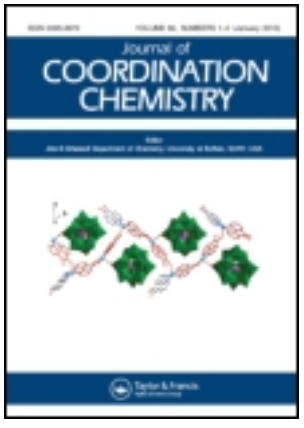

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Synthesis, crystal structure, interaction with DNA, and cytotoxicity in vitro of a new mixed ligand-nickel complex: $[Ni(DBMA)(en)(H_2O)_3]\cdot 3H_2O$

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Synthesis, crystal structure, interaction with DNA and cytotoxicity *in vitro* of a new mixed ligand-nickel complex: $[Ni(DBMA)(en)(H_2O)_3]\cdot 3H_2O$

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A mixed ligand-nickel complex of formula $[Ni(DBMA)(en)(H_2O)_3]\cdot 3H_2O$, where DBMA = 2,2-dibenzyl malonic acid, en = ethylenediamine, has been synthesized and characterized by elemental analysis, IR and single-crystal X-ray diffraction. The unit cell parameters for the complex are $a = 16.0214(16)$ Å, $b = 10.0801(10)$ Å, $c = 15.4024(15)$ Å, $\beta = 108.488(2)°$, $V = 2359.074(40)$ Å^3, $Z = 4$, space group *P2(1)/c*. The crystal system of the complex is monoclinic. Thermal stability of the water cluster by thermogravimetric analysis has been studied. Gel electrophoresis assay demonstrated the ability of the complex to cleave pBR322 plasmid DNA. The binding of the complex with HeLa cell DNA (HC-DNA) has been investigated by fluorescence spectra. Value of IC_{50} calculated for the complex shows that the complex exhibits good cytotoxicity against HeLa and KB cell lines.

Keywords: Nickel complex; X-ray analysis; Fluorescence spectra; Gel electrophoresis; Cytotoxicity *in vitro*

1. Introduction

Hydrogen bonding can be used to design and synthesize new materials. Frameworks based on transition metal complexes containing hydrogen bonding and water clusters with special properties attract attention in supramolecular chemistry and crystal engineering. Complexes with the same metal and ligand may form different structures because of different water clusters if the chemical environment is different [1–6].

Nickel is broadly used in nickel-cadmium batteries, steel industry, etc. Nickel is also an essential trace element with many biological effects. Nickel-containing enzymes include a rare bacterial class of superoxide dismutase and glyoxalase I enzymes in bacteria and several parasitic eukaryotic trypanosomal parasites (this enzyme in higher organisms, including yeast and mammals, uses divalent zinc, Zn^{2+}) [7–13]. Zhang [14], Guin [15] etc. demonstrated antimicrobial activity on the interaction with calf thymus DNA of Ni(II)

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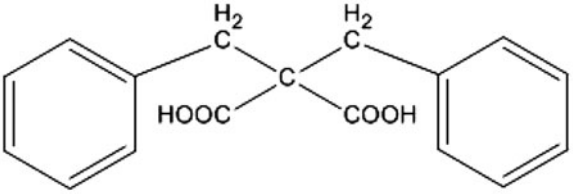
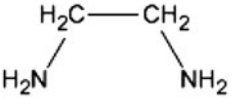
complexes. Manjunatha [16], Raman [17, 18] etc. synthesized a series of bivalent metal complexes and performed comparison experiments; the results provided Ni(II) with more effective antitumour activity.

Based on Ni(II), we synthesized $[Ni(DBMA)(en)(H_2O)_3]\cdot 3H_2O$ by DBMA (a) and en (b):



(a)



(b)

2. Experimental

2.1. *Materials*

All chemicals and reagents purchased were of reagent grade and used without purification unless otherwise noted.

2.2. *Physical measurements*

IR spectra were obtained as KBr disks on a Nicolet IR–470 spectrophotometer from 4000 to 400 cm^{-1}. Elemental analyses (C, H, and N) were performed on a Finnigan EA 1112 instrument.

