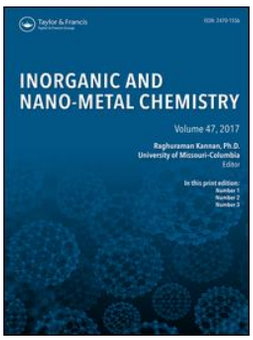

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Synthesis, catalysis, antimicrobial activity, and DNA interactions of new Cu(II)-Schiff base complexes

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ABSTRACT

Structural features and catalytic activities of five ternary copper (II)-Schiff base complexes are investigated. The ligands are derived from 3-methoxysalicylaldehyde (MS) or 4-diethylaminosalicylaldehyde (DS) and amino acids {L-phenylalanine (Phe), L histidine (His) or DL-tryptophan (Trp)}, as primary ligands, and 2,4′-bipyridyl (DP) as a secondary ligand. Cu(II)-complexes are characterized by various physicochemical tools. The catalytic efficiency of Cu(II)-complexes is studied in the oxidation of benzyl alcohol by an aqueous H_2O_2 in different reaction conditions. Temperature and catalyst features are involved in order to obtain the optimized catalytic oxidation conditions of benzaldehyde production. The Schiff base ligands and their ternary complexes are screened for their antimicrobial activities in various types of fungi and bacteria. The interaction between Cu(II)-complexes and (CT-DNA) was examined by employing various techniques, including viscosity, spectral and gel electrophoreses studies.

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KEYWORDS
Amino acid Schiff bases; benzyl alcohol; biological activities; catalytic oxidation; copper (II)

Introduction

Most attentions have been considered for the synthesis of *d*-block elements complexes with Schiff bases deduced from amino acids because of their high biological performances.[1–3] Salicylediene-Schiff base amino acid complexes are displayed as non-enzymes for the metal-pyridoxal derivatives as Vitamin B6, which are key intermediates in various metabolic reactions of amino acids derivatives catalyzed by enzymes. Moreover, Schiff base complexes deduced from amino acids are considered to construct a new type of potential antibacterial and anticancer reagents,[4] anti-inflammatory,[5] DNA cleavage,[2,6–8] antipyretic,[5,9] crystal engineering,[10] as well as, anti-corrosion agent.[11,12]

Copper (II) complexes have been well reported as effective catalysts for the regio- and chemoselective oxidation of alcohols to the corresponding aldehydes or ketones,[13–16] due to their easily synthesis, handling and interesting structural features.[17,18] Performance of copper-catalyzed oxidation processes with most environmentally friendly oxidants, that is, H_2O_2, is particularly of interest [19,20] in both academic fields and industry.[21,22] Stability, solubility, ligand steric hindrance and the redox properties of the copper catalyst could be easily adjusted by the linked organic ligands.[23–25]

Binding study of transition metal complexes with DNA have received considerable attention due to their prominence in chemotherapy, purposing of new classes of pharmaceutical molecules and molecular biology.[26,27] There have been several reports on Cu(II) Schiff bases complexes having various applications in catalysis, dye and food industry. Mixed ligand complexes were also found to show potent anti-bacterial, anti-fungal, anti-viral, antitumor, catalytic epoxidation activity, and DNA binding activity.[7,8,28] Recently, there has been a concern about the increase in the incidence of systemic fungal infections, which are potentially life-threatening.[29] Thus, designing and development of more effective antifungal agents are essential and the individual Schiff bases are considered to be effective antifungal medicines.[30]

From our research interest, the synthetic route and characterization of five ternary Cu(II) Schiff base complexes by complexation of Cu(II) ions with derived Schiff base ligands of amino acids and with 2,4′-bipyridyl, as secondary ligands, are presented and studied. The catalytic potential of Cu(II)-complexes was screened in the oxidation of benzyl alcohol in the presence of an external oxidant, that is, an aqueous H_2O_2, in various reaction conditions in order to present the efficiency of the organic nature of the ligands on the catalytic potential of Cu(II) ions and to describe proposed mechanistic pathway. Antimicrobial activities of the investigated ternary complexes are assessed to various types of bacteria and fungi. The Cu(II)-complex reactivity towards DNA is screened utilizing spectral investigations, viscosity and gel electrophoresis.

Experimental

Materials and measurements

All chemicals and reagents used in the synthesis of the ternary Cu(II)-complexes, 3-methoxysalicylaldehyde (MS),

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4-diethylaminosalicylaldehyde (DS), amino acids {L-Phenylalanine (Phe), DL-Tryptophan (Trp), L-Histidine (His)}, 2,4′-bipyridyl (DP), ethanol, dimethylformamide (DMF), copper acetate monohydrate, an aqueous H_2O_2 (30%), benzyl alcohol, and organic solvents were employed directly from commercial suppliers (Sigma-Aldrich, Acrös and Fluka) without any further purification or treatment.

IR spectra were registered by an apparatus of Shimadzu FT-IR model 8101 spectrometer using KBr pellets from 4000 to 400 cm^{-1}. Elemental analyses were measured using a CHNS-932 analyzer from LECO using standard conditions in Micro-Analytical Center at Cairo University. UV-Vis. spectra were measured on a PG spectrophotometer model T + 80 at 25 °C using 10 mm silica cells in the thermostatted cell holder. The thermostatted cell holder was supplied by an ultrathermostat water circulator (HAAKE Model F3-k). The TG/DT analyses were recorded on Shimadzu corporations TGA-60H thermal analyzer in dynamic nitrogen atmosphere (20 cm^3 min^{-1}) with heating rate 10 degrees min^{-1} from ambient temperature to 750 °C. Melting points were obtained by a Thermo Scientific 9100 apparatus. Magnetic susceptibility measurements of the metal complexes were done on a Gouy's balance at room temperature using $Hg[Co(SCN)_4]$ as a calibrant. Molar conductance was measured on an Elico CM-180 conductometer at 25 °C using DMF as a solvent. A HANNA 211 pH meter at 298 K equipped with a CL-51B joined electrode was used for pH measurements, calibrated against standard buffers (pH 4.02 and 9.18) before measurements. To investigate the 3D structure and molecular stability for the DSHDPCu complex, exact density functional theory (DFT) calculations were achieved using Gaussian 03 software package.[31] Calculations were carried out at DFT level of theory with pseudo potential functions, 6-311G (p,d) [32] basis set for ligand atoms, and LANL2DZ [33] basis set with effective core potential (ECP) for Cu^{2+} ion.

Synthesis of ternary Cu(II)-complexes

The ternary Cu(II) Schiff base complexes were synthesized by a common procedure as reported elsewhere for the binary ones.[24] In a general procedure, at room temperature in 40 mL of mixed aqueous-methanolic solution (1:1), amino acid (5 mmol, 0.83 g, 1.05 g, or 1.02 g of Phe, Trp, or His, respectively) was dissolved and then mixed with 50 mL of warm ethanolic solution of MS (5 mmol, 0.76 g) or DS (5 mmol, 0.99 g). The mixture was kept with stirring at 70 °C for 1 h and then treated with 40 mL of an aqueous solution (5 mmol, 1.00 g) of copper acetate monohydrate. The resulted reaction mixture was stirred at 70 °C for 3 h. An ethanolic solution (5 mmol, 0.79 g, 25 mL) of 2,4′-bipyridyl (DP) was added dropwisely to the reaction mixture with further stirring at 70 °C for 2 h. The product was extracted by solvent evaporation in vacuum. The residual was washed with water, ether and dried in oven. The final ternary complex was recrystallized in methanol.[28,34]

Catalytic procedures

Benzyl alcohol (0.13 mL, 1.0 mmol) was injected to a solution of Cu(II)-complexes (0.02 mmol) contacted to air in acetonitrile, as organic solvent (10 mL), at 50, 60, 80, or 90 °C in an oil bath with continuous stirring. The reaction was fed with an aqueous H_2O_2 (0.1 mL, 3 mmol, 30%) at the given temperature. The reaction was monitored by GC analyses, charged with computerized standard calibration curve. By comparing the retention times of the resulted oxidation product with the authentic samples, the products could be identified. Control reactions were carried out by withdrawing samples (ca. 0.2 mL) of the reaction mixture at the typical time. The taken samples were treated with MnO_2 (20 mg) to quench the excess H_2O_2 and with anhydrous sodium sulfate (20 mg) to absorb water, under the typical conditions in the catalytic runs. The resulting slurry was filtered on celite, and the filtrate was injected in the Gas Chromatography. This allowed independent measurements for each sample. The conversion of benzyl alcohol to benzaldehyde and/or benzoic acid was determined by the computerized standard calibration curves.[24]

Gas chromatography is computerized Agilent 5890A 19091J-413: 325 °C equipped with a flame ionization detector and a HP-5 capillary column (phenyl methyl siloxan 30 m × 320 µm × 0.25 µm). The temperature of injection was 250 °C. The initial temperature was 140 °C for 1 min, and then increased 10 °C per min to 250 °C, and held for 1 min at this temperature. Helium is the carrier gas (purity is 99.999%). All the catalytic processes were run at least in duplicate.

Antimicrobial evaluation

Two different concentrations (15 and 30 mg/mL) of each studied Cu(II)-complex in dimethylsulfoxide (DMSO) are displayed no antimicrobial activity versus any of the tested organisms. Ciprofloxacin and amphotricine B were employed as standards for antibacterial and antifungal activity, respectively.

Antibacterial bioassay

The agar well diffusion method in vitro was used to assess the antibacterial activity of the current Cu-complexes *versus* two Gram-positive (*Bacillus subtilis* and *Micrococcus luteus*) and one Gram-negative (*Escherichia coli)* bacterial strains. The tested organisms were mature on nutrient agar medium in petri plates. Molten nutrient agar was kept at 45 °C and saturated into the petri-dishes, allowing solidifying. After that, holes of 6 mm diameter were formed in the agar and these holes were completely stuffed with the test solutions of Cu-complexes. The plates were incubated for 24 h at 37 °C.[34]

Antifungal bioassay

The disk diffusion method was used to evaluate antifungal activity of all prepared Schiff base amino acid ligands and their corresponding ternary complexes contrast to three fungal cultures (*Asperagillus niger*, *Candida glabrata*, and

Saccharomyces cerevisiae). The tested fungi were vaccinated in Sbouraud dextrose broth medium and incubated for 48–72 h at 35 °C. The discs measuring 6 mm in diameter was synthesized from Whatman No.1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs soaked before in defined concentration of Cu(II)-complexes were put in Sabouraud dextrose Agar Plates. The dishes were inverted and incubated at 35 °C for 7 days.[35]

Reactivity of Cu-complexes towards calf thymus DNA (CT-DNA)

Electronic spectra detection of the reactivity

Absorption titrations were executed by the maintenance of the concentration of the complex constant and by various concentrations of CT-DNA from 3 to 30 µM. Interaction of Cu(II)-complexes with DNA was taken place in tris-HCl buffer (10 µM, pH 7.2). The Tris-HCl buffer solution used to control pH of the titration media. DNA purity was investigated by surveillance the ratio of the absorbance at 260 and 280 nm, indicating that the DNA was adequately free from protein contamination.[36] The formation constant K_b for the binding of Cu(II)-complexes with DNA, were specified from the spectroscopic titration values using Eq. 1:

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

where, [DNA] is the concentration per nucleotide, ε_a is the apparent extinction coefficient obtained by the ratio of A_{obs}/[complex]. The ε_f is the extinction coefficient of Cu(II)-complex in the presence of DNA and ε_b is the extinction coefficient for the ternary complexes in the fully bound form. The data were qualified to the above equation with a slope equal to $1/(\varepsilon_b - \varepsilon_f)$ and intercept equal to $1/[K_b(\varepsilon_b - \varepsilon_f)]$ and K_b was derived from the plot $[DNA]/(\varepsilon_a - \varepsilon_f)$ *contra* [DNA] slope and intercept. The criterion Gibbs free energy for DNA binding was derived from Eq. 2.

$$\Delta G_b^o = -RTlnK_b \quad (2)$$

where R and T are well known, the general gas constant and the absolute temperature and K_b is the binding constant.

