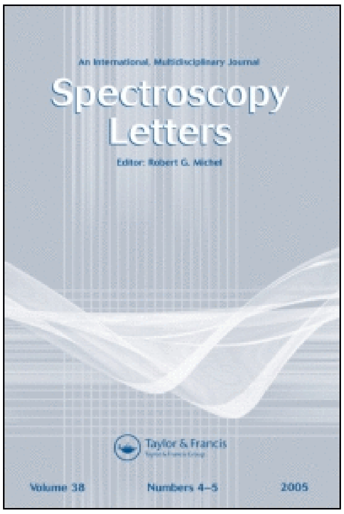

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INVESTIGATION ON SULFANILAMIDE AND ITS INTERACTION WITH SOME METALS AND LINCOMYCIN BY INFRARED SPECTROSCOPY

A. Topacli[a]; B. Kesimli[a]
[a] Department of Physics Engineering, Faculty of Engineering, University of Hacettepe, Ankara, Turkey

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INVESTIGATION ON SULFANILAMIDE AND ITS INTERACTION WITH SOME METALS AND LINCOMYCIN BY INFRARED SPECTROSCOPY

A. Topacli* and B. Kesimli

Department of Physics Engineering, Faculty of
Engineering, University of Hacettepe, Beytepe,
06532 Ankara, Turkey

ABSTRACT

In this work, the new cobalt and cadmium complexes of sulfanilamide were prepared and investigated by infrared spectrocopy. Their infrared spectra were compared with x-ray powder diffraction patterns of the complexes. The vibrations due to the anilino and sulfonamido groups are shifted with respect to the free sulfanilamide molecule in line with their coordination to the metal atoms. In addition, the low energy calculations were also carried out by using geometry optimization. The proposed structure for the complexes derived from the infrared spectra are consistent with the x-ray powder diffraction measurements and theoretical calculations. Among the studies, drug compounds, sulfanilamide-lincomycine interaction was obtained in methanol solution. The predicted structure of the product was given as a result of infrared studies.

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*Corresponding author.

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Key Words: Sulfanilamide; IR spectra; Metal complexes; X-ray diffraction

INTRODUCTION

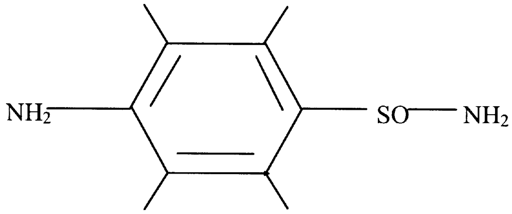
The sulfa drugs which are derivatives of sulfanilamide were the first effective chemotherapeutic agents to be widely used for the cure of bacterial infection in humans. Sulfanilamide are found to be active against several types of bacteria and used in treatment of diseases, *e.g.*, pneumonia, gonorrhea, meningitis, tonsilitis, sinus infections, etc. The orginally employed sulfanilamide is obsolute because of its high toxicity. The metal chelates of sulfa drugs have been found to be more bacteriostatic than the drugs themselves[1,2] Heavy metals, although only in traces, are essential for all forms of life. They are taken up by the living cell in the form of cations and their uptake is strictly regulated because most or all of them are toxic in excess. It should be noted that the infrared and x-ray powder diffraction data on sulfanilamide and its metal complexes are not plentiful in the literature. The synthesis and spectral characterization of Cu(II) complexes of sulfanilamide had been described by Narang[3] and Blasco[4]. They had reported the coordination of sulfanilamide through NH_2 (anilino) group. The shiff base ligand viz-*o*-vanilin-sulfanilamide its bipositive, tripositive, tetrapositive and uranyl metal complexes had also been synthesized and characterized by IR spectra[5]. Maurya and Patel[5] mentioned that in all the complexes the phenolic oxygen and azomethine nitrogen took part in the bonding of the metal-ligand by using infrared data. In our study, we reported the new sulfanilamide compounds of Co and Cd. The structures of the complexes are determined by infrared and x-ray powder diffraction techniques to provide a better understanding of the pharmacological studies.

