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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDIES OF METAL COMPLEXES OF SULFADIAZINE WITH N-ALKYL-N-PHENYLDITHIOCARBAMATE

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ABSTRACT. Co(II), Cu(II), Pd(II) and Pt(II) complexes of 4-amino-N-(2-pyrimidinyl)benzene sulfonamide (sulfadiazine) with some N-alkyl-N-phenyl dithiocarbamate have been synthesized and characterized by elemental analysis, conductivity measurements, UV-Vis and FTIR spectroscopy. The complexes are formulated as four coordinate MN_2S_2 species in which the metal ions are coordinated to one molecule of sulfadiazine through the pyrimidinyl and sulfulnamido nitrogen atoms and one molecule of dithiocarbamate through two sulfur atoms with both molecules acting as bidentate chelating ligands. The *in vitro* antibacterial activities of the complexes and sulfadiazine were evaluated against eight bacteria strains using the agar well diffusion method. The metal complexes showed varied antibacterial properties and their minimum inhibitory concentration (MIC) and maximum bactericidal concentration (MBC) were determined.

KEY WORDS: Sulfadiane, Dithiocarbamate, Metal complexes, Antibacterial, Drug resistance

INTRODUCTION

Sulfonamides are among the most widely used antibacterial agents in the world due to their excellent activity against bacterial diseases. Sulfonamides were introduced into therapy over a century ago for the prevention and cure of bacterial infections in humans [1]. Sulfadiazine is a sulfonamide with well known antibacterial activities [2, 3] and used clinically as a topical agent either alone or in combination with other compounds in the treatment of wound and burn infections [4-10]. Interest in the metal complexes of sulfadiazine is due to its use as pharmaceuticals. Zinc sulfadiazine is used to prevent bacterial infection in burned animal and silvadene (2-sulfanilamido pyrimidine-silver(I)) is used commercially for the treatment of topical burn [10, 11]. At present, the possibility of using metal complexes of sulfadiazine as antimicrobial agents has received some attention [12-14]. Metal complexes of dithiocarbamates are widely studied due to their biological, chemical, agricultural and industrial applications [15-17]. The presence of the dithiocarbamate moiety in some biologically active molecules has necessitated interest in their potentials for medical application [18].

At present, due to increase in resistance to current generation of antibiotics, efforts are being made to develop novel chemotherapeutic targets. In the search for novel compounds against drug resistance diseases, development of metal based pharmaceutical has received tremendous attention [19-26]. In continuation of our efforts to developed metal based chemotherapeutic agents [11, 27-32], we present the synthesis, characterization and *in vitro* antibacterial study of heteroleptic Co(II), Cu(II), Pd(II) and Pt(II) complexes of sulfadiazine and N-methyl-N-phenyl dithiocarbamate or N-ethyl-N-phenyl dithiocarbamate.

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EXPERIMENTAL

Materials and methods

All reagents and solvents were of analytical grade and used without further purification. Elemental analysis was carried out on a Perkin–Elmer elemental analyzer. Melting point determination was obtained with the Gallen Kamp melting point apparatus. Molar conductivity measurement (10^{-3} M solutions in dimethylformamide) was obtained on the CON 6/TDS conductivity meter. FTIR spectra of the complexes were recorded as KBr pellets on a Perkin-Elmer paragon 2000 spectrophotometer in the range 4000-370 cm^{-1}. Electronic spectra of complexes were recorded on a Perkin-Elmer Lambda 25 spectrophotometer. Sodium salt of N-methyl-N-phenyl dithiocarbamate (me-DTC) and N-ethyl-N-phenyl dithiocarbamate (et-DTC) was synthesized according to literature procedure [33].

Synthesis of the metal complexes

A solution containing 1 mmol of the respective metal salt was added to sodium sulfadiazine (1 mmol, 0.272 g) in 25 mL of distilled water. The mixture was refluxed for 1 h followed by the addition of N-methyl-N-phenyldithiocarbamate (1 mmol, 0.205 g) or N-ethyl-N-phenyl dithiocarbamate (1 mmol, 0.219 g) in 25 mL of distilled water. The reaction mixture was further refluxed for 3 h, cool to room temperature and filtered. The product was dried over $CaCl_2$.

