Some new Schiff Base Complexes of copper (II) and Their Biological Screening

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Abstract

Homodinuclear complexes of Cu(II) metal ions with three Schiff base ligands have been prepared andcharacterized.Theligandsare: dibenzoinlidenemalonoyldihydrazide($BMDH_4$),dibenzoinlidenesuccinyldihydrazide($BSDH_4$)and dibenzoinlidene phthaloyldihydrazide ($BPDH_4$) which are obtained by the reaction of malonoyldihy drazide,succinyl dihydrazide and phthalolyldihydrazide with benzoin in mole ratio1:2 The preparation of the complexes was carried out in both neutral and basic media and have been characterized by different phys- icochemically and they found to formulas$[Cu_2(LH_4)_2]X_4$ in neutral medium and $[Cu_2L_2]$in basic medium, respectively. Octahededral structure has been suggested for all the hexacoordinated complexes Furthermore thecomplexes have been found to be biologically active as demonstrated by antibacterial screening against four human pathogenic bacterial stains. It has been found that the complexes were more effective agent than the ligands (where X= Cl^-,NO_3^-).

Key words: acid hydrazide, Schiff base complexes, copper (II) complexes, antibacterial agents

بعض معقدات قواعد شيف للنحاس الثنائية ودراسة فعاليتها البايولوجية

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الخلاصة

تم في هذا البحث تحضير وتشخيص عدد من معقدات النحاس(II) ثنائية النوى المتجانسة مع ثلاث ليكاندات وهي ثنائي بنزونيليدين مالونويل ثنائي هيدرازيد($BMDH_4$) و ثنائي بنزونيليدين سكسنايل ثنائي هيدرازيد ($BSDH_4$) و ثنائي بنزونيليدين فثالوليل ثنائي هيدرازيد ($BPDH_4$) ، تم الحصول عليها من التفاعل بين الهيدرازيدات الحامضية مع البنزوين بنسبة مولالية 1: 2 . وتم تحضير المعقدات في كل من المحيطن المتعادل والقاعدي وشخصت هذه المعقدات باستخدام تقنيات مختلفة فيزياوية وكيميائية وطيفية.واستُنتج من هذاالدراسات ان معقدات الوسط المتعادل ايونية موجبة لها الصيغة العامة $[Cu_2(LH_4)_2]X4$ في حين معقدات الوسطالقاعدي متعادلة لها الصيغة العامة $[Cu_2L_2]0$(حيث ان $X= Cl^-,NO_3^-$) واوضحت هذه الدراسات ان لهذه المعقدات سداسية التناسق بنية ثماني السطوح الاكثر احتمالا. كما شخصت الفعالية البكتيرية للمعقدات على اربع جراثيم مرضية كمضدات للبكتيريا الموجبة والسالبة لصبغة كرام والمعزولة من حالات مرضية وقد اثبت المعقدات ان لها فعالية كمضدات للبكتيريا اكثرمن اليكاندات.

الكلمات الدالة: حامض الهيدرازيد، معقدات قواعد شيف، معقدات النحاس الثنائية، عوامل مضادة للبكتيريا

Introduction

Many Schiff bases and their complexes have been widely studied due to their use as a model for biological system. In addition , they exhibit a wide variety of industrial and pharmacological properties such as antinflammatory ,antimalarial antithelmentic activity, hypotensive actions ,and antitumor and carcinostatic activity[1-3] . Recently, considerable attention has been paid to chemistry of the metal complexes of Schiff bases containing oxygen, nitrogen and other donors because they offer many attractive properties such as displaying a double role of electron transport and light emission , higher thermal stability and easy sublimation[4-6]. Schiff bases derived from the reaction of the aldehy- des or ketones with hydrazides are very interesting since they are present in keto-enol forms and can form different types of complexes[7-9] In present work,new copper complexes formed with Schiff base ligands derived from benzoin and malonyl dihydrazide ($BMDH_4$), succinyldihydrazide ($BSDH_4$) and phthalolyldihydrazide ($BPDH_4$) have synthesized and characterized by different chemical, physical and spectral methods. Furthermore, the ligands and their complexes have been found to be biologically active demonstrated by antibacterial screening against four human pathogenic bacterial stains. It has been found that the complexes were more effective agents than the ligands.

