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THE REARRANGEMENT OF ORTHANILIC ACID TO SULPHANILIC ACID IN THE PRESENCE OF SULPHURIC ACID-S^{35} [1]

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Abstract—The conversion of orthanilic acid to sulphanilic acid has been studied in the presence of radiolabelled sulphuric acid-S^{35}. The rearrangement involved is irreversible and is shown to proceed in conc H_2SO_4 by an intermolecular mechanism, in common with similar rearrangements of the toluenesulphonic acids and the chlorobenzenesulphonic acids. The sulphonic acids involved in the present study exchange without isomerization to a limited extent under rearrangement conditions. Several reasons for this exchange are advanced and discussed.

THE isomerization outlined in Fig. 1, namely, the ultimate conversion to the thermodynamically more stable meta isomer of the *ortho* and *para* substituted benzene sulphonic acids, in conc sulphuric acid as reaction medium, has been realized partially ($o \rightarrow p$) for Y as Et,[2] OEt[3a] and NH_2[4] and fully ($o \rightarrow p \rightarrow m$) with Y as Me,[5]* Cl,[6] OH,[3] COOH[7] and SO_3H.[8] Despite the general reversibility of sulphonation, the transfer of the sulphonic acid group from the *ortho* to the *para* nuclear position in most of the instances listed above (except where Y is Me or Et) is irreversible due to the steric and dipole repulsions that arise when the sulphonic acid group occupies the *ortho* position. The reversibility of the *para* to *meta* conversion is well established for Y as Cl[6] and in fact probably occurs in all cases since the sulphonation of C_6H_5Y (Y being Me,[9] Cl,[9] SO_3H[8c]) for a sufficiently long time and at a sufficiently high temperature gives an equilibrium mixture of *para* and predominantly *meta* isomers (and a small amount of the *ortho* in the case of Y being Me). The isomeric transformations of the various toluene and chlorobenzene sulphonic acids are probably the most studied and those involving the aminosulphonic acids are possibly the least examined. With regard to the latter it is only known that

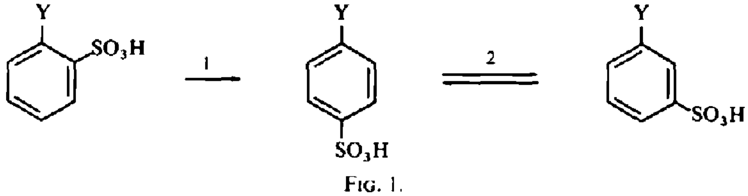

FIG. 1.

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[*] Shilov[5b] and Cerfontain[5d] (working under different conditions) found that the isomerization is intermolecular; Syrkin *et al.*[5c] (working at a lower temp), however, describe the mutual rearrangement of the *ortho* and the *para* isomers as being mainly intramolecular.

orthanilic acid is converted to sulphanilic acid in good yield[4] when heated with conc sulphuric acid at 180–190°. We now report the first study of this isomerization using sulphuric acid-S^{35}.

Our experimental conditions were similar to those of Bamberger except that we used the lower temperature of 156° for the rearrangement in order to be able to recover some unchanged orthanilic acid even after the rearrangement had progressed for some time. In all our runs we used a 1:5·6 molar ratio of sulphonic acid to sulphuric acid. In our work-up procedure we isolated initially 55–60% of orthanilic and/or sulphanilic acids and using the procedure of Bamberger an additional 11–13% of these acids could be recovered. We determined the relative amounts of each isomer present in each reaction mixture by separating them on an ion-exchange resin.[10] This method was used after we had failed to separate them by fractional crystallization of their S-benzylthiouronium derivatives—a method which has been suggested[11] for the separation of isomeric sulphonic acids.

Table 1 summarizes the data we obtained in a series of runs. The measured specific activities of orthanilic and sulphanilic acids, the per cent of each isomer recovered from the reaction mixture and the overall yield are recorded. The measured specific activities of both isomers have been corrected to allow for (a) hydrolysis of the sulphonic acid to form the correct quantity of sulphate, thus diluting the radiolabelled sulphate concentration, followed by (b) resulphonation from this mixed acid to form both labelled and unlabelled sulphonic acid randomly. We have also sulphonated aniline under rearrangement conditions and the only product is sulphanilic acid (approximately 30%). No orthanilic acid could be detected in the sulphonated product.

