culated on the basis of reasonable values for the moments of the polar structures. A quantum mechanical calculation of the relative energies of the structures explains the quantitative deviations from the amounts of the contributions to be expected merely on the basis of the number of contributing polar structures.

PRINCETON, NEW JERSEY RECEIVED NOVEMBER 19, 1948

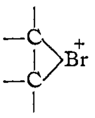
[CONTRIBUTION FROM THE WOLCOTT GIBBS LABORATORY OF HARVARD UNIVERSITY]

Kinetics of Hydrolysis and Displacement Reactions of β,β'-Dichlorodiethyl Sulfide (Mustard Gas) and of β-Chloro-β'-hydroxydiethyl Sulfide (Mustard Chlorohydrin)[1]

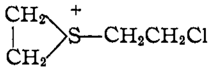
BY PAUL D. BARTLETT AND C. GARDNER SWAIN

Introduction

The existence of the ethylenebromonium ion (I) and its participation in bromination reactions were first postulated in 1937 by Roberts and Kimball.[2] An elegant demonstration of the participation of such ions in displacement reactions of β-bromoalkyl compounds was provided by Winstein and Lucas[3] in 1939. During World War II it was recognized by American workers that the closely analogous ethylenesulfonium ion (II) offered an attractive explanation of the *first-order* displacement reactions[4] of β,β'-dichlorodiethyl sulfide (mustard gas, III) a type of displacement kinetics not shown by any primary alkyl chloride.[5] Ogston, whose extensive studies of this reaction were the basis of most of the ideas used in the mustard program, observed certain facts which at the time appeared incompatible with the simple view of the mechanism expressed in eqn. 1 and indeed with any mechanism involving only this number of steps. The facts which presented the difficulty were: (1) that the "competition factor," defined as the ratio k_2/k_W for any molecule or ion X capable of reacting with the ethylenesulfonium ion, varied widely with the concentration of X in the case of chloride ion, whereas it was expected to be constant; and (2) that although, to a first approximation, the rates of reaction of mustard with all substances depended only upon the concentrations of mustard and of chloride ion, which are concerned in the first step of the mechanism, yet the initial measured first-order rate constant for the reaction of mustard with certain strong competitors such as sodium monothiophosphate was 10% greater than with water or weaker competitors.



I



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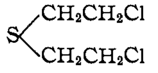

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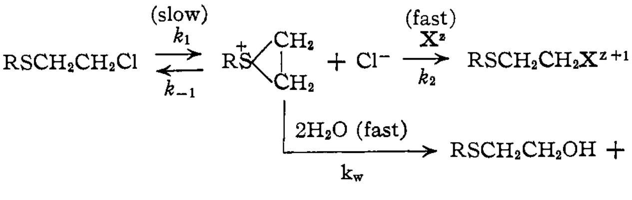
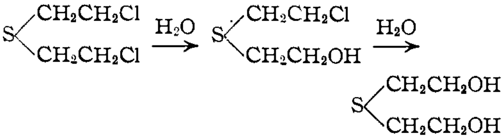


(1)

It was important to our work to obtain definite proof of the adequacy or inadequacy of Equation (1) to describe the displacement reactions of mustard gas. We therefore undertook some careful kinetic studies of the system and as a result were able to explain the above apparent anomalies satisfactorily within the scheme of Equation (1). The experimental approach had the following features. "Mustard chlorohydrin," β-chloro-β'-hydroxydiethyl sulfide, was prepared in a state of purity which permitted the two stages of mustard hydrolysis indicated in eqn. 2 to be studied separately. The progress of reaction was followed both by the convenient and accurate intermittent alkali titration of Peters and Walker[4] and by polarographic determination of the rate of liberation of chloride ion. The first of these methods was already adapted to following the kinetics of rapid reactions with half-periods of only a few minutes; we have adapted the polarographic method to the same purpose, thus permitting a comparison between the rates of liberation of chloride and hydrogen ions, which affords a test of the occurrence of appreciable concentrations of sulfonium ions during the reaction.



$$S\begin{matrix}CH_2CH_2Cl\\CH_2CH_2Cl\end{matrix} \xrightarrow{H_2O} S\begin{matrix}CH_2CH_2Cl\\CH_2CH_2OH\end{matrix} \xrightarrow{H_2O} S\begin{matrix}CH_2CH_2OH\\CH_2CH_2OH\end{matrix} \qquad (2)$$

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[1] This work was performed during 1943-1944 under Contract NDCrc 136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development.

[2] I. Roberts and G. E. Kimball, THIS JOURNAL, 59, 947 (1937).

[3] S. Winstein and H. J. Lucas, *ibid.*, 61, 1576, 1581, 2845 (1939).

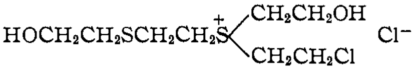
[4] R. A. Peters and E. Walker, *Biochem. J.*, 17, 260 (1923). A. G. Ogston, Peters Reports #34 (1941), #66 (1943), available through the British Ministry of Supply; *Trans. Faraday Soc.*, 44, 45 (1948).

[5] R. C. Fuson, C. C. Price and D. M. Burness, *J. Org. Chem.*, 11, 477 (1946). The hypothesis of the ethylenesulfonium ion was conceived independently by different workers. It was in use by the present authors late in 1941.

The ionic strength was controlled in all runs. The importance of these features will be brought out in the discussion which follows.

Experimental

Materials.—β-Chloro-β'-hydroxydiethyl sulfide (mustard chlorohydrin) was prepared by the method of Grant and Kinsey.[6] After the replacement of half of the hydroxyl of thiodiglycol by chlorine the unconverted thiodiglycol and sulfonium salts were removed by water–ether extraction, followed by a slow and incomplete removal of mustard by cyclohexane or petroleum ether. Judged by the halogen analyses, the best samples after this procedure contained 3–4% of mustard. The excess chlorine content was reduced to 2% by sublimation under a pressure of 3 × 10^{-5} mm. with efficient magnetic stirring of the liquid charge which was maintained at 0–5°. A middle fraction was melted off the Dry Ice–cooled condenser, weighed accurately, and immediately made into a 0.0187 *M* stock solution with undried Merck reagent acetone without allowing the undiluted chlorohydrin to be at room temperature for more than ten minutes. This solution showed no detectible hydrolysis when kept at 4° in a cold room over a period of two months. It was observed that undissolved mustard chlorohydrin developed about 5% of chloride ion in an hour, but that this chloride ion disappeared on solution of the material in acetone. The ionic material is presumably the dimer



$$HOCH_2CH_2SCH_2CH_2\overset{+}{S}\begin{matrix} CH_2CH_2OH \\ CH_2CH_2Cl \end{matrix}\ Cl^-$$

which is formed reversibly, and is present to an appreciable fraction at equilibrium in the chlorohydrin as solvent but not in acetone.

We investigated a sample of the chlorohydrin prepared by the photochemical reaction between monothioethylene glycol and vinyl chloride,[7] but could not get as pure material from it as by the method described.

