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Communication

Ferrocene-conjugated copper(II) dipyridophenazine complex as a multifunctional model nuclease showing DNA cleavage in red light

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Dedicated to the memory of Professor F. Albert Cotton

Abstract

The copper(II) complex $[Cu(L)(dppz)](ClO_4)_2$ (**1**) having a tripodal ligand ferrocenylmethylbis(2-pyridylmethylamine) (L) with a pendant ferrocenyl unit and a planar NN-donor dipyrido-[3,2-a:2′,3′-c]-phenazine (dppz) base is prepared and its DNA binding and cleavage properties studied. The complex is redox active showing cyclic voltammetric responses at 0.52 and –0.01 V vs. SCE due to Fe(III)/Fe(II) and Cu(II)/Cu(I) couples, respectively. The complex that binds to the major groove of DNA shows dual chemical nuclease activity involving both the metal centres. The complex displays efficient photo-induced DNA cleavage activity in visible laser light of 458 and 568 nm wavelengths forming cleavage active hydroxyl radicals. Significant DNA cleavage is also observed in red light of 647 nm within the photodynamic therapy (PDT) window.

Keywords: Bioorganometallic chemistry; Ferrocene; Copper(II) complex; Dipyridophenazine; DNA photocleavage; PDT window

1. Introduction

The current interests in bioorganometallic chemistry are mainly due to diverse biomedical applications of organometallic complexes [1–8]. Among various uses of organometallic complexes in biological studies, those targeted to anticancer applications are of particular importance [3,7–11]. Arene–ruthenium(II) complexes are reported to bind to the guanine base in double-stranded DNA and such complexes are promising candidates in chemotherapeutic applications [7]. Organometallic complexes could be suitably tailored for targeting tumour malignancy and as alternatives to *cis*-platin [3,7,9]. Considering stability and aqueous solubility of ferrocene and its diverse organometallic chemistry, several ferrocene-based complexes are subjected to chemotherapeutic applications [1,2]. It has been shown that the cytotoxic effect of the breast cancer drug tamoxifen can be augmented in the presence of a ferrocenyl unit conjugated to the drug [11]. In addition, peptide and nucleic acids conjugates of metallocenes have been used in biochemical studies [12,13].

The present work stems from our interest to develop the chemistry of ferrocene-conjugated 3d-metal complexes as model photonucleases for their potential use in photodynamic therapy (PDT). PDT is a non-invasive therapeutic treatment requiring photoactivation of the drug selectively at the tumour cells leaving the healthy cells unaffected [14]. Photofrin® is the FDA approved hematoporphyrin drug that shows anticancer activity on photoactivation at 630 nm generating cytotoxic singlet oxygen ($^1O_2$) species in a type-II process [14]. Transition metal complexes of heavier elements are used to photocleave DNA in visible light for their possible applications in PDT [5,15–19]. Our recent reports have shown that $3d^5$-iron(III) and $3d^9$-copper(II) complexes could be suitably designed to achieve oxidative cleavage of

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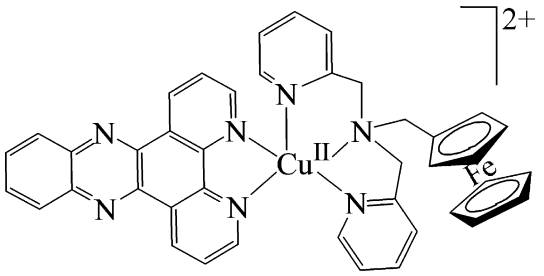
double-stranded DNA on photo-irradiation in red light by type-II or photo-redox pathways [20–22]. In this communication, we report a new copper(II)-dipyridophenazine complex $[Cu(L)(dppz)](ClO_4)_2$ (**1**), where L is ferrocenylmethylbis(2-pyridylmethylamine) having a pendant ferrocenyl unit and dppz is a planar heterocyclic base dipyrido-[3,2-a:2′,3′-c]-phenazine having a photoactive phenazine moiety (**I**). Complex **1** shows efficient DNA binding propensity, dual-functionality chemical nuclease activity involving both the metal centres and efficient photo-induced DNA cleavage activity in visible light. There are few reports of organometallic complexes showing photocleavage of DNA on irradiation with high pressure Hg lamp [23,24]. Observation of DNA cleavage by **1** in the PDT window of 630–800 nm is, however, unprecedented in the chemistry of bioorganometallic complexes. We have observed significantly high visible light-induced DNA cleavage activity of the present ferrocene–copper(II) complex (**1**) in comparison to its chloro analogue $[CuCl_2(L)]$ with a pendant ferrocenyl unit and the mono-dppz complex of copper(II) $[Cu(dppz)(H_2O)_2(NO_3)](NO_3)$ [25,26].



