Reactivity of $[Ru^{III}(edta)(H_2O)]^-$ with Nucleic Bases, Nucleosides and DNA (Calf-Thymus) in Aqueous Solution (etda = ethylenediamine-*N,N,N',N'*-tetraacetate)

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Reactions of $[Ru^{III}(edta)(H_2O)]^-$ (edta = ethylenediamine-*N,N,N',N'*-tetraacetate) with L' (L' = adenine, adenosine, cytosine, cytidine or thymine) and calf-thymus DNA were studied by spectrophotometric, electrochemical and kinetic methods. Spectral features of the substituted product $[Ru^{III}(edta)L']^-$ complexes were characterised by a strong ligand-to-metal charge transfer (l.m.c.t.) band in the UV region (293–309 nm). The $E_{\frac{1}{2}}$ values for the Ru^{III}–Ru^{II} couple for $[Ru^{III}(edta)L']^-$ are in the range −0.28 to −0.15 V (*vs.* saturated calomel electrode). Equilibration kinetics of complexation of $[Ru^{III}(edta)(H_2O)]^-$ with L' have been investigated using stopped-flow methods at 25 °C and pH 5.2. Equilibrium constants determined kinetically are in good agreement with those obtained spectrophotometrically. The reactivity of L' towards aqua-substitution of $[Ru^{III}(edta)(H_2O)]^-$ complex follows the sequence adenine > adenosine > cytosine > cytidine. On the basis of spectrophotometric, electrochemical and kinetic data and comparing the reactivity of $[Ru^{III}(edta)(H_2O)]^-$ with DNA bases and DNA (calf-thymus) itself it is proposed that the interaction of $[Ru^{III}(edta)(H_2O)]^-$ with DNA takes place through the adenine base unit in a kinetically preferred pathway.

The chemistry of pentadentate edta type complexes of ruthenium is of continued interest[1] due to their remarkable lability towards substitution reactions. In the past few years a substantial development in the catalytic system involving polyaminopolycarboxylate complexes of ruthenium-(II) and -(III) took place through which the catalytic ability of these complexes towards oxidation[2] and reduction[3] of organic compounds has been unambiguously demonstrated. Furthermore, a number of mixed-ligand complexes[4] of ruthenium-(II) and -(III) have been synthesised and characterised. We have been interested in studying the kinetic and mechanistic behaviour of $LRu^{III}(H_2O)^-$ complexes [L = ethylenediamine-*N,N,N',N'*-tetraacetate (edta), propylenedinitrilotetraacetate or *N'*-(2-hydroxyethyl)ethylenediamine-*N,N,N'*-triacetate] towards substitution reactions[5] and their possible application in the catalytic oxidation[2a–c] of organic substrates. The lability of the aqua molecule in $LRu^{III}(H_2O)^-$ complexes provides an advantage of easy co-ordination of substituting ligand to the metal centre for which a mixed-ligand product complex is formed through a rapid aqua-substitution step. Moreover, some potentially bidentate ligands were reported to form mixed-chelate ruthenium(III) complexes[1b,4b,5a] in a rapid aqua-substitution step followed by a slower ring-closing step[1b,5a] which involves the removal of the co-ordinated carboxylate arm of edta. In these mixed-chelate ruthenium(III) complexes, edta behaves as a tetradentate ligand leaving two carboxylate arms free.

The interest in the present work is related to the probability of using $[Ru^{III}(edta)(H_2O)]^-$ complexes as DNA binders. A number of amineruthenium complexes had been reported[6–8] to bind DNA (calf thymus) or to have shown antitumour activity[9,10] in resemblance to that of *cis*-$[Pt(NH_3)_2Cl_2]$.[11] However, these amineruthenium complexes, in particular ruthenium(III) species, are substitution inert *i.e.* undergo slow substitution processes. The edta type complexes of ruthenium(III) by virtue of their remarkable lability can be expected to show greater reactivity towards DNA binding than amine ruthenium complexes. Therefore, in order to examine the interaction of $LRu^{III}(H_2O)$ complexes with DNA, we have studied the reactions of $[Ru^{III}(edta)(H_2O)]^-$ with some DNA bases. Although synthesis of some Ru^{III}–edta–nucleoside complexes along with some spectral and electrochemical data had been reported earlier[12] there are no kinetic and equilibrium studies reported so far. The lack of this information (kinetic and equilibrium data) limits our ability to understand the mode of binding of $[Ru^{III}(edta)(H_2O)]^-$ towards DNA. In this work we report kinetic and equilibrium studies on the interaction of $[Ru^{III}(edta)(H_2O)]^-$ with adenine, adenosine, cytosine and cytidine in aqueous solution. We have extended our study to the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with single-strand DNA (calf thymus) itself to understand the probable mode of attachment in the Ru^{III}(edta)–DNA adduct.

