The Reaction of (Bipyridyl)palladium(II) Complexes with Thiourea − Influence of DNA and Other Polyanions on the Rate of Reaction

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$[Pd(bipy)(py)_2](PF_6)_2$ reacts stepwise with excess thiourea to give $[Pd(tu)_4](PF_6)_2$. The kinetics of the second step, which refers to the replacement of bipyridyl in $[Pd(bipy)(tu)_2](PF_6)_2$, have been studied in water and in the presence of calf thymus DNA, sodium polyriboadenylate, sodium polyvinylsulfonate or sodium polymetaphosphate at 25 °C and pH = 7 and a fixed sodium chloride concentration. The reaction follows a first order course and a plot of k_{obs} against [thiourea]^2 affords a straight line with a small intercept. DNA inhibits the process without altering the rate law. The k_{obs} values decrease systematically on increasing the DNA concentration eventually tending to a limiting value. The values are larger at higher ionic strengths and the other polyanions show similar behaviour. The influence of DNA on the kinetics can be related to steric inhibition caused by noncovalent binding with the complex. Upon interaction with DNA, $[Pd(bipy)(tu)_2]^{2+}$ gives rise to immediate spectroscopic changes in the UV/Vis region as well as induced circular dichroism suggesting that the complex, like similar platinum(II) and palladium(II) species of bipyridyl, intercalates with the double helix. Such a type of interaction hampers the attack of the nucleophile at the metal centre inhibiting the reaction. The decrease in the rate of ligand substitution upon decreasing salt concentration but at a given DNA concentration is due to the influence of ionic strength on the complex–DNA interaction. The reactivity inhibition by single-stranded poly(A), polyvinylsulfonate or polymetaphosphate can be accounted for in terms of self-aggregation of the complex induced by the polyanion.

Introduction

Since the discovery that square-planar complexes can intercalate[1] with DNA, many platinum(II) compounds containing aromatic ligands have been used[2] to study the basic features of this type of noncovalent interaction. These substances are thermodynamically stable and, furthermore, their kinetic inertness prevents undesired covalent interactions with the DNA nucleobases within the time needed for the experiments. The geometry and the ease of which their steric and electronic properties can be tuned by an appropriate choice of the ligands, renders platinum(II) complexes very suitable for studying intercalation with the DNA double helix. Palladium(II) complexes can also be used to study this type of noncovalent interaction with nucleic acids.[3] These substances share the thermodynamic stability and other chemicophysical properties of platinum(II) complexes but are less inert[4] and this feature makes them more amenable to study from a kinetic point of view. Various investigations have shown that the reactivity of a small molecule can be altered upon noncovalent interaction with DNA and RNA. Both inhibition[5] and enhancement[6] of reactivity of metal complexes have been observed. The influence on the kinetics may be related to the particular type of noncovalent interaction and, therefore, the study of the reactivity of a metal complex in the absence and in the presence of DNA or RNA can give interesting information about the interaction itself. In this paper we report the results of a kinetic investigation of the reaction between the palladium(II) complex $[Pd(bipy)(py)_2](PF_6)_2$ (bipy = 2,2′-bipyridyl; py = pyridine) and thiourea in water in the presence of double-helical DNA. The investigation was carried out at 25 °C and pH 7 at two different sodium chloride concentrations. In order to compare the influence of double stranded polyanions with single stranded, helical and random coiled polyanions, the reactions were studied in the presence of sodium polyriboadenylate [poly(A)], sodium polyvinylsulfonate (PVS) and sodium polymetaphosphate (PMP). In addition, the interaction of the complex with the polyanions has been studied by absorption and circular dichroism.

Results and Discussion

The electronic spectrum of $[Pd(bipy)(py)_2]^{2+}$ in water does not change over time although fast reversible spectro-

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scopic variations can be observed on changing the pH of the solution. Such variations are not expected on the basis of the nature of the complex. Accordingly, ^1H NMR experiments show the presence of signals due to free pyridine in D_2O solutions of $[Pd(bipy)(py)_2]^{2+}$. These signals are not present if the spectrum is run in a poorly coordinating solvent such as deuterated acetone. It appears, therefore, that the complex undergoes hydrolysis within the preparation times of the solutions. Hydrolytic equilibria are common for square-planar complexes and lead to a wide range of products. In the present case, precise indications of the nature of the products are difficult to obtain either by UV/Vis or NMR spectroscopic measurements. However, previous studies on platinum(II) and palladium(II) complexes have shown[7] that hydrolysis produces monomeric aqua and hydroxo species as well as oligomeric species with bridging hydroxo or aqua groups.

