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S_N2 Reactions in Dipolar Aprotic Solvents. Chlorine Isotopic Exchange Reactions of 2-Arylethyl Chlorides, Chloromethyl Aryl Ethers, and Chloromethyl Aryl Sulfides in Acetonitrile[1]

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The S_N2 reactions having a symmetrical transition state were studied in a dipolar aprotic solvent. A good Hammett correlation was found for the chlorine isotopic exchange reactions in acetonitrile between tetraethylammonium chloride and three types of substituted methyl chlorides, 2-arylethyl chlorides, chloromethyl aryl ethers, and chloromethyl aryl sulfides. The reaction constant was positive for 2-arylethyl chlorides and negative for the methyl chlorides possessing an α-heteroatom. The presence of oxygen and sulfur atom on the α-position to the reaction center resulted in a rate enhancement of about 10^5 times and 10^3 times, respectively. Features of the transition states of these S_N2 reactions are discussed.

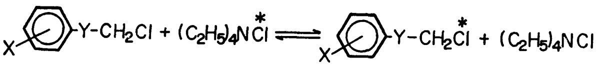
Nucleophilic substitution at a saturated carbon atom has been extensively studied.[3] As compared to abundant studies on unimolecular reactions, not much has been carried out on the features of the S_N2 reactions. Timing of bond-breaking and bond-forming and also the electronic requirement of the transition state are less extensively studied. Parker examined the solvent effect on bimolecular reactions.[4] However, little information is presented concerning the effect of the structures of the substrates.

In the present study, attempts were made to bring about a clean S_N2 reaction of which the examination of the Hammett relationship is feasible.

Methyl chlorides with a substituent at the α-position were prepared and subjected to isotopic exchange reaction in dry acetonitrile. Smaller solvation of anions in a dipolar aprotic solvent implies a slight change in anion solvation, minimizing the difficulties due to desolvation-solvation phenomena of anionic entities involved in an S_N2 displacement.[5] As is proved in this communication, kinetics suffered little from the change of ion-pair dissociation equilibria of the quaternary ammonium salt. In solvent acetonitrile, such a salt shows fairly good dissociation and little trouble is anticipated.

Results and Discussion

Three substituted methyl chlorides, 2-arylethyl chlorides, aryloxymethyl chlorides (chloromethyl aryl ethers), and arylthiomethyl chlorides (chloromethyl aryl sulfides) were prepared. These substrates were treated in dry acetonitrile with tetraethylammonium chloride-^{36}Cl. The reactions are summarized as follows.



(1)

I Y: CH_2, X: a) p-NO_2, b) m-Cl, c) p-Cl, d) H, e) p-CH_3, f) p-OCH_3, g) p-OC_3H_7-i
II Y: O, X: a) p-NO_2, b) m-Cl, c) p-Br, d) p-Cl, e) H, f) p-CH_3, g) p-OCH_3
III Y: S, X: a) p-NO_2, b) p-CN, c) m-CN, d) p-$COCH_3$, e) m-Cl, f) p-Cl, g) H, h) m-CH_3, i) p-CH_3, j) p-OCH_3

Rates of the bimolecular substitution reactions with a symmetrical transition state were followed by examining the radioactivities incorporated in the organic compounds and also the radioactivities remaining in the ionic chloride. In every case, a good first order kinetics was observed. Second order rate coefficients were deduced by dividing the observed first order rate constants by pertinent chloride concentrations. Typical kinetic data are given in Table 1.

Examination was made of the effect of ion-pair dissociation of the quaternary ammonium chloride in

TABLE 1. CHLORINE EXCHANGE BETWEEN CHLOROMETHYL PHENYL SULFIDE AND TETRAETHYLAMMONIUM CHLORIDE AT 20°C[a)]

Run	Time min	Radioactivity (cpm) benzene layer	Radioactivity (cpm) water layer	X_e[b)]	$k\times10^2$ l/mol min
1	25	1,510	15,720	8,620	3.84
	50	2,700	14,480	8,590	3.77
	75	3,740	13,370	8,560	3.83
	100	4,590	12,570	8,580	3.82
2	60	2,880	12,780	7,830	3.82
	90	3,830	11,670	7,750	3.79
	120	4,670	10,970	7,820	3.79
					av. 3.81

a) [Chloromethyl phenyl sulfide] = [Tetraethylammonium chloride] = 0.10M

b) The difference between Run 1 and Run 2 was due to the difference of specific radioactivity of used tetraethylammonium chloride.