Experimental

Materials.—The salt $K[Ru^{III}(Hedta)Cl]\cdot 2H_2O$ was prepared by following the published procedure[4a] and characterised. The $K[Ru^{III}(Hedta)Cl]$ complex is rapidly aquated when dissolved in water and exists predominantly in its most labile form $[Ru^{III}(edta)(H_2O)]^-$ in the pH range 5–6. Calf-thymus DNA (single strand, four base-pair) obtained from Sigma was purified by exhaustive dialysis against phosphate buffer and water. A solution of DNA (10^{-5} mol dm^{-3}) in phosphate buffer (pH 7.2) gave a ratio of UV absorbances at 260 and 280 nm of 1.80 indicating that the DNA is sufficiently free of protein.[13] The concentration of DNA is expressed here, in terms of nucleotide phosphate concentration calculated by UV-absorbance at 260 nm considering the absorption coefficient (ε_{260})[14] to be 6600 dm^3 mol^{-1} cm^{-1}. All other chemicals used were of A.R. grade. Double distilled water was used throughout the experiments.

Instrumentation and Techniques.—Absorption spectra of the experimental solutions were recorded with a Shimadzu UV/VIS

160 spectrophotometer equipped with a TCC 240A temperature controller. Absorption due to DNA was subtracted by adding equal amounts of DNA solution to both the sample and reference cells. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) measurements were carried out with Princeton Applied Research (PAR) electrochemical instruments in an aqueous medium using KCl as supporting electrolyte. A glassy carbon (Hg-drop electrode was avoided as it contaminates DNA solutions[15]) and a saturated calomel electrode (SCE) (as reference) were used for this purpose.

Kinetic Studies.—Kinetic measurements were carried out on a Hi-Tech (SF-51) stopped-flow spectrophotometer attached to an on-line data analyser (Apple IIe) with which the kinetic traces could be evaluated. All the reactions were monitored at 340 nm where a reasonable spectral difference between reactant and product exists. However, additional wavelengths (310 and 360 nm) were monitored routinely to assure that the results were independent of wavelengths. The instrument was thermostatted at ±0.1 °C. Rate-constant data were measured under pseudo-first-order conditions *i.e.* at least a 10-fold excess of nucleophile was used. Acetic acid–acetate buffer was used to maintain pH (5.2) of kinetic solutions (phosphate buffer was used to maintain the pH of DNA solution at 7.2). pH Measurements were carried out with a Digisun pH meter. Rate-constant data represented as an average of triplicate runs are reproducible within ±4%.

Results and Discussion

Complexation of $[Ru^{III}(edta)(H_2O)]^-$ *with DNA Bases* (L').—The reactions of $[Ru^{III}(edta)(H_2O)]^-$ with L' (L' = adenine, adenosine, cytosine and cytidine) in aqueous solution exhibit a characteristic ligand-to-metal charge transfer (l.m.c.t.) band of L' in the region 290–305 nm {Fig. 1 shows the typical spectral changes which occur immediately after mixing aqueous solutions of $[Ru^{III}(edta)(H_2O)]^-$ and adenine at pH 5.1}. The spectral data characteristic of $[Ru^{III}(edta)L']^-$ complexes are summarised in Table 1.