β,β'-Dichlorodiethyl sulfide (mustard gas) was prepared from thiodiglycol.[8] A fraction melting at 14.35 ± 0.10° was redistilled and a small middle fraction saved for kinetic purposes. It was apparently quite free from disulfide since a hydrolyzed solution gave no trace of a polarographic wave anywhere between the large sharp chloride and hydrogen waves at +0.20 and −1.5 volts, respectively, *vs.* the saturated calomel electrode. Determinate stock solutions were made by weighing 0.74–0.91 g. of mustard accurately on an analytical balance and making up to 250 cc. with undried Merck reagent acetone. No chloride ion could be detected in these freshly made solutions by distributing 25 cc. between benzene and water in a separatory funnel and titrating the water layer with 0.00500 *M* silver nitrate potentiometrically. After standing at room temperature for ten months the amount of ionic chloride corresponded to only 0.15% reaction in a kinetic run.

The sodium benzenesulfonate used to control the ionic strength was Eastman product repeatedly crystallized from 95% ethanol until the percentage of sodium chloride dropped from about 1% to under 0.00040%, corresponding to less than 0.2% of the chloride ion liberated in a kinetic run.

The 0.05 *M* benzenesulfonic acid used for neutralizations was Eastman practical grade and contained less than 0.0004% of chloride ion by titration. The shape of a titration curve with sodium hydroxide showed it to be free from weak acids.

A 0.0518 *M* sodium hydroxide solution was prepared from a filtered 50% solution with freshly boiled distilled water and properly protected from atmospheric carbon dioxide. It was standardized with 0.0499 *M* hydrochloric acid, which had been indirectly standardized by titration against weighed potassium acid phthalate.

In the intermittent titrations, we used 0.50 cc. per 100 cc. of aqueous reaction medium, of one of the following indicators: 0.1% aqueous brom thymol blue neutralized to *p*H 7.0; 1:3 0.1% aqueous cresol purple with 0.1% aqueous thymol blue neutralized to *p*H 8.0; or 1:2 0.1% aqueous brom cresol green with 0.1% aqueous methyl red neutralized to *p*H 5.1. This last mixture was partly insoluble and had to be shaken before use. The mixed indicators were kept in brown bottles. They gave distinctly sharper endpoints than single indicators. In all cases a standard cell, identical in size and shape to the reaction cell and containing 100 cc. of a phosphate buffer for the *p*H chosen, 5 cc. of acetone and 0.50 cc. of indicator, was clamped in the thermostat beside the reaction cell to make an accurate color comparison possible. The molarity of indicator used in a reaction was about 0.5% of the initial molarity of chlorohydrin or mustard.

Sodium monothiophosphate was shown by Ogston to be a useful competitor in reactions of mustard because at *p*H 8.0 it liberates hydrogen ion quantitatively when it reacts.

$$HPSO_3^= + RCl \longrightarrow RPSO_3^= + Cl^- + H^+$$

This compound was easily prepared by hydrolysis of Eastman practical grade thiophosphoryl chloride with sodium hydroxide. Twenty cc. of thiophosphoryl chloride was added to a solution of 48 g. of sodium hydroxide and 5 cc. of dioxan in 200 cc. of water, shaken with periodic cooling in a water-bath to prevent too rapid a reaction, then kept at 100° on the steam-bath for an hour to dissolve all the thiophosphoryl chloride. After evaporating somewhat in an open evaporating dish at room temperature and cooling in ice, 61 g. of large white crystals precipitated. These were collected, washed with alcohol and ether to dry, recrystallized from 69 cc. of water at 100° and finally cooled in ice yielding 48 g., then recrystallized several times more. The competitive power of the product, measured by the total amount (56%) of acid liberated on reaction with mustard with an equal molarity of the non-acid-liberating thiosulfate present, did not change with further crystallizations.

An acid titration of sodium monothiophosphate with a glass electrode showed two well defined waves with *pK* values of roughly 10.2 and 5.6 at 25°. Therefore at *p*H 7.9–8.0 it is most completely in the form of $HPSO_3^=$. At *p*H 8.0 Ogston reports that its "competition factor" is 3.8 × 10^4 compared to 2.7 × 10^4 for thiosulfate and 8.0 × 10^3 for hydroxyl ion.

The dry salt crystallized with its full twelve molecules of water seems to be stable over long periods of time. The partially dehydrated salt develops a pronounced odor of hydrogen sulfide in a few days. A 0.05 *M* solution decreases in iodine titer about 5% in a week at room temperature, faster after that. This is probably a chemical decomposition to phosphite and sulfur. In contrast to thiosulfate, one mole of thiophosphate equals two equivalents of iodine since the reaction product with iodine is colloidal sulfur.

$$PSO_3^{\equiv} + I_2 + H_2O \longrightarrow H_2PO_4^- + 2I^- + S$$

The titration is sharper with no buffering or added acid.

Aqueous solutions of sodium monothiophosphate are strongly alkaline. There should be no delay in degassing and using a solution which has been neutralized to *p*H 8.0 by an equivalent of acid preparatory to a run. The $HPSO_3^=$ ion is unstable and decomposes over a period of a day.

Apparatus.—The cell used for the intermittent titrations is shown in Fig. 1. It consisted of a 4.6 × 21 cm. test-tube with a capillary side tube entering near the bottom for a gas inlet. The shaft of a small glass propeller stirrer passed down through a glass sleeve in the rubber stopper in the top of the cell and rested in a small depression blown in the bottom of the cell which served as a bearing. The propeller was driven at high speed by an air blast directed on a small notched disc on the shaft outside the cell, and caused the gas bubbles entering below to break and com-

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[6] W. M. Grant and V. E. Kinsey, THIS JOURNAL, **68**, 2075 (1946).

[7] R. C. Fuson and J. B. Ziegler, Jr., *J. Org. Chem.*, **11**, 510 (1936).

[8] W. Steinkopf, J. Herold and J. Stöhr, *Ber.*, **53**, 1008 (1920).

pletely fill the solution. By turning of a stopcock the gas stream could be introduced into the cell over the surface through a tube in the rubber stopper instead of under the surface.

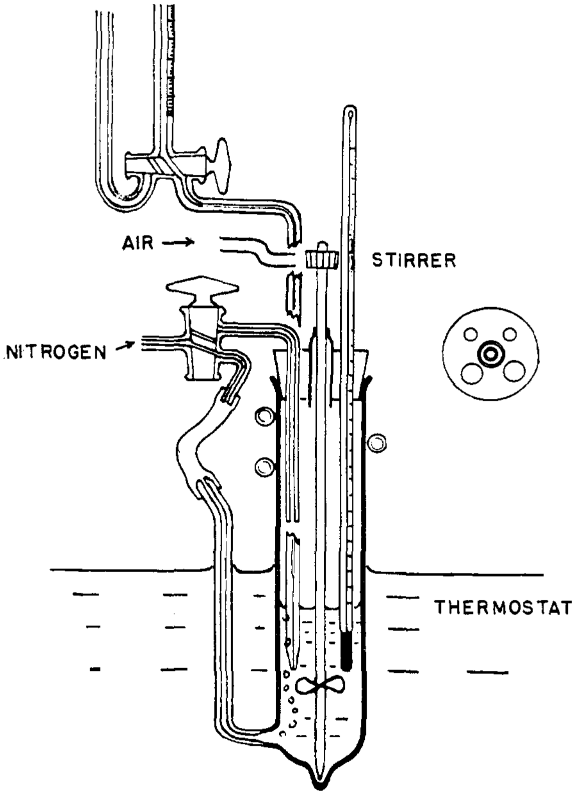

Fig. 1.—Apparatus for rapid intermittent titration of hydrogen ion liberated in hydrolysis of mustard and mustard chlorohydrin. Inset—top view of rubber stopper. Center hole, air-driven stirrer; upper holes, nitrogen inlet and thermometer; lower holes, microburet and nitrogen outlet.

