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카르보닐 탄소원자의 친핵성 치환반응(제 8 보). 염화포름산물과 치환아닐린 및 할라이드와의 반응에 관한 속도론적 연구

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Nucleophilic Substitution at a Carbonyl Carbon Atom(VIII). Kinetics and Mechanism of the Reactions of Chloloroformates with Substituted Anilines and Halides

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要 約. 염화포름산 메틸과 치환아닐린 및 염화포름산 페닐의 할로겐 교환반응을 속도론적으로 아세톤 속에서 연구하였다. 속도상수는 중간체를 동반하는 첨가-제거(S_AN) 메카니즘으로도 합리적으로 해석되나 분자궤도론적 및 동위원소 효과 연구결과를 고려할 때 1단계(S_N2) 메카니즘이 더욱 타당함을 알았다. 결론으로 반응성이 큰 친핵체들은 "늦은"형의 천이상태를 이루고 반응성이 작은 친핵체들은 "이른" 형의 천이상태를 이룬다는 것을 알았다.

ABSTRACT. Rate constants for the reaction of methyl chloroformate with substituted anilines, and for the halogen exchanges in phenyl chloroformate have been determined in acetone. Although the rate data can be interpreted equally well with the addition-eliminaiton mechanism (S_AN) involving an intermediate, results of MO and isotope effect studies strongly favor the synchronous (S_N2) mechanism for the reactions studied. It was concluded that for the fast reacting nucleophiles the transition state is of "late" type while for the slow reacting nucleophiles it is of "early" type.

INTRODUTION

Chloroformates have resonance stabilized ground state structures[1] and this is reflected in their reduced nucleophilic reactivities as compared with other carbonic acid derivatives.[2] Nucleophilic substitution reactions of chloroformates (ROCOCl) formally parallel those of other types of carboxylic acidesters.[3] From the mechanistic standpoint, the solvolytic reactions of chloroformates can be divided into two main types, unimolecular and bimolecular,[4]

where as the nonsolvolytic reactions proceed mainly through bimolecular mechanism.[5] The main problem in the reaction of a chloroformate with a non-solvolytic nucleophile such as amine and halide, however, is whether the bimolecular reaction takes place by a synchronous (S_N2) or an addition-elimination (S_AN) mechanism. In the latter, the reaction is believed to proceed through a tetrahedral intermediate.

We report here results of our structure-reactivity studies of chloroformates by theoretical as well as ay kinetic method. In this work we varied both the substrate, ROCOCl, where R= CH_3, C_2H_5, $(CH_3)_2$ CH, and C_6H_5, and the nucleophile, Cl^-, I^- and $XC_6H_4NH_2$ where X is the meta or para substituent. In the case of aniline, the reaction is represented as.

$$ROCOCl+2XC_6H_4NH_2 = ROCONHC_6H_4X+XC_6H_4NH^+{}_3Cl^- \quad (1)$$

EXPERIMENTAL

Ground State Electronic Structure Of Phenyl Chloroformate The CNDO/2 molecular orbital (MO) calculations were carried out on phenyl chloroformate similarly as described previously.[6] Standard values of bond lengths and bond angles[7] were used in determination of atomic coordinates in the molecule. The charge density, Z_c, and frontier electrondensity, f_c, of carbonyl carbon atomand the partial bond index of C-Cl bond, W_{C-Cl}, were then calculated for the lowest unoccupied molecular orbital (LUMO).[6]

Materials. Chloroformates and anilines were purified either by distillation after drying over sodium sulfate or by recrystallization. The purity was confirmed by measuring physical constants. The agreements with literature values were satisfactory in all cases.[8] Anilinium chlorides were prepared by passing HCl gas through aniline solutions and then recrystallized from acetone and ether. Acetone was distilled after drying over calcium sulfate and redistilled after drying over phosphorous pentoxide.

