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Coligand tuning of the DNA binding properties of half-sandwich organometallic intercalators: Influence of polypyridyl (pp) and monodentate ligands (L = Cl, $(NH_2)_2CS$, $(NMe_2)_2CS$) on the intercalation of (η^5-pentamethylcyclopentadienyl)-iridium(III)- dipyridoquinoxaline and -dipyridophenazine complexes

Sven Schäfer, William S. Sheldrick *

Lehrstuhl für Analytische Chemie, Ruhr-Universität Bochum, D-44780 Bochum, Germany

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Abstract

The DNA binding of polypyridyl (pp) (η^5-pentamethylcyclopentadienyl)iridium(III) complexes of the type $[(\eta^5\text{-}C_5Me_5)IrCl(pp)](CF_3SO_3)$ (pp = dpq, dppz, dppn) (**1**–**3**) and $[(\eta^5\text{-}C_5Me_5)Ir(L)(pp)](CF_3SO_3)_2$ (L = $(NH_2)_2CS$, pp = dpq, dppz, dppn) (**4**–**6**), (L = $(NMe_2)_2CS$, pp = dpq, dppz, dppn) (**7**–**9**) has been studied by UV/Vis spectroscopy, circular dichroism and viscosity measurements. Modest increases ΔT_m of 2–7 °C in the thermal denaturation temperature (for r = [complex]/[DNA] = 0.1) and the effectively unchanged values or decreases in viscosity observed for CT DNA after incubation with complexes **1**–**3** for 60 min are in accordance with thermodynamically preferred coordinative Ir-N (nucleobase) binding to the biopolymer. However, kinetically favoured intercalation for **2** and **3** leads to large initial hypochromic UV/Vis shifts for the π–π^* transitions of their polypyridyl ligands in the range 300–450 nm. As indicated by the large ΔT_m value of 14 °C and the marked increase in viscosity for **5**/CT DNA mixtures, dppz appears to present an optimum surface area for side-on intercalation for L = $(NH_2)_2CS$. Whereas lower values for these parameters suggest partial intercalation for the smaller dpq ligand of complex **4**, the ΔT_m value of only 2 °C and a decrease in DNA viscosity are in accordance with surface binding for the dppn complex **6**. In contrast, replacement of L = $(NH_2)_2CS$ in **6** by L = $(NMe_2)_2CS$ in **9** leads to very strong intercalative binding of the larger polypyridyl ligand with a binding constant $K_b = 1.0(6) \times 10^7$ M^{-1} following a possible change in the DNA structure from B to A, as suggested by CD spectroscopy. Viscosity studies and ΔT_m values for complexes **7** and **8** are in accordance with, respectively, partial and strong intercalative binding of these complexes into DNA. Circular dichroism measurements suggest that the presence of the bulky $(NMe_2)_2CS$ ligand causes significant distortions of the DNA structure for the larger dppz and dppn ligands.

Keywords: Bioorganometallic chemistry; Iridium; Polypyridyl ligands; Thiourea; DNA binding; Intercalation

1. Introduction

The intercalation of transition metal polypyridyl complexes into DNA has been the focus of numerous investigations in the past two decades [1–3]. Increasing the surface area of the polypyridyl ligand generally leads to a substantial increase in the intercalative binding strength [4]. As a result, octahedral complexes such as $[Ru(bpy)_2(dppz)]^{2+}$ [5] containing the extended heterocyclic ligand dppz (dipyrido[3,2-*a*:2′,3′-*c*]phenazine) have provided suitable tools for exploiting intercalative DNA interactions, for instance as molecular light switches [2]. Although Ru^{II} and Rh^{III} metallointercalators have been extensively studied, only a few reports of related compounds with a central Ir^{III} atom have previously appeared. These include $[Ir(bpy)(phen)(phi)]^{3+}$ (phi = 9,10-phenanthrenequinonediimine), which

* Corresponding author. Tel.: +49 234 32 24192; fax: +49 234 32 14420.
E-mail address: william.sheldrick@ruhr-uni-bochum.de (W.S. Sheldrick).

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has been employed to follow electron transfer in DNA [6], and luminescent dipyridoquinoxaline and dipyridophenazine complexes of the type $[Ir(ppy)_2(pp)](PF_6)$ [Hppy = 2-phenylpyridine; pp = 2-*n*-butylamidodipyrido[3,2-*f*:2′,3′-*h*]quinoxaline (dpq), dppz, benzo[*i*]dipyrido[3,2-*a*:2′,3′-*c*] phenazine(dppn)] [7].

We ourselves have recently demonstrated that bioorganometallic metallointercalators of the type $[(\eta^5\text{-}C_5Me_5)Ir(dppz)(peptide\text{-}\kappa S)]^{n+}$ ($n = 1$–3) with κ*S* coordinated methionine-containing peptides [8–10] exhibit strong intercalative binding into DNA with equilibrium constants K_b of up to $1.2 \times 10^6\ M^{-1}$. A side-on intercalation mode was established by 2D NOESY for the interaction of $[(\eta^5\text{-}C_5Me_5)Ir(dppz)(H_2metOMe)]^{3+}$ and the $(\eta^6\text{-}C_6Me_6)Ru^{II}$ complex $[(\eta^6\text{-}C_6Me_6)Ru(Ac\text{-}metOH)(dppz)]^{2+}$ (HmetOH = L-methionine) [11] with the hexanucleotide d(GTCGAC)$_2$. As mentioned above, the end-on intercalative binding affinity of polypyridyl complexes can normally be enhanced by extending the surface area of the heterocyclic pp ligand. For example, the expected trend is observed for the complexes $[Ir(ppy)_2(pp)](PF_6)$, whose DNA binding constants K_b increase from 1.2×10^4 over 2.0×10^4 to 7.8×10^4 in the series p = dpq, dppz, dppn [7]. A similar enhancement was reported for dppn in comparison to dppz in the Re^I complexes $[fac\text{-}Re(CO)_3(pp)(pyridine)](CF_3SO_3)$ [12–14]. Inspection of Fig. 1 suggests that replacement of dppz by dppn in organometallic complexes of the type $[(\eta^5\text{-}C_5Me_5)Ir(pp)L]^{2+}$ could favour the preferred side-on intercalation by enabling additional stacking with the adenine and cytosine bases of the left-hand strand. On the other hand, possible close non-bonding contacts between atoms of the additional six-membered ring of dppn and DNA riboses may prevent a favourable alignment of the polypyridyl ligand relative to the stacked nucleobase pairs of the double helix.

To establish whether there is, indeed, an optimum dipyridoquinoxaline or dipyridophenazine ligand size for side-on intercalation of such organometallic half-sandwich compounds, we have now studied the DNA binding properties for $[(\eta^5\text{-}C_5Me_5)IrCl(pp)](CF_3SO_3)$ (**1**–**3**) and $[(\eta^5\text{-}C_5Me_5)Ir\{(NR_2)_2CS\}pp](CF_3SO_3)_2$ (R = H, Me) (**4**–**9**) with pp = dpq, dppz, dppn. In contrast to typical metallointercalators [2], these $(\eta^5\text{-}C_5Me_5)Ir^{III}$ complexes contain an exchangeable anionic or neutral ligand L, whose variation may be expected to influence the nature and strength of the DNA interaction. Whereas rapid Cl^-/H_2O substitution followed by coordinative Ir-N(nucleobase) binding could be competitive with intercalation for **1**–**3**, complexes **4**–**9** containing the strong nucleophiles $(NH_2)_2CS$ and $(NMe_2)_2CS$ were chosen to explore the possible influence of additional groove binding (for $L = (NH_2)_2CS$) or steric bulk of the monodentate ligand L (for $L = (NMe_2)_2CS$). Thiourea ligands have been shown to play effectively no role in the DNA binding of the metallointercalator $[Pt(bpy)\{(NH_2)_2CS\}_2]$ [15], in which, however, they are sited *trans* rather than *cis* to the intercalating aromatic ligand as in **4**–**9**.

