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Influence of Steric Hindrance on the Antioxidant Activity of Some Schiff Base Ligands and Their Copper (II) Complexes

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ABSTRACT

Herein we report the synthesis, characterization and antioxidant activity of the Schiff base ligands (E)-4-bromo-2-((2-piperazine-1-yl)ethylimino)methylphenol and 2,2'-(1E,1E')-cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene))bismethan-1-yl-1-ylidene)bis (4-bromophenol) and their complexes of copper (II) ion. Antioxidant activities of the copper complexes were studied by ferric reducing antioxidant power (FRAP) assay according to the procedure reported by Benzie and Strain[1] which considered the reduction of ferric tripyridyl triazine complex to a ferrous complex at low pH by monitoring the change in absorption at 593nm. The overall results showed an increased in antioxidant activity with the increase in steric crowd. Similarly, the ligands show high activity than the complexes.

Key words: Synthesis, characterization, antioxidant activity.

INTRODUCTION

Interest in the symmetric and asymmetric synthesis of Schiff bases has increased significantly in recent years[2]. Diamines are known to coordinate to metal ions as bidentate ligands and forms both symmetric and asymmetric Schiff bases[3]. Being cancer one of the major leading diseases causing death in industrialized countries[4], as such, development of anticancer therapies is one of the fundamental goals in medicinal chemistry. It is well known that free radicals can damage protein, lipids and DNA of bio-tissues leading to the increased rates of cancer[1]. Fortunately, antioxidant can prevent this damage due to their free radical scavenging activity[9]. Hence it is of paramount importance to develop compounds with strong antioxidant activity and verify the factors affecting this biological activity. In this paper, we study the variation in antioxidant activity with increased steric crowd by measuring the activity of the Schiff base (E)-4-bromo-2-((2-piperazine-1-yl)ethylimino)methylphenol [$\mathbf{L_1}$] (less crowded) and 2,2'-(1E,1E')-cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)) bismethan-1-yl-1-ylidene)bis(4-bromophenol) [$\mathbf{L_2}$] (more crowded) against their Cu(II) complexes. The results were compared with that of Gallic acid and Vitamin C which are employed as reference standards to

ascertain the extent of antioxidant activity of the compounds under study.

MATERIALS AND METHODS

Materials

1-(2-Aminoethyl) piperazine, 5-bromosalicylaldehyde, cyclohexane-1, 2-diamine and $CuCl_2$ salts were purchased from Sigma-Aldrich. The spectroscopic grade DMSO-d_6 was obtained from Aldrich and all other solvents used were of analytical grade and used without further purifications.

Synthesis of the Schiff base L_1

The Schiff bases and their copper complexes were prepared according to the synthetic pathway shown in scheme1 and 2 following the procedure below:

A measured amount of 1-(2-aminoethyl)piperazine (0.13g, 1mmol) was dissolved in an absolute ethanol and added drop wise to the stirred ethanolic solution of (0.2g, 1mmol) Bromosalicylaldehyde at room temperature. The mixture is then refluxed for 1hr to give orange solution. After evaporating the solution using rotary evaporator, red oil was formed which on addition of solid sodium perchlorate (0.1g) produces yellow needle-like crystalline solids. Recrystallization was performed in methanol-chloroform mixture.

Synthesis complex [CuL_1]

A stoichiometric amount of $CuCl_2$ (0.17g, 1mmol) was dissolved in methanol and added to the stirred methanolic solution (0.3g, 1mmol) of the ligand at room temperature. A green precipitate was formed, which after stirring for 5min and settled is filtered. The filtrate is concentrated using rotary evaporator which on standing for 10 days gives black crystals. The crystals were isolated by filtration, washed with methanol and recrystallized to give pure and quality crystals.

Synthesis of the Schiff base L_2

Calculated amount of cyclohexane-1, 2-diamine (0.14g, 1mmol) was dissolve in an absolute ethanol and added drop wise to the stirred ethanolic solution (0.2g, 1mmol) of Bromosalicylaldehyde at room temperature and then refluxed for 1hr, to give yellow crystals. The crystals were removed by filtration, recrystallized in methanol and dried in a vacuum for further analysis.

