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DNA binding activity of novel discotic phenathridine derivative

Marichandran Vadivel [a,1], T. Aravinda [b,1], K. Swamynathan [a,b], B. Vinay Kumar [c], Sandeep Kumar [a,b,*]

[a] Soft Condensed Matter Department, Raman Research Institute, Sadashiva Nagar, Bengaluru 560080, India
[b] Department of chemistry, Nitte Meenakshi Institute of Technology, Gollahalli, Yelahanka, Bengaluru 560064, India
[c] Department of Chemistry, RNS Institute of Technology, Channasandra, Bengaluru 5600098, India

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ABSTRACT

Phenanthridine dyes are known for their stunning ability to bind with DNA through intercalation. They are widely used as the standard for DNA binding studies. In this report, we present the synthesis and characterization of a novel liquid crystalline phenanthridine derivative and its ability to bind with DNA. The Intrinsic binding constants K_b of compound **6** with CT–DNA was found to be $2.8 \times 10^4\ M^{-1}$ which is similar to the gold standard compound, ethidium bromide, binding constant. To the best of our knowledge, this is the first report on DNA binding studies of discotic mesogens in the field of liquid crystals.

1. Introduction

Supramolecular chemistry i.e. the chemistry beyond the molecules has triggered the thoughts of material chemists to come out of their shells in exploring new directions in the design of materials with immense potential. [1] The scope of supramolecular chemistry has been manifold since its inception. [2] The molecule of heredity i.e. DNA has shown the scientific world that nothing is impossible for them when it comes to their potential. Since their discovery by Watson and Crick, [3] DNA has unraveled many mysteries concerning its structure scope, and function, and still, it is unexhausted. DNA has been recognized as a site of the target for anticancer drugs, which can change DNA conformation and inhibit duplication or transcription because they showed great promise as a biological receptor for the development of chemotherapeutic agents. [4] DNA has been shown to have diverse interactions with varied molecules because DNA is undoubtedly a storehouse of genetic information. These small molecule binding studies with DNA can lead to better development of anti-cancer compounds. [5] These small organic compounds have been found to adopt different modes of binding with DNA which influences their pharmacological potential. Organic molecules bind to DNA either by intercalation or through grove binding. The intercalation model is often adopted by a pi fused system where they bind between adjacent base pairs of DNA. The groove binding molecules often causes slight perturbations as they fit themselves into the minor grooves of the nucleic acids. The intercalation mode of binding by organic pi fused systems with DNA has been first reported in acridine systems by Lerman et al. [6] They further documented that the intercalative binding is often operated through non-covalent interactions such as H-bonding and hydrophobic effect. The categories of compounds that have been reported for their binding with DNA comprise metal complexes, Schiff base derivatives, heterocyclic compounds, etc. There is a diverse number of reports on the DNA binding ability of transition metal (Pt, Ru, Cu, Pd, and Au) complexes with different ligands. [7–10] Cisplatin has been under the headlines due to its anticancer activity which is reported to have a mechanism of action through intercalative DNA binding. [11] These studies further reveal that complexes comprising of pi delocalized planar ligands afford a moderate to strong binding effect concerning DNA. Other notable ligands used for complexation with transition metals for DNA binding studies comprise acetylacetonato, [8] amine [12], arene [12,13], and Schiff base. [14] The derivatives of polycyclic heteroaromatic compounds have shown immense potential in binding with DNA due to their ability to interact with DNA through π–π interactions. [15]

Liquid crystalline systems are one of the best examples of self-assembled systems where the aggregation of molecules provides order and fluidity simultaneously as a function of temperature or solvent. [16] Discotic liquid crystals are compounds with a central rigid polyaromatic/heteroaromatic core surrounded by flexible tail functionalization at the periphery. [17,18]. The structural contrast i.e. rigidity of the central aromatic core and the flexibility of the peripheral chains within their chemical structure induces the self-assembly of these molecules into columnar structures. [19] This feasibility of these discotics assembling in columns imparts anisotropy in terms of their

* Corresponding author at: Soft Condensed Matter Department, Raman Research Institute, Sadashiva Nagar, Bengaluru 560080, India.
E-mail address: skumar@rri.res.in (S. Kumar).
[1] The authors have equally contributed to the work.

