BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 1632—1638 (1971)

The Hofmann Rearrangement. I. Kinetic Substituent Effects of *ortho*-, *meta*-, and *para*-Substituted *N*-Bromobenzamides[1]

Tsuneo Imamoto, Yuho Tsuno, and Yasuhide Yukawa

The Institute of Scientific and Industrial Research, Osaka Univervity, Yamadakami, Suita, Osaka

(Received September 25, 1970)

The kinetic substituent effects on the Hofmann rearrangements of *ortho*-, *meta*-, and *para*-substituted *N*-bromobenzamides were studied in an aqueous sodium hydroxide solution. The rate constants of the *meta*- and *para*-derivatives were correlated by means of our equation:

$$\log k/k_0 = -2.39(\sigma^0+0.41\Delta\bar{\sigma}_{\mathrm{R}}^{+}) + 0.002$$

The reaction rates of *ortho*-derivatives were found to be 2—20 times faster than those of the corresponding *para*-derivatives. The reaction mechanism of this rearrangement was discussed in terms of LFER, the *ortho*/*para* rate ratios, and the activation parameters; as a result, the concerted mechanism (the participation of the phenyl group in electron-deficient nitrogen at the transition state) was favored rather than the two-step mechanism. The similarity of the reaction mechanism of the Hofmann to the Lossen rearrangement was also shown on the basis of LFER.

The Hofmann reaction, the conversion of amide into primary amine uncontaminated with secondary amine, is one of the most useful reactions for organic syntheses.[2] The course of this reaction has already been demonstrated, as in the following scheme by isolating reaction intermediates:

$$\mathrm{R\text{-}CONH_2} \xrightarrow{\mathrm{OX^-}} \mathrm{R\text{-}CO\bar{N}^-\text{-}X} \xrightarrow{-\mathrm{X^-}} \mathrm{R\text{-}NCO} \xrightarrow{\mathrm{H_2O}} \mathrm{R\text{-}NH_2}$$

The rearrangement step, where the conjugate base of *N*-haloamide is converted accompanying the release of the halide ion into isocyanate, is the most important stage in the course of the Hofmann reaction. This rearrangement is well-known to be intramolecular from the results of many stereo-chemical and isotopic studies.[2,3] As for further details of the mechanism, however, only a few kinetic studies have been reported. Hauser and his co-worker,[4,5] in their kinetic study of substituted *N*-bromobenzamides, showed that electron-releasing substituents in the phenyl group accelerated the rate of the rearrangement and that electron-attracting substituents retarded it. Joshi *et al.*[6] reported the kinetic results of the rearrangements of three aliphatic *N*-bromoamides. In spite of these insufficient data, it has been formally speculated that the rearrangement proceeds through a two-step mechanism;[7] the release of the halide ion from the conjugate base of *N*-haloamide takes place in the first step, and the unstable univalent nitrogeneous intermediate thus formed rearranges immediately into isocyanate. Wright and Fry[8] recently investigated the isotope effect of this rearrangement using phenyl-1-^{14}C labeled *N*-bromobenzamide and suggested a concerted mechanism; the release of the halide ion and the migration of the phenyl group to nitrogen took place simultaneously. Joshi *et al.* also presented a similar mechanism in their paper. It appears, however, that the amount of data reported hitherto is not sufficient to support strongly the concerted mechanism, and the two-step mechanism has not yet been definitely excluded.

In order to elucidate the reaction mechanism more precisely, we have extensively studied kinetic substituent effects on the Hofmann rearrangement of substituted *N*-bromobenzamides.

Experimental

Materials. Various substituted *N*-bromobenzamides were prepared by a modification of Hauser's method.[4]

Finely-pulverized amide (0.1 mol) was added to an ice-cold hypobromite solution, freshly prepared from 0.2 mol of bromine, 0.5 mol of sodium hydroxide, and 300—800 m*l*

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[1] This paper is dedicated to Emeritus Professor Munio Kotake in commemoration of his 75th birthday.

[2] E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, John Wiley and Sons Inc., New York (1946); M. Matsuno, *J. Soc. Org. Synth. Chem. Japan*, *sp. ed.*, **29**, 563 (1968).

[3] T. J. Prosser and E. L. Eliel, *J. Amer. Chem. Soc.*, **79**, 2544 (1957).

[4] C. R. Hauser and W. B. Renflow, Jr., *ibid.*, **59**, 121 (1937).

[5] C. R. Hauser and S. W. Kantor, *ibid.*, **72**, 4284 (1950).

[6] K. M. Joshi and K. K. Shah, *J. Indian Chem. Soc.*, **43**, 481 (1966).

[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca and London (1969), p. 748; J. D. Roberts and M. C. Caserio, "Basic Principle of Organic Chemistry," Benjamin Inc., New York (1964), p. 655; D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill, New York (1969), p. 459.

