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Efficient nuclease activity of dinuclear iron(III) complex with ligand having carboxamido nitrogen donors

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ABSTRACT

A new dinucleating ligand N,N′-diphenyl-N,N′-di(pyridin-2-yl)oxalohydrazide ($GampH_2$) has been synthesized and $GampH_2$ gave rise to complex $[Fe_2(Gamp)(DMF)_2Cl_4]$, **1** with $FeCl_3$ salt and **1** was isolated as shiny blue crystalline solid. The molecular structure of complex **1** was characterized by X-ray crystallography. In this dinuclear complex, Fe–Fe separation was found to be 5.49 Å and variable temperature magnetic moment was examined. Electrochemical investigation afforded a quasireversible redox couple with $E_{1/2}$ value of 0.144 V vs Ag/AgCl. Complex **1** was efficient in DNA cleavage activity and enhancement of DNA cleavage was observed in the presence of 2-mercaptoethanol and hydrogen peroxide. Investigation of mechanism indicated possible involvement of hydroxyl radical in nuclease activity.

There has been considerable current interest in the studies on interaction of DNA with transition metal complexes because of their applications in the design and development of artificial nucleases, footprinting reagents, spectroscopic probes and chemotherapeutic agents which demand applications in medicinal chemistry and nucleic acid research [1–3]. Among the first row transition elements iron has got special interest due to its versatile coordination chemistry [4] and its redox properties [5]. In fact Fe-BLM causes DNA damage and it is clinically used for cancer treatment [6]. It is reported in the literature that deprotonated carboxamido nitrogen was bound to the iron center in Fe-BLM [7,8]. Therefore, the peptide bond (carboxamido nitrogen (N_{am})) linkage to metal center plays important role for inorganic as well as biological chemists because of their biomimetic and pharmaceutical relevances [9–13]. Indeed carboxamido nitrogen (N_{am}) is very important for several applications. Mascharak and co-workers reported the role of N_{am} for the coordination and photolability of NO [14]. Coordination chemistry of carboxamido nitrogen is also important for catalytic activity [15], prion protein research [16] and metal coordination in nitrile hydratase [17]. Recently, we have also communicated the role of carboxamido nitrogen in nuclease activity for manganese complexes [7]. We synthesized dinuclear iron complex with ligand having carboxamido nitrogen donors. It has been documented in the literature that dinuclear complexes exhibit higher nuclease activity compared to mononuclear complexes [18,19]. Recently, Peng et al. [20–22] reported dinuclear iron complexes derived from ligands containing phenolato donors and the complexes exhibited nuclease activity. In these reports the ligands were capable of binding more than one metal centers. On the other hand several dinuclear iron complexes were synthesized from bi, tri or tetradentate ligands and their DNA interaction studies were investigated [20–28]. However to the best of our knowledge there was no report on nuclease activity of dinuclear iron complexes with a dinucleating ligand having carboxamido nitrogen donor(s).

Herein we report the synthesis and characterization of a new dinucleating ligand ($GampH_2$) having two carboxamido nitrogen (N_{am}) donors (Scheme 1). Iron complex of $GampH_2$ was synthesized and molecular structure of the complex was determined by X-ray crystallography. Redox property was investigated. Nuclease activity and possible mechanism of DNA cleavage activity will be scrutinized in this report.

White solid of ligand ($GampH_2$) has been synthesized by refluxing 2-(1-phenylhydrazinyl)pyridine [29] (2 equiv.) with oxalyl chloride (1 equiv.) in dichloromethane, in the presence of the base triethylamine (5 equivalent) for 4 h. The ligand was characterized by IR, IR and NMR techniques and shown in supporting information (Fig. S1–S3). Reaction of deprotonated ligand (by sodium hydride) $GampH_2$ with $(Et_3N)[FeCl_4]$ salt (metal to ligand ratio 1:1) in dimethylformamide (DMF) and tetrahydrofuran (THF) solution afforded blue needle like crystals of complex **1**, $[Fe_2(Gamp)(DMF)_2Cl_4]$.