TABLE 1. SPECIFIC ACTIVITIES[a] OF ORTHANILIC AND SULPHANILIC ACIDS, THE PER CENT YIELD OF EACH ISOMER RECOVERED AND THE OVERALL YIELD

Reaction time (min)	Orthanilic acid			Sulphanilic acid			Overall yields (%)
	Specific activity (cpm/mmole × 10^5)		Yield[b]	Specific activity (cpm/mmole × 10^5)		Yield[b]	
	Actual	Corrected[c]		Actual	Corrected[c]		
22	0·168	0·168 (4·1)	100	—	—	0	70
45	0·483	0·527 (12·8)	43	3·68	4·02 (98)	57	65
60	0·483	0·541 (13·2)	23	3·45	3·86 (94)	77	70
75	0·490	0·558 (13·6)	11	3·27	3·73 (91)	89	71
90	0·580	0·663 (16·2)	5	3·27	3·74 (92)	95	63

[a] The figures in parentheses represent the per cent activity that the particular sample possessed in relation to the maximum.

[b] The percentage yields refer to the relative yields of monosulphonic acids recovered and not to the overall stoichiometry.

[c] These figures are corrected to allow for dilution of the radiolabelled acid by the inactive sulphonic acid group released as sulphuric acid by hydrolysis.

Our results show that the isomerization of orthanilic to sulphanilic acid is an intermolecular process. This conclusion is based on the specfic activities of the sulphanilic acid samples isolated. If the rearrangement proceeds according to an intermolecular mechanism than the sulphanilic acid isolated should have an activity approaching a value corresponding to the statistical equilibrium distribution of the radioactive sulphur atom between it and the medium. If the reaction proceeds by an intramolecular route then the sulphanilic acid isolated (and particularly the earlier fractions) would have an activity considerably lower than that of the product when equilibrium distribution of the radioactive sulphur is attained. These considerations will hold only if the direct exchange of the sulphonic acid group between the sulphonic acids involved in the rearrangement and the radiolabelled sulphuric acid takes place at a slower rate than the rate of the isomerization process. Our findings show that both orthanilic acid (Table 1) and sulphanilic acid (Table 2) exchange but, over the period of the rearrangement this exchange is not significant, except in the case of orthanilic acid, the activity of which reaches about 13 % after 1 hr.

TABLE 2. SPECIFIC ACTIVITIES OF SULPHANILIC ACID UNDER REARRANGEMENT CONDITIONS (AT 156°) AND OF SULPHURIC ACID

Reaction time (hr)	Compound	Specific activity[a] (cpm/mmole × 10^5)
1	Sulphanilic acid	0·1105 (2·7)
24	Sulphanilic acid	2·43 (59)
—	Sulphuric acid medium[b]	4·09 (100)

[a] The figures in parentheses represent the per cent activity that the particular sample possessed in relation to the maximum.

[b] The specific activity of the sulphuric acid stock solution was estimated via the formation of aniline sulphate quantitatively.

Our results are formally analogous to those of Shilov,[5b] who studied the reversible isomerization of *o*-toluenesulphonic acid to *p*-toluenesulphonic acid at 126° in the presence of sulphuric acid-S^{35}. He found that the *para* isomer isolated had the activity that it would be expected to have if it had been formed in an intermolecular process. The activity of the *ortho* isomer increased and it eventually reached the same activity as the *para* isomer formed in the rearrangement. This increase in the activity of the *ortho* isomer was mainly due to the partial reversibility of the *ortho* to *para* conversion.

Since the rearrangement of orthanilic acid to sulphanilic acid is irreversible the mechanism where the 13 % incorporation of radiosulphur into orthanilic acid occurs requires consideration. This incorporation may be due to either (a) direct replacement of the sulphonic acid group by an analogous group from an external sulphuric acid molecule and/or (b) the presence of undetectable small amounts of highly labelled sulphanilic acid in the small amounts of orthanilic acid, which were involved in the later reaction runs (Table 1). With regard to (a), it has been suggested that the replacement of HO_3S group by an analogous group from the surrounding sulphuric acid molecules may occur without being accompanied by hydrolysis and resulphonation.[12] Further it has been reported recently that sulphanilic acid underwent exchange to the extent of about 7% with the sulphuric acid of the medium[13] under conditions "where the possibility of exchange by a hydrolytic mechanism was substantially excluded". Undoubtedly orthanilic acid may be expected to undergo a similar exchange at least to the same extent as sulphanilic acid does.

EXPERIMENTAL

M.ps are uncorrected and were determined on an Electrothermal m.p. apparatus. IR spectra were determined in KBr pellets using a Perkin–Elmer 137B model IR spectrometer. Radioactive assays were carried out on a Nuclear Chicago D47Q gas-flow counter with a "Micromil Window".