[8] A. Fry, private communication; J. C. Wright and A. Fry, *J. Chem. Eng. News*, **1968**, No. 1, p. 28.

TABLE 1. SUBSTITUTED *N*-BROMOBENZAMIDES

Subst.	Mp °C (lit[3]))	Analysis (Calcd)				
		C%	H%	N%	Br%	Active Br%
p-CH_3O						33.09
						(34.73)
p-*t*-C_4H_9	117—118	51.46	5.49	5.61	31.07	31.07
		(51.58)	(5.51)	(5.47)	(31.20)	(31.20)
p-CH_3	136.0—137.5	45.01	3.67	6.60	37.28	36.50
	(131—133)	(44.89)	(3.77)	(6.54)	(37.33)	(37.33)
p-C_2H_5	93—94	46.66	4.25	6.07	34.40	33.87
		(47.39)	(4.42)	(6.14)	(35.02)	(35.02)
p-Ph	159—161	56.30	3.53	4.92	28.99	29.70
		(56.55)	(3.65)	(5.07)	(28.94)	(28.94)
Unsubst.	132.5—134.5	42.24	2.73	6.96	39.80	39.48
	(129—131)	(42.03)	(3.02)	(7.00)	(39.95)	(39.95)
p-F	168—170	38.60	2.39			36.95
		(38.56)	(2.31)			(36.65)
p-Cl	181—184	36.00	2.17	6.10		33.52
	(170—174)	(35.86)	(2.15)	(5.97)		(34.08)
p-Br	184—185	30.41	1.71	5.08	57.21	27.86
		(30.14)	(1.81)	(5.02)	(57.29)	(28.65)
p-NO_2	223—226	34.61	1.91	11.77		31.58
	(198—202)	(34.31)	(2.06)	(11.43)		(32.61)
m-CH_3	60—62	45.33	3.77	6.55	37.60	34.36
		(44.89)	(3.77)	(6.54)	(37.33)	(37.33)
m-Cl	111—113	36.02	2.03	6.03		33.82
	(102—105)	(35.86)	(2.15)	(5.97)		(34.08)
m-Br	126.5—127.5	30.44	1.70	5.11		28.11
	(122—126)	(30.14)	(1.81)	(5.02)		(28.65)
m-CF_3	120—121	35.64	1.90			29.34
		(35.83)	(1.88)			(29.82)
m-NO_2	183.0—186.5	34.03	2.24	11.62	32.72	31.96
	(173—176)	(34.31)	(2.06)	(11.43)	(32.61)	(32.61)
o-CH_3	101—102	45.39	3.76	6.75	37.08	36.44
		(44.89)	(3.77)	(6.54)	(37.33)	(37.33)
o-Cl	105.5—107.0	36.09	1.99	6.07		33.24
	(104—105)	(35.86)	(2.15)	(5.97)		(34.08)
o-Br	130—133	30.29	1.60	5.13	57.02	27.98
		(30.14)	(1.81)	(5.02)	(57.29)	(28.65)
o-NO_2	176—178	34.61	1.86	11.77	32.50	31.55
	(170—176)	(34.31)	(2.06)	(11.43)	(32.61)	(32.61)

of water. After vigorous stirring for 2—15 min, the reaction mixture was filtered rapidly with a suction into a solution of 30 m*l* of acetic acid in 70 m*l* of ice water. The *N*-bromoamide thus precipitated was collected, washed successively with 5% aqueous acetic acid and water, and dried at room temperature. The yields of the crude products were generally 80—90%. Unsubstituted, *p*-methyl, *p*-fluoro, *p*-phenyl, and *m*-chloro derivatives were recrystallized from dichloroethane; *m*-nitro and *p*-nitro derivatives, from acetic acid; *p*-chloro and *p*-bromo derivatives, from methanol; the *o*-nitro derivative, from dichloroethane-DMF (4 : 1), and the *m*-trifluoromethyl derivative, from dichloroethane-*n*-hexane (5 : 1). Better results were obtained in every case by recrystallization at a temperature lower than 60°C.

However, the acidification of the reaction mixture in the cases of *m*-methyl, *o*-methyl, *p*-methoxy, *p*-ethyl, and *p*-*t*-butyl derivatives did not give the precipitates, but a pasty mass. This was redissolved in a 3% sodium hydroxide solution at −5—0°C and filtered into cold aqueous acetic acid containing ice to give almost colorless precipitates of the corresponding *N*-bromoamide. This solid material was collected, washed with water, pressed to dry, and dissolved in chloroform or dichloroethane. Into this saturated solution, *n*-hexane was added until turbidity just appeared, and then the solution was cooled. *N*-Bromoamides containing more than 96% of the theoretical amount of active bromine could be obtained by this method.

These *N*-bromoamides were kept cold, away from the light.

