Friedel–Crafts acylation of benzene using the above mentioned acid halides is a result of some interest after the observations of Henne and Newman,[14] that aluminum chloride reacts with organic fluorides to produce aluminum fluoride and an organic chloride. The resistance to this reaction of the fluorine atoms in the trifluoromethyl group in this type of compound is a useful property. Tests revealed no inorganic fluoride in the reaction products.

1,1,1 - Trifluoro - 2,2 - dichloro - 2 - phenylethane failed to react with antimony trifluoride to prepare pentafluorophenylethane. This is unexpected due to the usual reactivity in the Swarts reaction of chlorine atoms adjacent to a phenyl group or a double-bonded carbon atom. The formation of benzotrifluoride by the action of hydrogen fluoride on benzotrichloride[15] (now accomplished in a pressure vessel at higher temperatures in excellent yield) is an indication of the ease of reaction of such a chlorine atom. In fact, even the fluorine atoms in benzotrifluoride are moderately reactive. This compound and related ones hydrolyze readily, if heated with 80% sulfuric acid. This reaction is useful for the identification of trifluoromethyl substituted aromatic compounds, and it is here used to prepare the carboxylic acids from such compounds for this purpose.

Pentafluorophenylethane would be expected to be prepared by the action of mercuric or silver fluoride on the 1,1,1-trifluoro-2,2-dichloro-2-phenylethane.

(14) Henne and Newman, THIS JOURNAL, **60**, 1697 (1938).
(15) Simons and Lewis, *ibid.*, **60**, 492 (1938).

The Grignard reaction has not previously been reported in the literature for use in connection with fluorine compounds of this type. It is used herein for two purposes. Trifluoroacetophenone reacted with a phenyl Grignard to form diphenyltrifluoromethylcarbinol. *m*-Bromobenzotrifluoride reacted with magnesium in ether to form a Grignard reagent from which *m*-methylbenzotrifluoride was prepared. An unexpected result was obtained in treating this Grignard reagent with dimethyl sulfate. A 65% yield of benzotrifluoride was obtained and only 9% of methylbenzotrifluoride was found.

Summary

1. Trifluoroacetyl chloride and bromide were prepared and their physical properties studied.

2. Trifluoroacetophenone was prepared by a Friedel–Crafts condensation in the presence of aluminum chloride.

3. Other new compounds reported are: *m*-bromobenzotrifluoride, 3,4-dibromobenzotrifluoride, *m*-methylbenzotrifluoride, trifluoroacetophenone-2,4-dinitrophenylhydrazone, 1,1,1-trifluoro-2,2-dichloro-2-phenylethane and diphenyltrifluoromethylcarbinol.

4. It was found that the Grignard reaction could be used in the synthesis of compounds containing the trifluoromethyl group.

5. A new qualitative test for fluoride ion based upon the precipitation of cerous fluoride is reported.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

The Resolution and Rates of Hydrolysis of *d,l*-α-Bromopropionic Acid and its Glycine Derivatives[1]

BY ALBERT F. CHADWICK[2] AND EUGENE PACSU

For the preparation of polypeptides consisting of optically active amino acids relatively large quantities of optically active α-halogen acids are required. One of the latter substances, active α-bromopropionic acid, was prepared by Walden,[3] Purdie and Walker[4] and also by Cowdrey, Hughes and Ingold,[5] from the calcium salt or the ethyl ester of active lactic acid and phosphorus pentabromide. Due to partial racemization during the reaction, the low yields, and also to the fact that it requires the preliminary preparation of pure *d*- and *l*-lactic acids, this method is unsuitable for the preparation of large quantities of

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(2) This paper is based upon a thesis submitted by Albert F. Chadwick, Allied Chemical and Dye Corporation Fellow in Chemistry, to the Faculty of Princeton University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Walden, *Ber.*, **28**, 1293 (1895).

(4) Purdie and Walker, *J. Chem. Soc.*, **67**, 914 (1895).

(5) Cowdrey, Hughes and Ingold, *ibid.*, 1208 (1937).

l-and*d*-α-bromopropionic acids. Another method, the value of which, however, is disputed by Timmermans and Jaffe,[6] is based on the reaction between *d*- or *l*-alanine and nitrosyl bromide.[7] The most obvious method of preparation of the two optically active α-bromopropionic acids is the resolution of the racemic compound by means of its alkaloid salts. Ramberg[8] experimented with the cinchonine salt in dilute aqueous solution, whereas Fischer and Warburg[7a] attempted resolution by crystallizing the various alkaloid salts of the racemic acid from water, alcohol or acetone. Their final conclusion was that there was no better method than the cinchonine procedure of Ramberg, but that it required some *twenty* recrystallizations to get a product which was nearly pure. They also observed that the cinchonine salt decomposed in aqueous solution at 50°, due to removal of bromide ion from the bromopropionate ion. To prevent this decomposition as much as possible they worked with a more dilute solution at 30–35° and evaporated it *in vacuo* to cause crystallization. Their final yield was 10% of the theoretical amount of *l*-acid with $[\alpha]^{20}D$ −26.7° (rotation −45.64°; 1-dm. tube; sp. gr., 1.708). Ramberg[9] later described the best procedure for the preparation of a very pure product with $[\alpha]^{20}D$ −29.0° (rotation −49.3°; 1-dm. tube; sp. gr., 1.700). Unfortunately, it can be obtained only in such a small yield that the method is impractical for synthetic purposes. Consequently, there is no method known by which pure *d*- or *l*-α-bromopropionic acid may be obtained in quantities great enough for use in synthetic experiments.

