

Nucleophilic Substitution at a Carbonyl Carbon Atom (Ⅵ)

Kinetic Studies of Halogen Exchanges in Benzoyl Chlorides.

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Abstract

Kinetic studies on the halide exchange reactions of substituted benzoyl chlorides have been carried out. The experimental result has been explained reasonably in terms of HSAB principle and EH-Theory, and addition elimination mechanism has been proposed for this type of reaction.

요 약

염화벤조일 치환체에 대한 할라이드 교환반응을 반응속도론적으로 연구하였다. HSAB 원리와 확장 Hückel 이론을 적용하여 실험 결과를 합리적으로 해석하였으며 이와 같은 유형의 반응에 대하여 첨가-제거 메커니즘이 합당함을 알았다.

1. Introduction

Nucleophilic substitution reaction at a carbonyl carbon atom has been a subject of extensive study with the view to clarifying the mechanism involved. The nucleophilic substitution reactions of derivatives of carboxylic acids, especially the hydrolysis of esters have been studied very thoroughly and the mechanism is well understood as addition elimination (S_N)¹⁾ However, the investigations of the kinetics of the hydrolysis and alcoholysis of acid chlorides have not led to completely concordant conclusions, and a reasonable explanation for all the data available seems to be lacking. Hudson and his coworkers,²⁾ Gold, Hilton and Jefferson³⁾, and Keily and Watson⁴⁾ have suggested that

aromatic acid chlorides may be hydrolyzed by either the S_N^1 or the S_N^2 mechanism. A few results of the kinetic studies of the nucleophilic substitution other than the solvolysis of acid chlorides have been reported,^{5, 6)} and the mechanism of these reactions have been shown to be of considerable complexity. The mechanism proposed can be classified into three categories; S_N^1 , S_N^2 and $S_A N$.¹⁻⁷⁾

In this work we have investigated the substituent effect on the rate of halide exchange of some substituted benzoyl chlorides in order to gain further insights as to the structure-reactivity relationship and hope to clarify the mechanism involved in the nucleophilic substitution at the carbonyl carbon atom of acid chlorides.

2. Experimental

(1) Materials

a) Benzoyl chloride (Chameleon, Japan) and m-chlorobenzoyl chloride (Aldrich Chem. Co., Inc.), were purified by distillation under reduced pressure. p-nitrobenzoyl chloride (Aldrich Chem. Co., Inc.) was purified by recrystallization from anhydrous carbon tetrachloride and was identified by m.p. 72° C. (lit.⁸⁾ 72°C). p-Toluoyl chloride was prepared from p-toluic acid with thionyl chloride and purified by vacuum distillation.

b) Aceton and acetonitrile were purified as described before^{9, 10)}

c) (Et)₄NCl, KI: G.R. grade sample was used without further purification.

d) Stock solution of (Et)₄NCl: The radioactive chlorine, Cl³⁶, purchased from Radiochemical Center, Amersham, Buckinghamshire, England in HCl³⁶ form was converted to (Et)₄NCl by adding the equivalent amount of (Et)₄NOH and then evaporated to dryness. Suitable amount of (Et)₄NCl carrier salt and radio isotopic (Et)₄NCl were dissolved in solvent.

(2) Kinetic Runs

a) Chloride exchange reactions were conducted as reported before.⁹⁾ Exchange rates were calculated by the equation.

$$k = \frac{-\ln(1-F)}{(a+b)t}, \quad F = \frac{x}{x_{\infty}}$$

In the above equation, *a* and *b* are the initial concentrations of the substrate and salt, respectively, and *x* and *x*_∞ are radioactivity of organic layer at time *t* and infinite time respectively.

b) Iodide exchange reactions

For the measurement of iodide exchange rate, conductivity method was adopted. Con-

ductance was measured by Beckman RC-18A model, conductivity cell, having the cell constant of the order of 0.5cm⁻¹, was used. Adjusting the concentration of the substrate as about a hundred fold greater than that of the salt, pseudo-first order rate constant was obtained by the Guggenheim method.¹¹⁾

$$k' = \frac{\ln(\lambda_t - \lambda_{t+\Delta})}{\Delta} + c$$

where λ_t and $\lambda_{t+\Delta}$ is conductance at time *t* and *t*+ Δ respectively. Second order rate constant was obtained from the first order rate constant divided by the initial concentration, of substrate, *a*.

$$k = k'/a$$

(3) Activation parameters

Activation energy was calculated from the Arrhenius plots, and the entropy of activation was calculated by the following equations.

