METAL COMPLEXES OF 4–AMINO–N–(3,4–DIMETHYL–5–ISOXAZOLYL) BENZENESULFONAMIDE (SULFISOXAZOLE)

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Absrrect

Certain antibacterial agents that, by virtue of their solubility properties (lower pKa values closer to the pH of urine), concentrate in the urine are effective in the treatment of infections of the urinary tract.[1] The more typical first time infections such as acute cystitis can be eradicated with use of either short acting sulfonamide of the antibiotic tetracycline. A β–lactam (penicillin or cephalosporin) or an aminoglycoside may be used to treat acute renal tissue infections. A combination of trimethoprim and sulfamethoxazole is a treatment of choice for chronic urinary tract infections. In addition, there is a group of antibacterial agents which include methanamine, nitrofurantoin, nalidixic acid, etc., are well suited for the treatment of chronic urinary tract infections. Because these drugs achieve significantly higher concentrations in the urine and in the kidneys as compared with other body fluids and tissues.

It is proposed to study the metal binding characteristics of some selected pharmaceuticals mentioned below.

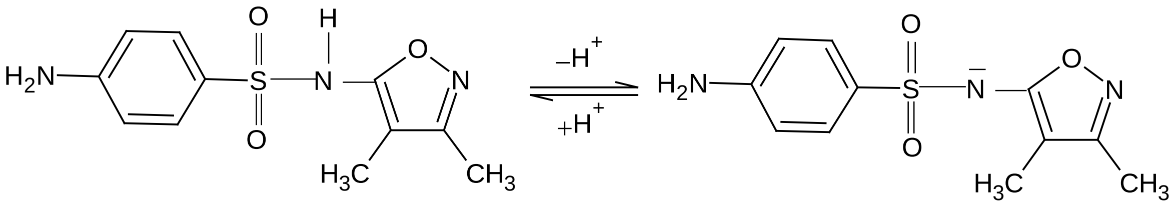
. In Sulfanilamide drugs such as sulfamethoxazole and sulfisoxazole are used as urinary antiseptics these heterocyclic derivatives of sulfanilamide, isoxazole ring nitrogen is also there in addition to aniline nitrogen, sulfonamide nitrogen and sulfonyl oxygen, capable of binding metal ions of interest

Keyword

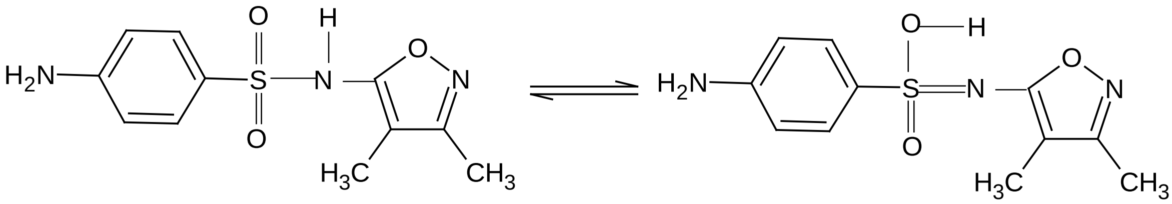
Sulfisoxazole,Metal Binding character

Introduction

Sulfisoxazole may be prepared by the reaction of 3,4–dimethyl–5–aminoisoxazole with N–acetyl–p–aminobenzene–sulfonyl chloride. The acetyl group is then cleaved to yield sulfisoxazole.[1] The pKa for sulfisoxazole has been determined spectrophotometrically and by the titration of sulfisoxazole in an excess of 0.1N sodium hydroxide solution with 0.1N hydrochloric acid solution to be 5.0



Sulfisoxazole, unlike sulfamethoxazole, can exhibit only amide–isoamide tautomerism in solution as shown below.



(AMIDE) (ISOAMIDE)

Sulfisoxazole, which was found to be stable in alkaline solution, was allowed to react with many metal salts and the products obtained were subjected to various methods of analysis to study the metal binding characteristics of sulfisoxazole.

Experimental Procedure

Conductivity Measurement[2]

Conductivity measurements for the metal complexes were carried out on a Metrohm 660 conductometer using a dip type cell incorporated with a temperature sensor

Magnetic Susceptibility Measruement[(3-5)]

Magnetic susceptibilities for the metal complexes were measured on a Cahn 2000 magnetic balance (Faraday) using $Hg[Co(NCS)_4]$ as calibrant.

Infrared Spectral Analysis[(6-7)]

Infrared spectra of the compounds were taken either as potassium bromide pellets or as nujol mull on a SP 1200 infrared spectrophotometer in the range 4000–400 cm^{-1}.

MATERIALS USED:

Pharmaceuticals used such as Sulfisoxazole (Sigma Chemical Co., USA).

Common organic solvents

Distilled water,Sodiium hydroxide solution, Methanol

Preparation of Metal Complexes of Sulfisoxazole

Sulfisoxazole (5 mmol) dissolved in distilled water (25 ml) by using aqueous sodium hydroxide solution (pH 8.0 to 10.0) was added slowly to an aqueous solution (10 ml) of metal salt (2.5 mmol) with continuous stirring. Stirring was continued for five to ten minutes. The precipitate obtained was filtered, washed with distilled water and then dried in a vacuum desiccator. Magnesium and copper complexes of sulfisoxazole were isolated from neutral methanolic solutions.