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[1] Presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970.

[2] To whom correspondences should be addressed.

[3] 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).

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

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

acetonitrile. A slight but not serious change in k_2 was observed in changing the concentration of the ammonium chloride present. This shows that a slight change in ion-pair dissociation equilibrium took place in the concentration range studied (an implication of essentially complete dissociation). The results are in contrast to reactions in dimethylformamide, where the rate increment of about 30% was observed for the seven fold variation in chloride ion concentration.6) A slight decrease in the rate observed in the presence of an inert salt may be attributed to a common ion effect which affects the ion-pair dissociation equilibrium in the reaction system.

The reaction was essentially of second order, first order in the substrate and also in tetraethylammonium chloride. Second order rate coefficients calculated were constant, the deviation being within the experimental error for the change in the ten fold variation of chloride concentration. The results for chloromethyl aryl ethers and sulfides present a rare case where molecularity of the reaction is well defined for the reaction of this class of compound. The results are shown in Table 2.

TABLE 2. EFFECT OF THE CHLORIDE ION CONCENTRATION ON THE RATE OF THE CHLORINE EXCHANGE IN THE PRESENCE AND ABSENCE OF TETRAETHYLAMMONIUM PERCHLORATE

	Y	X	T°C	[Cl⁻]M	[ClO$_4^-$]M	k l/mol min
Id	CH$_2$	H	50.0	0.10	—	1.85×10^{-3}
				0.05	—	1.86
				0.01	—	1.87
				0.05	0.05	1.76
				0.01	0.09	1.66
IIa	O	p-NO$_2$	−15.9	0.10	—	4.73×10^{-2}
				0.05	—	4.89
				0.01	—	5.05
				0.05	0.05	4.59
				0.01	0.09	4.47
IIIg	S	H	20.0	0.10	—	3.81×10^{-2}
				0.05	—	3.87
				0.01	—	3.90
				0.05	0.05	3.77
				0.01	0.09	3.80

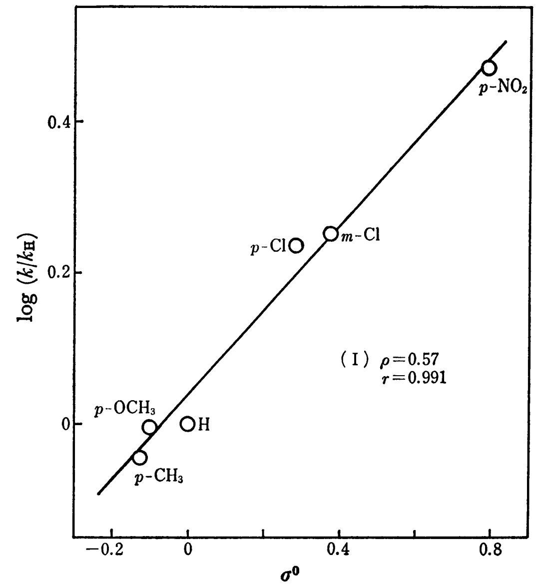

Fig. 1. a) Hammett plot for the chlorine exchange of 2-arylethyl chlorides (I) at 60°C.

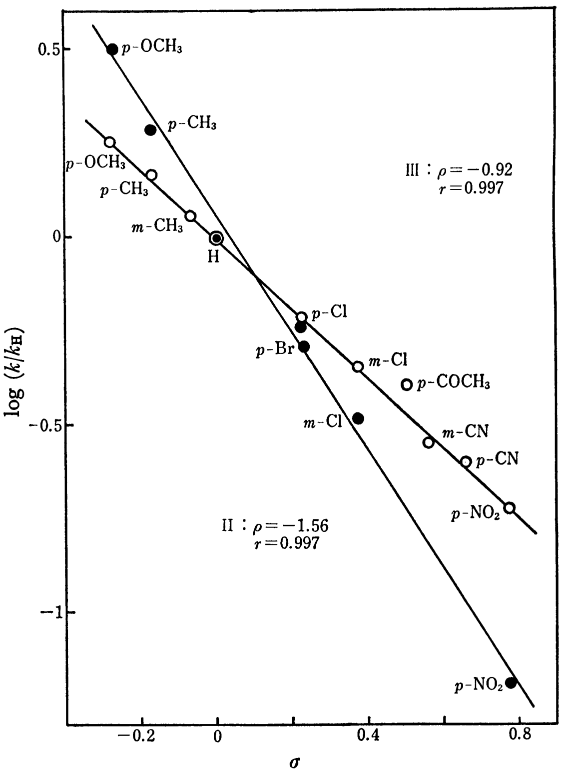

Fig. 1. b) Hammett plot for the chlorine exchange of chloromethyl aryl ethers (II: ●) and sulfides (III: ○) at −15.9°C and 20.0°C, respectively.

