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Auke Bult and Huub B. Klasen

The Characterization of the Silver Compounds of Some Sulfanilamide Derivatives

Laboratory for Pharmaceutical and Analytical Chemistry, State University of Groningen, Groningen, The Netherlands.
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The structures of 1 : 1 compounds of silver with twelve sulfanilamide derivatives are studied. In the compounds with sulfadimethoxine and sulfafenazole the silver ion is coordinated to the deprotonated amido nitrogen (amido-Ag structure). In the compounds with sulfadimidine, sulfamerazine, sulfamethoxazole, sulfamethoxydiazine, sulfamethoxy-pyrazine, sulfamethoxy-pyridazine, sulfamethylthiadiazole, sulfamoxol, sulfisomidine and sulfisoxazole the silver ion is coordinated to the nitrogen which is attached to the atom in the substituent (imido-Ag structure). In the compounds with sulfamerazine and sulfamethoxy-pyrazine the aromatic amine group is probably involved in coordination. The findings are discussed in relation to the results of a preliminary study on sulfadiazine silver. This silver compound is exceptional among the silver sulfanilamides because of its amido-Ag structure. There are indications that sulfadiazine silver has a high formation constant as compared with the other silver sulfanilamides.

Die Charakterisierung der Silber-Verbindungen einiger Sulfanilamid-Derivate

Die Strukturen von 1 : 1-Verbindungen des Silbers mit 12 Sulfanilamid-Derivaten werden untersucht. Im Sulfadimethoxin und Sulfafenazol ist das Silberion mit dem deprotonierten Amid-Stickstoff koordiniert (Amid-Ag-Struktur). Im Sulfadimidin, Sulfamerazin, Sulfamethoxazol, Sulfamethoxydiazin, Sulfamethoxy-pyrazin, Sulfamethoxy-pyridazin, Sulfamethylthiadiazol, Sulfamoxol, Sulfisomidin und Sulfisoxazol ist das Silberion mit dem Stickstoff im Substituenten R¹ koordiniert (Imid-Ag-Struktur). Im Sulfamerazin und Sulfamethoxy-pyrazin ist die aromatische Aminogruppe wahrscheinlich an der Koordination beteiligt.

Die Untersuchungsergebnisse werden bezugnehmend auf eine vorläufige Veröffentlichung über das Silber-Sulfadiazin diskutiert. Silber-Sulfadiazin stellt wegen seiner besonderen Struktur (Amid-Silberstruktur) eine Ausnahme unter den Silber-Sulfanilamiden dar. Es gibt Anzeichen dafür, daß Silber-Sulfadiazin eine besonders hohe Bildungskonstante im Vergleich zu den anderen Silber-Sulfanilamiden hat.

Silver sulfadiazine was reported to be particularly efficacious as a topical antibacterial agent for the control of *Pseudomonas* infection in burns¹). The mode of antibacterial action is different from that of sulfanilamides, because the drug is not antagonized in vitro by aminobenzoic acid. In binding studies using radioactive silver sulfadiazine prepared from radioactive ¹¹⁰Ag- and

1 Ch. L. Fox Jr., B. W. Rappole and W. Stanford, Surg. Gynecol. Obstet. 128, 1021 (1969).

^{35}S -tracers, the silver ion was found to bind to the *Pseudomonas* cells. No cellular binding of sulfadiazine was detected^{2,3}). The binding of silver to bacterial desoxyribonucleic acid was proposed as being important for inhibiting microbial growth. In another report, silver sulfadiazine was said to bind to cell membranes rather than to interact with cellular desoxyribonucleic acid⁴). Thus the role of the sulfadiazine moiety is unclear. One proposal suggests that sulfadiazine localizes the action of the drug to the microbial cells²). The sulfadiazine moiety as compared with a wide number of other sulfanilamides and related compounds offer definite advantages in treatment of burn infection. The unique property of silver sulfadiazine seems to be its moderate initial dissociation followed by a continued release of silver, over time. Most of the other silver compounds dissociate completely with rapid removal of all silver and binding of the silver to wound components or else dissociate only slightly without appreciable release of silver³).

The aims of this investigation were to obtain insight into the structures of the silver compounds of a number of sulfanilamide derivatives and to relate the results to the known structure of silver sulfadiazine. The structure is, among other physico-chemical properties, one of the factors determining the release of silver from these compounds and thus contributes to the different biological activity of the compounds. In table 1 the spectroscopic and conductivity data of the silver compounds are summarized.

