[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

Relative Reactivities of Organic Halides in Displacement Reactions. III. Reactions of Mercuric Nitrate with Some Bromoketones, Bromoesters and Bromoethers[1,2]

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Rate constants and relative rates have been determined for a series of bromoketones, bromoesters and bromoethers in their reaction with mercuric nitrate in aqueous dioxane. Here again, no alternation effects were observed; however, those compounds which have an oxygen atom at the δ-position were found to be remarkably more reactive than other homologs.

Introduction

It was shown in the work of Conant and his coworkers[4] that ω-chloroacetophenone reacts extremely rapidly with potassium iodide in absolute acetone, β-chloropropiophenone reacts rather slowly and γ-chlorobutyrophenone again reacts rather rapidly. This phenomenon of alternation of reactivities in homologous series also was observed by these workers in the reactions of chloroesters and chloroethers. They ascribed the phenomenon to "alternating polarity." Later Dewar[5] interpreted this concept of "alternating polarity" in terms of hyperconjugation. However, the reactions of bromoesters with piperidine studied by Drake and McElvain[6] did not show any alternation in rates. Recently the hydrolysis of a series of chloroethers was studied by Böhme and Sell[7] and also was found not to alternate in the reaction rates. Although the present investigation, which deals with the reactions of mercuric nitrate with bromoketones, bromoesters and bromoethers, also does not show any alternation of rates, it does indicate that all the compounds which have an oxygen atom at the δ-position, so that they are capable of forming furan-like five-membered rings, are more reactive than other homologs.

Experimental

Materials.—Eastman Kodak Co. C.P. ω-bromoacetophenone was recrystallized from ethanol twice and the sufficiently pure compound of m.p. 51° was used for the kinetic measurement.

β-Bromopropiophenone.—β-Bromopropionic acid (45 g.) was mixed with 82 g. of freshly prepared thionyl bromide[8] and the mixture was heated at 60° for two hours and the excess thionyl bromide was removed by suction, leaving the crude β-bromopropionyl bromide. Into the well-stirred mixture of 36 g. of aluminum chloride and 150 ml. of dry benzene, the crude β-bromopropionyl bromide was dropped as quickly as possible. The mixture was heated with stirring for an hour on the steam-bath and then the solution was poured into ice-water. The benzene layer was separated, washed several times with water and dried with Drierite for a few days. Upon removing benzene by distillation, the residue was distilled *in vacuo*. During the course of distillation, a large amount of the compound decomposed with the evolution of hydrogen bromide gas leaving a resinous substance in the distilling flask so that only 18 g. of white crystalline solid which boiled at 125° (14 mm.) was obtained (30% yield). The crude β-bromopropiophenone was recrystallized twice from low-boiling Skellysolve and the substance of m.p. 61° was used for the kinetic study.

Anal. Calcd. for C_9H_9BrO: C, 50.5; H, 4.3; Br, 37.5. Found: C, 50.6; H, 4.2; Br, 37.3.

γ-Bromobutyrophenone.—A solution of 35 g. of γ-bromobutyronitrile in 150 ml. of ether was added slowly to an ethereal solution of Grignard reagent made from 5 g. of magnesium and 31 g. of bromobenzene. Stirring was continued for about two hours until the formation of paste made further stirring impossible. The reaction mixture was decomposed by pouring it into a mixture of ice and hydrochloric acid, cooled in an ice–salt mixture. The upper layer was removed and the remaining solution extracted once with cold ether to take out bromobenzene, benzene and diphenyl which formed during the Grignard reaction.[9] The water layer was kept at room temperature overnight until a dark oil appeared on top. The oil was separated and the remaining water layer was extracted with ether. The combined oil and ether extract was dried over Drierite for a few days. Distillation gave 12 g. of crude γ-bromobutyrophenone boiling at 126–128° (3.5 mm.) (27% yield). This oil was redistilled twice through a small fractionating column and the fraction boiled at 149° (11 mm.) was used for the kinetic measurement; $n^{30}\mathrm{D}$ 1.5593.

Anal. Calcd. for $C_{10}H_{11}BrO$: C, 52.9; H, 4.9; Br, 35.2. Found: C, 53.3; H, 5.0; Br, 34.9.

Ethyl bromoacetate and ethyl β-bromopropionate were Eastman Kodak C.P. and Matheson Co. C.P., respectively. Both were carefully distilled under reduced pressure and the fractions boiling at 154–155° (735.5 mm.) and at 67–67.5° (12 mm.), respectively, were used for the kinetic measurements; $n^{30}\mathrm{D}$ for ethyl bromoacetate, 1.4467; $n^{30}\mathrm{D}$ for ethyl β-bromopropionate, 1.4490.

