

Title	ホフマン転位の研究
Author(s)	今本,恒雄
Citation	大阪大学, 1972, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/30685
rights	© The Chemical Society of Japan.
Note	

The University of Osaka Institutional Knowledge Archive : OUKA

https://ir.library.osaka-u.ac.jp/

The University of Osaka

THE HOFMANN REARRANGEMENT

TSUNEO IMAMOTO

The Institute of Scientific and Industrial Reseach Osaka University

CONTENTS

Chapter	1	Introduction and the Outline of the Investigation
		1
Chapter	2	Kinetic Substituent Effects of <u>ortho</u> -, <u>meta</u> -,
		and <u>para</u> -Substituted <u>N</u> -Bromobenzamides 16
Chapter	3	Kinetic Substituent Effects of <u>ortho</u> -, <u>meta</u> -,
		and <u>para</u> -Substituted <u>N</u> -Chlorobenzamides 32
Chapter	4	Kinetic Substituent Effects of 4- and 5-Substituted
		2-Chloro- <u>N</u> -chlorobenzamides
Chapter	5	Kinetic Isotope Effect of <u>N</u> -Chlorobenzamide 55
Chapter	6	The Formation of Benzoyl Chlorides from 1,2-Diben-
		zoylhydrazines or Dibenzoyldiimides
		(Supplementary Treatise)
		Acknowledgements 70

CHAPTER 1

INTRODUCTION AND THE OUTLINE OF THE INVESTIGATION

Among many organic reactions there are numerous cases in which an atom or a substituent is subjected to migrate to a new position in the same molecule. These kinds of reactions, rearrangements, have long been recognized to belong to a rather different category from other organic reactions, because of their abnormal characters of reaction. Much interest arising from such a recognition has been attracted to the reaction mechanisms of rearrangements, especially to those of 1,2-rearrangements. As the results, a large amount of the knowledge on the scope of 1,2-rearrangements has been brought about, with the general development of theories and experimental techniques in organic chemistry. The detailed structure of the transition state, however, has not yet been clarified in most rearrangements, for the lack of the effective methods to elucidate it.

While, V1958, Yukawa and Tsuno proposed the extended Hammett in equation (1), applicable to a large number of the electrophilic reactions of the benzene derivatives.¹⁾ After subsequent exami-

$$\log \underline{k}/\underline{k}_{0} = \varrho \left(\underline{\sigma} + \underline{r} \Delta \underline{\sigma}_{R}^{+} \right)$$
(1)

nation from the theoretical point of view, this equation was reformed to Eq. (2), which was termed the Linear Aromatic Substituent-Reactivity relationship (LArSR relationship).^{2,3)}

$$\log \underline{k}/\underline{k}_{o} = \underline{o} \left(\underline{o}^{\circ} + \underline{r} \Delta \underline{o}_{R}^{+} \right)$$
 (2)

One of the most important characters of this relationship consists in the resonance parameter, \underline{r} . That is, the \underline{r} -value has been proved, from empirical facts, to indicate the degree of the additional conjugation effect on the reactivity. This characteristic leads to the possibility that the transition state can be elucidated by means of the application of the LArSR relationship.

On the other hand, Bigeleisen et al. derived theoretical ^{equations} on isotope effects, and suggested that the determination

of kinetic isotope effect afforded valuable mechanistic informations.^{4,5)} Since then, isotope effects have been studied in wide variety of reactions. However, these studies are mostly concerned with hydrogen, and isotope effects of carbon have not yet been studied so much. This is mainly due to quite laborious works in the accurate measurements of isotopic ratios. Despite such difficult experiments, the determination of reliable values of carbon isotope effect is expected to play a decisive role, also in the investigation of the transition state of 1,2-rearrangement.

From these points of view, the present research has been directed to clarifying the precise mechanism of the Hofmann rearrangement, mainly by means of above two methods, the application of the LArSR relationship and the determination of carbon isotope effect.

The Hofmann reaction, the conversion of amide into primary amine by treatment with a hypohalite solution, is one of the most useful reactions for organic syntheses.⁶⁾ The course of this reaction has already been clarified, as in the following scheme:

 $R-CONH_2 \xrightarrow{OX} R-CON - X \xrightarrow{-X} R-N=C=0 \xrightarrow{H_2O} R-NH_2$

The most important stage in the course of this reaction is the rearrangement step in which the conjugate base of <u>N</u>-haloamide is converted into isocyanate. A large number of works have been devoted to the elucidation of the reaction mechanism of this step.

In 1932, Whitmore⁷⁾ suggested, on the basis of the electronic theory in organic chemistry, that the electron-deficiency of the nitrogen atom was the driving force of this rearrangement. Several stereo-chemical studies using optically active amides showed that the reaction proceeded with the complete retention of configuration.⁸⁻¹²) Prosser and Eliel¹³) observed no inter-crossing product,

<u>m</u>-deuteroaniline- 15 N, when the mixture of <u>m</u>-deuterobenzamide and benzamide- 15 N was treated with a hypobromite solution, and they strongly suggested an intramolecular character of the rearrangement.

As for the further details of the mechanism, however, a few kinetic studies have been reported. Hauser and his co-worker 14,15) measured the rates of the rearrangements of eight <u>meta</u>- and <u>para</u>-substituted <u>N</u>-bromobenzamides in an aqueous sodium hydroxide solution, and showed that the rearrangement was accelerated by an electron-releasing substituent. Joshi et al.¹⁶) reported the kinetic results of aliphatic <u>N</u>-bromoamides, and indicated the bulky group promoted the reaction rate.

In spite of these insufficient data, it has been formally inferred that the rearrangement proceeds through a two-step mechanism; 17 the release of the halide ion from the conjugate base of <u>N</u>-haloamide takes place in the rate-determining step, and then the unstable univalent nitrogenious intermediate formed rearranges immediately into isocyanate.

On the other hand, Wright and Fry^{18} recently investigated the isotope effect of this rearrangement using phenyl-l-¹⁴C labeled <u>N</u>-bromobenzamide, and suggested an alternative concerted mechanism; the release of the halide ion and the migration of the phenyl group to nitrogen atom took place simultaneously. However, their results have not yet been published in paper.

Two mechanisms mentioned above seem to be plausible. But no definite evidence has been found for respective ones, and the mechanism has not yet been established.

In order to find a clue to the elucidation of the mechanism, we began with the studies of the kinetic substituent effects of this rearrangement.

- 4 -

At first, the rates of the rearrangements of <u>meta</u>- and <u>para</u>substituted <u>N</u>-bromobenzamides were measured in an 0.5 <u>N</u> sodium hydroxide solution at various temperatures. Almost all the substi-

	EN	T OF	SUB	STITUTEI	$\sim N$	-BRO	MOBENZAMI	DES
Table	1,	KINE?	TIC	RESULTS	OF	THE	Hofmann	REARRANGE-

Subst.	$k_1 \times 10^4 (\text{sec}^{-1})$ 30.00°C	ΔH^{\pm} (kcal/mol)	ΔS^{\pm} (e.u.)
p-CH ₃ O	62.8 ⁿ)	25.48 ± 0.09	15.4 ± 0.3
p-t-C4H9	17.6 ^{a)}	27.34 ± 0.06	19.0 ± 0.2
p -CH $_3$	20.9ª)	27.03 ± 0.03	18.36 ± 0.11
p-C ₂ H ₅	19.6 ^{a)}	27.25 ± 0.11	18.9 ± 0.4
p-Ph	9.22ª)	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 <u>+</u> 0.13
p-NO ₂	0.121 ^{a)}	28.6 ± 0.39	13.4 ±1.3
m-CH ₃	12.5ª)	27.78 ± 0.09	19.8 ±0.3
m-CH ₃ O	4.09	27.52 ± 0.05	17.7 ±0.2
m-Cl	0.852	28.6 ± 0.2	17.1 ±0.7
<i>m</i> -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 $_{3}$ O	397ª)	26.2 ± 0.45	21.3 ± 1.5
$o\text{-}\mathrm{CH}_3$	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 ⁿ)	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.

tuents strictly obeyed firstorder kinetics, at least to 80% completion of the reaction. The rate constants at 30°C and the activation parameters obtained are summarized in Table 1.

The application of the LArSR relationship, Eq. (2) to the present data gave Eq. (3) with an excellent linear correlation. The comparatively large negative Q-value (-2.39) means that this rearrangement is a typical electrophilic

reaction.

 $\log \underline{k}/\underline{k}_{0} = -2.39 \ (\underline{\sigma}^{\circ} + 0.41 \ \underline{\Delta}\overline{\sigma}_{R}^{+} \) \tag{3}$

The other parameter, \underline{r} , was calculated to be 0.41. This value was first compared with those of other 1,2-rearrangements structurally analogous to the Hofmann rearrangement.

The <u>r</u>-value of the Beckmann rearrangement of acetophenoneoximes is found to be <u>ca</u>. 0,65.²⁾ The mechanism of this rearrangement has already been demonstrated to be a concerted one; the migratory group participates with the electron-deficient nitrogen in the transition state. The <u>r</u>-value of the Hofmann, which is smaller than that of the Beckmann rearrangement, might not necessarily support the concerted mechanism.

In contrast with the Beckmann rearrangement, the Curtius rearrangement in toluene has a large negative <u>r</u>-value (-1.04).^{3,19}

- 5 -

This value is exclusively attributable to the resonance stabilization effect in the initial state (Bond-energy effect). The large difference in the r-values between the Hofmann and the Curtius rearrangements clearly shows the Hofmann rearrangement being not predominantly controlled by the bond-energy effect.

On the other hand, it should not be overlooked to examine the two-step mechanism which had been inferred as a plausible one by several investigators.¹⁷⁾ The transition state in this mechanism closely resembles that of benzoate anion, and almost the same rvalue as the one of the Hammett's σ -constants (r=0.27) should be predicted for the mechanism. According to this prediction, the obtained r-value (0.41) seems not strongly support the two-step mechanism.

In order to clarify these ambiguous points, we subsequently measured the rates of ortho-derivatives at various temperatures. The ortho/para rate ratios and the relative activation parameters are listed in Table 2. It is noted that the ortho-derivative is

Subst.	Rel. rate ^{a)}	$k^o/k^{p\mathrm{b}}$	⊿l∠l <i>H</i> ≠ (kcal/mol)	∠1∠1 <i>S</i> ≒ (e.u.)
н	1.	1.	0.	0.
o-CH ₃ O	57.0	6.3	$+0.7\pm0.5$	$+5.9 \pm 1.8$
o-CH ₃	63.1	21.0	-0.2 ± 0.2	$+5.2 \pm 0.6$
0-C1	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) Rela	ative rate a	t 30.00°C	to the unsubstitut	cd N-bromo-

TABLE 2. EFFECTS OF ortho-substituents

amide.

b) The ortho/para rate ratio at 30.00°C.

more reactive than the corresponding para-derivative. Another noticeable fact is that this steric acceleration depends largely on the relative entropy of activation.

These facts can be rea-

sonably interpreted by considering the concerted mechanism rather than the alternative two-step mechanism. An ortho-substituent restricts the rotation of the phenyl ring, and lessens the entropy in the initial state more than that of the para-substituent. This entropy difference in the initial state should be reflected in the relative value of activation entropy of ortho- to para-derivatives, if the reaction proceeds through a concerted-type transition state.

On the contrary, in the two-step mechanism such difference of activation entropy can not be expected, since in this case the phenyl ring is not needed to twist to the amide group in the transition state.

As is suggested from the preceding discussion in terms of the \underline{r} -values, the concerted mechanism above supported is not well consistent with the rate effects of <u>meta</u>- and <u>para</u>-substituents.

This inconsistency can be dissolved by making the following assumption. The $d\pi$ - $p\pi$ conjugation on the nitrogen-bromine bond is important as a factor influencing the reactivity. As is illustrated in Formula (I), this conjugation is facilitated by a strongly



at the <u>para-position</u>, through the cross conjugation of the phenyl group with the carbonyl group. Therefore, such a substi-

electron-releasing conjugative substituent

tuent can also depress the reactivity in the initial state, with the increase of the bond-order of the N-Br bond. The substituent effect for this $d\pi$ -p π conjugation is expected to afford a negative <u>r</u>-value.

Taking account of these characteristics of the $d\underline{r}$ - $\underline{n}\underline{r}$ conjugation, following explanation may be possible for the substituent effect of <u>meta</u>- and <u>para</u>-derivatives. The comparatively large positive <u>r</u>-value owing to the participation of phenyl group with nitrogen atom in the transition state is partly compensated for by the negative <u>r</u>-value in the initial state. This compensation perhaps effects 0.41 as the observed <u>r</u>-value.

Two kinds of the conjugation effects have been inferred on the basis of the above working hypothesis, and then our attention is attracted to the effects of the leaving group in influencing the respective conjugations. Thus, the reaction rates of various substituted N-chlorobenzamides have been measured.

- 7 -

All the derivatives obeyed first-order kinetic law more strictly than those of <u>N</u>-bromo derivatives. The reproducibility of the rate constant from repeated runs was within 0.7%, and the

Subst. k1	$\times 10^4 (\text{sec}^{-1})$ 30.00°C	⊿H≠ (kcal/mol)	<i>∆S</i> ≠ (e. u.)
p-CH ₃ O	67.4 ^{a)}	24.89 ± 0.03	13.61 ± 0.10
p-C ₂ H ₅ O	70.9ª)	24.75 <u>+</u> 0.01	13.26 ± 0.04
p-CH ₃	23.64ª)	26.04 ± 0.02	15.33 ± 0.08
p-C ₂ H ₅	23.00 ^{a)}	26.04 ± 0.01	15.27 ± 0.05
Unsubst.	8.045	26.45 ± 0.05	14.55 ± 0.15
p-F	4.297	26.65 ± 0.02	13.97 ± 0.06
p-Cl	2.428	26.83 ± 0.02	13.43 ± 0.05
p-Br	2.219	26.88 ± 0.08	13.37 ± 0.28
p-NO ₂	0.1218	28.66 ± 0.06	13.52 ± 0.21
m-CH ₃	13.67ª)	26.27 ± 0.02	15.01 ± 0.06
m-CH ₃ O	5.008	26.49 ± 0.03	13.73 ± 0.11
m-Cl	1.061	27.35 ± 0.03	13.49 ± 0.09
m-Br	1.139	27.31 ± 0.10	13.51 ± 0.33
m-NO ₂	0.1272	28.48 ± 0.08	13.00 ± 0.28
$o\text{-}\mathrm{CH}_{3}$	575. 2)	25.2 ± 0.20	18.9 ± 0.66
o-Cl	12.78 ^{a)}	27.41 ± 0.02	18.64 ± 0.05
o-Br	15.16 ^{a)}	27.45 ± 0.01	19.09 ± 0.04
o-NO2	0.2258	29.01 ± 0.04	15.89±0.14

TABLE 3. KINETIC RESULTS OF THE HOFMANN REAR-RANGEMENT OF SUBSTITUTED N-CHLOROBENZAMIDES

a) Extrapolated from data at other temperatures.

plots of log $\underline{k}/\underline{T}$ vs. $1/\underline{T}$ gave an excellent straight line in every case. The rate constants at 30°C and the activation parameters obtained are given in Table 3.

An exceedingly excellent LFER was found between the <u>N</u>chloro- and <u>N</u>-bromo-series, with a slope of 0.97 and a correlation coefficient of 0.9999. This clearly indicates that the reaction mechanism

of <u>N</u>-chloro- and <u>N</u>-bromo-series are almost same; and also indicates that the contributions of respective conjugations are of the same degree for both series.

Further noticeable finding was that the <u>N</u>-chloro derivative was more reactive, even though slightly, than the corresponding <u>N</u>-bromo derivative. We ascribe this fact to the solvation effect and/or to the <u>dm-pm</u> conjugation effect on nitrogen-halogen bond, * by considering the relative values of activation parameters of <u>N</u>-chloro and <u>N</u>-bromo derivatives ($\Delta \Delta S^{\pm} = \underline{ca}$. -4 e.u. and $\Delta \Delta \underline{H}^{\pm} = \underline{ca}$. -1.3 kcal/mol).

