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Spectral Studies of Binary and Ternary Complexes of Some Sulfa-Drugs

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The complexes of Sulfamethazine (SMZ), Sulfathiazole (STZ) and Tolbutamide (TA) with Cu(II) and Fe(III) have been investigated. The formation of 1:1 and 1:2 species were inferred from electronic spectra and conductivity measurements. The bonding sites are the oxygen of sulphonamide group and heterocyclic nitrogen atom of aryl moiety. Interaction of Cu(II) and Fe(III) ions with salysaldehyde as the primary ligand and with SMZ, STZ and TA as secondary ligands has been studied spectrophotometrically. The data indicate the formation of ternary complexes with stoichiometric ratio of (1:1:1). Stability of binary and ternary complexes was found to be in the order. SMZ>STZ>TA

Key words: Binary and ternary complexes, Sulfadrugs, Sulfamethazine, Sulfathiazole, Tolbutamide.

Introduction

The reactions taking place in the natural systems are highly specific and selective. Metal ions activity participate in most of the reactions occuring in the biological systems which are dominated by mixed ligand and the systems as model have been proved useful in understanding the roles of metal ions in the biological systems (Martell and Sigel 1973; Perrin *et al* 1973; Chhorn Elsevier 1975; Sigel 1973-1985).

Sulphonamides group of compounds are well known for thier antibacterial actions (Yoe and Jone 1944; Lewis *et al* 1965; George and John 1977; Hans *et al* 1978; Misra *et al* 1982) and are found to inhibit the growth of many bacteria. The binary and ternary complexes of sulfadrugs are reported (Baltistuzzi *et al* 1991; Shvelashvili *et al* 1991) but the complexe formation of these drugs with Cu(II) and Fe(III) are not studied in solution spectrophotometrically. The present paper describes an equilibrium study of the binary and ternary interaction of Cu(II) and Fe(III) with salysaldehyde as the primary ligand and SMZ, STZ, TA as secondary ligands (Table 1).

Experimental

Solutions and measurements. Stock solutions (0.05) mol dm^{-3}) of copper nitrate and ferric nitrate were prepared by dissolving the appropriate amount in absolute ethanol. Stock solution (0.002 mol dm^{-3}) of sulfadrugs (The Nile company for pharm. Chem. Ind.) and (0.002 mol dm^{-3}) of salysaldehyde (Aldrich) solution were prepared, using absolute ethanol. The stoichiometry of the complex solution was determined by two spectrophotometric methods, molar ratio (Yoe and Jones 1944) and continuous variation method. Conductometric titrations were carried out at room temperature (30°C) titrating 25.0 ml $1.0x10^{-3}$ mol dm^{-3} of each of Cu(II) and Fe(III) ions with $1.0x10^{-2}$ mol dm^{-3} of ligand solution in 0.5 ml increment. The electronic spectromeasurements of freshly prepared solutions were obtained on Shimadzu UV-240, UV-Visible Recording Spectra Photometer, conductometric titrations were carried out using WPA, C.M. 25 Conductivity Meter.

Results and Discussion

Electronic absorption spectra study of binary complex. The electronic absorption spectra of the three subject sulfa-drugs compound Sulfamethazine (SMZ), Sulfathiazole (STZ) and Tolbutamide (TA) and their 1:1 metal chelates solutions are recorded in Fig (1) and presented in Table 1. In all measurements, the blank used is the corresponding ligand of the same concentrations as that in the test solution. The spectra of compounds in ethanol consist mainly of three bands (compound SMZ and STZ), and one band (compound TA). The shorter wavelength one appeared at 205 nm for SMZ and STZ or at 210 nm for TA can be assigned to II-II transition of the benzenoid system of compounds. The second band appeared in the UV region within the wavelength 268 nm and 270 nm for STZ and SMZ respectively may be used to have information about the extent of electron delocalization in sulfonamides. Number of hypotheses have been presented suggesting the following resonance structure (Commarato and Mortin 1970; Narang and Cupta 1975).

