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The Effect of the ω-Cyano Group on the Reactivity of Secondary Bromides in the Formolysis Reaction and on the Reactivity of Primary Bromides in the Reaction with Silver Nitrate[1–4]

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Several ω-cyano-2-bromoalkanes have been synthesized and their formolysis rates were determined. The reactivity of these compounds was found to decrease with a decrease in chain length and have a parallerism with a chemical shift ($\rangle$CH–, –CH$_3$) of NMR spectra. A similar sequence was observed in the reactivity of ω-cyano-1-bromoalkanes in the reaction with silver nitrate.

In the previous paper[6] of this series, rates of formolysis of several 5-substituted 2-bromopentanes were studied. While the 5-acetoxy and 5-bromo groups exhibited essentially no effect upon the reactivity, it was found that the methoxy group at the 5 position accelerated the formolysis by a factor of about thirty and that the cyano group at the same position caused nearly a five-fold retardation. The large accelerating effect of the methoxy group was ascribed to the five-membered ring neighboring group participation of the δ-methoxy group. This interpretation was confirmed later by Winstein and his co-workers.[7] As for the retarding effect of the ω-cyano group, the electrostatic attraction between the unshared electron pairs of covalently bonded bromine and the cyano group was suggested as a possible explanation, since the electron-withdrawing inductive effect is known to virtually disappear after being transmitted through more than three saturated methylene linkages in both S_N1 and S_N2 reactions[8,9] of primary organic halides. One way to test this assumption is to compare the reactivity of ω-cyanobromoalkanes of different methylene chain length, because direct electrostatic interactions of this nature should be quite insensitive to ring size. Therefore, the present investigation was undertaken to deal with the rates of formolysis of several 2-bromo-ω-cyanoalkanes, namely 2-bromo-3-cyanopropane, 2-bromo-4-cyanobutane, 2-bromo-5-cyanopentane and 2-bromo-6-cyanohexane. Contrary to our earlier expectation, the reactivity of 2-bromo-5-cyanopentane was much greater than that of 2-bromo-4-cyanobutane, which in turn, had remarkably greater reactivity than 3-cyano homolog, while the reactivity of 2-bromo-6-cyanohexane was found not to reach that of 2-bromobutane after being transmitted through four saturated methylene linkages, though it was greater than that of 2-bromo-5-cyanopentane.

The investigation has been extended to the kinetic study of the reaction of silver nitrate in absolute ethanol with 1-bromo-ω-cyanoalkanes, namely, 1-bromo-2-cyanoethane, 1-bromo-3-cyanopropane, 1-bromo-4-cyanobutane, 1-bromo-5-cyanopentane and 1-bromo-6-cyanohexane. Here again the reactivity was found to decrease as the cyano group more closely approached the reacting center and to be insensitive to the size of the chain length contrary to that expected from the assumption in the previous paper.[6]

Experimental

Materials. Commercially available extra pure 98% formic acid was diluted with distilled water to give a solution of specific gravity of 1.2086 at 20°C. This corresponds to 92.4% formic acid by weight. The purification of absolute ethanol and the preparation of a silver nitrate solution were discussed elsewhere.[10]

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[1] Contribution from the Department of Chemistry, Drexel Institute of Technology, Philadelphia, Pennsylvania, and the Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Osaka, Japan.

[2] Paper VII on "Relative Reactivities of Organic Halides in Displacement Reactions"; Paper VI, *J. Am. Chem. Soc.*, **79**, 3118 (1957).

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[4] Presented in part before the Fourth Delaware Valley Regional Meeting, Philadelphia, Pennsylvania, January 26, 1962.

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[6] S. Oae, *J. Am. Chem. Soc.*, **78**, 4032 (1956).

[7] S. Winstein, E. Allred, R. Heck and R. Glick, *Tetrahedron*, **3**, 1 (1958); E. L. Allred and S. Winstein, *J. Am. Chem. Soc.*, **89**, 3991 (1967).

[8] S. Oae and C. A. VanderWerf, *ibid.*, **78**, 4034 (1956).

[9] K. Akagi, S. Oae and M. Murakami, *ibid.*, **78**, 4032 (1956).

[10] S. Oae and C. A. VanderWerf, *ibid.*, **75**, 2724 (1953).

2-Bromo-6-cyanohexane was synthesized by a following method. Commercially available α-picoline was reduced to 2-methyl-piperidine by catalytic hydrogenation with Raney nickel at 200°C and 150 atm of hydrogen, and 2-methyl-piperidine thus prepared was converted to 1,5-dibromohexane by the von Braun reaction.[11] Equivalent amounts of 1,5-dibromohexane and sodium cyanide were refluxed in ethanol for 4 hr and 2-bromo-6-cyanohexane was obtained in a 25% yield. The fraction boiling at 103—103.5°C/2 mmHg was collected and used.