RESULTS AND DISCUSSION

The physical and analytical data of sulfisoxazole and its metal complexes are given in Table 1. The elemental analysis results for the metal complexes were found to be in agreement with the proposed molecular formulae.

Conductivity

The conductivity measurements on millimolar solutions of sulfisoxazole and its metal complexes in dimethylformamide were made at room temperature (300°k). The molar conductivity values calculated for sulfisoxazole, copper(II), zinc(II) and mercury(II) complexes were found to be much lower than the range of conductivity values reported in the literature for 1:1 electrolytes (see Table 2). The cobalt(II) complex has the value in the range (71.4 $ohm^{-1}.cm^2.mol^{-1}$) expected for 1:1 electrolytes (60 to 90 $ohm^{-1}.cm^2.mol^{-1}$). Magnesium(II) and nickel(II) complexes showed high values of molar conductivity probably due to solvolysis.[8]

Magnetic Susceptibility

The magnetic moment, μ calculated from the measured magnetic susceptibilities at room temperature for cobalt(II) and nickel(II) complexes was found to be in the range expected for six coordinate metal complexes containing three and two unpaired electrons, respectively (see Table 2). Cobalt(II) complex has magnetic moment of 5.23 BM while the nickel(II) complex has 3.60 BM. The lower

Infrared Spectral Study

Infrared spectra of sulfisoxazole and its metal complexes were recorded as nujol mull in the region 4000–400 cm^{-1} and as polyethylene film in the region 700–30 cm^{-1}. The important vibrational frequencies with tentative assignment to various vibrational modes of sulfisoxazole are given in Table 3.

IR Region 4000–3000 cm^{-1}

The ligand sulfisoxazole showed strong vibrational absorptions at 3480 and 3380 cm^{-1} which may be assigned to asymmetric and symmetric stretchings of aniline NH_2 groups, respectively (see Fig. 2).[1] A negative shift of 50–70 cm^{-1} with respect to these vibrational absorptions in the case of magnesium(II), cobalt(II) and nickel(II) complexes and relatively lesser negative shift of 20–30 cm^{-1} in the case of copper(II) and zinc(II) complexes were observed. Because of resonance contribution from aniline NH_2 group in the ligand molecule and also due to possible hydrogen bonding interaction between NH_2 group and sulfonyl oxygen of the neighbouring molecule, these negative shifts can not be attributed (satisfactorily) to the metal–ligand binding through aniline NH_2 nitrogen.[9] Though it is difficult to explain, a positive shift of 10–25 cm^{-1} in the case of mercury(II) complex may indicate that aniline NH_2 group remains free of metal binding. Another vibrational band at around 3300 cm^{-1}, expected due to the presence of sulfonamide NH group was not observed in the spectrum of the ligand, sulfisoxazole

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Table 1: Physical and Analytical Data of Sulfisoxazole and its Metal Complexes

S.No.	Compound[#]	Colour	M.P. (°C)*	Elemental Analysis							
				Calculated (%)				Found (%)			
				M	C	H	N	M	C	H	N
1.	Sulfisoxazole	White	213	–	49.43	4.90	15.72	–	49.31	4.35	15.59
2.	$Mg(SI)_2.H_2O$	White	266	4.23	45.96	4.56	14.62	4.54	45.75	4.21	14.26
3.	$[Co(SI)_2{-}(H_2O)_4]_2 3H_2O$	Pink	194 d	8.53	38.26	5.11	12.17	8.31	37.83	4.96	12.31
4.	$[Ni(SI)_2{-}(H_2O)_4]_2 2H_2O$	Bluish grey	199 d	8.39	37.78	5.19	12.02	8.88	37.86	4.84	12.20
5.	$[Cu(SI)Cl_2]_n$	Green	220 d	15.82	32.88	3.26	10.46	15.39	32.64	3.52	10.23
6.	$Zn(SI)_2.4H_2O$	White	225 d	9.76	39.43	4.81	12.54	9.14	39.87	4.79	12.75
7.	$Hg(SI)_2$	White	223	27.36	36.04	3.30	11.46	27.49	36.57	3.49	11.78

SI = deprotonated sulfisoxazole ($C_{11}H_{13}N_3SO_3$)

* d = decomposing

Table 2: Magnetic Susceptibility and Conductivity Data of Sulfisoxazole and its Metal Complexes

S.No.	Compound	Magnetic Moment, μ in BM#	Molar Conductivity, Λ_M in DMF ($ohm^{-1}.cm^2.mol^{-1}$)
1.	Sulfisoxazole ($C_{11}H_{13}N_3SO_3$)	–	5.3
2.	$Mg(SI)_2.H_2O$	diamagnetic	–*500
3.	$[Co(SI)_2–(H_2O)_4]_2 3H_2O$	5.23	71.4
4.	$[Ni(SI)_2–(H_2O)_4]_2 2H_2O$	3.60	–*295
5.	$[Cu(SI)Cl_2]_n$	1.46	30.3
6.	$Zn(SI)_2.4H_2O$	diamagnetic	24.2
7.	$Hg(SI)_2$	diamagnetic	8.5

Reported magnetic moment values are uncorrected for diamagnetism of the compounds studied.