It is interesting to note the mechanistic differences in the Hofmann, Lossen and Curtius rearrangements.

Table 4 shows the LFER between the Hofmann and the Lossen rearrangements. Excellent correlations are obtained regardless of the change of the leaving group. On the contrary, no apparent

- 8 -

TABLE 4. COMPARISON WITH THE LOSSEN REARRANGEMENT $X-C_{6}H_{4}-CON^{-}-OCO-C_{6}H_{4}-Y$

Subst. (Y)	Slope	Corr. coeff.	n ^{a)}
a-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

LFER has been observed between the Curtius and the Hofmann rearrangements, indicating a distinct difference in respective mechanisms.

a) The number of the species of substituent X.

The similarity and the

dissimilarity in the mechanisms are also reflected in the <u>ortho</u> effects (e.g., <u>ortho/para</u> rate ratios, and the relative activation parameters of <u>ortho-</u> to <u>para-substituents</u>). As is shown in Table 5, the <u>ortho/para</u> rate ratios of a given substituent is nearly equal regardless of the leaving group in Hofmann and Lossen rearrangements. Whereas, the quite large values are obtained in the Curtius rearrangement. Further remarkable difference is exhibited

Table 5 ,	ortho/para	RATE	RATIOS
X-0	C _a H ₄ -CO-	$N^{-}-Y$	

X/Y	Br	Cl			CO ₂ -	N ₂
CH ₃ O	6.3		8.5			150.
CH_3	21.0	24.3				131.
Cl	4.2	5.3		5.9		208.
Br	5.5	6.8		8.0		277.
NO_2	1.5	1.9			2.2	70.

	Table 6. Rei	LATIVE VALUES OF	ACTIVATION PARAM	METERS OF ortho- T	O <i>para</i> -DERIVATIVE	S	
	N-	Br	N-	Cl	N-	N-N ₂	
	$\Delta \Delta H^{\ddagger}$ (kcal/mol)	$\frac{\Delta\Delta S^{\pm}}{(e. u.)}$	$\Delta \Delta H^{\ddagger}$ (kcal/mol)	⊿⊿ ,5 ≑ (e. u.)	$\Delta \Delta H^{\ddagger}$ (kcal/mol)	$\frac{\Delta \Delta S^{*}}{(e. u.)}$	
CH3O	$+0.7\pm0.5$	$+5.9{\pm}1.8$		· · · · · · · · · · · · · · · · · · ·			
CH_3	-0.2 ± 0.2	$+5.2\pm0.6$	-0.8 ± 0.2	$+3.6\pm0.7$	-5.0 ± 0.3	$-6.4{\pm}0.8$	
Cl	$+1.0\pm0.2$	$+6.2 \pm 0.6$	$+0.6 \pm 0.0$	$+5.2\pm0.1$	-5.4 ± 0.6	-6.8 ± 1.9	
Br	$+0.7{\pm}0.1$	$+5.5 \pm 0.3$	$+0.6\pm0.1$	$+5.7\pm0.3$	-5.5 ± 0.2	-4.1 ± 0.7	
NO2	0.0 ± 0.8	$+0.8\pm2.5$	$+0.4{\pm}0.1$	$+2.4\pm0.4$	$-3.1{\pm}0.2$	-1.7 ± 0.5	

in the relative values of activation parameters. As is shown in Table 6, the <u>ortho/para</u> rate ratios depend largely on the entropy difference in the former two rearrangements, but rather on the enthalpy difference in the latter Curtius rearrangement. The entro-Py dependence is mostly caused by the participation of the phenyl group with nitrogen in the transition state, and the enthalpy dependence is referred to the exclusive significance of the bond-

- 9 -

energy effect in the initial state.

Several new knowledges have been derived from the data of <u>N</u>bromo and <u>N</u>-chloro derivatives. However, some of these are based on the working hypothesis on the <u>d</u><u>T</u>-<u>p</u><u>T</u> conjugation effect. Now, it remains necessary to prove the existence of this conjugation effect, by means of the application of a substituent effect. For this purpose, it is needed to ascertain the substituent effect in a system in which the amide group is sufficiently hindered from conjugating with the phenyl group in the initial state, and so the kinetic measurements of 4- and 5-substituted 2-chloro-<u>N</u>-chlorobenzamides have been carried out under the same reaction conditions as those employed in the preceding works.

The obtained rate constants and activation parameters are summarized in Table 7. Fig. 1 shows the plots of the logarithms

TABLE **7**, KINETIC RESULTS OF THE HOFMANN REAR-RANGEMENT OF *multi*-substituted *N*-chlorobenzamides

Subst.	$ k_1 \times 10^4 $ (sec ⁻¹)	⊿ <i>H</i> ≠ (kcal/mol)	ΔS^{\pm} (e. u.)
2-Cl-4-CH₃O	253ª)	25.05 ± 0.14	16.8 ± 0.47
2-Cl-4-CH ₃	48.8 ^{a)}	26.57 ± 0.03	18.52 ± 0.11
2-Cl-5-CH ₃	21.46 ^{a)}	27.02 ± 0.01	18.37 ± 0.03
2,4-di-Cl	5.446	27.44 ± 0.04	17.04 ± 0.14
2,5-di-Cl	2.059	27.86 <u>-</u> 0.05	16.48 <u>+</u> 0.16
2-Cl-4-NO ₂	0.2675	29.19 ± 0.06	16.82 ± 0.21
2,6-di-Cl	2.829	28.55 ± 0.04	19.39 ± 0.12
3,5-di-Cl	0.1715	28.10 ± 0.04	12.33 ± 0.14
3,5-di-Br	0.2084	27.94 ± 0.03	12.20 ± 0.11
2,5-di-Cl-4-CH ₃	7.226	27.04 ± 0.05	16.29 ± 0.15

a) Extrapolated from data at other temperatures.

of the relative rate constants of 2-chloro series <u>vs</u>. those of 2-unsubstituted series. All the <u>meta</u>-substituents form an excellent straight line with a slope of 0.930 and a correlation coefficient of 0.9999. Whereas, the electron-releasing conjugative substituents at

the <u>para-position</u> deviate upward from the correlation line. Each deviation, however, appears to be proportinal to the electronreleasing conjugative ability of its substituent. In fact, the least mean-square calculation using the values of $\Delta_{-R}^{=+}$ gives an excellent straight line with a correlation coefficient of 0.9999, including all the <u>para-substituents</u>. This correlation is illustrated in Fig. 2. The slope of the correlation line is 0.930, which is the same as that calculated from the all the <u>meta-substituents</u>

- 10 -





Fig. 2. Comparison with 2-unsubstituted derivatives with the application of the LArSR relationship.

and para-nitro substituent.

These facts evidently indicates that 2-chloro series is subjected with larger conjugation effect than the 2-unsubstituted se-The application of the LArSR relationship, Eq. (2), to the ries. present data affords the following equation with an excellent cor-The ρ -value (-2.21) is nearly equal to the one of relation.

$$\log \underline{k}/\underline{k}_{o} = -2.21 \ (\underline{\sigma}^{\circ} + 0.69 \ \underline{d}\underline{\sigma}_{R}^{+})$$
 (4)

unsubstituted series (-2.41), whereas the resonance parameter $(\underline{r}=0.69)$ is considerably larger than that of 2-unsubstituted series $(\underline{r}=0.41).$

These results are quite reasonably understood by the consideration of conjugation effects.

The conjugations applicable to the initial state are visualized in the Formulae (II) and (III). The through conjugation of carbonyl group with the phenyl group is restricted remarkably in the



2-chloro system (II), while not in the 2-unsubstituted system (III). The substituent effect on the conjugation effect in the 2-chloro system, therefore, is expected to be smaller

11 -

than the one in the 2-unsubstituted system.

On the other hand, in the transition state the degree of the conjugation in both series depends on the reaction mechanism (or on the structure of the transition state). In the two-step mecha-



nism the conjugation of phenyl group with amide group is restricted in the 2-chloro system (IV), while not in the 2-unsubstituted system (V). On the contrary, in the concerted mechanism the conjugation is expected to be almost the same for both 2-chloro and 2-unsubstituted system (VI) and (VII), since in this state the phenyl ring is twisted to the amide group almost at a right angle due to the effective overlap of orbitals.

These considerations can afford following predictions for the substituent effect of 2-chloro series:

- Two-step mechanism should effect an <u>r</u>-value smaller than
 0.41;
- Concerted mechanism should effect an <u>r</u>-value larger than
 0.41.

The comparatively large positive <u>r</u>-value (0.69) obtained in 2-chloro series, supports strongly the concerted mechanism, and affords a definite support to the existence of the $d\pi$ -p π conjugation on the nitrogen-halogen bond.

It has been concluded, from the kinetic substituent effects, that the Hofmann rearrangement proceeds through a concerted-type transition state. We have now intended to prove this mechanism from a different point of view.

- 12 -

Kinetic isotope effect study is the most useful method for this purpose. Especially carbon-14-isotope effect will play a quite decisive role to determine whether or not the mechanism is a concerted one.

The initial state, and the transition state for the concerted and the two-step mechanism, are schematically represented as follows:



T. S., Two-step

The most distinct difference in both mechanismslies in the variations of the total bondings at the phenyl-l- and carbonyl-carbons. In the case of the former concerted mechanism, the total bondings at respective carbons are remarkably varied in proceeding from the initial state to the transition state. On the contrary, in the latter two-step mechanism, the transition state resembles the initial state with respect to their bondings at respective positions.

Consequently, measurable kinetic isotope effects may be expected in the concerted mechanism, but no apparent effects should be observed in the latter two-step mechanism.

From these points of view, kinetic isotope effects of phenyl- $1-{}^{14}C$ and carbonyl- ${}^{14}C$ labeled <u>N</u>-chlorobenzamides have been studied.

The labeld <u>N</u>-chlorobenzamides have been prepared from the $benzoic-^{14}C$ acids by the usual method. The kinetic isotope effect was determined by measuring the specific activities of the benzamide which was derived quantitatively from the remaining reactant, <u>N</u>-

- 13 -

chlorobenzamide, at appropriate fractions of reaction. The reproducibility of the specific radioassay was within 0.25% in every case. The calculated isotope effect on the phenyl-l-carbon is given by

 $\underline{k}_{12}/\underline{k}_{14} = 1.0456 \pm 0.0012$

and that on the carbonyl-carbon by

 $\underline{k}_{12}/\underline{k}_{14} = 1.0447 \pm 0.0006$

These large isotope effects strongly support the concerted mechanism for the Hofmann rearrangement.

The details of the results and discussion will be described in succeeding chapters.

References

- Y. Yukawa and Y. Tsuno, <u>Bull. Chem. Soc. Japan</u>, <u>32</u>, 971 (1959).
 Y. Yukawa, Y. Tsuno, and M. Sawada, <u>ibid</u>., 39, 2274 (1960).
- 3) Y. Yukawa and Y. Tsuno, Nippon Kagaku Zasshi, 86, 873 (1965).
- J. Bigeleisen and M. Wolfsberg, "Advance in Chemical Physics,"
 <u>1</u>, 15 (1958).
- 5) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press Co., New York, N. Y., 1960.
- 6) E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, John Wiley and Sons Inc., New York (1946);

M. Matsuo, <u>J. Soc. Org. Synth. Chem., sp. ed</u>., <u>29</u>, 563 (1968).

- 7) F. C. Whitmore, <u>J. Amer. Chem. Soc.</u>, <u>54</u>, 3274 (1932).
- 8) W. A. Noyes and R. S. Potter, <u>ibid.</u>, <u>34</u>, 1067 (1912);
 W. A. Noyes and R. S. Potter, <u>ibid.</u>, <u>37</u>, 189 (1915).
- ⁹) E. S. Wallis and S. C. Nagel, <u>ibid.</u>, <u>53</u>, 2787 (1931).
- 10) A. Cambell and J. Kenyan, <u>J. Chem. Soc</u>., 25 (1946).
- ¹¹) E. S. Wallis and W. W. Moyer, <u>J. Amer. Chem. Soc.</u>, <u>55</u>, 2598 (1933).

- 12) F. Bell, <u>J. Chem. Soc.</u>, <u>1934</u>, 835.
- 13) T. J. Prosser and E. L. Eliel, <u>J. Amer. Che^m Soc.</u>, <u>79</u>, 2544 (1957).
- 14) C. R. Hauser and W. B. Renflow, Jr., <u>ibid.</u>, <u>59</u>, 121 (1937).
- 15) C. R. Hauser and S. W. Kantor, *ibid.*, <u>72</u>, 4284 (1950).
- 16) K. M. Joshi and K. K. Shah, <u>J. Indian Chem. Soc.</u>, <u>43</u>, 481 (1966).
- 17) 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," Mc Graw-Hill, New York (1969), p. 655.
- 18) A. Fry, private communication.
- 19) Y. Yukawa and Y. Tsuno, <u>J. Amer. Chem. Soc.</u>, <u>79</u>, 5530 (1957);
 Y. Yukawa and Y. Tsuno, <u>ibid.</u>, <u>80</u>, 6346 (1958).

CHAPTER 2

KINETIC SUBSTITUENT EFFECTS OF <u>ORTHO</u>-, <u>META</u>-, AND <u>PARA</u>-SUBSTITUTED <u>N</u>-BROMOBENZAMIDES *

* This work was published under the title of
"The Hofmann Rearrangement I," T. Imamoto, Y. Tsuno, and
Y. Yukawa, <u>Bull. Chem. Soc. Japan</u>, <u>44</u>, 1632 (1971).

The Hofmann reaction, the conversion of amide into primary amine uncontaminated with secondary amine, is one of the most useful reactions for organic syntheses.¹⁾ The course of this reaction has already been demonstrated, as in the following scheme by isolating reaction intermediates:

 $R-CONH_2 \longrightarrow R-CON-X \longrightarrow R-NCO \longrightarrow R-NH_2$

The rearrangement step, where the conjugate base of \underline{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.^{1,2)} As for further details of the mechanism, however, only a few kinetic studies have been reported. Hauser and his coworker, 3,4 in their kinetic study of substituted <u>N</u>-bromobenzamides, showed that electron-releasing substituents in the phenyl group accelerated the rate of the rearrangement and that electronattracting substituent retarded it. Joshi et al.⁵⁾ reported the kinetic results of the rearrangements of three aliphatic N-bromoamides. In spite of these insufficient data, it has been formally inferred that the rearrangement proceeds through a two-step mechanism;⁶⁾ the release of the halide ion from the conjugate base of \underline{N} -haloamide takes place in the first step, and the unstable uni-Valent nitrogeneous intermediate thus formed rearranges immediately into isocyanate. Wright and Fry⁷⁾ recently investigated the isotope effect of this rearrangement using phenyl-1- 14 C labeled <u>N</u>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 <u>et al</u>. also presented a similar echanism in their paper. It appears, however, that the amount of **Ata** reported hitherto is not sufficient to support strongly the

- 17 -

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 \underline{N} -bromobenzamides.

Experimental

<u>Materials</u>. Various substituted <u>N</u>-bromobenzamides were prepared by a modification of Hauser's method.³⁾

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 ml of water. After vigorous stirring for 2-15 min, the reaction mixture was filtered rapidly with a suction into a solution of 30 ml of acetic acid in 70 ml 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; mnitro and p-nitro derivatives, from acetic acid; p-chloro and pbromo 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 <u>m</u>-methyl, <u>o</u>-methyl, <u>p</u>-methoxy, <u>p</u>-ethyl, and <u>p-t</u>-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 al-most colorless precipitates of the corresponding <u>N</u>-bromoamide.

- 18 -

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. <u>N</u>-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 <u>N</u>-bromoamides are listed in Table 1.