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electronic behavior. [20] DNA has been no stranger to the mesogenic family as there are several reports on DNA-based liquid crystalline dispersions [21]. DNA has been shown to exhibit chromonic mesophases on mixing with water under certain conditions, promoted the scientist to explore the mesogenic potential of DNA-based systems especially in the field of therapeutics [22,23]. Phenanthridine, a polycyclic aromatic motif, has been part of the structure of diverse secondary metabolites. [24,25]. Phenanthridine derivatives are one of the most intensively studied categories of biologically active compounds with efficient DNA binding capability and they were reported to bind with DNA through intercalation. [26] The phenanthridine system (ethidium bromide & propidium iodide) has been applied as gold-standard DNA- and RNA-fluorescent markers and probes for cell viability. However, there is a notable problem prevalent among these systems regarding their mutagenicity and genotoxicity. [27] This report attempts to bridge the liquid crystalline order and DNA binding /cleavage ability of phenanthridine derivatives. Here we have studied mesomorphic phenanthridine derivative for its ability towards DNA binding.

2. Results and discussion

2.1. Synthesis and characterization

The phenanthridine derivative was synthesized as shown in Fig. 1. The commercially available catechol was alkylated using butyl bromide through Williamson reaction to form 1,2-dibutyloxy benzene. The alkylated catechol was oxidatively trimerized using ferric chloride through the Scholl reaction. The obtained triphenylene derivative was subjected to nitration using conventional nitrating agents HNO_3. The nitro product was reduced to an amine using Raney nickel as a reagent. The obtained amine was cyclized with acetaldehyde in presence of triflic acid to obtain the phenanthridine derivative. The structure of the compound was confirmed through NMR (Fig. 2) & elemental analysis. The detailed experimental procedure and spectral data are given in supporting information.

2.2. Mesomorphic characteristics

The liquid crystalline behavior of compound **6** was studied using polarizing optical microscopy (POM), differential scanning calorimetry (DSC), and X-ray diffractometry (XRD) (Fig. 3). Compound **6** showed mosaic textures under a polarizing microscope indicating the columnar order. The mesogenicity was further validated using DSC as they showed double melting behavior. Further, it was noticed that the compound was not crystallized immediately while cooling as shown in the thermogram. The enthalpy of the phase transition was found to be 6.67 Jg^{-1}. The morphology of columnar structure was studied through small-angle X-ray scattering (SAXS) which showed peaks in the small-angle region whose spacing is in the ratio 1: $1/\sqrt{3}$: 1/2:$1/\sqrt{7}$. They can be indexed into a two-dimensional hexagonal lattice. The lattice

