[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

The Effect of Halogen Atoms on the Reactivity of Other Halogen Atoms in the Same Molecule. VI. The S_N2 Reactivity of Methylene and Polymethylene Halides[1]

BY JACK HINE, STANTON J. EHRENSON AND W. H. BRADER, JR.

RECEIVED OCTOBER 15, 1955

The effect of various substituent halogen atoms on reactivity by the S_N2 mechanism has been studied by determining the rate constants for the reaction of sodium thiophenolate in methanol with CH_2I_2, $BrCH_2I$, $ClCH_2I$, FCH_2I, CH_2Br_2, $ClCH_2Br$, FCH_2Br, CH_2Cl_2, n-C_3H_7I, $I(CH_2)_3I$, $Br(CH_2)_3I$, $Cl(CH_2)_3I$, $F(CH_2)_3I$, n-$C_6H_{13}Br$, $Br(CH_2)_3Br$, $Cl(CH_2)_3Br$, $F(CH_2)_3Br$, $Cl(CH_2)_4I$ and $Cl(CH_2)_5I$. In the α-position, substituents have the following relative effect on reactivity: $H > CH_3 \sim C_2H_5 \sim F > Cl > Br < I$. In the γ-position the effect of the halogens is small, none changing the reactivity (compared to hydrogen as a substituent) by so much as 50%. Chlorine substituents in the δ- and ϵ-positions also have little effect on the reactivity.

Earlier reports from this Laboratory have described the effect of α-halogens[2] and β-halogens,[3] as substituents, on reactivity by the S_N2 mechanism.[4] The effect of α-halogens was studied by determining the reactivity of methylene halides toward sodium iodide in acetone and toward sodium methoxide in methanol. The small difference between the reactivity of a bromide and the corresponding iodide toward sodium methoxide made it very difficult to estimate how much of the reaction of bromoiodomethane involved displacement of iodide and how much involved displacement of bromide. This, in turn, made it difficult to draw any conclusion about the relative effect of α-bromine and α-iodine substituents on S_N2 reactivity. Since the difference in reactivities between bromides and iodides appears to be greater for reaction with sodium thiophenolate than for reaction with sodium methoxide,[5] we have determined the reactivities of methylene halides toward sodium thiophenolate. Furthermore, since FCH_2Br was found to be more reactive than C_2H_5Br toward sodium methoxide but less reactive toward sodium iodide in acetone, we felt it desirable to compare the reactivities of these two halides toward still another nucleophilic reagent.

To learn the effect of γ- and more distant halogen substituents we have also measured the reactivity of all of the trimethylene halides containing either bromine or iodine and also of 4-chlorobutyl iodide and 5-chloropentyl iodide toward sodium thiophenolate.

Experimental

Apparatus.—Kinetics were run, at temperatures other than 0°, as previously described.[3] Zero-degree runs were conducted in an air-insulated covered bath containing 18 liters of ice–water slurry. The temperature was found to remain at 0.0 to 0.1°.

Materials.—All the dihalides employed were fractionated (through a column packed with glass helices) immediately prior to use. When available for comparison, the refractive indices as well as the boiling points were used as indications of purity. Dihalides used, the preparations of which have not been previously described in this series,[1] were fluoroiodomethane, trimethylene chloroiodide, diiodide, bromoiodide, fluorobromide and fluoroiodide. Fluoroiodomethane was prepared from fluorobromomethane by the action of sodium iodide in methyl ethyl ketone, followed by fractionation under nitrogen and in the absence of light. Trimethylene chloroiodide, bromoiodide and fluoroiodide were prepared by the action of sodium iodide in acetone upon trimethylene chlorobromide, bromide and fluorobromide, respectively. Trimethylene iodide and fluorobromide were prepared by the methods of Bogert and Slocum,[6] and Hoffman,[7] respectively. The other halides employed were the best grades commercially available. Methanol purification followed the method described by Fieser.[8] Thiophenol, although more than 1% impure, was used in conjunction with approximately a 2% excess of sodium methoxide to prepare the sodium salt, and was standardized against methanolic iodine.

Kinetic Runs.—Procedures identical with those described previously[3] were used with the single exception that a standard iodine in methanol solution was used in titrating the unreacted thiophenol. Titration with standard $KI{\cdot}I_2$ in water[9] was found to be undesirable because the end-point is not sharp. Within about 5% of the true end-point an iodine color, which slowly fades, is noted. The true titer of the thiophenol may therefore be approached only slowly, and as a result less accurately, than is possible with the alcoholic iodine. The addition of water, in which the thiophenol and diphenyl disulfide are quite insoluble, in amounts *less* than necessary to precipitate the sulfur compounds is sufficient to obscure the end-point and has therefore been avoided.