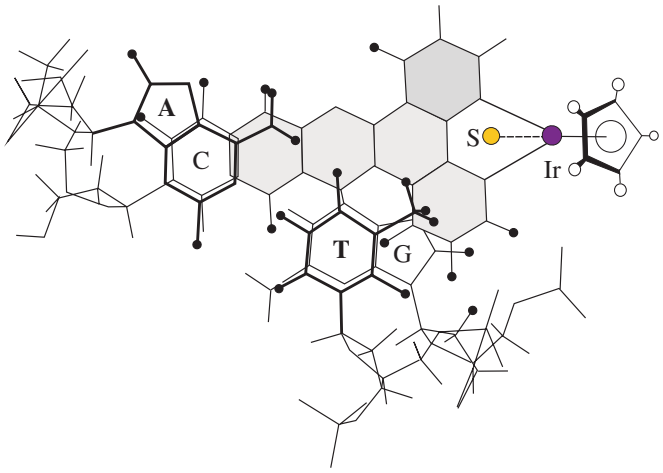


Fig. 1. Schematic illustration of the side-on intercalation of $[(\eta^5\text{-}C_5Me_5)Ir(H_2metOMe)(dppz)](CF_3SO_3)_3$ into the G_1T_2/C_6A_5 sequence of the hexanucleotide d(GTCGAC)$_2$ [8,11].

2. Results and discussion

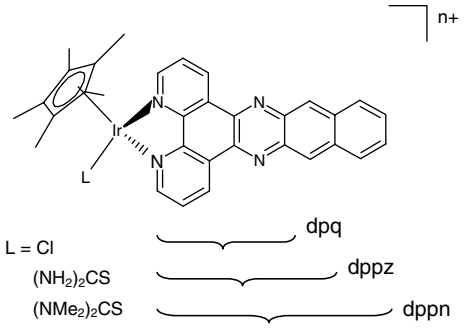
2.1. Synthesis of 1–9

The compounds of the type $[(\eta^5\text{-}C_5Me_5)RuCl(pp)](CF_3SO_3)$ (**1**–**3**) (pp = dpq, dppz, dppn) were prepared by refluxing the solvent complex $[(\eta^5\text{-}C_5Me_5)IrCl(acetone)_2](CF_3SO_3)$ with the appropriate polypyridyl ligand (pp) in CH_3OH/CH_2Cl_2 for 2 h. $[(\eta^5\text{-}C_5Me_5)IrCl(acetone)_2]^+$ can be obtained in situ by addition of two equivalents of $Ag(CF_3SO_3)$ to a solution of the dimeric starting compound $[\{(\eta^5\text{-}C_5Me_5)IrCl\}_2(\mu\text{-}Cl)_2]$ in acetone and subsequent filtration of the precipitated AgCl after stirring in the dark for 0.5 h. Following solvent substitution of the remaining chloride ligand in complexes **1**–**3** by treating these with a further equivalent of $Ag(CF_3SO_3)$ in acetone, addition of thiourea or tetramethyl thiourea to the in situ complexes $[(\eta^5\text{-}C_5Me_5)Ir(acetone)(pp)]^{2+}$ affords the series of compounds $[(\eta^5\text{-}C_5Me_5)Ir\{(NH_2)_2CS\}(pp)](CF_3SO_3)_2$ (**4**–**6**) and $[(\eta^5\text{-}C_5Me_5)Ir\{(NMe_2)_2CS\}(pp)](CF_3SO_3)_2$ (**7**–**9**) (pp = dpq, dppz, dppn) after refluxing for 2 h in CH_3OH/CH_2Cl_2. All complexes were characterised by ^1H and ^{13}C NMR, FAB MS and IR spectroscopy and gave satisfactory elemental analyses (see Scheme 1).

2.2. DNA binding studies

2.2.1. UV/Vis absorption and thermal denaturation

Melting temperature measurements for CT DNA in the presence of organometallic complexes such as **1**–**9** should provide a means of gauging the strength of polypyridyl intercalation, provided that the electrostatic and hydrogen bonding interactions may be regarded as remaining effectively unchanged by pp variation [8–11]. We have, for instance, previously demonstrated that the DNA melting temperature exhibits a systematic increase ΔT_m within the tricationic



Scheme 1. Structures of the complexes **1**–**9**.

series $[(\eta^6\text{-arene})Ru(dppz)(H_2metOMe)]^{3+}$ (HmetOH = L-methionine), when the biopolymer is treated with the complex at a 1:10 complex/[DNA] ratio ($r = 0.1$ for [DNA] = M(nucleotide)) in a 10 mM phosphate buffer at pH 7.2. The ΔT_m value increases from 6.5 (arene = C_6H_6) over 11.5 (arene = 1,3,5-$Me_3C_6H_3$) to 18.2 °C for C_6Me_6 as the aromatic coligand [11]. These changes correlate with a steady weakening of the Ru–N(dppz) bonds and, therefore, with a general increase in polypyridyl electron density within the series due to a concomitant strengthening of Ru-arene bonding in the order C_6H_6 < 1,3,5-$Me_3C_6H_3$ < C_6Me_6. ΔT_m values of, respectively, 6.9 and 7.8 °C were previously recorded for $[(\eta^5\text{-}C_5Me_5)$ Ir(dppz)(HglyglymetOH)$]^{2+}$ (HglyOH = glycine) and $[(\eta^5\text{-}C_5Me_5)Ir(dppz)(H_2metOMe)]^{3+}$, which exhibit strong intercalative binding into DNA, as confirmed by their binding constants K_b of 1.2×10^6 and 2.6×10^6 M^{-1} [8]. In contrast, only negligible increases of 1.7 and 1.4 °C are observed for the DNA melting temperature in the presence of the non-intercalating complexes $[(\eta^5\text{-}C_5Me_5)Ir(phen)(H_2metOMe)]^{3+}$ and $[(\eta^5\text{-}C_5Me_5)Ir(phen)(HcysOMe)]^{2+}$ (HcysOH = L-cysteine) [8].

Following an incubation period of 5 min, UV/Vis spectra for the buffered solutions of **4**–**9** (pH 7.2, 10 mM phosphate) with CT DNA exhibit no further changes, thereby indicating that achievement of equilibrium conditions is rapid. A pronounced decrease in absorbance at about 364 and 383 nm on UV/Vis titration of 20 μM solutions of the dppz complexes **5** and **8** with calf thymus DNA (CT DNA) and shifts of these absorption maxima to higher wavelengths are indicative of possible dppz intercalation into the biopolymer. The hypochromic shift $\Delta A/A$ of −44% at 383 nm with its associated red shift of 5 nm is depicted for $[(\eta^5\text{-}C_5Me_5)Ir\{(NMe_2)_2CS\}(dppz)](CF_3SO_3)$ (**8**) in Fig. 2a. Similar hypo- and bathochromic shifts were also observed for the spin-allowed π–π^* transitions of the dppn complexes **6** and **9** at about 327, 403 and 425 nm. Fig. 2b illustrates the $\Delta A/A$ value of −42% at 327 nm and the associated red shift of 6 nm for complex **9** on titration with CT DNA. The spectral changes observed here for **5**, **6**, **8** and **9** suggest that these $(\eta^5\text{-}C_5Me_5)Ir^{III}$ complexes may bind to DNA either by intercalation or by surface interaction with associated stacking of neighbouring dppz or dppn ligands. In contrast no effective change in absorption was recorded for the dpq complexes **4** and **7** in the range 320–430 nm.