Table 1: *The conductivity and spectroscopic data of the silver sulfanilamide derivatives*

no.	compound	$\Lambda_M(\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mole}^{-1})^a$			$\nu^*(\text{S-O})^b$ in cm^{-1}		$\Delta\nu(\text{N-H})$ in cm^{-1}
		aceto-nitrile	DMF	DMSO	R ² =H	R ² =Ag	
1	silver sulfadimethoxine	—	1.9	8.1	1240	1180	— 5
2	silver sulfafenazole · 1H ₂ O	—	4.8	22.0	1229	1177	—
3	silver sulfamerazine	—	—	—	1243	1193	— 85
4	silver sulfadimidine	—	2	6.5	1233	1195	+ 5
5	silver sulfamethoxydiazine	—	—	9.0	1222	1197	— 25
6	silver sulfamethoxypyrazine	54.5	19.0	19.0	1230	1206	—135
7	silver sulfamethoxazole	—	1.60	7.8	1228	1204	— 10
8	silver sulfisoxazole	—	—	22.5	1248	1212	— 35
9	silver sulfisomidine	—	—	8.8	1197	1192	— 5
10	silver sulfamethoxypyridazine	—	0.8	6.8	1218	1209	— 10
11	silver sulfamethylthiadiazole	—	9.5	12.9	1213	1207	+ 5
12	silver sulfamoxol	—	0.7	7.7	1202	1199	— 10

^aConcentration: 1×10^{-3} mole. The calculations of Λ_M are based on the assumed composition $[\text{AgL}_2]\text{Ag}$. Standard ranges of 1 : 1 electrolyte: acetonitrile 120–160, DMF 65–90, DMSO 23–42⁶). The missing values are due to insolubility of the compounds.

- 2 S. M. Modak and Ch. L. Fox Jr., *Biochem. Pharmacol.* 22, 2391 (1973).
- 3 Ch. L. Fox Jr. and S. M. Modak, *Antimicrob. Agents Chemother.* 6, 582 (1974).
- 4 J. C. Ballin, *J. Am. Med. Assoc.* 230, 1184 (1974).
- 5 M. S. Wyszor, *Chemotherapy* 21, 284 (1975).
- 6 W. J. Geary, *Coord. Chem. Rev.* 7, 81 (1971).

^bThe weighted average value of the symmetric and asymmetric ν (S-O) of SO₂.

$${}^c \Delta \nu (\overline{\text{N-H}}) = \nu (\overline{\text{N-H}})_{R^2} - \text{Ag} - \nu (\overline{\text{N-H}})_{R^2} = \text{H};$$

$\nu (\overline{\text{N-H}})$: the average value of the symmetric and asymmetric ν (N-H) of ⁴NH₂.

The values of ν^* (S-O) are the weighted average values of the symmetric and asymmetric ν (S-O) of the sulfanilamides and their silver compounds.

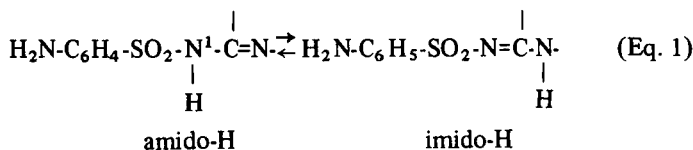
$$\left(\nu^* (\text{S-O}) = \sqrt{\frac{\nu (\text{S-O})_{\text{sym.}}^2 + \nu (\text{S-O})_{\text{assym.}}^2}{2}} \right)$$

Table 2 summarizes the elemental analyses of the compounds. All compounds have a 1 : 1 composition.

