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Environmentally benign synthesis of NO donar Schiff base and their Copper(II) complex: DNA binding and Photonuclease Studies.

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ABSTRACT

A pestle and mortar-assisted solvent-free condensation of salicylaldehyde and 2-aminopyridine efficiently afforded a NO donor Schiff base ligand in high yield. This is an environmentally benign method, as satisfactory results were obtained in solvent free conditions with excellent yields, short reaction time, and operational simplicity in the experimental procedure. Copper(II) complex of this ligand were synthesized. Schiff base ligand and its complex were characterized by their melting point, elemental analysis, IR and ^{1}H NMR spectra. In addition, DNA-binding properties of the metal complex were investigated using absorption spectroscopy, viscosity measurements and thermal denaturation methods. The DNA photoclevage experiment shows that, the complex act as effective DNA cleavage agent.

Keywords: Green synthesis; Schiff base; Metal complexes; DNA binding; DNA photocleavage.

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INTRODUCTION

One of the challenges for chemists is discovery and development of novel and simple environmentally safe chemical processes for selective synthesis of desired products by identifying alternate solvent free reaction conditions for much improved selectivity, energy conservation and less or no toxic waste generation and inherently safer chemical products. Therefore, to address depletion of natural resources and preservation of ecosystem it is just urgent to adopt so called "greener technologies" to make chemical agents for well being of human health. In recent years, environmentally benign synthetic methods have received considerable attention and some solvent-free protocols have been developed.[1,2] Schmeyers et al. reported the solid-state synthesis of various kinds of benzylideneaniline derivatives by grinding together solid anilines and solid benzaldehydes.[3] Varma et al. reported the clay catalyzed synthesis of imines and enamines under solvent-free conditions using microwave irradiation.[4]

Schiff's bases are reported to show characteristic biological activities including antibacterial, antifungal, anticancer and herbicidal properties.[5-7] It has been suggested that azomethine linkage (C=N) might be responsible for the biological activities of Schiff bases.[8] Other application of Schiff's bases includes industrial synthesis of high value life saving beta lactam7 antibiotics from class of penicillins and cephalosporins. Besides their utility in phosphorus chemistry Schiff's bases have been used for the preparation of a-aminophosphonate esters and H-phosphonate esters with repeatable Pudovik reaction.[9-11] They are also used as liquid crystals in analytical, medicinal, and polymer chemistry.[12-14] In addition, the schiff bases and their metal complexes exhibit interesting photophysical properties.[15] Salicylidimines show important photochromism where light absorption causes interconversion between enol-imine and keto-amine tautomers through intramolecular hydrogen transfer. Schiff base ligands have also been recognized as 'privileged ligands' and they are able to coordinate with various metals and stabilize them in various oxidation states, enabling the applications of Schiff base metal complexes in a large variety of useful catalytic transformations.[16-18] Particular attention has recently been paid to the synthesis and study of imino and diimino Schiff's bases and their complexes. This is due to various reasons, such as the biological activities of small organic molecules Schiff's base with metal cations have found broad applications in the field of interactions with biogenic macromolecules such as DNA, RNA, and peptides.[19-20] A systematic study of the influence of varying parameters on the interaction of metal complexes with DNA would be valuable in the rational design of new drugs and therapeutic reagents targeted to DNA. And it is possible to systematically vary parameters of interest by changing the properties of the

intercalating groups.[21,22] On the other hand, copper metal ions showed good biological activity. Recently, we found that, the large number of metal complexes exhibited interesting DNA binding properties. [23-25]

Considering the numerous applications of Schiff's bases in various fields of chemistry, there has been tremendous interest in developing efficient methods for their preparation. Although different research groups have developed various methods for different types of condensation reactions attempted so far, these methods suffer from drawbacks such as prolonged reaction times and low yields.[26-29] In such consequences we have developed a new solvent free, short time and high yielding protocol for the preparation of Schiff's bases using pestle and mortar assisted grinding technique. In the present work, we report our results for the preparation of Schiff's bases in solvent free solid medium under the aspect of environmentally benign processes with high yields, which are superior to conventional methods. Our new method has the advantage that neither acid catalysts nor aromatic solvents for azeotropic water separation are needed. Our group has continuously been interested in DNA interactions of Schiff based complexes and has reported the synthesis, DNA binding and cleavage activity of various metal complexes. [31-33] However, up to now the interactions of the copper metal complex of 2-((E)-(pyridine-2-ylimino)methyl) phenol with DNA have not been reported. This aroused our interest in the green synthesis of NNO donar schiff base ligand and its Cu(II) complex in view of evaluating their DNA-binding and cleavage properties.

