



Synthesis, Biological Activity and Thermal Characterization of Sulfadimidine with Transition Metals

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Abstract Synthesis, Characterization, Biological activity and Thermal analysis of sulfadimidine complexes with transition metals (Cr(III), Mn(II), Fe(III), Co (II), Ni(II), Cu(II), Zn (II), Cd(II) and Hg(II)) were discussed. It's obtained that sulfadimidine is a bidentate ligand through oxygen of sulfonyl group. From magnetic measurement and spectral data, octahedral structures were proposed for all complexes except for Cu had a tetrahedral structure. Hyper chemistry program confirmed binding sites of sulfadimidine. Sulfadimidine complexes show the same biological activity as the free ligand except for Co complex for some strains. From TG and DTA curves the thermal decomposition of the complexes were suggested .the thermal decomposition of the complexes ended with the formation of metal oxides as a final product except in case of Hg complex.

Keywords Sulfonamides-complexes- sulfadimidine –thermal analysis –biological activity

Introduction

Antibiotic drug containing sulfonyl group, Sulfonamides are one of the important class of synthetic organic compounds with great medicinal importance having a Sulfonamides functional group ($R_1-SO_2-NR_2R_3$) in their structures [1]. Sulfonamides contain multiple hydrogen bond acceptor and donor functional groups that allow cocrystal formation due to multiple supramolecular interactions and used the treatment of staphylococcal pyoderma [2-5] sulfadimidine is a bacteriostatic heterocyclic sulfonamide antibiotic which used widely in industry. It can act as anti infective agent, carcinogenic agent, ligand, anti microbial drug and anti bacterial agent [6]. It has wide antibacterial activity in spite of increasing antibiotic resistance. Cocrystallisation of Sulfadimidine with suitable cofomers may favourably alter its biopharmaceutical properties, such as dissolution, and ideally also its activity.

Experimental

Sulfadimidine and metal chloride [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)] were solvated with distilled water. The molar amount of the metal chloride salt was reacted with the calculated amount of the ligand with molar ratios (M:L) 1:1, 2:1 and 2:3. The reaction mixture was refluxed for about 50 min then left over- night, where the formed complexes were filtrated, then washed several times with a mixture of EtOH-H₂O and dried in a vaccum desiccator. The analytical results are given in Table1.The metal contents were analyzed based on atomic absorption technique using model 6650 Shimadzu-atomic absorption spectrophotometer and complexometric titration with standard EDTA solution using the appropriate indicator as reported [7-8]. The analysis of chloride contents of the complexes was examined by Volhard method [7] (Figure 1).



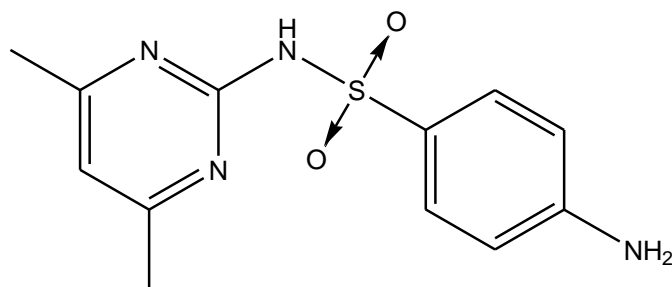


Figure 1: Structure of Sulfadimidine

Measurements

The infrared spectra of the sulfadimidine and their metal complexes were detected by Perkin Elmer spectrophotometer, Model 1430, the instrument was located at central lab of Alexandria University. The electronic spectra for the solid complexes were measured in Nujol mull spectra; the instrument was located at central lab of Alexandria University. Molar magnetic susceptibilities, constants were analyzed using Faraday's method at room temperature 25 °C.

The electron spin resonance spectra were tested by spectrometer operating at (9.1-9.8) GHz in a cylindrical resonance cavity with 100 KHz modulation, the instrument was located at central lab of Alexandria University. The g values were calculated by comparison with DPPH signal. Differential Thermal Analysis (DTA) and Thermo Gravimetric analysis (TG) of sulfadimidine and its complexes were carried out using a Shimadzu DTA/TGA-50 at central Lab., Tanta University. The rate of heating was 20 °C/min. The cell used was platinum and the atmospheric nitrogen rate flow was 15 ml/min. The biological screening of sulfadimidine and its metal complexes were examined against 5 microorganisms representing different microbial categories {two Gram-positive (*Staphylococcus aureus* ATCC6538P and *Bacillus subtilis* ATCC19659, two Gram negative (*Escherichia coli* ATCC8739 strain and *Pseudomonas aeruginosa* ATCC9027) and *Candida albicans* a fungi}, the. Computational chemistry programs are applied such as, hyperchem using PM3 semi-empirical and Molecular Mechanics Force Field (MM+) (Table 1).

Table 1: Elemental analysis, m.p, formula, stoichiometries and colour of sulfadimidine complexes

Complexes	Colour	Calculated/(Found)%					
		C	H	N	S	M	Cl
[Cr ₂ (Sd) ₃ Cl ₄]	Blue	43.60 (43.64)	4.78 (4.56)	15.64 (15.99)	8.95 (8.65)	9.68 (9.73)	9.9 (9.53)
[Mn ₂ (Sd)(H ₂ O) ₄ (OH) ₄]	Grey	27.23 (28.41)	5.14 (5.24)	10.59 (10.51)	6.06 (6.34)	20.76 (20.61)	-
[Fe ₂ (Sd) ₃ Cl ₄]	Dark red	42.18 (42.08)	4.38 (4.18)	15.53 (15.45)	8.89 (8.70)	10.32 (10.22)	9.83 (9.71)
[Co ₂ (Sd)(OH) ₄ (H ₂ O) ₄]	Dark pink	28.32 (28.54)	5.30 (5.42)	10.16 (10.46)	5.82 (5.94)	21.38 (21.13)	-
[Ni ₂ (Sd) ₃ Cl ₂ (H ₂ O) ₂]	Green	41.94 (41.82)	4.72 (4.91)	15.44 (15.66)	8.84 (8.92)	10.79 (10.60)	6.51 (6.49)
[Cu(Sd)Cl ₂]	Dark green	40.72 (40.66)	5.34 (5.11)	11.87 (11.77)	8.64 (8.50)	13.47 (13.19)	15.02 (15.38)
[Zn(Sd)(H ₂ O) ₂ (OH) ₂]	Pale Yellow	42.61 (42.51)	5.69 (5.54)	13.25 (13.34)	7.58 (7.62)	15.46 (14.23)	-
[Cd(Sd)(Cl) ₂ (H ₂ O) ₂]	White	32.75 (32.40)	4.33 (4.23)	11.75 (11.62)	6.72 (6.65)	23.58 (23.71)	7.44 (7.37)
[Hg ₂ (Sd) ₃ Cl ₂ (H ₂ O) ₂]	Brown	33.26 (33.05)	3.75 (3.56)	12.25 (12.31)	7.01 (7.02)	29.24 (29.1)	5.17 (5.33)



