With the small mixing device, where the mixing was much slower, considerably more tetrathionate was formed during the mixing than in the experiment of Table IV.[14] It is believed that the $S_2O_3^{=}$–$S_2O_3I^-$ reaction was more important in the former case because of the slowness of mixing, *i.e.*, the rates of the two fast reactions were both comparable with the rate of mixing. There may have been some relative slowness of mixing even in the experiment with the fast mixing device. Therefore, it is not possible to calculate the relative rates of the $S_2O_3^{=}$–I_3^- and $S_2O_3^{=}$–$S_2O_3I^-$ reactions; one can conclude only that the former is considerably faster than the latter.

BERKELEY 4, CALIF. RECEIVED JUNE 27, 1950

[14] Dodd and Griffith[4] also observed considerable tetrathionate formation in their experiments in which no special mixing was employed.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

On Cyclic Intermediates in Substitution Reactions. I. The Alkaline Hydrolysis of Some Aliphatic Bromoacids

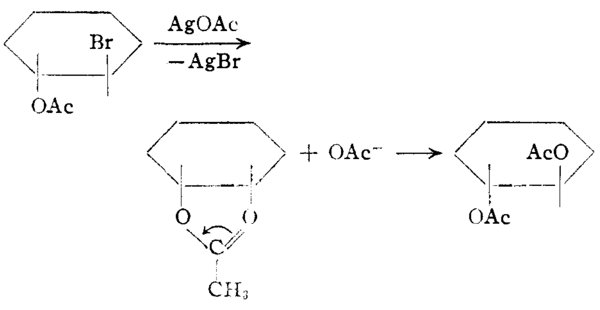
BY JOHN F. LANE AND HAROLD W. HEINE[1]

The rates of aqueous decomposition have been determined for a number of sodium salts of monobromoaliphatic acids in which the position of substitution of the bromine atom ranges from α to γ. It has been established that (1) the rates of decomposition, as measured by the release of bromide ion, are of the first order with respect to the ion of the haloacid; (2) the entropies of activation are positive, and, on the average, about 10 e.u.; (3) the heats of activation decrease in the order $\alpha > \beta > \gamma$.

These results are discussed in terms of a mechanism involving the formation of (increasingly strain-free) cyclic intermediates.

In recent years much evidence[2,3] has been collected to substantiate the idea that certain atoms or groups, capable of donating electrons, which are adjacent to carbon atoms undergoing nucleophilic substitution can, through the formation of cyclic intermediates, exert profound effects not only on the steric course of the displacement reaction, but also on its rate.

Evidence also has been obtained to show that such "neighboring-group" effects are produced by nucleophilic atoms not immediately adjacent to the carbon atom involved in the displacement reaction. Thus, Johannson[4] has reported the isolation of β-butyrolactone as an intermediate in the hydrolysis of β-bromobutyrate ion, and Winstein[3b] has found complete retention of configuration in the displacement of bromine by acetoxyl in the system



where a five-membered cyclic intermediate is postulated. Later investigations[3c] by this author and his co-workers have shown that the tendency of the acetoxyl group to participate in the displacement reaction exceeds by 3–4 kcal. that of methoxyl (which participates by means of a three-membered ring). Freundlich and Salomon[5] have also shown that the rates of formation of cyclic imines from monohalogenoamines are independent of the concentration of added hydroxyl ion and reach a maximum in the formation of a five-membered heterocycle, although their studies leave unanswered the question of whether differences in reactivity are attributable to heat effects or to entropy effects. In general, the information now available in the literature suggests that, other things being equal, the ease of participation of the neighboring nucleophilic atom increases with the strainlessness of the ring formed.

It is the purpose of this series to examine this matter further with quantitative studies on nucleophilic substitution in systems where the distance between the carbon atom on which displacement occurs and the participating neighboring group progressively increases while other variables are substantially constant. In the present study the sodium salts of a number of bromoacids, including the isomeric α-, β- and γ-bromocaproic acids have been chosen for investigation. These substances are soluble in water, and the kinetics of substitution (of oxygen for bromine) are easily followed by measuring the rate of release of the bromide ion. Here, of course, it is the carboxylate ion which plays the role of the neighboring group.