Today, there is also much concern about "Drug Interaction" because many patients receive more than one drug at a time. A drug interaction occurs whenever the presence of one chemical substance changes the pharmacological effects of a therapeutically administered drug[6]. These interactions can occur inside or outside the body. Much of the detailed knowledge of drug interactions has been gained from *in-vivo* (animal experimentation) and *in-vitro* (pharmaceutical interactions). We are interested in pharmaceutical interactions in this work. The doctors and nurses widely cause these interaction types during parentheral solution therapy. When different drug solutions are added to the infusion set, the color of the solution can change, crystals and precipitates can occur, gases can evolve and etc. as evidence of interactions. In this study, we also investigated precipitates which are the product of interaction between sulfanilamide and lincomycin, using infrared spectroscopy.

EXPERIMENTAL

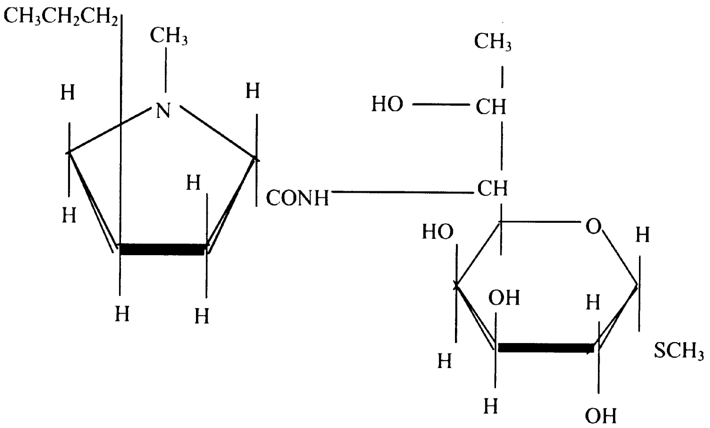
Synthesis

Sulfanilamide ($C_6H_8N_2O_2S$) was purchased from Sigma. The powder of sulfanilamide (Scheme 1) was crystallized in methanol solution at room temperature. The compounds were prepared in the following manner: 0.5 mmol of anhydrous metal acetate and 1 mmol of crystallized sulfanilamide were dissolved in hot methanol and mixed together under constant strirring to yield precipitates. The complexes were filtered and dried at room temperature for several days.



Scheme 1.

The colorless lincomycin ($C_{15}N_{15}O_2N$) crystals were obtained from ampul by evaporating the solution. Scheme 2 shows the chemical diagram of this molecule.



Scheme 2.

Measurements

The infrared spectra (IR) of the samples were recorded using a Perkin Elmer 621 spectrometer with the KBr techique, in the region 4000-400 cm^{-1}, which was calibrated by polystrene.

The powder X-ray diffraction patterns were recorded using a General Electronic XRD-700, SPG-2 manual spectrogonimeter employing CuK_α radiation ($\lambda = 1.5406$ Å) over the range 2θ, 5—50°.

RESULTS AND DISCUSSION

Infrared Studies

To our knowledge, few vibrational and structural studies have been reported for sulfanilamide and its metal complexes. The most significant frequencies of the IR spectra of the sulfanilamide and its copper complexes were given by Narang[3] and Blasco[4]. In our study, the comparison between the sulfanilamide wavenumbers observed in the infrared spectra of Co and Cd complexes and our measurements on crystalline sulfanilamide (Table 1) helped in elucidating out the structure of metal complexes.

In the sulfanilamide molecule, the aniline ring is connected through a sulfonamide group, as shown in Scheme 1. To simplify the interperation of complex IR spectra, the vibrations can be divided into two groups: the vibrations of the aniline ring and the sulfonamide group.

Aniline Ring Vibrations

The IR spectrum of sulfanilamide is shown in Fig. 1a; the vibrations of aniline have been discussed in relation to the most complete study published by Evans in 1960[7].