The <u>o</u>-methoxy- and <u>m</u>-methoxy-<u>N</u>-bromobenzamides were very unstable compounds, and the corresponding pure materials could not

	Mp °C	· · · · · · · · · · · · · · · · · · ·)			
Subst.	(lit ³⁾)	C%	H%	N%	Br ^{o/}	Active Br%
p-CH ₃ O						33.09 (34.73)
p-t-C ₄ H ₉	117—118	51.46 (51.58)	5.49 (5.51)	5.61 (5.47)	31.07 (31.20)	31.07 (31.20)
p-CH ₃	136.0 - 137.5 (131 - 133)	$45.01 \\ (44.89)$	3.67 (3.77)	6.60 (6.54)	37.28 (37.33)	36.50 (37.33)
p-C ₂ H ₅	93—94	$46.66 \\ (47.39)$	$4.25 \\ (4.42)$	6.07 (6.14)	$34.40 \\ (35.02)$	33.87 (35.02)
<i>p</i> -Ph	159—161	$56.30 \\ (56.55)$	3.53 (3.65)	4.92 (5.07)	28.99 (28.94)	29.70 (28.94)
Unsubst.	132.5 - 134.5 (129 - 131)	$\begin{array}{c} 42.24 \\ (42.03) \end{array}$	2.73 (3.02)	6.96 (7.00)	39.80 (39.95)	39.48 (39.95)
<i>p</i> -F	168—170	38.60 (38.56)	2.39 (2.31)			36.95 (36.65)
p-Cl	181—184 (170—174)	36.00 (35.86)	2.17 (2.15)	6.10 (5.97)		33.52 (34.08)
<i>p</i> -Br	184—185	$30.41 \\ (30.14)$	$1.71 \\ (1.81)$	5.08 (5.02)	57.21 (57.29)	27.86 (28.65)
p-NO ₂	223—226 (198—202)	$34.61 \\ (34.31)$	1.91 (2.06)	11.77 (11.43)		31.58 (32.61)
m-CH ₃	60—62	45.33 (44.89)	3.77 (3.77)	$6.55 \\ (6.54)$	37.60 (37.33)	34.36 (37.33)
m-Cl	111—113 (102—105)	36.02 (35.86)	$2.03 \\ (2.15)$	6.03 (5.97)		33.82 (34.08)
<i>m</i> -Br	126.5—127.5 (122—126)	$30.44 \\ (30.14)$	1.70 (1.81)	$5.11 \\ (5.02)$		28.11 (28.65)
m-CF ₃	120—121	35.64 (35.83)	1.90 (1.88)			29.34 (29.82)
m-NO ₂	183.0—186.5 (173—176)	$34.03 \\ (34.31)$	$2.24 \\ (2.06)$	$11.62 \\ (11.43)$	$32.72 \\ (32.61)$	$\begin{array}{c} 31.96 \\ (32.61) \end{array}$
$o\text{-}\mathrm{CH}_3$	101—102	$45.39 \\ (44.89)$	$3.76 \\ (3.77)$	$6.75 \\ (6.54)$	$37.08 \\ (37.33)$	36.44 (37.33)
o-Cl	105.5 - 107.0 (104 - 105)	36.09 (35.86)	1.99 (2.15)	6.07 (5.97)		33.24 (34.08)
o-Br	130	30.29 (30.14)	$1.60 \\ (1.81)$	5.13 (5.02)	57.02 (57.29)	27.98 (28.65)
0-NO2	176—178 (170—176)	$34.61 \\ (34.31)$	1.86 (2.06)	11.77 (11.43)	$32.50 \\ (32.61)$	31.55 (32.61)

Table	1.	SUBSTITUTED	N-BROMOBENZAMIDES
	••	SCDSTTOTDD	11 Diterio Delle Initio Ed

be obtained. In the cases of <u>p</u>-ethoxy- and <u>p</u>-phenoxybenzamides, because of accompanying bromination on the benzene ring, the compounds isolated were not the expected ones, but <u>m</u>-bromo-<u>p</u>-ethoxyand 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.⁸⁾ In a measuring flask we placed 200 ml of a standardized aqueous sodium hydroxide solution and immersed in a constant-temperature water bath (accuracy +0.01°C). A certain amount of N-bromoamide was weighed accurately into a 300-ml 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-m1 portion of the solution was pipetted out and transferred into 100 m $\underline{1}$ of an ice-cold 0.5 N HCl solution to which 2 ml of $^{2}_{\Lambda}20\%$ aqueous solution of potassium iodide had been added just before; the iodine thus liberated was titrated with an 0.025 \underline{N} Na₂S₂O₃ solution to the starch-iodide end-point.

In the cases of <u>m</u>-methoxy- and <u>o</u>-methoxy-benzamides, from which corresponding <u>N</u>-bromoamides could not be isolated, the kinetic measurements were carried out as follows. A hypobromite solution (0.025 mol/<u>1</u>, <u>f</u>=0.996) was prepared by the drop-by-drop addition of bromine to an ice-cold 0.5 <u>N</u> NaOH solution (<u>f</u>=1.000). Finely-pulverized pure amide (0.0055 mol) was added to 200 m<u>1</u> 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.

- 20 -

Results and Discussion

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

- A. Changing the concentration of <u>N</u>-bromoamide in a 1 <u>N</u> NaOH solution;
- B. Changing the concentration of sodium hydroxide, but keeping that of <u>N</u>-bromoamide constant $(0.05 \text{ mol}/\underline{1})$; and
- C. Changing the overall concentration, with the concentration ratio of \underline{N} -bromoamide to sodium hydroxide kept at 1:20.

The concentration factor for <u>N</u>-bromoamide and sodium hydroxide was 1.000 ± 0.003 in every case. The reaction temperatures were 20.00 $\pm0.01^{\circ}$ C for unsubstituted amide and $30.00\pm0.01^{\circ}$ C for <u>m</u>-chloro amide. The first-order rate constants were calculated by the least-squares method according to Eq. (1):

 $\underline{\mathbf{k}} \times \underline{\mathbf{t}} = 2.303 \times \log \left(\underline{\mathbf{a}} / \underline{\mathbf{a}} - \underline{\mathbf{x}}\right) \tag{1}$

where \underline{t} is the reaction time and where $\underline{a}-\underline{x}$ is the concentration





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



of <u>N</u>-bromoamide at time <u>t</u>. Almost all the cases obeyed firstorder kinetics, at least to 80% completion of the reaction (see Fig. 1). The observed rate constants are listed in Table 2.

	Conc. of amide (mol/l)	Conc. of NaOH (N)	$(k_1 \times 10^4 \text{ sec}^{-1})$ 20.00°C	m-Cl $k_1 \times 10^4 (\text{sec}^{-1})$ 30.00° C	$\frac{k_1(H, 20^{\circ}C)}{k_1(m-Cl, 30^{\circ}C)}$
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	$9.34{\pm}0.03$	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.	1.29ª)	7.85 ^{a)}	1.64

TABLE 2. EFFECT OF THE CONCENTRATIONS OF N-BROMOAMIDE AND NaOH

a) Extrapolated value.

In the case A, a very small rate enhancement was observed despite the increase in the concentration of <u>N</u>-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).⁹) The reaction involves a pre-equilibrium between <u>N</u>-bromoamide and its conjugate base, as is indicated by the following scheme. The relatively low

 $X-C_6H_4$ -CONHBr + $OH \longrightarrow X-C_6H_4$ -CON-Br + H_2O concentration ratio of sodium hydroxide to <u>N</u>-bromoamide releases a small amount of the <u>N</u>-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

- 22 -

products of <u>N</u>-bromoamide with amine or isocyanate.

From the above observations, it appears necessary to keep the initial concentration ratio [NaOH]/[Amide] at least <u>ca</u>. 10 to obtain a good kinetic result. The case C indicates the rates measured under reaction conditions in which the concentration ratio of <u>N</u>-bromoamide to sodium hydroxide kept at 1:20. The observed rate constants appeared to be given by the combined results of the con- * centration effects of <u>N</u>-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 <u>m</u>-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 <u>N</u>-bromobenzamides. Practically, fixed conditions with the respective concentrations of <u>N</u>-bromoamide and sodium hydroxide being $0.025 \text{ mol}/\underline{1}$ and $0.5 \underline{N}$ were employed throughout the series of runs as the most suitable standard from the experimental point of view.

<u>Substituent Effects</u>. The rates of the release of the bromide ion from the conjugate bases of various substituted <u>N</u>bromobenzamides were determined at various temperatures. The initial concentrations of <u>N</u>-bromoamide and sodium hydroxide were maintained at 0.025 mol/<u>1</u> and 0.5 <u>N</u> (<u>f</u>=1.000+0.003) respectively throughout the series. Plots of the $log(\underline{a}-\underline{x})$ against time <u>t</u> gave an excellent straight line, covering over 75% of the reaction, for almost all derivatives. In the cases of <u>P</u>-phenyl, <u>P</u>-fluoro, <u>P-t</u>-butyl and <u>o</u>-nitro derivatives, the reaction rates were gradually

- 23 -

increased as the reaction proceeded; thus, the rate constants were calculated from the plots of the initial stage of the reaction. The <u>m</u>-nitro and <u>p</u>-nitro derivatives behaved peculiarly; the firstorder plots provided a good straight line at temperatures over 45° C, but not at 30°C. Rate measurements of unsubstituted and <u>p</u>-methoxy derivatives were made not only by the general method but also by the conventional modification used for <u>o</u>-methoxy and <u>m</u>methoxy derivatives (see the Experimental section). The disagreement between the two methods did not exceed <u>ca</u>. 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.

Subst.	Temp. °C	$k_1 \times 10^4 \; (\text{sec}^{-1})$	Subst.	Temp. °C	$k_1 \times 10^1 (\text{sec}^{-1})$
p-CH₃O	13.00 10.00 5.00	$\begin{array}{cccc} 4.81 & \pm 0.02 \\ 2.92 & \pm 0.01 \\ 1.275 & \pm 0.001 \\ \end{array}$	m-CH ₃	23.00 15.00 8.00	$\begin{array}{rrrr} 4.120 & \pm 0.006 \\ 1.064 & \pm 0.002 \\ 0.3147 & \pm 0.0009 \end{array}$
	2.00	1.251 ± 0.003^{a} 0.771 ± 0.001	m-CH ₃ O	30.00 20.00	4.09 ± 0.004^{a} 0.847 $\pm 0.001^{a}$
p-t-C₄H9	$20.00 \\ 13.00 \\ 5.00$	$\begin{array}{rrrr} 3.63 & \pm 0.01 \\ 1.121 & \pm 0.003 \\ 0.274 & \pm 0.001 \end{array}$		15.00 10.00 0.00	$\begin{array}{r} 0.361 \pm 0.001^{a}) \\ 0.1503 \pm 0.0002^{a}) \\ 0.02447 \pm 0.00010^{a}) \end{array}$
p-CH₃	18.00 14.00 10.00 3.71	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	m-Cl	$38.00 \\ 30.00 \\ 23.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
p-C ₂ H ₅	20.00 13.00 5.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	<i>m</i> -Br	$38.00 \\ 30.00 \\ 23.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
p-Ph	25.00 18.00 10.00	$\begin{array}{cccc} 4.28 & \pm 0.01 \\ 1.40 & \pm 0.004 \\ 0.366 & \pm 0.002 \end{array}$	m-CF ₃	$\begin{array}{c} 45.00 \\ 35.00 \\ 30.00 \\ 23.00 \\ 15.00 \end{array}$	$\begin{array}{rrrr} 4.278 & \pm 0.009 \\ 0.946 & \pm 0.0006 \\ 0.4266 & \pm 0.0005 \\ 0.1341 & \pm 0.0002 \\ 0.03214 \pm 0.00004 \end{array}$
Unsubst.	25.00 20.00 10.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	m-NO ₂	$55.19 \\ 50.00 \\ 45.00$	$\begin{array}{ccc} 4.79 & \pm 0.02 \\ 2.30 & \pm 0.009 \\ 1.13 & \pm 0.003 \end{array}$
	0.00	0.0391 ± 0.0001	o-CH ₃ O	$5.00 \\ 0.00$	$\begin{array}{rrrr} 7.37 & \pm 0.02^{a} \\ 3.04 & \pm 0.01^{a} \end{array}$
p-F	$30.00 \\ 23.00 \\ 15.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	o-CH3	$5.00 \\ 3.00 \\ 2.00$	$\begin{array}{rrrr} 7.36 & \pm 0.02 \\ 5.19 & \pm 0.01 \\ 4.30 & \pm 0.005 \end{array}$
∲-Cl	$35.00 \\ 30.00 \\ 20.00$	$\begin{array}{rrrr} 4.346 & \pm 0.002 \\ 2.029 & \pm 0.004 \\ 0.4053 & \pm 0.0007 \end{array}$	o-Cl	0.00 25.00 18.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
<i>p</i> −Br	35.00 30.00 25.00 20.00	$\begin{array}{rrrr} 3.97 & \pm 0.007 \\ 1.834 & \pm 0.003 \\ 0.830 & \pm 0.001 \\ 0.365 & \pm 0.0004 \end{array}$	o-Br	10.00 25.00 18.00 10.00	$\begin{array}{cccc} 0.273 & \pm 0.0004 \\ 4.444 & \pm 0.005 \\ 1.368 & \pm 0.001 \\ 0.3268 & \pm 0.0007 \end{array}$
₱-NO2	$55.00 \\ 50.00 \\ 45.00$	$\begin{array}{rrrr} 4.85 & \pm 0.02 \\ 2.49 & \pm 0.01 \\ 1.18 & \pm 0.01 \end{array}$	$o-\mathrm{NO}_2$	$50.00 \\ 45.00 \\ 40.00$	$\begin{array}{rrrr} 3.74 & \pm 0.10 \\ 1.83 & \pm 0.02 \\ 0.871 & \pm 0.001 \end{array}$

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

a) Measured by using sodium hypobromite solution.

The present authors 10) have previously pointed out that the Linear Aromatic Substituent-Reactivity relationship (LArSR relationship, Eq. (2)) is one of the most useful tools for speculating on the reaction mechanism:

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

where $\underline{\sigma}^{\circ}$ is the normal substituent constant, where <u>r</u> is a constant depending on the resonance requirement in the reaction, and where $\varDelta \bar{\underline{\sigma}}_{R}^{+}$ measures the capacities of the substituents to supply electrons by resonance. It is of interest to discuss the reaction mechanism of the Hofmann rearrangement in terms of the above equation. First, the logarithms of the rate constants have been plotted against

ENT OF SUBSTITUTED N-bromobenzamides

Subst.	$k_1 \times 10^4 (\text{sec}^{-1})$ 30.00°C	⊿H≠ (kcal/mol)	ΔS^{\pm} (e.u.)
p-CH ₃ O	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 $_3$	20.9ª)	27.03 ± 0.03	18.36 ± 0.11
p-C ₂ H ₅	19.6 ^{a)}	27.25 ± 0.11	18.9 ± 0.4
$p ext{-Ph}$	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
$m-CH_3$	12.5ª)	27.78 ± 0.09	19.8 ±0.3
m-CH ₃ O	4.09	27.52 ± 0.05	17.7 ±0.2
m-Cl	0.852	28.6 ± 0.2	17.1 ± 0.7
$m ext{-Br}$	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 ₃ O	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
0-NO2	0.185 ^{a)}	28.6 ± 0.36	14.2 ± 1.2

a) Extrapolated from data at other temperatures.

TABLE 4. KINETIC RESULTS OF THE HOFMANN REARRANGE- Hammett's o constants in order to examine the applicability of the original Hammett equation, $\log k/k = 00$ to our data. A good overall linear relation with a q-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 is attributable to the experimental error. It would

be more reasonable to refer the deviation to the strongly electronreleasing conjugative ability of the methoxy group. That is, the Hofmann rearrangement may be considered to be a slightly more $\underline{\sigma}^+$ characteristic reaction than the dissociation of benzoic acids, from which the Hammett's $\underline{\sigma}$ constants are derived. The use of Eq.