2.3. *Syntheses of $[Ni(DBMA)(en)(H_2O)_3]\cdot 3H_2O$*

The complex was prepared as follows: an ethanol solution (10 mL) containing 0.15 mM of DBMA was added dropwise into 10 mL of a water solution containing 0.15 mM of $NiCl_2$ with stirring. The pH of the system was adjusted to 6.86 by addition of 0.1 M KOH (pH 1.0), after reacting 10 h at room temperature, then a 10 mL of water solution of en (0.15 mM) was added slowly and the mixture was allowed to react for 14 h at room temperature until the pH was constant at 7.34. After about 30 days, green transparent crystals were obtained, washed with ethanol, and dried in vacuum. The yield was 60%. For $C_{19}H_{34}N_2O_{10}Ni$ Anal. Calcd (%): C, 44.82; H, 6.73; N, 5.50. Found (%): C, 44.97; H, 6.68; N, 5.47. IR(neat) (cm^{-1}, *s*, strong; *m*, medium; *w*, weak): *v*(–O–H) 3332(*s*); *v*(–C–H) 3121(*m*); *v*(–C–H) 2957(*s*); *v*(C=O) 1590(*m*); *v*(C=C) 1418(*s*); δ(–C–H) 1379(*m*); *v*(–C–N) 1330(*m*).

Table 1. Crystallographic data, details of the experiment and refinement of the complex.

Parameter	Value
CCDC deposit no	875534
Empirical formula	$C_{19}H_{34}N_2O_{10}Ni$
Formula weight (g/M)	509.19
Crystal system, space group	Monoclinic, *P2(1)/c*
a (Å)	16.0214(16)
b (Å)	10.0801(10)
c (Å)	15.4024(15)
β (°)	108.488(2)
V (Å^3)	2359.1(4)
Z	4
θ range for data collection (°)	$2.42 < \theta < 26.02$
Crystal size	$0.12 \times 0.10 \times 0.08$ mm
Limiting indices	$-19 \leqslant h \leqslant 19$, $-9 \leqslant k \leqslant 12$, $-15 \leqslant l \leqslant 18$
Reflections collected/unique, $I > 2\sigma(I)$	12467/4631 ($R_{int} = 0.0186$)
Completeness (%)	99.6
Goodness-of-fit on F^2	1.031
F (000)	1080.0
Absorption coefficient (mm^{-1})	0.877
Final *R* indices ($I > 2\sigma(I)$)	$R_1 = 0.0300$, $wR_2 = 0.0786$
R indices (all data)	$R_1 = 0.0357$, $wR_2 = 0.0821$
Largest diffraction peak and hole (e Å^{-3})	0.34 and −0.25

Table 2. Selected bond lengths and angles in the complex.

Bond	*d* (Å)	Bond	*d* (Å)
Ni(1)–O(6)	2.0643(14)	Ni(1)–N(2)	2.0783(16)
Ni(1)–O(1)	2.0869(12)	Ni(1)–O(5)	2.0957(13)
Ni(1)–N(1)	2.0996(17)	Ni(1)–O(7)	2.1034(12)
Angle	***ω*** **(°)**	**Angle**	***ω*** **(°)**
O(6)–Ni(1)–N(2)	94.46(7)	O(6)–Ni(1)–O(1)	86.03(6)
N(2)–Ni(1)–O(1)	87.80(6)	O(6)–Ni(1)–O(5)	91.47(6)
N(2)–Ni(1)–O(5)	174.07(6)	O(1)–Ni(1)–O(5)	92.62(5)
O(6)–Ni(1)–N(1)	176.12(7)	N(2)–Ni(1)–N(1)	82.67(7)
O(1)–Ni(1)–N(1)	91.25(6)	O(5)–Ni(1)–N(1)	91.41(6)
O(6)–Ni(1)–O(7)	87.12(6)	N(2)–Ni(1)–O(7)	94.55(6)
O(1)–Ni(1)–O(7)	172.91(5)	O(5)–Ni(1)–O(7)	85.74(5)
N(1)–Ni(1)–O(7)	95.68(6)	C(18)–N(1)–Ni(1)	108.73(13)
C(19)–N(2)–Ni(1)	107.09(13)	C(17)–O(1)–Ni(1)	128.27(11)