-NH_2 Group Vibrations

Evans[7] reported the bands at 3440, 3360 and 1618 cm^{-1} were assigned to the asymmetrical stretching, symmetric stretching and scissoring modes, respectively of NH_2 in aniline. In this study, the ν(NH) stretching modes were observed near 3474 and 3372 cm^{-1}, respectively in the IR spectrum of sulfanilamide. Narang[3] and Blasco[4] had been observed these bands at 3470, 3472, and 3368 cm^{-1}, respectively. These bands were shifted to lower

Table 1. The Fundamental Wavenumbers (cm^{-1}) of Sulfanilamide in the Metal Complexes

Sulfanil-amide[a]	Sulfanil-amide[b]	Sulfanilamide (This Study)	Cd Complex	Co Complex	Assignments
3472	3470	3474	3454	3454	$\nu_{asym.}(NH_2)$
3368		3372	3371	3369	$\nu_{sym.}(NH_2)$
	3320	3350	3320	3319	$\nu_{asym.}(NH)_{sulfonamido}$
	3260	3261	3242	3232	$\nu_{sym.}(NH)_{sulfonamido}$
	1640	1627	1637	1632	$\delta(NH_2)$
		1597	1600	1598	ν_{ring}
		1505	1504	1501	ν_{ring}
1311	1350	1317	1311	1313	$\nu(SO_2)_{asym.}$
1145	1160	1144	1146	1145	$\nu(SO_2)_{sym.}$
900		897	900	899	$\nu(SN)$
		837	828	827	$\delta(CH)$
		680	680	682	$\nu(CS)$, $\rho(CH)$, γ (CCC)
		583	573	573	δ_s (SO_2)
		553	553	550	ρ_w (SO_2)

[a] Blasco et al.[3], [b] Narang et al.[4].

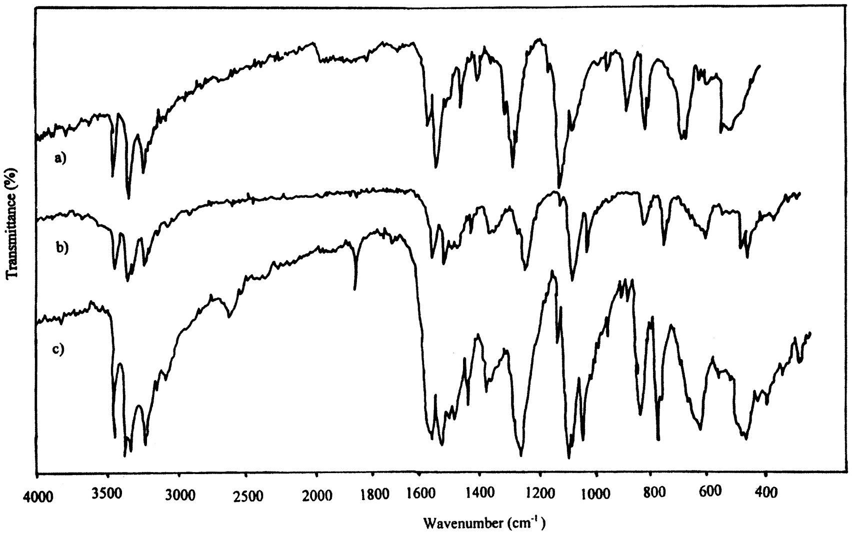


Figure 1. The infrared spectra of a) sulfanilamide b) cadmium complex of sulfanilamide c) cobalt complex of sulfanilamide.

frequencies with regard to the ligands, suggesting that the anilino group was involved in the coordination with the copper ions (Fig. 1). In our study, ν(NH_2) asymmetric and symmetric vibrations of the sulfanilamide shifted upon coordination toward a lower wavenumber when compared with the free sulfanilamide molecule in the IR spectra of Co and Cd complexes. Similar shifts had been observed with some metal complexes of sulfanilamide derivatives[8–10]. The NH_2 scissoring mode is observed at 1627 cm^{-1} in the IR spectrum of sulfanilamide. This vibration shows a small shift toward a higher wavenumber in the IR spectra of metal complexes. Kanagaraj et al.[8] had observed analogous effects in the Mn, Ni and Cu complexes of sulfamethoxazole. This conclusion is based on the fact that, one of the active binding sites of sulfanilamide is the aniline NH_2 group of sulfanilamide for the metal complexes.

In the IR spectrum of sulfanilamide, the ring stretching modes (at 1597 and 1505 cm^{-1}) have no significant shifts in wavenumbers compared to those in the metal complexes.