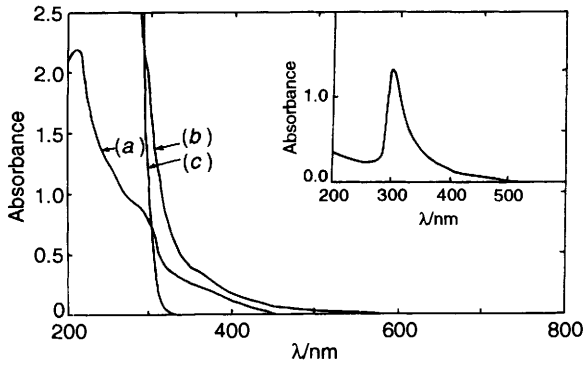


Fig. 1 Spectra of aqueous solutions of (*a*) $[Ru^{III}(edta)(H_2O)]^-$ and (*b*) $[Ru^{III}(edta)(H_2O)]^-$ + adenine in H_2O; $[Ru^{III}] = 5 \times 10^{-4}$ mol dm^{-3}, [adenine] = 5×10^{-3} mol dm^{-3}, pH 5.2 {inset, spectrum of $[Ru^{III}(edta)(adenine)]$ in the presence of adenine (5×10^{-3} mol dm^{-3})}. (*c*) Spectrum of adenine (5×10^{-3} mol dm^{-3}) in H_2O

Table 1 Spectral and electrochemical data for the reactions of $[Ru^{III}(edta)(H_2O)]^-$ with L' in aqueous solution at pH 5.2, I = 0.2 mol dm^{-3} (KCl)

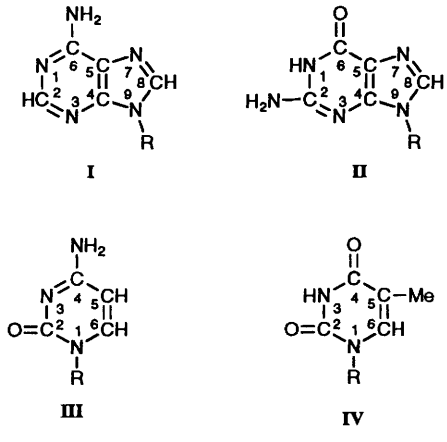
System *	λ_{max}/nm	$E_{\frac{1}{2}}$/V
$[Ru^{III}(edta)(H_2O)]^-$	283	−0.28
$[Ru^{III}(edta)(H_2O)]^-$ + adenine	292	−0.12
$[Ru^{III}(edta)(H_2O)]^-$ + adenosine	295	−0.15
$[Ru^{III}(edta)(H_2O)]^-$ + cytosine	301	−0.27
$[Ru^{III}(edta)(H_2O)]^-$ + cytidine	304	−0.27
$[Ru^{III}(edta)(H_2O)]^-$ + thymine	301	−0.26

* $[Ru^{III}] = 5 \times 10^{-4}$ mol dm^{-3}, $[L'] = 5 \times 10^{-3}$ mol dm^{-3}.

Electrochemical measurements both by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) on $[Ru^{III}(edta)(H_2O)]^-$ both in the absence and presence of L', were carried out in aqueous solution at pH 5.2. Cyclic voltammetry of $[Ru^{III}(edta)(H_2O)]^-$ in the absence of L' featured a pair of quasi-reversible anodic and cathodic waves, with $E_{\frac{1}{2}}$ [$=(E_{pc} + E_{pa})/2$] at −0.28 V (*vs.* SCE) and ΔE_p 90 mV (at a scan rate 100 mV s^{-1}). It was reported earlier[1a] that the reversibility of electrode reactions with $[Ru^{III}(edta)(H_2O)]^-$ complex is at its lowest at the glassy carbon electrode. In the presence of L' at the same concentration of $[Ru^{III}(edta)(H_2O)]^-$ the cathodic and anodic peak potentials shifted to appreciably more anodic values for L' = adenine or adenosine (Table 1), with values of ΔE_p in the range 90–120 mV, indicating that the same quasi-reversible nature of the electron-transfer process was maintained. Cyclic voltammetric potentials ($E_{\frac{1}{2}}$) for $[Ru^{III}(edta)L']^-$–$[Ru^{III}(edta)L']^{2-}$ redox couples are in Table 1. Based on a survey of the literature[16] on probable nucleoside sites for transition-metal ion binding it is assumed that in $[Ru^{III}(edta)L']$ complexes, adenine and adenosine bind through N^7 and cytosine and cytidine bind *via* N^3. The positive shift in peak potentials (Table 1) observed in $[Ru^{III}(edta)L']^-$ complexes (L' = adenine or adenosine) may be accounted for by π-interaction through the imidazole type N^7 site (Fig. 2) of purine bases which shifts some electron density from the metal to the ligand.

