greatly stabilized by the tetrahydrofuran type five-membered ring formation in the transition state.[22]

A six-membered ring could contribute to stabilizing the carbonium ion in the reaction of ϵ-bromoamyl ethyl ether, which is also a little faster than all the other homologs except the preceding one. It is interesting to note that cyclic sulfonium was reported to be the intermediate in the reaction between hydrobromic acid and phenyl δ-hydroxybutyl sulfide, which reacts far faster than its other homologs.[23] δ-Chlorobutyl phenyl sulfide was also reported to have much higher reactivity than γ-chloropropyl phenyl sulfide, suggesting that the δ-chloro-compound formed the cyclic sulfonium ion intermediate.[7] Freundlich and Solomon[24] also reported that δ-bromobutylamine reacted with sodium hydroxide, forming a five-membered ring far faster than its homologs, while ϵ-bromoamylamine was considerably higher in its reactivity.

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LAWRENCE, KANSAS

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[22] The same phenomenon was observed in the S$_N$1 hydrolysis of tetramethylene chlorohydrin by H. W. Heine, *et al.* (THE JOURNAL, **75**, 4778 (1953)). In this case, tetrahydrofuran was isolated as a main product.

[23] G. M. Bennett and A. N. Moses, *J. Chem. Soc.*, 2364 (1930).

[24] H. Freundlich and G. Solomon, *Ber.*, **66**, 355 (1933).

[CONTRIBUTION FROM THE INSTITUTE OF SCIENTIFIC AND INDUSTRIAL RESEARCH, OSAKA UNIVERSITY]

Relative Reactivities of Organic Halides in Displacement Reactions. IV. The Rates of Formolysis of Several Secondary Organic Bromides[1]

BY SHIGERU OAE[2]

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Several unsubstituted and ω-substituted secondary organic bromides have been synthesized and their formolysis rates determined. Unlike the case of primary bromides, the rates of 2-bromopropane, 2-bromobutane and 2-bromopentane were nearly equal. Among 5-substituted-2-bromopentane, the methoxy-compound showed remarkedly higher reactivity, while the cyano group was found to retard the reactivity.

Introduction

In the preceding two papers,[1,3] kinetic studies have been made of the reactions of several primary organic bromides with mercuric nitrate. In the reaction with mercuric nitrate, however, the attacking reagent is mercuric ion, which has been known to form a complex or even react with such functional groups as phenyl, carbonyl and hydroxyl groups.[4] In fact those organic bromides which have phenyl or acetoxy group did react rather slowly as compared to such simple normal alkyl bromides as n-butyl bromide.[3] Perhaps mercuric nitrate forms a loose complex with such functional groups as phenyl or acetoxy and reduces the electrophilicity toward bromide, thus lowering the rate of reaction. Therefore, one cannot discuss the reactivities of these compounds or compare the effects of these functional groups on the same basis as the simple alkyl bromides, such as n-butyl bromide, which would not form any complex with mercuric salts. In order to obtain more critical information on the real nature of the effect of substituents on reactivity, it is desirable to use a solvolysis-type reaction in which the solvent does not form any complex with such functional groups.

The present investigation deals with the rates of formolysis of secondary bromides. This reaction has been known to proceed through a pure S$_N$1 mechanism[5]; also, formic acid is considered neither to react nor form any complex with such functional groups. Thus, the rates of formolysis of 2-bromopropane, 2-bromobutane, 2-bromopentane, 2-bromo-5-methoxypentane, 2-bromo-5-acetoxypentane, 2,5-dibromopentane and 2-bromo-5-cyanopentane have been determined. Here again, a methoxy group at the δ-position was found to accelerate the reaction, while a cyano group at the same position was found to retard the reaction. Unlike the sequence of reactivities of n-alkyl bromides in the reaction with mercuric nitrate, *i.e.*, ethyl > n-propyl > n-butyl,[3,6] no such trend has been observed in the formolysis of secondary bromides: 2-bromopropane, 2-bromobutane and 2-bromopentane having nearly equal reaction rates.

Experimental

Materials.—Commercially available formic acid was dried over freshly prepared anhydrous copper sulfate[7] and then was distilled *in vacuo*, and the fraction boiling at 43° (50 mm.) collected and used for the kinetic measurement. The specific gravity was 1.1809, which corresponds to 78.55% formic acid by weight.