Results and Discussion

From IR spectra of sulfadimidine simple complexes, Table (2), it is obtained that sulfadimidine complexes, show broad bands in the 3400 – 3580 cm^{-1} region in all prepared complexes suggesting coordination with water except for Cr, Cu and Fe complexes.

Table 2: Fundamental infrared bands (cm^{-1}) of sulfadimidine and its metal complexes

Compound	$\nu(\text{NH}_2)$	ν ($\text{O} \leftarrow \text{S} \rightarrow \text{O}$)	$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{N})$
Sulfadimidine	3468	1354	1633	1086
[Cr ₂ (Sd) ₃ Cl ₄] (2:3)	3437	-	1630	1088
[Mn ₂ (Sd)(H ₂ O) ₄ (OH) ₄] (2:1)	3445	-	1631	1088
[Fe ₂ (Sd) ₃ Cl ₄] (2:3)	3437	1373	1630	1084
[Co ₂ (Sd)(OH) ₄ (H ₂ O) ₄] (2:1)	3471	1395	1632	1085
[Ni ₂ (Sd) ₃ Cl ₂ (H ₂ O) ₂] (2:3)	3433	1387	1631	1087
[Cu(Sd)Cl ₂] (1:1)	3449	1356	1630	1082
[Zn(Sd)(H ₂ O) ₂ (OH) ₂] (1:1)	3441	1390	1632	1087
[Cd ₂ (Sd) ₂ (Cl) ₂ (H ₂ O) ₂] (2:2)	3450	1313	1641	1084
[Hg ₂ (Sd) ₃ Cl ₂ (H ₂ O) ₂] (2:3)	3465	1302	1631	1085

It seems from the elemental analysis of the complexes and thermal analysis that all complexes contain water molecules or OH groups in their structures except for Cr, Cu and Fe. The broad band that appeared for sulfadimidine at 3468 cm^{-1} due to hydrogen bond. The sharp band of $\text{O} \leftarrow \text{S} \rightarrow \text{O}$ stretching vibration of sulfadimidine appears at 1354 cm^{-1} and shifted into 1360-1395 cm^{-1} in simple complexes that mean making of coordination bonding. The band at 1633 cm^{-1} corresponding to stretching vibration of $\text{C}=\text{N}$ of sulfadimidine but the complexes show at 1630-1633 cm^{-1} range that mean no shifting occur and no metal-ligand coordination. The narrow band of $\text{C}-\text{N}$ stretching vibration appeared at 1086 cm^{-1} of spectrum of sulfadimidine while for simple complexes is correspond to 1084-1088 cm^{-1} that meaning; there no shift occur leading to no metal ligand coordination occurs.

Electronic spectral and magnetic studies

The electronic absorption spectra for the blue chromium-complexes, [Cr₂(Sd)₃(Cl)₄] . showed three bands at 350, 370 nm and due to ${}^4\text{A}_{2g} \rightarrow {}^4\text{T}_{1g}(\text{F})$, Tables (3) and Figure (2). So this complex has octahedral geometry. Such O_h geometry is further deduced from the μ_{eff} value that equal 6.62 [9-10]. However, the Yellow electronic absorption spectrum of manganese-complexes [Mn₂(Sd)(H₂O)₄(OH)₄], Figure (3) and Tables (3), gave bands at 322, 335, 360 and 262, 446, 638 where the first band is due to $\pi - \pi^*$ while the second one is assigned to ${}^6\text{A}_{1g} \rightarrow {}^4\text{A}_{1g}$, while the third is due to ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}$ transition [9-10]. Its room temperature μ_{eff} value 5.64 of typified the existence of O_h configuration. The brown electronic absorption spectra of iron-complexes in Figure (9), Table (7). [Fe₂(Sd)₃(Cl)₄] gave bands at 408nm. These bands are due to CT ($t_{2g} \rightarrow \pi^*$) and CT ($\pi \rightarrow e_g$). Its room temperature μ_{eff} value 4.60 for iron typified the existence of O_h configuration [11-12]. The green electronic absorption spectra for Nickel-complexes, [Ni₂(Sd)₃Cl₂(H₂O)₂] showed bands at 435 nm due to ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$ transitions and this shows in Figures (4) and



Table (3) So this complex have octahedral geometry, further deduced from the μ_{eff} values which equals 2.72 [13-16]. The electronic absorption spectra of $[\text{Co}_2(\text{Sd})(\text{OH})_4(\text{H}_2\text{O})_4]$ and Figure (3), Table (3) and gave bands at 350, 370 nm bands are of charge transfer nature and the latter broad bands are assigned to ${}^1\text{A}_{1g}(\text{F}) \rightarrow {}^1\text{T}_{2g}(\text{P})$ transition with magnetic moment value equal 3.74 typified the existence of the complex in O_h geometry. The dark green copper –complexes in figure (5), Table (3). The complex $[\text{Cu}(\text{Sd})(\text{Cl})_2]$ showed band at 420nm and 430nm due to ${}^2\text{T}_{2g} \rightarrow {}^2\text{E}_g(\text{F})$. So that, this complex has tetrahedral geometry and deduced from μ_{eff} that equal 1.61 [17-19], while complexes of Zn(II), Cd(II) and Hg(II) exhibited only a high intensity band at 420-435 nm, which are assigned to ligand \rightarrow metal charge transfer. Owing to the d^{10} - configuration of Zn(II), Cd(II) and Hg(II), no d-d transition could be observed and therefore the stereochemistry around these metals in its complexes cannot be determined from ultraviolet and visible spectra. However, by comparing the spectra of these complexes and those of similar environments, an octahedral a structures suggested for these complexes [19], Figure (6,7).