Hammett relationship holds for these second order rate coefficients. Typical examples are given in Fig. 1 and the results are summarized in Tables 3, 4, and 5.

These tables clearly show that the reaction constant ρ was positive for the 2-arylethyl chlorides and negative for both the chloromethyl aryl ethers and sulfides. Such a trend is not without precedent but the present instance is perhaps the first case where linear free energy relationship holds. Negative ρ which holds for the varieties of the substituents is rarely reported.

As pointed out by Jaffé,7) S_N2 reactions of 2-arylethyl chlorides with iodide ion in acetone gave $\rho=0.590$ with a correlation coefficient $r=0.870$. An example of 2-chloroethyl aryl sulfides was also reported, where electron-withdrawing substituents accelerate the reaction, ρ being 0.626 with $r=0.918$.

In the present instance, the rate accelerating effect of the heteroatom located on α-position to the reaction center is fairly large. The oxygen accelerates the reaction by a factor of 10^5—10^6 and the sulfur atom by a factor of 10^2—10^3 compared to the 2-arylethyl system. These values are compatible with the one reported in

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6) D. Cook and A. J. Parker, *J. Chem. Soc.*, *B*, **1968**, 142.

7) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE 3. RATE CONSTANTS FOR THE CHLORINE EXCHANGE OF 2-ARYLETHYL CHLORIDES[a)]

	X	$k \times 10^3$ l/mol min		
		40.0°C	50.0°C	60.0°C
Ia	p-NO_2	1.63	5.68	16.7
Ib	m-Cl			10.1
Ic	p-Cl			9.76
Id	H	0.564	1.85	5.65
Ie	p-CH_3			5.11
If	p-OCH_3			5.60
Ig	p-OC_3H_7-i			5.54

a) [2-Arylethyl chloride] = [Tetraethylammoninm chloride] = 0.10M

TABLE 4. RATE CONSTANTS FOR THE CHLORINE EXCHANGE OF CHLOROMETHYL ARYL ETHERS[a)]

	X	k l/mol min			
		−21.3°C	−15.9°C	−10.0°C	0°C
IIa	p-NO_2		0.0473	0.112	0.362
IIb	m-Cl		0.241		
IIc	p-Br		0.374		
IId	p-Cl		0.425		
IIe	H	0.413	0.737	1.38	
IIf	p-CH_3		1.41		
IIg	p-OCH_3		2.33		

a) [Chloromethyl aryl ether] = [Tetraethylammonium chloride] = 0.10M

TABLE 5. RATE CONSTANTS FOR THE CHLORINE EXCHANGE OF CHLOROMETHYL ARYL SULFIDES[a)]

	X	$k \times 10^2$ l/mol min		
		20.0°C	30.0°C	40.0°C
IIIa	p-NO_2	0.715	2.27	6.46
IIIb	p-CN	0.939		
IIIc	m-CN	1.07		
IIId	p-$COCH_3$	1.55		
IIIe	m-Cl	1.71		
IIIf	p-Cl	2.31		
IIIg	H	3.81	10.9	27.3
IIIh	m-CH_3	4.29		
IIIi	p-CH_3	5.55		
IIIj	p-OCH_3	6.79		

a) [Chloloromethyl aryl sulfide] = [Tetraethylammonium chloride] = 0.10M

TABLE 6. ACTIVATION PARAMETERS FOR THE CHLORINE EXCHANGE REACTIONS OF ALKYL CHLORIDES

X-C_6H_4-Y-CH_2Cl

X	Y	E kcal/mol	$\Delta S^{\neq}$ e.u.(20°C)
H	CH_2	24.0	−6.8
	O	14.0	−14.9
	S	18.0	−13.8
p-NO_2	CH_2	24.2	−4.1
	O	17.7	−5.6
	S	20.1	−10.0

literature.[3c,8)] Ballinger and his co-workers[8c)] showed the accelerating effect of the α-heteroatom to be 10^5 for oxygen in a methoxy group in an S_N2 solvolysis of methoxymethyl chloride.