2-Bromopropane or isopropyl bromide was prepared by the method described in reference 8, using sodium bromide, sulfuric acid and isopropyl alcohol. In this case, heating was continued for a somewhat longer time than for the preparation of the primary bromide, in order to get the bromide in good yield.

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[1] Paper III, THIS JOURNAL, **78**, 4030 (1956).

[2] John Harrison Laboratory of Chemistry, University of Pennsylvania, Philadelphia 4, Pa.

[3] S. Oae and C. A. VanderWerf, THIS JOURNAL, **75**, 5037 (1953).

[4] I. Roberts and L. P. Hammett, *ibid.*, **59**, 1063 (1937).

[5] L. C. Bateman and E. D. Hughes, *J. Chem. Soc.*, 935 (1940).

[6] O. T. Benfey, THIS JOURNAL, **70**, 2163 (1948).

[7] A. Weissberger and E. Proskauer, "Organic Solvents," The Clarendon Press, Oxford, 1935, pp. 145.

[8] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 29.

2-Bromobutane or *sec*-butyl bromide was made by allowing 67 g. of phosphorus tribromide to react with 50 g. of *sec*-butyl alcohol according to the method described in reference 9; 85 g. of bromide which boiled at 89–90° was obtained, yield 93%. Redistillation gave a constant boiling fraction at 90°, which was used for the kinetic experiment.

2-Bromopentane was prepared in the usual manner by allowing 15 g. of phosphorus tribromide to react with 14 g. of 2-pentanol made from butyraldehyde and methylmagnesium iodide in 70% yield; the constant boiling fraction at 116° (15 g.) was obtained, yield 66%.

2,5-Dibromopentane was made by passing dry hydrogen bromide into 85 g. of boiling methyltetrahydrofuran[10] until no more hydrogen bromide was absorbed. Distillation, after thorough washing and drying, gave a constant boiling fraction at 62° (7.5 mm.), which was used for the kinetic study; $n^{25}\text{D}$ 1.5066.

2-Bromo-5-acetoxypentane.—This compound was prepared by the method described in reference 11 for the preparation of 4-chlorobutyl benzoate. To 38 g. of methyltetrahydrofuran containing a small portion of zinc chloride, 61 g. of acetyl bromide was added dropwise with cooling. Reaction took place vigorously with the evolution of heat. After the addition of acetyl bromide was over, the reaction mixture was washed with water, sodium carbonate solution and again with water, then dried over anhydrous sodium sulfate. Distillation gave 85 g. of a fraction boiling at 71–74° (8.5 mm.), yield 92%. After redistillation of the crude bromide, the constant boiling fraction 65° (7 mm.) was collected and was used for the kinetic experiment; $n^{25}\text{D}$ 1.4538.

Anal. Calcd. for $C_7H_{13}O_2Br$: Br, 38.2. Found: Br, 38.0.

2-Bromo-5-methoxypentane.—Metallic sodium (4.6 g.) was dissolved in 100 ml. of methanol and this solution was added dropwise to 46 g. of 2,5-dibromopentane with vigorous stirring and heating. Heating and stirring was continued for an additional 30 minutes to complete the reaction. Then about half of the methanol was distilled *in vacuo* and the remaining solution was poured into a large amount of water. The oil which separated was dried over calcium chloride. Distillation gave 22 g., b.p. 38–42° (7.5 mm.), yield 56%. The constant boiling fraction at 34–35° (7 mm.) was collected through redistillation and used for the kinetic study; $n^{25}\text{D}$ 1.4450.

Anal. Calcd. for $C_6H_{13}OBr$: Br, 44.1. Found: Br, 44.2.

2-Bromo-5-cyanopentane.—To 100 ml. of a boiling ethanol solution containing 69 g. of 2,5-dibromopentane was added 50 ml. of a 50% ethanol-water solution of 17.6 g. of sodium cyanide with vigorous stirring and refluxing. After the addition, stirring and heating were continued for an additional two hours. Then half the ethanol was distilled and the remaining mixture was poured into water. The oil (45 g.) was separated and dried over calcium chloride and then distilled *in vacuo*. The unreacted dibromide (11 g.) boiling at 52–53° (6 mm.) came over first and then 30 g. of a fraction boiling at 73–74° (6 mm.) was collected, yield 57%. Redistillation gave a constant boiling fraction at 85–86° (7.5 mm.) which was used for the kinetic measurement; $n^{25}\text{D}$ 1.4700.

Anal. Calcd. for $C_6H_{10}NBr$: Br, 45.4. Found: Br, 45.6.