(I)

2. Results and discussion

2.1. Synthesis and general aspects

Complex **1** as a purple–green solid is prepared in high yield by a synthetic procedure in which the ferrocenyl complex as a tripodal ligand is reacted with $[Cu(H_2O)_6](ClO_4)_2$ and dppz in MeOH. The complex is characterized from analytical and spectral data. The infrared spectrum shows the ClO_4 stretching frequency at 1088 cm^{-1}. The complex is 1:2 electrolytic in DMF. The electronic spectrum of the complex in Tris–HCl buffer medium containing 5%DMF (pH 7.2) displays two visible bands involving ferrocene (441 nm) unit and the copper(II) centre (560 nm) (Fig. 1) [25]. Complex **1** is redox active. It shows two cyclic voltammetric responses at 0.52 V and −0.01 V vs. SCE for the Fe(III)/Fe(II) and Cu(II)/Cu(I) couples, respectively, in MeCN–0.1 M TBAP (Fig. S1). The spectral and redox properties of complex **1** have similarity with its analogue $[CuCl_2(L)]$ [25].

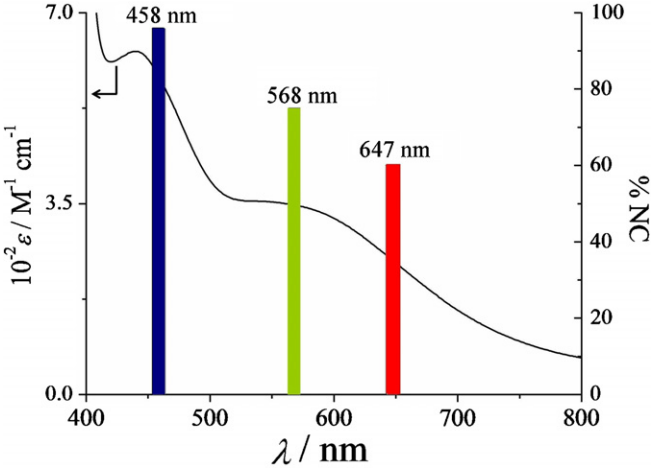


Fig. 1. The visible electronic spectrum of $[Cu(L)(dppz)](ClO_4)_2$ (**1**) in DMF–Tris buffer medium showing the visible bands and the extent of DNA cleavage on laser irradiations at 458, 568 and 647 nm wavelengths using Ar–Kr laser.

2.2. DNA binding studies

The DNA binding properties of the complex are studied by the absorption spectral titration technique, fluorescent ethidium bromide (EB) displacement assay, thermal denaturation and viscometric titration method. The absorption spectral method is used to determine the equilibrium-binding constant (K_b) of the complex to calf thymus (CT) DNA in which the change in absorption intensity of the ligand-based spectral band at 267 nm is monitored with increasing concentration of CT DNA (Fig. 2). A bathochromic shift of 2 nm of the spectral band along with 19% hypochromism is observed suggesting partial intercalation of the complex to DNA. The K_b and the binding site size (s) values are $2.5(\pm 0.4) \times 10^5$ M^{-1} and 0.2, respectively. The K_b value suggests good DNA binding propensity of the