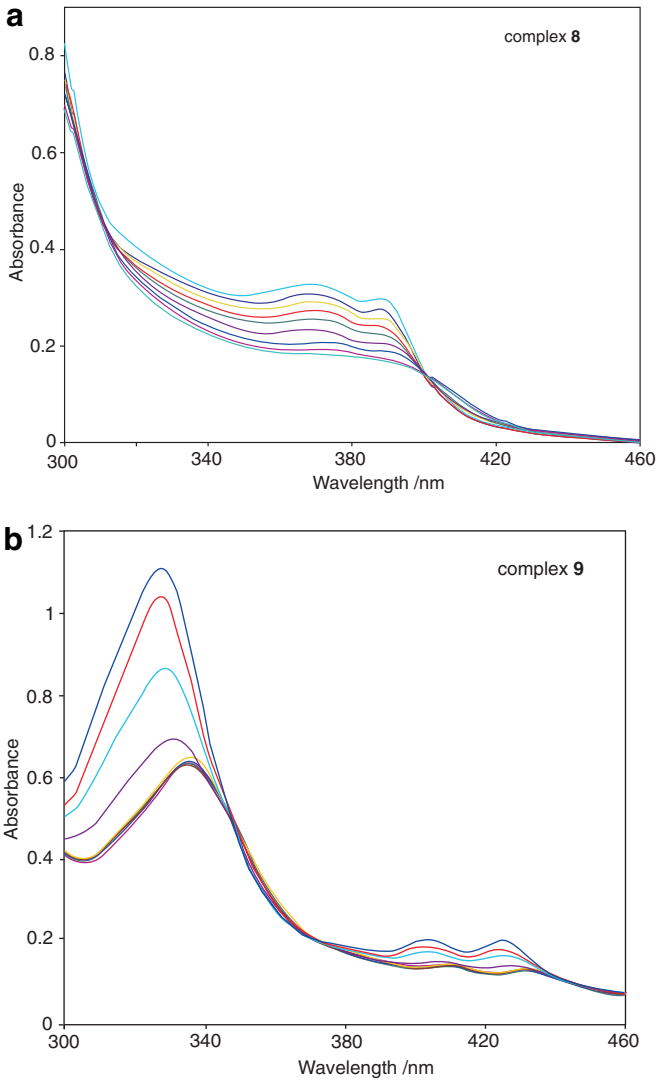


Fig. 2. UV/Vis spectra for the titrations of (a) $[(\eta^5\text{-}C_5Me_5)Ir(dppz)\{(NMe_2)_2CS\}](CF_3SO_3)_2$ (**8**) and (b) $[(\eta^5\text{-}C_5Me_5)Ir(dppn)\{(NMe_2)_2CS\}](CF_3SO_3)_2$ (**9**) (both 20 μM) in a 10 mM phosphate buffer (pH 7.2) with CT DNA [0–90 μM (nucleotide)].

The melting temperature shifts ΔT_m for the monocations of **1**–**3** and the dications of **4**–**9** are listed in Table 1. In the absence of intercalation, significantly higher ΔT_m values will generally be expected for the complexes **4**–**9** in comparison to **1**–**3** owing to their increased cationic charge $n = 2$. The very high values of 12–14 °C recorded for the thiourea and $(NMe_2)_2CS$ complexes **5**, **8** and **9** are in accordance with effective intercalation of the dppz or dppn ligands. Much lower melting temperature shifts of 6 and 4 °C are observed for the analogous dpq complexes **4** and **7**, but comparison with the negligible values of 2 °C registered for the chloro compounds $[(\eta^5\text{-}C_5Me_5)IrCl(pp)](CF_3SO_3)$ **1** and **3** (pp = dpq, dppn) suggests that **4** and **7** could possibly still exhibit a limited degree of intercalation. The minor increase in ΔT_m of 2 °C for complex **6**

Table 1
Melting temperature shifts ($r = 0.1$) and reduced viscosity concentration dependencies for the interaction of complexes $[(\eta^5\text{-}C_5Me_5)Ir(L)(pp)]^{n+}$ ($n = 1,2$) **1**–**9** with CT DNA in a phosphate buffer at pH 7.2

Compound	pp	L	n	ΔT_m (°C)[a]	v[b]
1	dpq	Cl	1	2	0.16
2	dppz	Cl	1	7	−1.63
3	dppn	Cl	1	2	−1.42
4	dpq	$(NH_2)_2CS$	2	6	0.67
5	dppz	$(NH_2)_2CS$	2	14	1.63
6	dppn	$(NH_2)_2CS$	2	2	−0.65
7	dpq	$(NMe_2)_2CS$	2	4	0.59
8	dppz	$(NMe_2)_2CS$	2	12	1.65
9	dppn	$(NMe_2)_2CS$	2	12	1.93

η = reduced viscosity for r = [complex]/[DNA] and η_0 = reduced viscosity of the DNA solution in the absence of complex, v gives the slope of the best fits for plots of $\ln(\eta/\eta_0)$ against $\ln(1 + r)$.
[a] Estimated errors of ±1 °C.
[b] Estimated standard deviations of ±0.02.

indicates an absence of dppn intercalation, which is at first sight surprising in view of the large increase (12 °C) recorded for the dppn complex **9** despite its bulkier tetramethyl thiourea ligand.

On mixing with CT DNA, the UV/Vis spectra of chloro complexes **2** and **3** initially exhibit large hypochromic shifts with values of $\Delta A/A$ at the absorption maxima between 300 and 430 nm reminiscent of those recorded for **8** and **9**. These initial spectral changes are followed by a slow increase in the absorbance values during the following 10–50 min. For instance a $\Delta A/A$ value of −49% was observed for the dppn complex **3** at 327 nm after 1 min. Following the subsequent increase in absorbance over the following 50 min to give a final value for $\Delta A/A$ of −30%, no further spectral changes were recorded. Taking these observations into account, the small ΔT_m value of 2 °C for **3** may be interpreted as indicating predominantly coordinative Ir-N7 (nucleobase) binding to DNA following initial rapid intercalation and slow subsequent substitution of the labile chloride ligands [16]. The final negative $\Delta A/A$ value suggests that the dppn ligands could be involved in stacking interactions with their neighbours. We have demonstrated that the more strongly κ*S* bound *N*-acetylmethionine methyl ester ligand in $[(\eta^5\text{-}C_5Me_5)Ir(dppz)(N\text{-}Ac\text{-}met\text{-}OMe\text{-}\kappa S)]^{2+}$ is slowly substituted by the thermodynamically favoured model base 9-ethylguanine [8]. A slight lowering of the DNA melting temperature has been reported for the Ru^{II} complex $[(\eta^6\text{-}p\text{-}cymene)RuCl(en)]^+$, which selectively binds to guanine bases at their endocyclic N7 position [17]. A modest ΔT_m value of 2 °C was also observed for complex **1**. In contrast to **1** and **3**, the dppz complex $[(\eta^5\text{-}C_5Me_5)IrCl(dppz)](CF_3SO_3)_3$ (**2**) exhibits a relatively high ΔT_m value of 7 °C. However, achievement of UV/Vis spectral stability is more rapid (10 min) for a mixture of complex **2** with CT DNA in comparison to **3**/[DNA] mixtures and the final spectrum exhibits absorbancy increases for the π–π* transitions in accordance with Ir-N(nucleobase) coordinative binding and negligible surface stacking.