Measurement of Rate Constants. Rates were followed by conductivity method using Beckman RC-18A type conductivity bridge. The temperature control was better than to ± 0.05 °C. Reaction solutions consisted of $1.1\sim3.7\times10^{-2}$ *M*. chloroformate and $1.1\sim8.1\times10^{-2}$ *M* aniline. The concentration of product anilinium chloride was determined from a conductivity—concentration plot constructed specially for each substituted anilinium chloride. A typical conductivity concentration curve is shown in *Fig.* 1. Second-order rate constants were then determined by use of the integrated second-order expression (2), where a and b are the initial concentration of substrate

$$K_2=\frac{1}{t\ (b-2a)}\ \ln\frac{a(b-2x)}{b(a-x)} \quad (2)$$

and nucleophile, and x is the concention of anilinium chloride determined from measured conductivity using a conductivity-concentration curve. Typical values are given in *Table* 1.

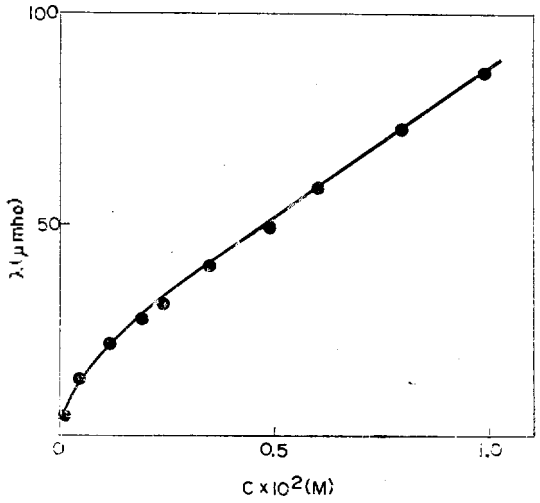
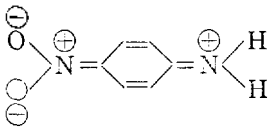


Fig. 1. Typical conductivity-concentration curve. For the reaction of methyl chloride, 1.243×10^{-2} *M* with aniline, 7.983×10^{-2} *M* in acetone at 25 °C.

Plots of $\log\frac{a(b-2x)}{b(a-x)}$ against t gave good straihgt lines in all cases and least square slopes were then used to calculate k_2 values. Product formed in this reaction, urethane, was confirmed by examining IR spectrum of the product.

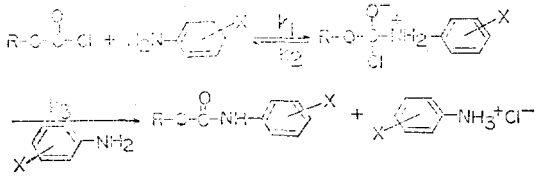
RESULTS AND DISCUSSION

The reaction was first order in both substrate and nucleophile, and hence over all second order, in the concentration range studied. Typical concentration dependence of the second order rate constant is shown in *Table* 2 for the reaction of methyl chloroformate with aniline. The errors in k_2 were less than ±3 % for the reactions with anilines and they increased to about twice for halide exchanges. *Table* 3 contains the second order rate constants obtained and activation parameters calculated for the reaction of methyl chloroformate with substituted anilines in dry acetone. It is evident that the nucleophilicity of aniline increases with the electron density on amine nitrogen as expected; electron donating substituent in aniline accelerates while electron withdrawing substituent deaccelerates the rate of reaction. The Hammett type plots of the rate constants against σ^- (for p-NO_2)[9] gave an excellent straight line of slope $\rho=-2.00$ with correlation coefficient $r=0.998$. Better Hammett type correlation with σ^- rather than σ for p-NO_2 group indicates that strong direct conjugation is operative between the substituent and reaction center of the nucleophile.[9]



(I)

The ρ value of -2.00 obtained with methyl chloroformate is to be compared with those obtained with ethyl chloroformate by Ostrogovich *et al.*[10] under the same reaction condition; values were $\rho=-5.56$ for electron releasing



(3)

Table 1. Typical kinetic run. Conductivities, λ, and concentration of anilinium chloride, x, for the reaction of methyl chloroformate, $1.243\times10^{-2}M$ with aniline, $3.983\times10^{-2}M$ in dry acetone at 25.0 °C

Time (sec)	λ (μ mho)	$x\times10^2$ (M)	$\log\frac{a(b-2x)}{b(a-x)}$
30	20.3	0.105	0.01481
60	28.7	0.195	0.02936
120	39.3	0.340	0.05748
180	48.0	0.463	0.08746
240	55.3	0.565	0.11833
300	61.0	0.644	0.14739
360	65.4	0.707	0.17486
420	69.1	0.759	0.20123
480	72.8	0.811	0.23187
540	75.9	0.855	0.26203
600	78.8	0.896	0.29457

Table 2. Concentration dependence of 2nd-order rate constants for the reaction of methyl chloroformate with aniline in dry acetone.