Because of this situation we attempted to resolve *d,l*-α-bromopropionylglycine rather than the uncoupled acid. With the negative charge of the carboxylate ion farther removed from the carbon–bromine bond it was thought that the alkaloid salts of this compound would be more stable in water to permit recrystallization than were those of the α-bromopropionic acid itself. Experiments carried out on the strychnine, brucine, quinine and cinchonine salts of *d,l*-α-bromopropionylglycine in aqueous, alcoholic and acetone solutions at different temperatures, ranging from 35° to the boiling points of the solvents employed, revealed the unexpected fact that the α-bromopropionylglycinate ion decomposes rapidly in solution, just as the α-bromopropionate ion does, yielding bromide ion. Another surprising discovery was that the *solid* brucine salt, in fact, any other alkaloid salt as well as the sodium salt, decomposed upon standing *even at room temperature*, yielding *d,l*-lactylglycine lactone and alkaloid hydrobromides or sodium bromide. The rate of this decomposition, which could be followed by titrating the bromide ion in the salts, was slow at first but it increased rapidly after a certain induction period. Our final conclusion reached from a systematic study of these reactions was that no practical method had been found by which the *d,l*-α-bromopropionylglycine could be resolved to give sufficiently pure active compounds in satisfactory yields.

The next obvious step was to find out what the stability of *d,l*-α-bromopropionylglycylglycine was. In this case it was thought that the charge of the carboxylate ion was certainly far enough removed from the carbon–bromine bond so that the ionization of the bromine atom in neutral solution would be very slow. It also seemed probable that the solid salts would be much more stable than were those of the α-bromopropionylglycine. The results of the measurements of the rates of ionization of the bromine atom in the α-bromopropionylglycylglycinate ion both in bicarbonate solution and in the solid state bore out the correctness of these suppositions; the rate in neutral solution was about one-twentieth that of α-bromopropionylglycinate ion, and in the solid state the decomposition was negligible. As to the resolution of *d,l*-α-bromopropionylglycylglycine, preliminary experiments showed that the alkaloid salts of this acid did not crystallize from aqueous solutions. Neither did the strychnine and cinchonine salts crystallize from acetone. The brucine and quinine salts, on the other hand, precipitated from the latter solvent in nearly quantitative yields, thus indicating practically no difference in the solubilities of the diastereomers. No better solvent could be found for the brucine salt, but the quinine salt crystallized in the right quantity from a 0.8% solution in ethyl acetate. After only three recrystallizations from this solvent the product was converted into the sodium salt, which showed $[\alpha]^{20}D$ 27.7° in aqueous solution. From the mother liquors an α-bromo-

(6) Timmermans and Jaffe, *Bull. chim. soc. belg.*, **46**, 471 (1937).

(7) (a) Fischer and Warburg, *Ann.*, **340**, 168 (1905); (b) Fischer and Raske, *Ber.*, **39**, 3981 (1906); (c) Abderhalden and Wybert, *ibid.*, **49**, 2456 (1916).

(8) Ramberg, *Ber.*, **33**, 3354 (1900).

(9) (a) Ramberg, *Ann.*, **349**, 324 (1906); (b) **370**, 234 (1909); *cf.* also note 6.

propionylglycylglycine with $[\alpha]^{20}D$ −18.0° was obtained. Fischer[10] had synthesized *d*-α-bromopropionylglycylglycine with $[\alpha]^{20}D$ 29.4° in alkaline solution from a *d*-α-bromopropionic acid that was 90% pure. Our experiments, therefore, indicate that the resolution of *d,l*-α-bromopropionylglycylglycine by its quinine salt is an entirely feasible method in that the salt is stable enough to permit recrystallizations even from hot solutions. However, a practical procedure would require a better solvent because the quantities of ethyl acetate used were far too great. To solve the original problem, the preparation of optically active α-bromopropionic acid in sufficiently large quantities, it is only necessary to hydrolyze the pure *d*- and *l*-α-bromopropionylglycylglycine when they are obtained. This hydrolysis takes place with no appreciable racemization in acidic hydrolyzing media. From this work the use of a *d,l*-α-halogen acyl dipeptide seems to be the best way of preparation of optically active α-halogen acids in good yield.

The Rates and Mechanisms of Removal of the Bromine Atom in *d,l*-α-Bromopropionate, *d,l*-α-Bromopropionylglycinate and *d,l*-α-Bromopropionylglycylglycinate Ions.—It has been shown by Hughes and Ingold[11] and others that there are two different mechanisms for the hydrolysis of aliphatic halides. Methyl and ethyl halides are nearly unreactive in acidic or neutral media but hydrolyze very readily in the presence of hydroxyl ions. This hydrolysis gives a good second-order rate constant, the actual rate being directly proportional to the concentrations of the halide and the hydroxyl ion. With *t*-butyl bromide the rate is independent of the hydroxyl ion concentration; the reaction gives a first-order constant regardless of the *p*H of the solution. Isopropyl halides fall in between these two extremes; in neutral and very dilute alkaline solutions they hydrolyze with a first-order rate, in very strong alkali the rate is second-order. With intermediate alkali concentrations the hydrolysis does not follow a simple kinetic mechanism but is a mixture of the first and second-order reactions.

Cowdrey, Hughes and Ingold[5] showed that α-bromopropionic acid itself reacted only very slowly with water. The α-bromopropionate ion, however, reacted in much the same way as the isopropyl halides; its first-order rate was faster than that of isopropyl bromide because of the negative charge on the carboxylate ion.

After it was found that α-bromopropionylglycine reacted unexpectedly rapidly in neutral solution, it was decided to measure the first- and second-order constants for the three compounds studied, *i. e.*, α-bromopropionic acid, α-bromopropionylglycine and α-bromopropionylglycylglycine. It was thought that these constants, as well as the activation energies involved, might give further insight into the reactivity of such compounds. It would supplement the information gained in the study of the ammonolysis[12] of similarly built α-halogen acids.

Materials.—***d,l*-α-Bromopropionic Acid.**—This acid was prepared according to Weinig[13] from *d,l*-α-bromopropionyl bromide.[14] Its b. p. was 106–108° at 12 mm.