2.2.2. Circular dichroism

Characteristic changes in the observed circular dichroism spectra of DNA in the range 220–300 nm provide a convenient means of monitoring conformational changes for the biopolymer. Although small molecules containing extended aromatic systems often generate CD bands between 300 and 400 nm on interaction with DNA, the appearance of such signals is generally not of diagnostic relevance, for an assignment of the binding mode. This is because the observed induced circular dichroism is caused by a rigid orientation of the molecule with respect to the double helix and this can result from external or groove binding as well as intercalation. However, we have previously established that the appearance of a negative CD band in the range 290–340 nm is characteristic for intercalating half-sandwich organometallic dppz complexes [10]. The appearance of such a pronounced negative band for the dppz complexes **5** and **8** (Fig. 3) correlates with their high ΔT_m values of 14 and 12 °C and indicates that these compounds are indeed efficient metallointercalators. In contrast, the absence of a negative band at about 300 nm for the chloride complex **2** is in accordance with predominant coordinative Ir-N(nucleobase) binding despite the observed rise of 7 °C in the DNA melting temperature. The significant decrease in the negative value of the molar ellipticity [θ] for the DNA band at about 243 nm upon interaction with **5** and **8** implies a significant alteration in the original B helical conformation. This may be due to possibly both the twofold positive charge of complexes **5** and **8** and their side-on intercalative binding mode. The observed approximate doubling of the positive [θ] value for the DNA band at about 270 nm caused by the tetramethyl thiourea complex **8** could indicate at least a partial B → A conformational change, possibly caused by the increased bulkiness of its $(NMe_2)_2CS$ ligand in comparison to thiourea in **5**.

Due to the absence of a characteristic negative band at about 300 nm, the CD spectra for the DNA interaction of the dpq complexes **1**, **4** and **7** provide no diagnostic information on possible intercalation. The molar ellipticities [θ] of the bands at about 243 and 270 nm are similar to those for CT DNA itself for the chloro complex **1**, as would be expected for the coordinative Ir-N(nucleobase) binding also indicated by the small ΔT_m value of 2 °C. As for the dppz complexes **5** and **8**, decreases in [θ] in the former band are apparent for the dpq complexes **4** and **7**. However, the changes are less pronounced for the smaller aromatic ligand and this is also the case for the observed increase in the [θ] value of the positive band at 270 nm for $[(\eta^5\text{-}C_5Me_5)Ir(dpq)\{(NMe_2)_2CS\}](CF_3SO_3)_2$ (**7**), in comparison to its dppz analogue **8**. These findings suggest that the DNA conformation is less influenced by interactions with the dpq complexes, possibly due to a significantly lower or negligible degree of intercalation. Inspection of Fig. 2 suggests that the possible area of overlap for the dpq ligand in a side-on intercalation mode would, indeed, be rather modest.

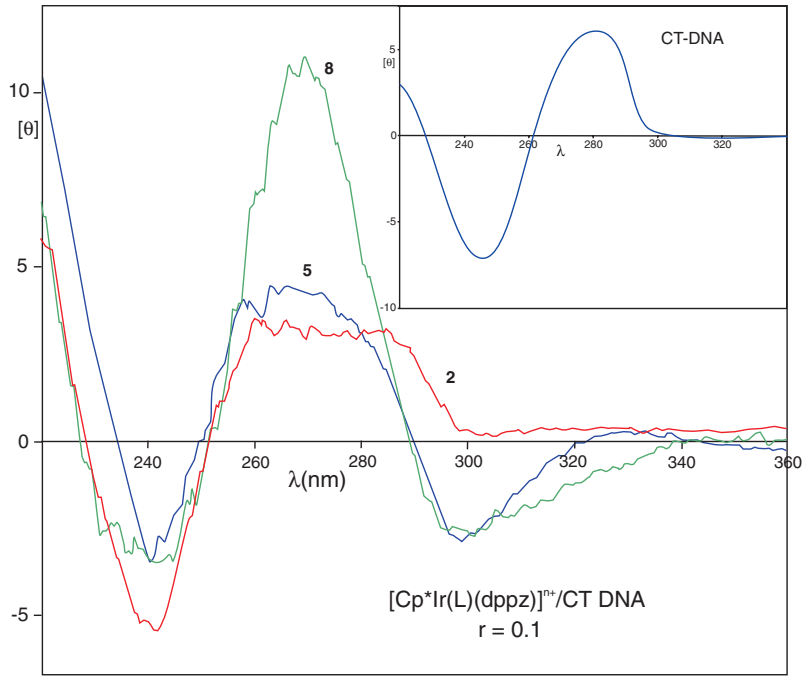


Fig. 3. CD spectra of mixtures of **2**, **5** and **8** (pp = dppz; X = Cl, $(NH_2)_2CS$, $(NMe_2)_2CS$) with CT DNA ($r = 0.1$) in a 10 mM phosphate buffer (pH 7.2) after 24 h incubation. Molar ellipticities [θ] are given in the units deg cm^2 dmol^{-1} 10^{-3}.

Perusal of Fig. 5 indicates that the CT DNA CD bands in the range 220–300 nm exhibit little change following incubation with the dppn complex [(η^5-C_5Me_5) IrCl(dppn)](CF_3SO_3), in agreement with observations for the analogous chloro complexes **1** and **2**. In contrast, the negative band at about 243 nm disappears completely for **9** and displays a very small [θ] value of only -1.8×10^3 deg cm^2 dmol^{-1} for complex **6**. This suggests that interaction with the dppn complexes [(η^5-C_5Me_5) Ir(dppn)(L)]$^{2+}$ [L = $(NH_2)_2CS$ **6**, $(NMe_2)_2CS$ **9**] must lead to massive distortions of the original B DNA conformation. In particular, the increase in [θ] to 10.2×10^3 deg cm^2 dmol^{-1} for the bulkier complex **9** is in accordance with the possible adoption of an A conformation, presumably to allow more

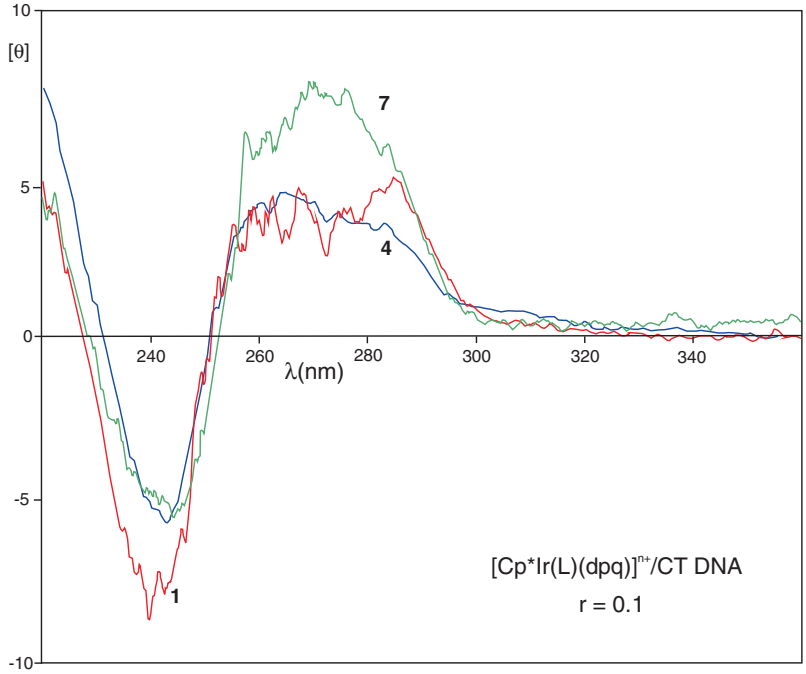


Fig. 4. CD spectra of mixtures of **1**, **4** and **7** (pp = dpq; X = Cl, $(NH_2)_2CS$, $(NMe_2)_2CS$) with CT DNA ($r = 0.1$) in a 10 mM phosphate buffer (pH 7.2) after 24 h incubation. Molar ellipticities [θ] are given in the units deg cm^2 dmol^{-1} 10^{-3}.

