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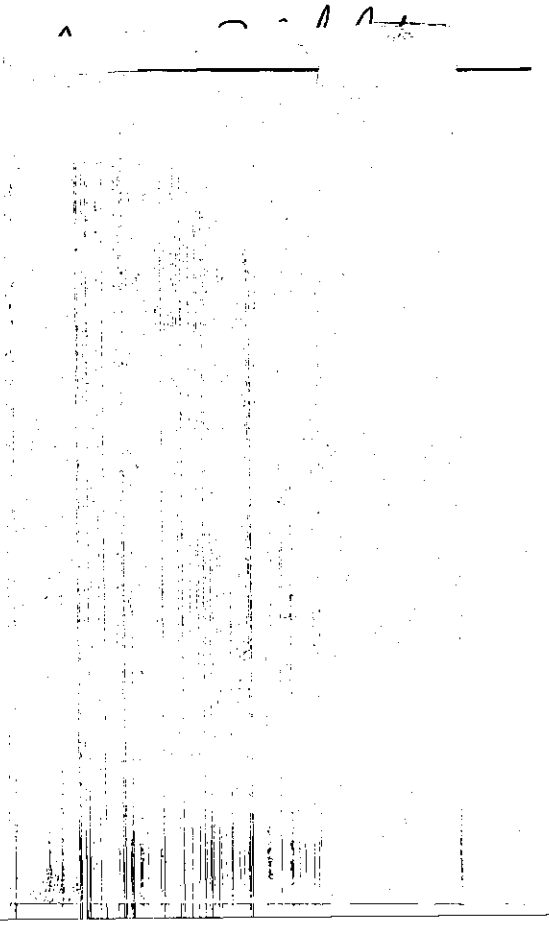

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MECHANISM OF NONACTIVATED AROMATIC NUCLEOPHILIC SUBSTITUTION

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Daniel Farmer Pinholster, Jr.

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GLOSSARY OF ABBREVIATIONS

TEG	Triethylene glycol
THP	Tetrahydropyran
THF	Tetrahydrofuran
IC	Intermediate complex
DMSO	Dimethyl sulfoxide
DMF	N, N-Dimethyl formamide
n.m.r.	Nuclear magnetic resonance
UV	Ultraviolet
IR	Infrared
SE-30	Silicone gum rubber
HMPT	Hexamethylphosphotriamide
MS	Mass spectrometer
AMU	Atomic mass units

SUMMARY

The research described herein is an attempt to establish a mechanism for nonactivated bimolecular aromatic nucleophilic substitution. A number of methods were used for this purpose.

The reaction of fluorobenzene with piperidine in triethylene glycol at 194 to 240°C follows second order kinetics. The rate constant was found to decrease as the piperidine concentration is increased. The decrease in the rate constant was rationalized in terms of a dielectric constant effect. These reactions were believed to proceed by a direct displacement reaction since product studies give no evidence of rearranged products.

A Hammett plot was obtained from the reactions of m- and p-substituted fluorobenzenes with piperidine in triethylene glycol at 194.5°C. The plot was linear with a rho value of + 4.42 and a correlation coefficient of 0.995. The substituents used were p-NO_2, m-NO_2, m-CF_3, m-Cl, p-Cl, m-Br, p-Br, m-I, p-I, m-F, p-F, m-OH, H, m-CH_3, p-CH_3. The rate constant at 194.5°C for the p-nitro substituent was obtained by extrapolation using energy of activation data. A linear Hammett plot implies that all the compounds react by the same mechanism. Since p-nitro-fluorobenzene has been postulated as proceeding through an intermediate complex mechanism, the conclusion was that it appeared all the reactants proceed by an intermediate complex mechanism.

Another method which was used for determining mechanism was the halogen order which is the rate of reaction of the different halobenzenes.

The rates of reaction of the four unsubstituted halobenzenes were obtained along with activation data. By comparing the halogen order of activated and non-activated halobenzenes at 100°C, it was found in both cases that F > Cl, Br, and I. Since activated cases go through an intermediate complex mechanism, and the same order F > Cl was found in nonactivated cases, the conclusion was that both cases go through an intermediate complex mechanism instead of a concerted S_N2 type displacement. At 200°C the order I > Br >> Cl was found. For these three halogens there were two conclusions. In an intermediate complex mechanism the order I > Br > Cl may be explained by a polarizability factor which is more effective I > Br > Cl. In terms of an S_N2 concerted type displacement, this is the order if bond breaking were important. Therefore, the conclusion that fluorobenzene goes by an intermediate complex mechanism may not necessarily be extended to the other halogens.

Bunnett used the element effect as a criterion for mechanism. This approach was also attempted in this work. If a number of leaving groups have approximately the same rate, then bond breaking is unimportant and the intermediate complex mechanism is indicated. Besides the halogens as leaving groups, an attempt was made to study the leaving ability of $-HNC_6H_5$, $-OC_6H_5$, $-NO_2$, $-SO_2C_6H_5$, and $-SC_6H_5$ where these groups were attached to benzene. These compounds, excluding the halobenzenes, failed to give proper rate data because of no reaction, tar formation, or reaction on sulfur. Therefore, the element effect could not be used.

Another method which failed was an attempt to show base catalysis (which implies an intermediate complex mechanism) in the reaction of fluorobenzene with piperidine in triethylene glycol. Due to a

complicating solvent effect and the inability to obtain accurate enough rate constants at 195°C, the point of base catalysis is still unclarified.

The last method was an attempt to trap the intermediate complex in the reaction of fluorobenzene with piperidine. The intermediate complex may be looked upon as a carbanion, and if the reaction of fluorobenzene with piperidine in triethylene glycol goes through an intermediate complex, the carbanion should undergo proton exchange on the ring. The results showed that the reaction of p-deuterio-fluorobenzene with piperidine in triethylene glycol at 225°C gave no exchange on the starting material and about six per cent on the product which was concluded as occurring on the IC. With m-deuterio-fluorobenzene no exchange occurred on the reactant or product.

Also, pentafluorobenzene reacted with sodium thiophenoxide in methanol-O-d at -30°C without exchange in the recovered product. Previous work has shown that reaction occurs greater than 90 per cent para to the hydrogen in pentafluorobenzene with various nucleophiles. If proton transfers to carbanions are diffusion controlled in this system these results are difficult to interpret. Since fluorobenzene showed deuterium exchange on the intermediate complex, it would appear that the activated pentafluorobenzene should also show deuterium exchange on the IC.

From the research presented the mechanism of activated and non-activated aromatic nucleophilic substitution was indicated to be similar and to involve the intermediate complex mechanism.

CHAPTER I

HISTORICAL BACKGROUND

Introduction

Aromatic nucleophilic substitution emerged as an important area of physical organic chemistry with the publication of reviews by Bunnett (1) and Miller (2) in the early nineteen-fifties. Since then there have been a prolific number of publications, most of them in the area of activated nucleophilic substitution. Only a small per cent of the papers deal with nonactivated bimolecular aromatic nucleophilic substitution, which may be defined as nucleophilic aromatic displacement on compounds having no substituent with a meta or para sigma value (σ) greater than 0.70. The value 0.70 allows one to omit most of the work in the activated case, especially with nitro substituted compounds. This definition is not a rigid one. For example, 3,5-bis-(trifluoromethyl)-chlorobenzene contains no substituent whose sigma value is greater than 0.70. But for displacement of chlorine the combined effect of two trifluoromethyl groups gives a sigma value 0.86. This compound is still considered in the nonactivated case. Table 1 organizes a number of substituents into four groups: activating, intermediate activating, halogens, and deactivating. Certain substituents in Table 1 can overlap two groups, yet these four classes provide a convenient basis for discussion. For example, although a m-$COCH_3$ has the same signa value as m-Cl, the p-$COCH_3$ is a strongly activating substituent, whose

true effect in terms of σ^- is + 0.874.

Table 1. Classification of Substituents

Activating ($\sigma > 0.70$)	Intermediate Activating	Halogens	Deactivating
NO_2	CN	F	NH_2
NO	CO_2H	Cl	p-OH
N_2^+	CO_2^-	Br	O^-
$N(CH_3)_3^+$	CO_2CH_3	I	alkyl
SO_2CF_3	CHO	H	
SO_2CH_3	COC_6H_5		
$SO_2C_6H_5$	$SOCH_3$		
$S(CH_3)_2^+$	SOC_6H_5		
	SO_2NH_2		
	SO_3^-		
	m-OH		

Although the nonactivated case has received less attention, this area is important industrially. For example, phenol has been made by the hydrolysis of chlorobenzene or benzenesulfonic acid. Aniline is produced commercially by ammonolysis of chlorobenzene at 200°C.

Therefore, this historical review emphasizes nonactivated bimolecular aromatic nucleophilic substitution. Copper catalyzed reactions are deleted. Other areas not included are activated nucleophilic substitution, reviewed by Bunnett, (1, 3) Miller (2), Sauer (4), and Ross (5); photonucleophilic displacement, reviewed by Pietra (6); heteroaromatic

substitution, reviewed by Illuminati (7) and Shepherd (8); and benzyne reactions, reviewed by Kauffman (9). Pentahalobenzenes, hexahalobenzenes, and other perhaloaromatics are considered part of the activated case and are not discussed (10).

Nonrearranging Reactions

Nucleophiles

Amines and Amides. Piperidine is frequently used as a nucleophile not only because of its high nucleophilicity, but also because of its ability to serve as a solvent. Tronov (11) early recognized the usefullness of piperidine in a study of the relative rates of halobenzenes with piperidine at 210°C. Berliner (12) repeated some of Tronov's work and extended the study to halonaphthalenes (Table 2). In naphthalenes the α position should be more reactive than the β, yet with piperidine the β isomer of the halonaphthalenes (reactions of fluoronaphthalenes with piperidine have not been determined) is more reactive. Petrenko-Kritschenko (13) found this earlier in the reaction of α and β chloronaphthalenes with piperidine. Berliner explained the increased reactivity of the β isomer as a result of the high temperatures used. The combination of the energy of activation and pre-exponential factor causes a reversal of the rates of the α and β isomers at a lower temperature. However, this cannot be, since Amstutz (14) found Berliner's values for the activation energy and pre-exponential factor to be in error for the bromonaphthalenes (Table 3). The values for the activation energy and entropy of activation are not so different to cause a reversal of rates at a lower temperature. Amstutz suggested that the peri-CH causes a

Table 2. Reaction of Halobenzenes and Halonaphthalenes with Piperidine at 165°C (12)

Substrate	k x 10^4 (hr^{-1})	Activation Energy (kcal/mole)	Pre-exponential Factor (log pZ)
1-I-$C_{10}H_7$	17.1	23.1 ± 0.95	8.76 ± 0.45
2-I-$C_{10}H_7$	21.1	24.6 ± 0.95	9.60 ± 0.45
1-Br-$C_{10}H_7$	8.56	24.9 ± 0.7	9.36 ± 0.35
2-Br-$C_{10}H_7$	14.9	27.6 ± 0.7	10.95 ± 0.35
1-Cl-$C_{10}H_7$	1.48		
2-Cl-$C_{10}H_7$	1.86		
C_6H_5I	9.4	23.6 ± 1.0	8.75 ± 0.5
C_6H_5Br	5.2		
C_6H_5Cl	0.62		

Table 3. Activation Data for Bromonaphthalenes with Piperidine (14)

Compound	Amstutz		Berliner	
	$\Delta E^{\neq}$	$\Delta S^{\neq}$	$\Delta E^{\neq}$	$\Delta S^{\neq}$
1-Bromonaphthalene	25.0 ± 0.8	-39.8	24.9 ± 0.7	-39.7
2-Bromonaphthalene	24.9 ± 1.0	-39.0	27.6 ± 0.7	-32.4

steric hindrance in the α isomer, which could increase the energy of activation and entropy of activation in the activated complex such that the values for the α and β isomers become the same. Characteristic of these nonactivated compounds is a high energy of activation, 20 to 30 kilocalories, and a very negative entropy of activation.

Amstutz (15) used piperidine as the nucleophile to study the effect of the substrate on reactivity (Table 4). The α and β positions in halonaphthalenes and haloanthracenes have similar reactivities. The activation energy decreases but only to a slight extent in the series chlorobenzene, 1-chloronaphthalene, and 1-chloroanthracene, while the rate increases indicating that the added aromatic rings exhibit essentially an inductive effect. Amstutz's work added much to the qualitative work by Lellman (16) on different nonactivated aromatic bromine compounds.

Amstutz (17) also published reactivity data of piperdine with halofurans (Table 5). Halofurans are very unreactive toward nucleophilic displacement, yet about ten times more reactive than halobenzenes, while having lower activation energies than halobenzenes. Note that it is the entropy of activation which determines the ten fold difference in the rates of chlorofuran and bromofuran.

Badger (18) attempted to include both activating and nonactivating substituents in a study of para substituted chlorobenzenes with piperidine in benzene under reflux conditions. The following gives the substituent and per cent of chloride liberated: nitro, 12.9; cyano, 5.0; azobenzene, 1.79; hydrogen, 1.29; and amino, 1.23. Since a number of authors have noted the unreactivity of chlorobenzene, even at temperatures

Table 4. Effect of the Substrate on Reactivity with Piperidine at 200°C (15)

Substrate	$k(hr^{-1})$	$\Delta E^{\neq}$ (kcal/mole)	log pZ
Chlorobenzene	0.00022	26.8 ± 1.4	7.71
1-Chloronaphthalene	0.00087	25.4 ± 1.0	7.74
2-Chloronaphthalene	0.0011	23.1 ± 0.5	6.67
1-Chloroanthracene	0.00074	23.8 ± 1.7	6.85
2-Chloroanthracene	0.00187	26.5 ± 2.0	8.48
9-Chloroanthracene	0.0155	20.1 ± 1.1	4.73
Bromobenzene	0.0038	24.1 ± 0.4	7.73
1-Bromonaphthalene	0.0059	25.0 ± 0.35	8.21
2-Bromonaphthalene	0.0105	25.0 ± 0.84	8.52
9-Bromoanthracene	0.063	16.0 ± 0.6	6.36

Table 5. Reactivity Data for the Reaction of Piperidine with Halofurans at 200°C (17)

Compound	$k(hr^{-1})$	$\Delta E^{\neq}$ (kcal/mole)	$\Delta S^{\neq}$ (e.u.)
2-Chlorofuran	0.0025	21.89 ± 0.36	-42.1 ± 1.5
2-Bromofuran	0.0230	21.69 ± 0.33	-39.1 ± 1.3
2-Iodofuran	0.050	23.6	-18.8 ± 1.2
5-Methyl-2-iodofuran	0.021	26.6 ± 0.75	-29.1 ± 2.4

greater than 200°C, Badger's data for chlorobenzene and p-chloroaniline is subject to doubt and may refer only to the residual chloride in the blank titration. A similar study by Bunnett (19) bears this out. Piperidine reacted with p-chlorobenzophenone and p-chlorobenzotrifluoride only 3.4 per cent and 1.2 per cent in three and a half days at 99°C in benzene. Although these two compounds are much more activated than chlorobenzene, they are still somewhat unreactive.

Aqueous ammonia reacts with nonactivated compounds at elevated temperatures. Chlorobenzene treated with aqueous ammonia at 300°C produces 30 per cent aniline, along with some phenol and phenyl ether (20). Shein (21, 22, 23) studied the ammonolysis of substituted chlorobenzenes at 250 to 300°C (Table 6). Shein (23) also investigated the kinetics of the reaction of 1,2,4,5-tetrachlorobenzene with ammonia. At temperatures below 250°C only one chlorine is replaced, but at a rate 10^5 times that of chlorobenzene. Since there is only a difference of four kilocalories in their activation energies, the difference in rates is due to the pre-exponential factor.

Hydrazine was used as a nucleophile with the different tetrafluorobenzenes at 90-130°C (24).

Although aminations with potassium amide of haloaromatics usually proceed through benzyne intermediates, some react by direct nucleophilic displacement. Bergstrom (25) showed that 1- and 2-fluoronaphthalenes with potassium amide produced only the corresponding amines. Phenyl trimethylammonium bromide reacted with potassium amide in liquid ammonia to give 95.8 per cent substitution at the C_1 carbon in the aniline produced. Sodium hydrazide or sodium methylhydrazide reacts in ether or

Table 6.. Reaction of Substituted Chlorobenzenes with Aqueous Ammonia at 270°C (21-23)

Substituent	$k(M^{-1}min^{-1})$	$\Delta E^{\neq}$(kcal/mole)	log A
2,4-di-CF_3	4.8×10^{-3}	29.5	
4-CH_3SO_2	1.9×10^{-3}	25.5	
2,5-di-CF_3	1.0×10^{-3}	21.6	
2,4,5-trichloro	1.05×10^{-4}*	31.0	9.1
4-SO_2NH_2	5.9×10^{-4}	22.9	6.3
4-CF_3	6.5×10^{-5}	27.8	
2-CF_3	5.1×10^{-5}	24.3	
H	4.5×10^{-9}	34.7	5.6

*statistically corrected

benzene at 30-35°C with p-fluorotoluene by direct displacement, whereas sodium dimethylhydrazide reacts only through a benzyne intermediate (27). Sodium hydrazide also reacts with 2-chloronaphthalene without rearrangement (28).

A number of examples of direct substitution by sodium piperidide and sodium diethyl amide are known (Table 7). These reagent have a greater nucleophilicity compared to potassium amide. It would be of interest to study the relative rates of reactivity of halobenzenes with amides by direct displacement, but in the cases studied only fluorobenzene allowed direct displacement.

Table 7. Reactions of Amides with Substituted Benzenes and Naphthalenes by Direct Displacement

Compound	Amine	Solvent	Base	Temperature °C	Reference
$(\underline{p}\text{-}CH_3C_6H_4)_2S$	piperidine	piperidine	$NaNH_2$	reflux	29
$\underline{p}\text{-}CH_3C_6H_4SO_2CH_3$	piperidine	piperidine	$NaNH_2$	reflux	30
$(\underline{p}\text{-}CH_3C_6H_4)_2SO_2$	piperidine	piperidine	$NaNH_2$	reflux	29
$C_6H_5SO_3C_6H_4CH_3\text{-}\underline{p}$	piperidine	piperidine	$NaNH_2$	reflux	29
$1\text{-}F\text{-}C_{10}H_7$	piperidine	piperidine	$NaNH_2$	reflux	31
1-and $2\text{-}CH_3SO_2C_{10}H_7$	piperidine	piperidine	$NaNH_2$	reflux	31
$2\text{-}SO_3H\text{-}C_{10}H_7$	piperidine	piperidine	$NaNH_2$	reflux	32
2-and $4\text{-}F\text{-}C_6H_4OCH_3$	piperidine	HMPT-THF	$NaNH_2$	50	33
2-and $4\text{-}F\text{-}C_6H_4CH_3$	piperidine	HMPT-THF	$NaNH_2$	50	33
2-and $4\text{-}F\text{-}C_6H_4OCH_3$	diethylamine	HMPT-THF	$NaNH_2$	45	33
2-and $4\text{-}F\text{-}C_6H_4CH_3$	diethylamine	HMPT-THF	$NaNH_2$	45	33
1-and $2\text{-}F\text{-}C_{10}H_7$	piperidine	ether	Li piperidide	30-35	34,35
$2\text{-}Cl\text{-}1\text{-}CH_3\text{-}C_{10}H_6$	piperidine	ether	Li piperidide	-----	28

Alkoxides. The most often used nucleophilic reagents are the alkoxides. The different studies are summarized in Table 8 and are discussed later. Alkoxides in protic solvents react with nonactivated haloaromatics without rearrangement (61). However, Shein (39) has pointed out that it is important to use glass ampoules instead of steel autoclaves, since iron catalyzes not only rearrangement but also reduction of the halogen compound. Even in glass ampoules Shein found one per cent m-chlorophenol from the reaction of p-dichlorobenzene with sodium methoxide in methanol at temperatures greater than 230°C.

Sodium Hydroxide and Sodium Cyanide Fusions. Fusions have a number of applications to synthesis, with the early work reviewed by Suter (63). Unfortunately, few mechanistic studies are available. The extent of direct displacement involved in alkali fusion of sulfanilic acid to produce p-phenolsulfonic acid is unknown (64). The same is true of alkaline fusion of benzenearsonic acid (65). The alkaline fusion of benzenesulfonic acid has been known since the work of Wurtz (66) and Kekule (67), yet the mechanism was only recently established as a direct displacement reaction (68). The benzyne mechanism was eliminated by using benzenesulfonic acid-1-^{14}C and finding 97 per cent activity in the C_1 carbon of the resulting phenol. Fusion of p-toluenesulfonic acid produced only p-cresol. Fusion of mesitylene sulfonic acid allowed a 30 per cent yield of mesitylenol, although, both ortho positions are blocked so that the benzyne mechanism cannot occur. The oxygen migration mechanism, involving initial hydroxyl attack on sulphur with subsequent migration of one of the sulfur oxygens, was also eliminated. When ^{18}O enriched potassium hydroxide was used, the ^{18}O activities of the resulting phenol and $K^{18}OH$

Table 8. Reactions of Alkoxides with Haloaromatics

Compound	Base	Solvent	Substituents (X)	References
C_6H_5X	$NaOCH_3$	CH_3OH	F, Cl, Br, I	11, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46
p-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	Cl, NH_2, CH_3, O^-, CO_2^-, F, Br, CF_3	36, 47, 46, 48, 49, 50, 51, 52
p-X-C_6H_4Cl	$NaOCH_3$	$CH_3OH \cdot H_2O$	NO_2, SO_2^-, SO_3^-, CO_2^-	53
p-X-C_6H_4Cl	$NaOCH_2CH_3$	CH_3CH_2OH	Cl, F, CF_3	54
m-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	NO_2, CF_3, Cl, O^-, NH_2	36, 46, 48, 50, 51, 52
m-X-C_6H_4Cl	$NaOCH_2CH_3$	CH_3CH_2OH	Cl, F, CF_3	54
o-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	NO_2, CF_3, CO_2^-, Cl, O^-, CH_3, NH_2	36, 47, 48, 50, 51, 52, 55, 56
o-X-C_6H_4Cl	$NaOCH_2CH_3$	CH_3CH_2OH	Cl, F	54
p-X-C_6H_4Br	$NaOCH_3$	CH_3OH	NO_2, Br, CH_3, NH_2, OCH_3, O^-	36, 38, 50
p-X-C_6H_4Br	$NaOCH_2CH_3$	CH_3CH_2OH	COC_6H_5, $COCH_3$	57, 58
m-X-C_6H_4	$NaOCH_3$	CH_3OH	Br, CO_2^-	36, 38
o-X-C_6H_4Br	$NaOCH_3$	CH_3OH	Br, CH_3, OCH_3	36, 38, 50
o-X-C_6H_4Br	$NaOCH_2CH_3$	CH_3CH_2OH	COC_6H_5, $COCH_3$	58
m-and p-X-C_6H_4F	$NaOCH_2CH_3$	CH_3CH_2OH	CF_3	54

Table 8. Reactions of Alkoxides with Holodromatics (Continued)

Compound	Base	Solvent	Substituents (X)	References
2,4-di-Cl-1-X-C_6H_3	$NaOCH_3$	CH_3OH	CF_3, NO, CHO, SO_3^-, COC_6H_5, I, Cl, Br, F, CN, CH_3, O^-, NH_2	36,52,55,59
2,5-di-Cl-1-X-C_6H_3	$NaOCH_3$	CH_3OH	CF_3, SO_3^-, F, Cl, Br, I, CO_2^-, NH_2, CH_3, O^-, S^-	36,49,55
3,4-di-Cl-1-X-C_6H_3	$NaOCH_3$	CH_3OH	CN, NO, COC_6H_5 F, Cl, Br, I, CH_3, CO_2^-, O^-, NH_2	60
3,5-di-X-C_6H_3Br	$NaOCH_3$	CH_3OH	Br	36
3,5-di-X-C_6H_3Cl	$NaOCH_3$	CH_3OH	Cl	52
2,4-di-X-C_6H_3Cl	$NaOCH_3$	$CH_3OH \cdot H_2O$	SO_3^-, CO_2^-	53
2,4,6-tri-X-C_6H_2Cl	$NaOCH_3$	CH_3OH	CF_3	55
1,2,4,5-tetrachlorobenzene	$NaOCH_3$	CH_3OH		36
tetrafluorobenzenes	$NaOCH_3$	CH_3OH		24
1-and 2-X-$C_{10}H_7$	$NaOCH_3$	CH_3OH	Cl	61
2-X-$C_6H_4CH_3$	K-t-BuO	DMSO	F	62

were the same. The alkaline fusion of benzenesulfinic gives only benzene (69).

The mechanism of alkaline fusion of diphenylsulfone (70) is not definitely established; however, evidence indicates that attack occurs both on sulfur and carbon and not by a benzyne mechanism. Both benzenesulfonic acid (71) and benzenesulfinic acid (72) have been isolated from this reaction.

A more complex situation exists in the alkaline fusion of halodiphenylsulfones and halobenzenesulfonic acids (72). In halodiphenylsulfones a nucleophilic attack on chlorine precedes attack at either the phenyl C_1 carbon or at sulfur since the halogen is activated by a phenyl sulfonyl group. Halobenzenesulfinic acids involve a sulfinate benzyne as an intermediate.

Fusion with sodium cyanide may occur by direct displacement since cyanide fusion of sodium 1-naphthalene sulfonate produces only 1-naphthonitrile (73).

Sodium Hydroxide Hydrolysis Reactions. Hydrolysis of nonactivated halobenzenes almost always produces rearranged products. This is true in the hydrolysis of chlorobiphenyls (74), halotoluenes (75), and haloalkylbenzenes (76). Hale and Britton summarized the early work (77). The question here is to what extent direct substitution is involved. By ^{14}C labeling experiments Roberts (78) found that in four molar sodium hydroxide chlorobenzene hydrolyses 16 per cent by direct displacement. Also, direct substitution is favored at lower temperatures and with the more ionizable halogen (Table 9).