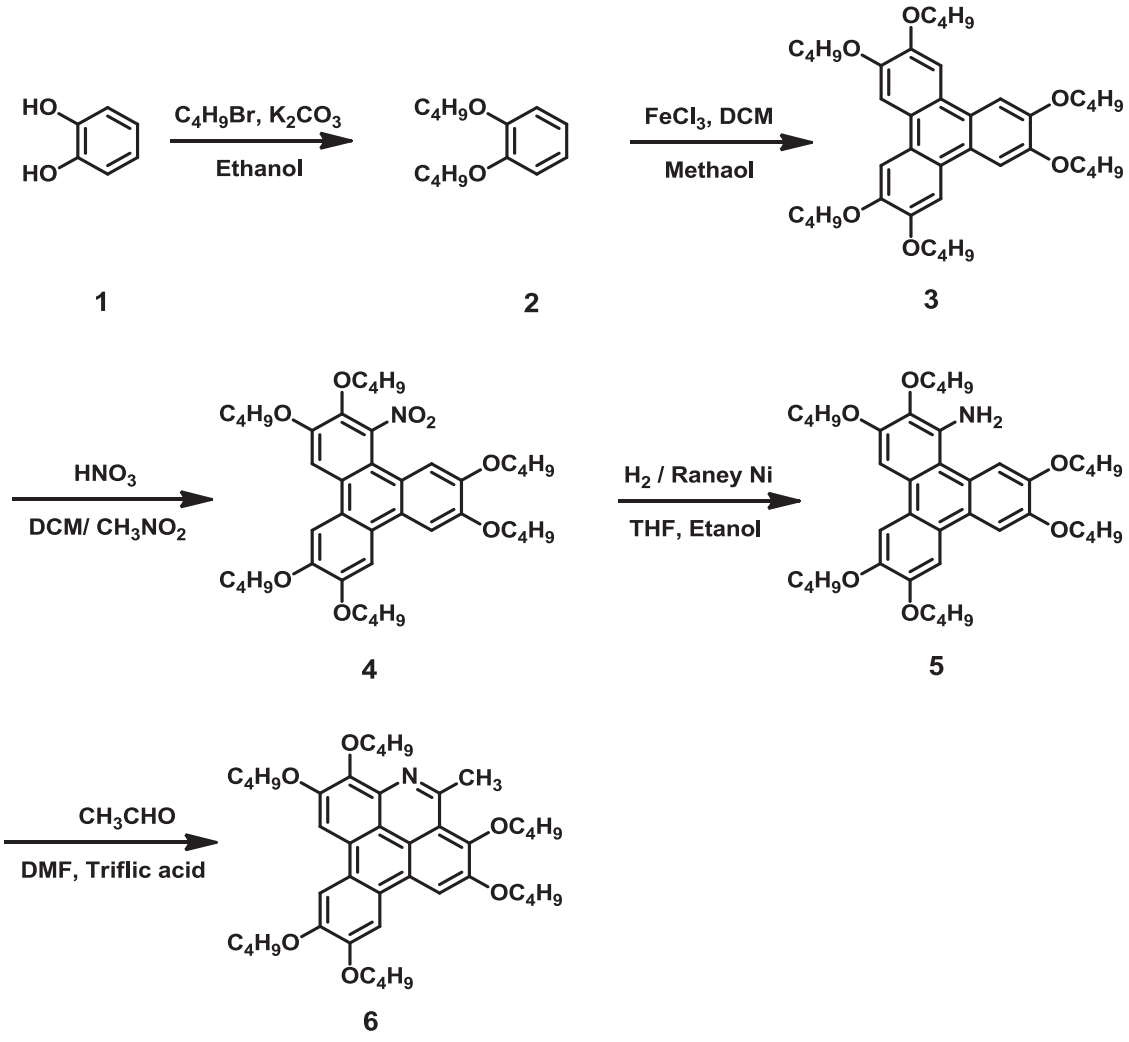

Fig. 1. Synthetic scheme for compound **6**.