Addition of sodium chloride, even in a large excess, to aqueous solutions of $[Pd(bipy)(py)_2]^{2+}$ alters the nature of the hydrolytic species in equilibrium without exchanging coordinated bipyridyl. However when thiourea is used, a bipyridyl is also replaced as well as the monodentate ligands coordinated to palladium. NMR spectra of the reaction mixtures in D_2O unambiguously show the signal corresponding to the released bipyridyl.

The rate of this process, which can be easily obtained by kinetic analysis of the spectroscopic variations over time (Figure 1), is largely independent of chloride and hydrogen ion concentration. Such independence suggests that the monitored process corresponds to the substitution of bipy in $[Pd(bipy)(tu)_2]^{2+}$ formed by the action of thiourea on the hydrolysis products [Equation (1)].

$$[Pd(bipy)(tu)_2]^{2+} + 2\,tu \rightarrow [Pd(tu)_4]^{2+} + bipy \qquad (1)$$

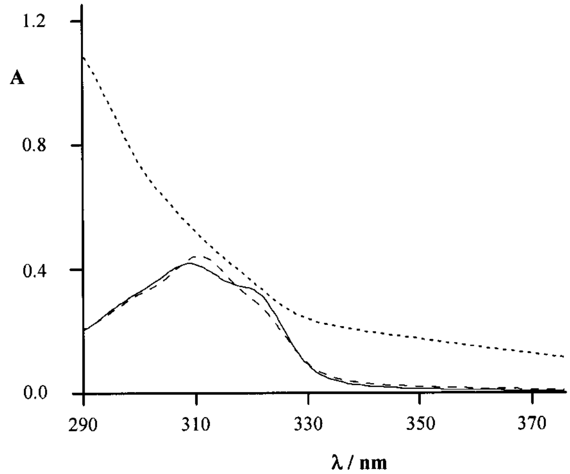


Figure 1. Spectroscopic changes at 25 °C and pH = 7 for the reaction of $[Pd(bipy)(py)_2]^{2+}$ in water (–), in the presence of Cl^- (– –) and with tu (···); $[Pd(bipy)]_{tot} = 3.75 \times 10^{-5}$ M

Thiourea, one of the strongest nucleophiles towards square-planar complexes,[4,8] replaces the monodentate ligands of the hydrolytic complexes in a fast step prior to substitution of bipy. In agreement with this observation, both the spectroscopic variations and the k_{obs} values are almost identical to those obtained upon treatment of a sample of independently synthesised $[Pd(bipy)(tu)_2]^{2+}$ with thiourea, under the same experimental conditions.

Under pseudo first-order conditions the reaction follows a first order course with respect to the complex. Plotting k_{obs} against $[tu]^2$ results in a straight line with a small intercept [Equation (2), Figure 2].

$$k_{obs} = k_1 + k_2 \cdot [tu]^2 \qquad (2)$$

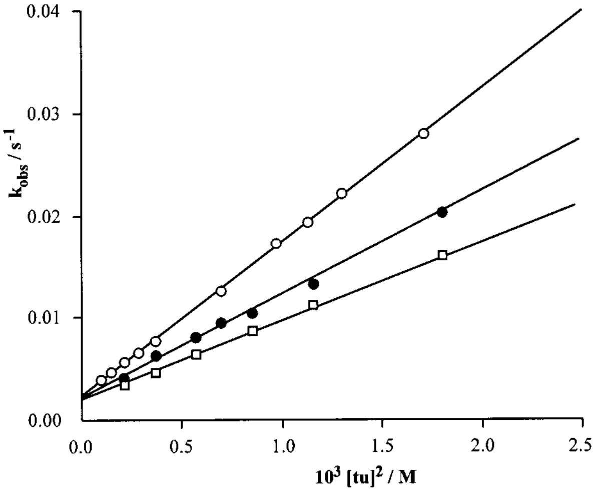
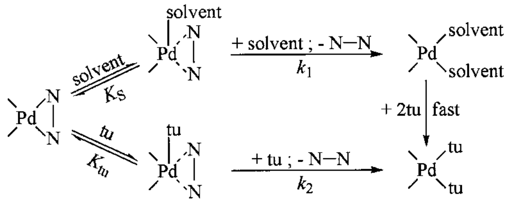


Figure 2. Plot of k_{obs} vs. $[tu]^2$ for reaction (1) [Equation (1)] at 25 °C and pH = 7; without DNA (open circles), in the presence of DNA at $I = 5.0 \times 10^{-2}$ M (filled circles), in the presence of DNA at $I = 2.2 \times 10^{-2}$ M, (squares) $[Pd(bipy)]_{tot} = 3.75 \times 10^{-5}$ M ; [DNA]/[complex] = 0.5

A possible mechanism that accounts for the experimental kinetic values is depicted below in Scheme 1.



