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Equilibrium and kinetic data for the interaction of diaqua-(*S*-methyl-L-cysteine)palladium(II) with biologically relevant ligands †

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The complex-formation equilibria of $[Pd(SMC)(H_2O)_2]^+$ (SMC = *S*-methyl-L-cysteine) with inosine, inosine-5′-monophosphate, guanosine-5′-monophosphate, L-glycine and 1,1-cyclobutanedicarboxylate have been studied. The stoichiometry and stability constants of the formed complexes are reported, and the concentration distribution of the various complex species has been evaluated as a function of pH. The kinetics and mechanism of the complex-formation reactions were studied as a function of nucleophile concentration, temperature and pressure. Two consecutive reaction steps, which both depend on the nucleophile concentration, were observed under all conditions. The negative entropies and volumes of activation support the operation of an associative complex-formation mechanism. The results are compared and discussed in reference to data reported for closely related systems in the literature.

Introduction

Palladium(II) complexes are suitable model compounds for mechanistic studies on the action of platinum(II) anticancer drugs, since they exhibit a 10^4 to 10^5-fold higher reactivity, whereas their structural and equilibrium behaviours are rather similar.[1] Work in our laboratories has concentrated on the kinetics and mechanisms of complex-formation and ligand substitution reactions of palladium(II) complexes with nucleobases, nucleosides, and nucleotides.[2–10] The goal of these studies was to contribute toward the mechanistic understanding of the interaction of the related anticancer drug cisplatin with DNA and its constituents. This work was extended to investigate the kinetic tuning of such complexes *via* steric and electronic effects. In this respect, the introduction of palladium–sulfur[11] and platinum–carbon[12,13] bonds resulted in a significant labilization of the *trans*-position in aqueous solution, which led to a significant increase in the rate of the ligand substitution reactions.

From another point of view, the chemistry of transition metal complexes containing sulfur donor amino acid ligands is of considerable biological importance, since chelation plays an important role in the biological activity of such ligands. Furthermore, the continued interest in platinum-based antitumor compounds is stimulated by the fact that certain tumors are resistant to the clinically used drugs cisplatin and carboplatin. It is now generally accepted that the interaction of cisplatin with DNA is responsible for its antitumor activity.[14,15] A number of reports have dealt with the interaction of cisplatin with L-methionine to produce *S*,*N*-chelated platinum(II) complexes.[16–18] Also, studies on the interaction of the drug carboplatin with sulfur-containing biomolecules suggest that long-lived Pt(II)–methionine adducts may be important metabolites *in vivo*.[19] The crystal structure of dichloro-(*S*-methyl-L-cysteine)palladium(II) shows that *S*-methyl-L-cysteine behaves as a bidentate ligand coordinated through sulfur and nitrogen to the palladium centre in which the carboxylic group is not involved in the coordination.[20] However, once such ligands are present in the coordination sphere of Pt(II) and Pd(II) complexes, they may affect the subsequent substitution behaviour.

In an effort to extend our earlier work,[5,6,11] we have now performed a detailed investigation of the complex-formation kinetics of $[Pd(SMC)(H_2O)_2]^+$, where SMC = *S*-methyl-L-cysteine, with inosine (INO), inosine-5′-monophosphate (5′-IMP), guanosine-5′-monophosphate (5′-GMP), 1,1-cyclobutanedicarboxylate (CBDCA) and L-glycine in an aqueous solution, as a function of nucleophile concentration, temperature and pressure.

Experimental

Materials

The complex $[Pd(SMC)Cl_2]\cdot H_2O$ was synthesized and characterized according to literature procedures for the synthesis of palladium and platinum complexes of *S*-methyl-L-cysteine, L-methionine and its derivatives,[21–24] but using 0.1M HCl as solvent instead of water. The chemical analysis and UV-VIS spectral data were in good agreement with those obtained in previous preparations. (Found: N, 4.24; C, 14.60; H, 3.35; S, 9.71. Calc.: N, 4.24; C, 14.52; H, 3.32; S, 9.68%.)

The complex was converted in solution into the diaqua form by treating it with 2 equivalents of $AgClO_4$, as described elsewhere.[25] The carboxylate group is protonated in acidic aqueous media. Deprotonation occurs above pH 2.5 to form $[Pd(SMC)(H_2O)_2]^+$. The ligands *S*-methyl-L-cysteine (Fluka), inosine, inosine 5′-monophosphate sodium salt hydrate, guanosine-5′-monophosphate sodium salt hydrate and 1,1-cyclobutanedicarboxylic acid were obtained from Sigma and

† Electronic supplementary information (ESI) available: kinetic data for the interaction of diaqua-(*S*-methyl-L-cysteine)palladium(II) with inosine, inosine-5′-monophosphate, guanosine-5′-monophosphate, L-glycine and 1,1-cyclobutanedicarboxylate as a function of temperature and pressure. See http://www.rsc.org/suppdata/dt/b2/b206068j/

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used without further purification. The pH of the solutions was adjusted with $HClO_4$ and NaOH to 2.50, and was 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 solutions to 0.1 M in the final reaction mixture.