The analytical data and melting points for *N*-bromoamides are listed in Table 1.

The *o*-methoxy- and *m*-methoxy-*N*-bromobenzamides were very unstable compounds, and the corresponding pure materials could not be obtained. In the cases of *p*-ethoxy- and *p*-phenoxybenzamides, because of accompanying bromination on the benzene ring, the compounds isolated were not the expected ones, but *m*-bromo-*p*-ethoxy- and *p*-(*p'*-bromophenoxy)-*N*-bromobenzamides.

Kinetic Measurements. The reaction rates were measured by titrating the residual amount of unrearranged *N*-bromoamide with a standardized sodium thiosulfate solution.[9]) In a measuring flask we placed 200 m*l* of a standardized aqueous sodium hydroxide solution and immersed in a constant-temperature water bath (accuracy ±0.01°). A

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[9]) Van Dam, *Rec. Trav. Chim. Pays-Bas*, **18**, 408 (1899); Van Dam and J. H. Aberson, *ibid.*, **19**, 318 (1900).

certain amount of *N*-bromoamide was weighed accurately into a 300-m*l* Erlenmeyer flask and immersed in the bath. After standing for one hour, the sodium hydroxide solution was transferred into the Erlenmeyer flask, and shaken vigorously until all of the *N*-bromobenzamide had been dissolved. The course of the reaction was followed by titrating a residual amount of active bromine with a sodium thiosulfate solution at moderate intervals; a 10-m*l* portion of the solution was pipetted out and transferred into 100 m*l* of an ice-cold 0.5 N HCl solution to which 2 m*l* of 20% aqueous solution of potassium iodide had been added just before; the iodine thus liberated was titrated with a 0.025 N $Na_2S_2O_3$ solution to the starch-iodide end-point.

In the cases of *m*-methoxy- and *o*-methoxy-benzamides, from which corresponding *N*-bromoamides could not be isolated, the kinetic measurements were carried out as follows. A hypobromite solution (0.025 mol/*l*, f=0.996) was prepared by the drop-by-drop addition of bromine to an ice-cold 0.5 N NaOH solution (f=1.000). Finely-pulverized pure amide (0.0055 mol) was added to 200 m*l* of this hypobromite solution at the reaction temperature, the mixture was shaken vigorously for a few minutes, and then the reaction was followed by the above procedure.

Results and Discussion

Effect of the Concentration. In order to examine the effects of the concentrations of *N*-bromoamide and sodium hydroxide on the reactivity, kinetic measurements of unsubstituted- and *m*-chloro-*N*-bromobenzamides were made in respect to:

A. Changing the concentration of *N*-bromoamide in a 1 N NaOH solution;

B. Changing the concentration of sodium hydroxide, but keeping that of *N*-bromoamide constant (0.05 mol/); and

C. Changing the overall concentration, with the concentration ratio of *N*-bromoamide to sodium hydroxide kept at 1 : 20.

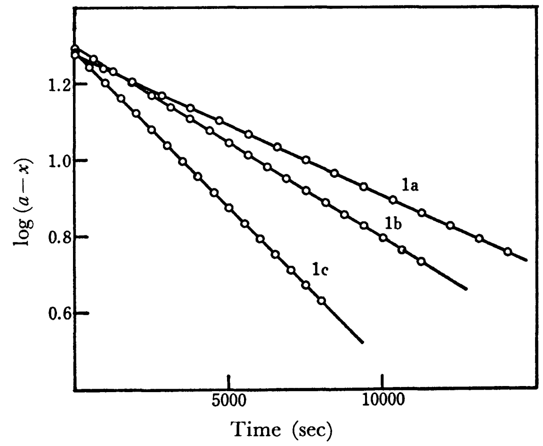

Fig. 1. Typical first-order plots.
1a: *m*-Cl; 0.05 mol/*l*, NaOH; 2 N, at 30.00°C.
1b: H; 0.025 mol/*l*, NaOH; 0.5 N, at 20.00°C.
1c: H; 0.1 mol/*l*, NaOH; 2 N, at 20.00°C.

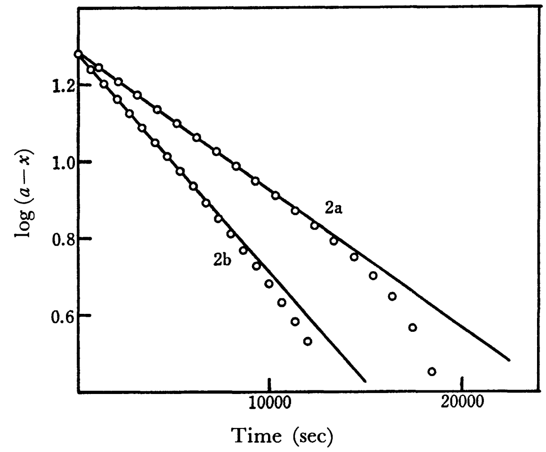

Fig. 1. First-order plots.
2a: *m*-Cl; 0.05 mol/*l*, NaOH; 0.1 N, at 30.00°C.
2b: H; 0.05 mol/*l*, NaOH; 0.1 N, at 20.00°C.