Scheme 1

This scheme implies the attack of a first thiourea molecule at the palladium atom with formation of an intermediate which leads to the product upon interaction with another thiourea molecule. $[Pd(tu)_4]^{2+}$ also forms through the customary solvolytic pathway.[8] The intermediates can be described as having a structure in which the ligand is monodentate but rapidly exchanging its point of attachment with the central atom.[9] From this scheme the following Equation (3) can be postulated.

$$k_{\mathrm{obs}} = \frac{k_1 K''_{\mathrm{S}} + k_2[\mathrm{tu}]^2 K_{\mathrm{tu}}}{\left(1 + K'_{\mathrm{S}} + [\mathrm{tu}]K_{\mathrm{tu}}\right)} \tag{3}$$

K'_S = [solvent]·K_S and K''_S = [solvent]^2·K_S. Taking into account that the intermediates could not be detected even using a large thiourea concentration, both K_{tu} and K_S should be very small and (K_{tu}·[tu] + K'_S) < 1. Therefore, rate law (3) is very similar to experimental rate law (2). When the reactions are conducted in the presence of DNA, no change in the rate law is observed and this suggests that the mechanism is the same as it is in water. However DNA influences the rate of reaction which becomes lower with respect to that in water (Figure 2).

In addition, the presence of DNA induces dependence of the kinetics on the ionic strength. Thus, when DNA is present, the kinetic values become significantly lower as the salt concentration decreases (Table 1).

Table 1. Values of rate constants for reaction (1) [Equation (1)] at 25 °C and pH = 7; $[\mathrm{Pd(bipy)}]_{\mathrm{tot}} = 3.75 \times 10^{-5}$ M

$10^3\ k_1$ [s^{-1}]	k_2 [M^{-2} × s^{-1}]
3.4 ± 0.3	15.1 ± 0.3[a]
2.0 ± 0.2	10.3 ± 0.7[b]
2.0 ± 0.3	7.6 ±0.5[c]

[a] Without DNA. [b] With DNA 1.87×10^{-5} M; $I = 5.0 \times 10^{-2}$ M. [c] With DNA 1.87×10^{-5} M; $I = 2.2 \times 10^{-2}$ M.

The inhibition caused by DNA depends on its concentration. In Figure 3 the k_{obs} values at fixed ionic strength and at a given thiourea concentration are plotted against the concentration of DNA.

On increasing the DNA concentration, there is a systematic decrease in the rate constants which tend to a limiting value. In addition, the sensitivity of the k_{obs} values to the DNA concentration change increases as the ionic strength is lowered. The presence of other polyanions also inhibits reaction (1) and again the presence of polymetaphosphate, poly(A) or polyvinylsulfonate does not change the rate law but the k_{obs} values become lower in all cases compared with those of the reaction in water. For these polyanions (Figure 4) the kinetic values are also less sensitive to their concentrations at higher ionic strengths.

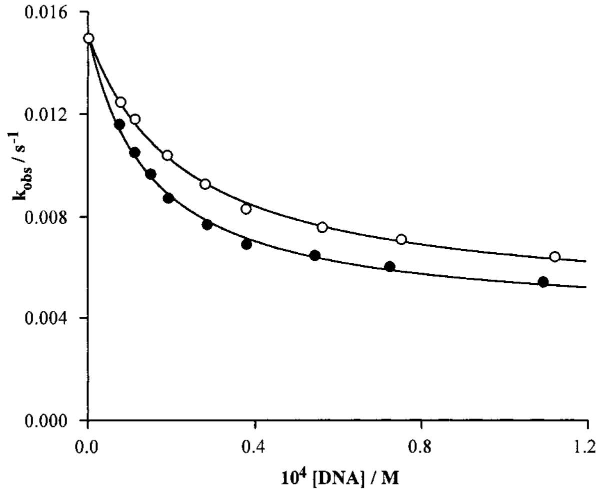


Figure 3. Plot of k_{obs} vs. [DNA] for reaction (1) [Equation (1)] at 25 °C and pH = 7; $[\mathrm{Pd(bipy)}]_{\mathrm{tot}} = 3.75 \times 10^{-5}$ M; [tu] = 2.91×10^{-2} M; $I = 5.0 \times 10^{-2}$ M (open circles); $I = 2.2 \times 10^{-2}$ M (filled circles)

