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An IR Study of the Structure of New Thiocarboxylic Acid *N*-(1-Arenesulfonamido-2-phenyl-2,2-dichloroethyl- and -2,2,2-trichloroethyl)amides

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Abstract — An IR study of thiocarboxylic acid *N*-(1-arenesulfonamido-2-phenyl-2,2-dichloroethyl- and -2,2,2-trichloroethyl)amides revealed intramolecular hydrogen bonds whose formation is accompanied by electron density delocalization and stabilization of conformations with quasiaromatic rings. Formation of chelate species was confirmed by AM1 calculations.

Among sulfamides exhibiting biological activity, polyfunctional haloalkylamides of sulfonic acids, synthesized by reactions of various nucleophiles with sulfonylimines derived from polyhalo aldehydes [1], have a peculiar steric structure. A combination of functional fragments differing in the steric configuration and of several electron-donor and proton-donor centers in polyfunctional molecules may favor formation of an intramolecular hydrogen bond and stabilization of the resulting chelate quasicyclic structure due to electron density delocalization [2]. A similar effect was observed previously with acetylacetone, thioacetylacetone, vinyl ketones, malonaldehyde, and enol forms of β-diketones, containing O=C–C=C–O–H and related fragments [3–6]. Neutron and X-ray diffraction studies showed that, in structures with intramolecular hydrogen bonds involving double bonds, quasiaromaticity of the chelate structures should be expected (the concept of resonance-assisted hydrogen bonding, RAHB) [2].

Proceeding with studies of the synthetic potential of the electron-deficient azomethine group in sulfonylimines derived from polyhalo aldehydes [1, 7–9], we studied reactions of *N*-(2,2,2-trichloroethylidene)-arenesulfonamides **I** and *N*-(2-phenyl-2,2-dichloroethylidene)arenesulfonamides **II** with thioacetamide and *N*-acetylthiourea. We prepared compounds in which formation of an intramolecular hydrogen bond is stereochemically possible. This allows us to study the mutual influence of conjugation and hydrogen bonding in polyfunctional molecules and to take into account this influence when evaluating the reactivity of sulfonamide derivatives. The hydrogen bonding is responsible for specific physicochemical properties of compounds and their peculiar behavior in chemical reactions; in particular, involvement of an amino group in hydrogen bonding can decrease its reactivity as a nucleophile by a factor of 100 [10].

The reactions were performed in benzene or trichloroethylene. We have found that thioamides react in the amide form to give the products of addition of the NH_2 group across the C=N bond of ethylidenamides **I** and **II**, *N*-(1-arenesulfonamidopolychloroethyl)thioamides **III**–**VI**. The reaction is complete in 5 h. The yield of amides **III**–**VI** is increased by heating of the reaction mixture.

$$ArSO_2N{=}CHCCl_2X + NH_2C(S)R \rightarrow ArSO_2NHCHCCl_2X, \quad \begin{array}{l} \\ | \\ NHC(S)R \end{array}$$

Ia, Ib, IIa, IIb **III**–**VI**

X = Cl, Ar = Ph (**Ia**), 4-ClC_6H_4 (**Ib**©); X = Ph, Ar = Ph (**IIa**), 4-ClC_6H_4 (**IIb**); R = Me, X = Cl, Ar = Ph (**III**); R = Me, X = Ph, Ar = 4-ClC_6H_4 (**IV**); R = NHC(O)Me, X = Cl, Ar = 4-ClC_6H_4 (**V**); R = NHC(O)Me, X = Ph, Ar = Ph (**VI**).

The products of addition of the isothiuronium form of the thioamides to **I** and **II** are not formed under these conditions. The products of simultaneous addition of the NH_2 and SH groups of thioureas to 2 equiv of ethylidenamides **I** and **II** were not obtained either.