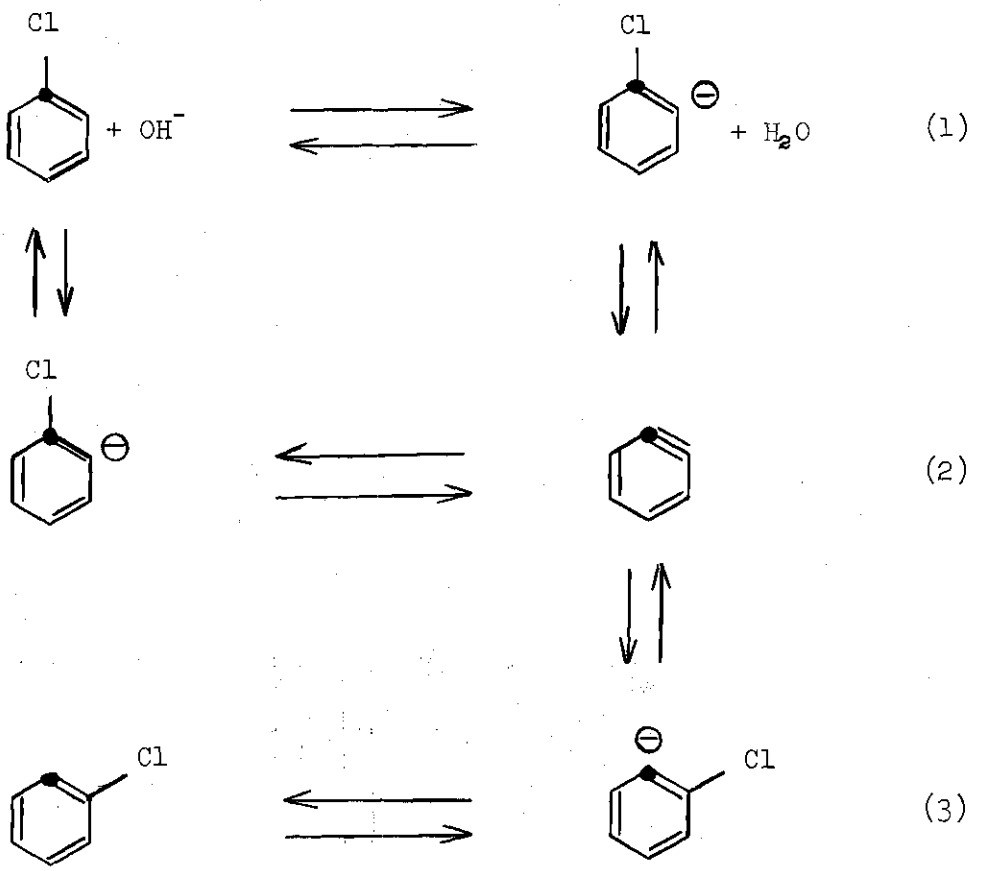
Table 9. Hydrolysis of p-Substituted Halotoluenes at 250°C (78)

Substituent	NaOH(M)	%Conversion	%m	%p
Cl	4	~0.3	~40-50	~50-60
Br	4	17	25.8	74.2
I	4	45	< 3	< 97

Important in the production of phenol from chlorobenzene is the hydrolysis of the by-product phenyl ether (79). Although Ambros (80) favored a benzyne mechanism, Dalman and Neumann (81) by using labeling techniques proved that the hydrolysis of phenyl ether occurs by a non-rearranging S_N2 type mechanism. Further, the hydrolysis of p, p′-ditolyl ether produces no m-cresol. The fact that ditolyl ethers hydrolyze less rapidly than phenyl ethers is consistent with an S_N2 mechanism (75).

Hydrolysis of p-dichlorobenzene (77) gives only p-chlorophenol, while p-difluorobenzene (82) gives only p-fluorophenol. Calcium hydroxide hydrolysis of p-bromofluorobenzene produces mainly p-fluorophenol (83).

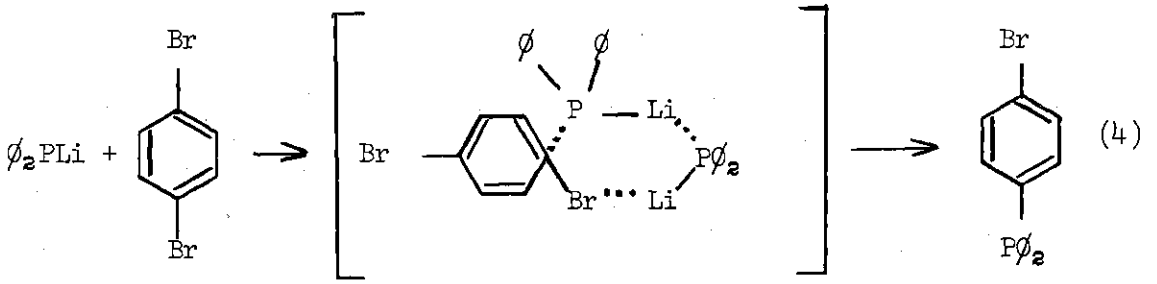
These alkaline hydrolyses are sometimes complicated by rearrangement of the reactant and the rearrangement is attributed to such processes illustrated by equations 1-3. In the partial hydrolysis of o-chlorotoluene, the recovered chlorotoluene contained ten per cent m-chlorotoluene (78).



Halides. Displacement by halides in aromatic nuclephilic substitution usually requires activation by one or more nitro or trifluromethylsulfonyl groups. The nonactivated case requires high temperatures for reaction. Iodide ion does not exchange with iodobenzene at 100°C in ethanol nor with m- and p-iodobenzoic acids at 100°C in acetone (84). Iodide does exchange with iodobenzene (85), p-iodophenol (86), p-iodotoluene (87), p-iodobenzoic acid (87), and 2-iodonaphthalene (88) at 185-240°C in either acetonitrile or 2-octanol. Iodide exchange of p-iodophenol in acetonitrile is bimolecular at 150°C and unimolecular at 200°C (87). Iodide exchange of p-iodophenol is second order in acetonitrile and first

order in 2-octanol (86). Interestingly, Roberts found that four molar sodium chloride effects direct displacement by chloride with p-iodotoluene (78). This is unusual in that the nucleophilic reactivity of the halides in protic solvents is I > Br > Cl > F.

Diphenyl Phosphide. Lithium diphenyl phosphide, a weak base, reacts with nonactivated aryl bromides and iodides in tetrahydrofuran at room temperature to give unrearranged products (89). The mechanism postulated (Eq. 4) involves a "push pull" type with two molecules of $LiP(Ph)_2$ participating.



(4)

Acetates and Carbonates. Weak bases, such as potassium carbonate (90) and sodium carbonate (91), are able to react by direct substitution at high temperatures. Sodium acetate at 340°C reacts mainly by an S_N2 mechanism with halotoluenes (78). p-Bromotoluene gave 30 per cent p-cresol and no m-cresol, while p-chlorotoluene gave a six per cent mixture of 95 per cent para and five per cent meta cresols when reacted with sodium acetate.

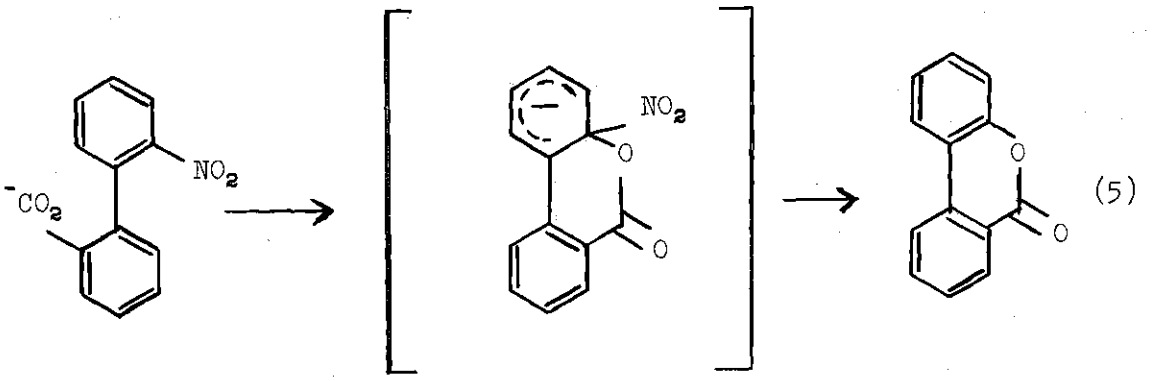
Thiophenoxide. The only mention in the literature of using thiophenoxide as a nucleophile with nonactivated compounds is by Bunnett (92) who noted its unreactivity.

Carbanions. Refer to the topic of the Truce-Smiles rearrangement.

Leaving Groups

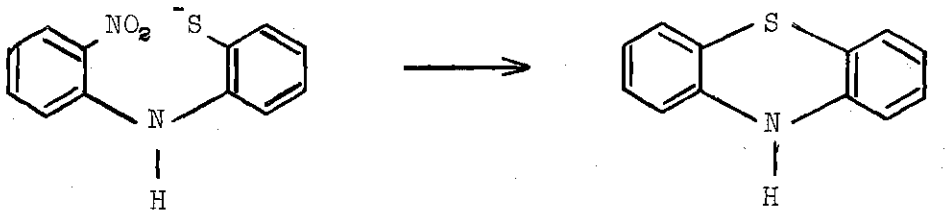
With the exception of the halogens which are discussed in the next section, the following is a discussion of the different leaving groups in nonactivated substitutions by an S_N2 mechanism.

Nitro. The known cases of displacement of nonactivated nitro groups involve intramolecular reactions. Hey and Rees (93) effected displacement of the nitro group in the biphenyl compound shown in Eq. 5 to produce 3,4-benzocoumarin.



(5)

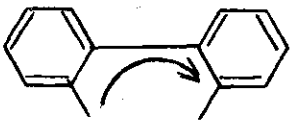
Davis and Wetzel (94) found intramolecular displacement of the nitro group by thiophenoxide ion (Eq. 6).



(6)

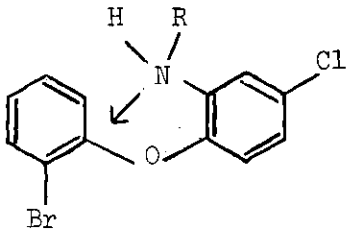
Benzenesulfonate ($OSO_2C_6H_5$). Benzenesulfonate is the leaving group in the reaction of p-cresyl benzenesulfonate with sodium amide in boiling piperidine (29).

Ammonia. Carbazole is produced from 2,2′-diaminobiphenyl by heating it in the presence mineral acid (95) or by heating the dry hydrogen bromide salt (96). Although the mechanism is unknown, an S_Ni mechanism involving intermediate I is suggested (96).



I

Phenoxide. As noted earlier, phenyl ether (81) is hydrolyzed by direct substitution. The intramolecular rearrangement of II involves loss of a phenoxy group (97).



II

Thiophenoxide. The reaction of di-(p-tolyl) sulfide with sodium amide in boiling piperidine, where $-SC_6H_4CH_3$-p is lost, gives only para substituted compounds (29).

Phenyl Sulfonyl and Methyl Sulfonyl. Phenyl sulfonyl is the leaving group in the S_N2 reaction of diphenylsulfone by alkaline fusion (70) and by amination (29). The Truce-Smiles rearrangement is an example of an intramolecular SO_2Ar leaving group. The methyl sulfonyl can also

leave by a S_N2 mechanism (30,31).

Sulfonate (SO_3^-). The alkaline fusion of benzene sulfonic acid occurs by an S_N2 type mechanism (68).

Phenyl Iodonium Group ($^+IC_6H_5$). Diaryl iodonium salts are important arylating agents, and reactions with numerous nucleophiles are known (98). These reactions have been explained as bimolecular nucleophilic dispacements (98) but little proof is available. Indeed, other mechanisms have been proven. With phenoxides (99) attack occurs on an ion pair or a complex [$Ar_2I^+\bar{O}$ Ar], while with amines a radical mechanism is indicated (100).

Halogen Order.

The halogens are discussed together as leaving groups because the halogen order is used as a criterion for explaining the mechanism of aromatic nucleophilic substitution. In the activated case the order is usually F >> Cl > Br > I. Since the loss of fluorine is faster than chlorine, there must be little bond breaking in the transition state. On the other hand, in the nonactivated case, the order is I > Br > Cl. Thus, one might conclude that a different mechanism is operating, possibly one similar to aliphatic S_N2 reactions where bond breaking is important.

Tronov and Krueger (11) are often quoted for their early study of halobenzenes with piperidine and sodium methoxide (Table 10). These reactions occur by direct displacement. Tronov's data is subject to doubt. Later values for the relative rates of halobenzenes (12) with piperidine are iodine, 14.6; bromine, 8.2; and chlorine, 1.0. For 1-halonaphthalenes (10) with piperidine the values are iodine, 11.4; bromine, 5.6; and chlorine, 1.0, and for 1-halofurans (17), iodine, 20; bromine 10; and

chlorine, 1. With sodium methoxide, bromobenzene reacts 4.5 times faster than chlorobenzene at 200°C (38,45).

Table 10. Relative Rates of Reaction of Halobenzenes with Piperidine and Sodium Methoxide (11)

Compound	$NaOCH_3$ (165°C)	Piperidine (210°C)
C_6H_5F	1	1
C_6H_5Cl	1.8	1.9
C_6H_5Br	4.4	74.5
C_6H_5I	35.6	132

The relative rates of fluorine and chlorine are important and affect the mechanistic interpretation of the reaction. Although the relative order I > Br > Cl > F which Tronov found was substantiated for I > Br > Cl, the position of fluorine was not verified by Bunnett (31). Bunnett challenged the position of fluorine in Tronov's order when he found that 1-fluoronapthalene reacted 36 per cent in 24 hours, while 1-bromonaphthalene reacted 49 per cent in 48 hours at 230°C. With sodium methoxide Miller (42) found the rate ratio of fluorobenzene to chlorobenzene to be approximately 100 at 202.5°C. This ratio compares favorably with the fluorine to chlorine ratio found in activated cases at 200°C: mononitro, 74.5; dinitro, 261 (42). This fact is used as evidence for the intermediate complex mechanism for nonactivated aromatic nucleophilic substitution. However, Miller's ratio is subject to considerable error since the chlorobenzene rate was only an estimate. Neither did Miller

take into account the consecutive demethylation reaction ($ArOCH_3 \rightarrow ArO^-$). Shein (46) took this into account in obtaining his value of 2.0×10^{-6} M^{-1} sec^{-1} at 202.5°C for chlorobenzene. Thus, the relative rate ratio of fluorine to chlorine is closer to forty.

Miller and Wrightson (54) looked at the fluorine to chlorine rate ratio as a function of the substituent on the ring (Table 11). The data shows that with sodium ethoxide the loss of fluorine is considerably faster than chlorine in all cases.

Substituent Effects

In aromatic nucleophilic substitution a substituent that is able to withdraw electrons mesomerically or inductively will activate, since a partial negative charge is developed in the ring in the transition state. Table 12 lists the activating powers of different substituents studied in the nonactivated case. Just as two nitro groups are more activating than one such group, addition of other substituents such as trifluoromethyl (Table 13) or chloro (Table 14) greatly activate.

Deactivating Substituents. These substituents include alkyl, amino, hydroxyl, and oxido. Little quantitative data is available with deactivating groups since in most cases no reaction is evident. With the methyl substituent, Van Lande (59) found that 2,4-dichlorotoluene reacted at 183°C with sodium methoxide 10.6 per cent while 1,3-dichlorobenzene reacted 38.9 per cent. From Table 5 iodofuran reacts 2.5 times faster than 5-methyl-2-iodofuran, the difference being determined by the activation energy. Qualitatively, the hydrolysis of phenyl ether is faster than p-tolyl ether (75).

Table 11. Rate Constants for Substituted Fluoro or Chlorobenzenes with Sodium Ethoxide at 150°C (54)

Compound	$k(M^{-1}hr^{-1})$	k_F/k_{Cl}
p-CF_3-C_6H_4	16	
		760
p-CF_3-C_6H_4Cl	0.021	
m-CF_3-C_6H_4F	0.39	
		186
m-CF_3-C_6H_4Cl	0.0021	
m-Cl-C_6H_4F	0.20	
		118
m-Cl-C_6H_4Cl*	0.00165	
p-Cl-C_6H_4F	0.042	
		84
p-Cl-C_6H_4Cl*	0.0005	

*Statistically corrected.

Table 12. Activating Ability of Substituents

Compound	Base	Temperature °C	Activation	Reference
p-X-C_6H_4Cl	$NaOCH_3$	150	$Cl > H > NH_2 \sim CH_3 \sim O^-$	50
p-X-C_6H_4Cl	$NaOCH_3$	190	$SO_2CH_3 > CF_3 > Cl > CO_2^- > H$	46,47,51
p-X-C_6H_4Cl	$NaOCH_3$	200	$COCH_3 > CF_3 > Cl > H$	45
p-X-C_6H_4Cl	NH_3	270	$SO_2CH_3 > SO_2NH_2 > CF_3 > H$	21
o-X-C_6H_4Cl	$NaOCH_3$	150	$Cl > H > NH_2 > CH_3$	50
o-X-C_6H_4Cl	$NaOCH_3$	190	$SO_2CH_3 > CF_3 > Cl \sim CO_2^- > H$	46,47,51
o-X-C_6H_4Cl	KOH	158	$SO_2C_6H_5 > SOC_6H_5$	101
p-X-C_6H_4Br	$NaOCH_3$	150	$Br > H \sim NH_2 > OCH_3 \sim CH_3$	50
p-X-C_6H_4Br	$NaOCH_2CH_3$	81	$SO_2CH_3 > COCH_3$	58
o-X-C_6H_4Br	piperidine	165	$SO_2CH_3 > COCH_3$	58
p-X-C_6H_4Cl	$NaOCH_3$	170	$SO_2^- > SO_3^- > CO_2^-$	53
2,4-di-Cl-1-X-C_6H_4	$NaOCH_3$	183	$SO_3^- > CO_2^- > Br \sim Cl > H > CH_3$	59
2,5-di-Cl-1-X-C_6H_4	$NaOCH_3$	180	$SO_3^- > CO_2^- > CH_2OH > C_6H_5 > F \sim CH_3$	49
3,4-di-Cl-1-X-C_6H_4	$NaOCH_3$	180	$I > Br > Cl > CH_3 > O^-$	60

Table 13. Kinetic Parameters of the Reaction of Substituted Chlorobenzenes with Sodium Methoxide at 120°C (55)

Substituent	k x 10^5 ($M^{-1}sec^{-1}$)	$\Delta E^{\neq}$	log A	Relative Rate
H	4.5 x 10^{-5}	37.3	11.4	1
4-CF_3	0.126	30.0	10.8	2.8 x 10^3
2,4(CF_3)2	65	24.0	10.1	1.4 x 10^6
2,4,6(CF_3)$_3$	6,600	20.1	10.0	1.5 x 10^8

Table 14. Kinetics of the Reaction of Chlorobenzenes with Sodium Methoxide at 210°C (51)

Compound	k x 10^{-5} ($M^{-1}sec^{-1}$)	$\Delta E^{\neq}$	log A	Relative Rate
Chlorobenzene	0.30	37.3	11.4	1
1,4-Dichlorobenzene	4.6*	33.6	11.2	15.3
1,2,4,5-Tetra-chlorobenzene	525*	26.0	10.2	1,750
Hexachloro-benzene	23,330*	22.0	10.1	76,600

*Statistically corrected.

The amino and oxido (O^-) groups are deactivating in all positions due to mesomeric release of electrons into the ring. No reaction occurs at 155°C with sodium methoxide with o- and p-chloroaniline nor with o- and p-chlorophenol, while the meta-oxido group is not so extremely deactivating (36).

Halogen Substituents. In activated nucleophilic substitution the halogen substituents are activating in all positions, except in the case of para fluorine. They activate inductively (F > Cl > Br > I) and deactivate mesomerically (F > Cl > Br > I) such that the relative strength of the two effects causes the order of reactivity to be meta greater than para. In the para position the order of activation is F < H < Cl < Br ~ I. The para fluorine substituent is interesting in that the balance between its inductive mesomeric effect causes the fluorine to have an effect similar to hydrogen.

In the nonactivated case halogens are activating in all positions, with the exception of para fluorine. With sodium methoxide at 190°C, the order of reactivity in dichlorobenzenes (51, 37, 102) and dibromobenzenes (38) is m > o > p (Table 15). In the para position the halogens activate in the order I > Br > Cl > H ~ F with nonactivated compounds (60).

Another important aspect in the substitution of halogens is the result of pitting different halogens against each other, such as p-bromofluorobenzene. The true effects in these competitive displacements of halogens are difficult to obtain in the activated case except in 3,5-dihalo-nitrobenzenes (103) or pentafluorohalobenzenes (104). In the nonactivated case little is known. In the reaction of p-chlorofluorobenzene

Table 15. Halogen Substituent Effects at 200° with Sodium Methoxide

Compound	k x 10^6 ($M^{-1}sec^{-1}$)	$\Delta E^{\neq}$	log A	Reference
C_6H_5Cl	0.16	37.3	11.4	46
o-$Cl_2C_6H_4$	3.4*	35.6	12.3	51
m-$Cl_2C_6H_4$	5.25*	35.1	12.2	51
p-$Cl_2C_6H_4$	2.3*	33.1	11.2	51
C_6H_5Br	0.71	35.9	11.4	38
o-$Br_2C_6H_4$	14.0*	33.1	11.7	38
m-$Br_2C_6H_4$	19.8*	34.6	12.7	38
p-$Br_2C_6H_4$	6.0*	36.3	12.9	38

*Statistically corrected.

with sodium methoxide at 183°C, the fluorine is displaced 96 per cent and the chlorine 0.5 per cent (49). This may be explained by the fact that fluorobenzene is faster than chlorobenzene and that the p-fluorine substituent is deactivating toward nucleophilic displacement. In the same study p-bromochlorobenzene gives 90 per cent bromide displacement and only a trace of chloride displacement. Table 15 shows bromobenzene to be 4.5 times faster than chlorobenzene. Thus this cannot alone explain why such a small amount of chloride ion is produced. The calcium hydroxide hydrolysis of p-bromofluorobenzene produces mainly p-fluorophenol (83). This reaction is postulated as an S_N2 type displacement since no

meta products are obtained. Unless bromobenzene is much faster than fluorobenzene this mechanism is incorrect since fluorine deactivates nucleophilic displacement. Also, there are known cases of benzyne reactions occuring without rearrangement (see Miller, Ref. 112, Chap. 2).

Intermediate Activating Substituents. The trifluoromethyl group activates strongly inductively. Reactivity data show that p-CF_3 is more activating than m-CF_3. In substituted trifluoromethylbenzenes the k_p/k_m for loss of fluorine with sodium ethoxide (54) is 41, for loss of chlorine k_p/k_m is 10 at 150°C, and for loss of chlorine at 200°C with sodium methoxide (46) k_p/k_m is 5.9. In the series of mono and polytrifluoromethylbenzenes (105) reacting with sodium alkoxides the following is the order of decreasing activity: 2,4,6-tri-CF_3 > 2,4-di-CF_3 > 2,6-di-CF_3 > 2,5-di-CF_3 > p-CF_3 > o-CF_3 > 3,5-di-CF_3 ~ m-CF_3.

The carboxylate group is weakly activating ortho and para with alkoxides. The 2-chlorine is principally displaced in 2,5-dichlorobenzene carboxylate (49). p-Bromobenzene carboxylic acid reacts 14 per cent with sodium methoxide at 155°C in 50 hours, while the m-bromo isomer does not react (35). With sodium methoxide, p-chlorobenzoic acid is only 25 times more reactive than chlorobenzene at 190°C, while o-chlorobenzoic acid is 75 times faster than chlorobenzene (46, 47).

The sulfonate group is only two to three times more activating than the carboxylate group in nonactivated compounds (53). The sulfonate group activates ortho and para, since the 4-chlorine is displaced in sodium 3,4-dichlorobenzenesulfonate (60), and the 2-chlorine is displaced in sodium 2,5-dichlorobenzenesulfonate (49). Chlorobenzene-2,4,6-trisulfonic acid is much less activated compared to 2,4,6-tris

(trifluoromethyl)chlorobenzene (53, 55).

Data on the remaining intermediate activating substituents are sparse. The following is a list of these substituents along with references: aceto (19, 46, 58), COC_6H_5 (19, 58), $N_2C_6H_5$ (18), and phenyl (49).

Side Reactions. In nonactivated compounds, many substituents are destroyed under the condition necessary for nucleophilic displacement. Other reactions may occur to complicate the kinetic picture.

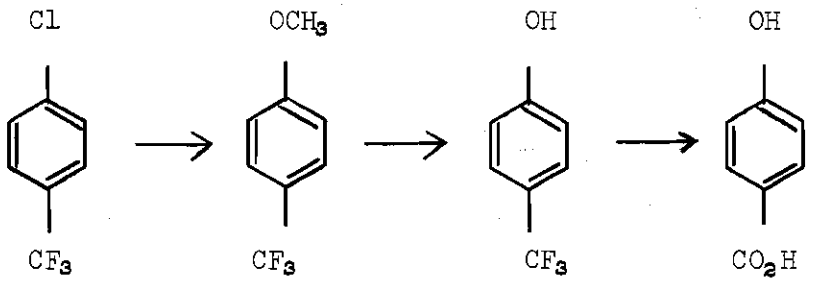
The reductive removal of halogen (Ar-Br → Ar-H) has been found in many systems and is important in determining kinetics. In water, o-chlorophenol is reduced to phenol up to 40 per cent in acidic, basic, or neutral conditions at 250°C (107). p-Dibromobenzene gives phenetole, bromobenzene, and benzene at 185°C with sodium ethoxide in ethanol (57). In the sodamide and boiling piperidine system iodonaphthalene gives six per cent naphthalene (31). The mechanism is probably a nucleophilic displacement on halogen, the order of reactivity being I > Br > Cl.

Saponification is a complicating side reaction with the cyano substituent (59, 60). Benzophenones with sodium methoxide at 180°C produce an amount of benzhydrol (49). An aldehyde substituent undergoes a Cannizzaro reaction under the same conditions (49, 59). Substituted acetophenones undergo aldol condensations at 100°C in sodium methoxide.

A general reaction occurring with sodium methoxide and other alkoxides, to a lesser extent, is demethylation of anisoles, initially formed from the halogen compound. The cleavage of anisoles proceeds by a bimolecular nucleophilic displacement; bond breaking occurs between the methyl group and the oxygen. This reaction must be accounted for in

the kinetics since base is used. With sodium methoxide at 150°C the rate of reaction of 1,2,4,5-tetrachlorobenzene is only twice as fast as demethylation of the anisole (109), while with sodium ethoxide cleavage of the phenetole produced is only 1/20th as fast as aromatic nucleophilic substitution (108).

Demethylation is kinetically important when an ortho or para trifluoromethyl group is present, since o- and p-trifluoromethyphenols readily lose fluoride ion in base. Shein (110, 111) studied the effect of hydrolysis of the trifluoromethyl group on kinetics in aromatic nucleophilic substitution and confirmed the scheme in Equation 7.



