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Characterization of Silver Sulfadiazine and Related Compounds

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Abstract □ Silver sulfonamides can be successfully recrystallized from strong ammonia solution. The spectral characterization of silver sulfadiazine, silver sulfamethazine, silver sulfanilamide, and silver sulfapyridine indicates that the silver sulfonamide formed on reaction of silver nitrate with the free sulfonamide or its sodium salt is correctly represented by a classical salt structure. Complexations of silver sulfonamides with morpholine yield 1:1 crystalline complexes, which can be analyzed by NMR spectroscopy directly. Spectral studies of the silver sulfonamides were carried out using an indirect NMR technique.

Keyphrases □ Silver sulfadiazine and related compounds—recrystallization and spectral characterization, structure determination □ Silver sulfonamides—recrystallization and spectral characterization, structure determination □ Sulfonamides, silver—recrystallization and spectral characterization, structure determination □ NMR spectroscopy—structure determination, silver sulfonamides

Since 1968, interest in silver sulfadiazine has increased steadily due to its effectiveness in the topical treatment of *Pseudomonas* infections associated with thermal burns. The compound contains both silver with its oligodynamic effect and sulfonamide antibiotic activity to give a broad range of effectiveness against microorganisms. Silver ion in solution is toxic, but salts of silver have been shown to be safe and effective against bacteria in concentrations as small as 1 ppb. When used in combination with, or when reacted with, a sulfonamide, silver offers additional advantages in the treatment of burns. These include the lack of sensitization characteristics of antibiotics usually employed for these conditions, the broader range of antibacterial activity as well as activity against mycotic and viral infections, and the failure of organisms to develop resistant strains to silver-ion activity.

Silver sulfadiazine offers many therapeutic advantages in topical use over other silver salts. Fox (1) reported that, unlike silver nitrate, silver sulfadiazine is odorless, stainless, easy to apply, and painless and often reduces the need for skin grafts. In addition, the compound does not deplete the applied area of essential body salts and, therefore, does not require simultaneous administration of supplementary fluids as is necessary with silver nitrate. Sulfonamides used as sodium salts are also inferior to their silver salts, because the sodium derivatives have been shown to cause extensive tissue damage because of their high alkalinity.

The proven efficacy of silver sulfadiazine in the treatment of *Pseudomonas* infections in burns has been reported (2–4), but little information about the physical and chemical properties of this compound is available. It was reported (5) that silver sulfadiazine is poorly water soluble and that the silver ion is firmly bound to the nitrogen, but no positive evidence for this claim was given. Wruble (6) prepared colloidal silver preparations of sulfadiazine and other sulfonamides and indicated structural formulas but without any supportive spectral or analytical data. A silver–sulfadiazine chelate ring complex was reported (7) for the precipitate obtained after mixing a sodium sulfadiazine solution with a silver nitrate solution. The chelate structure is just one of several proposed structures for silver sulfadiazine and related

Table I—Elemental Analyses and Melting Points of Silver Aminosulfonamides

Complex	Melting Point	Analysis, %	Calc.	Found
Morpholine silver sulfadiazine	263–265°	C	37.83	37.59
		H	4.08	4.24
		N	15.75	15.65
Morpholine silver sulfapyridine	220–223°	C	40.65	40.91
		H	4.32	4.46
		N	12.64	12.44

silver sulfonamides. No conclusive evidence about the structures has been reported.

The preparation of crystalline silver sulfonamides has not been indicated since all previous reports refer to silver sulfadiazine and the other silver sulfonamides as colloids or precipitates. The intents of this study were to purify and crystallize the silver sulfonamides prepared and to establish the structures for these compounds using spectral analytical methods. During this investigation, additional reactions of the silver sulfonamides with amines were studied and the results indicate complex formation with different stoichiometry than that previously reported (8). Additional studies on the physical properties of the silver sulfonamides are underway, and the results will be reported subsequently.

EXPERIMENTAL

Equipment—A grating IR spectrophotometer[1] and an NMR spectrometer[2] were used.