The influence of the polyanion on the rate of bipyridyl substitution cannot be explained on the basis of concentration effects[10] arising from a particular distribution of the reactants driven by electrostatic interactions. While the dicationic complex tends to concentrate around the polyanion, the uncharged thiourea has no preference for any particular region of the solution. The inhibiting effect seems to be steric in origin and can be interpreted on the basis of noncovalent interactions between the complex and the

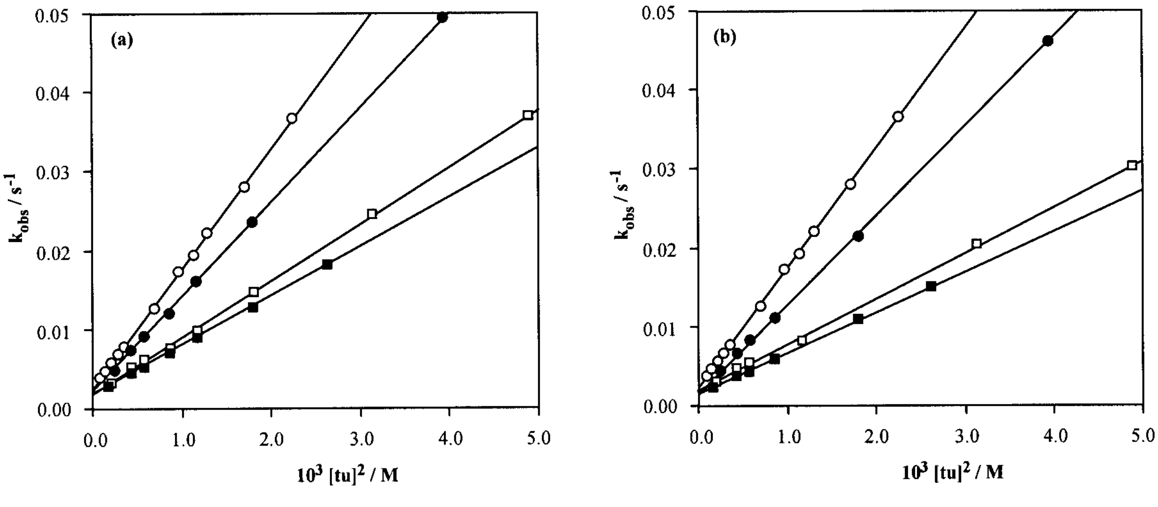


Figure 4. Plot of k_{obs} vs. [tu]^2 for reaction (1) [Equation (1)], at 25 °C and pH = 7, in water (open circles) and in the presence of polyanions (a) at $I = 5.0 \times 10^{-2}$ M and (b) at $I = 2.2 \times 10^{-2}$ M; $[\mathrm{Pd(bipy)}]_{\mathrm{tot}} = 3.75 \times 10^{-5}$ M, [PMP] = 7.50×10^{-5} M (filled circles), [Poly(A)] = 3.75×10^{-5} M (open squares), [PVS] = 1.87×10^{-5} M (filled squares)

polyanions. In principle, due to the lability of palladium(II) complexes, covalent binding could also occur with the DNA nucleobases. However, under our experimental conditions, the complex and the DNA are initially separate. The biopolymer is then added together with thiourea in a large excess. Thiourea is a much stronger nucleophile than the nucleobases and competition between the two nucleophiles is, therefore, highly unlikely.

In the absence of thiourea, addition of any of the polyanions to $[Pd(bipy)(tu)_2]^{2+}$(the actual chemical species involved in the process studied) produces immediate spectroscopic variations characterised by hypochromism (Figure 5 and 6).