Instrumentation

Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. UV-VIS spectra were recorded on Shimadzu UV 250 and Hewlett-Packard 8452A diode-array spectrophotometers with thermostated 1.00 cm quartz Suprasil cells. pH titrations were performed on an automatic titrator (Metrohm 702 SM Titrino). Kinetic measurements were carried out on an Applied Photophysics SX.18MV stopped-flow instrument coupled to an online data acquisition system. Kinetic measurements at ambient pressure were performed on a Durrum D110 stopped-flow instrument attached to an online data acquisition system[26] with which the kinetic traces were evaluated using the KINFIT (OLIS, Bogart, GA) set of programs. Experiments at elevated pressure (up to 130 MPa) were performed on a homemade high-pressure stopped-flow unit.[27] The temperature was controlled throughout all kinetic experiments to ±0.1 °C. All kinetic measurements were performed under pseudo-first-order conditions, *i.e.* at least a 10-fold excess of the nucleophile was used.

pH titrations

The titroprocessor was calibrated with standard buffer solutions prepared according to NBS specifications.[28] The acid dissociation constants of 1,1-cyclobutanedicarboxylic acid, inosine, inosine-5′-monophosphate and guanosine-5′-monophosphate, were determined by titrating 0.10 mM samples of each with standard NaOH solution. 5′-IMP and 5′-GMP were prepared in equimolar $HClO_4$ solution in order to protonate the phosphate group. The acid dissociation constants of the coordinated water molecules in $[Pd(SMC\text{-}H)(H_2O)_2]^{2+}$ were determined by titrating 0.098 mM of the complex with NaOH. The formation constants of the complexes were determined by titrating solution mixtures of $[Pd(SMC\text{-}H)(H_2O)_2]^{2+}$ (0.098 mM) and the ligand in the concentration ratio 1:1 for CBDCA and glycine, and ratio 1:2 (Pd:ligand) for the DNA constituents. The titration solution mixtures each had a volume of 40 ml and the titrations were carried out at 25 °C and 0.1 M ($NaClO_4$) ionic strength. A 0.091 M NaOH solution was used as titrant.

The equilibrium constants evaluated from the titration data (summarized in Table 1), are defined by eqns. (1) and (2).

$$pM + qL + rH \rightleftarrows (M)_p(L)_q(H)_r \quad (1)$$

$$\beta_{pqr} = [(M)_p(L)_q(H)_r]/[M]^p[L]^q[H]^r \quad (2)$$

(Charges are omitted for simplicity)

M, L and H represent $[Pd(SMC)(H_2O)_2]^+$, nucleophile and proton, respectively. The calculations were performed using the program MINIQUAD-75.[28] The stoichiometry and stability constants of the complexes formed were determined by fitting various possible composition models. The selected model gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drift in the magnitude of various residuals, as described elsewhere.[29] Concentration distribution diagrams were obtained using the program SPECIES.[30]

Kinetics measurements

The spectral changes resulting from mixing complex and nucleophile solutions were recorded over the wavelength range 220 to 550 nm to establish a suitable wavelength at which kinetic measurements could be performed. Reactions were initiated by mixing equal volumes of the complex and ligand solutions directly in the stopped-flow instrument and were followed for at least eight half-lives. Complex-formation was monitored as an increase in absorbance at 315 or 320 nm, and as a decrease in absorbance at 420 nm under pseudo-first-order conditions, with the nucleophile in at least a 10-fold excess. The observed pseudo-first-order rate constants, k_{obsd}, were calculated as average values from five to eight independent runs. Two exponential functions could be fitted to all kinetic traces. The faster step was attributed to the substitution of water in the *trans*-position to the sulfur donor, and the slower step to the displacement of the other coordinated water molecule. The temperature dependence of k_{obsd} was studied in the interval 5–25 °C. Experimental data are reported in Tables SI–SIII (see ESI †) and are summarized in Figs. 1 and 2.

The pressure dependence of the observed rate constants was studied at 25 °C, in the range 0.1–130 MPa. The observed pseudo-first-order rate constants, k_{obsd}, were calculated as average values from three to five independent runs. The high pressure kinetic data are listed in Tables SIV–SVI (ESI †) and are summarised in Fig. 3.