Table 3: Nujol mull electronic absorption spectra λ_{max} (nm), room temperature effective magnetic moment values (μ_{eff} 298 K) and geometries of sulfadimidine metal complexes

Complex	λ_{max} (nm)	μ_{eff}	Geometry
$[\text{Cr}_2(\text{Sd})_3\text{Cl}_4(\text{H}_2\text{O})_2]$ (2:3)	350,370	6.62	O_h
$[\text{Mn}_2(\text{Sd})(\text{H}_2\text{O})_4(\text{OH})_4]$ (2:1)	322, 335, 360	5.64	O_h
$[\text{Fe}_2(\text{Sd})_3\text{Cl}_4(\text{H}_2\text{O})_4]$ (2: 3)	408	4.60	O_h
$[\text{Co}_2(\text{Sd})(\text{H}_2\text{O})_4]$ (2:1)	350,370	3.74	O_h
$[\text{Ni}_2(\text{Sd})_3\text{Cl}_4(\text{H}_2\text{O})_4]$ (2:3)	435	2.72	O_h
$[\text{Cu}(\text{Sd})\text{Cl}_2]$ (1: 1)	420,430	1.61	T_d
$[\text{Zn}(\text{Sd})(\text{H}_2\text{O})_2(\text{OH})_2]$ (1:1)	380	Diamagnetic	O_h
$[\text{Cd}(\text{Sd})(\text{Cl})_2(\text{H}_2\text{O})_2]$ (1:1)	420	Diamagnetic	O_h
$[\text{Hg}_2(\text{Sd})_3\text{Cl}_2(\text{H}_2\text{O})_2]$	335	Diamagnetic	O_h