(7)

Linear Free Energy Relationships. The Hammett plot is one method of correlating and predicting reactivity. This is a plot of the log of the rate constant against the sigma value, a measure of the substituent effect. Table 16 accumulates the sigma values used in aromatic nucleophilic substitution. The σ^- value is used for para substituents since a partial negative charge may be placed at the carbon attached to the substituent in the transition state. The σ^- values found in aromatic nucleophilic substitution are classed according to whether the nucleophile is piperidine or methoxide.

Table 16. Sigma Values (111)

Substituent	σ_m	σ_p^-($NaOCH_3$)	σ_p^-(piperidine)	σ_p^-(other)
CH_3	-0.069	-0.221, - 0.237	-0.169	
$COCH_3$	+0.376	+0.874		
COC_6H_5		+0.767, + 0.879		
CO_2^-	-0.10	+0.16, + 0.135	+0.283	
CF_3	+0.43	+0.746	+0.668	
NH_2	-0.16	-0.87	-0.789	
O^-	-0.708			
F	+0.337	-0.015	-0.118	-0.05[113]
Cl	+0.373	+0.244, + 0.265	+0.151, + 0.196*	
Br	+0.391	+0.289, + 0.338	+0.181, + 0.241*	
I	+0.352	+0.299, + 0.318	+0.148, + 0.266*	
SOC_6H_5				
$SO_2C_6H_5$		+1.117		
SO_2CH_3	+0.60	+1.05		
SO_3^-	+0.05	+0.186		
SO_2NH^-		+0.363		

*In benzene solvent.

Table 17. Hammett Plots

Substrate	Reagent	Solvent	Temperature °C	Rho	Reference	Substituents
m- and p-X-C_6H_4F	$NaOCH_3$	CH_3OH	0	9.2	37	p-N_2^+, p-NO_2, H, m-NO_2
m- and p-X-C_6H_4F	$NaOCH_3$	CH_3OH	50	8.47	37	
p-X-C_6H_4Br	piperidine	C_6H_6	99	4.87	19	NO_2, SO_2CH_3, CN, $COCH_3$
p-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	50	8.47	45	CF_3, $COCH_3$, NO_2, Cl
m- and p-X-C_6H_4Br	$NaOCH_3$	CH_3OH	100	5.2	38	H, p-Br, p-SO_2CH_3, p-NO_2, m-Br
m- and p-X-C_6H_4Br	$NaOCH_3$	CH_3OH	150	4.5	38	
m- and p-X-C_6H_4Br	$NaOCH_3$	CH_3OH	200	3.9	38	
m- and p-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	100	5.6	46	p-NO_2, p-SO_2CH_3, p-CF_3, m-CF_3, m-Cl
m- and p-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	150	4.9	46	
m- and p-X-C_6H_4Cl	$NaOCH_3$	CH_3OH	200	4.3	46	
4 and 5-X-2-CF_3-C_6H_3Cl	$NaOCH_3$	CH_3OH	50	5.3	55	H, 4-CF_3, 4-NO_2, 5-CF_3
4 and 5-X-2-CF_3-C_6H_3Cl	$NaOCH_3$	CH_3OH	100	4.7	55	
4 and 5-X-2-CF_3-C_6H_3Cl	$NaOCH_3$	CH_3OH	150	4.2	55	

Table 17 summarizes some Hammett plots which include both activating and nonactivating substituents. In most cases the rho (ρ) values, measures of the effect of the substituent on the reaction center, are from plus four to plus five at temperatures greater than 150°C. These rho values decrease with increasing temperature.

The ortho:para Ratio.

The ortho:para ratio has received much attention in the activated case, especially the effect of the nitro group. When the ortho:para effect of another substituent is in question a nitro group may mask the true ortho:para ratio. The substituents discussed in this section are CO_2^-, CF_3, $SO_2C_6H_5$, SOC_6H_5, Br, CH_3, $COCH_3$, COC_6H_5, and Cl, in compounds containing no nitro groups. The substituents are discussed according to Miller's (112) classification: (1) attached by the positive end of a dipole (CO_2^-, $COCH_3$, COC_6H_5, SOC_6H_5, $SO_2C_6H_5$), (2) electrically neutral-no unshared pairs (CF_3, CH_3), and (3) electrically neutral-unshared pairs (Cl, Br).

(1) The first is carboxylate. Table 18 shows the data on the ortho:para effect of carboxylate with anoid nucleophiles. In activated cases carboxylate (114, 115) is weakly activating para but deactivating ortho with sodium methoxide. Miller has ascribed this ortho deactivation to the electrostatic repulsion between the negatively charge carboxylate and the negatively charged methoxide, along with an added steric effect. Whereas in the activated case the ortho:para ratio is less than one with alkoxides, in the nonactivated case the ortho:para ratio is greater than or equal to one. This reversal of the ortho:para ratio is due to the differences in reaction temperature. If the ortho:para ratio for the activated compounds are calculated at 190°C, the ratio becomes greater

Table 18. The ortho:para Effect of Carboxylate

Compound	Base	Temperature °C	k x 10^4 ($M^{-1}sec^{-1}$)	% Br^-	Reference
o-$BrC_6H_4CO_2^-$	$NaOCH_3$	155		14.4	36
p-$BrC_6H_4CO_2^-$	$NaOCH_3$	155		14.0	36
o-$ClC_6H_4CO_2^-$	$NaOCH_3$	190	0.5		47
o-$ClC_6H_4CO_2^-$	$NaOCH_2CH_3$	190	0.7		47
p-$ClC_6H_4CO_2^-$	$NaOCH_3$	190	0.17		47
p-$ClC_6H_4CO_2^-$	$NaOCH_2CH_3$	190	0.064		47

Table 19. The ortho:para Ratio of SOC_6H_5 and $SO_2C_6H_5$ in Aqueous DMSO at 158°C (101)

Compound	Base	k x 10^5 ($M^{-1}sec^{-1}$)
o-Cl-$C_6H_4SOC_6H_5$	KOH	1.9
p-Cl-$C_6H_4SOC_6H_5$	KOH	3.3
o-Cl-$C_6H_4SO_2C_6H_5$	KOH	193
p-Cl-$C_6H_4SO_2C_6H_5$	KOH	374

than one.

The data on the $SO_2C_6H_5$ and SOC_6H_5 are in Table 19. Since the coplanarity of these substituents with the ring is unnecessary for valence shell expansion of the sulfur, the ortho compound should activate more than para. Since this is not the case in Table 19, there must be a steric factor associated with the ortho substituent.

The ortho:para effect of the $COCH_3$ and COC_6H_5 substituents is seen in Table 20. The ortho:para effect of these substituents follows the pattern with nitro substituents, that of ortho activation with amines and para activation with alkoxides. Bunnett ascribes the ortho activation with amines to "built-in solvation" (116) which is an electrostatic interaction between the developing positively charged amine nitrogen and the negatively charged oxygens of the nitro group.

(2) The second classification deals with trifluoromethyl and methyl groups. The trifluoromethyl group should have a negligible steric effect with small nucleophiles. The greater inductive effect of the ortho trifluoromethyl group should therefore be more activating than the para, and this is observed in activated compounds (37). Table 21 shows that the ortho:para ratio is less than or equal to one in non-activated compounds. Here again the ortho isomer will become faster than the para at some lower temperature due to the lower activation energy of the ortho compound.

Data on the methyl group is limited to the findings of Lande (59), who noted that the 2-chlorine is displaced in 2,4-dichlorotoluene with sodium methoxide at 183°C, which parallels the activated cases (see Ref. 112, p. 106). The cause of an ortho:para ratio greater than one with

Table 20. The ortho:para Ratio of $COCH_3$ and COC_6H_5 (58)

Compound	Base	Temperature °C	$k(M^{-1}sec^{-1})$	% Br^-
o-Br-$C_6H_4COCH_3$	piperidine	165		84.0
p-Br-$C_6H_4COCH_3$	piperidine	165		26.1
o-Br-$C_6H_4COCH_3$	$NaOCH_2CH_3$	81	4.4×10^{-6}	
p-Br-$C_6H_4COCH_3$	$NaOCH_2CH_3$	81	35.0×10^{-6}	
o-Br-$C_6H_4COC_6H_5$	piperidine	165		25.8
p-Br-$C_6H_4COC_6H_5$	piperidine	165		4.3
o-Br-$C_6H_4COC_6H_5$	NaOH	75		0.6
p-Br-$C_6H_4COC_6H_5$	NaOH	75		2.4

Table 21. The ortho:para Ratio of the Trifluoromethyl Substituent

Compound	Base	Temperature °C	$k \times 10^4 (M^{-1}sec^{-1})$	$\Delta E^{\neq}$	log A	Reference
o-Cl-C_6H_4	$NaOCH_3$	190	1.8	29.5	10.2	48
o-Cl-$C_6H_4CF_3$	n-$C_5H_{11}ONa$	190	1.4	32.7	11.6	48
p-Cl-$C_6H_4CF_3$	$NaOCH_3$	190	3.9	30.0	10.8	48
p-Cl-$C_6H_4CF_3$	n-$C_5H_{11}ONa$	190	1.4	36.7	13.3	48
o-Cl-$C_6H_4CF_3$	NH_4OH	270	0.0084	24.3		21
p-Cl-$C_6H_4CF_3$	NH_4OH	270	0.1	27.8		21

methyl is uncertain. Bunnett has suggested a polarizability factor or a solvation favoring the ortho position (117, 118).

(3) Table 22 lists the ortho:para effects of chlorine and bromine. These halogens have a conjugative destabilization which operates better from the para position, and an inductive stabilization more effective from the ortho position. The result is greater ortho activation. p-Dibromobenzene has a higher energy of activation than the ortho compound, while the opposite is found in dichlorobenzene.

Shein also studied solvent effects on the ortho:para ratio of substituted chlorobenzenes where the substituents are SO_2CH_3, CO_2^-, Cl, and CF_3 (47, 48, 119, 120).

Solvent Effects.

Aromatic nucleophilic reactions are usually carried out in protic solvents. In the nonactivated case few solvent studies are available, and they are limited to alkoxide nucleophiles. Shein (38, 47, 48, 110, 121) studied the rates of reaction of aromatic chloro and bromo derivatives with sodium methoxide and higher alkoxides in their corresponding alcohols. The rates are determined by the nucleophilicity of the alkoxide and by the polarity of the medium. In all cases studied, except o-chlorobenzoic acid and o-chlorophenyl methyl sulfone, the rates decrease as the length of the alkoxide chain increases. A few other studies involve binary mixtures (119, 210) of benzene, heptane, or p-xylene with alcohols, with the corresponding alkoxides as nucleophiles. There is one study in methanol-water mixture (122). The rates are explained by specific and nonspecific solvation by the alcohol.

There has been recent interest in studying aromatic nucleophilic

Table 22. The ortho:para Ratio of Chlorine and Bromine

Compound	Base	Temperature °C	k x 10^5 ($M^{-1}sec^{-1}$)	$\Delta E^{\neq}$	log A	Reference
1,2-$Br_2C_6H_4$	$NaOCH_3$	190	13.0	33.1	11.7	38
1,4-$Br_2C_6H_4$	$NaOCH_3$	190	5.6	36.3	12.9	38
1,2-$Cl_2C_6H_4$	$NaOCH_3$	190	3.6	35.6	12.3	39
1,4-$Cl_2C_6H_4$	$NaOCH_3$	190	1.5	33.0	10.7	39
1,2-$Cl_2C_6H_4$	$NaOCH_2CH_3$	150	2.2			54
1,4-$Cl_2C_6H_4$	$NaOCH_2CH_3$	150	1.7			54
2-F-C_6H_4Cl	$NaOCH_2CH_3$	150	480.0			54
4-F-C_6H_4Cl	$NaOCH_2CH_3$	150	70.0			54

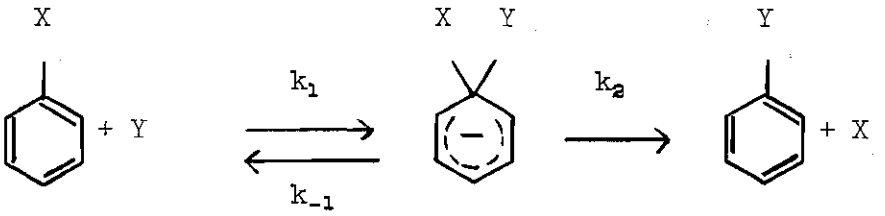
substitutions in dipolar aprotic solvents. The only study in the non-activated case is that of Cram (62) who found a marked rate enhancement in the reaction of o-fluorotoluene with sublimed potassium tert-butoxide in dimethyl sulfoxide over ordinary protic solvents.

Mechanism

Since there is proof that nonactivated halobenzenes can react by bimolecular nucleophilic substitution, the question remains as to whether the reaction occurs by an intermediate complex mechanism, as in activated cases, or by a mechanism similar to a one step S_N2 aliphatic displacement. Many authors (1, 12, 15, 123) have concluded that metastable intermediates, such as the cyclopentadienyl anion, play little or no part in the reaction and that this should be reflected in the partial breaking of the carbon halogen bond in the transition state. As carbon halogen bond stretching becomes important, the rate of loss of fluorine and chlorine should become closer than in the activated case where formation of the intermediate complex is usually rate determining. But, as Miller and Shein have shown, the rate ratio of fluorobenzene and chlorobenzene is similar to the ratio in the activated case when compared at the same temperature. To incorporate this fact into any one step mechanism requires an early transition state where carbon halogen bond breaking is unimportant. Brower (124) concluded from a pressure study that the transition state resembles the reactants.

In an intermediate complex mechanism with nonactivated compounds the formation of the intermediate should be rate determining because of its instability compared to nitro activated intermediates. But, kinetically, three possibilities exist (Eq. 8). The derived kinetic expression,

(Eq. 9), indicates that if $k_2 \gg k_{-1}$, the formation of the intermediate complex is rate determining and $k = k_1$. This case is kinetically indistinguishable from a one step S_N2 mechanism. If $k_{-1} \gg k_2$,



(8)

$$k = k_1 k_2/(k_{-1} + k_2) \tag{9}$$

then the overall rate is $k = k_1 k_2/k_{-1}$, and the rate is dependent on the concentration of the complex times the rate of conversion to products. If k_2 and k_{-1} are comparable, the rate is affected by bond formation and bond rupture. In an intermediate complex mechanism an early transition state is unnecessary to fit the fluorine to chlorine rate ratio.

Although there are a number of methods for distinguishing between these two mechanisms, only the halogen order has been studied. Whatever the mechanism, the high positive rho values from Table 17 show that substituents have a significant effect on the transition state.

Rearranging Reactions

Sommelet-Hauser Rearrangement

This rearrangement reaction (125, 126) has been included in a review (2) of aromatic nucleophilic substitution. This reaction will

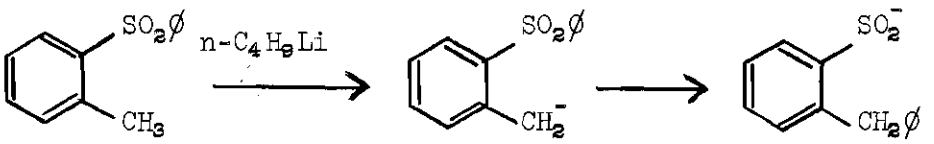
not be discussed since evidence has shown that this reaction actually involves a tight ion pair mechanism (127).

Competitive (Benzyne: Addition-Elimination)

In reactions involving benzynes the presence of rearranged products does not always mean that the benzyne reaction is the only mechanism. Listed here are methods of showing the presence of direct substitution. (1) One can use ^{14}C labeling, as in C_1 labeled chlorobenzene (78). If benzyne is the only mechanism, then the one position of the product will be equally distributed between labeled carbon and unlabeled carbon. (2) The whole series of halogens may be run (31, 34). If the ratio of products such as m- and p-cresols from p-halotoluenes is different for one halogen, then this halogen involves some direct substitution. (3) In aminations, if the addition of free amine enhances the amount of direct substitution product (34) then some direct substitution is occurring due to the reversal of metalation. (4) If the addition of a proton source, such as methanol, to the system produces a greater per cent of unrearranged product then direct substitution is occurring due to reversal of metalation (128).

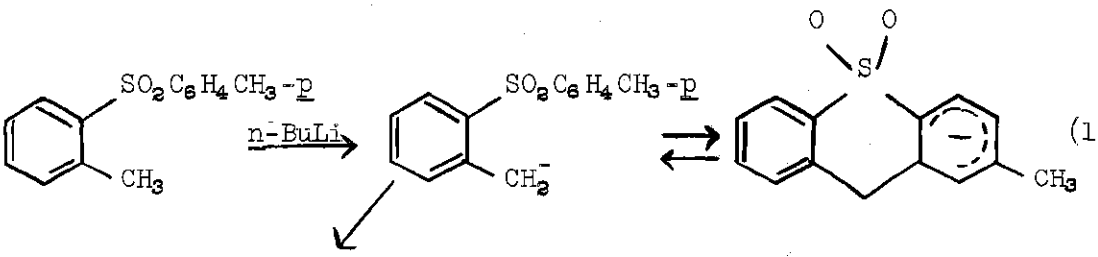
Truce-Smiles Rearrangement

Although the Smiles (1) rearrangement usually occurs only with activating nitro groups present, the Truce-Smiles reaction may be considered part of the nonactivated case. This reaction, first studied by Truce (129, 120, 131), is a base induced intramolecular rearrangement of o-methyldiaryl sulfones to o-benzylbenzenesulfinic acids (Eq. 10).

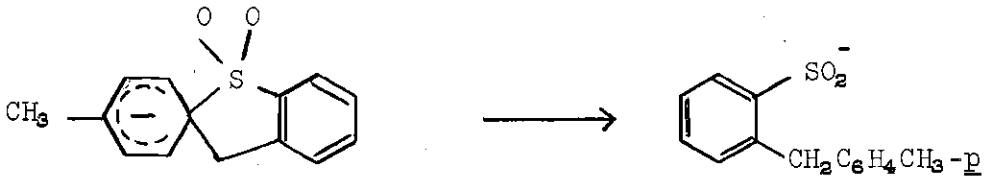


(10)

Later, Drozd (132, 133) showed this reaction is more complex than simple direct displacement and involves more than one intermediate (Eq. 11, 12).

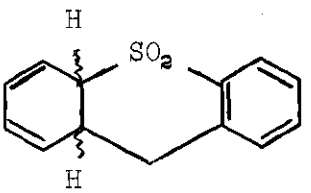


(11)



(12)

In almost all cases, compounds similar to III may be isolated. However, if a good leaving group (Cl, OCH_3) is placed ortho to the SO_2

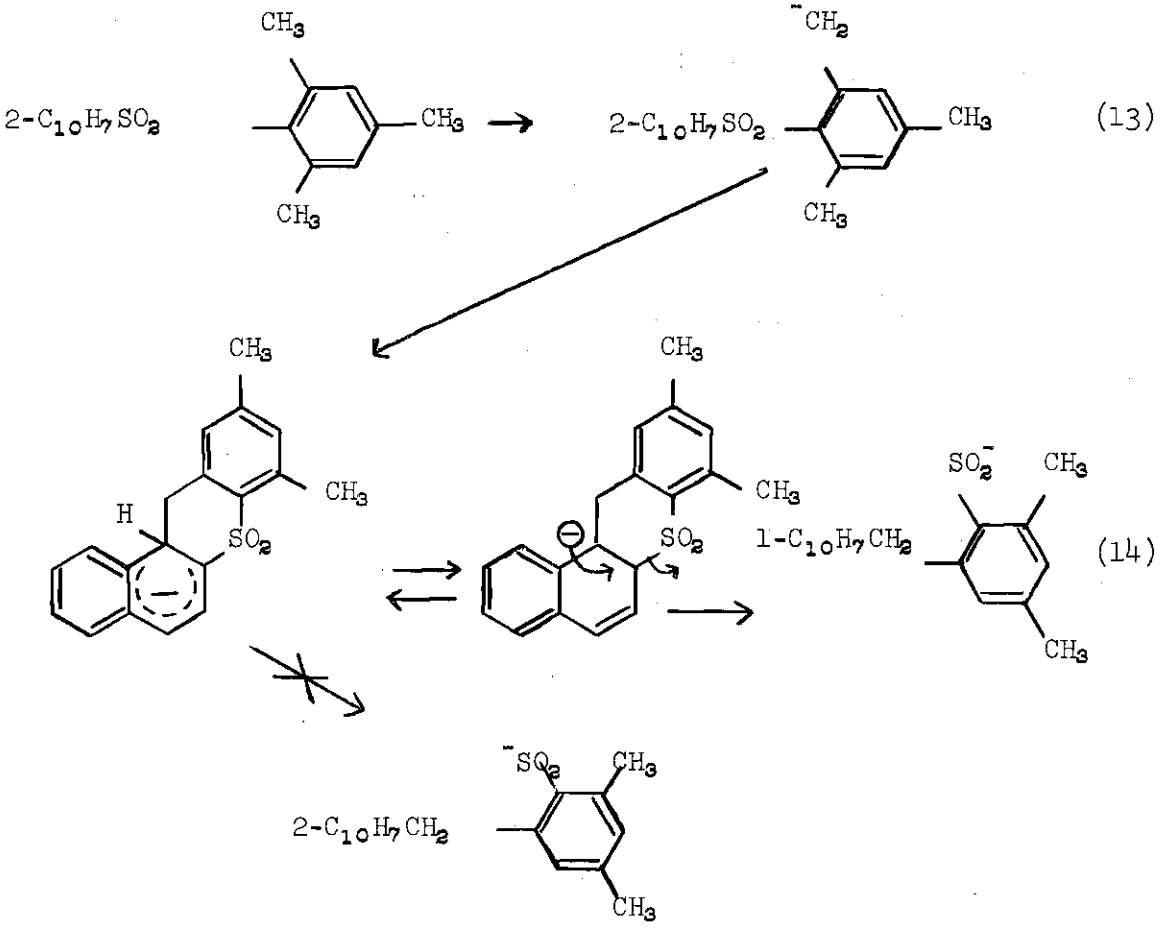


III

group in the ring not containing o-methyl groups, then the chlorine or methoxy group is displaced by the carbanion in an intramolecular

nucleophilic cyclization (134). This reaction occurs because of the strong ortho activation of the methoxy group by a phenylsulfonyl substituent.

Interestingly, the mesityl naphthyl sulfones (135, 136) with potassium tert-butoxide in dimethyl sulfoxide do not undergo the Truce-Smiles rearrangement, but follow a cine mechanism, specifically the AE^2_a (Eq. 13, 14).



This reaction involves an intramolecular nucleophilic addition of the carbanion across the 1, 2 bond of naphthalene, followed by base catalyzed β-elimination of the sulfone group. The AE_a mechanism has previously been shown to occur in some heterocyclic systems (130, 137).

Miscellaneous

Azulene

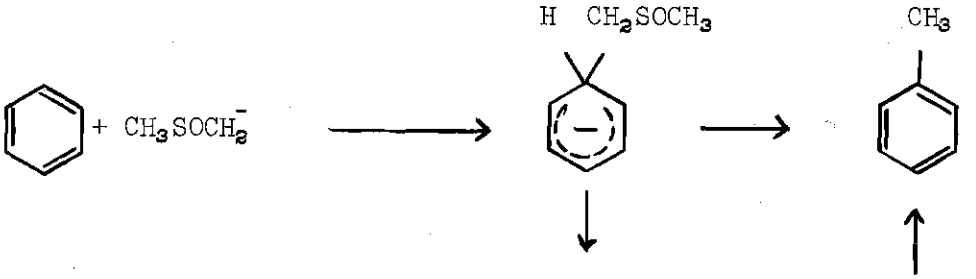
Azulene is interesting in that this aromatic compound needs no activating substituents to facilitate nucleophilic displacement. The seven membered ring is activated by the negative polarization of the smaller ring, activating greatest at the 4, 6, 8 positions (138). The compound 6-chloro-4,8-dimethylazulene reacts with piperidine, aniline, sodium ethoxide, sodium sulfide, or sodium azide at temperatures less than 140°C without rearrangement (139).

Nucleophilic Aromatic Alkylation

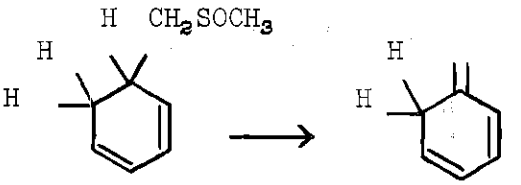
This reaction involves methylation of condensed aromatic compounds by means of methylsulfinyl or methylsulfonyl carbanions. Table 23 gives the compounds methylated, excluding heterocyclics, and the conditions used. The mechanism proposed involves nucleophilic attack on the aromatic ring by the carbanion. The resulting sigma complex may break down by either a hydride shift, or by protonation of the sigma complex, elimination of methylsulfinic acid, and fast aromatization (Eq. 15, 16). The latter route is supported by the fact that 9-deuteriophenanthrene loses approximately 50 per cent deuterium in the monomethylated product (140).

Table 23. Methylation of Aromatic Compounds

Compound	Base	Position Methylated	% Product	Reference
Benzene	NaH, DMSO		0	140
Anthracene	NaH, DMSO	9	77	140
Anthracene	NaH, DMSO	9,10	13	140
Phenanthrene	NaH, DMSO	9	86	140
Benzene	K-t-BuO, DMSO		0	141
Anthracene	K-t-BuO, DMSO	9	45	141
Naphthalene	K-t-BuO, DMSO	1	14.5	141
Anthracene	NaH, HMPA, $C_6H_5SO_2CH_3$	9	53	142
Anthracene	NaH, HMPA, $C_6H_5SO_2CH_3$	9,10	10	142



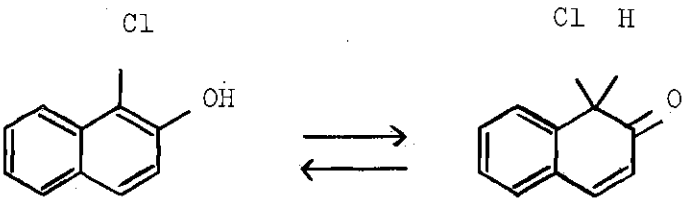
(15)



(16)

Keto-enol Equilibrium

The reactions of amines with 1-halogeno-2-naphthols at 100°C yield the unrearranged 1-amino-2-naphthols (143, 144). Similarly, 4-bromo-1-naphthol reacts with aniline at 100°C in diethylene glycol (145). These compounds are much more reactive compared to 1-halonaphthalenes and may be explained by a keto-enol pre-equilibrium (146) where the reactive species is the keto tautomer (Eq. 17).

