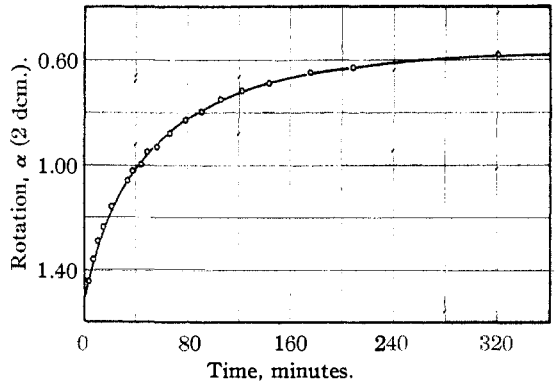

Fig. 2.—Diacetone-sorbose and tosyl chloride at 23 ± 2°.

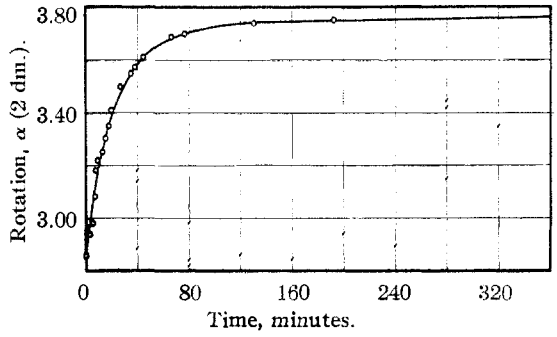

Fig. 3.—Diacetone-galactose and tosyl chloride at 23 ± 2°.

Experimental

1,2;5,6-Diisopropylidene-D-glucofuranose.—A sample of this substance obtained from the Corn Products Refining Co., contained a considerable amount of monoacetone glucose. It was dissolved in water and extracted three times with very small portions of benzene to remove colored impurities. After a treatment with decolorizing carbon, the colorless aqueous solution was extracted five times with chloroform; the extract was dried with sodium sulfate, filtered, and concentrated to crystallization. The product after a recrystallization from benzene and drying, melted from 109.5–110° (cor.) and rotated[6] −17.6° (*c*, 2.040; H_2O).

1,2;3,4-Diisopropylidene-D-galactopyranose.—This was prepared exactly as described previously.[2]

2,3;4,6-Diisopropylidene-L-sorbofuranose.—The dark-brown distillate supplied by Hoffmann-LaRoche was dissolved in ether and most of the coloring matter was removed by extractions with 20% KOH solution and then by carbon treatment. Almost colorless crystals were obtained when the dried ether extract was evaporated. A final recrystallization from petroleum ether (b. p. 30–60°) yielded white crystals melting from 77.5–78.5°.

Toluenesulfonyl Chloride.—Eastman Kodak Co. product melting 68.5–69.0° (cor.) was employed.

Pyridine.—A colorless fraction dried over KOH and boiling at 115.3–115.5° was used.

The Rate Measurements.—The method described for the case of triphenylchloromethane was duplicated.[2] The reactions took place in a constant-temperature room at 23 ± 2°.

Summary

1. The rates of reaction of *p*-toluenesulfonyl chloride with diacetone glucose, diacetone sorbose and diacetone galactose at a molar ratio of 8 to 1 in pyridine solution, have been measured polarimetrically.

2. The reactions were pseudounimolecular and gave times of half-change in the ratio 74.2: 2.1: 1 in the order named.

3. The "selectivity" of *p*-toluenesulfonyl chloride toward primary hydroxyl groups as compared with secondary ones is of the same order as the "selectivity" of triphenylchloromethane.

(6) Specific rotation of the D line of sodium at 24°.

CAMBRIDGE, MASS. RECEIVED AUGUST 11, 1942

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Solubilities of Orthanilamide, Metanilamide and Sulfanilamide[1a]

BY R. H. KIENLE AND J. M. SAYWARD[1b]

In connection with a broad program of research on chemotherapeutic agents of the sulfanilamide type, a study of certain physical chemical properties of sulfanilamide and its therapeutically inactive isomers was undertaken. Any distinction found between the active para compound and the inactive ortho and meta isomers might contribute to the explanation of the therapeutic activity of sulfanilamide.