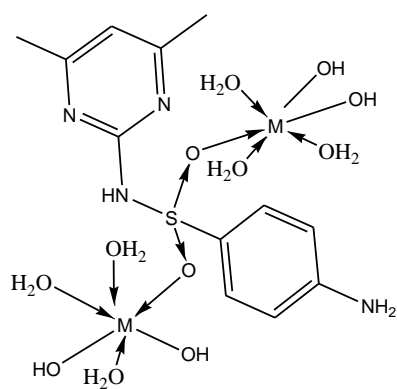


Figure 2: $M(\text{Fe,Cr})$ -Sulfadimidine complex

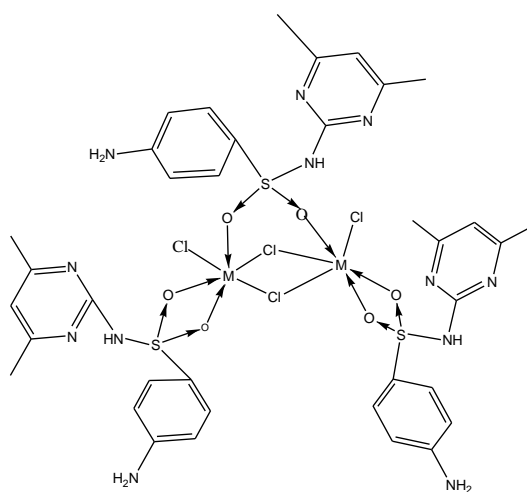


Figure 3: $M(\text{Mn,Co})$ -Sulfadimidine

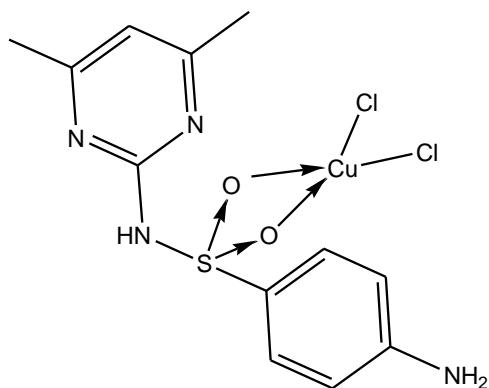


Figure 4: Cu-Sulfadimidine complex

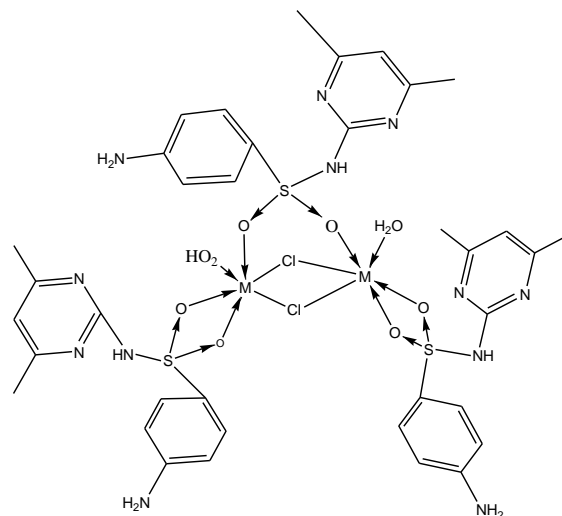


Figure 5: M-Sulfadimidine complex

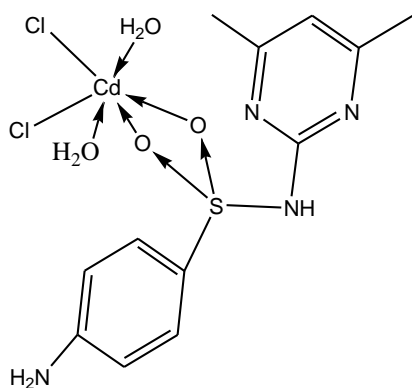


Figure 6: Cd-Sulfadimidine complex

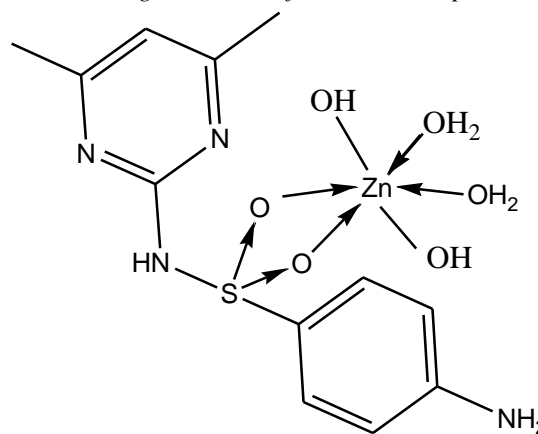


Figure 7: Zn-Sulfadimidine complex

From hyper chem program charge density of sulfadimidine atoms is calculated. Figure (8) confirmed sulfadimidine coordination through sulfonyl group which has highest charge.

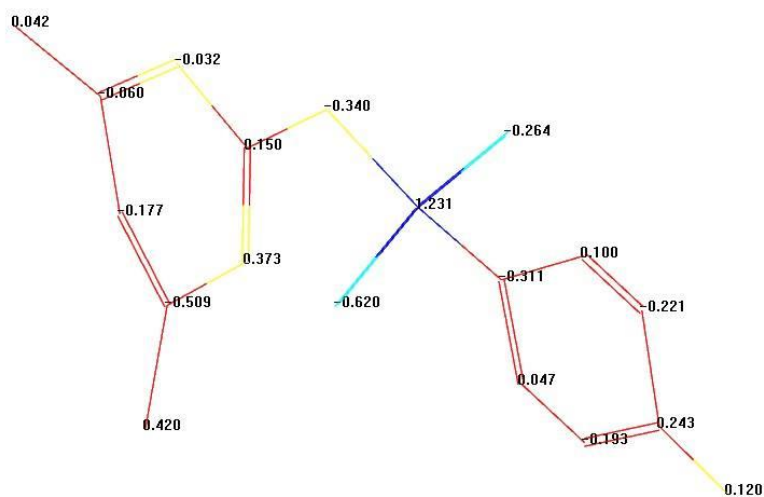


Figure 8: Charge density of sulfadimidne atoms



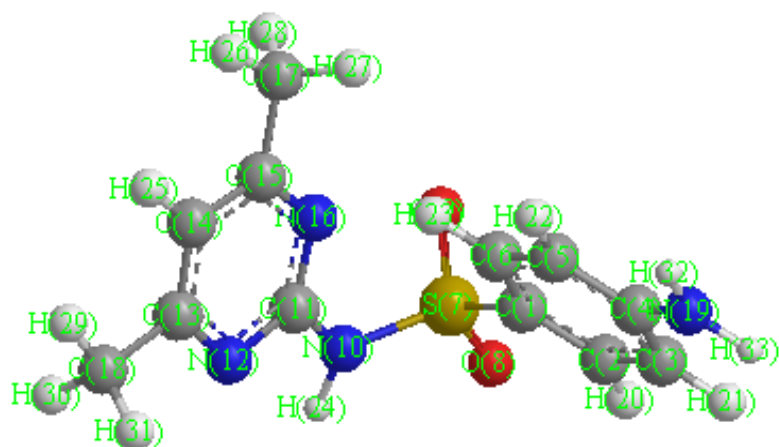
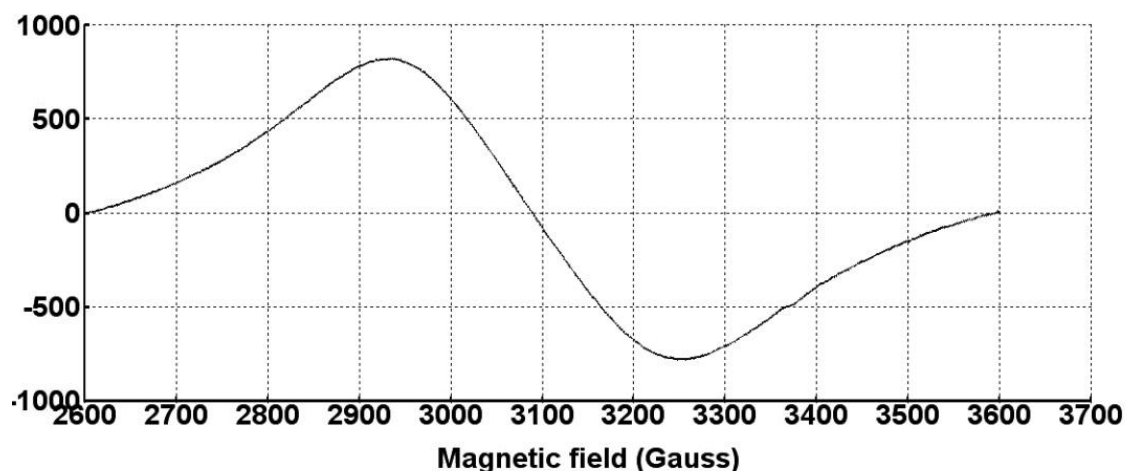


Figure 9: Structure of sulfadimidine

Figure 10: ESR of $[Cu(Sd)Cl_2]$

The room temperature polycrystalline X-band ESR spectral pattern of $[Cu(Sd)Cl_2]$ complex, Figure(10) is isotropic nature with $g_s=1.15$ and value of $A=6\text{ cm}^{-1}$

Biological Activity

Biological activity is a property that used to characterize drug effect on living things. To study biological activity of sulfadimidine and diminazine, we depend on five micro organisms that represent different microbial classes. Those five organisms involved {two Gram-positive (*Staphylococcus aureus* ATCC6538P and *Bacillus subtilis* ATCC19659), two Gram negative (*Escherichia coli* ATCC8739 strain and *Pseudomonas aeruginosa* ATCC9027) bacteria and *Candida albicans* as fungi were used, in this study there are six complexes of different metal ions are used (Zn, Cu, Co, Mn). In this study two different broadly antibiotics (Ciprofloxacin and Clotrimazole) are used as references.

