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Luminescent Ir(III) Complex Exclusively Made of Polypyridine Ligands Capable of Intercalating into Calf-Thymus DNA

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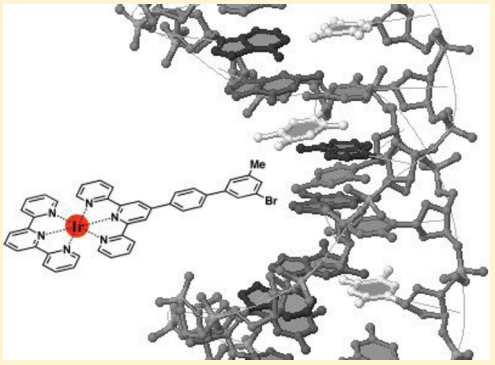
Supporting Information

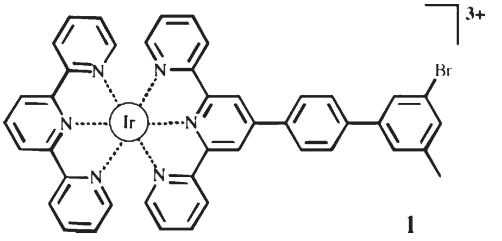
ABSTRACT: Efficient intercalation of a luminescent Ir(III) complex exclusively made of polypyridine ligands in natural and synthetic biopolymers is reported for the first time. The emission of the complex is largely enhanced in the presence of [poly(dA−dT)$_2$] and strongly quenched in the presence of [poly(dG−dC)$_2$]. By comparing the emission decays in DNA and in synthetic polynucleotides, it is proposed that the emission quenching of the title compound by guanine residues in DNA is no longer effective over a distance of four dA−dT base pairs.



Design of luminescent metal complexes capable of intercalating between DNA base pairs is an extensively investigated topic.[1,2] Specific interaction of metal complexes with DNA strands, coupled with modification of luminescence outputs, allows such systems to efficiently perform the function of probes of DNA sites. Moreover, beside the probing function, interaction of photoactive metal complexes with DNA can also yield information on the DNA electron/hole transport ability,[3,4] obtain photoreactions involving DNA sites, leading to specific DNA damage,[5,6] and assemble elaborate, interesting supramolecular architectures.[7]

Several ligands have proven to be quite useful to generate luminescent metal complexes with intercalating properties: examples are extended polycyclic aromatic species like dipyrido[3,2-a:2′,3′-c]phenazine (dppz) and 1,10-phenanthrolino[5,6-*b*]-1,4,5,8,9,12-hexaazatriphenylene (PHEHAT) and their derivatives.[8−10] By using such ligands, polypyridine complexes of several metals have been designed as luminescent and/or photoactive species capable of intercalating between DNA base pairs, the more used being Ru(II), Re(I), Rh(III), and Pt(II).[1−3,5−10] More recently, even Ir(III) luminescent complexes have been reported to interact with DNA or biological systems,[4,11] but up to now only cyclometalated Ir(III) species have been investigated to this regard.

Here we report the first example, to the best of our knowledge, of luminescent Ir(III) complexes, whose coordination sphere is *exclusively* made of polypyridine ligands, which feature intercalation between DNA base pairs. Moreover, the 4-biphenyl-terpyridine moiety is here identified as an efficient structural motif for promoting intercalation of octahedral metal complexes within DNA base pairs.



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EXPERIMENTAL SECTION

Compound **1** was available, as hexafluorophosphate salt, from a former work.[12] Compounds [Ru(bpy)$_2$(dppz)]$^{2+}$ and [Ir(terpy)$_2$]$^{3+}$ (**2**) have been prepared, as hexafluorophosphate salts, following literature procedures.[13,14] Calf thymus DNA, [poly(dA−dT)$_2$], and [poly(dC−dG)$_2$] were purchased from Sigma Chemical Co. DNA was purified as previously described;[15] [poly(dA−dT)$_2$] and [poly(dC−dG)$_2$] were dissolved as received in the phosphate buffer containing the desired amount of NaCl to adjust the ionic strength. Their concentrations, expressed in base pairs, were determined spectrophotometrically using the molar absorptivities:[16] 1.32 × 10^4 M^{-1} cm^{-1} (258 nm), 1.32 × 10^4 M^{-1} cm^{-1} (262 nm), and 1,68 × 10^4 M^{-1} cm^{-1} (254 nm) for