The presence of noncovalent interactions between a small molecule and a chiral polyanion such as DNA or poly(A) is also indicated by the appearance of a CD signal in the spectroscopic region where the bound molecule absorbs. This CD signal is due to induced circular dichroism as a result of the rigid orientation assumed by the bound substance with respect to the helical axis of the polyanion. Figure 7 shows the CD spectra of the complex in the presence of increasing amounts of DNA and poly(A).

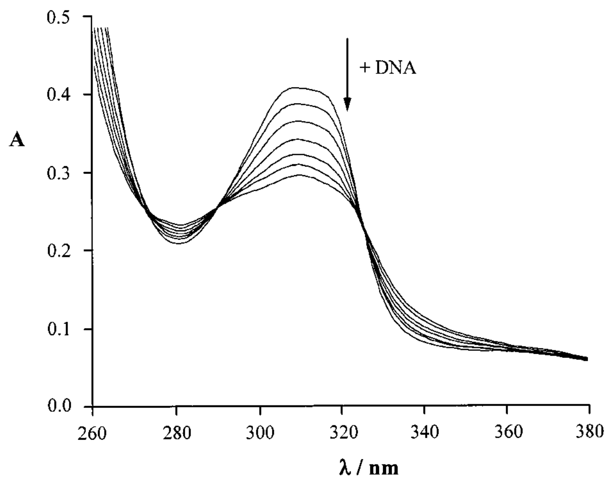


Figure 5. Spectroscopic changes for the interaction of $[Pd(bipy)(tu)_2]^{2+}$ (3.75×10^{-5} M) with DNA, at 25 °C and pH = 7; $I = 2.2 \times 10^{-2}$ M; [DNA]/[complex] = 0, 0.27, 0.52, 0.84, 1.14, 1.55, 2.03

As is well known, small molecules can interact noncovalently with double stranded DNA[11] either by surface binding or by intercalation. Both binding modes and especially intercalation imply shielding of the reaction centre, reducing the effectiveness of the incoming ligand and lowering the rate of substitution. Though neither absorption nor circular dichroism experiments can establish the type of noncovalent interaction between a small molecule and the DNA double helix, previous investigations[2d] have shown that $[Pt(bipy)(py)_2]^{2+}$, as well as many other dicationic platinum(II) and palladium(II) complexes of bipyridyl, intercalate with DNA. Similar conclusions can also be drawn for $[Pd(bipy)(tu)_2]^{2+}$ and its precursor $[Pd(bipy)(py)_2]^{2+}$. The binding constant for the interaction of $[Pd(bipy)(tu)_2]^{2+}$ with DNA at 25 °C and $I = 2.2 \times 10^{-2}$ M, obtained by the analysis of the spectrophotometric titration data via the McGhee von Hippel[12] equation is $(1.0 \pm 0.1) \times 10^5$ M^{-1}. Such a value is of the same order of magnitude as other similar platinum(II) and palladium(II) complexes.[2b,2d,3]

Intercalation may well account for the observed rate effect. Shielding of both sides of the square plane by the nucleobases hampers the attack of the incoming nucleophile thus inhibiting the substitution process. The decrease in the rate of ligand substitution at a given DNA concentration, as the salt concentration is reduced, is due to the influence[13] of ionic strength on the complex-DNA interaction. Due to competition of the interacting small molecule and the other cations present in solution for the anionic phosphate groups of DNA, ionic strength destabilises any type of noncovalent interaction between cationic species and this biopolymer. In addition, ionic strength influences DNA conformation. Increasing ionic strength reduces repulsion between phosphate groups allowing adjacent base pairs to get closer thus disfavouring intercalation. For the other polyanions, where intercalation is not possible, the reactivity inhibition can be interpreted on the basis of self-aggregation of the complex. Stacking of aromatic rings produces hypochromism[14] as experimentally observed upon interac-