Synthesis of complex [CuL_2]

A stoichiometric amount of $CuCl_2$ (0.17g, 1mmol) was dissolved in methanol and added to the stirred methanolic solution (0.48g, 1mmol) of the ligand at room temperature. A green precipitate was formed after stirring for about 2min which was allowed to settle and then filtered and dried in a vacuum.

Mass Spectra

The mass spectra of the ligand **L1** was

Table 1

Compounds	m/z
L1($C_{13}H_{18}BrN_3O$)	130, 312, 313, 314, 312,
L2($C_{20}H_{20}Br_2N_2O_2$)	467.19, 479.9,481.9,477.9,480.9, 478, 482, 483, 480

Table 2

Compound	ν(N-H)	ν(C-H) aliphatic	ν(C=N)	ν(C-C) Aromatic	ν(C-N)	ν(O-H)	ν(C-H) aromatic	ν(M-O)	ν(M-N)
L1($C_{13}H_{18}BrN_3O$)	3421	2736	1638	1458	1176	3421	688	-	-
CuL1($C_{13}H_{18}BrN_3O$)	3413	2947	1635	1478	1182	-	694	624	554
L2($C_{20}H_{20}Br_2N_2O_2$)	none	2926	1630	1475	1184	3434	628	-	-
CuL2($C_{20}H_{20}Br_2N_2O_2$)	none	2935	1630	1455	1175	-	647	570	513

recorded at room temperature and showed a molecular ion peak at m/z 130 which is assignable to the decomposition of N-(Aminoethyl)piperazine and another peak at m/z 311.06(100%) which is attributed to the decomposition of the whole compound. Other peaks were observed at 313(97%), 314(14.8%), 312(14.3%). While the Ligand L2 shows molecular ion peaks at of 467(100%), 479(97%), 481(51.33%), 477(51.2%), 480(21.9%) and 478(11.5%). As shown in the table below

Table 3

Compound	Chemical shifts in ppm				
	O-H	N-H	CH_2	Ar-Br	C=N
L1	4.32	2.17	2.51	7.37	8.29
L2	3.5	none	2.52	7.25	8.98

Table 4

Compound	Wave length	Absorption	Description
L1	279	3.073	π-π^*
	303	3.135	n-π^*
	312	3.135	n-π^*
	344	3.135	n-π^*
L2	267	2.916	π-π^*
	321	3.263	n-π^*
CuL1	274	2.552	π-π^*
	377	1.554	L-MCT
	636	0.144	d-d
CuL2	272	2.592	π-π
	372	1.418	L-MCT
	588	0.354	d-d

Table 5: Antioxidant activity

200	0.263	0.261	0.256	0.26	0.144
400	0.379	0.41	0.383	0.391	0.275
600	0.52	0.545	0.585	0.55	0.434
800	0.707	0.703	0.704	0.705	0.589
1000	0.841	0.809	0.925	0.858	0.742

Infra red spectra

The IR spectra of the ligand L1 showed a broad band in the region 3400cm^{-1} which is assignable to N-H amine group. Appearance of this peak in the spectra of both the ligand and its Cu (II) complex indicates that the secondary amine at the extreme end of the structure is free from complexation. However, the spectrum of the ligand shows sharp absorption at1640.cm^{-1} which is due to azomethine –C=N-, this absorption seems to shift to a lower frequency in the spectra of the complex which indicates the involvement –C=N- nitrogen in the coordination to metal ion[5,6]. Assignment of the proposed coordination site is further supported by the appearance of medium bands at 554cm-1 which could be attributed to ½(M-N) and 624cm-1 for ν(M-O)[7,3].