MATERIALS AND METHOD

Chemicals and instrumentations

All reagents and solvents required were of AR grade, purchased commercially. All the solvents were purified by distillation and used. Salicylaldehyde, 2-aminopyridine, $Cu(OAc)_2.H_2O$ and *Tris*–HCl were purchased from Merck (India), calf thymus (ds)DNA and super coiled (SC) pUC19 DNA were purchased from Bangalore Genie (India), Agarose (molecular biology grade) and ethidium bromide were purchased from Himedia. *Tris*–HCl buffer solution used for binding and cleavage studies was prepared using deionised double distilled water. Melting points were determined in open capillaries and were uncorrected. Microanalyses (C, H and N) were performed in Carlo-Erba 1106-model 240 Perkin-Elmer analyzer. IR spectra were recorded with Shimadzu model FT-IR spectrophotometer by using KBr pellets. UV–visible absorption spectra were recorded using Shimadzu model UV-1650PC spectrophotometer at room temperature. ^{1}H-NMRspectra was recorded on a Bruker FT NMR spectrometer (300 MHz) at 25 ^{0}C in DMSO

with TMS as the internal reference. Viscosity measurements were carried out on semimicro dilution capillary viscometer (Viscomatic Fica MgW) with a thermostatic bath D40S at room temperature. Thermal denaturation studies were carried out with a Perkin–Elmer Lambda 35 spectrophotometer.

Synthesis of 2-((E)-(pyridine-2-ylimino)methyl) phenol, ligand (L)

The Schiff base was synthesized using solvent free grinding method. Eqvimolar (0.01 mol) mixture of salicylaldehyde (1.047ml) and 2-aminopyridine (1.882gm) was grinded for 12 minutes using mortar and pestle yielded yellow solid. Thus obtained product was collected and recrystallized from hot absolute ethanol and dried under vacuum desiccator over anhydrous calcium chloride. Elemental analysis and Melting points were measured for the prepared Schiff bases. The results obtained were in good agreement with the calculated values. The prepared Schiff bases have the following structural formula **Figure 1.**

(HL) Yellow solid; Yield 89%; mp 65 ^{o}C ; Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found: C, 72.63; H, 4.54; N, 13.84 %. IR (KBr): ν (cm^{-1}): 3427, 2559, 1646, 1275, 989.

^{1}H NMR (CDCl3) δ (ppm):): 6.8-7.9 (m, 8H), 9.45 (s,1H), 13.62 (s,1H).;

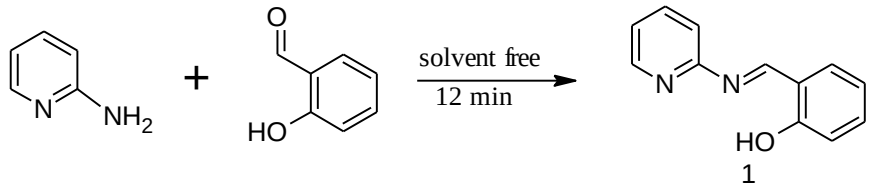

Figure 1. Scheme of ligand (HL) synthesis.

Synthesis of Copper(II) Complex of (HL)

A simple method was adopted for the preparation of the complex [Cu(L)$_2$·2H$_2$O]. The hot ethanolic solution of ligand (HL) and ethanolic solution Cu(OAc)$_2$.H$_2$O in 2:1 molar ratio respectively were mixed. The mixture was refluxed for about 1–2 h, at 80±5 °C, lead to complex precipitation. The obtained complexes were kept in a vacuum desiccator.

Green solid; Yield 78%; FW 493.5 ; Anal. Calcd for $C_{24}H_{22}CuN_4O_4$: C, 58.35; H, 4.45; N, 11.34; Cu, 12.86. Found: C, 58.24; H, 4.37; N, 11.22; Cu, 12.69%. IR (KBr): ν (cm^{-1}): 3346, 1629, 1547, 1030, 1318, 816, 463, 446;

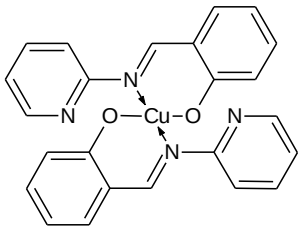

Figure 2. Proposed structure of Cu(II) complex.

