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The Fine Structure of Sulfanilamide

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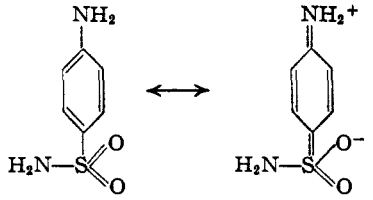
The physical properties of sulfanilamide (its solubility, low in non-polar, and high in polar solvents, its absorption spectrum,[1] its high electric moment[2]) may be explained by the assumption of a charged structure contributing to the actual state of the molecule. The possibility that S=O double bonds participate in such resonating systems as



has, however, been doubted occasionally on the strength of the hypothesis that S=O is not a real double bond, but a "semipolar" bond system.[3]

A decision appeared possible by the application of a method first used by Birtles and Hampson[4] in the case of 4-nitroaniline. If the high dipole moment of sulfanilamide is due to a contributing charged structure, ortho-substituents bulky enough to prevent the necessary monoplanar arrangement of the substituents of the double bond, should make the charged form incapable of existence and should, therefore, reduce the electric moment.

2,3,5,6-Tetramethylsulfanilamide has, indeed, a lower moment (5.3 ± 0.8) than the parent substance (6.63). According to Kumler and Halverstadt[2] the theoretical value for the moment of sulfanilamide (and, of course, its tetramethyl derivative), should be 5.82, if the classical formula is correct.

For the sake of comparison, it is interesting to note that in contradistinction with the behavior of sulfanilamide, the moments of methyl 2,3,5,6-tetramethylbenzoate (2.6 ± 0.4) and 2,3,5,6-tetramethylphenylurethan (3.1 ± 0.8 in benzene; 3.2 ± 0.4 in dioxane) are somewhat higher than those of the parent substances, methyl benzoate (1.9 ± 0.5)[5] and phenylurethan (2.56 ± 0.03), respectively. The reason for this phenomenon is obscure; in neither case a significant contribution of a charged form is to be expected; in the latter, the acylation of the amino-group prevents its participation in such a formula.[6]

(1) Kumler and Strait, THIS JOURNAL, **65**, 2349 (1943); Kumler, *ibid.*, **68**, 1184 (1946). See also Halverstadt and Kumler, *ibid.*, **63**, 624 (1941); Kumler and Daniels, *ibid.*, **65**, 2190 (1943).

(2) Kumler and Halverstadt, *ibid.*, **63**, 2182 (1942).

(3) See, *e. g.*, Arndt and Martius, *Ann.*, **499**, 228 (1932).

(4) Birtles and Hampson, *J. Chem. Soc.*, 10 (1937).

(5) Previous values: 2.06, 1.8, 1.91, 1.83, 1.9 (*Trans. Faraday Soc.*, **30**, LI (1934)). See also Halverstadt and Kumler, THIS JOURNAL, **64**, 2988 (1943).

(6) Prof. Norman R. Jones has also found some unexpected features in the absorption spectra of the above substances. He will report on his findings independently.

Some preliminary observations on the biological activity of tetramethyl-sulfanilamide may be of interest.[7] The substance showed no bactericidal or bacteriostatic action *in vitro*, perhaps due to its low solubility in water. *In vivo*, however, it showed approximately the same activity as sulfaguanidine, especially against gram-negative bacteria.

Experimental

Durene was prepared according to v. Braun and Nelles[8] and aminodurene according to Willstätter and Kubli,[9] who also described briefly the **N-acetyl derivative** (m. p. 207°). If in its preparation (5 g. of aminodurene, 15 cc. of acetic anhydride on the water-bath for thirty minutes; cooling; filtration; recrystallization from glacial acetic acid) the reaction mixture is heated to the boiling point, the **N,N-diacetyl derivative**, m. p. 137°, is formed.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2. Found: C, 72.0; H, 8.3.

By treatment with the theoretical amount of 15% methanolic potassium hydroxide solution (two hours), one acetyl group is split off.

The N-Acetyl-2,3,5,6-tetramethylaminobenzenesulfonamide.—N-Acetylaminodurene (0.9 g.) was added slowly to chlorosulfonic acid (10 g.) at 10–15°. The reaction was completed at 55–60° (ninety minutes) and the product poured on iee, filtered, washed with water and boiled for ten minutes with 15% aqueous ammonia; from glacial acetic acid, m. p. 262°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2S$: C, 53.3; H, 6.7. Found: C, 53.6; H, 6.7.

Boiling 15% aqueous potassium hydroxide, 10% alcoholic potassium hydroxide solution or 10% alcoholic hydrochloric acid left the substance unattacked; the last-mentioned reagent at 180° gave aminodurene, m. p. 75°.

For the synthesis of tetramethylsulfanilamide, the following route proved more successful:

N-Carbethoxyaminodurene (2,3,5,6-tetramethylphenylurethan).—To a well-agitated mixture of aminodurene (1 g.), sodium carbonate (0.53 g.) and benzene (15 cc.), ethyl chlorocarbonate (2 g.) was added at room temperature. The reaction was completed at 80° (ten minutes) and the reaction product recrystallized successively from dilute acetic acid and benzene or petroleum ether. It formed needles of m. p. 154–155°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.6; H, 8.6. Found: C, 70.8; H, 8.8.

N-Carbethoxy-2,3,5,6-tetramethylaminobenzenesulfonamide.—The preceding substance (0.5 g.) was added slowly with agitation and cooling (0°) to chlorosulfonic acid (10 cc.). After thirty minutes at room temperature, the product was poured on ice, and the waxy solid filtered, washed with ice water and boiled for five minutes with 15% aqueous ammonia. It crystallized from 50% acetic acid in platelets, m. p. 225° (dec. 230°); yield, 61%.