T (°C)	Concentration (M)		$k_2\times10^{-2}$ (l mol^{-1} sec^{-1})
	$a\times10^{-2}$	$b\times10^{-2}$	
15	1.884	6.168	4.78
	1.516	4.013	4.62
	0.942	3.994	4.85
		mean	4.75±0.10
25	1.001	4.205	7.62
	1.243	3.983	7.49
	1.549	3.996	7.31
		mean	7.47±0.15

a : substrate, b : nucleophile.

Table 3. Rate constants and activation parameters for the reactions of methyl chloroformate (MCF) with substituted anilines in anhydrous acetone.

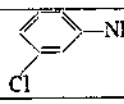
Nucleophile	(Nuclephilo) $\times 10^2$ (M)	(MCF) $\times 10^2$ (M)	($^\circ$C)	k_2 (l mol^{-1} sec^{-1})	$\Delta H^{\neq}$ (k cal mol^{-1})	$\Delta S^{\neq}$ (e. u.)
p-Methylaniline	3, 579	1, 145	25. 0	1.22×10^{-1}	1. 1	−59. 0
	4, 038	1. 365	15. 0	9.44×10^{-2}		
	4, 119	1, 272	5. 0	8.09×10^{-2}		
m-Methylaniline	3, 944	1, 249	25. 0	8.44×10^{-2}	6. 7	−41. 0
	4, 730	1, 169	15. 0	6.16×10^{-2}		
	5, 029	1, 873	5. 0	3.43×10^{-2}		
Aniline	3, 983	1, 243	25. 0	7.49×10^{-2}	7. 5	−38. 5
	4, 018	1. 516	15. 0	4.62×10^{-2}		
	5, 015	2, 127	5. 6	2.82×10^{-2}		
p-Chloroaniline	5, 986	1, 518	35. 0	3.51×10^{-2}	10. 0	−32. 9
	7, 180	1, 659	25. 0	1.82×10^{-2}		
	7, 345	2, 170	15. 0	5.60×10^{-3}		
m-Chloroaniline	6, 037	1, 554	35. 0	1.40×10^{-2}	8. 6	−39. 2
	6, 990	1. 975	25. 0	8.27×10^{-3}		
	8, 000	2, 091	20. 1	6.03×10^{-3}		
p-Nitroaniline	6, 947	2, 995	45. 0	4.99×10^{-4}	11. 9	−36. 4
	8, 022	3, 738	35. 0	2.59×10^{-4}		
	4, 68[illegible]	2, 057	25. 0	1.29×10^{-4}		
m-Nitroaniline	6, 045	2, 366	45. 0	6.03×10^{-3}	5. 8	−50. 6
	7, 045	3, 300	35. 1	3.96×10^{-3}		
	5, 484	1, 937	25. 0	3.02×10^{-3}		

substituents and $\rho=-1.57$ for electron withdrawing substituents. Assuming an S_AN mechanism, (3), they interpreted the large negative value of ρ for the electron releasing substituents as an indication of the rate determining splitting of the intermediate (k_3) while relatively low negative value for electron withdrawing groups as reflecting rate determining attack (k_1) in forming the intermediate due to their diminished nucleophilicity. According to this criterion, the rate determining step seems to be the nucleophilic attack for the reaction of methyl chloroformate with anilines. This does not necessarily mean that the reaction proceeds via an intermediate since one-step mechanism (S_N2) is also consistent with the rate determining attack. The Brønsted plot[9] using data in *Table* 4 gave a straight line of slope $\beta=0.756$ with correlation coefficient $r=0.993$. Although the use of pKa values in water may not be justified, the magnitude of β obtained for the reaction of methyl chloroformate with anilines implies that considerable degree of bond formation is achieved at

Table 4. Basicities and rate constants for the reaction with methyl chloroformate for substituted anilines at 25 °C.