Table 2. Effect of the concentrations of *N*-bromoamide and NaOH

	Conc. of amide (mol/*l*)	Conc. of NaOH (N)	H ($k_1 \times 10^4$ sec^{-1}) 20.00°C	*m*-Cl $k_1 \times 10^4$ (sec^{-1}) 30.00°C	$\frac{k_1(\text{H, 20°C})}{k_1(m\text{-Cl, 30°C})}$
Case A	0.100	1.000	1.582±0.003	9.76±0.09	1.62
	0.0500	1.000	1.579±0.003	9.56±0.02	1.65
	0.0250	1.000	1.548±0.002	9.52±0.01	1.63
	0.0125	1.000	1.540±0.002	9.44±0.01	1.63
	0.00625	1.000	1.534±0.003	9.34±0.03	1.64
Case B	0.0500	2.000	1.932±0.002	11.63±0.01	1.66
	0.0500	1.000	1.579±0.002	9.56±0.02	1.65
	0.0250	1.000	1.548±0.002	9.52±0.01	1.63
	0.0500	0.500	1.409±0.001	8.81±0.01	1.60
	0.0250	0.500	1.401±0.002	8.52±0.02	1.64
	0.0500	0.250	1.361±0.001	8.39±0.008	1.62
	0.0500	0.100	1.33 ±0.006	8.3 ±0.02	1.60
Case C	0.100	2.000	1.958±0.004	11.81±0.01	1.66
	0.0500	1.000	1.579±0.002	9.56±0.02	1.65
	0.0250	0.500	1.401±0.002	8.52±0.02	1.64
	0.0125	0.250	1.319±0.002	8.20±0.02	1.61
	0.00500	0.100	1.301±0.002	7.96±0.03	1.63
	0.	0.	1.29[a]	7.85[a]	1.64

[a] Extrapolated value.

The concentration factor for *N*-bromoamide and sodium hydroxide was 1.000±0.003 in every case. The reaction temperatures were 20.00±0.01°C for unsubstituted amide and 30.00±0.01°C for *m*-chloro amide. The first-order rate constants were calculated by the least-squares method according to Eq. (1):

$$k \times t = 2.303 \times \log (a/a-x) \qquad (1)$$

where t is the reaction time and where $a-x$ is the concentration of *N*-bromoamide at time t. Almost all the cases obeyed first-order kinetics, at least to 80% completion of the reaction (see Fig. 1). The observed rate constants are listed in Table 2.

In the case A, a very small rate enhancement was observed despite the increase in the concentration of *N*-bromoamide from 0.00625 to 0.1 mol/*l*. On the other hand, in the case B, the rate constant considerably depended on the concentration of sodium hydroxide, but tended to converge to a constant value as it approached an infinite dilution. The extremely small concentration of sodium hydroxide, however, gave an anomaly. In the case B with 0.1 N NaOH, the solution was gradually darkened as the reaction proceeded, and the dark brown precipitates appeared after the reaction was about half completed. The reaction rate increased with the progress of reaction (see Fig. 2).[10] The reaction involves a preequilibrium between *N*-bromoamide and its conjugate base, as is indicated by the following scheme. The relatively low concentration

$$\text{X-C}_6\text{H}_4\text{-CONHBr} + \text{OH}^- \rightleftharpoons \text{X-C}_6\text{H}_4\text{-CON}^-\text{-Br} + \text{H}_2\text{O}$$

ratio of sodium hydroxide to *N*-bromoamide releases a small amount of the *N*-bromoamide reactant, which then reacts rapidly with the rearranged products to lose its active bromine. The dark brown precipitates are considered to be the reaction products of *N*-bromoamide with amine or isocyanate.

From the above observations, it appears necessary to keep the initial concentration ratio [NaOH]/[Amide] at least *ca.* 10 to obtain a good kinetic result. The case C indicates the rates measured under reaction conditions in which the concentration ratio of *N*-bromo-