Ethyl γ-bromobutyrate was prepared in one step by the same procedure that was used for the preparation of ethyl phenylacetate,[10] starting from γ-bromobutyronitrile, ethanol and sulfuric acid as a catalyst. The fraction boiling at 61–62.5° (11.5 mm.) was collected. The yield, 20 g. (50%), $n^{25}\mathrm{D}$ 1.4540, was the same as was prepared by other workers using a different method.[11]

Eastman Kodak C.P. β-bromoethyl acetate was redistilled and the fraction boiling at 155° (741 mm.) was used; $n^{30}\mathrm{D}$ 1.4516.

γ-Bromopropyl acetate[12] was prepared by allowing γ-bromopropyl alcohol and acetic anhydride to react in the presence of dry zinc chloride. The fraction boiling at 71–72° (12 mm.) was collected and used; yield 88%, $n^{30}\mathrm{D}$ 1.4543.

δ-Bromobutyl acetate was prepared by refluxing equimolar amounts of tetramethylene bromide and dry potassium acetate in methanol for ten hours. After three successive fractionations, the fraction boiling at 95–96° (14 mm.) was collected and used. The product is identical to that made previously by another method[13]; $n^{30}\mathrm{D}$ 1.4602.

ε-Bromoamyl acetate[14] was made by the same method as was used for the preparation of δ-bromobutyl acetate and

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[1] Paper II, THIS JOURNAL, **75**, 5037 (1953).

[2] Presented at the 6th General Meeting of the Japanese Chemical Society, Kyoto, April, 1953.

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

[4] J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924); J. B. Conant, W. R. Kirner and R. E. Hussey, *ibid.*, **47**, 478, 488 (1925).

[5] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, pp. 157–159.

[6] W. V. Drake and S. M. McElvain, THIS JOURNAL, **56**, 697 (1934).

[7] H. Böhme and K. Sell, *Ber.*, **81**, 123 (1948).

[8] R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1516 (1946).

[9] J. B. Conant, J. B. Segur and W. R. Kirner, *ibid.*, **46**, 1882 (1924).

[10] *Organic Syntheses*, Coll. Vol. I, p. 265.

[11] E. Peril and S. M. McElvain, THIS JOURNAL, **55**, 1233 (1933).

[12] J. S. Allen and H. Hibbert, *ibid.*, **56**, 1398 (1934).

[13] L. M. Smorgouskii and Y. L. Gol'dfarb, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1113 (1940); *C.A.*, **35**, 4011 (1941).

[14] C. L. Wilson, *J. Chem. Soc.*, 48 (1945).

the fraction of b.p. 106–107° (12 mm.) was collected and used for this experiment; $n^{30}\text{D}$ 1.4641.

Eastman Kodak C.P. β-bromoethyl ethyl ether was washed, dried and distilled under the atmospheric pressure and the fraction boiling at 124.5° (737 mm.) was collected and used for the kinetic experiment.

γ-Bromopropyl ethyl ether[15] was made by allowing 100 g. of γ-bromopropyl alcohol to react with 100 ml. of ethanol in the presence of 10 ml. of concd. sulfuric acid at 145–155° in the usual manner.[16] The fraction of b.p. 40° (12 mm.) was collected and used. The yield was rather poor, $n^{30}\text{D}$ 1.4446.

δ-Bromobutyl ethyl ether[17] was prepared by allowing sodium ethoxide to react with tetramethylene bromide in boiling ethanol. The yield of the fraction, boiling at 170–175° (738 mm.) was 40%. This was refractionated through an efficient column and the material boiling at 69° (15 mm.) was collected, $n^{30}\text{D}$ 1.4490.

ε-Bromoamyl ethyl ether was prepared in the same manner as in the previous homolog, starting from pentamethylene bromide and sodium ethoxide in ethanol. The yield of the fraction boiling between 185–192° (741 mm.) was 48%. Careful refractionation gave the constant boiling fraction at 85° (14 mm.) used for the kinetic experiment; $n^{30}\text{D}$ 1.4520.

Kinetic Determination and Rate Calculations.—Kinetic measurements and rate calculations were made by procedures reported previously.[1] With the use of rather weakly acidic dioxane solutions, hydrolysis of esters was negligible in the course of the kinetic runs, except in the case of ethyl bromoacetate, which reacted so slowly with mercuric nitrate that appreciable hydrolysis occurred. In this case, the analysis was made up to 15% of completion of the reaction in order to avoid the large error due to the side reaction of hydrolysis.

Results and Discussion

The reaction velocity constants at 40.05° are shown in Table I.