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DNA, [poly(dA−dT)$_2$], and [poly(dC−dG)$_2$], respectively. All the experiments with DNA and synthetic polynucleotides were carried out at 25 °C and pH 7, in a phosphate buffer 1×10^{-3} M and enough NaCl to give the desired ionic strength value.

Absorption spectra were recorded with a JASCO V570 or a Cintra 20 GBC spectrophotometers. For luminescence spectra, a Jobin Yvon-Spex Fluoromax P spectrofluorimeter was used, equipped with a Hamamatsu R3896 photomultiplier, and the spectra were corrected for photomultiplier response using a program purchased with the fluorimeter. Luminescence lifetimes were determined by time-correlated single-photon-counting (TCSPC) with an Edinburgh OB900 spectrometer (light pulse: Hamamatsu PL2 laser diode, pulse width 59 ps at 408 nm). Experimental uncertainties are as follows: absorption maxima, 2 nm; emission maxima, 5 nm; excited state lifetimes, 10%, unless otherwise stated.

Circular dichroism experiments were performed by a Jasco J-810 spectropolarimeter.

The thermal denaturation temperature of compound−DNA mixtures (1:10) was determined in 1×10^{-3} M phosphate buffer (pH 7) solutions containing the compound (7.8×10^{-6} M) and 2×10^{-3} M NaCl. Melting curves were recorded at 260 nm. The temperature has been increased at a rate of 0.5 °C/min by using a PTP-1 Peltier system.

Viscosity titrations were performed by means of a Cannon-Ubbelhode semimicrodilution viscometer (Series No. 75, Cannon Instrument Co.), thermostatically maintained at 25 °C in a water bath. The viscometer contained 2 mL of sonicated DNA solution, in 1×10^{-3} M phosphate buffer (pH = 7) and 1×10^{-2} M NaCl. The compound solution ($(1.7-2.5) \times 10^{-4}$ M), containing also DNA (6.0×10^{-4} M) at the same concentration as that in the viscometer, was delivered in increments of 90−380 μL from a micropipet. Solutions were freed of particulate material by passing them through nylon Acrodisc syringe filters before use. Flow times were measured by hand with a digital stopwatch. Reduced viscosities were calculated by established methods and plotted as $\ln \eta/\eta_0$ against $\ln (1 + r)$ for rodlike DNA (600 base pairs) (η = reduced viscosity of the biopolymer solution in the presence of compound; η_0 = reduced viscosity of the biopolymer solution in the absence of compound; $r = [\text{compound}]_{\text{bound}}/[\text{biopolymer}]_{\text{tot}}$).

Spectrophotometric titrations were performed by adding to a complex solution [$(3.7-4.2) \times 10^{-5}$ M] successive aliquots of DNA, containing also the complex, in a 10 mm stoppered quartz cell and recording the spectrum after each addition. The data were analyzed by a nonlinear least-squares fitting program, applied to the McGhee and von Hippel equation.[17] The binding constant, K_B, was determined by the program, using the extinction coefficient of the compounds, the free complex concentration, and the ratio of bound complex per mole of DNA. Extinction coefficient for bound compound was determined by Beer's law plots in the presence of a large excess of DNA.