Reagents were added from a 5-cc. microburet with its long capillary tip below the surface of the solution in the cell. The microburet and all other burets, pipets and volumetric flasks used in this work were standardized.

The reaction cell for following chloride liberation with the dropping mercury electrode was identical with the cell used for the intermittent titrations except that it was modified into an H-cell by blowing a side tube and auxiliary cell into the side of the reaction cell. The side tube had a 2.5-cm. medium-coarse fritted disc on the reaction side. This was covered with a plug of 3% agar gel containing 0.15 *M* sodium benzenesulfonate. A saturated mercurous sulfate electrode was made so that it could be readily removed and stored in a bottle containing saturated potassium sulfate when not in use. When placed in this cell it was covered with 0.15 *M* sodium benzenesulfonate to the same height as the solution in the reaction half.

Intermittent Titration for Hydrogen Ion.—Appropriate amounts of reagents and stock solutions were made up to 100 cc. with water in a volumetric flask. This solution was introduced into the titration cell. Purified nitrogen was then passed for forty-five minutes through this solution and through the acetone stock solution of mustard or chlorohydrin, the gas being first saturated with water in the one case and acetone in the other. The temperature in the cell was brought to exactly 23.70°; then 4.96 cc. of the acetone stock solution was added rapidly from a syringe pipet, the stopwatch being started when the addition was half complete. There was an immediate temperature rise to 25.00° and the total volume was 104.2 cc. The cell, air blast for the stirrer, buret, etc., were all on the same vertically sliding mount so that the cell could be dropped into position in the thermostat at 25.00° without delay.

The Peters-Walker intermittent titration might well be called the kineticist's dream. The rate of reaction of mustard or of its chlorohydrin is independent of the *p*H over a wide range; it is therefore possible to read the buret, add a small increment of alkali to the reaction, and watch for the color-change of the indicator, which marks the point at which an amount of acid has been produced exactly equivalent to the first increment of alkali. When this color change occurs the time is noted, the buret is read again and another increment of standard base is added to the reacting solution. It has been amply verified that it makes no difference whether the reaction is conducted on the acid or alkaline side of the change-point, or, as in our experiments, on the two sides alternately. The time of color change of the indicator could be noted within one second. The first such point was usually obtained about forty seconds after the beginning of the reaction. In these experiments, the standard 0.0518 *M* base was added in increments of 0.200 cc.

As an infinite time or 100% point, 13.3 times the half life was used. This corresponds to 99.99% completion for a first order reaction. This figure always checked the figure calculated from the weighing data within 3%. Corrections were made in the data when the temperature at one minute was more than 0.05° removed from 25.00°, by adding to all times 1.2% of their value multiplied by the average deviation in tenths of a degree up to 70% reaction. This is the calculated correction based on a 3.3-fold change of rate between 25 and 35°. Runs deviating by more than 0.2° were discarded.

Polarographic Determination of Chloride.—A preliminary polarogram on a hydrolyzed solution of 0.00097 *M* mustard gas showed sharp chloride and hydrogen ion waves with half-wave potentials of +0.20 and −1.5 volts *vs.* the saturated calomel electrode. The hydrogen wave had a pronounced maximum, but the chloride did not appear to have one. There was no sign of a wave between the two. The plateau region of the chloride wave began at about +0.25 volt. Since the half-wave potential of chloride increases 59 millivolts for each tenfold decrease in concentration we selected 0.35 volt to be sure of being on the plateau at 2% reaction. This corresponds to −0.05 volt *vs.* our saturated sulfate electrode.

The ordinary polarographic technique of averaging the current by use of a ten- to twenty-second period galvanometer would result in too much lag to follow accurately a reaction with a half-life of three minutes. Therefore a Moll microgalvanometer with a full period of one-fifth of a second was used with a scale at 1.2 meters distance to follow the entire current swing during the life of each drop. The maximum of the swing was recorded. The circuit was connected as shown in Fig. 2. Since the cell resistance was of the order of 100 ohms and the maximum current was about 10 microamperes, the internal voltage drop and hence the applied voltage varied during the course of a run by about 1 millivolt. Also the voltage, which was set at 0.05 volt, was that applied to the cell in series with the galvanometer and its series and shunt resistances, and differed by several millivolts from that applied to the cell itself. However this arrangement of the circuit caused no error because of the way in which chloride was measured.

The galvanometer was first standardized with a 0.0499 *M* solution of hydrochloric acid as follows. One hundred cc. of 0.15 *M* sodium benzenesulfonate and 4.96 cc. of acetone were placed in the reaction cell, the dropping electrode inserted, known amounts of hydrochloric acid from zero to 4 cc. added from the 5-cc. microburet, and the maximum of the fifth or any following swing recorded after each increment. The first two or three swings were abnormally large until the region near the tip of the electrode had been partially depleted of chloride and a steady state had established itself. This variation in local con-

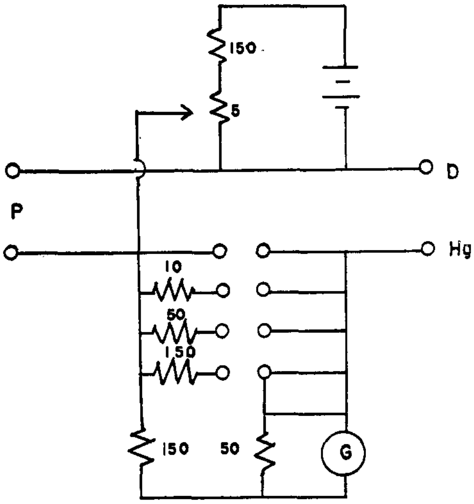

Fig. 2.—Circuit used in polarographic determination of chloride ion: P, to potentiometer; D, dropping electrode; Hg, mercurous sulfate electrode; G, galvanometer. The numbers are resistances in ohms.

centration because of electrolysis by the drop is the principal source of error in this analysis. Since the initial galvanometer reading is the same in a kinetic run as in the standardization, the resulting plot of galvanometer reading *vs.* cc. of hydrochloric acid enables kinetic data to be translated into per cent. reaction directly.

It was found that thiodiglycol did have a small effect on the current. For example, 0.0036 M added thiodiglycol gave a current four times the normal residual current, or one equal to that obtained at 35% reaction with the chlorohydrin. It might seem, therefore, that there are two serious errors in this procedure other than difference in local depletion of chloride between the standardization and the run: first, the volume is increased 4% in the standardization, not at all in the run; second, thiodiglycol accumulates as a reaction product, but is not present in the standardization. However these "errors" are proportional to the measured percentage reaction, which in turn is based on the final *observed* current, and so are not errors at all.

The procedure followed was the same as that in the runs with intermittent titration for hydrogen ion up to a point fifteen seconds after the start of the run. Then the stirrer and the thermostat motor and heater were turned off (to eliminate vibrations) and the nitrogen stream diverted to pass over the surface. The first galvanometer reading was usually obtained at about thirty seconds. Since the hydrogen ion liberated is not neutralized, the pH falls steadily to nearly 3.0 by the end of the reaction.