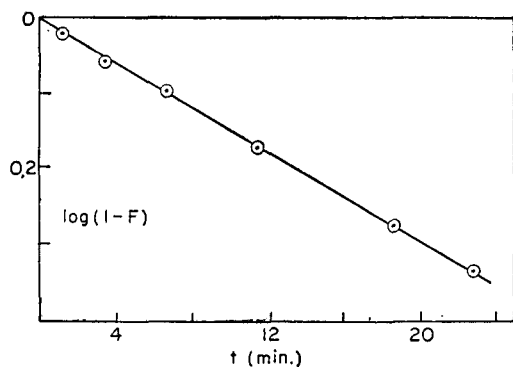
$$\Delta H^\ddagger = E_a - RT$$

$$k = \frac{RT}{Nh} \cdot e^{xp(\Delta S^\ddagger/R)} \exp(-\Delta H^\ddagger/RT)$$

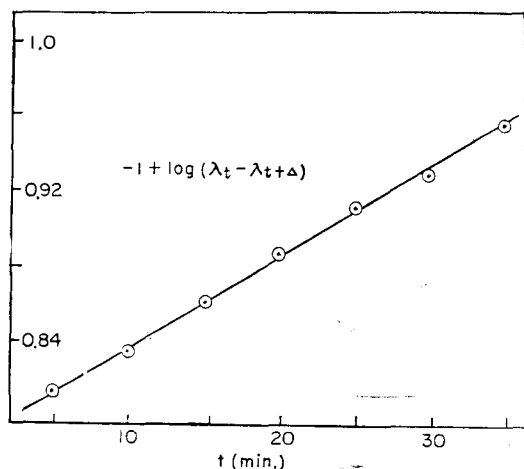
3. Results and Discussion

Linearities of the plot log(1-*F*) versus *t* for the chlorine exchange and that of log($\lambda_t - \lambda_{t+\Delta}$) versus *t* for the iodine exchange are satisfactory as can be seen from the typical plots given in Fig.1 and Fig.2.

Rate constants for chlorine exchange reactions of some substituted benzoyl chlorides in anhydrous acetonitrile are summarized in Table 1. It can be seen that bond formation is important in this reaction since the electron withdrawing substituent enhances while electron donating substituent reduces the rate. This safely eliminates the S_N¹ mechanism, where bond breaking is far more important, leaving S_N² and S_AN as possible mechanisms for the chlorine exchange of benzoyl chloride.

Fig. 1. Typical Plot of $\log(1-F)$ vs. t for chlorine exchange of benzoyl chloride.

reaction: $\phi\text{COCl} + \text{Cl}^{*-} \rightarrow \phi\text{COCl}^* + \text{Cl}^-$
 Solvent: CH_3CN
 temp: 0°C
 $(\phi\text{COCl}) = 6.23 \times 10^{-4}\text{M}$
 $(\text{Et}_4\text{NCl}) = 3.85 \times 10^{-4}\text{M}$
 $k_{\text{obs}} = 0.608 \text{ M}^{-1} \text{ sec}^{-1}$

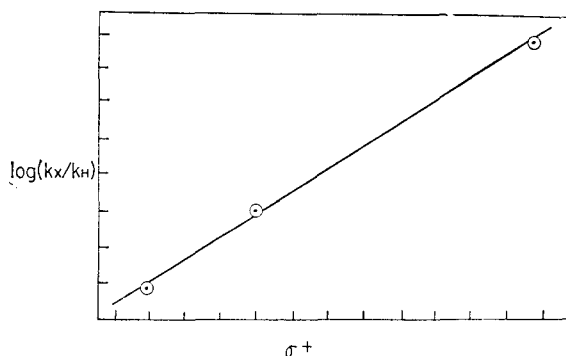
Fig. 2. Guggenheim Plot for iodide exchange of benzoyl chloride.

reaction: $\phi\text{-COCl} + \text{I}^- \rightarrow \phi\text{COI} + \text{Cl}^-$
 Solvent: acetone
 temp.: 25°C
 $(\phi\text{-COCl}) = 5.82 \times 10^{-3}\text{M}$
 $(\text{KI}) = 5.73 \times 10^{-4}\text{M}$
 $k_{\text{obs}} = 3.47 \times 10^{-3} \text{ M}^{-1} \text{ sec}^{-1}$

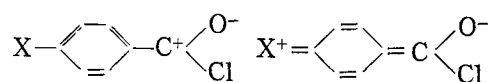
Fig. 3. shows the linear correlation between logarithmic ratio of rate constants, $\log(k_X/k_H)$, and σ^+ substituent constants for the para substituted derivatives, with $\rho = +1.29$. The Hammett plot with the normal substituent constant σ is found less satisfactory. The

Table 1. Summary of rate constants $k(\text{l} \cdot \text{mole}^{-1} \cdot \text{sec}^{-1})$ for chlorine exchange of benzoyl chloride in acetonitrile.

