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Solubility Studies of Silver Sulfonamides

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Abstract □ The solubilities of silver sulfapyridine, silver sulfamethazine, and silver sulfamethizole as a function of pH were determined in nitric acid–potassium nitrate, acetate, and sulfonic acid buffers. All silver sulfonamides showed an increase in solubility with increasing hydrogen-ion concentration, a behavior which closely paralleled the protonation of the *p*-amino function of the sulfonamide. A silver-ion selective electrode was used to measure silver-ion concentration in solution and the methods of known subtraction and known addition were used to measure total silver. Both silver sulfamethizole and silver sulfamethazine were ionized completely in solution. Silver sulfapyridine was ionized completely only in the more acidic pH 2–3 range. A comparison of the physical properties of the silver salts for which mortality studies were available revealed a unique set of properties for silver sulfadiazine.

Keyphrases □ Silver sulfonamides, various—aqueous solubility, effect of pH □ Solubility, aqueous—various silver sulfonamides, effect of pH □ Antibacterials—various silver sulfonamides, aqueous solubility, effect of pH

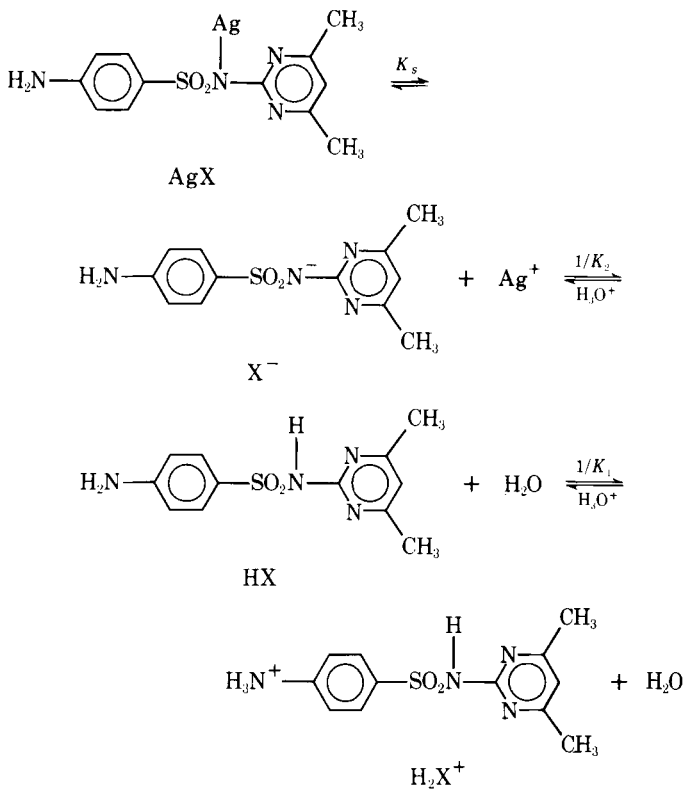
While some silver salts have been tested for effectiveness against *Pseudomonas* infections, the unique activity of silver sulfadiazine remains impressive but incompletely explained. The solubility and ionization properties of this compound were reported (1) and the drug was characterized as a practically insoluble salt having a solubility product of 8.1×10^{-12} at 25° and 0.1 *M* ionic strength. In the presence of a nitrate buffer under these experimental conditions, the silver ion was dissociated completely from the sulfadiazine moiety and therefore free to precipitate or complex with any suitable ligand. In the presence of endogenous chloride ion, silver sulfadiazine did not cause the rapid precipitation of silver chloride, under physiological conditions, even though the solubility product of silver chloride was exceeded (2). Further studies of the behavior of silver sulfadiazine in the presence of chloride ion are indicated for a better understanding of this phenomenon.

Other silver sulfonamides have been compared to silver sulfadiazine for anti-infective activity and reaction with human serum and DNA. Differences between the reactions of the other sulfonamides to those of silver sulfadiazine were postulated to relate to the ionization constants for the sulfonamide moieties (2). However, a comparison of the literature values of the amide hydrogen ionization constants with the reported behavior for the reaction of the silver compounds with serum does not indicate that a simple ionization phenomenon is involved. The solubility of these salts should be considered, as well as the tendency of free silver ions to complex with many endogenous biological substances.

This solubility study was undertaken to determine the properties of some silver sulfonamides other than silver sulfadiazine to provide more information about their behavior in aqueous solution. The solubility and ionization properties of silver sulfamethazine, silver sulfamethizole, and silver sulfapyridine are reported. A possible correlation between the physical properties of the silver salts and their biological activity is proposed.

EXPERIMENTAL

Equipment—Potentiometric measurements were made using a pH meter[1], accurate to ±0.001 pH unit, in a thermostated bath regulated at 25 ± 0.1°. Silver-ion concentration was measured with a silver-ion se-



Scheme I—Silver sulfamethazine dissolution

[1] Digital 112 research pH meter, Corning Scientific Instruments, Medfield, Mass.