The shunts on the galvanometer made it possible to decrease the sensitivity several times as the reaction proceeded. Thus large, easily measured deflections were obtained on the meter scale at all percentage reactions. A standardization curve was prepared for each sensitivity.

Table I gives data on the machine-made capillaries which we used. The drop time given is that observed during the runs, *i.e.*, in the salt solutions with the voltage applied. Since the two runs on mustard, 100 and 105, gave the same results, the drop time does not seem to be an important factor affecting the accuracy by this method.

TABLE I

Run no.	Capillary	Length, cm.	Height of Hg above tip, cm.	Drop time, sec.
74	A	4.5	65	1.02
101	A	4.5	57.5	1.20
100	A	4.5	57.5	1.22
105	B	11	65	2.22

Results with Mustard Chlorohydrin.—Data for seventeen typical kinetic runs on the hydrolysis and displacement reactions of mustard chlorohydrin at 25° in water containing 5% acetone are plotted in Fig. 3. To avoid confusion in the figure, not all the experimental points are plotted, but a selection to avoid superposition of points as far as possible. All the plots are seen to be linear when the logarithm of mustard chlorohydrin concentration, as inferred from the production of hydrogen or chloride ion, is plotted against time, up to 90% reaction and beyond. There were no points which were not on the lines.

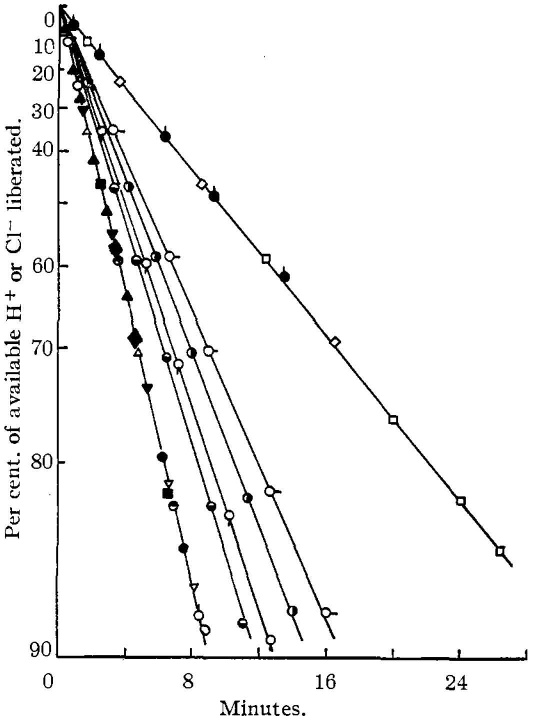

Fig. 3.—Logarithmic plots of seventeen experiments on hydrolysis and displacement reactions of mustard chlorohydrin (β-chloroethyl-β'-hydroxyethyl sulfide). Points plotted are selected to avoid overlapping. The ordinate scale is a logarithmic one, the ordinates being proportional to log C_0/C as inferred from chloride ion determinations in runs 74 and 101, and from hydrogen ion titrations in the other fifteen runs. All runs are at ionic strength 0.144 except those designated "no inert salt." The significance of the points is as follows: ▲, Run 74 (chloride ion determined); ▼, Run 101 (chloride ion determined); △, Run 63; ▽, Run 76; ○, Run 116, 0.00096 M NaH_2PO_4; ȯ, Run 123, no inert salt; ◓, Run 122, 0.00192 M NaCl; ●̇, Run 111, 0.142 M NaCl; □, Run 125, 0.142 M NaCl, 0.00096 M NaH_2PO_4; ◇, Run 126, 0.142 M NaCl, immediate additions of NaOH; ◒, Run 117, 0.192 M NaCl; ♀, Run 121, 0.0192 M NaCl, no inert salt; ◑, Run 118, 0.0385 M NaCl; o-, Run 119, 0.0385 M NaCl, no inert salt; ●, Run 127, 0.127 M, NaCl, 0.0043 M sodium monothiophosphate (P); ■, Run 64, 0.0043 M P; ◆, Run 77, 0.0043 M P.

In all the runs not otherwise described the ionic strength was 0.144, being brought to this value by adding the necessary amount of sodium benzenesulfonate. The initial molarity of mustard chlorohydrin in each case was 0.00089 *M*.

Ten of the runs have the same first order rate constant within the experimental error, 0.260 ± 0.016 min.$^{-1}$ These ten include two runs in which the percentage reaction figures represent chloride ion liberated as a percentage of total chloride liberated up to a time equal to 13.3 times the half-life (99.99% reaction). They also include eight runs in which the percentage figures represent hydrogen ion liberated as a percentage of total hydrogen ion at 13.3 times the half-life. Of the eight hydrogen-ion runs having the same rate constant, two were like the chloride-ion runs in having no added competitors (only the usual inert salt addition to bring the ionic strength up to 0.144 *M*); one had 0.00096 *M* monosodium phosphate added to keep the *p*H below 6.0, and was followed with a *p*H 5.1 indicator; one had the inert salt omitted; one had 0.00192 *M* chloride added; three had 0.0043 *M* sodium monothiophosphate added; and one of these also had 0.127 *M* chloride added.

The other seven runs all had considerable amounts of added chloride, and the data represent hydrogen ion liberated. In three of these runs the chloride ion concentration was 0.142 *M*, and accordingly the usual addition of inert salt to make the total ionic strength up to 0.144 ± 0.003 *M* was omitted. One of the three runs was done in the usual way with the brom thymol blue indicator yellow and blue about equal amounts of time; one had 0.00096 *M* monosodium phosphate added to keep the *p*H below 6.0, and was followed with a *p*H 5.1 indicator; and in the other, which had brom thymol blue and no buffer, additions of sodium hydroxide equivalent to 25% reaction were made as soon as each end-point was reached to keep the *p*H above 10.0 half of the time. The three runs have the same rate constant within experimental error, showing the unimportant part played by *p*H in this reaction. The other four runs represent intermediate amounts of chloride added, with and without inert salt added to make the ionic strength up to 0.144 *M*.

It is qualitatively predicted from eqn. 1 that a sufficiently high concentration of chloride ion should be able to reconvert an appreciable fraction of the ethylenesulfonium ion into starting material in competition with water and the other reagents present. Such an effect would appear as a simple lowering of the first-order rate constant for the over-all reaction, as can be shown by a simple derivation based on eqn. 1.

The fact that the logarithmic plots are linear shows that concentrations of chloride ion up to 0.00089 *M* produce no observable effect of this kind. Nor does any effect appear at a chloride ion concentration of 0.00192 *M* (Run 122). At ten times this concentration of chloride ion there is a marked retardation of hydrolysis (Runs 117 and 121) but no effect upon the rate of reaction in the presence of monothiophosphate (Run 127) even by 0.127 *M* sodium chloride. These results provide a basis for calculating the competition factor of chloride ion, as will be done in a later section, and they emphasize the fact that the competition factor of thiophosphate is enormously greater than that of chloride ion.

