

S_N2 Reactions in Dipolar Aprotic Solvents. II. Direct Displacement Reactions of Substituted Benzyl Chlorides with Halide Anion in Acetonitrile.

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The S_N2 reactions of benzyl chlorides were studied in a dipolar aprotic solvent, acetonitrile. Chlorine-chlorine isotopic exchange reactions and displacement reactions with fluoride anion gave concaved Hammett relationships as are the cases with most of the benzylic reactions.

These results imply that "tightening factors" of the S_N2 transition state, namely a symmetrical transition state and a transition state involving a very hard nucleophile, are not effective enough to secure a tight transition state for any set of the S_N2 reactions.

The presence of the ion-molecule interaction in the ground state is suggested from nmr data.

In the previous report of this series, the present authors studied the chlorine-chlorine isotopic exchange reactions in a dipolar aprotic solvent, acetonitrile, and presented good Hammett relationships for the S_N2 reactions of the substituted methyl chlorides.¹⁾ In a separate paper, the authors also suggested that the use of a soluble fluoride in a dipolar aprotic solvent would offer a powerful means of examining the nature of many bimolecular reactions.²⁾

Recently, in a study of the direct displacement reaction of substituted benzyl bromides, Parker explained the relative rates and the variation in the solvent activity coefficient in terms of a spectrum of transition states with varying looseness or tightness.^{3,4)}

In the present communication, the authors studied the chlorine-chlorine isotopic exchange reaction of substituted benzyl chlorides and also studied a direct displacement reaction of such chlorides with fluoride anion in acetonitrile. Examination of the effect of the "tightening factors", a symmetrical transition state and a transition state involving a very hard nucleophile, is feasible with such Finkelstein reactions.⁴⁾

RESULTS AND DISCUSSION

Nine different kinds of substituted benzyl chlorides were used for the chlorine-chlorine isotopic exchange reaction with tetraethylammonium chloride-³⁶Cl as the chloride source. In a previous report,¹⁾ the present authors showed that, in a concentration range studied, this salt showed little change in an ion-pair dissociation equilibrium and that observed rate coefficients of the exchange reaction remained essentially constant. In the present

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Displacement Reaction of Benzyl Chlorides with Halide Anion

Table 1. Second Order Rate Constants for the Chlorine Exchange of Benzyl Chlorides.

$$\text{X-C}_6\text{H}_4\text{-CH}_2\text{Cl} + \text{*Cl}^\ominus \longrightarrow \text{X-C}_6\text{H}_4\text{-CH}_2\text{*Cl} + \text{Cl}^\ominus$$

X	$k_2 \times 10^2$ 1/mol min	
	in acetonitrile ^{a)} (20°)	in acetone ^{b)} (25°)
<i>p</i> -NO ₂	3.47	111 (240°)
<i>m</i> -NO ₂	2.46	—
<i>m</i> -CF ₃	1.76	—
<i>m</i> -Cl	1.35	—
<i>p</i> -Cl	1.81	29.8
H	1.23	16.9
<i>m</i> -CH ₃	1.25	10.3
<i>p</i> -CH ₃	1.83	27.1
<i>p</i> -OCH ₃	4.52	—

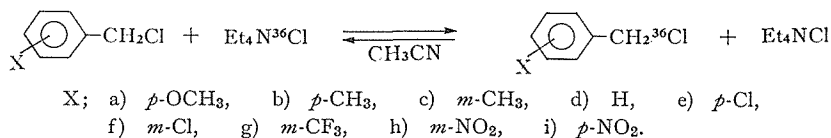
a) Present work. [Benzyl chloride] = [Tetraethylammonium chloride] = 0.10 M

b) Ref. 5 b)

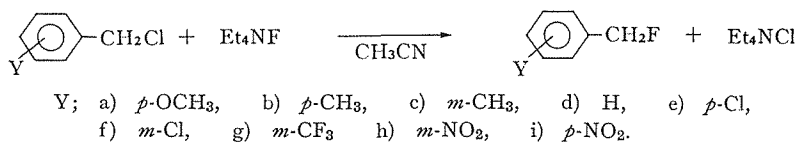
c) Ref. 6

study, following reactions were examined and proved to give good second-order kinetics throughout the course of the reactions.