- 25 -

(2) gives a better linearity, including the <u>p</u>-methoxy group, with a correlation coefficient of 0.997, as is shown in Fig. 3.

$$\log k/k_0 = -2.39(\sigma^0 + 0.41\,\varDelta\,\overline{\sigma}_{R}) + 0.002 \tag{3}$$

For the interpretation of the above derived parameters, especially of the resonance parameter, \underline{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 $d\pi$ -pp 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 electronreleasing conjugative groups at the <u>para-position</u>. For instance, the <u>p</u>methoxy group, a typical electron-re-

leasing 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

- 26 -

orbital, resulting in a relative increase in the $d\pi$ -pp conjugation on the N-Br bond. Therefore, if the present reaction is controlled solely by the $d\pi$ -pp conjugation effect at the initial state, the resonance parameter, <u>r</u>, in the LArSR relationship Eq. (2) may be expected to be negative, as has been observed in the Curtius rearrangement in toluene (<u>r</u>=-1.04)¹¹) and in the Wolff rearrangement (<u>r</u>=-1.7).¹²) In the present Hofmann rearrangement, however, comparatively large positive <u>r</u>-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.

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, where the release of the bromide ion takes place at the first step and the univalent nitrogeneous intermediate formed rearranges immediately into iso-

cyanate. 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 process. In the former model, the substituent effect on the stabilization of this state is expected to afford a small positive <u>r</u>-value (a value of the same order as for $\underline{\sigma}$, <u>r</u>=0.27), since its electronic nature resembles closely that of the benzoate anion. On the other hand, in the latter model, a strongly electronreleasing conjugation is required for the partial bond formation between the phenyl group and nitrogen, and thus a large positive <u>r</u>-value should be observed, as in the Beckmann rearrangement of acetophenone oximes (r=0.60-0.65). The observed <u>r</u>-value (0.41), however, appears too large for the (III) model and, on the contrary,

- 27 -

too small for the (IV) model. Its <u>r</u>-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 <u>r</u>-value due to the electrophilic conjugative effect at the transition state (IV) may be somewhat compensated for by the negative <u>r</u>-value resulting from the <u>d\pi-p</u> conjugation on the N-Br bond at the initial state.

It is also of interest to discuss the effect of <u>ortho</u>-substituents with regard to the reaction mechanism. The polar effect of the <u>ortho</u>-substituent is generally recognized to be nearly equal to that of <u>para</u>-substituent;¹³⁾ thus, the rate ratio and the relative value of the activation parameters of <u>ortho</u>- to <u>para</u>substituent can be taken as measures of <u>ortho</u> effects reflecting the reaction mechanism. The <u>ortho/para</u> rate ratios and the relative values of activation parameters are summarized in Table 5. It may be noted that comparatively large <u>ortho/para</u> rate ratios

Subst.	Rel. rate ^{a)}	$k^{o}/k^{p\mathrm{b}}$	$\frac{\Delta \Delta H^{\ddagger}}{(\text{kcal/mol})}$	<i>∆∆S</i> ≠ (e.u.)
Н	1.	1.	0.	0.
o-CH₃O	57.0	6.3	$+0.7{\pm}0.5$	$+5.9\pm1.8$
o-CH3	63.1	21.0	-0.2 ± 0.2	$+5.2 \pm 0.6$
o-Cl	1.23	4.2	$+1.0\pm0.2$	$+6.2 \pm 0.6$
o-Br	1.44	5.5	$+0.7 \pm 0.1$	$+5.5 \pm 0.3$
$o-NO_2$	0.027	1.5	0.0 ± 0.8	$+0.8{\pm}2.5$

TABLE 5. EFFECTS OF ortho-SUBSTITUENTS

a) Relative rate at 30.00°C to the unsubstituted N-bromoamide.

b) The ortho/para rate ratio at 30.00°C.

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 <u>ortho</u>-substituent restricts the rotation of the

phenyl ring and lessens the entropy in the initial state more than does that of the corresponding <u>para</u>-substituent. If the reaction Proceeds by the two-step mechanism, the difference in the entropy of the <u>ortho</u>- and <u>para</u>-derivative 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 <u>para</u>-derivative is lowered below that of corres-

- 28 -

ponding <u>ortho</u>-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 <u>ortho</u> 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 <u>ortho</u> group. This effect increases the conjugation of the carbonyl group with the nitrogen orbital, but decreases the <u>dT-pT</u> conjugation on the N-Br bond. The smaller <u>dTpT</u> conjugation may play a role in bringing about the rate acceleration.

Hauser and Renflow had measured the rates of eight <u>meta-</u>, <u>para-</u> and two <u>ortho-</u>substituted <u>N</u>-bromobenzamides in a l <u>N</u> 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 <u>p</u>-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-worker¹⁴⁾ 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

- 29 -

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 $d\pi$ -pp conjugation in the Hofmann rearrangement, on the depression of the reactivity should not be neglected.

Table 6. Comparison with the Lossen rearrangement $X-C_6H_1-CON^--OCO-C_6H_1-Y$

Subst. (Y)	Slope	Corr. coeff.	n^{a}
o-NO2	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
Н	1.15	0.999	5

 $\begin{array}{c}
 & & & & & \\ & & & & \\ & & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\$

a) The number of the species of substituent X.

References

- E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, John Wiley and Sons Inc., New York (1946); M. Matsuo, <u>J. Soc</u>. <u>Org. Synth. Chem. Japan, sp. ed.</u>, <u>29</u>, 563 (1968).
- 2) T. J. Prosser and E. L. Eliel, <u>J. Amer. Chem. Soc.</u>, <u>79</u>, 2544 (1957).
- 3) C. R. Hauser and W. B. Renflow, Jr., *ibid.*, 59, 121 (1937).
- 4) C. R. Hauser and S. W. Kantor, <u>ibid.</u>, <u>72</u>, 4284 (1950).
- 5) K. M. Joshi and K. K. Shah, <u>J. Indian Chem. Soc.</u>, <u>43</u>, 481 (1966).
- 6) 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," Mc Graw-Hill, New York (1969), p. 655.
- 7) A. Fry, private communication; J. C. Wright and A. Fry, <u>J</u>. <u>Chem. Eng. News</u>, 1968, No. 1, p. 28.

- 8) Van Dam, <u>Rec. Trav. Chim. Pays-Bas</u>, <u>18</u>, 408 (1899); Van Dam and J. H. Aberson, <u>ibid</u>., <u>19</u>, 318 (1900).
- 9) The rate constant under these reaction conditions was calculated from the first-order plots of the initial stage of the reaction.
- 10) Y. Tukawa, Y. Tsuno, and M. Sawada, <u>Bull. Chem. Soc. Japan</u>, <u>39</u>, 2274 (1966); Y. Yukawa and Y. Tsuno, <u>Nippon Kagaku Zasshi</u>, <u>86</u>, 873 (1965).
- 11) Y. Yukawa and Y. Tsuno, <u>J. Amer. Chem. Soc.</u>, <u>79</u>, 5530 (1957);
 Y. Yukawa and Y. Tsuno, <u>ibid.</u>, <u>80</u>, 6346 (1958).
- 12) Y. Yukawa, Y. Tsuno, and T. Ibata, <u>Bull. Chem. Soc. Japan</u>, <u>40</u>, 2613 (1967).
- 13) R. W. Taft. Jr., "Steric Effects in Organic Chemistry," John Wiley and Sons Inc., New York (1956), p. 556.
- 14) W. B. Renflow and C. R. Hauser, <u>J. Amer. Chem. Soc.</u>, <u>59</u>, 2308 (1937); R. D. Bright and C. R. Hauser, <u>ibid.</u>, <u>61</u>, 618 (1939).

CHAPTER 3

KINETIC SUBSTITUENT EFFECTS OF <u>ORTHO</u>-, <u>META</u>-, AND <u>PARA</u>-SUBSTITUTED <u>N</u>-CHLOROBENZAMIDES *

* This work was published under the title of "The Hofmann Rearrangement II", T. Imamoto, Y. Tsuno, and Y. Yukawa, <u>Bull. Chem. Soc. Japan</u>, <u>44</u>, 1639 (1971).

- 32 -

As has been described in the preceding chapter, the kinetic substituent effects on the Hofmann rearrangement of substituted <u>N</u>-bromobenzamides were studied in order to elucidate the mechanism precisely. The results appeared to suggest that this rearrangement proceeded through a concerted-type transition state; the dissociation of the nitrogen-bromine bond and the migration of the phenyl group to nitrogen took place simultaneously. Furthermore, the results indicated that the contribution of the <u>dT-pT</u> conjugation to the nitrogen-bromine bond in the initial state was also an important factor in depressing the reactivity.

It remains necessary to examine whether or not these qualities of the rearrangement are changed by the substitution of the leaving group, bromide, for chloride. In the present study, the substituent effects of substituted <u>N</u>-chlorobenzamides have been determined, and the results are discussed in terms of the effects of the leaving group on the reactivity.

Experimental

<u>Materials</u>. Various substituted <u>N</u>-chlorobenzamides, but not <u>m</u>- and <u>p</u>-methoxy and <u>p</u>-ethoxy derivatives, were prepared by a modification of Elliott's method.¹⁾ Ten grams of pure amide was dissolved in 10% hydrochloric acid, and chlorine gas was passed into this solution for one hour. The <u>N</u>-chloroamide thus precipitated was collected, washed with water, and dried <u>in vacuo</u>. The yields of the crude products were generally 70-80% of the theoretical amounts.

In the cases of <u>m</u>- and <u>p</u>-methoxy and <u>p</u>-ethoxy benzamides, chlorination on the benzene ring was also present and the corresponding pure <u>N</u>-chloroamides could not be isolated by the above method. However, these <u>N</u>-chloroamides could be obtained by the application of the method of Altenkirk and Israelstam.²⁾ Ten

- 33 -
grams of pure amide and 0.4 g of borax were dissolved in methanol, and into this solution an equimolar quantity of <u>t</u>-butyl hypochlorite was added at room temperature. After standing in the dark for <u>ca</u>. 15 hr, the reaction mixture was diluted with water to twice the original volume. The <u>N</u>-chloroamide thus precipitated was collected, washed with water, and dried <u>in vacuo</u> (yield 50-70%).

The crude <u>N</u>-chloroamides were recrystallized from dichloroethane or from a mixed solvent of methanol and dichloroethane. The analytical data and melting points for <u>N</u>-chlorobenzamides are listed in Table 1.

Cubat	Mp °C	Analysis (Calcd)				
Subst.	(lit ³⁾)	C %	Η%	N %	Cl%	Active Cl%
p-CH ₃ O	$ \begin{array}{r} 142-143 \\ (142-143) \end{array} $	51.77 (51.77)	4.40 (4.34)	7.47 (7.55)	18.94 (19.10)	19.00 (19.10)
p-C ₂ H ₅ O	128.0-129.0	$54.04 \\ (54.15)$	5.08 (5.05)	6.88 (7.02)	17.91 (17.76)	17.69 (17.76)
<i>p</i> -CH ₃	153.5 - 154.5 (147)	$56.87 \\ (56.65)$	4.60 (4.75)	8.38 (8.26)	20.79 (20.90)	20.52 (20.90)
p-C ₂ H ₅	106.5—107.0	$58.49 \\ (58.86)$	5.41 (5.49)	$7.69 \\ (7.63)$	19.18 (19.31)	19.23 (19.31)
Unsubst.	117.0—118.0 (117—118)	$53.93 \\ (54.04)$	3.67 (3.89)	9.00 (9.00)	22.98 (22.79)	22.48 (22.79)
<i>p</i> -F	178—180	$\begin{array}{c} 48.28 \\ (48.44) \end{array}$	3.02 (2.90)			20.13 (20.43)
p-Cl	196—198 (194—195)	$44.05 \\ (44.24)$	$2.58 \\ (2.65)$	7.46 (7.37)	$37.48 \\ (37.31)$	18.46 (18.66)
<i>p</i> -Br	198—199	35.86 (35.86)	$2.01 \\ (2.15)$	5.99 (5.97)		15.00 (15.12)
<i>p</i> -NO ₂	230—233 (200—202)	41.99 (41.92)	$2.19 \\ (2.51)$	13.78 (13.97)	17.70 (17.68)	16.98 (17.68)
m-CH ₃ O	103.0-103.5 (165-166)	$51.90 \\ (51.77)$	$4.29 \\ (4.34)$	7.55 (7.55)	19.27 (19.10)	18.86 (19.10)
m-Cl	121 - 122 (119 - 120)	$44.14 \\ (44.24)$	$2.54 \\ (2.65)$	7.60 (7.37)	37.37 (37.31)	18.30 (18.66)
<i>m</i> -Br	127.0-127.5	35.81 (35.86)	2.08 (2.15)	$6.00 \\ (5.97)$		14.85 (15.12)
m-NO ₂	188—189 (184)	42.21 (41.92)	$2.37 \\ (2.51)$	$14.02 \\ (13.97)$	$17.82 \\ (17.68)$	17.41 (17.68)
0-CH3	87.0—88.5 (88—89)	56.28 (56.65)	$4.63 \\ (4.75)$	8.14 (8.26)	$20.80 \\ (20.90)$	20.54 (20.90)
0-C1	107.0—107.5 (105—106)	44.10 (44.24)	$2.46 \\ (2.65)$	7.55 (7.37)	37.20 (37.31)	18.44 (18.66)
o-Br	149.0-150.5 (151-152)	36.00 (35.86)	1.96 (2.15)	6.02 (5.97)		14.98 (15.12)
0-NO2	172—173	41.89 (41.92)	2.22 (2.51)	14.30 (13.97)	17.82 (17.68)	17.45 (17.68)

TABLE 1. SUBSTITUTED N-CHLOROBENZAMIDES

<u>Kinetic Measurements</u>. The rates of the rearrangement of the substituted <u>N</u>-chlorobenzamides except those of the <u>m</u>-methyl derivative were measured by the same method as was previously used for <u>N</u>-bromobenzamides. The initial concentrations of <u>N</u>-chloroamide and sodium hydroxide were $0.025 \text{ mol}/\underline{1}$ and $0.5 \underline{N}$ respectively.

In the case of <u>m</u>-methyl benzamide, from which the corresponding <u>N</u>-chloro derivative could not be isolated,³⁾ the kinetic measurements were carried out as follows. Finely-pulverized amide (0.0055 mol) was added at the reaction temperature to 200 m<u>l</u> of a hypochlorite solution (0.025 mol/<u>l</u>, <u>f</u>=1.000), freshly prepared by passing chlorine gas into an ice-cold 0.5 <u>N</u> (<u>f</u>=1.000) NaOH solution. The mixture was shaken vigorously for a few minutes, and then the reaction was followed by titrating the residual active chlorine with a 0.025 <u>N</u> Na₂S₂O₃ solution.

In order to compare the two rate constants, that obtained by the usual method and that obtained by the conventional modification applied to the <u>m</u>-methyl derivative, the rates of the <u>m</u>-chloro derivative were measured at 30° C by both the above methods. The rate constant obtained by the latter method was, at most, <u>ca</u>. 2% smaller than the constant obtained by the former method.

Results and Discussion

The rates of the release of the chloride ion from the conjugate bases of substituted <u>N</u>-chlorobenzamides were measured under the same reaction conditions as were used for the previous <u>N</u>-bromo series. All the runs strictly obeyed first-order kinetics, at least to 75% completion of the reaction, except for those of <u>m</u>-methyl derivative. Some examples of first-order plots are shown in Fig. 1. In the case of the <u>m</u>-methyl derivative, the rates of which were measured by using a hypochlorite solution, a short induction period was observed when the reaction was about 15% ^{complete} (see Fig. 1),⁴⁾ and the rate constants were calculated from the first-order plots, excluding the induction period.

- 35 -



Fig. 1. Typical first-order plots. la: *m*-CH₃, at 15°C; lb: *p*-F, at 25°C lc: *p*-Cl, at 30°C; ld: H, at 25°C. The reproducibility of the rate constant obtained from repeated runs was within 0.7%, and the plots of log $\underline{k}/\underline{T}$ vs. $1/\underline{T}$ gave an excellent straight line in every case. The observed rate constants are listed in Table 2. The rate constants at 30°C and the derived activation parameters are summarized in Table 3.