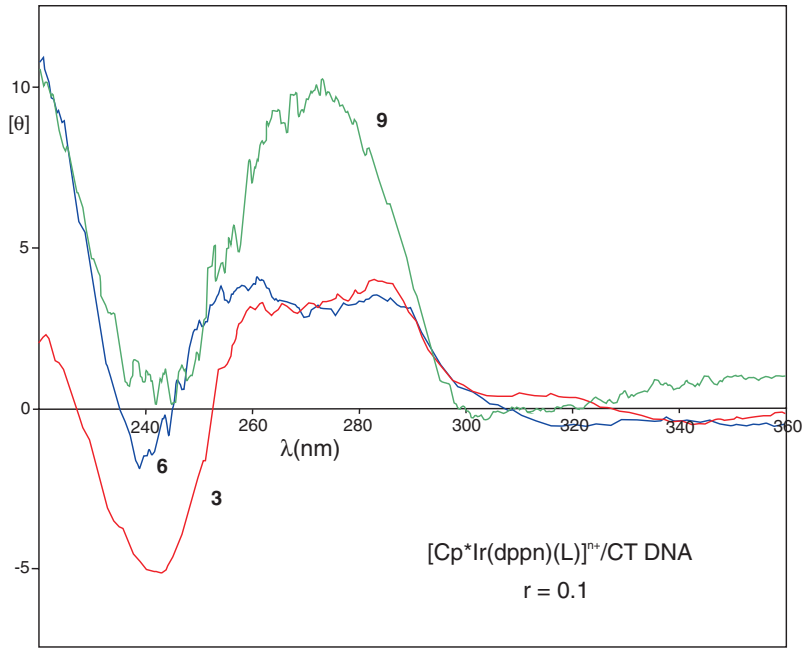


Fig. 5. CD spectra of mixtures of **3**, **6** and **9** (pp = dppn; X = Cl, $(NH_2)_2CS$, $(NMe_2)_2CS$) with CT DNA ($r = 0.1$) in a 10 mM phosphate buffer (pH 7.2) after 24 h incubation. Molar ellipticities [θ] are given in the units deg cm^2 dmol^{-1} 10^{-3}.

effective intercalation of the larger dppn ligands, while at the same time reducing non-bonded contacts to the $(NMe_2)_2CS$ methyl groups. In A DNA, the base pairs are inclined at 71–77° to the helix axis and therefore offer a potentially larger total surface area to an intercalating aromatic ligand.

2.2.3. Viscometric titrations

The most convincing evidence for DNA intercalation is generally provided by viscosity measurements [15,18]. Insertion of ligands such as dppz or dppn between adjacent nucleobase pairs leads to lengthening and stiffening of the double helix, i.e. to structural changes that are reflected in an increase in DNA viscosity [18,19]. Fig. 6 illustrates the dependence of the logarithmic relative reduced viscosity $\ln(\eta/\eta_0)$ on the concentration function $\ln(1 + r)$ with $r = [\text{complex}]/[\text{DNA}]$ for the $(NMe_2)_2CS$ complexes **7**, **8** and **9**. The slopes (v) of the viscometric titration analyses (Table 1) correlate well with the observed ΔT_m values for these compounds and confirm DNA lengthening in all three cases. Effective intercalation is indicated for the dppz and dppn complexes by the calculated slope values of 1.65 and 1.93. It is important to note that overall DNA lengthening still prevails for mixtures of **8** and **9** with the biopolymer despite its possible conformation change leading to the shorter and fatter A form. The significantly lower value of 0.59 for the dpq complex **7** suggests, in accordance with its ΔT_m value of only 4 °C, that surface binding may be competitive with intercalation for the smaller dpq ligand. As indicated by the CD spectrum of **7** in Fig. 4, such external binding apparently leaves B DNA in an essentially unperturbed form.

The observed slope value of $v = 1.63$ for the dppz complex $[(\eta^5\text{-}C_5Me_5)Ir(dppz)\{(NH_2)_2CS\}](CF_3SO_3)_2$ (**5**) is closely similar to that of 1.65 registered for the analogous tetramethyl thiourea complex **8** and in accordance with effective intercalation of this dipyridophenazine ligand. As for complex **7**, only partial intercalation is indicated for $[(\eta^5\text{-}C_5Me_5)Ir(dpq)\{(NH_2)_2CS\}](CF_3SO_3)_2$ (**4**) by the much lower increase in DNA viscosity ($v = 0.67$) in the presence of the less extensive dpq ligand. In striking contrast to the other thiourea complexes and to its tetramethyl

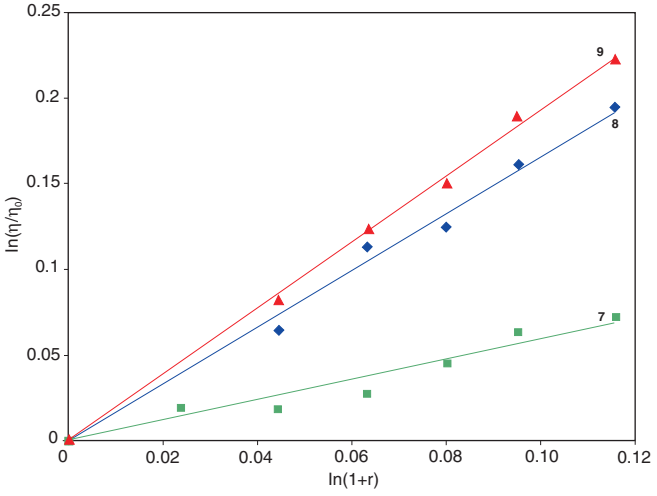


Fig. 6. Viscometric titration of sonicated DNA with the complexes **7**–**9** (pp = dpq, dppz, dppn; X = $(NMe_2)_2CS$) in a 10 mM phosphate buffer (pH 7.2): η = reduced viscosity of the DNA solution in the presence of a complex, η_0 = the reduced viscosity of the DNA solution without the complex, $r = [\text{complex}]/[\text{DNA}]$.

thiourea analogue **9**, $[(\eta^5\text{-}C_5Me_5)Ir(dppn)\{(NH_2)_2CS\}](CF_3SO_3)_2$ (**6**) causes a significant decrease in viscosity for [complex]/[DNA] mixtures in the range $0 < r < 0.12$. This finding is in accordance with an absence of intercalation already indicated by the negligible ΔT_m value of 2 °C and suggests that hydrophobic interaction of **6** with the DNA surface and associated dppn stacking may possibly lead to kinks or bends in the double helix [20,21]. Viscosity decreases are also observed for the chloro complexes **2** and **3**, for which the predominant coordinative Ir-N7 binding to the DNA purine bases may be assumed to invoke similar distortions in the double helix structure. In contrast, a very small increase is observed for the DNA viscosity ($v = 0.16$) on mixing with the dpq complex **1**. This suggests that coordinative Ir-N(nucleobase) binding may have little influence on the DNA structure in the presence of the smaller dpq ligand.

On taking the thermal denaturation and viscosity studies for **4**–**6** into account, it may be concluded for $L = (NH_2)_2CS$ that dppz will present an optimum aromatic surface area for side-on intercalation into B DNA and that steric interactions may prevent intercalation of the more extensive dppn ligand. How is it then possible to explain the ΔT_m value of 12 °C and the significant increase in viscosity for the interaction of dppn complex **9** with DNA? The CD spectra of Fig. 5 suggest that intercalation of the longer dihydrophenazine ligand may be associated with a stabilization of the shorter A DNA conformation, whose inclined parallel base pairs would offer a larger total surface area for base stacking. It seems possible that groove binding involving N–H···O hydrogen bonding between the thiourea ligands and the DNA double helix may prevent this conformational change for complex **6** and thereby prevent dppn intercalation. Steric interactions involving the bulkier tetramethyl thiourea ligands may also play a role in facilitating the B → A DNA change in the presence of **9**.