***d,l*-α-Bromopropionylglycine.**—It was prepared according to Fischer[15] and recrystallized from a concentrated ether solution by addition of petroleum ether; m. p. 100–103°.

***d,l*-α-Bromopropionylglycylglycine.**—The substance was synthesized according to Fischer's procedure for the preparation of *l*-α-bromopropionylglycylglycine.[16] Diketopiperazine prepared according to Fischer[17] from glycine ethyl ester hydrochloride[18] was combined with *d,l*-α-bromopropionyl chloride which was obtained by the method that Fischer had used for *l*-α-bromopropionyl chloride.[19] After recrystallization from about three parts of water the substance melted at 164–166° (cor.).

Method of Rate Measurement.—The rates of ionization of the bromine atom were measured by an experimental technique much the same as that used in measuring the rates of ammonolysis.[12] The constant temperature bath was the same as used before (±0.05°). The acid to be used was weighed out into a volumetric flask and then heated to the bath temperature. For the runs with alkali the calculated quantity of preheated standard alkali solution was then added plus enough water to bring the solution up to the desired volume. In the case of the neutral reactions a preheated solution of sodium bicarbonate of the correct concentration was added. Samples were taken at convenient intervals and run into strong nitric acid to stop the reaction. The samples were titrated for bro-

(10) Fischer, *Ber.*, **41**, 860 (1908).
(11) Hughes and Ingold, *Trans. Faraday Soc.*, **34**, 202 (1938).
(12) Chadwick and Pacsu, THIS JOURNAL, **63**, 2427 (1941).
(13) Weinig, *Ann.*, **280**, 247 (1894).
(14) (a) Volhard, *ibid.*, **242**, 141 (1887); (b) Zelinsky, *Ber.*, **20**, 2026 (1887).
(15) Fischer, *Ann.*, **340**, 128 (1905).
(16) Fischer, *Ber.*, **39**, 2921 (1906).
(17) Fischer, *ibid.*, **39**, 2930 (1906).
(18) Harries and Weiss, *Ann.*, **327**, 365 (1903).
(19) Fischer, *ibid.*, **340**, 171 (1905); (b) Freudenberg and Markert, *Ber.*, **60**, 2447 (1927).

mide ion by a modified Volhard titration.[20] In calculating the rate constants from the results of the titrations the first sample was taken as the starting point of the reaction in most cases because the temperature was usually a little low in the intervals preceding the titration and with the fast reactions it was also difficult to determine the exact starting point. In general, the constants obtained represented excellent values with an average deviation of only ±1 to 2%. Preliminary experiments on the solutions of the sodium salts showed that the first-order constants drop rapidly as the reaction progresses, because the hydrogen bromide produced makes the solution acidic and the α-bromo acid ions are then changed back into the undissociated acid, the bromine atom of which is very stable. Because of this the constants for the first-order reactions were obtained by buffering the solutions with an excess of sodium bicarbonate. By this method constants were obtained which showed no variations outside the limits of experimental error. Since the first-order reaction is fast enough with the first two of the three compounds, a pure second-order reaction cannot be measured easily. To evaluate the pure second-order constants it was necessary to integrate the formula for the rate of the simultaneous first- and second-order reactions. In the following formulas x is the concentration of the Br ion, a is the initial concentration of the OH ion, b is the initial concentration of the bromo acid, k_1 is the first-order rate constant, and k_2 is the second-order rate constant.

$$dx/dt = k_1(b - x) + k_2(a - x)(b - x) \quad (1)$$

$$dt = \frac{dx}{[(k_1 + k_2a) - k_2x](b - x)} \quad (2)$$

$$t = \int_{x=0}^{x=y} \left[\frac{1}{k_1 + k_2(a - b)} \ln \frac{b - x}{(k_1 + k_2a) - k_2x}\right] \quad (3)$$

$$t = \frac{1}{k_1 + k_2(a - b)} \ln \frac{b[k_1 + k_2(a - y)]}{(b - y)(k_1 + k_2a)} \quad (4)$$

$$\frac{t[k_1 + k_2(a - b)]}{2.303} = \log \frac{b[k_1 + k_2(a - y)]}{(b - y)(k_1 + k_2a)} \quad (5)$$

Because the final expression, equation (4), contains a transcendental function of k_2, it must be solved by separating the logarithmic part of the expression from the rest as is shown in equation (5). Using the values of k_1 obtained from the buffered reactions and assuming a series of values for k_2, the two functions represented by the two sides of equation (5) were plotted on the same coordinates. The intersection of the two curves was taken as the value of k_2. By this means the second-order constants were determined for α-bromopropionic acid and α-bromopropionylglycine. It was found, however, that these k_2 constants increased with higher initial concentrations of alkali. As the concentrations used were such that the activity of the sodium hydroxide was at its minimum,[21] the use of activity in place of concentration in the formula did not correct the difficulty. To check the possibility of a salt effect, in one experiment a 0.4 N sodium hydroxide solution was made, by addition of sodium nitrate, 1 N with respect to sodium ion concentration. This caused an increase in the rate constant so that the value observed was nearly that which was obtained using 1 N alkali. This made it necessary to check the first-order constants for salt effect, because they were obtained in dilute sodium bicarbonate solutions and could not be assumed to be necessarily the same in strong sodium hydroxide solutions. The effect was measured by adding sodium nitrate to the dilute sodium bicarbonate solutions so that the final salt concentration would be the same as that present in the runs made in determining the k_2 constants. The results of all these measurements were sets of ten constants, five at each of two temperatures, for α-bromopropionate ion and also for α-bromopropionylglycinate ion. These constants are included in Table I. The constants for α-bromopropionylglycylglycinate ion are also listed in Table I but their measurement presented an entirely different set of problems. In the first place, the first-order reaction was so slow that its contribution was negligible when the OH ion concentration was high. Therefore, it was unnecessary to use the complicated expression for evaluating the k_2 constants. Actually, the first-order reaction was so slow that its measurement was quite difficult. Bicarbonate solutions lose carbon dioxide slowly upon standing and become basic. When the first-order reaction is rapid this is offset by the acidity which is produced by the reaction itself when the hydrogen bromide is liberated by the hydrolysis of the C–Br bond. In the present case where the k_1 is very small the solution gradually becomes basic and the second-order reaction begins to be appreciable. This caused the k_1 constants to increase gradually after about the first quarter of the reaction had been completed. During the first period the constants were good enough so that the value was taken as the true k_1.