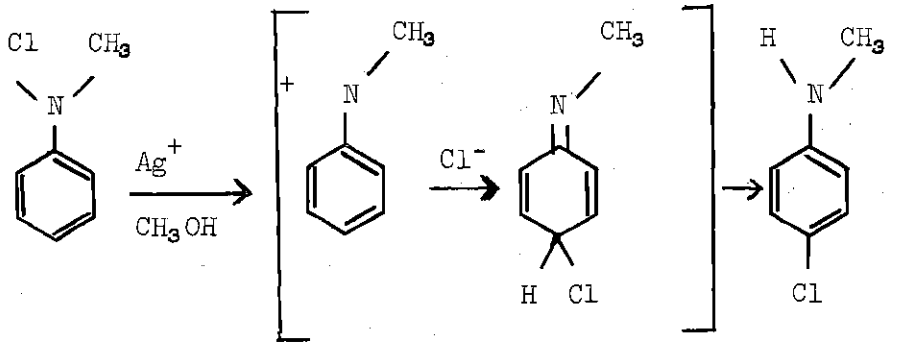


(17)

Hydroxyl groups are very deactivating toward nucleophilic substitution. This reaction is not considered as an aromatic nucleophilic displacement but serves to illustrate the fact that in nonactivated cases other mechanisms may take precedence over direct displacement.

Anilenium Ion

The reaction of N-chloro-N-methylaniline with methanolic silver perchlorate at -20°C produces chloro or methoxy substituted N-methylanilines in the ortho or para positions (147). This reaction proceeds by a loss of chloride ion with subsequent nucleophilic attack by methanol or chloride ion on the intermediate anilenium ion (Eq. 18).



(18)

Although this reaction involves nucleophilic attack by chloride on an aromatic ring, there is no anoid leaving group but merely a prototropic rearrangement to form the product. This mechanism is similar to the acid catalyzed rearrangement of phenyl hydroxylamine to p-aminophenol (148, 149).

Description of Research

There is no extended study of the mechanism of nonactivated aromatic nucleophilic substitution. It is known that these reactions are second order when alkoxides are used as nucleophiles and that

displacement can occur without rearrangement on nonactivated compounds. Yet the details of this mechanism remain obscure. It is the intent of this research to help elucidate the mechanism of this reaction by using a number of methods. Also, previous to this research, there were no second order rate data on the reaction of nonactivated halobenzenes with amine nucleophiles. The data obtained show that solvent studies on nonactivated halobenzenes are certainly feasible with amine nucleophiles and should open up a broad area where research has been limited.

CHAPTER II

EXPERIMENTAL

Chemicals

Triethylene glycol (Fisher) was distilled using a distilling head fitted with 1000-ml round-bottomed flask containing about 500-ml of triethylene glycol. Rapid stirring with a one inch magnetic stirring bar was necessary to reduce bumping. Insulating the pot with cotton helped reduce bumping. The colorless liquid was collected at 110°C/5 mm and was stored in a stoppered round-bottomed flask under nitrogen.

Piperidine (Fisher) was purified by distillation from sodium. About 150-ml of piperidine and five g of sodium was placed in a 250-ml round-bottomed flask and refluxed a minimum of six hours through a two-foot vacuum-jacketed column filled with glass beads. The amount of decomposition in the pot was lessened if the apparatus was flushed with nitrogen previous to distillation. A middle third, b. p. 105°C/736 mm, (lit. 105°C)(115) was collected and stored in a brown bottle under nitrogen. There was always about one per cent pyridine in the distilled piperidine.

The substituted liquid anilines (Table 24) used to prepare the phenyl piperidines were purified by distillation using Bantam Ware apparatus. In all cases the compound was used immediately after distillation.

p-Nitroaniline was not reacted with 1,5-dibromopentane.

Table 24. Data on Substituted Anilines

Substituent	Boiling Point	Boiling Point (lit).	Source
p-Methoxy	77°C @ 0.5 mm		Eastman
m-Methoxy	80.5°C @ 0.5 mm	81-86°C @ 2 mm (150)	Aldrich
m-Methyl	56°C @ 0.5 mm	121°C @ 57 mm (151)	Eastman
Hydrogen	43.5°C @ 1.5 mm	112.9°C A 75.8 mm (151)	Eastman
m-Fluoro	45.5°C @ 0.5 mm	64-66°C @ 4 mm (152)	Peninsular
p-Fluoro	38.2°C @ 0.5 mm	98-99°C @ 33 mm (153)	Peninsular
m-Chloro	72°C @ 1 mm	118.5°C @ 21 mm (154)	Eastman
m-Bromo	91°C @ 2 mm	91°C @ 2 mm (154)	Eastman

m-Aminobenzotrifluoride (Eastman) was used without purification. p-Chloroaniline (Aldrich) was also used without purification, m.p. 68-70°C. m-Nitroaniline (Aldrich) was not purified, m.p. 112-113°C.

p-Toluidine (Matheson, Coleman, & Bell) was sublimed at room temperature, m.p. 42-43. p-Bromoaniline (Eastman) was recrystallized from ethanol-water, m.p. 56-58°C.

A large number of halobenzenes was used in this research. Those liquid halobenzenes, purified by distillation, are listed in Table 25. These compounds were distilled using either a Nester Faust spinning band eight inch (stainless steel) column or Bantam Ware. The purified material was collected and stored in brown bottles under nitrogen. They were then checked for purity by gas liquid chromatography.

p-Bromochlorobenzene (Eastman) was recrystallized from ethanol-water, m.p. 62-65°C. p-Fluorophenol (Pierce) was sublimed at room temperature under 1 mm pressure, m.p. 45. 7-47°C. p-Chlorophenol (Eastman) was also sublimed at room temperature, m.p. 38-40°C. Diphenylsulfone (Aldrich) was recrystallized from 60:40 v/v benzene-petroleum ether. The colorless crystals melted at 121.5-123.5. Diphenylamine (Eastman) was distilled (b.p. 136°C/3 mm) on Bantam Ware. Phenyl ether (b.p. 26°C/1 mm) and nitrobenzene (b.p. 41°C/0.5 mm) were distilled using Bantam Ware. Diphenyl sulfide (Eastman) and p-chlorotoluene were also purified by distillation. Compounds not purified are in Table 26. The perchloric acid used in titrating was Baker Reagent grade, 70-72 per cent.

Isooctane, used as the solvent for UV samples, was Fisher Certified A. C. S. Spectraanalyzed.

The Beckman pH meter was standardized at pH seven with Fisher Buffer Solution.

Table 25. Data on Distilled Halobenzenes

Compound	Boiling Point	Source
Fluorobenzene	83°C @ 736 mm	Eastman
Chlorobenzene	128-129°C @ 737 mm	Eastman
Bromobenzene	153.4-154.5°C @ 737 mm	Columbia
Iodobenzene	104°C @ 75 mm	Eastman
4-Fluoronitrobenzene	34°C @ 0.5 mm	Peninsular
3-Fluoronitrobenzene	33°C @ 0.1 mm	Columbia
3-Fluorobenzotrifluoride	93.5-94°C @ 740 mm	Peninsular
3-Fluorophenol	30°C @ 0.5 mm	Pierce
4-Chlorofluorobenzene	67°C @ 95 mm	Columbia
3-Chlorofluorobenzene	59°C @ 72 mm	Eastman
1,3-Difluorobenzene	81°C	Eastman
1,4-Difluorobenzene	87°C	Peninsular
4-Bromofluorobenzene	148-149°C @ 737 mm	Eastman
3-Bromofluorobenzene	144-145.5 @ 737 mm	Pierce
4-Fluoroidobenzene	36°C @ 2 mm	Peninsular
3-Fluoroiodobenzene	36-38°C @ 0.5 mm	Peninsular
3-Fluoroanisole	59°C @ 50 mm	Pierce
4-Fluoroanisole	58.5°C @ 45 mm	Peninsular
4-Fluorotoluene	115°C	Eastman
3-Fluorotoluene	114.5-115.5°C	Eastman
3-Bromochlorobenzene	37°C @ 1 mm	Eastman

Table 25. (Continued)

Compound	Boiling Point	Source
4-Bromotoluene	35°C @ 0.5 mm	Columbia
1,3-Dibromobenzene	52°C @ 0.5 mm	Eastman
3-Bromoidobenzene	59-61°C " 0.5 mm	Eastman
3-Chloroiodobenzene	82°C @ 2 mm	Eastman

Table 26. Compounds Not Purified

Compound	Melting Point	Source
1,3-Diiodobenzene		Eastman
1,4-Diiodobenzene	125.5-127°C	Eastman
3-Bromonitrobenzene	52-53.6°C	Eastman
3-Iodonitrobenzene	34.8-36.0°C	Eastman
1,4-Dibromobenzene	84-85.7°C	Eastman
4-Bromoiodobenzene	86-87.5°C	Eastman
4-Chloroidobenzene	55-56°C	Eastman
Pentafluorobenzene		Peninsular

Methanol-O-d was previously prepared by Dr. C. L. Liotta and was shown to be of high deuterium content by n.m.r.

Eastman labeled 1,5-dibromopentane was distilled (b.p. 65°C/2 mm) with Bantam Ware.

Instrumentation

pH Meter and Titration Apparatus

The titration of piperidine was done with a Beckman Zeromatic II with reference calomel and glass (Beckman) electrodes. A magnetic stirrer was used to speed up equilibrium in the titration vessel, a 50-ml beaker. The perchloric acid was delivered from a 50-ml burette with a Teflon stopcock.

Infrared Instrument

The infrared spectra were obtained on a Perkin Elmer 457 Grating Infrared Spectrophotometer. The fast scan was used with a normal slit width. Calibration was by a factory supplied polystrene film and the 1601.4 cm^{-1} peak was usually used. Liquids were run as a film and solids as a KBr pellet.

Ultraviolet Spectrophotometer

The UV spectra were run on a Cary Model 14 Recording Spectrophotometer. All spectra were at room temperature and all in isooctane solvent.

Melting Point Apparatus

A Mel-temp was used to get melting points. Fisher capillary tubes were used. The values obtained are uncorrected.

Nuclear Magnetic Resonance Spectrophotometer

The n.m.r. data were obtained on a Varian A-60 D with the RF field at 0.01 or less.

Constant Temperature Baths

For reactions at temperatures less than 100°C a Precision Scientific water bath model 161 was used. A mercury thermoregulator capable of ± 0.03°C was used along with an NBS calibrated 100°C thermometer. For reactions greater than 100°C an American Instrument Company Type R oil bath was used. This bath holds about 20 gallons of Extra Hecla Super Cylinder Oil (Mobile Oil Company). This bath uses a bimetal regulator capable of ± 0.2°C at 190°C. The oil bath must be well vented to protect against escaping vapors. The thermometer was a 360°C type in divisions of one °C.

Gas-Liquid Chromatography Instruments

The gas chromatographs used were an Aerograph 90-P and an F and M Model 700, both with thermal detectors. Most data was collected using an SE30 one-half or one-quarter inch column.

Index of Refraction

A Bausch and Lomb Abbe-3L refractometer was used to get the indexes of refraction. This instrument is fitted with a bath to maintain a 25°C reading.

Weighing Balances

Reaction samples were weighed out on a Mettler Type 15 balance and micro samples on a Mettler Type B 6 balance.

Mass Spectrometer

All mass spectra data was obtained on a Varian instrument. This instrument is fitted with a gas chromatograph such that combination MS-GLC may be run.

Preparation of Solutions

Sodium hydroxide solution was made up by weighing out a known amount of solid sodium hydroxide (Fisher) and dissolving in one liter of distilled water such that the resulting solution was 0.10-0.11 molar. The solution was kept in a tightly closed polyethylene bottle and checked regularly for changes in concentration.

The sodium hydroxide solution was standardized with potassium acid phthalate which had been dried overnight in an oven at 100°C. Approximately 0.1 g of the solid was weighed into each of three 50-ml beakers. Fifteen milliliters of distilled water was added to each beaker

and then stirred to dissolve the solid as rapidly as possible. These solutions were titrated with approximately 0.10 molar sodium hydroxide solution using a ten milliliter burette. One drop of 0.3% phenolphthalein in ethanol was put in each beaker and titrated to a light pink color.

Perchloric acid was used to titrate piperidine. Approximately 0.12 and 0.24 molar perchloric acid solutions were prepared by adding about 14 g or 28 g of 70-72% $HClO_4$ to one liter of water. These solutions were standardized with the standardized sodium hydroxide solution. The sodium hydroxide solution was placed into the ten milliliter burette and used to titrate five milliliters of perchloric acid solution in a 25-ml beaker. A five milliliter pipette was used to measure $HClO_4$ solution. Using phenolphthalein indicator, three titrations were performed on each solution.

Syntheses and Product Identification

Reactions of 1,5-Dibromopentane with Substituted Anilines

The products obtained from the reaction of substituted fluorobenzenes with piperidine were prepared by a different method. The procedures followed were those of Scholtz and Wasserman (155) and Sommers and Aaland (156). The properly substituted anilines were reacted with 1,5-dibromopentane with or without a solvent. The products were identified by n.m.r., IR, UV, index of refraction, and melting point. Two general procedures (A and B) were used.

Procedure A is exemplified by p-toluidine. In a 50-ml Erlenmeyer flask was placed p-toluidine (8.52 g, 0.0795 mole) and 1,5-dibromopentane (3.56 g, 0.0155 mole). The solution was mixed and stoppered with a cork.

The flask was placed on a steam bath for five minutes. (Reactions run at temperatures greater than 100°C were carried out in sealed glass ampoules.) The solution developed a dark brown color and as it cooled became a syrupy solid. Water was added to the mass to dissolve the hydrogen bromide salt and then was poured into a 100-ml separatory funnel. Ether was added to the flask to dissolve the remaining material and was poured into the separatory funnel. Concentrated sodium hydroxide was added to the water in the separatory funnel until it became basic to litmus paper. The water was extracted twice with ether. The water was checked again to be sure it remained basic. After placing the ether extract on a rotary evaporator, the ether was removed and the remaining oil distilled using Bantam Ware. A colorless liquid was collected at 102°C/1 mm and was identified as N-(p-tolyl)-piperidine. The yield, based on 1,5-dibromopentane, was 42 per cent.

Procedure B is exemplified by m-nitroaniline. In a 250-ml round-bottomed flask was placed m-nitroaniline (13.35 g, 0.0965 mole), anhydrous sodium carbonate (10.74 g), 1,5-dibromopentane (19.52 g, 0.085 mole), 30-ml of o-xylene, and a one inch magnetic stirring bar. A reflex condenser was attached to the round bottom flask and the flask was placed in an oil bath at 135°C. The mixture was kept at the temperature for 17 hours while stirring. It was then cooled and the pH adjusted to one with hydrochloric acid. The solution was extracted with ether and the ether discarded. The remaining aqueous layer was made basic with sodium hydroxide solution and extracted twice with 50-ml portions of ether. The ether was removed on a rotary evaporator and to the residue was added 50-ml of light petroleum ether. This solution was warmed and filtered while warm to

remove most of the m-nitroaniline. The cooled petroleum ether solution was placed on a rotary evaporator and then the remaining oil was distilled on Bantam Ware. A bright red liquid [N-(m-nitrophenyl)-piperidine] was collected at 150°C/1 mm in a 23.8 per cent yield.

Data on compounds prepared by procedures A and B are in Table 27.

The p-bromoaniline reaction was worked up differently from the rest. After reaction, 50-ml of water was added and adjusted to pH seven with dilute sodium hydroxide. The precipitated solid was filtered with a Buchner funnel. The solid collected was warmed in n-hexane. The n-hexane was separated from any undissolved liquid. The solution was cooled in an ice bath and filtered. The filtered n-hexane was cooled in a dry ice-acetone bath and the resulting precipitate collected and sublimed in vacuo at 55°C. This compound was identified as N-(p-bromophenyl)-piperidine.

The m- and p-hydroxyl derivatives were prepared from the corresponding methoxyl compounds by the reaction with aqueous hydrogen bromide. In a 100-ml round-bottomed flask was placed 4.18 g of N-(m-methoxyphenyl)-piperidine and 50-ml of 48 per cent hydrogen bromide. This was refluxed 16 hours while stirring. The solution was cooled and made neutral with concentrated sodium hydroxide solution. The solution was extracted with ether and the ether extract placed on a rotary evaporator. The resulting solid was sublimed at 110°C. The m-piperidino-phenol (157) was collected in a 36 per cent yield, m.p. 120-122°C (lit. m.p. 123-124°C) (156). A similar reaction was run on N-(p-methoxyphenyl)-piperidine. The solid collected was sublimed at 110°C and identified as p-piperidinophenol. The yield was 70 per cent, m.p. 158-160°C, decomp.

Table 27. Preparation of N-(X-Phenyl)-Piperidines

X	Method	Yield (%)	Reaction Temperature (°C)	Reaction Time	Boiling Point	N^{25}_D	Melting Point
m-CF_3 (158)	A	50	135	30 min.	106°C @ 2 mm	1.5006	---
p-Br (159,160)	A	37	Steam bath	15 min.	---	---	71-72 (lit. 77°C (161)
m-Br	A	82	135	30 min.	113-115°C 1 mm	1.5949	---
p-Cl (155)	B	29	125	10 hours	112°C @ 1 mm	---	65-67°C
m-Cl	A	54	130	15 min.	110°C @ 0.5 mm	1.5769	---
m-F (162)	A	54	125	15 min.	90°C @ 1 mm	1.5446	---
p-F	A	68	105	5 min.	82.5°C @ 1 mm (lit. b.p. 70°C @ 3 mm (168)	1.5360	---
H	A	64	27	2 hours	82.5°C @ 1 mm (lit. 129-132°C @20 mm (164)	1.5620 (1.5601) (165)	---
m-CH_3 (155, 165)	A	32	Steam bath	30 min.	103°C @ 2 mm (lit.b.p. 132.5°C @ 12 mm (166)	1.5549 (1.5555) (166)	---
p-CH_3 (155, (159	A	42	Steam bath	5 min.	102°C @ 1 mm	1.5526 (1.5529)(166)	---

Table 27. (Continued)

X	Method	Yield (%)	Reaction Temperature (°C)	Reaction Time	Boiling Point	N^{25}_D	Melting Point
m-CF_3 (158)	A	50	135	30 min.	106°C @ 2 mm	1.5006	---
m-OCH_3	A	57	Steam bath	15 min.	102°C @ 0.5 mm	1.5576	---
p-OCH_3	A	68	Steam bath	5 min.	111°C @ 1.0 mm	1.5501	---
m-NO_2	B	24	135	17 hours	150°C @ 1 mm	1.5965	---

The N-(p-nitrophenyl)-piperidine was not prepared from the aniline since this compound has been well characterized in the literature. The reactions of m- and p-iodoanilines with 1,5-dibromopentane produced only tarry material by either precedure A or B.

Besides the data in Tables 27 and 28, these products were identified also by n.m.r. and IR. For the n.m.r. spectra an external reference (tetramethylsilane in chloroform) was used. All the products showed a broad absorption (0.4 τ wide) with a maximum occurring around 8.6-9.0 τ which integrated to six protons. Another broad absorption (about 0.4 τ wide) with a maximum occurring at 7.0-7.5 τ integrated to four protons. These four protons are the methylene hydrogens attached to nitrogen. The aromatic protons show up in the area of 2.6-3.6 τ and integrate to four protons. The IR spectra show bands for CH_2 bending and strecthing, aromatic C-H bending and stretching, C-N aliphatic and aromatic, and C=C stretch.

N-(m- or p-R-Phenyl)-piperidines from Aromatic Nucleophilic Substitutions

This procedure describes the isolation of the products from the reactions of piperidine with the substituted fluorobenzenes which were used to construct the Hammett plot. Products were isolated in all cases except m-fluoroidobenzene and m-bromofluorobenzene.

A reaction sample which was about 0.5 molar halobenzene and 1.2-1.5 molar piperidine in triethylene glycol solvent was made up in a 50-ml volumetric flask. The solution was transferred to a glass ampoule (70-ml volume) and sealed. The reaction vessel was heated to 194-195°C (except p-nitrofluorobenzene) for a time which allows 40-60 per cent reaction as determined from the kinetic data. After reaction the ampoule

Table 28. UV Data on N-(X-Phenyl)-Piperidines*

Prepared from the Anilines			Product from Piperidine with m- or p- Fluorobenzenes	
X	λ max	ε max	λ max	ε max
m-CH_3	256	12,200	--	--
p-Cl	261	17,000	261	16,800
m-Cl	249	13,900	249	13,600
p-F	248	9,300	249	8,650
m-F	254	14,800	254	13,400
m-Br	261	13,300	--	--
p-Br	263	17,100	263	17,200
m-CF_3	259.5	14,000	259.5	15,000
m-NO_2	250	20,500	251	20,000
H	254	12,300	254	12,100

*Isoctane solvent.

was opened and the contents poured into a 250-ml separatory funnel and extracted twice with 50-ml portions of ether. The ether layer was collected and extracted with 20-ml of water to get rid of any triethylene glycol. The ether is then placed on a rotary evaporator and the remaining material was either distilled, sublimed, and/or analyzed by gas-liquid chromatography. Those products which were distilled are in Table 29. The N-(p-bromophenyl)-piperidine was sublimed at 61°C, m.p. 73-74°C.

Table 29. N-(m- or p-X-Phenyl)-piperidines Isolated from the Reaction of Piperidine with the Corresponding m- or p-Substituted Fluorobenzenes in Triethylene Glycol at 194.5°C.

X	Boiling Point	Melting Point
H	92°C @ 0.5 mm	
m-F	81.5°C @ 0.5 mm	
p-Cl	110°C @ 0.5 mm	64-66°C
m-NO_2	157°C @ 2 mm	
p-F	75°C @ 1 mm	
m-OH	120°C @ 1 mm	120-122°C
m-Cl	70°C @ 1.5 mm	
p-CH_3	106°C @ 1.5 mm	
m-CF_3	81-83°C @ 0.5 mm	
m-CH_3	110°C @ 1 mm	

The reaction with p-nitrofluorobenzene was over in about 20 minutes at room temperature. The product isolated was recrystalized from methanol, m.p. 99-101°C. All of these products were compared to the products made from the anilines by means of n.m.r., IR, UV, and gas-liquid chromatography. In all cases the corresponding products were identical, with no rearranged products indicated. In the cases of m-fluoroidobenzene and m-bromofluorobenzene the products were identified by gas-liquid chromatography.

The products of similar reactions of substituted bromobenzenes (H, m-Br, p-Br, m-Cl, p-Cl, m-I, p-I, m-NO_2) at 205°C and m- and p-chloroidobenzenes, chlorobenzene, and iodobenzene at 195°C were identified by gas-liquid chromatography.

In order to check for displacement by piperidine of both halogens in dihalobenzenes, m-dipiperidinobenzene was synthesized. Into a 70-ml glass ampoule was placed 3.8 g N-(m-fluorophenyl)-piperidine, 11.1 g piperidine, and 37.3 g of triethylene glycol. The ampoule was sealed and heated to 257°C for three days. After reaction the sample was worked up as the other fluorobenzenes had been and distilled on Bantam Ware. A yellow oil (0.5 g) was collected at 185-190°C and 0.5 mm, a 10% yield. The product m-dipiperidino-benzene was identified by n.m.r., mass spectrometry, and gas-liquid chromatography.

Further Studies of the Products from Nucleophilic Displacements by Piperidine

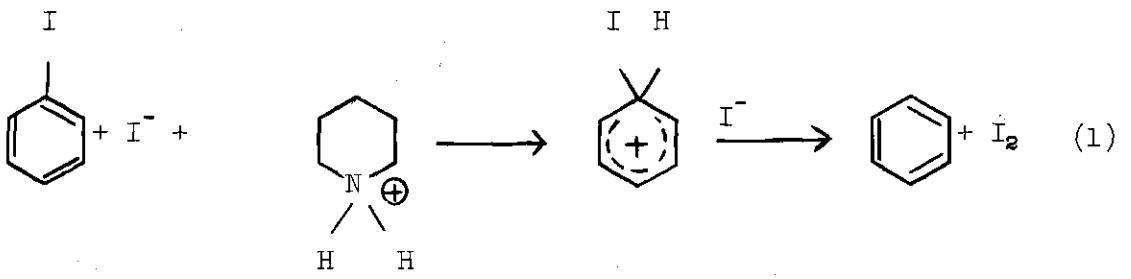
These studies are principally gas-liquid chromatography studies. In all the nucleophilic displacement reactions the products were checked by GLC with the known compounds made from the anilines. Checks were also made for rearranged products which would be indicative of a benzyne reaction. No rearranged products were found. A GLC check was also made for reduction of the halobenzenes, e.g., iodobenzene to benzene.

A GLC study was made to determine if rearranged products were present in the reaction of certain substituted fluorobenzenes (m-NO_2, m-F, p-F, m-I, p-I, m-OH) since the corresponding m and p isomers of the products could easily be separated on an SE30 column. A check for any o products was made only in the reaction of m-diiodobenzene with piperidine.

In no case was any rearranged products observed within one to three per cent accuracy. The m and p isomers of the chloro, bromo, and methyl products could not be separated by GLC. A check was made for rearrangements in the reaction of m and p-fluorotoluenes with piperidine by n.m.r. The methyl peaks of the m and p products appeared at different tau values as shown by mixing the two products and determining the n.m.r. Within a few percent accuracy no rearranged products were found. It is possible that any benzyne intermediate may be intercepted by triethylene glycol. This aromatic ether would be readily dealkylated to the phenol by piperidine. Although no check was made for this reaction, it would be difficult to interpret any products observed as being produced by any benzyne intermediate since the corresponding alkoxide of triethylene glycol ($ROH + C_5H_{11}N \rightleftarrows RO^- + C_6H_{12}N^+$) could also react by direct substitution.

Reductive halogen removal appeared to occur in all reactions where a bromine or iodine was present, the removal of iodine being faster than bromine. No chlorine or fluorine reductive removal was observed. The reduction occurred on both reactants and products. The mechanism is not a homolytic cleavage of the carbon halogen since no benzene was produced when iodobenzene and triethylene glycol were heated at 240°C for 24 hours. Also, the amount of reduction increased with time as the piperidine concentration decreased. Another point concerning reduction is that N-(p-I-phenyl)-piperidine was reduced much faster than p-diiodobenzene. When iodobenzene (0.6 g), piperidine hydrochloride (0.07 g), and TEG (5.7 g) were heated to 240°C for 24 hours a substantial amount of benzene was formed. This data is more consistent with a mechanism (Eq. 1) where there

is proton attack on the ring to form a sigma complex with subsequent nucleophilic displacement on iodine by iodide, rather than a mechanism of nucleophilic displacement on iodine in iodobenzene by piperidine which would go by a carbanion mechanism.