Table 2: Analytical data of the silver sulfanilamide derivatives

compound	Ag		C		H		N		S	
	calc.	found	calc.	found	calc.	found	calc.	found	calc.	found
1	25.86	26.0	34.53	34.4	3.14	3.0	13.43	13.3	7.69	7.7
2	24.56	23.8	40.98	41.7	3.41	3.4	12.75	12.6	7.30	6.9
3	29.06	28.6	35.57	35.4	2.99	2.9	15.10	14.9	8.64	8.5
4	28.01	28.1	37.40	37.2	3.40	3.3	14.55	14.7	8.32	8.2
5	27.86	27.6	34.10	34.3	2.86	2.9	14.48	14.5	8.28	8.3
6	27.86	27.7	34.10	34.2	2.86	2.8	14.48	14.6	8.28	8.3
7	29.95	29.4	33.33	33.8	2.80	2.8	11.69	12.0	8.90	9.0
8	28.83	28.8	35.29	34.9	3.23	3.2	11.23	10.9	8.57	8.4
9	28.01	28.2	37.40	37.1	3.40	3.3	14.55	14.4	8.32	8.3
10	27.86	27.3	34.10	33.2	2.86	2.7	14.48	14.2	8.28	8.1
11	28.60	28.4	28.64	27.8	2.40	2.3	14.86	14.9	17.0	16.2
12	28.83	28.3	35.29	33.8	3.23	3.0	11.23	10.8	8.57	8.2

From the excellent IR studies on the amido-H/imido-H tautomerism of sulfanilamides (Eq.1) it is known that the value of ν^* (S-O) is



indicative of the tautomeric form present in the solid state (KBr): amido-H: 1228–1256 cm⁻¹, imido-H: 1198–1206 cm⁻¹ ^{7,8}). The sulfanilamides 1–8 have the

7 P. G. de Benedetti, A. Rastelli, A. Albasini, M. Melegari and G. Vampa, Atti. Soc. Nat. Mat. Modena, 105, 73 (1974).

8 A. Rastelli, P. G. de Benedetti, A. Albasini, G. Vampa and M. Melegari, Farmaco, Ed. Sci. 29, 654 (1974).

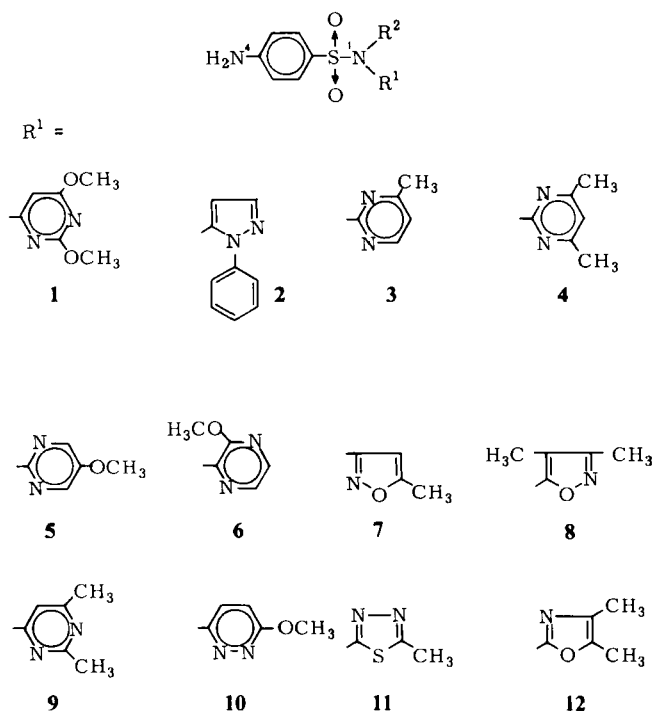
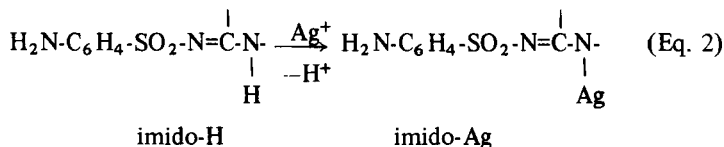


Fig. 1: Structure formulas of the sulfanilamides; R² = H or Ag.

amido-H form and 9–12 the imido-H form, the tautomeric forms of 5 and 10 are somewhat uncertain, a further study on this subject is in progress.

The formation of a silver compound is based on the substitution of the amido or imido hydrogen, respectively by silver.

The substitution of the imido hydrogen by silver (Eq. 2) will cause only small changes in the electronic structure of SO₂ and therefore ν* (S-O) will be nearly unaffected.



