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Preparation and Antibacterial Activity of Copper and Cobalt Complexes of 4-Chloro-3-nitrobenzoate with a Nitrogen Donor Ligand

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Copper and cobalt complexes with 4-chloro-3-nitrobenzoate (ClNBz) and the nitrogen ligands 1,3-diaminopropane (1,3-DAP) or *o*-phenylenediamine (*o*-PDA), were prepared and characterized. The complexes [Cu(ClNBz)$_2$(1,3-DAP)] (1), [Cu(ClNBz)(*o*-PDA)]Cl (2), [Co(ClNBz)$_2$(1,3-DAP)] (3) and [Co(ClNBz)$_2$(*o*-PDA)$_2$] (4) were characterized by FTIR, UV–Visible absorption, elemental analysis and thermal analysis. Complex [Cu(ClNBz)(*o*-PDA)]Cl (2) shows high antibacterial activity as indicated by its ability to inhibit the growth of *Staphylococcus aureus*, *Enterococcus faecalis*.

Key words complex; antibacterial; thermal analysis

Carboxylate ligand are of great interest due to their various coordination modes to transition metals.[1—4)] Mononuclear carboxylate copper and nickel complexes in the presence of nitrogen donor ligands have been isolated in neutral or cationic form.[5—9)] The antifungal and antibacterial properties of a range of copper(II) complexes have been evaluated against several pathogenic fungi and bacteria.[10—13)] In addition to its ability to combat infection or neoplastic disease, an antibiotic must exhibit selective toxicity, chemical stability, and optimun rates of bio-transformation and elimination.[14,15)] In this paper we report the synthesis of copper(II) and cobalt(II) complexes with mixed ligands: 4-chloro-3-nitrobenzoic acid (ClNBz) and 1,3-diamino propane (1,3-DAP) or *o*-phenylenediamine (*o*-PDA).

The antimicrobial efficiency of the complex (**2**) [Cu(ClNBz)(*o*-PDA)]Cl has been tested on four different bacteria.

Experimental

Physical Measurements Infrared spectra (200—4000 cm^{-1}) were recorded on a Shimadzu (Prestige 41) FT-IR spectrophotometer with samples prepared as KBr pellets. Elemental analysis was performed on Flash EA1112 series "THERMO." UV–Visible spectra were recorded on a Ciba Corning 2800 dual beam spectrophotometer. Thermal analysis was performed on Setaram-Labsys instrument using TG-DSC module. The heating rate was 3 °C/min. Dry nitrogen was passed over 15 mg of the sample placed in a platinum crucible.[16)]

Preparation of the Complexes Preparation of (**1**): 1,3-Diaminopropane (0.8 ml, 10 mmol) was added to 4-chloro-3-nitrobenzoic acid (2.00 g, 10 mmol) in 50 ml ethanol. A solution of $CuCl_2 \cdot 2H_2O$ (1.7 g, 10 mmol) in 10 ml ethanol was then added dropwise with stirring. The color of the mixture changed from light yellow into blue, then into green, and a precipitate of green color settled out. The reaction was stirred further for 1 h, then left to stand for 24 h. The green powder product was collected by filtration, washed with water and ethanol and then dried over P_2O_5. Yield 65%.

Anal. Calcd for $C_{20}H_{26}Cl_2CuN_6O_8$: C, 39.19; H, 4.28; N, 13.71. Found: C, 39.02; H, 4.01; N, 13.42. UV–Vis: λ_{max} (DMSO, nm)=265 and 675.

Preparation of (**2**): 1,2-Phenylenediamine (1.08 g, 10 mmol) was added to 4-chloro-3-nitrobenzoic acid (2.02 g, 10 mmol) in 40 ml of hot ethanol. Ten millimoles of $CuCl_2 \cdot 2H_2O$ in 15 ml ethanol was added dropwise to the above solution with stirring. The solution color changes from yellowish orange into light green, and a precipitate settled out. The reaction was stirred further for 1 h, then left to stand for 24 h. The blue solid was collected by filtration, washed with ethanol and dried in vacuum over P_2O_5. Yield 65%.

Anal. Calcd for $C_{13}H_{11}Cl_2CuN_3O_4$: C, 38.3; H, 2.72; N, 10.31; Found %C=38.22. Found: C, 38.22; H, 2.68; N, 10.26. UV–Vis: λ_{max} (DMSO, nm)=288, 355, 420, and 665.

Preparation of (**3**): $CoCl_2 \cdot 6H_2O$ (1.2 g, 5 mmol) was added to a mixture of 1,3-diaminopropane (0.4 ml, 5 mmol) and 4-chloro-3-nitrobenzoic acid (1.01 g, 5 mmol) in ethanol (40 ml). The solution color changed from pale yellow into purple, and a precipitate formed. The violet product was obtained as above. Yield 60%.