(1)

In the reactions where rate constants were obtained, reduction was no greater than 10 per cent on any reactant. The iodobenzene reaction at 223°C gives about seven percent benzene. The reaction with bromobenzene at 223°C gives less than one per cent benzene. The reaction of p-dibromobenzene at 205°C with piperidine in TEG gives 10 per cent bromobenzene. In other reactions where rate constants were obtained, the reduction of bromine or iodine in the reactant was less, usually one to two per cent. The reductive removal of bromine or iodine in the products was greater than in the reactants although the meta halogen was much less reductively removed than the para halogen in the products. The reaction of m-dibromobenzene at 205° gives less than one per cent N-phenylpiperidine, whereas p-dibromobenzene gives more N-phenylpiperidine. The reduction in all these reactions was not enough to affect the rate plot since the plots remained linear.

An extended GLC study was made of mixed dihalobenzenes in order to determine the amount of displacement of each halogen. In each case a reaction sample was made up about 0.50 molar in the dihalide and 1.2-1.5

molar in piperidine in triethylene glycol. These samples were heated up to 195° (except m- and p-bromochlorobenzene at 205°C) to a time amounting to 40-60 per cent reaction as determined from the kinetic data. The samples were opened and poured into a round bottom flask and 150-ml of water added and continuously extracted with ether for a minimum of 16 hours. The extract was placed on a rotary evaporator and the residue subjected to a GLC analysis. The per cent of each product was determined by gas chromatography by cutting out the peaks and weighing the paper. Three GLC's were run for each reaction.

A complication in determining accurate percentages was taking into account the reduction of a bromine or iodine in the products. In all the reactions except p-halofluorobenzenes the products were well separated on the gas chromatograph. In the p-halofluorobenzenes the products, (N-(p-fluorophenyl)-piperidine produced from displacement of chlorine, bromine, or iodine and N-phenylpiperidine produced by reduction) could not be separated on GLC. Another procedure was used to check that peak. Since these two products don't separate on the gas chromatograph, one can inject the reaction mixture into the gas chromatograph connected to a mass spectrometer and take a spectrum of the peak containing N-phenylpiperidine and/or N-(p-fluorophenyl)-piperidine. The height of the parent ions gave the ratio of the two products from which a per cent may be calculated. It was shown that the mass spectrum of N-(p-fluorophenyl)-piperidine gave no peak at the parent ion of N-phenylpiperidine. The results showed no reduction occurred in the reaction of p-chlorofluorobenzene. The only peak observed in the mass spectrum was that of N-(p-fluorophenyl)-piperidine. In the p-bromofluorobenzene reaction

the mass spectrum showed this peak to be 75.6 per cent p-fluoro product and 24.4 per cent N-phenylpiperidine. In the reaction of p-fluoroiodobenzene the mass spectrum of this VPC peak showed 12.4 per cent p-fluoro product and 87.6 per cent N-phenylpiperidine. From this data and the gas chromatograph data the actual percentage of N-(p-fluorophenyl)-piperidine could be obtained. This GLC-MS technique was not necessary with m-halofluorobenzene since N-phenylpiperidine and N-(m-fluorophenyl)-piperidine can be separated on the gas chromatograph.

A check was made to see if the per cent N-phenylpiperidine calculated from the peak heights of the MS of N-phenylpiperidine and N-(p-F-phenyl)-piperidine correlated with a known mixture of these two compounds. N-Phenylpiperidine (0.0399g) and N-(p-F-phenyl)-piperidine (0.03989) were weighed into a vial and mixed. The GLC-MS was then run. From the known weights 52.7% N-phenylpiperidine was calculated to be in the mixture. From the parent peak heights in the MS an average value of 58% N-phenylpiperidine was calculated. Thus, the MS gave a value 9.3% too high for the N-phenylpiperidine. Hence, the correct values for the VPC peak containing these two compounds were (24.4%)(90.7) = 22% for N-phenylpiperidine and 78% for N-(p-F-phenyl)-piperidine in the p-bromofluorobenzene reaction. For the p-fluoroiodobenzene reaction the values became 79% for N-phenylpiperidine and 21% for N-(p-F-phenyl)-piperidine.

In the reactions of m-bromofluorobenzene, m-chlorofluorobenzene, m-fluoroiodobenzene, m-bromochlorobenzene, and m-chloroiodobenzene no reduction product was observed. In the reaction of p-bromochlorobenzene 4.7 per cent of the total products was N-phenylpiperidine and was assumed to come from N-(p-bromophenyl)-piperidine. In the reaction of p-

chloroiodobenzene, the N-phenylpiperidine was assumed to come from N-(p-iodophenyl)-piperidine. In the reactions of m- and p-bromoiodobenzenes the N-phenylpiperidine (less than 3 per cent of the total products) observed was not taken into account since both the iodo and bromo products are capable of reductive removal of halogen. It was not necessary to consider reduction of the reactant, i.e. p-bromochlorobenzene to chlorobenzene, in the product analysis since the monohalobenzenes react much slower than the dihalobenzenes.

The results of this mixed dihalobenzene study are in Table 30. In all these reactions of dihalobenzenes there was a peak in the gas chromatograph for dipiperidinobenzene which was usually one to two per cent of the total products.

There is good precision in the values in Table 30. The value found for chlorine displacement in p-chlorofluorobenzene varied 0.27-0.31% varied 73.4-75.2%. In m-fluoroiodobenzene the value for fluorine displacement varied 88.0-89.2%. The attenuation factor was four which occurred between the peaks of the products of the p-chlorofluorobenzene reaction, the difference in attenuation for other reactions being two or one. Also, a mixture of N-(m-F-phenyl)-piperidine (19.5 mole %) and N-(m-Br-phenyl)-piperidine was made up and the GLC determined. The weight of the peaks cut out showed the mole % of the fluoro compound to be 19.7%.

As noted earlier, N-(m- and p-iodophenyl)-piperidine could not be prepared from the anilines. These products were prepared by the reaction of piperidine with diiodobenzene. In a small glass ampoule piperidine (6-ml) and p-diiodobenzene (0.6 g) were placed and heated to 195°C for

Table 30. Experimental Per Cent Displacements in Mixed Dihalobenzenes

Para Compounds		%	Meta Compounds		%
Fluorine	Displacement	99.71	Fluorine	Displacement	97.09
Chlorine	"	0.29	Chlorine	"	2.91
Bromine	"	80.87	Bromine	"	83.31
Chlorine	"	19.13	Chlorine	"	16.69
Bromine	"	1.06	Bromine	"	10.6
Fluorine	"	98.94	Fluorine	"	89.4
Iodine	"	74.5	Iodine	"	83.72
Chlorine	"	25.5	Chlorine	"	16.28
Iodine	"	3.00	Iodine	"	11.3
Fluorine	"	97.00	Fluorine	"	88.7
Bromine	"	60.6	Bromine	"	48.0
Iodine	"	39.4	Iodine	"	52.0

for 15 hours. The sample was then analyzed by GLC. The reaction was worked up by adding 50-ml of water and removing the solid by filtration. The solid was dissolved in ether and extracted with ten per cent hydrochloric acid. The aqueous layer was made neutral, cooled in an ice bath, and filtered. This solid is sublimed at 50°C in vacuo. There was collected 0.155 grams of N-(p-iodophenyl)-piperidine, m.p. 73-74.5°C.

Similarly, in a 50-ml ampoule were placed 5 g m-diiodobenzene and 33-ml piperidine, then sealed, and heated at 200°C for 19 hours. After reaction no work up was carried out but the reaction mixture was analyzed by gas liquid chromatography. It was shown that the product, N-(m-

iodophenyl)-piperidine, contained no para product within three per cent accuracy. The GLC also showed peaks for iodobenzene, N-phenylpiperidine, and m-dipiperidinobenzene.

The last study of mixed dihalobenzenes was the reaction of sodium methoxide with p-bromofluorobenzene. This reaction was run to show that p-fluorine is deactivating not only with amine nucleophiles but also with alkoxides. Sodium (0.2 g) was reacted with anhydrous methanol (6-ml) and then 1.5 g of p-bromofluorobenzene was added. This solution was sealed in a glass ampoule and heated to 180°C for three hours. After reaction concentrated HCl was added until the solution became acidic. Then the solution was analyzed on the gas chromatograph to get the per cent displacement of each halogen by weighing the peaks cut out of the gas chromatograph chart. The results showed 99.96 per cent displacement of fluoride and 0.04 per cent displacement of bromide. The products analyzed were the anisoles, since no measurable quantity of the phenols, p-fluorophenol and p-bromophenol, could be detected in the gas chromatograph.

Deuterated Compounds

The preparation of piperidine-1-d followed the procedure of Heacock and Marion (167). In a beaker containing cold piperidine (35-ml), 20 per cent HCl was added until about pH five (Litmus paper) was reached. This solution was put into a 500-ml round-bottomed flask and warmed to 60°C and the water pulled off by a vacuum pump. A powdery white solid remained. To this solid was added 25-ml D_2O and warmed to 80°C for 15 minutes while shaking. Then the water was again removed under pressure. This was repeated twice. Then to the dry salt was added 15-ml. D_2O and

and then NaOD in D_2O until pH 12 was reached. This solution was poured into a dropping funnel. This dropping funnel was fitted to a 500-ml round bottom flask flushed with N_2 containing 200-ml of anhydrous ether and clean sodium (25 g). The piperidine-D_2O solution was added to the ether dropwise, keeping the ether in an ice bath. After addition, the solution was distilled from sodium and 25-ml piperidine-1-d was collected at 104-105°C/745 mm. The n.m.r. showed 97 per cent deuteration.

The NaOD in D_2O was prepared by adding D_2O dropwise to 100 ml of dry tetrahydrofuran containing sodium. After addition, the tetrahydrofuran was removed by distillation.

Thiophenol-S-d was prepared by shaking thiophenol (10-ml) with 50-ml of D_2O and a few drops of concentrated hydrochloric acid at room temperature for 15 minutes. The thiophenol was separated with a separatory funnel and distilled. The n.m.r. showed 92 per cent deuteration.

Fluorobenzene-4-d (168, 169) was prepared by a Grignard reaction with p-bromofluorobenzene. The apparatus consisted of a 250-ml round-bottomed flask with three necks. In these necks was fitted a dropping funnel, a mechanical stirrer, and a condenser joined to the flask by an elbow which allowed the condenser to be used for refluxing or distillation. All the glass parts had previously been cleaned in basic cleaning solution and dried in an oven overnight at about 100°C. The magnesium turnings were rinsed in anhydrous ether and placed in the oven overnight. The apparatus was assembled and magnesium (6.1 g) was added. The system was flushed with dry nitrogen which was bubbled through concentrated sulfuric acid. A crystal of iodine was added to the magnesium. Then 100-ml of anhydrous ether (Fisher), which had been dried further over

sodium, was added to the flask and a drying tube containing P_2O_5 was fitted to the reflux condenser. The dropping funnel contained 24.6 g of p-bromofluorobenzene. The halide was added over a one hour period, maintaining a gentle reflux, and then the entire mixture refluxed for one additional hour. Another dropping funnel was put on containing D_2O (2.5-ml). The D_2O was added, maintaining a gentle reflux. Using a steam bath the ether and deuterated fluorobenzene were distilled off. This mixture was then distilled through a Nester Faust spinning band column to give 4.5 g of fluorobenzene-4-d. By mass spectrometry the compound showed to be more than 99 per cent deuterated.

A similar reaction was carried out on m-bromofluorobenzene (19.3 g) and magnesium (12 g) to obtain fluorobenzene (6.1 g). This compound, fluorobenzene-3-d, distilled at 82.5°C-83.0°C at 745 mm and was 98 per cent deuterated.

A similar Grignard reaction was carried out on N-(p-bromophenyl)-piperidine. This compound was prepared by heating piperidine (32.6 g) and p-dibromobenzene (15.6 g) in a sealed glass ampoule at 195°C for two days. By distillation 15.2 g of N-(p-bromophenyl)-piperidine was obtained. For the Grignard reaction 30 g of the bromo compound was used and a 50-fold excess of magnesium. The setup was the same as before except that tetrahydrofuran was used as the solvent instead of ether. After reaction and addition of D_2O, the THF solution was poured off. The solid remaining in the flask was rinsed with THF and the two liquid portions were combined. The THF was removed on a rotary evaporator and the distillation with Bantam Ware gave 9.5 g of N-(phenyl-4-d)-piperidine with 97% deuteration.

Kinetic Procedures and Related Studies

This first procedure was used for all the second order rate data, except p-fluoronitrobenzene. The reaction solution was made up in a 50-ml volumetric flask. The flask was weighed and then fluorobenzene, piperidine, and triethylene glycol are then weighed, respectively, into the flask. Before getting the final weight, the flask was equilibrated for ten minutes at 25.0°C and then filled to the mark with TEG. The flask was shaken to insure mixing. From this solution seven ampoules were made up containing six to seven milliliters of solution. The ampoules were flushed with nitrogen and sealed. These ampoules were placed in the oil bath at the proper temperature and an initial sample was removed after two minutes. Only in the reaction of m-fluoronitrobenzene at 195°C was it necessary to take into account the initial warm up period, which was determined to be 80 seconds. After the ampoules were taken out of the bath and cooled, they were opened and approximately three milliliters of the sample were taken up with a pipette and placed in a 50-ml beaker which has been previously weighed. After obtaining the weight of the sample, a one inch stirring bar and 15-ml of water were added. The sample was titrated immediately with perchloric acid to pH 6.5. This was the end point determined for the titration of piperidine. This end point was satisfactory because product titration was unimportant at that pH, except for the p-amino or p-hydroxy products. Each ampoule allowed two titrations.

The reactions were allowed to proceed no more than 40% completion. This was necessary to minimize any salt effect produced by the build up of the piperidine hydrohalide salt. The concentration of the

aromatic halide was 0.5-0.55 molar and piperidine was 1.3-2.5 molar. At these concentrations a significant amount of halide ion was produced. Very little decomposition was noted in these reactions. The solutions did develop a very pale yellow color when heated and it was this color which prohibited a colorimetric fluoride titration. A small amount of etching occurred when fluoride ion was produced. For this reason also the reactions were limited to 40 per cent completion.

The ampoules were made from Pyrex glass. At temperatures below 230°C a 19 millimeter standard wall type was used while above 230°C a 3/4 inch heavy wall type was used.

A few miscellaneous experiments were carried out which were related to the kinetic procedure. One was a check on the decomposition of the reaction solution. Piperidine and triethylene glycol were heated up to 195°C and the piperidine was titrated to determine if any base had been lost. In a 50-ml volumetric flask was placed piperidine (5.5g) and TEG (48.8g) at 25°C, the volume of the solution being 50-ml. Six reaction ampoules were made up, each containing about six milliliters. An initial sample was titrated and a sample was taken out of the bath each day for five days and titrated. The difference between the first sample and the last was 0.18 ml out of 27-ml. Although the solution became light yellow, decomposition to any appreciable extent was not apparent.

From activation energy data the rates of bromobenzene and fluorobenzene at 225°C are $5.9 \times 10^{-3} M^{-1} hr^{-1}$ and $5.25 \times 10^{-3} M^{-1} hr^{-1}$. These rate constants are based on titration of piperidine. It was of interest to check these rate constants by a method based on the products. This

was easily done by making up the reaction solutions of bromobenzene and fluorobenzene exactly the same. After reaction the same quantities of each solution were injected into the gas chromatograph. The relative peak areas of the product of each reaction gives the relative rates. Based on a 50-ml volume, the reaction solutions were made up exactly 0.553 molar in halobenzene and 1.580 molar in piperidine. The sealed ampoules were heated to 225°C for 68 hours. After reaction the two reaction solutions were analyzed by GLC. Three samples, each of two microliters, were injected into the GLC. The peak areas were cut out and weighed. The relative rate ratio obtained was Br/F = 0.98. This is within 10 per cent error of the results of the titration method.

A reaction was carried out to show that these high temperature reactions approach 100 per cent completion. A reaction ampoule was made up of m-difluorobenzene (2.8g), piperidine (11.4g), and TEG (38.8g). The ampoule was heated to 205°C for 42 hours. The sample was worked up by adding water and extracting with ether. After the ether was taken off the residue was analyzed by GLC, specifically the relative peak areas N-(m-fluorophenyl) piperidine and m-dipiperidinobenzene were obtained. Then the residue was distilled on Bantam Ware and 4.06g of N-(m-fluorophenyl) piperidine was obtained. From this data and the GLC data, 97.7 per cent of the total products, calculated on the basis of m-difluorobenzene, was accounted for. This was good evidence that these reactions are well defined, barring the presence of reductive halogens (bromine and iodine).

These data also shows that an equilibrium between TEG and piperidine ($ROH + C_5H_{11}N \rightleftarrows RO^- + C_5H_{12}N^+$) is not appreciable, or the total

reaction products with piperidine would have been lowered by alkoxide reaction with m-difluorobenzene. This conclusion is also drawn from the fact that the dielectric constant of TEG is so low as not to favor any charge build up as in the above equilibrium.

The next procedure describes the reaction of p-nitrofluorobenzene with piperidine in TEG. A known amount of p-nitrofluorobenzene was weighed into a 50-ml volumetric flask and filled to the mark with TEG, which had been equilibrated at 25.0°C. A similar flask was made up for piperidine. The two volumetric flasks were placed in the bath. For other reaction temperatures they were made up at those temperatures. Now two five milliliter syringes were calibrated for three milliliter volumes. From the average weights of these volumes of TEG and the known density (1.1254, Handbook of Chemistry and Physics, 41st Ed.) of TEG, a true volume is calculated. From the piperidine solution three milliliters were syringed into a 25-ml Erlenmeyer flask which has a stopper and a magnetic stirring bar (water driven stirrer). Then three milliliters of the fluoro solution is injected, the timer being started at half injection. The reaction mixture was quenched by quickly pouring 15-ml of iced water into the reaction flask and then titrated immediately. This method does not require any density correction.

The next procedure was one in which piperidine was the nucleophile and the solvent. Conditions were set up to run under pseudo-unimolecular conditions. For example, the relative rates of the monohalobenzenes in piperidine may be obtained by making up reaction ampoules which contain the same number of moles of halobenzene and piperidine. All samples react for the same time period. Since the product was the same in these

cases, the relative rates may be obtained by injecting the same sample size (two microliters) into the gas chromatograph. The weight of the cut out product peaks is proportional to the relative rates.

There were two reaction samples for each compound and two GLC's run for each sample. The reaction samples were made up by weighing the materials directly into the ampoules. In the first series of reactions, monohalobenzenes (0.0051 mole) and piperidine (5.91g., 0.0695 mole) were heated to 196°C for 22 hours; in the second series m-nitroholobenzenes (0.00525 mole) and piperidine (0.067 mole) were heated to 168°C for 40 minutes; in the third series p-halotoluenes (0.00206 mole) except p-iodotoluene, and piperidine (0.0405 mole) were heated to 237°C for 24 hours. All these samples were analyzed by determining the GLC's, cutting out and weighing the product peaks.

Treatment of Kinetic Data

The kinetic expression used to calculate the second order rate constants is Eq. 2 (170),

$$\frac{1}{2A_o - B_o} \ln \frac{B_o}{A_o} \frac{A_o - x}{B_o - 2x} = kt \qquad (2)$$

where 2x is the decrease in piperidine concentration with time. A_o is initial halogen concentration and B_o is the initial piperidine concentration. The stoichiometry of the reaction is A + 2B → C + D, where A is halogen and B is piperidine and D is the piperidine salt. The kinetic expression may be simplified for plotting (Eq. 3). Then one can plot

$$\log \frac{B_o}{A_o} + \log \frac{A_o - x}{B_o - 2x} = \frac{kt}{2.303} (2A_o - B_o) \qquad (3)$$

Then one can plot log $(A_o - x/B_o - 2x)$ against time and the slope is $\frac{k}{2.303} (2A_o - B_o)$. A typical rate data sheet is given in Table 31. The first rate constant obtained from the plot has units of 3g/mm·hr, since the solutions were made up on a weight basis. It is a simple matter to change to a volume basis. The weight and the volume at 25°C is known for the original solution; hence, the density is known. First a small volume correction is applied to correct the density to the reaction temperature. Then it is a simple matter to calculate how many milliliters are in three grams of solution (Z).

The density correction factor was obtained using triethylene glycol to represent the reaction solution (see Appendix A). A 50-ml volumetric flask of TEG was made up at 22°C and weighed. It was then equilibrated at 48°C and the excess TEG above the mark was taken out and the flask weighed. This was also done at 72°C. The weight at each temperature was then plotted against temperature and extrapolated to the reaction temperatures. The weight of 50-ml of TEG at 25°C divided by the weight of 50-ml at the reaction temperature, say 195°C, is then the density correction factor. The values obtained at different temperatures are 195°C, 1.128; 204.5°C, 1.135; 223.5°C, 1.142; 239.5°C, 1.167; 257°C, 1.183.

One other kinetic expression must be explained. In the case of mixed dihalobenzenes, e.g., p-bromofluorobenzene, either halogen is capable of being displaced. It is still possible to determine the rate

Table 31. Rate Data Sheet

Nucleophile (b): Piperidine — M(b) 1.9107
Halide (a): p-Difluorobenzene — M(a) 0.5275
Temperature: 195°C — N_{HClO_4} 0.2272
Aliquot: 3.0 grams*

Sample	Ml of $HClO_4$/ 3g	mm (B_o-2x)	2x	2x/2	$A_o-x/3g$	A_o-x/B_o-2x	log A_o-x/B_o-2x	Time (hr.)
1	23.41	5.3181	0	0	1.4682	0.2761	-0.5590	0
2	22.45	5.1004	0.2177	0.1088	1.3594	0.2665	-0.5742	49.6
3	21.36	4.8534	0.4647	0.2323	1.2359	0.2546	-0.5941	117.6
4	20.14	4.5769	0.7412	0.3706	1.0976	0.2398	-0.6201	197.5
5	19.11	4.3418	0.9762	0.4881	0.9801	0.2257	-0.6464	285.6
6	18.03	4.0969	1.2212	0.6106	0.8576	0.2093	-0.6792	381.7

Density Correction Factor = 1.128 — Slope = $3.062 \times 10^{-4} hr^{-1}$

$x(g/50\ ml) = 53.893\ (25°C)$ — $k = \frac{slope \times 2.303}{2A_o - B_o} = 2.961 \times 10^{-4}$ 3g/mmxhr

$x'(g/50\ ml) = \frac{53.893}{1.128} = 47.777\ (195°C)$ — $k' = k \cdot Z = 9.294 \times 10^{-4} M^{-1} hr^{-1}$

$y(g/1\ ml) = 0.9555$ — $k'(stat.corr.) = 4.65 \times 10^{-4} M^{-1} hr^{-1}$

$Z(ml/3g.) = 3.139$

*Each aliquot was only approximately three grams. After titration the ml of $HClO_4$ used was then calculated for exactly 3.0 grams in order to put all samples on the same weight basis.

constant for each halide by knowing the total rate constant which comes from the titration of the total piperidine lost. The total rate constant is simply determined as in other reactions and this value is multiplied by the per cent of each product (Table 30) to obtain the individual rate constants. The total rate constant, obtained by titrating piperidine, is a true value whether the halogens react 99:1 or 50:50. This is true because both reactions depend on the same reactants. This is expressed in the following equations, using p-bromofluorobenzene as an example. The value k_F is the rate constant for loss of fluoride, k_{Br}, the rate constant for loss of bromide, k_T, the total rate constant, and A and B, the concentrations of piperidine and p-fluorobenzene, respectively.

$$\frac{dA}{dt} = k_F\ (A)(B) + k_{Br}\ (A)(B) \tag{4}$$

$$\frac{dA}{dt} = (k_F + k_{Br})\ (A)(B) \tag{5}$$

$$\frac{dA}{dt} = k_T\ (A)(B) \tag{6}$$

where $k_T = k_F + k_{Br}$.

Reactions with Deuterated Compounds

The purpose of these reactions is to look for deuterium exchange on the intermediate Meisenheimer complex.

The first compound studied was fluorobenzene-4-d. The reaction studied was that of fluorobenzene-4-d with piperidine in triethylene

glycol. Five reaction ampoules were made up from a solution of fluorobenzene-4-d (2.3g., 0.0237 mole), piperidine (4.6g., 0.0574 mole), and TEG (57.0g., 0.380 mole). They were reacted at 223°C and samples taken out at 4, 7.6, 16.2, 26.2, and 44 hours, the last sample corresponding to 35 per cent reaction. The last sample was cooled and opened. The ampoule was connected to a vacuum pump and the piperidine and unreacted fluorobenzene collected in a dry ice acetone trap. The trap was a preparative gas chromatograph collection tube. This collected material was injected into the mass spectrometer. Compared to a pure sample of fluorobenzene-4-d there was no change in the relative heights of the m and m^{-1} peaks. No exchange occurred on the reactant. The solution left in the ampoule was poured on water, extracted with ether, and placed on a rotary evaporator. The residue was injected into the mass spectrometer and showed about 50 per cent deuterium exchange in the product. In order to determine if this was exchange on the product or the intermediate, it was necessary to make a time study of the product. If a plot of per cent hydrogen in the product against time goes to zero, then exchange occurred in the intermediate. The remainder of the samples was analyzed and per cent hydrogen in the product was calculated to be 48 per cent at 44 hours, 24.5 per cent at 26.2 hours, 12.6 per cent at 16.2 hours, 6.66 per cent at 7.6 hours, and 5.75 per cent at 4 hours. A second reaction showed the following per cent hydrogen at the given times: 23.2 per cent at 26.0 hours, 14.7 per cent at 15.9 hours, 9.25 per cent at 7.8 hours, and 8.23 per cent at 4.2 hours. Ampoules were made up from a reaction solution of fluorobenzeye-4-d (2.3g., 0.0237 mole), piperidine (4.4g, 0.0518 mole), and TEG (57.5g, 0.384 mole). Extrapolation to zero time showed

7.00 per cent. The peak heights from the mass spectra were obtained from a five AMU expansion around the parent ion. The whole spectra included only six AMU. In the following mass spectral analysis use the assignments below. The mass spectral analysis for the per cent hydrogen :

$$160 = (m - 2)_D$$
$$160 = (m - 1)_H$$
$$161 = m_H + (m - 1)_D$$
$$162 = m_D$$

incorporation in the product N-(phenyl-4-d)-piperidine was complicated by the fact that the $(m - 1)_D$ peak was greater than the m_D peak. However, the per cent hydrogen could be found easily if the analysis is based on the $(m - 1)_D$ and $(m - 1)_H$ peaks. Since the $(m - 2)_D$ peak is negligible, any peak at 160 represents the $(m - 1)_H$. If the value at 160 is multiplied by the $m_H/(m - 1)_H$ ratio in pure N-phenylpiperidine, the resulting value represents the amount of m_H peak in 161. Subtracting the value from the total value at 161 gives the amount of $(m - 1)_D$ in 161. Thus, the per cent hydrogen in the product is calculated from the $(m - 1)_H$ and $(m - 1)_D$ values. The plot of per cent hydrogen against time gave an average value of 6.31 per cent hydrogen at zero time. This number is small, but if real this does provide a new insight into determining intermediates in aromatic nucleophilic substitution.