Found: C, 44.23; H, 6.37%. Calcd for $C_7H_{12}NBr$: C, 44.23; H, 6.03%. n_D^{30} 1.4784.

2-Bromo-5-cyanopentane was prepared by a procedure described.[6]

2-Bromo-4-cyanobutane was made similarly, starting from 1,3-dibromobutane and sodium cyanide. The fraction boiling at 86—86.5°C/8 mmHg was collected and used.

Found: C, 37.74; H, 5.08%. Calcd for C_5H_8NBr: C, 37.74; H, 4.98%. n_D^{30} 1.4692.

2-Bromo-3-cyanopropane was made similarly, starting from 1,2-dibromopropane and sodium cyanide. The fraction boiling at 65°C/75 mmHg was collected and used.

Found: C, 32.30; H, 4.16%. Calcd for C_4H_6NBr: C, 32.46; H, 4.16%. n_D^{30} 1.5147.

1-Bromo-2-cyanoethane was an Eastman white labeled product. 1-Bromo-3-cyanopropane, 1-bromo-4-cyanobutane, 1-bromo-5-cyanopentane and 1-bromo-6-cyanohexane were obtained from Aldrich Chemical Company. All were washed with diluted alkaline solutions, dried over anhydrous calcium chloride and carefully fractionated. Boiling points and refractive indices of the respective compounds are shown below. (Table. 1)

TABLE 1. PHYSICAL CONSTANTS OF ω-CYANO-1-BROMOALKANES

Compound	Boiling point	Refractive index
1-Bromo-2-cyanoethane	76.2—76.3°C/9 mmHg	1.4768
1-Bromo-3-cyanopropane	99.6—99.9°C/14 mmHg	1.4753
1-Bromo-4-cyanobutane	108.4—108.6°C/9.4 mmHg	1.4754
1-Bromo-5-cyanopentane	118.0—118.2°C/7 mmHg	1.4744
1-Bromo-6-cyanohexane	133.5—134.5°C/7.6 mmHg	1.4728

2-Bromobutane and 1-bromopentane were both Eastman white labeled products and were purified as in the previous work.[6,8]

Determination of Rate Constant. Kinetic measurements and rate calculations for the formolysis of secondary bromides were made by the same procedure previously used.[6] In this case, 5 m*l* portions were sealed in ampoules and the reaction was carried out at 85.00±0.01°C, 95.00±0.01°C and 105.00±0.01°C, respectively, while the titration was accomplished by Volhard's method, using ammonium alum as the indicator. First order rate constants were calculated according to the equation,

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

The activation parameters were obtained graphically.

Isolation of Product in the Reaction of 2-Bromobutane with Formic Acid. A solution of 2-bromobutane in 90% formic acid was refluxed on a steam bath for 48 hr. This was poured into cold water and extracted with ether. The ethereal extracts were washed three times with water, three times with diluted sodium carbonate and three times again with water. They were dried over potassium carbonate and the solvent was distilled to give a pale yellow residue. This was found to have very similar index of refraction, infrared spectrum and identical retention time in the vapor phase chromatograph with an authentic sample of secondary butyl formate prepared by the method of Pickard, Kenyon and Hunter.[12]

Primary bromides are known to react with ethanolic silver nitrate to give the corresponding nitrate ester.[10] 1-Bromo-5-cyanopentane was treated in the same concentration solutions as those used for the kinetics, but allowed to reflux on a steam bath for several days. The silver bromide was filtered, followed by evaporation of the solvent, removal of any additional solid and distillation of the filtrate through a packed column. The yellow distillate, bp 113—114°C/15 mmHg, showed infrared bands at 1276 cm^{-1} and 1632 cm^{-1}, indicating the presence of nitrate ester and a strong aliphatic ether band at 1108 cm^{-1} in addition to those bands present in the starting material.[13]

Result and Discussion

The first-order rate constants, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of secondary bromides at 85.0°C, 95.0°C and 105.0°C are given in Table 2.