TABLE 3. RATE CONSTANTS OF THE HOFMANN REARRANGEMENT OF SUBSTITUTED *N*-BROMOBENZAMIDES

Subst.	Temp. °C	$k_1 \times 10^4$ (sec^{-1})
p-CH_3O	13.00	4.81 ±0.02
	10.00	2.92 ±0.01
	5.00	1.275 ±0.001
		1.251 ±0.003[a]
	2.00	0.771 ±0.001
p-*t*-C_4H_9	20.00	3.63 ±0.01
	13.00	1.121 ±0.003
	5.00	0.274 ±0.001
p-CH_3	18.00	3.148 ±0.004
	14.00	1.626 ±0.002
	10.00	0.819 ±0.001
	3.71	0.2682 ±0.0008
p-C_2H_5	20.00	4.05 ±0.02
	13.00	1.263 ±0.002
	5.00	0.308 ±0.001
p-Ph	25.00	4.28 ±0.01
	18.00	1.40 ±0.004
	10.00	0.366 ±0.002
Unsubst.	25.00	3.13 ±0.005
	20.00	1.401 ±0.002
		1.370 ±0.001[a]
	10.00	0.250 ±0.0004
	0.00	0.0391 ±0.0001
p-F	30.00	3.51 ±0.004
	23.00	1.15 ±0.01
	15.00	0.300 ±0.002
p-Cl	35.00	4.346 ±0.002
	30.00	2.029 ±0.004
	20.00	0.4053 ±0.0007
p-Br	35.00	3.97 ±0.007
	30.00	1.834 ±0.003
	25.00	0.830 ±0.001
	20.00	0.365 ±0.0004
p-NO_2	55.00	4.85 ±0.02
	50.00	2.49 ±0.01
	45.00	1.18 ±0.01
m-CH_3	23.00	4.120 ±0.006
	15.00	1.064 ±0.002
	8.00	0.3147 ±0.0009
m-CH_3O	30.00	4.09 ±0.004[a]
	20.00	0.847 ±0.001[a]
	15.00	0.361 ±0.001[a]
	10.00	0.1503 ±0.0002[a]
	0.00	0.02447±0.00010[a]
m-Cl	38.00	3.06 ±0.004
	30.00	0.852 ±0.002
	23.00	0.2789 ±0.0005
m-Br	38.00	3.318 ±0.006
	30.00	0.929 ±0.002
	23.00	0.2997 ±0.0005
m-CF_3	45.00	4.278 ±0.009
	35.00	0.946 ±0.0006
	30.00	0.4266 ±0.0005
	23.00	0.1341 ±0.0002
	15.00	0.03214±0.00004
m-NO_2	55.19	4.79 ±0.02
	50.00	2.30 ±0.009
	45.00	1.13 ±0.003
o-CH_3O	5.00	7.37 ±0.02[a]
	0.00	3.04 ±0.01[a]
o-CH_3	5.00	7.36 ±0.02
	3.00	5.19 ±0.01
	2.00	4.30 ±0.005
	0.00	2.976 ±0.011
o-Cl	25.00	3.78 ±0.003
	18.00	1.144 ±0.002
	10.00	0.273 ±0.0004
o-Br	25.00	4.444 ±0.005
	18.00	1.368 ±0.001
	10.00	0.3268 ±0.0007
o-NO_2	50.00	3.74 ±0.10
	45.00	1.83 ±0.02
	40.00	0.871 ±0.001

a) Measured by using sodium hypobromite solution.

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[10] The rate constant under this reaction conditions was calculated from the first-order plots of the initial stage of the reaction.

amide to sodium hydroxide kept at 1:20. The observed rate constants appeared to be given by the combined results of the concentration effects of *N*-bromoamide (case A) and sodium hydroxide (case B).

The rate constants independent of the initial concentration can be obtained by the extrapolation of the observed rate constants to an infinite dilution. However, they are only approximate and are not as precise as those measured directly. It is very noticeable that the rate ratios of the unsubstituted derivative to the *m*-chloro derivative are almost the same under these conditions. This indicates that any reaction conditions within the limits examined may be employed to ascertain the relative change in the rates of various substituted *N*-bromobenzamides. Practically, fixed conditions with the respective concentrations of *N*-bromoamide and sodium hydroxide being 0.025 mol/*l* and 0.5 N were employed throughout the series of runs as the most suitable standard from the experimental point of view.

Substituent Effects. The rates of the release of the bromide ion from the conjugate bases of various substituted *N*-bromobenzamides were determined at various temperatures. The initial concentrations of *N*-bromoamides and sodium hydroxide were maintained at 0.025 mol/*l* and 0.5 N ($f=1.000\pm0.003$) respectively throughout the series. Plots of the $\log(a-x)$ against time t gave an excellent straight line, covering over 75% of the reaction, for almost all derivatives. In the cases of *p*-phenyl, *p*-fluoro, *p*-*t*-butyl, and *o*-nitro derivatives, the reaction rates were gradually increased as the reaction proceeded; thus, the rate constants were calculated from the plots of the initial state of the reaction. The *m*-nitro and *p*-nitro derivatives behaved peculiarly; the first-order plots provided a good straight line at temperatures over 45°C, but not at 30°C. Rate measurements of unsubstituted and *p*-methoxy derivatives were made not only by the general method but also by the conventional modification used for *o*-methoxy and *m*-methoxy derivatives (see the Experimental section). The disagreement between the two methods did not exceed *ca.* 2% of the rate constant. The obtained rate constants are listed in Table 3. The rate constants at 30.00°C and the activation parameters derived are also shown in Table 4.