It was possible to show that exchange does indeed occur on the product. A reaction sample of piperidine (0.72g), N-(phenyl-4-d)-piperdince (0.29), piperidine hydrochloride (0.06g), and TEG (7.6g) was made

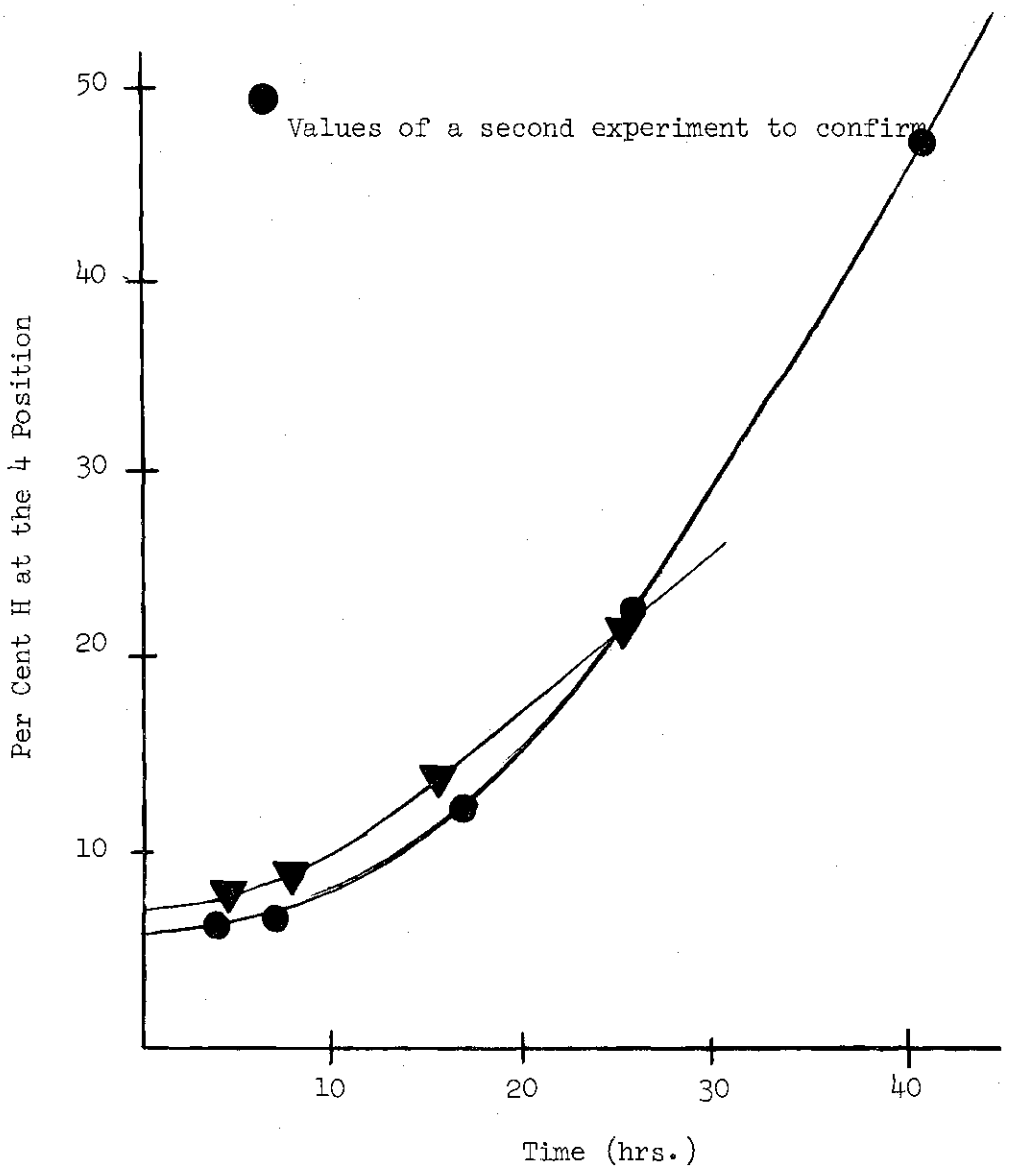
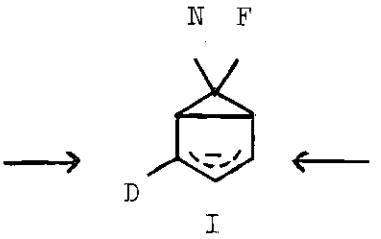


Figure 1. Plot of the Per Cent Hydrogen Incorporation into N-(Phenyl-4-d)-piperidine vs. Time in the Reaction of Piperidine with Fluorobenzene-4-d at 225°C in TEG.

up. This sample was supposed to represent the concentrations of the compounds at about 20 per cent reaction, with the absence of fluorobenzene. Piperidine was used as the base because it did not react with N-(phenyl-4-d)-piperidine by nucleophilic displacement. The ampoule was heated to 223°C for 55 hours and the phenyl piperidine extracted and analyzed as before. The mass spectrum showed 50 per cent exchange.

Fluorobenzene-3-d was also reacted with piperidine and checked for deuterium exchange. It was thought that the reaction intermediate could cyclize in a thermal disrotatory fashion to intermediate I. Here the higher charge densities are located at the arrows. It would have



I

been preferred to have had fluorobenzene-3, 5-d_2. Six reaction samples were made up from a solution of fluorobenzene-3-d (2.3g), piperidine (4.8g), and TEG (58.4g). An ampoule was run at 223°C for 44 hours and the contents analyzed as before. The mass spectra showed no exchange on fluorobenzene-3-d or on N-(phenyl-3-d)-piperidine.

Then the activated compound pentafluorobenzene was used. Since nucleophilic displacement on pentafluorobenzene occurs greater than 90 per cent <u>para</u> (10, 171-176) to the hydrogen, the intermediate complex would prefer to protonate at the position of the hydrogen. Reaction samples were made up from a solution of pentafluorobenzene (4.51g), piperidine-1-d (5.6g), and methanol-O-d to make 50-ml. The samples were

run 80°C and samples taken out at 1.7, 7, 14.2, and 24 hours, the last corresponding to 50 per cent reaction. Each sample was analyzed by pouring onto cold water extracting with ether, and placing on a rotary evaporator to remove the ether. The residue was analyzed by mass spectrometry. The spectra showed complete deuterium incorporation in the product, N-(2,3,5,6-tetrafluorophenyl)-piperidine, at all times; therefore, this reaction system could not be used.

A reaction was also run with pentafluorobenzene and sodium methoxide in methanol-O-d at 25°C. The reaction solution was made up by reacting sodium (0.68g) with methanol-O-d (30-ml). Pentafluorobenzene (4.33g) was added and the solution quickly made up to 50-ml with methanol-O-d. The solution as immediately thermostated at 25°C. Samples (4-ml) were withdrawn at intervals up to 24 hours. By titration the reaction was shown to have proceeded 30 per cent at 24 hours. The samples were expelled into ice water (50-ml) and extracted with ether. The ether was rotovaped and the oily residue was run on the MS. In all the samples there appeared to be complete deuteration in the product 4-d-2,3,5,6-tetrafluoroanisole. The deuterium exchange was concluded as occurring on the product and/or reactant and not on the intermediate complex. This conclusion is based on a mass spectral analysis of the product. Let $m_H = 180$ and $m_D = 181$. The pure protonated product gave values for the peak heights $m_H = 64.0$ and $(m - 1)_H = 32$. The product isolated from the reaction in methanol-O-d gave values $m_D = 64.0$ and $(m - 1)_D = 4.0$. A simple calculation showed that there was 1.2 per cent hydrogen in the deuterated product. If exchange had occurred on the intermediate complex, and assuming only one exchange on the IC, then a k_H/k_D of 80 would

have been necessary to cause 98.8 per cent exchange. This value is very high, so exchange is occurring on the product. This system did not prove fruitful to study deuterium exchange on the IC.

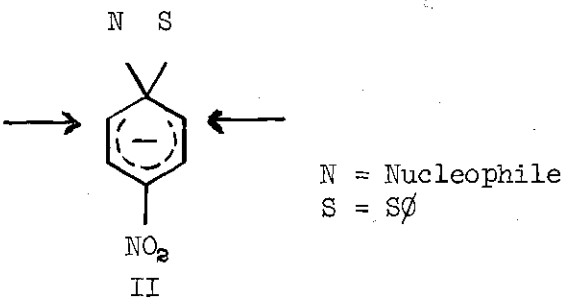
Therefore, thiophenoxide was used as the nucleophile because of its high nucleophilicity and low basicity. It was found that thiophenoxide reacted with pentafluorobenzene only very slowly at 25°C in methanol. A higher temperature was undesirable for fear of deuterium exchange on the reactant. A temperature less than 25°C would be better since the intermediate complex should be more stable at lower temperatures. Therefore, a mixed solvent of methanol and dimethylformamide (Fisher Spectra-analyzed) was used which allowed reactions to be run at -30°C. The bath used for these low temperature reactions was an Ultra Kryomat TK30D from Lauda Instruments.

Pentafluorobenzene (4.5g) was weighed into a 25-ml volumetric flask and filled to the mark with dimethylformamide. Another solution was made up by reacting 0.68g of sodium with 20-ml of methanol-O-d. After sodium reaction this was poured into a 25-ml volumetric flask and 3.5g of thiophenol-O-d was added and filled to the mark with methanol-O-d. The reaction solution was made up in a ten milliliter volumetric flask. Into the flask is placed six milliliters of DMF and two milliliters of the pentafluorobenzene solution. This was cooled to -60°C in a dry ice acetone bath and two milliliters of the thiophenoxide solution is added. The resulting solutions have a 10 per cent excess of thiophenol. This reaction solution was then placed in the bath at -30°C and allowed to react 22 hours, which was about 50 per cent reaction. After reaction, the solution was poured on iced water (the pH remained about 7.5) and the

oil in the bottom of the beaker was taken up by microliter syringe and injected into the mass spectrometer. The samples checked showed practically no deuterium incorporation in the product, 2,3,5,6 tetrafluorophenyl phenyl sulfide. The MS values for the pure protonated product are m_H, 98.0 and $(m + 1)_H$, 15.5, while the values for the product obtained from the deuterated solvent are m_H, 98.3 and $(m + 1)_H$, 17.0

The conclusion was that no exchange occurred, but the very first time this reaction was run, exchange on the product (about 60 per cent) was observed. New solutions of thiophenoxide in methanol-O-d and pentafluorobenzene in dimethyl formamide were subsequently prepared a number of times and the reaction solution made up. Since no exchange was ever found with subsequent solutions, it may be possible that the first solution did not contain a 10 per cent excess of thiophenol over thiophenoxide such that some sodium methoxide was present to cause exchange.

The last compound studied was that of p-fluoronitrobenzene. It was thought that protonation could occur at the two or six positions on the intermediate complex II. A thiophenoxide solution was made up exactly



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as before. Also, a solution of p-fluoronitrobenzene (3.1g) in 20-ml of DMF was made up. The same procedure was used here as with pentafluorobenzene. Reactions were run at -30°C for eight hours and at 0°C for 30

minutes. The work up was the same as pentafluorobenzene and the mass spectra showed no deuterium incorporation into the product, 4-nitrophenyl phenyl sulfide.

CHAPTER III

DISCUSSION AND RESULTS

Rate Data

Table 32 gives the 2nd order rate coefficients for the reaction of aryl halides with piperidine in triethylene glycol at temperatures ranging from 194-257°C. The error in temperature at 194-233°C was ± 0.5 and at 240-257°C the error was ± 0.8°C.

Table 32. Second Order Rate Data for Reactions Carried Out in Triethylene Glycol**

Compound	Molarity (Halogen)	Molarity (Piperidine)	Rate Constant ($M^{-1}hr^{-1}$)	Temperature °C
Fluorobenzene	0.5774	1.1879	1.18×10^{-3}	194.5
Fluorobenzene	0.5860	2.5718	1.01×10^{-3}	194.5
Fluorobenzene	0.5983	1.8659	1.09×10^{-3}	194.5
Fluorobenzene	1.0881	2.5036	8.91×10^{-4}	195.4
Fluorobenzene	0.5387	1.3736	1.929×10^{-3}	204.5
Fluorobenzene	0.5781	1.3538	1.958×10^{-3}	204.5
Fluorobenzene	0.5769	1.5060	1.144×10^{-2}	239.5
Fluorobenzene	0.5781	1.3451	1.09×10^{-2}	239.5
Chlorobenzene	0.5693	1.4198	5.82×10^{-4}	223.5
Chlorobenzene	0.5760	1.4986	1.622×10^{-3}	239.5
Chlorobenzene	0.5771	1.2938	1.389×10^{-3}	239.5
Chlorobenzene	0.5715	1.4145	3.708×10^{-3}	257
Chlorobenzene	0.5650	1.4030	3.829×10^{-3}	257
Bromobenzene	0.5798	1.3560	1.946×10^{-3}	204.5
Bromobenzene	0.5739	1.3708	5.606×10^{-3}	223.5
Bromobenzene	0.5817	1.3701	5.618×10^{-3}	223.5
Bromobenzene	0.5745	1.4538	1.50×10^{-2}	239.5
Bromobenzene	0.5763	1.3481	1.842×10^{-3}	204.5
Iodobenzene	0.5626	1.4108	1.589×10^{-3}	195
Iodobenzene	0.5600	1.3774	1.593×10^{-3}	195
Iodobenzene	0.5636	1.3482	2.99×10^{-3}	205.5
Iodobenzene	0.5772	1.3434	3.02×10^{-3}	205.5

Table 32.

Compound	Molarity (Halogen)	Molarity (Piperidine)	Rate Constant ($M^{-1}hr^{-1}$)	Temperature °C
Iodobenzene	0.5649	1.4067	9.557×10^{-3}	223.5
Iodobenzene	0.5730	1.4380	8.695×10^{-3}	223.5
p-Fluorotoluene	0.5402	1.1804	1.965×10^{-4}	194.5
p-Fluorotoluene	0.5412	1.7747	2.015×10^{-4}	194.5
pFluorotoluene	0.5363	2.4490	1.931×10^{-4}	194.5
m-Fluorotoluene	0.5382	1.2764	7.72×10^{-4}	194.5
m-Fluorotoluene	0.5375	1.6873	8.145×10^{-4}	194.5
m-Fluorotoluene	0.5231	2.1503	7.513×10^{-4}	194.5
p-Difluorobenzene*	0.5285	1.1824	7.514×10^{-4}	194.5
p-Difluorobenzene*	0.5212	2.5503	4.63×10^{-4}	194.5
p-Difluorobenzene*	0.5275	1.9107	4.64×10^{-4}	194.5
p-Chlorofluorobenzene	0.5476	1.2167	1.00×10^{-2}	194.5
p-Chlorofluorobenzene	0.5295	1.9755	9.018×10^{-3}	194.5
p-Chlorofluorobenzene	0.5196	2.6884	7.915×10^{-3}	194.5
p-Bromofluorobenzene	0.5098	1.3847	1.681×10^{-2}	194.5
p-Bromofluorobenzene	0.5401	1.3145	1.650×10^{-2}	194.5
p-Fluoroiodobenzene	0.5117	1.4380	2.592×10^{-2}	194.5
p-Fluoroiodobenzene	0.5212	1.3711	2.78×10^{-2}	194.5
m-Difluorobenzene*	0.5264	1.1728	2.895×10^{-2}	194.5
m-Difluorobenzene*	0.5336	1.8740	2.74×10^{-2}	194.5
m-Difluorobenzene*	0.5286	2.5778	2.394×10^{-2}	194.5
m-Chlorofluorobenzene	0.5198	1.2096	4.781×10^{-2}	194.5
m-Chlorofluorobenzene	0.5050	1.8118	3.628×10^{-2}	194.5
m-Chlorofluorobenzene	0.5402	2.5374	3.653×10^{-2}	194.5
m-Bromofluorobenzene	0.5115	1.3954	6.563×10^{-2}	194.5
m-Bromofluorobenzene	0.5031	1.3637	6.505×10^{-2}	194.5
m-Fluoroidobenzene	0.5399	1.5636	5.665×10^{-2}	194.5
m-Fluoroidobenzene	0.5365	1.6490	5.638×10^{-2}	194.5
m-Fluorophenol	0.5535	1.1944	4.576×10^{-3}	194.5
m-Fluorophenol	0.5524	1.8405	3.992×10^{-3}	194.5
m-Fluorophenol	0.5568	2.3823	3.41×10^{-3}	194.5
m-Fluorobenzotrifluoride	0.5588	1.3540	6.61×10^{-2}	194.5
m-Fluorobenzotrifluoride	0.5521	1.9016	6.185×10^{-2}	194.5
m-Nitrofluorobenzene	0.5230	1.2106	5.966×10^{-4}	67.8
m-Nitrofluorobenzene	0.5157	1.2359	4.886×10^{-3}	93.7
m-Nitrofluorobenzene	0.5151	1.144	1.554×10^{-2}	115
m-Nitrofluorobenzene	0.5445	1.3628	0.9292	195
m-Nitrofluorobenzene	0.6571	1.7746	0.9582	195
p-Nitrofluorobenzene	0.5554	1.1969	5.0×10^{-1}	25.0
p-Nitrofluorobenzene	0.5403	1.2108	5.06×10^{-1}	25.0
p-Nitrofluorobenzene	0.5459	0.9878	2.21	50.0
p-Nitrofluorobenzene	0.5541	1.1721	2.10	50.0
p-Nitrofluorobenzene	0.5180	1.2700	5.507	67.0

Table 32.

Compound	Molarity (Halogen)	Molarity (Piperidine)	Rate Constant ($M^{-1}hr^{-1}$)	Temperature °C
p-Dibromobenzene*	0.5649	1.5823	1.167×10^{-2}	204.5
p-Bromochlorobenzene	0.5627	1.3808	6.914×10^{-3}	204.5
m-Bromochlorobenzene	0.5616	1.3808	2.23×10^{-2}	204.5
m-Dibromobenzene	0.5640	1.4809	2.03×10^{-2}	204.5
m-Bromofluorobenzene	0.4928	1.4598	1.002×10^{-1}	204.5
m-Nitrobromobenzene	0.5002	1.4018	0.2663	204.5

*Statistically Corrected
**The rate constants for mixed dihalobenzenes are total rate constants and have not been multiplied by the per cent fluorine displacement in Table 30.

Hammett Plot

The Hammett plot may be used as a mechanistic tool. If all the points lie on a straight line, all the compounds are assumed to proceed by the same mechanism. If one point is far off the line, this compound is regarded as having a different mechanism of reaction. If the plot is curved, then either a change in the rate determining step (concave down) or a change in the mechanism (concave up) has occurred (177, 178). Some explanation may be helpful at this point. Let Equation 1 represent a reaction where C is an intermediate complex in aromatic nucleophilic

$$A + B \underset{}{\overset{k_1}{\rightarrow}} C \overset{k_2}{\rightarrow} D + E \qquad (1)$$

substitution. Then k_1 is increased by electron withdrawing groups and has a positive slope in Figure 1. The value k_2 is speeded up by electron

releasing groups since the intermediate complex is destabilized. The rate determining step is the slow step in Figure 2. The concave down dotted line represents the slow step found for each sigma value and a curved plot similar to this would represent a change in the rate determining step.

The concave up case is illustrated in Figure 3, where a change in mechanism occurs. Assume a reaction can go by two different mechanisms to produce the same product, depending on the substituent which path is taken (Eqs. 2, 3).

$$A + B \rightarrow C \rightarrow P \qquad (2)$$

$$A + B \rightarrow D \rightarrow P \qquad (3)$$

Let C and D represent the two mechanisms for reaction. Specifically, the two mechanisms are the intermediate complex mechanism and an S_N2 concerted type displacement in aromatic nucleophilic substitution. Substituents will affect the rates in a different manner for each reaction and may be illustrated by Figure 3. The reaction path which predominates for each substituent is the fastest rate constant, and the concave up dotted line portrays the result.

In actual fact the lines in Figure 3 should appear as in Figure 4 since both reactions discussed are speeded up by electron withdrawing groups. Therefore, a Hammett plot (Figure 6) was constructed from the data in Table 32 on the reaction of substituted fluorobenzenes with piperidine in TEG at 194.5°C (179). The plot was found to be linear