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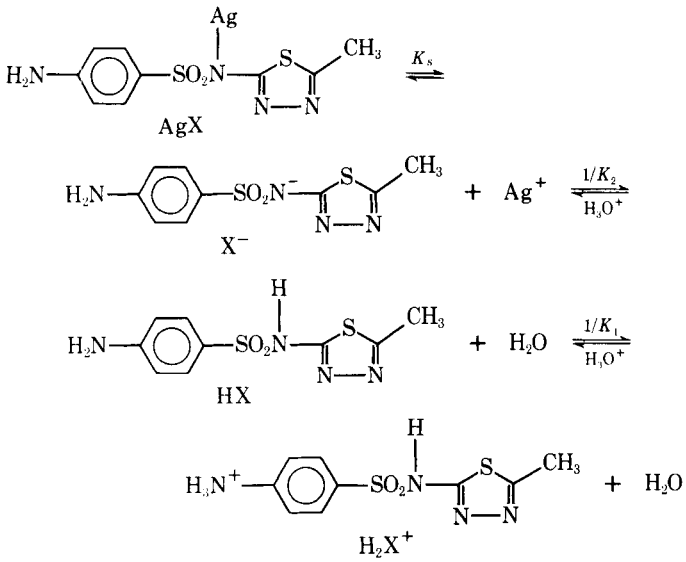


Scheme II—Silver sulfamethizole dissolution

lective electrode[2]. Hydronium-ion concentration was measured with a pH electrode[3]. A double-junction silver chloride reference electrode[4] with a filling solution of 10% KNO_3 was used to eliminate the possible precipitation of silver chloride in the sample solutions.

Reagents—All reagents used were analytical or USP grade, unless otherwise stated. The water had a specific conductivity of $1–10 \times 10^{-7}$ ohm^{-1} cm^{-1}. Silver sulfamethazine, silver sulfapyridine, and silver sulfamethizole were prepared by the method of Rosenzweig and Fuchs (3) and recrystallized from concentrated ammonia (4). The sulfonic acid[5] and acetic acid buffers were prepared with a total molar concentration of 0.05 *M*. The nitric acid buffers were prepared by dilution of 0.1 *M* HNO_3. All buffers were adjusted to an ionic strength of 0.1 *M* with potassium nitrate.

Preparation of Equilibrium Mixtures—Procedures similar to those previously reported were utilized (1). The recrystallized and dried silver sulfonamides were screened through an 80-mesh standard screen[6], and a 100-mg sample was added to either 25 or 27 ml of nitric acid buffer, 27 ml of acetate buffer, or 27 ml of sulfonic acid buffer. For measurement of total silver, 27 ml of buffer was used.

The mixtures were adjusted to a constant ionic strength of 0.1 *M* and placed in paraffin-coated vials with paraffin-sheet[7]-covered rubber closures. The vials were rotated end over end in the thermostated bath until equilibrium solubility was obtained (3–7 days).

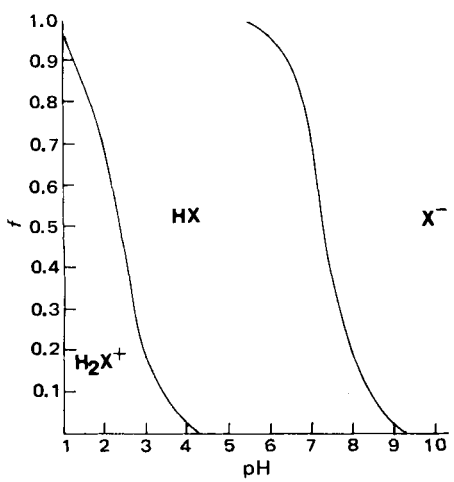


Figure 1—*Distribution diagram: fraction of sulfamethazine present as some particular form, f, as a function of pH; pK_1 = 2.36 and pK_2 = 7.38 (8).*

[2] No. 94-16, Orion Research, Cambridge, Mass.
[3] Triple-Purpose pH electrode, Corning Scientific Instruments, Medfield, Mass.
[4] No. 90-02, Orion Research, Cambridge, Mass.
[5] United States Biochemical Corp., Cleveland, Ohio.
[6] W. S. Tyler Co., Minton, Ohio.
[7] Parafilm, American Can Co., Neenah, Wis.

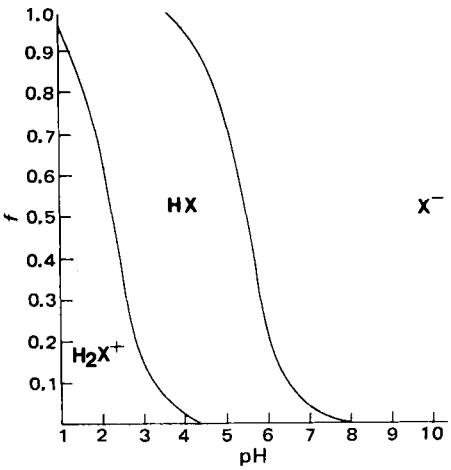


Figure 2—*Distribution diagram: fraction of sulfamethizole present as some particular form, f, as a function of pH; pK_1 = 2.20 and pK_2 = 5.45 (8).*

Measurement of Silver—The equilibrated mixtures were filtered through 20M glass filtering crucibles. The solutions were analyzed at 25 ± 0.1° in paraffin-coated beakers for silver ions with a silver-ion selective electrode[2] standardized at 25 ± 0.1° and 0.1 *M* ionic strength using procedures reported earlier (1, 5, 6).

Measurement of pH—The pH was measured with a pH electrode standardized using buffers meeting National Bureau of Standards requirements (7).