Reactions involving all the dihalides except methylene fluorobromide were run batchwise in erlenmeyer flasks, samples being withdrawn at various times. The low boiling point of CH_2BrF (18°) necessitated separate weighings of the halide for each point (into 50-ml. volumetric flasks containing 20 ml. of methanol). The volumetric flasks, which served as the reaction vessels, were thermostated and the standard thiophenolate added.

Results

The specific rate constants for the reactions of the monohalides, fluoromethyl halides and polymethylene halides were calculated from the unmodified integrated second order rate equation

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

where $a = [RX]_0$, $b = [C_6H_5SNa]_0$, $x = \Delta[RX]_t$ and t = time (seconds). Since this equation is suitable only if the reaction stops at the replacement of one halogen, it was necessary to use a five- to twelve-fold excess of halide with trimethylene dibromide and diiodide to prevent the rate constants from "drifting." For the other methylene halides we used an equation derived on the assumption that the displacement of the first halogen from a molecule

---

(1) For Part V of this series see ref. 2.

(2) J. Hine, C. H. Thomas and S. J. Ehrenson, THIS JOURNAL, **77**, 3886 (1955).

(3) J. Hine and W. H. Brader, Jr., *ibid.*, **75**, 3964 (1953).

(4) For the significance of the term S_N2 see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, chap. VII.

(5) Chloroiodomethane is about six times as reactive as chlorobromomethane toward sodium thiophenolate (Table II) but only about twice as reactive toward sodium methoxide.[2]

(6) M. T. Bogert and E. M. Slocum, THIS JOURNAL, **46**, 763 (1924).

(7) F. W. Hoffman, *J. Org. Chem.*, **14**, 1056 (1940).

(8) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Inc., Boston, Mass., 1941, p. 359.

(9) P. Klason and T. Carlson, *Ber.*, **39**, 738 (1906).

was followed quite rapidly by the displacement of the second

$$k = \frac{2.303}{t(2a - b)} \log \frac{b(a - x)}{a(b - 2x)}$$

a, b, x and t having the same significance as before. Data on a typical run is shown in Table I. Points taken before four minutes and/or 15% reaction and after 90% reaction and those whose deviations were more than four times the average were rejected.

TABLE I

REACTION OF METHYLENE IODIDE WITH SODIUM THIOPHENOLATE IN METHANOL AT 40°

$[C_6H_5SNa]_0 = 0.02412\ N$, $[CH_2I_2]_0 = 0.01440\ N$

Time (sec.)	0.0304 N I_2, ml.	$k \times 10^4$, l./mole. sec.
0	15.87	
630	11.41	208.8
975	9.68	216.6
1140	9.06	216.0
1335	8.46	213.0
1575	7.67	217.3
1775	7.07	221.8
2325	6.01	217.2
	Av.	215.8 ± 2.8

The average rate constants and mean deviations are listed in Tables II and III.

TABLE II

KINETIC CONSTANTS FOR REACTIONS OF METHYLENE HALIDES WITH SODIUM THIOPHENOLATE IN METHANOL

Halide	10^4k (l./mole. sec.) 0.0°	10^4k (l./mole. sec.) 40°	$\Delta H^{\ddagger}$ (kcal.)	$\Delta S^{\ddagger}$ (e.u.)
ICH_2I[a]	1.19 ± 0.01	108 ± 2	18.6	− 8.5
$BrCH_2I$	0.811 ± .018	79.8 ± 1.6	18.9	− 7.9
$ClCH_2I$	1.83 ± .03	149 ± 3	18.1	− 9.2
FCH_2I	47.9 ± .9	964 ± 20[b]	15.9	−10.8
C_2H_5Br[c]	3.79 ± .06	182 ± 3[d]	18.1	− 7.7
$BrCH_2Br$[a]	0.0798 ± .0004	10.0 ± 0.2	20.0	− 8.7
$ClCH_2Br$	.228 ± .002	25.1 ± .3	19.4	− 8.6
FCH_2Br	1.98 ± .03	152 ± 5	17.9	− 9.9
$ClCH_2Cl$[a]	0.0214 ± .0010[e]	0.222 ± 0.007	21.1	−12.5

[a] The observed rate constants have been divided by two to get the rate constant per iodine, bromine or chlorine. [b] At 30°. [c] Data from ref. 3. [d] At 34.6°. [e] At 20.35°.

