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S_N2 Reactions in Dipolar Aprotic Solvents. III. Chlorine Isotopic Exchange Reactions of Cinnamyl Chlorides and 3-Aryl-2-propynyl Chlorides. Effect of the Unsaturated Group Adjacent to the Reaction Center

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Chlorine isotopic exchange reactions of substituted cinnamyl chlorides and 3-aryl-2-propynyl chlorides with tetraethylammonium chloride-^{36}Cl were studied in acetonitrile. In both cases, the electron-donating groups accelerated the reaction. An acceptable linear Hammett relationship was found for the propynyl chlorides. Cinnamyl chlorides gave a linear relationship for the *m*-substituted compounds superposed by a concaved U-shaped relationship of *p*-substituted compounds. Both classes of compounds showed 10^{2-3} times of rate enhancement, compared with 2-arylethyl chlorides in the similar isotopic exchange reaction. Features of these S_N2 reactions are discussed.

Many works have been carried out to further our understanding of the bimolecular nucleophilic substitution at a saturated carbon atom,[2] an important reaction in organic chemistry.

Of the bimolecular nucleophilic substitutions at a saturated carbon atom, the Finkelstein reaction is one of the most thoroughly studied.[3] However, not many works have been carried out dealing with the Hammett type analysis to reveal the electronic requirement of the reaction center in a transition state.

The authors presented an example of a Hammett analysis in which the heteroatom adjacent to the S_N2

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[2] a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd Edition, Cornell Univ. Press, Ithaca, New York (1969) p. 418. b) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Pub. Co., London (1963). c) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York (1962).

[3] For instance, P. B. D. de la Mare, *J. Chem. Soc.*, **1955**, 3169, and succeeding papers.

reaction center accelerates the reaction by a conjugative stabilization of the transition state.[4] The authors also showed that, in the Finkelstein reaction with benzyl chloride, chloride and fluoride anions behave similarly and the substituent effect can be rationalized in terms of the importance of the approach of a nucleophile superposed by the stabilization of the transition state.[5]

The rate enhancing effect of the unsaturated bond in an S_N2 reaction is well-known.[6] However, a further advance can be anticipated from systematic studies of the symmetrical exchange reaction of these classes of compounds.

The authors studied the chlorine-chlorine isotopic exchange reactions of the nuclear substituted cinnamyl chlorides and 3-aryl-2-propynyl chlorides in solvent acetonitrile to examine the effect of the carbon to carbon multiple bond adjacent to the S_N2 reaction center. Comparison was made with the results obtained for the other modified methyl chlorides to reveal the dominating factors of these reactions.

Results and Discussion

Nine kinds of nuclear substituted cinnamyl chlorides and eight kinds of 3-aryl-2-propynyl chlorides were treated with tetraethylammonium chloride-^{36}Cl in dry acetonitrile, as shown in the following scheme.

$$\text{X-Ph-Y-CH}_2\text{Cl} + (\text{C}_2\text{H}_5)_4\text{N}\overset{*}{\text{Cl}} \rightleftharpoons \text{X-Ph-Y-CH}_2\overset{*}{\text{Cl}} + (\text{C}_2\text{H}_5)_4\text{NCl}$$

I Y: CH^t=CH, X: a) p-NO$_2$, b) m-NO$_2$, c) m-CF$_3$, d) m-Cl, e) p-Cl, f) H, g) m-CH$_3$, h) p-CH$_3$, i) p-OCH$_3$

II Y: C≡C, X: a) p-NO$_2$, b) m-CF$_3$, c) m-Cl, d) p-Cl, e) H, f) m-CH$_3$, g) p-CH$_3$, h) p-OCH$_3$

The advantage of using the dipolar aprotic solvent has been reported.[7] In the present cases, a good second-order kinetics holds, the second-order rate coefficients remaining virtually constant in varying concentration of nucleophile and also on addition of an inert salt, tetraethylammonium perchlorate (Table 1).

The results are given in Table 2 together with the rate coefficients for the Finkelstein reaction of benzyl chloride with chloride ion and fluoride ion.

The rate data for the unsubstituted modified methyl chlorides are collected in Table 3 to show the relative effectiveness of the group adjacent to the S_N2 reaction center.