RESULTS AND DISCUSSION

The analytical method and the acid–base properties of silver sulfadiazine were discussed previously (1). Similar systems are proposed for the silver salts of sulfamethazine, sulfamethizole, and sulfapyridine.

The equilibria of the saturated solutions of silver sulfamethazine and silver sulfamethizole (Schemes I and II) are described by Eqs. 1–5:

$$K_s = [Ag^+][X^-] \quad \text{(Eq. 1)}$$

$$\frac{1}{K_2} = \frac{[HX]}{[H_3O^+][X^-]} \quad \text{(Eq. 2)}$$

$$\frac{1}{K_1} = \frac{[H_2X^+]}{[HX][H_3O^+]} \quad \text{(Eq. 3)}$$

$$S = [Ag^+] \quad \text{(Eq. 4)}$$

$$S = [H_2X^+] + [HX] + [X^-] \quad \text{(Eq. 5)}$$

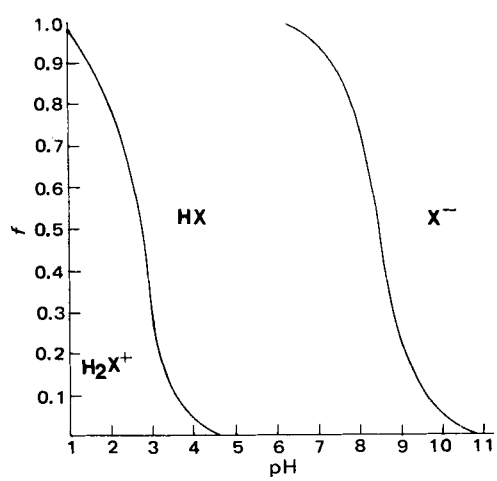


Figure 3—*Distribution diagram: fraction of sulfapyridine present as some particular form, f, as a function of pH; pK_1 = 2.58 and pK_2 = 8.43 (8).*

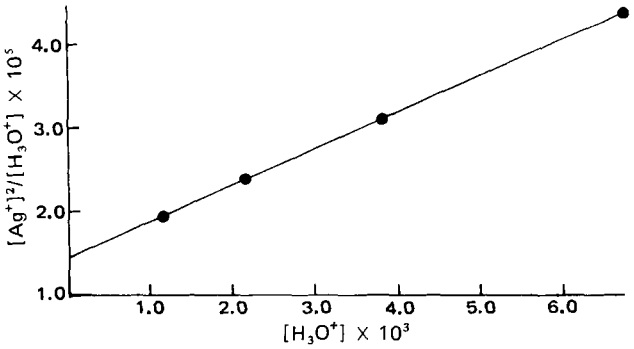


Figure 4—*Equilibrium values of* $[Ag^+]^2/[H_3O^+]$ versus $[H_3O^+]$ *for silver sulfamethazine in nitric acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*

where S is the total molar solubility of the silver sulfonamide. Substitution of Eqs. 1–4 into Eq. 5 and rearrangement give:

$$S^2 = [Ag^+]^2 = \frac{[H_3O^+]^2K_s}{K_1K_2} + \frac{[H_3O^+]K_s}{K_2} + K_s \qquad \text{(Eq. 6)}$$

which describes the solubility of these silver sulfonamides in terms of only the silver- and hydronium-ion concentrations of the saturated solutions. The parameter K_s is the apparent solubility product, and K_1 and K_2 are the apparent dissociation constants of the N^4- and N^1-hydrogens, respectively. Equation 6 may be simplified by using the limiting conditions of low (2–4) and high (5–9) pH. These approximations were derived by using distribution diagrams for the sulfonamides (Figs. 1 and 2), calculated using ionization constants determined by Bell and Roblin (8), noting which species of sulfonamide was not present in the pH range of interest, and neglecting this term in the mass balance equation (Eq. 5).

In the low pH range, Eq. 6 may be approximated to give:

$$S^2 = [Ag^+]^2 = \frac{[H_3O^+]^2K_s}{K_1K_2} + \frac{[H_3O^+]K_s}{K_2} \qquad \text{(Eq. 7)}$$

by neglecting the X^- species in Eq. 5. This equation may be linearized by dividing both sides by the hydronium-ion concentration, giving:

$$\frac{[Ag^+]^2}{[H_3O^+]} = \frac{[H_3O^+]K_s}{K_1K_2} + \frac{K_s}{K_2} \qquad \text{(Eq. 8)}$$

When $[Ag^+]^2/[H_3O^+]$ is plotted against $[H_3O^+]$, a linear relationship should exist with an intercept of K_s/K_2 and a slope of $(K_s/K_2)(1/K_1)$. From the slope and intercept, K_1 may be determined experimentally.

At the higher pH range (5–9), Eq. 6 may be approximated to give:

$$S^2 = [Ag^+]^2 = \frac{[H_3O^+]K_s}{K_2} + K_s \qquad \text{(Eq. 9)}$$

where the H_2X^+ species in Eq. 6 has been neglected. The application of Eq. 9 to the experimental data in the presence of the acetate and sulfonic acid buffer systems does not adequately represent the system because of apparent complexation of the free silver ion with the buffer. This results in an increased value of the solubility, S, and subsequently a higher value for K_s, the apparent solubility product.