Nucleophile	log k_2	pKa
p-Methylaniline	−0. 9136	5. 08
m-methylaniline	−1. 0737	4. 71
Aniline	−1. 1255	4. 59
p-Chloroaniline	−1. 7399	3. 98
m-chloroaniline	−2. 0825	3. 52
p-Nitroaniline	−3. 8898	0. 99
m-Nitroaniline	−2. 5200	2. 46

Table 5. Summary of 2nd-order rate constants and activation parameters for the nucleophilic reactions of chloroformates in acetone.

Substrate (R) ROCOCl	$\Delta H^{\neq}$ [a] (K cal mol^{-1})	$\Delta S^{\neq}$ [a] (e. u.)	Nucleophile:  (25°C)	Nucleophile: Cl^- (°C)	Nucleophile: I^- (45°C)
CH_3	8.6	−39.2	8.27×10^{-3}	1.51×10^{-2}**	3.03×10^{-2}*
CH_3CH_2	9.8***	−33.1***	5.36×10^{-3}***	7.29×10^{-3}*	2.67×10^{-3}*
$(CH_3)_2CH$	14.8	−20.0	3.47×10^{-3}	4.89×10^{-4}*	2.67×10^{-4}*
C_6H_5	7.5	−35.1	3.66×10^{-1}	1.23×10^{-1}	1.75×10^{-4}

*Calculated from ref. 5, **ref. 5, ***ref. 10.

[a] activation parameters for the nucleophilic reactions of chloroformates with *m*-chloroaniline in the anhydrous acetone at 25 C.

the transition state. Activation parameters in *Table* 3 are characterized by the large negative entropy of activation (−32.9∼−59.0 e. u.) and small enthalpy of activation (1.1∼11.9 kcal/mol). Both of these are general characteristics of a bimolecular S_N reaction.[10]

Rate constants for reactions of chloroformates with *m*-chloroaniline, Cl^-, and I^- determined are summarized in *Table* 5 together with other relevant data for comparison. For the fast reacting nucleophiles, anilines and Cl^-, the reactivity decreases in the order of $C_6H_5OCOCl > CH_3OCOCl > C_2H_5OCOCl > (CH_3)_2CHOCOCl$, while for relatively slow reacting I^-, C_6H_5OCOCl becomes the least reactive.

Queen has reported[11] results of the hydrolysis of a series of alkyl chloroformates and phenyl chloroformate. Data extracted from his paper are presented in *Table* 6. Queen assumed the sudden increase in entropy of activation for isopropyl chloroformate hydrolysis to follow from a change in mechanism from bimolecular for phenyl, methyl, and ethyl chloroformates towards unimolecular for secondary alkyl chloroformate. He then proposed a mechanism proceeding through a tetrahedral intermediate for the bimolecular solvolysis, as opposed to the one-step mechanism proposed by Kivinen[12] for the solvolysis of ethyl chloroformate. For the solvolysis of isopropyl chloroformates concurrent S_N1 mechanism was proposed. It was emphasized however that other explanation are also possible, and thus he did not rule out the possibility of S_N2 mechanism for the reactions he studied. Since the present work is concerned with non-solvolytic reactions in acetone, our data are not directly comparable to those of Queen. However for fast reacting nucleophiles sequence of reactivity is the same in the two cases excepting of course isopropyl for which concurrent S_N1 mechanism is most probably operating. It is readily seen from *Tables* 5 and 6 that the nitrogen nucleophile reacts faster than the oxygen nucleophile towards chloroformates

Table 6. Rate constants and activation parameters for hydrolysis of chloroformates (ROCOCl) in water.

R	10^4k (s^{-1})*	$\Delta H^{\neq}_{298}$ (kcal/mol)	$\Delta S^{\neq}_{298}$ (e. u.)
CH_3	1.23	16.2	−19.1
C_2H_5	0.76	17.1	−17.0
$(CH_2)_2CH$	2.36	24.1	+10.1
C_6H_5	34.6	14.1	−19.8

*Determined at slightly varying temperatures within the range 10±0.2 °C.