The data, Table (4), allows the following observations and conclusions:

Sulfadimidine ligand showed similar activities for all five micro organisms. All investigated complexes showed similar activity for *Staphylococcus aureus*, *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Bacillus subtilis* except $[Co_2(Sd)(OH)_4(H_2O)_4]$ that has higher activity to *Staphylococcus aureus*.



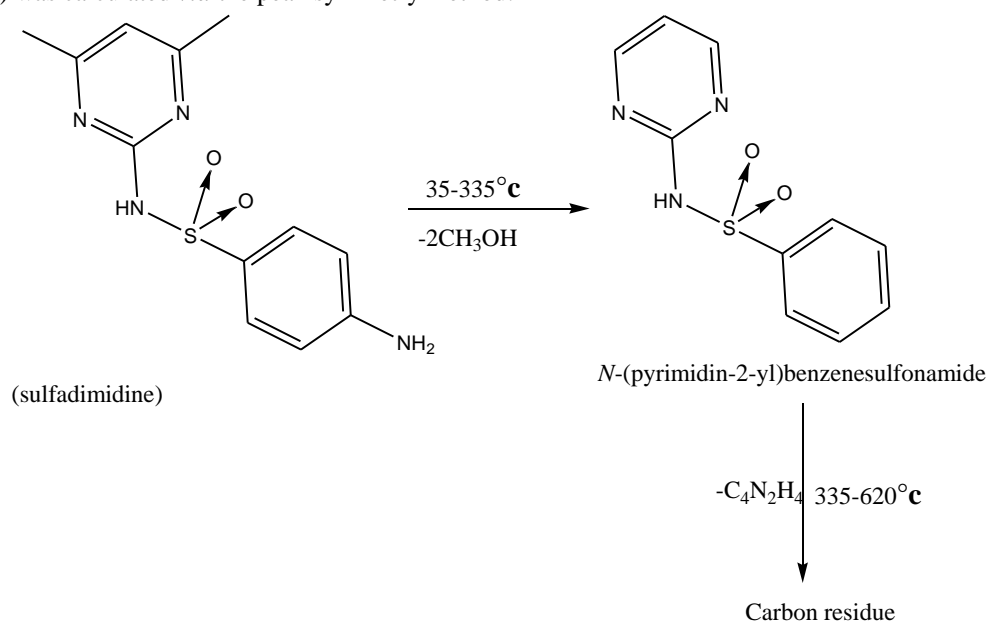
Table 4: The antibacterial activity of the free ligands and its complexes against some reference strains expressed in absolute activity (AU)

Compounds	<i>Candida albicans</i>		<i>Escherischia coli</i>		<i>Pseudomonas aeruginosa</i>		<i>Staphylococcus aureus</i>		<i>Bacillus subtilis</i>	
	Blank	Cpd	Blank	Cpd	Blank	Cpd	Blank	Cpd	Blank	Cpd
Sulfadimidine	9	9	9	9	9	9	9	9	9	9
[Zn(Sd) (H ₂ O) ₂ (OH) ₂]	9	9	9	9	9	9	9	9	9	9
[Cu (Sd)(Cl) ₂]	9	9	9	9	9	9	9	9	9	9
[Co ₂ (Sd)(OH) ₄ (H ₂ O) ₄]	9	9	9	9	9	9	9	13	9	9
Ciprofloxac	-	-	9	30	9	30	9	30	10	30
Clotrimazole	9	18	-	-	-	-	-	-	-	-

Thermal Analysis

The thermal behavior of Sulfadimidine and some metal complexes were investigated by thermograms (TG, DT) [20-25]. The DTA and TG analysis data is presented in Table 5. The DTA curves showed endothermic and exothermic peaks depend on temperature.