(1a) Presented at the 103rd meeting of the American Chemical Society, Memphis, Tenn., April, 1942.

(1b) Present address: Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut.

The present paper reports on the water-solubilities of the three sulfanilamide isomers. The results led to dilatometry and manometric drying of the solid phase of sulfanilamide. Microscopical and X-ray investigation of the three isomers is expected to be published at a later date by our Laboratories. Solubilities were also determined at 37° in buffered solutions.

Experimental

Materials.—Sulfanilamide (U. S. P.) from plant production was recrystallized from alcohol and from hot water.

Orthanilamide was synthesized by standard methods

from *o*-nitrochlorobenzene by oxidizing the disulfide, amidating and reducing. The product was recrystallized repeatedly from hot water (using traces of hydrosulfite to prevent discoloration), once from diluted alcohol, and once from cold diluted acetone.

Metanilamide was prepared from nitrobenzene by converting to the sulfonyl chloride, amidating and reducing. It was recrystallized repeatedly from hot water (also using hydrosulfite), from hot alcohol and from hot diluted acetone.

Titration with nitrite indicated that the products were 100.0 ± 0.3% pure. Elementary analyses and mixed melting point determinations with materials furnished by Dr. E. H. Northey[2] confirmed these values.

Buffered solutions used in measuring solubility at various *p*H values are listed with their ionic strengths (calculated from dissociation constants) in Table III.

Determination of Solubilities.—Half-filled bottles containing excess solid were rotated, usually overnight, in a water thermostat controlled to ±0.02° by an all-glass mercury–toluene regulator. Equilibrium was approached usually from above and during twelve hours or more (overnight); exceptions are indicated in Table I and Fig. 1. It will also be noted that approach toward equilibrium from below and shorter runs in general gave equivalent results. Sampling was accomplished by forcing the solution, with air pressure, through a glass wool immersion filter into a 15–25-cc. pycnometer immersed in the bath. The pycnometer (resembling a pipet bulb) was closed by two stopcocks, cleaned, dried, cooled and weighed, after which the contents were flushed into a volumetric flask. Duplicate aliquots were acidified (10 cc. of concentrated hydrochloric acid per 25-cc. sample), iced below 15°, and titrated with *N*/25 sodium nitrite to first blue on starch–iodide paper.

TABLE I

Temp., °C.	Solubilities, g./100 g. Orthanilamide S	Orthanilamide 2σ	Metanilamide S	Metanilamide 2σ	Sulfanilamide S	Sulfanilamide 2σ
23.0	0.65		1.14		0.64	
					.64	
24.0	.67		1.21		.69	
26.0	.75		1.34		.77	
27.0					.82[b]	±0.012
					.82[b,a]	
					.82	
					.83	
28.0	.82		1.48	±0.018	.87	
	.82		1.49		.87	
30.5	.91				1.01	
31.7					1.08	
					1.08[a]	
33.0	1.01		1.89		1.19	
34.0	1.05				1.26	
					1.27[a]	±0.015
					1.27	
35.5	1.11		2.19		1.37	
37.0	1.20	±0.024	2.37	±0.031	1.47	±0.010
	1.20		2.36[a]		1.47	
	1.20[a]		2.35[a]		1.47[a]	
	1.18[b]		2.34[b]		1.47[a]	
					1.46[b]	
37.05	1.19					
39.0			2.58		1.61	
					1.61	
42.0	1.46		3.01		1.84	
46.0	1.70		3.70		2.21	
50.0	2.00[b]		4.58[b]		2.68[b]	

[a] Equilibrium approached from below. [b] Duration less than twelve hours.

(2) Observed melting points for experimental, Northey's, and mixed samples: orthanilamide, 155.2, 155.3, 154.8; metanilamide, 142.1, 141.9, 142.1; sulfanilamide, 165.9, 165.8, 166.0.