RESULTS AND DISCUSSION

Compound **1**, recently reported by our groups,[12] exhibits a relatively strong emission (Φ = 0.02) in acetonitrile deareated solution, with lifetime in a time regime of a few microseconds. The emission has been assigned to a mixed ^{3}MLCT/^{3}LC (MLCT = metal-to-ligand charge transfer; LC = ligand centered) state. Such emissive properties (see Figure 1) are retained in aqueous buffered solution (1×10^{-3} M phosphate buffer, pH 7, and 2.1×10^{-2} M NaCl); emission decay is monoexponential, yielding a lifetime of 3.6 μs (Φ = 0.06). The luminescence of **1** is strongly affected by the presence of calf-thymus DNA (see Figure 1): the emission intensity steeply decreases, and at the end of titration, emission decay requires at least three components to be reasonably fitted (see Supporting Information). The dominant component is quite short-lived (5 ns), a second component corresponds to a lifetime of about 60 ns, and a third one corresponds to a longer-lived species (900 ns). A further minor component, with a lifetime in the range 10−18 μs, has to be considered to justify the long tail of the emission decay.[18] The absorption spectrum (dominated by spin-allowed LC bands with MLCT bands contributing to low-energy absorption;[12] $\varepsilon_{370\ \text{nm}}$ 21 800 M^{-1} cm^{-1} in buffered solution) is also strongly affected by the presence of DNA. The addition of the biopolymer, in fact, produces hypochromism and a red-shift of the absorption maxima, while net isosbestic points (Figure 2) show the presence of only two absorbing species, the free and the bound complex. Moreover, as expected for noncovalent interactions, the spectral changes can be fully reversed by addition of NaCl.

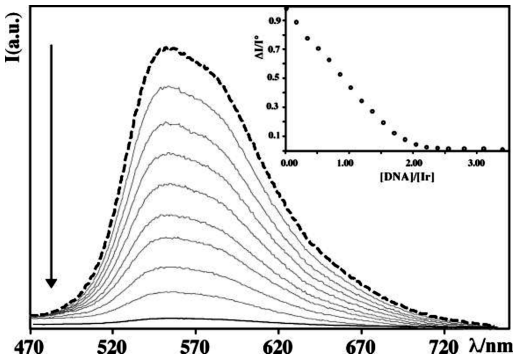

Figure 1. Emission spectrum of **1** (1×10^{-5} M) in buffered solution upon successive addition of calf-thymus DNA (intensity changes at fixed wavelength and various [DNA]/[Ir] ratios in the inset). Excitation is performed at an isosbestic point, 384 nm.

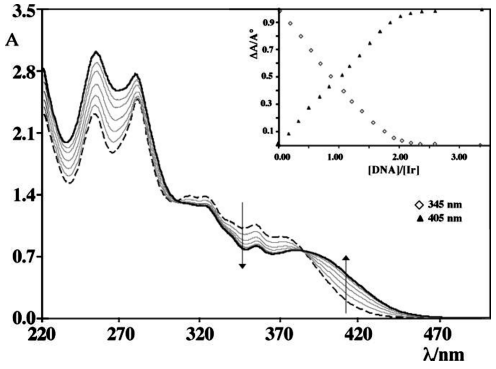

Figure 2. Absorption spectrum of **1** (4.2×10^{-5} M) in buffered solution upon successive addition of calf-thymus DNA (inset: absorption changes at two fixed wavelengths and different [DNA]/[Ir] ratios).

Whereas some interaction between **1** and DNA was expected, due to the relatively high positive charge of the iridium complex (3+), such significant effects on absorption and luminescence spectra can hardly be attributed to simple electrostatic interactions. Moreover, the appearance of induced CD signals upon addition of DNA (in the region where the compound DNA assembly absorbs) strongly suggests the occurrence of a more intimate interaction, that is, intercalation or groove binding. Indeed, the absorption, emission, and CD spectra of the parent compound $[Ir(terpy)_2]^{3+}$ (**2**; terpy = 2,2′:6′,2″-terpyridine) do not exhibit any substantial change in the presence of DNA (see Supporting Information) in the same conditions, in spite of the identical charge of **1** and **2**.