Experimental

1-Starting materials:

All the chemicals used were supplied from Fluka, BDH, Aldrich, Merck, Acid hydrazides , malonyl , succinyl and phthaloyl dihydrazides were prepared by the condensation of the corresponding esters and hydrazine hydrate in 1: 2 molar ratio according to the reported procedure[10].

2- Analysis and physical measurements:

Copper contents were determined by applying precipitation method after the decomposition of the complexes with concentrated nitric acid[11] . Electronic spectra were recorded on Shimadzu UV-160 spectrophotometer for 10^{-3} M for complexes in DMF at 25°C using 1 cm quartz cell. Infrared absorption was recorded on a Perkin-Elmer 580 spectrophotometer as KBr Pelletes in the range 400-4000 cm^{-1}. Molar conductance of the complexes was measured at room temperature for 10^{-3} M in DMF solution using conductivity bridge type LF-42.Magnetic susceptibility of the complexes was measured by Bruker-BM6.

3- Synthetic methods:

A- The Schiff base ligands were prepared by the condensation of benzoin (0.02mole, 4.7g) and one of the following ,acid dihydrazide in(2:1) molar ratio in 20 ml ethanol. [malonyldihydrazide (MDH_2)(0.01mole,1.43g) or succinyldihydrazide (SDH_2)(0.01, 1.5g) or phthaloyldihydrazide (PDH_2)(0.01 mole , 2.15g)] . The reaction mixture was heated under reflux for 3-9 hrs. After cooling, fine precipitate was formed which was filtered off, washed with cold ethanol and dried.

B- Preparation of the complexes (1:1 molar ratio ,copper salts: ligand)

A general procedure has been used for the preparation of the complexes in neutral and basic medium .In neutral medium ,a solution of 0 .5g of nickel chloride or nickel nitrate in 10 ml of ethanol has been added to the solution of one of acid dihydrazides [($BMDH_4$,1.93g or 1.07g) or ($BSDH_4$,1.98g or 1.10g) or ($BPDH_4$, 2.16g or 1.20g)].An ethanolic mixture containing 1:1 molar ratio of copper (II) salt and the ligand has been refluxed for about three hours. After cooling the separated complexes were filtered off , recrystallized from hot water and dried.The alkaline medium complexes have been prepared by applying the same above amounts except that the ligands were treated with 1M KOH solution .Complete precipitation of the complexes were achieved at pH 9-10. The mixtures were left to stand or 30 minutes, then filtered off, recrystallized from hot water and dried.

4- Biological activity:

The antibacterial activity of the ligands and their complexes were selected for screening by disc diffusion technique[12]. The test disc was containing 20microgram of the compound. The activity was shown against the *S.aureus*, *E.Coli*, *P.mirabilis* and *k.pneumoniae* . The antibiotic Vancomycin and gentamycin were used as control drugs. The inhibition zone (in mm) for the copper complexes and ligands tested for antibacterial are listed in Table (1).

Table (1): The antibacterial activities of the ligands and their complexes

Compound	Test organism			
	Gr^+	Gr^-		
	s.aureus	*E.coli*	*k.pneumoniae*	*P.mirabilis*
$BMDH_4$	4	-	-	5
$[Cu_2(BMDH_4)_2]Cl_4$	8	10	6	8
$[Cu_2(BMD)_2]$	10	8	5	3
$[Cu_2(BMDH_4)_2](N0_3)_4$	7	7	8	8
$BSDH_4$	4	-	-	3
$[Cu_2(BSDH_4)_2]Cl_4$	11	8	10	6
$[Cu_2(BSD)_2]$	13	4	3	4
$[Cu_2(BSDH_4)_2](N0_3)_4$	11	5	9	5
$BPDH_4$	7	5	3	5
$[Cu_2(BPDH_4)_2]Cl_4$	10	7	8	4
$[Cu_2(BPD)_2]$	9	7	3	6
$[Cu_2(BPDH_4)_2](N0_3)_4$	10	5	6	4
Cancomycin	15	-	-	-
Gentamicin	-	17	14	17

The value is the inhibition zone diameter subtracted disc diameter.
S= sensitive, zone diameter nor more than 6mm less than control
MS= moderately sensitive, zone diameter of 6-12 mm less than control
R= resistant, zone diameter of 12 mm or less than control

