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Synthesis and characterization of some metalcomplexesderived from *L*-lysine dihydrochloride with some metal ionsbytribochemical reactions

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ABSTRACT

Four new complexes with the general formula, $R_2[MCl_4]$(R=*L*-lysine dihyrochloride),were synthesized by grinding *L*-lysinedihyrochloride and MX_2 in the solid state in a mortarbytribochemical reaction. The isolated complexes with the general formula, $R_2[MCl_4]$, derived fromCu^{2+},Ba^{2+},Cd^{2+} and Pd^{2+}chloridesarecharacterized by elemental analyses, conductivities, spectral (IR, UV-Vis, Far-IR)and magnetic measurements. Spectral and magnetic measurements suggest that the metal ions form tetrahedral geometry around the metal ion. The $[MCl_4]$ anion and its counter ions are connected through a hydrogen bonds between Cl of the anion and OH (carboxylate)formingO-H···Cl interaction. Molar conductance values of complexes suggest the electrolytic nature of these complexes in DMSO but easily dissociated in H_2O indicating that the hydrogen bond formed is very weak. The results of Far-IR spectra suggest the stretching and bendingvibrations of M-Cl. Also, the isolated complexes were tested against different types of cancer and some the complexes give promising results.

KEYWORDS

Tribochemical reactions;
Tetrahalometallate complexes;
Spectroscopic studies;
Far-FTIR;
Biological activity.

INTRODUCTION

The study of the biological role of metal ions has a long history in medicine, pharmacology, toxicology and recently the extent and variety of metal ions involvement have been appreciated. The metal behavior in *vivo* which cannot be over emphasized is essentially that of the complex ion. Properties such as the effective size and solubility of a metal ion in *vivo* are a function of ligand and solvent present as well as of the metal ions themselves. The chemistry of these ions in *vivo* is that of ions which present in an excess of competing groups.

Tetrachloropalladate(II)complex with glutamine of the formula, $[PdCl_4][(L\text{-Glutamine})_2]$, was prepared and characterized*via* IR spectroscopy[1]. The compound was found cytotoxic to TA98 and TA100 bacterial cells of salmonella typhimurium. The structure of {3-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-ylidene}{1-[2-(4-methoxyphenyl) ethyl]-4-

piperidin-1-io} ammoniumtetrachlorocuprate(II), $[C_{28}H_{33}FN_4O]$ $[CuCl_4]$, was also investigated by Parvez et al[2]. The geometry around Cu is flattened tetrahedral with significantly different Cu-Cl distances which lie in the range 2.1968(14)-2.2861(12) Å. The compound, $[C_8H_{22}N_2][CuCl_4]$, which was composed of one *N,N,N',N'*-tetramethylbutane-1,4-diammonium cation and a tetrachlorocuprate(II) anion was investigated by Elangovan et al[3]. The anion was mononuclear and has a flattened tetrahedral geometry. Two new compounds, bis-(*DL*-erythro-a-2-piperydylium-2,8-bis(trifluoromethyl)-4-qinolinemethanol) tetrachlorocuprate (II) tetrahydrate,$[LH]_2[CuCl_4].4H_2O$ (*L*=mefloquine) andbis(*DL*-erythro-2-piperydylium-2,8-bis (trifluoromethyl)quinolinemethanol) tetrabromocadmate (II) bis (methanol) $[LH^+]_2$ $[CdBr_4]^{2-}.2CH_3OH$, were studied byJoshua et al[4]. The two compounds were characterized by elemental analysis, ^{1}H-NMR andIR spectroscopy. Adams et al[5]reported thereactions of $Pd^{2+}$and Pd^{2+}chloride complexes with imidazole and pyrazole or their hydrochloridein solidstate. The salts are shown to produce metal complex salts and coordination compounds. Thus, $K_2[MCl_4]$ or MCl_2 can be ground with imidazolium chloride ($[H_2im]Cl$ to produce salts of the type $[H_2im]_2[MCl_4]$. The synthesis and crystal structure of thermochromic, yellow benzimidazoliumtetrachlorocuprate (II),$[C_7H_7N_2]_2$ $[CuCl_4]$,have been reported[6]. The compound crystallizes in the C2/c space group and contains discrete tetrahedral $[CuCl_4]^{2-}$species. The role of the water molecule on the solid state, yellow $\rightleftharpoons$/green thermochromic transformation,was discussed. A series of new complex salts of the type $[A]_2[MCl_2I_2]$ where A=1,3,5-trimethylpyridinium cation, M=Mn^{2+},Co^{2+}, Ni^{2+},Cu^{2+} and Zn^{2+},were prepared by thereaction of the metal chloride and 3,5-trimethylpyridinium iodide in (1:2) molar ratio andcharacterized by elemental analysis, molar conductance, IR, Uv/Vis., spectral studies andmagnetic measurements[7]. The crystal structure of 1,3,5-trimethylpyridinuimiodide wasdetermined by single crystal x-ray crystallography. The complex salts of the type $[R]_2[MCl_4]$ {where *R* = $[CN_4(C_6H_5)_3]_2$,*M* = Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}}, were prepared and characterized by elemental analysis, molar conductance, IR and UV/Vis spectral studies and magnetic measurements. The crystal structure of$[CN_4$ $(C_6H_5)_3]_2[CuCl_4]_2$was determined by single crystal X-ray crystallography[8]. The structure consisted of anionpart and 2,3,5-(triphenyl) tetrazoliumcation as counter ion. The copper complex has a distorted-tetrahedral geometry and the $[CuCl_4]$ anion and its counter ions are connected through a hydrogen bonds between Cl of the dianion and hetero aromatic rings by Cl-π, π-π and O-H ··· π, interactions.