Table 1 Equilibrium constants for CBDCA, INO, 5′-IMP and 5′-GMP complexes with $[Pd(SMC)(H_2O)_2]^+$ at 25 °C and 0.1 M ionic strength

System	*p*	*q*	*r*[a]	log *β*[b]
$[Pd(SMC)(H_2O)_2]^+$	1	0	−1	−4.13(0.05)
	2	0	−1	−0.01(0.05)
	1	0	−2	−15.77(0.07)
CBDCA	0	1	1	5.59(0.01)
	0	1	2	8.56(0.01)
	1	1	0	6.61(0.03)
	1	1	1	9.69(0.05)
INO	0	1	1	8.80(0.01)
	1	1	0	6.94(0.05)
	1	1	1	11.00(0.03)
	1	2	0	10.27(0.05)
5′-IMP	0	1	1	9.04(0.01)
	0	1	2	15.21(0.01)
	0	1	3	16.22(0.07)
	1	1	0	7.45(0.09)
	1	1	1	14.10(0.07)
5′-GMP	0	1	1	9.51(0.01)
	0	1	2	15.68(0.01)
	0	1	3	17.99(0.01)
	1	1	0	11.96(0.09)
	1	1	1	18.75(0.07)
	1	1	2	22.00(0.06)

[a] *p*, *q* and *r* are the stoichiometric coefficients corresponding to $[Pd(SMC)(H_2O)_2]^+$, ligand and H^+, respectively. [b] Standard deviations are given in parentheses.

Results and discussion

Equilibrium studies

The acid–base equilibria of $[Pd(SMC)(H_2O)_2]^+$ were characterized by fitting the potentiometric titration data to various acid–base models. The best model, selected according to the above-mentioned method of calculation, was found to be consistent with the deprotonation of two coordinated water molecules and formation of hydroxo and μ-hydroxo species, as given in eqn. (3).

$$\underset{100}{[Pd(SMC)(H_2O)_2]^+} \rightleftarrows \underset{10\text{-}1}{[Pd(SMC)(H_2O)(OH)]} + H^+ \quad (3a)$$

$$\underset{10\text{-}1}{[Pd(SMC)(H_2O)(OH)]} \rightleftarrows \underset{10\text{-}2}{[Pd(SMC)(OH)_2]^-} + H^+ \quad (3b)$$

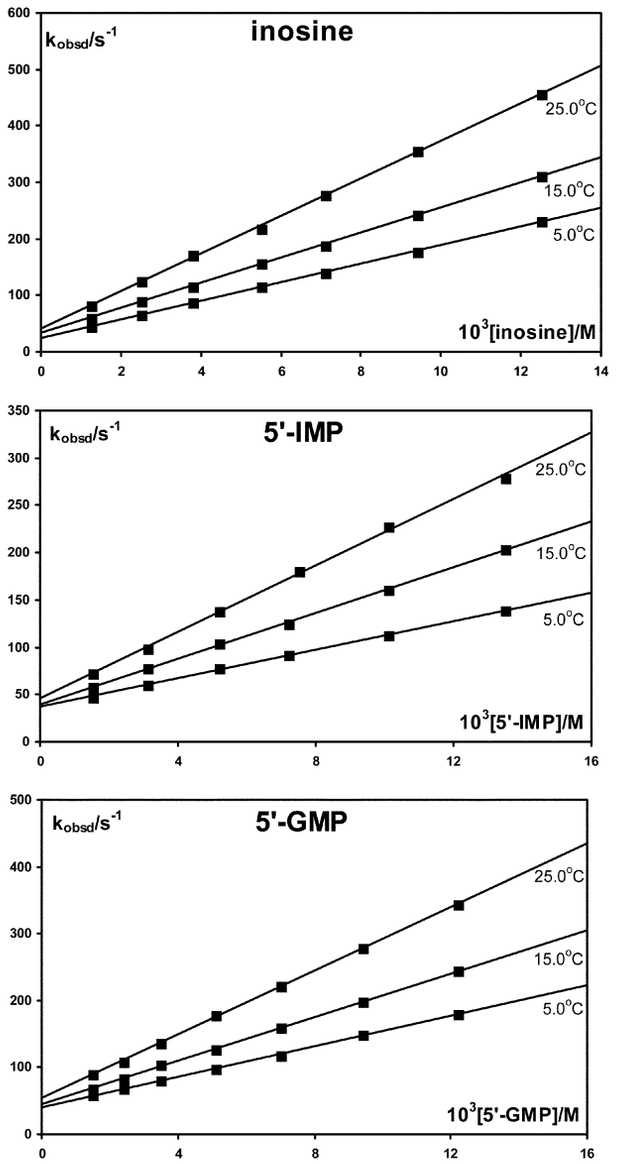

Fig. 1 Observed pseudo-first-order rate constants, k_{obsd}, as a function of excess nucleophile concentration and temperature for the first reaction with $[Pd(SMC)(H_2O)_2]^+$.

