

Coordination Compounds of Cobalt, Nickel, Copper, and Zinc with N^1, N^2 -Bis(pyridin-2-ylmethylidene)benzene-1,2-diamine and Its Derivatives

E. Pahontu^a, A. P. Gulea^b, D. Poirier^c, and V. I. Tsapkov^b

^a Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

^b State University of Moldova, A. Mateevici st. 60, Chişinău, 2009 Moldova
e-mail: guleaurelian@gmail.com

^c Laval University, Québec, Canada

Received January 23, 2014

Abstract—*o*-Phenylenediamine reacts with 2-formyl-, 2-acetyl-, or 2-benzoylpyridine in ethanol in the presence of cobalt, nickel, copper, or zinc chlorides to form monomeric complexes $ML^{1-3}Cl_2 \cdot nH_2O$ {M = Co, Ni, Cu, Zn; $L^1 = N^1, N^2$ -bis(pyridin-2-ylmethylidene)benzene-1,2-diamine, $L^2 = N^1, N^2$ -bis(pyridin-2-ylethylidene)benzene-1,2-diamine, $L^3 = N^1, N^2$ -bis[phenyl(pyridin-2-yl)methylidene]benzene-1,2-diamine; $n = 0-3$ }. The condensation products (L^1-L^3) act in the complexes as tetradentate *N,N,N,N*-ligands. Thermolysis of the complexes occurs in two stages: dehydration (70–95°C) and complete degradation (320–450°C). At concentrations of 10^{-5} – 10^{-7} M, the complexes inhibit in vitro growth and proliferation of HL-60 human promyelocytic leukemia cells.

Keywords: coordination compounds, azomethines, Schiff bases, anticancer activity

DOI: 10.1134/S1070363214090217

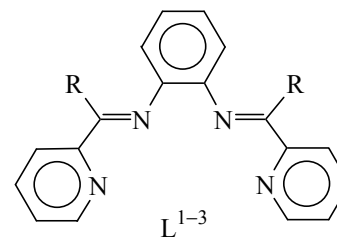
Azomethines are among nitrogen-containing compounds that most readily form complexes with transition metal ions [1–3]. The interest in such complexes is associated with their potential practical use as dyes, polymer stabilizers, and catalysts; they can also be used in analytical practice for isolation and separation of metals, and in medicine [4–11].

In the present paper we describe the synthesis, structure, and physicochemical and anticancer properties of cobalt, nickel, copper, and zinc complexes of the condensation products (L^1-L^3) of *o*-phenylenediamine with 2-formyl-, 2-acetyl-, and 2-benzoylpyridine (Scheme 1).

Reaction of hot (50°–55°) ethanol solutions of *o*-phenylenediamine with 2-formyl-, 2-acetyl-, or 2-benzoylpyridine with cobalt, nickel, copper, and zinc chloride (reagent molar ratio 1 : 2 : 1) resulted in formation of finely crystalline compounds **I–XII**. Their elemental analyses (Table 1) suggested the composition $M(L^{1-3})Cl_2 \cdot nH_2O$ [M = Co (**I**, **V**, **IX**), Ni (**II**, **VI**, **X**), Cu (**III**, **VII**, **XI**), Zn (**IV**, **VIII**, **XII**)];

$L^{1-3} = L^1$ (**I–IV**), L^2 (**V–VIII**), L^3 (**IX–XII**); $n = 0$ (**II**, **IV**, **VI**, **VIII**, **X**, **XII**), 1 (**III**), 2 (**VII**, **XI**), 3 (**I**, **V**, **IX**). Complexes **I–XII** are insoluble in ether, sparingly soluble in water and alcohols, and readily soluble in dimethylformamide, dimethyl sulfoxide, and acetonitrile. Their yields and physicochemical characteristics are listed in Table 1. Judging from the elemental analyses of complexes **I–XII**, we can assume that, like in [12–14], they are formed by metal-template condensation of *o*-phenylenediamine with 2-acetylpyridines to form Schiff bases L^1-L^3 whose

Scheme 1.



R = H (L^1), CH_3 (L^2), C_6H_5 (L^3).