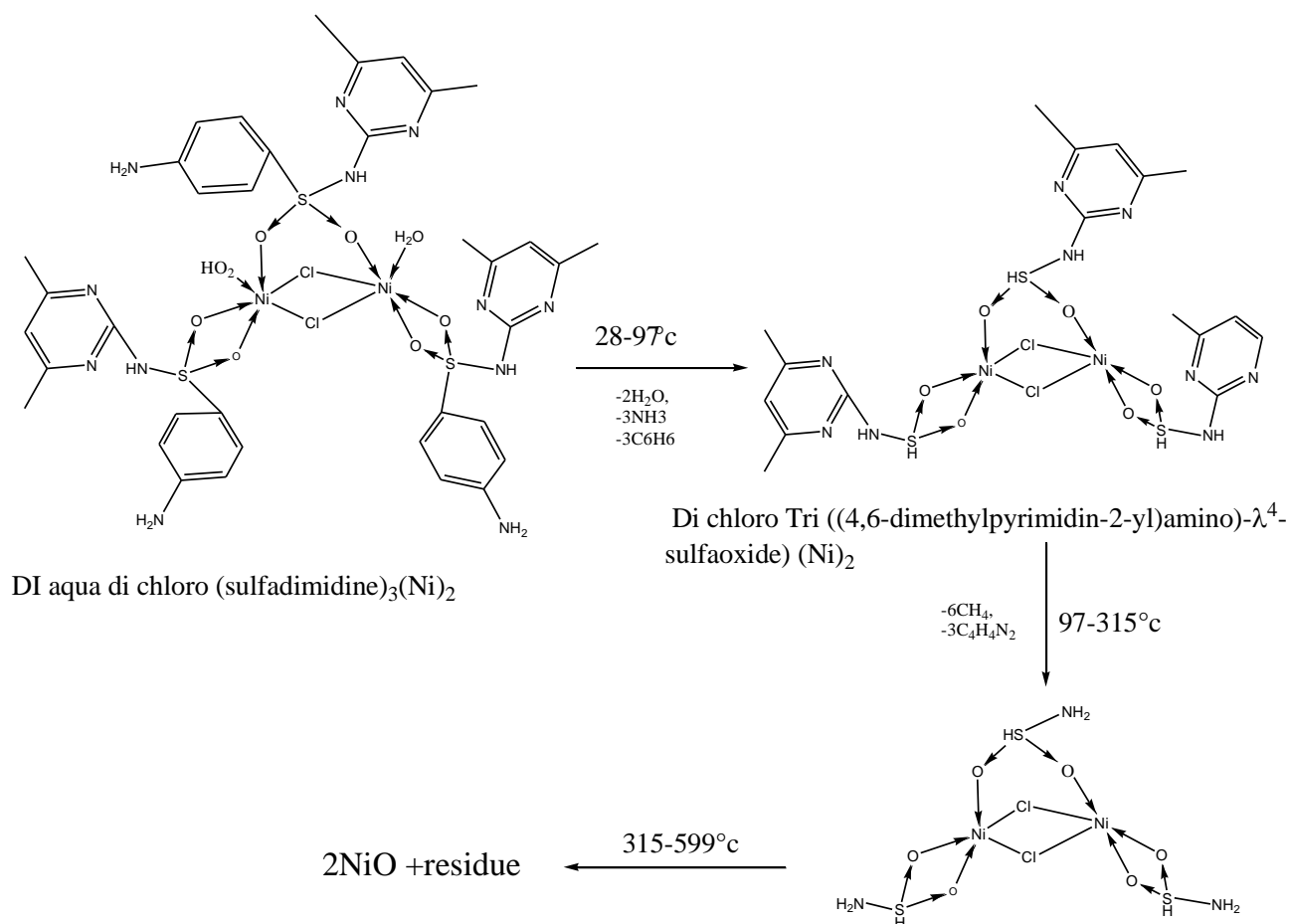
The TGA data of sulfadimidine showed well defined two peaks, in the following scheme (1), Figure (11) while DTA data gave two peaks Figure(12), Table (5) at 118.9°C and 474.5°C. first one is endothermic and second is exothermic with activation energies 38.93 and 2.14kJ/mole, respectively and the order of first reaction is first order and order of second one is second order. Based on least square calculations, the ln ΔT versus 103/T plots, for all complexes gave straight lines from which the activation energies were calculated (Table 6). The order of chemical reactions (n) was calculated via the peak symmetry method.



Scheme 1: Theromolysis of sulfadimidine

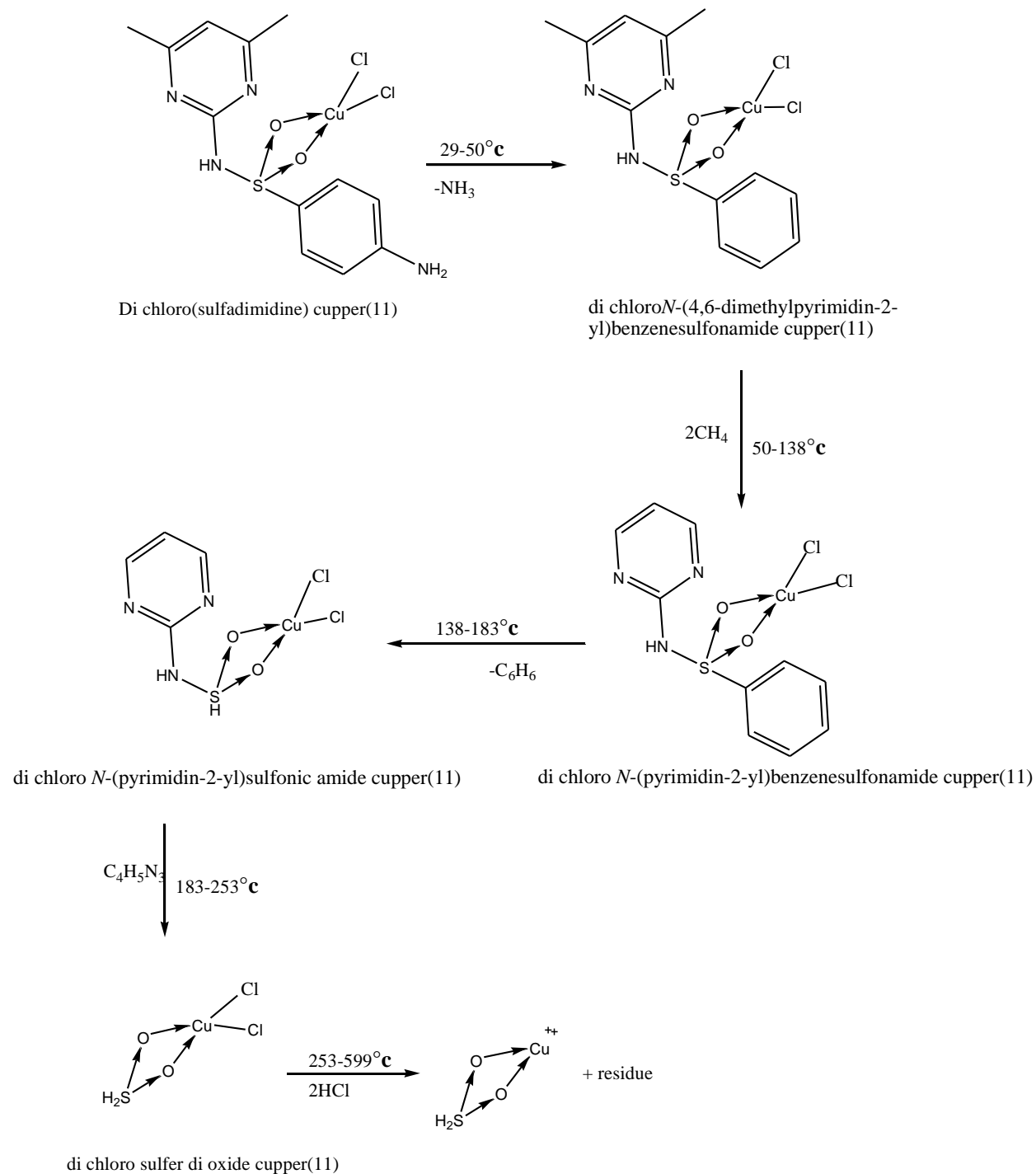
The TGA data of [Ni₂(Sd)₃ (Cl)₂(H₂O)₂] complex showed well defined three peaks, in the following scheme (2), Figure (13) while DTA data gave two peaks Figure(14), Table (5) at 99°C and 360°C. The first one is endothermic and second is exothermic with activation energies 18.41 and 23.04 kJ/mole, respectively and the order of first reaction is second order and order of second one is third order.