Spectral changes which occurred in the reactions of $[Ru^{III}(edta)(H_2O)]^-$ with L' are shown in Fig. 1. A suitable wavelength can be selected in the range 310–360 nm for kinetic investigations. The reactions of $[Ru^{III}(edta)(H_2O)]^-$ with L' were followed as an absorbance increase at 340 nm, and in all cases (except adenine) absorbance–time traces were found to be single exponential. The rate of formation of $[Ru^{III}(edta)L']^-$ was found to be first order with respect to $[Ru^{III}(edta)(H_2O)^-]$ concentration. The values of k_{obs} increased linearly by increasing [L'] with a significant intercept (Fig.3). The general kinetic behaviour observed for the reactions of $[Ru^{III}(edta)(H_2O)]^-$ with L' can be interpreted by equation (1) for which a rate expression is given by equation (2).

$$[Ru^{III}(edta)(H_2O)]^- + L' \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [Ru^{III}(edta)L']^- + H_2O \quad (1)$$



	R = H	R = ribose unit
I	adenine	adenosine
II	guanine	guanosine
III	cytosine	cytidine
IV	thymine	thymidine

Fig. 2 Schematic representation of purine and pyrimidine bases

Table 2 Rate and equilibrium constant data for the reaction $[Ru^{III}(edta)(H_2O)]^- + L' \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [Ru^{III}(edta)L']^- + H_2O$[a]

L'	k_1/dm^3 mol^{-1} s^{-1}	k_2/s^{-1}	$K (= k_1/k_2)$/dm^3 mol^{-1}	K_m[b]/dm^3 mol^{-1}	k_3[c]/s^{-1}
Adenine	400 ± 10	2.30 ± 0.20	171	*d*	0.18 ± 0.03
Adenosine	110 ± 4	0.77 ± 0.30	153	168	
Cytosine	1.8 ± 0.3	0.024 ± 0.005	75	72	
Cytidine	1.5 ± 0.4	0.033 ± 0.006	46	40	

[a] $[Ru^{III}] = 5 \times 10^{-4}$ mol dm^{-3}, pH 5.2, 298 K, $I = 0.2$ mol dm^{-3} (KCl). [b] Determined spectrophotometrically in the wavelength range 320–340 nm. [c] Ring-closure step. [d] Equilibrium constant could not be determined spectrophotometrically due to interference from the ring-closure step.

$$k_{obs} = k_1[L'] + k_2 \quad (2)$$

The slopes and intercepts of the k_{obs} *vs.* [L'] plots (Fig. 3) give the values of k_1 and k_2 respectively, which are listed in Table 2.

Comparing our experimental results to those reported earlier for aqua-substitution reactions[1-3] of $[Ru^{III}(edta)(H_2O)]^-$, it is seen that the pyrimidine and purine bases used here are poor nucleophiles towards the substitution process. The weak product-complex $[Ru^{III}(edta)L']^-$ so formed in the substitution process suffers reverse aquation [k_2 step in equation (1)] and exists in equilibrium with $[Ru^{III}(edta)(H_2O)]^-$. The values of equilibrium constant (K) determined spectrophotometrically[17] for the process outlined in equation (1) are in good agreement with those values determined kinetically (k_1/k_2). The agreement between K and k_1/k_2 demonstrates that the slopes and intercepts of the plots of k_{obs} *vs.* [L'] (Fig. 3) correspond to k_1 and k_2, respectively, in equation (1).

A study of the rate constant data (Table 1) suggests that adenine is the most reactive nucleophile studied, towards aqua substitution of $[Ru^{III}(edta)(H_2O)]^-$. The reactivity of L' towards binding with $[Ru^{III}(edta)(H_2O)]^-$ decreases in the following order: adenine > adenosine > cystosine > cytidine.

The rate constants for the substitution reactions of $[Ru^{III}(edta)(H_2O)]^-$ with nucleic bases are slightly higher than those observed for the same reactions with nucleosides. A similar trend was also observed in the equilibrium constant (K) values. From this trend, it is established that the presence of the ribose unit in the nucleosides does not significantly alter the nucleophilicity of the corresponding nucleic bases but does increase the size of the nucleophile so slightly reducing their reactivity relative to that of the nucleic bases studied here.