-*SO_2 Group Vibrations*

The SO_2 asymmetric and symmetric stretching vibrations are strongly active in the region 1335 ± 25 cm^{-1} and 1150 ± 15 cm^{-1} [11]. As seen from Fig. 1, the sharp and intense bands at 1317 and 1144 cm^{-1} are assigned to the asymmetric and symmetric SO_2 modes of free sulfanilamide, respectively. These bands show no significant change in metal complexes. Similar effect had been observed in copper complexes of sulfanilamide[3,4] and metal complexes of viz *o*-vanilin-sulfanilamide[5]. The scissoring and wagging vibrations of the SO_2 group occur at 570 ± 60 cm^{-1} and 520 ± 40 cm^{-1}, respectively[11]. As seen from Fig. 1a, these bands are observed at 583 and 553 cm^{-1} in IR spectrum of sulfanilamide. We did not observe any significant shifts in the scissoring and wagging modes of sulfonamide group in comprasion to those of metal complexes. This result suggest little or weak interaction between sulfonyl oxygen and metal ions.

-*NH_2 Group Vibrations*

The NH_2 asymmetric and symmetric bands of sulfonamide group are observed around 3355 ± 35 cm^{-1} and 3250 ± 20 cm^{-1}, respectively[11]. Narang et al.[3] and Maurya et al.[5] had described these vibrations at 3320, 3260 cm^{-1} and 3320, 3230 cm^{-1}, respectively. These bands either showed upward shift or no change in their position in the complexes indicating the reluctance of sulfonamide nitrogen towards coordination. In our study, the NH_2 asymmetric and symmetric stretching vibrations of sulfonamide groups are observed at $3350\,cm^{-1}$ and $3261\,cm^{-1}$ in the IR spectrum of sulfanilamide. These vibrations are shifted to lower wavenumbers (about 3320 and $3235\,cm^{-1}$) with regard to the ligand, suggesting that the NH_2 group of sulfonamide is involved in the coordination with the metal ions.

-S-N Stretching Vibration

The S-N stretching vibration exhibits a moderate band in the region $905 \pm 30\,cm^{-1}$ [11]. Blasco et al.[4] had observed this vibration at $900\,cm^{-1}$ in the IR spectrum of sulfanilamide. In our study, the band at $897\,cm^{-1}$ due to the ν (S-N) vibration of sulfanilamide are found unshifted in the spectra of metal complexes. Similar effect had been observed in copper complex of sulfanilamide[4]. This result suggested the absence of any interaction between sulfonamide nitrogen and Cu(II) ion[4]. Our result also indicated that the SN group remain free of metal coordination for Cd and Co complexes.

Sulfanilamide and Lincomycin Interactions

There are several reports of drug-drug interactions in the world literature. In this part of our study drug-drug interaction has been investigated between these compounds by using infrared (IR) spectroscopy. The wavenumbers of sulfanilamide observed in the IR spectra of its interacted compound with lincomycin were compared with those of free sulfanilamide. Investigations of the infrared spectrum of interacted compound indicated that the vibrations due to the the anilino and sulfonamido nitrogens are shifted with respect to the free molecule in line with their coordination to the lincomycin. The analyses of the IR spectra of sulfanilamide and its interaction compound with lincomycin have been the most used techique applied to the knowledge of the interaction between sulfanilamide and lincomycin molecule.

In this study, the ν(NH) stretching modes (at 3474 and $3372\,cm^{-1}$) in the IR spectrum of sulfanilamide (Fig. 1a) shifted to lower frequencies (3440 and $3340\,cm^{-1}$) in the spectrum of interacted compound (Fig. 2). The NH_2 scissoring mode observed at $1619\,cm^{-1}$ in sulfanilamide shows slightly a shift toward a higher wavenumber in the IR spectrum of interacted compound (Fig. 2). Similar changes are observed in Co and Cd complexes of sulfanilamide. This conclusion is based on the observed negative shift in