TABLE 2. RATE CONSTANTS OF THE HOFMANN REARRANGEMENT OF SUBSTITUTED N-CHLOROBENZAMIDES

Subst.	Temp. °C	$k_1 \times 10^4 (\text{sec}^{-1})$	Subst.	Temp. °C	$k_1 \times 10^4 (\text{sec}^{-1})$
p-CH ₃ O	13.00 10.00	5.456 ± 0.001 3.414 ± 0.009 1.507 ± 0.009		40.00 30.00	$\begin{array}{c} 0.5807 \pm 0.0001 \\ 0.1218 \pm 0.0002 \end{array}$
	0.00	1.507 ± 0.003 0.6492 ± 0.0009	m-CH ₃	$15.00 \\ 10.00$	$\begin{array}{rrrr} 1.341 \ \pm \ 0.002^{a}) \\ 0.5852 \ \pm \ 0.0005^{a}) \end{array}$
p-C₂H₅O	13.00 10.00 5.00	5.826 ± 0.007 3.629 ± 0.008 1.619 ± 0.002	m-CH ₃ O	5.00 30.00 25.00	$0.2487 \pm 0.0005^{*}$ 4.999 ± 0.008 2.355 ± 0.002
<i>p</i> -CH ₃	15.00	0.7000 ± 0.0019 2.364 ± 0.004 1.011 ± 0.002		20.00 15.00	$\begin{array}{r}1.085 \pm 0.0008\\0.4812 \pm 0.0002\end{array}$
	5.00	0.4448 ± 0.0007 0.1843 ± 0.0003	m-Cl	$\begin{array}{c} 38.00\\ 30.00 \end{array}$	3.500 ± 0.001 1.061 ± 0.0006 1.043 ± 0.0023
p-C ₂ H ₅	20.00	5.091 ± 0.006 2.302 ± 0.002		20.00	0.2181 ± 0.0003
	10.00 5.00	$\begin{array}{r} 1.012 \pm 0.001 \\ 0.4333 \pm 0.0004 \end{array}$	<i>m</i> -Br	$38.00 \\ 30.00 \\ 20.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
Unsub st.	30.00 25.00 20.00 15.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	m-NO ₂	50.00 45.00 40.00 30.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
<i>p</i> -F	$30.00 \\ 25.00 \\ 20.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$o ext{-} ext{CH}_{3}$	5.00 0.00	$\begin{array}{rrrr} 12.3 & \pm & 0.07 \\ 5.23 & \pm & 0.010 \end{array}$
	15.00	0.4075 ± 0.0004	o-Cl	$20.00 \\ 15.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
p-Cl	$35.00 \\ 30.00 \\ 25.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$		$\begin{array}{c} 10.00 \\ 5.00 \end{array}$	$\begin{array}{r} 0.4794 \pm 0.003 \\ 0.1964 \pm 0.0010 \end{array}$
	20.00	0.5129 ± 0.0004	o-Br	$20.00 \\ 15.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
∲-Br	35.00 30.00 35.00	$\begin{array}{rrrr} 4.633 & \pm & 0.003 \\ 2.219 & \pm & 0.002 \\ 1.021 & \pm & 0.001 \end{array}$		$10.00 \\ 5.00$	$\begin{array}{c} 0.5667 \pm 0.0004 \\ 0.2313 \pm 0.0006 \end{array}$
	20.00	0.4654 ± 0.0005	$o-NO_2$	$50.00 \\ 45.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$
<i>p</i> -NO ₂	50.00 45.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$		40.00 30.00	$\begin{array}{r} 1.095 \pm 0.001 \\ 0.2258 \pm 0.0002 \end{array}$

a) Measured by using sodium hypochlorite solution.

The rate constant at 30°C is found to be slightly larger than that of the corresponding <u>N</u>-bromoamide, and the chloride/bromide rate-ratio is calculated to be <u>ca</u>. 1.2:1 in every substituent. It should be noted that the observed rate-ratio is considerably

Table 3. Kinetic results of the Hofmann rearrangement of substituted N-chlorobenzamides

Subst.	$k_1 \times 10^1 (\text{sec}^{-1})$ 30.00°C	ΔH^{i} (kcal/mol)	<i>∆S</i> ≠ (e. u.)
p-CH ₃ O	67.4 ^{a)}	24.89 ± 0.03	13.61 ± 0.10
p-C₂H₅O	70.9ª)	24.75 ± 0.01	13.26 ± 0.04
p-CH ₃	23.64 ^{a)}	26.04 ± 0.02	15.33 ± 0.08
$p-C_2H_5$	23.00 ^{a)}	26.04 ± 0.01	15.27 ± 0.05
Unsubst.	8.045	26.45 ± 0.05	14.55 ± 0.15
p-F	4.297	26.65 ± 0.02	13.97 ± 0.06
p-Cl	2.428	26.83 ± 0.02	13.43 ± 0.05
p-Br	2.219	26.88 ± 0.08	13.37 ± 0.28
$p-NO_2$	0.1218	28.66 ± 0.06	13.52 ± 0.21
m-CH ₃	13.67 ^{a)}	26.27 ± 0.02	15.01 ± 0.06
m-CH ₃ O	5.008	26.49 ± 0.03	13.73 ± 0.11
m-Cl	1.061	27.35 ± 0.03	13.49 ± 0.09
<i>m</i> -Br	1.139	27.31 ± 0.10	13.51 ± 0.33
m-NO ₂	0.1272	28.48 ± 0.08	13.00 ± 0.28
o-CH3	575.ª)	25.2 ± 0.20	18.9 ± 0.66
o-Cl	12.78 ^{a)}	27.41 <u>+</u> 0.02	18.64 ± 0.05
o-Br	15.16 ^{a)}	27.45 ± 0.01	19.09 ± 0.04
$o-NO_2$	0.2258	29.01 <u>+</u> 0.04	15.89 ± 0.14

a) Extrapolated from data at other temperatures.

different from that of the usual alkyl halide reported hitherto in various nucleophilic substitution reactions and elimination reactions. That is, an alkyl chloride reacts 10-1000 times slower than the corresponding bromide,⁵) whereas in the Hofmann rearrangement the <u>N</u>-chloroamide is slightly more reactive than the <u>N</u>-bromoamide. This result might possibly be referred to

the fact that the bond-breaking of the nitrogen-halogen bond does not take place in the rate-determining step, but this possibility is entirely obviated by the kinetic results on the Lossen rearrangement. Hauser <u>et al</u>.⁶⁾ had studied the kinetic substituent



effect on the Lossen rearrangement of dihydroxamates (I), and obtained a comparatively large positive o-value (+1.0). This result

evidently indicates that the rate-determining step involves the bond-cleavage of the nitrogen-oxygen bond. From the similarity of the reaction mechanism of the Lossen to that of the Hofmann rearrangement, it is also clear that the dissociation of the nitrogenhalogen bond in the Hofmann rearrangement takes place in the ratedetermining step. The data on the relative reactivities of the \mathbb{N} -chloro and \mathbb{N} -bromo derivatives can be rather reasonably interpreted by considering the effect of solvation at the initial and the transition states. The reactant molecule, the conjugate base of \mathbb{N} -haloamide, is strongly solvated by the hydrogen bond with the amide group, at which a large negative charge is acquired.

- 37 -

Both N-chloro and N-bromo derivatives, however, will be subjected to almost the same degree of the solvation, since this solvation is controlled for the most part by the large acquired negative charge at the amide group, with a minor influence by the halogen atom. On the other hand, at the transition state the solvent water molecule is strongly hydrogen-bonded with a large negative charge on the halogen atom. Therefore, the degree of the solvation is proportional to the ion potential of the halide ion itself; the N-chloro derivative is more solvated than the N-bromo derivative. The difference in the solvation effect in the transition state can be estimated to be one of the main factors in increasing the reactivity of N-chloroamide relative to that of N-bromoamide. This consideration is supported by the fact that the relative values of the activation entropy and the activation enthalpy have found to be approximately -4 e. u. and -1.3 kcal/mol respectively.

In addition to the solvation effect, the effect of the $d\pi$ -pp conjugation on the nitrogen-halogen bond seems to be an important factor in increasing the reactivity. Therefore, if the $d\pi$ -pp conjugation on the N-Br bond is stronger than that of the N-Cl bond, the reactivity of the N-bromoamide will be relatively more depressed than that of the N-chloroamide. The above assumption regarding the relative strength of the $d\pi$ -pp conjugation on the nitrogen-halogen bond may be supported by the data on the $d\pi$ -pp conjugation of the carbon-halogen bond.⁷⁾ This might lead to a subsequent conclusion that, in the Hofmann rearrangement, the effects of the solvation and the $d\pi$ -pp conjugation on the relative reactivity are so important as to overcome the effects of the polarization and the <u>o</u>-bond strength of the nitrogen-halogen bond.

The application of LFER to the present data will provide ^{Valuable} informations on the effect of the leaving group on the ^{reactivity} as well as on the more precise reaction mechanism of

- 38 -

this rearrangement. In a preceding study of the substituent effect of the <u>N</u>-bromoamides, it has been inferred that the most important factors characterizing the Hofmann rearrangement are the $d\underline{r}$ -p<u>r</u> conjugation on the N-Br bond in the initial stage and the participation of the phenyl group migrating to electron-deficient nitrogen in the transition state.

These two factors can be influenced by the substituent on the migrating phenyl group, especially by the electron-releasing conjugative substituent at the para-position. In the initial state, such a substituent increases the $d\pi$ -p π conjugation on the nitrogenbromine bond by the aid of the cross conjugation effect of the carbonyl group, as is indicated in Formula (II), and makes it more difficult to release the bromide ion from the reactant molecule.



On the other hand, in the transition state, the same electron-releasing conjugative substituent facilitates the additional conjugation of the phenyl group with electron-deficient

nitrogen, with a considerable stabilization of the transition state, and promotes the rate acceleration.

It is one of the purpose of the present study to examine the effect of the leaving group on the conjugation effects mentioned above. The logarithms of the relative rate constants of <u>meta</u>-and <u>para</u>-substituted <u>N</u>-chlorobenzamides have been plotted against those of <u>N</u>-bromoamides. An excellent linear relation has been observed except for the nitro group,⁸⁾ as shown in Fig. 2. The slope of the correlation line and its correlation coefficient are calculated as 0.97 and 0.9999 respectively. Furthermore, as may be anticipated from the above results, the application of the Linear Aromatic Substituent-Reactivity relationship (LArSR relationship; $\log \underline{k}/\underline{k}_{o} = \varrho(\underline{\sigma}^{\circ} + \underline{r}\underline{A}\overline{\underline{\sigma}}_{R}^{\pm})$) to the present data gives almost the same



values of the reaction constant, \underline{o} , and of the resonance parameter, \underline{r} , as those of the <u>N</u>-bromo series. These results obviously indicate that the

 $\log k/k_0 = -2.43(\sigma^0 + 0.41 \varDelta \overline{\sigma}_R) + 0.02$ conjugation effects in both the initial and the transition states are also important factors for the reaction of <u>N</u>chloroamides; furthermore, it

Fig. 2. Comparison of N-chloro with N-bromo derivatives.

may be concluded that the substituent effect for each conjugation effect is almost the same for both the <u>N</u>-chloro and <u>N</u>-bromo series. This conclusion does not conflict with the earlier estimation of the relative strength of the $d\underline{\mathcal{M}}$ - $p\underline{\mathcal{M}}$ conjugation of N-Cl and N-Br bonds; such a small difference in the strength of the $d\underline{\mathcal{M}}$ - $p\underline{\mathcal{M}}$ conjugation will not be so sensitively reflected in the substituent effect as to give a certain trend to the correlation plots.



Fig. 3. Application of the LArSR relationship.

It is also of interest to discuss the effect of the leaving group on the <u>ortho</u> effect. The <u>ortho/para</u> rate ratios for several substituents observed in Hofmann, Lossen and Curtius rearrangements are listed in Table 4. In the case of the <u>N</u>-bromo series, the <u>ortho/para</u> rate ratio varies over a considerably wide range, depending on the substituent, but it tends to decrease with an increase of the electron-attracting character of the substituent except for the methoxy group. This tendency appears also in the present <u>N</u>-chloro series and in the Lossen rearrangement. Another noticeable fact is the relative values of the activation parameters of <u>ortho-</u> and <u>para-substituents</u>. In both the <u>N</u>-chloro and <u>N</u>-bromo series, similar values of $\Delta M H^{\ddagger}$ and ΔS^{\ddagger} are observed in a given substituent except for nitro groups,⁹) as is shown in Table 5. These facts apparently indicate that the <u>ortho</u> effects in the Hofmann and the Lossen rearrangements are almost the same in every leaving group.

TABLE 4. ortho/para rate ratios $X-C_{6}H_{4}-CO-N^{-}-Y$							
				CI	NO ₂		
X/Y	Br	Cl			CO ₂ -	≥ N₂	
CH ₃ O	6.3		8.5			150.	
CH_3	21.0	24.3				131.	
Cl	4.2	5.3		5.9		208.	
Br	5.5	6.8		8.0		277.	
NO_2	1.5	1.9			2.2	70.	
	Table 5. Rei	LATIVE VALUES OF	ACTIVATION PARAM	IETERS OF ortho- TO	<i>para-</i> derivative	5	
	N-	Br	N-Cl		N-N ₂		
	$\Delta \Delta H^{\ddagger}$ (kcal/mol)	$\frac{\Delta \Delta S^{\pm}}{(e. u.)}$	$\Delta \Delta H^{\ddagger}$ (kcal/mol)	∆∆ 5 ≠ (e. u.)	$\Delta \Delta H^{\ddagger}$ (kcal/mol)	$\frac{\Delta\Delta S}{(e. u.)}$	
CH ₃ O	$+0.7\pm0.5$	$+5.9\pm1.8$					
CH3	-0.2 ± 0.2	$+5.2 \pm 0.6$	-0.8 ± 0.2	$+3.6\pm0.7$	-5.0 ± 0.3	$-6.4{\pm}0.8$	
Cl	$+1.0\pm0.2$	$+6.2 \pm 0.6$	$+0.6 \pm 0.0$	$+5.2 \pm 0.1$	-5.4 ± 0.6	-6.8 ± 1.9	
Br	$+0.7 \pm 0.1$	$+5.5 \pm 0.3$	$+0.6\pm0.1$	$+5.7 \pm 0.3$	-5.5 ± 0.2	-4.1 ± 0.7	
NO ₂	0.0 ± 0.8	$+0.8{\pm}2.5$	$+0.4{\pm}0.1$	$+2.4\pm0.4$	-3.1 ± 0.2	$-1.7{\pm}0.5$	

On the other hand, the Curtius rearrangement, of which leaving group is a nitrogen molecule, is expected to be considerably different from the Hofmann and the Lossen rearrangements with respect to the reaction mechanism. The structure of the transition state of the Curtius rearrangement is considerably closer to that of the initial state, since, in this rearrangement, a stable nitrogen molecule is released in the rate-determining step. The reactivity, therefore, depends greatly on the strength of the N-N₂ bond.¹⁰) In the case of an <u>ortho</u>-substituent, the bond-order of the N-N₂ bond is reduced by the steric restriction of the through conjugation of the phenyl group with the carbonyl group with an

- 41 -

elevation in the reactivity. The exclusive significancy of this Bond-energy effect on the Curtius rearrangement is evidently reflected in the <u>ortho</u> effects—the quite large <u>ortho/para</u> rate ratios and the enthalpy dependency of their rate ratios (see Tables 4 and 5). It is especially to be noted that the <u>ortho</u> effects on the Curtius rearrangement are in marked contrast to those on the Hofmann and the Lossen rearrangements, which are caused both by the bond-energy effect in the initial state and by the participation of the phenyl group migrating to nitrogen in the transition state.