Results and Discussion

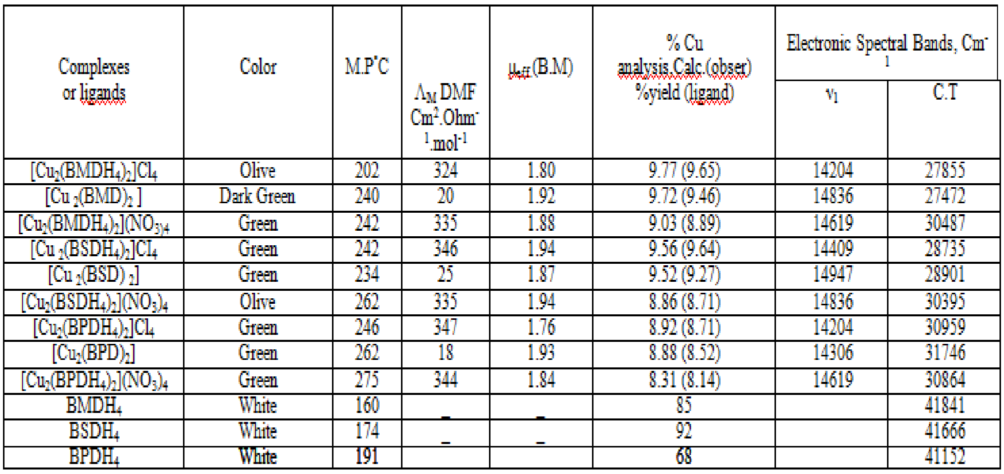
The reaction of the two copper (II) salts with the ligands in both neutral and basic solution may be represented in the following two reactions: -

$$2CuX_2.nH_2O + 2LH_4 \longrightarrow [Cu_2 (LH_4)_2]X_4 + 2nH_2O….. \text{ Type I}$$

$$2CuX_2.nH_2O + 2LH_4 + 2KOH \longrightarrow [Cu_2L_2]+2KX+(2n+2)\ H_2O+3H_2 \text{ .. Type II}$$

Where X = Cl^-, NO^-_3; LH_4 = $BMDH_4$, $BSDH_4$, $BPDH_4$ and L are the tetrabasic anionic species were obtained from neutral and alkaline solutions, respectively . For all the complexes, the metal contents and the molar conductance values are in a good agreement with the given formulations Table (2).

Table (2): Some physical and spectral data of the complexes



Complexes or ligands	Color	M.P°C	Λ_M DMF $Cm^2.Ohm^{-1}.mol^{-1}$	μ_{eff} (B.M)	% Cu analysis.Calc.(obser) %yield (ligand)	Electronic Spectral Bands, Cm^{-1}	
						ν_1	C.T
$[Cu_2(BMDH_4)_2]Cl_4$	Olive	202	324	1.80	9.77 (9.65)	14204	27855
$[Cu_2(BMD)_2]$	Dark Green	240	20	1.92	9.72 (9.46)	14836	27472
$[Cu_2(BMDH_4)_2](NO_3)_4$	Green	242	335	1.88	9.03 (8.89)	14619	30487
$[Cu_2(BSDH_4)_2]Cl_4$	Green	242	346	1.94	9.56 (9.64)	14409	28735
$[Cu_2(BSD)_2]$	Green	234	25	1.87	9.52 (9.27)	14947	28901
$[Cu_2(BSDH_4)_2](NO_3)_4$	Olive	262	335	1.94	8.86 (8.71)	14836	30395
$[Cu_2(BPDH_4)_2]Cl_4$	Green	246	347	1.76	8.92 (8.71)	14204	30959
$[Cu_2(BPD)_2]$	Green	262	18	1.93	8.88 (8.52)	14306	31746
$[Cu_2(BPDH_4)_2](NO_3)_4$	Green	275	344	1.84	8.31 (8.14)	14619	30864
$BMDH_4$	White	160	-	-	85		41841
$BSDH_4$	White	174	-	-	92		41666
$BPDH_4$	White	191			68		41152

The solid complexes are colored, conductance in DMF indicate their ionic and non ionic nature[13,14] .

The coordination sites of the ligands were inferred by infrared spectroscopy, which is considered a useful technique for probing the structure of Schiff base complexes. The infrared data of the main absorption bands of the ligands and the complexes are given in (Table 3).