The spectra of the ligand L2 shows sharp absorption 1630.cm^{-1} which is assignable to –C=N- of the azomethine, this absorption drops to a lower frequency of 1630. -1591.cm-1 in the complex indicating the coordination of –C=N- to the central metal ion. Also, the proposed coordination site was supported by the appearance of band regions at 513cm-1 for ν(M-N) and 570cm-1 which is assignable to ν(M-O) respectively as shown in the table below

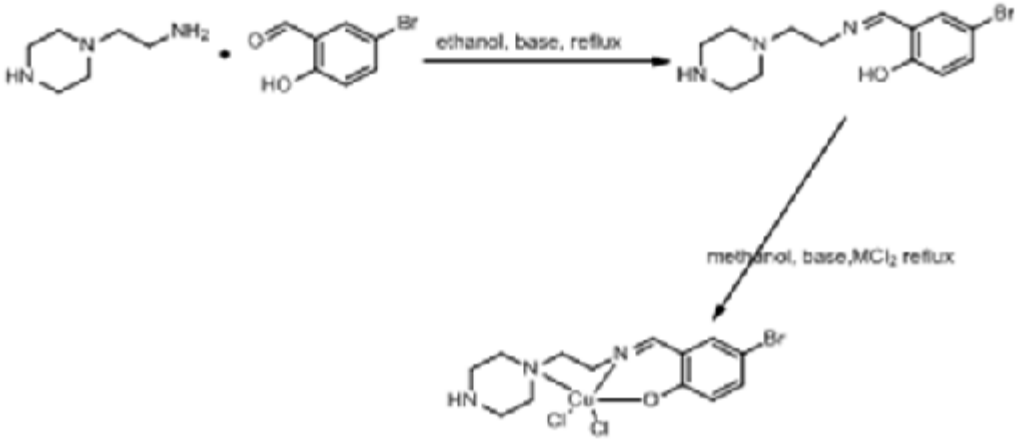
Table 6

Samples	rep1	rep2	rep3	Mean	avg-blnk	frap value
L2	0.245	0.239	0.235	0.240	0.124	176.7
L1	0.215	0.23	0.219	0.221	0.105	150.5
CuL2	0.182	0.16	0.175	0.172	0.056	80.5
CuL1	0.155	0.137	0.147	0.146	0.030	43.3
GA 10x	2.227	2.134	2.135	2.165	2.049	2927.6
AA 10x	1.161	1.1156	1.234	1.170	1.054	1506.0

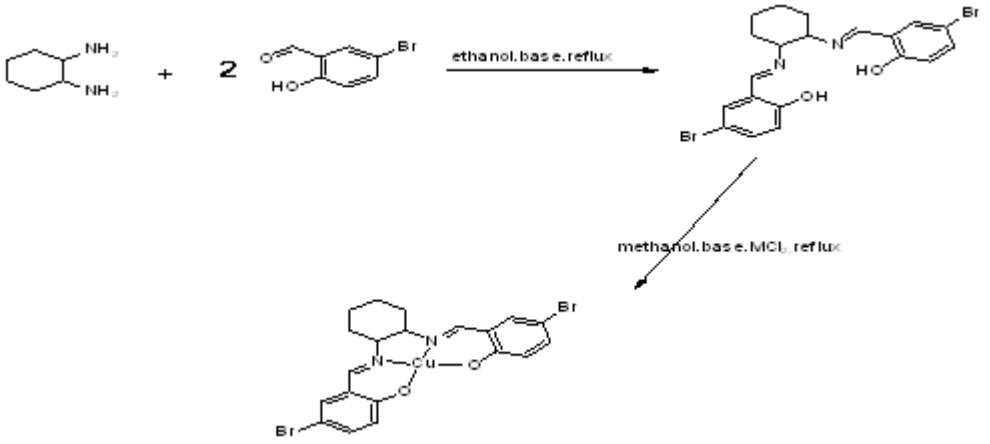
^{1}H-NMR spectra

The HNMR spectra of the compound L1 was recorded in $CDCl_3$ and the following signals were observed. N-H amine was observed at 2.17ppm, methylene (CH_2) with 1-α-N(C) C and 1-β-N-C at 2.51ppm, the chemical shift at 4.32ppm can be assign to aromatic alcohol while at 7.37ppm the shift can be attributed to aromatic bromide. Azomethine was observed at 8.29ppm.

The spectrum of the L2 shows aromatic alcohol at 3.5ppm, methylene CH_2 at 2.52ppm, aromatic bromide at 7.25ppm and azomethine at 8.98 as shown in table 3.