(20) Caldwell and Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(21) Harned and Hecker, THIS JOURNAL, **55**, 4838 (1933).

TABLE I

RATES OF IONIZATION OF THE BROMINE ATOM OF *d,l*-α-BROMO ACID IONS IN NEUTRAL AND ALKALINE MEDIA AT DIFFERENT TEMPERATURES

Start, min.	*N* Solution	Temp., °C.	*N* NaOH soln.	*N* Sod. bicarb. soln.	*N* Sod. nitrate soln.	$10^4 \times k_1$ min.$^{-1}$	$10^4 \times k_2$ min.$^{-1}$ mole^{-1} liter
			(1) *d,l*-α-Bromopropionate Ion				
10	0.2090	49.2	1.0700			9.3	74.0
15	.1970	49.2	0.3970			8.5	54.0
30	.0404	49.2		0.2		8.3	
0	.0393	49.2		.2	0.40	8.5	
90	.0388	49.2		.2	.95	9.3	
5	.2050	59.7	1.0250			42.0	203.0
10	.2080	59.7	0.4160			40.0	156.0
20	.0420	59.7		.2		40.0	
25	.0420	59.7		.2	.40	40.0	
25	.0400	59.7		.2	.95	42.0	
			(2) *d,l*-α-Bromopropionylglycinate Ion				
20	0.1920	49.2	1.0000			10.8	123.0
20	.1960	49.2	0.4000			10.9	107.0
30	.0390	49.2		0.2		11.7	
0	.0396	49.2		.2	0.40	10.9	
0	.0392	49.2		.2	.95	10.8	
5	.1940	59.7	.9760			42.0	350.0
11	.1950	59.7	.3880			42.0	290.0
25	.0393	59.7		.2		44.0	
45	.0393	59.7		.2	.40	42.0	
20	.0392	59.7		.2	.95	42.0	
			(3) *d,l*-α-Bromopropionylglycylglycinate Ion				
0	0.2000	49.2	1.0000				800.0[a]
0	.2010	49.2	0.4020				650.0[a]
0	.0403	49.2		0.2		0.7	
0	.2020	59.7	1.0100				very fast
0	.2000	59.7	0.4000				1770.0[a]
0	.4020	59.7		0.2		2.2	

[a] By extrapolation.

More difficulty was encountered in the determination of the second-order constants for the α-bromopropionylglycylglycinate ion. It was found that they dropped very rapidly throughout the course of the reaction. The explanation for this was found, however, in some work done by Abderhalden and Zeisset,[22] who followed the hydrolysis of the bromine atom and simultaneously measured the rate of splitting of the peptide bonds by alkali in α-bromopropionylglycylglycine. They found that by the time the bromine was 70% removed one mole of free amino group had been liberated. The second amide linkage was split much more slowly. Because of the negative charge on the carboxylate ion it is most likely that the amide linkage farthest from it is attacked and split first by the OH^- ions. This follows from the observation by Hammel[23] that diglycylglycine hydrolyzes much more rapidly in alkaline solution than does glycylglycine. In the case of the α-bromopropionylglycylglycine the basic hydrolysis produces glycylglycinate ion and α-bromopropionate ion. Since the bromine is removed ten times faster from α-bromopropionylglycinate ion than from α-bromopropionate ion, the reason for the drop in the observed k_2 is obvious. What is being measured changes, as the peptide bond hydrolysis proceeds, from the second-order constant for the starting compound to that for the α-bromopropionate ion. The k_2 constants in Table I for α-bromopropionylglycylglycinate ion were obtained by plotting the observed constants against the bromide ion concentration and extrapolating back to the zero point. Because of this these constants are not as accurate as are those for the other two compounds. In the case of the reaction with 1 *N* alkali at 59.7° the rate was so fast that the constant could not be measured. The first reading was so far along the curve that any extrapolation would have been mere guesswork. At both temperatures the two

(22) (a) Abderhalden and Zeisset, *Fermentforschung*, **11**, 170 (1930). *cf.* (b) Abderhalden, Dienerstein and Genes, *ibid.*, **10**, 532 (1929).

(23) To be published shortly.

curves for the 1 N and 0.4 N alkali concentrations crossed each other. The easiest explanation for this fact would be that the rate of hydrolysis of the peptide linkage increases more rapidly with the increasing alkali concentration than does the rate of bromine removal.

From the values of the various constants at the two temperatures the changes in heat and entropy during the formation of the activated complex were calculated from the equation for absolute reaction rates[24]

$$k' = \frac{k_0 T}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R}$$

where $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are the changes in heat and entropy during the formation of the transition state, k_0 and h are the Boltzmann and Planck constants, respectively. $\Delta H^{\ddagger}$ is identical with the heat of activation of the reaction and may be calculated for the various compounds by plotting $\ln k'/(k_0 T/h)$ against $1/T$ and multiplying the slope of the curve so obtained by R. Substitution of these $\Delta H^{\ddagger}$ values in the above equation leads to the evaluation of $\Delta S^{\ddagger}$, the entropy of activation. All these values for both the first- and second-order reactions are listed in Table II. As only two temperatures were used and they were only 10° apart, the values are probably no more accurate than ±0.5 kcal. for the first two compounds. Because the constants themselves are less certain for the α-bromopropionylglycylglycinate ion, the error here is probably about ±1 kcal.