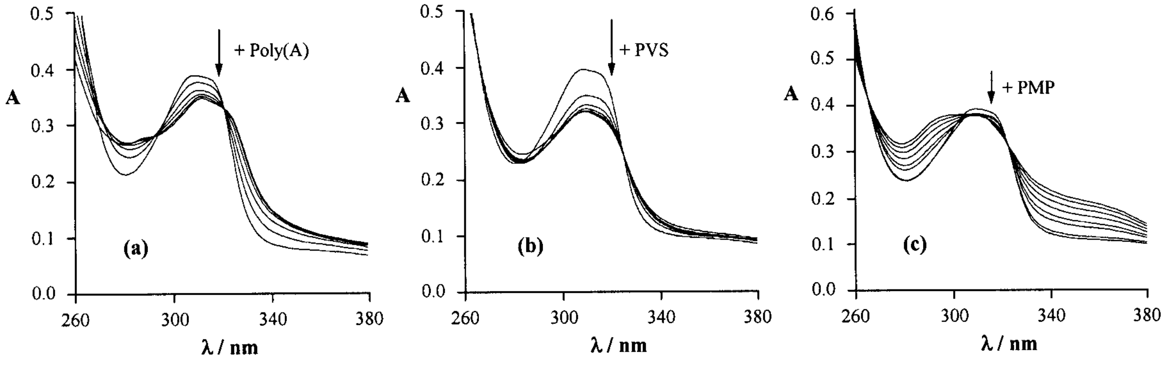


Figure 6. Spectrophotometric titration of $[Pd(bipy)(tu)_2]^{2+}$ (3.75×10^{-5} M), at 25 °C and pH = 7, with (a) poly(A) ([poly(A)]/[complex] = 0, 0.55, 1.02, 1.43, 1.79, 2.11), (b) PVS ([PVS]/[complex] = 0, 0.007, 0.014, 0.020, 0.027, 0.033), and (c) PMP ([PMP]/[complex] = 0, 5.8, 11.5, 22.5, 43.4, 80.9, 113.5, 142.2, 167.6); $I = 2.2 \times 10^{-2}$ M

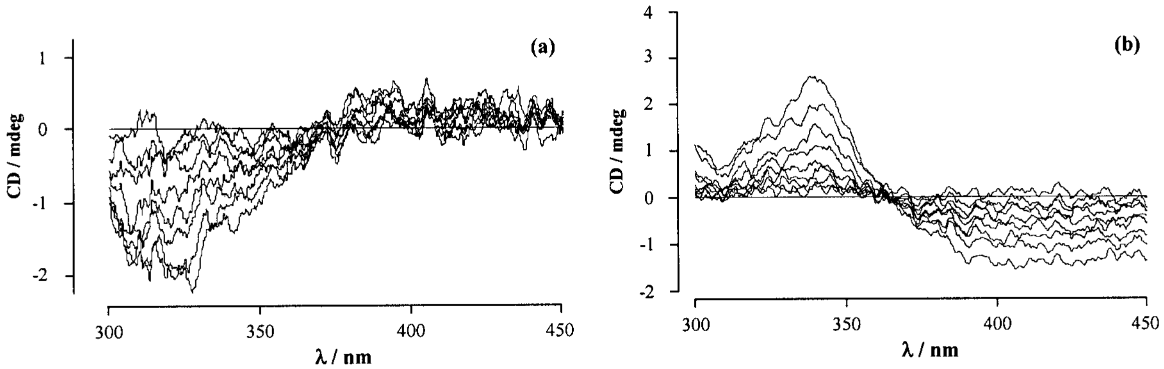
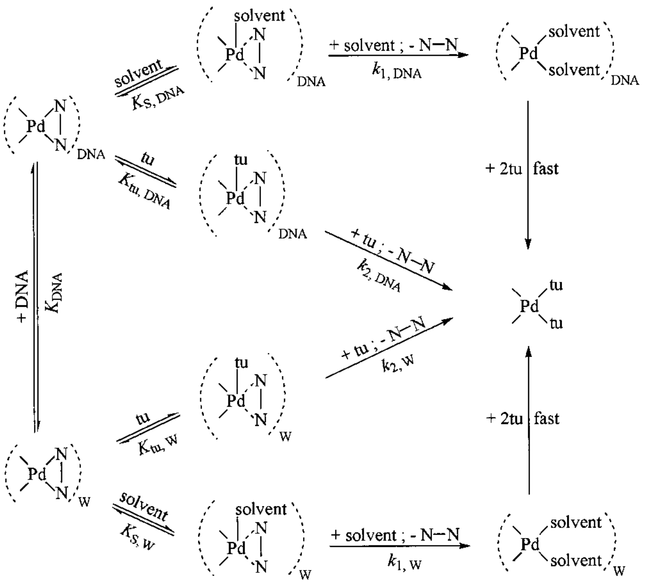