Method of Rate Measurement.—The measurements were carried out in a water-bath in which the temperature was thermostatically controlled to ±0.02°. Ordinarily a quantity of halogen acid sufficient to make the concentration of the sodium salt lie within the range 0.05–0.1 *M* was added to a solution 0.25 *M* in sodium bicarbonate which had been previously brought to the desired temperature. The rate of reaction was then followed by removing aliquot samples at convenient time inter-

---

[1] William F. Meredith Fellow in Rutgers University, 1946–1947. Department of Chemistry, Bucknell University, Lewisburg, Penna.

[2] W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1208 (1937).

[3] S. Winstein, *et al.*, THIS JOURNAL, (a) **61**, 1576 (1939); (b) **64**, 2780, 2778 (1942); (c) **70**, 821, 828 (1948).

[4] H. Johannson, *Ber.*, **48**, 1256 (1915); **55**, 647 (1922); *cf.* A. R. Olson and R. J. Miller, THIS JOURNAL, **60**, 2687 (1938).

[5] H. Freundlich and G. Salomon, *Z. physik. Chem.*, **166**, 161 (1933).

vals and delivering them into an excess of 1 N nitric acid to stop the reaction. After the excess of unreacted halogen acid had been extracted with chloroform, the bromide ion was determined by the Volhard method.

To check the possibility of a salt effect a few runs were made on sodium α-bromocaproate at ionic strengths higher than 0.25. In general for these reactions it was easily demonstrated that the rate of production of bromide ion conformed to a first order law.

Difficulty was encountered only with sodium γ-bromocaproate, for which substance the calculated rate constants at 0°, based on infinity values obtained at room temperature, exhibited marked downward drifts. Subsequent investigation, in which the infinity values were determined at 0° showed that the reaction reached completion when only 85% of the total expected bromide ion had been released. When it was assumed that this quantity represented the actual amount of γ-bromoacid present, satisfactory constants were obtained. Pending a more detailed investigation of this matter it seems reasonable to assume that the γ-bromocaproic acid used (which was prepared either by the addition of hydrogen bromide to 2-hexenoic acid or by the action of hydrogen bromide on γ-caprolactone) was contaminated to the extent of about 15% by the less reactive β-isomeride. For this reason it was decided to investigate, in addition to γ-bromocaproic acid, the next lower homolog, γ-bromovaleric acid which could be obtained as a pure, crystalline substance.

Typical rate data for two of the acids are given in Table I. Table II summarizes the complete data on first-order rate constants for all of the acids studied.

TABLE I

RATES OF AQUEOUS DECOMPOSITION OF SOME BROMOACIDS IN 0.25 M SODIUM BICARBONATE

Time (min.)	Vol. of 0.1 N AgNO$_3$ (ml.)	10^3k_1 (min.$^{-1}$)
Sodium α-bromocaproate, t = 49.20°		
83.75	0.96	1.48
158.5	1.70	1.47
253.0	2.52	1.46
321.8	3.03	1.44
392.2	3.53	1.44
∞	7.84	(mean) 1.46
Sodium α-bromocaproate, t = 59.60°		
10.36	0.60	6.15
30.00	1.63	6.10
60.02	3.04	6.23
90.13	4.23	6.33
119.8	5.15	6.29
179.8	6.56	6.24
239.9	7.52	6.19
380.0	8.80	6.20
∞	9.79	(mean) 6.22
Sodium β-bromocaproate, t = 30.80°		
55.70	2.68	5.60
85.85	3.79	5.58
115.6	4.81	5.69
142.6	5.56	5.72
206.0	6.86	5.66
∞	9.97	(mean) 5.64

TABLE II

RATE CONSTANTS FOR THE FIRST-ORDER DECOMPOSITION OF α-, β- AND γ-BROMOACIDS IN 0.25 M SODIUM BICARBONATE

Acid	Temp., °C.	10^3k_1(min.$^{-1}$)	Mean
α-Bromocaproic	49.20	1.46	1.46
		1.47	
	59.60	6.22	6.24
		6.26	
		6.28[a]	
		6.29[b]	
		6.39[c]	
		6.33[d]	
α-Bromopropionic	59.75	4.22	4.25
		4.28	
	69.40	15.7	15.6
		15.6	
β-Bromocaproic	30.80	5.61	5.64
		5.64	
		5.66	
	40.20	22.5	22.3
		22.5	
		21.9	
β-Bromopropionic	50.00	10.3	10.3
		10.3	
	62.75	58.7	58.7
γ-Bromocaproic	0.00	14.8	14.8
		14.9	
γ-Bromovaleric	0.00	10.3	10.3
		10.3	
		10.4	
	5.41	23.1	23.0
		22.9	

[a] μ = 0.35. [b] μ = 0.45. [c] μ = 0.75. [d] μ = 1.25 (added sodium nitrate).