2.4. *X-ray structure determination*

The crystal structure of the complex was determined by singe-crystal X-ray diffraction. A suitable single crystal was mounted in a glass fiber capillary. Data were collected on a Bruker Smart 1000 CCD X-ray single-crystal diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at 293(2) K with the *ω* scan technique. The structure was solved by direct methods and refined by full-matrix least squares procedures with SHELXTL-97 [19–21]. A summary of the crystallographic data and structural parameters are listed in table 1. Selected bond lengths (Å) and angles (°) are shown in table 2. The geometrical parameters of hydrogen bonds for water clusters are shown in table 3.

Table 3. Geometrical parameters of hydrogen bonds (D–H···A) for water clusters in the complex (D for donor, A for acceptor).

Names	Lengths (H···A) (Å)	Lengths (D–H···A) (Å)	Angles (D–H···A) (°)
O7–H7OA···O5	2.00	2.808(2)	167
O2W–H2WB···O7	2.07(3)	2.900(2)	163(3)
O2W–H2WA···O3	2.02(3)	2.750(2)	176(4)
O7–H7OB···O4	1.76(3)	2.5793(19)	172(3)
O3W–H3WB···O3	2.02(3)	2.859(2)	164(3)
O5–H5A···O3W	1.90	2.714(2)	170
O5–H5B···O2	1.86(3)	2.6389(19)	166(3)
O3W–H3WA···O1W	2.09(3)	2.850(3)	161(3)
O6–H6B···O2W	1.95(3)	2.708(2)	176(3)
O1W–H1WB···O3	2.30(3)	2.948(2)	152(3)
O1W–H1WA···O2	1.96(3)	2.802(2)	171(3)

Supplementary material for the structure has been deposited with the Cambridge Crystallographic Data Center (No. 875534; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

2.5. *Thermogravimetric analysis*

The thermal stability of the water cluster by thermogravimetric analysis (TGA) has also been studied. The TGA result of the complex is provided in Supplementary material.

2.6. *Agarose gel electrophoresis*

The complex as a DNA cleavage agent was examined using supercoiled pBR322 plasmid DNA as the target. The efficiency of cleavage was probed using agarose gel electrophoresis [22–24]. For the gel electrophoresis experiment, pBR322 plasmid DNA (0.5 mg/mL) was treated with the complex (dissolved in DMF) in Tris buffer (50 mM Tris-acetate, 18 mM NaCl buffer, pH 7.2) and the content was incubated for 1 h at room temperature. The sample was electrophoresed for 1 h at 120 V on 0.8% agarose gel in Tris-acetate buffer. After electrophoresis, the gel was stained with 1 mg/mL ethidium bromide and photographed under UV light [25, 26].

2.7. *Fluorescence spectra*

EtBr (ethidium bromide) is a conjugated planar molecule. Its fluorescence intensity is very weak, but it is greatly increased when EtBr is specifically intercalated into the base pairs of double-stranded DNA [25, 27]. Enhanced fluorescence can be quenched, at least partially, by addition of a second molecule [28, 29] which could compete with EtBr to bind with DNA. This is proof that the complexes intercalate to DNA base pairs [30–32]. The quenching extent of fluorescence of EtBr-DNA is used to determine the extent of binding between the complex and DNA. The emission spectrum of EtBr bound to DNA in absence and presence of the complex is given in figure 1. The addition of the complex to DNA pretreated with EtBr caused appreciable reduction in the emission intensity, indicating the replacement of EtBr by the complex [33].