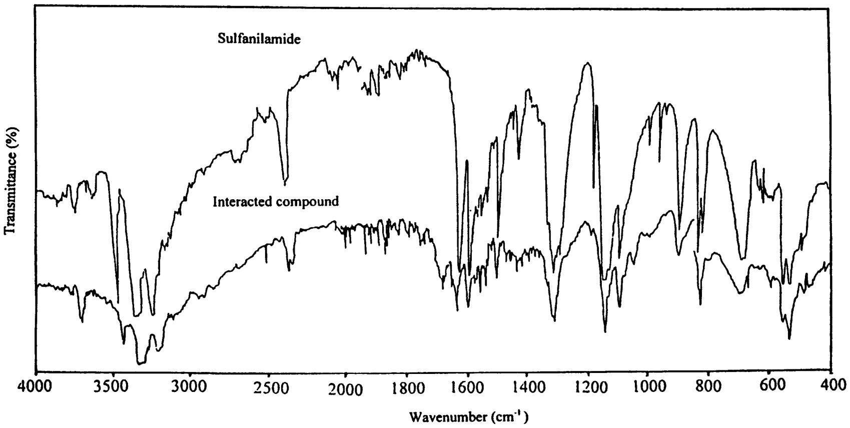


Figure 2. The infrared spectrum of the interacted compound of sulfanilamide and lincomycin.

interacted compound due to the ν(NH) stretching vibrations which may be due to the possible interaction between the anilino group of sulfanilamide and lincomycin molecule. In the IR spectrum of interacted compound (Fig. 2), the symmetric stretching mode of NH_2 in the sulfonamido group is also shifted to a lower frequency (3230 cm^{-1}) in comparsion to the band (3261 cm^{-1}) in sulfanilamide. This result suggests an interaction between sulfonamide nitrogen and lincomycin.

In the IR spectrum of interacted compound, the ring stretching modes (1597 and 1505 cm^{-1}) have no significant shifts in wavenumber compared to those in the free sulfanilamide. The SO_2 asymmetric and symmetric stretching vibrations (1317 and 1144 cm^{-1}) are sligthly shifted to a lower frequency region (1306 and 1140 cm^{-1}) with respect to those of sulfanilamide in the IR spectrum of interacted compound. We did not observe any significant shifts in the scissoring and wagging modes of the sulfonamide group in comprasion to those of interacted compound. The sligthly shifted vibrational bands due to the sulfonyl group suggest little or weak interaction between sulfonyl oxygen of sulfanilamide and lincomycin. The ν(SN) vibration of sulfanilamide are also found to be almost the same in wavenumber in interacted compound.

The interactions of lincomycine and some sulfonamide compound had been already observed clinically[6]. In this study, lincomycin was interacted with sulfonamide *in vitro*; these two drug compounds will probably also interact *in-vivo*.