TABLE II

THE HEATS AND ENTROPIES OF ACTIVATION OF THE HYDROLYSIS AT 59.7° OF THE *d,l*-α-BROMOPROPIONATE, *d,l*-α-BROMOPROPIONYLGLYCINATE AND *d,l*-α-BROMOPROPIONYLGLYCYLGLYCINATE IONS

	From k_2, 0.2 N salt, 0.4 N sod. hydr.		From k_1, 0.04 N salt, 0.2 N sod. bicarb.	
	Heat $\Delta H^{\ddagger}$	Entropy $\Delta S^{\ddagger}$	Heat $\Delta H^{\ddagger}$	Entropy $\Delta S^{\ddagger}$
Substance	kcal.	e.u.	kcal.	e.u.
Sodium *d,l*-α-bromopropionate	21.0	−4.4	31.4	24.2
Sodium *d,l*-α-bromopropionylglycinate	19.7	−7.0	26.4	9.4
Sodium *d,l*-α-bromopropionylglycylglycinate	19.8	−3.1	22.7	− 7.7

Discussions of the Results

From the data accumulated the mechanisms of the various reactions can be postulated. Cowdrey, Hughes and Ingold[5] showed that in the second-order reaction of the optically active α-bromopropionate ion with hydroxyl ion Walden inversion always occurred to better than 90%. This indicates that the OH^- approaches the α-carbon from the side opposite to the bromine and pushes the latter out to form the inverted lactic acid. Such a reaction should theoretically be slowed up by the presence of the negative charge on the carboxylate ion. As this charge is more remote from the C–Br bond in the glycine derivatives, it would be expected that their rates of reaction should be greater. Such was actually the case, α-bromopropionylglycinate reacting about twice as fast and α-bromopropionylglycylglycinate reacting about ten times as fast as the α-bromopropionate ion. Most of this difference in rate should theoretically show up in the activation energy, $E = \Delta H^{\ddagger} + RT$, because the OH^- ion has to do more work in approaching the molecule the greater the negative charge is in the part of the molecule approached. The observed activation energies for the k_2 constants of the three compounds do not vary much but, as a change in rate of ten or eleven times only corresponds to a change in activation energy of about 1.6 kcal. at 60°, this difference is within the limits of error in the measurement of the energies.

The salt effect mentioned above is qualitatively just what would be expected for a reaction of this sort[25] between two ions of like charge. By the Debye–Hückel theory the rates should be nearly doubled by increasing the ionic strength of the solution from 0.6 to 1.2 N. The effect is actually less than that because the concentrations are in the range where the Debye–Hückel theory becomes inadequate. Several runs were made with the sodium salt of α-bromopropionylglycine and even lower concentrations of alkali. As is to be expected the effect becomes less noticeable in the more dilute solutions. With 0.3880 N sodium hydroxide the value for k_2 at 59.7° is 0.029 min.$^{-1}$ mole^{-1} liter. With 0.2 N alkali has dropped to 0.025 and with 0.04 N solutions of both the sodium hydroxide and the sodium salt k_2 is still about 0.025. In this last case the k_2 is not very accurate because the first-order reaction predominates.

No work has been done on the glycine derivatives of optically active α-bromopropionate ion but they would almost certainly show Walden inversion as the active α-bromopropionate ion itself did. Inactive lactylglycine was isolated as the product of hydrolysis of the *d,l*-α-bromo-

(24) Wynne-Jones and Eyring, *J. Chem. Phys.*, **3**, 492 (1935).

(25) Glasstone, Laidler and Eyring, "Theory of Rate Processes," Chapt. VIII, York, Pa., 1941.

propionylglycinate ion. It checked exactly with the compound prepared by Fischer.[26] No attempt was made to isolate a product from the reaction of α-bromopropionylglycylglycinate ion because the latter suffered cleavage at the peptide bonds during the reaction.

As to the first-order reaction of the α-bromopropionate ion, Hughes and Ingold[5] found that the reaction was accompanied by almost complete retention of configuration. They postulated that this retention was due to the fact that the negative carboxylate group approached the α-carbon from the rear as the Br^- ion left and formed a betaine-like inner salt. This inner salt stabilized the carbonium ion in a pyramidal form with the opposite configuration from the original. The solvent molecule then attacked it from the side which the Br^- left and the original configuration was retained. Kenyon and Phillips[27] as well as Winstein and Lucas[28] went further and postulated a completely covalent α-lactone as the intermediate. There was no real proof for this theory but the latter authors cited the example of the β-lactone studied by Olson.[29] As the experimental phenomena can be very well explained without assuming the actual formation of an α-lactone, there is no advantage to be had from the theory. Therefore, it seems best to assume the Hughes mechanism as the correct one for the first-order removal of the bromine from α-bromopropionic acid.

Regarding the first-order reaction of the α bromopropionylglycinate ion, the observed rate constants are nearly the same as those for the α-bromopropionate ion itself, but there is a great difference in the activation energies. Furthermore, the effect on the rate constant of changing the ionic strength of the solution is exactly the opposite for the two substances. As the negative charge in α-bromopropionylglycinate ion is farther removed from the C–Br bond its effect on the reaction rate should be much smaller if the mechanism of the reaction is the same for the two compounds. This lessening of the effect of the negative charge was actually observed in the case of the second-order reactions which went by the same mechanism in the two cases. As may be seen from Table I, the observed k_1 constants for α-bromopropionylglycinate were about the same at higher temperature while they were even greater at the lower temperature. Therefore, some factor other than the position of the negative charge in the two molecules must account for the great reactivity of the sodium α-bromopropionylglycinate in neutral solution. The observed activation energy, $E = \Delta H^{\ddagger} + RT$, for the first-order reaction of α-bromopropionate ion is 32 kcal., while that for the α-bromopropionylglycinate ion is 27 kcal. If the other factors were the same this should mean that the latter substance should react a thousand times faster. As the rates are actually of the same order of magnitude, there must be a great difference in the entropy values of the two substances (Table II).