Antibacterial studies

The antibacterial activities of the metal complexes were determine using agar well diffusion method [34, 35] using eight bacteria isolates: *Staphylococcus aureus (ATCC 6538)*, *Streptococcus faecalis (ATCC 29212)*, *Bacillus cereus (ATCC 10702)*, *Bacillus pumilus (ATCC 14882)*, *Escherichia coli (ATCC 8739)*, *Pseudomonas aeruginosa (ATCC 19582)*, *Proteus vulgaris (ATCC 6830)*, and *Klebsiella pneumonia (ATCC 10031)* typed cultures as obtained from the American Type Culture Collection (ATCC). The inoculated organisms in nutrient broth media together with the prepared liquid Mueller-Hinton agar were poured into plates and allowed to solidify. Wells were bored into the solidified agar medium using a sterile 6 mm cork borer. The wells were then filled up with the solution of prepared metal complexes ensuring that the each solution does not spill to the surface of the medium. The plates were allowed to stand for between 1-2 hours to allow proper inflow of the complex solution into the medium before incubating at 37 ^{o}C. The plates were observed for the zones of inhibition after 24 hours.

Minimum inhibitory concentration (MIC) of the complexes

Macro-broth dilution technique [36, 37] was used to determine the MIC with few modifications. The MIC was taken as the lowest concentration of the tested antibiotics that shows no visible bacterial growth [38]. Serial dilution of the complexes stock solution i.e. complex in the sterilized dissolving solvent (1:10 of DMF and distilled water respectively) was done by introducing an equal volume of complex stock solution into the same volume of sterilized distilled water, this was followed by taking the same volume of diluted stock solution into another distilled water of the same volume in a test tube to attain a second dilution concentration, this process continued to give final concentrations of 20.00, 10.00, 5.00, 2.50, 1.25, 0.63, 0.31 0.16 and 0.08 mg/mL in a case and 0.50, 0.25, 0.13, 0.06, 0.03, 0.02 and 0.01 mg/mL in another case in duplicates. 2 mL of different concentration of the prepared complexes was introduced one after the other to 18 mL of pre-sterilized molten nutrient agar. The mixture

was then poured into sterile plates and allowed to set. To the solidified nutrient agar mixture, bacterial isolates with standardized inoculums was streaked on it. The plates were incubated at 37 ^{o}C for 24 hours after which they were examined for the presence or the absence of growth.

Minimum bacteria concentrations (MBC) of the complexes

Minimum bacteria concentrations of the complexes were determined with the method of Olorundare *et al.* [39] using samples of organisms were taken from plates which were used for the MIC test with no visible growth. These were sub-cultured on to freshly prepared nutrient agar medium by streaking. These plates were incubated at 37 ^{o}C for 24 hours. MBC was taken as the lowest concentration of complexes at which all bacteria are killed.

RESULTS AND DISCUSSION

Synthesis

The complexes synthesized are formulated as [M(SD)(me-DTC)] and [M(SD)(et-DTC)], where M = Co, Cu, Pd and Pt; SD = sulfadiazine, me-DTC = N-methyl-N-phenyl dithiocarbamate and et-DTC = N-ethyl-N-phenyl dithiocarbamate. The formation of the Co and Cu complexes can be represented by the general equation:

$$NaSD + NaR\text{-}DTC + MX_2Cl_2 \rightarrow [M(SD)(R\text{-}DTC)] + 2NaCl \quad (R = \text{methyl or ethyl, } M = Co, Cu)$$

The formation of the Pd and Pt complexes can be represented by the following equations:

$$[PdCl_2(CH_3CN)_2] + NaSD + NaR\text{-}DTC \rightarrow [Pd(SD)(R\text{-}DTC)] + 2NaCl + 2CH_3CN$$

$$[PtCl_2(COD)] + NaSD + NaR\text{-}DTC \rightarrow [Pt(SD)(R\text{-}DTC)] + 2NaCl + COD$$

Table 1. Analytical data and some physical properties of the complexes.