IR spectral studies of **1** shows $\nu_{C=O}$ stretching frequency at 1606 cm^{-1}. Coordination of deprotonated $Gamp^{2-}$ to iron metal center was observed by shifting of $\nu_{C=O}$ from 1674 cm^{-1} in free ligand to 1606 cm^{-1} in metal complex. The decrease in $\nu_{C=O}$ frequency in complex **1** clearly indicated that the binding of deprotonated ligand to the metal center and the decrease of $\nu_{C=O}$ were due to the generation of partial double bond character in carbonyl moiety after complex

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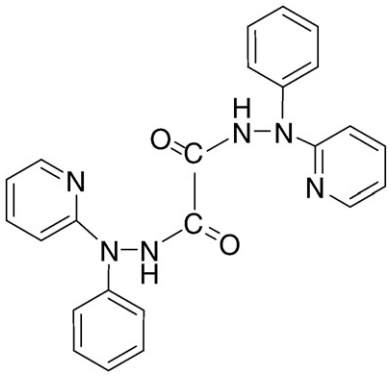

Scheme 1. Schematic representation of ligand $GampH_2$.

formation. Similar red shift of $\nu_{C=O}$ has been noted with other Fe(III) complexes with coordinated carboxamido nitrogens [30]. This result was further supported by disappearance of ν_{N-H} (3242 cm^{-1}) in complex **1**. UV–vis spectra of complex **1** was recorded in acetonitrile showing peak at 238 nm ($\varepsilon = 24{,}600\ M^{-1}\ cm^{-1}$) and shoulder at 270 nm ($\varepsilon = 21{,}330\ M^{-1}\ cm^{-1}$) which were assigned to be ligand based π–π*, n–π* transitions [29]. Small humps near 320 nm ($\varepsilon = 18{,}220\ M^{-1}\ cm^{-1}$) and 350 nm ($\varepsilon = 14{,}680\ M^{-1}\ cm^{-1}$) were due to charge-transfer transitions from the coordinated chloride to the metal center [31,32] and a broad band at 562 nm ($\varepsilon = 2346\ M^{-1}\ cm^{-1}$) was also assigned as ligand to Fe(III) charge transfer transition. The molar conductivity value (8.0 $\Lambda_m/\Omega^{-1}cm^2mol^{-1}$ in DMF) represents neutral or non-electrolytic behavior of complex **1** [33].

Molecular structure of dinuclear iron complex $[Fe_2(Gamp)(DMF)_2Cl_4]$ (**1**) depicted in Fig. 1. All the crystallographic parameters are tabulated in Table S1. Needle shaped blue crystals of **1** were obtained by slow evaporation of dimethylformamide:tetrahydrofuran (1:5) solution within a week. The X-ray crystal structure of **1** revealed that both the iron centers were octahedrally coordinated by two oxygen atoms from the carbonyl group (O_{ox}), two carboxamido nitrogens (N_{am}) and two pyridine nitrogens (N_{py}) from the ligand and the remaining terminal coordination site was occupied by four chloride and two solvent molecules. In complex **1**, Fe – N_{am}, Fe – N_{py} and Fe – O_{ox} bond lengths were 2.071(4) Å, 2.152(4) Å and 2.017(4) Å respectively and they are consistent with the values reported for Fe^{III} metal center by Wieghardt and coworkers [34]. The equatorial Fe – Cl1 bond length (*trans* to carboxamido nitrogen was 2.2691(14) Å), however, the axial Fe – Cl2 bond length was 2.3209(14) Å, which was longer than equatorial Fe – Cl1 distance. The short distance of Fe – Cl1 may be due to the *trans* effect of carboxamido nitrogen [35]. The Fe – O_{DMF} bond lengths was 2.112(4) Å which was quite large than reported literature value [36]. The bond lengths Fe – Cl, Fe – N and Fe – O were quite long which represented high-spin d^5 configuration of metal center [34,31]. The flexibility of the ligand was expressed by the small chelated bite angles between the carboxamido and pyridine nitrogen atoms, with 72.88(15)° for N1 – Fe1 – N2 as well as carboxamido nitrogen and oxygen from $-_{C=O}$ moiety with 78.41(15)° for N1 – Fe1 – O2. The angles between the chloride ligands and solvent molecule (dimethylformamide) were significantly larger than 90°, with values 94.81(5)° for Cl1 – Fe1 – Cl2, 103.83(11)° and 97.83(11)° for O2 – Fe1 – Cl1 and O2 – Fe1 – Cl2 respectively. These values expressed the distortion from octahedral geometry and consistent with reported literature values [31,32]. There are two types of non-covalent interactions observed in packing diagram of complex **1**. First, a hydrogen bonding between axial chlorine atom and pyridyl hydrogen atom (distance — 2.865 Å) and second, non-covalent interaction between aromatic hydrogen and carbon atom of dimethylformamide (distance — 2.857 Å) (Shown in supporting information (Fig. S7)). We would like to mention here that the bond distances observed after structure calculation were similar to the distances in high-spin Fe(III) complexes [34,31].