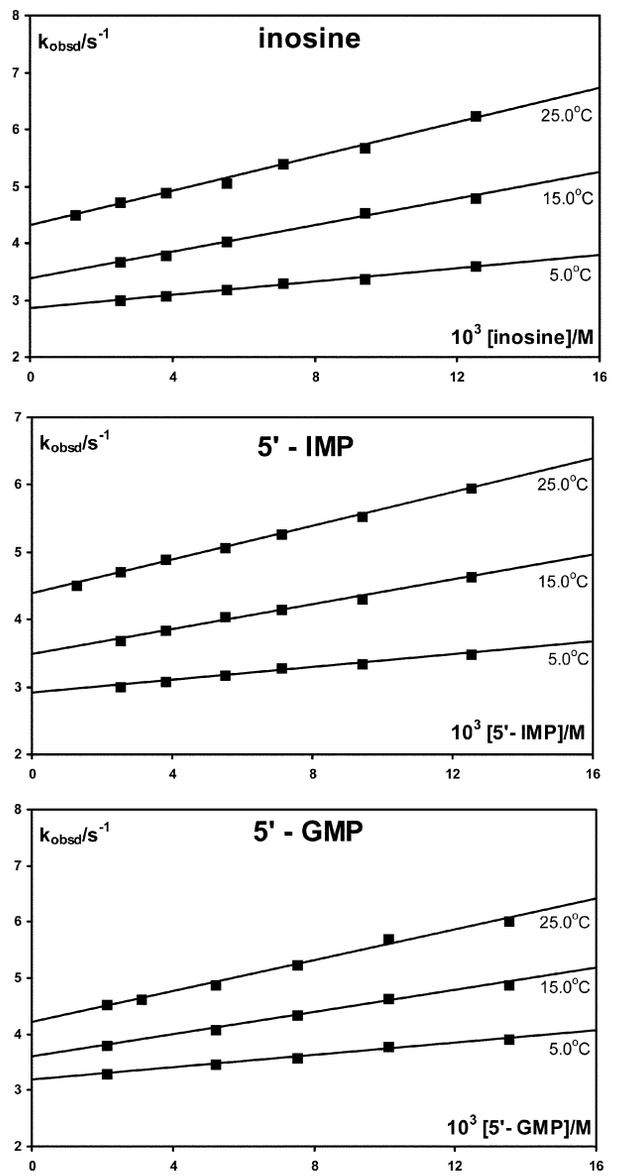

Fig. 2 Observed pseudo-first-order rate constants, k_{obsd}, as a function of excess nucleophile concentration and temperature for the second reaction with $[Pd(SMC)(H_2O)_2]^+$.

$$\underset{100}{2[Pd(SMC)(H_2O)_2]^+} \rightleftharpoons \underset{20\text{-}1}{[Pd(SMC)(H_2O)]_2OH} + H^+ \quad (3c)$$

The pK_a value of the carboxylic acid group of coordinated *S*-methyl-L-cysteine was too low to be determined potentiometrically. pK_{a_1} and pK_{a_2} of the coordinated water molecules are 4.13 and 11.64, respectively. pK_{a_1} corresponds to deprotonation of the coordinated water molecule *trans* to the coordinated amino group. pK_{a_2} has a significantly higher value than the corresponding Pd–diimine complexes. This is due to the strong *trans* labilization effect of sulfur on the coordinated water molecule. The μ-hydroxo species (20-1) is assumed to form through dimerization of the Pd(II) complex *via* a hydroxy group bound in the positions *trans* to the coordinated amino group. The formation of the dihydroxo-bridged dimer (20-2), found for most Pd–diimine complexes, is not favoured in the case of the Pd–SMC complex. This may be accounted for on the basis that the strong labilization effect of the S donor atom will cause the dimeric form (20-2) to be strained and, consequently, energetically not favoured.

A dimer with a single hydroxo bridge is formed with $[Pd(SMC)(H_2O)_2]^+$. The dimerization reaction can be reformulated as:

$$\underset{(100)}{[Pd(SMC)(H_2O)_2]^+} + \underset{(10\text{-}1)}{[Pd(SMC)(H_2O)(OH)]} \rightleftharpoons \underset{(20\text{-}1)}{[(SMC)(H_2O)Pd\text{-}OH\text{-}Pd(H_2O)(SMC)]^+}$$

The equilibrium constant (K) for the dimerization reaction was determined to be $\log K = 4.12$ ($= \log \beta_{20\text{-}1} - \log \beta_{10\text{-}1}$). The equilibrium constant for the corresponding dimerization of $[Pd(dien)(H_2O)]^+$ was previously found to be $\log K = 2.12$.[31] The difference may be explained in terms of the difference in the Lewis acidity of Pd(II) in $[Pd(SMC)(H_2O)_2]^+$ and $[Pd(dien)(H_2O)]^+$, where the former complex has a higher Lewis acidity than the latter. The difference in Lewis acidity is also reflected in the pK_a value of the first coordinated water molecule, where pK_a of $[Pd(dien)(H_2O)]^{2+}$ is 7.74 and the corresponding value for $[Pd(SMC)(H_2O)_2]^+$ is 4.13.