DNA-binding experiments

The DNA-binding and cleavage experiments were performed at room temperature. The DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient (6600 M^{-1} cm^{-1}) at 260 nm.[34] The absorption titration experiments and viscosity measurements experiments involving the interaction of the complexes with calf thymus (CT) DNA were carried out in Tris-HCl buffer containing (5mM Tris, pH 7.1, 50mM NaCl) 5% DMF at room temperature. Phosphate buffer (1Mm phosphate, pH 7, 2mM NaCl) was used for thermal denaturation. Absorption titration experiments were carried out by varying the DNA concentration and maintaining the complex concentration constant. Due correction was made for the absorbance of DNA itself. Absorbance values were recorded after each successive addition of DNA solution and equilibration (ca. 10 min). The absorption data were analysed for an evaluation of the intrinsic binding constant K_b using the following equation (1)

$$[DNA]/(\varepsilon_a-\varepsilon_f) = [DNA]/(\varepsilon_b-\varepsilon_f) + 1/K_b(\varepsilon_a-\varepsilon_f) \quad (1)$$

where [DNA] is the concentration of DNA in base pairs, ε_a corresponds to the apparent absorption coefficient $A_{abs}/[M]$, ε_f corresponds to the extinction coefficient for the free metal [M] complex and ε_b corresponds to the extinction coefficient for the metal [M] complex in the fully bound form. In plots of $[DNA]/(\varepsilon_a-\varepsilon_f)$ Vs [DNA], K_b is given by the ratio of slope to the intercept.

Viscosity measurements were carried out using a semimicro dilution capillary viscometer at room temperature. Flow time was measured with a digital stopwatch, and each sample was measured three times, and an average flow time was calculated. Data were presented as (η/η_o) versus [complex]/[DNA], where η is the viscosity of DNA in the presence of the complex and η_0 is that of DNA alone.[34-36]

Thermal denaturation experiments were carried out with a Shimadzu Model UV-160A spectrophotometer coupled to a temperature controller (Model TCC-240A) by monitoring the absorption at 260nm of CT-DNA at various temperatures.[37-38]

DNA Cleavage Experiments

For the gel electrophoresis experiments, supercoiled pUC19 DNA was treated with Co(III) and Ni(II) complexes in Tris buffer (50 mM *Tris*–acetate, 18 mM NaCl, pH 7.2), and the solution was irradiated at room temperature with a UV lamp (365 nm, 10 W). After being incubated at 37°C for 1 h, electrophoresis was carried out at 50 V for 2 h in *Tris*–borate EDTA (TBE) buffer. Electrophoresis was carried out and bands were visualized by UV light and photographed to determine the extent of DNA cleavage from the intensities of the bands using UVITEC Gel

Documentation System.[39-40]

RESULTS AND DISCUSSION

Characterization of ligand and complex

The elemental analytical data and IR data of the new complex are summarized in experimental section. These data were in agreement with the theoretical values within the limit of experimental error and confirmed the formula of the complex $[Cu(HL)_2 \cdot 2H_2O]$. Complex shows solubility in DMF, DMSO and in buffer (pH 7.2) solution. The IR spectra of complex indicate that the *ν*(C=N) band of the ligand at 1646 cm^{-1} due to the azomethine linkage was shifted towards lower frequency 1629 cm^{-1}, indicating that the ligand coordinate to metal ion via the azomethine nitrogen. A broad band at 3346 cm^{-1} found in spectra of complex can be assigned to stretching frequency of OH indicating the presence of water of hydration and/or coordinated water.The absence of band due to phenolic OH group at 3427 cm^{-1} and increase in frequency of phenolic C-O vibration from 1275 cm^{-1} of ligand to 1318 cm^{-1} in the spectra of metal complex suggests the coordination of ligand to the metal via deprotonation, which infers that azomethine-nitrogen and phenolic-oxygen as the coordination sites of the monobasic bidentate ligand which form cationic four-coordinate chelate.[34, 41-42] Besides, two non-ligand peaks at 463 cm^{-1} and 446 cm^{-1} of complexes were assigned to ν(Cu-N) and ν(Cu-O) stretching vibrations respectively. \The electronic spectra of the free ligand and complexes measured in DMSO are dominated by intense ligand-centred transitions in the near UV. However, the complex exhibits prominent transitions in the visible region not seen in the spectrum of the free ligand. The bands exhibited by the ligand at 250–280 and 350 nm can be assigned to azomethine group π-π* and n-π*transitions, respectively. The bands were observed at 310–315 nm, 420–430nm and 540–550nm in the spectrum of the complex ,which are assigned to the O-Cu charge transfer transition, N-Cu charge-transfer transition, being overlapped by the π-π* and n-π*transitions of the ligand and d-d transition of the divalent copper(II) respectively . On the basis of above evidence and analyses, the suggested structure of the complex with square-planar geometry are shown in **Figure 2**