The spectra of complex solutions show that the band of both Fe(III) and Cu(II) complexes are split into several components. These split components are observed for the shorter as well as for the longer wavelengths. The lower energy split in the

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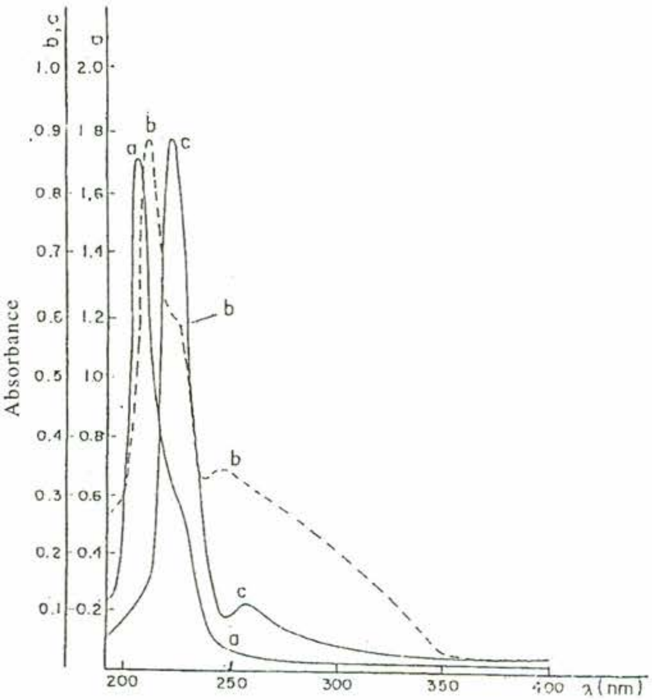


Fig 1. Absorption spectra of (1:1) tolbutamide (TA)-metal ions chelates: a, Free tolbutamide = 4×10^{-6} mol dm^{-3}; b, Fe(III)-TA= [Fe(III)]-[TA]=1×10^{-4} mol dm^{-3}; c, Cu (II)-TA= [Cu(II)]-[TA]=1×10^{-4} mol dm^{-3}.

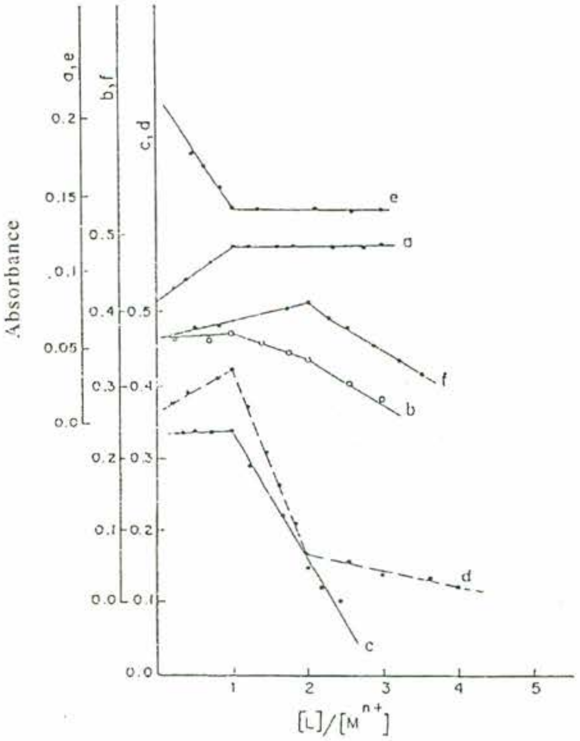


Fig 2. Molar ratio method of L-M^{-4} chelates:
i- SMZ-M^{n+} a, [Cu^{2+}] = 2.0×10^{-4} mol dm^{-3}, λ = 300 nm
b, [Fe^{3+}] = 1.6×10^{-4} mol dm^{-3}, λ = 300 nm
ii- STZ-M^{n+} c, [Cu^{2+}] = 1.2×10^{-4} mol dm^{-3}, λ = 267 nm
d, [Fe^{3+}] = 1.0×10^{-4} mol dm^{-3}, λ = 290 nm
iii- TA-M^{n+} e, [Cu^{2+}] = 1.8×10^{-4} mol dm^{-3}, λ = 260 nm
f, [Fe^{3+}] = 1.6×10^{-4} mol dm^{-3}, λ = 260 nm