Anal. Calcd for $C_{17}H_{16}C_{12}CoN_4O_8$: C, 38.22; H, 3.02; N, 10.49. Found: C, 38.09; H, 2.98; N, 10.22. UV–Vis: λ_{max} (DMSO, nm)=268, 570, 600 and 670.

Preparation of (**4**): A 15 ml ethanolic solution of $CoCl_2 \cdot 6H_2O$ (2.38 g, 10 mmol) was added slowly with stirring to a solution of 1,2-phenylenediamine (1.08 g, 10 mmol) and 4-chloro-3-nitrobenzoic acid (2.00 g, 10 mmol) in 40 ml of hot ethanol. While the metal solution was added, the reaction solution color changed from yellowish orange into dark blue, and a precipitate formed. The brownish red powder was collected and dried as before. Yield 60%.

Anal. Calcd for $C_{26}H_{22}Cl_2CoN_6O_8$: C, 46.17; H, 3.28; N, 12.43, Found: C, 46.06; H, 3.14; N, 12.19. UV–Vis: λ_{max} (DMSO, nm)=300, 444, 505 and 555.

Discussion

IR and UV Spectra IR spectral data for the complexes are listed in Table 1. Two very strong bands attributed to ν_{asym} (CO_2) and the symmetric ν_{sym} (CO_2) streching vibrations, in the regions 1600—1630 cm^{-1} and 1350—1520 cm^{-1} respectively, were observed for the complexes. The green (**1**) and blue (**2**) copper complexes exhibit d–d transitions at 675 nm with 1,3-diaminopropane and at 665 nm with *o*-phenylenediamine ligand, while the violet (**3**) and red (**4**) cobalt complexes display d–d transitions at 600 and 670 nm with 1,3-diaminopropane, and at 505 and 555 nm with *o*-phenylenediamine ligand. The octahedral nature of the cobalt complexes is reflected in observing two visible d–d transitions. This is in agreement with the split of the degeneracy of the eg orbitals due to strong Jahn–Teller distortion. Such split

Table 1. Infrared Spectral Data and Modes of Coordination of Carboxylate as Monodentate and Bidentate Ligand

Complex number	IR (KBr, cm^{-1})		$\Delta\nu$ (cm^{-1})	Carboxylate binding mode
	ν_{sym} (COO$^-$)	ν_{asym} (COO$^-$)		
1	1607	1417	190	Unidentate
2	1628	1509	119	Bidentate
3	1628	1521	107	Bidentate
4	1614	1354	260	Unidentate

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of the d–d visible band is absent for the tetrahedral copper complexes.

The conclusions about the coordination modes of the carboxylate ligands, is based on the magnitude of the difference between the wavenumbers of the symmetric and asymmetric modes. A difference close to 200 cm^{-1} or above is indicative of a unidentate binding mode, and that close or less than 100 is indicative of the carboxylato acting as a bidentate ligand.17) The results are well supported by the elemental analysis data. The formation of unidentate complexes with copper and bidentate complexes with cobalt for each type of the diamine ligand is consistent with the tetrahedral nature of the copper complexes and the octahedral nature of the cobalt complexes,18,19) as shown in Fig. 1.