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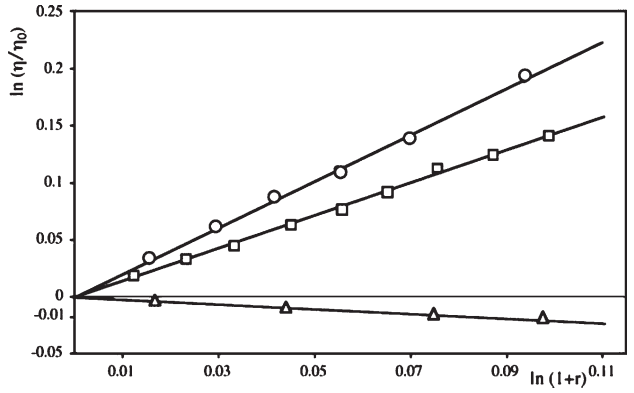

Figure 3. Viscometric titrations of calf-thymus DNA solutions (6.0×10^{-4} M) with $[Ru(bpy)_2(dppz)]^{2+}$ (○), **1** (□), and **2** (△) at 25 °C and pH 7 (1×10^{-3} M phosphate buffer, and 1.0×10^{-2} M NaCl). η_0 = reduced viscosity of the DNA solution; η = reduced viscosity of the DNA solution in the presence of compounds; $r = [\text{compound}]_{\text{bound}}/[\text{DNA}]_{\text{tot}}$.

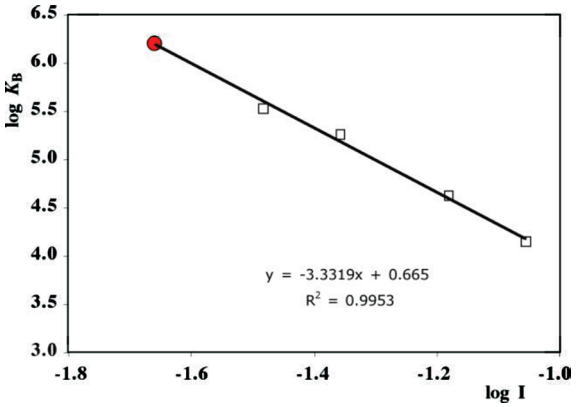

Figure 4. Plot (logarithmic scale) of association constant (K_B) vs ionic strength (I). Squares refer to experimental values. Red circle is an extrapolated value, which is in very good agreement with the experimental value at 2.2×10^{-2} M ionic strength.

To discriminate between intercalation and external binding, we performed DNA melting temperature experiments and viscometric titrations. Upon interaction with a cationic species, in fact, the double helix stability usually increases and so does the DNA melting temperature, ΔT_m. At a 3×10^{-3} M ionic strength value, the DNA melting temperature is affected by **1** (ΔT_m = 10.1 (±0.5) °C) similar to what happens in the presence of the well-known[8−10] DNA intercalator $[Ru(bpy)_2(dppz)]^{2+}$ (ΔT_m = 13.2 (±0.5) °C), while the increase due to $[Ir(terpy)_2]^{3+}$ is very small (ΔT_m = 1.9 (±0.5) °C). Although the increase in denaturation temperature is not specific of any particular type of noncovalent interaction, the ΔT_m values may give some indications on the binding mode. Large increases in melting temperature are observed, in fact, only for the strongest type of interaction, i.e., intercalation. Viscosity can give better indications on the binding mode of a small molecule to DNA. While intercalation results in a substantial change of the double helix, the other types of interaction produce only subtle changes in the structure and the DNA remains essentially in an unperturbed B DNA form. In particular, the former type of interaction causes lengthening and stiffening of the helix which result in an increase of the DNA solution viscosity.

The result of the viscometric titration of rodlike DNA (about 600 base pairs long) with increasing amounts of **1** is shown in Figure 3, where it is compared with those obtained for $[Ru(bpy)_2(dppz)]^{2+}$ and $[Ir(terpy)_2]^{3+}$ complexes: **1** has a behavior quite similar to that of the Ru(II) compound, while the bis-terpyridine Ir(III) complex does not produce any increase of DNA viscosity and rather gives rise to a small decrease of it.