In continuation of our earlier work [9-13] we extend our studyto synthesize new metal complexes derived from *L*-lysinedihyrochloridewith some metal ions by tribochemical reactions. Also, one of our main goals of this work is to study the biological activity of the isolated complexes against different types of cancer.

EXPERIMENTAL

Materials and methods

Carbon, hydrogen and nitrogen contents were determined at the MicroanalyticalUnit, Cairo University, Egypt. The metal contents (Pd and Cd) were determined by complexometric titration using Xylenol orange as indicator[14]. Cu and Ba contents were performed with AAS (flame absorption) model Perkin-Elmer in the Micro Analytical Center, Faculty of Science at Cairo University. The conductance measurements in DMSO were carried out using a conductivity bridge TDS model 72 at Domiat University, Egypt. IR spectra were recorded on an 800-PC FTIR Schimadzu spectrophotometer using KBr pellets (4000-400 cm^{-1})atCairo University. Far-IRspectrawere recorded using spectrophotometer model 6300 FTIR in the Egyptian Petroleum Research Institute. Magnetic moments were determined using a Sherwood balance at room temperature (25°C) with $Hg[Co(NSC)_4]$ as a celebrant at Mansoura University. Diamagnetic corrections for *L*-lysine.2HCl and the metal atoms were computed using Pascal's constants[15]. Electronic spectra of the complexes in Nujol mulls were recorded on a Unicam UV2 spectrophotometer at Mansoura University.

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Synthesis of ligands and metal complexes

The synthesis of the metal complexes with the general formula, $R_2[MCl_4]$, were obtained by grinding equivalent amounts of the solid metal salts under investigation with *L*-lysine.2HClby tribochemical reaction. The mixtureswere mixed and grinded in agate mortar at room temperature till the reactants become in fine powder. The complexes were dried in an oven at 60 °C and kept in desiccators over $CaCl_2$.

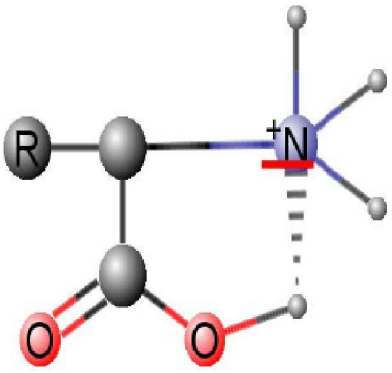
Biological activity

Cytotoxicity assay

Evaluation of the cytotoxicity of the prepared complexes against HCT-116 (colon) and MCF-7 (breast) cell lines was carried out in the Regional Center for Mycology and Biotechnology (Al-Azhar University). Doxorubicin and Vinblastine were used as standard drugs. The cells were seeded in 96-well plate at a cell concentration of 1×10^4 cells per well in 100µL of growth medium. Fresh medium containing different concentration of the test sample was added after 24h of seeding,serial two-fold dilution of tested chemical compound were added to confluent cell monolayer dispensed into 96-well flat-bottomed microtiter plates (Falcon,NJ,USA)using multichannel pipette. The microtiter plates were incubated at 37°C in humidified incubator with 5% CO_2 for a period of 48h. Different concentrations of the sample (50,25,12.5,6.25,3.125 and 1.56µg) were added and the incubation was continued for 48h and a viable cell yield was determined by a colorimetric method, after end of the incubation period, medium were aspirated and the crystal violet solution (1%) was added to each well for at least 30 minutes. The stain was removed and the plates were rinsed using tap water until all excess stain is removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly and then the absorbance of the plates was measured after gently shaken on microplate reader[16]. The relationship between the surviving fraction and