Complexes	Molecular formulae	Colour	Analytical data (%) C Found (calc.)	H Found (calc.)	N Found (calc.)	Yield (%)	M.P. (ºC)	Cond. µS
[Co(SD)(me-DTC)]	$C_{18}H_{18}N_5O_2S_3Co$	Green	44.40 (43.99)	3.99 (3.69)	13.97 (14.25)	76	214-215	2.47
[Cu(SD)(me-DTC)]	$C_{18}H_{18}N_5O_2S_3Cu$	Brown	43.12 (43.58)	3.13 (3.66)	14.07 (14.12)	79	208-210	2.11
[Pt(SD)(me-DTC)]	$C_{18}H_{18}N_5O_2S_3Pt$	Yellow	34.04 (34.45)	3.02 (2.89)	10.96 (11.16)	97	167-170	3.07
[Pd(SD)(me-DTC)]	$C_{18}H_{18}N_5O_2S_3Pd$	Orange	39. 80 (40.11)	3.04 (3.37)	11.80 (12.11)	85	225-227	1.53
[Co(SD)(et-DTC)]	$C_{19}H_{20}N_5O_2S_3Co$	Green	45.03 (45.14)	3.55 (3.99)	14.08 (13.85)	80	209-211	3.80
[Cu(SD)(et-DTC)]	$C_{19}H_{20}N_5O_2S_3Cu$	Brown	44.55 (44.74)	3.50 (3.95)	13.22 (13.73)	89	199-201	6.96
[Pt(SD)(et-DTC)]	$C_{19}H_{20}N_5O_2S_3Pt$	Yellow	35.05 (35.57)	3. 52 (3.14)	11.22 (10.91)	92	206–209	1.19
[Pd(SD)(et-DTC)]	$C_{19}H_{20}N_5O_2S_3Pd$	Orange	40.88 (41.27)	3.11 (3.65)	12.32 (12.66)	84	199-202	1.27

All complexes are air stable and insoluble in most solvent except DMSO and DMF. They are all non-electrolyte in DMF with conductivity values of 1.53–6.96 μS. The analytical data of the complexes are presented in Table 1.

Infrared spectra of the complexes

The infrared spectra of the ligands and their respective metal complexes were compared and assigned on careful comparison. Relevant IR bands are presented in Table 2. The bands in the region of 3450-3200 cm^{-1} due to symmetrical and asymmetrical stretching modes of NH_2 in the spectrum of the sulfadiazine ligand undergo only slight changes in the spectra of the complexes. This indicates that the NH_2 group of free sulfadiazine molecule is not affected by coordination to the metal ions [27]. The coordination of the metal ions to sulfadiazine affected the symmetrical and asymmetrical stretching modes of the SO_2. The bands which occurs at 1332 and 1163 cm^{-1} in the free sulfadiazine ligands shifted to a lower wavenumber in all the complexes. The ν_{SN} on the other hand shifted to a higher wavenumbers by about 31-47 cm^{-1} in complexes with N-methyl-N-phenyl dithiocarbamate, while in the N-ethyl-N-phenyl dithiocarbamate complexes, a shift to lower wavenumbers of 31-51 cm^{-1} was observed. These observations confirmed the coordination of the metal ions to sulfadiazine through the sulfonamide N atom. The ν(C=N) stretching vibration bands that occurs at 1631 and 1586 cm^{-1} in the free sulfadiazine ligand shifted in all complexes, and this confirms the coordination of the metal ions through the pyrimidinyl N(1) atom of sulfadiazine.

Table 2. Relevant infrared frequencies (cm^{-1}) for the ligand and complexes.

Compound	ν(N-H)as	ν(N-H)s	ν(C=N)	ν(SO)as	ν(SO)s	ν(CS)	ν(SN)
$C_{10}H_9N_4O_2SNa$	3419	3370	1631 1586	1332	1163	–	941
Co(SD)(me-DTC)	3431	–	1619 1595	1292	1069	1017	983
Cu(SD)(me-DTC)	3450	3370	1631 1593	1278	1128	1020	972
Pt(SD)(me-DTC)	3414	–	1619 1594	1266	1116	1024	974
Pd(SD)(me-DTC)	3437	–	1619 1593	1266	1133	1024	988
[Co(SD)(et-DTC)]	3435	–	1619 1595	1280	1129	1068	990
[Cu(SD)(et-DTC)]	3450	3370	1631 1593	1280	1128	1019	972
[Pt(SD)(et-DTC)]	3419	–	1643 1593	1283	1129	1024	992
[Pd(SD)(et-DTC)]	3436	–	1619 1593	1283	1129	1025	991