All these experiments definitely confirm the intercalation of **1** within DNA base pairs. The binding constant value for this interaction, estimated by the McGhee−Von Hippel equation applied to the absorption spectra titration, is 1.6 (±0.5) × 10^6 M^{-1} at a 2.2×10^{-2} M ionic strength value, and the number of sites not occupied about 1.8.[17]

Since the K_B value is quite large, according to the Record−Manning theory we decided to test its value also by performing titrations at different (higher) ionic strengths and to extrapolate the value at 2.2×10^{-2} M ionic strength.[19]

The titrations were carried out in 1×10^{-3} M phosphate buffer, pH 7, at different ionic strength values (in 3.2×10^{-2} M, 4.3×10^{-2} M, 6.5×10^{-2} M, and 8.7×10^{-2} M NaCl). The extrapolated K_B value at 2.2×10^{-2} M ionic strength is shown in Figure 4 and perfectly agrees with the value obtained by the experimental determination at 2.2×10^{-2} M ionic strength.

Since **2**, made of two terpy ligands, clearly does not intercalate, the intercalation ability of **1** can be attributed to the terpy-substituted ligand: the 4-biphenyl-terpyridine moiety is therefore suggested to be responsible for the intercalation process. Large polyaromatic moieties are known to be suitable intercalator motifs;[20] however, this is the first case in which a biphenyl-substituted terpyridine is shown to exhibit clear DNA intercalation ability in an octahedral compound.

To rationalize the effect of DNA on the luminescence properties of **1** we performed experiments with synthetic polynucleotides. Figure 5 shows the changes of the emission of **1** in the presence of $[poly(dA-dT)_2]$: the emission intensity is largely enhanced and lifetime increases to 27 μs. This effect is attributed to intercalation between DNA base pairs, which protects the excited state of **1** from molecular oxygen quenching and possibly also decreases the efficiency of radiationless transitions by inhibiting some vibrations acting as accepting modes. Also, the emission spectrum is slightly red-shifted, indicating stabilization of the excited state.[21] On the contrary, the emission of **1** is strongly quenched (Figure 5) in the presence of increasing amounts of $[poly(dG-dC)_2]$; at the end of the titration process, only a very weak emission remains, which exhibits a lifetime of 5 ns.[22] The emission quenching of **1** with $[poly(dG-dC)_2]$ is attributed to an electron transfer process involving guanine moieties, according to general findings.[1,2] In the present case, driving force for the reductive electron transfer quenching of **1** emission by guanine bases is thermodynamically allowed by about 0.26 eV.[23] The electron transfer rate constant (k_{el}) for such a process can be estimated from the equation $k_{el} = (1/\tau) - (1/\tau^0)$; where τ and τ^0 are the quenched and unquenched excited state lifetimes of **1**, respectively. Whereas the quenched lifetime of **1** (5 ns) is experimentally well-defined, it is not obvious to assign the value for the unquenched emission: in fact, in the absence of the electron transfer process, the emission of **1** in $[poly(dG-dC)_2]$ should be close to that in $[poly(dA-dT)_2]$, as intercalation of **1** in $[poly(dG-dC)_2]$ or $[poly(dA-dT)_2]$ should have similar effects on oxygen quenching and radiationless decay. For such reasons, we assume for τ^0 the value of 27 μs. So, k_{el} is estimated to be 2×10^8 s^{-1}, a value which agrees with