The identity of the rates in Runs 116 and 123, with and without inert salt, shows that the initial cyclization is insensitive to ionic strength, while the distinct difference in rate between Nos. 117 and 121 shows that the *reverse* reaction between sulfonium ion and chloride ion must be retarded by an increase in ionic strength. This, too, will be treated quantitatively below. It is immediately obvious, however, that in kinetic experiments with sodium chloride as the only added salt, the determined competition factor of chloride ion will be lower, the higher the sodium chloride concentration, as a result of this property.

Since there is no evidence of any difference between the rates of appearance of hydrogen ion and of chloride ion (runs 63, 74, 76, 101), there is no accumulation during the hydrolysis of either an ethylenesulfonium ion or a dimeric sulfonium ion, to any extent observable by our technique.

Finally, the total absence of any effect of sodium monothiophosphate on the rate of hydrolysis of, or displacement in, mustard chlorohydrin strongly suggests that the difunctional character of mustard itself is somehow responsible for the accelerating effect noted by Ogston in the presence of thiophosphate and other competitors.

Results with Mustard.—Figure 4 shows data for eleven typical kinetic runs on mustard, temperature, solvent and ionic strength being the same as in the case of the chlorohydrin. In contrast to the case of the chlorohydrin, none of the first-order plots is linear, all being convex upward. Since the hydrolysis and displacement reactions of mustard involve the replacement of both chlorine atoms, the nature of the reacting molecule changes from the early to the late part of the reaction, and the reaction in the case of mustard is a succession of two reactions, one of mustard and one of the chlorohydrin. Unless both species undergo cyclization at identical rates, it is evident that a logarithmic plot based upon the evolution of chloride ion or of hydrogen ion must show curvature, and the type of curvature observed indicates that k_1 for mustard is lower than for the chlorohydrin. This would be expected on the basis of the reasoning developed in connection with the so-called nitrogen mustards.[9]

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[9] (a) P. D. Bartlett, S. D. Ross and C. G. Swain, THIS JOURNAL, **71**, 1415 (1949); (b) see also B. Cohen, E. R. Van Artsdalen and J. Harris, *ibid.*, **70**, 281 (1948).

Five of the runs fit the same curve on this plot and therefore are described by the same pair of first order rate constants within the experimental error. These are runs without effective competitors added. Two of the five represent liberation of chloride ion, and the other three liberation of hydrogen ion. One of the hydrogen ion runs was done by the ordinary technique with the *p*H varying from 4 to 10; one had 0.00096 *M* sodium dihydrogenphosphate buffer to keep the *p*H below 6.0 and was followed with a *p*H 5.1 indicator, and the other had 0.00192 *M* chloride added.

Four of the curves give data for the liberation of hydrogen ion in runs with considerable amounts of added chloride. Except for their curvature they are similar to the curves obtained with the chlorohydrin. However, the remaining curve in Fig. 2 gives data for liberation of hydrogen ion in two runs with 0.0043 *M* added sodium monothiophosphate. In contrast to the case with chlorohydrin this curve differs from the normal curve without competitors, the rate of reaction here being considerably greater than the normal rate.

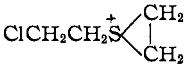
When a concentration of chloride (0.00192 *M*) twice that formed by 100% reaction was added at the start (run 8), the initial rate was the same as without additions within experimental error. Therefore this increase in rate with thiophosphate added is too large to be explained as an elimination of reversal by chloride ion. It is easy to see why the later stages of the reaction with thiophosphate should be faster than the later stages of the simple hydrolysis, for the substance undergoing reaction is a sulfide containing in the one case the group $-CH_2CH_2SPO_3^=$ and in the other case the group $-CH_2CH_2OH$, of which the former, with its double negative charge, should be more base-strengthening than the latter and should therefore contribute more to the reactivity of the sulfide sulfur in the cyclization step.

Quantitative Treatment of Results

Notation.—For the equations to follow, it will be convenient to establish the following notation. The symbols for molecular species will denote molecules in chemical equations, and their concentrations in moles per liter when in mathematical equations.

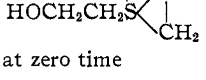
M = mustard, $(ClCH_2CH_2)_2S$
C = mustard chlorohydrin, $ClCH_2CH_2SCH_2CH_2OH$
V = $ClCH_2CH_2SCH_2CH_2SPO_3^=$
P = $PSO_3^=$

M* = mustard ethylenesulfonium ion,



$ClCH_2CH_2\overset{+}{S}(CH_2)_2$

C* = chlorohydrin ethylenesulfonium ion,



$HOCH_2CH_2\overset{+}{S}(CH_2)_2$

Subscript zero refers to concentration at zero time
k_1, k_{-1}, k_2, k_w as defined in eqn. 1.

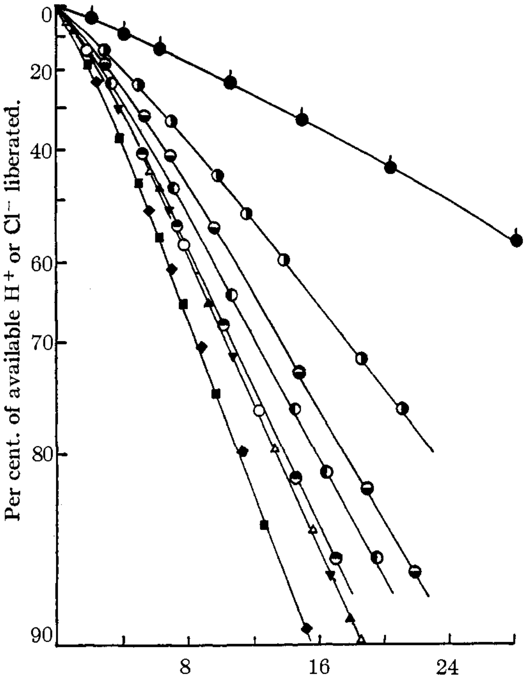


Fig. 4.—Logarithmic plots of eleven experiments on hydrolysis and displacement reactions of mustard (β,β′-dichlorodiethyl sulfide). Points plotted are selected to avoid overlapping. The ordinates are proportional to log $(Cl^-)_\infty/((Cl^-)_\infty - (Cl^-))$ in runs 100 and 105, and to log $(H^+)_\infty/((H^+)_\infty - (H^+))$ in the other nine runs, the subscript $_\infty$ referring to the concentration at the end of the reaction. All runs are at ionic strength 0.144. The significance of the points is as follows: ▲, run 100 (chloride ion determined); ▼, run 105 (chloride ion determined): △, run 28; ○, run 114, 0.00096 *M* NaH_2PO_4; ◓, run 8, 0.00192 *M* NaCl; ◐, run 19, 0.0096 *M* NaCl; ◒, run 9, 0.0192 *M* NaCl; ◑, run 20, 0.0385 *M* NaCl; ●, run 21, 0.142 *M* NaCl; ■, run 16, 0.0045 *M* sodium monothiophosphate (P); ◆, run 18, 0.0045 *M* P.

k_{1M}, k_{1C}, k_{1V}, etc., are the k_1's for the reactions of M, C and V, respectively
$F^{\mu}_{Cl^-} = (k_{-1}/k_w)$ at the ionic strength μ.
$F^{\mu}_X = (k_2/k_w)$ at the ionic strength μ

These are the competition factors of Ogston, except that the ionic strength was not specified in Ogston's work.