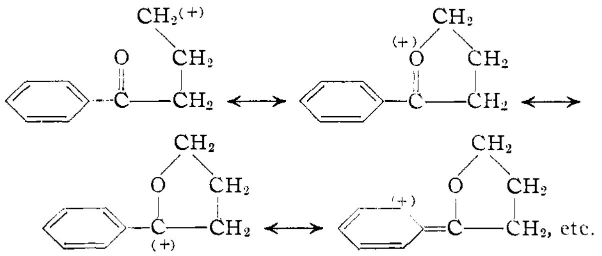
TABLE I

RATE CONSTANTS OF REACTION OF BROMOKETONES, BROMOESTERS AND BROMOETHERS WITH MERCURIC NITRATE AT 40.05°

Compound	$10^3 \times k$, mole^{-1} sec.^{-1} l.	Relative reactivity (*n*-butyl bromide as 1)
n-Butyl bromide	4.2[a]	1.0
ω-Bromoacetophenone	0.23	0.055
β-Bromopropiophenone	1.3	0.31
γ-Bromobutyrophenone	[b]	71.1
Ethyl bromoacetate	0.13	0.031
Ethyl β-bromopropionate	0.43	0.10
Ethyl γ-bromobutyrate	5.2	1.24
β-Bromoethyl acetate	2.0	0.48
γ-Bromopropyl acetate	2.0	.48
δ-Bromobutyl acetate	2.2	.52
ε-Bromoamyl acetate	2.0	.48
β-Bromoethyl ethyl ether	0.43	.10
γ-Bromopropyl ethyl ether	1.4	.33
δ-Bromobutyl ethyl ether	33.8	8.0
ε-Bromoamyl ethyl ether	5.0	1.2

[a] 1.1 at 25.0°. [b] Too fast to be measured at 40.05°; 78.3 at 25°. [c] Based upon the value at 25.0°

In contrast to the extremely high reactivities of ω-haloacetophenone and of ethyl haloacetate in S_N2 reactions, the reactivities of both ω-bromoacetophenone and ethyl bromoacetate are low in the present reaction as well as in the similar reactions with silver nitrate.[18] The low reactivities of these compounds in S_N1 type[19] reaction would best be ascribed to the lower electron density on the α-carbon due to the strong electron-attracting inductive effect of the carbonyl group, which makes the separation of halogen anion more difficult. The rather low reaction rates of both β-bromopropiophenone and ethyl β-bromopropionate seem to indicate that the inductive effect of the carbonyl group is still effective at the β-position. The extremely high reactivity of γ-bromobutyrophenone is understandable if the possible resonance with a large contribution from the benzene ring is considered to be operating in the resulting carbonium ion



A furan type five-membered ring can also be formed in the resulting carbonium ion of ethyl γ-bromobutyrate, which also showed high reactivity. This is compatible with the postulate of Winstein and his co-workers[20] that the cyclic orthoacetate type intermediate occurs in the S_N1 type reaction of 2-acetoxy-3-bromobutane. Moreover, it was reported recently that 2-ethyl-2-cyanotetrahydrofuran formed as the result of a reaction between γ-bromopropyl ethyl ketone with cuprous cyanide in toluene.[21] These postulates are further affirmed by the fact that β-bromoethyl acetate reacts here with moderate velocity, in spite of its rather strong electron attractive acetoxy group at the β-position and that its reactivity is larger than β-bromoethyl ethyl ether.

The reactivities in the hydrolysis of chloroethers were shown by Böhme and Sell[7] to increase with the increase of the number of methylene groups between oxygen and halogen, but their experiments did not extend to the 5-methylene group. In the present experiments, reactivities increased with the increase in the number of connecting methylene groups up to δ-bromobutyl ethyl ether and then decreased in the succeeding homolog, *i.e.*, ε-bromoamyl ethyl ether. δ-Bromobutyl ethyl ether, furthermore, showed remarkably high reactivity and even ε-bromoamyl ethyl ether has rather high reactivity, which could not be observed in the work of Böhme and Sell.[7] This is conceivable, because the bromide has higher polarizability than chloride and by using such a strong electrophilic reagent as mercuric nitrate instead of water–dioxane mixture, the bromides would become more sensitive to influence by the rest of the molecule. In this case, the carbonium ion resulting from the hydrolysis of δ-bromobutyl ethyl ether would be

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(15) R. L. Frank, F. F. Woodward and P. J. Canterino, *J. Polymer Sci.*, **3**, 39 (1948); *C.A.*, **42**, 3987 (1948).

(16) L. C. Swallen and C. E. Boord, THIS JOURNAL, **52**, 651 (1930).

(17) V. Prelog and K. Bozicevic, *Ber.*, **72B**, 1103 (1939).

(18) M. Murakami, S. Oae and S. Takeuchi, *Boll. Chem. Soc. Japan* **24**, 1 (1951).

(19) See C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, pp. 357–360.

(20) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2780, 2787 (1942); **65**, 613 (1943).

(21) H. Normant, *Compt. rend.*, **232**, 1942 (1951); *C. A.*, **46**, 5036 (1952).

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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[22] The same phenomenon was observed in the S_N1 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).

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

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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_N1 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).

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[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.