Materials and Reagents—All chemicals used were of analytical or reagent grade. Silver nitrate and sodium sulfadiazine were supplied commercially[3].

Sulfadiazine, sulfamethazine, and sulfapyridine were recrystallized from 95% ethanol. The sulfanilamide was recrystallized from distilled water.

Synthesis of Sodium Salts of Sulfonamides—The sodium salts of sulfadiazine, sulfamethazine, sulfapyridine, and sulfanilamide were prepared by dissolving 1.0 g of the sulfonamide base in 7% excess of 5 *N* NaOH and adding distilled water to form a clear solution, which was evaporated to dryness. The sodium salts were recrystallized from 95% ethanol and vacuum dried overnight. IR spectra were obtained using potassium bromide disks.

Synthesis of Silver Salts of Sulfonamides—Silver sulfadiazine was prepared by the method of Braun and Towle (9) and vacuum dried overnight at 40°. The silver salts of sulfamethazine, sulfapyridine, and sulfanilamide were prepared by the method of Rosenzweig and Fuchs (8) and vacuum dried overnight at 40°.

Purification of Silver Sulfonamides—The dried silver sulfonamides were dissolved in ammonium hydroxide with gentle heating, if needed. The solution was filtered and allowed to evaporate partially at room temperature. The colorless crystals remaining after partial evaporation were filtered and washed with distilled water and acetone. The silver sulfadiazine was vacuum dried overnight at 40°. Silver sulfamethazine, silver sulfapyridine, and silver sulfanilamide were dried at 110° for 72 hr. The melting decomposition points of the silver sulfonamides are as follows: silver sulfadiazine, 286–288°; silver sulfamethazine, 298–299°; silver sulfapyridine, 248–250°; and silver sulfanilamide, 212–215°. IR spectra were obtained using potassium bromide disks.

NMR—A procedure for the determination of active hydrogen by NMR was described previously (10), and a similar method was used to study the silver sulfonamides. The NMR spectra of the silver sulfonamides were obtained by preparing a sample tube containing 40 mg of the silver sulfonamide, 0.25 ml deuterated trifluoroacetic acid[4] (CF_3COOD), and 4 mg of sodium 2,2-dimethyl-2-silapentane-5-sulfonate[4] (I) as the reference standard. Another sample tube was prepared containing 0.25 ml deuterated trifluoroacetic acid and 4 mg of I as the reference standard.

The NMR spectrum of both samples was scanned up to 980 Hz. The number of exchangeable hydrogens was obtained by integrating the residual OH peak at 11–12 ppm of deuterated trifluoroacetic acid in both samples at a constant instrument setting. These integrations were carried out by successively removing and replacing the sample tubes for each integration. By subtracting the average height of the residual OH peak in deuterated trifluoroacetic acid from the average height of the residual OH peak in the silver sulfonamide spectrum and dividing by the height contributed by one hydrogen as determined from the average integral heights of the other peaks on the spectrum, the number of active hydrogens was determined.

Synthesis of Silver Aminosulfonamides—One gram of the silver sulfonamide was dissolved in 40 ml of warm morpholine[5]. The solution was filtered and the complex was forced out of solution with approximately 100 ml of anhydrous ether[5] and recrystallized from a morpholine–ether solvent system. The elemental analyses and melting points of the silver aminosulfonamides are given in Table I. NMR spectra of the complexes were obtained in deuterated dimethyl sulfoxide[4] with scanning up to 980 Hz.

Table II—Asymmetric SO_2 Stretching Vibrational Frequencies (Centimeters^{-1})

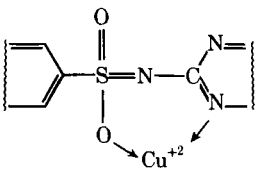
Compound	Free Base	Sodium Salt	Silver Salt
Sulfanilamide	1320	1190	1250
Sulfadiazine	1330	1430	1425
Sulfamethazine	1315	1430	1425
Sulfapyridine	1270	1330	1310

RESULTS AND DISCUSSION

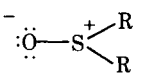
IR—Spectral identification of the structures of the silver sulfonamides requires a pure and preferably crystalline material and solution of the compound in the analytical solvent. Previously prepared silver sulfonamides have been colloidal in nature and insoluble in the commonly used spectroscopic solvents.