Discussion.—For purposes of discussing the relative reactivities of the substances studied it is desirable to compare the contributions made to the total free energy of activation by heat and entropy effects. These may be estimated from the experimental data by means of Eyring's equation[6]

$$k = \frac{\mathbf{k}T}{\mathbf{h}} e^{\Delta S^{\ddagger}/R} e^{-\Delta H^{\ddagger}/RT}$$

for temperature dependence of the reaction rate. Furthermore, with the aid of this equation, rates can be compared at a standard temperature (25°). Accordingly, values of thermodynamic parameters of activation are presented in Table III, together

TABLE III

THERMODYNAMICS OF ACTIVATION, TOGETHER WITH ESTIMATED RATES OF DECOMPOSITION AT 25° FOR SOME BROMOACIDS IN 0.25 M SODIUM BICARBONATE

Acid	$\Delta H^{\ddagger}$ (kcal.)	$T\Delta S^{\ddagger}$ (kcal.)	$\Delta F^{\ddagger}$ (kcal.)	k_1 min.$^{-1}$
α-Bromopropionic	29.7	3.4	26.3	2.5×10^{-5}
β-Bromopropionic	28.7	3.8	24.9	2.1×10^{-4}
α-Bromocaproic	29.2	3.1	26.1	3.3×10^{-5}
β-Bromocaproic	27.1	3.5	23.6	2.1×10^{-3}
γ-Bromovaleric	22.2	1.5	20.7	0.33

---

(6) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 196.

with estimated values of the specific rate constants at 25°.

First, it is to be noted that the entropy is positive and, on the average, about ten entropy units ($T\Delta S^{\ddagger}$ 3 kcal.).[7] Such a positive entropy effect has already been noted for the first-order hydrolysis of α-bromopropionate ion by Chadwick and Pacsu.[8] These investigators, following a suggestion of Eyring, have interpreted this as most probably due to a freeing of water molecules (oriented stiffly or "frozen" around the carboxylate ion) as the transition state is formed. Such "melting" can only occur if the carboxylate ion itself effects substitution with attendant formation of an α-lactone. From the results presented here it appears that this effect is characteristic of those participations by the carboxylate-ion which involve the formation of three-, four- and five-membered cyclic intermediates.

Second, the variation of reactivity with the location of the bromine atom in the chain seems to be attributable primarily to changes in the heat of activation. This, of course, is in harmony with the prediction of the strain theory,[9] if the substitution is internal, involving in each case the formation of the corresponding lactone. Since the five-membered ring may be considered strainless, it may be inferred that the absorption of about 5 kcal. of strain energy attends the formation of a four-membered ring (β-caprolactone), while about 7 kcal. are absorbed in the formation of a three-membered ring (α-caprolactone).

It is to be noted in passing that the β-bromocaproate ion is approximately ten times as reactive as the β-bromopropionate ion. This enhancement in rate is undoubtedly due to the stabilizing effect of alkyl substitution on formation of small rings, a phenomenon first noted and discussed by Winstein.[3c]

Taken as a whole the results suggest that in a substitution process involving the formation of a three-, four- or five-membered cyclic intermediate, variations in the size of the ring formed and in the total number of carbon atoms in the molecule produce only minor variations in the entropy of activation. As a result the speed of such a process is governed largely by the heat of activation which increases markedly with the strain attending ring formation.

Experimental

dl-α-**Bromocaproic Acid.**—This acid was prepared from *n*-caproic acid according to the procedure in "Organic Syntheses."[10] By this method there was prepared, from 12 g. of freshly dried and distilled *n*-caproic acid, 16.9 g. of product boiling at 122–125° (8 mm.).

Anal. Calcd. for $C_6H_{11}O_2Br$: Br, 40.9. Found: Br, 40.0.

dl-β-**Bromocaproic Acid.**—The method used for obtaining this compound was similar to that described by Fittig and Baker.[11] Fifteen grams of 2-hexenoic acid, prepared by the procedure of Goldberg and Linstead,[12] was dissolved in 40 ml. of 48% HBr. The reaction mixture was saturated with a current of dry hydrogen bromide at 0°. It was then allowed to stand at room temperature for 2 days after which it was poured rapidly onto crushed ice, whereupon an oily brown precipitate formed. The crude bromoacid (18 g.) so obtained was separated from the aqueous layer, taken up in pentane, dried and stored overnight in the refrigerator. The colored pentane extract was treated with activated carbon and filtered. Upon removal of most of the solvent under reduced pressure the product crystallized as white burr-like crystals and was immediately filtered and dried in a vacuum desiccator kept in the refrigerator. The purified bromoacid melted at 35°.