The species distribution diagram for the hydrolysed species is shown in Fig. 4. The concentrations of μ-hydroxo (20-1) and

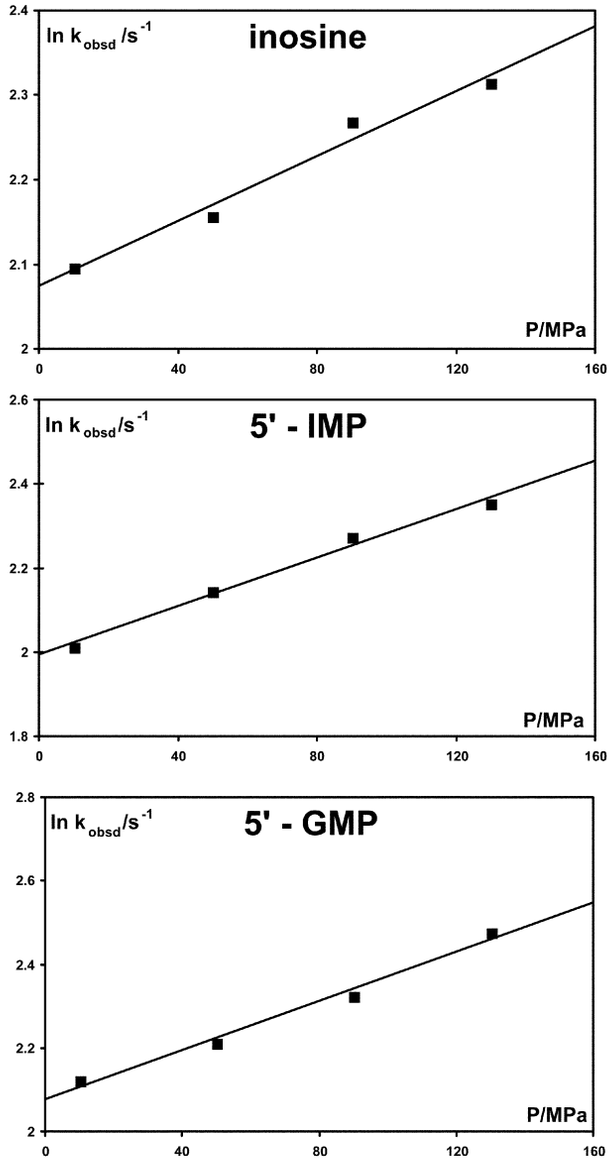

Fig. 3 Observed pseudo-first-order rate constants, $\ln k_{obsd}$, as a function of pressure for the second reaction with $[Pd(SMC)(H_2O)_2]^+$.

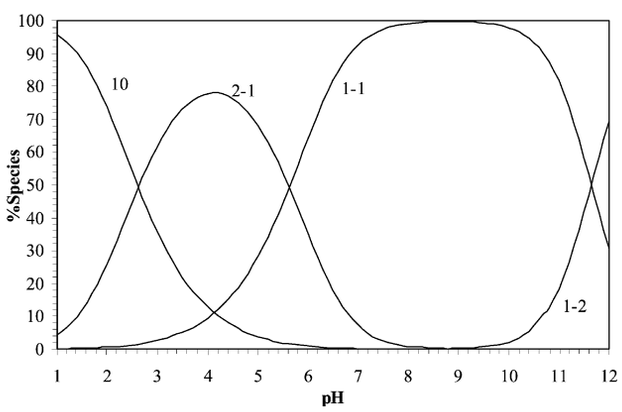

Fig. 4 Distribution of various species as a function of pH in the $[Pd(SMC)(H_2O)_2]^+$ system at a concentration of 2.47 mM.

monohydroxo (10-1) species increase with increasing pH, attaining a maximum of 78% at pH 4.2 and 100% at pH 8.4, respectively. However, the dihydroxo (10-2) species starts to form at pH 9.5 and its concentration increases with increasing pH. The main species present under physiological conditions are the monohydroxo and μ-hydroxo species, which can interact with DNA constituents.

Complex-formation equilibria involving CBDCA

Analysis of the titration data for the Pd(SMC)–CBDCA system showed the formation of the 1:1 species and its protonated form. The stability constant of the CBDCA complex (6.61) is lower than the corresponding complex of Pd(pic) (pic = 2-picolylamine) (7.34)[32] and of Pd(aliphatic amine) (7.17).[33] The high stability constant of the Pd(pic)–CBDCA complex results from the π-acceptor property of the pyridyl group. The lowest stability constant of Pd(SMC)–CBDCA is most probably due to a labilization effect of the thioether group. The pK_a of the protonated species is 3.08, a value lower than that of free H-CBDCA$^-$, indicating acidification by 2.51 pH units (5.59–3.08) upon coordination to Pd(II) through one carboxylate group. The pK_a value of this protonated species for the corresponding bipyridyl complex was estimated previously from UV-VIS measurements to be *ca.* 2.5 at 25 °C and 0.1 M ionic strength.[33] The distribution curve, Fig. 5, shows that the