Anal. Calcd. for $C_{13}H_{20}O_4N_2S$: C, 52.0; H, 6.7. Found: C, 52.0; H, 6.6.

2,3,5,6-Tetramethyl-aminobenzenesulfonamide.—The N-carbethoxy- compound was hydrolyzed with boiling

(7) Thanks are due for these data to Dr. Olitzki of the Department of Hygiene, Hebrew University, Jerusalem.

(8) v. Braun and Nelles, *Ber.*, **67**, 1094 (1934).

(9) Willstätter and Kubli, *ibid.*, **42**, 4151 (1909).

c	δ	ϵ	n^2	P	$P_{E^1/_2}$	$\overline{P}$	$\overline{P}_E$	$\overline{P}_{A+O}$
(1) Methyl benzoate in benzene; t = 26.0°								
0	0.8744	2.2700	2.2231	26.629	25.834	....	...	....
0.0148	.8788	2.3115	2.2237	27.297	25.996	78.11	36.81	41.30
.0251	.8818	2.4270	2.2243	29.042	26.113	126.62	36.97	89.65
.0312	.8836	2.5131	2.2261	30.286	26.203	146.92	37.68	109.24
$\overline{P}_{A+O}$ (average) = 80.06; μ = 1.9 ± 0.5								
(2) Methyl 2,3,5,6-tetramethylbenzoate in benzene; t = 26.5°								
0	0.8716	2.2690	2.2228	26.596	25.916	....	...	....
0.0060	.8737	2.3138	2.2238	27.430	26.088	173.24	54.78	118.56
.0076	.8743	2.3392	2.2240	27.844	26.148	187.21	55.77	131.44
.0123	.8759	2.4331	2.2249	29.307	26.279	247.36	55.48	191.88
$\overline{P}_{A+O}$ (average) = 147.29; μ = 2.6 ± 0.4								
(3) 2,3,5,6-Tetramethylsulfanilamide in dioxane; t = 35.0°								
0	1.0248	2.2290	2.0079	24.930	21.567	....	...	....
0.0017	1.0279	2.2792	2.0087	25.658	21.597	450.66	39.11	411.55
.0024	1.0288	2.3288	2.0096	26.368	21.620	626.60	43.74	582.76
.0031	1.0297	2.3861	2.0107	27.141	21.642	742.79	45.92	696.87
$\overline{P}_{A+O}$ (average) = 563.76; μ = 5.3 ± 0.8								
(4) Phenylurethan in benzene; t = 26.8°								
0	0.8710	2.2684	2.2201	26.615	25.889	....	...	....
0.0068	.8734	2.3204	2.2225	27.498	26.049	157.24	23.67	133.57
.0097	.8745	2.3342	2.2231	27.750	26.109	149.99	22.75	127.24
.0156	.8766	2.3910	2.2238	28.678	26.225	129.20	21.59	137.61
$\overline{P}_{A+O}$ (average) = 132.81; μ = 2.56 ± 0.03								
(5) 2,3,5,6-Tetramethylphenylurethan in benzene; t = 35.0°								
0	0.8619	2.2720	2.2171	26.950	26.117	....	...	....
0.0045	.8662	2.3041	2.2177	27.509	26.211	151.73	47.10	104.63
.0060	.8676	2.3569	2.2183	28.303	26.248	253.20	48.02	205.18
.0088	.8703	2.4430	2.2189	29.581	26.312	324.91	48.20	276.71
$\overline{P}_{A+O}$ (average) = 195.51; μ = 3.1 ± 0.8								
(6) 2,3,5,6-Tetramethylphenylurethane in dioxane; t = 35.0°								
0	1.0366	2.2310	2.0079	24.695	21.351	....	...	....
0.0055	1.0368	2.2935	2.0116	25.785	21.583	223.60	63.69	159.91
.0069	1.0369	2.3529	2.0133	26.652	21.653	308.32	65.12	243.20
.0090	1.0370	2.3711	2.0161	26.964	21.760	277.93	67.00	210.93
P_{A+O} (average) = 204.68; μ = 3.2 ± 0.4								

15% aqueous sodium hydroxide solution (forty-five minutes), the solution carefully neutralized with acetic acid and the product recrystallized from 50% alcohol. It formed needles of m. p. 177–178°.

Anal. Calcd. for $C_{16}H_{16}O_2N_2S$: C, 52.6; H, 7.0; N, 12.3. Found: C, 52.5; H, 7.2; N, 12.4.

2,3,5,6-Tetramethylbenzoic Acid.—The Grignard compound, prepared from bromodurene (10 g.) and magnesium (10 g.) in ether–benzene (75 and 30 cc.), was treated with dry gaseous carbon dioxide. The acid was recrystallized from dilute alcohol and had m. p. 178°; yield, 50%.[10] The **methyl ester**, from the acid (0.4 g.) and dimethyl sulfate (2.5 g.) at room temperature, was best purified by sublimation *in vacuo* (100–110° (25 mm.)). It formed prismatic plates of m. p. 60–61°.[11]

(10) Beilstein, Vol. IX, p. 564.

Measurements

c = concentration; δ = density; ϵ = dielectric constant; n = refractive index; $P^1/_2$ = total polarization of the solution, $P_{E^1/_2}$ = electron polarization of the solution; $\overline{P}$,$\overline{P}_E$ = the same for the solute; $\overline{P}_{A+O}$ = atomic and orientation polarization for the solute.

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(11) Jacobson, *Ber.*, **22**, 1223 (1889); Meyer and Woehler, *ibid.*, **29**, 2572 (1896).