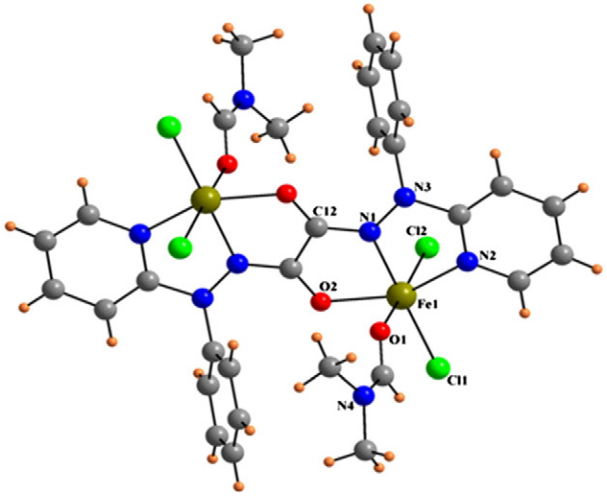

Fig. 1. Ball and stick representation of $[Fe_2(Gamp)(DMF)_2Cl_4]$ (**1**). Selected bond lengths (Å) and angles (°): Fe1 – N1 2.071(4), Fe1 – N2 2.152(4), Fe1 – O2 2.017(4), Fe1 – Cl1 2.2691(14), Fe1 – Cl2 2.3209(14), Fe1 – O1 2.112(4), N1 – Fe1 – N2 72.88(15), N1 – Fe1 – O2 78.41(15), N1 – Fe1 – O1 84.34(15), N1 – Fe1 – Cl1 174.68(12), N1 – Fe1 – Cl2 89.63(11), N2 – Fe1 – Cl1104.24(12), N2 – Fe1 – Cl2 88.60(11), Cl1 – Fe1 – Cl2 94.81(5), O1 – Fe1 – N1 84.34(15), O1 – Fe1 – N2 85.90(15), O1 – Fe1 – O2 84.81(15), O1 – Fe1 – Cl2 172.81(11), O1 – Fe1 – Cl1 91.03(11), O2 – Fe1 – Cl1 103.83(11), O2 – Fe1 – Cl2 97.83(11), O2 – Fe1 – N2 150.53(15).

Magnetic property of dinuclear iron (magnitude of the intermolecular Fe – Fe separation was 5.49 Å) complex **1** has been studied by SQUID magnetometer in the range 5–300 K at an external field of 5 T. The variable-temperature (5–300 K) magnetic susceptibility (χ_m) of complex **1** and plot of $\chi_m T$ vs T is shown in Fig. S8. The magnetic moment of complex **1** at 300 K was about 7.8 BM and as the temperature lowered magnetic moment decreases monotonically from 7.8 BM to 1.4 BM (at 5 K). This decrease at low temperature represented the spin of two ferric centers were weakly antiferromagnetically coupled [34,37].

The electrochemistry of the dinuclear complex was studied by cyclic voltammetry. The neutral uncomplexed ligand does not show any cyclic voltammogram over the range from −0.2 to 0.4 V; hence the curve shown here attributed to the redox activity of complex **1**. Cyclic voltammetry of the complex **1** was recorded in acetonitrile with TBAP as supporting electrolyte vs Ag/AgCl. Cyclic voltammogram of complex **1** showed a quasireversible peak and shown in Fig. 2. The $E_{1/2}$ value of Fe(III)/Fe(II) couple for complex **1** was 0.144 V vs Ag/AgCl.