A significant rate enhancement as compared with the chlorine-chlorine isotopic exchange reaction of 2-arylethyl chloride was observed for the three classes of compounds in Table 2. Thus benzyl chloride, cinnamyl chloride, and 3-aryl-2-propynyl chloride showed fairly similar reactivity, and all reacted about 10^2 times more rapidly in the S_N2 isotopic exchange reaction than 2-arylethyl chloride. However, the double bond in cinnamyl chloride seemed to exert a more pronounced effect than the triple bond and direct linkage in other classes. Sulfur atom in the chloromethyl aryl sulfides seemed to be more effective than the unsaturated groups in Table 3 in accelerating the Finkelstein reaction.

Electron-donating groups on the phenyl ring faciliated the chlorine-chlorine exchange reaction of cinnamyl chlorides as well as the same reaction of 3-aryl-2-propynyl chlorides. The rate data are plotted against Hammett σ to give the relationships given in Figs. 1 and 2.

As is shown in Fig. 2, the Hammett plot for the 3-aryl-2-propynyl chlorides gives an acceptable linear relation ($\rho=-0.19$, $r=0.919$[8]). Similarly, the m-substituted cinnamyl chloride gives a straight line ($\rho=-0.19$, $r=0.962$[8]) superposed by a concaved U-

Table 1. Effect of the chloride ion concentration on the rate of chlorine exchange in the presence and absence of tetraethylammonium perchlorate

	Y	X	T°C	[RCl]	[Cl$^-$]	[ClO$_4^-$]	$k\times10^2$ l/mol·min
Ie	CH=CH	p-Cl	20	0.10	0.10	—	2.63
				0.10	0.03	—	2.72
				0.10	0.01	—	2.80
				0.10	0.03	0.07	2.56
				0.10	0.01	0.09	2.55
Ii	CH=CH	p-OCH$_3$	20	0.10	0.10	—	7.42
				0.05	0.10	—	7.40
IId	C≡C	p-Cl	30	0.10	0.10	—	3.32
				0.10	0.03	—	3.36
				0.10	0.01	—	3.48
				0.10	0.03	0.07	3.15
				0.10	0.01	0.09	3.17

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[4] J. Hayami, N. Tanaka, S. Kurabayashi, Y. Kotani, and A. Kaji, This Bulletin, **44**, 3091 (1971).

[5] J. Hayami, N. Tanaka, and N. Hihara, *Bull. Inst. Chem. Res., Kyoto Univ.*, **50**, 354 (1972).

[6] a) L. F. Hatch, L. B. Gordon, and J. J. Russ, *J. Amer. Chem. Soc.*, **70**, 1093 (1948). b) L. F. Hatch and H. E. Alexander, *ibid.*, **72**, 5643 (1950). c) L. F. Hatch and V. Chiola, *ibid.*, **73**, 360 (1951). d) C. A. Vernon, *J. Chem. Soc.*, **1954**, 4462.

[7] a) A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965). b) A. J. Parker, *Quart. Rev.* (London), **1962**, 163.

[8] The correlation factor obtained for these compounds is not satisfactory, but the rather poor linearity does not affect a general discussion of the present work. Jaffé reported that there were not enough examples of good linear relationship for systems with $|\rho|\leqq0.2$.[9]

[9] H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE 2. SECOND ORDER RATE COEFFICIENTS OF FINKELSTEIN REACTIONS (X-Ph-Y-CH_2Cl + Halide) AT 20°C. $k\times10^2$ l/mol·min

X \ Y	CH=CH	C≡C	None[a)]	
			Cl^-	F^-
p-NO_2	2.34	0.90	3.47	—
m-NO_2	1.93	—	2.46	5.71
m-CF_3	1.96	0.841	1.76	2.94
m-Cl	2.13	0.860	1.35	1.59
p-Cl	2.63	0.964	1.81	2.29
H	2.54	0.914	1.23	1.59
m-CH_3	2.64	1.07	1.25	1.48
p-CH_3	3.18	1.15	1.83	2.29
p-OCH_3	7.42	1.15	4.52	3.26

a) Ref. 5.

TABLE 3. EFFECT OF THE GROUP ADJACENT TO THE REACTION CENTER. RELATIVE RATE OF FINKELSTEIN REACTIONS OF MODIFIED METHYL CHLORIDES (20°C)

Y	Halide	$k\times10^2$ (l/mol·min)	Relative rate
O	Cl	1500[a,b)]	400000
S	Cl	3.81[b)]	1020
CH=CH	Cl	2.54	680
C≡C	Cl	0.914	250
None	Cl	1.23[c)]	330
None	F	1.59[c)]	430
CH_2	Cl	0.00372[a,b)]	1

a) Calculated from the the data at other temperatures.
b) Ref. 4. c) Ref. 5.

shaped line for p-substituted compounds.