longer wavelength band has been related to binuclear nature of copper and iron complexes (Ross *et al* 1964; Limey and Saxena 1985). These behaviour may be due to (L-M^{+n}) charge transfer band (Tashika and Taknashi 1967; Sigel 1980; Limey and Saxena 1985; Sigel 1973 and 1985) indicating coordination of the ligand to metal as a result of the high positive charge of the coordinated metal ion. The stoichiometry of the chelated formed in solution, from the reaction of each of the ligand under study (SMZ, STZ, TA) with the metal ions used, was investigated using molar ratio and continuous variation methods (Fig 2). In all concentration as in the solutions of the chelate, the results reveal the possible formation of 1:1 (M:

Table 1
The maximum wavelength and extinction coefficient of the free ligand and their metal binary and ternary complexes

Ligand	Free ligands		Binary complexes				Ternary complexes			
			Cu (II)		Fe (III)		Cu (II)		Fe (III)	
	λ_{max}	$\varepsilon_{max}\times10^{-3}$	λ_{max}	$\varepsilon_{max}\times10^{-3}$	λ_{max}	$\varepsilon_{max}\times10^{-3}$	λ_{max}	$\varepsilon_{max}\times10^{-3}$	λ_{max}	$\varepsilon_{max}\times10^{-3}$
SMZ	205	28.0	230	4.0	-	-	-	-	-	-
	212 sh	26.0	240	4.0	240	48.75	280	3.38	290	5.25
	270	31.5	310	1.65	2.85	25.0	390	1.88	360	2.88
STZ	205	27.0	220	4.31	210	9.95	-	-	-	-
	268	23.25	270	2.67	240 sh	3.6	275	6.06	275	6.0
	295	26.25	-	-	270	4.0	395	2.25	365	3.0
TA	210	41.50	230	8.8	2.15	-	-	-	-	
	-	-	260 sh	1.2	225 sh	3.63	280	613	285	6.13
	-	-	-	-	240 sh	2.06	395	1.88	360	2.75

λ_{max}, nm; ε_{max}, mole^{-1} cm^{2}; sh, shoulder

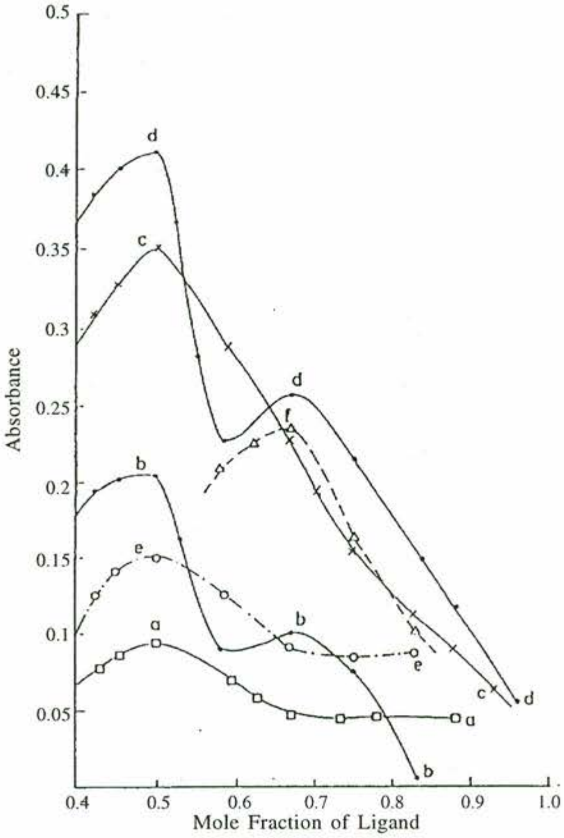


Fig 3. Continuous variation method of L-M^{n+} chelates:

i- Total concentration;
  a, [SMZ+Cu(II)] = 3.6×10^{-4} mol dm^{-3}, λ_{sh} = 310 nm
  b, [SMZ+Fe(III)] = 2.4×10^{-4} mol dm^{-3}, λ_{sh} = 310 nm
ii- Total concentration;
  c, [STZ+Cu(II)] = 2.4×10^{-4} mol dm^{-3}, λ = 267 nm
  d, [STZ+Fe(III)] = 2.4×10^{-4} mol dm^{-3}, λ = 209 nm
iii- Total concentration
  e, [TA+Cu(II)] = 2.4×10^{-4} mol dm^{-3}, λ = 260 nm
  f, [TA+Fe(III)] = 2.4×10^{-4} mol dm^{-3}, λ = 260 nm

ligand) in case of Cu(II) with all ligands or 1:1 and 1:2 in case of Fe(III). The apparent formation constants (K_f) of the formed complexes species in solution were calculated from the spectrophotometric data. The K_f values are collected in Table 2 together with ΔG values.

The results of conductometric titrations of the metal ions with the ligands used (Fig. 3) are in accordance with those obtained from the spectrophotometric methods. The observed gradual increase of conductance on increasing ligand ion concentration is due to the replacement of hydrogen ions of sulfonamide group (SO_2NH group) of ligand by the metal ions forming metal-ligand complexes. It is evident from the results Table 2 that the stability constant values of the metal chelate, decreases in the following order:

SMZ > STZ > TA

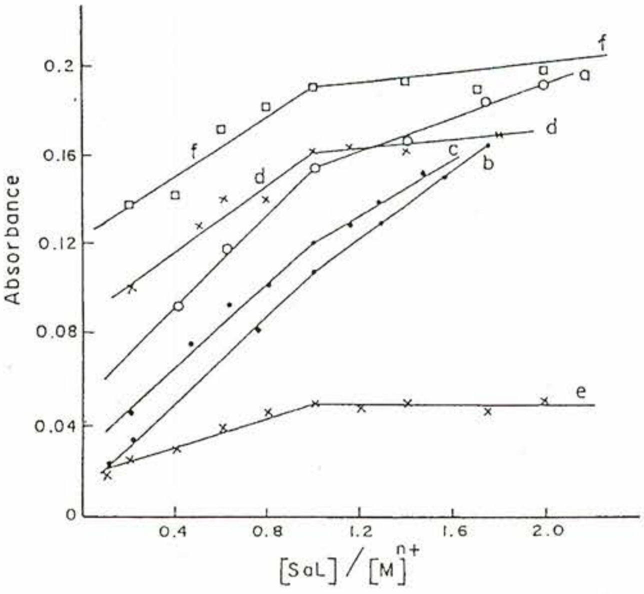


Fig 4. Molar ratio method for (1:1:1) ternary complexes sulfadrugs:

a,Cu(II)-SA-TA= [Cu(II)]-[TA] = 8×10^{-5} mol dm^{-3}, λ = 390 nm
b,Cu(II)-SA-STZ= [Cu(II)]-[STZ] = 8×10^{-5} mol dm^{-3}, λ = 390 nm
c,Cu(II)-SA-SMZ= [Fe(III)]-[SMZ] = 8×10^{-5} mol dm^{-3}, λ = 385 nm
d,Fe(III)-SA-SMZ= [Fe(III)]-[SMZ] = 8×10^{-5} mol dm^{-3}, λ = 330 nm
e,Fe(III)-SA-STZ= [Fe(III)]-[STZ] = 8×10^{-5} mol dm^{-3}, λ = 320 nm
f,Fe(III)-SA-TA= [Fe(III)]-[TA] = 8×10^{-5} mol dm^{-3}, λ = 320 nm.