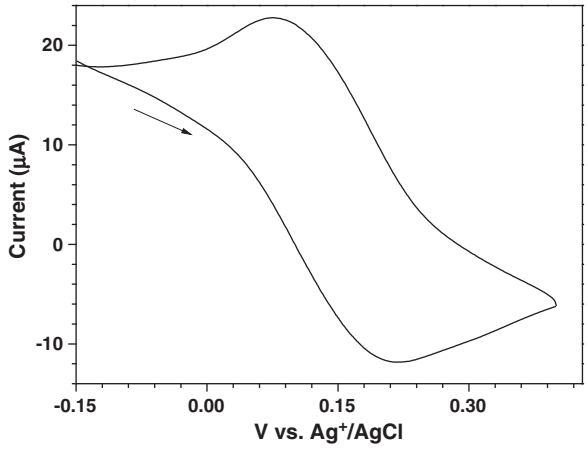

Fig. 2. Cyclic voltammogram of 10^{-3} M solution of complex **1** using working electrode: glassy-carbon, reference electrode: Ag/AgCl; auxiliary electrode: platinum wire, scan rate 0.1 V/s.

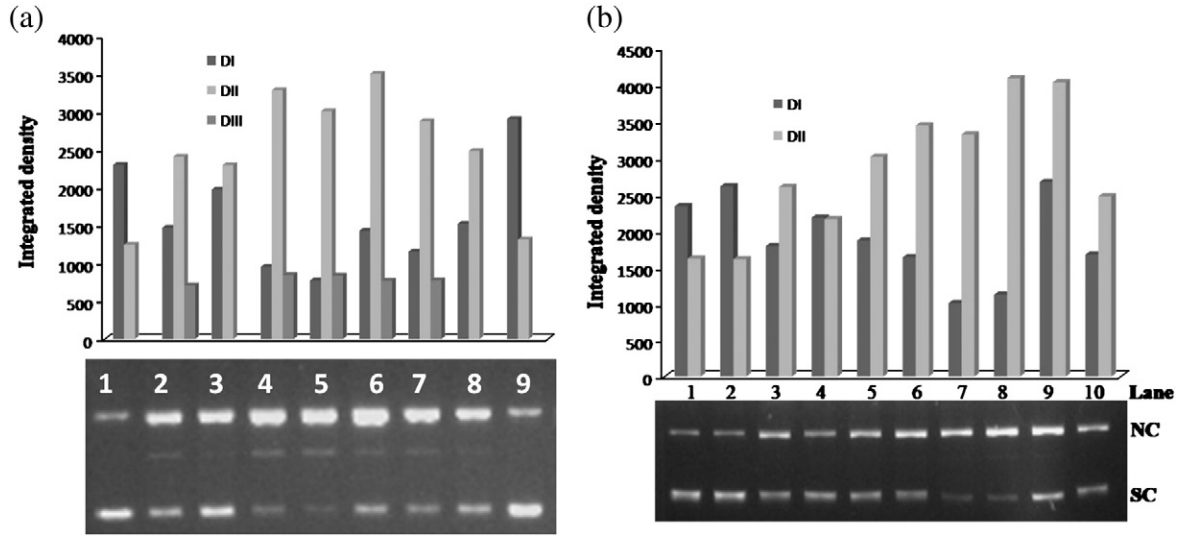

Fig. 3. Gel electrophoresis separations showing the cleavage of supercoiled *pBR322* DNA (60 ng) by complex **1** incubated at 37 °C for 3 h. (a) Key, lane 1: DNA, lanes 2–8: DNA + H_2O_2 (200 μM) + **1** = 10, 15, 30, 40, 50, 60, 70 μM respectively, lane 9: DNA + H_2O_2 (200 μM). (b) Key, lane 1: DNA, lane 2: DNA + **1** (50 μM), lane 3: DNA + **1** (100 μM), lanes 4–7: DNA + **1** (50 μM) + BME = 50, 100, 150, 200 μM respectively, lanes 8–9: DNA + BME (200 μM) + **1** = 10, 70 μM respectively, lane 10: DNA + BME (200 μM).