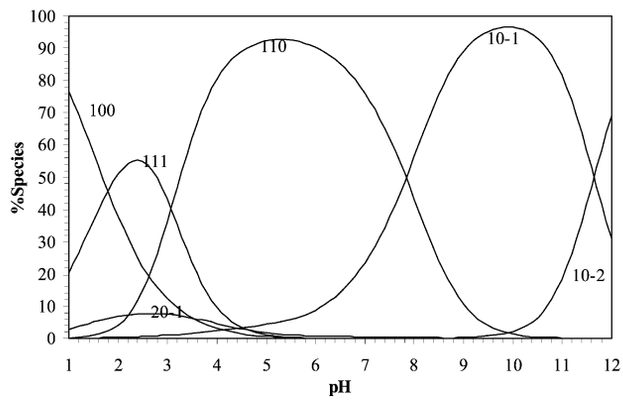

Fig. 5 Distribution of various species as a function of pH in the Pd(SMC)–CBDCA system at a concentration of 2.47 and 2.50 mM, respectively.

protonated species (111) predominates at low pH with a maximum concentration of 55% at pH 2.5. The ring-closed form (110) predominates with a maximum formation degree of 92% at pH 5.2. At higher pH, CBDCA is displaced by hydroxyl ions to give hydroxo complexes. The concentration of the ring-closed form contributes significantly in the physiological pH range.

Complex-formation equilibria involving DNA constituent

The purines inosine, inosine-5′-monophosphate and guanosine-5′-monophosphate have two metal ion binding sites, *viz.* N_1 and N_7. The pH-dependent binding of these N-donors has been reported before.[4] The results showed that inosine forms 110, 111 and 112 complexes. The 111 species is formed in the acidic pH range and corresponds to the N_7 coordinated complex, whereas the N_1 nitrogen is in the protonated form. The pK_a of the protonated complex ($\log \beta_{111} - \log \beta_{110}$) amounts to 5.04. The lowering of the pK_a of N_1H upon coordination has been reported before.[34] The speciation diagram for the inosine complex is given in Fig. 6. The protonated species predominate with a maximum concentration of 39% at pH 1.0. Increasing pH is accompanied by a decrease in the protonated species, an increase in the concentration of the hydrolysed Pd(II) complex, and an increase in the 110 and 120 complexes. The 110 complex reaches a maximum concentration of 38% at pH 6.7, *i.e.* in the physiological pH range. 5′-GMP forms complexes with stoichiometric coefficients of 110, 111 and 112. However, 5′-IMP only forms 110 and 111 complexes. The 1:2 complex is not formed as a result of *trans*-labilization by the S donor, and in order to avoid steric interaction between the incoming and coordinated ligand. The pK_a values of the protonated 5′-GMP complex are 6.79 ($\log \beta_{111} - \log \beta_{110}$) and 3.25 ($\log \beta_{112} - \log \beta_{111}$). These values correspond to the PO_2–OH and N_1H groups,

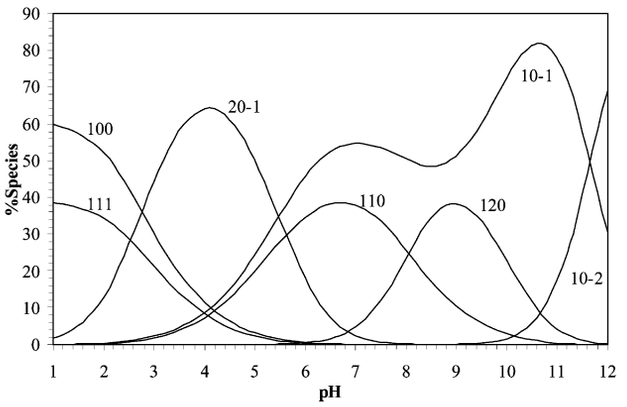

Fig. 6 Distribution of various species as a function of pH in the Pd(SMC)–INO system at a concentration of 2.47 and 5.00 mM, respectively.

respectively. The latter assignment is based on the fact that N_7 is coordinated to Pd(II), and as a result N_1H is acidified and its pK_a value is lowered significantly. The pK_a of the protonated 5′-IMP complex is 6.66. This value may correspond to an average of the pK_a values for PO_2–OH and N_1H. It should be noted that the 5′-GMP complex (110) is significantly more stable than the inosine and 5′-IMP complexes. This may be plausible due to hydrogen bonding between the exocyclic amino group of 5′-GMP and the carboxylate group of coordinated *S*-methyl-L-cysteine. This interaction will contribute to the stability of the formed complex. The high stability of the 5′-GMP complex in comparison to that of the inosine and 5′-IMP complexes is reflected in the concentration distribution diagrams for these complexes in Figs. 6–8. The 5′-GMP complexes 110, 111 and 112 form the major contribution, whereas hydroxo species are not formed at all.

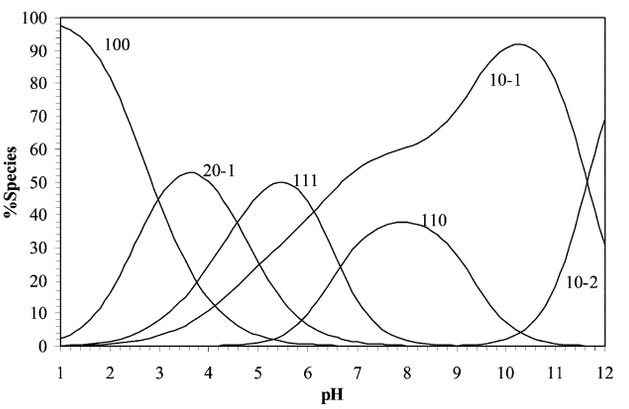

Fig. 7 Distribution of various species as a function of pH in the Pd(SMC)–IMP system at a concentration of 1.235 and 2.50 mM, respectively.