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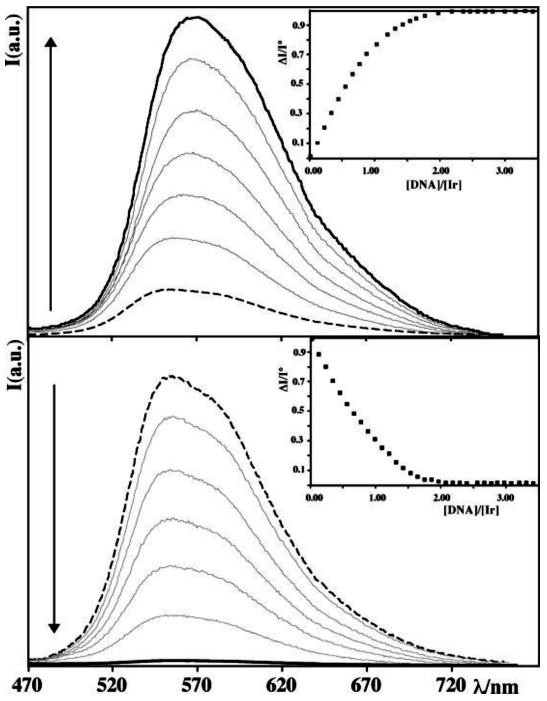

Figure 5. Emission spectral changes of **1** (1×10^{-5} M) in buffered solution upon successive addition of [poly(dA−dT)$_2$] (top) and of [poly[(dG−dC)$_2$] (bottom). Emission intensity changes at fixed wavelengths are shown in the insets. Excitation at 384 nm, an isosbestic point.

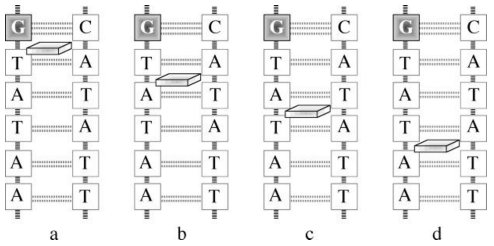

Figure 6. Schematization of the possible situations (see text). The intercalated **1** is shown as a perpendicular object. The guanine quencher units are highlighted in gray.

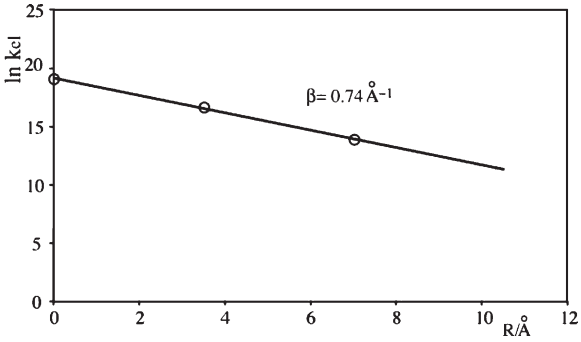

Figure 7. Distance dependence of ln k_{el}, according to eq 1.

several rate constants measured for the same process in luminescent metal complexes/DNA assemblies.[5]

Further information can be inferred by the titration curves of the emission of **1** by [poly(dG−dC)$_2$] and [poly(dA−dT)$_2$]: the slopes are practically identical for both emission titrations (see Figure 5, insets), suggesting that there is no preferential binding of **1** for A−T or C−G sites. Furthermore, the fittings of the titration data give similar binding constant values (K_B = 1.4 (±0.5) × 10^6 M^{-1} for [poly(dA−dT)$_2$] and K_B = 1.5 (±0.5) × 10^6 M^{-1} for [poly(dG-dC)$_2$]).

With the information inferred from emission changes of **1** in the presence of synthetic polynucleotides in our hands, we are now able to rationalize the emission behavior of **1** in calf-thymus DNA. The shorter-lived component of the emission, with a 5 ns lifetime, can be attributed to metal complexes inserted within C−G sites; the other components can be attributed to metal complexes inserted into A−T sites, and having guanine residues at various distance from the complex, so featuring slower electron transfer rate constants.