Viscosity menstruations detection of the reactivity

Viscosity titration experiments carried out with different concentrations of Cu(II)-complexes at constant CT-DNA concentration (250 µM). Flow time was specified with a digital stopwatch. Each sample was measured at least three times and median flow time was enumerated. Data were presented as $(\eta/\eta^o)^{1/3}$ *vs* binding ratio ([complex]/[DNA]),[37] where η was the viscosity value for DNA in presence of the ternary complex and η^o was the viscosity value of CT-DNA alone.

Agarose gel electrophoresis detection of the reactivity

With the gel electrophoresis probe, a solution of Cu(II)-complex in DMF was added to the CT-DNA sample and incubated for 30 min at 37 °C. 1% agarose gel was prepared in TBE buffer (45 µM tris, 45 µM boric acid and 1 µM EDTA, pH is 7.3), the solidified gel was putted in electrophoresis chamber flooded with TBE buffer. After that, 20 microns of each of the incubated complex-DNA mixtures (mixed with bromophenol blue dye) were loaded on the gel and electrophoresis was accomplished under TBE buffer system at 100 V for 2 h. At the end of electrophoresis, that is, the end of DNA movement, the electric current was turned off. The gel was visualized under UV light using a transilluminator and snapshotted with a Panasonic DMC-LZ5 Lumix Digital Camera.[38]

Results and discussion

Synthesis and characterization of Cu(II)-complexes

The condensation of amino acid with salicylaldehyde (1:1) in an aqueous-ethanolic mixture is well known for the formation of salicylediene-amino acid Schiff base ligands. An aqueous solution of copper acetate (1:1) was added to the synthesized ligand followed by addition of 2,4′-bipyridyl as a secondary ligand in an ethanolic solution (1:1) to afford ternary Cu(II)-Schiff base salicylediene-amino acid complexes with a general formula $[Cu(HL)(DP)(H_2O)(CH_3COO)].nH_2O$ where HL is the Schiff base salicylediene-amino acid ligands and DP is 2,4′-bipyridyl. Cu(II)-complexes are characterized by CHN microanalyses (EA), conductivity measurements and magnetic susceptibility (Table 1). IR spectra, UV-Vis spectra and thermogravimetric analysis (TGA) (Table 2) of the studied complexes are also reported. The CHN microanalyses' values of all complexes agree (±0.2%) with the expected suggested structure of the investigated complexes (Table 1).

The conductivity measurements carried out in DMF and gave very low data, as recorded in Table 1. The results demonstrate that all ternary Cu(II)-complexes are non-electrolytic, as observed for the previously reported corresponding binary Cu(II)-complexes.[28,34] Magnetic susceptibility measurements (Table 1) of the ternary Cu(II)-complexes suggest an octahedral geometrical structure.[28,34] The coordination of the octahedral structure is completed with water molecules and an acetate anion with presence of crystalline water molecules (Scheme 1). All complexes (MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, and DSHDPCu) are para-magnetic. Unfortunately, all trials to confirm the molecular structure of the Cu-complexes by X-ray single-crystal analysis were unsuccessful. The synthesized complexes are insoluble in water and poorly soluble in ethanol and methanol. They are soluble in DMF and DMSO.

The IR spectra of the coordinated ligands and the corresponding ternary Cu-complexes (Table S1 in the supplementary materials). The IR spectral results of the free ligands display broad bands around 3441–3389 cm^{-1} due to the vibrational band of the hydroxyl-phenolic group, with the presence of intramolecular hydrogen bonding between phenolic hydrogen and the azomethine group nitrogen.[24] IR spectral data supported the mode of complexation of the studied complexes. In particular, the presence of the -OH phenolic group bands around 3574–3403 cm^{-1} with an observable intense of the bands elucidates that the oxygen of

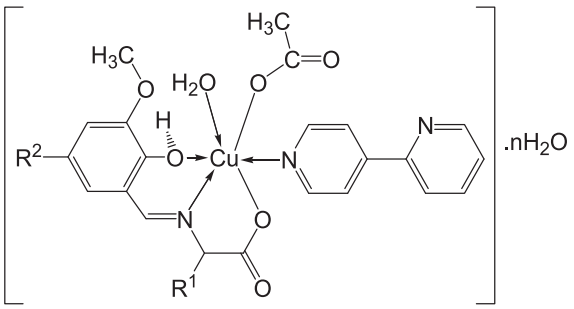
Table 1. Physico-chemical characteristic data of the ligands and their ternary Cu(II)-complexes.

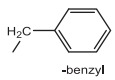
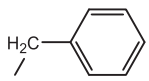
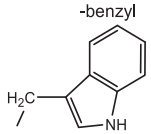
Comp.	Empirical formula (M.W., g mol^{-1})	μ_{eff} (B.M.)	Λ_m, (Ohm^{-1} cm^2 mol^{-1})	m.p. (°C)	Elemental Analysis found (calc.)			UV-Vis. spectra		
					C %	H %	N %	λ_{max} (nm)	ε_{max} (dm^3 mol^{-1} cm^{-1})	Assignment
MST	$C_{17}H_{17}NO_4$ (299.0)	–	–	220	67.70 (67.73)	5.62 (5.68)	4.50 (4.58)	419	136	$n\rightarrow\pi^*$
								249	116	$\pi\rightarrow\pi^*$
MSPDPCu	$C_{29}H_{31}N_3O_8Cu$ (612.5)	1.82	12.14	250	56.72 (56.60)	4.99 (5.04)	6.78 (6.81)	637	305	*d-d* ($2E_g \rightarrow 2T_{2g}$)
								398	556	LMCT band
								246	1770	$\pi\rightarrow\pi^*$
MSP	$C_{19}H_{18}N_2O_4$ (338.0)	–	–	240	67.28 (67.31)	5.10 (5.22)	8.05 (8.18)	431	100	$n\rightarrow\pi^*$
								315	31	$n\rightarrow\pi^*$
								247	37	$\pi\rightarrow\pi^*$
MSTDPCu	$C_{31}H_{36}N_4O_{10}Cu$ (687.5)	2.15	9.76	265	53.92 (54.01)	5.20 (5.24)	8.02 (8.14)	650	1320	*d-d* ($2E_g \rightarrow 2T_{2g}$)
								462	2710	LMCT
								393	2100	LMCT
								308	1770	LMCT
								284	1630	$\pi\rightarrow\pi^*$
DSP	$C_{20}H_{24}N_2O_3$ (340.0)	–	–	160	70.40 (70.52)	6.98 (7.06)	8.11 (8.23)	389	75	$n\rightarrow\pi^*$
								250	136	$\pi\rightarrow\pi^*$
DSPDPCu	$C_{32}H_{42}N_4O_9Cu$ (689.9)	2.00	3.77	260	55.52 (55.59)	6.22 (6.29)	8.02 (8.12)	602	164	*d-d* ($2E_g \rightarrow 2T_{2g}$)
								387	892	LMCT
								244	1272	$\pi\rightarrow\pi^*$
DST	$C_{22}H_{25}N_3O_3$ (379)	–	–	200	69.58 (69.66)	6.52 (6.60)	10.97 (11.08)	397	93	$n\rightarrow\pi^*$
								247	111	$\pi\rightarrow\pi^*$
DSTDPCu	$C_{34}H_{41}N_5O_8Cu$ (710.5)	1.89	5.20	230	57.32 (57.40)	5.66 (5.73)	9.77 (9.83)	568	510	*d-d* ($2E_g \rightarrow 2T_{2g}$)
								402	1500	LMCT
								242	1940	$\pi\rightarrow\pi^*$
DSH	$C_{17}H_{22}N_4O_3$ (330)	–	–	275	61.82 (61.91)	6.67 (6.72)	16.97 (17.02)	397	76	$n\rightarrow\pi^*$
								249	101	$\pi\rightarrow\pi^*$
DSHDPCu	$C_{29}H_{44}N_6O_{11}Cu$ (715.5)	1.83	4.10	258	48.51 (48.64)	6.11 (6.15)	11.68 (11.74)	625	256	*d-d* ($2E_g \rightarrow 2T_{2g}$)
								414	1004	LMCT
								244	1220	$\pi\rightarrow\pi^*$

UV-Vis. Spectral data, λ_{max} (nm) and ε_{max} (dm^3 mol^{-1} cm^{-1}) [ligand] = [complexe] = 1.0×10^{-5} mol dm^{-3} in DMF at 25 °C.[28,34]

Table 2. TGA data of the ternary Cu(II)-complexes.

Complex	*T* (°C)	Fragment loss (%) Molecular formula	Weight loss (%) M.W.	Found	Calc.
MSTDPCu	18.7–100.8	H_2O	18	2.93	2.99
	102.5–251.6	$C_{10}H_8N_2+H_2O$	174	28.37	28.41
	252.9–355.0	$C_{16}H_{15}NO$	237	38.71	38.79
	356.3–403.3	$C_3H_4O_5$	120	19.43	19.50
Residue	>750	Cu	63.5	10.29	10.33
MSPDPCu	33.7–190.9	$3H_2O$	54	8.09	8.11
	190.9–352.8	$C_{18}H_{16}N_2O_2 + H_2O$	310	44.97	45.09
	352.8–508.6	$C_{13}H_{12}N_2O_4$	260	37.79	37.82
Residue	>750	Cu	63.5	9.19	9.24
DSTDPCu	30.9–155.8	$2H_2O$	36	5.23	5.29
	157.0–363.3	$C_{12}H_{10}N_2O_2 + H_2O$	232	32.59	32.64
	364.5–735.6	$C_{22}H_{25}N_3O_3$	379	53.30	53.34
Residue	>750	Cu	63.5	8.89	8.92
DSPDPCu	21.7–82.8	$3H_2O$	54	7.65	7.71
	84.5–258.8	$C_{11}H_{15}NO + H_2O$	195	28.17	28.28
	260.1–359.6	$C_{18}H_{16}N_3$	274	39.69	39.74
	360.9–460.4	$C_3H_3O_4$	103	14.87	14.92
Residue	>750	Cu	63.5	9.19	9.21
DSHDPCu	23.2–133.2	$5H_2O$	90	12.52	12.59
	134.5–220.7	$C_{11}H_{15}ON + H_2O$	195	27.21	27.25
	222.0–303.9	$C_{15}H_{14}N_5$	264	36.85	36.90
	305.3–428.0	$C_3H_3O_4$	103	14.33	14.40
Residue	>750	Cu	63.5	8.77	8.82