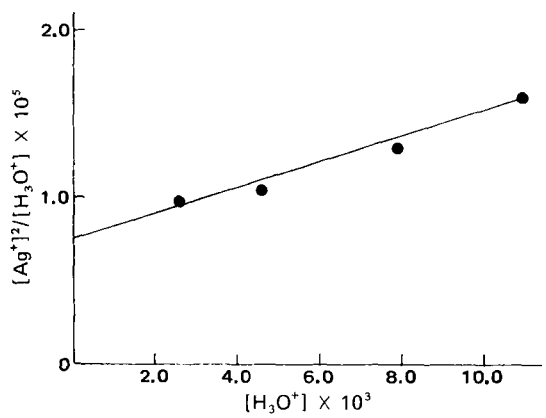
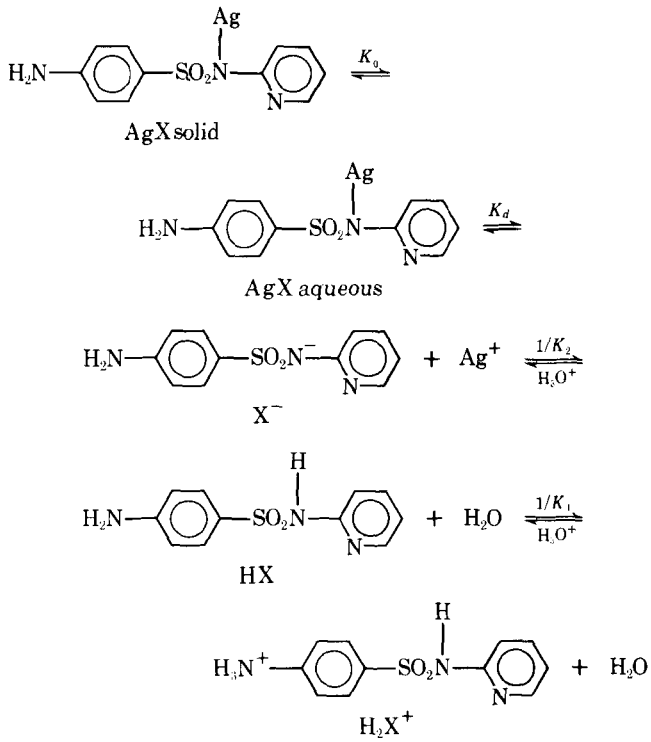


Figure 5—*Equilibrium values of* $[Ag^+]^2/[H_3O^+]$ versus $[H_3O^+]$ *for silver sulfamethizole in nitric acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*



Scheme III—Silver sulfapyridine dissolution

A suitable modification of Eq. 9 to include this complexation may be made by using a conditional solubility product K_s' defined by:

$$K_s' = [Ag^+]'[X^-] \qquad \text{(Eq. 10)}$$

where $[Ag^+]'$ represents the concentration of all silver in solution, irrespective of the form of the silver. Equation 9 may now be rewritten as:

$$S^2 = \frac{[H_3O^+]K_s'}{K_2} + K_s' \qquad \text{(Eq. 11)}$$

where S is the total molar solubility and K_2 is defined by Eq. 2. A plot of S^2 *versus* $[H_3O^+]$ would be expected to be linear with an intercept of K_s' and a slope of K_s'/K_2, from which K_2 may be determined experimentally.

The silver sulfapyridine equilibria shown in Scheme III may be described by the following equations:

$$K_0 = \frac{[AgX]_{(soln)}}{[AgX]_{(s)}} \qquad \text{(Eq. 12)}$$

$$K_d = \frac{[Ag^+][X^-]}{[AgX]_{(soln)}} \qquad \text{(Eq. 13)}$$

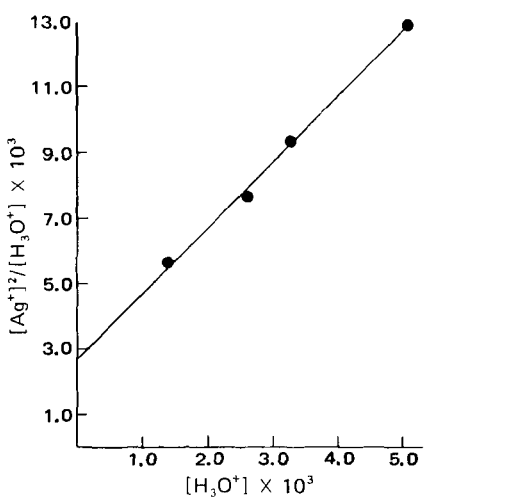


Figure 6—*Equilibrium values of* $[Ag^+]^2/[H_3O^+]$ versus $[H_3O^+]$ *for silver sulfapyridine in nitric acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*

Table I—Amino pK Values Calculated from Plots of Eq. 9 [a]

Silver Sulfonamide	Experimental $pK_1 \pm SD$	r	p
Silver sulfamethazine	2.47 ± 0.002	0.9998	>0.001
Silver sulfamethizole	2.00 ± 0.01	0.9957	>0.01
Silver sulfapyridine	2.88 ± 0.02.	0.9985	>0.01

[a] Degrees of freedom equals 2.