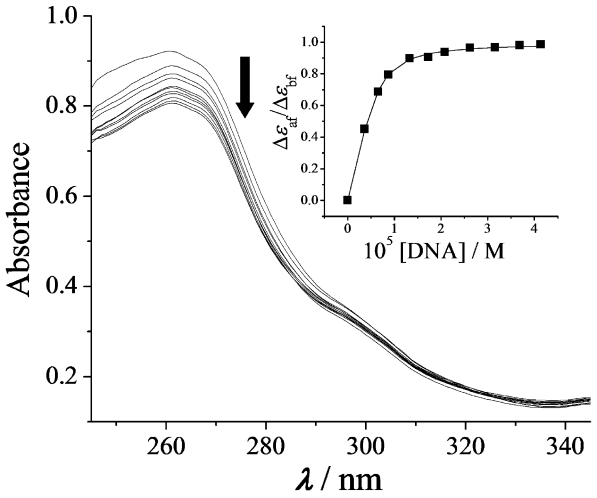


Fig. 2. Spectral traces showing the effect of addition of CT DNA (230 μM NP) to a 25 μM complex solution in Tris–HCl buffer (pH 7.2) having 6%DMF with the inset showing $\Delta\varepsilon_{af}/\Delta\varepsilon_{bf}$ vs. [DNA] plot.

complex. The planer extended phenazine ring of dppz facilitates DNA binding.

The emission spectral method is used to get an estimate on the relative binding affinity of the complex to CT DNA with respect to EB. The emission intensity of EB is used as a spectral probe as EB shows reduced fluorescence in buffer solution because of solvent quenching and an enhancement of the emission intensity on intercalation to CT DNA [27]. The apparent binding constant (K_{app}) of **1**, determined using the formula $K_{app}[complex] = K_{EB}[EB]$, is $1.6 \times 10^6\ M^{-1}$(Fig. S2). We have done viscometric studies to determine the possibility of any intercalation mode of binding of the dppz ligand in **1** considering that intercalation results in large increase in viscosity of the DNA solution. Addition of the complex in increasing concentration (0–268 μM) to the CT DNA solution (130 μM) in 5 mM Tris–HCl buffer results only in minor change in viscosity and the $(\eta/\eta_0)^{1/3}$ vs. R = [complex]/[DNA] plot suggests primarily groove binding nature of the complex (Fig. S3). Thermal denaturation study showing small change in the DNA melting temperature (T_m) on addition of the complex to CT DNA indicates primarily groove-binding nature of the complex. The low ΔT_mvalue of 2.0 °C could be due the steric bulk of the complex (Fig. S4).

2.3. DNA cleavage studies

2.3.1. Chemical nuclease activity

Since the complex has redox active Fe(II) and Cu(II) centers, the chemical nuclease activity of the complex is studied using 3-mercaptopropionic acid (MPA) as a reducing agent and H_2O_2 as an oxidizing agent in 50 mM Tris–HCl/NaCl buffer (pH 7.2). Ferrocene (Fc) and [$CuCl_2$(L)] (**2**) are used as controls. While complex **1** (15 μM) displays efficient cleavage of supercoiled (SC) pUC19 DNA (0.2 μg, 33.3 μM) in the presence of MPA or H_2O_2 making it an artificial chemical nuclease of dual-functionality, both Fc and **2** do not show any apparent chemical nuclease activity even though they have redox active metal center(s) (Fig. 3). Complex **1** does not show any DNA cleavage in dark in absence of MPA or H_2O_2 indicating no hydrolytic cleavage activity. Complex **1** shows ~89% SC DNA damage in the presence of 500 μM MPA and ~72% DNA cleavage from SC to its nicked circular (NC) form in the presence of 200 μM H_2O_2. MPA or H_2O_2 alone is cleavage inactive under similar conditions.

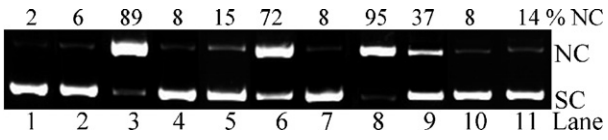


Fig. 3. Gel diagram showing the chemical nuclease activity of [Cu(L)(dppz)]$(ClO_4)_2$ (**1**, 15 μM) using SC pUC19 DNA (0.2 μg, 33.3 μM bp): lane-1, DNA control; lane-2, DNA + **1**; lane-3, DNA + MPA + **1**; lane-4, DNA + DMSO + MPA + **1**; lane-5, DNA + catalase (2 units) + MPA + **1**; lane-6, DNA + H_2O_2 + **1**; lane-7, DNA + DMSO + H_2O_2 + **1**; lane-8, DNA + distmycin-A (100 μM) + MPA + **1**; lane-9, DNA + methyl green (100 μM) + MPA + **1**; lane-10, DNA + H_2O_2 + ferrocene (15 μM); lane-11, DNA + MPA + [Cu(L)Cl_2] (15 μM). MPA and H_2O_2 alone gave ~8% NC form. Concentrations of MPA and H_2O_2 are 500 and 200 μM, respectively. Incubation time in dark is for 2 h.