Complex Abbr.	R^1	R^2	n
MSTDPCu	H	—CH_3 -methyl	2
MSPDPCu	H	 -benzyl	3
DSTDPCu	—$N(Me)_2$	—CH_3 -methyl	2
DSPDPCu	—$N(Me)_2$	 -benzyl	3
DSHDPCu	—$N(Me)_2$	 -methyl-indolyl	5

Scheme 1. The Synthetic and tentative molecular structure of Cu-complexes.

the hydroxyl group is coordinated to central metal ion without deprotonation.[39] Moreover, $\overline{\nu}_{(C\text{-}O)}$ (phenolic) vibration of the ligands of the same group are observed in the region from 1293 to 1235 cm^{-1}, with a remarkable shift to lower frequency region after complexation remarkably elucidating the coordination of phenolic oxygen. The ligands show specific $\overline{\nu}_{(CH=N)}$ vibration in the region from 1651 to1628 cm^{-1}, but, the $\overline{\nu}_{(CH=N)}$ in the Cu(II)-complexes are observed with a little shift in the region 1627–1588 cm^{-1}. The $\overline{\nu}_{(CH=N)}$ stretching vibrational frequency is considerably moved to a lower frequency, supporting the coordination of the central metal ion with the azomethine nitrogen lone pair (CH = N).[28,40] The Schiff base amino acid ligands exhibit other two intense bands in the region from 1443 to 1362 and from 1599 to 1573 cm^{-1} that matched for symmetric vibrational and asymmetric vibrational frequencies of the carboxylate group (COO^-), respectively. the symmetric and asymmetric bands of the coordinated COO^- group to the Cu^{2+} ion were shifted to lower frequencies from 1344 to 1392 and from 1514 to 1572 cm^{-1}.[24] Moreover, the bands appeared at 739–702 cm^{-1} and 506–558 cm^{-1} are resulted from $\overline{\nu}_{(M\text{-}N)}$ and $\overline{\nu}_{(M\text{-}O)}$ stretching bonds in the Cu(II)-complexes, respectively.[39] The bands, which found in the region from 823 to 987 cm^{-1} correspond to the vibrational bonding of the labile coordinated water molecules to Cu^{2+} ion.[28]

The electronic absorption spectra data of the synthesized ligands and their corresponding ternary Cu-complexes are reported at the absorption wavelength range from 200 to 800 nm and 25 °C. The wavelengths at the characteristic maximum absorption band (λ_{max}) and the molar absorptivity (ε) of the variance bands of the Cu(II)-complexes (Figure S1 in the supplementary materials) are listed in Table 1. An intense band observed in the range from 247 to 250 nm is appreciated for $\pi\rightarrow\pi^*$ transitions originating in the aromatic moiety. The bands in the region from 315 to 431 nm range are attributed to $n\rightarrow\pi^*$ transitions originating in the CH = N azomethine. The appearance of bands at 308–462 nm is due to ligand-to-metal charge transfer (L→MCT) from ligand to the metal ion. The broad bands from 568 to 650 nm are mainly due to the central metal ion d→d transition.

TGA supplied more information about the thermal stability of the current Cu(II)-complexes and more information about the water molecules of the crystalline lattice or the coordination sphere. The experimental results are given in Table 2 exhibiting the presence of coordinated water molecules and water molecules in the crystal lattice of the investigated ternary complexes. From the thermograms, there are 3 decomposition steps. In the first step, a small weight percentage loss which attributed to a loss of water molecules in the crystalline lattice in the range of 110 to 130 °C. In the second step, a maximum weight percentage loss is due to the loss of the water molecules in the coordination sphere from 180 to 200 °C. Finally, as observed in the last decomposition step, a gradual weight loss could be detected for a complete degradation of ligand moiety around Cu(II) ion.[28,34]

The pH profile (Figure S2, supplementary materials) presents a wide stability pH range from 3 to 10 for all ternary Cu(II)-complexes. The wide stability pH range could illustrate that the formed complex is greatly stabilized by chelation to the Schiff base-salicylediene amino acids, as reported for the primary Cu(II)-complexes.[34]

DFT calculations

The ternary complex stability is due to the formation of a five-membered ring between the Cu(II) and DSH ligand.

Also the coordinated water tends to form hydrogen bond with the acetate group. Figure 1a,b suggests that the ternary complex shows significant small (HOMO-LUMO) energy gap (∼2.71 eV) comparing with the non-bound ligand (4.13 eV). The calculation of HOMO, LUMO, energy gap (ΔE), chemical hardness (μ), chemical reactivity (η) and electrophilicity index (ε) were tabulated in Table 3. Chemical hardness (μ) in a coordinated molecular structure points to the resistance to any change in the electron distribution or charge transfer. The stability and reactivity of a molecular system is associated with their chemical hardness. The chemical hardness corresponds to the energy gap amidst HOMO and LUMO depending upon the foundation of frontier molecular orbitals. The larger value the energy gap refers to the harder and the more stable molecule. Chemical Reactivity (η) is a measurement of the molecule electronegativity. The greater η means the higher reactivity and less stability of the characteristic complex. Electrophilicity chart (ε) measures the capacity of a molecular species to gain electrons.

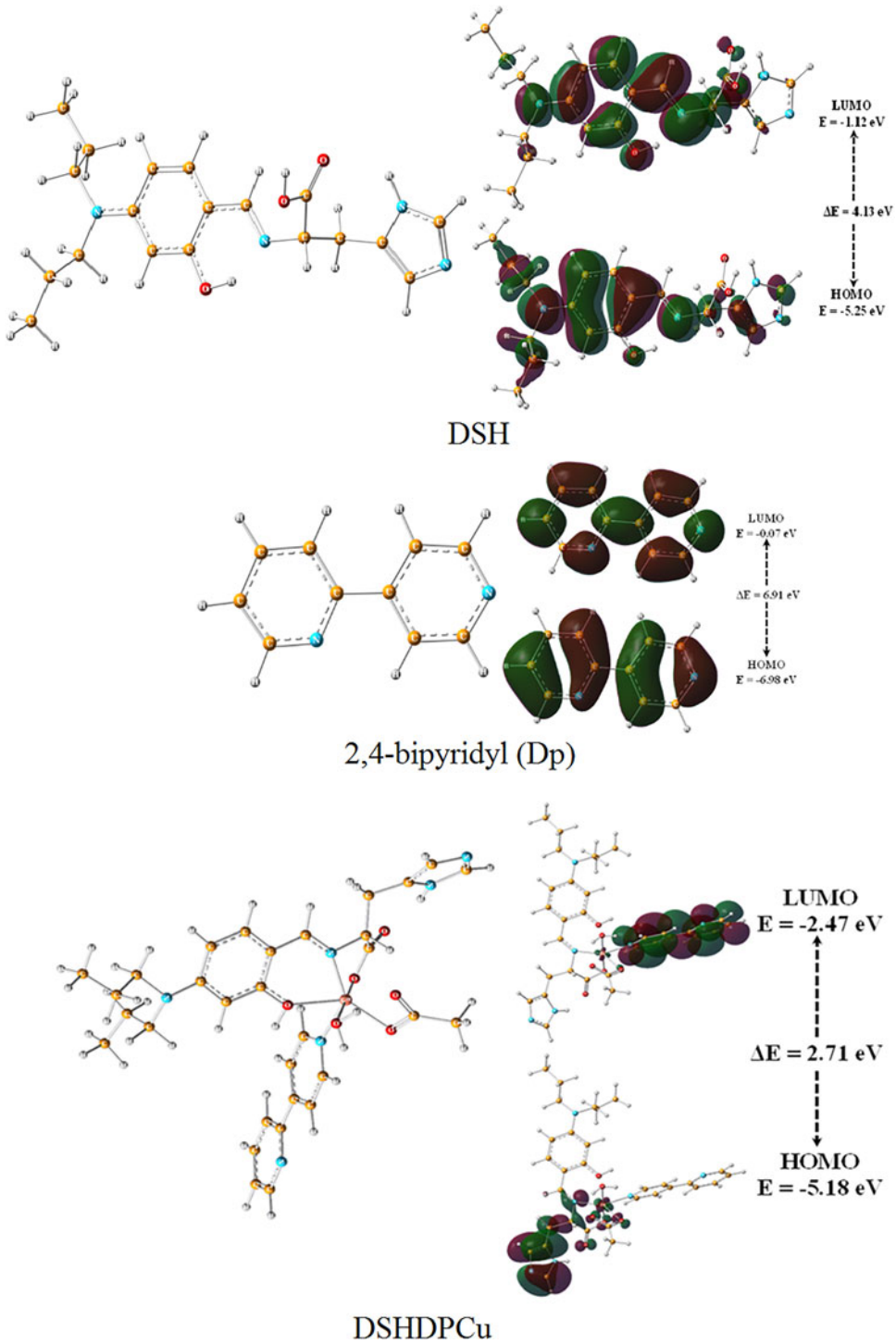


Figure 1. Optimized structures of: (a) DSH ligand as primary ligand, Dp as secondary ligand (2,4-bipridyl) and the Cu(II)-complex (DSHDPCu). (b) The calculated energy gap of the HOMO-LUMO molecular orbitals.

Table 3. The calculated HOMO-LUMO, energy gap (ΔE), chemical hardness (μ), chemical reactivity (η), and electrophilicity index (ε).

Complex	HOMO	LUMO	ΔE	μ	η	ε
DSHDPCu	−5.18	−2.47	2.71	1.36	−3.83	5.40
DSH	−1.12	−5.25	4.13	2.07	3.19	2.45
DP	−0.07	−6.98	6.91	3.46	3.53	1.80

Catalytic reactivity

The catalytic potential of the Cu-complexes was investigated in the oxidation of benzyl alcohol (**A**) by an aqueous H_2O_2, as a green oxidizing agent, to the corresponding carbonyl compound, that is, benzaldehyde (**BA**), in various reaction conditions. A series of standard experiments implied that the presence of the complex catalyst and the external oxidant are essential for such catalytic oxidation (Table 4). In order to find the optimized reaction procedures, the effect of various reaction parameters were studied that probably control the chemoselective conversion. Temperature, catalyst type and solvent are the factors that have been studied to optimize the catalytic oxidation of benzyl alcohol.

Oxidation processes of **A** (1.0 mmol) carried out by aqueous H_2O_2 (3.00 mmol) in acetonitrile (10 mL) at various temperatures catalyzed by MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, or DSHDPCu (0.02 mmol) and the results are presented in Table 4. The amounts of products (benzaldehyde, benzoic acid (**BZ**), or other unknown side products), thus obtained, were analyzed by GC. The controlled catalytic processes using Cu(II)-complex were afforded **BA**, as the major welcomed product, which obtained in the highest scale with some other side products in various conditions, Table 4. No oxidation was observed of **A** by an aqueous H_2O_2 in the absence of any Cu(II)-complex catalyst.

Temperature effect

The catalytic processes were followed in various reaction temperatures, 50, 60, 80, and 90 °C and the resulted GC measurement results are collected in Table 4. At low temperature, 50 °C, the conversion of **A** to **BA** catalyzed by MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, or DSHDPCu was low, but the chemoselectivity was excellent (100%) with good chemoselectivity up to 71–77% after 6 h (entries 1–4).