We have investigated the stability of our complex in phosphate buffer at pH 7.2 and the complex was observed in buffer solution by UV–vis spectral studies with repetitive scans for 5 h. It has been found out that the complex is generating new species in the phosphate buffer solution as the spectra obtained after 5 h are different to that of ligand. This is probably due to the coordination of H_2O molecule and/or dissociation of Cl^- ion. Electronic spectra for this study were furnished in the Fig. S6 in the supporting information. We were unable to find out the binding constant of the complex with calf thymus DNA (CT DNA) because we did not observe appreciable change in UV–vis spectra during our DNA titration experiment [29]. The DNA cleavage behavior of the complex **1** was studied under physiological conditions (37 °C) and observed by the transformation of the supercoiled form (SC) to the nicked (NC) and linear (LC) forms of plasmid DNA (60 ng) in Tris–boric acid–EDTA buffer. The nuclease activity of the complex **1** was examined by gel electrophoresis, which allowed quantitative evaluation of different forms of the DNA by plotting their integrated densities graphs [28]. The nuclease activity was performed in 10% acetonitrile solution and no cleavage was found in the presence of acetonitrile (Fig. S9, lane 6). Nuclease activities were performed in the absence as well as in the presence of reducing (BME) and oxidizing (H_2O_2) agents. Complex **1** alone cleaved *pBR322* plasmid DNA without any oxidizing or reducing agent at high concentrations (150–200 μM), however, no LC form was observed (Fig. S9, lanes 3–5). Gel electrophoresis experiment was investigated with the variation of incubation time in presence of complex also. The electrophoresis data afforded enhancement of nuclease with increase in incubation time (Fig. S9, lanes 8–10). Complex **1** efficiently cleaved DNA in the presence of H_2O_2 shown in Fig. 3(a). A 10–70 μM of complex is sufficient for production of LC form of DNA in the presence of 200 μM of H_2O_2 (Fig. 3(a), lanes 2–8). Complex **1** also exhibited DNA cleavage in the presence of BME with increasing amount of BME (50–200 μM) where integrated density of NC form started increasing with incubation time