The results clearly indicate that low reactivity of 2-bromo-5-cyanopentane is not the unique phenomenon. In fact, the rate decreases with the decrease in chain length. However, when one plots the logarithms of the rates against *n*, one finds that 2-bromo-3-cyanopropane falls off the line while the others are in a fairly good correlationship (Fig. 1). Apparently the formolysis of this particular bromide proceeds through a different path. Indeed, both the enthalpy and entropy of activation of the reaction are vastly different from those of the other compounds. The strong electron-withdrawing inductive effect of ω-cyano group probably makes the S_N1 type heterolysis of C–Br bond so difficult that S_N2 type process, in which formolysis is assisted by the nucleophilic attack of formate, becomes predominant. As one expected, the NMR chemical shifts of methyne proton at 2 position of substitued

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[11] Adapted from a method of J. Von Braun, " Organic Syntheses," Coll. Vol. I, p. 428 (1941).

[12] R. H. Pickard, J. Kenyon and H. Hunter, *J. Chem. Soc.*, **1923**, 123.

[13] L. J. Bellamy, " The Infra-red Spectra of Complex Molecules, " John Wiley and Sons, Inc., New York, N.Y. (1958).

TABLE 2. FIRST-ORDER RATE CONSTANTS, AND ACTIVATION PARAMETERS OF FORMOLYSIS OF SECONDARY ORGANIC BROMIDES IN 92.4% FORMIC ACID

Compound	Temp (°C)	k_1(sec^{-1})	$\Delta H^{\ddagger}$(kcal/mol)	$\Delta S^{\ddagger 95°C}$(e.u.)
$NCCH_2CHBrCH_3$	85.0	$1.31\pm0.11\times10^{-6}$		
	95.0	$2.19\pm0.07\times10^{-6}$		
	105.0	$4.12\pm0.03\times10^{-6}$	15.3	−43.1
$NC(CH_2)_2CHBrCH_3$	85.0	$5.68\pm0.05\times10^{-6}$		
	95.0	$1.44\pm0.04\times10^{-5}$		
	105.0	$3.44\pm0.13\times10^{-5}$	25.9	−16.1
$NC(CH_2)_3CHBrCH_3$	85.0	$1.99\pm0.06\times10^{-5}$		
	95.0	$6.19\pm0.03\times10^{-5}$		
	105.0	$1.37\pm0.08\times10^{-4}$	25.6	−9.87
$NC(CH_2)_4CHBrCH_3$	85.0	$2.49\pm0.08\times10^{-5}$		
	95.0	$7.53\pm0.05\times10^{-5}$		
	105.0	$1.89\pm0.01\times10^{-4}$	25.1	−9.96
$CH_3CH_2CHBrCH_3$	85.0	$1.62\pm0.02\times10^{-4}$		
	95.0	$3.97\pm0.04\times10^{-4}$		
	105.0	$9.77\pm0.30\times10^{-4}$	24.0	−9.29

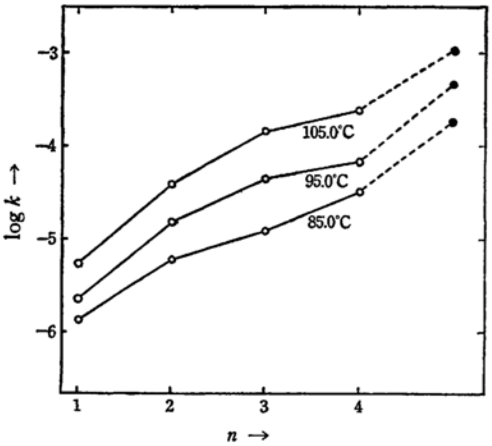

Fig. 1. Correlationship between the formolysis rates of $NC(CH_2)_nCHBrCH_3$ and n.
—○— $NC(CH_2)_nCHBrCH_3$
—●— $CH_3CH_2CHBrCH_3$

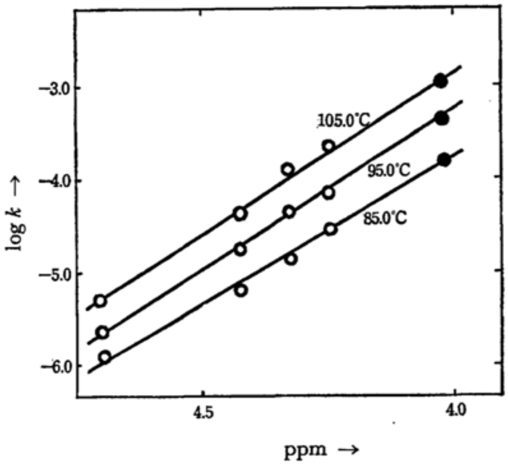

Fig. 2. Correlationship between the formolysis rates and NMR methyne chemical shifts of $NC(CH_2)_nCHBrCH_3$ and $CH_3CH_2CHBrCH_3$.
—○— $NC(CH_2)_nCHBrCH_3$
—●— $CH_3CH_2CHBrCH_3$