TABLE III

KINETIC CONSTANTS FOR REACTIONS OF POLYMETHYLENE HALIDES WITH SODIUM THIOPHENOLATE IN METHANOL

Halide	10^4k (l./mole. sec.) 0.0°	10^4k (l./mole. sec.) 19.95°	$\Delta H^{\ddagger}$ (kcal.)	$\Delta S^{\ddagger}$ (e.u.)
C_3H_7I	14.7 ± 0.3	128 ± 1	16.7	−10.3
$I(CH_2)_3I$[a]	20.1 ± .3	181 ± 3	17.0	− 8.6
$Br(CH_2)_3I$	21.8 ± .4	191 ± 4	16.8	− 9.2
$Cl(CH_2)_3I$	15.7 ± .2	138 ± 1	16.8	− 9.7
$F(CH_2)_3I$	11.2 ± .1	104 ± 1	17.2	− 9.0
$Cl(CH_2)_4I$	23.9 ± .2	204 ± 4	16.6	− 9.7
$Cl(CH_2)_5I$	22.9 ± .2	195 ± 1	16.5	−10.0
C_3H_7Br[b]	2.56 ± .03	25.6 ± 0.3[c]	17.7	−10.0
C_4H_9Br[b]	2.77 ± .03	26.9 ± .3[c]	17.7	−10.0
$C_6H_{13}Br$	3.14 ± .02	77.8 ± .4[d]	17.4	−10.8
$Br(CH_2)_3Br$[a]	2.89 ± .04	29.9 ± .1	18.1	− 8.4
$Cl(CH_2)_3Br$	2.54 ± .04	70.6 ± .4[d]	18.0	− 8.9
$F(CH_2)_3Br$	1.86 ± .02	52.6 ± .4[d]	18.1	− 9.1

[a] The observed rate constants have been divided by two to get the rate constant per iodine or bromine. [b] Data from ref. 3. [c] At 20°. [d] At 29.4°.

Enthalpies and entropies of activation were calculated from the absolute rate equation[10]

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

The values of $\Delta H^{\ddagger}$ are estimated to be reliable within 0.4 kcal. and the $\Delta S^{\ddagger}$ values within 1.0 e.u.

From the data of Tables II and III, iodides may be seen to be considerably more reactive than the corresponding bromides. However, although most of the reaction of bromoiodides is due to iodine, the amount of reaction due to bromine is enough to warrant an estimation of the correction necessary for this factor. Perhaps as reliable an estimate as any would be based on the assumption that the reactivity of bromomethyl bromide is to that of iodomethyl bromide as the reactivity of bromomethyl iodide is to that of iodomethyl iodide. From this assumption and the data of Table II we get

$$\frac{10 \times 10^{-4}}{(79.8 \times 10^{-4}) - y} = \frac{y}{108 \times 10^{-4}}$$

or

$$y = 62.5 \times 10^{-4} \text{ l./mole. sec.}$$

and

$$(79.8 \times 10^{-4}) - y = 17.3 \times 10^{-4} \text{ l./mole. sec.}$$

where y is the rate constant for the displacement of iodine and $(79.8 \times 10^{-4}) - y$ is the rate constant for the displacement of bromine from bromoiodomethane by sodium thiophenolate at 40°. Similarly, the rate constant for the displacement of iodide from trimethylene bromoiodide at 19.95° may be estimated to be 156×10^{-4} and that for displacement of bromine 35×10^{-4} l./mole. sec. These estimates are certainly not entirely reliable since they are based on assumptions of a type shown by other data in Tables II and III to be not generally true. Since the corrections for bromine displacement are not too large, the estimates of the reactivity of the iodine atoms are probably relatively reliable.

Discussion

The data obtained on methylene halides are like those reported previously[2] in that as α-substituents, each of the four halogens (compared to hydrogen) decreases the S_N2 reactivity. The data are like those obtained in the reaction with sodium iodide in acetone in that ethyl bromide is more reactive than fluoromethyl bromide. A new, unexpected result is that fluoromethyl iodide is more than three times as reactive as *n*-propyl iodide although fluoromethyl bromide is only 80% as reactive as *n*-propyl bromide.

With γ-halogen substituents the reactivity decreases with increasing electronegativity, but this correlation of reactivity with electron-withdrawing power may not be extended to γ-hydrogen and γ-methyl substituents. No striking effect results from δ- or ε-chlorine substituents.

A comparison of the activation parameters and the estimated experimental errors therein shows that in several cases differences in enthalpies of activation contribute to the differences in reactivity but in few, if any, cases can we be sure that entropy differences contribute to the differences in

---

[10] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 14.

reactivity. The data presented herein will be discussed in a subsequent, more general article on the effect of structure on reactivity.

Acknowledgments.—The authors would like to express their gratitude to the National Science Foundation for a grant in support of this investigation and to the Dow Chemical Company for samples of methylene bromide and bromochloromethane.

