

NUCLEOPHILE-SUBSTRATE COMPLEX IN SOLUTION. DETECTION OF CHLORIDE-ORGANIC CHLORIDE ASSOCIATION AND THE POTENTIAL ROLE OF THE COMPLEXES IN THE S_N2 REACTION¹⁾

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Two important factors, the approach of the nucleophile and the stabilization of the transition state, govern the rate of the S_N2 reactions.³⁾

In a Hammett type analysis of the Finkelstein reaction of modified methyl chlorides, the present authors reported the example in which the approach of a nucleophile is a major factor (2-arylethyl chlorides) and in which the stabilization of the transition state plays an important role (chloromethyl aryl ethers and sulfides). There are intermediate cases, represented by benzylic compounds, where both effects can be observed depending on the substituent.

Naturally, even in cases where negative ρ values were observed, the approach of a nucleophile should certainly be involved and merely is masked in the predominating effect of transition state stabilization.

In an effort to estimate these two factors separately, the present authors tried to detect the ground state association of a nucleophile and a substrate.

Lemieux, Martin, and one of the present authors (J.H.) have reported a specific interaction of a strong nucleophile with an organic molecule.⁴⁾

As is shown in Figure 1, the low field shift of the pmr signal was observed for modified methyl chlorides after the addition of tetraethylammonium chloride to the solution in acetonitrile. Addition of tetraethylammonium chloride gave similar results with haloform and with β -glucopyranosyl derivatives in an aprotic solvent.

The equilibrium constants and complex shifts of the anion complexes analyzed by the Scott-Benesi-Hildebrand method⁵⁾ are shown in the Table.

As shown in the Table, the equilibrium constants are not large, however, the complex shift is large enough to suggest a close contact of chloride anion to the molecule. Interestingly, equilibrium constants K gave fairly good linear Hammett relationship as shown in Figure 2.

As proposed previously, these phenomena can be attributed to the 1 : 1 anion-molecule association.⁴⁾ The trend in the magnitude of the shift of individual hydrogens in one molecule, $\Delta_C(\alpha) > \Delta_C(o) > \Delta_C(m)$, implies a rear-side coordination of a chloride ion with respect to the chlorine bonded to the carbon, an S_N2 reaction center. A possible model of the complex for *p*-nitrobenzyl chloride is shown in Scheme 1.

Positive values of ρ observed for the equilibrium constants, as well as the suggested configuration of the complex in Scheme 1, imply that this complexing should have an important bearing upon the approaching step in the S_N2 reaction.

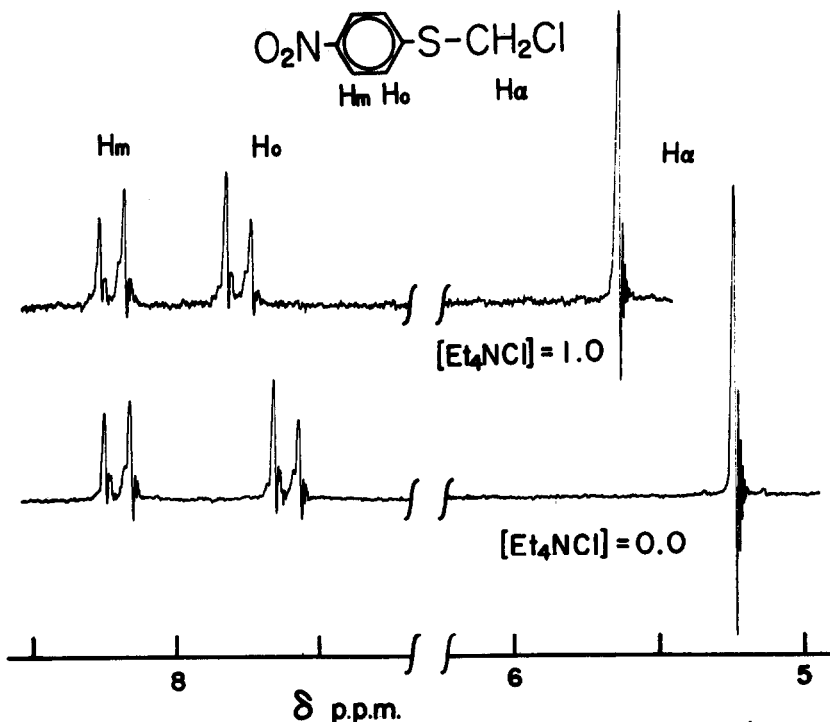
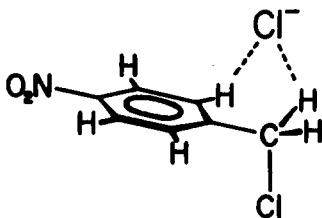


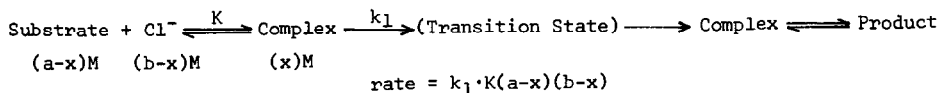
Figure 1. Change of pmr spectra of chloromethyl p-nitrophenyl sulfide in acetonitrile after addition of tetraethylammonium chloride. (at 100MHz, δ from TMS)



(Scheme 1) A possible configuration of chloride complex of p-nitrobenzyl chloride. Cl^- may lie in the plane which bisects the H-C-H angle and involves the C-Ph bond.

As has been reported previously,³⁾ every symmetrical substitution reaction studied, including benzyl chlorides and chloromethyl aryl sulfides down to a fairly low concentration of both of the nucleophile and the substrate, followed second-order kinetics.