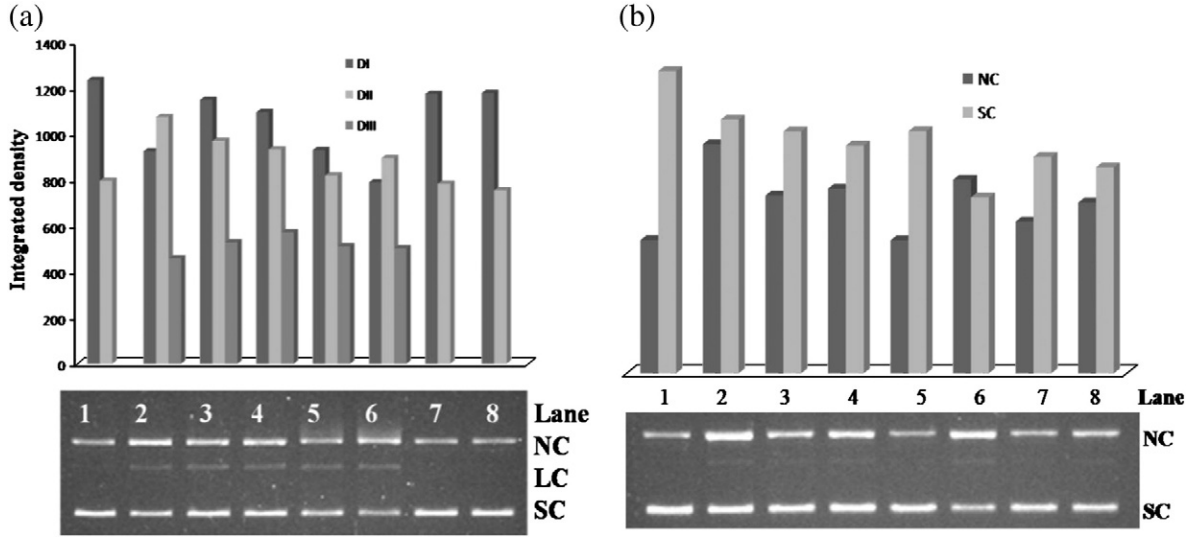

Fig. 4. Gel electrophoresis separations showing the cleavage of supercoiled *pBR322* DNA (60 ng) by complex **1** (50 μM) and H_2O_2 (200 μM) incubated at 37 °C for 3 h. (a) Key, lane 1: DNA, lane 2: DNA + **1** + H_2O_2, lanes 3–8: DNA + **1** + H_2O_2 + EtOH (20 mM), NaN_3 (20 mM), urea (20 mM), D_2O (20 mM), DMSO (20 mM), KI (20 mM) respectively. (b) Key, lane 1: DNA, lane 2: DNA + **1** + BME, lanes 3–8: DNA + **1** + BME + DMSO (20 mM), NaN_3 (20 mM), KI (20 mM), D_2O (20 mM), urea (20 mM), EtOH (20 mM) respectively.

(Fig. 3(b), lanes 4–7). In Fig. 3, it is clear that at high concentration of H_2O_2 and BME (200 μM) complex **1** showed efficient nuclease activity. In the control experiment, H_2O_2 and BME itself did not show DNA cleavage (Fig. 3). The nuclease activity at the lower concentration of the complex was not enough when only complex was utilized; however, the *enhancement* of the DNA cleavage activity with the addition of H_2O_2 and BME is important and integral part of this study. For example, the work reported by Borras and coworkers [37] described the nuclease activity by the complex only as well as the complex in the presence of H_2O_2/BME. The activity was found to be in the range 25–30 μM. Hence no enhancement was observed, however the activity for **1** in the presence of H_2O_2 and BME is similar to the work described by Borras and coworkers. In a recent report by Chakravarty and coworkers [38] Fig. 5 clearly showed the activity of the iron complex at a concentration of 30 μM. Of course our molecule is not efficient like the complexes described by Mandal and coworkers [39]. However to the best of our knowledge there was no report on nuclease activity of dinuclear iron complexes with a dinucleating ligand having carboxamido nitrogen donor(s).

Investigation of mechanism of DNA cleavage was performed in the presence of several quenchers eg. NaN_3 (singlet oxygen quencher), DMSO, urea, EtOH, KI and D_2O (hydroxyl radical quenchers) [7,29,33]. Addition of singlet oxygen quencher NaN_3 did not show any inhibition of DNA cleavage in the presence of oxidizing agent H_2O_2. Addition of D_2O significantly inhibited the cleavage of DNA in the presence of H_2O_2 which ruled out the possible role of singlet oxygen in cleavage pathway (Fig. 4(a)). However, hydroxyl radical scavengers such as DMSO and KI (Fig. 4(a), lanes 7, 8) inhibited the nuclease activity and hence hydroxyl radical was probably responsible for nuclease activity. Similar observation was made during the investigation of mechanism of nuclease activity in the presence of reducing agents BME (Fig. 4(b)). Moreover NaN_3 did not inhibit and D_2O did not enhance the nuclease activity of **1** in the presence of BME (Fig. 4(b)). These results indicated the involvement of hydroxyl radicals as the reactive oxygen species in the nuclease activity of complex **1** in the presence of H_2O_2 and BME [7,29]. For further confirmation of role of hydroxyl radical we tried to do rhodamine B Assay [40]. We cannot predict with confirmation with the data obtained from the assay, however we got some indication regarding the role of hydroxyl radical. There are two important points we would like to mention here. First, there was an increase in absorbance of 552 nm band of rhodamine B due to the addition of our complex **1** which indicated probable interaction of dye with metal complex. Second, we saw the decrease in the absorbance of 552 nm band similar to the data obtained by using iron salt and H_2O_2. These data support our observation during inhibition studies.

In conclusion, a novel dinuclear iron(III) complex was synthesized and spectroscopically characterized. Molecular structure of this complex was determined by X-ray crystallography. Redox property of the metal center was investigated and variable temperature magnetic moment measurement afforded weak antiferromagnetically coupled iron centers. The complex itself was efficient in cleaving DNA at high concentration, however, the efficiency was increased with the increase in incubation time. Moreover, we have found out the enhancement of nuclease activity in the presence of H_2O_2 as well as BME. Preliminary results on investigation of mechanism predicted possible role of hydroxyl radicals in DNA cleavage activities. Detail of the mechanism of such activity and biological applications are under progress.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.inoche.2012.02.042.

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