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Ionic Silver Compounds of Sulfanilamide Derivatives and Related Substances

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Coordination of Ag(I) with the anion of a sulfanilamide (L) usually produces a non-conducting compound of the composition AgL. However, with sulfamethoxy-pyrazine and sulfacetamide an ionic compound $[AgL_2]Ag$ is formed. Model substances demonstrate that the presence of one suitable donor atom (the deprotonated acidic N) results in the formation of ionic compounds of type $[AgL_2]Na$ and $[AgL_2]Ag$. The presence of an aromatic NH_2 group as the second donor group results in the formation of only one type, namely $[AgL_2]Ag$. The silver compounds were studied by the use of conductivity, UV and IR measurements.

Ionische Silber-Verbindungen von Sulfanilamid-Derivaten und verwandten Stoffen.

Die Koordination von Ag(I) mit dem Anion eines Sulfanilamids (L) führt meistens zu einer nichtleitfähigen Verbindung der Zusammensetzung AgL. Mit Sulfamethoxy-pyrazin und Sulfacetamid bilden sich leitfähige Verbindungen der Zusammensetzung $[AgL_2]Ag$. Modellverbindungen zeigen, daß sich in Anwesenheit eines geeigneten Donoratoms (die deprotonierte Säure N) ionische Verbindungen des Types $[AgL_2]Na$ und $[AgL_2]Ag$ bilden. Die Gegenwart einer aromatischen NH_2 -als zweiter Donorgruppe führt nur zur Bildung eines Typs, nämlich $[AgL_2]Ag$. Von allen Silber-Verbindungen wurde die Leitfähigkeit bestimmt sowie UV- und IR Spektren aufgenommen.

In two preceding studies the preparation and characterization of 22 silver compounds of sulfanilamides and related substances was described^{1,2}. The compounds were non-ionic and had the composition AgL (L = mono-anion of the sulfanilamide HL) with the exception of three compounds (compounds no. 1, 2 and 4 in table 1). These compounds had ionic character and the composition $[AgL_2]Ag$ was proposed. An investigation of the origin of this distinct character is the subject of this study. The results of this investigation may be of value for the design of antibacterial agents from silver sulfanilamide class. The commonly used antibacterial agent in the treatment of extensive burns silver sulfadiazine (Flammazine[®], Philips-Duphar, The Netherlands) has a very low water solubility: 0.2 mg/100 ml³. The study of the relationship between physico-chemical parameters and antibacterial activity of the silver sulfanilamides is in progress.

Table 1: The conductivity and spectroscopic data of the silver compounds.

Composition silver complex	No.	ligand = L	Λ_M ($\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mole}^{-1}$) ^a	DMF	DMSO	ν^* (S-O) ^e in cm^{-1}	ν (C=O) ^e in cm^{-1}
AgL	1	sulfamethoxy-pyrazine ^b	54.5 (32)	19.0 (28)	19.0 (51)	1206	
	2	sulfacetamide ^c	75.6 (45)	33.2 (48)	18.75 (50)	1204	1580
	3	benzenesulfonylacetamide	80.8 (48)	34.3 (50)	16.6 (44)	1206	1585
	4	benzenesulfonamidobenzene ^c	87.4 (52)	36.5 (53)	15.9 (42)	1190	
	5	carbutamide	69.5 (41)	17.9 (26)	10.7 (28)	1206 ^f	1588
	6	tolbutamide	73.8 (44)	27.1 (40)	16.8 (45)	1202 ^f	1587
	7	saccharin	63.4 (37)	25.0 (36)	18.4 (49)	1214	1610/1575
	8	barbiturates ^d	93. (55)	30 (44)	16 (43)		≈ 1570 ^g
[AgL ₂]Na	3a	benzenesulfonylacetamide	174.0 (103)	83.3 (122)	43.7 (116)	1222	1617
	4a	benzenesulfonamidobenzene	189.1 (112)	82.4 (120)	37.3 (98)	1194 ^f	
	6a	tolbutamide	129.8 (77)	78.6 (115)	35.5 (94)	1202	1623
	7a	saccharin	141.1 (83)	81.4 (119)	51.5 (137)	1206	1650/1622
AgNO ₃	8a	barbiturates ^d	95 (56)	46 (67)	19 (51)		≈ 1610 ^g
			169.2	68.5	37.6		

^a Concentration: $1 \cdot 10^{-3}$ mole. The calculations of Λ_M for AgL are based on the assumed composition [AgL₂]Ag. Standard ranges of 1 : 1 electrolyte: acetonitrile: 120–160, DMF: 65–90, DMSO: 23–42^h. The Λ_M values of silver nitrate are also given in the table. The values between brackets are the percentage conductivity related to silver nitrate.