Scheme 1



Scheme 2

Physical and analytical data

Compound	Formula	Colour	M.P/D.T	%Yeid	Calc.(found)		
					C	H	N
L1	$C_{13}H_{18}BrN_3O$	red	40	72	50(48)	5.8(5.6)	13.5(12.9)
L2	$C_{20}H_{20}Br_2N_2O_2$	yellow	130	87	50(48.7)	4.2(3.9)	5.8(4.9)
CuL1	$Cu(C_{13}H_{18}BrN_3O)$	deep green	328	65	35(34)	3.8(3.6)	9.4(9.2)
CuL2	$Cu(C_{20}H_{20}Br_2N_2O_2)$	green	346	80	39(36)	2.9(2.8)	4.6(4.5)

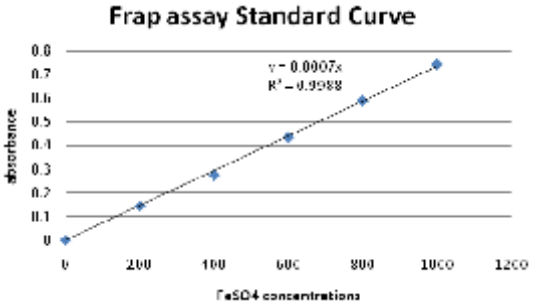


Fig. 1

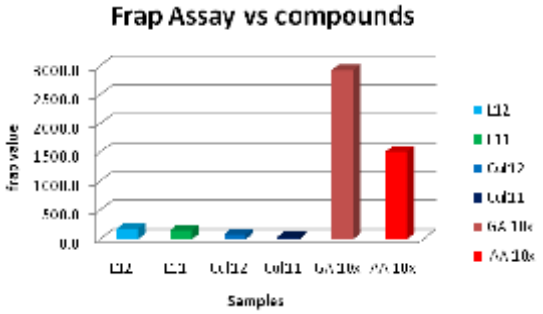


Fig. 2

UV-Visible

The UV-Visible spectra of the complexes were carried out in DMSO and their tentative assignments are as follows:

The spectra of L1 shows absorption of 3.073 at 279nm which is assignable to π-π* electronic transition this is followed with a bathochromic shift at wavelength 303nm and remain constant at wavelengths 312nm, and 344nm, this is attributed to n-π* electronic transition due to nitrogen groups found in the various part of the ligand. However, the spectra of its complex (CuL1) shows absorption of 2.552 at 274nm which is assignable to π-π* this absorption then move to a high wavelength of 377nm which is very close to the wavelength of 344nm found in the ligand and can be attributable to ligand-metal charge transfer, another absorption at 636nm was observed and can be assign to d-d electronic transition in Cu (II). The spectra of L2 shows absorption at 267nm which correspond to π-π* electronic transition, a bathochromic shift occur at 321nm which is assignable to n-π* electronic transition, its CuL2 complex shows absorption at 272nm which can be attributed to π-π* electronic transition, another absorption at 372nm in relation to the absorption at 321nm in the spectra of the ligand can be assignable to ligand-metal charge transfer, while absorption at 588nm can be attributed to d-d electronic transition as shown in the table 4 below.

Biological Activity

The antioxidant activity results presented in figure 13 showed that the synthesized ligands and their metal (II) complexes posses antioxidant activity. The compounds were screened for their antioxidant activity and the scavenging ability of the ligands as well as their complexes against hydroxyl radicals were tested as a function of concentration from 0-0.8μM as shown in figure 13. It can be seen that the inhibitory effects of complexes on the hydroxyl radicals are related to concentration. The scavenging activities was found to be more on the ligands than on their Cu(II) complexes and is increase with increasing steric crowding according to the following order L2>L1>CuL2>CuL1 detail was shown on the tables 5 & 6 and figures 1& 2 below.

CONCLUSION

The synthesized compounds showed antioxidant properties. By comparison, the ligands showed high antioxidant activity than their Cu (II) complexes. However, none of the compounds were found to have high activity than vitamin C and/or Gallic acid. L2 reveals the highest radical scavenging activity among the series whereas the compound CuL1 reveals the lowest. The different relative scavenging activity of the individual compounds against different radicals may be attributed to steric crowd, number of free hydroxyl groups and other factors such as stereoselectivity of the radicals or the solubility of these compounds in different testing systems may also affect the capacity of individual compounds to react and quench different radicals[8].

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