References

- 1) G. R. Elliott, <u>J. Chem. Soc.</u>, <u>121</u>, 203 (1922).
- B. Altenkirk and S. S. Israelstam, <u>J. Org. Chem.</u>, <u>27</u>, 4532 (1962).
- 3) Chlorination with chlorine gas gave solely a pasty mass.
- 4) The induction period may be caused by the <u>N</u>-chlorination of the amide with hypochlorite at the initial stage of the reaction.
- 5) A. Streitwieser, Jr., "Solvolytic Displacement Reactions,"
 Mc Graw-Hill Book Company, Inc., New York (1962), p. 29;
 C. K. Ingold, "Structure and Mechanism in Organic Chemistry,"
 Cornell University Press, Ithaca and London (1969), p. 453.
- 6) W. B. Renflow and C. R. Hauser, <u>J. Amer. Chem. Soc.</u>, <u>78</u>, 5002 (1937); R. D. Bright and C. R. Hauser, <u>ibid.</u>, <u>61</u>, 618 (1939).
- 7) Although the data on the relative strength of the <u>dT-pT</u> conjugation on the nitrogen-halogen bond have not yet been reported, its relative strength may be presumed to be the order, F (C1 ≤ Br ≤ I, from that of <u>dT-pT</u> conjugation on the carbon-halogen bond; J. Hine and P. D. Langford, <u>J. Amer. Chem. Soc</u>., <u>78</u>, 5002 (1956); J. Hine, N. W. Burske, M. Hine, and P. D. Langford, <u>ibid</u>., <u>79</u>, 1406 (1957).

- 42 -

- 8) The deviations of the nitro groups are attributable to the uncertainty of the rate constants of the nitro- \underline{N} -bromobenz-amides.
- 9) The comparatively large disagreement of the nitro groups is caused by the uncertainty of the activation parameters of <u>N</u>bromoamides. The p-nitro-<u>N</u>-bromobenzamide did not obeyed first-order kinetics at 30°C due to accompanying hydrolysis of the reactant molecule itself, and the reaction rates were measured at 45-55°c where satisfactory first-order plots were obtained. The narrow temperature range and the side reaction may afford considerable uncertainty to the derived values of activation parameters. In the case of <u>o</u>-nitro-<u>N</u>-bromobenzamide the reaction rate gradually increased as the reaction proceeded, and the rate constants were calculated from the initial stage of the reaction. Therefore, the activation parameters of this derivative may be also attended with large uncertainty.
- 10) Y. Yukawa and Y. Tsuno, <u>J. Amer. Chem. Soc.</u>, <u>79</u>, 5530 (1957);
 Y. Yukawa and Y. Tsuno, <u>ibid.</u>, <u>80</u>, 6346 (1958).

۰.,

CHAPTER 4

KINETIC SUBSTITUENT EFFECTS OF 4- AND 5-SUBSTITUTED 2-CHLORO-<u>N</u>-CHLOROBENZAMIDES *

* This work was published under the title of "The Hofmann Rearrangement III," T. Imamoto, Y. Tsuno, and Y. Yukawa, <u>Bull. Chem. Soc. Japan</u>, <u>44</u>, 1644 (1971). As has been described in the preceding chapters, kinetic studies of the Hofmann rearrangement of <u>mono</u>-substituted <u>N</u>-bromoand <u>N</u>-chloro-benzamides were carried out with a view to elucidating its precise reaction mechanism. From the results, we concluded that the bond-energy effect in the initial state and the participation of the migrating phenyl group with electron-deficient nitrogen in the transition state were important factors in characterizing the rearrangement.

In order to establish the existence of the above two factors, a kinetic study of the rearrangement of 4- and 5-substituted 2chloro-<u>N</u>-chlorobenzamides has been undertaken, and a further attempt has been made to evaluate each of them semi-quantitatively on the basis of LFER.

In this chapter we will report these kinetic results, along with those of a few other disubstituted <u>N</u>-chlorobenzamides, and will discuss the reaction mechanism of the Hofmann rearrangement.

Experimental

<u>Materials</u>. <u>Disubstituted benzamides</u> were prepared by the usual methods and were identified by elementary analysis. The melting points of these amides are listed in Table 1.

<u>Disubstituted</u> N-<u>chlorobenzamides</u> were prepared by the methods described in the preceding chapter. The melting points and the analytical data of these <u>N</u>-chloroamides are listed in Table 1.

<u>Kinetic Measurements</u>. The reaction rates were determined according to the procedure described in the preceding chapter. The initial concentrations of <u>N</u>-chloroamide and sodium hydroxide employed were $0.025 \text{ mol}/\underline{1}$ and $0.5 \underline{N}$ respectively.

Results and Discussion

The rates of the release of the chloride ion from the

- 45 -

	A * 1	N-Chloroamides					
Subst.	Amides Mp °C	Mp °C			Analysis (Ca	lcd)	
		(lit a)	C%	H%	N%	Cl%	Act. Cl%
2-Cl-4-CH ₃ O	161.5-162.5	128.5—129.0	43.63 (43.67)	3.33 (3.21)	6.29 (6.37)	32.33 (32.22)	16.28 (16.11)
2-Cl-4-CH ₃	180—181	119—120	47.06 (47.09)	$3.45 \\ (3.46)$	6.84 (6.86)	34.58 (34.75)	17.21 (17.37)
2-C1-5-CH ₃	185.5-186.0	121-122	46.88 (47.09)	$3.39 \\ (3.46)$	6.83 (6.86)	34.62 (34.75)	17.13 (17.37)
2,4-di-Cl	193—194	136—137	37.41 (37.46)	1.71 (1.80)	6.13 (6.24)	47.20 (47.38)	15.79 (15.79)
2,5-di-Cl	160.0-160.5	158.0-158.5	37.29 (37.46)	1.77 (1.80)	6.00 (6.24)	47.20 (47.38)	15.64 (15.79)
2-Cl-4-NO ₂	171.0-171.5	190—200 (184—185)	35.97 (35.77)	1.67 (1.72)	12.19 (11.92)	30.24 (30.17)	14.56 (15.08)
2,6-di-Cl	202-203	190—192	37.52 (37.46)	1.87 (1.80)	6.42 (6.33)	47.50 (47.38)	15.64 (15.79)
3,5-di-Cl	161—162	198—200	37.59 (37.46)	1.71 (1.80)	6.33 (6.33)	47.20 (47.38)	15.44 (15.79)
3,5-di-Br	187	212-214	26.75 (26.83)	1.23 (1.29)	4.26 (4.47)		11.38 (11.31)
3,5-di-NO2	183—184	176—177 (168)	34.26 (34.23)	1.44 (1.64)	$17.28 \\ (17.11)$	14.31 (14.44)	14.16 (14.44)
2,5-di-Cl-4-CH ₃ b)		171—173	40.14 (40.29)	2.30 (2.54)	5.85 (5.87)	44.45 (44.59)	14.77 (14.86)

TABLE 1. DISUBSTITUTED BENZAMIDES AND THEIR N-CHLORO-DERIVATIVES

a) B. Altenkirk and S. S. Israelstam, J. Org. Chem., 27, 4532 (1962).

b) This N-chloroamide was obtained by the treatment of 2-chloro-4-methylbenzamide with chlorine gas under the same reaction condition as applied for the other amides.

conjugate bases of <u>multi</u>-substituted <u>N</u>-chlorobenzamides were measured under the same reaction conditions as those used in connection with the preceding kinetics of <u>mono</u>-substituted <u>N</u>-chlorobenzamides. All the runs except those of the 3,5-dinitro derivative strictly obeyed first-order kinetics, at least to 75% completion of the reaction.¹⁾ The reproducibility of the rate constant from repeated runs was within 0.7%, and the plots of $\log \frac{k}{T} \frac{vs}{s} \frac{1}{T}$ gave an excellent straight line in every case. The observed first-order rate constants are listed in Table 2. The rate constants at 30.00°C and the derived activation parameters are summarized in Table 3.

As a result of the previous kinetic studies of the Hofmann rearrangement of <u>mono</u>-substituted <u>N</u>-bromo- and <u>N</u>-chloro-benzamides, it was suggested that the bond-energy effect in the initial state and the participation of the phenyl group with electron-deficient nitrogen were important factors in controlling the reactivity. The most interesting point in connection with these two factors

			MANUELAL OF MALL-SUBSTITUTED AV-CHLOROBENZAMIDES
Subst.	Temp. °C	$k_1 \times 10^1 (\text{sec}^{-1})$	Subst. $k_1 \times 10^4$ ΔH^{\pm} ΔS^{\pm} (e. u.)
2-01-4-01130	$4.00 \\ 0.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{c} 2-\text{Cl}-4-\text{CH}_{3}\text{O} & 253^{\text{a}} \\ 2 \text{Cl}-4-\text{CH}_{3}\text{O} & 253^{\text{a}} \\ 2 \text{Cl}-4-\text{CH}_{3} & 25.05\pm0.14 & 16.8\pm0.47 \\ 2 \text{Cl}-4-\text{CH}_{3} & 25.05\pm0.14 & 16.8\pm0.47 \\ 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} \\ 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} \\ 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} \\ 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} & 2 \text{Cl}-4-\text{CH}_{3} \\ 2 \text{Cl}-4-\text{CH}_{3}$
2-Cll-CH ₃	17.00 13.00	6.478 ± 0.016 3 358 ± 0.006	2-Cl-4-CH ₃ $+3.8^{a_1}$ $26.3/\pm0.03$ 18.52 ± 0.11 2-Cl-5-CH ₃ 21.46^{a_1} 27.02 ± 0.01 18.37 ± 0.03
	10.00	2.021 ± 0.005 0.8150 ± 0.0016	2,4-di-Cl 5.446 27.44 \pm 0.04 17.04 \pm 0.14
	0.00	0.8439 ± 0.0018 0.4995 ± 0.0011	$2,0.39$ 27.86 ± 0.05 16.48 ± 0.16 $2-Cl-4-NO_{2}$ 0.2675 29.19 ± 0.06 16.82 ± 0.21
2-Cl-5-CH ₃	20.00	4.495 ± 0.008	2,6-di-Cl 2.829 28.55 ± 0.04 19.39 ± 0.12
	10.00	1.976 ± 0.002 0.8443 ± 0.0016	3,5-di-Cl 0.1715 28.10±0.04 12.33±0.14
	0.00	0.3495 ± 0.0003	$2,5-di-Cl-4-CH_{2}$ 7.226 27.94 ± 0.03 12.20 ± 0.11 $2,5-di-Cl-4-CH_{2}$ 7.226 27.04 ± 0.05 16.29 ± 0.15
2,4-di-Cl	$\begin{array}{c} 30.00 \\ 25.00 \end{array}$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	a) Extrapolated from data at other temperatures.
	$20.00 \\ 15.00$	1.118 ± 0.002 0.4822 ± 0.00004	
2,5-di-Cl	35.00	4.406 ± 0.003	consists in the effects of the
,	$30.00 \\ 25.00 \\ 20.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	para-substituted electron-re-
2-Cl-4-NO ₂	45.00	2.755 ± 0.006 1 311 ± 0.002	leasing conjugative groups on
	35.00 30.00	$\begin{array}{c} 0.5979 \pm 0.0006 \\ 0.2675 \pm 0.0003 \end{array}$	the reactivity. In the transi-
2,6-di-Cl	35.00 30.00	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	tion state these substituents
	25.00 20.00 15.00	1.259 ± 0.0009 0.5453 ± 0.0003 0.2270 ± 0.0002	facilitate the additional con-
3,5-di-Cl	$\begin{array}{c} 50.00\\ 45.00\end{array}$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	jugation of the phenyl group
	$\begin{array}{c} 40.00\\ 30.00 \end{array}$	0.7902 ± 0.0007 0.1715 ± 0.0002	with electron-deficient nitro-
3,5-di-Br	$50.00 \\ 45.00$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	gen, with a considerable stabi-
	$\begin{array}{c} 40.00\\ 30.00 \end{array}$	$\begin{array}{r} 0.9545 \ \pm \ 0.0008 \\ 0.2084 \ \pm \ 0.0003 \end{array}$	lightion of its state. In the
2,5-di-Cl-4-CH ₃	30.00	7.23 ± 0.01	iization of its state. In the
	25.00 20.00 15.00	3.354 ± 0.004 1.518 ± 0.002 0.6620 ± 0.0009	initial state, however, such
			substituents increase the bond-

TABLE 2. RATE CONSTANTS OF THE HOFMANN REAR-RANGEMENT OF *mulli*-substituted N-chlorobenzamides

TABLE 3. KINETIC RESULTS OF THE HOFMANN REAR-RANGEMENT OF multi-substituted N-chlorobenzamide

order of the nitrogen-halogen bond through the cross-conjugation of the carbonyl group with the phenyl group and with the nitrogen orbital, and lead to a rate retardation with a stabilization of the initial state. The former conjugation effect is expected to give a comparatively large positive value of the resonance parameter, \underline{r} , of the LArSR relationship, whereas the latter effect will rather afford a negative \underline{r} -value. The resonance parameter (\underline{r} =0.41) for the rearrangement of <u>mono</u>-substituted <u>N</u>-chlorobenzamides can be qualitatively interpreted in terms of the mutual compensation of the conjugation effects in the initial and the transition states. In order to establish these theories, it is necessary to ascertain the substituent effect in a system where the amide group is sufficiently hindered from conjugating with the phenyl group in the initial state, and so the kinetic study of 4- and 5-substituted 2-chloro-N-chlorobenzamides has been undertaken. The chloro group at the <u>ortho</u>-position has been chosen as the most suitable group in satisfying the following requirements: sufficient steric effect to restrict the through-conjugation of the amide group with the phenyl group in the initial state, measurable rates, and the easily-available amides.

The logarithms of the relative rate constants of the present 2-chloro series have been plotted against those of the preceding 2-unsubstituted series. As is illustrated in Fig. 1, all the <u>meta-</u> substituents and the <u>para-nitro</u> substituent form an excellent straight line with a slope of 0.930 and a correlation coefficient of 0.9999, whereas the electron-releasing conjugative substituents at the <u>para-position</u> deviate upward from the correlation line. Each deviation, however, appears to be proportional to electronreleasing conjugative ability of its substituent. In fact, the least-mean-square calculation using the values of the electron-



Fig. 1. Comparison with 2-unsubstituted derivatives.



Fig. 2. Comparison with 2-unsubstituted derivatives with the application of the LArSR relationship.

- 48 -

releasing conjugative ability $(\Delta \bar{e}_R^+)^{2}$ gives an excellent straight line with a correlation coefficient of 0.9999, including all the <u>para</u>-substituents, as is shown in Fig. 2. The slope of the correlation line is 0.930, which is the same as that calculated from all the <u>meta</u>-substituents and the <u>para</u>-nitro substituent. This fact evidently indicates that the reactivity of the 2-chloro series that is subjected to a larger additional conjugation effect than \bigwedge_{0} of the 2-unsubstituted series. The application of the LArSR relationship



Fig. 3. Application of the LArSR relationship.





to the present data gives a good linearity, as is shown in Fig. 3. Although the calculated reaction

$$\log k/k_0 = -2.21(\sigma^0 + 0.69 \varDelta \overline{\sigma}_R^+) + 0.03$$

constant ($\underline{\varrho}$ =-2.21) is nearly equal to the value of the 2-unsubstituted series ($\underline{\varrho}$ =-2.43), the resonance parameter (\underline{r} =0.69) is considerably larger than that of the 2-unsubstituted series (\underline{r} =0.41).

The conjugations applicable p. to the initial state are visualized The through-conjugation of the carbonyl

group with the phenyl group is remarkably restricted in the 2-chloro system (I), while it is not in the 2-unsubstituted system (II). The substituent effect on this conjugation effect

in the 2-chloro series, therefore, is expected to be smaller than that in the 2-unsubstituted series.

On the other hand, in the transition state the degree of the conjugation in both series depends on the reaction mechanism (or on

- 49 -



the structure of the transition state). In the two-step mechanism, the conjugation of the phenyl group with the amide group is restricted in the 2chloro system (III), but not in the 2-unsubstituted system (IV). On the contrary, in the concerted mechanism the degree of the conjugation may be expected to be almost the same for both the 2-chloro and 2-unsubstituted system (V and VI), since in this state

the phenyl ring is twisted almost at a right angle to the amide group due to the effective overlap of orbitals.

