[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Kinetics of the Reactions of Thiosulfate Ion with Methyl and Isobutyl Bromides

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A recent paper[2] from this Laboratory has described an accurate kinetic study of the reaction of ethyl, *n*-propyl and isopropyl bromides with thiosulfate ion under strictly comparable conditions. The work was undertaken in order to determine quantitatively the comparative importance of energies and entropies of activation in the interpretation of the relative reactivities of saturated alkyl halides toward nucleophilic reagents in bimolecular displacement reactions of the type

$$RX + B^- \longrightarrow RB + X^-$$

The results show that the difference in reactivities between ethyl and isopropyl bromides is due primarily to a difference in heats of activation while the difference in reactivities between ethyl and *n*-propyl bromides is accounted for solely by an entropy decrease.

It was important to extend the study to include other members of the series in which α- or β-hydrogens have been replaced by methyl groups, CH_3—, CH_3CH_2—, $(CH_3)_2CH$—, $(CH_3)_3C$— and CH_3CH_2—, $CH_3CH_2CH_2$—, $(CH_3)_2CHCH_2$—, $(CH_3)_3CCH_2$— in order to ascertain to what extent these same energy and entropy effects are found.

t-Butyl and neopentyl bromides were omitted from the study, the former because of the predominance of unimolecular reaction with the solvent, the latter because its reaction rate is too slow for accurate measurement.

The reaction of methyl bromide posed more than the usual difficulties, not only because it is so rapid but also because the change in thiosulfate ion concentration during the reaction corresponds to only about 90 mole % of the methyl bromide added. This fact had led a previous observer[3] to suppose the reaction to be reversible. The situation had to be investigated before the kinetics of the reaction could be studied. The results are discussed in a later section.

There follows a description of the kinetics of the reactions of thiosulfate ion with methyl bromide between 0 and 20° and with isobutyl bromide between 12.5 and 50°.

Experimental

Apparatus.—The thermostats used were accurate to ±0.01°. Thermometers were calibrated by the National Bureau of Standards.

Volumetric apparatus was calibrated for each temperature and solvent composition for which it was to be used.

Materials.—The reactions were carried out in a solvent 50% water and 50% U. S. P. ethyl alcohol by volume (44.05% alcohol by weight). The measured density was $d^{25}{}_4$ 0.9229.

The $Na_2S_2O_3 \cdot 5H_2O$ used was Baker & Adamson reagent grade, free from sulfate ion.

Methyl bromide (Matheson & Co.) was passed from a tank through Drierite into cold absolute alcohol until the concentration of the solution was approximately 0.3 *M*. The solution was stored at 8°, but never kept more than a few days.

One sample of isobutyl bromide, an Eastman Kodak Co. product, was fractionated in a 24-in. column packed with glass helices and the main fraction, boiling within a 0.1° range, used. This was analyzed by allowing a sample weighed in a sealed ampule to hydrolyze in the presence of excess 1 *N* alcoholic sodium hydroxide for one week at 50° and determining the bromide ion produced by the Volhard titration. The result corresponded to 98.4 mole % isobutyl bromide.

A second sample from the Paragon Chemical Co., b. p. 91–93°, was first partially hydrolyzed to remove any tertiary alkyl halide, then fractionated and the fraction boiling between 90–92° collected. This fraction was washed with concentrated sulfuric acid, water and potassium carbonate solution, distilled from dry potassium carbonate, and the fraction boiling at 91.2° (uncor.) used. The bromine analysis indicated 99.9 mole % isobutyl bromide. The refractive index (Abbe refractometer) was $n^{20}{}_D$ 1.435.

The primary standard for the determination of sodium thiosulfate was resublimed iodine; that for the Volhard titrations was both dried sodium chloride and dried silver nitrate.

The Thiosulfate Reaction with Methyl Bromide.—Reaction mixtures were prepared in volumetric flasks, whose stoppers were sealed with silicone grease, from an alcoholic solution of methyl bromide, an aqueous solution of sodium thiosulfate and 50% alcohol, all at thermostat temperature. The flasks were held in the thermostat and sampled at appropriate intervals by an automatic pipet which delivered into an amount of iodine solution just insufficient to react with the thiosulfate. The titration was completed with 0.005 *N* iodine solution using starch indicator. At the same time that the reaction solution was prepared a sample of the alcoholic methyl bromide solution was delivered into excess 1 *N* sodium hydroxide solution, allowed to hydrolyze at room temperature for twenty-four hours, and titrated for bromide ion. An "infinity" titer on the reaction mixture was obtained from a sample of the mixture which had reacted at least ten times the half time of the reaction. Sampling times were read from a continuous electric timer.