Materials. Sulphanilic acid (B.D.H. AnalaR), orthanilic acid (K & K Laboratories) and conc H_2SO_4 (B.D.H. AnalaR, density 1·865) were used as obtained. Aniline was distilled over Zn dust before use. The aniline–sulphonic acids were characterized by formation of their S-benzylthiouronium derivatives; sulphanilic acid m.p. 182°, lit.[14] m.p. 182°, orthanilic acid m.p. 132°, lit.[14] m.p. 132°. Amberlite resin IRA-400 (Cl) (B.D.H.) was used as obtained. The HCl for use in the ion-exchange experiments was prepared from M & B "Volucon" standards.

Radioactive assays. Samples of finite thickness were used with appropriate corrections for efficiency and self-absorption. All materials were crystallized from water to constant activity. The activity of the H_2SO_4 stock soln was determined by the preparation of a solid derivative therefrom, namely, by the reaction of two moles of aniline, in EtOH, and one mole of radioactive H_2SO_4. The yield of aniline sulphate was quantitative.

Rearrangement runs. We first carried out a number of trial runs in order to determine the extent of the rearrangement for various times and temps under Bamberger's conditions, i.e. employing an orthanilic to H_2SO_4 ratio of 1:5·6. The following represents the conditons of a typical run. Orthanilic acid (2 g) was added to a Pyrex glass ampoule, followed by H_2SO_4 (3·4 ml). The ampoule was sealed and immersed in a thermostatically controlled bath at 156° for 60 min. The cooled ampoule was broken and its contents added to ice-cold water (about 20 ml). An additional quantity of water (about 10 ml) was used to wash out any remaining product. The white crystalline ppt (1·12 g) represented 55% of the original sulphonic acid and was crystallized from water. The crystallized derivative gave an S-benzylthiouronium derivative which had a m.p. below that of either the S-benzylthiouronium derivatives of orthanilic acid or sulphanilic acid. This material was therefore assumed to be a mixture of orthanilic and sulphanilic acids. Prior to this experiment a number of other experiments were carried out in order to determine the optimum conditions for studying the rearrangement. The results of these experiments are shown in Table 3.

Since the rearrangement went at an appreciable rate at 156°, we decided to carry out more exact studies at this temp. In a typical run the procedure was as described above, except that the composition of the solid reaction mixture was determined more accurately by separating the isomers in this mixture on an

TABLE 3. SCREENING RUNS ON THE REARRANGEMENT

Reaction time	Temp	M.p. of S-benzylthiouronium derivative of product	Conclusion
7 hr[a]	180°	183°	Orthanilic absent
30 min	180°	184°	Orthanilic absent
1 hr	75°	135°	Sulphanilic absent
2 hr	122°	134°	Sulphanilic absent
2 hr	138°	133°	Sulphanilic absent
2 hr	156°	183°	Orthanilic absent
25 min	156°	132°	Sulphanilic absent
1 hr	156°	70–75°	Mixture

[a] Conditions under which Bamberger carried out the rearrangement.

ion-exchange resin (see below). The aqueous mother liquor (about 30 ml) was then diluted with water (to about 200 ml) and the sulphate present was removed as $BaSO_4$. Excess Ba was removed by passing through CO_2 gas. The soln was then concentrated and an additional 13% of monosulphonated products were recovered. This material was also separated on an ion-exchange resin and the proportion of *ortho* to *para* isomer was found to be the same as that in the initially isolated sulphonic acid mixture. It was therefore assumed that in the other runs the ratio of *ortho* to *para* isomers was the same in both the product initially isolated and the product isolated on concentration of the aqueous extract. The per cent yield of each isomer in Table 1 therefore represents the total amount of that isomer in the reaction mixture after rearrangement for the appropriate time.

Separation of isomers. This has been described elsewhere.[10] In a typical case the separation involved in brief, addition of the isomer mixture (dissolved in 150 ml water) to an Amberlite IRA-400 (Cl) resin followed by elution with HCl ranging in strength from 0·01 to 0·1N and collection of between 70 and 80 fractions (each containing 50 ml). A flow rate of 5 ml per min was maintained. The progress of the separation was followed by determining the IR spectrum of every fifth fraction. Usually a recovery of about 90% of each isomer could be achieved.

Sulphonation run. Aniline (0·02 mole, 1·52 ml) and H_2SO_4 (0·132 mole, 6·91 ml) were maintained at 156° for 1 hr 15 min. The reaction mixture was added to water and neutralized with $Ba(OH)_2$aq. The $BaSO_4$ formed was filtered off, after the mixture had been steam distilled to remove unreacted aniline. Excess Ba ion was removed by passing CO_2 gas through the soln. Concentration of the clear soln yielded a white solid identified as a Ba salt, which on conversion to the free acid gave a brilliant white material (0·941 g). This material was added to an ion-exchange resin and eluted with HCl of progressively increasing strength. All fractions gave a small quantity of a white solid identified as sulphanilic acid. The total yeild of sulphanilic acid was 27·5%.

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