Table (3): Important IR spectral bands (cm^{-1}) of the free ligands and their complexes

Compound	ν_{OH}	ν_{NH}	$\nu_{C=0}$	$\nu_{C=N}$	δ_{OH}	ν_{C-O}	$\nu_{C=N-N=C}$ azine chromophore	ν_{N-N}	ν_{M-O}	ν_{M-N}	ν_{Cl^-} ionic	νNO^-_3 ionic
$BMDH_4$	3400	3250	1685	1630	1255	1200	-	1035	-	-	-	-
$[Cu_2(BMDH_4)_2]Cl_4$	3300	3240	1665	1605	1235	1175	-	1045	435	480	570	-
$[Cu_2(BMD)_2]$	-	-	-	1595	-	1175	1575	1045	440	475	-	-
$[Cu_2(BMDH_4)_2](NO_3)_4$	3280	3250	1665	1605	1235	1180	-	1045	440	480	-	1380,720
$BSDH_4$	3410	3300	1695	1615	1275	1220	-	1030	-	-	-	-
$[Cu_2(BSDH_4)_2]Cl_4$	3310	3300	1675	1575	1255	1190	-	1055	430	470	585	-
$[Cu_2(BSD)_2]$	-	-	-	1585	-	1200	1550	1055	435	480	-	-
$[Cu_2(BSDH_4)_2](NO_3)_4$	3310	3300	1675	1575	1255	1190	-	1054	430	470	-	1380,720
$BPDH_4$	3500	3200	1675	1625	1275	1205	-	1020	-	-	-	-
$[Cu_2(BPDH_4)_2]Cl_4$	3400	3200	1650	1585	1255	1180	-	1050	440	480	600	-
$[Cu_2(BPD)_2]$	-	-	-	1605	-	1180	1575	1055	435	470	-	-
$[Cu_2(BPDH_4)_2](NO_3)_4$	3400	3195	1650	1595	1235	1175	-	1055	440	480	-	1380,720

For Type I complexes, $[Cu_2(LH_4)_2]X_4$, the stretching and deformation vibrations of OH groups were shifted to lower frequency by about 100 -120 and 10 - 40 cm^{-1}, respectively. Compared to their positions in the free ligands spectrum indicating coordination of alcoholic hydroxyl groups through their oxygen atoms. In addition, the stretching vibration of C-O single bond split into two peaks due to (C-O $_{H}$ ^{M}) which support the above suggested coordination of the hydroxyl groups without deprotonation[13]. The negative shift of about 10 -25 cm^{-1} in the stretching frequency of carbonyl group suggests coordination through the carbonyl oxygen atom as observed in similar acid hyrazide and hydrazine complexes [15,16] . The C=N stretching band shows negative shift of about 10 - 40cm^{-1},indicating the involvement of azomethine nitrogen atom in complex formulation[17,18] while the NH remains almost unaffected compared to the free ligand spectrum.

In the infrared spectra of type II complexes, [Cu_2L_2] the absence of the bands due to OH-stretching and deformation vibrations was attributed to the coordination of the ligand through deprotonanon of the alcoholic hydroxyl groups.The stretching band of the azomethine group was also shifted by about (10 -40cm^{-1}),suggesting coordination through azomethine nitrogen similar to that which occurred in type I complexes.On the other hand , the absence of the stretching band due to NH and C=O mioety was attributed, as reported for similar cases[19] to the presence of the enol tautomer. In these complexes,the new bands located at1625 -1630 and1550-1570 cm^{-1} were assigned to the combined stretching vibration of [(O-C=N)+ (C=N)] and the str- etching vibration of azine chromophore, respectively[20]. The presence of these bands is strong evidence for the enolization deprotonati- on in alkaline solution.