Particularly, at 60 °C, both of chemoselectivity and the conversion were remarkable enhanced up to 70, 65, 71, 68, and 62% yield of **BA** with very little amount of **BZ** and the reactant **A** after 2 h, catalyzed by MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, and DSHDPCu, respectively (entry 6). Prolongation of time up to 6 hours, the chemoselectivity percentages of the catalytic processes were reduced with little improvement of the conversion, as see in entries 7 and 8 for all Cu-catalysts. The optimized oxidation reaction conditions for the catalytic potential of MSTDPCu, DSTDPCu, MSPDPCu, and DSPDPCu were found at 80 °C for 2 h with very good chemoselectivity (91, 92, 92, and 93%, respectively) and excellent conversion (98, 96, 99, and 97%, respectively). With DSHDPCu, the maximum chemoselectivity was 87% and conversion was 100% after 3 h at 80 °C. Conclusively, MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu,

Table 4. Oxidation of benzyl alcohol catalyzed by Cu(II)-complexes using an aqueous H_2O_2.

			Yield, %												Conversion, % (Selectivity, %)									
			A[a]					BA[b]					BZ											
Entry[a]	T, °C	t, h	MSTDPCu	DSTDPCu	MSPDPCu	DSPDPCu	DSHDPCu	MSTDPCu	DSTDPCu	MSPDPCu	DSPDPCu	DSHDPCu	MSTDPCu	DSTDPCu	MSPDPCu	DSPDPCu	DSHDPCu	MSTDPCu	DSTDPCu	MSPDPCu	DSPDPCu	DSHDPCu
1	50	1	65	68	62	74	73	35	32	31	26	27	0	0	0	0	0	35 (100)	32 (100)	31 (100)	26 (100)	27 (100)
2		2	62	62	57	61	64	38	38	42	38	38	0	0	1	3	1	38 (100)	38 (100)	43 (98)	41 (93)	39 (97)
3		4	50	50	52	52	52	49	47	42	42	40	1	3	6	5	8	50 (98)	50 (94)	48 (87)	47 (89)	48 (83)
4		6	42	39	48	41	46	41	47	38	44	41	17	14	14	15	13	58 (71)	61 (77)	52 (73)	59 (75)	54 (76)
5	60	1	51	48	43	49	50	49	52	57	51	50	0	0	0	0	0	49 (100)	52 (100)	57 (100)	51 (100)	50 (100)
6		2	30	33	27	28	35	70	65	71	68	62	0	2	2	4	3	70 (100)	67 (97)	73 (97)	72 (94)	65 (95)
7		4	25	23	25	23	21	67	66	63	64	58	8	11	12	13	11	75 (89)	77 (86)	75 (84)	77 (83)	69 (84)
8		6	12	15	12	17	14	54	48	46	48	47	34	37	42	35	33	88 (61)	85 (56)	88 (52)	83 (58)	80 (60)
9	80	1	41	39	38	34	42	59	61	62	66	58	0	0	0	0	0	59 (100)	61 (100)	62 (100)	66 (100)	58 (100)
10		2	2	4	1	3	12	89	88	91	90	71	9	8	8	7	17	98 (91)	96 (92)	99 (92)	97 (93)	88 (81)
11		4	0	0	0	0	0	71	68	74	70	87	25	32	26	30	13	100 (71)	100 (68)	100 (74)	100 (70)	100 (87)
12		6	0	0	0	0	0	54	49	52	49	65	46	51	48	51	35	100 (54)	100 (49)	100 52	100 70	100 71
13	90	1	10	11	9	11	14	80	79	79	78	80	10	10	12	11	6	90 (89)	90 (88)	91 (87)	89 (88)	86 (93)
14		2	0	1	0	0	2	72	67	65	62	66	28	32	35	38	32	100 (72)	99 (67)	100 (65)	100 (62)	98 (66)
15		4	0	0	0	0	0	46	42	39	35	41	54	58	61	65	59	100 (46)	100 (42)	100 (39)	100 (35)	100 (41)

[a]The oxidation of benzyl alcohol (**A**) (1.0 mmol) by an aqueous H_2O_2 (3.00 mmol) catalyzed by Cu(II)-complexes (0.02 mmol) in 10 mL acetonitrile for 6 h, at 50, 60, 80 or 90 °C.
[b]The yield based on GC results, selectivity control of the target oxide product, benzaldehyde (**BA**) and other side product, benzoic acid (**BZ**).

or DSHDPCu afforded high catalytic potential towards oxidation of benzyl alcohol by an aqueous H_2O_2 with very good yield of **BA** (entries 10 and 11) at 80 °C in acetonitrile. In particular, after longer time of the catalytic processes, the amount of **BA** was reduced with enhancing the amount of **BZ**, as shown in entry 12. This could be due to the further oxidation of **BA** to **BZ** in the presence of excess amount of the oxidant, an aqueous H_2O_2.

Nerveless, at 90 °C after 1 h (entry 1), the catalytic potential of all Cu(II)-catalysts was very good with excellent conversion 90, 90, 91, 89, and 86% with MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, or DSHDPCu, respectively (entry 13). The control chemoselective product percentages of **BA** were very good 89, 96, 87, 88, and 93% in presence of very little amounts of the reactant **A**. After 2 h, chemoselectivity was remarkably reduced to 72, 67, 65, 62, and 66% using either, MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, or DSHDPCu, respectively (entry 14), which influenced by the high reaction temperature, that is, 90 °C. Entry 15 presents a high reducing in the percentages of the target product (**BA**) due to the continuous further oxidation of **BA** to **BZ**.

Catalyst type effect

All the above catalyst complexes have very good to excellent catalytic potential towards selective oxidation of **A** to **BA** under the optimized catalytic conditions. The solubility of the catalyst complex has more attention on the catalytic activity in a homogeneous system.[22,34] The polarity of the current Cu(II)-complexes [40] may have an observable impact on their alternative catalytic potentials for the benzyl alcohol oxidation by an aqueous H_2O_2 based on structure-activity relationship.[41,42] According to Cu(II)-complex chemical structures, $\mathbf{R^1}$ and $\mathbf{R^2}$ may have strong impact on the structural features and their catalytic potentials, that is, steric demand, polarity and solubility (Scheme 1).[43] In MSTDPCu and DSTDPCu, $\mathbf{R^1}$ is -CH_2-CH_3, whereas, in MSPDPCu and DSPDPCu, $\mathbf{R^1}$ is -CH_2-Ph. The less organic nature of $\mathbf{R^1}$ increases the catalysts' solubility in the high polar organic solvent, that is, acetonitrile, and so may enhance the catalytic potential in the benzyl alcohol oxidation homogeneously. Obviously, MSPDPCu and DSPDPCu, with $\mathbf{R^1}$ = -CH_2-Ph, are less soluble in acetonitrile which may influence their catalytic reactivity towards benzyl alcohol oxidation by an aqueous H_2O_2. Additionally, the aqueous solution of H_2O_2 may have an observable impact on the catalytic reactivity of Cu(II)-complexes. In such more polar reaction media (aqueous-acetonitrile media), the catalytic potential of DSHDPCu is poor for the control oxidation of **A** to **BA**. This could be attributable to the less polarity and solubility of DSHDPCu depending upon the more organic nature of $\mathbf{R^1}$ group (-CH_2-indolyl). On the other hand, it is highly remarked that $\mathbf{R^2}$ in *p*-position (H- in MSPDPCu or $(Me)_2N$- in DSTDPCu) has no observed effect on the catalytic activity of all Cu(II)-complexes (Scheme 1).[44]

Proposed catalytic mechanism

Oxidation of benzyl alcohol using an aqueous H_2O_2 catalyzed by MSTDPCu, DSTDPCu, MSPDPCu, DSPDPCu, or DSHDPCu was subjected, to explore the highest catalytic efficiency of Cu(II)-catalysts. Table 4 utilizes their catalytic potentials by the yield of the oxidation products in acetonitrile. Inspections of those results indicate several useful features. The structural features of the characteristic Cu^{2+}-complex with tridentate Schiff base ligands have an effective role for the control oxidation and chemoselectivity.[45] Cu-complexes with tri-coordinating ligand is octahedral geometry, which is highly stable and strongly closed complexes. This could be the reason for their good/moderate catalytic potentials, as reported for many copper (II)-complexes.[22,42,46,47] However, the presence of a labile coordinated solvent molecule (water as an active coordination site) or the acetate anion may be useful for catalytic oxidation reactions.

Cu(II)-catalysts were initiated by adding an aqueous H_2O_2. This could be detected by an observable shift of the characteristic absorption maximum wavelength (λ_{max}), Figure 2a,b, of MSTDPCu and DSTDPCu, respectively. The addition of an aqueous H_2O_2 to MSTDPCu or DSTDPCu solution (in acetonitrile) probably causes electron and oxygen transfers from H_2O_2 to Cu^{2+} within coordination of H_2O_2 molecule to Cu^{2+} ion (Scheme 2, I), through formation peroxo-intermediate Cu-OOH_2 [48] (Scheme 2, II) followed by formation of Cu^{2+}=O species [22] by exploring the coordinated water molecule (Scheme 2, III). In another word, electron and oxygen transfers from the more environmentally benign oxidant, an aqueous H_2O_2, to the catalyst would be easier in the presence of a labile coordinated water molecule through the coordination to Cu^{2+} ions, as observed previously.[49] The peroxo-intermediate was subjected by other groups in acidic media by protonation of H_2O_2 [46] or directly linkage between Cu^{2+} ions and H_2O_2.[23] In particular, this behavior could be explained by the repeated visible spectral scans in the catalytic process before and just after addition of the oxidant, H_2O_2 (Figure 2a,b). This small remarkable shift at the maximum absorption bands, from 398 and 389 nm to 408 and 421 nm after adding an aqueous H_2O_2 to MSTDPCu and DSTDPCu, respectively, in the oxidation reaction of **A**, may be attributable for electron and oxygen transfers to central metal ion Cu^{2+} in MSTDPCu or DSTDPCu from the oxygen source, an aqueous H_2O_2, affording Cu^{2+}=O in the reaction media through formation of peroxo-intermediate (II), as shown in Scheme 2. Exploration of water molecule in the oxygen transfer step of Cu^{2+} ions in the catalytic process would be favorable in acetonitrile, as a polar organic solvent.