TABLE 1 : Elemental analyses and some physical data of the metal complexes

Complex; chemical formula	M.p., °C	$\lambda_{max.}$	Λ_m (DMSO; $ohm^{-1}cm^2 mol^{-1}$)	$U_{eff.}$ (B.M)	C% F(Calc.)	H% F(Calc.)	N% F(Calc.)	M% F(Calc.)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2[CuCl_4]$; $C_{12}H_{30}N_4O_4CuCl_4$(1)	180	304.00 380.00 718.00	----	2.06	30.0 (29.8)	6.1 (6.1)	11.3 (11.2)	12.7 (12.7)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2$ $[BaCl_4]$; $C_{12}H_{30}N_4O_4BaCl_4$ (2)	257	248.00 288.00 306.00 416.00	115	Diamag.	24.4 (25.1)	4.6 (5.3)	9.3 (9.8)	24.4 (23.9)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2$ $[CdCl_4].2H_2O$; $C_{12}H_{30}N_4O_4CdCl_4$(3)	234	254.00 384.00 414.00 564.00	----	Diamag.	23.9 (24.7)	5.6 (5.9)	9.5 (9.6)	19.7 (19.2)
$[NH_2\text{-}HC\text{-}COOH\text{-}(CH_2)_4\text{-}NH_3]_2$ $[PdCl_4]$; $C_{12}H_{30}N_4O_4PdCl_4$(4)	200	238.00 358.00 400.00 420.00 420.00	115	Diamag.	27.4 (26.6)	5.5 (5.6)	10.3 (10.3)	19.7 (19.6)



R = $-(CH_2)_2-NH_3^+$

Figure 1 : Hydrogen bond in lysine.2HCl

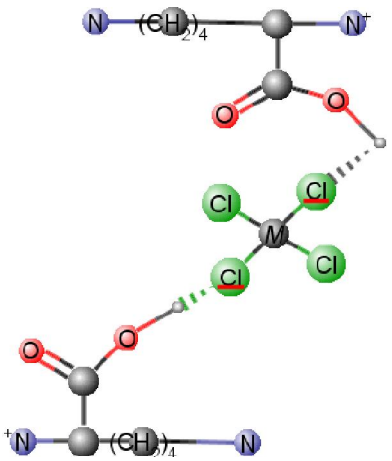


Figure 3 : The structure of the complexes with the formula $R_2[MCl_4]$

drug concentration was plotted to get the survival curve of each tumor cell line after specific compound was added. Inhibition of cell proliferation (IC_{50}) for test compounds (A, B and D) (µg sample/ L) were recorded. The $IC_{50}$is the concentration of treatment required to induce 50% inhibition of cell growth[16].

RESULTS AND DISCUSSION

The analytical data of the complexes are listed in TABLE 1. Comparison of the elemental analyses for the calculated and found percentage indicates that the compositions of the complexes coincide with proposed formulae. All the complexes are decomposed in water but freely soluble in DMF and DMSO. The decomposition of complexes in H_2O is mainly due to the weak hydrogen bond formed within the complex. The values of molar conductance in DMSO TABLE 1suggest that all the complexes are

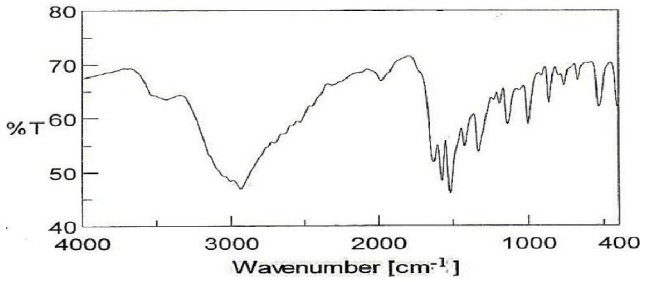


Figure 2 : IR spectrum *L-l*ysinetetrachloropalladate(II) in KBr

electrolytic in nature[17]. The melting points of the solid complexes TABLE1 lie in the180-257 °Crangesuggestthat the strength of the bond between *L*-lysine.2HCl and the metal ions are quite stable.