Scheme 2: Thermolysis of $[Ni_2(Sd)_3(Cl)_2(H_2O)_2]$ complex

The TGA data of $[Cu(Sd)Cl_2]$ complex showed well defined five peaks, in the following scheme (3), Figure (15) and while DTA data gave two peaks Figure(16), Table (5) at 164.9°C and 347.1°C first one is endothermic and second is exothermic with activation energies 32.01 and 21.26 kJ/mole, respectively and the order of first reaction is first order and order of second one is first order.



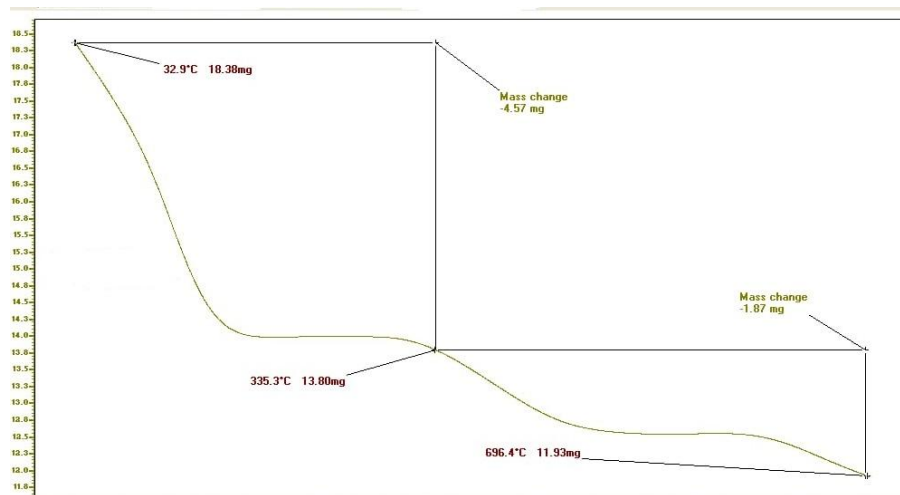


Figure 11: TGA of sulfadimidine

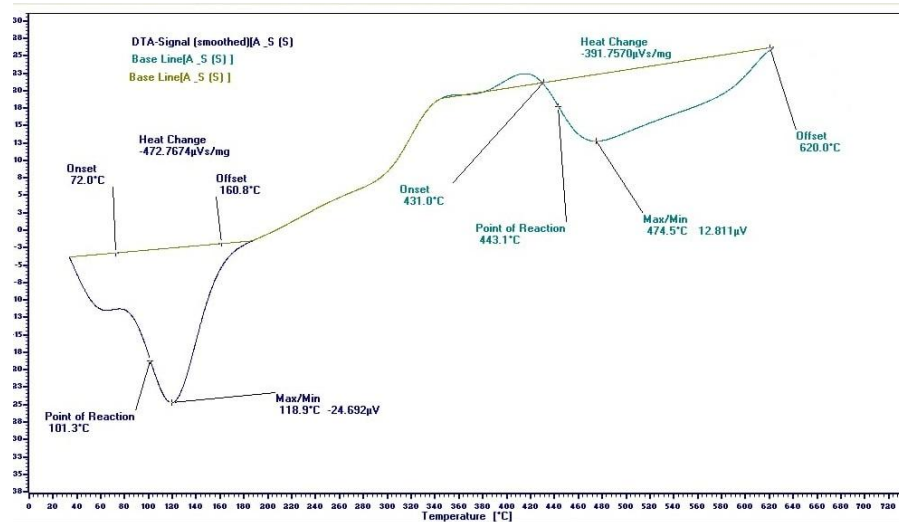


Figure 12: DTA of sulfadimidine

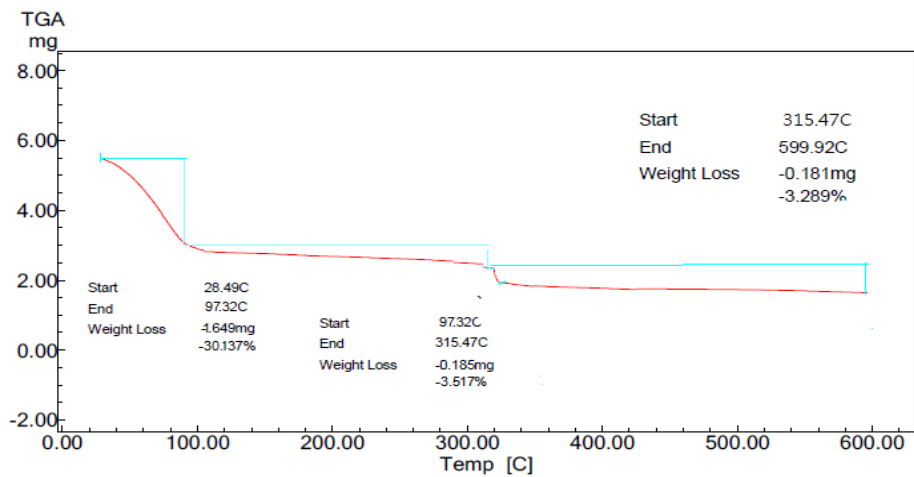


Figure 13: TGA of Ni-sulfadimidine complex

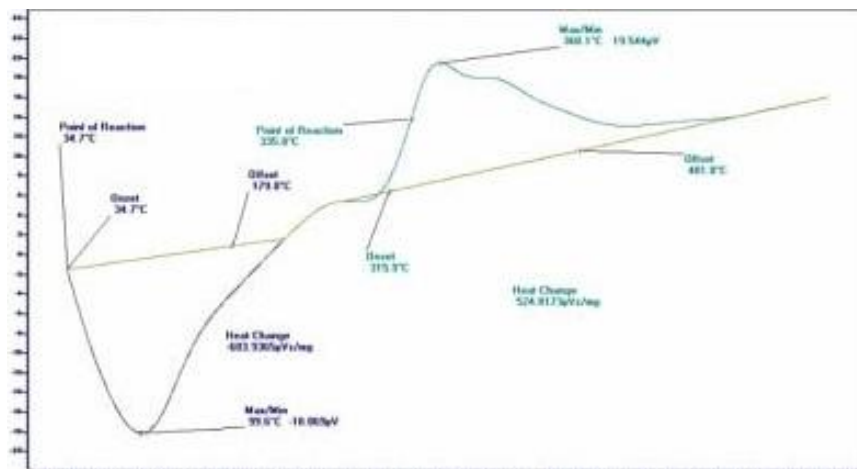


Figure 14: DTA of Ni-sulfadimidine complex

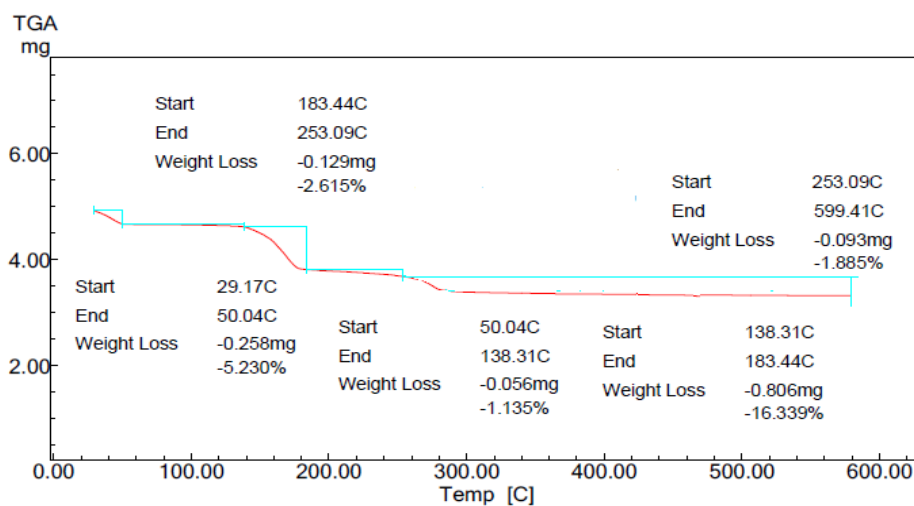


Figure 15: TGA of Cu-sulfadimidine complex

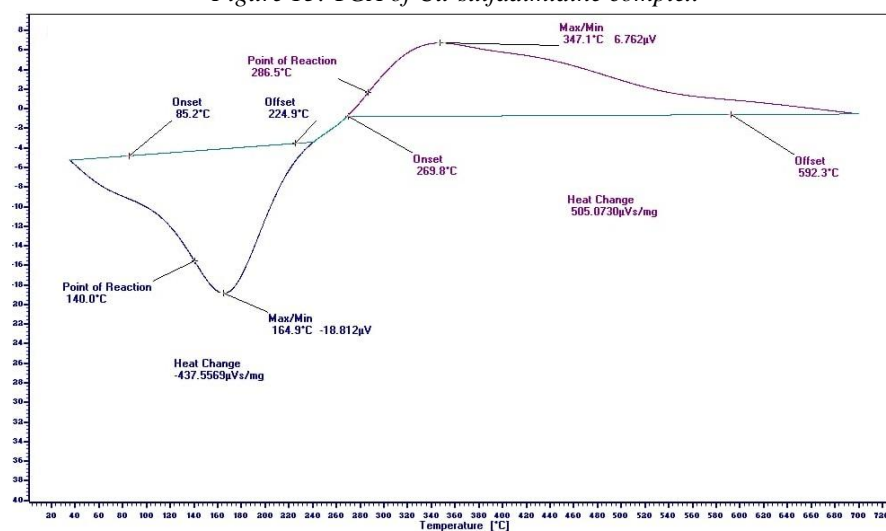