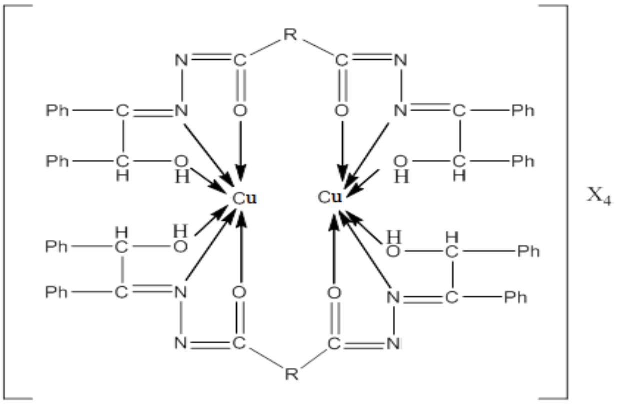
In all complexes of both types, positive shift of about 10 - 30 cm^{-1} was observed in the stretching vibration of N-N band , since the shift is less than 50 cm^{-1} only one nitrogen atom is involved in bonding [21]. In addition to the above mentioned perturbation in infrared spectra,new bands around 470-480and435-440cm^{-1} were observed and tentatively assigned to M-N and M-O stretching modes, respect- ively[22] . The band located at 1380, 720 and 760 cm^{-1} in nitrate complexes, were attributed to ionic nitrate groups, while the new band located at 575-600 cm^{-1} in complexes might be due to the interaction of chloride ion with other atoms in the molecule and thus, suggesting uncoordinated chloride ion[23] .These observations are in accordance with the conductivity data and the given general formula for these complexes (Type I).

The electronic spectra of Cu(II) complexes(Table 1) showed only one broad band centered at 14204-14947cm^{-1} due to the transition $^2Eg \rightarrow {}^4T_{2g}$ of ^2D state . This band has been compartable both in position and width with the earlier reported octahedral complexes Because the eg state has been highly affected by Jahn Taller effect, therefore, copper(II)complexes had distorted octahedral geometry[24]. In addition, high intensity bands were observed in the ultraviolet region of the spectra and assigned to C-T transitions which due to the partial electron density migration from the filled ligands π-orbital to the empty metal π-orbitals. The observed CT bands suggested the presence of some π-character in coordination bonds between the metal ions and the ligand . All the complexes showed magnetic behavior corresponds to the presence of one unpaired electron and (Table 1) are in good agreement with the distorted octahedral structure[25] and in the range

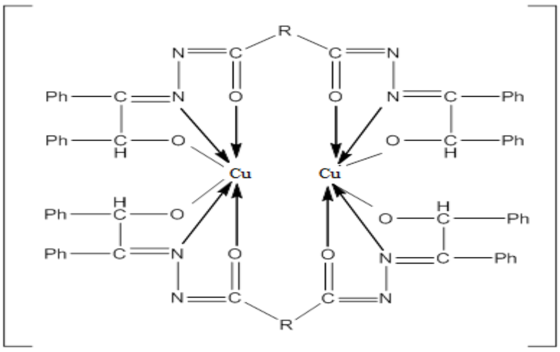
(1.76-1.94) B .M. The antibacterial agents were known to attack the bacterial cell in a variety of ways such as killing or of cell wall, protein and nucleic acid through their effects on the synthesis of ribonucleic acid which could be resulted from the inhibition action of bacterial DNA enzyme which caused the separation of supercoiling or decantenation or unknotting of the DNA. Numerous experiments have been done to determine the antibacterial influence of the complexes (Table 3,4 & Fig. 2). The chemical complexes had a good ability to attack the cell wall of the bacteria through the heavy metal ions which preferentially bind to SH(sulfhydryl group) of the cell enzyme more strongly, it is logical to assume that the complexes screened were involved in a competitive equilibria involving the SH group of the cell enzyme.

Conclusion

According to the above studies, it was concluded that all the ligands act as neutral hexadentate in neutral solution giving cationic complexes and coordinating through alcoholic oxygen, carbonyl oxygen and azomethine nitrogen atoms. In basic medium neutral complexes were obtained (Fig. 1)