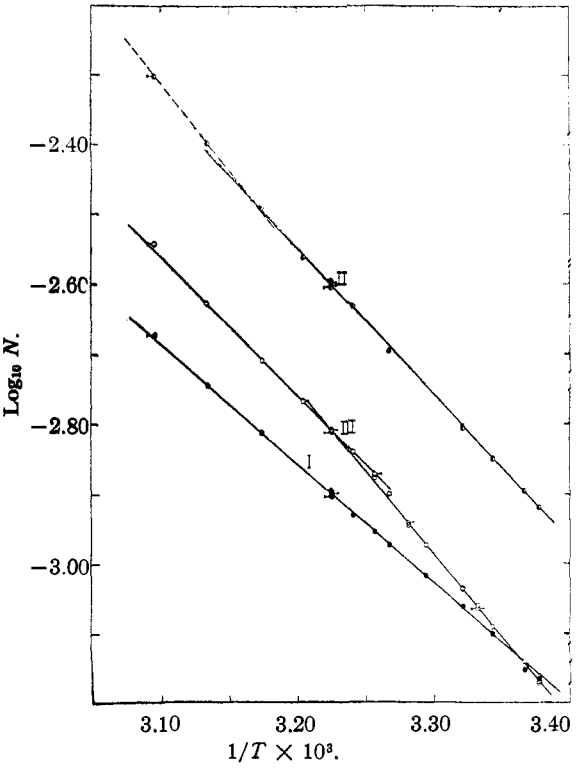

Fig. 1.—Solubility of sulfanilamide isomers in water; I, ●, orthanilamide; II, ◐, metanilamide; III, ○, sulfanilamide; ○–+ equilibrium approached from below; ●–○, duration of experiment less than twelve hours.

In buffered solutions at 37° the solubility was determined by drawing the sample directly into a volumetric pipet, yielding results on a volume basis.

Accuracy of the experimental results, based on the estimated error in weighing and in titration, is taken to be about ±0.01 g./100 g. of solution. This corresponds to ±0.012 × 10^{-3} in mole fraction (±0.0024 in log *N*); these limits are indicated by the size of the circles in Fig. 1. The precision of the results has been calculated in those cases where several determinations were carried out at one temperature. Values of 2 σ vary from 0.01 to 0.03 g./100 g.—see Table I. The consistency with which the experimental points fall on straight lines in the log *N versus* $1/T$ plot, Fig. 1, is also indicative of the degree of reproducibility.

Dilatometry.—The dilatometers were of the Bouyoucos type, 100-ml. capacity, with ground stoppers. They were suspended with capillaries immersed in a glass thermostat controlled to ±0.1°. They were charged with about 35 g. of sulfanilamide hydrate crystals (large plates formed from a 1.75% solution by slow cooling below 40°) suspended in toluene or Solvesso No. 2. Readings of the capillary level were taken periodically until essentially con-

stant at each temperature. Above 37° this required many hours.

Manometric Drying.[3]—The apparatus consisted of a mercury manometer, cold trap and vacuum pump connected to a flask in a thermostat at 21°. In the flask was placed a thin layer of ground-up, wet crystals prepared as for dilatometry. During evacuation, pressures were read at intervals (four minutes after closing the connection to the pump). After a definite fall in pressure a sample of the crystals was removed and analyzed both by drying at 110° and by titrating with nitrite.

Results

Solubilities of orthanilamide, metanilamide and sulfanilamide, as directly determined by weight in the temperature range 23–50°, are given in Table I. Values of 2 σ were calculated where duplicate data made this possible.

Solubilities by volume do not differ from values on the weight basis by more than 0.01 g./100 cc. This follows as, over the range 23–50°, the densities of the solutions varied only as follows: orthanilamide, 0.999 to 0.995; metanilamide, 1.000 to 1.001; sulfanilamide, 0.999 to 0.996 g./100 cc.

The experimental aqueous solubility data are plotted in Fig. 1, using $\log_{10} N$ and $1/T$ as coordinates. The discontinuity in the curve for sulfanilamide indicates a phase transition, which was confirmed by dilatometry (see below) as well as by the microscopical and X-ray investigations. Manometric drying, reported below, has shown the transition to involve a monohydrate.