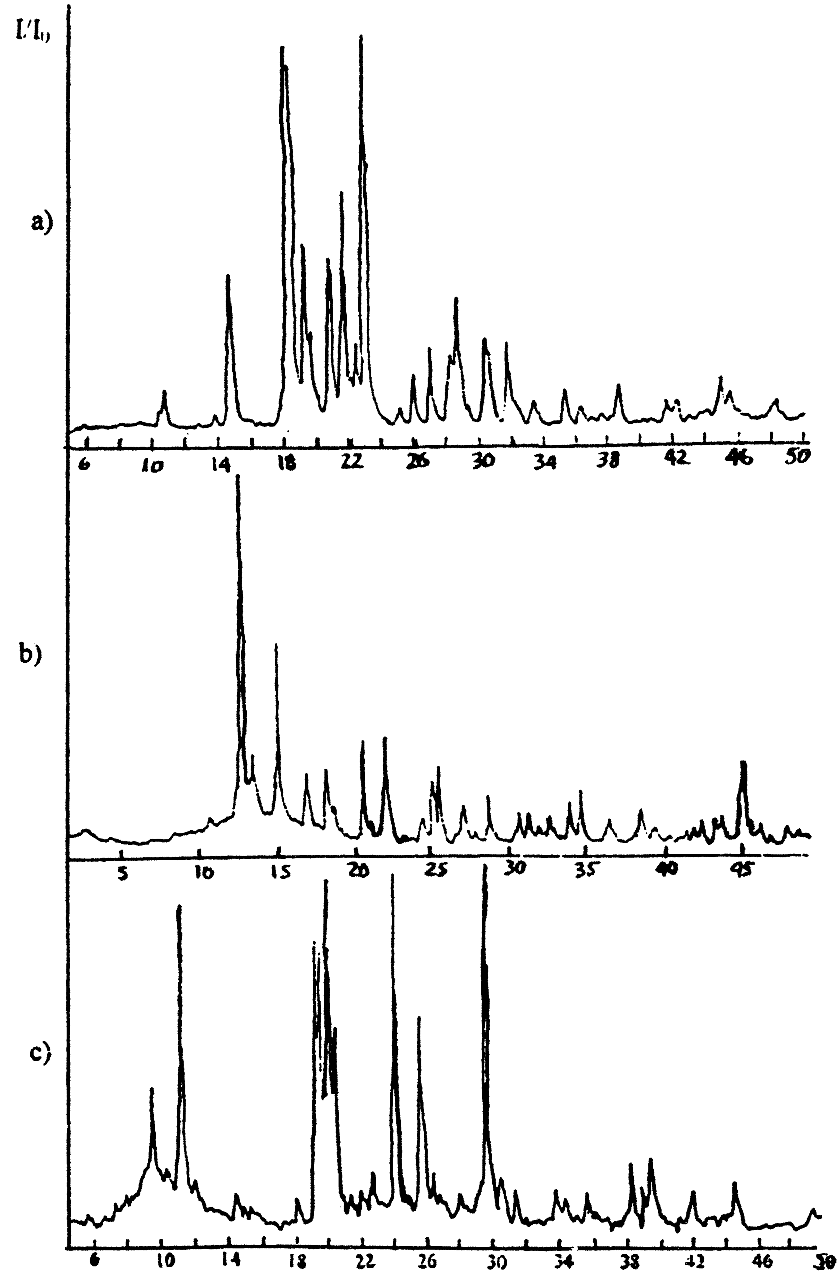


Figure 3. The diffraction patterns of a) sulfanilamide b) Cd $(CH_3COO)_2$ c) Cd complex.

Table 2. The CuK$_\alpha$ x-ray Powder Diffraction Analysis for Sulfanilamide, Cd(acetate), and Cd Complex of Sulfanilamide

Sulfanilamide			Cd(acetate)			Cd complex		
I/I_o	2θ(°)	d(Å)	I/I_o	2θ(°)	d(Å)	I/I_o	2θ(°)	d(Å)
11.96	10.70	8.26	100.00	12.75	6.95	44.06	9.60	9.21
40.17	14.50	6.10	29.36	13.25	7.23	22.88	10.50	8.42
97.43	18.00	4.92	59.63	15.00	5.91	89.83	11.40	7.76
91.45	18.20	4.86	23.85	16.75	5.29	19.49	12.00	7.37
47.86	19.00	4.66	24.77	18.25	4.86	16.10	14.50	6.11
23.93	19.40	4.57	33.03	20.75	4.28	14.40	18.20	4.87
48.72	20.60	4.31	33.95	22.25	3.99	79.66	19.30	4.59
61.54	21.40	4.15	16.51	24.50	3.63	77.12	19.60	4.53
22.22	22.20	3.99	21.10	25.00	3.56	96.61	20.00	4.44
100.00	22.80	3.89	25.69	25.50	3.49	68.64	20.20	4.04
5.98	25.00	3.55	14.68	27.20	3.27	56.78	20.50	4.33
13.67	25.90	3.43	17.43	28.75	3.11	15.25	21.50	4.13
20.51	26.90	3.31	19.27	34.60	2.59	16.95	22.20	4.00
18.80	28.20	3.16	24.77	44.80	2.02	21.19	22.90	3.88
34.19	28.50	3.13				97.46	24.20	3.67
5.98	29.20	3.05				61.01	25.80	3.45
22.22	30.40	2.93				21.19	26.50	3.36
22.22	31.60	2.82				16.95	28.20	3.16
15.38	33.20	2.69				100	29.80	2.99
9.40	35.20	2.54				20.34	30.60	2.92
5.98	36.10	2.48				16.95	31.60	2.83
11.11	38.40	2.34				16.95	33.80	2.65
5.98	41.30	2.18				15.25	34.40	2.61
6.84	42.00	2.14				16.95	35.70	2.51
11.96	44.70	2.02				23.73	38.40	2.34
9.40	45.20	2.00				17.79	39.10	2.31
						25.42	39.60	2.27
						16.95	42.00	2.15
						19.49	44.70	2.02
						13.56	49.40	1.84