Table 4. Kinetic results of the Hofmann rearrangement of substituted *N*-bromobenzamides

Subst.	$k_1\times10^4$ (sec^{-1}) 30.00°C	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e.u.)
p-CH_3O	62.8[a)]	25.48±0.09	15.4 ±0.3
p-*t*-C_4H_9	17.6[a)]	27.34±0.06	19.0 ±0.2
p-CH_3	20.9[a)]	27.03±0·03	18.36±0.11
p-C_2H_5	19.6[a)]	27.25±0.11	18.9 ±0.4
p-Ph	9.22[a)]	26.93±0.08	16.4 ±0.3
Unsubst.	6.96[a)]	27.83±0.04	18.77±0.14
p-F	3.51	27.90±0.11	17.7 ±0.4
p-Cl	2.029	27.79±0.03	16.23±0.10
p-Br	1.834	27.95±0.04	16.57±0.13
p-NO_2	0.121[a)]	28.6 ±0.39	13.4 ±1.3
m-CH_3	12.5[a)]	27.78±0.09	19.8 ±0.3
m-CH_3O	4.09	27.52±0.05	17.7 ±0.2
m-Cl	0.852	28.6 ±0.2	17.1 ±0.7
m-Br	0.929	27.95±0.04	16.57±0.13
m-CF_3	0.4266	29.03±0.09	17.2 ±0.3
m-NO_2	0.113[a)]	28.8 ±0.29	13.7 ±0.9
o-CH_3O	397[a)]	26.2 ±0.45	21.3 ±1.5
o-CH_3	439[a)]	26.8 ±0.16	23.6 ±0.5
o-Cl	8.56[a)]	28.8 ±0.15	22.4 ±0.5
o-Br	10.0[a)]	28.60±0.04	22.10±0.14
o-NO_2	0.185[a)]	28.6 ±0.36	14.2 ±1.2

a) Extrapolated from data at other temperatures.

The present authors[11)] have previously pointed out that the Linear Aromatic Substituent-Reactivity relationship (LArSR relationship, Eq. (21)) is one of the most useful tools for speculating on the reaction mechanism:

$$\log k/k_0 = \rho(\sigma^0 + r\Delta\bar{\sigma}_R^+) \qquad (2)$$

where σ^0 is the normal substituent constant, where r is a constant depending on the resonance requirement in the reaction, and where $\Delta\bar{\sigma}_R^+$ measures the capacities of the substituents to supply electrons by resonance. It is of interest to discuss the reaction mechamism of the Hofmann rearrangement in terms of the above equation. First, the logarithms of the rate constants have been plotted against Hammett's σ constants in order to examine the applicability of the original Hammett equation, $\log k/k_0=\rho\sigma$ to our data. A good overall linear relation with a ρ-value of -2.52 is observed with the correlation coefficient of 0.994, while *p*-methoxy and *p*-*t*-butyl derivatives deviate a little. There is no reason to consider that the deviation of the *p*-methoxy group

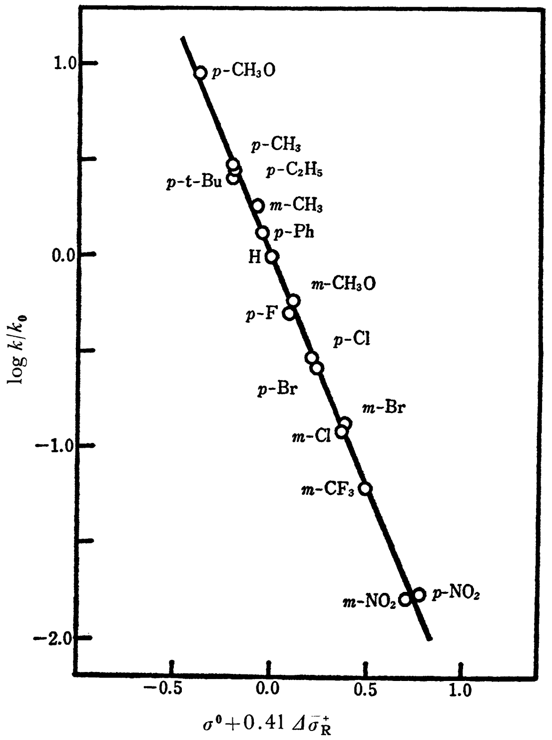

Fig. 3. Application of the LArSR relationship.