2.2.4. DNA binding parameters

Binding constants K_b in the range $0.2\text{–}1.2 \times 10^6\ M^{-1}$ have been determined for least-squares fits to UV–Vis titration data of complexes of the type $[(\eta^5\text{-}C_5Me_5)\text{-}Ir(dppz)(peptide\text{-}\kappa S)]^{2+}$ with CT DNA using the hypochromic absorption shifts at $\lambda = 364$ nm and the model of Bard [22] and Thorp [23]. The corresponding site sizes s between 1.53 and 2.06 are in accordance with intercalative binding [8]. It is of interest to compare these values with those of complexes **8** and **9**, for which the presence of the bulky tetramethyl thiourea ligands might be expected to lead to less stable intercalation. Figs. 2a and b depict the UV–Vis spectra recorded for buffered 10 μM solutions of **8** and **9** in the presence of increasing quantities of CT DNA in the range 10–90 μM. Isosbestic points at, respectively, 399 and 346/437 nm are apparent in accordance with a simple equilibrium distribution between DNA-bound and free $(\eta^5\text{-}C_5Me_5)Ir^{III}$ complexes. Data recorded at, respectively, 383 and 327 nm were fitted graphically for **8** and **9**

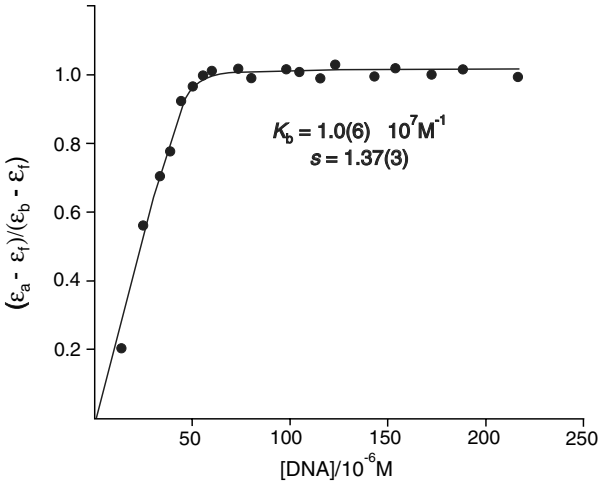


Fig. 7. Best least-squares fit to the model of Bard and Thorp [22,23] for the UV/Vis titration data of **9** with CT DNA (Fig. 2).

(Fig. 7) using the model of Bard and Thorp to afford K_b values of respectively $2.9(6) \times 10^6$ and $1.0(6) \times 10^7\ M^{-1}$. Corresponding site sizes of 1.79(7) and 1.37(3) were obtained.

It is interesting to note that much more stable DNA binding is observed for complex **9** in comparison to **8** despite the possible B → A DNA conformational change that is apparently required for dppn intercalation. The enhanced binding affinity of **9** is presumably due to the larger surface area of its dppn ligand as reported for $[Ir(ppy)_2(dppn)](PF_6)$ ($K_b = 7.8 \times 10^4\ M^{-1}$) in comparison to $[Ir(ppy)_2(dppz)](PF_6)$ ($K_b = 2.0 \times 10^4\ M^{-1}$) [7]. The site size factors s of, respectively, 1.79 and 1.37 are relatively low for exclusively intercalative binding and this suggests that additional surface stacking of the polypyridyl ligands may possibly augment the DNA interaction at low [DNA] concentrations.

3. Conclusions

Our present results demonstrate that the DNA binding of organometallic half-sandwich complexes of the type $[(\eta^5\text{-}C_5Me_5)Ir(L)(pp)](CF_3SO_3)_n$ ($L = Cl$, $n = 1$; $L = (NH_2)_2CS$, $(NMe_2)_2CS$, $n = 2$) is influenced by both the size of the polypyridyl ligand and the nature of the monodentate ligands L. The following conclusions may be drawn:

1. Following initial kinetically preferred intercalation for $L = Cl$ (**1**–**3**), relatively slow substitution of the labile chloride ligands leads to thermodynamically preferred coordinative Ir-N7(Nucleobase) binding to DNA.
2. When thiourea is employed as the monodentate ligand, dppz presents an optimum aromatic surface area for side-on intercalation into B DNA. Partial intercalation may still be possible for the smaller dpq ligand but steric interactions apparently prevent intercalation of the more extensive dppn surface.

3. When thiourea is replaced by its bulkier tetramethyl derivative, strong intercalative binding with a high K_b value of $1.0(6) \times 10^7\ M^{-1}$ is also observed for dppn following a possible change in the DNA structure from B to A.

This means that the mode of DNA binding (i. e. coordinative, surface or intercalative) for the dppn complexes **3**, **6** and **9** is determined solely by the nature of monodentate ligand L! Moreover, as demonstrated for $L = Cl^-$, the release of the monodentate ligand can lead to a change in the complex binding mode and to significant alterations in the DNA structure. As it should be possible to tune the time required for such changes by varying the nucleophilicity of the ligand L [24], this opens opportunities for the use of such organometallic complexes for controlled two-stage reactions with DNA.

4. Experimental

Solvents were dried and distilled before use. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer, IR spectra as KBr discs on a Perkin–Elmer 1760 spectrometer and LSIMS data (liquid secondary ion mass spectrometry) on a VG Autospec instrument using 3-nitrobenzyl alcohol as the matrix. An Analytik Jena SPECORD 200 was employed for UV–Vis measurements and CD spectra were registered on a Jasco J-715 instrument in the range 220–400 nm for 1:10 complex/[DNA] mixtures [DNA concentration in M(nucleotide)] in a 10 mM phosphate buffer at pH 7.2. Elemental analyses were performed on a Vario EL (Elementar Analysensysteme).

$IrCl_3 \cdot xH_2O$ and $Ag(CF_3SO_3)$ were obtained from Chempur, thiourea and $(Me_2N)_2CS$ from Acros. The starting complex $[\{(\eta^5\text{-}C_5Me_5)IrCl\}_2(\mu\text{-}Cl_2)]$ [25,26], $[(\eta^5\text{-}C_5Me_5)IrCl(dppz)](CF_3SO_3)$ (**2**) and the polypyridyl ligands dpq [27], dppz [28] and dppn [12] were synthesised according to literature procedures.

4.1. Preparation of *1* and *3–9*

4.1.1. $[(\eta^5\text{-}C_5Me_5)IrCl(dpq)](CF_3SO_3)$ (*1*)

Two equivalents of $Ag(CF_3SO_3)$ (25.7 mg, 0.1 mmol) were added to $[\{(\eta^5\text{-}C_5Me_5)IrCl\}_2]$ (40.0 mg, 0.05 mmol) in 10 ml acetone and stirred in the dark for 0.5 h. Filtration of the resulting AgCl precipitate and subsequent solvent removal under vacuum afforded $[(\eta^5\text{-}C_5Me_5)IrCl(acetone)_2](CF_3SO_3)$, which was stirred with the ligand dpq (23.2 mg, 0.1 mmol) in CH_3OH/CH_2Cl_2(1/1, 10 ml) at 55 °C for 2 h. Following volume reduction of the resulting clear solution to 2 ml and addition of CH_3OH (3 ml), the product was precipitated with diethyl ether, washed and dried in vacuo. Yield: 60% (45 mg). Anal. Found: C, 40.1; H, 3.0; N, 7.4, S, 4.1; M: 744 g/mol; $C_{25}H_{23}F_3IrN_4O_3S$,Calc.: C, 40.4; H, 3.1; N, 7.5; S, 4.3. FAB MS: *m/z* 745 (1%) $[M]^+$, 709 (1%) $[M-Cl]^+$, 595 (100%) $[M-CF_3SO_3]^+$, 560 (15%) $[M-CF_3SO_3-Cl]^+$, 363 (25%) $[Cp^*IrCl]^+$, 329 (10%) $[Cp^*Ir]^+$. ^1H NMR (d_6-DMSO): δ 1.72 (s, 15H, Cp^*), 8.3 (m, 2H, dpq), 9.35 (s, 2H, dpq), 9.5 (dd, 2H, dpq), 9.7 (dd, 2H, dpq). ^{13}C NMR (d_6-DMSO): δ 8.1 (CCH_3), 89.2 (CCH_3), 128.5, 129.1, 135.4, 138.8, 146.9, 147.7, 153.3 (dpq).