X-Ray Studies

We also recorded the x-ray powder diffraction patterns of sulfanilamide, metal acetate and metal complexes of sulfanilamide for comparative purposes. Fig. 3 shows the x-ray diffraction patterns of sulfanilamide, $Cd(CH_3COO)_2$ and the Cd complex of sulfanilamide.

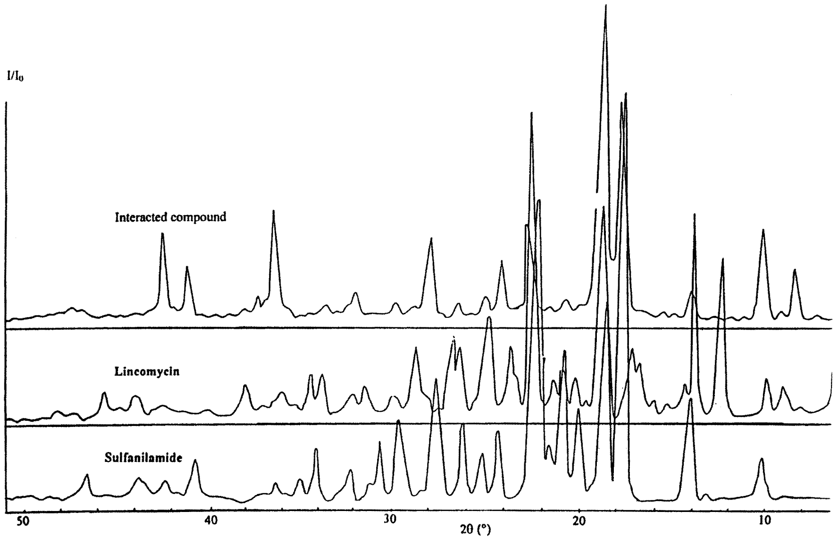


Figure 4. The diffraction patterns of sulfanilamide, lincomycin, and their interacted compound.

The patterns of metal complexes are not simply a statistical mixture of the patterns of sulfanilamide and cadmium acetate. The Bragg angles (2θ), interplanar spacing (d) and relative intensities (I/I_0) of the samples are given in Table 2. The sharp peaks of the pattern of cadmium complex shows the increased degree of crystallinity. Since the most intense peak

Table 3. The Low Energy Values (kcal/mol) of Cadmium Complex According to the Probable Binding of Different Groups of Sulfanilamide

Groups	Energy (kcal/mol)
SO_2, NH_2	47
SO_2, SO_2	138
$NH_{anilino}$, $NH_{anilino}$	37
$NH_{sulfonamido}$, $NH_{sulfonamido}$	74
$NH_{anilino}$, $NH_{sulfonamido}$	13
SO_2, $NH_{sulfonamido}$	100

Table 4. The Low Energy Values (kcal/mol) of Cobalt Complex According to the Probable Binding of Different Groups of Sulfanilamide

Groups	Energy (kcal/mol)
SO_2, $NH_{anilino}$	53
SO_2, SO_2	160
$NH_{anilino}$, $NH_{anilino}$	34
$NH_{sulfonamido}$, $NH_{sulfonamido}$	79
$NH_{anilino}$, $NH_{sulfonamido}$	21
SO_2, $NH_{sulfonamido}$	101

positions are placed in the low 2θ range, a large unit cell and low symmetry can be indicated.