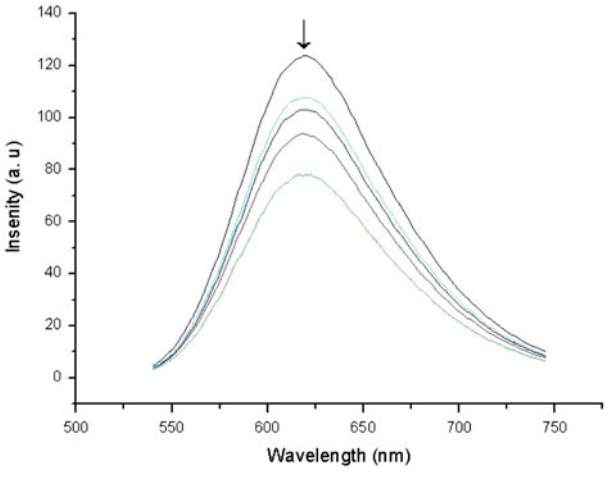


Figure 1. Emission spectrum of EtBr bound to DNA in the presence of the complex ([EtBr] = 1.0 mM, [DNA] = 5.0 mM, [complex] = 0–37.5 mM, λ_{ex} = 526 nm). The arrow shows the intensity changes on increasing the complex concentration.

2.8. *Cytotoxicity* in vitro *study*

The cytotoxicity of the complex was investigated on HeLa and KB cells. The cell lines were grown in 25 cm^2 tissue culture flasks in an incubator at 37 °C in a humidified atmosphere consisting of 5% CO_2 and 95% air. The cells were maintained in logarithmic growth phase in complete medium consisting of RPMI 1640, 10% (v/v) heat-inactivated fetal calf serum, 20 mM Hepes, 0.112% $NaHCO_3$, and 2 mM glutamine. Cell viability was assessed by the microculture tetrazollium [3, 4] assay [34, 35]. In brief, cells were seeded into a 96-well culture plate at 2×10^5 cells/well in a 100 mL culture medium. After incubation for 24 h, cells were exposed to the tested complex of serial concentrations. The complex was dissolved in DMF and diluted with RPMI 1640 or DMEM (dulbecco's modified eagle medium) to the required concentrations prior to use (0.1% DMF final concentration). The cells were incubated for 72 h, followed by addition of 20 mL MTT solution (5 mg/mL) to each well and further cultivated for 4 h. The media with MTT were removed and 100 mL of DMSO was added to dissolve formazan crystals at room temperature for 30 min. The absorbance of each cell at 450 nm was determined by analysis with a microplate spectrophotometer. The IC_{50} values were obtained from the results of quadruplicate determinations of at least three independent experiments.

In another trial the effect on cell growth for the complex was studied by culturing the cells in medium alone for 24 h, followed by 72 h treatment with 3 mg/mL concentrations. The viable cells remaining at the end of the treatment period were determined by MTT

Table 4. Cytotoxicity of the complex against selected human tumor cells after 72 h of incubation.

	IC_{50}/μM	
Test complex	HeLa	KB
Complex	8 ± 1	6 ± 1

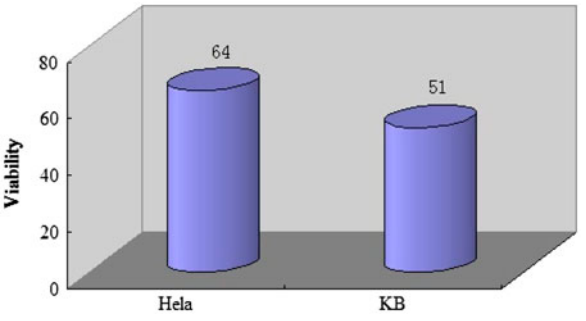


Figure 2. Effect of 3.0 mg/mL of the complex on selected human tumor cells viability after 72 h of incubation. All determinations are expressed as percentage of the control (untreated cells).

assay and calculated as percentage of control, treated with vehicle alone (DMSO) under similar conditions.

The IC_{50} values of the complex are shown in table 4. The cytotoxicity results are depicted in figure 2.

3. Results and discussion

3.1. *X-ray determination*

The crystal structure of the complex was determined by X-ray crystallography as shown in figure 3. In the asymmetric unit of the complex, there are one Ni, one DBMA, three waters, and one en (figure 3). Ni is six-coordinate through coordination to four oxygens [O(1), O(5), O(6), O(7)] of one carboxylate from DBMA, three waters and two nitrogens [N(1), N(2)] of one chelating en. The coordination angles around Ni are 82.67°–176.12°. There are also three free waters in each asymmetric unit of the complex that hydrogen bond [36].