Table II—Amide pK Values Calculated from Plots of Eq. 11 [a]

Silver Sulfonamide	Experimental $pK_2 \pm SD$	r	p
Silver sulfamethazine	7.29 ± 0.06	0.9779	>0.05
Silver sulfamethizole	5.45 ± 0.06	0.9914	>0.01
Silver sulfapyridine	8.46 ± 0.07	0.9288	>0.1

[a] Degrees of freedom equals 2.

$$K_d K_0 = [Ag^+][X^-] = K_s \quad \text{(Eq. 14)}$$

$$\frac{1}{K_2} = \frac{[HX]}{[H_3O^+][X^-]} \quad \text{(Eq. 2)}$$

$$\frac{1}{K_1} = \frac{[H_2X^+]}{[HX][H_3O^+]} \quad \text{(Eq. 3)}$$

$$S = [Ag^+] + [AgX]_{(soln)} \quad \text{(Eq. 15)}$$

$$S = [H_2X^+] + [HX] + [X^-] + [AgX]_{(soln)} \quad \text{(Eq. 16)}$$

Substituting Eq. 13 into Eq. 15 gives:

$$\frac{S}{[Ag^+]} = 1 + \frac{[X^-]}{K_d} \quad \text{(Eq. 17)}$$

If $S/[Ag^+]$ is plotted against $[X^-]$, a linear plot should result with an intercept of 1 and a slope of $1/K_d$.

Equating Eq. 15 with Eq. 16 gives:

$$[Ag^+] = [H_2X^+] + [HX] + [X^-] \quad \text{(Eq. 18)}$$

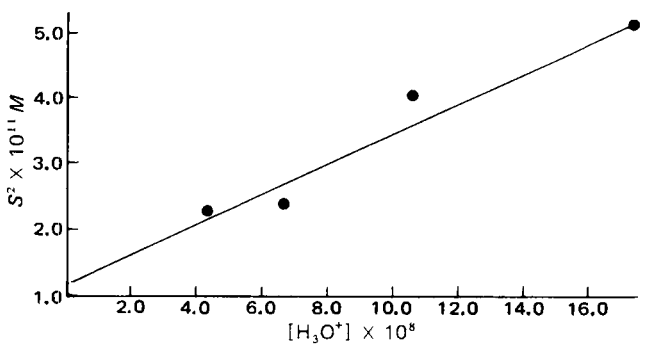


Figure 7—*Equilibrium values of* S^2 versus $[H_3O^+]$ *for silver sulfamethazine in 0.05* M 2-(N-*morpholino*)*propanesulfonic acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*

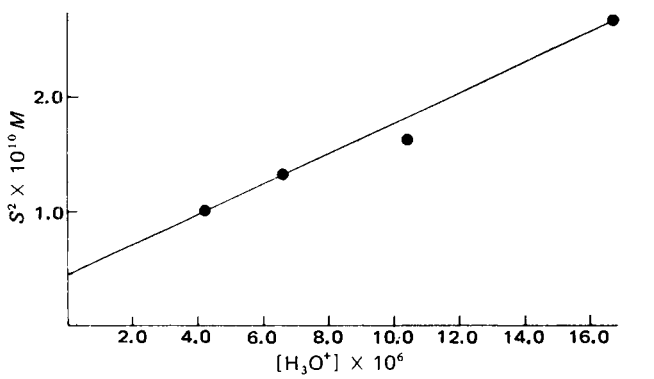


Figure 8—*Equilibrium values of* S^2 versus $[H_3O^+]$ *for silver sulfamethizole in 0.05* M 2-(N-*morpholino*)*propanesulfonic acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*

Table III—Comparison of Total Silver Sulfamethazine Molar Solubility, *S*, Determined by the Method of Known Subtraction with the Molar Concentration of the Silver Ion Determined by Direct Potentiometry on Identical Samples at 25 ± 0.1°, 0.1 *M* Ionic Strength, in Nitric Acid Buffer

	pH 2.186		pH 3.970	
	$S \times 10^3$	$[Ag^+] \times 10^3$	$S \times 10^4$	$[Ag^+] \times 10^4$
	1.194	1.185	0.992	1.028
	1.191	1.185	0.9689	1.003
	1.191	1.171	0.9813	1.041
	1.218	1.194	1.1010	1.170
	1.194	1.157	0.9945	1.053
	1.204	1.166		
Mean	1.198	1.176	1.010	1.059

Table IV—Comparison of Total Silver Sulfamethizole Molar Solubility, *S*, Determined by the Method of Known Subtraction with the Molar Concentration of the Silver Ion Determined by Direct Potentiometry of Identical Samples at 25 ± 0.1°, 0.1 *M* Ionic Strength, in Nitric Acid Buffer

	pH 1.931		pH 2.565	
	$S \times 10^4$	$[Ag^+] \times 10^9$	$S \times 10^4$	$[Ag^+] \times 10^4$
	4.073	4.052	1.477	1.486
	4.077	4.068	1.491	1.486
	4.088	4.068	1.477	1.492
	4.062	4.036	1.459	1.475
	4.120	4.099	1.482	1.486
	4.080	4.021	1.476	1.475
Mean	4.084	4.057	1.477	1.483

Substituting Eqs. 1–3 into Eq. 18 gives:

$$[Ag^+]^2 = \frac{[H_3O^+]^2 K_s}{K_1 K_2} + \frac{[H_3O^+] K_s}{K_2} \quad \text{(Eq. 19)}$$

Equation 19 describes silver sulfapyridine solubility in terms of only the silver- and hydronium-ion concentrations of the saturated solutions. This equation may be simplified by applying the limiting conditions of low (2–4) and high (5–9) pH, as done previously utilizing the sulfapyridine distribution diagram (Fig. 3) calculated with the values of Bell and Roblin (8). When using these approximations, Eq. 19 reduces to Eq. 7 in the low pH range and to Eq. 9 at the higher pH range. Again Eq. 9 is modified to give Eq. 11 to include the complexation of the silver ion with the sulfonic acid buffer.