In discussing the results, three factors are conceivable in determining the rate of the S_N2 reactions. Besides the solute-solvent interactions and steric effects, which are similar or essentially similar to those of all the reaction systems studied, the following factors have been proposed and successfully applied to rationalize the S_N2 reactions:[10)] a) approach of the nucleophile; b) stabilization of the transition state by the electron-donating conjugation with the incipient pseudo-p-orbital; and c) the "neighboring orbital overlap," an interaction which involves both the substrate and nucleophile.

The rate determining approach of a nucleophile is a characteristic feature of the S_N2 reaction, a dominating factor when there is no group that stabilizes the transition state of such a reaction. An example was presented for the Finkelstein reaction of 2-arylethyl chlorides where a good linear Hammett relationship with positive value of ρ was obtained.[4)] For modified methyl chlorides, at least for the examples studied in the present paper, the nucleophilic approach may be rather a common factor while the other two effects should be discriminating. The polar effect alone cannot account for the rate differences between 2-phenylethyl chloride and benzyl chloride.[11)] Thus the rate enhancement should be attributed to the conjugative interaction involving the reaction center.

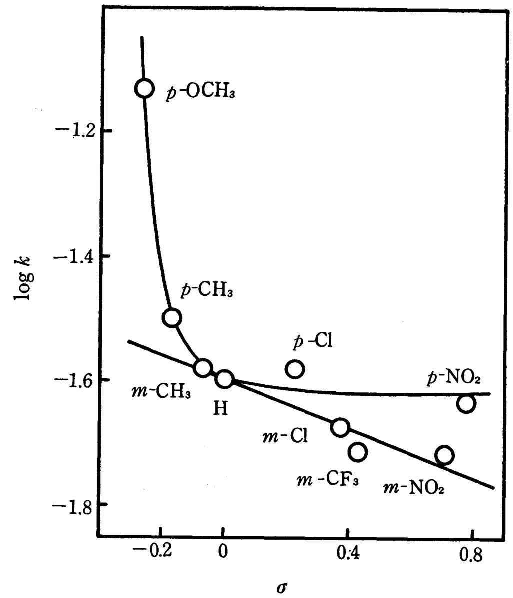

Fig. 1. Hammett plot for the chlorine exchange of substituted cinnamyl chlorides (I) at 20°C. $\rho=-0.19$, $r=0.962$

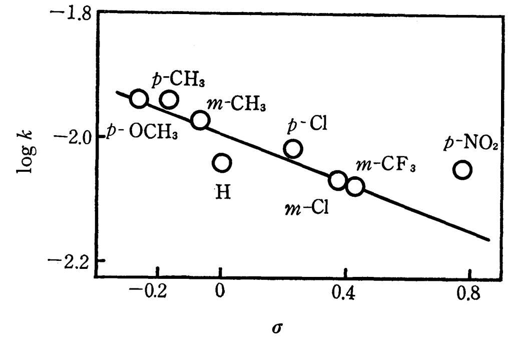

Fig. 2. Hammett plot for the chlorine exchange of 3-aryl-2-propynyl chlorides (II) at 20°C. $\rho=-0.19$, $r=0.919$

Negative ρ values found for the cinnamyl and 3-aryl-2-propynyl chlorides indicate that an electron-donating effect is dominant in these reactions. Stabilization would be attributed to an electron-donating conjugation. The cinnamyl system seems to exert a somewhat larger effect than the 3-aryl-2-propynyl system does. Taking into account the fact that an acceptable linear Hammett relationship holds for both of the p- and m-substituted 3-aryl-2-propynyl chlorides and that the ethynylic linkage is a rather poor transmitter of the conjugative effect but a good transmitter of the polar effect,[12)] the effect in this system should be ascribed to the electron-donating conjugation of the triple bond itself with the reaction center.

[10)] Ref. 2c. pp. 26—29.

[11)] The difference in $\sigma^*(\sigma^*_{Ph}-\sigma^*_{PhCH_2}=0.4)$ predicts a rate enhancement not more than several times for a conceivable reaction parameter ($\rho=1$—2) for such a reaction.