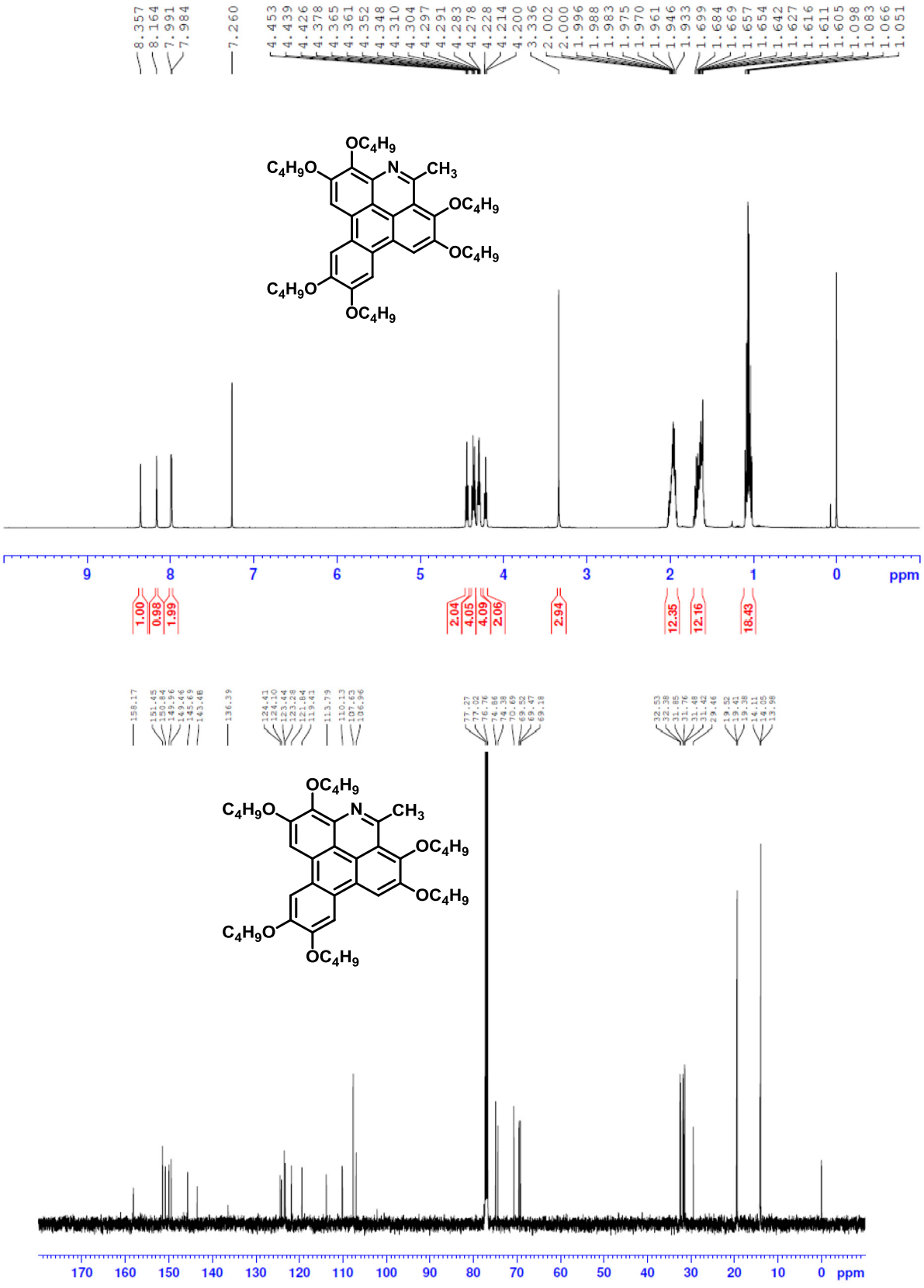

Fig. 2. ^{1}H (top) & ^{13}C (bottom) NMR spectra of compound **6**.

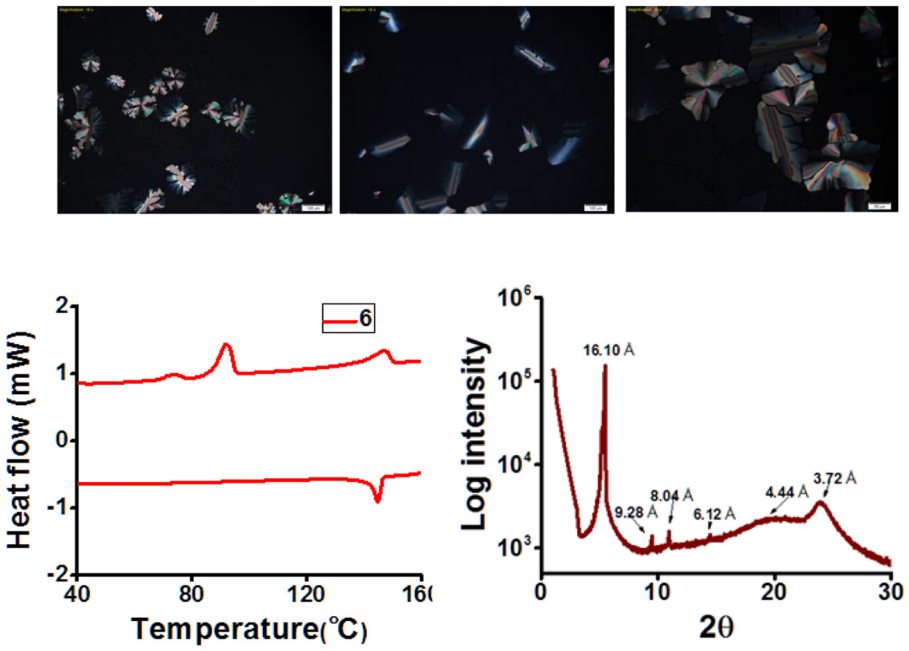

Fig. 3. Mesomorphic characterization of compound **6**.

parameter obtained through diffraction pattern was used to calculate lattice area, lattice volume. From all the above-mentioned data, the number of molecules occupying a single slice of columns was found to be around 1 (Table 1). Based on this we have proposed the hexagonal packing of molecules in their mesophase that has been given in the proposed model as shown in Fig. 4.