4.1.2. $[(\eta^5\text{-}C_5Me_5)IrCl(dppn)](CF_3SO_3)$ (*3*)

Preparation as for **1** with the ligand dppn (33.2 mg, 0.1 mmol). Yield: 73% (62 mg). Anal. Found: C, 46.4; H, 3.3; N, 6.3, S, 3.3; M: 844 g/mol; $C_{33}H_{27}F_3IrN_4O_3S$, Calc.: C, 46.9; H, 3.2; N, 6.6; S, 3.8. FAB MS: *m/z* 809 (2%) $[M-Cl]^+$, 695 (100%) $[M-CF_3SO_3]^+$, 660 (15%) $[M-CF_3SO_3-Cl]^+$, 363 (40%) $[Cp*IrCl]^+$. ^1H NMR (d_6-DMSO): δ 1.74 (s, 15H, Cp*), 7.7 (m, 2H, dppn), 8.3 (m, 2H, dppn), 8.4 (m, 2H, dppn), 9.13 (s, 2H, dppn), 9.4 (dd, 2H, dppn), 9.7 (dd, 2H, dppn). ^{13}C NMR (d_6-DMSO): δ 8.1 (CCH_3), 89.3 (CCH_3), 127.8, 127.9, 128.4, 128.9, 130.1, 134.5, 135.6, 137.8, 140.2, 149.6, 153.4(dppn).

4.1.3. $[(\eta^5\text{-}C_5Me_5)Ir(dpq)\{(NH_2)CS\}](CF_3SO_3)_2$ (*4*)

Two equivalents of $Ag(CF_3SO_3)$ (25.7 mg, 0.1 mmol) were added to a solution of $[\{(\eta^5\text{-}C_5Me_5)IrCl\}_2(\mu\text{-}Cl)_2]$ (40.0 mg, 0.05 mmol) in 10 ml acetone and stirred in the dark for 0.5 h. Filtration of the precipitate AgCl and subsequent solvent removal under vacuum afforded $[(\eta^5\text{-}C_5Me_5)IrCl(acetone)_2](CF_3SO_3)$, which was stirred with the ligand dpq (23.2 mg, 0.1 mmol) at 55 °C for 2 h. Following solvent removal, the resulting residue of complex **1** was dissolved in 10 ml acetone and treated with a further equivalent of $Ag(CF_3SO_3)$. After stirring in the dark for 0.5 h, filtration of AgCl and solvent removal, the remaining solid was dissolved in 10 ml of a 1:1 CH_3OH/CH_2Cl_2 mixture and treated with thiourea (7.6 mg, 0.1 mmol). The solvent was then refluxed for 12 h and subsequently reduced in volume to 2 ml. Following addition of 2 ml of CH_3OH, the product was precipitated by addition of diethyl ether, washed and dried in vacuo. Yield: 62% (58 mg). Anal. Found: C, 34.7; H, 3.0; N, 9.3, S, 10.2; M: 934 g/mol; $C_{27}H_{27}F_6IrN_6O_6IrS_3$, Calc.: C, 34.7; H, 2.9; N, 9.0; S, 10.3. FAB MS: *m/z* 957 (3%) $[M+Na]^+$, 785 (20 %) $[M-CF_3SO_3]^+$, 709 (5%) $[M-CF_3SO_3-\{(NH_2)_2CS\}]^+$, 635 (25%) $[M-2CF_3SO_3]^+$, 560 (65%) $[M-2CF_3SO_3-\{(NH_2)_2CS\}]^+$, 403 (85%) $[Cp^*Ir(\{(NH_2)_2CS\}]^+$. ^1H NMR (d_6-DMSO): δ 1.75 (s, 15H, Cp*), 7.5 (s, br, 4H, $\{(NH_2)_2CS\}$), 8.4 (m, 2H, dpq), 9.3 (dd, 2H, dpq), 9.4 (s, 2H, dpq), 9.7 (dd, 2H, dpq). ^{13}C NMR (d_6-DMSO): δ 7.8 (CCH_3), 91.9 (CCH_3), 128.8, 129.4, 135.3, 139.0, 146.8, 147.8, 153.6 (dpq), 170.8 ($SC(NH_2)_2$).

4.1.4. $[(\eta^5\text{-}C_5Me_5)Ir(dppz)\{(NH_2)_2CS\}](CF_3SO_3)_2$ (*5*)

Preparation as for **4** with the ligand dppn (28.2 mg, 0.1 mmol). Yield: 69% (68 mg). Anal. Found. C, 38.0; H, 3.1; N, 9.0; S, 9.9; M: 984 g/mol; $C_{31}H_{29}F_6IrN_6O_6S_3$, Calc.: C, 37.8; H, 3.0; N, 8.5; S, 9.8. FAB MS: *m/z* 835 (5%) $[M-CF_3SO_3]$, 759 (1%) $[M-CF_3SO_3-\{(NH_2)_2CS\}]^+$, 685 (6%) $[M-2CF_3SO_3]^+$, 610 (10%) $[M-2CF_3SO_3-\{(NH_2)_2CS\}]^+$, 403 (15%) $[Cp*Ir(\{(NH_2)_2CS\})]^+$. ^1H

NMR (d_6-DMSO): δ 1.77 (s, 15H, Cp*), 7.5 (s, br, 4H, {$(NH_2)_2CS$}), 8.2 (m, 2H, dppz), 8.4 (m, 2H, dppz), 8.6 (m, 2H, dppz), 9.3 (dd, 2H, dppz), 9.8 (dd, 2H, dppz). ^{13}C NMR (d_6-DMSO): δ 8.3 (CCH_3), 92.3 (CCH_3) 129.5, 129.7, 130.5, 133.2, 136.0, 140.0 142.3, 149.6, 154.1(dppz), 171.2 ($SC(NH_2)_2$).

*4.1.5. [(η^5-C_5Me_5)Ir(dppn){$(NH_2)_2CS$}]$(CF_3SO_3)_2$ (**6**)*

Preparation as for **4** with the ligand dppn (33.2 mg, 0.1 mmol). Yield: 44% (45 mg). Anal. Found: C, 40.7; H, 3.0; N, 8.9; S, 8.8; M: 1034 g/mol; $C_{35}H_{31}F_6IrN_6O_6S_3$, Calc.: C, 40.7; H, 3.0; N, 8.1; S, 9.3. FAB MS: *m*/*z* 1057 (3%) $[M+Na]^+$, 885 (10%) $[M-CF_3SO_3]^+$, 809 $[M-CF_3SO_3-\{(NH_2)_2CS\}]^+$, 735 (15%) $[M-2CF_3SO_3]^+$, 660 (50%) $[M-2CF_3SO_3-\{(NH_2)_2CS\}]^+$, 403 (100%) $[Cp^*Ir\{(NH_2)_2CS\}]^+$. ^{1}H NMR (d_6-DMSO): δ 1.77 (s, 15H, Cp*), 7.6 (s, br, 4H, {$(NH_2)_2CS$}), 7.8 (m, 2H, dppn), 8.4 (m, 2H, dppn), 8.5 (m, 2H, dppn), 9.2 (dd, 2H, dppn), 9.28 (s, 2H, dppn), 9.8 (dd, 2H, dppn). ^{13}C NMR (d_6-DMSO): δ 7.8 (CCH_3), 91.9 (CCH_3), 127.9, 128.1, 128.5, 129.3, 130.5, 134.7, 135.6, 137.8, 140.5, 149.8, 153.6(dppn), 170.8 ($SC(NH_2)_2$).