Indeed, there are several possible situations for the intercalated **1** with regard to guanine residues (Figure 6): (a) intercalation close to a dC−dG base pair; (b) intercalation within two dA−dT base pairs, with a guanine residue just beside the intercalation site; (c) intercalation within two dA−dT base pairs, with a guanine residue separated by a further dA-dT site; (d) the same as case c, but with two dA−dT sites interposed between a guanine residue and the intercalation site. Cases where the luminescent species are separated from guanine residues by three or more dA−dT sites can also be present, but are not expressly considered here. Moreover, it should be considered that guanine residues can be on both sides of the intercalation site (with reference to Figure 6, we mean above and below the intercalation site, that is a symmetric situation) or on a single site only (an asymmetric condition; in Figure 6 only this case is represented, for simplicity reasons). When guanine bases are on both sides of the intercalation sites, the measured electron transfer rate constant should be twice that measured when a single guanine is present. However the occurrence of a symmetric situation is half as probable as the asymmetric situation. So, also considering that the emission would be more quenched for the symmetric case than for the asymmetric one, most likely the emission lifetime of the chromophore immersed in a symmetrically populated guanine environment is below the safely detectable limit. Because of the arguments mentioned above, it is not surprising that the emission decay of **1** in calf thymus DNA is complicated. However, as it is well-known that distance dependence of the electron transfer rate constant also occurs in DNA, we can make some tentative attributions. The shorter lifetime of **1** in DNA has been attributed (see above) to case a, the lifetime of about 60 ns can be attributed to **1** in the b situation, case c could be responsible for the 900 ns emission lifetime, and case d could reflect longer-lived (>10 μs) intercalated species, although the emission component connected with such a situation could overlap with the unquenched **1**.

According to the above hypothesis, rate constants for guanine-to-**1** electron transfer in intercalated situation are 2.0×10^8 s^{-1} for case a, 1.7×10^7 s^{-1} for case b, and 1.1×10^6 s^{-1} for case c. Assuming that case a corresponds to donor−acceptor partners in direct contact (that is R, the electron transfer donor−acceptor distance, is assumed to be 0), R is approximately 3.5 and 7.0 Å for cases b and c, respectively. Equation 1, where k_{et}^0 is the electron transfer rate constant at contact distance between donor and acceptor (2.0×10^8 s^{-1} in our case) and β is the so-called electronic attenuation factor (sometimes also called distance decay constant),[25] provides Figure 7, which indicates a value of 0.74 $Å^{-1}$

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for β, not far from the value of 0.64 $Å^{-1}$ reported for photoinduced electron transfer in DNA hairpins.[26] The difference in the β values is acceptable, even considering that β is not only a bridge-dependent factor, but it also depends on the donor−acceptor partners.[25]

$$\ln k_{el} = \ln k_{el}^{0} - \beta R \quad (1)$$

Equation 1 predicts a lifetime of about 13 μs for case d, which is in good agreement with the longer emission lifetime component of the decay of **1** emission in DNA, and also suggests that reductive electron transfer of the excited state of **1** by guanine residues in our system is no longer effective over a distance of four dA−dT base pairs.

CONCLUDING REMARKS

In conclusion, we reported the first example of an Ir(III) complex exclusively made of polypyridine-type ligands which exhibits intercalation in DNA base pairs, and also identified a new intercalating structural motif. By taking advantage of the information gained by the use of synthetic nucleotides, the complicated emission decay of **1** in the presence of DNA is interpreted with the distance dependence of electron transfer quenching, also indicating that the quenching is no longer effective over a distance of four dA−dT base pairs in the present system.

ASSOCIATED CONTENT

Supporting Information. General information and details on calculation of binding constants, emission decay analysis, circular dichroism experiments and absorption spectra changes (including four figures and one table). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The red-shift of the emission of the intercalated compound could be due to forced planarization of the intercalating ligand.

(22) Both in the presence of [poly(dA−dT)$_2$] and [poly(dG−dC)$_2$] the absorption spectrum changes of **1** are practically identical to that occurring in the presence of calf-thymus DNA.

(23) The driving force of the process, ΔG, is approximated by the equation $\Delta G = (eE_{ox} - eE_{red} - E_{00})$, where E_{ox} is the oxidation potential of guanosine sites, estimated to be +1.06 vs SCE,[24] E_{red} is the reduction potential of **1**, −1.21 vs SCE, and E_{00} is the energy of **1** excited state, taken as the maximum of the emission spectrum at 77 K, 2.53 eV.[12] The Koopman theorem is assumed as valid and the work term is neglected.

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