2.3. DNA binding activity

The absorption spectroscopy is one of the most effective approaches to probe the binding interaction between compound **6** with the DNA helix. The electronic absorption spectra of compound **6** displayed intense absorption bands at 280 nm because of the intraligand $\pi \rightarrow \pi^*$ transitions as illustrated in Fig. 5. Upon the addition of increasing concentration of DNA to the test compounds in (5 mM Tris HCl/50 mM NaCl) buffer solution, there was a decline in the absorption intensity of the intraligand absorption band 'hypochromism' with a red-shift in wavelength for an active stacking interaction between the heterocyclic chromophore and the base pairs of DNA. These spectral studies implied that compounds show better binding property with DNA and interact by intercalation, and hypochromism is proportional to the intensity of intercalative interaction. [28] The Intrinsic binding constants K_b of compound **6**, with CT–DNA was found to be $2.8 \times 10^4\ M^{-1}$. Phenanthridine-based ligands have been reported to be one of the excellent intercalators with binding constants ranging from 10^4 to 10^5 determined through diverse methods. The gold standard compound Ethidium bromide showed a binding constant of around 10^4. [25,27]. Our compound **6** was found to have a binding constant in the order of 10^4 implies that our molecule can be as potent binder as that of the gold standard ligand ethidium bromide. Further one of the points worth mentioning here that the synthetic feasibility concerning compound **6** is good with the cheaper precursors compared to that of ethidium bromide.

2.4. DNA cleavage activity

The plasmid pUC19 DNA cleavage assays were investigated using agarose gel electrophoresis to probe the DNA cleavage activities of the compound **6**. DNA cleavage has been investigated under anaerobic conditions by observing the conversion of super-coiled DNA (Form I) to nicked DNA (Form II) and linear DNA (Form III). There was no DNA cleavage for the control under which the compound was absent (lane 1). Compound 6 can cause apparent plasmid DNA cleavage at 25 μM and 50 μM concentrations. DNA cleavage was found to be successful (lanes 2–3) at higher concentrations (As shown in Fig. 6), respectively.

At a concentration of 25 μM, compounds will enable the conversion of super-coiled DNA from Form I to III that is a nicked and linear form of

Table 1
d spacing of compound **6**.

Compound	Phase	$d_{observed}$ (Å)	$d_{calculated}$ (Å)	Miller indices (*h*,*k*)	Parameters
6	Col_h 90° C	16.10 9.28 8.04 6.12 4.44(h_a) 3.72(h_c)	16.10 9.26 8.06 6.14	10 11 20 21	a = 18.59 Å S_h = 299.79 Å^2 V_h = 1113.31 Å^3 Z = 1.08

Layer spacing obtained from XRD for **6**. (**a** = lattice parameter = $\sqrt{(4/3)} \times d_{10}$; lattice area $S_h = a^2 \sin 60°$; lattice volume $\mathbf{V_h} = a^2 \sin 60° \times h_c$ (h_a if h_c is not observed); No of molecules per slice of column (**Z**) = $(\sqrt{3} \times N_a \times \rho \times a^2 \times h)/2$ M; N_a = Avogadro number; ρ = Density in Kg/m^3; **a** = lattice parameter; hc = core peak (h_a if core is not observed); M = molecular weight in Kg/m^3).

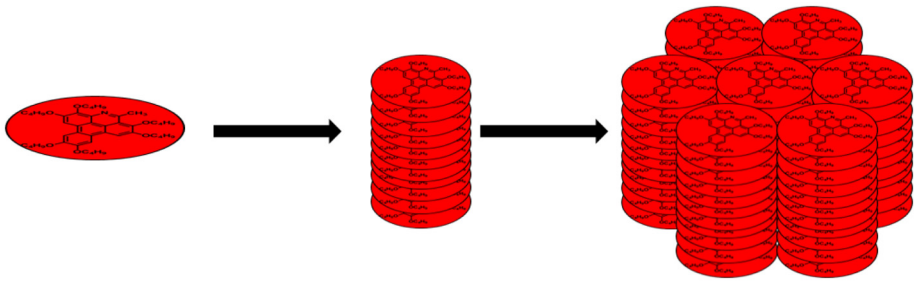

Fig. 4. Possible arrangement of molecule **6** in the columnar phase.