Figures 4–6 display linear plots of Eq. 9. The pK_1 values for the amino dissociation constants are summarized in Table I. As shown in Figs. 7–9, plots of the equilibrium values of S^2 *versus* $[H_3O^+]$ are linear. The pK_2 values for the amide dissociation constants are summarized in Table II.

The possibility of intact silver sulfonamide in solution in the lower pH range was investigated. The total molar solubility, S, as determined by the method of known subtraction was compared with the molar concentration of the free silver ion, $[Ag^+]$, by direct potentiometric analysis of identical samples under the given experimental conditions. Only the

Table V—Calculation of the Solubility Product of Silver Sulfamethazine from Eq. 21 at 25 ± 0.1° and 0.1 *M* Ionic Strength

pH	f_0	S^2	K_s [a]
2.174	2.551×10^{-6}	1.477×10^{-6}	3.77×10^{-12}
2.421	6.323×10^{-6}	5.897×10^{-7}	3.72×10^{-12}
2.668	1.455×10^{-5}	2.606×10^{-7}	3.79×10^{-12}
2.934	3.265×10^{-5}	1.151×10^{-7}	3.76×10^{-12}
		Mean	$(3.76 \pm 0.03)10^{-12}$

[a] K_s reported as mean ± *SD*.

Table VI—Calculation of the Solubility Product of Silver Sulfamethizole from Eq. 21 at 25 ± 0.1° and 0.1 *M* Ionic Strength

pH	f_0	S^2	K_s [a]
1.965	1.583×10^{-4}	1.733×10^{-7}	2.74×10^{-11}
2.102	2.526×10^{-4}	1.051×10^{-7}	2.65×10^{-11}
2.345	5.448×10^{-4}	4.693×10^{-8}	2.56×10^{-11}
2.598	1.132×10^{-3}	2.508×10^{-8}	2.85×10^{-11}
		Mean	$(2.70 \pm 0.12)10^{-11}$

[a] K_s reported as mean ± *SD*.

Table VII—Comparison of Total Silver Sulfapyridine Molar Solubility, *S*, Determined by the Method of Known Subtraction with the Molar Concentration of the Silver Ion Determined by Direct Potentiometry on Identical Samples at 25 ± 0.1°, 0.1 *M* Ionic Strength, in Nitric Acid Buffer

	pH 2.294		pH 2.486	
	$S \times 10^3$	$[Ag^+] \times 10^3$	$S \times 10^3$	$[Ag^+] \times 10^3$
	8.973	8.143	5.472	7.425
	8.889	8.018	5.514	7.514
	9.030	8.143	5.579	7.632
	9.030	8.143	5.304	7.484
	8.889	8.018	5.514	7.514
			5.660	7.454
Mean	8.962	8.093	5.508	7.504

Table VIII—Comparison of Total Silver Sulfapyridine Molar Solubility, *S*, Determined by the Method of Known Subtraction with the Molar Concentration of the Silver Ion Determined by Direct Potentiometry on Identical Samples at 25 ± 0.1°, 0.1 *M* Ionic Strength, in Nitric Acid Buffer

	pH 2.583		pH 2.848	
	$S \times 10^3$	$[Ag^+] \times 10^3$	$S \times 10^3$	$[Ag^+] \times 10^3$
	5.366	4.540	3.031	2.954
	5.336	4.488	2.974	2.874
	5.356	4.401	2.866	2.774
	5.346	4.505	2.979	2.863
	5.366	4.470	2.788	2.678
	5.356	4.436		
Mean	5.354	4.473	2.928	2.839

extremes of the low pH range were studied for silver sulfamethazine and silver sulfamethizole. For silver sulfapyridine, the entire low pH range was studied.

When tested by one-way analysis of variance, the means displayed in Tables III and IV were found not to be statistically different at the 1% confidence level. Therefore, in the low pH range, silver sulfamethazine and silver sulfamethizole are completely dissociated and the solubility is given by Eqs. 4 and 5. The solubility product is given by Eq. 1. By substituting Eqs. 2 and 3 into Eq. 5, an expression may be derived giving the ratio, f_0, of the sulfonamide anion to the total solubility, where:

$$f_0 = \frac{[X^-]}{S} = \left(1 + \frac{[H_3O^+]}{K_2} + \frac{[H_3O^+]^2}{K_1K_2}\right)^{-1} \quad \text{(Eq. 20)}$$

Combining this expression with Eqs. 1 and 4 gives:

$$K_s = f_0S^2 \quad \text{(Eq. 21)}$$

Application of Eq. 21 to the experimental data at the low pH range for silver sulfamethazine and silver sulfamethizole is given in Tables V and VI, where f_0 was calculated using the experimentally determined dissociation constants.