^b Data derived from ²; ^c Data derived from ¹; ^d Data derived from ⁴.

^e The weighted average value of the symmetric and asymmetric ν (S-O) of SO₂ (in KBr).

^f Nujol value is given. ^g Band position of the lowest ν (C=O).

In table 1 the spectroscopic and conductivity data of the investigated silver compounds are summarized. For most ligands two types of complexes were prepared namely compounds of composition AgL and $[\text{AgL}_2]\text{Na}$. L is the deprotonated ligand i. e. the acidic proton is substituted by Ag(I) . The analytical data of the silver compounds not described before are given in table 2.

Table 2: Analytical data of the silver compounds.

com- pound	Ag		C		H		N		S		Na	
	calc.	found	calc.,	found	calc.,	found	calc.,	found	calc.,	found	calc.,	found
3	35.3	34.4	31.4	31.5	2.6	2.7	4.6	4.5	10.5	10.5		
5	28.5	27.7	34.9	34.8	4.3	4.3	11.1	11.2	8.5	8.4		
6	28.6	27.5	38.2	38.6	4.5	4.5	7.4	7.4	8.5	8.5		
7	37.2	36.7	29.0	29.1	1.4	1.4	4.8	4.8	11.1	11.1		
3a	20.5	20.3	36.4	36.8	3.1	3.2	5.3	5.2	12.1	12.1	4.4	3.9
4a	18.1	18.1	48.4	48.2	3.4	3.4	4.7	4.8	10.8	10.7	3.9	3.6
6a	16.1	16.8	43.0	43.1	5.1	5.2	8.4	8.3	9.6	9.4	3.4	3.4
7a	21.8	23.0	33.9	33.0	1.6	1.8	5.7	5.7	13.0	12.7	4.6	4.3

The formation of ionic, conducting Ag(I) compounds is only possible when one suitable donor atom per L (mono-anion) is present as is found with the barbiturates⁴). The composition AgL can be described as $[\text{AgL}_2]\text{Ag}$. As a logical consequence the counter-ion Ag^+ can be substituted by another cation. These we have already described for barbiturate compounds of the type $[\text{AgL}_2]\text{Na}$ ⁴). The same complexing properties that occur with the barbiturates are also found with the ligands forming the compounds **3/3a**, **4/4a**, **6/6a** and **7/7a** (table 1). These ligands also have one suitable donor atom namely the deprotonated N atom. The attempted synthesis of compounds of the type $[\text{AgL}_2]\text{Na}$ was not successful for the ligands **1**, **2** and **5**. These ligands have as a common structural element the presence of an aromatic 4- NH_2 group. Comparison of the ligand pairs **2**, **3** and **5**, **6** which differ in the presence or absence of a NH_2 group, clearly shows the importance of this function in the inhibition of the preparation of the compounds $[\text{AgL}_2]\text{Na}$. The involvement of the NH_2 group in the AgL complex formation with the ligands **1**, **2** and **5** is also demonstrated by their IR spectra. The shift of $\nu(\text{NH}_2)$ indicates a $\text{H}_2\text{N} \leftarrow \text{Ag}$ interaction^{1,2}). These three ligands act as a bidentate.

The presentation of compounds **3a**, **4a**, **6a** and **7a** by $[\text{AgL}_2]\text{Na}$ is supported by their conducting properties. The Λ_M values in the three solvents are in the range of an 1 : 1 electrolyte. The theoretical assumption of a mixture of AgL and NaL is out of the question due to the method of preparation (NaL is soluble in aqueous solution) and their IR spectra (not an addition of AgL and NaL). The presentation of the compounds **3**, **4**, **6** and **7** by $[\text{AgL}_2]\text{Ag}$ instead of AgL is also supported by their conducting properties in the three solvents. The lower Λ_M values as compared with the corresponding $[\text{AgL}_2]\text{Na}$ compounds can be attributed to a smaller ionic mobility of Ag^+ . The shift of $\nu^*(\text{S-O})$ and $\nu(\text{C=O})$ to lower frequencies upon complexation of HL to $[\text{AgL}_2]^{(-)}$ is in agreement with former