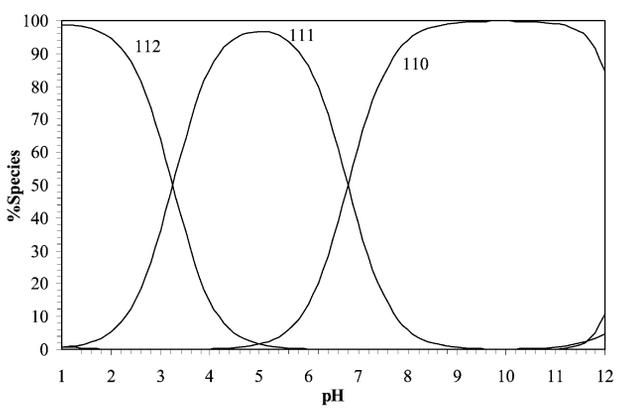

Fig. 8 Distribution of various species as a function of pH in the Pd(SMC)–5′-GMP system at a concentration of 1.235 and 2.50 mM, respectively.

Kinetic studies

The reaction of $[Pd(SMC)(H_2O)_2]^+$ with the selected nucleophiles occurs in two subsequent steps. Both reaction steps exhibit linear dependencies of k_{obsd} on the nucleophile concentration with significant intercepts (see Figs. 1 and 2). This suggests that both substitution processes are reversible and proceed according to the reactions given in eqns. (4) and (5). The observed rate constants for the two reactions can be expressed as given in eqn. (6).

$$[Pd(SMC)(H_2O)_2]^+ + Nu \underset{H_2O}{\overset{k_1,k_{-1}}{\rightleftharpoons}} [Pd(SMC)(Nu)(H_2O)]^+ + H_2O \quad (4)$$

$$[Pd(SMC)(Nu)(H_2O)]^+ + Nu \underset{H_2O}{\overset{k_2,k_{-2}}{\rightleftharpoons}} [Pd(SMC)(Nu)_2]^+ + H_2O \quad (5)$$

$$k_{obsd1} = k_{-1} + k_1[Nu] \text{ and } k_{obsd2} = k_{-2} + k_2[Nu] \quad (6)$$

Values for the rate constants and thermal activation parameters estimated from the data in Figs. 1 and 2 are summarized in Table 2. The reactions for the second step are significantly slower than for the first step. The faster reaction step with the larger absorption change was attributed to the substitution of the first coordinated H_2O in the *trans* position to the S donor atom of *S*-methyl-L-cysteine, whereas the slower reaction was assigned to the displacement of the other H_2O molecule. This is due to the strong *trans* labilization effect of coordinated sulfur. Inosine (INO), inosine-5′-monophosphate (5′-IMP) and guanosine-5′-monophosphate (5′-GMP) can coordinate to metal ions *via* N_1 and N_7. Under our experimental conditions (pH 2.5) only the N_7 position of INO, 5′-IMP and 5′-GMP will bind to the central metal atom, since at this pH the N_1 position is protonated.[35] Binding through the N_7 position in a neutral or weakly acidic medium has been verified.[36–39] On average, k_1 is *ca.* 10^2 times faster than k_2, whereas k_{-1} is on average *ca.* 10 times faster than k_{-2}, with the result that K_1 (= k_1/k_{-1}) is *ca.* 10 times larger than K_2 (= k_2/k_{-2}).

The introduction of an *S*-amino acid ligand into the Pd(II) coordination sphere results in an increase in substitution reactivity. Such a labilization has clearly been illustrated by an earlier study from this laboratory,[11] and can also be seen from a comparison of the results of the present study with those for related Pd(II) complexes which are chelated through nitrogen atoms only.[2–6] The kinetic data clearly show that inosine is more reactive toward $[Pd(SMC)(H_2O)_2]^+$ than either 5′-IMP and 5′-GMP, which can be attributed to a primary process that involves partial pre-association of the metal complex with the phosphate group in 5′-IMP and 5′-GMP, and so slows down the actual substitution reaction. This is in good agreement with the results for the same ligands reacting with $[Pd(met)Cl_2]^+$ (met = L-methionine) and $[Pd(pic)(H_2O)_2]^{2+}$.[3,11] This effect is not so large in the case of the second substitution process. The forward and reverse reactions for both reaction steps (4) and (5) are characterized by significantly negative activation entropies, which is in line with an associative substitution mechanism. The activation entropies for the reverse reactions k_{-1} and k_{-2} are indeed more negative than the forward reactions due to the lower magnitude of these first-order rate constants and a compensation effect as a result of the exceptionally low the activation enthalpies for the these reactions. This suggests that the complexes produced are rather labile and can easily aquate to form the corresponding aqua complexes.