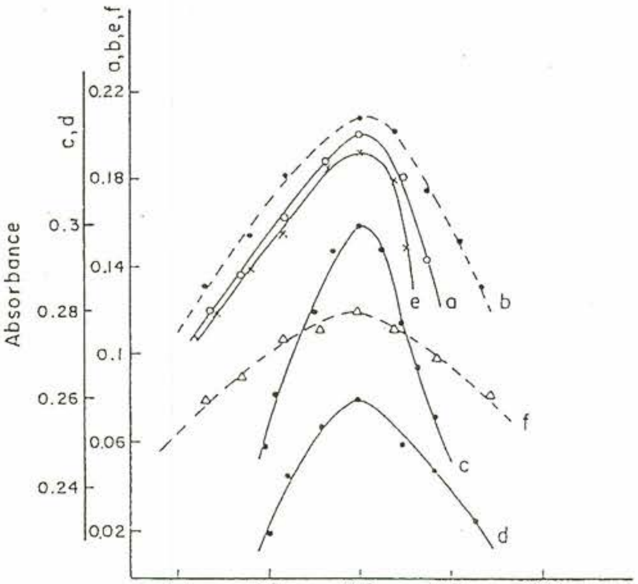


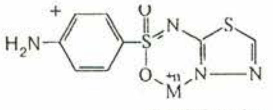
Fig 5. Continuous variation method for (1:1:1) ternary complexes sulfadrugs, total concentration, 3.6×10^{-4} mol dm^{-3}:

a, Cu(II)-SA-SMZ; λ, 390 nm; b,Cu(II)-SA-SMZ;λ,395nm;
c, Fr(III)-SA-SMZ; λ, 360nm; d,Fe(III)-SA-TA;λ,365nm.
e, Cu(II)-SA-TA; λ, 390 nm; f, Fe(III)-SA-STZ; λ, 365 nm.

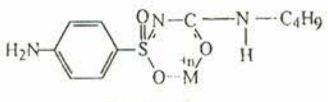
The formation constant of the 1:1 (M-L) chelates decreases as the valency of the metal decreases.

Fe(III) > Cu(II)

The intermolecular C.T. which took place within the chelated ligand under investigation can be suggest as below



(STZ) Complex



(TA) Complex

Accordingly, the longer wavelength band observed in the spectra of all chelates formed is ascribed to an intermolecular C. T. transition within the established six member chelated ring.

In order to apply the spectrophotometric methods for the microdetermination of the metal ions Cu(II) Fe(III), a constant concentration of the ligand (coluoring agent) is mixed with different concentrtions of the tested metal ion. The molar absorptivity values of the chelate formed are high (Table 3). This values would suggest the validity of the method for the microdetermination of the elements under investigation. It is found that the minimum amount which can be measured for each of the metal ions runs in the following order.

SMZ > STZ > TA

This behaviour is in line with general order of stability of the chelates of the studied metal ions, which decreases in the same direction.

Table 2

Formation constant and free energy changes (ΔG^* in K cal mole^{-1} at 25°C) of Cu(II) and Fe(III), sulfa-drug chelates

Method	Ratio	Binary complexes			
		Cu(II)		Fe(III)	
		β	ΔG*	β	ΔG*
		Chelates of tolbutamide (TA)			
MR	1:1	4.6×10^4	5.970	-	-
MR	1:2	-	-	3.15×10^8	10.881
CV	1:1	7.4×10^4	6.683	-	-
CV	1:2	-	-	3.55×10^8	11.735

β, ± (1.5-2.1%); ΔG*, ± (0.09-0.12%).

Table 3

The maximum wavelength and extinction coefficient of the free sulfa-drugs and their metal chelates

ligand	Free ligands		Cu(II)		Fe(III)	
	λ_{max}	$\varepsilon_{max} \times 10^{-3}$	λ_{max}	$\varepsilon_{max} \times 10^{-3}$	λ_{max}	$\varepsilon_{max} \times 10^{-3}$
Tolbutamide	210	41.5	230	8.80	215	5.50
(TA)	-	-	260 sh	1.20	225 sh	3.625
	-	-	-	-	240 sh	2.062