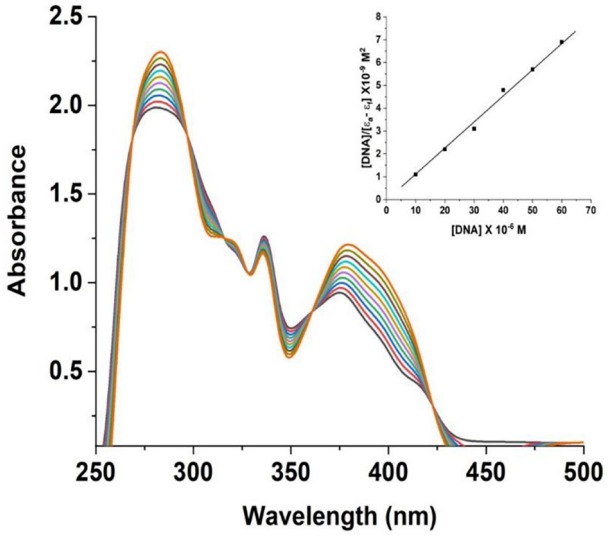

Fig. 5. Absorption spectra for **6** in Tris–HCl buffer upon addition of calf thymus DNA. Concentration of compound **6** = 0.5 mM, [DNA] = 0–100 μM. Inner graph of [DNA]/($\varepsilon_a - \varepsilon_f$) vs. [DNA] for titration of DNA with Compound **6**.

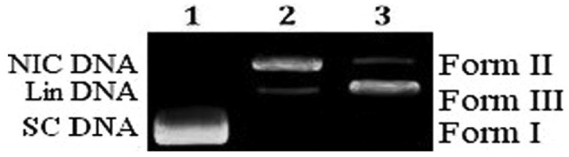

Fig. 6. Gel electrophoresis diagrams showing UV light –induced DNA (SC-pUC19, 0.5 μM). Cleavage activity of compound **6** (25 μM & 50 μM) at 360 nm.

pUC19 DNA. The intensity of Form I pUC19 DNA decreased steadily with the enhancing concentration of these compounds (**lanes 2–3**), while form III increased. However, for pUC19 DNA the compound showed significantly higher cleaving ability [29].

3. Conclusions

We have attempted to study the DNA binding and cleavage ability of the newly synthesized discotic Phenanthridine derivative. The novel compound 2,3,6,7,10,11-hexabutoxy-5-methylnaphtho[1,2,3,4-*lmn*] phenanthridine was found to show hexagonal columnar phase over a wide range of temperature. The synthesized compound was found to have good DNA binding ability which was confirmed from the spectrophotometric study. Further, the cleavage studies confirm its excellent cleaving potential at two different concentrations. To the best of our knowledge, this report is the first account of the DNA binding ability of any discotic mesogen.

4. Experimental

All the chemicals and reagents were purchased from Sigma Aldrich, Himedia, and used directly. The AR grade solvents were distilled and dried using corresponding protocols before usage. The crude products were subjected to column chromatography using silica gel (100–200 mesh) and recrystallized using suitable solvents. Calf thymus DNA (CT–DNA) and supercoiled (SC) pUC19 DNA, were ordered from Sigma-Aldrich and were used as purchased from Bangalore Genei (India). Ethidium bromide and agarose (molecular biology grade) have been received from SD fine chemicals. Tris–HCl buffer solutions were formulated using double-distilled deionized water for binding and cleavage practices. All the intermediates and final products structure were confirmed by NMR, Mass, Elemental analysis. ^{1}H NMR and ^{13}C NMR (Nuclear magnetic resonance spectroscopy) were recorded on Bruker 500 MHz instrument using $CDCl_3$ as a solvent and trimethyl silane as an internal standard. Chemical shift values are given in ppm and the solvent $CDCl_3$ peaks appear at ^{1}H NMR: δ = 7.23 ppm and ^{13}C NMR δ = 77.0 ppm. Peak multiplicity is given as s = singlet, d = doublet, t = triplet, m = multiplet, b = broad peak. Mass spectra were recorded on a Micro Mass ESI-TOF spectrometer. Elemental analysis was done by using the Elementar Vario MICRO Select instrument. Samples were placed between the glass slides and kept inside Mettler FP82HT hot stage which is controlled by Mettler FP90 central processor and the liquid crystal textures were recorded using Olympus BX51 polarizing optical microscope (Olympus, Tokyo, Japan). Mettler Toledo DSC instrument was used to record the phase transition temperatures of all the compounds. The peak temperatures are given in °C and corresponding enthalpy values are given in J g^{-1}. Panalytical (Empyrean) X-ray diffractometer was used to further confirm the mesophase structure of all compounds. Absorption studies were carried out by Perkin Elmer UV–Vis-lambda 35 double-beam spectrophotometer.