Figure 16: DTA of Cu-sulfadimidine complex



Table 5: DTA analysis of Sulfadimidine and its metal complexes

Complex	Type	T _m (°C)	E _a kJ mol ⁻¹	n	α _m	ΔS [#] kJ K ⁻¹ mol ⁻¹	ΔH [#] kJ mol ⁻¹	Z S ⁻¹
Sulfadimidine	Endo	118.9	38.93	1.0	0.62	-0.28	-33.68	0.039
	Exo	474.5	31.68	2.2	0.47	-0.33	-156.78	0.005
[Cr ₂ (Sd) ₃ Cl ₄]	Endo	101	75.70	1.3	0.56	-0.27	-27.78	0.090
	Exo	382.7	30.04	1.7	0.52	-0.30	-116.68	0.009
[Co ₂ (Sd)(OH) ₄ (H ₂ O) ₆]	Endo	82	50.14	2.4	0.46	-0.27	-22.55	0.073
	Exo	478	32.89	1.0	0.62	-0.30	-147.14	0.008
[Ni ₂ (Sd) ₃ (Cl) ₂ (H ₂ O) ₂]	Endo	99.6	18.41	1.9	0.50	-0.28	-28.54	0.022
	Exo	360.1	23.04	2.6	0.44	-0.30	-110.22	0.007
[Cu (Sd)(Cl) ₂]	Endo	164.9	32.01	1.0	0.61	-0.29	-47.88	0.023
	Exo	347.1	21.26	0.6	0.72	-0.30	-106.22	0.007
[Zn(Sd) (OH) ₂ (H ₂ O) ₂]	Endo	253.7	46.43	0.6	0.72	-0.29	-74.70	0.022
	Exo	329	90.53	3.4	0.40	-0.29	-96.46	0.033

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