In the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with adenine we found two clearly different absorption–time profiles at 320 nm. These are characterised by a rapid growth (*ca.* 1 s) followed by a slower decay (*ca.* 60 s) as shown in Fig. 4. It is thus clear that there are two consecutive reaction steps. The corresponding two-exponential fit [Fig. 4(*a*) and (*b*)] results in rate constants (k_{obs}) of 6.41 and 0.18 s^{-1} (25 °C, pH 5.0, $[Ru^{III}] = 5 \times 10^{-4}$ mol dm^{-3}, [adenine] = 1.05×10^{-2} mol dm^{-3}). The values of the observed rate constant for the rapid first step increased linearly with adenine concentration (as observed for other nucleophiles *viz.* cytosine, adenosine, cytidine). However, the rate constant values corresponding to the slower decay step were found to be independent of adenine concentration. On the basis of earlier reports on the kinetics of chelate formation of 2-thioxopyridine[16] and 2-thioxopyrimidine[5a] with Ru^{III}–edta, the present kinetic observations may be interpreted in terms of a rapid formation of the mono-ligated product $[Ru^{III}(edta)L']^-$ followed by a ring-closure step (ligand independent) in which the exocyclic NH_2 group (at C^6) is co-ordinated to the ruthenium centre by displacement of a co-ordinated carboxylate group of edta (Scheme 1). It is of interest that this ring-closure step was only kinetically observable with adenine. The absence of a ring-closure step for adenosine, cytosine and cytidine may be explained in terms of their poorer

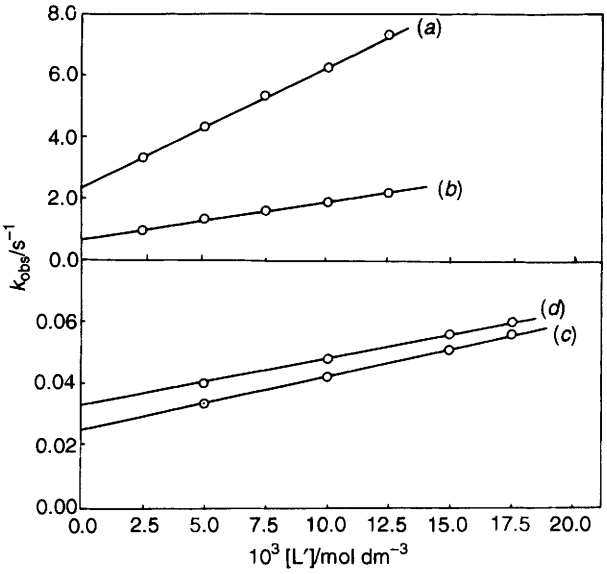


Fig. 3 Plot of k_{obs} *vs.* [L'], $[Ru^{III}] = 5 \times 10^{-4}$ mol dm^{-3}, 298 K, pH 5.2, $I = 0.2$ mol dm^{-3} (KCl). L' = (*a*) adenine, (*b*) adenosine, (*c*) cytosine and (*d*) cytidine

nucleophilicity or by steric factors.* The kinetics of the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with thymine could not be studied owing to insufficient absorption change in the spectra of reactant and products while guanine was found to be insoluble at the specified experimental conditions. On the basis of experimental observations discussed so far it can be concluded at this stage that the complexation reactions of $[Ru^{III}(edta)(H_2O)]^-$ with adenine and adenosine are more favourable (both kinetically and thermodynamically) compared to the reactions with cytosine or cytidine.

Reaction of $[Ru^{III}(edta)(H_2O)]^-$ *with DNA.*—Due to very limited stock of DNA available only a few experiments were performed. Fig. 5 shows the spectrum of the reaction mixture obtained upon addition of excess DNA (in phosphate buffer) to a solution of $[Ru^{III}(edta)(H_2O)]^-$. The absorption band at 295 nm resembles that exhibited by the $[Ru^{III}(edta)(adenosine)]^-$ complex. Changes in absorption at 310 nm upon variation of the concentration of DNA are given in Table 3 for the purpose of calculating binding constants (K_b). The value of K_b determined spectrophotometrically[17] (by using the data in Table 3) was 144 dm^3 mol^{-1}. A plot of $1/\Delta A$ *vs.* 1/[DNA] gave a good straight line with a regression factor (r) value of 0.999. CV and DPV of $[Ru^{III}(edta)(H_2O)]^-$ both in the absence and presence of DNA are shown in Fig. 6. The cyclic voltammetric behaviour of $[Ru^{III}(edta)(H_2O)]^-$ in the presence of DNA

* Negligible absorbance change upon ring-closure in these systems cannot however be fully discounted.