The complex is self-assembled from 1-D zigzag polymeric coordination chains formed by hydrogen bonding (the distances are 2.5793(19)–2.948(2) Å) (figure 4). The 2-D plane

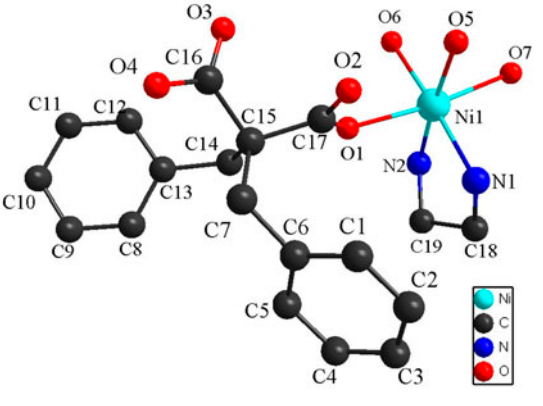


Figure 3. ORTEP representation (50% probability) of the complex; some atoms are omitted for clarity.

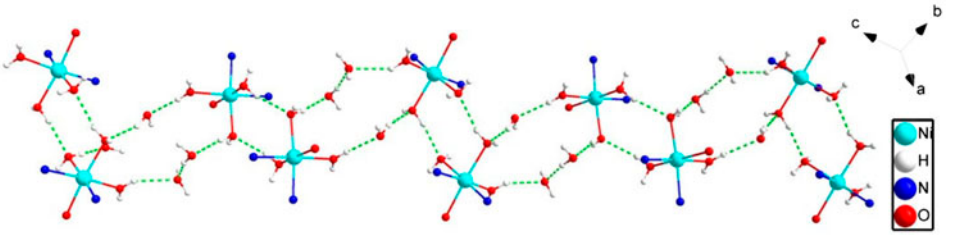


Figure 4. 1-D chain structure formed by hydrogen bonding; some atoms are omitted for clarity.

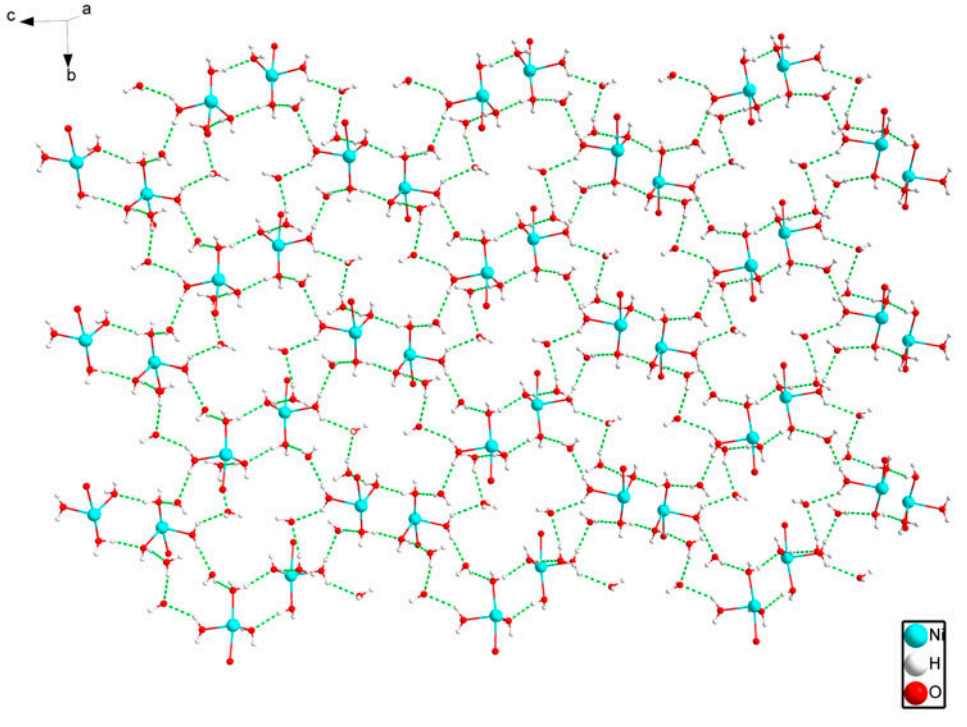


Figure 5. 2-D planar structure formed by hydrogen bonding; some atoms are omitted for clarity.