Table 7. Results of the CNDO/2 MO calculations for ground statesof chloroformates.[5]

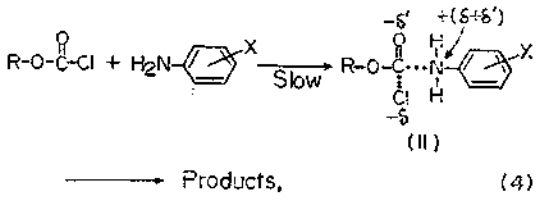
Substrate	$\varepsilon^{LU}_{(eV)}$	Z_c	f^{LU}_c	$\frac{f^{LU}_c}{\varepsilon^{LU}_{ROCOCl}-\varepsilon^{HO}_{Cl}}$	W^{LU}_{C-Cl}
CH_3OCOCl	3.1	+0.4904	0.9458	0.1039	0.6596
C_2H_5OCOCl	3.3	+0.4895	0.9428	0.1014	0.6494
$(CH_3)_2CHOCOCl$	3.3	+0.4912	0.9332	0.1003	0.6334
C_6H_5OCOCl	2.1	+0.4549	0.6003	0.0741	0.7053

*ε^{LU} : energy of LUMO, ε^{HO} : energy of the highest occupied MO.

and this is entirely due to an enthalpic effect.

Results of MO calculations are summarized in *Table* 7. According to the generalized perturbation theory of reactivity, nucleophilic substitutions are either charge controlled or orbital (or frontier) controlled when bond formation is the rate determining.[13] In the former the reactivity is dictated by the total charge density on the reaction center, Z_c, while in the latter it is determined mainly by frontier electron density, f^{LU}_c. The theory further postulates that the reactivity of frontier controlled reaction is proportional to f^{LU}_c divided by the energy difference of frontier orbitals of the two reacting species.[13] This quantity is calculated and given in the fifth column of *Table* 7. It can be concluded from *Table* 7 that irrespective of whether the reactions studied are charge controlled or frontier controlled, phenyl chloroformate should be the least reactive, which is contrary to our rate results for the fast reacting nucleophiles. Thus MO results suggest that the rate of reaction of chloroformate with fast reacting nucleophiles is not determined by the easiness of bond formation alone. MO theoretical explanation of rate results is only possible by assuming S_N2 mechanism for the reaction in which synchronous bond breaking occurs in one-step displacement, (II), i.e., the"late" type.

Since LUMOs are antibonding, σ^*, bond breaking should be easier for the substrate with large partial bond index, W^{LU}_c—Cl. This value and hence the easiness of bond breaking decreases in the order $C_6H_5OCOCl > CH_3OCOCl > C_2H_5OCOCl > (CH_3)_2CHOCOCl$, which is exactly the rate sequence for fast reacting nucleophiles.



(4)

The charge density, Z_c, in *Table* 7 shows that C_6H_5O group tends to release electron since the positive charge on the carbonyl carbon atom is the smallest in phenyl chloroformate campared with those in other chloroformates. The electron releasing phenoxy group decreases the positive charge on the carbon atom of the chlorocarbonyl group and thus reduces the strength of the carbon-halogen bond. Formation of transition state which involves partial bond breaking of this carbon-halogen bond will be made easier with phenyl chloroformate, and the rate will increase only if the rate determining bond breaking is assumed.

Similar conclusion was reached by Elliot and Mason[14] on the basis of isotope effect studies on the benzoylation of aniline. They found that breaking of a nitrogen-hydrogen bond is not involved in the rate determining step. The two, MO and isotpoe effect results, complements each other in favor of the S_N2 mechanism with the "late" transition state of the type (II), for the

reaction of chloroformates with fast reacting nucleophiles. For the slow reacting nucleophile, I^-, however the bond formation and bond breaking may not be significant at the transition state and an "early" transition state proposed previously [15] may be more appropriate. We therefore conclude that for the fast reacting nucleophiles the bond breaking occurs synchronously with the bond formation and the easiness of bond breaking dictates the rate, while for the slow nucleophiles the bond breaking is not significant and an "early" transition state is formed.

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