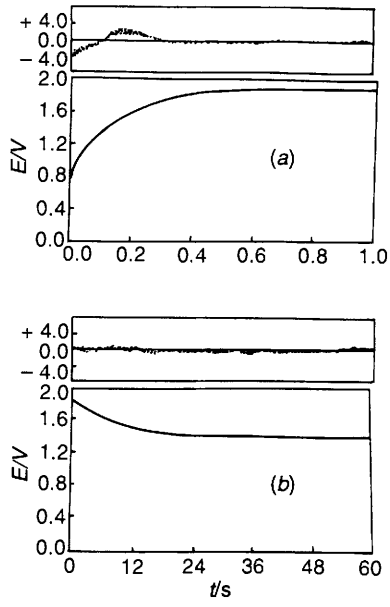
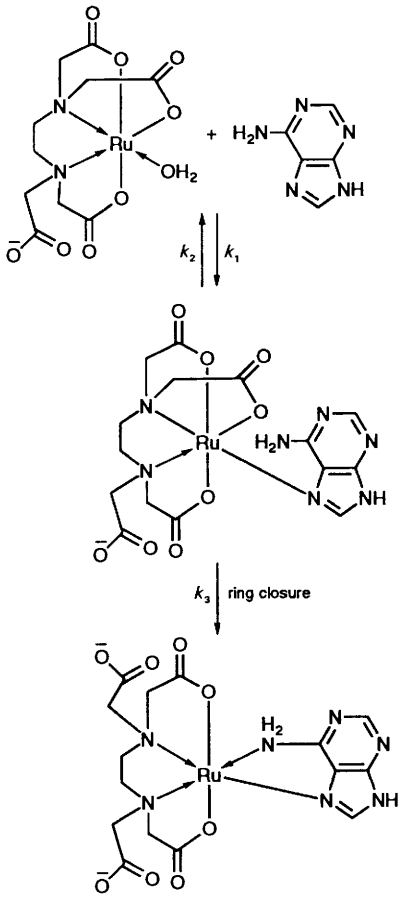


Fig. 4 Typical kinetic traces recorded for the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with adenine, $[Ru^{III}] = 5 \times 10^{-4}$ mol dm^{-3}, [adenine] = 1.05×10^{-2} mol dm^{-3}, $I = 0.2$ mol dm^{-3} (KCl), pH 5.0, 298 K. The difference (residual in %) between experimental and fitted traces is given at the top of the figures



Scheme 1

was found to be similar to that observed for the $[Ru^{III}(edta)(adenosine)]^-$ complex. The redox potential ($E_{\frac{1}{2}}$) corresponding to the Ru^{III}–Ru^{II} redox couple estimated (in presence of excess DNA at pH 7.2) from voltammetric measurements is −0.15 V, the same value as obtained for the $[Ru^{III}(edta)(adenosine)]^-$ complex.

Kinetics of the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with DNA were studied at 320 nm where an appreciable absorption change occurs (and spectrum of DNA itself is featureless). A typical kinetic trace obtained under pseudo-first-order conditions of excess DNA is shown in Fig. 7. The trace shown in Fig. 7 clearly exhibits a single exponential feature. The single-exponential nature of the traces did not change even at the highest time base (500 s) of the stopped-flow instrument. This would seem to indicate the absence of any other consecutive reactions. The reaction of $[Ru^{III}(edta)(H_2O)]^-$ with DNA exhibits very similar kinetic behaviour to that observed in the reaction with

Table 3 Spectrophotometric data for the interaction of $[Ru^{III}(edta)(H_2O)]^-$ with DNA in aqueous solution[a]

10^2 [DNA]/mol dm^{-3}	λ_{max}/nm	Absorbance (A) at 310 nm	ΔA[b]
0.0	283	0.451 (A_0)[c]	0.0
0.16	295	0.507	0.056
0.41	295	0.567	0.116
0.61	296	0.592	0.141
1.23	296	0.634	0.183

[a] $[Ru^{III}] = 4 \times 10^{-4}$ mol dm^{-3}, pH 7.2 (phosphate buffer), 298 K. [b] $\Delta A = A - A_0$. [c] A_0 is the absorbance of $[Ru^{III}(edta)(H_2O)]^-$ (at 310 nm) in the absence of DNA.