At the optimized reaction temperature of the catalytic process and from the repeated spectral scans of the absorption bands for MSTDPCu and DSTDPCu (Figure 3a,b, respectively), it rationalizes that the catalysts are stable in the catalytic conditions without decomposition of the catalysts in the reaction media. These spectral observations are in stark contrast with previous reports [24] since catalytic oxidation of benzyl alcohol using Cu(II)-complexes was discussed for the reaction of Cu^{2+} ion in the catalyst complex with H_2O_2 to form an oxide intermediate of the catalyst complex Cu^{2+}=O with exploring of water molecule.[15,46]

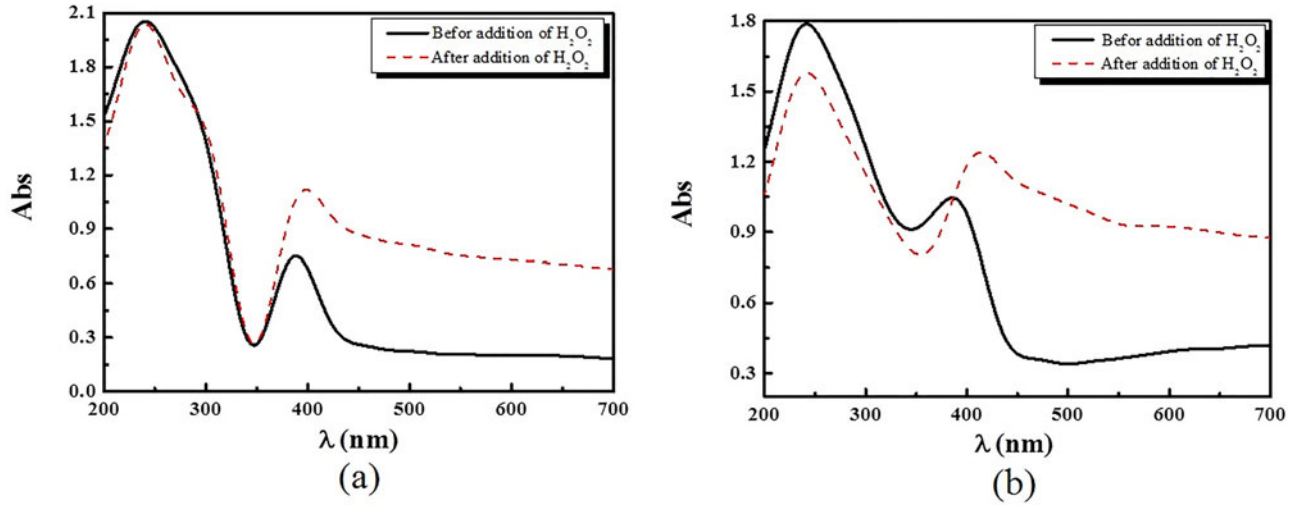
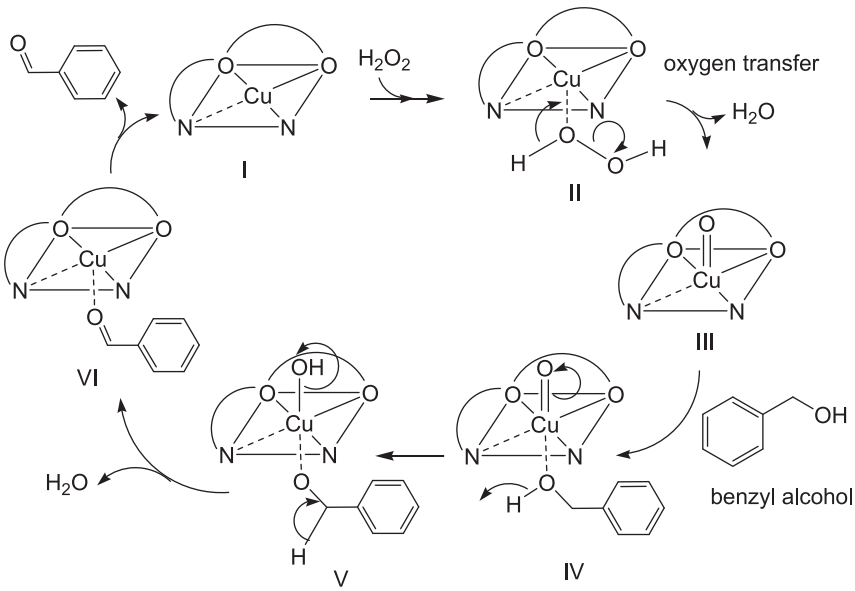


Figure 2. Molecular spectral scan of (a) MSTDPCu (b) DSTDPCu (0.02 mmol) before and after addition of an aqueous H_2O_2 (3.00 mmol) at 60 °C in acetonitrile.



Scheme 2. Proposed mechanistic pathway for the oxidation of alcohols by an aqueous H_2O_2 solution catalyzed by Cu(-complexes.

The stability of Cu^{2+} species in the catalytic process against an aqueous H_2O_2 is demonstrated by monitoring the repeated molecular visible spectral scans of the catalyst complex in the reaction media (Figure 3a,b). The intensity of the characteristic absorption visible bands has little shifted within the catalytic runs. The initial shift in the intensity upon addition of the oxidant and benzyl alcohol may be due to the production of new active species by coordination of benzyl alcohol to Cu^{2+} ions (Scheme 2, III).[15,45] The fourth step of the mechanism is the formation another active species (IV) by an approach of the oxo-copper species, Cu^{2+}=O, to benzyl alcohol. This could be taken place by the coordination of the oxygen atom of OH group of benzyl alcohol to the Cu^{2+}=O species (Scheme 2, IV).[24] The little shift of the repeated visible spectral scan of the complex catalysts after addition of an aqueous H_2O_2 and benzyl alcohol to the reaction mixture could probably prove that proposal. Moreover, the continuous shift of λ_{max} for MSTDPCu or DSTDPCu, respectively, (Figure 3a,b) might be attributed to the oxidation of benzyl alcohol to benzaldehyde within release of a water molecule (Scheme 2, V), as expected previously.[22,47] The final stage of the catalytic cycle involves extraction with reduction of the activated intermediate (IV) to reform the initial catalyst (I) and to begin e new catalytic cycle (Scheme 2).

It is widely reported that the change of oxidation state of the central metal ion in the catalyst in oxidation processes could be observed and detected by repeated spectral scan of the characteristic absorption band or by cyclic voltammetry.[50] Our mechanism supports strongly the probability of oxidation state changing of Cu^{2+} ion in its catalyst to Cu^{3+} with electron transfer.[50]

Biological studies

Antimicrobial studies

The antimicrobial effectiveness of Cu-complexes was presented in Figures 4 and 5 (Tables S2 and S3 in the

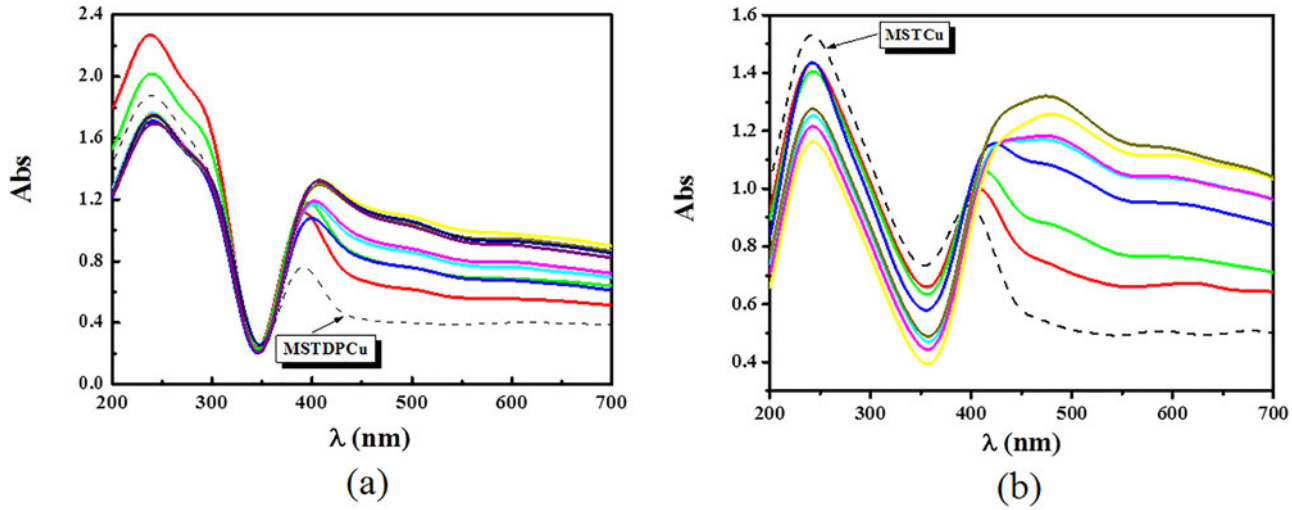


Figure 3. Repeated molecular spectral scan of the oxidation of benzyl alcohol by an aqueous H_2O_2 catalyzed by (a) MSTDPCu and (b) DSTDPCu at 60 °C in acetonitrile with interval time 20 min.

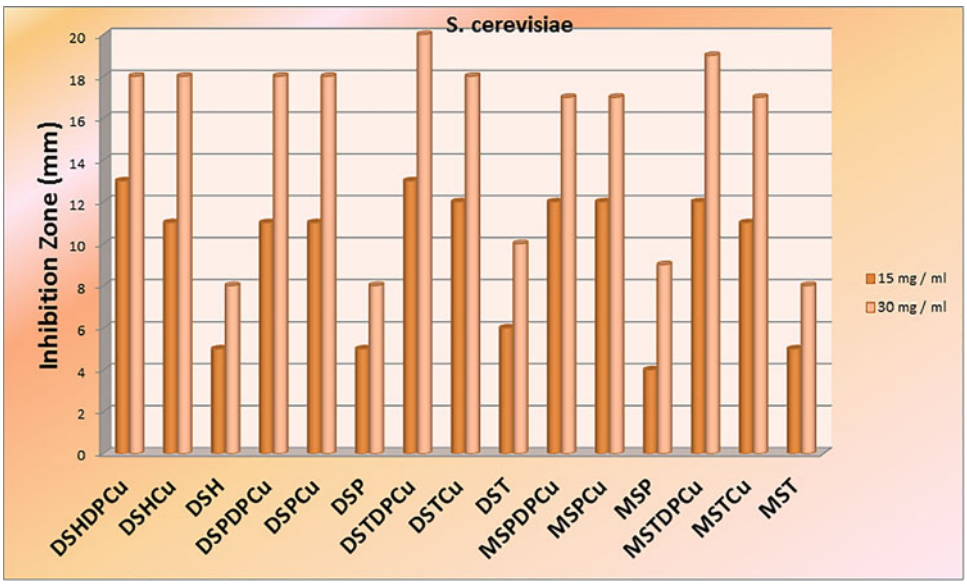


Figure 4. Antifungal results of the investigated Schiff base amino acids and their binary and ternary complexes against *S. cerevisiae* fungi.