[12)] For a reaction involving the rate determining approach of an anion, a triple bond exerts an almost similar effect as a double bond as long as there is no pronounced effect of conjugation. Thus for the base catalyzed hydrolysis of ethyl cinnamate, ρ was reported to be 1.3 while the same reaction with ethyl 3-arylpropiolate gave $\rho=1.1$. (cf. R. M. O'Ferrall and S. I. Miller, *J. Amer. Chem. Soc.*, **85**, 2440 (1963), and I. J. Solomon and R. Filler, *ibid.*, **85**, 3492 (1963).)

Table 4. Comparison of the rate of Finkelstein reaction of benzyl chlorides with chloride and fluoride[a)]

	p-OCH$_3$	p-CH$_3$	m-CH$_3$	H	p-Cl	m-CF$_3$	m-NO$_2$	p-NO$_2$
k_{Cl^-}/k_{F^-}	1.39	0.80	0.84	0.77	0.79	0.60	0.43	<0.60[b)]

a) Ref. 5. b) $k_{Cl^-}(p\text{-NO}_2)/k_{F^-}(m\text{-NO}_2)$

The U-shaped Hammett plot for the p-substituted cinnamyl chlorides suggests an operation of an additional conjugation through the double bond, an effect not operative in the present instance of the ethynylic linkage. This additional rate enhancement definitely shows that the cinnamyl system is a good transmitter of a conjugative effect even in the S_N2 transition state. A similar observation for the benzyl chloride is common, an example having been given[13)] (Table 2).

The increment of the rate constant from the value predicted by the ρ-σ relationship for m-substituted compounds is a measure of the perturbing effect of a p-substituent. Such increments for the benzyl chlorides[14)] are plotted against a similar increment observed in the cinnamyl chlorides, and shown in Fig. 3.

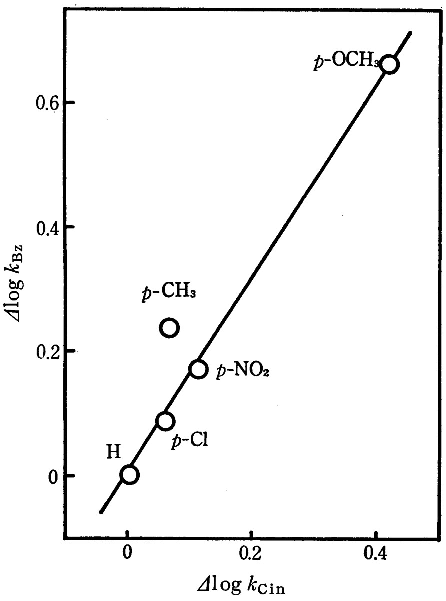

Fig. 3. Rate increment by p-substituents. Comparison of benzyl chlorides ($\Delta\log k_{Bz}$) with cinnamyl chlorides ($\Delta\log k_{Cin}$).

A fairly good linear relationship was obtained which implies the common nature of the reactivity of two classes of compounds. A most interesting observation is that the linear relationship also includes p-nitro substituent which shows a rate enhancement hardly interpreted.

The concept of "neighboring orbital overlap" is quite attractive to rationalize the rate accelerating effect by p-cyano and p-nitro substituents.[10)] The trend has often been reported and is also observed in the present cases (Figs. 1 and 2).

In a trial to reveal the contribution of the effect, the reaction of benzyl chlorides with fluoride anion in acetonitrile[5)] has quite an important bearing.

If the "neighboring orbital overlap" is operative in the present instances of chlorine-chlorine isotopic exchange reaction, the overlap should serve as a retarding factor for the organic halides with an electron-donating substituent, while the S_N2 reaction with fluoride anion should be essentially free of this overlap.[15)]

Thus the ratio of the second-order rate coefficients of these two Finkelstein reactions, k_{Cl^-}/k_{F^-}, should be lower for benzyl chlorides with effective electron-donating substituent and higher for benzyl chlorides with strongly electron-attracting substituent whose rate enhancement due to the overlap is expected. This is not the case with the two Finkelstein reactions of the substituted benzyl chlorides (Table 4). The finding would be an indication against the operation of the "neighboring orbital overlap."

However, there can be another explanation for the rate ratio in Table 4. Tightening of the transition state, which is possibly brought about by the involvement of a very "hard" nucleophile (fluoride anion), should result in a lower k_{F^-} for compounds with electron-donating substituent and a higher k_{F^-} for compounds with electron-attracting substituent. Thus, the effect of "neighboring orbital overlap" can be counteracted, or could be apparently counterbalanced depending upon the degree of tightening. In an extreme case, in which tightening is overwhelming, importance of the approach of a nucleophile becomes dominating and the contribution of conjugative stabilization plays only a minor role. The effect of the overlap can thus easily be masked.