To reconcile the plausible second-order kinetics and the formation of the 1 : 1 complex, the path of this reaction can be written as Scheme 2 (Path A). The association complex plays (Scheme 2. Path A)



the role of the direct precursor, and the rate-determining step in this scheme should be the unimolecular scrambling among the complex thus producing the exchanged complex.

Table. Complex Formation between Modified Methyl Chlorides and Chloride Ion in Acetonitrile at ca. 32°C.

Substrate	Substituent	$\Delta_{1,0}$ (ppm) ⁶⁾	Δ_c (ppm) ⁷⁾	K (l/mol)		
Ar-S-CH ₂ Cl	p-NO ₂ (α)	-0.400	-1.229	0.493		
		(o)	-0.168	-0.584	0.405	
		(m)	-0.027	-0.089*	-	
	m-Cl	-0.292	-1.307	0.297		
	p-Cl	-0.286	-1.422	0.256		
	H	-0.227	-1.634	0.163		
	p-OCH ₃	-0.197	-1.715	0.124		
	ArCH ₂ Cl	p-NO ₂ (α)	-0.191	-0.943	0.258	
			(o)	-0.142	-0.681	0.269
			(m)	-0.046	-0.220*	-
m-NO ₂		-0.202	-1.202	0.205		
m-CF ₃		-0.154	-1.244	0.144		
p-Cl		-0.135	-1.256	0.122		
H		-0.092	-1.295	0.077		
p-CH ₃		-0.081	-1.464	0.059		
p-OCH ₃		-0.091	-1.789	0.054		

* Calculated from average K obtained for other protons.

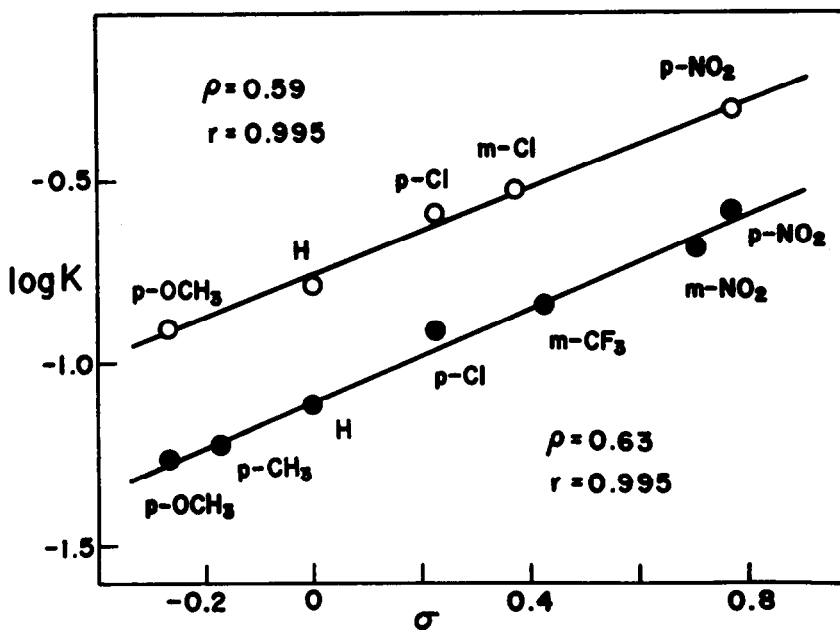
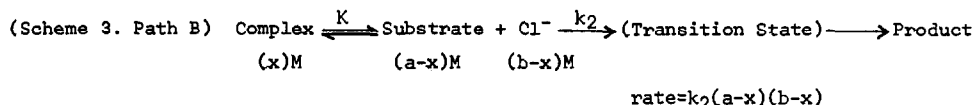


Figure 2. Hammett plot for complex formation of chloromethyl aryl sulfides (o) and benzyl chlorides (●).

However, there is a possibility that this complex may play no major role in the substitution reaction but may only correspond to a subsidiary equilibrium (Path B).



Kinetically, Path A and Path B are not distinguishable. However, when one takes into consideration the presence of the chloride ion in the proximity of the reaction center at the backside of the leaving group and also takes into consideration the similarity of the ρ_K to the ρ_k for the isotopic exchange reaction of 2-arylethyl chlorides, in which the manifestation of the approach of the nucleophile is suggested by this positive ρ_k value (+0.57), it is plausible to prefer the conclusion that some of the bimolecular nucleophilic substitution (S_N2) involve the rate-determining collapse of the association complex and proceed through Path A in the Scheme 2.

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REFERENCES AND FOOT-NOTE

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 - 4) J. S. Martin, J. Hayami, and R. U. Lemieux, *Can. J. Chem.*, **46**, 3263 (1968).
 - 5) The equilibrium constant, K , and the limiting shift of the complex, Δ_c , can be estimated by the plot according to the Scott-Benesi-Hildebrand equation, $[I]/\Delta = 1/K\Delta_c + [I]/\Delta_c$. An initial estimate of Δ_c and K was made with total concentration of chloride ion $[I]_0$ as the approximation to the real concentration $[I]$. Then the equilibrium analysis was repeated with a better value of $[I]$ obtained with the approximate K . c.f. Ref. 4.
 - 6) Observed low-field shift at the concentration, $[\text{Substrate}] = 0.1M$, $[\text{Et}_4\text{NCl}] = 1.0M$.
 - 7) General trend of the increasing complex shift with the decreasing stability of the complex may not be fortuitous. As the magnitude of the dipole, the driving force of the complexing, decreases by the interaction with the electron-donating substituent the closer approach of the anion may be necessary to secure the interaction, thus increasing the limiting shift.
- At the very extreme of the weak complexing, the free energy of the complexing would become high enough to reach the level of the free energy of activation for the rate-determining step (classical S_N2 attained).