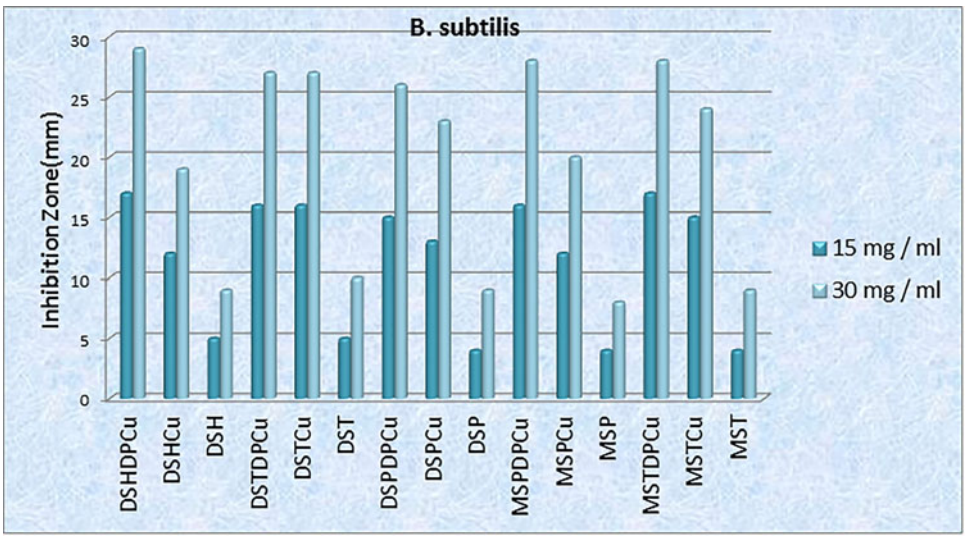


Figure 5. Antibacterial studies of the ligands and their binary and ternary complexes against *B. subtilis* bacteria.

supplementary materials). The antimicrobial activity of Cu(II)-complexes were derived by Eq. 3 (Table 5):

$$\text{Activity index} = \frac{\text{Inhibition Zone of compound (mm)}}{\text{Inhibition Zone of standard drug (mm)}} \times 100 \quad (3)$$

The reactivity of the antimicrobial reagents could be classified according to the bacteria structure and/or the function affected by the reagents. Such reactivity could depend upon other factors, which have been reported previously.[28,34]

So, the mode of action of the Cu-complexes may include the formation of a hydrogen bond through azomethine group (CH = N) with the active centers of cell components [28,51] resulting in involvements with the normal process. The sensibility of confirmed strains of bacteria to the ligands and their corresponding Cu-complexes was estimated by measuring the magnitude of the bacteriostatic diameter. The antimicrobial screening results showed marked enhancement inactivity on coordination with the ternary complexes possess biological activity. The ligand within N- and O-donor centers might reduce production of the enzyme since the enzymes which demand these groups for their activity appear to be especially more susceptible to extinction by the metal ions rely on chelating. The theory states that the polarity of the metal ion is minimized on complexation justified the partial sharing of its positive charge with donor groups. Subsequently, the positive charge is delocalized over the entire ring, which causes the enhanced lipophilicity of the compound through cell membrane of the pathogen.[52] The low results can be attributed either to the inability of the complexes to diffuse into the negative bacteria cell membrane and hence they become impotent to intervene with its biological activity or they can prevalent and become inactivated by obscure cellular mechanisms, that is, bacterial enzymes.[53] Compared with binary complexes, it is found that ternary complexes more reactive than binary complexes.[54]

Table 5. Results of activity index (%) for antimicrobial assay of the prepared Schiff base amino acid ligands and their Cu(II)-complexes.

Comp.	Activity index (%)					
	Bacteria			Fungi		
	B. subtilis	*E. coli*	M. *luteus*	*A. niger*	*C. glabrata*	*S. cerevisiae*
MSP	24.2	25.0	28.6	37.9	35.3	39.1
MSPDPCu	84.8	82.1	85.7	86.2	94.1	78.3
MST	27.3	28.6	26.2	34.5	41.2	34.8
MSTDPCu	84.8	78.6	83.3	93.1	82.4	82.6
DSP	27.3	28.6	26.2	27.6	41.2	34.8
DSPDPCu	78.8	71.4	78.6	86.2	82.4	82.6
DST	30.3	35.7	28.6	34.5	47.1	43.5
DSTDPCu	81.8	78.6	80.9	89.7	88.2	86.9
DSH	27.3	28.6	23.8	31.0	47.1	34.8
DSHDPCu	87.9	85.7	88.1	86.4	82.4	82.6

DNA binding studies

CT-DNA plays an influential role in the life process since it contains all the genetic information for the cellular assignment. However, DNA is the main intracellular aim of anticancer drugs, could be damaged under diverse conditions such as interactions with some small molecules. This creator DNA damage in cancer cells could block the division of cancer cells and result in cell expiration. Cu(II)-complexes show the properties of efficacious binding, as well as, cleave the double-stranded DNA. Such features could be governed by physiological conditions, which are of great importance since these could be employed as diagnostic agents in medicinal and genomic investigation.

Electronic spectra studies

Titration with electronic absorption spectroscopy is an efficacious method to investigate the binding mode of DNA with a metal complex.[7] If the binding process is intercalation, the orbital of intercalated ligand could couple with the orbital of the base pairs, curtailment the $\pi \rightarrow \pi^*$ transition energy and resulting in bathochromism. If the coupling orbital is partially engaged by electrons, it results in lowering the transition eventualities and resulting in hypochromism.[54] Moreover, a supplement for augmenting amounts of CT-DNA resulted in a decrease of absorbance for each investigated Cu(II)-complex. The electronic absorption spectra of the studied complexes in the lack and presence of various concentrations of buffered CT-DNA are given in Table 6 and Figure 6. The binding constant (K_b) was higher in the sequence: DSTDPCu > MSTDPCu > DSPDPCu > DSHDPCu > MSPDPCu. From a comparison between the value of binding constant (K_b) of ethidium bromide, the known DNA intercalator (EB, $K_b = 1.4 \times 10^6\ \text{mol}^{-1}\,\text{dm}^{-3}$) and the values of the binding constants (K_b) of the prepared ternary Cu(II)-complexes, it is found that all the prepared ternary complexes have high values of binding constants (K_b) near to the control (EB). These results promise that these complexes could be used in cancer therapy.

Table 6. Spectral parameters for DNA interaction with the prepared ternary complexes.

Complex	λ_{max} free (nm)	λ_{max} bound (nm)	Δn (nm)	Chromism (%)[a]	Type of Chromism	$10^5\ K_b\ \text{mol}^{-1}\text{dm}^3$	$\Delta G^{\neq}$ kJ mol^{-1}
MSPDPCu	644	645	1	34.4	Hypo	2.5	−30.8
	395	387	8	17.9	Hypo		
MSTDPCu	644	636	8	27.2	Hyper	4.6	−32.3
	401	387	14	35.2	Hypo		
DSPDPCu	597	617	20	90.0	Hypo	3.2	−31.4
	387	370	17	30.0	Hypo		
DSTDPCu	573	598	25	96.0	Hypo	24.3	−36.4
	403	386	17	43.0	Hypo		
DSHDPCu	631	661	30	88.7	Hyper	2.9	−31.1
	414	373	41	38.3	Hypo		

[a]Chromism (%) = $(A_{free} - A_{bound})/A_{free}$.

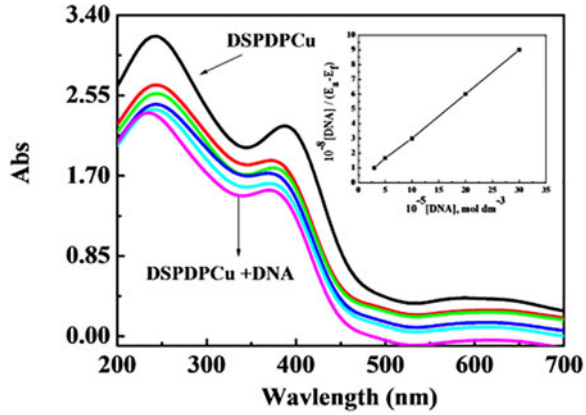


Figure 6. Electronic spectral scans of the interaction of DSPDPCu (2.5×10^{-3} mol dm^{-3}) in 0.01 mol dm^{-3} tris buffer (pH 7.2 at 25 °C) with CT – DNA (3–30 μM intervals).

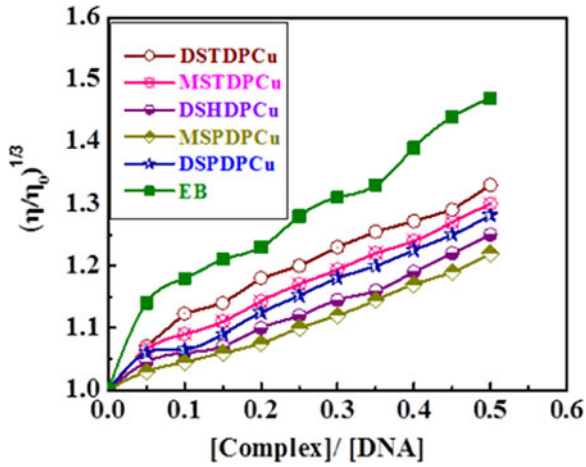


Figure 7. The effect of concentration of the ternary Cu-complexes on the viscosities of DNA at [DNA] = 0.5 μM, [complex], [EB] = 25 250 μM and 25 °C.

DNA binding analysis using viscosity

The relative viscosity of DNA solution increases worthy as the amount of the Cu(II)-complex magnifies, but the increase is less than that detected for the typical intercalator EB, registering that intercalative, as shown in Figure 7. This may due to the infusion of aromatic ring in Schiff base ligand into the DNA base pairs and give rise to a bend in the DNA helix, rise in the separation of the base pairs at the intercalation site, subsequently increasing in DNA molecular length (Scheme 3).

DNA binding analysis using agarose gel electrophoresis

With agarose gel electrophoresis, DNA binding studies are substantial for the rationalistic design and construction of

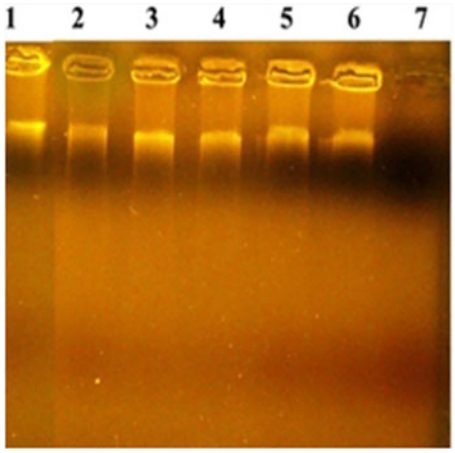
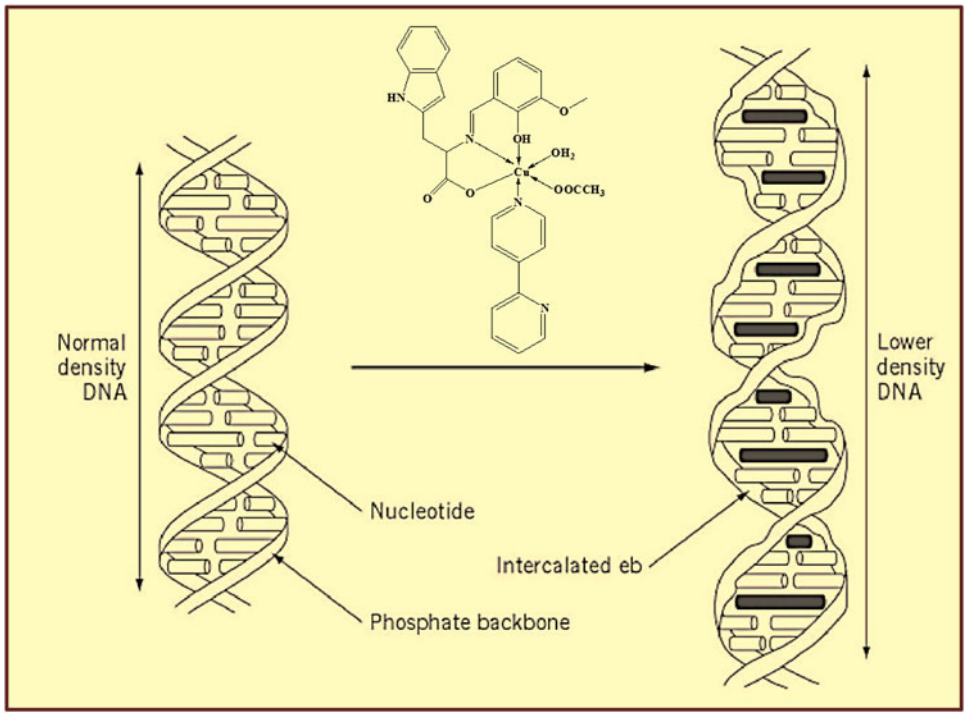


Figure 8. DNA binding of ternary Cu- complexes based on gel electrophoresis, Lane 1: CT – DNA, Lane 2: CT – DNA + DSTDPCu, Lane 3: CT – DNA + MSTDPCu, Lane 4: CT – DNA + DSPDPCu, Lane 5: CT – DNA + DSHDPCu, Lane 6: CT – DNA + MSPDPCu, Lane 7: MSPDPCu.