Formation of **III**–**VI** was proved by ^{1}H NMR spectroscopy, and their composition was confirmed by elemental analysis (Table 1). In the ^{1}H NMR spectra of **III**–**VI** (in DMSO-d_6), the protons of the SO_2NH–

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Table 1. Yields, melting points, ^{1}H NMR spectra, and elemental analyses of amides **III**–**VI**

Comp. no.	Yield, %	mp, °C	^{1}H NMR spectrum (DMSO-d_6), δ, ppm					
			CH	NH	CH_3	Ar	$J(SO_2NH, CH)$, Hz	J[C(S)NH, CH], Hz
III	78	106–108	6.91 d.d	9.16 d, 10.34 d	2.14 s	7.51–7.82 m	10.0	9.0
IV	88	153–154	6.95 d.d	8.79 d, 10.14 d	2.07 s	7.53, 7.72 (*AA*'*BB*') 7.39–7.66 m	10.0	9.1
V	67	155–156	6.69 d.d	9.65 d, 11.36 d, 11.49 s	2.02 s	7.59, 7.89 (*AA*'*BB*')	10.1	9.7
VI	64	143–144	6.84 d.d	9.00 d, 11.26 d, 11.14 s	1.96 s	7.42–7.79 m	10.0	9.6

Comp. no.	Found, %				Formula	Calculated, %			
	C	Cl	N	S		C	Cl	N	S
III	31.97	28.85	7.51	17.88	$C_{10}H_{11}Cl_3N_2O_2S_2$	33.21	29.41	7.75	17.73
IV	43.12	24.11	6.15	14.90	$C_{16}H_{15}Cl_3N_2O_2S_2$	43.90	24.29	6.40	14.65
V	29.54	31.92	9.31	14.83	$C_{11}H_{11}Cl_4N_3O_3S_2$	30.09	32.29	9.57	14.60
VI	45.60	15.18	9.22	14.61	$C_{17}H_{17}Cl_2N_3O_3S_2$	45.74	15.89	9.41	14.36

CHNHC=S fragment give a characteristic group of signals: a doublet of doublets in the range 6.69–6.95 ppm (CH) and two doublets (SO_2NH and NHC=S) of equal intensity in lower field (Table 1). Also, the ^{1}H NMR spectra of **III**–**VI** contain proton signals of aromatic rings and methyl groups with the relative integral intensities consistent with the suggested structures.

In IR study of structural features of **III**–**VI**, we proceeded from the fact that these compounds combine amide, thioamide, and sulfonamide fragments. Whereas amide and thioamide fragments are characterized by so-called "amide conjugation" between the lone electron pair of the nitrogen atom and the π system of the carbonyl and thiocarbonyl groups, the conjugation in the SO_2N group, according to the IR spectra and dipole moments, is insignificant or absent at all [11]. However, the extent of participation of pharmacophoric sulfonamide group in intramolecular interactions in biologically active compounds is very important [1, 12, 13].

Comparative analysis of the IR spectra of **III**–**VI** and of amides and thioamides modeling their molecular fragments shows that the ν(NH), ν(C=O), and [ν(C=S)] frequencies in **III**–**VI** (Table 2) are appreciably lower than those in usual N-substituted amides [ν(NH) 3440–3470, ν(C=O) 1680–1700 cm^{-1}], thioamides [ν(NH) 3440–3400 cm^{-1}], and sulfonamides [ν(NH) 3409 cm^{-1}], suggesting that these groups are involved in hydrogen bonding [14–17]. The lack of the concentration dependence of the frequencies and intensities of these bands indicates that the hydrogen bonds in **III**–**VI** are intramolecular.

In the IR spectra of **III**–**VI**, the intensity ratio of the ν(C=O) [ν(C=S)], amide II, and amide III bands differs from that characteristic of amides. In particular, the amide II and amide III bands are very weak relative to the carbonyl and thiocarbonyl bands, whereas in the IR spectra of usual amides and thioamides these bands have comparable intensity [14–17]. There are also some other differences in the spectra of **III**–**VI** and related model compounds. Furthermore, appreciable differences are observed within the series **III**–**VI**: In the spectra of more complex compounds **V** and **VI**, there are additional bands of variable intensity at 1500 and 1640 cm^{-1}.

As the solutions of **III**–**VI** are heated to 100°C, new stretching vibration bands of free NH, C=O, and C=S groups appear (Table 2), suggesting cleavage of hydrogen bonds. Interaction of arenesulfonamides with DMSO and THF is also accompanied by cleavage of H bonds and simultaneous formation of new intermolecular complexes with the ν(NH) bands at 3050–3200 cm^{-1}. Under these conditions, the intensity ratio of the ν(C=O) [ν(C=S)], amide II, and amide III bands becomes typical of amides and thio-

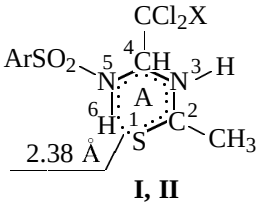
Table 2. Absorption frequencies (ν, cm^{-1}) of the main functional groups in the IR spectra ($C_2H_2Cl_4$) of arenesulfonamides **I**–**IV** at 20°C (data for 100°C in parentheses)