The IR spectra of sulfonamides reacted with copper ion were investigated (11) and indicated a difference in the SO_2 absorption of the free sulfonamides when compared to the copper reaction product. The proposed chelate structure, II, for sulfadimethoxine, sulfamerazine, and sulfadimethoxypyridine was based on SO absorption band shifts from 1316 to 1282 cm^{-1}, indicating coordination of the metal with oxygen. This shift to a lower SO stretching frequency is seen with metal complexes with sulfoxides where Structure III dominates where there is oxygen coordination (12). It seemed reasonable to investigate the IR spectra of the silver sulfonamides to determine if a similar SO shift is seen with the silver as was reported with copper (Table II).

The shifts in the SO bands of the silver and sodium salts are similar. The SO shifts for sulfanilamide are toward lower frequency



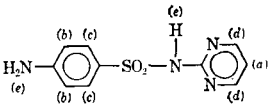
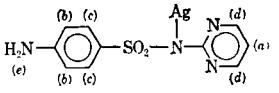
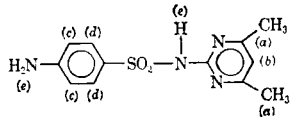
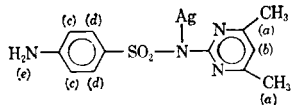
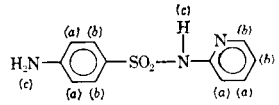
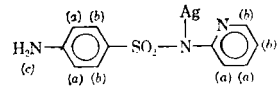
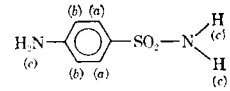
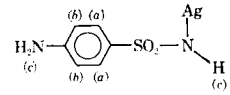
II



III

[1] Perkin-Elmer 457.
[2] Varian T60.
[3] Marion Laboratories, Kansas City, Mo.
[4] Merck Sharp and Dohme of Canada Limited.
[5] Fisher Scientific Co., Fair Lawn, N.J.

Table III—NMR Spectra of Silver Sulfonamide Analogs (Parts per Million) (in Deuterated Trifluoroacetic Acid Using I as the Reference)[a]

Compound	*a*	*b*	*c*	*d*	*e*	Number of Active Hydrogens per Mole	
						Theoretical	Found
	7.60 t	7.90 d	8.46 d	9.03 d	11.75 s	3	2.67
	7.30 t	7.80 d	8.36 d	8.93 d	11.75 s	2	1.67
	2.72 s	7.13 s	7.83 d	8.35 d	11.56 s	3	3.00
	2.66 s	7.0 s	7.70 d	8.21 d	11.9 s	2	2.13
	7.83 m	8.36 m	11.53 s	—	—	3	3.01
	7.83 m	8.35 m	11.68 s	—	—	2	1.89
	7.75 d	8.13 d	10.86 s	—	—	4	3.97
	7.71 d	8.15 d	11.35 s	—	—	3	2.64

[a] s = singlet, d = doublet, m = multiplet, and t = triplet.

for the salts, whereas the shifts for the other sulfonamides are toward higher frequency. The shift to lower frequency for silver and sodium sulfanilamide could indicate possible oxygen coordination with the silver and sodium ions in sulfanilamide. The SO shifts to higher stretching frequency for salts of sulfadiazine, sulfamethazine, and sulfapyridine indicate little if any oxygen coordination with the sodium or silver ions. Therefore, these data suggest that the silver salts of substituted sulfonamides do not involve coordination with oxygen but have a classical salt structure similar to the sodium salts.