The results are given in Table 1 with similar data of Lee for the exchange reaction in acetone as a solvent.^{5b)}



For a displacement reaction with fluoride anion, nine different kinds of benzyl chlorides were utilized. Which are shown in the following scheme:



Sometimes difficulty was encountered in getting a reproducible reactivity of the fluoride specimen.* Accordingly, control experiments with the unsubstituted benzyl chloride were always undertaken to secure a relative reactivity between the substituted benzyl chlorides.

* The fluctuating reactivity may be caused by a trace amount of water²⁾. The reaction mixture also contained some 0.01 to 0.02% of water which is sufficient to deactivate up to 10⁻² M of the tetraethylammonium fluoride.

Table 2. Relative Rates of the Displacement of Chloride Anion from Benzyl Chloride with Fluoride Anion in Acetonitrile.^{a)}

Y	Relative Rate	
	0°	20°
<i>p</i> -NO ₂	420 ^{b)}	—
<i>m</i> -NO ₂	3.30	3.59
<i>m</i> -CF ₃	—	1.85
<i>m</i> -Cl	—	1.00
<i>p</i> -Cl	1.69	1.44
H	1.00 ^{c)}	1.00 ^{c)}
<i>m</i> -CH ₃	—	0.90
<i>p</i> -CH ₃	—	1.44
<i>p</i> -OCH ₃	1.87	2.05

a) Rates of the chloride ion liberation.

[Benzyl chloride] = 0.03 M, [Tetraethylammonium fluoride] = 0.06 M

b) A complex reaction took place.

[Benzyl chloride] = 0.015 M, [Tetraethylammonium fluoride] = 0.03 M

c) $k_H(0^\circ) = 0.191 \times 10^{-2}$ 1/mol min, $k_H(20^\circ) = 1.59 \times 10^{-2}$ 1/mol min,

$k_H(40^\circ) = 12.4 \times 10^{-2}$ 1/mol min.

$\Delta H^\ddagger(20^\circ) = 17.1$ Kcal/mol, $\Delta S^\ddagger(20^\circ) = -16.5$ e. u.

With the correction by control experiments, the relative rates were reproducible and were essentially independent of the reactivity of the fluoride used in each run. Results are given in Table 2.

Relative rates of the chlorine-chlorine isotopic exchange reaction, which are given in Table 1, are in fair agreement with the rate reported by others.⁵⁾ Both the electron-donating substituents and the electron-withdrawing substituents accelerate the reaction. Table 1 also shows that, provided the correction be made of the ion-pair dissociation, chlorine isotopic exchange reactions in acetone are some ten to seventy times faster than the same reaction in acetonitrile.^{5,6)} A similar trend was pointed out by Parker in other cases where the bimolecular reaction is slower in DMF or in acetonitrile than in acetone.⁷⁾ At present, no reasonable explanation can be given to the acceleration of Finkelstein reaction in acetone.

The rate data of the displacement reaction with fluoride, which are given in Table 2, show a similar trend as the chlorine-chlorine exchange reaction.

One exception can be furnished by *p*-nitrobenzyl chloride. The rate of the chloride ion liberation was about 400 times faster for this compound than for the unsubstituted benzyl chloride. Such a rate enhancement is of without precedent* for an S_N2 reaction and it is highly probable some reaction other than a direct displacement is taking place. Indeed, no *p*-nitrobenzyl fluoride was isolated from the kinetic run. *p,p'*-dinitrostilbene was isolated instead.

* Generally, the *p*-nitro-group in benzylic system accelerates S_N2 reactions by a factor of 6 or so⁸⁾.