The x-ray diffraction patterns of sulfanilamide, lincomycin and interacted compound also are recorded. If there is a pharmaceutical interaction in solution, the x-ray diffraction pattern of the interacted compound is not a

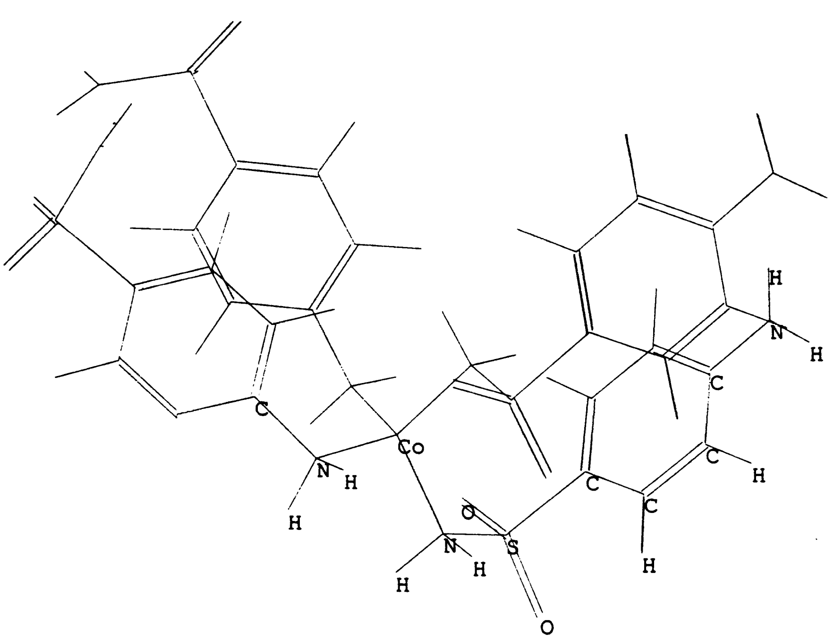


Figure 5. The probable structure of Co complex.

statistical sum of that of lincomycin and sulfanilamide. As seen from Fig. 4, it can be said that some peak locations and intensities changed due to an interaction between lincomycin and sulfanilamide molecules. Therefore x-ray studies are in agreement with the data from the infrared spectra of the samples.

Theoretical Studies

In addition, the low energy calculations (Table 3 and Table 4) were also carried out by using geometry optimization by means of the HYPERCHEM program. The proposed structure for the metal complexes of sulfanilamide derived from the infrared spectra are consistent with the low energy values.

CONCLUSION

In conclusion, sulfanilamide acts as a bidendate ligand, binding the metal ions through anilino and sulfonamide nitrogens. Fig. 5 and Fig. 6

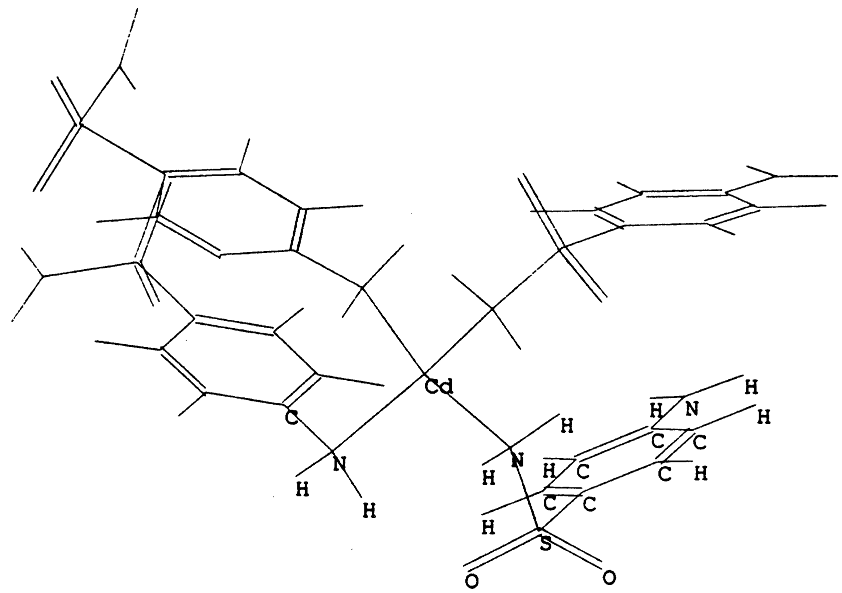


Figure 6. The probable structure of Cd complex.

show the probable structure of Co and Cd complexes in three dimensions, respectively.

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