Comp. no.	ν(NH)	Amide II	Amide III	ν(C=S) or ν(C=O)
I	3382, 3350 (3400, 3420)	1550 (1505)	1280 (1300)	1210 (1240)
II	3375, 3340 (3405, 3420)	1530 (1500)	1290 (1310)	1200 (1235)
III	3390, 3340, 3310 (3402, 3420, 3450)	1530–1550 (1510)	1260 (1300)	1660 (1700)
IV	3390, 3350, 3310 (3400, 3420–3440)	1530–1560 (1510)	1270 (1310)	1660 (1700)

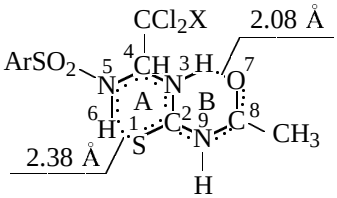
amides, and the absorption at 1500 and 1640 cm^{-1} in the IR spectra of **V** and **VI** fully disappears.

To explain the unusual spectroscopic behavior, determine the molecular and electronic structure, and reveal major conformations of **III**–**VI**, we performed AM1 calculations with full geometry optimization, based on data from the Cambridge Structural Database [18, 19]. The calculations showed that the thermodynamically preferable forms of **III**–**VI** are arenesulfonamide forms with an intramolecular hydrogen bond and *Z* conformation of the thioamide and amide fragments [with respect to the relative arrangement of the oxygen (sulfur) atom of the carbonyl (thiocarbonyl) group and NH hydrogen atom].

According to the calculations, the distance between the H-bonded atoms is considerably shorter than the sum of the van der Waals radii, which is characteristic of chelate forms [20]. The hydrogen bond energy in **III** and **IV** is 3.7 and 4.0 kcal mol^{-1}, respectively. For **V** and **VI**, the energy of each of the two types of intramolecular hydrogen bonds, which are not complementary, was estimated from successive structure calculations as the energy boundary between the conformers with the hydrogen bond and without it; we obtained for **V** and **VI** the values of 3.6 and 4.05 (ring A), and 4.6 and 4.8 kcal mol^{-1} (ring B), respectively.



I, II



III, IV

Comparison of the torsion angles shows that H-bonded chelate ring B is virtually planar, whereas in pseudorings A the NH group of the sulfonamide moiety deviates from the plane of the other atoms (Table 3). The internal bond angles in the H-bonded rings in **III**–**VI** are smaller than those in the corresponding open conformations and in common amides and thioamides. For example, the mean (S)OCN bond angles in amides and thioamides are 124.7° and 122.9°, respectively, whereas the related angles in **III**–**VI** are 122.0° and 120.7°, respectively. The increased N^5–H^6 and N^3–H bond lengths in **III**–**VI** (1.04 Å) and C^8=O^7 bond lengths in **V** and **VI** (1.245 Å) also indicate that these atoms participate in a hydrogen bond (Table 3), whereas the bond length in a free NH group is 0.988 Å according to our calculations and 0.99–1.009 Å according to [19].

Comparative analysis of the bond π orders (P^{π}) for the conformations of **III**–**VI** with the hydrogen bond and without it revealed their appreciable alternation. This may be due to formation of quasiaromatic structures as a result of electron density delocalization in the heteroconjugated system. Variation of P^{π} is especially significant in pseudorings B of bicyclic systems of **V** and **VI**, which is quite understandable, since a planar H-bonded cross-conjugated system is formed. The π order of the C^2–N^3 bond changes most significantly upon H bonding, suggesting transformation of the amide conjugation. This apparently accounts for an unusual intensity ratio of the bands in the IR spectra of **III**–**VI** and for appearance of additional absorption in the spectra of **V** and **VI**, characterizing the whole cross-conjugated system with delocalized bonds. The unexpected results are somewhat increased P^{π} of the S^1–N^2 bond and decreased order of the S=O bond (Table 4). This indicates that the sulfonamide fragment is sensitive to the "electronic pressure" [21] from the chelate group, causing strengthening of the S–N bond.