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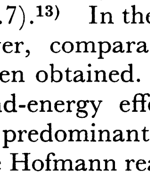
11) Y. Yukawa, Y. Tsuno, and M. Sawada, This Bulletin, **39**, 2274 (1966); Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965).

is attributable to the experimental error. It would be more reasonable to refer the deviation to the strongly electron-releasing conjugative ability of the methoxy group. That is, the Hofmann rearrangement may be considered to be a slightly more σ^+-characteristic reaction than the dissociation of benzoic acids, from which the Hammett's σ constants are derived. The use of Eq. (2) gives a better linearity, including the *p*-methoxy group, with a correlation coefficient of 0.997, as is shown in Fig. 3.

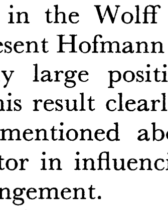
$$\log k/k_0 = -2.39(\sigma^0 + 0.41\,\Delta\bar{\sigma}_R^+) + 0.002 \qquad (3)$$

For the interpretation of the above derived parameters, especially of the resonance parameter, *r*, it will be very useful to consider the effect of the conjugation in the initial and the transition states.

In the conjugations applicable for the initial state, the *dπ–pπ* conjugation on the N–Br bond (I) may be considered to be important as the factor influencing the reactivity; the contribution of this conjugation leads to an increase in the bond-order of the N–Br bond and makes it more difficult to release the bromide ion from the reactant molecule (the Bond-energy Effect). The degree of this conjugation can be affected by the substituent on the migrating phenyl group, especially by electron-releasing conjugative groups at the *para*-position, For instance, the *p*-methoxy group, a typical electron-releasing conjugative group, will produce a considerable increase in the above conjugation effect through the cross conjugation of the carbonyl group. As is indicated by Formula (II), the methoxy group particularly strengthens the conjugation of the carbonyl group with the phenyl group, while it weakens the conjugation of the carbonyl group with the nitrogen orbital, resulting in a relative increase in the *dπ–pπ* conjugation on the N–Br bond. Therefore, if the present reaction is controlled solely by the *dπ–pπ* conjugation effect at the initial state, the resonance parameter, *r*, in the LArSR relationship Eq. (2) may be expected to be negative, as has been observed in the Curtius rearrangement in toluene ($r = -1.04$)[12] and in the Wolff rearrangement ($r = -1.7$).[13] In the present Hofmann rearrangement, however, comparatively large positive *r*-value (0.41) has been obtained. This result clearly indicates that the bond-energy effect mentioned above is not necessarily a predominant factor in influencing the reactivity of the Hofmann rearrangement.

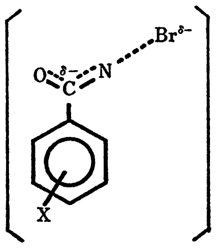


(I)

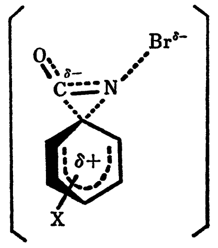


(II)

On the other hand, the following two models may be assumed as probable structures of the transition state. The (III) model corresponds to the two-step mechanism,



(III)



(IV)

where the release of the bromide ion takes place at the first step and the univalent nitrogeneous intermediate formed rearranges immediately into isocyanate. The other model (IV) corresponds to the concerted mechanism (or the one-step mechanism), where the release of the bromide ion and the migration of the phenyl group to the nitrogen are simultaneous processes. In the former model, the substituent effect on the stabilization of this state is expected to afford a small positive *r*-value (a value of the same order as for σ, $r=0.27$), since its electronic nature resembles closely that of the benzoate anion. On the other hand, in the latter model, a strongly electron-releasing conjugation is required for the partial bond formation between the phenyl group and nitrogen, and thus a large positive *r*-value should be observed, as in the Beckmann rearrangement of acetophenone oximes ($r=0.60$—0.65). The observed *r*-value (0.41), however, appears too large for the (III) model and, on the contrary, too small for the (IV) model. Its *r*-value does not entirely support either of the above two models without considering the effect of the conjugation at the initial state. It is a rather plausible explanation for the present data that the large positive *r*-value due to the electrophilic conjugative effect at the transition state (IV) may be somewhat compensated for by the negative *r*-value resulting from the *dπ–pπ* conjugation on the N–Br bond at the initial state.