Figure 7. CD spectroscopic titration of $[Pd(bipy)(tu)_2]^{2+}$ (3.75×10^{-5} M) with (a) DNA and (b) poly(A) at 25 °C and pH = 7; $I = 2.2 \times 10^{-2}$ M

tion with the polyanions, while for poly(A) the observed hypochromism could be caused either by interaction of the adenine rings with the bipyridyl rings or by self stacking of the bipyridyl rings. Only the latter type of interaction is conceivable for PVS and PMP. In both cases, however, the interaction shields the reaction centre thus hampering attack of the nucleophile at palladium and so lowering the rate of reaction. Rate effects of other palladium(II) complexes upon the reaction with thiourea in the presence of polyvinylsulfonate have been previously reported.[6b] The observed acceleration of the rate of ethylenediamine substitution both for complexes of the type $[Pd(N{-}N)_2]^{2+}$ (N−N = ethylenediamine or *N*,*N*-substituted ethylenediamine) and $[Pd(bipy)(en)]^{2+}$ has been accounted for in terms of the enhanced acidity of the surfaces of the polyanions. These processes are acid catalysed and proceed faster in the proximity of a polyanion where the pH is lower than in the bulk.[15] In the case of $[Pd(bipy)(en)]^{2+}$, catalysis is observed even though the bipyridyl moieties undergo stacking and slow down the process. The accelerating effect, due to polyanion local acidity, probably prevails over the inhibition caused by stacking. The rate of bipyridyl replacement in $[Pd(bipy)(tu)_2]^{2+}$ is independent of the solution acidity and only inhibition, most likely due to self-stacking of the complexes, can occur as experimentally observed. The influence of the ionic strength on the rate of the reaction is similar to that observed for DNA and is again due to competition between the complex and the other cations present in solution for the negative charges of the polyanion.

The dependence of the k_{obs} values on the DNA concentration can be reasonably interpreted by assuming that the dicationic complex is partitioned between the DNA pseudo-phase and the bulk solution (Scheme 2). The DNA pseudo-phase includes the double helix itself, in which the complex is intercalated, and its electrostatic environment.

Taking into account that noncovalent interactions are much faster than the covalent steps involved in the scheme, the rate law according to Equation (4) may be deduced, where $K'_{S,W} = K_{S,W}\cdot[\text{solvent}]$, $K''_{S,W} = K_{S,W}\cdot[\text{solvent}]^2$, $K'_{S,DNA} = K_{S,DNA}\cdot[\text{solvent}]$, $K''_{S,DNA} = K_{S,DNA}\cdot[\text{solvent}]^2$; $k_{1,W}$ and $k_{1,DNA}$ are, respectively, the rate constants for replacement of monocoordinated bipyridyl by water in the bulk phase and in the DNA pseudophase, while $k_{2,W}$ and $k_{2,DNA}$ are the rate constants for replacement of monocoordinated bipyridyl by thiourea in the bulk phase and in the DNA pseudophase. $K_{S,W}$ and $K_{S,DNA}$ are, respectively, the equilibrium constants for formation of the monosubstituted solvo-intermediate in water and in the DNA pseudophase, while $K_{tu,W}$ and $K_{tu,DNA}$ are the equilibrium constants for formation of the monosubstituted thiourea-intermediate in water and in DNA pseudophase, respectively. K_{DNA} is the equilibrium constant for partitioning of the complex in water and in the DNA pseudophase.



Scheme 2

$$k_{obs} = \frac{k_{1,W}K''_{S,W} + k_{2,W}K_{tu,W}[tu]^2 + [DNA]\left(k_{1,DNA}K''_{S,DNA}K_{DNA} + k_{2,DNA}K_{tu,DNA}K_{DNA}[tu]^2\right)}{1 + [DNA]\left(K_{DNA} + K_{DNA}K'_{S,DNA} + K_{DNA}K_{tu,DNA}[tu]\right) + K'_{S,W} + K_{tu,W}[tu]} \tag{4}$$

In the absence of DNA Equation (4) coincides with Equation (3). When the concentration of DNA is large enough, for a given thiourea concentration, the rate constant

k_{obs} assumes a constant value which is lower than that in water [Equation (5)].[16]

$$k_{obs} = \frac{k_{1,DNA} K''_{S,DNA} + k_{2,DNA} K_{tu,DNA}[tu]^2}{1 + K'_{S,DNA} + K_{tu,DNA}[tu]} \qquad (5)$$

The good agreement between the experimental plot of k_{obs} against [DNA] and that obtained by fitting the data in accordance with Equation (4) supports the proposed scheme. In addition, the value of the binding constant of 6.5×10^4 M^{-1}, obtained from the fitting of the kinetic data[17] to the same equation at $I = 2.2 \times 10^{-2}$ M, is in fair agreement with that of $(1.0 \pm 0.1) \times 10^5$ M^{-1} determined spectrophotometrically under the same experimental conditions.