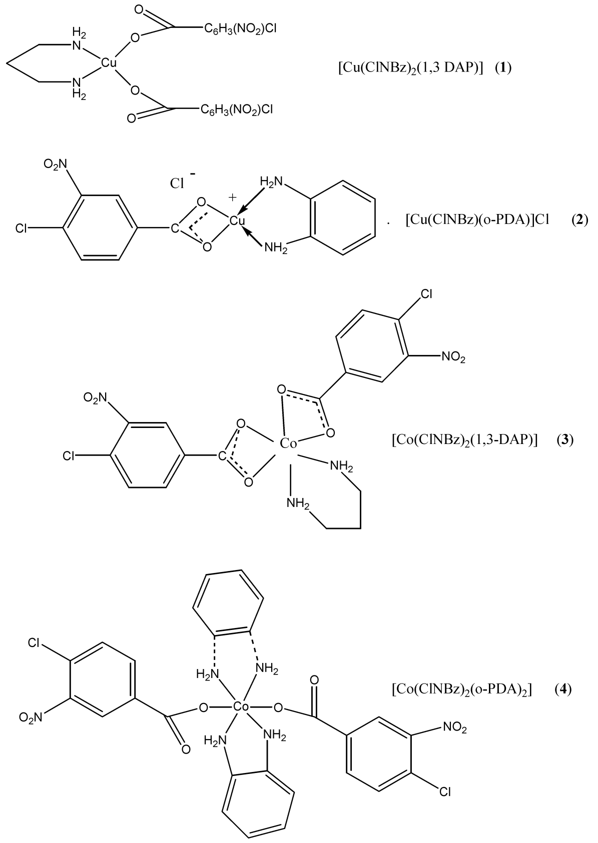

Fig. 1. Predicted Structures of Complexes

Thermal Analysis The results of thermogravimetric analysis for the prepared metal complexes are shown in Figs. 2—5. The data are listed in Table 2. We have previously prepared and determined the crystal structure of $Cu_2(ClNBz)_4(MeOH)_2$ complex.20) The compounds was heated to 700—800 °C, all relevant weight loss were completed by 650 °C. The TGA curve reveals that the complexes is stable up to 100 °C. The exothermic processes occurring at about 250 and 350 °C are due to the loss of 4-Cl,3-nitrobenzoate in all the complexes containing these ligands, except for $Co(ClNBz)_2$(1,3-DAP) (**3**) where those peaks shift to lower temperatures at 177 and 265 °C. Moreover, these peaks are absent in the case of Cu(1,3-diaminopropane)$_2$Cl$_2$ instead an endothermic peak occurred at 311 °C with $\Delta H = 473.6$ J/g. On the other hand [Cu(ClNBz)(*o*-PDA)]Cl (**2**), shows a sharp exothermic peak at 145 °C with $\Delta H = -364.47$ J/g accompanied by a mass loss of 11.7% which could be attributed to a loss of NO_2 group (theor. loss 12.3%).

Antimicrobial Activity For metal complexes showing antibacterial activity the following five principal factors have been considered: (i) The chelate effect: Ligand like bipyridine, phenanthroline, *o*-phenyldiamine bound to metal ions in a bidentate fashion show higher antimicrobial efficiency than complexes with unidentate N-donor ligands *e.g.* pyridine.21) (ii) The total charge of the complex: Generally the antimicrobial efficiency decreases in the order cationic>neutral>anionic complex. This behaviour may be related to the redox potential which is decreased in the same order. (iii) The nature of the ion neutralizing the ionic complex. (iv) The nature of the N-donor ligands, and (v) The nuclearity of the metal center in the complex: Dinuclear complex are more active than uninuclear ones.

The antimicrobial activity of the copper complex (**2**) was studied using the minimal inhibitory concentration (MIC) method. This was determined according to the NCCLS standards. A set of 10 tubes, each containing 1 ml of Mueller–Hinton broth was used. One milliliter of the 10 mg/ml of stock solution of compound in DMSO or ethanol was added to the first tube, mixed and then 1 ml was transferred to the second tube in a serial two-fold dilution.