λ_{max}, nm; ε_{max}, mole^{-1} cm^2; sh, shoulder

Electronic absorption spectra study of ternary complexes. The visible spectra of SMZ, STZ and TA or SA exhibit an absorption band at about 270 nm however the spectrum of the reaction mixture of solution containing sulfadrugs and salysaldehyde and Cu(II) or Fe(III) ion recorderd against a blank solution containing the same concentration of the salysaldehyde and sulfadrugs shows an apparent new band at 360 nm for Fe(III)/SA/SMZ or Fe(III)/SA/TA, 365 nm for Fe(III)/SA/STZ, 390 nm for Cu(II)/SA/SMZ 395 nm for Cu(II) SA/TA or Cu(II)/SA/STZ. The later band is presumably due to the formation of a mixedligand complex with metal. The spectophotometric method was applied for ascertaining the stoichiometry (Mukherjee and Ghoshal 1985). The relations obtained are characterised by a maximum at a point corresponds mole fraction equal to 0.5 for continuous variation method and 1.0 for molar ratio method. This suggests that, the ternary complex formed was the stoichiometric 1:1:1. The apparent stability constants (K_f) of the complexes formed in solution are determined utilizing the following equation in the case of the type (1:1:1)

$$B_1 = \frac{A/Am}{(1-A/Am)^2 C}$$

Table 4

Formation constant of mixed ligand complexes and free energy changes (ΔG^* in Kcal mole^{-1} at 25°C) of Cu(II) and Fe(III), sulfadrugs and salysaldehyde chelates

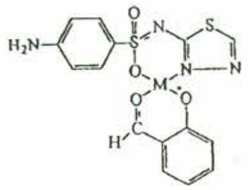
Method	Ratio	Ternary complexes			
		Cu(II)		Fe(III)	
		β	ΔG*	β	ΔG*
		Chelates of sulfamethazine (SMZ)			
MR	1:1:1	2.09×10^6	8.092	6.29×10^7	9.985
CV	1:1:1	1.8×10^6	8.009	7.74×10^7	10.101
		Chelates of sulfathiazole (STZ)			
MR	1:1:1	2.84×10^6	8.263	1.51×10^7	9.192
CV	1:1:1	2.65×10^6	8.224	1.01×10^7	8.968
		Chelates of tolbutamide (TA)			
MR	1:1:1	1.04×10^6	7.704	6.68×10^6	8.738
CV	1:1:1	1.68×10^6	7.971	7.09×10^6	8.772

β, ± (1.5-2.1%); ΔG*, ± (0.09-0.12%).

Where Am the limiting absorbance, corresponds to the concentration of MI at full colour development; A, corresponds to the concentration of the complex molecules existing in equilibrium and C is the initial concentration of the metal ion. In all cases for spectral measurements of the solutions prepared for the two above mentioned spectrophotometric methods. The blank used was a solution of salysaldehyde and sulfadrugs of the same concentration as in the test ternary component solution. This was made in order to cancel the effect of the absorption of unreacted SA and sulfadrugs. The values of B_1 and ΔG^* are shown in Table (4) Fig. (4,5). The results indicate that the formation constant values of the (1:1:1) mixed ligand decreases in the following order.

SMZ > STZ > TA

This order is in accordance with the decrease in basicity of these ligand (PK's = 8.5, 8.35 and 6.35 respectively), where the bonding in the mixed ligand complexes occurs through oxygen atoms of both sulfonamide group of sulfadrugs and aldehydic group of salysaldehyde. On the other hand, the chelation with metal ions also involve the liberation of atoms of the phenolic group of salysaldehyde and the imine group of the sulfa-drugs moiety. The structure of the 1:1:1 ternary complexes can be represented schematically as below:



(SMZ ternary complex)

With respect to metal ions it is evident that, the values of formation constant of the Fe(III) ternary chelates are higher than that of Cu(II) chelates. This suggests that, the stability of the chelate is expected to decrease as the valency of the metal decreaces. This behaviour is in line with the general order of stability of the binary complexes of these metal ions as determined by the spectophotrometric method.

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