DNA binding studies

Absorption spectroscopic studies

Electronic absorption spectroscopy is usually employed to determine the binding of complexes with the DNA helix through the changes observed in the absorbance and shift in the wavelength. In the absence and presence of CT-DNA the absorption spectra of Cu(II) complex are illustrated

in **Figure 3**. The interaction of Cu(II) complex with CT-DNA was monitored by the red shift (the bathochromic effect) in UV–visible spectra. The observed maximum wavelength of Cu(II) complex was shifted from 428 nm to 432 nm when it was mixed with CT-DNA (**Figure 3**). A complex bound to DNA through intercalation is characterized by the change in absorbance (hypochromism) and red shift in wavelength, due to a strong stacking interaction between the aromatic chromophore and the DNA base pairs.[43,44] The extent of hypochromism is commonly consistent with the strength of the intercalative interaction.The percentage hypochromicity for the metal complexes was determined from (εf – εb)/εf ×100, where εf is the extinction coefficient of the free metal complex and εb is the extinction coefficient of the bound metal complex.

The percentage hypochromism of Cu(II) complexes were found to be 21.5 and. The half-reciprocal plots for binding of complex with CT DNA were presented (Figure **3**). The complex exhibited the similar absorption spectra pertaining to the chromophore. To further illustrate the DNA binding strength, the intrinsic binding constant K_b was determined for Cu(II) complex which was found to be $3.5\times10^4\ M^{-1}$. The binding constants of these metal complexes were lower in comparison to those observed for typical classical intercalators (ethidium-DNA,$1.4\times10^6\ M^1$).[45]