The acceleration may be ascribed to the electron deficiency of the reaction center caused by the presence of an electronegative heteroatom. This can be ruled out by the negative ρ found for the isotopic exchange reactions. The results show definitely that the effects of the α-oxygen and of the α-sulfur atom are due to electron-donation. The electron-donating conjugation of oxygen and sulfur seems to surpass the electron-withdrawing inductive effect in this case.

In other words, in the case of the S_N2 reaction of chloromethyl aryl ethers and sulfides, the important factor should be the stabilization of the transition state by the electron-donating conjugation of an α-heteroatom with the reaction center. The conjugation brings about the delocalization of the developing fractional positive charge on the central carbon atom. The $2p$–$2p$ overlap between carbon and oxygen may exert a larger effect than $2p$–$3p$ overlap provided by sulfur.[8a)] The smaller activation energy for the ethers may support this interpretation. An electron-donating group can facilitate the bond dissociation in a nucleophilic displacement, and also can retard the bond formation to the incoming nucleophile. Accordingly, the effect of such a group should be self-canceling and should not reflect on the rate of the bimolecular symmetrical substitution.

In the case of 2-arylethyl chlorides, the ease of approach of the entering chloride ion seems to be essential.[9)] The effect of substituents is essentially polar (inductive), and the linear free energy relationship with a positive ρ holds for Taft's σ^0,[10)] a polar parameter.

It should be noted that as far as the S_N2 reactions in the present instance are concerned, there seems to be no clue to the fact that the ion-pair mechanism of Sneen[11)] is operative. Potential cation from 2-arylethyl chlorides may accept the participation of aryl group (*cf.* ethylenephenonium cation), showing the accelerating effect by electron-donating substituents which generally obeys the ρ–σ^+ relationship. However, this is not the case. Also in the other two cases, where electron-donating substituents accelerated the reaction, ion-pair mechanism is less probable. Hammett ρ values were −1.56 and −0.92 for these compounds. These values seem too small to imply the interaction of an α-heteroatom with the fully developed

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8) a) M. Murakami and S. Oae, *Nippon Kagaku Zasshi*, **72**, 595 (1951). b) H. Böhme and A. Dörries, *Chem. Ber.*, **89**, 719 (1956). c) P. Ballinger, P. B. D. De La Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, **1955**, 3641.

9) The polar effect observed in the present study is tentatively ascribed to the importance of bond formation at the transition state. The interpretation based on a field effect proposed by Holtz and Stock is noteworthy. However, the establishment of ρ-σ^0 rather than ρ-σ_I relationship seems to prefer the present interpretation. H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **87**, 2404 (1965).

10) a) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960). b) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 878 (1965).

11) R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 362 (1969).

positive center.[12)]

A report was given by the authors showing that the E2 reaction from 2-arylethyl chlorides in acetonitrile gave a ρ value close to 2.[13)] This implies that electronic requirement of the S_N2 reaction with chloride ion is quite different from that of the E2 reaction promoted by fluoride ion.

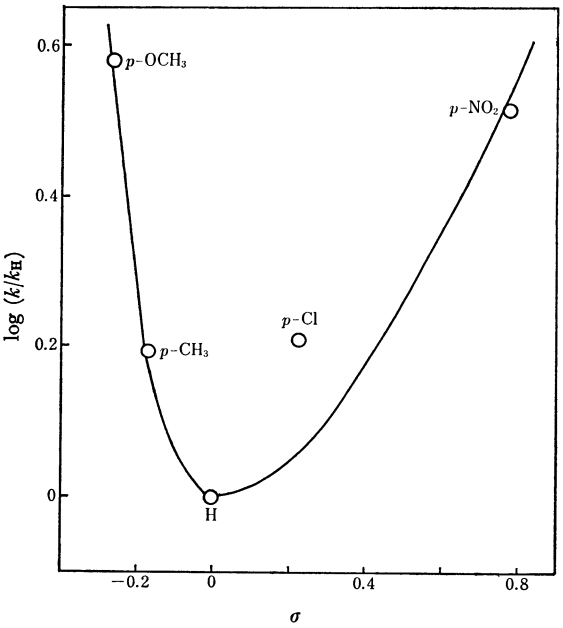

Fig. 2. Hammett plot for the chlorine exchange of benzyl chlorides at 40.0°C.