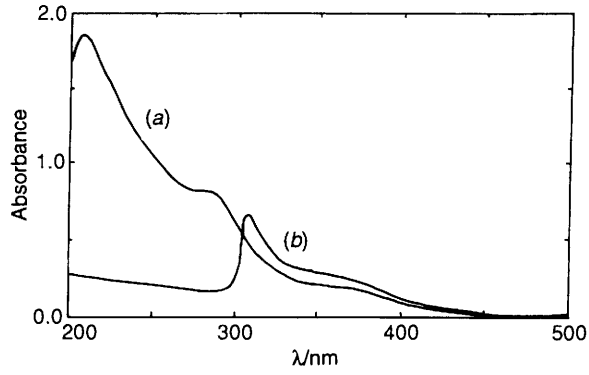


Fig. 5 Spectra of aqueous solutions of $[Ru^{III}(edta)(H_2O)]^-$ (4×10^{-4} mol dm^{-3}) in the absence (*a*) and in the presence of DNA (*b*) (1.23×10^{-2} mol dm^{-3}) at pH 7.2

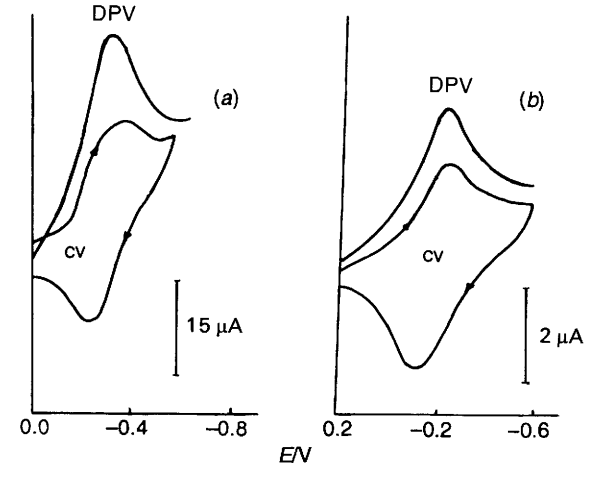


Fig. 6 CV and DPV of $[Ru^{III}(edta)(H_2O)]^-$ in the absence (*a*), and in the presence of DNA (*b*) at pH 7.2. Scan rate 100 mV s^{-1} for CV and 10 mV s^{-1} for DPV; $[Ru^{III}] = 4 \times 10^{-4}$ mol dm^{-3}, [DNA] = 1.23×10^{-2} mol dm^{-3}

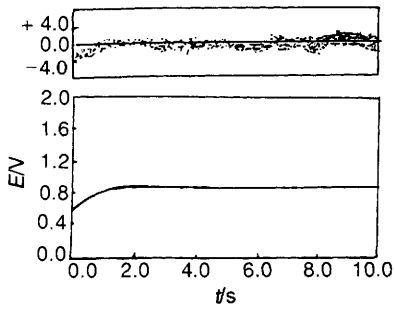


Fig. 7 Kinetic trace for the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with DNA, $[Ru^{III}] = 4 \times 10^{-4}$ mol dm^{-3}, $[DNA] = 0.41 \times 10^{-2}$ mol dm^{-3}, pH 7.2, 298 K. The difference between experimental and fitted traces is given at the top of the figure

nucleosides. The rate law derived for the reaction is outlined in equation (3).

$$k_{obs} = k_f[DNA] + k_r \quad (3)$$

The values of k_f and k_r are 120 ± 4 dm^3 mol^{-1} s^{-1} and 0.85 ± 0.05 s^{-1} respectively at 25 °C (pH 7.2).

On the basis of above experimental facts and comparison of the spectrophotometric, electrochemical and kinetic data (Tables 1 and 2) with those obtained in the reaction of $[Ru^{III}(edta)(H_2O)]^-$ with DNA we propose that the binding of $[Ru^{III}(edta)]$ to single-strand calf-thymus DNA (in which the various component monomeric bases are exposed for co-ordination) probably occurs *via* adenine in a kinetically favoured rapid aqua-substitution step. Our experimental results reported here clearly demonstrate (for the first time) the ability of a ruthenium(III) complex to bind DNA in a stopped-flow time-scale. As the biological action both of carcinogenic and antitumour agents is believed to be attributed to covalent binding to DNA, our results may be of importance (especially with regard to the lability of the system) in the evaluation of the oncological properties of $[Ru^{III}(edta)(H_2O)]^-$. Studies relating to the redox properties of the DNA-bound Ru^{III}–edta complex are in progress.

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