In examining the infrared spectra of dithiocarbamate complexes, the three main area of interest are: the region 1580-1450 cm^{-1} due to ν(C–N) stretching vibrations, the region 1060-940 cm^{-1} due to ν(C–S) and the region 430-250 cm^{-1} due to the ν(M–S). In the dithiocarbamate ligands, the bands in the region 1430-1454 cm^{-1} assigned to the ν(C–N) stretching vibrations shifted in the spectra of all complexes to 1451-1494 cm^{-1}. The shift is caused by increased electron delocalization towards the metal ion upon coordination and confirmed the coordination of the metal ions to the dithiocarbamate ligands. The coordination increases the double bond

character of the C–N bond, and this is responsible for the shift in the *v*(C–N) stretching vibrations. In dithiocarbamate complexes, the *v*(C–S) symmetrical and asymmetrical stretching vibrations are diagnostics of the coordination mode of the ligand to the metal ions. The *v*(S–C–S) mode is expected to be in the region 1000±70 cm^{-1} and the number of bands observed in this region can be used to determine the binding mode of the dithiocarbamate ligand. A single sharp band at about 970 cm^{-1} is attributed to *v*(C–S) stretching vibration of symmetrically coordinated dithiocarbamate ligand while two peaks in the region 1002-1017 cm^{-1} indicate unsymmetrically coordinated ligands. In the metal complexes of the sulfadiazine with dithiocarbamate ligands the *v*(C–S) could not be properly assigned because it occurs at almost the same region as the *v*(C–N) of the sulfadiazine ligand. In all the complexes, three bands in the region 980-1002 cm^{-1} are assigned to *v*(C–S) stretching vibrations. The M–N bond is assigned to the band at about 453-458 cm^{-1}, while the M–S is assigned to the bands at about 334 cm^{-1}

Electronic spectra of metal complexes

In the electronic spectra of regular tetrahedral Cu(II) complexes, a single broad band of 10^2 molar absorptivity located near the IR region is usually observed while Cu(II) complexes in square planar geometries normally show two bands in the visible regions [40]. The Cu(II) complexes showed very broad bands at 450 nm and another band of low intensity at about 640 nm. These bands can be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions in a square planar environment. The splitting of the absorption bands of [Cu(SD)(et-DTC)] might be attributed to Jahn-Teller distortions which normally results in unsymmetrical bands or due to the occurrence of multiple bands. Co(II) occurs in a variety of structural environments and gives varied spectra and magnetic properties [41]. For tetrahedral Co(II) complexes, two principal bands are expected with the lowest energy band being in the infrared region. The spectra of the Co(II) complexes are similar with an asymmetrical broad band that peaks at about 620 nm that may be assigned to the $^4T_{2g} \rightarrow {}^4T_{1g}$ transitions in tetrahedral environment. Pd(II) and Pt(II) typically form square planar complexes with their electronic spectra dominated by charge transfer bands. The Pd(II) complexes showed very week bands at about 450 nm that typical of a square planar d^8 complexes while the Pt(II) show little or no d-d transitions. The proposed structures for the complexes are shown in Figure 1.

M = Co, Cu, Pd and Pt

Figure 1. Proposed structures for the complexes.

Antibacterial studies of metal complexes of sulfadiazine

All metal complexes as well as the sulfadiazine ligand show positive activities against some of the selected bacterial isolates at 40 mg/mL concentration (Table 3). The highest zone of inhibition of 27 mm can be seen with [Co(SD)(et-DTC)] against *Escherichia coli* cultures. The lowest MIC value of 0.16 mg/mL was observed with [Co(SD)(et-DTC)], and its activity was shown against gram positive *Bacillus pumilus.* [Cu(SD)(et-DTC)] and [Pt(SD)(me-DTC)] have MIC value of 0.31 mg/mL each, which makes them the second most active antimicrobial agents after [Co(SD)(et-DTC)] (Table 4). However, it can also be seen that the complexes with N-ethyl-N-phenyl dithiocarbamate is more active than the complexes with N-methyl-N-phenyl dithiocarbamate. In general, the metal complexes have a much higher antimicrobial potency than the free sulfadiazine ligand. The MBC values of the complexes once again showed that [Co(SD)(et-DTC)] is a stronger antimicrobial agent with MBC value of 0.31 mg/mL. A value greater than the dilution concentration of 20 mg/mL can be observed in MBC values of sulfadiazine which shows that it is the least active compared to the metal complexes (Table 5).

Table 3. Zone of inhibition in mm exhibited by sulfadiazine and the complexes at 40 mg/mL.