Closed glass tubes were introduced to the flask as samples were removed to keep the level of the liquid high enough to be reached by pipet. Reactions run with and without these pieces showed no distinguishable difference in rate.

Some of the possible causes for the failure of the decrease in thiosulfate titer in this reaction to be equivalent to the methyl bromide present were eliminated by the following experiments.

Thiosulfate is stable to air in the presence of the reaction products since the thiosulfate titer of solutions remaining at the completion of reaction was not changed by bubbling air saturated with the solvent through the solution for one half hour. Titer before, 13.57; after, 13.63; in another experiment, before, 14.44; after, 14.48.

Silicone grease has no effect on thiosulfate solution. Closed pieces of glass tubing coated with the grease were left in a reaction mixture for five hours: titer before, 22.69; after, 22.67.

Loss from volatilization of methyl bromide is negligible.

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[1] Dissertation submitted by Phyllis Marguerite Dunbar in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University, New York, N. Y.

[2] Crowell and Hammett, THIS JOURNAL, **70**, 3444 (1948).

[3] Moelwyn-Hughes, *Trans. Faraday Soc.*, **37**, 279 (1941).

A 0.01 M solution of methyl bromide in 50% alcohol was sampled six times over a period of three days by the method used in sampling the reaction mixtures for the thiosulfate reaction. The sample was hydrolyzed by alkali and titrated by the Volhard method. The first and last samples differed in titer by 0.02 ml. of 0.032 N potassium thiocyanate. If this were a real difference it would represent a 0.5% loss in methyl bromide. Further three pairs of identical runs were made in which one flask of the pair was sampled at the normal intervals and the other titrated only after the reaction had gone to completion. The titers of the first "opened" runs were indistinguishable from those of the other "closed" runs.

"Opened"	"Closed"
17.65 ml.	17.74 ml. of 0.005894 N iodine
17.98	17.96 ml. of 0.005894 N iodine
22.71	22.66 ml. of 0.003147 N iodine

The reaction is not reversible. Two reaction mixtures of 0.01 M methyl bromide and 0.02 M sodium thiosulfate in water–alcohol solvent were allowed to go to completion. At this time the iodine titers on 10-ml. samples were 28.76 ml. and 28.83 ml. of a 0.005065 N solution. This indicated that a 0.004 M bromide ion solution had been formed. Then 0.2 g. of sodium bromide was added to the 230 ml. of reaction mixture left in each flask, tripling the bromide ion concentration. After twelve hours, 10-ml. samples were again titrated. The titers were 28.75 and 28.82 ml., respectively.

A second methyl bromide does not react with the $CH_3SSO_3^-$ produced in the reaction. A reaction between 0.005 M methyl bromide and 0.01 M sodium thiosulfate in 50% water–alcohol at room temperature was carried to completion. Titration of 10-ml. samples with standard iodine solution showed that, for duplicate experiments, an amount of thiosulfate equivalent to 93.1 and 93.3% of the methyl bromide put into the reaction mixture had reacted. Ten ml. of 0.25 M methyl bromide and 10 ml. of 0.5 M sodium thiosulfate were added to this same mixture and the fresh reaction thus started allowed to go to completion. Titration with iodine showed that this time 89.9 and 91.8% of the methyl bromide had reacted. A second set of determinations on solutions in which the concentrations of the reactants had been doubled gave 90.9 and 88.4% of the first samples reacting and 92.6 and 90.2% of the second.

The Thiosulfate Reaction with Isobutyl Bromide.—Reaction mixtures were prepared by bringing a solution of a known amount of sodium thiosulfate in 50% alcohol (prepared either from the hydrated salt or from a concentrated aqueous solution plus enough alcohol to compensate for the water added) to thermostat temperature, breaking under the solution a sealed ampule containing a known amount of isobutyl bromide, mixing and adding the requisite amount of 50% alcohol at thermostat temperature to bring to volume. Stoppers were again sealed with silicone grease. Samples were delivered at suitable intervals into 100 ml. of ice-water and titrated with 0.03 N iodine using starch indicator. The temperature at the end of the titration was about 10°.