If the reaction proceeds through the two-step mechanism, the reactivity of the 2-chloro series should be considerably affected by the steric restriction of the conjugation in both the initial and transition states. The substituent effect of the conjugation effect on the 2-chloro series is expected to be smaller than that on the 2-unsubstituted series; the r-value of the 2-chloro series should be smaller than the value (0.41) of the 2-unsubstituted series. On the other hand, if the reaction proceeds through the concerted mechanism, the r-value to be observed on the 2-chloro series will be larger than the value of the 2-unsubstituted series, since the effect of the conjugation in the transition state is almost the same for both the 2-chloro and 2-unsubstituted series; further, the substituent effect on the conjugation effect in the initial state is reduced for the 2-chloro series more than for the 2-unsubstituted series. The comparatively large positive <u>r</u>-value (0.69) resulting in the 2-chloro series strongly supports the concerted mechanism rather than the two-step mechanism.

It is of interest to discuss the effect of the introduction

- 50 -

of the chlorine atom into the <u>ortho</u>-position in relation to the above discussion of the substituent effect of 4- and 5-substituted 2-chloro-<u>N</u>-chlorobenzamides. The relative reactivities among unsubstituted, 2-chloro, 4-chloro, 2,4-dichloro, and 2,6-dichloro derivatives are listed in Table 4. The first introduction of the chlorine atom at the <u>ortho</u>-position effects a small rate acceleration ($\underline{k}_{2-C1}/\underline{k}_{H} = 1.6$), whereas the second one at another <u>ortho</u>-position effects rather a rate retardation ($\underline{k}_{2,6-diC1}/\underline{k}_{2-C1} = 0.22$). The steric rate effect of the <u>ortho</u>-substituent can be

TABLE 4.	
k_{2-C1}/k_{H}	= 1.6
$k_{2,6-d1-C1}/k_{H}$	= 0.35
$k_{2,6-di-Cl}/k_{2-Cl}$	= 0.22
k_{2-C1}/k_{4-C1}	= 5.3
$k_{2,6-d1-C1}/k_{2,4-d1-C1}$	= 0.52

qualitatively evaluated by means of the <u>ortho/para</u> rate ratios, since the polar effect of the <u>ortho</u>-substituent is generally recognized to

be nearly equal to that of the corresponding <u>para</u>-substituent. The $\underline{k}_{2-C1}/\underline{k}_{4-C1}$ value of the present reaction is calculated to be 5.3, indicating considerable steric acceleration due to the first introduction of the <u>ortho</u>-chloro substituent. The value of $\underline{k}_{2,6-diC1}/\underline{k}_{2,4-diC1}$, which corresponds to the steric rate effect due to the other <u>o</u>-chloro substituent, is calculated to be 0.52, indicating that the steric effect of the other <u>o</u>-chloro substituent ent affords a rather small rate retardation.

From these results, it would be reasonable to consider that the first introduction of the chloro substituent at the <u>ortho</u>-position effects a large steric effect to restrict the conjugation of the phenyl group with the carbonyl group considerably. The observed value of the resonance parameter of the 2-chloro series, therefore, may be attributed for the most part to the conjugation effect in the transition state. This value can be compared with the <u>r</u>value of the Beckmann rearrangement, the reaction mechanism of which is estimated to be a concerted one. The <u>r</u>-value of the Beckmann rearrangement under various conditions has been calculated

- 51 -

to be <u>ca</u>. 0.65. If the substituent effect on the conjugation in the transition state of the Hofmann rearrangement has an <u>r</u>-value of about 0.7, the effect of the <u>d</u> π -<u>p</u> π conjugation in the initial state in the 2-unsubstituted series might be estimated to be <u>ca</u>. -0.3 as a resonance parameter by the subtraction of the value of 0.7 from the observed <u>r</u>-value (0.41) of the 2-unsubstituted series. This estimated <u>r</u>-value of the bond-energy effect due to the <u>d</u> π -<u>p</u> π conjugation of the nitrogen-chlorine bond is reasonable as compared with the observed <u>r</u>-values of the Curtius and the Wolff rearrangements, which are characterized exclusively by the bond-energy effect of the N-N₂ bond.³

It is also of interest to discuss the substituent effects on the Hofmann rearrangement in terms of the derived activation parameters. The plots of $\underline{A} \underline{H}^{\ddagger} \underline{vs}$. $\underline{AS}^{\ddagger}$ are shown in Fig. 4, along with those of the meta- and para-substituents of the 2-unsubstituted



series studied previously. In the case of the 2-unsubstituted series the enthalpy of activation varies from <u>ca</u>. 24.5 to <u>ca</u>. 28.5 kcal, although the entropy of activation varies merely from <u>ca</u>. 13 to <u>ca</u>. 15 e.u. This enthalpy dependency of the substituent effect on the reactivity is presumably caused both by the bond-energy effect in the initial

state and by the additional conjugation effect of the phenyl group in the transition state, rather than by the solvation effect. The solvation effect is surely considered to play an important role in the reactivity; however, the substituent effect on it appears to be almost the same throughout the series. Another noticeable

- 52 -

fact is shown by the plots of the 2-chloro series, which form a pattern similar to that of the 2-unsubstituted series, though they deviate in parallel fashion by <u>ca</u>. 3 e.u. and <u>ca</u>. 0.5 kcal from the corresponding plots of the 2-unsubstituted series. This fact shows that the reaction mechanism of the 2-unsubstituted and 2chloro series are substantially the same. In the 3,5-dichloro and 3,5-dibromo derivatives, excellent additivities are found not only in the free energy of activation but also in the entropy and the enthalpy of activation. These additivities also indicate that the reaction mechanism of this rearrangement does not change with the change in the polar effect, at least not in the cases examined. The 2,6-dichloro derivative, however, does not retain any additivity. The failure of the additivity in the free energy of activation may be attributed to the entropy of activation, as is indicated in Fig. 4. The entropy gain caused by the concerted mechanism is perhaps saturated by the first introduction of the chlorine atom. The second introduction will afford rather rate retardation because of the additional polar effect.

References

- In the case of 3,5-dinitro derivative excellent first-order plots were not obtained especially at the temperature lower than 45°C. This anomaly is presumably caused by accompanying the hydrolysis of the reactant conjugate base of <u>N</u>-chloroamide.
- Y. Yukawa, Y. Tsuno, and M. Sawada, <u>Bull. Chem. Soc. Japan</u>, <u>39</u>, 2274 (1966).
- 3) The <u>r</u>-values of the Curtius rearrangement in toluene and of the Wolff rearrangement in toluene are -1.04 and -1.7, respectively; Y. Yukawa and Y. Tsuno, <u>J. Amer. Chem. Soc.</u>, <u>79</u>, 5530 (1957); Y. Yukawa and Y. Tsuno, <u>ibid.</u>, <u>80</u>, 6346 (1958);

- 53 -

Y. Yukawa, Y. Tsuno, and T. Ibata, <u>Bull. Chem. Soc. Japan</u>, <u>40</u>, 2613 (1967); Y. Yukawa, Y. Tsuno, and T. Ibata, <u>ibid.</u>, <u>40</u>, 2618 (1967).

•

CHAPTER 5

KINETIC ISOTOPE EFFECT OF <u>N</u>-CHLOROBENZAMIDE *

,

* This work was published under the title of
"The Hofmann Rearrangement IV," T. Imamoto, S. G. Kim,
Y. Tsuno, and Y. Yukawa, <u>Bull. Chem. Soc. Japan</u>, <u>44</u>,
2776 (1971).

- 55 -

The most important stage in the course of the Hofmann reaction is the rearrangement step in which the conjugate base of <u>N</u>haloamide is converted into isocyanate accompanying the release of a halide ion. With a view to clarifying the precise reaction mechanism of this step, we have investigated this rearrangement kinetically. Kinetic results of the rearrangements of various substituted <u>N</u>-bromo- and <u>N</u>-chlorobenzamides in an aqueous sodium hydroxide solution have been reported. These results could be interpreted by considering a concerted mechanism (path (A)) rather than an alternative two-step mechanism (path (B)).



We have now studied the kinetic isotope effect of this rearrangement using phenyl-1- 14 C and carbonyl- 14 C labeled <u>N</u>-chlorobenzamides in order to demonstrate this concerted mechanism.

Results and Discussion

The rate of the rearrangement of the non-labeled <u>N</u>-chlorobenzamide was measured at $15.00\pm0.01^{\circ}$ C by the iodometric method. The initial concentrations of <u>N</u>-chloroamide and sodium hydroxide were 0.05 <u>M/1</u> and 0.5 <u>N</u>, respectively.¹⁾ The first-order kinetic plots formed straight line to at least 85% completion of the reaction. The rate constant obtained from repeated runs was <u>k</u>₁=7.830 $\pm 0.009 \times 10^{-5} \text{ sec}^{-1}$. This value is larger by <u>ca</u>. 1% than the one reported previously. The slight difference in the rate constant refers to the change of the initial concentration of <u>N</u>-chloroamide from 0.025 to 0.05 <u>M/1</u>.

Determination of the kinetic isotope effect was carried out

- 56 -

under the same reaction conditions by measuring the specific activities of the benzamide derived quantitatively from the remaining reactant N-chlorobenzamide. Labeled N-chlorobenzamide, prepared from commercial benzoic-¹⁴C acid, was dissolved in an aqueous sodium hydroxide solution. A certain amount of the reaction solution was pipetted out at intervals and transferred into hydrochloric acid containing excess potassium iodide. After reduction of the liberated iodine with a sodium thiosulfate solution, the benzamide was extracted and purified by recrystallization. The specific activity of the benzamide thus obtained was determined by an equilibrium voltage method with an ionization chamber and a vibrating reed electrometer connected to a digital integrating voltmeter. These results are listed in Table 2. The kinetic isotope effect was calculated by the least-squares method according to the equation

$$\log A_x = \log A_0 - (1 - k_{14}/k_{12}) \log (1 - x) \tag{1}$$

where <u>x</u> is the fraction of reaction calculated from the reaction time and the rate constant ($\underline{k}_1 = 7.830 \times 10^{-5} \text{ sec}^{-1}$), and \underline{A}_x and \underline{A}_o are specific activities at $\underline{x} = \underline{X}$ and $\underline{x} = 0$ respectively. Fig. 1 shows the plots of the log \underline{A}_x <u>vs</u>. log(1-<u>x</u>). The calculated



kinetic isotope effect on the phenyl-l-carbon is given by $k_{12}/k_{14} = 1.0456 \pm 0.0012$

and that on the carbonyl-carbon by $k_{12}/k_{14} = 1.0447 \pm 0.0006$

Theoretical and experimental studies on the isotope effect lead to the conclusion that the variation of bonding at a labeled position from the initial state

 t_0 the transition state in the rate-determining step is the most

- 57 -

important factor to cause a kinetic isotope effect.^{2,3)} Thus it is necessary, for elucidation of the precise reaction mechanism of the present Hofmann rearrangement, to examine the variations of the total bondings at respective labeled positions in <u>N</u>-chlorobenzamide for the proposed mechanisms.

The initial and the transition states for the concerted and two-step mechanisms may be schematically represented as follows.



In the former mechanism, bondings at the labeled positions change remarkably in proceeding from initial to transition states, and measurable kinetic isotope effects can be expected in this mechanism. On the contrary, if the reaction proceeds through the two-step mechanism, no apparent kinetic isotope effect should be observed, since the transition state resembles the initial state with respect to the bondings at labeled positions.

Thus the apparent kinetic isotope effects on phenyl-1- and carbonyl-carbons evidently indicate the concerted mechanism for the Hofmann rearrangement.⁴⁾

In addition to the present Hofmann rearrangement, the kinetic isotope effects of Beckmann, Wolff and Schmidt rearrangements have been studied in our laboratory by the use of phenyl-1-¹⁴C and carbonyl-¹⁴C labeled compounds. The obtained results are summarized in Table 1. An important working hypothesis in the course

- 58 -

of these studies is that the apparent observation of the kinetic isotope effect on phenyl-l-carbon indicates the participation of the phenyl group with electron-deficient migration terminus in the transition state. This suggest the Hofmann and the Beckmann rearrangements proceed through a concerted type transition state. In the cases of other Wolff and Schmidt rearrangements, where kinetic isotope effects on the phenyl-l-carbon were not observed within experimental error, the migration of the phenyl group might not take place in the rate-determining step.

On the other hand, application of the following LArSR relationship (linear aromatic substituent-reactivity relationship) is useful to elucidate the mechanism of organic reactions. In particular, empirical facts on the resonance parameter r have enabled

$$\log \underline{k}/\underline{k}_{O} = \varrho \left(\underline{\sigma}^{\circ} + \underline{r} \Delta \overline{\underline{\sigma}}_{R}^{+} \right)$$
(2)

.

to evaluate quantitatively the degree of conjugation effect us on the reactivity.5)

The calculated r-values of Hofmann, Beckmann and Wolff rearrangements are given in Table 1. Comparatively large positive

· · · · · · · · · · · · · · · · · · ·	Temp. (°C)	Phenyl-1-C	Carbonyl-C k_{12}/k_{14}	r-Value
Hofmann rearrangement	15.00±0.01	1.0456±0.0012°)	1.0447 ± 0.0006^{a}	0.41^{0} $(0.69)^{h}$
Beckmann	60.00 ± 0.01	1.018 ±0.009め		
rearrangement	60.00 ± 0.01	1.025 ± 0.008^{b}		0.6329
6	40.00 ± 0.01	1.026 ± 0.003^{b}		0.6001)
	71.30 ± 0.01	$1.052 \pm 0.017^{\circ}$	$1.00 \pm 0.01^{\circ}$	
Wolff rearrangement	30.00 ± 0.01	1.00 ± 0.01^{d}	1.00 ± 0.01^{d}	-1.7^{k}
Schmidt	45.00 ± 0.01	$1.00 \pm 0.02^{\circ}$	$1.045 \pm 0.02^{\circ}$	
rearrangement	45.00 ± 0.01		1.066 ± 0.022	

TABLE 1	ι.	KINETIC ISOTOPE EI	FFECTS AND	r-values of 1	,2-REARRANGEMENTS

a) Present results. b) Acetophenone oxime, in coned. H₂SO₄. Y. Yukawa, S. G. Kim, T. Ando, and T. Kawakami, unpublished.

c) Acetophenone oxime-acetate, in Beckmann mixture. Y. Yukawa and S. G. Kim, unpublished.

d) a-Diazoacetophenone, in t-butyl alcohol containing silver benzoate and triethylamine. Y. Yukawa : d T. Ibata, This Bulletin, 42, 802 (1959).

c) Acetophenone, in aqueous trichloroacetic acid containing sodium azide. Y. Yukawa and K. Toriyama, unpublished.
f) Benzophenone, in aqueous trichloroacetic acid containing sodium azide. Y. Yukawa and K. Toriyama apublished.

g) N-Chlorobenzamides, in 0.5 N NaOH, at 30°C. Ref. 2. h) 2-Chloro 4- and 5-substituted N-chlorobenzamides, in 0.5 N NaOII, 30°C. Ref. 3.

i) Acetophenone oximes, in sulfuric acid, 51°C. P. J. McNulty and D. E. Pearson, J. Amer. Chem. Soc., 81, 612 (1959). j) Acetophenone oxime-picrates, in dichlorobutane, 70°C. R. Huisgen, J. Witte, H. Walz, and W. Jira, Ann. Chem., 604, 191 (1957).

k) a-Diazoacetophenones, in toluene containing silver benzoate and triethylamine. Y. Yukawa, Y. Tsuno, and T. Ibata, This Bulletin, 40, 2618 (1967).

<u>r</u>-values of the former two rearrangements indicate the additional conjugation effect to the reaction center with the stabilization of the transition state. In contrast, the large negative <u>r</u>-value of the Wolff rearrangement shows that the resonance stabilization of the initial state is the most important factor in the reactivity.