Scheme 3. Diagrammatic interaction of the ternary Cu-complexes with CT-DNA.

new and more effective drugs targeted to DNA. The interaction of the investigated Cu(II)-complexes with CT-DNA was studied by gel electrophoresis and the results were performed in Figure 8. The cleavage efficiency of ternary complexes was compared to that of the control is due to their efficacious DNA binding ability. The variation in DNA cleavage efficacy of the investigated complexes was due to their variation in binding ability of complexes to DNA. The intensity of lanes was higher in the sequence: DSTDPCu > MSTDPCu > DSPDPCu > DSHDPCu > MSPDPCu. Interestingly, there are agreements between the three methods of the interaction with DNA (electronic spectra, viscosity measurements and gel electrophoresis) and by comparing with binary complexes; it is found that the ternary complexes are more reactive than binary complexes.[53]

Conclusion

Ternary Cu(II)-complexes have been prepared in ethanol using Schiff base amino acids that were derived from MS or DS with α-amino acids (L-phenylalanine (Phe), L-histidine (His), DL-tryptophan (Trp)) as a primary ligand, and 2,4-bipyridyl (DP) as secondary ligand. IR, UV-Visible, thermal analysis, conductance measurements, magnetic susceptibilities menstruation, and elemental analysis were utilized to confirm their formation. The catalytic efficiency in the oxidation of benzyl alcohol by an aqueous H_2O_2 in different reaction conditions of the current complex catalysts has been investigated. The results illustrate that Cu(II)-complexes are good effective catalysts for the control conversion to the chemoselective product, benzaldehyde. Based upon spectroscopic investigation, octahedral geometry of complexes is proposed. The *in vitro* biological evaluations of complexes against various pathogenic bacterial strains show that ternary metal complexes manifestation higher antimicrobial activity than free ligands. The interaction between ternary complexes and DNA is strongly progressed. These findings clearly indicate that ternary transition metal-based complexes have many practical applications, like the new therapeutic reagents for diseases.

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References

[1] Low, M. L.; Maigre, L.; Tahir, M. I. M.; Tiekink, E. R. T.; Dorlet, P.; Guillot, R.; Ravoof, T. B.; Rosli, R.; Pages, J.-M.; Policar, C.; et al. New Insight into the Structural, Electrochemical and Biological Aspects of Macroacyclic Cu(II) Complexes Derived from S-Substituted Dithiocarbazate Schiff Bases. *Eur. J. Med. Chem.* **2016**, *120*, 1–12. DOI: 10.1016/j.ejmech.2016.04.027.

[2] Theetharappan, M.; Subha, L.; Balakrishnan, C.; Neelakantan, M. A. Binding Interactions of Mixed Ligand Copper(II) Amino Acid Schiff Base Complexes with Biological Targets: Spectroscopic Evaluation and Molecular Docking. *Appl. Organometal. Chem.* **2017**, *31*, e3713. DOI: 10.1002/aoc.3713.

[3] Shabbir, M.; Akhter, Z.; Ahmad, I.; Ahmed, S.; McKee, V.; Ismail, H.; Mirza, B. Copper (II) Complexes Bearing Ether Based on Donor Bidentate Schiff Bases: Synthesis, Characterization, Biological and Electrochemical Investigations. *Polyhedron* **2017**, *124*, 117–124. DOI: 10.1016/j.poly.2016.12.039.

[4] Demirci, S.; Doğan, A.; Türkmen, N. B.; Telci, D.; Rizvanov, A. A.; Şahin, F. Schiff base-Poloxamer P85 Combination Demonstrates Chemotherapeutic Effect on Prostate Cancer Cells in Vitro. *Biomed. Pharmacother.* **2017**, *86*, 492–501. DOI: 10.1016/j.biopha.2016.11.101.

[5] AlAjmi, M. F.; Hussain, A.; Alsalme, A.; Khan, R. A. In Vivo Assessment of Newly Synthesized Achiral Copper(II) and Zinc(II) Complexes of a Benzimidazole Derived Scaffold as a Potential Analgesic, Antipyretic and anti-Inflammatory. *RSC Adv.* **2016**, *6*, 19475–19481. DOI: 10.1039/C5RA25071D.

[6] Singh, B. K.; Rajour, H. K.; Prakash, A. Synthesis, Characterization and Biological Activity of Transition Metal Complexes with Schiff Bases Derived from 2-Nitrobenzaldehyde with Glycine and Methionine. *Spectrochim. Acta A* **2012**, *94*, 143–151. DOI: 10.1016/j.saa.2012.03.077.

[7] Reddy, P. R.; Shilpa, A.; Raju, N.; Raghavaiah, P. J. Synthesis, Structure, DNA Binding and Cleavage Properties of Ternary Amino Acid Schiff Base-Phen/Bipy Cu(II) Complexes. *Inorg. Biochem.* **2011**, *105*, 1603–1612. DOI: 10.1016/j.jinorgbio.2011.08.022.

[8] Ma, X.-F.; Li, D.-D.; Tian, J.-L.; Kou, Y.-Y.; Yan, S.-P. DNA Binding and Cleavage Activity of Reduced Amino-Acid Schiff Base Complexes of Cobalt(II), Copper(II), and Cadmium(II). *Transit. Met. Chem.* **2009**, *34*, 475–481. DOI: 10.1007/s11243-009-9219-7.

[9] Adam, M. S. S.; Elsawy, H. Biological Potential of Oxo-Vanadium Salicyledieneamino-Acid Complexes as Cytotoxic, Antimicrobial, Antioxidant and DNA Interaction. *J. Photochem. Photobiol. B* **2018**, *184*, 34–43. DOI: 10.1016/j.jphotobiol.2018.05.002.

[10] Krishnamohan Sharma, C. V. Crystal Engineering – Where Do We Go from Here? *Cryst. Growth Des.* **2002**, *2*, 465–474. DOI: 10.1021/cg0200356.

[11] Abd El-Lateef, H. M.; Adam, M. S. S.; Khalaf, M. M. Synthesis of Polar Unique 3d Metal-Imine Complexes of Salicylidene Anthranilate Sodium Salt. Homogeneous Catalytic and Corrosion Inhibition Performance. *J. Taiwan Inst. Chem. Eng.* **2018**, *88*, 286–304. 88, DOI: 10.1016/j.jtice.2018.04.024.

[12] Adam, M. S. S.; Abd El-Lateef, H. M.; Soliman, K. A. Anionic Oxide-Vanadium Schiff Base Amino Acid Complexes as Potent Inhibitors and as Effective Catalysts for Sulfides Oxidation: Experimental Studies Complemented with Quantum Chemical Calculations. *J. Mol. Liq.* **2018**, *250*, 207–322.

[13] Gao, I.-J.; Ren, Z.-G.; Lang, J.-P. Oxidation of Benzyl Alcohols to Benzaldehydes in Water Catalyzed by a Cu(II) Complex with a Zwitterionic Calix[4]Arene Ligand. *J. Organomet. Chem.* **2015**, *792*, 88–92. DOI: 10.1016/j.jorganchem.2015.02.008.

[14] Chattopadhyay, T.; Kogiso, M.; Asakawa, M.; Shimizu, T.; Aoyagi, M. Copper(II)-Coordinated Organic Nanotube: A Novel Heterogeneous Catalyst for Various Oxidation Reactions. *Catal. Commun.* **2010**, *12*, 9–13. DOI: 10.1016/j.catcom.2010.07.013.

[15] Ramakrishna, D.; Bhat, B. R. A Catalytic Process for the Selective Oxidation of Alcohols by Copper (II) Complexes. *Inorg. Chem. Commun.* **2011**, *14*, 690–693. DOI: 10.1016/j.inoche.2011.02.007.

[16] Parmeggiani, C.; Cardona, F. Transition Metal Based Catalysts in the Aerobic Oxidation of Alcohols. *Green Chem.* **2012**, *14*, 547–564. DOI: 10.1039/c2gc16344f.

[17] Puterova-Tokarova, Z.; Mrazova, V.; Boca, R. Magnetism of Novel Schiff-Base Copper(II) Complexes Derived from Aminoacids. *Polyhedron* **2013**, *61*, 87–93.

[18] Wang, M.-Z.; Li, Y.; Ji, J.-J.; Huang, G.-L.; Zhang, X.; Li, S.-H.; Yang, X.-J. Novel Hybrids of Cu^{2+} Ternary Complexes of Salicylidene-Amino Acid Schiff Base with Phenanthroline (or Bipyridine) Intercalated in Mg/Al-NO_3-Layered Double

Hydroxide. *Chin. Chem. Lett.* **2013**, *24*, 593–596. DOI: 10.1016/j.cclet.2013.03.040.

[19] Piera, J.; Backvall, J. E. Catalytic Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer—A Biomimetic Approach. *Angew. Chem. Int. Ed.* **2008**, *47*, 3506–3523. DOI: 10.1002/anie.200700604.

[20] Islam, S. M.; Roy, A. S.; Mondal, P.; Mubarak, M.; Mondal, S.; Hossain, D.; Banerjee, S.; Santra, S. C. Synthesis, Catalytic Oxidation and Antimicrobial Activity of Copper(II) Schiff Base Complex. *J. Mol. Catal. A* **2011**, *336*, 106–114. DOI: 10.1016/j.molcata.2011.01.006.

[21] Moradi-Shoeili, Z.; Amini, Z.; Boghaei, D. M.; Notash, B. Synthesis, X-Ray Structure and Ascorbic Oxidation Properties of Ternary α-Amino Acid Schiff Base-Bipy Cu(II) Complexes as Functional Models for Ascorbic Oxidase. *Polyhedron* **2013**, *53*, 76–82. DOI: 10.1016/j.poly.2013.01.020.

[22] Steves, E.; Stahl, S. S. Copper(I)/ABNO-Catalyzed Aerobic Alcohol Oxidation: Alleviating Steric and Electronic Constraints of Cu/TEMPO Catalyst Systems. *J. Am. Chem. Soc.* **2013**, *135*, 15742–15745. DOI: 10.1021/ja409241h.

[23] Zueva, E.; Walton, P.; McGrady, J. E. Catalytic Alcohol Oxidation by an Unsymmetrical 5-Coordinate Copper Complex: Electronic Structure and Mechanism. *Dalton Trans.* **2006**, 159–167. DOI: 10.1039/B512298H.

[24] Adam, M. S. S. Catalytic Potentials of Homodioxo-Bimetallic Dihydrazone Complexes of Uranium and Molybdenum in a Homogeneous Oxidation of Alkenes. *Monatsh. Chem.* **2015**, *146*, 1823–1836. DOI: 10.1007/s00706-015-1477-9.