$b = (Cl^-)_0$

$$k_{bC} = \frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0 = b}}{C} \text{ for chlorohydrin}$$

$$k_{bM} = \frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0 = b}}{M} \text{ for mustard}$$

Ionic Strength Effects.—We shall now consider quantitatively the dependence of the competition factor upon the concentration of the competitor. The kinetic results with the chlorohydrin show that, within the accuracy of the experiments, the rate of hydrolysis or displacement is determined entirely by k_{1C} when there is no added chloride ion, and k_{WC} may be considered to be infinitely great compared to k_{1C}.[10] This is an extreme not reached in any of the nitrogen mustards, but approached with increasing chlorination in the series: $ClCH_2CH_2N(C_2H_5)_2$, $(ClCH_2CH_2)_2NC_2H_5$, $(ClCH_2CH_2)_3N$.[9] It is reasonable that decreasing basicity of the basic center should increase the values of the ratios k_w/k_1, k_2/k_1 and k_{-1}/k_1 thus decreasing the extent to which the ethylene-onium intermediate accumulates during reaction.

Since k_{WC} is large relative to k_{1C}, the following simplified treatment is valid: In the absence of added chloride ion

$$\frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0 = 0}}{C} = k_{1C} = k_0$$

In the presence of an added excess of chloride ion such that its concentration b remains approximately constant during reaction, and in the absence of other competitors

$$\frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0 = b}}{C} = k_{1C}\frac{k_{WC}}{k_{WC} + k_{-1C}\, b} = k_{bC}$$

The ratio of rates in presence and absence of added chloride ion is thus equal to $k_{WC}/(k_{WC} + k_{1C}b)$ or to $1/(1 + F_{Cl}b)$, the special form for chloride ion of a general expression derived by Ogston and applied by him and by Clark, Cohen and Harris[11] to the estimation of competition factors for the bifunctional reagent, mustard. The explicit form for F_{Cl} is

$$F_{Cl} = \frac{1}{b}\left[\frac{k_0}{k_{bC}} - 1\right] \qquad (3)$$

The nature of this equation is such as to magnify errors in the kinetic runs when two runs with rates differing only slightly are used to determine competition factors. For example, if F_{Cl} is determined from Runs 76 and 117, and the rate of each reaction is subject to a maximum uncertainty of 6%, the maximum uncertainty in F_{Cl} becomes 52%. Nevertheless, if we use the four runs, 76, 111, 117 and 118, at ionic strength 0.144, to calculate $F_{Cl}^{0.144}$, we obtain values of 18.1, 15.6 and 16.6, which are all within less than 8% of the weighted mean of 16.9. From this value for the competition factor we can calculate back the relative rates in the three runs with chloride added with a mean deviation of 2.7%. However, this procedure applied to Runs 119 and 121 with sodium chloride but without inert salt, at lower ionic strengths, yields calculated values of relative rate deviating from the observed by 7.8 and 12%, outside the experimental error in both cases. It appears from these results that the competition factor of chloride ion is a function of ionic strength, but not of chloride ion concentration at constant ionic strength.

From the Bronsted rate equation[12] and the limiting Debye-Hückel equation,[13] one can predict semi-quantitatively for a dilute solution how the rate constant for a reaction between oppositely charged ions should respond to changes in ionic strength. The constant k_{-1} is of this type, while k_1 and k_w are not and should show a zero salt effect by the Bronsted theory. Then using the Debye–Hückel relation for the activity coefficient of ions

$$-\log \gamma = 0.5Z^2\sqrt{\mu} - \beta\mu \qquad (4)$$

and the Brönsted law applied to k_{-1}

$$k_{-1} = k_{-1}^{0}\frac{\gamma_{C^+}\gamma_{C^-}}{\gamma^*} \qquad (5)$$

we obtain

$$\log_{10} k_{-1} = \log_{10} k_{-1}^{0} - \sqrt{b} + (\beta_{C^+} + \beta_{Cl} - \beta^*)b \qquad (6)$$

or

$$\log_{10} F_{Cl^-} = \log_{10}\left(\frac{k_{-1}^{0}}{k_w}\right) - \sqrt{b} + (\beta_{C^+} + \beta_{Cl^-} - \beta^*)b \qquad (7)$$

if the total ionic strength is due to added chloride. Here the γ's are activity coefficients, μ is the ionic strength, $Z = 1 =$ the valence of each reacting ion, k_{-1}^{0} and the β's are constants independent of the conditions. If the cyclic intermediate, C^*Cl^-, has a minimum in its mean activity coefficient curve at 1.0 ± 0.5 M ionic strength as do most uni-univalent electrolytes, then $\beta_{C^+} + \beta_{Cl^-} = 0.50 \pm 0.20$. Since the transition state is a neutral molecule, β^* is negative,[14] and $-\beta^*$ probably adds about 0.20 more to the sum. We shall use 0.70 as the estimated value of $\beta_{C^+} + \beta_{Cl^-} - \beta^*$. (The results of the calculation are not much affected by a variation of ± 0.20 in its assumed value.) We shall use the experimental data to determine $(k^0 - 1/k_w)_{\mu=0}$, which should be a *true constant*. This might be called the "competition factor at zero ionic strength," and will be denoted by F_{Cl}^{0}. Its value is calculated from the competition factors in Table II. The

TABLE II

F_{Cl} AS A FUNCTION OF IONIC STRENGTH; APPLICATION OF THE DEBYE–HÜCKEL LIMITING LAW TO RUNS WITHOUT INERT SALT

Run	b	$\frac{k_b}{k_0}$	obs. F_{Cl}^{μ}	Calculated using $F_{Cl}^0 = 32.2$ F_{Cl}^{μ}	$\frac{k_b}{k_0}$	Deviation, %
123	0	1.00	..	32.2	1.00	
121	.0192	0.70	22.4	24.2	0.682	−2.6
119	.0385	.54	22.1	21.8	.545	+0.9
111	.142	.28	18.1	17.0	.294	+5.0
					Mean	2.8%

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(10) Calculations based on eqn. 1 without this simplification show that the assumption $k_w/k_1 = \infty$ introduces about a 3% error into the calculated competition factor of chloride ion if k_w is actually as small as 30 k_1, and a negligible error, for these experiments, if $k_w \gg 100\ k_1$.

(11) W. M. Clark, B. Cohen and J. Harris, N. D. R. C. Report, June 1, 1942.

(12) J. N. Bronsted, *Chem. Revs.*, **5**, 265 (1928).

(13) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

(14) E. Hückel, *Physik. Z.*, **26**, 93 (1925).

weighted mean value for F^0_{Cl} is 32.2; using this value and calculating back, we obtain the calculated values of F^μ_{Cl} and of k_b/k_0 shown in the fifth and sixth columns of Table II. It will be noted that the value of $F^{0.142}_{Cl}$ calculated is 17.0, compared with the mean value of 16.9 obtained from the four runs made at ionic strength 0.144. The mean deviation of the calculated relative rates from the observed is 2.8%, satisfactorily within the experimental uncertainty.