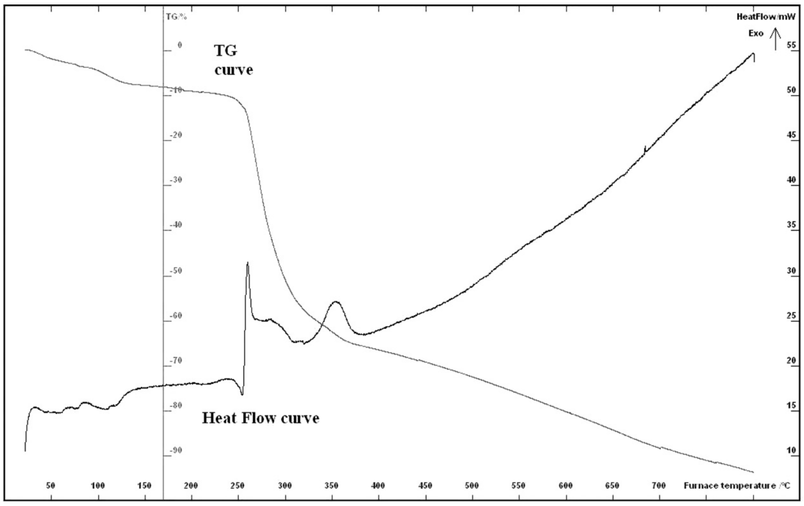

Fig. 2. Thermal Analysis of $Cu(ClNBz)_2(MeOH)_2$

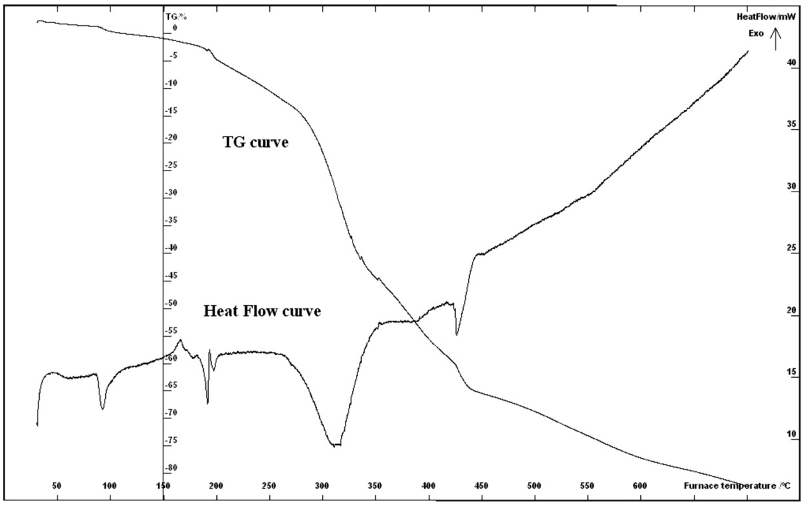

Fig. 3. Thermal Analysis of Cu(1,3-DAP)$_2$Cl$_2$

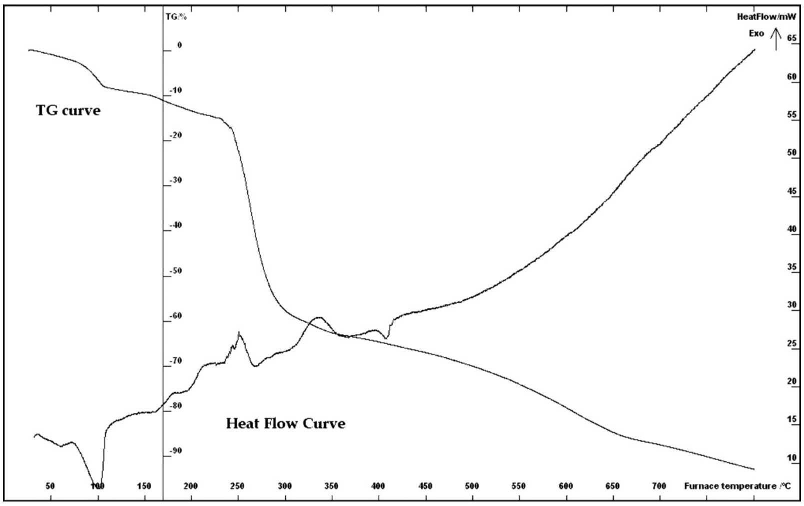

Fig. 4. Thermal Analysis of Cu(ClNBz)$_2$(1,3-DAP) (**1**)

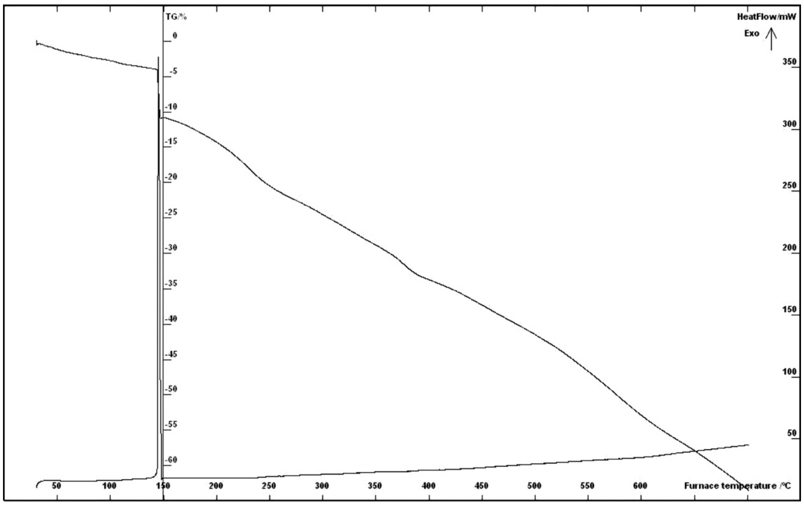

Fig. 5. Thermal Analysis of [Cu(ClNBz)(*o*-PDA)]Cl (**2**)