[25] Mannam, S.; Alamsetti, S. K.; Sekar, G. Aerobic, Chemoselective Oxidation of Alcohols to Carbonyl Compounds Catalyzed by a DABCO-Copper Complex under Mild Conditions. *Adv. Synth. Catal.* **2007**, *349*, 2253–2258. DOI: 10.1002/adsc.200700213.

[26] Wang, X. Y.; Zhang, J.; Li, K.; Jiang, N.; Chen, S. Y.; Lin, H. H.; Huang, Y.; Ma, L. J.; Yu, X. Q. Synthesis and DNA Cleavage Activities of Mononuclear Macrocyclic Polyamine Zinc(II), Copper(II), Cobalt(II) Complexes Which Linked with Uracil. *Bioorg. Med. Chem.* **2006**, *14*, 6745–6751. DOI: 10.1016/j.bmc.2006.05.049.

[27] Gupta, K. C.; Sutar, A. K. Catalytic Activities of Schiff Base Transition Metal Complexes. *Coord. Chem. Rev.* **2008**, *252*, 1420–1450. DOI: 10.1016/j.ccr.2007.09.005.

[28] Abdel-Rahman, L. H.; Abu-Dief, A. M.; Ismael, M.; Mohamed, M. A. A.; Hashem, N. A. Synthesis, Structure Elucidation, Biological Screening, Molecular Modeling and DNA Binding of Some Cu(II) Chelates Incorporating Imines Derived from Amino Acids. *J. Mol. Struct.* **2016**, *1103*, 232–244. DOI: 10.1016/j.molstruc.2015.09.039.

[29] Shokohipour, Z.; Chiniforoshan, H.; Momtazi-Borojeni, A. A.; Notash, B. A. Novel Schiff Base Derived from the Gabapentin Drug and Copper (II) Complex: Synthesis, Characterization, Interaction with DNA/Protein and Cytotoxic Activity. *J. Photochem. Photobiol. B* **2016**, *162*, 34–44. DOI: 10.1016/j.jphotobiol.2016.06.022.

[30] Chandraleka, S.; Ramya, K.; Chandramohan, G.; Dhanasekaran, D.; Priyadharshini, A.; Panneerselvam, A. Antimicrobial Mechanism of Copper (II) 1,10-Phenanthroline and 2,2′-Bipyridyl Complex on Bacterial and Fungal Pathogens. *J. Saudi Chem. Soc.* **2014**, *18*, 953–962. DOI: 10.1016/j.jscs.2011.11.020.

[31] Frisch, M. J. *Gaussian 03, Revision C. 01*; Gaussian, Inc.: Wallingford, CT, **2004**.

[32] Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self Consistent Molecular Orbital Methods. IX. An Extended Gaussian-Type Basis for Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1971**, *54*, 724–728. DOI: 10.1063/1.1674902.

[33] Hay, P. J.; Wadt, W. R. Ab Initio Effective Core Potentials for Molecular Calculations. Potentials for the Transition Metal Atoms Sc to Hg. *J. Chem. Phys.* **1985**, *82*, 270–283. DOI: 10.1063/1.448799.

[34] Abdel Rahman, L. H.; Abu-Dief, A. M.; Hashem, N. A.; Seleem, A. A. Recent Advances in Synthesis, Characterization and Biological Activity of Nano Sized Schiff Base Amino Acid M(II) Complexes. *Int. J. Nano. Chem.* **2015**, *1*, 79–95.

[35] Hegazy, W. H.; Al-Motawa, I. H. Lanthanide Complexes of Substituted -Diketone Hydrazone Derivatives: Synthesis, Characterization, and Biological Activities. *Bioinorg. Chem. Appl.* **2011**, *2011*, 1–10. DOI: 10.1155/2011/531946.

[36] Abdel-Rahman, L. H.; Adam, M. S. S.; Abu-Dief, A. M.; Moustafa, H.; Basha, M. T.; Aboraia, A. S.; Al-Farhan, B. S.; Ahmed, H. E. Synthesis, Theoretical Investigations, Biocidal Screening, DNA Binding, in Vitro Cytotoxicity and Molecular Docking of Novel Cu(II), Pd(II) and Ag(I) chlorobenzylidene Schiff Base: Promising Antibiotic and Anticancer Agents. *Appl. Organometal. Chem.* **2018**, *32*, e4527. DOI: 10.1002/aoc.4527.

[37] Adam, M. S. S.; Youssef, M. M.; Abo Elghar, M. F.; Hafez, A. M.; El-Ayaan, U. Synthesis and Characterization of Binary and Ternary Oxovanadium Complexes of N,N'-(2-Pyridyl)Thiourea and Curcumin. Catalytic Oxidation Potential, Antibacterial, Antimicrobial, Antioxidant and DNA Interaction Studies. *Appl. Organometal. Chem.* **2017**, *31*, e3650. DOI: 10.1002/aoc.3650.

[38] Cohen, G.; Eisenberg, H. Viscosity and Sedimentation Study of Sonicated DNA–Proflavine Complexes. *Biopolymers* **1969**, *8*, 45–55. DOI: 10.1002/bip.1969.360080105.

[39] Lekha, L.; Kanmani, R. K.; Rajagopal, G.; Easwaramoorthy, D. J. Schiff Base Complexes of Rare Earth Metal Ions: Synthesis, Characterization and Catalytic Activity for the Oxidation of Aniline and Substituted Anilines. *J. Organomet. Chem.* **2014**, *753*, 72–80. DOI: 10.1016/j.jorganchem.2013.12.014.

[40] Adam, M. S. S.; Mohamad, A. D. M. Catalytic (ep)Oxidation and Corrosion Inhibition Potentials of Cu^{II} and Co^{II} Pyridinylimino Phenolate Complexes. *Polyhedron* **2018**, *151*, 118–130. DOI: 10.1016/j.poly.2018.05.035.

[41] Liu, E.; Zhang, Y. Z.; Li, L.; Yang, C.; Fettinger, J.; Zhang, G. New Copper(II) Species from the Copper/2,2′-Bypyridine and Copper/4-Dimethylaminopyridine Catalyzed Aerobic Alcohol Oxidations. *Polyhedron* **2015**, *99*, 223–229. DOI: 10.1016/j.poly.2015.07.080.

[42] Rayati, S.; Ghaemi, V. A.; Sadeghzadeh, N. Electronic Effects of Substituents on the Oxidation Potentials of Vanadyl Complexes with Tetradentate Schiff Base Ligands Derived from 1,2-Propylenediamine. *Catal. Commun.* **2010**, *11*, 792–796. DOI: 10.1016/j.catcom.2010.02.017.

[43] Adam, M. S. S.; Hafez, A. M.; El-Ghamry, I. Catalytic Performance of Binary and Ternary Oxovanadium Complexes of Dipyridinyl-Urea in (ep)Oxidation of Cis-Cyclooctene and 1-Octene. *React. Kinet. Mech. Cat.* **2018**, *124*, 779–805. DOI: 10.1007/s11144-018-1399-8.

[44] Adam, M. S. S. Catalytic Activity of Nickel(II), Copper(II) and Oxovanadium(II)-Dihydroindolone Complexes towards Homogeneous Oxidation Reactions. *Appl. Organometal. Chem.* **2018**, *32*, e4234. DOI: 10.1002/aoc.4234.

[45] Banu, K. S.; Chattopadhyay, T.; Banerjee, A.; Bhattacharya, S.; Zangrando, E.; Das, D. Catechol Oxidase Activity of Dinuclear Copper(II) Complexes of Robson Type Macrocyclic Ligands: Syntheses, X-Ray Crystal Structure, Spectroscopic Characterization of the Adducts and Kinetic Studies. *J. Mol. Catal. A* **2009**, *310*, 34–41. DOI: 10.1016/j.molcata.2009.05.016.

[46] Biswas, S.; Dutta, A.; Debnath, M.; Dolai, M.; Das, K. K.; Ali, M. A Novel Thermally Stable Hydroperoxo–Copper(II) Complex in a $Cu(N_2O_2)$ Chromophore of a Potential N_4O_2 Donor Schiff Base Ligand: Synthesis, Structure and Catalytic Studies. *Dalton Trans.* **2013**, *42*, 13210–13219. DOI: 10.1039/c3dt51359a.

[47] Abdel-Rahman, L. H.; Abu-Dief, A. M.; Adam, M. S. S.; Hamdan, S. K. Some New Nano-Sized Mononuclear Cu(II) Schiff Base Complexes: Design, Characterization, Molecular Modeling and Catalytic Potentials in Benzyl Alcohol Oxidation.

Catal. Lett. **2016**, *146*, 1373–1396. DOI: 10.1007/s10562-016-1755-0.

[48] Sun, Y.; Bi, S.; Song, D.; Qiao, C.; Mu, D.; Zhang, H. Study on the Interaction Mechanism between DNA and the Main Active Components in Scutellaria baicalensis Georgi. *Sens. Actuators B Chem.* **2008**, *128*, 799–810. DOI: 10.1016/j.snb.2007.09.082.

[49] Adam, M. S. S.; Al-Omair, M. A.; Ullah, F. Catalytic Comparison of Various Polar Zn(II)- and VO(II)-Schiff Base Complexes in (ep)Oxidation Processes of 1,2-Cyclohexene and Cyclohexane. *Res. Chem. Intermed.* **2019**, *45*, 4653–4675. DOI: 10.1007/s11164-019-03855-8.

[50] Hoover, J. M.; Ryland, B. L.; Stahl, S. S. Copper/TEMPO-Catalyzed Aerobic Alcohol Oxidation: Mechanistic Assessment of Different Catalyst Systems. *ACS Catal.* **2013**, *3*, 2599–2605. DOI: 10.1021/cs400689a.

[51] Abdel-Rahman, L. H.; El-Khatib, R. M.; Nassr, L. A. E.; Abu-Dief, A. M.; Lashin, F. E.-D. Design, Characterization, Teratogenicity Testing, Antibacterial, Antifungal and DNA Interaction of Few High Spin Fe(II) Schiff Base Amino Acid Complexes. *Spectrochim. Acta A* **2013**, *111*, 266–276. DOI: 10.1016/j.saa.2013.03.061.

[52] Sharma, A. K.; Chandra, S. Complexation of Nitrogen and Sulphur Donor Schiff's Base Ligand to Cr(III) and Ni(II) Metal Ions: Synthesis, Spectroscopic and Antipathogenic Studies. *Spectrochim. Acta A* **2011**, *78*, 337–342. DOI: 10.1016/j.saa.2010.10.017.

[53] Yousef, T. A.; Abu El-Reash, G. M.; El-Gammal, O. A.; Bedier, R. A. Co(II), Cu(II), Cd(II), Fe(III) and U(VI) Complexes Containing a NSNO Donor Ligand: Synthesis, Characterization, Optical Band Gap, in Vitro Antimicrobial and DNA Cleavage Studies. *J. Mol. Struct.* **2012**, *1029*, 149–160. DOI: 10.1016/j.molstruc.2012.06.050.

[54] Begum, M. S. A.; Saha, S.; Nethaji, M.; Chakravarty, A. R. Iron(III) Schiff Base Complexes of Arginine and Lysine as Netropsin Mimics Showing at-Selective DNA Binding and Photonuclease Activity. *J. Inorg. Biochem.* **2010**, *104*, 477–484. DOI: 10.1016/j.jinorgbio.2010.01.001.