This great variation in activation energies is much different from the case of the second-order reactions where the difference was small but was still large enough to account for the observed difference in rates, and the entropies were all of the same order of magnitude. The salt effect in the two cases is small, the greatest difference measured being only about ten per cent. The two compounds, however, show definitely different behavior in this respect. The first-order constant increases with increasing ionic strength of the solution for α-bromopropionic acid but the constant for α-bromopropionylglycine decreases under the same conditions. The former effect is just what would be expected in the case of a neutral molecule reacting to form ions.[25] Although the α-bromopropionate ion is not neutral to start with, two more charges are produced in a part of the molecule where there were none at the start. As will be shown, the best explanation for the first-order reaction of α-bromopropionylglycine is a sort of internal bimolecular reaction between the carboxylate group and the C–Br group. This is in effect a reaction between an ion and a neutral molecule. The direction of the salt effect cannot be predicted easily but it may be either positive or negative in a case of this kind. The fact that the constant decreases with increasing ionic strength is in agreement with this.

The best explanation of the first-order reaction of α-bromopropionylglycinate is that it is a lactonization. The molecule curls around so that the carboxylate group with its negative charge approaches the carbon to which the bromine is bonded and pushes the bromine out much as the hydroxyl ion does in the second-order reaction.

(26) Fischer, *Ber.*, **40**, 409 (1907).
(27) Kenyon and Phillips, *J. Chem. Soc.*, 303 (1936).
(28) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939).
(29) (a) Olson and Miller, *ibid.*, **60**, 2687 (1938); *cf.* (b) Olson and Hyde, *ibid.*, **63**, 2459 (1941).

The first product in that case would be a diketomorpholine derivative which would hydrolyze in aqueous solution to give lactylglycine. This morpholine derivative has been isolated from the reaction in the solid state. It apparently has a measurable rate of hydrolysis in neutral aqueous solution but it reacts so rapidly with alkali that it is impossible to follow the course of hydrolysis accurately. The rapidity of this alkaline hydrolysis is to be expected because it is a δ-lactone. The lactone must hydrolyze during the course of the reaction because an unbuffered solution becomes acidic as the reaction proceeds. One good proof for the mechanism, of course, would be to observe the effect of the reaction upon the optical activity of the compound. That, however, would have required an optically active starting material, the search for which was the original cause for this study. If the postulated mechanism is the correct one, the net optical effect of the reaction should be a rather complete Walden inversion. The rate determining removal of the bromine should invert the configuration because it is a bimolecular substitution similar to the reaction with OH^- ion which also causes complete inversion. The hydrolysis of the δ-lactone should leave the configuration inverted because it is similar to the hydrolysis of an ester and therefore should occur with no effect upon the active center, the split being between the oxygen and the carbonyl carbon.

With α-bromopropionylglycylglycinate the rate of reaction is much slower as was predicted. If the mechanism were the same this would probably mean a higher activation energy, whereas it is actually much lower than that for either of the other two reactions. The entropy value, $\Delta S^{\ddagger} = -7.7$ e. u., is so much lower than for the other two reactions that it offsets the low activation energy and the reaction itself is slower. A nine-membered ring is rather improbable so that a lactonization does not seem to be the answer. Neither should the effect of the negative carboxylate group be important in forcing an ionization. Therefore, the reaction is probably somewhat similar to that of the ester or amide of α-bromopropionic acid. The reaction of the former with methyl alcohol was studied by Cowdrey, Hughes and Ingold.[5] They concluded that it was actually a bimolecular reaction with the solvent, resulting in practically complete inversion. It would be very instructive to determine the optical effect of this reaction but it seems quite safe to assume that this is a first-order bimolecular reaction of the bromo compound with the solvent. It should result in complete inversion.

The postulated mechanisms for the solvolysis of the three compounds do not satisfactorily account for the magnitudes and the peculiar variations in heats and entropies of activation. In spite of a striking difference in the heats of activation the actual rates of hydrolysis for the three substances are not very different. It may be said that this might conceivably be due to the fact that although the individual k_1 values are quite accurately measured, making the free energies of activation accurate, the E's might be inaccurate making the differences spurious. However, the reproducibility and consistency of the experimental results indicate that the individual activation energies are known to within less than a large calorie and certainly preclude uncertainties of a magnitude comparable to those deviations observed. Therefore, experimental error must be discarded as an explanation of the variations in the activation energies. Since these substances possess charged carboxyl groups which are strongly hydrated, it is natural to inquire whether the activated complex may not involve a disappearance of this ion with a release of the bound water molecules. When a water molecule changes from the liquid state to water of crystallization, the decrease in entropy, 4.7 e. u., is very nearly the same as in the process of freezing, 1440/273 = 5.3 e. u.[30] If 5.3 e. u. be approximately the entropy decrease of a bound water molecule over that in the liquid, and if it be assumed that the entire observed entropy change is due to the release of water molecules, then it could be stated that upon activation the α-bromopropionate ion releases about five water molecules, the α-bromopropionylglycinate ion about two and that the α-bromopropionylglycylglycinate ion binds one molecule. Further, each molecule of water upon being melted from the carboxylate ion would absorb about 1.44 kcal., the heat of melting of a mole of ice. This absorbed energy should appear as an increase in the energy of activation. Therefore, it is to be expected that the activation energy for the α-bromopropionate ion should exceed that of the α-bromopropionylglycylglycinate ion by about $6 \times 1.44 = 8.6$ kcal. as compared with the

(30) Wenner, "Thermochemical Calculations," McGraw-Hill Book Co., New York, N. Y., 1941, p. 178.