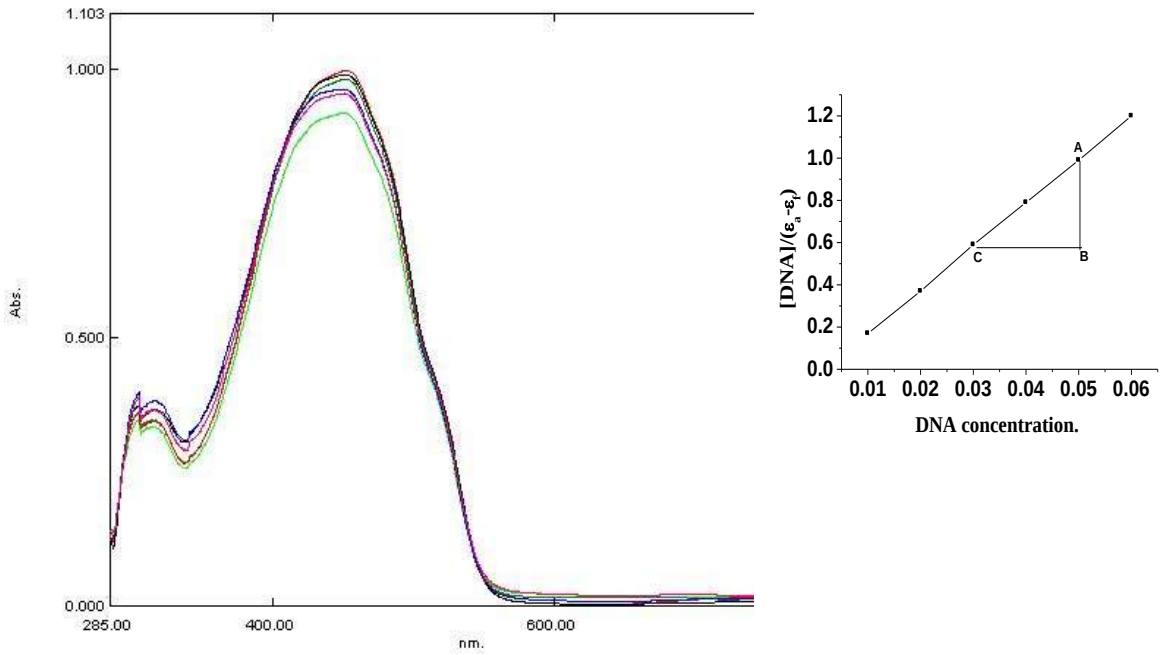

Figure 3. Absorption spectra of Cu(II) complex in *Tris*-HCl buffer upon addition of DNA. [Co(III)] = 0.5 μM, [DNA] = 0-100 μM. Arrow shows the absorbance changing upon increase of DNA concentration. The inner plot of [DNA]/(ε_a-ε_f) *vs* [DNA] for the titration of DNA with complex (I), $K_b = 3.5\times10^4\ M^{-1}$.

Viscosity measurements

In the absence of crystallographic structure data, hydrodynamic methods which are sensitive to DNA length increases are regarded as the least ambiguous and the most critical tests of binding in solution. A classical intercalative mode demands that the DNA helix must lengthen as base pairs are separated to accommodate the binding ligand, leading to the increase of DNA viscosity.[46, 47] The effects of complex together with the viscosity of rod-like DNA are shown in **Figure 4**. On increasing the amounts of complex, the relative viscosity of DNA increases steadily. The experimental results suggest that complexes bind to DNA through a classical intercalation mode. This helps complex intercalate into the DNA base pairs deeply.[48, 49]

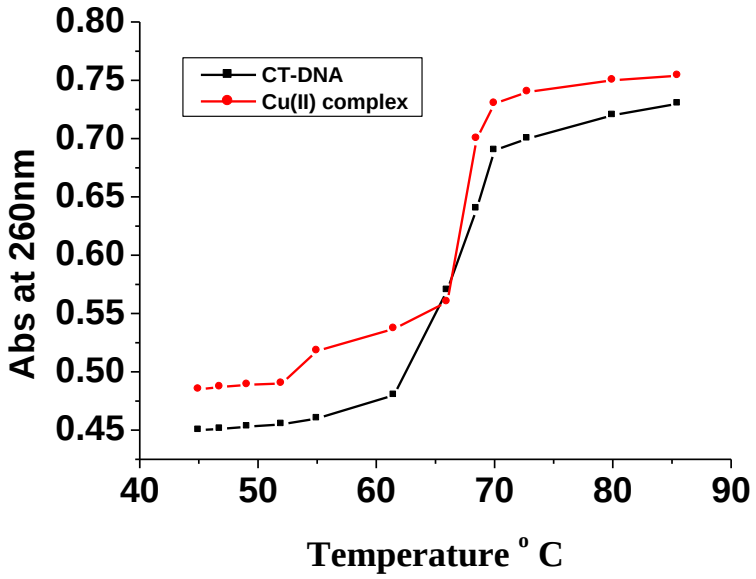

Figure 4. Plot of relative viscosity vs [Complex]/[DNA]. Effect of Cu(II) complex on the viscosity of CT-DNA at 25 ± 0.1^{0}C. Complex = 0-160 µM, [DNA] = 150 µM.

Thermal denaturation studies

The thermal behavior of DNA is a measure of the stability of DNA double helix temperature. An interaction between DNA and complexes were indicated by the increase in the thermal melting temperature (T_m). Thermal denaturation experiments also revealed the intercalation of these complexes with DNA. The CT-DNA alone melt at 61±1°C (10 mmol NaCl, 1 mmol phosphate) in the absence of any added complex. The T_m of DNA was increased by 4±1 °C in presence of complex at [DNA nucleotide phosphate]/[complex] = 25 **Figure 5.** The σ_T values of DNA were also increased by 4±1 °C for these complexes. The increase T_m and σ_T of DNA could be interpreted in terms of the stabilization that results from the intercalation of these metal complexes with DNA. The observations made during the absorption titration, viscosity

measurements and thermal denaturation experiments are reminiscent of those reported earlier for various metallointercalators, thus suggesting that the complexes bound to DNA by intercalations.[50-52]