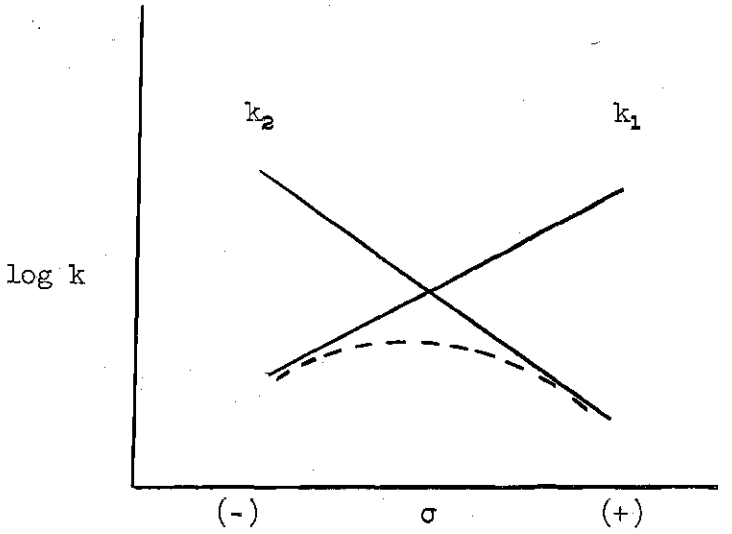


Figure 2. Change in the Rate Determining Step

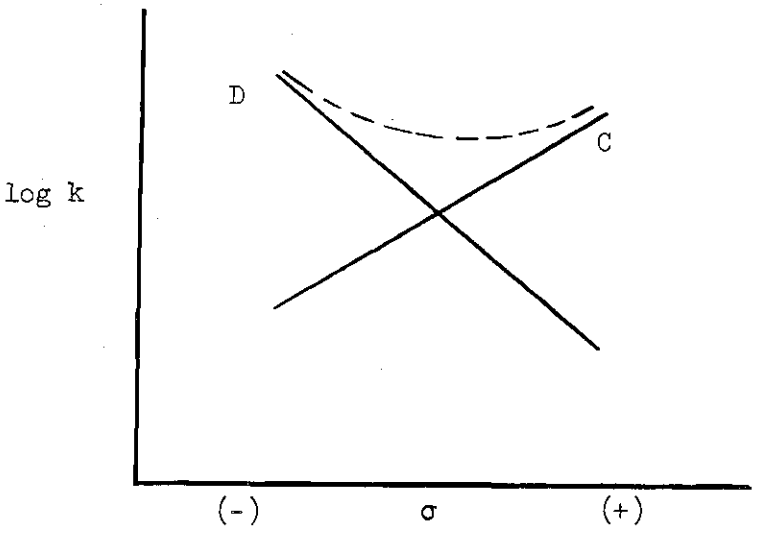


Figure 3. Change in Mechanism

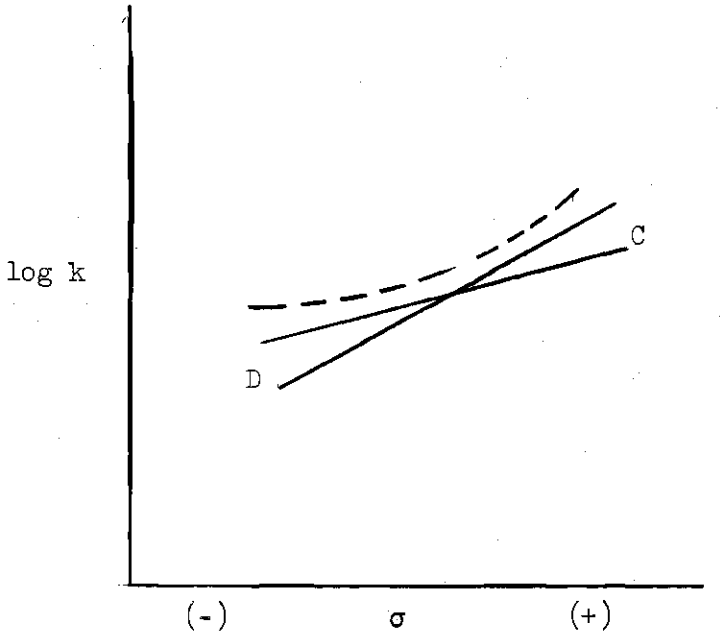


Figure 4. Change in Mechanism in Aromatic Nucleophilic Substitution

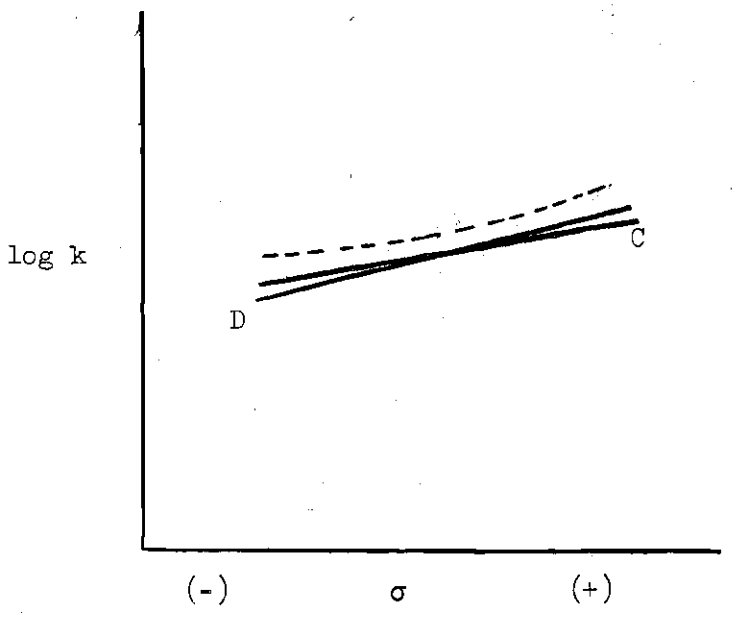


Figure 5. Slight Change of Mechanism

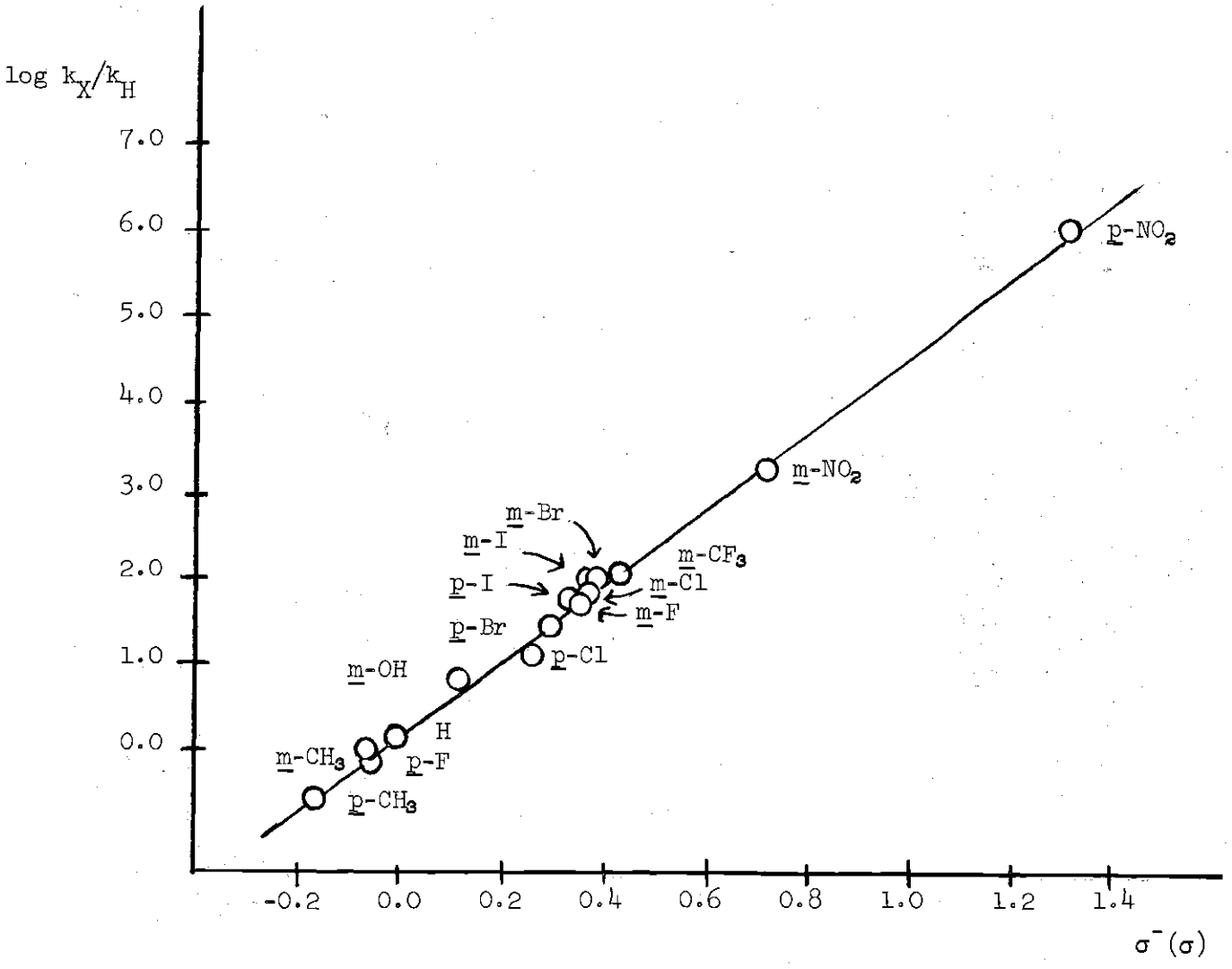


Figure 6. Hammett Plot for the Reaction of m- and p-Substituted Fluorobenzenes with Piperidine in Triethylene Glycol at 194.5°C.

with a rho value of + 4.41 and a correllation coefficient (180) of 0.9945. The rate constants and sigma values used are in Table 33. The rate constants used for the Hammett plot are not an average of the three values for each substituent in Table 32 because of the solvent effect. The concentration of halobenzene was about the same for all cases. In order to negate the solvent effect and obtain the values in Table 33, the rate constants were plotted against the piperidine concentration and the rate constant at 1.5 molar piperidine was chosen. The rate constants for halofluorobenzenes have also been multiplied by the per cent fluoride displacement found in Table 30. The rho value was determined by the computer on linear least square plot.

The conclusion from the Hammett plot is that the compounds react by the same mechanism since a straight line was obtained. The mechanism proposed is the intermediate complex mechanism since p-nitrofluorobenzene falls on the Hammett plot. This compound has been postulated as proceeding by an intermediate complex mechanism (181).

There are a few points of criticism concerning the mechanism proposed. Suhr (181) postulated that p-nitrofluorobenzene reacts with piperidine by an intermediate complex mechanism based on the observation of base catalysis. Bunnett (182) has divided base catalyzed reactions into two classes on the basis of the catalyzed and uncatalyzed rates. Ratios of catalyzed to uncatalyzed rates of about five are considered as mild base catalysis and ratios of 50 or greater are considered as strong base catalysis. The values Suhr found in protic solvents are four to five. These values are small and may not be base catalysis at all.

Table 33. Hammett Plot Data for Substituted Fluorobenzenes

Substituent	$k(M^{-1}sec^{-1})$	Sigma Value**
p-NO_2	1.75×10^{-1}	1.27
m-NO_2	2.54×10^{-4}	0.71
m-CF_3	1.83×10^{-5}	0.43
m-I	1.38×10^{-5}	0.352
m-Br	1.37×10^{-5}	0.391
m-Cl	1.20×10^{-5}	0.373
m-F*	7.81×10^{-6}	0.337
p-I	7.27×10^{-6}	0.318
p-Br	4.56×10^{-6}	0.289
m-OH	1.18×10^{-6}	0.121
p-Cl	2.66×10^{-6}	0.244
H	3.14×10^{-7}	0
p-F*	1.38×10^{-7}	-0.05
m-CH_3	2.21×10^{-7}	-0.069
p-CH_3	5.55×10^{-8}	-0.170

*Statistically corrected
**Taken from Table 16

A second criticism is illustrated in Figure 5. If the mechanism does change on going from activating to nonactivating substituents, the effect of the substituents may be closely the same for each mechanism. In this case the lines tend to overlap and it would be difficult to see any change in the mechanism. This is possible but the correlation coefficient (0.9945) obtained is considered excellent and would indicate only one line may be drawn.

Substituent Effects

The meta halogens (Table 33) activate inductively. The order of activation is I ≅ Br > Cl > F which indicates that within the series the relative rates are determined by the mesomeric effect of the halogens. Fluorine has the greatest inductive effect of the halogens, yet the m-fluorine compound has the slowest rate. Other orders for meta halogens found in aromatic nucleophilic substitution are Br > I > Cl (183, 184), Br > Cl > I (183), and Br > Cl > I F (103). The fact that iodine shifts around in the order indicates that this substituent has a greater temperature dependence than the others.

The para halogens in Table 33 are all activating except the p-fluoro substituent, which is deactivating. The para halogens are less activating than the meta halogens. The order of activation is I ≅ Br > Cl > F. This is the order generally found in aromatic nucleophilic reactions (37, 183-7). The order within the para halogens is governed by the mesomeric effect, which is more effectively destabilizing in the para position than the meta. The result is that para fluorine is actually destabilizing.

The position of p-fluorine relative to a hydrogen substituent is particularly interesting. In aromatic nucleophilic reactions p-fluorine is found to be deactivating (37, 187, 172, 176), activating (186, 184) and the same as hydrogen (185). In similar reactions where a partial negative charge is placed into the ring in the transition state, such as the ionization of phenols (188) and anilines (188, 112), the p-fluorine substituent is deactivating. The destabilizing effect of fluorine on delocalized carbanions appears to be a general phenomenon and has been observed by a number of authors (189-192). One explanation is an orbital penetration which is a repulsive interaction between the filled p-orbitals on carbon and the filled π-electrons on fluorine (193-195). The other explanation (189) is a weakening of the C-F bound due to the greater electronegativity of the sp^2 carbon compared to sp^3 carbon. It is Streitwieser's (190) contention that quantum mechanical calculations should distinguish between the two explanations.

It was hoped to have obtained some quantative data on the extremely deactivating effects of the p-amino and p-hydroxyl groups. When p-fluoroaniline and p-fluorophenol were heated separately in piperidine at 240° C for three days no reaction was observed as evidenced by gas chromatography analysis. It was thought that since these two groups are so deactivating, they might be displaced instead of fluorine but no N-(p-F-phenyl)-piperidine was observed by GLC.

Related to substituent effects is the data in Table 30 which gives the per cent displacement of each halogen in mixed dihalobenzenes. It is necessary to bring some order to this data and show why one halogen is displaced over another. If the data can be explained by electronic

factors, then one can apply the Hammett equation (Eq. 4). Although this

$$\log k_X/k_H = \rho_Y(\sigma_X - \sigma_H) \tag{4}$$

is the usual form of the Hammett equation, a different situation exists with the mixed diahalobenzenes because the reaction centers are not the same. Consider m-bromofluorobenzene as an example. When fluorine is displaced the rate constant is k_F because fluorine is indeed being displaced. The substituent is bromine, so the sigma value used is for m-Br. The reaction center is at fluorine, so the rho value is ρ_F. When bromine is displaced the rate constant is k_{Br}. The substituent is fluorine so the sigma value is for m-F. The reaction center is at bromine so the rho value is ρ_{Br}. This is shown below (Eq. 5, 6) where k_F^o is the reference compound (fluorobenzene) for fluorine displacement and k_{Br}^o is the reference compound for bromine displacement (bromobenzene). These two equations may be subtracted and rearranged to obtain Eq. 7, where the

$$\log k_F/k_F^o = \rho_F\sigma_{Br} \tag{5}$$

$$\log k_{Br}/k_{Br}^o = \rho_{Br}\sigma_F \tag{6}$$

$$\log k_F/k_{Br} = \rho_F\sigma_{Br} - \rho_{Br}\sigma_F - \log k_{Br}^o/k_F^o \tag{7}$$

last term is simply the logarithm of the relative rates of the displacement reaction of bromobenzene and fluorobenzene. If one calculates the ratio of k_F/k_{Br}, this can easily be changed to a per cent displacement

for each halogen.

Since the sigma values and the rates of the unsubstituted halobenzenes are known, it is necessary to estimate the rho values ρ_F, ρ_{Br}, ρ_{Cl}, ρ_I. The rho value for fluorine displacement may be obtained from the data in Table 33. The rho value for bromine displacement can be obtained from the data in Table 32 on substituted bromobenzenes at 204.5°C. The calculated rho value is + 3.05. Previously, Dr. C. L. Liotta had obtained a rho value of + 2.78 for the reaction of substituted chlorobenzenes with piperidine in triethylene glycol at 242°C (unpublished). What is wanted is a rho value at 195°C. From Table 17 rho values increase with a decrease in temperature. An increase of 0.3 to 3.08 for the rho value at 195°C is reasonable. A rho value for iodine displacement in triethylene glycol solvent could be obtained but would be difficult because reduction of iodine competes with displacement. An indirect method was used to get an approximation of a rho value for iodine displacement. From Table 34 the relative rates of displacement reaction of bromo- and iodobenzene are known at 196°C and also the relative rates of reaction of m-bromo- and m-iodonitrobenzene at 168°C with piperidine as the nucleophile and solvent are known. The rate of reaction of m-iodonitrobenzene at 195°C could not be obtained because of iodine reduction. By plotting the logarithm of the values in Table 34 against the sigma value for each substituent, the relative rho value for bromine and iodine displacement may be obtained. The difference in the slopes is + 0.57 = $\rho_{Br} - \rho_I$. Since the rho value for substituted bromobenzenes with piperidine in TEG is known, one can calculate the rho value for iodine. The rho value calculated for iodine displacement is 3.05 -

0.57 = 2.48. This rho value should be near the expected value. The fact that bromo- and iodobenzene were not run at the same temperature as m-bromo- and m-iodonitrobenzene is not important since bromobenzene and iodobenzene have essentially the same activation energy (Table 35). Also, the relative rates of reaction of bromo- and iodobenzenes in TEG and piperidine solvents are essentially the same.

Using these rho values and the proper sigma values, σ^- for para substituents, the calculated per cent displacement on each compound was obtained (Table 35).

Considering the accuracy of the values used to calculate the data in Table 35, this method explains satisfactorily the per cent displacements. With the para compounds σ^- values work better than σ values.

This method of explaining the per cent displacement in mixed dihalobenzenes may be presented graphically in Figure 7. Consider m-bromofluorobenzene. Although the rates of fluorobenzene and bromobenzene are about the same with piperidine, in m-bromofluorobenzene the fluorine is displaced 89.4 per cent and bromine 10.6 per cent. The sigma values for m-Br and m-F differ only by less than 0.02. Therefore, the high fluorine reactivity in m-bromofluorobenzene is due to a higher rho value for fluorine displacement.

Halogen Order and Activation Data

The halogen order is important in determining the mechanism of aromatic nucleophilic substitution. Table 35 gives the relative rates and activation data of the halobenzenes using the data in Table 32. The error in the activation energy was determined from the known errors in

Table 34. Relative Rates of Substituted Halobenzenes in Piperidine

	m-NO_2 (168°C)	p-CH_3 (237°C)	H(196°C)
F	48.7	2.1	4.5
Cl	1	1	1
Br	5.9	9.21	10.3
I	3.3	---	14.9

Table 35. Calculated Per Cent Displacement in Mixed Dihalobenzenes*

Para Compounds	Using σ^-	Using σ	Meta Compounds	
Fluorine Displacement	96.5	87.5	Fluorine Displacement	84
Bromine Displacement	3.5	12.5	Bromine Displacement	16
Fluorine Displacement	99.4	99.0	Fluorine Displacement	97.8
Chlorine Displacement	0.6	1.0	Chlorine Displacement	2.2
Fluorine Displacement	96	88.5	Fluorine Displacement	78.5
Iodine Displacement	4	11.5	Iodine Displacement	21.5
Bromine Displacement	89	91.5	Bromine Displacement	90
Chlorine Displacement	11	8.5	Chlorine Displacement	10
Bromine Displacement	53.5	57.1	Bromine Displacement	50.5
Iodine Displacement	46.5	42.9	Iodine Displacement	49.5
Iodine Displacement	87.2	89.5	Iodine Displacement	92
Chlorine Displacement	12.8	10.5	Chlorine Displacement	8

*The values used to calculate these per cents are in Appendix B.

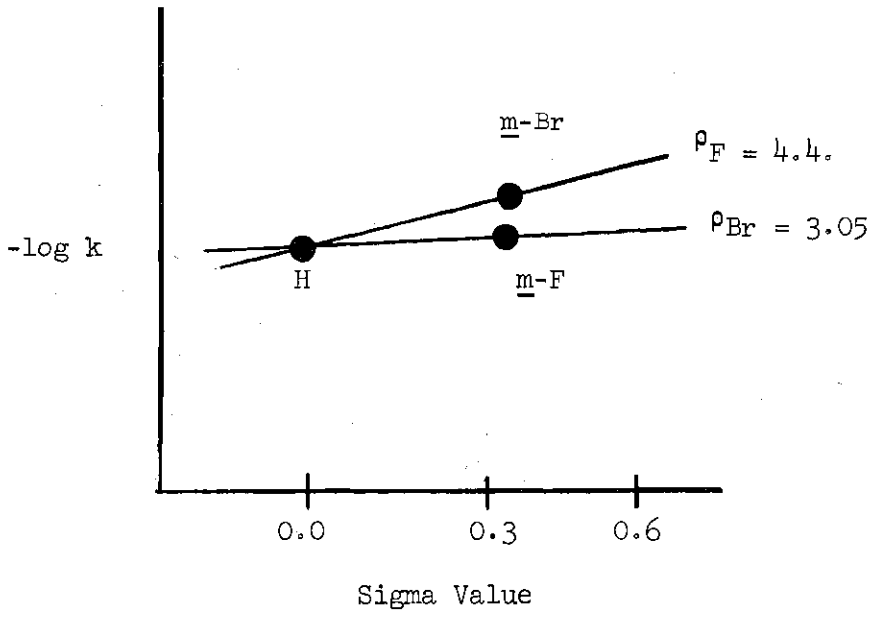


Figure 7. Graphical Representation of the Reactivity in Mixed Dihalobenzenes.

rate constants and temperatures by the method found in Benson (see Ref. 170, p. 94).

Table 36. Activation Data and Relative Rates of Halobenzenes with Piperidine in TEG

	$\Delta E^{\neq}$ (kcal/mole)	log A	$\Delta G^{\neq}$ 200°C	$\Delta S^{\neq}$ 200°C	Relative Rates (195°C)
F	24.42 ± 0.8	4.92	43.7 ± 1.2	-42.6 ± 0.85	11.4
Cl	29.21 ± 1.1	6.03	46.1 ± 1.6	-32.6 ± 1.2	1.0
Br	28.17 ± 0.8	6.56	43.9 ± 1.2	-34.8 ± 0.85	10.6
I	28.58 ± 1.1	6.95	43.4 ± 1.6	-33.9 ± 1.2	16.6

Also determined were the relative rates of halobenzenes in piperidine where piperidine is the nucleophile and solvent (Table 34).

Although the activation energies and relative rates of chlorobenzene, bromobenzene, and iodobenzene have been determined a number of times previously with piperidine, this is the first time that the correct position of fluorine has been determined quantitatively in the halogen order. The order obtained in Table 36 $I > Br \sim F \gg Cl$ is difficult to explain without the activation energies. It is important that the reaction rate of fluorobenzene with piperidine is greater than chlorobenzene, since this implies that there is little bond breaking in the transition state. The activation energies show that the value for fluorine is about 4.5 kilocalories less than the value for chlorine. This means that as the temperature is decreased the rate of fluorobenzene becomes even faster than chlorobenzene. The relative rates of fluorobenzene to chlorobenzene calculated at 100°C is 38 which is comparable to activated

compounds in that F >> Cl at 100°C. Comparing at the same temperatures, the relative rates of fluorobenzene to chlorobenzene will not be as high as the ratio of, say, p-nitrofluorobenzene to p-nitrochlorobenzene simply because the rho value for fluorobenzenes is higher than the rho value for chlorobenzene. Since the rate ratios (F/Cl) of activated and non-activated cases are similar, it may be concluded that both cases go through an intermediate complex mechanism.

The relative rates of the halobenzenes I > Br >> Cl may be explained by a polarizability factor which is more favorable I > Br > Cl. Thus, to explain the whole order, I > Br ~ F >> Cl, a combination of inductive effects and polarizability effects is necessary.

One consequence of the halogen order is the reason why fluorine is usually much faster than the remaining halogens with hard nucleophiles. The usual explanation is that the high electronegatively of fluorine creates a partial positive charge at the attached carbon which makes it more susceptible to nucleophilic displacement.

An attempt was made to place this question on a quantitative basis. The argument is based on the assumption that one is dealing with the intermediate complex mechanism with the first step rate determining. In the halobenzenes the halogen is attached to an sp^2 carbon and in the intermediate complex the halogen is attached to an sp^3 carbon. In a comparison of the whole series of halobenzenes with the same nucleophile, the only process necessary to compare is the change in energy in going from the halogen carbon sp^2 bond to the halogen carbon sp^3 bond. Since only hard nucleophiles are used, polarizability factors should not be very important. Thus, it is necessary to know the difference in bond

energy of a C_{sp^3} - X (where X is a halogen) bond and a C_{sp^3} - X bond. The difference for fluorine is greater than for the other halogens because it is this process which explains the greater reactivity of fluorine. The excess energy is related to the difference in the known activation energy of an aromatic nucleophilic displacement reaction of fluorine, and chlorine, bromine, or iodine.

From a number of aromatic nucleophilic substitution reactions where the activation energies of all the halogens are known, the activation energy of fluorine is 3.9-4.6 kilocalories less than chlorine, 3.6-4.8 kilocalories less than bromine, and 4.3-5.5 kilocalories less than iodine. Based on the previous assumption, the lower activation energy for fluorine is reflected in its higher reactivity.

One can calculate bond dissociation energies from the Pauling equation, Eq. 8:

$$BE_{A-B} = \frac{BE_{A-A} + BE_{B-B}}{2} + 23\ (X_A - X_B)^2 \qquad (8)$$

where X is the electronegativity. Equations 9, 10 and 11 show the development of this procedure,

$$BE_{C_{sp^2}-F} = \frac{BE_{C_{sp^2}-C_{sp^2}} + BE_{F-F}}{2} + 23(X_{C_{sp^2}} - X_F)^2 \qquad (9)$$

$$BE_{C_{sp^3}-F} = \frac{BE_{C_{sp^3}-C_{sp^3}} + BE_{F-F}}{2} + 23(X_{C_{sp^3}} - X_F)^2 \qquad (10)$$

$$(BE_{C_{sp^3}-F} - BE_{C_{sp^2}-F}) - (BE_{C_{sp^3}-Y} - BE_{C_{sp^2}-Y}) =$$

$$-46\,(X_{C_{sp^2}} - X_{C_{sp^3}})(X_F - X_Y) \qquad (11)$$

where Y is either chlorine, bromine, or iodine. Hines (189) value of 0.093 for the difference in the electronegativity of an sp^2 carbon and an sp^3 carbon is used. The Pauling electronegativities used are 4.00, 3.00, 2.80, and 2.50 for fluorine, chlorine, bromine, or iodine, respectively. The values for Eq. 11 are + 4.3, + 5.1, + 6.4 for Y equal to chlorine, bromine, and iodine respectively. These values are larger than expected because the transition state occurs about 80 per cent along the reaction coordinate in going from sp^2 to sp^3. This means that the difference in the electronegativity of the sp^2 and sp^3 carbons is not 0.093 but about 80 per cent of 0.093. Eighty per cent of these values gives 3.4, 4.05, and 5.1 which agree well with the values from activation energy data.

Element Effect

It was hoped to have found the leaving ability of other groups beside the halogens. Then it would have been possible to use the "element effect" as a criterion of mechanism (196). Bunnett found that the rates of reaction of six 1-substituted-2,4-dinitrobenzenes with piperidine differed by only 4.7. Bunnett concluded that these compounds reacted by an intermediate complex mechanism and that bond breaking was not important in the transition state. A rate difference of only 4.7 is incompatible with a concerted S_N2 type mechanism where bond breaking

is important. The leaving groups involved five different elements (S, O, Cl, Br, I) attached to the carbon at the reaction center.

An attempt was made to use the "element effect" as a criterion for mechanism in nonactivated aromatic nucleophilic substitution. Reaction samples of phenyl ether and piperidine in TEG were made up and reacted at 240°C for 14 days. About 10 per cent of the base was consumed and the solution became very dark brown, but no N-phenylpiperidine could be observed by gas chromatography. A similar reaction was run with nitrobenzene for five hours at 240°C. Base was used up and a large amount of black tar was found, but no N-phenylpiperidine. A similar reaction was run on diphenyl sulfone at 240°C for 13 days. Base was used up and no N-phenylpiperidine was observed by gas chromatography. A large amount of benzene was observed indicating attack or sulfur. A reaction with diphenyl amine at 240°C for 12 days showed a 10 per cent loss of base but no N-phenylpiperidine. A reaction ampoule was made up with diphenyl sulfide and piperidine as nucleophile and solvent and heated at 196°C for 22 hours. No N-phenylpiperidine was observed by gas chromatography. Because of the inability of these compounds to undergo aromatic nucleophilic substitution under these conditions, the "element effect" could not be used as a criterion for mechanism.

Base Catalysis

An attempt was made to show whether amine catalysis by piperidine was present in the reaction of m-difluorobenzene with piperidine in TEG at 194.5°C. It was necessary to circumvent the solvent effect. First, reactions were run at three different concentrations of piperidine, say one, two, and three molar. Then a reaction was run which

was one molar piperidine and one molar dioxane (or tetrahydropyran). Also a reaction was run which was one molar in piperidine and two molar dioxane (or THP). Dioxane and tetrahydropyran are used because they have similar solvation properties as piperidine but were much less effective toward base catalysis. A plot was made of rate constant against the concentration of piperidine, one, two, and three molar. On the same graph was plotted rate constant of one molar piperidine, of one molar piperidine plus one molar dioxane (plotted as "two molar" piperidine), and of one molar piperidine plus two molar dioxane (plotted as "three molar" piperidine). A more negative slope for the latter line than the former indicates base catalysis, while lines which overlap indicate no base catalysis. The pertinent data is in Table 37.

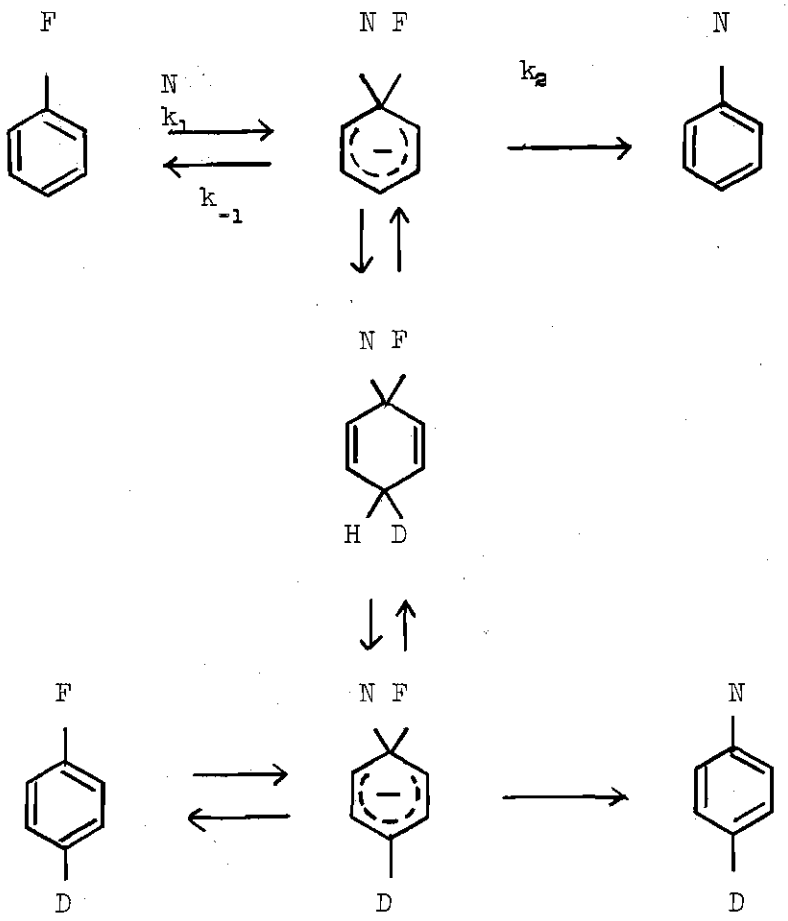
Table 37. Amine Catalysis Data

M(Halide)	M(Piperidine)	M(Dioxane)	M(THP)	$k(M^{-1}hr^{-1})$
0.5264	1.1728			2.945×10^{-2}
0.5336	1.8740			2.79×10^{-2}
0.5286	2.5778			2.433×10^{-2}
0.5270	1.1756		0.6799	2.645×10^{-2}
0.5218	1.1742		1.4155	2.722×10^{-2}
0.5298	1.1630	0.6790		3.32×10^{-2}
0.5180	1.1580	1.2913		2.49×10^{-2}

A plot of the data in Table 37 as outlined above showed no definite trend with either dioxane or tetrahydropyran. This may be due to the inability to obtain accurate enough rate constants. It was impossible to draw any concrete conclusions concerning amine catalysis from the data.