*4.1.6. [(η^5-C_5Me_5)Ir(dpq){$(NMe_2)_2CS$}]$(CF_3SO_3)_2$ (**7**)*

Preparation as for **4** with the ligand dpq (23.2 mg, 0.1 mmol) and tetramethyl thiourea (10.2 mg, 0.1 mmol). Yield: 64% (53 mg). Anal. Found: C, 37.5; H, 3.6; N, 8.2; S, 9.8; M: 990 g/mol; $C_{31}H_{35}F_6IrN_6O_6S_3$,Calc.: C, 37.6, H, 3.6, N, 8.5, S, 9.7. FAB MS: *m*/*z* 1011 (1%) $[M+Na]^+$, 841 (10%) $[M-CF_3SO_3]^+$, 709 (25%) $[M-CF_3SO_3-\{(NMe_2)_2CS\}]^+$, 560 (50%) $[M-2CF_3SO_3-\{(NMe_2)_2CS\}]^+$. ^{1}H NMR ($d_6$-DMSO): δ 1.79 (s, 15H, Cp*), 2.35 (s, 12H, $SC(NMe_2)_2$), 8.4 (m, 2H, dpq), 9.43 (s, 2H, dpq), 9.5 (dd, 2H, dpq), 9.8 (dd, 2H, dpq). ^{13}C NMR (d_6-DMSO): δ 7.7 (CCH_3), 42.6 ($SC(N(CH_3)_2)_2$), 92.2 (CCH_3), 128.9,129.4,135.9, 138.9, 147.1, 147.4, 153.9 (dpq), 176.8 ($SC(NH_2)_2$).

*4.1.7. [(η^5-C_5Me_5)Ir(dppz){$(NMe_2)_2CS$}]$(CF_3SO_3)_2$ (**8**)*

Preparation as for **4** with the ligand dppz (28.2 mg, 0.1 mmol) and tetramethyl thiourea (10.2 mg, 0.1 mmol). Yield: 60% (62 mg). Anal. Found: C, 39.8; H, 3.9; N, 7.6; S, 9.0; M: 1040 g/mol; $C_{35}H_{37}F_6IrN_6O_6S_3$, Calc.: C, 40.4; H, 3.6; N, 8.1; S, 9.3. FAB MS: *m*/*z* 1062 (1%) $[M+Na]^+$, 891 (5%) $[M-CF_3SO_3]^+$, 759 (40%) $[M-CF_3SO_3-\{(NMe_2)_2CS\}]^+$, 610 (85%) $[M-2CF_3SO_3-\{(NMe_2)_2CS\}]^+$. ^{1}H NMR ($d_6$-DMSO): δ 1.76 (s, 15H, Cp*), 2.38 (s, 12H, $SC(NMe_2)_2$), 8.2 (m, 2H, dppz), 8.4 (m, 2H, dppz), 8.6 (m, 2 H, dppz), 9.5 (dd, 2H, dppz), 9.9 (dd, 2H, dppz). ^{13}C NMR (d_6-DMSO): δ 8.2 (CCH_3), 43.1 ($SC(N(CH_3)_2)_2$), 92.7 (CCH_3), 129.6, 129.8, 130.5, 133.3, 136.6, 139.8, 142.5, 149.1, 154.4 (dppz), 177.1 ($SC(NH_2)_2$).

*4.1.8. [(η^5-C_5Me_5)Ir(dppn){$(NMe_2)_2CS$}]$(CF_3SO_3)_2$ (**9**)*

Preparation as for **4** with the ligand dppn (33.2 mg, 0.1 mmol) and tetramethyl thiourea (10.2 mg, 0.1 mmol). Yield: 72% (79 mg). Anal. Found: C, 43.1; H, 3.3; N, 7.5; S, 9.3; M: 1090 g/mol; $C_{39}H_{39}F_6IrN_6O_6IrS_3$, Calc.: C, 43.1; H, 3.6; N, 7.7; S, 8.8. FAB MS: *m*/*z* 941 (2%) $[M-CF_3SO_3]^+$, 809 (5%) $[M-CF_3SO_3-\{(NMe_2)_2CS\}]^+$, 660 (10%) $[M-2xCF_3SO_3-\{(NMe_2)_2CS\}]^+$. ^{1}H NMR ($d_6$-DMSO): δ 1.76 (s, 15H, Cp*), 2.44 (s, 12H, $SC(NMe_2)_2$), 7.8 (m, 2H, dppn), 8.4 (m, 2H, dppn), 8.5 (m, 2H, dppn), 9.30 (s, 2H, dppn), 9.4 (dd, 2H, dppn), 9.8 (dd, 2H, dppn). ^{13}C NMR (d_6-DMSO): δ 8.2 (CCH_3), 43.1 ($SC(N(CH_3)_2)_2$), 92.7 (CCH_3), 128.4, 128.6, 129.0, 129.8, 131.0, 135.2, 136.6, 138.4, 140.8, 149.7, 154.4 (dppn), 177.2 ($SC(NH_2)_2$).

4.2. DNA binding studies of **8** and **9**

The thermal denaturation temperatures T_m of 1:10 complex/DNA mixtures [DNA concentration = M (nucleotide)] were determined in a 10 mM phosphate buffer at pH 7.2. Melting curves were recorded in 1 °C steps in the range 60–90° at 260 nm with an Analytik Jena SPECORD 200 spectrometer connected with a Peltier temperature controller. T_m values were calculated by determining the midpoints of melting curves from the first-order derivatives. The experimental ΔT_m values of Table 1 are estimated to be accurate within ±1 °C. Concentrations of CT DNA were determined spectrophotometrically using the molar extinction coefficient $\varepsilon_{260} = 6600\ M^{-1}\ cm^{-1}$ [29].

All electronic absorption titrations were performed at 293 K. After sonication, buffered solutions of CT DNA gave a UV absorbance ratio A_{260}/A_{280} of ca. 1.90, indicating that the DNA was sufficiently free of protein [30]. 20 μM solutions of the individual metal complexes were treated with DNA over a range of molarities 10–250 μM (nucleotide). All UV–Vis spectra were measured after equilibration, i.e. no further change in the monitored absorbance. Titration curves were constructed from the fractional change in absorbance as a function of DNA concentration according to the model of Bard and Thorp [22,23] for non-cooperative non-specific binding for one type of discrete DNA binding site.

$$(\varepsilon_a - \varepsilon_f)/(\varepsilon_b - \varepsilon_f) = (b - \{b^2 - 2K_b^2 C_t[\mathrm{DNA}]/s\}^{1/2})/2K_b C_t. \quad (1)$$

Eq. (1) was used to fit the absorption data by least-squares refinement of binding constants (K_b) and site sizes (s) with $b = 1 + K_b C_t + K_b[\mathrm{DNA}]/2s$, where ε_a is the extinction coefficient of the complex in the absence of DNA, ε_b the extinction coefficient of the complex when fully bound to DNA (i.e. no absorption change on further addition of DNA), K_b the equilibrium constant in M^{-1}, C_t the total metal complex concentration, [DNA] the DNA concentration in M(nucleotide) and s the binding site size. Values of ε_b were obtained by extrapolation from the y intercept of plots of $\varepsilon_a/\varepsilon_f$ vs. 1/[DNA]. The K_b and s values of **8** and **9** are those for the best least-square fits to the individual UV/Vis titration curves using the program ORIGIN 6.0.

4.3. Viscosity measurements

Viscosities for complex/sonicated DNA mixtures were determined using a Cannon-Ubbelhode semi-micro dilution viscometer (Series No 75, Cannon Instrument Co.) held at a constant temperature of 25 °C in a water bath. The viscometer contained 2 ml of 0.4 mM sonicated DNA solution in a 10 mM phosphate buffer (pH 7.2). O.2 mM complex solutions also containing sonicated DNA at the same concentration as in the viscometer (0.4 mM) were added in increments of 100 μl from a micropipet. Solutions were passed through filters to remove particulate material prior to use. Reduced viscosities η were calculated by literature methods [18] and plotted as $\mathrm{In}(\eta/\eta_0)$ (η_0 = reduced viscosity of the DNA solution in the absence of complex) against $\mathrm{In}(1 + r)$ for rod-like DNA (approximately 600 bp).

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