S. Suvachittanont and R. van Eldik, *J. Chem. Soc.*, *Dalton Trans.*, 1995, 2027.
13 T. Rau, M. Shoukry and R. van Eldik, *Inorg. Chem.*, 1997, **36**, 1454.
14 H. Hohmann, B. Hellquist and R. van Eldik, *Inorg. Chim. Acta*, 1991, **188**, 25; H. Hohmann, S. Suvachittanont and R. van Eldik, *Inorg. Chim. Acta*, 1990, **177**, 51.
15 F. F. Prinsloo, J. J. Pienaar and R. van Eldik, *J. Chem. Soc.*, *Dalton Trans.*, 1995, 3581.
16 M. Schmülling, A. D. Ryabov and R. van Eldik, *J. Chem. Soc.*, *Dalton Trans.*, 1994, 1257.
17 M. Schmülling, D. M. Grove, G. van Koten, R. van Eldik, N. Veldman and A. L. Spek, *Organometallics*, 1996, **15**, 1384.
18 H. Hohmann and R. van Eldik, *Inorg. Chim. Acta*, 1990, **174**, 87.
19 B. McCormick, E. N. Jr. Jaynes and R. I. Kaplan, *Inorg. Synth.*, 1971, **13**, 217.
20 G. Mahal and R. van Eldik, *Inorg. Chem.*, 1985, **24**, 4165.
21 A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, 1970, **92**, 5432.
22 N. S. Kurnakov, *Russ. Phys.-Chem. Soc.*, 1893, **25**, 565.
23 L. Zhu and N. M. Kostic, *Inorg. Chim. Acta*, 1994, **217**, 21; T. Rau, R. Alsfasser, A. Zahl and R. van Eldik, *Inorg. Chem.*, in the press.
24 M. Kotowski and R. van Eldik, *Inorganic High Pressure Chemistry*, ed. R. Eldik, Elsevier, Amsterdam, 1986, p. 219.
25 M. Shoukry and R. van Eldik, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 2673.
26 H. Sigel, S. S. Massoud and N. Corfu, *J. Am. Chem. Soc.*, 1994, **116**, 2958.
27 T. Rau and R. van Eldik, *Chem. Ber.*, 1997, **130**, 1551.
28 K. A. Mitchell and C. M. Jensen, *Inorg. Chem.*, 1995, **34**, 4441; L. Kumar, N. R. Kandasamy and T. S. Srivastava, *Inorg. Chim. Acta*, 1982, **67**, 139.
29 P. Haake and P. A. Cronin, *Inorg. Chem.*, 1963, **2**, 879.

Paper 8/04141E