These results suggest that the displacement reaction upon *p*-nitrobenzyl chloride with its conjugate base, $\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}^-\text{Cl}$, followed by an E2 reaction was involved in this reaction.^{*,9)} The details of the reaction of fluoride anion with nitro compounds is the subject of a forthcoming paper.

The plot of second-order rate coefficients in Table 1 and 2 against Hammett σ gives a concaved, shallow U-shaped, free-energy relationship. These results are shown in Fig. 1 and 2.

Figure 1 and 2 clearly show that both an electron-withdrawing group and an electron-donating group accelerate the Finkelstein reaction of benzyl chlorides with chloride anion and with fluoride anion, as are the cases with most of the $\text{S}_{\text{N}}2$ reactions of benzylic compounds.⁸⁾ The present result indicates that the fluoride behaves as a typical halide anion in the Finkelstein reactions.

These substituent effects can be rationalized in terms of a spectrum of variable looseness or tightness of the transition states as proposed by Parker.³⁾ These results also indicate that the "tightening factor" of the transition state, the introduction of a strong nucleophile which is identical with the leaving group or the involvement of a hardest and small-sized nucleophile, is not effective enough to secure a tight transition state for an any set of $\text{S}_{\text{N}}2$ reactions. In a sense, these findings may serve as an additional evidence

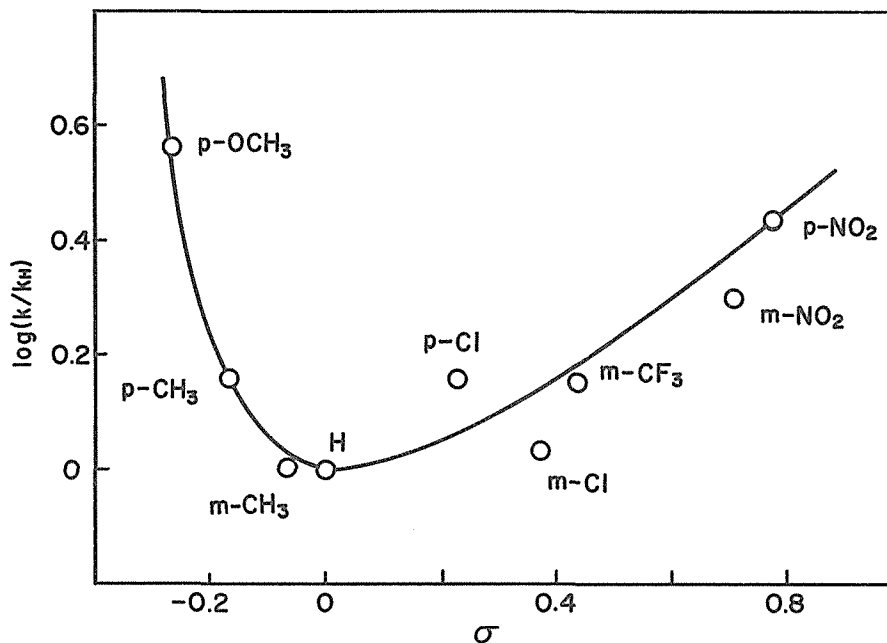


Fig. 1. Hammett plot for the chlorine-chlorine isotopic exchange of benzyl chlorides at 20.0°C.

* A kind of oxidative mechanism, perhaps similar to the oxidative coupling of *p*-nitrotoluene reported by Russel, may also be operative. c.f. G. Russel, A. J. Moye, E. G. Janzen, S. Mak and E. R. Talaty, *J. Org. Chem.*, **32**, 137 (1967); G. Russel and E. G. Janzen, *J. Amer. Chem. Soc.*, **89**, 300 (1967).