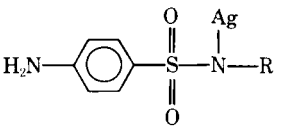
The amide–amine region of the IR spectra was investigated to determine the presence or absence of the amide hydrogen in silver sulfadiazine. This region for the silver and sodium sulfonamides was very similar to that of the free sulfonamide base. Thus, it was impossible to determine the presence or absence of the amide hydrogen on the basis of IR data alone.

NMR—Because the results obtained from the IR data were inconclusive relative to the presence of an amide hydrogen in the silver sulfonamides, NMR studies were undertaken. NMR studies of the free sulfonamide bases in deuterated dimethyl sulfoxide are well documented (13).

Deuterated dimethyl sulfoxide did not prove to be a suitable solvent for the silver sulfonamide salts. Various amines were tried as solvents, but none provided the solubility needed to obtain a NMR spectrum. Deuterated trifluoroacetic acid was found to be the solvent of choice. The exchange of the deuterium of the acid with the active hydrogens of the sulfonamides was utilized as a method for counting the number of active hydrogens in the compounds. The acid also has the advantage of forming stable solutions with the silver sulfonamides studied; in addition, the residual OH peak at 11.34 ppm of the acid is easily integrated because of its position downfield from the rest of the spectrum.

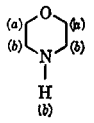
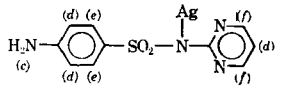
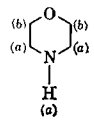
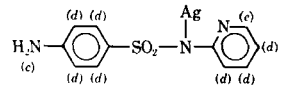
The exchange reactions occur rapidly enough to give one peak for the exchanged protons. In this case the integrated peak height at 11–12 ppm minus the integrated peak height of the residual OH in the deuterated trifluoroacetic acid at 11.34 ppm represents the total active hydrogen content of the silver sulfonamide. The results (Table III) indicate the complete displacement of the amido hydrogen by the silver in the reaction of a solution of silver nitrate with a solution of the free sulfonamide base or a solution of the sodium salt of the sulfonamide.

Additional NMR data of the silver sulfonamides complexed with morpholine were studied. The morpholine complexes of the prepared silver sulfonamides were synthesized to make them soluble in deuterated dimethyl sulfoxide. Only the morpholine complexes of silver sulfadiazine and silver sulfapyridine were soluble



IV

Table IV—NMR Spectra of Silver Sulfonamide Morpholine Complex (Parts per Million) (in Deuterated Dimethyl Sulfoxide Using I as the Reference)[a]

Compound	*a*	*b*	*c*	*d*	*e*	*f*
	2.9 m	3.7 m	5.6 s	6.75 m	7.78 d	8.51 d
						
	2.9 m	3.7 m	5.8 m	7.1 s	—	—
						

[a] s = singlet, d = doublet, m = multiplet, and t = triplet.

enough in deuterated dimethyl sulfoxide to obtain a NMR spectrum. Rosenzweig and Fuchs (8) indicated that the silver sulfonamides form a dimorpholinamino complex. The data (Tables III and IV) indicate that only a monomorpholinamino complex is formed under the experimental conditions used. These data also suggest that the amido hydrogen is absent in the silver sulfadiazine–morpholine complex.

It was concluded from the studies using deuterated trifluoroacetic acid and complexation data that the amide hydrogen is not present in silver sulfonamides and that Structure IV represents the compound.

SUMMARY

The first successful crystallization of silver sulfonamides has been achieved. The spectral characterization of these compounds, including silver sulfadiazine, silver sulfamethazine, silver sulfanilamide, and silver sulfapyridine, indicates that silver ion reacts with the sulfonamide displacing the amide hydrogen to give a classical silver sulfonamide salt.

Complexation studies of silver sulfonamides with morpholine indicate that one morpholine reacts with one silver sulfonamide to give a stable complex which is soluble in deuterated dimethyl sulfoxide. Although the morpholine complexes could be analyzed directly with NMR solvents, the silver sulfonamides could only be analyzed by an indirect method. IR data were inconclusive in establishing the structures of the silver sulfonamides.

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