* High values of molar conductivity possibly due to solvolysis.

Table 3: Infrared Spectral Data of Sulfisoxazole and its Metal Complexes*

Assignment	SI	Mg–SI	Co–SI	Ni–SI	Cu–SI	Zn–SI	Hg–SI
$\nu_{O-H}(H_2O)$	–	–	3500 3100vb,s	3500 3100vb,s	–	3500 3100vb,s	–
νN–H	3480s 3380s	3420s 3315s	3410s 3330s	3410s 3330s	3460s 3365s	3350s –	3505s 3390s
δNH2+ Isoxazole ring vibration	1645m 1635m	– 1635m	1650m 1625m	1640m –	1650w 1515m	1650w –	1650m 1640m
νC=C (phenyl ring)	1595m 1505m	1600m 1505m	1605m 1505m	1615m 1510m	1595m 1505m	1615m 1520m	1610m 1520m
Isoxazole ring stretching	1465s 1380s	1465s 1380s	1465s 1380s	1480s 1395s	1465s 1380s	1480s 1395s	1480s 1395s
νSO2 Asymmetric symmetric	1345s 1170s	– 1165s	1340vw 1160s	1355vw 1175m	– 1155s	1330m 1155s	1355m 1155s
νC–N	1320s 1300m –	1300s 1285s 1225s	1300w 1285s 1235s	1305m 1250s –	1320w 1270m –	1270s 1250s –	1320s 1290m –
Aromatic C–H in–plane bending	1095s	1095s	1095s	1110s	1090s	1095s	1100s

* Spectra recorded in nujol; vibrational frequencies in cm^{-1};

SI = Sulfisoxazole; vibrational band description: s = strong, m = medium, w = weak, vw = very weak and vb = very broad

Thermal Decomposition Study[10]

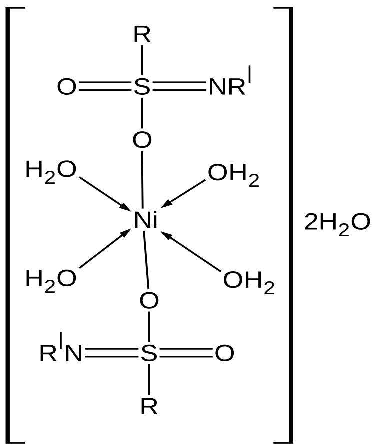
The thermal properties of sulfisoxazole in the melting region depend greatly on the previous thermal history of the sample. When a thermogram was obtained using a heating rate of 10°C/minute in static air, an endotherm (melting) starting at 230°C and an exotherm (decomposing) at 255°C were observed. Above 270°C, the ligand decomposed continuously and the crucible was found empty at around 565°C.

CONCLUSION

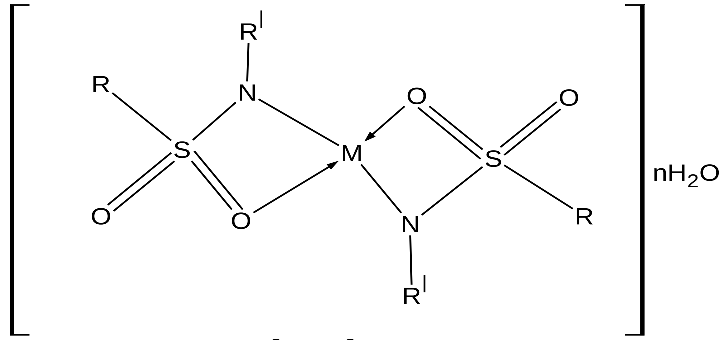
The various physico–chemical methods of analysis of metal complexes of sulfisoxazole showed that sulfisoxazole acts as a bidentate ligand binding the metal ion through sulfonyl oxygen and sulfonamide nitrogen (deprotonated) in the case of magnesium(II), zinc(II) and mercury(II) complexes.

In the nickel(II) complex of the type $[Ni(SI)_2(H_2O)_4]2H_2O$, the ligand probably acts as an anionic monodentate ligand binding the metal ion through sulfonyl oxygen. The cobalt(II) complex of the type $[Co(SI)_2(H_2O)_4]_2 3H_2O$ might contain deprotonated sulfisoxazole binding the metal ion only through sulfonyl oxygen. However, in the absence of detailed structural investigation like single crystal X–ray diffraction study, these suggestions remain tentative.

The following structures are proposed for some of the metal–sulfisoxazole complexes studied.



R = $-C_6H_4.NH_2$
R^I = 3,4–Dimethyl–5–isoxazolyl moiety



M = Zn^{2+}, Hg^{2+}
R = $-C_6H_4.NH_2$
R^I = 3,4–Dimethyl–5–isoxazolyl moiety
n = 0 or 4

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