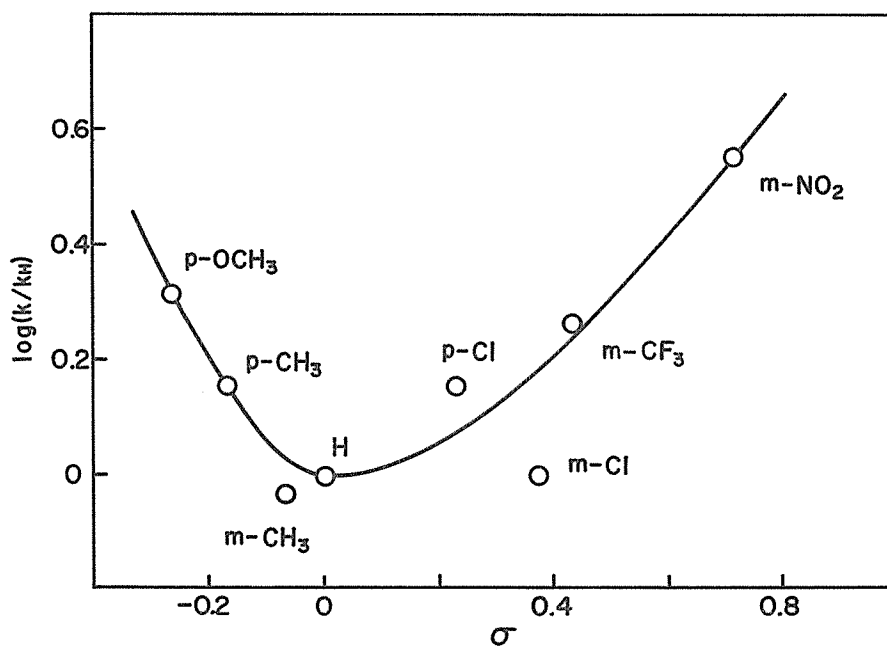


Fig. 2a. Hammett plot for the reaction of benzyl chlorides with tetraethylammonium fluoride at 20.0°C.

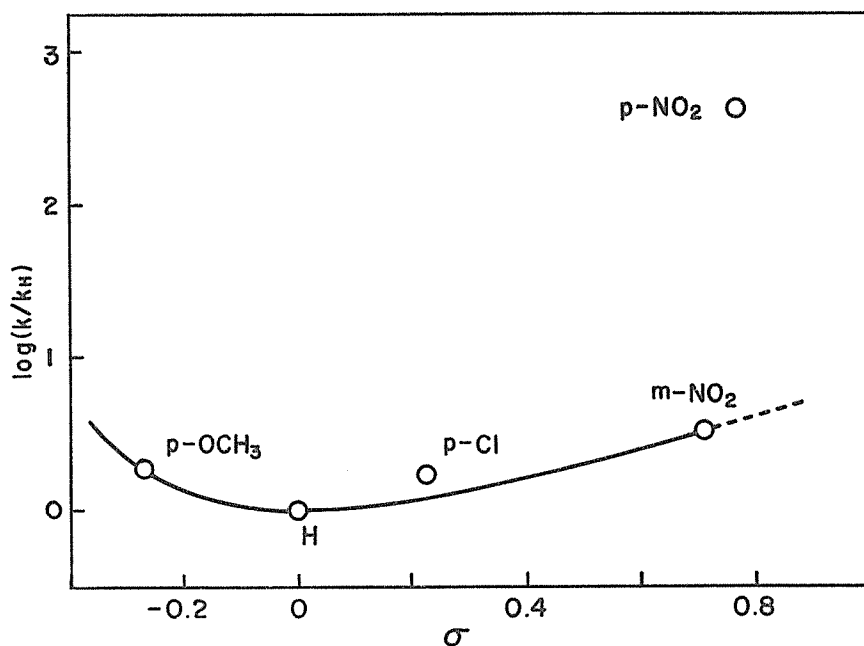


Fig. 2b. Hammett plot for the reaction of benzyl chlorides with tetraethylammonium fluoride at 0°C.

of the assumptions in Ingold's calculation of rate data.¹⁰⁾ The difference in the rate of any set of Finkelstein reactions are assumed to be independent of a solvent and of a salt effect. This assumption implies that the structure of the transition state of an S_N2 reaction of such a type should be affected little by the change of a solvent and by the change of a nucleophile. Accordingly, the soundness of a research which utilizes solvent effect (or salt effect) is vindicated.