*4.1. Experimental procedure for synthesis of 2,3,6,7,10,11-hexabutoxy-5-methylnaphtho[1,2,3,4-lmn]phenanthridine (**6**) [30]*

Compounds **1**,**2**,**3**,**4** and **5** were prepared as reported in the literature. [31,32] A mixture of compound 5 (1 eq) and acetaldehyde (2 eq) in dry DMF (10 ml) and 1% triflic acid were heated to 100 °C. The reaction was monitored using TLC. Water (20 ml) was added to the reaction mixture after completion of the reaction. The mixture was alkalized with 15% NaOH solution and extracted using dichloromethane and washed with brine. The organic layer was dried using anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by column chromatography using petroleum ether: ethyl acetate (90:10) as eluent to give yellow solid (60%).^{1}H NMR (500 MHz, CDCl3), δ (ppm) = 8.35 (s,1H), 8.16 (s, 1H), 7.98 (d,

2H), 4.43 (t, 2H, $J = 7$ Hz), 4.28–4.46 (m, 4H), 4.214 (t, 2H, 7 Hz) 3.34 (s, 3H), 1.61–1.69 (m, 12H), 1.52 (m, 12H), 1.05 (m, 18H). ^{13}C NMR (500 MHz, $CDCl_3$), δ (ppm) = 158.1, 151.4, 150.8, 149.9, 149.4, 145.6, 143.4, 136.3, 124.4, 124.1, 123.4, 123.2, 121.8, 119.4, 113.7, 110.1, 107.6, 106.9, 74.8, 74.3, 70.6, 69.5, 69.4, 69.1, 32.5, 32.3, 31.8, 31.4, 29.4, 19.5, 19.4, 19.3, 14.1, 14.05, 13.98; Cr 91.82 ($\Delta H = 12.47$ Jg^{-1}) Col_h 146.83($\Delta H = 6.67$ Jg^{-1})I; I 144.81 (($\Delta H = -6.48$ Jg^{-1}) Col_h. Elemental analysis calculated for $C_{44}H_{61}NO_6$: C, 74.63; H, 9.10; N, 2.07; found: C, 74.58; H, 9.08; N, 1.86 (expt.)

4.1.1. DNA interaction experiments

The concentration of CT-DNA dissolved in a buffer (5 mM tris (hydroxymethyl) aminomethane with 50 mM NaCl, pH 7.2,) [$C_{(p)}$] was measured at 260 nm (6600 M^{-1} cm^{-1}) using its extinction coefficient. [33] The absorption of CT-DNA was also evaluated at 260 nm (A_{260}) by 280 nm (A_{280}) to verify the purity level. The proportion of A_{260}/A_{280} was found to be in the range of 1.8 to 1.9, confirming the absence of protein with CT-DNA. The absorption titration test was performed using a range of DNA concentrations (0 to 100 μM) by keeping constant compound concentration (0.5 μM). The absorption spectrum was taken for every successive addition of DNA to 2, 3, 6, 7, 10, 11-hexabutoxy-5-methylnaphtho [1, 2, 3, 4-lmn] phenanthridine (**6**) and contrast (about 10 min). To achieve the constant of intrinsic attachment, K_b:

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

where ε_a, ε_f and ε_b are the apparent, free, and bound compound extinction coefficients, respectively. A plot of $[DNA]/(\varepsilon_a - \varepsilon_f)$ versus [DNA] gave a slope of $1/(\varepsilon_b - \varepsilon_f)$ and an intercept y equal to $1/K_b(\varepsilon_b - \varepsilon_f)$, where K_b is the ratio of the slope to the intercept y.

4.1.2. DNA cleavage experiments

For the gel electrophoresis analysis, supercoiled pUC19 DNA has been treated with compound **6**. The study was conducted in 2 ml quantity comprising pUC19 DNA of 5 μmol/l phosphate solution mixed with 10 μmol NaCl, pH 7.4, with distinct compounds level (25–50 μmol/l). The sample was mixed with 0.5 ml of 0.25% bromophenol yellow, 0.25% xylene cyanol FF, 30% glycerol, and the sample was then examined using 1% agarose electrophoresis by submerging the gel in Tris-borate buffer (1 μmol/l EDTA, 45 μmol/l Tris-borate) and running at 50 V for 2.5 h. The untreated pUC19 DNA was kept as parallel control. The gel was dyed with ethidium bromide (1 μg/ml) and then photographed under UV light. [34]

Declaration of Competing Interest

We declare that we don't have any conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2021.115798.

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