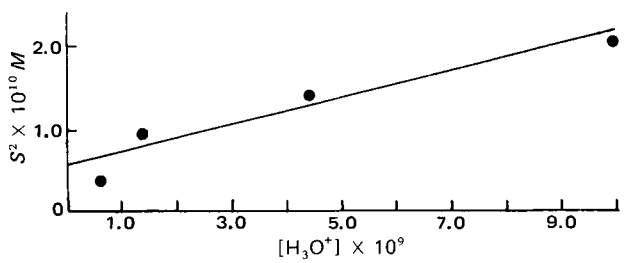


Figure 9—*Equilibrium values of* S^2 versus $[H_3O^+]$ *for silver sulfapyridine in 0.05* M *2-(N-morpholino)propanesulfonic acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*

Plots of the molar solubility of silver sulfamethazine and silver sulfamethizole over the low pH ranges studied are displayed in Figs. 10 and 11.

As shown in Scheme III, the existence of intact silver sulfapyridine in solution was proposed for the low pH nitric acid buffers. This condition is due to the high solubility of silver sulfapyridine at the low pH values studied, pH 2.294–2.583. This solubility increase is due to the effect of K_2 in Eq. 7, because K_2 is inversely proportional to solubility. The total molar solubility as determined by the method of known subtraction was compared with the molar concentration of free silver ion by direct potentiometric analysis on identical samples under the given experimental conditions for every value in the pH range studied.

When tested by one-way analysis of variance, the means displayed in Tables VII and VIII were statistically different at the 1% confidence level. At the average pH of 2.848, the values of free and total silver are not statistically different, because the decreased solubility of silver sulfapyridine does not allow enough silver or sulfonamide ions in solution to ion pair at pH 2.848. Therefore, in the pH 2.294–2.583 range, the solubility of silver sulfapyridine is given by Eq. 15. Figure 12 displays Eq. 17 ($r = 0.6893$, $p > 0.01$, 15 df), where each value represents greater than the average of five or six determinations. The intercept is 0.93 ± 0.078 SD, and the reciprocal of the slope gives (6.828 ± 2.336 SD) 10^{-9} for K_d. The intercept, 0.93, for Eq. 17 compares well with the expected value of 1, further confirming the assumption of intact silver sulfapyridine in solution in the pH range studied.

The solubility product of silver sulfapyridine is defined by Eq. 14. Substituting Eq. 20 into Eq. 14 gives:

$$K_s = f_0[Ag^+]S \quad \text{(Eq. 22)}$$

Application of Eq. 22 to the experimental data at the low pH range for silver sulfapyridine is illustrated in Table IX. The value of K_0 was found

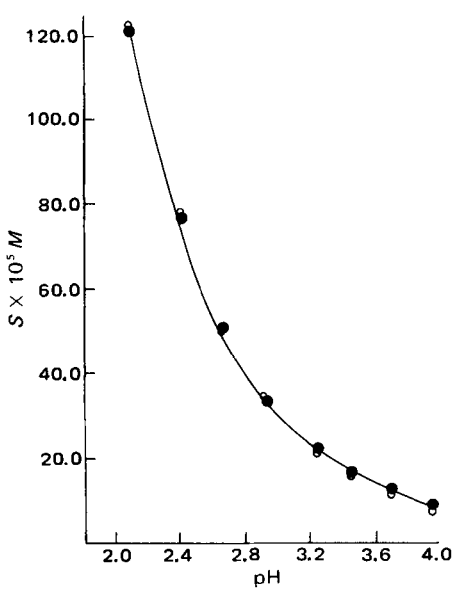


Figure 10—*Molar solubility,* S, *of silver sulfamethazine* versus *pH at 0.1* M *ionic strength and 25 ± 0.1°. Key:* ●, *calculated from Eq. 7; and* ○, *experimental values.*

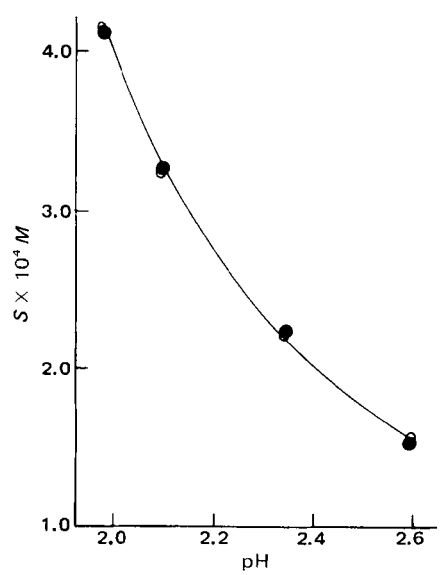


Figure 11—*Molar solubility,* S, *of silver sulfamethizole against pH at 0.1* M *ionic strength and 25 ± 0.1°. Key:* ●, *calculated from Eq. 7; and* ○, *experimental values.*

Table IX—Calculation of the Solubility Product of Silver Sulfapyridine from Eq. 22 at 25 ± 0.1° and 0.1 *M* Ionic Strength

pH	f_0	$[Ag^+]$	S	K_s
2.294	1.418×10^{-7}	8.093×10^{-3}	8.890×10^{-3}	1.02×10^{-11}
2.486	3.066×10^{-7}	5.508×10^{-3}	7.504×10^{-3}	1.27×10^{-11}
2.583	4.480×10^{-7}	4.473×10^{-3}	5.354×10^{-3}	1.07×10^{-11}
2.848	1.184×10^{-6}	2.828×10^{-3}	2.937×10^{-3}	9.80×10^{-12}
			Mean	$(1.09 \pm 0.13)10^{-11}$

[a] K_s reported as mean ± *SD*.

to equal 1.58 ± 0.25 *SD* × 10^{-3} on substitution of the experimentally determined values of K_s and K_d into Eq. 14.