$X\phi\text{COCl} + \text{Cl}^{*-} \rightarrow X\phi\text{COCl}^* + \text{Cl}^-$		
X	T°	
	0	-10
p- CH_3	0.208	0.077
H	0.608	0.268
m-Cl	4.27	1.92
p- NO_2	5.41	2.21

**Fig. 3.** The plot of $\log(k_X/k_H)$ vs. σ^+ for chlorine exchanges of benzoyl chloride in acetonitrile at 0°C . (where $X = \text{p-NO}_2$, p-H and p-CH_3 .)

positive ρ value for the $\rho\sigma^+$ plot is generally interpreted as due to the resonance stabilization of the electron donating para substituent in the ground state. For benzoyl chloride the following resonance stabilization is indeed highly plausible.



Thus electron donating group stabilizes this resonance structure by dispersing the positive charge. This ground state stabilization must be destroyed when the anion attacks the benzoyl chloride. The more stabilized reactants i.e., with the strong electron donating substituents, react more slowly so that a positive value is to be expected in the $\rho\sigma^+$ plot.

Similar plots were obtained for the reaction between malonitrile anion and benzaldehydes¹²⁾ with $\rho = +1.45$ and for the reaction of benzoyl chlorides with aniline^{6,9)} where ρ was $+0.794$. In these reactions the prime importance is the bond formation, and bond breaking contributes far negligibly. Therefore the reactions are considered to proceed via some intermediates, i.e., via the S_N mechanism.

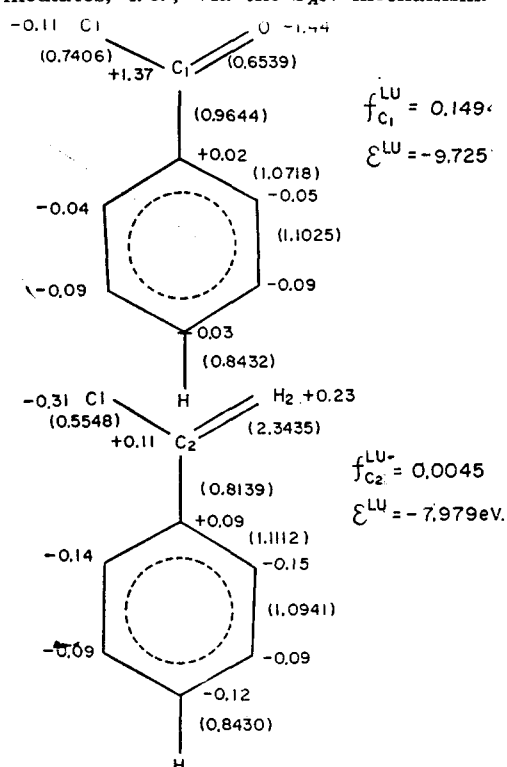
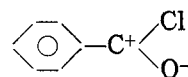


Fig. 4. The EHMO results for benzoyl chloride and benzyl chloride¹³⁾. Formal charges of atoms and bond populations (in parenthesis) are shown.

Fig. 4. shows the structural characteristics obtained from the extended Hückel molecular orbital (EHMO) calculations for benzoyl and benzyl chloride.¹³⁾ Comparison of these MO results for the two compounds provides us the following useful information.

(1) The carbonyl carbon center is highly charged due to the electronegative carbonyl oxygen as compared with the saturated

carbon center. Thus the resonance form,



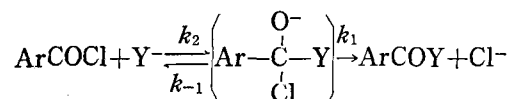
contributes strongly to the ground state of benzoyl chloride. This supports the contention of the extra stabilization effect of electron donating para substituent discussed above.

(2) Bond strength of C-Cl is greater in benzoyl chloride than that in benzyl chloride. This implies that leaving ability may be less for Cl in benzoyl chloride compared to that in benzyl chloride. Therefore the mechanism, in which addition precedes elimination, i.e., S_N mechanism may be preferred.