The U-shaped Hammett plots were reported for the S_N2 reactions of benzyl halides in some cases.[14)] The authors carried out the chlorine exchange reaction between substituted benzyl chlorides and tetraethylammonium chloride. The symmetrical S_N2 reaction showed an ordinary U-shaped Hammett plot as shown in Fig. 2. The result implies that the tightening factor in a symmetrical transition state after Parker[15)] is not effective enough to make the intrinsically loose transition state tighter.

Experimental

Preparation of materials. a) 2-Arylethyl chlorides (Ib—Ig) were prepared from corresponding 2-arylethyl tosylates by heating to reflux with tetraethylammonium chloride in acetonitrile. The products were purified by distillation under reduced pressure. 2-*p*-Nitrophenylethyl chloride (Ia) was obtained by nitration of 2-phenylethyl chloride (Id).

b) Chloromethyl aryl ethers (IIa—IIg) were prepared from sodium aryloxymethanesulfonates with phosphorus pentachloride, and purified by vacuum distillation except for chloromethyl *p*-nitrophenyl ether (IIa) and chloromethyl *p*-bromophenyl ether (IIc) which were recrystallized from petroleum ether containing a small amount of benzene.[16)]

c) Chloromethyl aryl sulfides (III) were prepared by either of the two following methods. (A). Corresponding thiophenols were allowed to react with paraformaldehyde and gaseous hydrogen chloride in methylene chloride. (B). Corresponding methyl aryl sulfides were chlorinated with sulfuryl chloride in methylene chloride.[17)] Chloromethyl *p*-nitrophenyl sulfide (IIIa) and chloromethyl *p*-cyanophenyl sulfide (IIIb) were purified by recrystallization from methylene chloride. Chloromethyl *m*-cyanophenyl sulfide (IIIc) and chloromethyl *p*-acetylphenyl sulfide (IIId) were recrystallized from methylene chloride after distillation under reduced pressure. The structures of new compounds were confirmed by their NMR and IR spectra and by elemental analyses.

Physical constants of alkyl chlorides (I, II, III) are summarized in Tables 7,8, and 9.

Table 7. Physical constants of 2-arylethyl chlorides

	X	Bp °C/mmHg (Mp °C)	(lit)
Ia	p-NO$_2$	(49.0)	(48—49)[a)]
Ib	m-Cl	130—131/35	
Ic	p-Cl	84.0/4	82—83/3[b)]
Id	H	86.0/18	90/25[c)]
Ie	p-CH$_3$	66.5/3	67/4[c)]
If	p-OCH$_3$	94.0/3	95/4[c)]
Ig	p-OC$_3$H$_7$-i	106.0/5	

a) Ref. 18 b) Ref. 19 c) Ref. 13

Table 8. Physical constants of chloromethyl aryl ethers

	X	Bp °C/mmHg (Mp °C)	(lit)[a)]
IIa	p-NO$_2$	(34.0—34.5)	(36—37)
IIb	m-Cl	82.0—83.0/6	112—113/18
IIc	p-Br	(52.0—52.5)	(55—56)
IId	p-Cl	87.0—88.0/6	120—124/18
IIe	H	86.0—87.0/17	88—89/15
IIf	p-CH$_3$	98.5—99.0/16.5	106—108/20
IIg	p-OCH$_3$	98.5—99.0/5.5	140—141/18

a) Ref. 16

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12) The observed rate constants, or ρ values, can be affected by the ion-pair return that makes the interpretation of ρ values ambiguous.[a)] It is quite plausible, however, that the solvent separated ion-pair intermediate is effectively intercepted by chloride and/or perchlorate ion, and external ion-pair return from this intermediate is minimized by the presence of tetraethylammonium salt in a concentration range studied.[b)] It is difficult to confirm or disprove the intervention of an intimate ion-pair. However the enhanced internal return should result in a high ρ value reaching the limiting value for S_N1 reactions. Bordwell and his coworkers reported that an S_N1 reaction of chloromethyl aryl sulfides gave $\rho = -2.6$ at 34.85°C.[c)] a) S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, **34**, 3127 (1969). b) S. Winstein and A. H. Fainberg, *J. Amer. Chem. Soc.*, **80**, 459 (1958); E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958). c) F. G. Bordwell, G. D. Cooper, and H. Morita, *J. Amer. Chem. Soc.*, **79**, 376 (1957).

13) J. Hayami, N. Ono, and A. Kaji, This Bulletin, **44**, 1628 (1971).