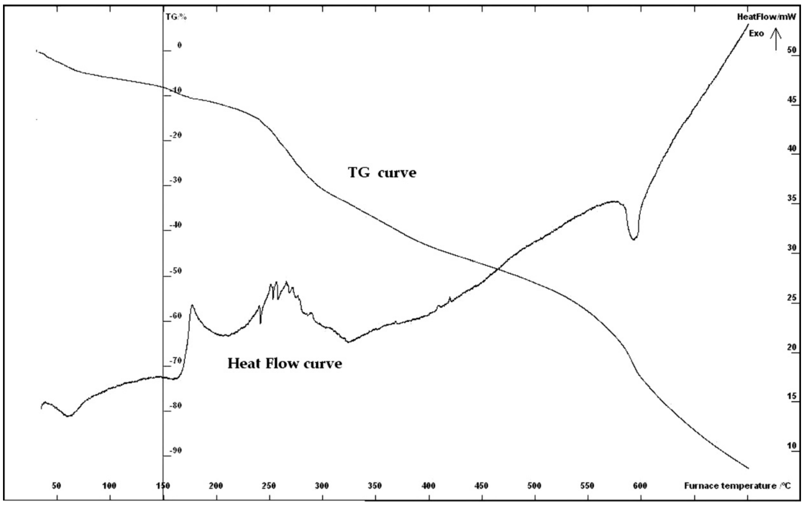

Fig. 6. Thermal Analysis of $Co(ClNBz)_2(1,3\text{-}DAP)$ (**3**)

Table 2. Thermal Analysis Data, TG and DSC for the Complexes

T (°C)	% Mass loss	Enthalpy change ΔH (J/g) (Process)
	$[Cu(1,3\text{-}DAP)2Cl_2]$	
92.48	1.66	32.34 (Endo)
165.76		−21.73 (Exo)
191.44	6.29	23.01 (Endo)
310.89	37.77	473.58 (Endo)
389.2	13.1	15.33 (Endo)
426.28	8.84	22.94 (Endo)
525	13.33	
	$[Cu_2(ClNBz)_4((MeOH)_2]$	
48.2	4.14	24.35 (Endo)
100.01	12.13	275.7 (Endo)
257.27	49.42	−200.17 (Exo)
337.45	4.24	−80.68 (Exo)
525	26.71	
	$[Cu(ClNBz)_2(MeOH)_2]$	
110.5	6.81	39.55 (Endo)
259.68	52.05	−289.05 (Exo)
352.77	6.16	−134.42 (Exo)
525	23.9	
	$[Cu(ClNBz)_2(1,3\text{-}DAP)]$ (**1**)	
101.42	7.8	123.76 (Endo)
162.65	5.2	22 (Endo)
195.41		12.95 (Endo)
250.36	47.23	−46.22 (Exo)
335.33		−88.46 (Exo)
407.79		17.49 (Endo)
550	26.62	
	$[Cu(ClNBz)(o\text{-}PDA)]Cl$ (**2**)	
145	11.1	−364.47 (Exo)
230	10.05	
290	6.31	
380	4.92	
435	5.76	
580	16.01	
	$[Co(ClNBz)_2(1,3\text{-}DAP)]$ (**3**)	
63.01	5.08	50.28 (Endo)
150	4.7	
163.01		86.17 (Endo)
177.06		−77.31 (Exo)
265.84	23.04	−353.62 (Exo)
330	11.97	
593.88		206.95 (Endo)
	$[Co(ClNBz)_2(o\text{-}PDA)_2]$ (**4**)	
69.2	10.74	189.8 (Endo)
197.94		56.4 (Endo)
223.66	16.56	−249.68 (Exo)
395	15.58	
610	24.36	

Table 3. Antimicrobial Activity of Copper Complex $[Cu(ClNBz)(o\text{-}PDA)]Cl$ (**2**) Using the Minimal Inhibitory Concentration Method

Organism	MIC of copper *o*-phenylenediamine benzoate complex	MIC of $CuCl_2$ (Reference)
Staphylococcus aureus-ATCC 25923	39 μg/l	312 mg/l
Enterococcus faecalis-ATCC 25922	39 μg/l	312 mg/l
Escherichia coli-ATCC 27853	625 μg/l	156 mg/l
Pseudomonas aeruginosa-ATCC 29212	625 μg/l	156 mg/l

Then 1 ml of the bacterial suspension containing 10^6 colony forming unit (CFU)/ml was added to each tube. The tubes were shaken and incubated at 35 °C for 24 h. The tube with no turbidity and highest dilution reflect the MIC.

The efficiency of complex (**2**) *o*-phenylenediamine-4-chloro-3-nitrobenzoate copper(II) chloride against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa* are listed in Table 3. A MIC of 39 μg/l reflects a high antibacterial activity against the first two types of bacteria listed. The antibacterial activity of the above complex is consistent with the fact that the carboxylate group in this complex is in its bidentate mode. The high activity of the complex correlates very well with its cationic nature.[22]

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