Solvolysis Reaction.—A methyl bromide–thiosulfate reaction mixture of the usual composition was allowed to stand at 20° for a time sufficient to allow the reaction with thiosulfate to go to completion, and samples were titrated with 0.01 N sodium hydroxide and phenolphthalein. The titer corresponds to a solvolysis of less than 1% of the methyl bromide. Indeed the data of Dostrovsky and Hughes[4] on the solvolysis of methyl bromide in 50% water–alcohol at 95° and that of Grunwald[5] for the same reaction at 50° indicate that only 0.01% of the methyl bromide would solvolyze.

An isobutyl bromide–thiosulfate reaction mixture of the usual composition except that it contained 0.02 N sodium acetate was allowed to react at 25°. Samples removed at intervals and titrated in ice-water with sodium hydroxide indicated that less than 0.5% of the total reaction was due to solvolysis. Similar titration of an isobutyl bromide–thiosulfate reaction mixture which had reacted to completion at 50° showed acid equivalent to less than 0.9% of the isobutyl bromide.

Calculations

The rate of reaction for each individual run was calculated from the second order rate equation

$$kt = \frac{1}{b - a} \ln \frac{a(b - x)}{b(a - x)}$$

The initial thiosulfate concentration, a, was determined by titration with standard iodine solution and the initial concentration of the alkyl halide, b, assumed to be equal to the total amount of thiosulfate reacting and thus equivalent to the difference between the initial thiosulfate titer and the titer at "infinite" time. The units of k are l./mole-sec.

A plot of the quantity $1/(b - a) \ln [a(b - x)]/[b(a - x)]$ *versus* time was found to be a straight line for both compounds, and while in most cases this quantity was determined only up to 50% reaction, in several experiments it was followed and found to give a straight line to 80% reaction. Therefore the slopes of the plots were calculated by the method of least squares. The slopes are tabulated in Tables I and II.

TABLE I

SPECIFIC RATES OF THIOSULFATE REACTION WITH METHYL BROMIDE

Temp., °C.	$10^2 k$ l./mole-sec.	No. of runs	Av. deviation
20.00	5.73	9	0.047
10.00	2.235	4	.015
0.00	0.8095	4	.0028

TABLE II

SPECIFIC RATES OF THIOSULFATE REACTION WITH ISOBUTYL BROMIDE

Temp., °C.	$10^5 k$ l./mole-sec.	No. of runs	Av. deviation
50.00	26.00	2	0.02
37.50	7.60	5	.05
25.00	2.02	4	.02
12.50	0.459	2	.0005

The curves for the methyl bromide reaction were consistently found to have a negative intercept on the time axis, the values of which averaged −20.1 sec. at 20°, −35.7 sec. at 10° and −124 sec. at 0°. The negative intercept would indicate a faster rate during the first few per cent. of reaction. However, since this was comparable at all temperatures it cancels out in the activation energy and entropy computations.

Since the curves were straight lines it was not necessary to use the graphical method of Crowell and Hammett[2] for the calculation of the energies and entropies of activation. The energy of activation, $E^{\ddagger}$, was calculated from the Arrhenius equation. The results are given in Table III.

Relative heats of activation and entropies of

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(4) Dostrovsky and Hughes, *J. Chem. Soc.*, 164 (1946).

(5) Ernest Grunwald, data to be published.

TABLE III

ENERGIES, HEATS AND ENTROPIES OF ACTIVATION OF THE REACTIONS BETWEEN THIOSULFATE ION AND METHYL AND ISOBUTYL BROMIDES

Methyl bromide	$E^{\ddagger}$, kcal./mole	$\Delta H^{\ddagger}-\Delta H^{\ddagger}_0$, kcal./mole	$\Delta S^{\ddagger}-\Delta S^{\ddagger}_0$, cal./mole-deg.
0–10°	15.6	−2.9	−0.6
10–20°	15.5	−3.0	−0.7
Av.	15.6	−2.9	−0.6
Isobutyl bromide			
12.5–25°	20.0	1.5	−2.6
25 –37.5°	19.5	1.0	−4.0
37.5–50°	19.6	0.9	−3.7
Av.	19.7	1.1	−3.4

activation were determined on the basis of the reaction of ethyl bromide as standard.

Errors

The probable error of the individual rate determinations for the reaction of methyl bromide with thiosulfate ion is less than 1% for all runs at all temperatures. The average deviations of the individual points from a straight line are 0.4 l./mole at 20°, 0.6 l./mole at 10° and 0.3 l./mole at 0°. The average deviation of the rates is 0.3% at 0°, 0.7% at 10° and 0.8% at 20°.