observed value of 8.7 kcal., while the activation energy of the former ion should exceed that of the α-bromopropionylglycinate ion by about $3 \times 1.44 = 4.3$ kcal. as compared with the observed value of 5 kcal. This picture shows a gratifying self consistency. The negative value, $\Delta S^{\ddagger} = -7.7$ e. u., for the α-bromopropionylglycylglycinate ion simply means that in forming the activated complex only the one water molecule which is to provide the OH^- ion to replace the bromide ion is in effect frozen. The carboxylate ion on the latter substance is so far away from the bromine atom that there is no tendency to form a lactone between the charged oxygen atom and the carbon atom beginning to lose the bromide ion. In the case of α-bromopropionate ion the activated complex does produce strong attraction between these elements and releases six water molecules previously surrounding the carboxylate ion, but immobilizes the one which is to provide the OH^- ion. In the α-bromopropionylglycinate ion there is already a weak lactone bond in the normal state partially interfering with the hydration of the carboxylate ion, and this bond is tightened in the active state with the melting of three water molecules and the immobilizing of one. In this presentation the neglect of all entropy changes except those of hydration and dehydration is undoubtedly an oversimplification, but the rough picture, which seems reasonable *a priori*, provides a consistent and, in the opinion of the authors, substantially correct interpretation of the peculiar variations in heat and entropy.

Reactions in the Solid State

As was mentioned earlier in this paper it was found that the brucine salt of α-bromopionylglycine decomposed in the solid state, even at room temperature. In order to understand this reaction it was first necessary to identify the products. One of them was brucine hydrobromide. The presence of bromide ion was the evidence which proved that the reaction had taken place. The only method which completely separated the brucine hydrobromide from the other product was vacuum distillation of the decomposed salt. At 1.5 mm. a white solid started to sublime at low temperature. At 150° this compound distilled over and it was recrystallized from ether. From a series of tests it appeared that the compound was the lactone of *d,l*-lactylglycine. An analysis for the elements and the titration of the compound corroborated this conclusion; m. p. 98°; calcd. for $C_5H_7O_3N$: C, 46.49, H, 5.47, N, 10.85; found: C, 46.40, H, 5.50, N, 10.51. The substance is very soluble in water, alcohol, acetone and chloroform, moderately soluble in ethyl acetate and ether, and slightly soluble in hot carbon tetrachloride. An attempt was made to improve the yield of the compound by separating it from the brucine hydrobromide by solvent extraction. The pure compound was not obtained by this method as the removal of all of the hydrobromide was impossible. Better success was obtained in the recovery of the product from the reaction of the sodium salt. This salt was prepared in absolute ethanol solution and precipitated with ether. No rate measurements could be made with it because it is too hygroscopic. It decomposed on heating much as the brucine salt did. A small amount of the lactone sublimed during the heating but it was not much because the rest of the reaction products sintered down to a hard solid lump. By the extraction of the finely ground substance about 40% of the lactone was isolated.

The rates of the solid phase reaction on the brucine salt of α-bromopropionylglycine were followed by means of the Volhard titration as in the case of the reactions in solution. In the experiments at 45.1° a constant temperature water-bath was used with a variation of ±0.2°. The runs at 56.1° were made in a drying apparatus using boiling acetone. In the former case the salt was put in a glass container and at suitable intervals samples were removed, weighed and titrated for bromide ion. Because strong nitric acid reacts with brucine, giving a red color, it was found necessary to use sulfuric acid in the titration. This did not lower the accuracy of the titration. In the experiments at 56.1° each sample was weighed into a small platinum boat. At the desired times the boats were removed from the drying apparatus and their contents were washed out and titrated.

The run with added brucine hydrobromide was made by the same method as the experiments with the pure salt at 56.1°. The mixture was made by saturating the acetone solution of brucine with brucine hydrobromide before adding it to the solution of α-bromopropionylglycine. The two salts crystallized together. Titration of the mixture for bromide ion gave the quantity of brucine hydrobromide present.

The results of these experiments are summarized in Table III.

TABLE III

REACTION OF THE BRUCINE SALT OF *d,l*-α-BROMOPROPIONYLGLYCINE IN THE SOLID STATE

Time, hrs.	Sample, g.	Milliequiv. of Br′	% Br as Br′
	(a) Temperature, 45.1°		
4	0.1928	0.011	3.4
9.75	.2709	.056	12.5
23.50	.2351	.232	59.6
28.50	.2624	.320	73.7
36.25	.2982	.388	78.5
48	.2853	.399	84.5
480	.2176	.331	92.0
	(b) Temperature, 56.1°		
Min.			
30	0.2567	0.008	1.9
60	.2598	.018	4.2
90	.2590	.045	10.5
120	.2597	.090	21.0
210	.2699	.228	51.0
300	.2718	.302	67.1
360	.2703	.323	72.1
2880	.2568	.367	86.0

(c) With 7.6% added brucine hydrobromide

Time, min.	Sample, g.	Sample wt. − wt. of bruc. hydrobromide	Total mill. eq. Br − mill. eq. from bruc. hydrobromide	% Bromoprop.-glyc. decomposed
30	0.1458	0.1347	0.014	6.3
60	.1459	.1348	.026	11.7
85	.1443	.1333	.042	19.0
110	.1544	.1427	.063	26.6
210	.1119	.1034	.073	42.1
320	.1624	.1501	.132	53.0
2280	.1345	.1243	.191	92.7

The reaction in the solid state followed an S-shaped curve. It started with a long induction period, then became very rapid. After the reaction was about 75% complete this rapid rate dropped off and the reaction neared completion very slowly. The reaction was found to have a great dependence on the temperature, the rate being doubled for about a five degree increase in the temperature.