Table 5. Activation parameters for Finkelstein reactions of modified methyl chlorides[a)]

Y	X	E_a kcal/mol	$\Delta S^{\neq}$ e.u. (20°C)
O[b)]	H	14.0	−14.9
O[b)]	p-NO$_2$	17.7	−5.6
S[b)]	H	18.0	−13.8
S[b)]	p-NO$_2$	20.1	−10.0
CH=CH	H	19.6	−9.1
CH=CH	p-Cl	19.3	−10.1
C≡C	H	20.6	−7.7
C≡C	p-Cl	21.0	−6.2
None	H	18.1	−15.8
None[c)]	H	17.1	−16.5
CH$_2$[b)]	H	24.0	−6.8
CH$_2$[b)]	p-NO$_2$	24.2	−4.1

a) Reaction with chloride ion. b) Ref. 4. c) Reaction with fluoride ion. Ref. 5.

[13)] G. M. Bennett and B. Jones, *J. Chem. Soc.*, **1935**, 1815.

[14)] A linear relationship (ρ=0.36, r=0.905) was tentatively given from the data for the benzyl chlorides with m-substituent (m-NO$_2$, m-CF$_3$, m-Cl, and H, m-CH$_3$).

[15)] It is commonly accepted that the rate-controlling effect of this nature is more pronounced in cases in which the entering and leaving groups are not first row elements. (*cf.* Ref. 2c, p. 28).

TABLE 6. PHYSICAL CONSTANTS OF SUBSTITUTED CINNAMYL CHLORIDES

	X	bp °C/mmHg (mp°C)	Solvent	(lit)
Ia	*p*-NO_2	(56.0—56.5)	CH_3OH	(58.5—59.5)[a] (58—60)[b]
Ib	*m*-NO_2	(83.0—83.5)	CH_3OH	(78)[a]
Ic	*m*-CF_3	79.0—79.5/3		
Id	*m*-Cl	112.0—113.0/6		90/0.1[a]
Ie	*p*-Cl	(41.0—41.5)	CH_3OH	95/0.6[a]
If	H	116.0—118.0/16 (7.0—8.0)		94/2[c] (7—8)
Ig	*m*-CH_3	86.5—87.0/3		
Ih	*p*-CH_3	(38.5—39.0)	*n*-C_6H_{14}-C_6H_6	(39.5—40.0)[d]
Ii	*p*-OCH_3	(73.0—74.0)	*n*-C_6H_{14}-C_6H_6	(71.5—73.0)[e]

a) Ref. 20. b) Ref. 21. c) Ref. 6b. d) Ref. 22. e) Ref. 19.

However, the use of the fluoride anion failed to substantiate the tight transition state as is proved by the U-shaped Hammett plot concave upward of the reaction with benzyl chlorides.[16]

As to the relative effectiveness of the group adjacent to the S_N2 reaction center in promoting the reactions of the modified methyl chlorides, the present work furnishes the order $O \gg S > CH{=}CH > \text{None (benzyl)} \gtrsim C{\equiv}C \gg CH_2$. This can be rationalized in terms of the relative effectiveness of the conjugative stabilization of the transition state, oxygen and sulfur atom being more effective than the unsaturated group. The data of activation energy support this explanation (Table 5).

As the rate enhancement due to the effective conjugation implies loose transition state,[17] a study of the secondary deuterium isotope effect should be quite interesting. The work is now in progress and the results will be the subject of the forthcoming paper.[18]

Experimental

Preparation of Materials. Cinnamyl chloride (If) and *p*-nitrocinnamyl chloride (Ia) were prepared from the corresponding cinnamyl alcohols by the standard method with thionyl chloride in dry benzene. Other cinnamyl chlorides (Ib, c, d, e, g, h) were prepared from the corresponding 1-arylallyl alcohols[19] by passing gaseous hydrogen chloride through their ethereal solutions. After being passed through a short column of alumina with *n*-hexane-benzene mixture as an eluent, cinnamyl chlorides were purified by distillation under reduced pressure or by recrystallization from the solvent listed in Table 6.