The individual rate determinations for the reaction of the isobutyl bromide with thiosulfate ion have a probable error of 0.4% or less. The average deviation of the rates is 0.1% at 12.5°, 0.8% at 25°, 0.7% at 37.5° and 0.1% at 50°.

Since the rates are accurate to better than 1%, the energies of activation should not be in error to more than 0.2 kcal./mole, and the entropies of activation to greater than 0.4 cal./deg.

In the case of isobutyl bromide three of the runs at 37.50° and two of those at 25° were made with a different sample of bromide from that used in the other runs, at a time separated by several months from the others, and with new thermostat settings. The differences between the two sets of measurements were not significant.

Results

The results of the study are shown in Tables I through IV.

TABLE IV

SUMMARY OF THE DATA ON THE REACTIONS OF THIOSULFATE ION WITH ALKYL HALIDES

	MeBr[a]	EtBr[b]	*n*-PrBr[b]	*i*-PrBr[b]	*i*-BuBr
Rate at 12.5°C., $k \times 10^4$ l./mole-sec.	285	2.43	1.266	0.0677	0.0459
$\Delta H^{\ddagger}-\Delta H^{\ddagger}_0$, kcal./mole	−2.9	(0)	−0.5	1.6	1.1
$\Delta S^{\ddagger}-\Delta S^{\ddagger}_0$. cal./mole-deg.	−0.6	(0)	−3.0	−0.9	−3.4

[a] Concn. of MeBr and $S_2O_3^=$ is one-tenth of that used in the other reactions. [b] Data for these compounds were obtained from the work of Crowell and Hammett.[2]

Tables I and II show the rates of the methyl bromide and isobutyl bromide reactions, respectively. The latter were determined upon 0.046–0.048 *M* isobutyl bromide and 0.097–0.101 *M* sodium thiosulfate alcohol–water solutions. The methyl bromide reactions were 0.0046–0.0050 *M* in methyl bromide and 0.0098–0.010 *M* in thiosulfate ion except for two cases in which the methyl bromide was 0.0036 *M*. These latter two were included since they reacted at a rate well within the range of experimental results.

A change of solvent composition by 2% to 48% water–52% alcohol by volume increased the rate of the isobutyl bromide–thiosulfate reaction 5%. The values were $k = 4.81 \times 10^{-3}$ and 4.78×10^{-3} l./mole-sec.

The experimental activation energies and relative heats and entropies of activation for the reactions are listed in Table III, and Table IV puts the results obtained in this paper and those from that of Crowell and Hammett[2] in convenient form for comparison. In the work on methyl bromide the concentrations of both the methyl bromide and the thiosulfate ion were only one-tenth of those used for the other alkyl halides. The other reactions are strictly comparable with respect to concentrations and solvent.

The rapidity of the methyl bromide reaction provided some difficulty. This was surmounted by working both at low temperatures and low concentrations, which brought the rate of reaction within measurable range but necessitated extreme precision in order to obtain the specific rates within the desired 1% limit of error.

The amount of thiosulfate used up in the reaction with methyl bromide corresponded to from 89.5 to 93.8% of the methyl bromide added as determined by analysis, the individual averages being 89.9% at 20°, 92.1% at 10° and 92.6% at 0°. This parallels the results of Moelwyn-Hughes[3] which indicate that the reaction between methyl bromide and thiosulfate ion in water solution is only 86% quantitative. Moelwyn-Hughes suggested that this indicated a reversibility of the reaction, but this we have disproven, as shown in the experimental section. The experiments there described also prove that the effect is not due to air oxidation of thiosulfate, to the effect of silicone grease, to evaporation of methyl bromide, to solvolysis of methyl bromide, or to further reaction of methyl bromide with $CH_3SSO_3^-$. Furthermore, the fact that the second order law is followed closely makes any complication involving successive reactions of any sort improbable. It therefore appears highly probable that the effect in question arises from the presence of a parallel second order reaction between methyl bromide and thiosulfate whose product reduces iodine. Such a product might be $CH_3OSO_2S^-$. This being the case the procedure adopted of calculating the rate constant of the process $CH_3Br + S_2O_3^= \rightarrow CH_3SSO_3^- + Br^-$ from the infinity titer rather than from the known concentration of methyl bromide is sound and the activation energies and entropies obtained from the temperature coefficient of these rate constants apply to this reaction.