Although these experiments do not cover a range sufficient to establish the validity of this treatment in any unique way, it is clear that the variation of competition factor with concentration of the competitor, previously thought to be an obstacle to the acceptance of the simple ethylenesulfonium ion mechanism, is an entirely normal effect of ionic strength which would be predicted on the basis of accepted theories. Such variation should, of course, be exhibited by other competitors bearing an ionic charge, though not by neutral competitors. Linstead and Doering[15] found that the competition factors of acetate ion for mustard in 0.05 *M*, 0.19 *M* and 0.4 *M* acetate solutions were 8.2, 5.4 and 4.7, respectively, this variation being of the general sort called for by the present theory.

The Determination of k_{1M}.—The value of k_1 for mustard itself should be the same with all competitors, and the question remains: is the initial slope of a line such as those in Fig. 4 an adequate measure of the initial k_1? This question can be answered quantitatively by using the first-order rate constant evaluated for mustard chlorohydrin and the equation for successive first-order reactions. It is seen from Fig. 4 that the logarithmic curves of fraction of total available hydrogen ion remaining unliberated are smooth curves showing no resolution into initial and final linear portions. In past work[4] k_{1M} has been estimated as the slope of the earliest portion of such a curve for which experimental points were available, the hope being that the small amount of C or V formed during such interval would not appreciably affect the rate of production of hydrogen ions. Whether this is true or not obviously depends upon the relative magnitudes of k_{1M} and k_{1C} or, in the case at hand of the use of a strong competitor, the relative magnitudes of k_{1M} and k_{1V}. Our direct measurement of k_{1C} offers a means of determining k_{1M} from the kinetic data on mustard without making any approximation about limiting slopes. We need only assume that with mustard, as with the chlorohydrin, $k_w >> k_{-1}$, so that the entire process may be treated as a pair of consecutive irreversible first-order reactions.

In such a system the liberation of hydrogen ion should closely follow the law[16]

$$[H^+] = M_0\left[2 - \left(\frac{k_{1M} - 2k_{1C}}{k_{1M} - k_{1C}}\right)e^{-k_{1M}t} - \frac{k_{1M}}{k_{1M} - k_{1C}}\,e^{-k_{1C}t}\right] \quad (8)$$

From the work with mustard chlorohydrin we know that in runs with no added chloride ion and with no added competitor, $k_{1C} = 0.260 \pm 0.016$ min.$^{-1}$. For this value of k_{1C}, a value of $k_{1M} = 0.155 \pm 0.010$ gives the closest agreement between the curve calculated from eqn. 8 and the experimental curves for mustard under these same experimental conditions. With this value of k_{1M} the calculated curve lies slightly above the experimental up to 70%, slightly below beyond 70%, but the deviations in time at 50% and 90% are within 1 and 3%, respectively, or well within the experimental error.

Similarly we can determine the k_{bM} corresponding to various amounts of added chloride. From the values of k_{bM} we can then calculate the competition factor of chloride at 0.144 *M* ionic strength for M*, *i.e.*, in the first of the two processes making up the reaction. We can then compare the competition factor of chloride for M* with the corresponding factor of chloride for C*, which determines the reactivity of chloride in the second half of the reaction.

Table III gives the data for the runs with chloride added, all done at an ionic strength of 0.144 *M*, and the calculated values of k_{bM} and k_{bC}/k_{bM}. It is reasonable to assume that the competition factors at zero ionic strength would also be the same for mustard as for the chlorohydrin, *viz.*, 32. Thus the discriminating ability of an intermediate between competitors is not affected to a detectable extent by differences in structure of the sort existing between mustard and mustard chlorohydrin.

TABLE III

DETERMINATION OF k_{bM} AT DIFFERENT CHLORIDE ION CONCENTRATIONS AT 25° IN WATER CONTAINING 5% ACETONE

Run	b	$t_{70\%}$	k_{bC}	k_{bM}	k_{bM}/k_{bC}
28	0.0000	10.30	0.260	0.155	0.595
8	.0019	10.55	.260	.152	.585
9	.0192	13.65	.194	.118	.610
20	.0385	17.65	.153	.090	.590
21	.142	38.70	.072	.041	.570
					Av. .59

With the values at hand for k_{1M}, k_{1C} and F^μ_{Cl}, the entire curves for mustard with various amounts of chloride added can be calculated within experimental error.

The course of the displacement experiments with sodium monothiophosphate differs from that of the hydrolytic experiments in that the ethylenesulfonium ions, when formed, react exclusively with thiophosphate ion. The kinetic equation for the two successive reactions is accordingly identical with Equation (8) except

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(15) R. P. Linstead and W. E. Doering, NDRC Report, April 15, 1942.

(16) C. G. Swain, THIS JOURNAL, **66**, 1696 (1944); A. Rakowski, *Z. physik. Chem.*, **57**, 321 (1907).

for the replacement of k_{1C}, wherever it occurs, by the hitherto unknown constant k_{1V}. Since the other constant of this equation k_{1M}, is now known, it becomes possible to determine the value of k_{1V} in the same manner as was just done using eq. 8.[16] A calculated curve using $k_{1V} = 0.70$ approximates the experimental curve most closely, and the sensitivity of the calculated curve to the assumed value suggests the limits ± 0.05 for this constant. The calculated curve has the same general shape as the experimental, lying above it throughout but always within 2% of it on the time coördinate.

Thus both hydrogen ion and chloride ion are liberated by mustard in dilute solution according to the equation

$$[H^+] = [Cl^-] = a\left[2 - \left(\frac{k_{1M} - 2k_{1'}}{k_{1M} - k_{1'}}\right)e^{-k_{1M}t} - \left(\frac{k_{1M}}{k_{1M} - k_{1'}}\right)e^{-k_{1'}t}\right]$$

where $k_{1M} = 0.155$, and $k_{1'} = 0.260$ ($= k_{1C}$) or 0.70 ($= k_{1V}$) according to whether or not thiophosphate is added. From this equation it would seem that it should have been possible to estimate k_{1M} from the initial slope of a simple logarithmic plot [ln $(2a - H^+)$ *vs.* t], instead of by the curve-fitting method which we actually employed. The limiting initial slope on such a plot is $k_{1M}/2$. Ogston, Linstead and others used early points, with the origin, to measure the initial rate in this way. However, the value obtained is far from correct if any realizable fraction of the curve is used to define the slope. Even if points be used as early as 5.0% of total reaction, which are the earliest points that we have been able to obtain by the intermittent titration technique, the estimates of the initial rate so reached are still in error by 6% in the runs without thiophosphate added, and by 16% in the runs with thiophosphate added (see Table IV). This difference in errors is the cause of Ogston's observation that the initial rate with thiophosphate added was about 10% faster than without the addition. The present study accounts for this observation on the basis that the first rate constant (and initial rate) is the same under both conditions, and that only the second rate constant differs, according to whether the second step is ionization of chlorohydrin or of thiophosphate displacement product.