For mechanistic investigations, the chemical nuclease activity of **1** has been studied in the presence of various additives. Addition of hydroxyl radical scavengers like DMSO and catalase causes significant reduction in the DNA cleavage activity in the presence of MPA. This indicates the formation of hydroxyl radical (·OH) as a cleavage active species. The chemical nuclease activity in the presence of H_2O_2 also follows hydroxyl radical pathway (Fig. 3). The reaction in the presence of MPA involves Cu(II)/Cu(I) couple forming Cu(I) that activates molecular oxygen to generate hydroxyl radical cleaving DNA by abstracting deoxyribose sugar hydrogen atom [28]. The reaction with H_2O_2 involves the oxidation of Fe(II) of the ferrocenyl moiety to Fe(III) that generates hydroxyl radicals [29]. We have explored the DNA binding property of the complexes using DNA groove binders distamycin-A and methyl green. Addition of minor groove binder distamycin-A (200 μM) has no effect on the chemical nuclease activity of **1**. The major groove binder methyl green, however, significantly inhibits the DNA cleavage suggesting major groove binding nature of the dppz complex **1**.

2.3.2. DNA photocleavage activity

Photo-induced DNA cleavage activity of **1** along with ferrocene (Fc) and the chloro analogue **2** as controls is studied using pUC19 DNA (33.3 μM, 0.2 μg) in Tris–HCl/NaCl buffer (50 mM, pH 7.2) on irradiation with monochromatic visible light of 458, 568 and 647 nm wavelengths using a continuous-wave (CW) argon–krypton mixed gas ion laser (100 mW laser power). The extent of cleavage of SC DNA to its NC form is shown in Figs. 1, 4a. The choice of wavelengths for photo-irradiation of the complex is based on its spectral behavior showing two visible bands at 440 and 560 nm. While complex **1** is found to be cleavage active at all three wavelengths used, the controls using Fc and [$CuCl_2$(L)] do not show any DNA cleavage activity. The ligand dppz alone is also cleavage inactive. The photoactive dppz ligand when bound to the copper(II) ion seems to generate activated species in a metal-assisted process. The dppz ligand thus plays dual role in showing DNA binding propensity and generating the photo-activated species. The mono-dppz copper(II) complex [Cu(dppz)$(H_2O)_2(NO_3)$](NO_3) used as a control shows reduced DNA photocleavage activity under similar experimental conditions (Fig. 4a, lane-9). The formation of ferrocene–copper(II) conjugate with a bound dppz ligand has positive effect on the visible light-induced DNA cleavage activity.

The mechanistic aspects of the DNA photocleavage activity of **1** are investigated using various additives (Fig. 4b). Addition of singlet oxygen quencher sodium azide has no apparent effect on the DNA cleavage activity. This excludes the type-II pathway involving the formation