formed by hydrogen bonding (the distances are 2.5793(19)–2.948(2) Å) (figure 5) is further extended to the 3D structure. All hydrogen bonds are within the normal range [36].

3.2. *Thermogravimetric analysis*

TGA shows that the complex loses solvated water below 90 °C, with 10.91% weight loss (Calcd 10.61%). The remaining water was lost at 180–270 °C, 10.44% weight loss, consistent with that calculated (10.61%). With the temperature increase from 270 to 500 °C, a total of 67.84% was lost, which corresponds to removal of the organic species (Calcd 78.00%). Only 10.81% of the total weight was NiO remaining.

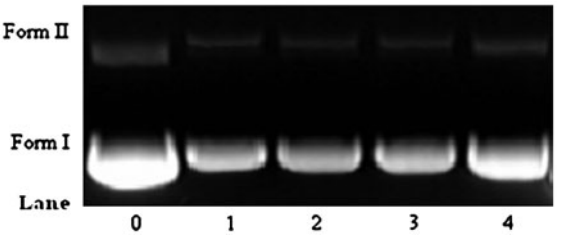


Figure 6. Cleavage of pBR322 DNA (0.5 mg/mL) in the presence of the complex: Lane 0, DNA alone; (Lanes 1–4) at different concentrations of complex: (1) 5 mM; (2) 2.5 mM; (3) 1.25 mM; (4) 0.625 mM.

3.3. *Agarose gel electrophoresis*

When circular plasmid DNA is studied by electrophoresis, the fastest migration will be observed for the supercoiled form (Form I). If one strand is cleaved, the supercoils relax to produce a slower-moving nicked circular form (Form II). The complex cleaved both the supercoiled Form (I) and the nicked Form (II) of pBR322 plasmid DNA (figure 6). A little DNA-cleavage was observed for the control in which metal complex was absent (Lane 0). The complex cleaves plasmid DNA at 0.625 mM. With increasing concentration of the complex (Lanes 1–4), the amount of Form I and Form II of pBR322 DNA decreased gradually, but both Form I and Form II of all lanes (Lanes 1–4) are less than Lane 0. The capability of cleavage of pBR322 DNA by the complex indicates efficient DNA-cleavage. Similar observations have been reported for other complexes [37–42].

3.4. *Fluorescence spectra study*

The emission spectra of EtBr bound to DNA in absence and presence of the complex are given in figure 1. Addition of the complex to DNA pretreated with EtBr causes appreciable reduction in the emission intensity, indicating replacement of EtBr by the complex [33, 43], indicating the complex binds to DNA by intercalation. This is quite different from the binding of Pt(II) complexes with DNA, which is linked by N7 of adjacent purine bases of DNA and form intrastrand cross-links [44–46].

3.5. *Cytotoxicity* in vitro *study*

In vitro cytotoxic studies show that the complex exhibits higher cytotoxic activity against KB cell lines than HeLa cell lines. IC_{50} calculated for the complex shows that the complex exhibits good cytotoxicity against HeLa and KB cell lines.

4. Conclusion

A nickel complex has been synthesized and characterized. The crystal structure of the complex was determined by single crystal X-ray diffraction. TGA shows that every complex unit contains three solvated waters and three coordinated waters. The DNA binding properties of the complex were examined by fluorescence spectra. The results support the fact that the complex binds to DNA by intercalation. The capability of cleavage of

pBR322 DNA by the complex was investigated by agarose gel electrophoresis; the results indicate that the complex exhibits efficient DNA-cleavage. IC_{50} calculated for the complex shows that the complex exhibits good cytotoxicity against HeLa and KB cell lines.

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