It is of interest to compare these \underline{r} -values with the kinetic isotope effects on phenyl-l-carbons. The positive \underline{r} -value indicates an apparent isotope effect and the large negative \underline{r} -value no effect. This leads to the conclusion that not only the application of the LArSR relationship but also the isotope effect study on phenyl-lcarbon are useful for the elucidation of the precise reaction mechanism of 1,2-rearrangement.

Experimental

N-Chlorobenzamide-(Phenyl- $1-^{14}$ C). Materials. A mixture of 10.0 g of phenyl-1-¹⁴C labeled benzoic acid (supplied from NENC, USA) and 27 g of purified thionyl chloride was refluxed for 2 hr. The excess thionyl chloride was removed by azeotropic distillation adding twice 10 ml of absolute benzene. The benzoyl chloride obtained was added dropwise to 70 ml of 28% aqueous ammonia with stirring at 0-5°C. The benzamide precipitated was collected, washed with water and dried, mp 126.5-127.5°C. yield 8.11 g (82%). This crude amide was recrystallized three times from dichloroethane-ligroin (1:1), 6.60 g, mp 127.5-128.5°C. Specific activity 2.830 mCi/mol. The obtained pure amide (6.37 g) was dissolved in 400 ml of 3 N HCl and chlorine gas was passed for The N-chloro derivative thus precipitated was collected, 2 hr. washed with water and dried in vacuo, 6.91 g (84%), mp 114-116°C. This was recrystallized twice from dichloroethane-ligroin (1:2), 5.38 g, mp 117.0-118.0°C (reported 117.0-118.0°C). Active chlorine: found 22.85%, calcd. 22.79%. Specific activity 2.830 mCi/mol. - 60 -

N-<u>Chlorobenzamide-(Carbonyl-¹⁴C)</u>. Carbonyl-¹⁴C labeled benzoic acid (supplied from RCC, England) (10.0 g) was converted into <u>N</u>-chlorobenzamide (4.95 g) by the same procedure as described in the preceding part. Benzamide: mp 127.5-128.5°C, specific activity 2.961 mCi/mol. <u>N</u>-chlorobenzamide: mp 117.0-118.0°C, specific activity 2.960 mCi/mol, active chlorine; found 22.73%, calcd. 22.79%.

No mutual contamination of the phenyl-l- 14 C and the carbonyl- 14 C labeled <u>N</u>-chlorobenzamides was indicated by comparing the specific activities of the derived acetanilides with those of the respective reactant <u>N</u>-chlorobenzamides- 14 C.

Determination of the Rate Constant. Kinetic Procedure and Preparation of the Sample for Assay. In a measuring flask was placed 400 ml of a standardized aqueous sodium hydroxide solution (0.500 N), and the flask was immersed in a constant temperature bath (15.00+0.01°C). Labeled N-chlorobenzamide (3.112 g) was weighed into a 500-ml Erlenmeyer flask and immersed in the same bath. After being kept for several hr, the sodium hydroxide soluwith tion was transferred into the Erlenmeyer flask Avigorous swirling. A certain amount of the reaction solution was pipetted out at intervals and transferred into 15 m $\underline{1}$ of 6 \underline{N} HCl containing 700 mg of potassium iodide. A sodium thiosulfate solution (0.3 N) was added dropwise until the color of the liberated iodine disappeared. The residual unrearranged benzamide was extracted with five 50 ml portions of dichloromethane. The solvent was evaporated and the residue was stirred with 50 ml of dichloroethane. A small amount of the undissolved salts was excluded by filtration. The filtrate was evaporated to give pale yellow needles, ca. 120 mg, mp 125-127°C. This was recrystallized five times from toluene to afford 40-50 mg of sample for assay, colorless plates, mp 127.5-128.5°C.

- 61 -

<u>Measurements of Specific Activity</u>. About 7-8 mg of accurately weighed benzamide-¹⁴C was burned by means of a combustion furnace for micro-elemental analysis, and the carbon dioxide gene-

TABLE	2.	Specific	ACTIV	TTIES	OF	RESIDUAL
	UN	REARRAN	GED BE	ENZAN	AIDE	5

No. Time		Frac- tion of	Specific f (mCi/	activity mol)
1.0.	(min)	reac- tion (%) Phenyl-1- ¹⁴ C	Carbonyl-14C
1	0	0	2.8404 ± 0.0024^{a}	2.9567±0.0016*)
2	57.1	23.5	2.8666 ± 0.0014	2.9877 ± 0.0024
3	114.2	41.5	2.9011 ± 0.0022	3.0257 ± 0.0033
4	171.3	55.3	2.9357 ± 0.0024	3.0629 ± 0.0020
5	228.4	65.8	2.9805 ± 0.0010	3.0914±0.0016
6	285.5	73.9	3.0101 ± 0.0011	3.1287 ± 0.0004
7	342.6	80.0	3.0389 ± 0.0029	3.1690 ± 0.0040

a) The sample was obtained by treatment of pure N-chlorobenzamide with potassium iodide in aqueous acetic acid. rated was introduced into a 200-m<u>1</u> ionization chamber. The chamber was set on a Takeda-Riken RS-84 vibrating reed electrometer connected to a digital integrating voltmeter. The ion current was recorded as relative voltage every ten

seconds for 1 hr, and the mean value of the voltage was obtained with the standard deviation of $\pm 0.2\%$. The radio activity of the sample was calculated by calibrating of the obtained voltage with that of the standard chamber. Specific activity measurements were carried out at least twice for each sample. Reproducibility of the specific radioassay was within 0.25% in every case. The results are given in Table 2. The error indicates the standard deviation from the mean value.

<u>References</u>

- From the results of the preliminary experiment on the recovery and the purification of the residual unrearranged benzamide,
 0.05 M/1 was employed as the most suitable initial concentration of N-chloroamide.
- J. Bigeleisen and M. Wolfsberg, "Advanced in Chemical Physics,"
 <u>1</u>, 15 (1958).
- 3) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press Co., New York, N. Y. 1960.
- 4) Wright and Fry studied the kinetic isotope effect of the Hofmann rearrangement using phenyl-1-¹⁴C and carbonyl-¹⁴C labeled

- 62 -

 \underline{N} -bromobenzamides, and also supported the concerted mechanism. Their results, however, have not yet been published. A. Fry, private communication.

5) Y. Yukawa, Y. Tsuno, and M. Sawada, <u>Bull. Chem. Soc. Japan</u>, <u>39</u>, 2274 (1966); Y. Yukawa and Y. Tsuno, <u>Nippon Kagaku Zasshi</u>, <u>86</u>, 783 (1965).

CHAPTER 6

(SUPPLEMENTARY TREATISE)

THE FORMATION OF BENZOYL CHLORIDES FROM 1,2-DIBENZOYL-HYDRAZINES OR DIBENZOYLDIIMIDES *

* T. Imamoto, Bull. Chem. Soc. Japan, in press.

•

The reaction of acid hydrazide with chlorine was reported by Carpino.^{1,2)} He obtained acid chlorides in good yields from the corresponding hydrazides by successive treatments with hydrogen chloride and chlorine. Later, Kissinger and Ungnade showed that the prior conversion of acid hydrazide to the hydrochloride was not necessarily needed.³⁾

The path of the reaction was proposed by Carpino, as in the following scheme (1).²⁾ This mechanism appears to be reasonable, $\begin{array}{c} \text{R-CONHNH}_2 \xrightarrow{\text{HC1}} & \text{R-CONHNH}_3 \text{C1} \xrightarrow{\text{C1}_2} \\ \hline & & \\ \text{(R-CO-N=N-C1)} \xrightarrow{\text{-N}_2} & \text{R-COC1} \end{array}$

(1)

for his reaction conditions. However, in the cases of no concomitant addition of hydrogen chloride (Kissinger's conditions), the reaction seems not to proceed solely through the above path (1).

In order to clarify the reaction paths, we first carried out the isolation of the intermediates under the Kissinger's conditions, using benzoylhydrazine as a representative acid hydrazide.

When benzoylhydrazine was treated with chlorine in nitromethane without prior conversion to the hydrochloride, large amounts of white precipitates appeared at the initial stage of the reaction. These precipitates completely disappeared by further introduction of chlorine to give benzoyl chloride in good yield (78%). The precipitates were identified as the mixture of benzoylhydrazine hydrochloride and 1,2-dibenzoylhydrazine (mol ratio: ca. 4:1).

On the other hand, no 1,2-dibenzoylhydrazine was detected at any stage of the reaction under the Carpino's conditions.

These results indicate that not only benzoylhydrazine hydrochloride but also 1,2-dibenzoylhydrazine may be the precursors of benzoyl chloride under the Kissinger's conditions. This was supported by the result of the reaction of pure 1,2-dibenzoylhydrazine with excess chlorine in nitromethane or dichloromethane; benzoyl chloride was obtained in the yields of 76% and 82% in respective - 65 -

solvents.

Further, several 1,2-bis(substituted benzoyl)hydrazines were allowed to react with chlorine. Table 1 shows the yields of the corresponding chlorides obtained. In the cases of <u>m</u>-chloro and <u>p</u>-chloro derivatives, the reaction rates were fairly slow, and the chlorides were scarcely obtained.

It is well known 1,2-diaroylhydrazine is oxidized by halogen to afford diaroyldiimide. $^{4,5)}$ This suggests that dibenzoyldiimide is also the precursor of benzoyl chloride. Thus, we treated dibenzoyldiimide with chlorine in the same solvents as the cases of the preceding dibenzoylhydrazines. The reaction proceeded quite smoothly at room temperature. The yields of benzoyl chloride are also shown in Table 1, along with those of other chlorides.

These results lead to the conclusion that 1,2-diaroylhydrazine and diaroyldiimide are also the precursors of the corresponding acid chloride. In other words, acid chloride is formed through the paths (1) and (2), under the Kissinger's conditions.⁶⁾

 $2 \text{ R-CONHNH}_2 \xrightarrow{\text{Cl}_2} \text{ R-CONHNHCO-R} \xrightarrow{\text{Cl}_2} \text{ R-CONHNHCO-R} \xrightarrow{\text{Cl}_2} \text{ (2)}$

Experimental

<u>Isolation of Intermediates.</u> Into a solution of 3.91 g of benzoylhydrazine in 120 m<u>l</u> of anhydrous nitromethane, dry chlorine gas was passed at about 0.5 m<u>l</u>/sec with stirring for 5 min. The white precipitates thus formed were collected, washed with nitromethane, and dried. This material (1.99 g) was then triturated with 40 m<u>l</u> of water, followed by filtration leaving colorless powder (0.43 g), mp 238-240°C. The filtrate was evaporated to afford colorless crystals (1.50 g), mp 192-194°C(decomp.).

The two substances above separated were identified, as 1,2dibenzoylhydrazine and benzoylhydrazine hydrochloride, respectively,

- 66 -

	X-C ₆ H ₄ -CON	HNHCO-C ₆ H ₄ -X	X-C ₆ H ₄ -CON=N	NCO-C6 ^H 4-X	
Solvent X	CH ₃ NO ₂	CH ₂ Cl ₂	CH ₃ NO ₂	CH2C12	
Н	76%	82% ^a)	79%	89%	
<u>р</u> -сн ₃ о	87 ^{c)}	49 ^{b)} _{+ 44} c)	11 ^{b)} + 81 ^c)	93 ^b)	
P-CH3	82	87	86	91	
<u>o</u> -CH ₃	81	90	81	90	
<u>o</u> -C1	79	88			

a) The reaction time was 10-30 hr at room temperature.

c) 3-Chloro-4-methoxybenzoyl chloride.

b) p-Anisoyl chloride.

by comparing their infrared spectra with those of authentic samples.

<u>1,2-Dibenzoylhydrazines.</u> These were prepared by the usual method.⁷⁾ Melting points of new hydrazines are as follows: 1,2-bis(<u>o</u>-methylbenzoyl)hydrazine, 219-220°C; 1,2-bis(<u>o</u>-chlorobenzoyl) hydrazine, 219-221°C; 1,2-bis(<u>m</u>-chlorobenzoyl)hydrazine, 272-274°C.

<u>Dibenzoyldiimides.</u> General procedures are as follows. 1,2-Dibenzoylhydrazine (0.20 mol) was saturated in dimethylformamide. Bromine (48 g, 0.30 mol) was added dropwise into this solution with vigorous stirring for 10 min. After the addition of bromine, stirring was continued for 2 hr, and then the reaction mixture was poured into <u>ca</u>. 3 <u>1</u> of ice-water. The precipitated solid was collected, washed with water, and dried <u>in vacuo</u> at 50-60°C. The yield of the crude product was 87-94%. This crude diimide was recrystallized from n-hexane-benzene(2:1).

Melting points of bis(substituted benzoyl)diimides are as follows: H, 119-121°C (lit,⁸⁾119.5-121.5°C); <u>p</u>-CH₃O, 136-137°C (lit,⁸⁾131.5-132.0°C); <u>p</u>-CH₃, 120-121°C (lit,^{5e)}118°C); <u>o</u>-CH₃, 106-107°C.

The Reaction of 1,2-Dibenzoylhydrazines with Chlorine. 1,2-Dibenzoylhydrazine (6-8 g) was suspended in 50 m<u>1</u> of nitromethane or dichloromethane. Chlorine gas was passed slowly into this suspension at room temperature until the dibenzoylhydrazine was completely dissolved. This required 1-5 hr. The solvent was removed by rotary evaporation, and the liquid was distilled under reduced pressure.

The benzoyl chlorides obtained were identified by comparing their infrared spectra with those of authentic samples.

The Reaction of Dibenzoyldiimides with Chlorine. Dibenzoyldiimides were treated with chlorine under the same conditions as the cases of the preceding dibenzoylhydrazines. The reactions were completed within 30 min.

- 68 -

References

- 1) L. A. Carpino, <u>Chem. Ind.</u> (London), 123 (1956).
- 2) L. A. Carpino, <u>J. Amer. Chem. Soc.</u> <u>79</u>, 96 (1957).
- L. W. Kissinger and H. E. Ungnade, <u>J. Org. Chem.</u>, <u>24</u>, 1244 (1959).
- 4) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. II,
 W. B. Benjamin, Inc., New York (1966), p. 119.
- 5) a) R. Stolle and A. Benrath, <u>Ber.</u>, <u>33</u>, 1770 (1900);
 - b) R. Stolle and A. Benrath, <u>J. prakt. Chem.</u>, (ii), <u>70</u>, 263 (1900);
 - c) E. Mohr, <u>ibid.</u>, (ii), <u>70</u>, 281 (1904);
 - d) R. Stolle, <u>Ber.</u>, <u>45</u>, 245 (1912);
 - e) L. Horner and W. Naumann, <u>Ann.</u>, <u>587</u>, 93 (1954).
- 6) Dibenzoyldiimide could not be isolated under these reaction conditions. However, we observed that reddish orange color, which was perhaps due to dibenzoyldiimide being formed, appeared in the course of the reaction, and that this color faded just when the reaction was completed.
- 7) H. H. Hatt, "Organic Syntheses," Coll. Vol. II, p. 208 (1966).
- J. E. Leffler and W. B. Bond, <u>J. Amer. Chem. Soc.</u>, <u>78</u>, 335 (1956).
ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Professor Yasuhide Yukawa and Professor Yuho Tsuno who conceived the problem and gave many suggestions. Appreciation is also due to Dr. S. G. Kim and Dr. M. Sawada for their kind advice and valuable discussion. Heartful thanks are due to Dr. T. Ando, Dr. Y. Kusuyama, Miss M. Fujio, Mr. T. Fujii, Mr. Y. Takai, and many members of the Yukawa Group, in many respects.

The author is grateful to Mr. T. Fujino and Mr. T. Shishido for their kindness to elementary analysis.

Great gratitude is also made to Mr. and Mrs. Sasagawa, who took care of the author in his livelihood.

Finally, the author would like to express his heartful appreciation to his mother, Mrs. Michi Imamoto, for her constant encouragement during the course of studies.

1971, 12, Tsuneo Imamoto