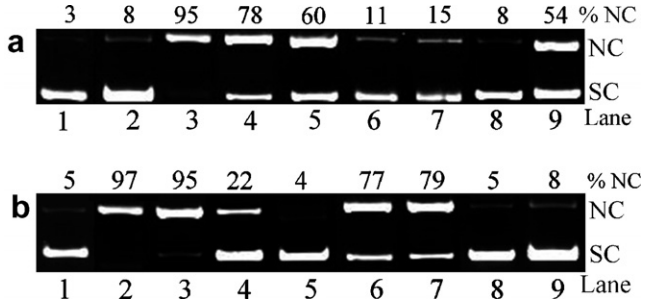


Fig. 4. (a) Gel diagram showing the cleavage of SC pUC19 DNA (0.2 μg, 33.3 μM bp) by $[Cu(L)(dppz)](ClO_4)_2$ (**1**) and other complexes (20 μM) in visible wavelengths for 2 h exposure time: lane-1, DNA control (458 nm); lane-2, DNA + dppz (458 nm); lane-3, DNA + **1** (458 nm); lane-4, DNA + **1** (568 nm); lane-5, DNA + **1** (647 nm); lane-6, DNA + ferrocene (458 nm); lane-7, DNA + $[CuCl_2(L)]$ (458 nm); lane-8, DNA + $[CuCl_2(L)]$ (568 nm); lane-9, DNA + $[Cu(dppz)(H_2O)_2(NO_3)](NO_3)$ (568 nm). (b) Gel diagram showing the photocleavage of SC pUC19 DNA (0.2 μg, 33.3 μM bp) by **1** (20 μM) in the presence different additives: lane-1, DNA control; lane-2, DNA + **1** (458 nm); lane-3, DNA + NaN_3 + **1** (458 nm); lane-4, DNA + DMSO + **1** (458 nm); lane-5, DNA + catalase + **1** (458 nm); lane-6, DNA + **1** (568 nm); lane-7, DNA + NaN_3 + **1** (568 nm); lane-8, DNA + DMSO + **1** (568 nm); lane-9, DNA + catalase + **1** (568 nm) (DMSO, 4 μL; $[NaN_3]$, 200 μM; catalase, 2 units).

of singlet oxygen as the reactive species. Hydroxyl radical scavengers DMSO and catalase significantly inhibit the photocleavage activity at both 458 and 568 nm. The results indicate the formation of hydroxyl radical via a photo-redox pathway [30]. Such a pathway is known to occur for copper(II) complex having accessible redox potential and quasi-reversible Cu(II)/Cu(I) couple [22]. Further studies are on to understand the mechanistic role of the ferrocenyl moiety in the photocleavage reaction.

3. Conclusion

We present here the hitherto unknown chemistry of bio-organometallic complexes showing visible light-induced DNA cleavage activity. Complex **1** is successfully designed to have a ferrocenyl unit conjugated with a copper(II) complex having photoactive and DNA binder dipyridophenazine ligand for multifunctional oxidative DNA cleavage activity. The complex shows efficient DNA major groove binding propensity. We have observed rare dual-functionality in the chemical nuclease activity using both oxidizing (H_2O_2) and reducing (MPA) agents involving respective Fe(II) and Cu(II) centres. The mechanistic pathway involves formation of hydroxyl radical as the cleavage active species. The bioorganometallic complex **1** displays unprecedented photo-induced DNA cleavage activity in visible light. The oxidative photocleavage of DNA occurs via metal-assisted photosensitization process forming hydroxyl radical in a photo-redox pathway. Observed DNA cleavage at 647 nm is of significance as it offers further scope of tailoring such complexes for potential PDT applications considering the versatility of the ferrocene chemistry and the utility of the complexes having bio-essential transition metal ions in the PDT chemistry. Further work in that direction is in progress.

4. Experimental

4.1. Materials and measurements

The reagents and chemicals were obtained from commercial sources. The supercoiled (SC) pUC19 DNA (caesium chloride purified) was procured from Bangalore Genie (India). Ferrocene, calf thymus (CT) DNA, agarose (molecular biology grade), distamycin-A, methyl green, catalase and ethidium bromide (EB) were from Aldrich-Sigma (USA). Tris(hydroxymethyl)aminomethane–HCl (Tris–HCl) buffer was prepared using deionized and sonicated triple distilled water. Ferrocenylmethylbis(2-pyridylmethylamine) (L), $[CuCl_2(L)]$ (**2**), $[Cu(dppz)(H_2O)_2(NO_3)](NO_3)$ and dipyrido-[3,2-a:2′,3′-c]phenazine (dppz) were prepared following literature procedures [25,26,31].

