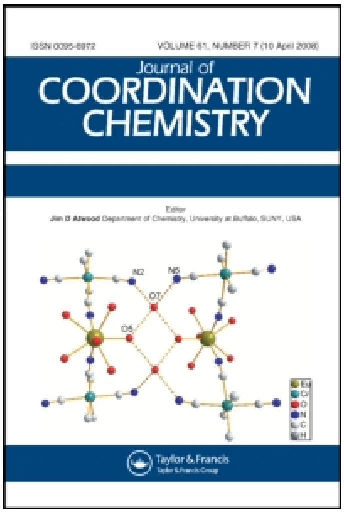

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Synthesis, characterization and susceptibility of bacteria against Sulfamethoxydiazine complexes of copper(II), zinc(II), nickel(II), cadmium(II), chromium(III) and iron(III)

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SYNTHESIS, CHARACTERIZATION AND SUSCEPTIBILITY OF BACTERIA AGAINST SULFAMETHOXYDIAZINE COMPLEXES OF COPPER(II), ZINC(II), NICKEL(II), CADMIUM(II), CHROMIUM(III) AND IRON(III)

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Complexes of sulfamethoxydiazine with Cu(II), Zn(II), Ni(II), Cd(II), Cr(III) and Fe(III) have been synthesized and characterized on the basis of conductivity measurements, elemental analyses, UV, IR, ^{1}H NMR and thermal studies. It is shown that sulfamethoxydiazine behaves as a bidentate ligand, binding the metal ion through the sulfonyl oxygen and sulfonamide nitrogen. *In vitro* susceptibility tests of these complexes against *Escherichia coli, Bacillus subtilis, Proteus vulgaris* and *Staphylococcus aureus* were carried out. The results show that the antibacterial activities of the complexes of Zn(II), Cu(II), Cr(III) and Fe(III) are, in general, stronger than that of sulfamethoxydiazine, while the complexes of Cd(II) and Ni(II) are less active.

Keywords: Synthesis; Characterization; Antibacterial activity; Sulfamethoxydiazine complexes

INTRODUCTION

Sulfa drugs are widely used for the treatment of various infectious diseases. The clinical application of complexes of sulphadiazine with silver(I) and zinc(II) in burn therapy aroused interest in metal complexes of sulfa drugs [1–3]. Since the number of synthesized metal complexes of antibiotic sulfa drugs has been increasing, the interaction of metal ions with drugs administered for therapeutic reasons has become a subject of considerable importance.

In order to understand drug–metal ion interactions, we have studied sulfamethoxydiazine and its complexes. Sulfamethoxydiazine is used for the treatment of urinary tract infections. Its antibacterial activity and protection for patients are stronger than those of other sulfa drugs, but research concerning its complexation with biologically

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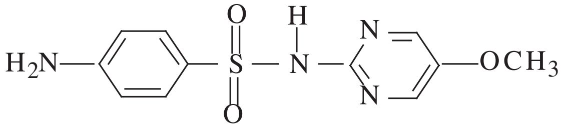


FIGURE 1 Structure of sulfamethoxydiazine (HSMD).

important metals has not been reported. This article reports, for the first time, the preparation of transition metal complexes with sulfamethoxydiazine and their physical, spectral and antibacterial activity. The intention was to study the coordination of sulfamethoxydiazine with metal ions and whether the antibacterial activity of sulfamethoxydiazine is enhanced by complexation with metals. The structure of sulfamethoxydiazine is shown in Fig. 1.

EXPERIMENTAL

Materials

The compounds $CuCl_2 \cdot 2H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$, $ZnSO_4 \cdot 7H_2O$, $NiCl_2 \cdot 6H_2O$, $CrCl_3 \cdot 6H_2O$, $CdCl_2 \cdot 1/2H_2O$ were of A.R. grade. Sulfamethoxydiazine (Kunshan Xingyu Trading Company, China) was used directly without further purification. All other chemicals used were of A.R. grade.

Preparation of Metal Complexes

Sulfamethoxydiazine (1.4 g, 5 mmol) in distilled water (20 mL) was adjusted to pH 8.0–10.0 by the addition of powdered sodium hydroxide. The ligand solution was then added to an aqueous solution (10 mL) of the metal salt (2.5 mmol) with continuous stirring at room temperature. Stirring was continued for 1–2 h. The precipitate obtained was filtered, then washed three times with distilled water, dried in vacuum for 10 h and kept in a desiccator filled with anhydrous calcium chloride. The yields of metal complexes were in the range 60–85%.