A possible discontinuity at about 43° in the case of metanilamide is also shown. Dashes have been used for the higher temperature line, because only two points determine it, and the 50° point is perhaps unreliable since equilibrium was approached during only 3.3 hours. If the dashed line is correct, the main portion of the curve represents a metastable equilibrium, for it corresponds to higher solubilities than would the extension of the dashed line. (In the microscopical work, various modifications of the anhydrous solid phases of all three isomers were observed. In preparing crystals for this examination it appeared that a transformation for metanilamide may occur near 43°.)

Equations expressing the relation of temperature and solubility, in terms of mole fraction, have been derived from the straight lines of Fig. 1. The general equation is

$$\log N = a(1/T) + b \qquad (1)$$

where N is mole fraction and T is degrees absolute. Values of the constants, a and b, are given in Table II. Solubility as g./100 g. of solution may be derived from mole fraction by the relation

$$S = (17{,}214N)/(18.02 + 154N) \qquad (2)$$

Differential heats of solution have been calculated from the lines of Fig. 1, using the Schröder equation

$$\log N_2 - \log N_1 = \frac{\Delta H}{4.575}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad (3)$$

where ΔH is heat of solution in calories per mole, values for which appear in Table II. Taking the heat of transition as the difference between the heats of solution of the two forms, the heat absorbed by the hydrate → anhydrous transition of sulfanilamide at 37° is 1810 cal./mole.

TABLE II

Compound	Heat of solution, cal./mole	Constants for solubility equation a	b
Orthanilamide	7,820	−1710	2.615
Metanilamide	9,570	−2091	4.156
Sulfanilamide (< 37°)	10,860	−2373	4.844
Sulfanilamide (> 37°)	9,050	−1978	3.570

Qualitative independent evidence of the transition of sulfanilamide, indicated by the solubility data, was sought in a dilatometric investigation. Such was found, there being a distinct increase in volume, evidenced by a discontinuity in the temperature–volume curve, which occurred within 2–4° above 37°. Suspended or negligible rate of transformation close to the transition point accounts for the higher temperature observed in these experiments. Figure 2 portrays the curves obtained from two such experiments.

It had been noticed early that platy sulfanilamide crystals grown at ordinary temperatures changed when exposed to air (or to alcohol or acetone), becoming opalescent, even at room temperature. This change could be forestalled in a saturated or a controlled humidity (such as over 18% sulfuric acid). Crystals rinsed with alcohol gave evidence of water content in rough moisture determinations. Manometric dehydration was undertaken to determine the composition of the hydrate thus indicated.

Hydrate existence of orthanilamide or metanilamide had not been indicated either by change in appearance or by weight loss on drying, so manometric drying was not carried out in these cases.

In Fig. 3 is a graph of observed vapor pressure as wet crystals of sulfanilamide hydrate were

(3) These measurements were carried out by Drs. W. L. Seaman and J. J. Freeman, of the Calco Laboratories, to whom grateful acknowledgment is made.

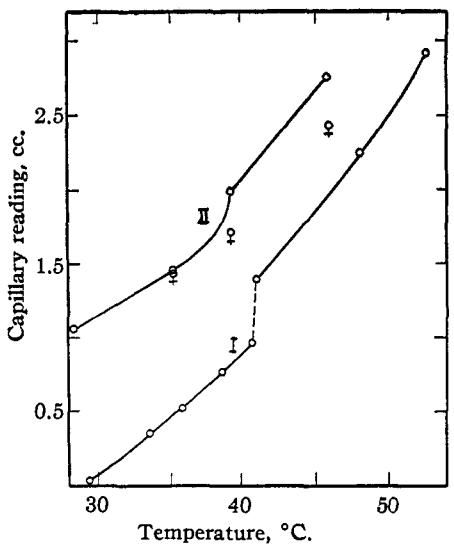

Fig. 2.—Dilatometry of sulfanilamide monohydrate: O, final readings; ♀, non-equilibrium points one hour after temperature change (Curve II).

dried at 21°, plotted against time. The first plateau, of course, corresponds to saturated solution wetting the crystals. After a sudden fall in pressure, another step occurs; crystals removed from the system at this point analyzed 9.4% water by drying and 9.1% by titration; theory for the monohydrate is 9.4%. Such a determination was carried out on two samples, from separate preparations of crystals, with the same results. Further dehydration, during which the temperature was raised to 30° and alcohol–carbon dioxide used on the cold trap, reduced the pressure to a few tenths of a millimeter. Drying at 110° of a sample removed at this point showed only 0.5% loss in weight.