The elemental analysis was done using a Thermo Finnigan FLASH EA 1112 CHNS analyzer. The infrared, electronic and fluorescence spectra were recorded on Perkin Elmer Lambda 35, Perkin Elmer spectrum one 55 and Perkin Elmer LS 50B, respectively, at 25 °C. Magnetic susceptibility data at 298 K for the polycrystalline sample of the complex was obtained using Model 300 Lewis-coil-force magnetometer of George Associates Inc. (Berkeley, USA) make. Molar conductivity measurement was done using a Control Dynamics (India) conductivity meter. Cyclic voltammetric measurement was made at 25 °C on a EG& G PAR 253 VersaStat potentiostat/galvanostat using a three electrode configuration consisting of a glassy carbon working, a platinum wire auxiliary and a saturated calomel reference (SCE) electrode. Ferrocene ($E_{1/2} = 0.42$ V) was used as a standard in MeCN–0.1 M $[Bu^n_4N]ClO_4$ (TBAP). DNA binding studies by UV–Visible and DNA melting method were done using Cary 300 bio UV–Vis spectrometer with a Cary temperature controller.

4.2. Synthesis

A methanolic solution (7.0 mL) of ferrocenylmethylbis(2-pyridylmethylamine) (L, 0.2 g, 0.5 mmol) was reacted with a methanolic solution (7.0 mL) of $[Cu(H_2O)_6](ClO_4)_2$ (0.18 g, 0.5 mmol) under an inert nitrogen atmosphere. The green solution thus obtained was magnetically stirred for 1.0 h followed by cooling in an ice bath. To the cold solution was added a methanolic solution (10.0 mL) of dppz (0.14 g, 0.5 mmol) with continuous stirring for 45 min. The solid thus obtained was isolated, washed with cold ether–methanol mixture until the washings were no longer coloured and the product was finally dried *in vacuo* over P_4O_{10}. Yield: 0.3 g, 64%. Anal. Calc. for $C_{41}H_{33}Cl_2CuFeN_7O_8$: C, 52.27; H, 3.53; N, 10.41. Found: C, 51.92; H, 3.26; N, 10.23%. FT-IR (KBr): 3436br, 3079w, 2923m, 2853w 1611m, 1495m, 1448m, 1361w, 1088vs (ClO_4^-), 818m, 765m, 623m, 490w cm^{-1}(br, broad; vs, very strong;

s, strong; m, medium; w, weak). ESI-MS: m/z 841 $(M-ClO_4)^+$ in MeCN (Fig. S5). UV–Visible in DMF–Tris buffer mixture [λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$)]: 560 (350), 441 (630), 380 (10300), 361 (9950), 267 (56100). Λ_M, $S\,m^2\,mol^{-1}$ in DMF at 25 °C: 156. μ_{eff}, $1.81\mu_B$ at 298 K. Cyclic voltammetric data [$E_{1/2}$, V (ΔE_p, mV)] vs. SCE at $50\,mV\,s^{-1}$ scan rate in MeCN–0.1 M TBAP: 0.52 (70) Fe(III)/Fe(II) couple; −0.01 (140) Cu(II)/Cu(I) couple; − 1.16 (120), −1.69 (220) for the dppz ligand.

Solubility and stability: The complex showed high solubility in DMF, MeCN and less solubility in MeOH and CH_2Cl_2. The complex was soluble and stable in aqueous DMF. The perchlorate salts being potentially explosive, only small quantity of the complex was handled with precautions.

4.3. DNA binding and cleavage studies

DNA binding and cleavage experiments were carried out using CT DNA and supercoiled pUC19 DNA (0.2 μg, 33.3 μM bp), respectively, in Tris–HCl/NaCl buffer (pH 7.2) by following methods reported elsewhere [32]. The light source used for DNA photocleavage study was tunable wavelength Spectra Physics Water-Cooled Mixed Gas Ion Laser Stabilite 2018-RM with laser power meter model 407A (100 mW, CW beam diameter at $1/e^2 = 1.8\,mm \pm 10\%$, beam divergence = 0.7 mrad ± 10%). The complex and reagent concentrations corresponded to those in the 20 μL sample volume (solution pathlength = 5 mm). The extent of DNA cleavage was determined from the intensities of the bands in the agarose gels using a UVI-TECH Gel Documentation System. The experimental error in measuring the band intensities varied from 3% to 6%. The method of Bard et al. was used for K_b and s determination [33].

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2007.10.027.

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