Physical Measurements

Melting points were determined on an XRC-1 micromeltingpoint apparatus. Conductivity measurements were made on a DDS-12A conductometer in DMF at room temperature. The elemental analyses were carried out on a PE-2400 elemental analyzer. Metals were determined by standard literature procedures [4]. Infrared spectra were recorded in KBr discs on Bio-Rad FTS-40 spectrophotometer in the range of 4000–400 cm^{-1}. The electronic spectra were recorded on a PE-17 UV-Vis spectrophotometer. Proton magnetic resonance spectra were obtained on a DPX-400 NMR spectrometer using TMS as reference in DMSO-d^6 at room temperature. Thermograms were recorded on a DT-40 thermal analyzer in N_2 with a heating rate of 10°C per minute.

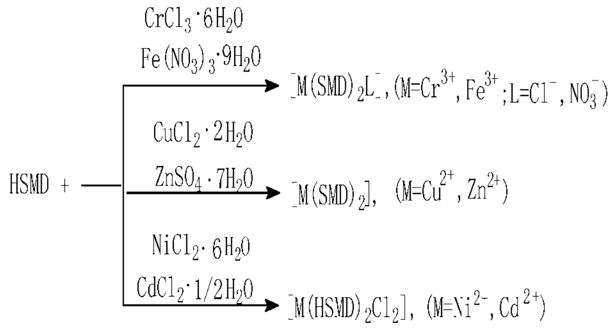
Antibacterial Measurements

The ligand and its complexes were tested for their antibacterial activity using the paper disc diffusion method. The bacteria used usually had to be cultured in the nutrient agar-agar at 16–18°C for 24 h. Circles of filter paper (6-mm diameter) were first soaked in the DMF solution of the tested compound, disinfected under high pressure for 20 min then dried at 80°C. The strips obtained were then put in contact with the cultured bacteria on the nutrient agar-agar at 37°C for 24 h. The activity against bacteria of the compound was determined by the zone of inhibition. Each solution was tested twice as parallel analysis.

RESULTS AND DISCUSSION

Physical Properties and Elemental Analysis

The physical and elemental analysis data of sulfamethoxydiazine and its metal complexes prepared are given in Table I. The relevant chemical reactions are summarized below:



The complexes are soluble in DMF but insoluble in water, methanol, ethanol, benzene and CCl_4. All complexes are stable in air.

The values of the conductivities of millimolar solutions of the metal complexes in DMF at room temperature were lower than expected for 1:1 electrolytes (65–90 $ohm^{-1}\,cm^2\,mol^{-1}$), which indicates that these compounds are non-electrolytes [5]. The thermograms of the metal complexes showed first decomposition (endothermic) at 80–140°C corresponding to loss of water molecules and formation of the corresponding metal oxides or sulfate at high temperatures.

Infrared Spectral Studies

The important IR frequencies of these compounds are given in Table II. Sulfamethoxydiazine shows two strong vibrational bands at 3465 and 3378 cm^{-1} which may be assigned to asymmetric and symmetric stretching vibrations of the aniline (NH_2) group, respectively [6]. A shift to lower frequency with respect to these bands in the spectra of the metal complexes cannot be attributed to metal–ligand binding through the aniline NH_2 nitrogen. A shift could arise from a resonance contribution

TABLE I Physical and analytical data of sulfamethoxydiazine and its metal complexes

Compound	*Formula* (*Formula Weight*)	*Yield* (%)	*Color*	*M.p* (°C)	*Elemental analysis Found* (*Calcd.*) (%)				*Molar conductance* (ohm cm^2 mol^{-1})
					M	*C*	*H*	*N*	
HSMD	$C_{11}H_{12}N_4O_3S$ (280.31)	–	White	210	–	47.13	4.32	19.99	–
$[Cu(SMD)_2] \cdot 3H_2O$	$C_{22}H_{28}CuN_8O_9S_2$ (676.17)	85	Green-yellow	232	8.98 (9.37)	38.62 (38.96)	3.05 (3.27)	16.45 (16.52)	3.7
$[Ni(HSMD)_2Cl_2] \cdot 5H_2O$	$C_{22}H_{34}Cl_2N_8NiO_{11}S_2$ (780.45)	70	Green	> 300	7.70 (7.52)	33.97 (33.86)	3.81 (4.39)	14.27 (14.36)	1.6
$[Zn\ (SMD)_2] \cdot 4H_2O$	$C_{22}H_{30}N_8O_{10}S_2Zn$ (695.98)	78	White	288	9.41 (9.37)	37.76 (37.85)	3.81 (4.33)	15.82 (16.06)	7.8
$[Cd(HSMD)_2Cl_2] \cdot H_2O$	$C_{22}CdCl_2H_{26}N_8O_7S_2$ (761.92)	75	White	240	14.92 (14.75)	34.63 (34.68)	3.20 (3.44)	14.72 (14.71)	1.4
$[Fe(SMD)_2(NO_3)] \cdot H_2O$	$C_{22}FeH_{24}N_9O_{10}S_2$ (694.47)	82	Brown-yellow	187	8.17 (8.04)	37.86 (38.05)	3.19 (3.48)	16.12 (16.14)	1.8
$[Cr(SMD)_2Cl] \cdot 2H_2O$	$C_{22}ClCrH_{26}N_8O_8S_2$ (681.67)	60	Grey-green	185	7.44 (7.23)	36.65 (36.62)	3.76 (3.83)	16.49 (16.38)	2.4