Experimental Section

Synthesis. [Pd(bipy)(py)$_2$](PF$_6$)$_2$: The compound was prepared according to a general procedure previously described[3,4] by heating an aqueous suspension of [Pd(bipy)Cl$_2$] with an excess of pyridine to reflux. After dissolution of the solid, NH_4PF_6 was added and the resultant complex precipitated as a pale yellow substance which was recrystallised from water-acetone. **[Pd(bipy)(tu)$_2$](PF$_6$)$_2$:** The compound was prepared in a similar way by treating [Pd(bipy)Cl$_2$] with thiourea in a ratio of 1:2. Both complexes were characterised by elemental analysis and ^{1}H NMR spectroscopy in [D$_6$]acetone.

DNA: Calf thymus DNA was purchased from Sigma Chemical Co. and purified as described previously.[18] DNA concentration, expressed in base pairs, was calculated spectrophotometrically using an ε_{260} value of 1.31×10^4 M^{-1}·cm^{-1}.[19] NaCl and other chemicals were of reagent grade and were used without further purification.

Poly(A): Polyadenylic acid was purchased from Pharmacia Co. and used as received. The Poly(A) concentration was calculated spectrophotometrically using an ε_{258} value of 9.8×10^3 M^{-1}·cm^{-1}.[20]

PVS and PMP: Sodium polyvinylsulfonate and sodium polymetaphosphate were also of reagent grade (Aldrich).

Methods: All experiments were carried out at 25 °C in a phosphate buffer 1×10^{-3} M ([KH_2PO_4]/[Na_2HPO_4] = 1.61) to maintain pH = 7 and sufficient NaCl to give the desired ionic strength. The pH was measured with a Radiometer PHM 62 instrument. Absorption spectra were recorded using a Lambda 5 Perkin−Elmer spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker ARX-300 spectrometer. CD spectra were recorded with a J-810 Jasco polarimeter.

Kinetics: The kinetics of ligand substitution were followed spectrophotometrically in the range of 320−400 nm at 25 °C. In order to avoid competing covalent binding of the complex to the DNA nucleobases, the biopolymer was added to the complex and placed in a cuvette preheated to 25 °C together with thiourea. The concentration of the latter was at least twenty times larger than that of the DNA and the complex. A Perkin−Elmer Lambda 5 spectrophotometer was used to monitor the process. The absorbance changes were displayed on a PC interfaced with the spectrophotometer and pseudo first-order rate constants k_{obs} were obtained from nonlinear least-squares fits of the experimental data to $A_t = A_\infty + (A_0 - A_\infty)\exp(-k_{obs}t)$, where A_0, A_∞ and k_{obs} are the parameters to be optimised (A_0 = absorbance after mixing of the reagents, A_∞ = absorbance at completion of reaction). The k_{obs} values were reproducible to better than ±5%.

Binding Constant Determination: To a solution of complex (3.75×10^{-5} M) were added successive aliquots of DNA, also containing the complex, in a 10-mm stoppered quartz cell and a spectrum was recorded after each addition. The spectrophotometric data were analysed by a non least-squares fitting program using the McGhee and von Hippel equation.[12] The binding constant K_B was determined by the program using the extinction coefficient, the free complex concentration and the ratio of bound complex per mole of DNA. The extinction coefficient for the bound complex was determined by Beer's law plots in the presence of a large excess of DNA.

Supporting Information: All the kinetic data are available (see also footnote on the first page of this article).

Acknowledgments

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[16] K_{DNA} is expected to be very large as experimentally found for many (bipyridine)platinum(II) and -palladium(II) complexes. Therefore, the values in parentheses both in the numerator and the denominator of Equation (4) should be much larger than the other terms.

[17] Owing to the large value of K_{DNA} the denominator of Equation (4) is approximately equal to K_{DNA}[DNA]. Thus, the value of the parameter P_3 obtained from the fitting of the kinetic data to $k_{obs} = (P_1 + P_2[DNA])/(1 + P_3[DNA])$ corresponds essentially to the value of K_{DNA}.

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