The silver compounds 9–12 meet this condition. Upon substitution ν* (S-O) shifts between –3 and –9 cm⁻¹ and the value of ν* (S-O) for these silver compounds coincide with the value range of imido-H. The ν* (S-O) values of the silver compounds 3–8 belong to the same value range as the silver compounds discussed before and this strongly indicates the same type of coordination

e.g. imido-Ag. The substitution reaction can be described by amido-H \rightarrow imido-Ag. The ν^* (S-O) values of the silver compounds of **1** and **2** are lower and belong to the value range for amido-Ag found in a preliminary study (1171–1178 cm^{-1})⁹. In this study the silver compounds of sulfonamides including some sulfanilamides (sulfadiazine, sulfathiazol, sulfanilamide) were studied. Now the substitution reaction is amido-H \rightarrow amido-Ag. The lower values of ν^* (S-O) can be explained by the close proximity of the silver atom situated at N¹. The lowering may be supported by a S-O \cdots Ag interaction. Such a rather weak interaction is found for instance with silver sulfadiazine¹⁰.

The amido-Ag structure of **1** is striking because the silver compounds **3–6**, **9** and **10** with similar structures to the parent compounds have an imido-Ag structure. It is possible that steric hindrance plays a role here. In the silver compound of **2** the most suitable donor atom is occupied by phenyl.

Considering the entire group of sulfanilamides the formation of silver compounds with an imido-Ag structure seems to be preferred. The amido-Ag structure of silver sulfadiazine as shown by X-ray analysis¹⁰ is therefore unexpected and an exceptional case.

It is known that silver(I) prefers the formation of two and four coordinate complexes with linear and tetrahedral geometry respectively¹¹.

This implies for a 1 : 1 complex the presence of two and four donor atoms per ligand molecule respectively. If we suppose linear coordination for the compounds discussed previously then a second donor atom per sulfanilamide is needed. The potential donor atoms left are ⁴NH₂, O of SO₂ and in most cases one or more donor atoms in the substituent R¹. In favourable conditions the involvement of ⁴NH₂ in coordination can be derived from the IR spectra. It is known that metal ion coordination with an amine group results in lowering of ν (N-H). The complicating factor in the case of sulfanilamides is that in the solid state the aromatic amine group is involved in hydrogen bonding and this also results in lowering of ν (N-H). The results of the preliminary study⁹ indicate that coordination causes a shift of the average ν (N-H) of ⁴NH₂ of about -50 cm^{-1} and more: $\Delta\nu$ (N-H). Probably, as can be seen from table 1 the aromatic amine groups of compounds **3** and **6** are involved in coordination. The shift of compound **2** is not observable because of strong deformation of the absorption bands.

The second donor site of the remaining silver compounds is most probably situated at substituent R¹. R¹ of the compounds **7**, **8** and **12** however, does not have a suitable donor atom left (only ether O). In these compounds with the imido-Ag structure only ¹N seems to be available for coordination.

Because of the linear structure (and also in the case of tetrahedral geometry) the silver compounds are polymers. This property is responsible for the insolubility of

9 A. Bult and H. B. Klasen, *J. Pharm. Sci.* **67**, 284 (1978).

10 D. S. Cook and M. F. Turner, *J. Chem. Soc., Perkin II* **1975**, 1021.

11 F. A. Cotton and G. Wilkinson, „Advanced Inorganic Chemistry”, 3rd. ed., p. 1044, Interscience Publishers, New York 1972.

the compounds in nearly all solvents. All compounds but **3** dissolve to some extent in DMSO. This solvent has strong dissociative and solvolytic effects.

The conductivity data given in table 1 show that all compounds except one are neutral and non-conducting. Only **6** has conducting properties but the values of Λ_M are rather low for a 1 : 1 electrolyte of the composition $[\text{AgL}_2]\text{Ag}$ (L = anion of the sulfanilamide).

The neutral complexes have rather variable Λ_M values in DMSO (theoretical prediction $\Lambda_M \approx 0$). This conductivity is caused by the partial dissociation of the compound: $(\text{AgL})_n \rightleftharpoons n\text{Ag}^+ + n\text{L}^-$. The variation of Λ_M is related to the degree of dissociation and the value of Λ_M is an indication of that degree. The stability of the silver sulfanilamide compound decreases with the increase of the Λ_M value. Comparison of the Λ_M value of silver sulfadiazine (2.2)⁹ with the Λ_M values mentioned in table 1 demonstrates that this value is rather low. This indicates a high formation constant for silver sulfadiazine in comparison with all other silver sulfanilamides.