TABLE II Infrared spectral data and electronic spectral bands of sulfamethoxydiazine and its metal complexes

Compounds	$\nu_a(NH_2)$ (cm^{-1})	$\nu_s(NH_2)$ (cm^{-1})	$\nu(NH)$ (cm^{-1})	$\delta(NH_2)$ (cm^{-1})	$\nu_a(SO_2)$ (cm^{-1})	$\nu_s(SO_2)$ (cm^{-1})	*Heterocyclic ring vibration* (cm^{-1})	*Electronic spectral band* (nm)
HSMD	3465 m	3378 m	3231 m	1631 m	1320 s	1153,1141s	1569,1282 m	276, 290
$[Cu(SMD)_2] \cdot 3H_2O$	3454 m	3366 m	–	1629 m	–	1127 m	1550, 1280 m	274, 286, 350 ($\varepsilon = 1.2 \times 10^3$ mol^{-1} cm^{-1})
$[Ni(HSMD)_2Cl_2] \cdot 5H_2O$	3454 m	3362 m	3230 w	1629 m	–	1131 m	1551, 1278 m	276, 286, 360 ($\varepsilon = 2.0 \times 10^3$ mol^{-1} cm^{-1})
$[Cd(HSMD)_2Cl_2] \cdot H_2O$	3463 m	3359 m	3231 w	1625 m	–	1131 m	1549, 1276 m	276, 286,356 ($\varepsilon = 1.8 \times 10^3$ mol^{-1} cm^{-1})
$[Zn(SMD)_2] \cdot 4H_2O$	3458 m	3365 m	–	1628 m	–	1134 m	1548, 1274 m	270, 290
$[Fe(SMD)_2(NO_3)] \cdot H_2O$	3420 m	3340 m	–	1630 m	1305 m	1128 m	1548, 1262 m	276, 280
$[Cr(SMD)_2Cl] \cdot 2H_2O$	3440 m	3342 m	–	1630 m	1305 m	1125 m	1548, 1270 m	274, 286, 380 ($\varepsilon = 2.5 \times 10^3$ mol^{-1} cm^{-1})

from the aniline NH_2 group or a bonding interaction between the NH_2 group and the sulfonyl oxygen of a neighboring molecule of sulfamethoxydiazine [7]. In the range 3200–3500 cm^{-1}, a broad, strong peak shows the presence of water molecules. The absence of a vibrational band at 3231 cm^{-1} (due to sulfonamide NH stretching in the free ligand [6]) in the complexes of Cu(II), Zn(II), Cr(III) and Fe(III) indicates that the sulfonamide NH group was deprotonated during complex formation [8]. However, the complexes of Cd(II) and Ni(II) did show a very weak vibrational band at 3231 cm^{-1}.

The medium vibrational band at 1629 cm^{-1} in the spectrum of the ligand may be due to the NH bending vibration coupled with heterocyclic ring C–N stretching vibrations and this band remains unshifted, further indicating the absence of coordination of the aniline NH_2 group. The bands at 1320 and 1153 (1141) cm^{-1} in the case of the ligand may be assigned to asymmetric and symmetric stretching vibrations of the sulfonyl group, respectively [6]. The absence of a band at 1320 cm^{-1} in the case of the Cu(II), Ni(II), Cd(II) and Zn(II) complexes, and a shift to lower frequency in the Fe(III) and Cr(III) complexes, indicate that coordination of sulfamethoxydiazine to the metal ion occurs through the sulfonyl oxygen. A shift to lower frequency for the asymmetric SO_2 stretch further supports this assertion. The phenyl ring frequencies [9] at 1600–1500 cm^{-1}, an X-sensitive (X = substituent) aromatic mode [10] at 1000–1090 cm^{-1} and frequencies in the range [10,11] 1580–1560 and 1280–1295 cm^{-1} due to heterocyclic ring vibrations were found unaltered in the complexes. The band at 1091 cm^{-1} due to the $\nu_{(C\text{–}O\text{–}C)}$ vibration [12] remains unaffected in the complexes, indicating that the oxygen in the heterocyclic ring is not involved in coordination to the metal ion. The presence of additional infrared bands at 1270 cm^{-1} [$\nu_a(NO_2)$] and 998 cm^{-1} [$\nu_s(NO_2)$] in the spectrum of the Fe(III) complex indicates the presence of chelating nitrate ion [13].