Table 1. Physicochemical characteristics of cobalt, nickel, copper, and zinc complexes of N^1, N^2 -bis(pyridin-2-ylmethylidene)-benzene-1,2-diamine and its derivatives

Comp. no.	Yield, %	$M_{\text{eff}}^{\text{a}}$, BM	$\kappa,^{\text{a}}$ $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$	Found, %			Formula	Calculated, %			Complete decomposition temperature, °C
				Cl	M ^b	N		Cl	M ^b	N	
I	62	4.90	4	14.79	12.47	11.71	$\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{CoN}_4\text{O}_3$	15.08	12.75	11.92	380
II	67	3.07	2	16.80	14.00	13.31	$\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{N}_4\text{Ni}$	17.05	14.12	13.50	380
III	78	1.84	2	16.07	14.35	12.52	$\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{CuN}_4\text{O}$	16.17	14.58	12.76	350
IV	70	^c	3	16.59	15.17	12.98	$\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{N}_4\text{Zn}$	16.82	15.40	13.27	410
V	62	4.84	2	14.03	11.57	10.95	$\text{C}_{20}\text{H}_{24}\text{Cl}_2\text{CoN}_4\text{O}_3$	14.25	11.85	11.24	410
VI	65	2.99	3	15.14	12.49	11.84	$\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_4\text{NiO}$	15.37	12.77	12.12	400
VII	79	1.96	3	14.38	12.94	11.39	$\text{C}_{20}\text{H}_{22}\text{Cl}_2\text{CuN}_4\text{O}_2$	14.64	13.20	11.55	360
VIII	78	^c	4	15.50	14.17	12.15	$\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_4\text{Zn}$	15.78	14.44	12.44	450
IX	70	5.10	5	11.17	9.20	8.77	$\text{C}_{30}\text{H}_{28}\text{Cl}_2\text{CoN}_4\text{O}$	11.41	9.49	9.00	360
X	72	3.07	3	12.23	10.14	9.70	$\text{C}_{30}\text{H}_{22}\text{Cl}_2\text{N}_4\text{Ni}$	12.50	10.39	9.86	350
XI	74	1.87	4	11.41	10.17	8.93	$\text{C}_{30}\text{H}_{26}\text{Cl}_2\text{CuN}_4\text{O}_2$	11.66	10.51	9.20	320
XII	72	^c	2	12.09	11.08	9.49	$\text{C}_{30}\text{H}_{22}\text{Cl}_2\text{N}_4\text{Zn}$	12.37	11.32	9.76	380

^a At 294 K. ^b (M) Metal. ^c Diamagnetic complex.

subsequent reaction with cobalt, nickel, copper, and zinc chlorides gives rise to complexes **I–XII**.

The molar electrical conductivities of the complexes in DMF show that they all are nonelectrolytes ($\kappa = 2\text{--}5 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$).

To gain insight into the mode of coordination of ligands $L^1\text{--}L^3$ with central ions, we compared the IR spectra of the parent compounds and complexes **I–XII**, as well as published IR spectra of transition metal complexes of similar Schiff bases [10–14]. In the compounds studied azomethines $L^1\text{--}L^3$ behave as tetradentate ligands and coordinate to the complexing ion via the pyridine and azomethine nitrogen atoms, forming three five-membered metallocycles. Evidence for this conclusion is provided by the fact that the $\nu(\text{C}=\text{N})$ band is shifted red by 25–20 cm^{-1} compared to the respective band in the spectra of similar Schiff bases [1–14]. Moreover, the IR spectra of all the complexes show new bands at 530–510 and 430–405 cm^{-1} , assignable to $\nu(\text{M}\text{--}\text{N})$ ($\text{M} = \text{Co}, \text{Ni}, \text{Cu}, \text{Zn}$). Involvement of other functional groups of azomethines $L^1\text{--}L^3$ in coordination can be excluded, because their characteristic absorption bands appear in the same regions as in the spectra of *o*-phenylenediamine, 2-acylpyridines, as well as transition metal complexes of similar Schiff bases, described in the literature.

Magnetochemical study of complexes **I–XI** at room temperature (294 K) showed (Table 1) that the cobalt and nickel complexes are paramagnetic, and, judging from their magnetochemical characteristics, the central atoms in them have a pseudo-octahedral ligand environment (electron states $t_{2g}^5 e_g^2$ and $t_{2g}^6 e_g^2$, respectively). The effective magnetic moments of the copper complexes correspond to spin values for one unpaired electron. These experimental data point to a monomeric structure of the complexes.

Thermal analysis of compounds **I–XII** (Table 1) revealed a two-stage thermolysis. The DTA curves show an endotherm at 70–95°C, which, as judged from the fairly low temperature, corresponds to dehydration. The second thermal effect observed in the DTA curves of the complexes at 320–450°C is an exotherm and assignable to thermo-oxidative decomposition of coordinated azomethines $L^1\text{--}L^3$. The complete decomposition temperature depends on the nature of the central atom and inner-sphere ligands and varies in the series $t(\text{Zn}) > t(\text{Co}) \geq t(\text{Ni}) \geq t(\text{Cu})$ for the same ligand and $t(L^2) > t(L^1) > t(L^3)$ for the same metal.