Anal. Calcd. for $C_6H_{11}O_2Br$: Br, 40.0. Found: Br, 40.8.

dl-γ-**Bromocaproic Acid.**—This compound was prepared by two different methods: **Procedure A.**—2-Hexenoic acid (9.4 g., b.p. 115–117° (26 mm.) m.p. 12°) was treated with hydrogen bromide.[13] The resultant bromoacid was isolated according to the procedure of Boorman, Linstead and Rydon.[14] Nine grams of product was obtained (b.p. 104–108° (3.1 mm.); n^{20}D 1.4800).

Anal. Calcd. for $C_6H_{11}O_2Br$: Br, 40.9. Found: Br, 40.8.

Procedure B.—*dl*-γ-Caprolactone (7 g., b.p. 97° (16.4 mm.)), which had been synthesized by the isomerization of 2-hexenoic acid according to the procedure of Linstead,[15] was dissolved in 2.8 g. of water and the solution saturated with a current of hydrogen bromide at 0°. The mixture was left standing overnight at room temperature, and finally heated to 100°. It was poured over crushed ice, the precipitated bromoacid taken up in petroleum ether (b.p. 60–70°) and dried over sodium sulfate. The product, after removal of the solvent, boiled at 116° (2.8 mm.); 6.7 g., n^{20}D 1.4796.

Anal. Calcd. for $C_6H_{11}O_2Br$: Br, 40.9. Found: Br, 40.0.

dl-γ-**Bromovaleric Acid.**—This substance was prepared according to Wohlgemuth[16] by the action of hydrogen bromide on *dl*-γ-valerolactone and was purified by freezing a concentrated solution in light petroleum, decanting the supernatant liquid and subjecting the residual solid acid to distillation. The product so obtained boiled at 113° (7.4 mm.); m.p. 18°.

dl-α-**Bromopropionic Acid.**—A sample of this compound was kindly donated by Dr. Robert Feller of this Laboratory. Its boiling point was 102° (19 mm.).

Anal. Calcd. for $C_3H_5O_2Br$: Br, 62.1. Found: Br, 62.0.

β-**Bromopropionic Acid.**—This compound was purchased from Paragon Laboratories, East Orange, N. J. Its melting point upon recrystallization from petroleum ether was 62–63°.

Acknowledgment.—The authors wish to express their sincere thanks for generous financial assistance, provided in the academic year 1946–1947 by the Titanium Alloy Manufacturing Division, National Lead Co., Niagara Falls, New York, and in the year 1947–1948 by the Rutgers University Research Council, which made this study possible.

NEW BRUNSWICK, NEW JERSEY RECEIVED AUGUST 25, 1950

---

[7] Since the heat of activation is precise to only 1 kcal., the observed variations in $T\Delta S^{\ddagger}$ are not considered particularly significant.

[8] A. P. Chadwick and E. Pacsu, THIS JOURNAL, **65**, 392 (1943). The value of 24 e.u., reported by these investigators for the first-order hydrolysis of α-bromopropionate ion, is too high and is apparently caused by an arithmetical error. Recalculated values from their data are $\Delta H^{\ddagger}$ = 31.3 kcal., $T\Delta S^{\ddagger}$ = 4.8 kcal., $\Delta F^{\ddagger}$ = 26.5 kcal. (25°), which compare reasonably well with the corresponding quantities determined here.

[9] A. Baeyer, *Ber.*, **18**, 2277 (1885).

[10] "Organic Syntheses," Coll. Vol. I, edited by H. Gilman and A. H. Blatt, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 115.

[11] R. Fittig and C. F. Baker, *Ann.*, **283**, 117 (1894).

[12] A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 2343 (1928).

[13] S. E. Boxer and R. P. Linstead, *ibid.*, 740 (1931).

[14] E. J. Boorman, R. P. Linstead and H. N. Rydon, *ibid.*, 568 (1933).

[15] R. P. Linstead, *ibid.*, 115 (1932).

[16] H. Wohlgemuth, *Ann. chim.*, [9] **2**, 292 (1914).