Electronic Spectra

The UV spectra of the ligand and the complexes in the range 190–400 nm are given in Table II. Sulfamethoxydiazine shows two absorption bands at 276 and 290 nm in DMF, which may be assigned to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions of the aromatic ring and heterocylic ring. The complexes show absorption bands at shorter or similar wavelengths. Additional bands at 350–380 nm ($\varepsilon = 1.0 \times 10^3$–$2.5 \times 103$ mol^{-1} cm^{-1}) are observed for the complexes of Ni(II), Cu(II), Cr(III) and Cd(II), which may be due to charge transfer from the ligand to metal [14].

^{1}H NMR Spectra

The proton magnetic resonance spectrum of the ligand shows a broad singlet at 11.01 ppm, which may be assigned to the sulfonamide NH proton. The absence of this proton signal in the spectra of the Cu(II) and Zn(II) complexes indicates that the sulfonamide NH group is deprotonated during complex formation [8]. For the Ni(II) and Cd(II) complexes, the NMR spectrum does not show the disappearance of the –NH– proton signal. The other proton signals could be assigned to aromatic CH protons [5.25 (s)] and [4.24 (s)], aniline NH_2 proton [3.30 (s)], methyl proton [2.51 (s)] and heterocyclic ring CH proton [7.52 (s)]. The Cr(II) and Fe(II) complexes are too paramagnetic to obtain the spectra.

Summary

From the elemental analytic data and spectral studies of the sulfamethoxydiazine metal complexes we may conclude that under alkaline conditions the sulfonamide NH group is deprotonated except in the case of Ni(II) and Cd(II) complexes. Sulfamethoxydiazine probably acts as a bidentate ligand, binding to the metal through the sulfonyl oxygen and sulfonamide nitrogen (Fig. 2).

Antibacterial Activity

The ligand and its complexes were tested for their antibacterial activity using the paper disc diffusion method. The bacteria used include *Escherichia coli, Bacillus subtilis, Proteus vulgaris* and *Staphylococcus aureus*. The test data are given in Table III. Generally, the activity against bacteria is represented by the disc size (D). $D \geq 17$ mm

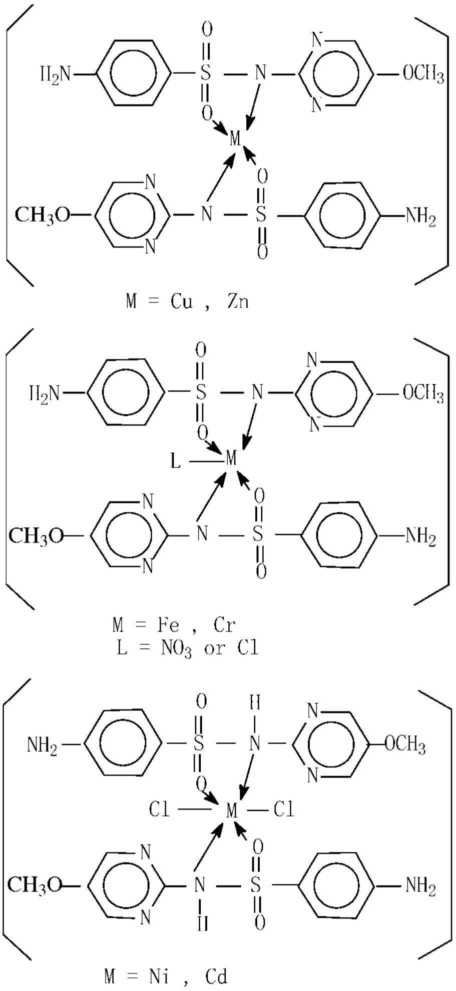


FIGURE 2 Suggested structures of the complexes.