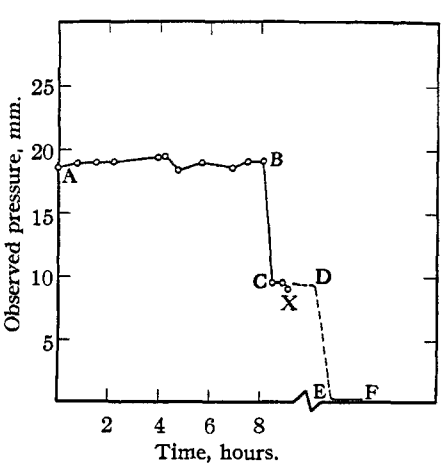

Fig. 3.—Manometric drying of sulfanilamide monohydrate: A-B, wet crystals; C-D, monohydrate; E-F, anhydrous solid; sample removed at X contained 9.4% of water; A-B and C-D at 21°, E-F at 30°.

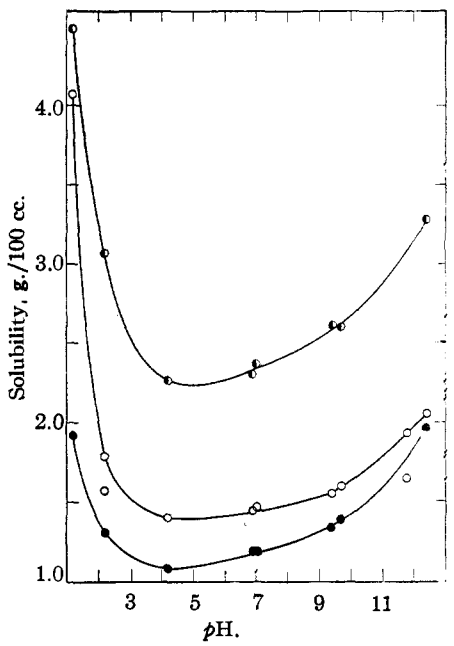

Fig. 4.—Solubility of sulfanilamide isomers in buffer solutions at 37°: ●, orthanilamide; ◐, metanilamide; O, sulfanilamide.

Solubility data at 37° in buffered solutions of various *p*H values appear in Table III. Figure 4 shows solubility to be minimum at *p*H 4.5–5.0. Solubility increases markedly above *p*H 9 and below *p*H 3. Sulfanilamide shows an especially great increase below *p*H 2. Different buffers of the same *p*H may give different results (Table III); the curves in Fig. 4 were drawn for corresponding buffers for the three isomers.

TABLE III

SOLUBILITY AND *p*H AT 37.0°

*p*H	Components	Ionic strength	Solubility, g./100 cc. Orth-anil-amide	Met-anil-amide	Sulf-anil-amide
1.2	KCl	0.12	1.92	4.48	4.07
2.2	KCl	.06	..	..	1.57
2.2	Phthalate	.05	1.31	3.07	1.79
4.2	Phosphate–citric acid	.84	1.08	2.26	1.40
6.9	Phosphate	.03	1.19	2.30	1.44
(5.7)	Distilled water	..	1.19	2.36	1.47
9.4	Boric acid-KCl	.08	1.34	2.61	1.55
9.7	Boric acid-KCl	.09	1.39	2.60	1.60
11.8	Glycine	.11	..	..	1.93
11.8	Citrate	.40	..	..	1.65
12.4	Borate	.23	1.96	3.28	2.05

Discussion

Several types of sulfanilamide crystals have been noted by Van Zyp.[4] Undoubtedly one of these

(4) Van Zyp, *Pharm. Weekblad*, **75**, 585 (1938).

is the hydrate form, but neither composition nor temperature conditions of formation were specified.