It is also of interest to discuss the effect of *ortho*-substituents with regard to the reaction mechanism. The polar effect of the *ortho*-substituent is generally recognized to be nearly equal to that of *para*-substituent;[14] thus, the rate ratio and the relative value of the activation parameters of *ortho*- to *para*-substituent can be taken as

TABLE 5. EFFECTS OF *ortho*-SUBSTITUENTS

Subst.	Rel. rate[a]	k^o/k^p[b]	$\Delta\Delta H^{\ddagger}$ (kcal/mol)	$\Delta\Delta S^{\ddagger}$ (e.u.)
H	1.	1.	0.	0.
o-CH_3O	57.0	6.3	$+0.7\pm0.5$	$+5.9\pm1.8$
o-CH_3	63.1	21.0	-0.2 ± 0.2	$+5.2\pm0.6$
o-Cl	1.23	4.2	$+1.0\pm0.2$	$+6.2\pm0.6$
o-Br	1.44	5.5	$+0.7\pm0.1$	$+5.5\pm0.3$
o-NO_2	0.027	1.5	0.0 ± 0.8	$+0.8\pm2.5$

a) Relative rate at 30.00°C to the unsubstituted *N*-bromoamide.
b) The *ortho*/*para* rate ratio at 30.00°C.

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[12] Y. Yukawa and Y. Tsuno, *J. Amer. Chem. Soc.*, **79**, 5530 (1957); Y. Yukawa and Y. Tsuno, *ibid.*, **80**, 6346 (1958).

[13] Y. Yukawa, Y. Tsuno, and T. Ibata, This Bulletin, **40**, 2613 (1967).

[14] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," John Wiley and Sons Inc., New York (1956), p. 556.

measures of *ortho* effects reflecting the reaction mechanism. The *ortho/para* rate ratios and relative value of activation parameters are summarized in Table 5. It may be noted that comparatively large *ortho/para* rate ratios are observed, and that these values depend mainly on the difference in the entropy of activation, except for the case of the nitro group. The introduction of an *ortho*-substituent restricts the rotation of the phenyl ring and lessens the entropy in the initial state more than dose that of the corresponding *para*-substituent. If the reaction proceeds by the two-step mechanism, the difference in the entropy of the *ortho*- and *para*-derivatives in the initial state will not have any effect on the relative value of the entropy of activation. However, in the case of the concerted mechanism, the entropy of activation of the *para*-derivative is lowered below that of corresponding *ortho*-derivative by the restriction of the motion of the phenyl ring on proceeding from the reactant to the transition state; therefore, it can be expected that the relative value of the entropy of activation, $\Delta\Delta S^{\ddagger}$, depends considerably on the difference in entropy in the initial state. The observed value of $\Delta\Delta S^{\ddagger}$ can be qualitatively interpreted by the above considerations. On the other hand, the following explanation of the *ortho* rate effects is also probable. The through-conjugation between carbonyl and phenyl groups is weakened by reduced co-planarity due to the introduction of the *ortho* group. This effect increases the conjugation of the carbonyl group with the nitrogen orbital, but decreases the $d\pi$–$p\pi$ conjugation on the N–Br bond. The smaller $d\pi$–$p\pi$ conjugation may play a role in bringing about the rate acceleration.

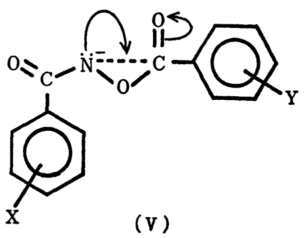
Hauser and Renflow had measured the rates of eight *meta*-, *para*-, and two *ortho*-substituted *N*-bromobenzamides in a 1N aqueous sodium hydroxide solution at 30°C. Logarithms of our rate constants have been plotted against theirs. An excellent correlation results, with a correlation coefficient of 0.9999 and a slope of 1.000 except for nitro and *p*-methoxy derivatives, which are attended with large experimental uncertainty in Hauser's data. This fact indicates that the mechanism of this reaction is little affected by a minor change in the reaction conditions.

The Lossen rearrangement, of which the leaving group is carboxylates as a substitute for halide, is expected to be analogous to the Hofmann rearrangement with respect to the reaction mechanism. Hauser and his co-worker[15] had reported the kinetic results of the decomposition of potassium dihydroxamates (R–CON–OCOR$'$)$^-$K$^+$, where R and R$'$ were various substituted phenyl groups. As is shown in Table 6, the LFER between the Lossen rearrangement and the Hofmann rearrangement is excellent regardless of the different leaving groups. These satisfactory linear relationships suggest that the mechanisms of the two reactions are almost the same. It is conceivable that the contribution of the homo-conjugation (Formula V), which may be compared with the $d\pi$–$p\pi$ conjugation in the Hofmann rearrangement, on the depression of the reactivity should not be neglected.

TABLE 6. COMPARISON WITH THE LOSSEN REARRANGEMENT X-C_6H_4-CON$^-$-OCO-C_6H_4-Y

Sutst. (Y)	Slope	Corr. coeff.	n[a]
o-NO_2	0.98	1.000	3
m-NO_2	1.15	1.000	3
m-F	1.25	1.000	2
o-Cl	1.06	0.999	5
H	1.15	0.999	5

a) The number of the species of substituent X.



(V)

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[15] W. B. Renflow and C. R. Hauser, *J. Amer. Chem. Soc.*, **59**, 2308 (1937); R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).