TABLE III *In Vitro* susceptibility test of sulfamethoxydiazine and its complexes

Compound	*Disc concention* (μg/disk)	*Disc size* (mm)							
		E. coli		*P. vulgaris*		*S. aureus*		*B. subtilis*	
HSMD	25	10	10	10	10	16	16	9	9
	50	10.4	10.4	11	11	17	16.8	10.4	10.4
	100	11	11.2	12	12.5	17.9	18	11	11
$[Zn(SMD)_2] \cdot 4H_2O$	25	9.5	9.2	9	9	16.8	16.5	8.5	8.4
	50	10	10	10.4	10.8	17.6	17.6	9	9
	100	11.1	11	11.8	11.8	19	19	10.4	10
$[Cd(HSMD)_2Cl_2] \cdot H_2O$	25	9.8	9	8	8	9.2	9	8	8
	50	10	10.5	8.5	8.6	10	10	8.5	8.5
	100	11	11.3	10	10	12	12	9.2	9
$[Ni(HSMD)_2Cl_2] \cdot 5H_2O$	25	8	7.8	6.8	7	10	10.5	8	8.4
	50	8.8	8.7	7.5	7.5	11.6	11.6	9	9
	100	10	9.8	9.2	9	12.4	12.4	10	10.3
$[Cu(SMD)_2] \cdot 3H_2O$	25	8.1	8	9	9	17	17	8	8
	50	8.8	8.8	10.8	10.8	17.4	17.6	9	9.2
	100	10	10	11.5	11.5	18.9	19	10	10
$[Cr(SMD)_2Cl] \cdot 2H_2O$	25	9.5	9	10	10	16.5	16.4	10	10
	50	10	9.8	11.6	11.6	17	17	11	11
	100	12	11.5	12	12	19.2	19	12	12
$[Fe(SMD)_2(NO_3)] \cdot H_2O$	25	9.8	9.5	10	10.3	16.1	16	10	10.6
	50	11	10.8	11.2	11	17	17.3	11	11
	100	11.3	12	11.8	12	18	18	11.8	11.5
DMF	AR	0	0	0	0	0	0	0	0
$[Cr(SMD)_2Cl] \cdot 2H_2O$	25		10		11.6				11
	50								
	100								
DMF	AR								

corresponds to a high antibacterial effect; $D = 13-16$ mm to a medium antibacterial effect; $D \leq 12$ mm to a weak antibacterial effect. The test data suggest that the antibacterial abilities against *S. aureus* of the Zn(II), Cu(II) and Cr(III) complexes are basically stronger than that of sulfamethoxydiazine, but the Cd(II) and Ni(II) complexes generally have weaker antibacterial activities against all four bacteria than other compounds. The test data suggest that for the complexes of Zn(II), Cr(III), and Fe(III), the antibacterial activities against all four bacteria are larger than or similar to that of sulfamethoxydiazine but for the Cd(II) and Ni(II) complexes, the antibacterial activities are weaker than the ligand. While the Cu(II) complex shows different susceptibility against *S. aureus* is stronger than and the susceptibility against others is weaker. Meanwhile, all six compounds listed have lower antibacterial activities against *E. coli*, *P. vulgaris* and *B. substilis* than against *S.aureus*. All six compounds listed have lower antibacterial activities against *E. coli*, *P. vulgaris* and *B. substilis* than against *S. aureus*.

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References

[1] Wilson and Gisvold's, Textbook of Organic Medicinal and Pharmaceutical Chemistry (J.P. Lippincott, Philadelphia 1982), 8th Edn.
[2] S. Garg and S.S, Gupta, *J. Indian Chem. Soc.* **62**, 780 **(**1985).
[3] J.K. Gupta and N.K. Jha, *Croat. Chem. Acta* **60**, 303 (1987).
[4] The Handbook of Analytical Chemistry (Chemical Industry Press, Beijing, 1982), Vol 2.
[5] W.J. Geary, *Coord. Chem. Rev.* **1**, 81 (1971).
[6] L.J. Barami, Infrared Spectra of Complicated Molecules (Science Press, Beijing, 1975).
[7] G. Kanagaraj and G.N. Rao, *Indian J. Chem.* **32A**, 594 (1993).
[8] G. Kanagaraj and G.N Rao, *Synth. React. Inorg. Met.-Org. Chem.* **22**, 559 (1992).
[9] M. Goldstein, M.A. Russell and H.A. Williams, *Spectrochim. Acta* **25A**, 1275 (1969).
[10] I.A. Brownlie, *J. Chem. Soc.* 3062, (1950).
[11] L.N. Short and H.W. Thompson, *J. Chem. Soc.*, 168, (1952).
[12] S. Gu, R. Deng and J. Wu, *Chem. J. Chinese Universities* **7**, 575 (1987).
[13] Y. Zhongben, Infrared and Raman Spectra of Inorganic and Coordination Compounds (Chemical Industry Press, Beijing, 1986).
[14] D. Jin Douman and W. Zhu, Physical Methods in Coordination Chemistry (Science Press, Beijing, 1996).