Hudson and Klopman have pointed out that electron-attracting substituents in benzylic compounds may promote conjugation between the π -orbital of the benzene ring and the pseudo- p -orbitals.¹¹⁾ The importance of such an interaction has been pointed out as a "neighboring orbital overlap" which facilitate some displacement reactions of a substituted benzyl system by increasing the interaction energy with the nucleophile and hence the bond-forming energy.¹²⁾

By nmr studies of a dipolar aprotic solvent containing a strong nucleophile, one of the present authors has proved that a kind of the interaction is operative between a nucleophile and an S_N2 reaction center even in the ground state.¹³⁾ Present authors also detected, by nmr spectroscopy, a similar ion-molecule association in a solution containing benzyl chloride and halide ion. As are shown in Table 3, the absorption signal of the benzylic proton moves downfield on addition of tetraethylammonium chloride to a solution in acetonitrile. The magnitude of such a downfield shift is dependent on chloride concentration in solution.

Although the calculations of the equilibrium constant and of an energy of complexing have not yet been complete, these observations qualitatively but definitely show that

Table 3. Complexes of Benzyl Chlorides with Chloride Anion in Acetonitrile.
(at ca. 32°C)

Substituent	[Cl ⁻] (mol/l)	Shift (Hz)
<i>p</i> -NO ₂	1.40	24.8
	1.00	19.1
	0.80	15.6
	0.60	12.5
	0.40	8.5
<i>m</i> -NO ₂	1.40	26.6
	1.00	20.2
	0.40	9.0
<i>m</i> -CF ₃	1.00	15.4
<i>p</i> -Cl	1.40	18.2
	1.00	13.5
	0.80	11.0
	0.60	8.5
	0.40	5.8
H	1.00	9.2
<i>m</i> -CH ₃	1.00	9.1
<i>p</i> -CH ₃	1.00	8.1
<i>p</i> -OCH ₃	1.00	9.1

a hydrogen-bonding type interaction is operative* in the ground state. The magnitude of the shift shows that the interaction is most significant in *p*-nitro and *m*-nitro derivatives and then gradually falls off to *m*-methyl and *p*-methoxy derivatives. Still, a solution of *m*-methylbenzyl chloride and tetraethylammonium chloride in acetonitrile showed the downfield shift without doubt. One important finding is concerned with *p*-nitrobenzyl chloride in which ring proton is also affected by the addition of chloride ion. The magnitude of the complexing shift are as follows** : benzyl proton (19.1 Hz), *o*-proton (14.2 Hz), and *m*-proton (4.6 Hz). Such a trend in the nmr spectrum strongly suggest that the chloride anion is located somewhere close to α -proton and to *o*-proton in the benzylic system.

The ion-molecule interaction observed in the present study may have some implication upon the rate enhancement typical of the benzylic compounds. However, the main factor that resulted in an enhanced rate compared with the reaction of the phenethyl halide¹⁾ may be of a conjugative one, probably without the contribution of "neighboring orbital overlap"***. These effects seem to be superposed by an inductive effect which assists an approach of the nucleophile to the reaction center and also by the conjugative effect of the ordinary sense (especially for compounds with a strongly electron-donating substituent(s)).

EXPERIMENTAL

Materials. Substituted benzyl chlorides were prepared from the corresponding alcohols by standard methods. Physical constants of these compounds are given in Table 4.

Table 4. Physical Constants of Benzyl Chlorides.