Complexes	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. faecalis*	*B. cereus*	*B. pumilus*	*K. pneumonia*	*P. vulgaris*
[Cu(SD)(me-DTC)]	NI	N1	NA	16.0	23.0	N1	NI	NI
[Cu(SD)(et-DTC)]	20.0	20.0	NA	26.0	NI	NI	20.0	NI
[Co(SD)(me-DTC)]	17.0	NI	NA	NI	14.0	23.0	NI	NI
[Co(SD)(et-DTC)]	20.0	22.0	NA	NI	12.0	27.0	NI	NI
[Pd(SD)(me-DTC)]	11.0	12.0	NI	NI	10.0	NI	11.0	NI
[Pd(SD)(et-DTC)]	24.0	NI	25.0	NI	22.0	NI	NI	20.0
[Pt(SD)(me-DTC)]	23.0	24.0	NI	25.0	23.0	24.0	11.0	13.0
[Pt(SD)(et-DTC)]	22.0	NI	23.0	NI	22.0	NI	NI	25.0
Sulfadiazine	20.0	NI	22.0	22.0	24.0	NI	24.0	20.0

NI = no inhibition observed; NA = not applicable.

Table 4. MIC values (mg/mL) for sulfadiazine and the complexes.

Complexes	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. faecalis*	*B. cereus*	*B. pumilus*	*K. pneumonia*	*P. vulgaris*
[Cu(SD)(me-DTC)]	NI	N1	NA	1.25	0.63	N1	NI	NI
[Cu(SD)(et-DTC)]	0.31	0.31	NA	1.25	NI	NI	0.63	NI
[Co(SD)(me-DTC)]	5.0	NI	NA	NI	5.0	1.25	NI	NI
[Co(SD)(et-DTC)]	0.63	0.63	NA	NI	1.25	0.16	NI	NI
[Pd(SD)(me-DTC)]	10.0	10.0	NI	NI	10.0	NI	10.0	NI
[Pd(SD)(et-DTC)]	10.0	NI	20.0	NI	10.0	NI	NI	20.0
[Pt(SD)(me-DTC)]	10.0	10.0	NI	0.31	10.0	0.31	0.31	10.0
[Pt(SD)(et-DTC)]	10.0	NI	5.0	NI	10.0	NI	NI	10.0
Sulfadiazine	20.0	NI	22.0	22.0	24.0	NI	26.0	20.0

NI = no inhibition observed; NA = not applicable.

Table 5. MBC values (mg/mL) for sulfadiazine and the complexes.

Complexes	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. faecalis*	*B. cereus*	*B. pumilus*	*K. pneumonia*	*P. vulgaris*
[Cu(SD)(me-DTC)]	NI	N1	NA	2.5	1.25	N1	NI	NI
[Cu(SD)(et-DTC)]	0.31	0.31	NA	2.5	NI	NI	0.63	NI
[Co(SD)(me-DTC)]	10.0	NI	NA	NI	5.0	2.5	NI	NI
[Co(SD)(et-DTC)]	1.25	0.63	NA	NI	2.5	0.31	NI	NI
[Pd(SD)(me-DTC)]	>20.0	20.0	NI	NI	20.0	NI	20.0	NI
[Pd(SD)(et-DTC)]	20.0	NI	20.0	NI	20.0	NI	NI	20.0
[Pt(SD)(me-DTC)]	>20.0	>20.0	NI	1.25	20.0	1.25	5.0	>20.0
[Pt(SD)(et-DTC)]	20.0	NI	10.0	NI	>20.0	NI	NI	20.0
Sulfadiazine	20.0	NI	22.0	22.0	24.0	NI	26.0	20.0

NI = no inhibition observed; NA = not applicable.

CONCLUSIONS

Heteroleptic Co(II), Cu(II), Pd(II) and Pt(II) complexes of sulfadiazine and some N-alkyl-N-phenyldithiocarbamate was synthesized and characterized by elemental analysis, conductivity measurements, electronic and FTIR spectroscopy. Four coordinate tetrahedral geometryies are proposed for the Co(II) complexes while square planar geometries are proposed for the Cu(II), Pd(II) and Pt(II) complexes. The antibacterial studies of the complexes against eight bacterial isolates showed varied antibacterial activities with [Co(SD)(et-DTC)] being the most active. The minimum inhibitory concentrations and the maximum bactericidal concentrations for the complexes were also determined.

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