TABLE IV

ERRORS INVOLVED IN CALCULATING k_1M FROM INITIAL SLOPE OF OVER-ALL CURVE FOR REACTION OF MUSTARD GAS

Rate constants		Point	Used	k_1 Calcd. from point	Error,
k_1	k_2	t	%H^+	and origin	%
0.155	0.260	$^1/_2$	4.0	0.162	4.5
.155	.260	1	8.2	.171	10
.155	.700	$^1/_2$	4.3	.177	14
.155	.700	1	9.3	.196	26

Experimental Errors.—Our best estimate of the maximum error in the runs with intermittent titration for hydrogen ion is ± 6% in the rate constant or time value for 50% reaction. This corresponds to a 2.0% analytical error in the 50% point if the zero point is correct, or a 1.0% error in opposite directions in each. In the polarographic chloride runs a reasonable estimate of the maximum uncertainty is about ± 10% in rate constant. The largest uncertainty in the runs with intermittent titration was in the matching of color against the standard color at the zero point and endpoints. This was greatest with the *p*H 5.1 indicator and the *p*H 8.0 indicator in runs with sodium monothiophosphate added where it amounted to ± 0.015 cc. (± 1.5 divisions on the microburet) or 0.9% of the total reaction. The "time of mixing" error was under five seconds (3% in rate constant at 50% reaction). Standardization of glassware and factors of solutions were accurate to 0.5% (< 2% in rate constant), temperature control to 0.05°, *p*H of end-points to 0.2 *p*H unit, solution volume to 2%, ionic strength to 2%. In the polarographic runs the larger 3% error in individual chloride values was due to electrolysis at the dropping electrode and local depletion of the chloride concentration near the drop during the run.

Effect of Dimerization.—Since the absolute chloride and hydrogen ion values are the same within experimental error during the first 70% of reaction, it is clear that the C–C dimer, $HOCH_2CH_2SCH_2CH_2S^+(CH_2CH_2Cl)CH_2CH_2OH\text{-}Cl^-$, does not accumulate as an intermediate during the early stages of the reaction. Such an accumulation would be kinetically equivalent to accumulation of C^+.

The average final end-point in 15 runs without added thiophosphate was 1.700 cc., with an average deviation of 0.017 cc. The average endpoint in three runs with added thiophosphate was 1.737 cc., with an average deviation of 0.018 cc. This 0.037 cc. difference in endpoint is outside the experimental error and corresponds to the production of 2.2% of the hydrolyzed dimer, $HOCH_2CH_2SCH_2CH_2S^+(CH_2CH_2OH)_2Cl^-$, in the runs without thiophosphate added. However, there is an uncertainty in this value of at least ± 50%. Two sets of paired runs, with and without thiophosphate added, indicated only 1.2% dimer. In the preceding analysis of the experimental data we have neglected the effect of this dimer formation and based percentage reaction on the final endpoints actually observed in each individual run. If 2.2% of the carbon were side-tracked by dimer formation, and half of this dimer were formed by the time of 50% reaction there would be no error resulting from this procedure. Even if we assume that as little as one quarter of the total dimer is formed up to 50% reaction, the time and rate constant at 50% reaction would still be in error by less than 3.5%. This is less than the experimental error. If we had done kinetic runs with the initial molarity of C greater than 0.001 *M*, it would have been necessary to take this dimerization into account in the quantitative treatment.

Summary

The rate of hydrolysis of β,β′-dichlorodiethyl sulfide (mustard gas) and of β-chloro-β′-hydroxydiethyl sulfide (mustard chlorohydrin) in aqueous solution containing 5% of acetone at 25° has been measured at different concentrations of chloride and monothiophosphate ions and at controlled ionic strength. The rate of liberation of hydrogen ions, measured by the intermittent titration method of Peters and Walker, is identical within the experimental uncertainty with the rate of liberation of chloride ions, followed polarographically with a short-period galvanometer, a fact which shows that neither ethylenesulfonium ions nor any dimeric sulfonium ions accumulate appreciably during reaction.

The results of 17 runs on mustard chlorohydrin and 11 runs on mustard have been interpreted in some detail by means of the mechanistic scheme of eq. 1, involving a rate-determining formation of an ethylenesulfonium ion followed by competition for this ion by water, chloride ion and other competitors such as thiophosphate ion, all at rates much greater than that of the initial cyclization. The "competition factor" of chloride ion, defined as the ratio of the rate constants for reaction of the ethylenesulfonium intermediate with chloride ion and with water, is shown to be independent of the chloride ion concentration at constant ionic strength, but to depend upon ionic strength in a manner predictable from the Brønsted rate equation and the limiting Debye–Hückel law for the activity coefficient of an ion.

By first determining the strictly unimolecular rate constant (0.260 ± 0.016 min.$^{-1}$) for hydrolysis or displacement of mustard chlorohydrin and then introducing this into the equation for two successive unimolecular reactions, the first rate constant for mustard has been calculated as 0.155 ± 0.010 from the data covering the two steps in its hydrolysis to thiodiglycol, which are not resolvable by any simpler method. From this constant and the data for displacement of the two chlorines successively by monothiophosphate, the constant for cyclization of the S-2-(2-chloroethylthio)-ethyl monothiophosphate ion is determined to be 0.70 ± 0.05. The fact that this ion cyclizes more than twice as fast as mustard chlorohydrin produced, in earlier experiments, the false appearance of mustard having a faster initial reaction in the presence of thiophosphate than in its absence.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 24, 1948

[CONTRIBUTION FROM THE WOLCOTT GIBBS LABORATORY OF HARVARD UNIVERSITY]

Kinetics and Mechanism of the Reactions of Tertiary β-Chloroethylamines in Solution. III. β-Chloroethyldiethylamine and tris-β-Chloroethylamine[1]

BY PAUL D. BARTLETT, SIDNEY D. ROSS AND C. GARDNER SWAIN

In the first[2] and second[3] papers of this series the existence of a general mechanism was established whereby a tertiary β-chloroethylamine undergoes internal cyclization to an ethylene-immonium ion as a first step common to hydrolysis, dimerization and displacement reactions. By quite different methods in the cases of methyl-bis-β-chloroethylamine and ethyl-bis-β-chloroethylamine it was possible to determine the separate rate constants for the steps in this mechanism, and to show how the observed difference between predominating hydrolysis and predominating dimerization rested upon moderate differences between the relative values of the constants for these two homologs.

Two other tertiary β-chloroethylamines have been examined more briefly and such quantitative information about them as was obtained is here presented. In the case of β-chloroethyldiethylamine the ethylene-immonium ion is comparatively stable and its formation can be observed uncomplicated by other reactions. We have not determined the rates of reaction of this ion with displacing reagents, although such measurements should present no difficulties. In the case of tris-β-chloroethylamine hydrolysis occurs to bis-β-chloroethylethanolamine hydrochloride with much less accumulation of the intermediate ethyleneimmonium ion than in the previous cases; in this respect this amine is intermediate between the other "nitrogen mustards" and β,β-dichlorodiethyl sulfide ("mustard gas").[4] In the presence of alkali to neutralize the liberated hydrochloric acid, the hydrolysis proceeds through successive stages to triethanolamine.[5]

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(1) The work described in this paper was performed under Contract NDCrc-136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development in 1942 and 1943.

(2) Part I: P. D. Bartlett, S. D. Ross and C. G. Swain, THIS JOURNAL, **69**, 2971 (1947).

(3) Part II: P. D. Bartlett, J. W. Davis, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2977 (1947).

(4) P. D. Bartlett and C. G. Swain, *ibid.*, **71**, 1406 (1949).

(5) C. Golumbic, M. A. Stahmann and M. Bergmann, *J. Org. Chem.*, **11**, 550 (1946).