TABLE 7. PHYSICAL CONSTANTS OF 3-ARYL-2-PROPYNYL DERIVATIVES

	X	Chloride bp°C/mmHg (mp°C)	Alcohol bp°C/mmHg (mp°C)
IIa	*p*-NO_2	(65.5—66.0)	
IIb	*m*-CF_3	80.0—80.5/4	103.5—105.0/3
IIc	*m*-Cl	108.0—108.5/6.5	122.5—124.0/3
IId	*p*-Cl	99.5—100.5/2.5 (26.4—26.6)[a]	138—140/6 (78.0—78.5)
IIe	H	78.5—79.0/5[b]	139—141/18[e]
IIf	*m*-CH_3	97.0—98.0/5.5	115.5—117.0/4
IIg	*p*-CH_3	92.0—92.5/4	116.5—117.5/4 (25.0—26.0)
IIh	*p*-OCH_3	126—129/3[c] (22.5—23.0)[d]	146—148/4 (62.0—63.0)

a) CH_3OH. b) Ref. 23. c) Crude material. d) *n*-hexane-benzene. e) Ref. 20 and 24.

3-Aryl-2-propynyl chlorides. 3-Aryl-2-propynyl alcohols were prepared from the corresponding arylacetylenes. As an example, phenylacetylene (20 g, 0.20 mol) in 50 ml of ether was added to ethereal solution of 0.22 mol of ethyl magnesium bromide in 150 ml of ether. The resulting solution was stirred overnight at room temperature. Powdered paraformaldehyde (10 g, 0.33 mol as CH_2O), dried in a vacuum dessicator for a few days, was added to this solution in small portions. After being refluxed for three hours, the solution was worked up as usual. Distillation gave 16.5 g (63%) of 3-phenyl-2-propynyl alcohol. 3-Aryl-2-propynyl chlorides (IIb—IIh) were obtained from the corresponding alcohols by the reaction with thionyl chloride.

3-*p*-Nitrophenyl-2-propynyl chloride (IIa) was prepared by nitration of 3-aryl-2-propynyl chloride (IIe). Under vigorous stirring 1g of IIe was added slowly into 20 ml of fuming nitric acid (d. 1.50) at −30°C. After the addition was complete, the solution was stirred for another minute,

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[16] The observed trend that the rate ratio is slightly larger for the strongly electron-donating substituent and smaller for the strongly electron-attracting substituent was pointed out previously.[5] This can be a reflection of the tightening of the transition state, although it is not overwhelming.

[17] A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

[18] Normal isotope effects were found; 5% for *p*-methyl and *p*-methoxy benzyl chloride, about 10% for chloromethyl aryl ethers and sulfides. Cinnamyl chloride also exhibited about 5% isotope effect. The positive effect definitely supports the concept of loose transition state and a conjugative interaction. cf. Preprint p. 21, 23rd Symposium on Organic Reaction Mechanism, Kobe, October 1972 and also N. Tanaka, A. Kaji, and J. Hayami, *Chem. Lett.*, **1972**, 1223.

[19] W. N. White and W. K. Fife, *J. Amer. Chem. Soc.*, **83**, 3846 (1961).

[20] G. Cignarella, E. Occelli, and E. Testa, *J. Med. Chem.*, **8**, 326 (1965).

[21] N. V. Smirnova, A. P. Arendaruk, D. D. Smolin, and A. P. Skoldinov, *Med. Prom. S. S. S. R.*, **12**, 31 (1958).

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[23] M. Nagawa, H. Ito, and A. Terada, Jap., 10919 (1964).

[24] a) E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, **1954**, 1854. b) C. Moureu and H. Desmots, *C. R. Acad. Sci. Paris*, **132**, 1224 (1901).

and the mixture was poured into ice water. The organic compounds were extracted with benzene. The benzene extract was dried with anhydrous magnesium sulfate and the solution was concentrated under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane-benzene as an eluent. Recrystallization from methanol gave pure IIa.

These chlorides decomposed gradually on standing. Fresh samples were therefore used for the kinetic experiment immediately after purification. Purification was affected by column chromatography on alumina followed by distillation or recrystallization.

The structures of these unsaturated chlorides were confirmed by their NMR and IR spectra. Physical constants are summarized in Tables 6 and 7.

Preparation and purification of tetraethylammonium salts and acetonitrile were undertaken as described previously.[4)]

Kinetic Measurements. Batch method was utilized. A modification was made by use of toluene as an extracting solvent instead of benzene.

Tracer experiments were carried out at Radioisotope Research Center of Kyoto University. Sincere thanks are due to the staff of this institution. The work was supported by the Ministry of Education and Saneyoshi Shogakkai.