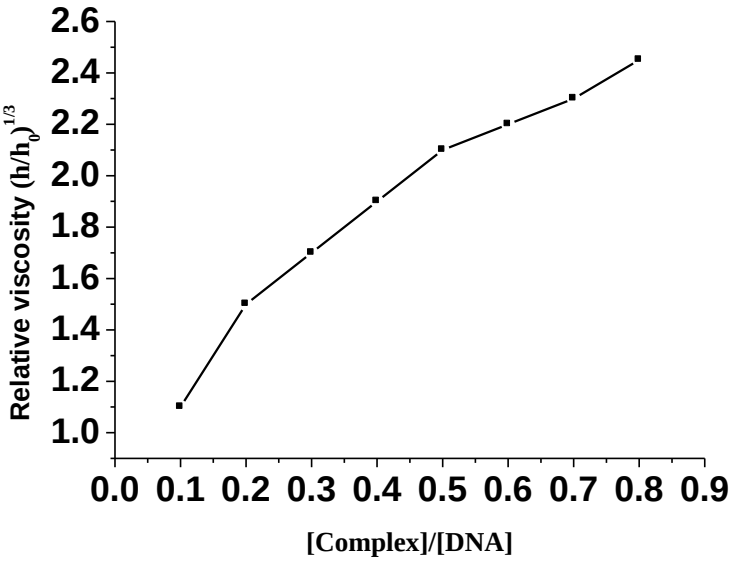

Figure 5. Thermal denaturation of CT-DNA in the absence and presence of Cu(II) complex. [DNA]= 50 µM, [complex] = 10 µM, Buffer: Phosphate

DNA cleavage activity

DNA cleavage was analyzed by monitoring the conversion of supercoiled DNA (Form I) to nicked DNA(Form II) and linear DNA (Form III) under anaerobic conditions. No DNA cleavage was observed for the control in which metal complex was absent (lane 1). Complex can induce the obvious cleavage of the plasmid DNA at the concentration of 20 µM, 40 µM and 60 µM. It was shown that, at lower concentrations, DNA cleavage was not effective (lane 2) **Figure 6**.

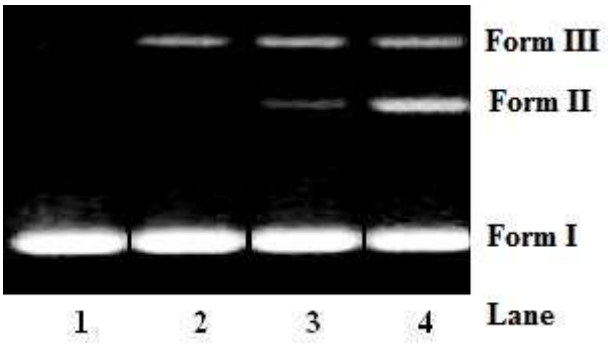

Figure 6. Light-induced DNA cleavage by Cu(II) complex. Supercoiled DNA runs at position I (SC), nicked DNA at position II (NC) and Linear DNA at position III (LC). The complex was irradiated with UV light at 365 nm, Lane; 1: control DNA (absence of complex), Lane; 2: 20 µM; Lane; 3: 40 µM; Lane; 4: 60µM; Cu(II)complex respectively.

At the concentration of 60 μM, complexes can almost promote 75% conversion of supercoiled DNA to nicked and linear DNA (Form I to III). With increasing concentration of these complexes (lanes 2-4), the amount of Form I of pUC19 DNA diminished gradually, whereas Form III increased. Higher concentrations were not examined because of the precipitation of complex in the reaction mixture. It was found that copper complex as a potent nuclease mimic in terms of molecular structure. Chemical environment and their geometric structures may also affect the nucleolytic efficiency of copper complex.[53,54]

CONCLUSION

NO donar Schiff base ligand and Cu(II) complex have been efficiently synthesized by solvent free green method and characterized. The DNA-binding properties of these complexes were examined by absorption spectra, viscosity measurements and thermal denaturation studies. Experimental results indicate that the complexes were bound to CT-DNA via intercalation. The binding constant shows that the DNA-binding affinity Kb 3.5×10^{4} M^{-1}. Upon irradiation at 365 nm, Cu(II) complex can efficiently cleave the plasmid pUC19 DNA. The DNA-cleavage efficiency of the Cu(II) complex may be considered due to the increased binding affinity of the complex to DNA. Information obtained from the present work will be helpful in understanding the mechanism of metal complexes with nucleic acids and should be useful in the development of potential probes of DNA structure and conformation.

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