The rate of the studied reactions is such that the pressure dependence of the reactions could only be studied for the second reaction step, *i.e.* reaction (5). Furthermore, the absorbance change associated with the second reaction step is such

Table 2 Rate constants and activation parameters for the reactions of $[Pd(SMC)(H_2O)_2]^+$ with INO, 5′-IMP and 5′-GMP

First reaction

L	k_1^{298}/M^{-1} s^{-1}	$\Delta H_1^{\neq}$/kJ mol^{-1}	$\Delta S_1^{\neq}$/J K^{-1} mol^{-1}
INO	$(3.32 \pm 0.02) \times 10^4$	22 ± 1	−84 ± 4
5′-IMP	$(1.75 \pm 0.04) \times 10^4$	26 ± 1	−75 ± 3
5′-GMP	$(2.38 \pm 0.02) \times 10^4$	24 ± 1	−80 ± 4

L	k_{-1}^{298}/s^{-1}	$\Delta H_{-1}^{\neq}$/kJ mol^{-1}	$\Delta S_{-1}^{\neq}$/J K^{-1} mol^{-1}
INO	42 ± 2	16 ± 1	−160 ± 3
5′-IMP	49 ± 3	7 ± 1	−190 ± 5
5′-GMP	53 ± 1	8 ± 1	−186 ± 5

Second reaction

L	k_2^{298}/M^{-1} s^{-1}	$\Delta H_2^{\neq}$/kJ mol^{-1}	$\Delta S_2^{\neq}$/J K^{-1} mol^{-1}	$\Delta V_2^{\neq}$/cm^3 mol^{-1} [a]
INO	$(1.51 \pm 0.03) \times 10^2$	31 ± 2	−98 ± 6	−5.4 ± 0.6
5′-IMP	$(1.24 \pm 0.02) \times 10^2$	31 ± 3	−102 ± 8	−7.1 ± 0.4
5′-GMP	$(1.37 \pm 0.06) \times 10^2$	30 ± 2	−104 ± 7	−7.3 ± 0.6

L	k_{-2}^{298}/s^{-1}	$\Delta H_{-2}^{\neq}$/kJ mol^{-1}	$\Delta S_{-2}^{\neq}$/J K^{-1} mol^{-1}
INO	4.31 ± 0.04	12 ± 2	−194 ± 6
5′-IMP	4.39 ± 0.02	12 ± 1	−194 ± 4
5′-GMP	4.33 ± 0.04	12 ± 2	−192 ± 6

[a] Values determined from the pressure dependence of k_{obsd2} at high nucleophile concentration.

that the effect of pressure on this reaction could only be studied at high nucleophile concentration, *i.e.* where reaction (5) is shifted more towards the product side. Thus the observed rate constant is a combination of both the forward and reverse reactions and the observed activation volume should be interpreted accordingly. Plots of ln k_{obsd2} *vs.* pressure are linear (see Fig. 3 and Tables SVII–SIX in the ESI†) and the volumes of activation were calculated from the slopes (= $-\Delta V^{\neq}/RT$). The derived values of $\Delta V_2^{\neq}$ are listed along with the thermal activation parameters in Table 2. The significantly negative activation volumes support the mechanistic conclusion based on the activation entropies, suggesting that the activation process in the present systems is strongly dominated by bond making. This further supports the assignment of an associative complex-formation mechanism, in agreement with that reported for substitution reactions of square-planar complexes in general.[1–11]

The substitution behaviour of the $[Pd(SMC)(H_2O)_2]^+$ complex is very similar to that reported for related Pd(II) complexes which are chelated through nitrogen donor atoms only. The labilization effect of the S donor ligand merely causes the rate constant for the first substitution reaction to differ significantly from that for the second reaction step. It is reasonable to expect a similar behaviour for the corresponding Pt(II) complex.

Finally, a comparison of the stability constant values obtained from potentiometric and kinetic data are made for inosine. The stability constant of the 1:1 complex formed in the acidic pH range (where N_7 is coordinating) obtained from potentiometric measurements log K_1 = 2.22 (= log β_{111} − log β_{011}) is in good agreement with the value obtained from the kinetic investigation, *viz.* log K_1 = 2.89 (= $k_1/k_{-1} = 3.3 \times 10^4/42$). In the case of IMP and GMP there is an extra phosphate group and an exocyclic amino group in GMP. This will result in the formation of various acid–base forms, which may react with $[Pd(SMC)(H_2O)_2]^+$. Consequently, a comparison of kinetic and potentiometric data does not give good results. In addition, the stability constants of the 1:2 complexes of inosine, IMP and GMP, obtained from the kinetic data, are log K_2 = 1.54, 1.45 and 1.50, respectively. These values are relatively small such that the potentiometric measurements will not be able to detect the formation of these species, unless a high concentration of ligand is used.

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