ATLANTA, GEORGIA

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Structural Effects in the Reactivity of Primary Amines with Piperonal[1]

BY RICHARD L. HILL AND THOMAS I. CROWELL

RECEIVED DECEMBER 5, 1955

The rate of the uncatalyzed, second-order reaction of piperonal with a series of primary aliphatic amines, RNH_2, has been measured at 0, 25 and 45°. The values of k do not parallel the basicity of RNH_2. However, a linear relation between log k and the free energies of dissociation of the corresponding addition compounds, $RNH_2 \cdot B(CH_3)_3$, is observed, showing that similar structural effects are present in the two reactions. Several other reactions show this correlation. Heats and entropies of activation have been calculated.

While the reactivity of aldehydes and ketones with semicarbazide has been the subject of several investigations,[2] the effect of the structure of the amine on the rate of carbonyl addition reactions has not been elucidated. The formation of the Schiff base from an aldehyde and a primary amine in alcoholic solution is a suitable example for such a study. In the absence of acid catalysts, it is a rapid, second-order reaction.[3] This paper describes the kinetics of the reaction of piperonal with a series of aliphatic primary amines in methanol, at three different temperatures.

The observed rate constants, k, are given in Table I. The basicity of the amine in water (or in methanol, which would be closely comparable)[4] is not a good index of the rate. Bell[5] has shown that the apparent basicities of amines in aqueous solution are markedly affected by solvation and that the dissociation constant in an aprotic solvent is preferred when the Brønsted catalysis law is to be applied. These solvent effects serve mainly to differentiate the three classes of amines, however, and probably are not the cause of a poor correlation between basicity and rate of reaction of a series of primary amines.

TABLE I

RATE OF SCHIFF BASE FORMATION FROM RNH_2 AND PIPERONAL

R	$10^2\ k$, liters/mole-sec. 0.00°	24.97°	45.00°
Me	1.92	5.55	11.4
Et	0.952	2.88	6.00
n-Pr	1.04	3.15	6.40
i-Pr	0.267	0.895	1.98
n-Bu	1.15	3.37	6.83
i-Bu	1.13	3.16	6.23
s-Bu	0.292	0.940	2.00
t-Bu	0.0267	0.115	0.299

A correlation appears, however, when a different reference acid is used in estimating basicity. A linear relation is found between log k and the standard free energies of dissociation of the corresponding amine–boron trimethyl addition compounds.[6] These quantities (log k_0 and $\Delta F°_{100}$) are plotted in Fig. 1. Similar linear plots are obtained with log k_{25} and log k_{45}. While the existence of such correlations probably is not general and would depend on the choice of substrates and of reference acids, here it indicates that changes in the various structural parameters produce similar effects on the rate of Schiff base formation and the extent of association of $RNH_2 \cdot B(CH_3)_3$. According to Brown and co-workers, many of these effects are steric in nature[6]; they have already shown, moreover, that hindered bases react slowly in displacement reactions.[7]

The same kind of correlation may be found in other cases where the reactivities of amines have been compared. Besides the well known cases where a series of basic catalysts obeys the Brønsted catalysis law, or a series of substituted anilines follows the Hammett equation,[8] there are several comparisons involving the amines of Table I. The data of Brady and Cropper[9] for the reaction of amines with 2,4-dinitrochlorobenzene, and the data of Arnett, Miller and Day[10] for the aminolysis of methyl acetate are shown in Fig. 2. The transannular interaction between a carbonyl group and a nitrogen atom in a nine-membered ring has been measured by the shift in the carbonyl frequency in the infrared.[11] Because of the essential similarity of this interaction to the first step of Schiff base formation and because the effects of methyl, isopropyl and *t*-butyl groups on the nitrogen atom were reported,[11] the shift in carbonyl frequency is

---

[1] Presented at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, April 1, 1955.

[2] J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932); F. H. Westheimer, *ibid.*, **56**, 1964 (1934); F. P. Price and L. P. Hammett, *ibid.*, **63**, 2387 (1941).

[3] (a) T. I. Crowell and D. W. Peck, *ibid.*, **75**, 1075 (1953); (b) G. Kresze and H. Manthey, *Z. Elektrochem.*, **58**, 118 (1954); (c) G. Vavon and P. Montheard, *Bull. soc. chim.*, **7**, 551 (1940).

[4] L. G. Goodhue and R. M. Hixon, THIS JOURNAL, **57**, 1688 (1935).

[5] R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).

[6] H. C. Brown and G. K. Barbaras, THIS JOURNAL, **75**, 6 (1953).

[7] H. C. Brown and N. R. Eldred, *ibid.*, **71**, 445 (1949).

[8] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 189.

[9] C. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

[10] E. McC. Arnett, J. G. Miller and A. R. Day, THIS JOURNAL, **72**, 5635 (1950).

[11] N. J. Leonard and M. Oki, *ibid.*, **76**, 3463 (1954).