Thus, the revealed intramolecular hydrogen bonds stabilize the forms of **III**–**VI** in which the S=C–N–H and O=C–N–H fragments have the *Z* conformation. The spectroscopic and quantum-chemical parameters

Table 3. Geometric parameters of conformations of **III**–**VI** with intramolecular hydrogen bonds, according to AM1 calculations

Parameter	III	IV	V	VI
		Angle, deg		
$S^1C^2N^3C^4$	3.7	2.3	5.5	6.0
$C^2N^3C^4N^5$	35.3	36.3	38.5	39.9
$N^3C^4N^5H^6$	60.7	60.1	62.1	61.7
$O^7C^8N^9C^2$	–	–	0.1	0.2
$C^8N^9C^2N^3$	–	–	1.9	2.3
$C^9C^2N^3C^4$	–	–	4.1	4.9
		Bond length, Å		
$S^1=C^2$	1.590	1.590	1.627	1.163
$C^8=O^7$	–	–	1.245	1.245
$N^5–H^6$	1.010	1.010	1.020	1.020
$N^3–H$	0.988	0.988	1.040	1.040
$C^2–N^3$	1.366	1.366	1.371	1.372

of **III**–**VI** adequately reflect formation of quasiaromatic forms with fairly strong hydrogen bonds and strong delocalization of the electron density, demonstrating synergism in the effects of conjugation and hydrogen bonding.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer. Samples of **III**–**VI** were prepared as KBr pellets and as 0.04–0.005 M solutions in $CHCl_3$ and $C_2H_2Cl_4$; such concentrations exclude association of the molecules. Measurements at variable temperature were performed with a Carl Zeiss cell equipped with a calibrated thermocouple. The measurement scale in the amide I–amide III absorption range was 100/100 cm^{-1} at the measurement time of 22 min and resolution of 1 cm^{-1}. In the ν(NH) range, the resolution was 2 cm^{-1}. The ^1H NMR spectra were recorded on a Bruker DPX-400 spectrometer (400.13 MHz) in DMSO-d_6. The quantum-chemical calculations were performed in the RHF approximation by the AM1 method with full geometry optimization [17].

***N*-(1-Benzenesulfonamido-2,2,2-trichloroethyl)-thioacetamide III.** A 2.87-g portion of **Ia** [8] was stirred with 2.25 g of thioacetamide in 10–15 ml of dry benzene for 5 h at 50°C under argon. The precipitate was filtered off, washed with 50 ml of water, and dried. Yield of amide **III** 2.82 g (78%).

***N*-[1-(4-Chlorobenzene)sulfonamido-2-phenyl-2,2-dichloroethyl]thioacetamide IV** was prepared similarly from 1.81 g of **IIb** [9] and 0.75 g of thioacetamide in 1.93 g yield (88%).

***N*-[1-(4-Chlorobenzene)sulfonamido-2,2,2-trichloroethyl]-*N'*-acetylthiourea V.** A 0.59-g portion of acetylthiourea was added to a solution of 1.61 g of **Ib** [8] in trichloroethylene. The mixture was stirred with heating to 70–80°C for 1 h and then allowed to stand at room temperature for a day. The precipitate was filtered off and washed with CCl_4. Yield of **V** 1.47 g (67%).

***N*-(1-Benzenesulfonamido-2-phenyl-2,2-dichloroethyl)-*N'*-acetylthiourea VI.** A mixture of 1.64 g of **IIa** [9] and 0.59 g of acetylthiourea in 10 ml of benzene was refluxed with stirring for 4 h, after which the solvent was distilled off. The residue was recrystallized from ethanol. Yield of **VI** 1.43 g (64%).

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Table 4. Bond π orders (P^{π}) in (a) H-bonded and (b) open (without hydrogen bonds) conformations of arenesulfonamides **III**–**VI**, calculated by the AM1 method

Bond	III		IV		V		VI	
	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
$N^5–XC4$	0.078	0.061	0.075	0.061	0.080	0.063	0.075	0.052
$C^4–N^3$	0.058	0.062	0.051	0.060	0.058	0.068	0.051	0.062
$N^3–C^2$	0.292	0.280	0.310	0.280	0.304	0.239	0.320	0.245
$C^2=S^1$	0.694	0.704	0.684	0.701	0.560	0.584	0.543	0.580
$C^2–N^9$	–	–	–	–	0.181	0.238	0.178	0.235
$N^9–C^8$	–	–	–	–	0.197	0.157	0.202	0.162
$S^1–N^2$	0.075	0.070	0.079	0.073	0.077	0.071	0.079	0.073
S=O	0.354	0.380	0.352	0.370	0.356	0.377	0.358	0.380

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