Polymorphism of sulfanilamide has been described by Watanabe,[5] working in Japan. By means of X-ray study three forms of the solid were defined. The crystals studied were all obtained from alcohol; hence Watanabe could not have obtained the hydrate which is the main feature of this investigation.

Since 37° is body temperature, the sulfanilamide hydrate or transition thereof may hypothetically bear some relation to therapeutic activity, perhaps as a water carrier in biological coupled reactions or as an energy transfer mechanism.

The behavior in buffers bears out the hypothesis that sulfanilamide and its isomers may behave as ampholytes, with minimum solubility at an "isoelectric point" (*p*H 4.5–5.0 at 37°). The solubility increase for sulfanilamide at *p*H 1.2 appears to be exceptionally large.

The similarity of "isoelectric point" of sulfanilamide with that of blood serum proteins may be involved in therapeutic activity.

(5) Watanabe, *Naturwissenschaften*, **29**, 116 (1941); *Chem. Abs.*, **36**, 695 (1942).

The authors are indebted to Dr. G. L. M. Christopher for help rendered in the preparation of this paper and to Dr. M. L. Crossley for the encouragement to carry through this type of investigation.

Summary

1. The aqueous solubilities of orthanilamide, metanilamide and sulfanilamide have been determined in the range 23–50°.

2. Heats of solution calculated from the solubility data are: orthanilamide 7820; metanilamide 9570; sulfanilamide below 37°, 10,860, above 37°, 9050 cal./mole.

3. The discontinuity in the solubility curve of sulfanilamide at 37° represents a transition, confirmed by dilatometry, and shown by analysis to involve a monohydrate.

4. Solubilities in buffered solutions of *p*H 1.2 to 12.4 at 37° exhibit a minimum for all three isomers at *p*H 4.5–5.0, with striking increase above *p*H 9 and below *p*H 3, especially for sulfanilamide below *p*H 2.

BOUND BROOK, NEW JERSEY RECEIVED MAY 7, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reactions in Solutions Containing O_3, H_2O_2, H^+ and Br^-. The Specific Rate of the Reaction $O_3 + Br^- \longrightarrow$

BY HENRY TAUBE

When ozone and bromide ion are mixed in acid solution, the net reaction

$$O_3 + 2H^+ + 2Br^- = O_2 + Br_2 + H_2O$$

takes place so rapidly that a direct measure of the specific rate is not possible. In the present paper, experiments on the measurement of this specific rate by an indirect method are reported. The system studied contained acid, O_3, Br^- at a relatively low concentration and H_2O_2. Hydrogen peroxide possesses the properties that at low (Br^-), it rapidly reduces bromine to Br^-,[1] that the reaction with Br^- under the present conditions is negligibly slow, and that the direct interaction with ozone is also slow.[2] The net reaction which takes place in this mixture is

$$H_2O_2 + O_3 = 2O_2 + H_2O \qquad (A)$$

It has been shown[2] that this reaction is accelerated by Br^-, and that the catalytic decomposition of ozone

$$2O_3 = 3O_2 \qquad (B)$$

which accompanies reaction A in a mixture of H_2O_2, O_3 and acid is suppressed by low concentrations of Br^-.

The experiments consisted of a study of the variation of the rate of A with (O_3), (H_2O_2), (H^+) and (Br^-). Analysis of the data showed that three distinct paths are available for reaction A. Mechanisms for these paths, consistent with the data, and with other work in this field are proposed.

(1) Bray and Livingston, THIS JOURNAL, **50**, 1663 (1928).
(2) Taube and Bray, *ibid.*, **62**, 3357–3373 (1940).

Experimental

Acid solutions of O_3 at 0° were prepared as described[2]; redistilled water was used for the most part. Merck's inhibitor free Superoxol was used to make up the solution of H_2O_2. A stock supply of sodium perchlorate solution was prepared by neutralizing perchloric acid with C. P. sodium carbonate.