The presented physicochemical data allows us to propose the following distribution of chemical bonds in complexes **I–XII** (Scheme 2).

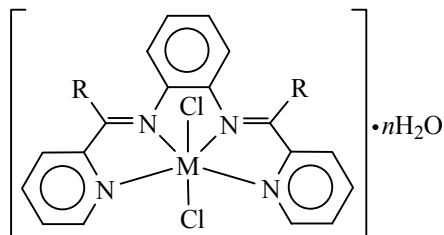
As shown in [15–17], many coordination compounds of 3d elements with pyridine-derived ligands are capable of selectively inhibiting growth of cancer cells. In this connection we tested complexes **I–XII** for anticancer activity in vitro on HL-60 human promyelocytic leukemia cells. The complexes inhibited growth of this kind of cells (Table 2) at the same level as chemotherapeutic agents (Doxorubicin) applied in medicine to treat leukemia [10]. At the concentration of 10^{-5} M complexes **I–XII** inhibit growth and proliferation of 48.3 to 2.2% of cancer cells, at $c = 10^{-6}$ M they inhibit from 17.7 to 3.2% cancer cell, and at $c = 10^{-7}$ M, up to 14.2% cancer cells; at lower concentrations complexes **I–XII** exhibit no anticancer activity. As seen from Table 2, the anticancer activity of the complexes is primarily dependent on the nature of the central atom and substituent R and varies in the series $\text{Cu} \geq \text{Ni} > \text{Co} > \text{Zn}$ for the same substituent and $\text{C}_6\text{H}_5 > \text{H} > \text{CH}_3$ for the same metal.

EXPERIMENTAL

The resistances of solutions of complexes **I–XII** in DMF (20°C, $c = 0.001$ M) were measured with an R-38 slidewire bridge. The IR spectra were measured on a Specord M-80 spectrophotometer for suspensions in mineral oil; before measurements the samples were dried to constant weight in an oven at 105°C. The effective magnetic moments of compounds **I–XII** were determined by the Gouy method. The molar magnetic susceptibilities with diamagnetic corrections were calculated from theoretical magnetic susceptibilities of organic compounds. The derivative thermoanalytical curves of complexes **I–XII** were obtained on a Paulik–Paulik–Erdely derivatograph at 20–1000°C in air (reference Al_2O_3 , corundum crucible).

The anticancer activity of complexes **I–XII** was studied in vitro on HL-60 human promyelocytic leukemia cells by the standard procedure described in [18].

Scheme 2.



$\text{M} = \text{Co}, \text{Ni}, \text{Cu}, \text{Zn}; \text{R} = \text{H}, \text{CH}_3, \text{C}_6\text{H}_5; n = 0-3.$

Table 2. Fractions (%) of HL-60 human promyelocytic leukemia cells inhibited by cobalt, nickel, copper, and zinc complexes of N^1, N^2 -[bis(pyridin-2-yl)methylidene]benzene-1,2-diamine and its derivatives

Comp. no.	Concentration, M		
	10^{-5}	10^{-6}	10^{-7}
I	19.9	16.4	14.2
II	42.1	17.4	11.4
III	47.3	4.5	0
IV	14.7	3.2	0
V	16.7	15.3	0.5
VI	34.5	16.0	0.5
VII	46.8	17.0	11.1
VIII	12.1	1.8	1.4
IX	2.2	6.2	3.4
X	48.3	16.7	7.9
XI	25.2	13.5	10.8
XII	36.6	17.7	10.2
Doxorubicin	76.4	73.9	15.7

Dichloro[N^1, N^2 -bis(pyridin-2-ylmethylidene)benzene-1,2-diamine]cobalt trihydrate (I**).** A solution of 10 mmol of cobalt chloride hexahydrate in 20 mL of alcohol was added to a solution of 10 mmol of *o*-phenylenediamine and 20 mmol of 2-formylpyridine in 30 mL of alcohol under continuous stirring and heating (50–55°C). The reaction mixture was heated for 50–60 min. The dark brown precipitate that formed after cooling to room temperature and slow evaporation was filtered off on a glass frit, washed with a little alcohol and ether, and dried in air to constant weight.

Compounds **II–XII** were synthesized in a similar way from *o*-phenylenediamine, 2-formylpyridine, 2-acetylpyridine, or 2-benzoylpyridine and cobalt, nickel, copper, or zinc chloride hydrates, taken in a 1 : 1 : 1 molar ratio. The yields of complexes **I–XII** and their selected physicochemical characteristics are presented in Table 1.

ACKNOWLEDGMENTS

The work was financially supported by the Academy of Sciences of the Republic of Moldova and

the National Research Council of Romania (project 13.820.08.01/RoF).

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