There are many cases[31] where such an S-shaped curve for a solid reaction has been shown to indicate a reaction occurring on the surface. At first there is no solid–solid interface so that the reaction proceeds only very slowly. After a small amount of the products has formed the reaction accelerates. As the concentration of the products increases, more solid–solid interface is formed and the reaction proceeds more and more rapidly. After the reaction is half-way completed the active surface area begins to decrease and the reaction again slows up. If this be the case for the reaction being studied, the addition of one of the products to the salt as an impurity should remove the induction period because the necessary solid–solid interfaces are already present. This phenomenon was found to take place. One run was made with a brucine salt containing 7.6% of added brucine hydrobromide (Table IV(c)). The induction period was practically removed but the reaction of the mixture never reached the high rate with which the pure salt reacted.

One experiment was made by heating the brucine salt of α-bromopropionylglycylglycine. After fifteen days at 56.1° the salt showed only a trace of bromide ion, thus indicating that the decomposition had been negligible. The heating was then continued at 100°. After seventeen days at this temperature about 30% of the salt had decomposed. This is, of course, very much slower than the reaction of the brucine salt of α-bromopropionylglycine, which was more than 80% decomposed after one hour at 100°. No induction period was observed but no attempt can be made to explain this reaction without more information about it. It would be useless to investigate the product until the salt has been much more completely decomposed.

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Summary

Resolution of inactive α-bromopropionic acid by fractionate crystallization of the alkaloid salts is impractical because of the low yield, which is mainly due to the rapid decomposition of the salts in neutral solutions. While it was found that the *d,l*-α-bromopropionylglycinate ion is equally unstable, good results were obtained with the *d,l*-α-bromopropionylglycylglycinate ion.

The rates of the removal of the bromine atom in *d,l*-α-bromopropionate, *d,l*-α-bromopropionylglycinate and *d,l*-α-bromopropionylglycylglycinate ions were measured. The first- and second-order rate constants were determined at two temperatures, and the changes in heat and entropy during the formation of the activated complex were calculated. From these data the mechanisms of the reactions were postulated. Regarding the first-order reactions it was possible to correlate the peculiar variations in heat and

(31) Schwab, Taylor and Spence, "Catalysis," Chapt. XVIII.

entropy with the dehydration of the carboxylate ion in the activated state.

The rate of decomposition in the solid state of the brucine salts of *d,l*-α-bromopropionylglycine and *d,l*-α-bromopropionylglycylglycine was followed by means of titration of the bromide ion. From the former substance the lactone of *d,l*-lactylglycine was isolated. The decomposition followed an S-shaped curve. Addition of brucine hydrobromide to the brucine salt resulted in the elimination of the induction period.

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The Inversion of Menthone with Hydrogen Chloride in Benzene

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In a preceding paper it was shown that the rather complex kinetics of the inversion of menthone by trichloroacetic acid are adequately understood if we assume that the sterical rearrangement takes place by interaction of a binary menthone-acid complex with a further molecule of the monomeric acid.[1] The results of some experiments with hydrogen chloride[2] as a catalyst are in agreement with a similar assumption.

Dry solutions of menthone and of hydrogen chloride in benzene were mixed, the rotations (ρ) measured at certain times (t) and the reaction rates ($k + k'$) calculated as stated before.[1] The concentration of the acid in the reaction mixtures was determined after the completion of the reaction. The constancy of the rate coefficients is illustrated by Table I.

TABLE I

MENTHONE 0.5 MOLE/LITER; BENZENE 20.0 ± 0.1°

HCl 0.024 mole/liter			HCl 0.047 mole/liter		
t	ρt	$(k + k')10^4$	t	ρt	$(k + k')10^4$
0	−1.79	...	0	−0.66	...
5.0	−1.38	119	4.9	+0.08	354
13.1	−0.81	120	8.2	+0.40	337
30.2	+0.01	118	13.3	+0.78	335
49.9	+0.62	121	18.4	+1.04	332
64.9	+0.88	119	27.0	+1.31	335
99.8	+1.22	118	38.3	+1.49	353
∞	+1.42	...	∞	+1.59	...

Table II gives the results for a series of concentrations of hydrogen chloride. They agree with similar measurements by Tubandt covering part of the range of the acid concentrations,[3] and show that the reaction rate is proportional to the *square* of the concentration of the catalyst.

The inversion with trichloroacetic acid proceeded the more slowly, the higher the concentration of the menthone. Table III shows that the inversion with hydrogen chloride is not affected in a similar way by the menthone concentration.

TABLE II

MENTHONE 0.5 MOLE/LITER; BENZENE, 20.0 ± 0.1°

[HCl] mole/liter × 10^3	$(k + k')10^4$	$((k + k')/[HCl]^2)10$
4.8	6.7	29.1
12.0	21.5	14.9
16.6	46.3	16.8
24.0	119.9	20.8
32.0	197.8	19.3
47.0	335.0	15.2
92.0	1329.0	15.7

TABLE III

[HCl] mole/liter × 10^3	Menthone mole/liter	$(k + k')10^4$
26.5	0.5	144
26.5	0.75	155
26.4	1.00	154
26.7	1.50	155

To discuss the results, we write M for the menthone, A for the acid, MA for their binary complex, [] to indicate concentrations, and m and a for the total concentrations of menthone and of acid. For convenience, we consider the sterical rearrangement as going in one direction only, $(k + k') = \kappa$. If the inversion takes place by interaction of the binary menthone–acid complex with a further molecule of the acid, the inversion rate $r = \kappa[MA][A]$.[1] At variance with the experiments with trichloroacetic acid, the experiments with hydrogen chloride were carried out with low concentrations of the acid and a large *excess of menthone* over the latter. This technique was necessary to keep the reaction rates low enough and the angles of rotation high enough for observation. With trichloroacetic acid, the association of the catalyst had to be

(1) Weissberger, THIS JOURNAL, **65**, 245 (1943).
(2) A. Dörken, Dissertation, Leipzig, 1934.
(3) Tubandt, *Ann.*, **389**, 41 (1905); **354**, 259 (1907).