Determination of Rate Constants.—Kinetic measurements and rate calculations were made by the same procedure which was used by Hughes and his co-workers.[5] In this case, since all the organic bromides were non-volatile and the reaction temperature was set at 85°, the reaction was carried out not in sealed tubes but in a glass-stoppered bottle, except in the case of isopropyl bromide, which was formolyzed in sealed tubes. Into a 200-ml. glass-stoppered reaction flask containing 78.5% formic acid, a calculated amount of organic bromide was placed so that the concentration of the solution was exactly 0.2 *N* with respect to the bromide. From time to time 5 ml. of the reaction mixture was pipetted into about 50 ml. of ice-water, extracted twice with 25 ml. of ether, then poured into a solution containing a definite amount of silver nitrate. The excess silver nitrate was titrated with ammonium thiocyanate, using iron alum as the indicator. The rate was calculated according to the equation

$$k = \frac{2.303}{t} \log \frac{a}{a - x}$$

Results and Discussion

The first-order rate constants of various organic bromides at 85 ± 0.1° are listed in the Table I.

TABLE I

FIRST-ORDER RATE CONSTANTS OF FORMOLYSIS OF VARIOUS SECONDARY ORGANIC BROMIDES IN 78.5% FORMIC ACID AT 85.0 ± 0.1°

Compound	$10^5 \times k$, mole^{-1} sec.$^{-1}$ l.
2-Bromopropane	6.37
2-Bromobutane	6.74
2-Bromopentane	6.50
2-Bromo-5-methoxypentane	188.6
2-Bromo-5-acetoxypentane	6.4[a]
2,5-Dibromopentane	6.3[b]
2-Bromo-5-cyanopentane	1.40

[a] The rate of reaction increased as the reaction proceeded for this compound. This is probably because of the hydrolysis of the acetoxy group in the reaction process. Once the acetoxy group hydrolyzed, the resulting 2-bromo-5-hydroxypentane would react rapidly with formic acid. In the case of this compound and of 2,5-dibromopentane, rate calculations were made up to 30% completion of the reaction and the mean value of *k* was obtained. [b] In this case, the formolysis of primary bromide should be taken into consideration; as soon as the primary bromide hydrolyzes, the resulting 2-bromo-5-hydroxypentane would hydrolyze immediately. Thus, the hydrolysis of the primary bromide would cause the dissociation of two bromide anions. As for the rate of hydrolysis of the primary bromide, the rate of *n*-butyl bromide was taken as the approximate value. The value in Table I was calculated from the amount of observed titration value minus twice the titration value of *n*-butyl bromide at the same time interval.

In the reaction of primary bromides with mercuric nitrate, the following order of reactivities was observed: ethyl > *n*-propyl > *n*-butyl,[3,6] and we expected that the same sequence would exist in the reactivities of secondary bromides in the formolysis reactions, *i.e.*, 2-bromopropane > 2-bromobutane > 2-bromopentane. However, there were no significant differences in their reactivities. Within small differences, 2-bromobutane had the highest rate, while 2-bromopropane had the lowest, but these differences are too small to be discussed in terms of electrical effect of the substituents.

The ethoxy group at the δ-position had a large accelerating effect on the reactivity in the reaction of primary bromide with mercuric nitrate. Here again, in the formolysis of secondary bromides, a methoxy group at the δ-position has shown a large accelerating effect. As shown in Table I, 2-bromo-5-methoxypentane formolyzed about 30 times faster than 2-bromopentane. This could be ascribed to the resonance participation of the oxygen atom of the methoxy group in the formation of a tetrahydrofuran type five-membered ring in the transition state. The driving force *L* of the methoxy group would be calculated from the equation, $L = RT \ln k/k_{\text{H}}$, in which k and k_{H} are the observed rates of formolysis of 2-bromo-5-methoxypentane and that of 2-bromopentane, respectively, similar to the driving force of the neighboring group effect

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(9) Reference 8, p. 34.

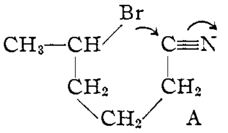
(10) Obtained through the kindness of the Du Pont Chemical Company, Del.

(11) *Org. Syntheses*, **29**, 30 (1949).

by Winstein and co-workers[12]; it was found to be 2.37 kcal./mole.

It is rather strange that acetoxy and bromo groups at the δ-position were found to have no significant effect upon the rates, when one recalls that the neighboring group effects of those groups at the β-position are quite large,[12] especially in the case of a bromo group which is fairly nucleophilic in nature.