(3) The frontier orbital [lowest unoccupied (LU) MO] electron density, f_c^{LU} , of carbonyl carbon atom is much greater than that of benzyl carbon. Since the magnitude of f_c^{LU} reflect the reactivity of S_N reaction where bond formation is of major importance in rate determining step, the S_N reactivity of benzoyl chloride is expected to be greater than that of benzyl chloride. This agrees well with the experimental results. (Table 2)

(4) The energy of LUMO, ϵ^{LU} , for benzoyl chloride is lower. This is another factor in favor of enhanced S_N reactivity toward a halide nucleophile according to the perturbational theory of reactivity.¹⁴⁾

The experimental as well as the MO theoretical results obtained appear to support the S_N mechanism for the halogen exchanges in benzoyl chlorides. Thus,



Application of the steady state approximation for tetrahedral intermediate yield,

$$\text{Rate} = \frac{k_1 \cdot k_2}{k_1 + k_{-1}} [\text{ArCOCl}][\text{Y}^-]$$

Since $k_1 = k_{-1}$ for chloride exchange reactions,

$$\text{Rate} = \frac{k_2}{2} [\text{ArCOCl}] [\text{Cl}^-]$$

where the factor 1/2 indicates that the intermediate formed has the same probability of decomposing into the reactants or into the products. In this case addition step is the rate determining. Since $k_{-1} \gg k_1$ for iodide exchange reactions¹⁵⁾.

$$\text{Rate} = \frac{k_2 k_1}{k_{-1}} [\text{ArCOCl}] [\text{I}^-].$$

Assuming k_1/k_{-1} for I^- exchange as $\sim 10^{-2}$ from Litvinenko's data,¹⁵⁾ the relative reactivity of the Cl^- to I^- becomes $\sim 10^2$, that is, addition of Cl^- to carbonyl carbon center of acid chloride is favored hundred fold compared to the addition of I^- .

In Table 2, the rate constants for the halide exchange reactions of benzoyl chloride in dry acetone are compared with those of benzyl chloride¹⁶⁾ and methyl chloroformate.¹⁰⁾ From the data of Table 2, it can be seen that carbonyl center in benzoyl chloride is highly reactive toward Cl^- ion in comparison with the saturated carbon center in benzyl chloride.

On the other hand the rate constants for the iodide exchange reactions are comparable

Table 2. Summary of rate constants k ($\text{l} \cdot \text{mole}^{-1} \cdot \text{sec}^{-1}$) for halogen exchanges of benzoyl chloride methyl chloroformate and benzyl chloride in acetone.

Substrate	T°C	N^-	Cl^-	I^-
ϕCOCl	-10		0.616	
	0		1.85	2.69×10^{-4}
	25			3.47×10^{-3}
CH_3OCOC	25		*0.282	* 1.10×10^{-3}
$\phi\text{CH}_2\text{Cl}$	25		** 2.83×10^{-3}	** 1.62×10^{-3}

* from Ref. 10

** from Ref. 16

magnitude.

Table 3. Summary of activation parameters for halide exchanges of benzoyl chlorides

(1) For $\text{X}\phi\text{COCl} + \text{Cl}^-$ in acetonitrile

X	E_a (kcal)	ΔS^\ddagger (e. u.)
p- CH_3	13.6	-13.5
H	11.3	-20.2
m-Cl	11.0	-17.3
p- NO_2	12.3	-11.9

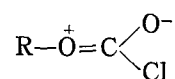
(2) For $\phi\text{COCl} + \text{Y}^-$ in acetone

Y^-	E_a (kcal)	ΔS^\ddagger (e. u.)
Cl^-	15.1	-3.9
I^-	14.0	-26.2

In terms of HSAB principle¹⁷⁾ carbonyl carbon center in benzoyl chloride may be considered as hard (highly positive) acid while saturated carbon center in benzyl chloride belongs to borderline case. Therefore, it is expected that the reaction of benzoyl chloride with Cl^- ion, which is relatively hard, will be very fast while the reaction with I^- ion, which is relatively soft, will be very slow.

From this consideration, reasonable explanation for the fast rate ($\sim 3\text{M}^{-1} \cdot \text{sec}^{-1}$ at -10°C) of benzoyl chloride with ethoxide ion in 80% alcoholic acetone,¹⁸⁾ can be given. Ethoxide ion is hard base due to its high proton basicity, so that its reaction rate with benzoyl chloride acting as hard acid may be very fast.

The somewhat slow rate of chloride exchange reactions of methyl chloroformate¹⁰⁾ may be attributed to the reduction of hardness of the ester carbon center due to the resonance contribution:



In Table 3, activation energies and the entropies of activation are summarized. We may conclude that this type of reaction is entropy controlled.

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