The UV spectra of the silver compounds, as far as soluble, gave little information. The spectra resemble these of the parent compounds.

Thus it can be concluded that the imido-Ag structure is common structural feature of silver sulfanilamides. The formation of silver compounds with an amido-Ag structure occurs in cases where the formation of an imido-Ag structure is more or less unfavourable. The exceptional position of silver sulfadiazine among the silver sulfanilamides is due to the presence of its unexpected amido-Ag structure. Also there are indications that this compound has a relatively high formation constant. The stability of these compounds needs further research.

Another useful field of investigation is the estimation of the crystal structure of these compounds (especially the geometry of the coordinated silver). The (polymeric) structure is an important factor in the release of silver. The results of this investigation will be used as basis for the development of other silver sulfadiazine like compounds.

The authors are indebted to Dr. A.S. Horn and Mrs. A. Gerbrands for their help in preparing the manuscript.

Experimental

Reagents and chemicals

All chemicals used were of analytical or reagent grade. The sulfanilamides were supplied commercially or isolated from commercial available tablets (7 supplied by Hoffmann-La Roche B.V., Holland; 12 supplied by Nordmark-Werke GmbH, Hamburg, Germany).

Equipment and analyses

IR spectra: Beckman Acculab 2 (KBr, Nujol); *UV spectra:* Perkin Elmer 124 (methanol); *conductivity measurements:* Radiometer conductivity meter, type CDM^{2d} with a conductivity cell type CDC 104.

The silver was analyzed by *Volhard* titration after decomposition of the compound with 65 % nitric acid. The elemental analyses were performed by the Analytical Department of the Chemical Laboratories, University of Groningen.

Synthesis of silver sulfanilamides

0.03 mole of the sulfanilamide were dissolved in a mixture of 30 ml of 1.0 N NaOH and 70 ml of water, with gentle heating. After dilution of the solution with water to 300 ml a solution of 0.03 mole of silver nitrate in 100 ml of water was added dropwise with stirring. After 1 hr. the white precipitate was separated, washed with water and dried at 120° C.

The synthesis of a silver compound with sulfaganidine failed.

Address: Dr. A. Bult, 9713 AW, Ant. Deusinglaan 2, Groningen, The Netherlands. [Ph 929]

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Richard Neidlein*, Karl F. Cepera¹⁾ und Alfred Hotzel

Spektroskopische Untersuchungen an Thia-pseudophenalenonen²⁾³⁾

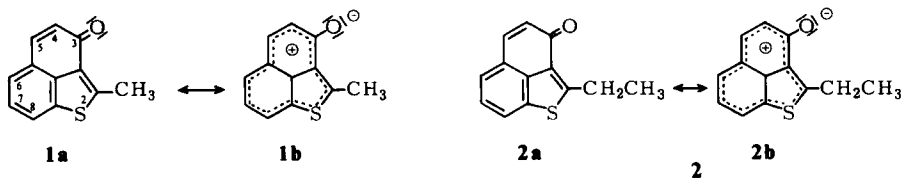
Aus dem Pharmazeutisch-Chemischen Institut der Universitäten Karlsruhe (TH) und Heidelberg. (Eingegangen am 23. November 1977)

Es werden die ¹H-NMR-, IR- und Massenspektren der Thiapseudophenalenone 1, 2 und 5 diskutiert.

Spectroscopic Studies of Thiapseudophenalenones

The ¹H-NMR, infrared and mass spectra of the thiapseudophenalenones 1, 2 and 5 are discussed

Die beiden Thia-pseudophenalenone 2-Methyl-3-oxo-3H-naphtho(1.8-bc)thiophen (1) und 1-Äthyl-3-oxo-3H-naphtho(1.8-bc)thiophen (2) sind in einfacher Weise zugänglich¹⁾. Im Folgenden soll über die Ergebnisse der physikalisch-chemischen und spektroskopischen Messungen berichtet werden.



* Herrn Professor Dr. O.E. Schultz mit den besten Wünschen zum 70. Geburtstag gewidmet.

1 Dissertation K.F. Cepera, Heidelberg 1977.

2 26. Mitt. „Heterocyclische 12- π - und 14- π -Systeme“.

3 Teilweise vorgetragen beim 26-th International Congress of Pure and Applied Chemistry (IUPAC), Tokyo/Japan, 4. bis 10. September 1977.