14) a) S. Sugden and J. B. Willis, *J. Chem. Soc.*, **1951**, 1360. b) G. M. Benett and B. Jones, *ibid.*, **1935**, 1815. c) H. Franzen and I. Rosenberg, *J. Prakt. Chem.*, (2) **97**, 82 (1918).

15) A. J. Parker, Ref. 4, p. 15.

16) H. J. Barber, R. F. Fuller, M. B. Green, and H. T. Zwartouw, *J. Appl. Chem.* (London), **1953**, 266.

17) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955).

18) E. Ferber, *Ber.*, **62**, 187 (1929).

19) C. H. Depuy and C. A. Bishop, *J. Amer. Chem. Soc.*, **82**, 2535 (1960).

TABLE 9. PHYSICAL CONSTANTS AND ANALYTICAL DATA OF CHLOROMETHYL ARYL SULFIDES

	X	Bp °C/mmHg (Mp °C)	Analysis found (calcd)			Method	(lit.)
			C%	H%	N%		
IIIa	p-NO$_2$	(63.5—64.0)				B	(62—64)[a]
IIIb	p-CN	(60.5—61.0)	52.50 (52.32	3.16 3.29	7.38 7.63)	B	
IIIc	m-CN	120.0—121.0/0.4 (31.5—32.0)	52.28 (52.32	3.07 3.29	7.37 7.63)	B	
IIId	p-COCH$_3$	140.5/0.75 (43.0)	54.04 (53.86	4.50 4.52)		A	
IIIe	m-Cl	94.5/0.7				B	115—116/5[a]
IIIf	p-Cl	109—111/4.0				A	128—129/12[a]
IIIg	H	115.5—116.0/20				A	106—109/12[b]
IIIh	m-CH$_3$	88.5—89.0/1.3				B	125/16[a]
IIIi	p-CH$_3$	87.0/0.8				A	125—126/15[a]
IIIj	p-OCH$_3$	105.0/0.7				A	141—142/12[b]

a) Ref. 12 b) Ref. 17

d) Tetraethylammonium chloride labeled with Cl-36 was prepared by titration of tetraethylammonium hydroxide with hydrochloric acid labeled with Cl-36. Tetraethylammonium chloride having suitable specific radioactivity was obtained by dilution and recrystallization with non-active tetraethylammonium chloride from chloroform containing a small amount of petroleum ether. Essentially no loss of radioactivity due to exchange reaction between chloroform and the chloride was observed. The reagent was dried *in vacuo* at 110°C before use. Acetonitrile was purified according to the procedure described previously.[20]

Kinetic measurements. Batch method was used for kinetic runs. Aliquots of the acetonitrile solutions of an alkyl chloride and tetraethylammonium chloride were put separately into an ampoule with double stems, and the tube was flame-sealed. After the temperature equilibrium was attained, the kinetic run was initiated by inverting and shaking the ampoule. The reactions of 2-arylethyl chlorides and chloromethyl aryl sulfides were quenched by cooling with an acetone-dry ice bath at appropriate intervals. Organic chloride was taken up in benzene while ammonium chloride was extracted in water. The reaction of chloromethyl aryl ethers was carried out in an ampoule equipped with a double rubber septum. The reaction was quenched by addition of a mixture of diisopropyl ether and n-hexane (10:1) precooled in an acetone-dry ice bath. The resulting mixture was extracted with three 5 ml portions of water. In all cases, the organic layer containing alkyl chlorides, and the aqueous layer containing tetraethylammonium chloride was made up to 25 ml. Chlorine-36 radioactivity was measured by liquid scintillation counting.[21] Exchange rates were calculated by the equation[22]

$$k = \frac{1}{t}\frac{1}{a+b}\ln\frac{X_e}{X_e-X},$$

where t, time; a, b, initial concentration; X, radioactivity of organic layer at time t; X_e, radioactivity of organic layer at infinite time.

Blank tests were performed with the non-active materials. Titration proved that alkyl chlorides underwent essentially no hydrolysis during extraction.

The tracer experiments were carried out at Radioisotope Research Center of Kyoto University. Sincere thanks are due to the staff of this institution.

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[20] R. U. Lemieux and J. Hayami, *Can. J. Chem.*, **43**, 2162 (1965).

[21] Nuclear Chicago 6801 liquid scintillation counter was utilized with dioxane base organic phosphor solution (7 g PPO, 0.050 g POPOP, 120 g naphthalene, and 1000 ml of dioxane). Radioactivity measurements were made long enough to secure the standard errors below ±1%.

[22] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York (1961), p. 192.