A plot of the molar solubility of silver sulfapyridine over the low pH range is displayed in Fig. 13. The open circles represent experimentally determined values, and the closed circles represent values calculated using Eq. 17 in the form:

$$S = \left(\frac{[H_3O^+]^2 K_s}{K_1 K_2} + \frac{K_s}{K_2}[H_3O^+]\right)^{1/2}\left(1 + \frac{f_0 S}{K_d}\right) \qquad \text{(Eq. 23)}$$

The solubility data obtained may be used to establish a possible correlation between physically measurable properties of the silver salts of certain weak acids and their anti-infective activities. Plots of percent mortality, as reported[8] (9) for burned mice infected with *Pseudomonas aeruginosa*, *versus* log K_s and log K_2 were attempted using data for silver compounds mutually investigated. There was little correlation between percent mortality and log K_s or log K_2 for the silver salts plotted. There was a large disparity in biological effectiveness for silver sulfonamides of similar log K_s values.

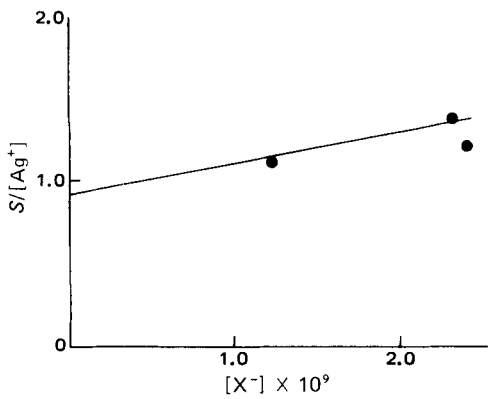


Figure 12—*Equilibrium values of* S/[Ag^+] *against* [X^-] *(sulfapyridine anion) for silver sulfapyridine in nitric acid buffer at 0.1* M *ionic strength and 25 ± 0.1°.*

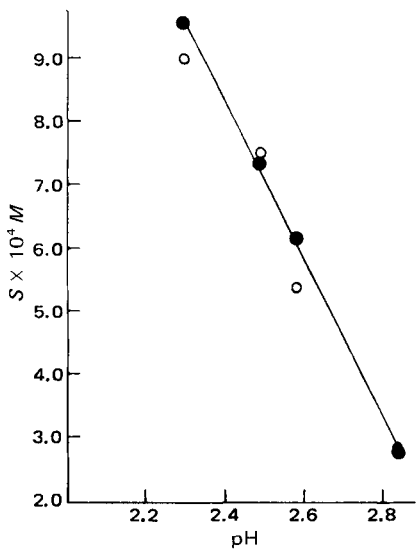


Figure 13—*Molar solubility,* S, *of silver sulfapyridine* versus *pH at 0.1* M *ionic strength and 25 ± 0.1°. Key:* ●, *calculated from Eq. 23; and* ○, *experimental values.*

[8] J. Stanford, Columbia University College of Physicians and Surgeons, New York, N.Y., personal communication, 1976.

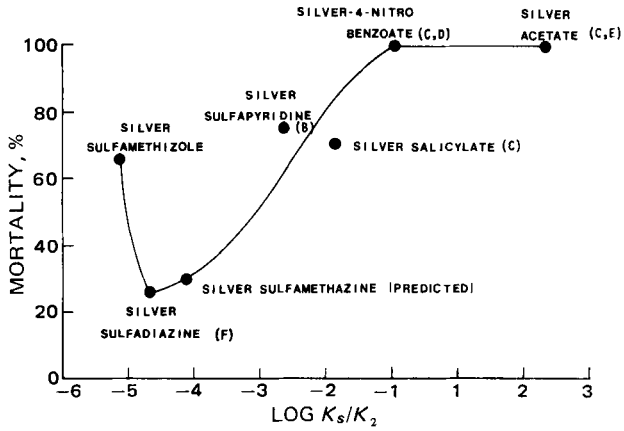


Figure 14—*Percent mortality* versus *log* K_s/K_2. *Percent mortality was taken from Ref. 9, except as indicated. Key: B, percent mortality from J. Stanford (see footnote 8); C,* K_2 *from Ref. 12; D,* K_s *from Ref. 10; E,* K_s *from Ref. 11; and F,* K_s *from Ref. 1.*

However, by combining K_s with K_2, the percent mortality *versus* log K_s/K_2 plot (Fig. 14) reveals a minimum for silver sulfadiazine as compared to other silver salts of weak organic acids. The K_2 values (dissociation constant for monoprotonated acid) and solubility products for silver 4-nitrobenzoate, silver salicylate, and silver acetate are literature values (10–12). The K_2 value for silver sulfadiazine was determined previously (1). The percent mortality value for silver sulfamethazine was predicted using the experimentally determined value for the log K_s/K_2 ratio. For this set of data, the efficacy of silver sulfadiazine in the treatment of burn wound sepsis apparently is directly related to its unique physical–chemical properties, where the dissociation and solubility are involved in providing the most favorable concentration of the silver ion for anti-infective activity.

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