observations about the substitution of H in HL by metal ions (Ag, Na, Zn, Co, Cu)^{1,2,4,6,7}. The values of $\nu^*(\text{S-O})$ for $[\text{AgL}_2]\text{Na}$ and $[\text{AgL}_2]\text{Ag}$ are about equal; the $\nu(\text{C=O})$ values of $[\text{AgL}_2]\text{Ag}$ are lower (about 30 to 40 cm^{-1}) as for $[\text{AgL}_2]\text{Na}$ and may indicate a $\text{C=O} \leftarrow \text{Ag}$ interaction. Possibly the counterion Ag^+ interacts with C=O in the solid state.

The remaining problem that requires interpretation is the nature of the silver compounds **1**, **2** and **5**. As previously concluded the ligands are, at least in the solid state, bidentate. In contrast with the AgL compounds reported in the preceding studies^{1,2} these compounds have conducting properties. The values of Λ_M are about equal to the compounds $[\text{AgL}_2]\text{Ag}$ discussed above. This indicates the same ionic structure in solution. There is also a good resemblance between the IR-spectra of the closely related pairs of silver compounds **2-3** and **5-6**. The band positions of $\nu^*(\text{S-O})$ and $\nu(\text{C=O})$ are nearly equal. These facts also indicate a $[\text{AgL}_2]\text{Ag}$ structure in the solid state.

The UV-spectra of $[\text{AgL}_2]\text{Na}$ and $[\text{AgL}_2]\text{Ag}$ are similar or nearly similar as was expected. The band positions are only slightly different from HL but significantly different from L (anion). These findings agree with our former results¹.

The reaction of the ligands with the silver ion discussed so far can be summarized by the following equations:

- a) $\text{Ag}^+ + 2 \text{L}^- \rightarrow [\text{AgL}_2]^-$
- b) $[\text{AgL}_2]^- + \text{Na}^+ \rightarrow [\text{AgL}_2]\text{Na} \downarrow$
- c) $[\text{AgL}_2]^- + \text{Ag}^+ \rightarrow [\text{AgL}_2]\text{Ag} \downarrow$

In the case where $[\text{Ag}]/[\text{L}] \leq 0.5$ the ligands **3**, **4**, **6** and **7** react according to the equations a) and b) and the ligands **1**, **2** and **5** according to the equations a) and c). In the latter case the complex anions $[\text{AgL}_2]^-$ are coupled by Ag^+ via the interaction with the aromatic NH_2 groups. In the case where $[\text{Ag}]/[\text{L}] \approx 1$ all ligands follow the reactions a) and c). Here the "excess" Ag^+ substitutes Na^+ in equation b) in the case of the ligands **3**, **4**, **6** and **7**.

In contrast with the preceding compounds the silver sulfanilamides reported before^{1,2} are formed according to the reaction:

- d) $\text{Ag}^+ + \text{L}^- \rightarrow \text{AgL} \downarrow$

Because of the presence of two or more donor atoms per L the formation of polymeric compounds is likely. This polymerisation has been confirmed with silver sulfadiazine⁸.

It remains unclear why the ligands **1**, **2** and **5** produce conducting silver compounds and the other sulfanilamides non-conducting silver compounds.

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Experimental

Reagents and chemicals

All chemicals used were of analytical grade. The drugs were supplied commercially. The preparation of benzenesulfonamidobenzene was described¹ previously. Benzenesulfonylacetamide was prepared

by condensation of benzenesulfonamide with acetic anhydride in pyridine and recrystallized from an acetone-water mixture mp. 115–117° (lit.: 111–113°C).

Equipment and analyses

IR spectra: Perkin Elmer, model 577 (KBr, Nujol). Other details have been previously described^{1,2}.

Synthesis of the silver compounds

The procedure has been previously described^{1,2}.

Synthesis of silver sodium compounds

0.02 mole of the sodium salt of the sulfonamide or related compound were dissolved in 20 ml of water (or 0.02 mole of the sulfonamide were dissolved in 20 ml of 1 N-NaOH) with gentle heating. To the clear solution was added dropwise with stirring a solution of 0.01 mole of silver nitrate in 20 ml of water.

After 0.5 hr. the white precipitate was separated, washed with a small quantity of water and dried at 105°C.

The attempted synthesis of a silver sodium compound with sulfamethoxypyrazine, sulfacetamide and carbutamide was unsuccessful.

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