Discussion

The results show, with one exception, an increase in activation energy when α- or β-hydrogens are replaced by methyl groups. The activation energy of the ethyl bromide reaction is 2.9 kcal. greater than that of the methyl bromide reaction. As would be expected, the effect of the introduction of a second methyl group on the α-carbon, 1.6 kcal., is not as great as that caused by the introduction of the first group. Entropy differences for the reactions of the members of the α-methylated series are small. The exact value of the isopropyl bromide reaction is uncertain. The value for the methyl bromide reaction is just on the border line of significance since it is only 0.2 cal. greater than the probable error.

The one exception is found on the introduction of the first methyl group on a β-carbon. As one goes from the ethyl to the n-propyl reaction the activation energy drops slightly, yet the reaction rate is halved due to a 3 cal./deg. drop in the entropy of activation. However, upon introduction of a second methyl group, *i. e.*, the reaction of isobutyl bromide, the drop in reaction rate is again primarily due to a 1.7 kcal. rise in the activation energy. The entropy has not decreased significantly. This result is in close agreement with the calculations of Dostrovsky, Hughes and Ingold[6] which predict a rise of 1.4 kcal. in the activation energy because of increased steric hindrance.

The data are consistent and, with exception of the reaction of n-propyl bromide, they are in agreement with explanations of the decrease in reactivity accompanying α- or β-methylation which are based on increased energy barriers to the activated complex caused by significantly increased polar and steric effects.

Summary

The rates of reaction of methyl bromide with thiosulfate ion in 50% water–alcohol solvent were measured at 0, 10 and 20° and those of isobutyl bromide with thiosulfate ion at 12.5, 25, 37.5 and 50°. From the rates of reaction the energies and relative heats and entropies of activation of the reactions were computed.

The amount of thiosulfate ion used up in the methyl bromide reaction corresponds to only 90 mole % of that required to react with all of the methyl bromide added. This has been investigated and it has been shown that this incompleteness of reaction does not interfere with the kinetics.

(6) Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 173 (1946).

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[CONTRIBUTION NO. 75 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Kinetics of Acid-catalyzed Esterification of Dimethylsubstituted Benzoic Acids

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The rates of acid-catalyzed esterification of the monomethyl substituted benzoic acids have been previously reported.[2] It was found that substitution of a methyl group in the meta or para position of benzoic acid did not greatly alter the rate constant, while similar substitution in the ortho position caused the esterification rate to drop to one-third of that of benzoic acid. Hartman and Borders also reported that for each of the toluic acids, the activation energies were considerably lower (1100 to 1700 calories per mole) than for benzoic acid.

Since little work has been done on the dimethyl substituted benzoic acids, it seemed of interest to prepare the various isomers, and to measure their esterification rates. In addition, benzoic acid was also studied for comparison purposes.

Experimental

Merck reagent grade, primary standard **benzoic acid** was used without further purification. The dimethylbenzoic acids were prepared and recrystallized in the manner previously described.[3] Table I shows the melting points and neutral equivalents of the materials used.

TABLE I

MELTING POINTS AND NEUTRAL EQUIVALENTS OF ACIDS ESTERIFIED

Acid	Cor.[a] m. p., °C.	Neutral equivalent Found	Theoretical
Benzoic	121.0–121.6	122.3	122.0
2,3-Dimethylbenzoic	144.5–145.5	150.4	150.2
2,4-Dimethylbenzoic	125.2–125.8	150.0	150.2
2,5-Dimethylbenzoic	133.9–134.6	150.2	150.2
2,6-Dimethylbenzoic	115.5–116.2	150.5	150.2
3,4-Dimethylbenzoic	168.6–169.2	151.0	150.2
3,5-Dimethylbenzoic	173.2–173.8	150.8	150.2

[a] All melting points have been corrected for emergent thermometer stem and were determined in an aluminum melting-point block.

Methanol was obtained in a pure, dry state, as in previously reported work, by careful fractionation of methyl alcohol through a 5-ft. helix-packed column. The method used to ob-

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* Harvard University Ph.D. 1934.

(1) Tennessee Eastman Fellow, 1947–1948.

(2) Hartman and Borders, THIS JOURNAL, **59**, 2107 (1937).

(3) Smith and Stanfield, *ibid.*, **71**, 81 (1949).