It is also interesting that the cyano group retards the reaction. In this case, since the cyano group is highly electron-withdrawing, there would be a fairly large electrostatic attraction between the nucleophilic bromo group and the carbon atom of the cyano group, as shown in (A); and in order for the bromide to formolyze, it would be necessary to break this attraction, which would require a small amount of energy and in turn would result in the retardation of the reactivity. Another possible explanation is based upon a purely inductive mechanism. Since the cyano group is highly electron withdrawing, the simple inductive effect could have caused the retardation of SN1 reactivity of the bromide, while the bromo group in 2,5-dibromopentane, although quite strongly electron withdrawing, might have canceled out its effect by its nucleophilic participation from the back side at the transition state, which would hardly be possible in the case of cyano group. However, the latter explanation seems to be less probable, because the inductive effect is not usually transmitted through more than three saturated methylene linkages.[3,13]



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[12] S. Winstein and E. Grunwald, THIS JOURNAL, **70**, 928 (1948).

[13] See succeeding paper, Paper V of this series, *ibid.*, **78**, 4034 (1956).

OSAKA, JAPAN

[CONTRIBUTION FROM THE INSTITUTE OF SCIENTIFIC AND INDUSTRIAL RESEARCH, OSAKA UNIVERSITY]

Effect of Substituent on the Reactivity of ω-Substituted Primary Alkyl Halide in the Reaction with Sodium Thiosulfate[1,2]

BY KATSUHIKO AKAGI, SHIGERU OAE[3,4] AND MASUO MURAKAMI

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Rate constants, heat of activation and entropies of activation have been determined for several series of ω-substituted primary alkyl halides in their reaction with sodium thiosulfate in 50% ethanol. No alternation effects were observed in most of the series. In all series examined, electron-withdrawing substituents were found to increase the value of the heat of activation.

Since the well-known work of Conant and his co-workers,[5] the phenomenon of alternating reactivities has been re-observed or re-interpreted by many other workers[6] from time to time. Among all, Dewar's interpretation by means of hyperconjugation seemed to be elegant and in fact the decomposition rates of ω-nitrosoacetaminoalkylbenzenes were very well explained by his theory.[7] However, the particular phenomenon was not observed in the SN1 type reactivities of ω-substituted primary alkyl halides in the reaction with mercuric nitrate.[8] Therefore, the alternation of reactivities in the reaction with potassium iodide in acetone, which was referred to by Dewar for his interpretation of the alternation effect, does not seem to originate from pure electrical effect, such as the "alternating polarity," as far as this particular reaction is concerned.

Meanwhile, there is a possibility that the steric effect is responsible for the alternation of reaction rates. As is known in the case of ethylene dihalides the *trans* form is considered to be the most stable form at the normal state.[9] But the *trans* form is sterically handicapped for SN2 reaction and therefore would isomerize to the *gauche* or *cis*-form in the transition state. This process would consume a small amount of energy. If the energies required in this process are varied alternatively according to the number of the chain, it would affect the activation energy and in turn would cause the alternation of reaction rates. However, this assumption was found to be implausible. We have chosen *cis*- and *trans*-dichloropropenes as the similar models. Fisher–Hirschfelder models of these compounds clearly show that the *trans* form is sterically more favorable than the *cis* form in the SN2 reaction. And yet there was found no practical difference in the values of their heats of activa-

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[1] Paper V on "Reactivities of Organic Halides in Displacement Reactions"; Paper IV, THIS JOURNAL, **78**, 4032 (1956).

[2] Presented at the 8th General Meeting of the Japanese Chemical Society, Tokyo, April, 1955.

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[4] To whom requests for reprints should be addressed.

[5] J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924); J. B. Conant, W. R. Kirner and R. B. Hussey, *ibid.*, **47**, 488 (1925).

[6] E. Müller, "Neuere Anschaungen der organischen Chemie," Julius Springer, Berlin, 1940, pp. 66–73; M. J. B. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, 1949, pp. 157–159.

[7] M. Murakami and K. Akagi, *J. Chem. Soc., Japan*, **75**, 532 (1954).

[8] (a) S. Oae and C. A. VanderWerf, THIS JOURNAL, **75**, 5037 (1953); (b) S. Oae, *ibid.*, **78**, 4030 (1956).

[9] L. N. Ferguson, "Electron Structures of Organic Molecules," Prentice Hall Book Co., New York, N. Y., 1952, pp. 93–100.