IR spectra of the complexes derived from L-lysine.2HCl

The IR spectrum of the free ligand (*L*-lysine.2HCl) shows the absence of any bands in the 3400-3100 cm^{-1}regions. This suggests that the two NH_2groups of *L*-lysine.2HCl are changed to NH_3^+as well as the absence of H_2O molecules in the compound as shown in Figure 1. Severalbandsare observed at 3024, 2814, 1725, 1620 and 1571 cm^{-1}. The first two strong bandsaremainly due to the strong hydrogen bond between the OH and NH_3 (N….H-O) vibration. The latter two bands at 1620, and 1571cm^{-1} are attributed to the ν_{as}(COO) and ν_s(COO) vibrations[18-22], respectively.The IR spectrum of the *L-l*ysinetetrachloropalladate(II) in KBrcomplex is recorded in Figure 2.

The most important bands in the metal complexes,$[NH_3$-CH(COOH)-$(CH_2)_4$-$NH_2]_2[CuCl_4]$ (1),$[NH_3$-CH(COOH)-$(CH_2)_4$-$NH_2]_2[BaCl_4]$ (2),$[NH_3$-CH(COOH)-$(CH_2)_4$-$NH_2]_2[CdCl_4]$(3), $[NH_3$-CH(COOH)-$(CH_2)_4$-$NH_2]_2[PdCl_4]$ (4), are observed in the regions 3493-3409, 3234-3002, 2927-2900, 1735-1681and 1680-1587 cm^{-1}. The observation of the bands in the 3493-3409 and3234-3002 regions assigned to NH_2 vibration indicating that one of the NH_3^+ group in the free ligand is changed toNH_2 on complex formation. These bans are assigned to $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ vibrations, respectively. The band observed in the 2927-2900 regions isν(CH) vibration. The last two bands are assigned toν_{as}(COO) and ν_s(COO) vibrations[20-22], re-

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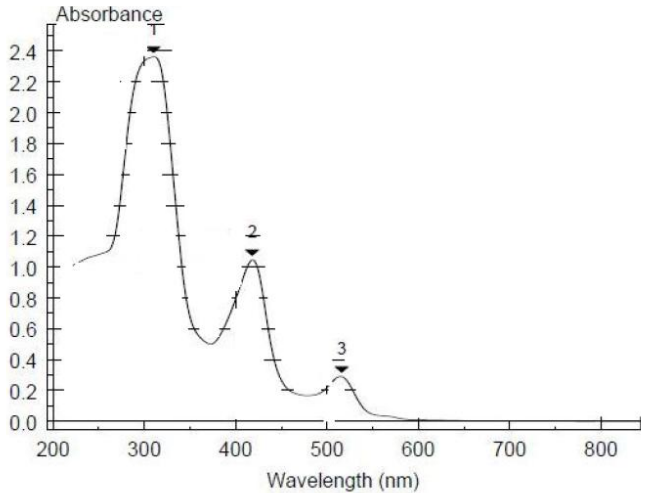

Figure 4 : The electronic spectrum of the Cu^{2+}complex

spectively. Also, the band observed at 1585 cm^{-1} is assigned to NH_3^+ group suggests that the ligand is mainly existed in the form of Zwitterion. Also, the data obtainedsuggest that the ligand is bonded to the metal ions forming a complex of the type $[L]^{2+}[MX_4]^{2-}$. Finally, the bands observed in all complexes in the 1900-2000 and 2600-2500cm^{-1} region suggests the presence of O-H….Cl hydrogenbond[23]as shown in Figure 3.

Electronic spectraand magnetic measurements

The electronic spectrum of the Cu^{2+}complex is shown in Figure 4. All the complexes show two main bands in the 272-418 and 374-516 nm regionswhich are assigned to $\pi\rightarrow\pi^*$(COOH) and $n\rightarrow\pi^*$(COOH) transitions[24], respectively. The Cu^{2+} complex exhibits three bands at310, 385 and 520nm. The first two bands are due to charge-transferwhile the third band is due to d-d transition. The observation of these bands suggests that the Cu^{2+}complex has a distorted-tetrahedral geometry around the Cu^{2+}ion[25]. The value of magnetic moment for the Cu^{2+}complex (2.06BM)suggests the absence of Cu-Cu interactions.

Far-IR spectra of the metal complexes

The Far-IR spectrum (600-50 cm^{-1}) of the tetrahalopalladate(II) complex of the general formula, $L_2[PdCl_4]$, is recorded in Figure 5. The spectra in the complexes show two bands in the 265-295 and 54-84 cm^{-1}regions assigned to ν(M-Cl) stretching[26] and ν(Cl-M-Cl) bending, respectively.