Substituent	Bp °C/mmHg (Mp °C)	(lit.)
<i>p</i> -NO ₂	(72.5–73.0)	(72.5) ^{a)}
<i>m</i> -NO ₂	(45.0)	(45.5) ^{a)}
<i>m</i> -CF ₃	80.5–81.0/22	
<i>m</i> -Cl	96.5–97.5/16	104/17 ^{a)}
<i>p</i> -Cl	(28.0–28.5)	(29) ^{a)}
H	76.8–77.0/24.5	66–67/16 ^{a)}
<i>m</i> -CH ₃	56.5–57.0/2.5	65/5 ^{b)}
<i>p</i> -CH ₃	88.5/17	81/15 ^{a)}
<i>p</i> -OCH ₃	70.5/0.5	92.5/1.5 ^{c)}

a) G. M. Bennett and B. Jones, *J. Chem. Soc.*, (1935), 1815.

b) "Dictionary of Organic Compounds", Eyre and Spottiswoode (Publishers) Ltd., London, 1965, p 695.

c) C. G. Swain and W. P. Langsdorf, *J. Amer. Chem. Soc.*, **73**, 2813 (1951).

* A result of the Scott-Benesi-Hildebrand analysis¹³⁾ showed the equilibrium constant of the *p*-nitrobenzyl chloride-chloride anion complexing in acetonitrile to be 0.26 l mole⁻¹. The analysis also showed that the limiting shift of this complexing is about 0.94 ppm.

** In the presence of 1.0 M of tetraethylammonium chloride.

*** Streitwieser suggested that such "neighboring orbital overlap" is not pronounced with an entering group of first row element.¹²⁾ Unexpectedly low reactivity of the fluoride ion observed in the present study may have some implication upon such a suggestion. However, the rate ratio k_{Cl^-}/k_{F^-} suggests there is no significant rate enhancement for the isotopic exchange reaction of *p*-nitrobenzyl chloride over the Cl-F exchange reaction.

Tetraethylammonium chloride- ^{36}Cl was prepared from hydrochloric acid- ^{36}Cl (RCC-CIS-1; $15\ \mu\text{Ci/ml}$) by neutralizing with tetraethylammonium hydroxide, about 5% excess of the hydroxide being used. Water was removed from the solution by successive azeotropic distillation from acetonitrile solution. The crystalline residue, which was essentially free of water, was recrystallized from chloroform-hexane and the purified salt was dried at 110°C *in vacuo*. Inactive chloride was added when a dilution was necessary.

Tetraethylammonium fluoride was prepared as reported previously.²⁾ Acetonitrile was purified and dried as described previously and was stored in a bottle equipped with a drierite tube and with a stopcock, the open end of which was stoppered with a rubber septum. Aliquots of acetonitrile were withdrawn with a hypodermic needle through this septum.¹⁴⁾

Kinetic Measurements. Chlorine-chlorine isotopic exchange reactions were undertaken batch-wise. The detailed procedure was described in a previous report.¹⁾

A similar procedure was adopted for the reaction with fluoride. After the reaction mixture was quenched, the organic halides were taken up in toluene while the ionic halides were extracted into aqueous solution. The amount of liberated chloride was determined by titration with mercuric nitrate.¹⁵⁾ Control runs were always made with the unsubstituted benzyl chloride to guarantee a relative rate for the substituted benzyl chlorides.

Reaction of *p*-Nitrobenzyl Chloride with Fluoride Anion. In a sealed ampoule, flushed with nitrogen, a brilliant yellow or orange coloration took place on admixture of a solution of tetraethylammonium fluoride and a solution of *p*-nitrobenzyl chloride in acetonitrile. This color faded away quite rapidly and was followed by the gradual development of a fine deep purple. The purple color is quite stable in an inert atmosphere, but disappeared rapidly in contact with oxygen. This decoloration was accompanied with a deposition of beautiful golden yellow needles. The needles had a mp 297°C , and also showed a satisfactory elemental analysis for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$. This compound was identified as *p,p'*-dinitrostilbene by comparison with the authentic sample.

Nmr Measurement. A weighed amount of benzyl chlorides and tetraethylammonium chloride were dissolved in purified dry acetonitrile containing about 1% of TMS as an internal standard. Usually 0.1 M solution of substrate was used. Nmr spectra were taken with JEOL's PS-100 nmr spectrometer operated at 100 MHz.

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