[$Cu_2(LH_4)_2$]X_4

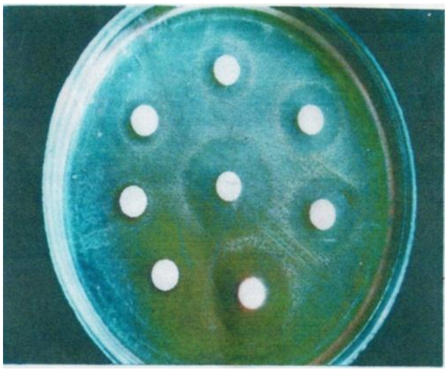


– Cu_2L_2 –

R= CH_2, CH_2CH_2 or Ph X = Cl^- or NO_3^-

Fig. (1): The proposed structures of complexes

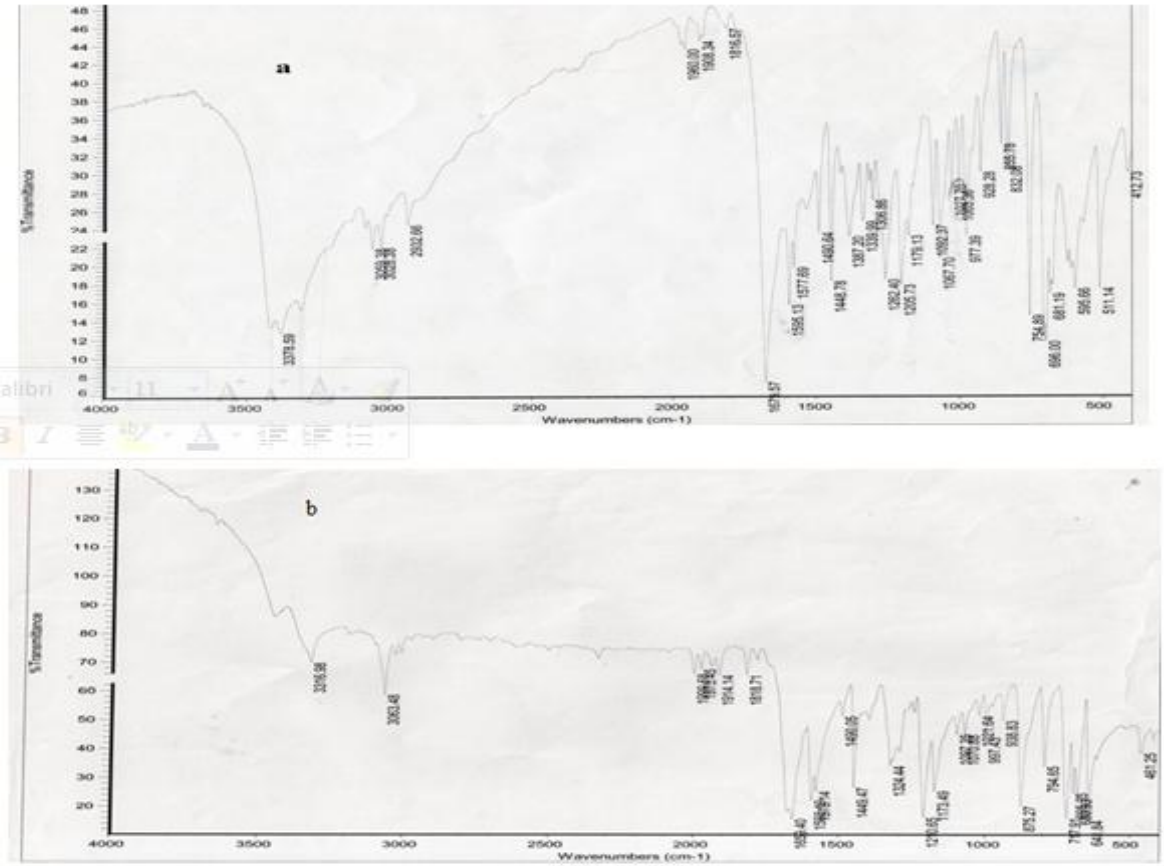
and the hexadentate action of the ligand was satisfied by coordination through both deprotonated alcoholic oxygen, enolic oxygen and azomethine nitrogen atoms .In neutral medium (cationic complexes) ,the chloride ion joint to the copper ion in ionic manner . In all cases the same complexes were obtained with respect to mole ratio
(1: 1 or 2:2 ligand : metal) and an octahedral structure was suggested.Therefore,we concluded the most of the complexes acquire a good antibacterial activity, this may be due to interaction of the metal ion more strongly than the donor atoms in the ligands and these observations have been consistent with that observed by many authors[26] as shown in (Table 3) and Figure (2).



Effect of some complexes on S. Aureus

Fig (2): Antibacterial activity of different concentration of complex $[Cu_2(BSD)_2]$ on E. Coli

IR Spectra OF (a) $BMDH_4$ and (b)$[Cu_2(BPD)_2]$



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