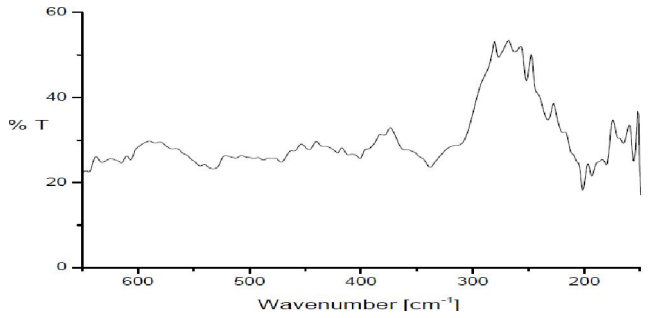

Figure 5 : Far-IR spectrum of$L_2[PdCl_4]$

Evaluation of cytotoxic activity on human tumor cell lines

Activity against breast cancer cell lines (MCF-7)

The data illustrate that the order of theactivity of the complexes against breast cancer is in the order: 3>1>4>2with IC_{50} values of (0.47, 6.0, 34.3 and37.0μg/mL). Doxorubicin (DOX) a drug with antineoplastic activity was used in this study as standard drug, since it is widely used in the treatment of tumor cells. Bis-*L*-lysinetetrachlorocadmate (3) is promising to inhibit the growth of breast cancer lines whilebis-*L*-lysinetetrachloropalladate complex(4) shows the least antitumor activity due toits low solubility.

Activity against cervical cancer

All tested compounds are effective against HELA (Cervical cancer) illustrate that the order of their activities is 3>1>4>2. Bis-*L*-lysine tetrachlorocadmate(3) andbis-*L*-lysinechlorocuprate (1) are very successful to inhibit the growth of the cervical cancer. Thebis-*L*-lysinetetrachlorobarimate (2) hasthe worst effect.

Activity against colon cancer

The activity of tested compounds against HCT (colon cancer) illustrates that the order of their activities is in the order: 3>1>2>4. Bis-*L*-lysinetetrachlorocadmate(1) is very potential agent to inhibit the growth of the colon cancer followed by bis-*L*-lysinediiododichlorocadmate (I_e) and bis-*L*-lysinetetrachloropalladate (4) has the lowest potent activity. Cytotoxic activities of these complexesare mainlydue their differential solubility.

TABLE 2 : Inhibition of cell proliferation (IC_{50} µg sample/L) for complexes

Complex	Breast cancer	Cervical cancer	Colon cancer	Larynx cancer	Hepatocellular cancer
Bis-*L*-lysinetetrachlorocuprate(II)(1)	6.0	9.3	6.9	9.7	10.9
Bis-*L*-lysinetetrachlorobarimate(II)(2)	37.0	37.6	36.6	40.0	32.1
Bis-*L*-lysinetetrachlorocadmate(II)dihydrate(3)	0.47	0.47	0.73	0.51	0.69
Bis-*L*-lysinetetrachloropalladate(II)(4)	34.3	16.5	47.8	40.0	21.8

Activity against larynx cancer

The activity of compounds under investigation against HEP2 (Larynx cancer) shows that the order of their activities is as follow: 3>1>2≈4.

Both of bis-*L*-lysinetetrachlorocadmate(3) andbis-*L*-lysinetetrachloropalladate (1) are the most potent while bis-*L*-lysinetetrachlorobarimate (2) andbis-*L*-lysinetetrachloropalladate(4) are the least effective in activity against HEP2 (Larynx carcinoma).

Activity against heptacellular cancer

The activities of compound against HEPG2 (Heptacellular cancer) illustrate that the order of their activities is as follow:3>1>4>2. Bis-*L*-lysinetetrachlorocadmate (3), and bis- *L*-lysinetetrachlorocuprate(1) are very successful to inhibit the growth of the heptacellular cancer. Both the bis-*L*-lysinetetrachloropalladate (4) andbis- *L*-lysinetetrachlorobarimate (2) show less activity. All the data are recorded in TABLE 2.

Cadmium and copper complexes(3 and 1) are the most active compounds against all tumor cell lines. Theresults suggest that the positively charged polar head of the complexes provides the basis for its anticancer specificity, whereas the amino acid tail may aid in its insertion into the plasma membrane altering its mosaic structure in response to the negative trans-membrane potential. It should be also noted that effects of these complexes are found to be dependent on the typeof the tested tumor cell line. Results illustrated that cadmium complex shows excellent cytotoxic activity, which can be attributed to the ability of cadmium complex to produce non-covalently interact with DNA double helix rather than forming coordinated covalent adducts with DNA. The non-covalent DNA interactions included intercalative, electrostatic and groove binding of metal complexes along the major or minor DNA groove. In most cases, the metal acted as an inorganic modifier of the organic backbone of the bioactive molecule and ligands granted DNA affinity and specificity[27].

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