2-bromoalkanes can be correlated with the methylene chain lengths, while a rough linear correlationship is observed between the rates and the NMR chemical shifts of these organic bromides. (Fig. 2) A similar relationship between the chemical shifts and the electron-withdrawing properties has been reported in the case of ω-nitroalkanes,[14] however, in this case the inductive and/or field effects disappear rapidly after being transmitted through more than four methylene linkages. Perhaps in the case of nitro group, negative oxygen atoms display negative field effect and decrease the electron-withdrawing effect so markedly beyond more than two methylene groups away. While cyano group being uncharged yet electronegative and polarizable, may perturb the electrons further away, both directly and indirectly. From the NMR data, the transmission coefficient, ε, of cyano group is calculated to be 0.45—0.50. Transmission coefficient has been accepted to be nearly constant, *i.e.*, 0.35, in many reactions.[15] Therefore the value we obtained is somewhat larger than the ordinary one. In this case not only an inductive effect through methylene but also some field effect of highly electro-negative groups are in operation. To clarify this problem, $\rho\sigma^*$

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[14] W. Hofman, L. Stefariak, T. Urbanski and M. Witanowski, *J. Am. Chem. Soc.*, **86**, 554 (1964).

[15] M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3539, 3548 (1961).

treatment[16] was carried out in which σ^* values were calculated by using the transmission coefficient obtained in this experiment. A very good linear correlationship was found as in Fig. 3. This may mean that the formolysis of ω-cyano-2-bromoalkanes is controlled by the inductive effect alone.

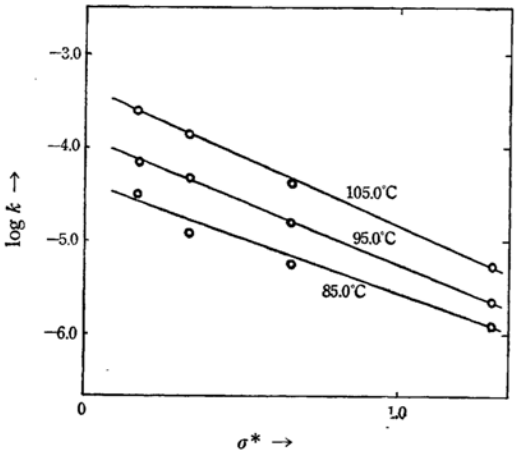

Fig. 3. Correlationship between the formolysis rates of $NC(CH_2)_nCHBrCH_3$ and σ^* of $-(CH_2)_n-CN$.

The second order rate constants for the reaction of the primary bromides with silver nitrates in absolute ethanol at 50.04±0.02°C are tabulated in Table 3.

There are numerous sources of evidence to support the fact that carbon-halogen bond fission is the rate determining step for the reaction between silver nitrate and alkyl halides. Therefore, one would expect that the slow reacting primary 1-bromo-ω-cyanoalkanes would show a similar sequence of reactivities in the reaction with silver nitrate. In fact, the cyano group was found to retard the reactivity considerably as it approaches closer to the reacting site. However, in this case the retarding effect of the cyano group virtually disappeared beyond three saturated methylene groups.

TABLE 3. SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF PRIMARY BROMIDES WITH SILVER NITRATE IN ABSOLUTE ETHANOL AT 50.04±0.02°C

Compound	$k_2 \times 10^4$ $l\ mol^{-1}sec^{-1}$
1-Bromo-2-cyanoethane	2.98
1-Bromo-3-cyanopropane	5.01
1-Bromo-4-cyanobutane	14.0
1-Bromo-5-cyanopentane	23.4
1-Bromo-6-cyanohexane	21.6
1-Bromopentane	16.9

It is interesting to note that 1-bromo-5-cyanopentane and 1-bromo-6-cyanohexane were found to react faster than 1-bromo-pentane. This may be due to an altering of the electron-withdrawing ability of the cyano group by coordination with silver ion, as is known to occur in ũ bonded systems, or by some interaction with solvent such as hydrogen bonding.[17]

The presence of an ether in the product may be accounted for by a transition state model in which silver ion is exerting an attracting force on the halogen which results in partial carbonium ion character at the seat of reaction. Displacement could be effected by nitrate ion to give the expected product or by solvent with the subsequent loss of a proton to give rise to the ethoxy derivative.

We are indebted to Mr. Clyde Zault who checked some of the kinetic runs.

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[16] R. W. Taft, Jr., "Separation of Polar, Steric, and Resonance Effects in Reactivity," in "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Wiley and Sons, Inc., New York (1956), p. 595.

[17] P. von R. Schleyer and A. Allerhand, *J. Am. Chem. Soc.*, **84**, 1322 (1962).