Deuterium Exchange

The object of the deuterium exchange study was to find exchange on the intermediate complex, which can be thought of as a conjugate base (carbanion) of a carbon acid. This was a novel idea. Deuterium exchange on carbanions have been studied for many years but deuteration produced a stable product. When deuteration of the intermediate complex occurs, another metastable intermediate is formed which then deprotonates to produce either reactant or product. The full reaction scheme is presented below. where N refers to the nucleophile.



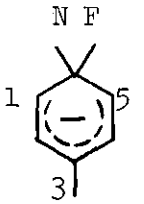
It is possible with this scheme to find deuterium in the reactant and/or product. If k_1 is rate determining, then no deuterium will be found in the reactant, but could be found in the product. This technique for detecting the intermediate complex is more useful than base catalysis since the observation of base catalysis can only be seen when the rate of decomposition of the intermediate complex depends on k_{-1} and k_2, or k_2 alone.

Ideally, a system should be chosen where deuterium exchange does not occur on the reactant or product. Then any exchange which occurs will be on the intermediate complex. A system should be chosen where proton transfers to the conjugate base of carbon acids are known to be diffusion controlled or where the rates approach diffusion controlled rates. This eliminates the necessity of knowing the rates of decomposition of the intermediate complex to reactant and product.

If no deuterium exchange is found in an aromatic nucleophilic substitution reaction, then it can be said that the mechanism occurred by a concerted S_N2 type mechanism. This means that the decomposition of any intermediate occurs faster than diffusion controlled rates, which is essentially a concerted S_N2 mechanism. Deuterium exchange can not occur during this mechanism because there is only one degree of freedom going across the barrier.

The reaction of p-deuterio-fluorobenzene with piperidine in TEG at 223°C showed 5.65 and 7.0 per cent proton incorporation into the product. This was concluded as having been incorporated by proton exchange on the intermediate complex. An analysis of this system was necessary to show if the small amount of exchange has any real significance.

Proton transfer in this system to the conjugate base of a carbon acid was diffusion controlled. Ritchie (197) showed that proton transfers in methanol become diffusion controlled only when the ΔpK is 18 or greater. The ΔpK in the fluorobenzene reaction refers to the difference in acidity of the protonated intermediate complex and TEG. The pK_a of TEG is about 14-15. The acidity of the protonated intermediate complex may be estimated to be about 35 from the acidity of the α proton in propene (35.5) and cycloheptatriene which is 36 (198). Thus, the ΔpK was about 20 which is greater than the value necessary for diffusion controlled proton transfers. Another point is that in the intermediate complex, positions 1, 3, or 5 may be protonated, yet deuterium is at only position 3 (for numbering of the intermediate complex see I).



I

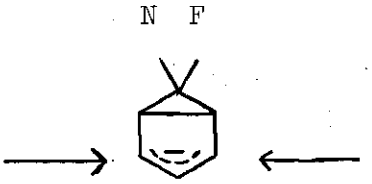
To a first approximation, exchange is equally probable at the 1, 3, or 5 positions. Hence, a maximum of only 33.3 per cent exchange may be seen in the 4-d-fluorobenzene reaction. This value becomes even less when the k_H/k_D isotope effect is considered, since the loss of deuterium is being observed on the intermediate complex. If k_H/k_D were ten, it would be difficult to see any exchange on the intermediate complex since the proton would be preferably lost. Fortunately, a maximum value for the k_H/k_D may be calculated at 225°C. Hine gives a value of four (199).

From Melander's book a maximum value of 3.7, considering only stretching frequencies, and 4.2, considering stretching and bending, may be calculated (200). Although the calculated values vary, a choice of four for the maximum value of k_H/k_D seems plausible. Therefore, the minimum amount of deuterium exchange that can be observed is 33.3% x 1/5 = 6.66%. The experimental values 5.66 and 7.00 per cent agree very well with the calculated values and indicated that exchange did occur on the intermediate complex.

In the above argument the 1, 3, and 5 positions of the intermediate complex were considered equally probable toward protonation. There is the possibility that protonation may prefer the 3 position, which would raise the calculated value of 6.66 per cent. Deuterium exchange on the 6, 6-dimethyl-cyclohexadienyl anion showed exchange favors the 3 position at least eight to one over the 1 or 5 positions (201, 202). Recent molecular orbital calculations show a higher charge density at the 3 position than the 1 or 5 positions (203). This data indicates that the calculated value 6.66 per cent should be greater. But it must be pointed out that in 6,6-dimethyl-cyclohexadienyl anion the methyl groups are electron donating, whereas in the intermediate complex two electronegative groups (N and F) tend to increase the charge at the 1 and 3 positions. Therefore, there is actually no data which would eliminate a statistical proton attack at the 1, 3, or 5 positions.

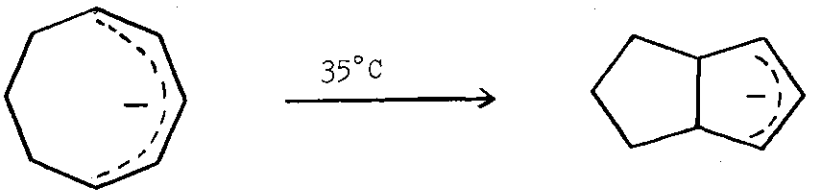
The similar reaction with m-deuterio-fluorobenzene showed no deuterium exchange. Based on the above conclusions, the intermediate complex II was not an intermediate in this reaction. In this intermediate the electron density is highest at the positions indicated. The

disrotatory cyclization (Figure 8) of a cyclohexadienyl anion to anion II is thermally favored (204) and the thermal cyclization of a pentadienyl



II

to a cyclopentenyl anion (Eq. 12) has been shown to occur (205).



(12)

The reaction of pentafluorobenzene with sodium thiopenoxide in methanol-O-d and DMF showed no deuterium exchange. Again the ΔpK is at least twenty since fluorine greatly destabilizes delocalized carbanions which makes the intermediate complex more basic. Deuteration of the IC should prefer to occur at the hydrogen position, para to nucleophilic attack, since fluorine should destabilize the negative charge on the carbon to which it is attacked such that the greatest electron density is at the hydrogen position. The solvent used was DMF: methanol-O-d (80:20). Ritchie (197) has shown that proton transfers become diffusion controlled in DMSO at a ΔpK of ten. Rates in DMSO and other dipolar aprotic solvents (206) such as N, N-dimethyl formamide approach

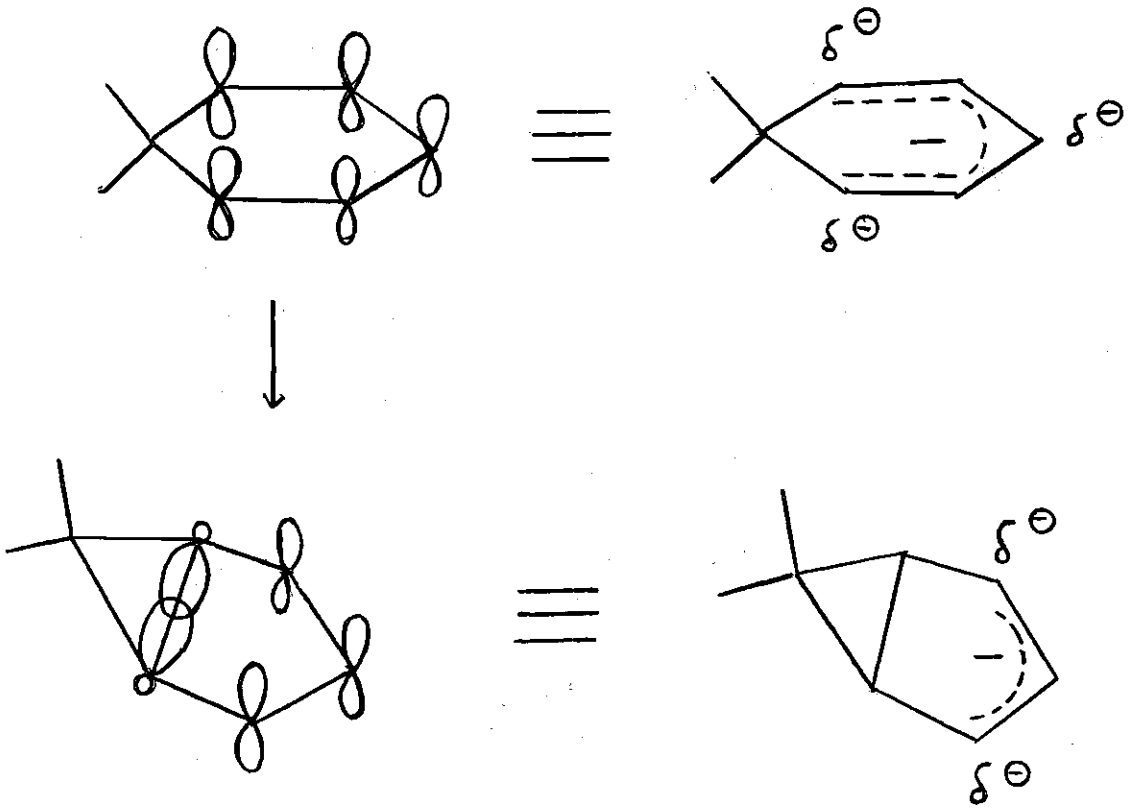


Figure 8. Orbital Picture for the thermal Disrotatory Cyclization of Cyclohexadienyl Anion to Cyclopentenyl Anion.

diffusion control at a lower ΔpK than protic solvents because the anion has a smaller solvation sphere and hence has to lose a smaller energy of solvation to accept a deuterium. Certainly, in the solvent mixture used here, the intermediate complex should be less solvated than in pure methanol-O-d.

The fact that no deuterium exchange occurred in the pentafluorobenzene reaction leads to the conclusion that the reaction does not proceed through an intermediate complex. This conclusion is tentative, since pentafluorobenzene is an activated compound and activated aromatic nucleophilic substitution reactions are generally thought of as proceeding through an intermediate complex. The same statements may be said concerning the reaction of thiophenoxide with p-nitrofluorobenzene in DMF: methanol-O-d, where no deuterium exchange was observed. There is the possibility of preferential deuteration on an oxygen of the nitro group in the intermediate complex. Neutral Meisenheimer complexes have been observed which contain the NO_2H function (207, 208).

The true value of this deuterium exchange method has yet to be realized. It should greatly extend the ability to detect intermediate complexes in aromatic nucleophilic substitution.

CHAPTER IV

CONCLUSIONS

The results in Chapter III indicate that the mechanism of nonactivated bimolecular aromatic nucleophilic substitution goes through an intermediate complex. This is based on the evidence, firstly, that a linear Hammett plot was obtained from the rate constants of the reaction of piperidine with activated and nonactivated meta and para substituted fluorobenzenes. Secondly, fluorobenzene reacts faster than chlorobenzene with piperidine. Thirdly, it appears that deuterium exchange was observed on the intermediate complex in the reaction of p-deuterio-fluorobenzene with piperidine in TEG.

CHAPTER V

RECOMMENDATIONS

The Hammett plot (Figure 6) was constructed to observe curvature in the line. It is possible that the curvature occurred in the neighborhood of the p-NO_2 substituent since there are only two substituents in the range 0.6 σ - 1.4 σ. In order to look for curvature on this area, another Hammett plot should be constructed from the rates of reaction of m- and p-substituted fluorobenzenes with piperidine in TEG using substituents with σ_m or σ_p^- values greater than 0.70.

In the deuterium exchange section, reactions might also be run with chlorobenzene, bromobenzene, and iodobenzene with piperidine in an effort to find intermediate complexes in these reactions. Another reaction that could be run with fluorobenzene is that of fluorobenzene-2, 6-d_2 with piperidine-1-d in deuterated (ROD) triethylene glycol. In this latter case the observation of incorporation of deuterium in the four position of the product is not hampered by the k_H/k_D ratio, and more exchange would be seen in the product.

APPENDICES

APPENDIX A

In making the density correction factor, the temperature dependence of the density was obtained using triethylene glycol to represent the reaction solution. This was done because the reaction solution contained volatile piperidine and fluorobenzene which could evaporate causing inaccurate density data. It is necessary to see if the change in density with temperature of TEG is similar to the reaction solution.

First, a check was made to see if the temperature dependence of the volume is affected by the piperidine concentration. Two TEG solutions were made up at 25°C, one 0.5 molar in fluorobenzene and 1.0 molar in piperidine, and another 0.5 in fluorobenzene and 2.0 molar in piperidine. The weights of these solutions were obtained at temperatures up to 60°C. For each solution a plot was made of the weight of 50-ml of the solution against temperature, and the slopes obtained. The slopes were very similar for each solution, 3.57 for the 1.0 molar piperidine solution and 3.48 for the 2.0 molar piperidine solution. So, the piperidine concentration doesn't appreciably affect the density change with temperature. Since the slope for the pure TEG solution was 3.45, the use of TEG to represent the reaction solution appears to be valid.

APPENDIX B

Below are the values used to calculate the per cent displacements in Table 35.

	σ_m	σ_p	$\bar{\sigma_p}$	ρ	Relative Rates
F	0.337	0.062	-0.05	+4.41	11.4
Cl	0.373	0.227	0.244	3.08	1.0
Br	0.391	0.232	0.289	3.05	10.6
I	0.352	0.276	0.318	2.48	16.6

BIBLIOGRAPHY*

1. J. F. Bunnett and R. E. Zahler, Chem. Rev., 49, 273 (1951).

2. J. Miller, Rev. Pure and Appl. Chem., 1, 171 (1951).

3. J. F. Bunnett, Quart. Rev. (London), 12, 1 (1958).

4. J. Sauer and R. Huisgen, Angew. Chem., 72, 294 (1960).

5. S. D. Ross in A. Streitwieser, S. G. Cohen, and R. W. Taft (Eds.), Progress in Physical Organic Chemistry, Vol. 1, Interscience, New York, N. Y., 1963, p. 31.

6. F. Pietra, Quart. Rev. (London), 23, 504 (1969).

7. G. Illuminati in A. Katritzky (Ed.), Advances in Heterocyclic Chemistry, Vol. 3, Academic Press, New York, N. Y., 1964, p. 285.

8. R. G. Shepherd and T. L. Fedrick, in A. R. Katritzky (Ed.), Advances in Heterocyclic Chemistry, Vol. 4, Academic Press, New York, N. Y., 1965, p. 145.

9. T. Kaufman, Angew. Chem. Intern., Ed. Engl., 4, 543 (1965).

10. J. Tatlow, Endeavor, 22, 89 (1963).

11. B. Tronov and E. Krueger, J. Russ. Phys.-Chem. Soc., 58, 1270 (1926); Chem. Abstr., 21, 3887 (1927).

12. E. Berliner, M. Quinn, and P. Edgerton, J. Am. Chem. Soc., 72, 5305 (1950).

13. P. Petrenko-Kritschenko, Chem. Ber., 62, 581 (1929).

14. K. Brower and E. Amstutz, J. Org. Chem., 18, 1025 (1953).

15. K. Brower and E. Amstutz, J. Org. Chem., 21, 890 (1956).

16. E. Lellman and M. Buttner, Chem. Ber., 20, 680 (1887); ibid., 23, 1383 (1890).

*Periodical abbreviations follow those in Access, 1969.

17. D. Manly and E. Amstutz, J. Org. Chem., 22, 133 (1957); R. Petfield and E. Amstutz, ibid., 19, 1944 (1954).

18. G. Badger and J. Cook, J. Chem. Soc., 1109 (1947).

19. J. F. Bunnett and A. Levitt, J. Am. Chem. Soc., 70, 2778 (1948).

20. K. Meyer and F. Bergius, Chem. Ber., 47, 3155 (1914).

21. S. M. Shein and L. Kozorez, Izv. Sib. Otd. Okad. Nauk SSSR, Ser. Khim. Nauk, 2, 85 (1965) [Chem. Abstr., 64, 1917 (1966)] ibid., 3, 105 (1965) [Chem. Abstr., 64, 19347 (1966)].

22. S. M. Shein and L. Kozorez, Kinet. Catal. (USSR), 5, 651 (1964).

23. S. M. Shein and L. Kozorez, J. Org. Chem. USSR, 2, 1066 (1966).

24. J. Burdon and W. B. Hollyhead, J. Chem. Soc., 6326 (1965).

25. R. Urner and F. Bergstrom, J. Am. Chem. Soc., 67, 2108 (1945).

26. J. D. Roberts and L. Carlsmith, J. Am. Chem. Soc., 78, 601 (1956).

27. T. Kaufman and H. Henkler, Chem. Ber., 96, 3159 (1963).

28. R. W. Hoffman, Dehydrobenzene and Cycloalkynes, Academic Press, New York, N. Y., 1967, p. 29.

29. S. Oae, N. Furukawa, and H. Tanaka, Bull. Chem. Soc. Jap., 41, 1463 (1968).

30. W. Bradley, J. Chem. Soc., 458 (1938).

31. J. F. Bunnett and T. Brotherton, J. Am. Chem. Soc., 78, 6265 (1956).

32. J. F. Bunnett and T. Brotherton, Chem. Ind. (London) 80 (1957).

33. P. Caubere and M. Hochu, Bull. Soc. Chim. Fr., 2854 (1969).

34. J. Sauer, A. Hauser, and R. Huisgen, Chem. Ber., 91, 1461 (1958).

35. J. Sauer, R. Huisgen, W. Mack, and I. Ziegler, Chem. Ber., 92, 441, (1959).

36. R. Clark and R. Ball, Trans. Royal Soc. of Canada, 21, Sect. 3, 311 (1927).

37. J. Miller, Aust. J. Chem., 9, 61 (1956).

38. S. M. Shein and V. Evstifeev, Org. Reactiv. (USSR), 5, 159 (1968).

39. S. M. Shein and V. Evstifeev, Sib. Chem. J., 227 (1967).

40. S. Carra and P. Beltrame, Gazz. Chim. Ital., 89, 2027 (1959); Chem. Abstr., 55, 5419 (1961).

41. F. Blau, Monatsh, 7, 621 (1886).

42. J. Miller, Chem. Ind. (London),954 (1957).

43. C. Bevan, J. Chem. Soc., 3091 (1954).

44. J. Miller, J. Chem. Soc., 750 (1956).

45. J. Miller, J. Chem. Soc., 3492 (1963).

46. S. Shein and V. Evstifeev, J. Gen. Chem. USSR, 38, 480 (1968).

47. S. M. Shein and V. Litvak, and Khmetinskaya, J. Org. Chem. USSR, 4, 632 (1968).

48. S. M. Shein and V. Evstifeev, J. Org. Chem. USSR, 4, 637 (1968).

49. T. DeCrauw, Rec. Trav. Chim. Pays-Bas, 50, 753 (1931).

50. E. Kryuger and M. Bednova, J. Gen. Chem. (USSR), 3, 67 (1933); Chem. Abstr., 28, 1593 (1934).

51. S. Shein and V. Ignatov, J. Org. Chem. USSR, 2, 1062 (1966).

52. A. Holleman, Rec. Trav. Chim. Pays-Bas, 24, 194 (1905).

53. W. Davis and E. Wood, J. Chem. Soc., 1122 (1928).

54. W. Miller and J. Wrightson, Absts. of Papers of the 112th Meeting of the Am. Chem. Soc., 1947, p. 16J.

55. S. M. Shein and V. Evstifeev, J. Gen. Chem. USSR, 38, 485 (1968).

56. A. Kipriyanov and E. Suich, Ukr. Khim. Zh., 1, 94 (1932); Chem. Zentralbl., II, 1339 (1933).

57. L. Balbiano, Gazz. Chim. Ital., 11, 396 (1881) [see reference 1, p. 279].

58. Y. Ogata and M. Tsuchida, J. Org. Chem., 20, 1631 (1955).

59. L. Van Lande, Rec. Trav. Chim. Pays-Bas, 51, 98 (1932).

60. G. Kraay, Rec. Trav. Chim. Pays-Bas, 49, 1082 (1930).

61. S. M. Shein and V. Ignatov, J. Org. Chem. USSR, 2, 706 (1966).

62. D. J. Cram, B. Richborn, and G. R. Knox, J. Am. Chem. Soc., 82, 6412 (1960).

63. C. M. Suter, The Organic Chemistry of Sulfur, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 420.

64. N. Vorozhtsov and M. Shemyakin, Chem. Ber., 69, 148 (1936).

65. W. La Coste, Justus Liebig's Ann. Chem., 208, 9 (1881).

66. C. Wurtz, Justus Liebig's Ann. Chem., 144, 121 (1867).

67. A. Kekule, Compt. rend., 64., 753 (1866).

68. S. Oae, M. Kise, N. Furukawa and M. Kawanishi, Bull. Chem. Soc. Jap., 39, 1212 (1966).

69. R. Otto, Justus Liebig's Ann. Chem., 145, 322 (1868).

70. S. Oae and N. Furukawa, Bull. Chem. Soc. Jap., 39, 2260 (1966).

71. C. Ingold and J. Jessop, J. Chem. Soc., 708 (1930).

72. S. Oae and N. Furukawa, Bull. Chem. Soc. Jap., 41, 949 (1968).

73. F. C. Whitmore and A. L. Fox, J. Am. Chem. Soc., 51, 3363 (1929).

74. E. C. Britton, U. S. Pat. 1,996,744, April 9, 1935; Chem. Abstr., 29, 3354 (1935).

75. R. Shreve and C. J. Marsel, Ind. Eng. Chem., 38, 254 (1946).

76. V. Meharig, J. Am. Chem. Soc., 54, 2920 (1932).

77. W. Hale and E. Britton, Ind. Eng. Chem., 20, 114 (1928).

78. J. D. Roberts and A. Bottini, J. Am. Chem. Soc., 79, 1458 (1957).

79. H. Clough, "Manufacture of Synthetic Phenol by the Chlorination Route," A. G. Leverkusen, PB 97853, 1947, p. 37.

80. A. Luttringhaus and D. Ambros, Chem. Ber., 89, 463 (1956).

81. G. Dalman and F. Neumann, J. Am. Chem. Soc., 90, 1601 (1968).

82. F. Swartz, Bull. Acad. roy. Belg. Classe des sci., 241 (1913), [Chem. Zent. II, 760 (1913)].

83. M. Boudakian, R. Eber, and R. McArthur, J. Org. Chem., 26, 4641 (1961).

84. H. McKay, Nature, 139, 283 (1937).

85. A. Kristjanson and C. A. Winkler, Can. J. Chem., 29, 154 (1951).

86. S. May and R. Daudel, J. Chim. Phys., 53, 274 (1956).

87. S. May, A. Fava, and B. Giraudel, C. R. Acad. Sci., Paris, 236, 286 (1953).

88. S. May and I. Estelles, C. R. Acad. Sci. Paris, 234, 433 (1952).

89. A. Aguiar and K. Rubenstein, J. Org. Chem., 28, 2091 (1963).

90. S. Tijmstra, Chem. Weekblad, 5, 96 (1908).

91. E. C. Britton, U.S. Pat. 1,959,283, March 15, 1931; Chem. Abstr., 28, 4433 (1934).

92. J. F. Bunnett and W. D. Merritt, Jr., J. Am. Chem. Soc., 79, 2967 (1957).

93. D. Hey and C. Rees, J. Chem. Soc., 4579, (1962).

94. F. Davis and R. Wetzel, Tetrahedon Letters, 51, 4483 (1969).

95. E. Tauber and R. Lowenhertz, Chem. Ber., 24, 1033 (1891).

96. D. Allen and I. Millar, J. Chem. Soc., (c), 2406, (1968).

97. G. Bonvicino, R. Hardy, Jr., and L. Yogodzinski, J. Org. Chem., 27, 4272 (1962).

98. M. Beringer and E. Gindler, J. Am. Chem. Soc., 75, 2708 (1953).

99. M. Beringer and E. Gindler, J. Am. Chem. Soc., 77, 3203 (1955); M. Beringer and M. Mausner, ibid., 80, 4535 (1958).

100. G. G. Lyatiev, O. A. Ptitsyna, and O. A. Reutov, J. Org. Chem. USSR, 5, 390 (1969); ibid., 5, 400 (1969); ibid., 5, 695 (1969).

101. S. Oae and Y. Khim, Bull. Chem. Soc. Jap., 40, 1716 (1967).

102. A. Holleman and W. de Mooy, Rec. Trav. Chim. Pays-Bas, 33, 1 (1915).

103. C. W. Bevan and J. Hirst, Chem. Ind. (London), 341 (1966).

104. E. T. McBee, P. Graham, and R. Bolt, J. Am. Chem. Soc., 69, 947 (1947).

105. E. T. McBee, P. Graham, and R. Bolt, J. Am. Chem. Soc., 69, 947 (1947).

106. D. Hammick and R. B. Williams, J. Chem. Soc., 211 (1938).

107. W. Gleim, U.S. Pat., 2,766,295, Oct. 9, 1956, Chem. Abstr., 51, 8790 (1957).

108. S. M. Shein and V. Ignatov, J. Gen. Chem. USSR, 33, 2578 (1963).

109. S. M. Shein and V. Ignatov, J. Gen. Chem. USSR, 32, 3168 (1962).

110. S. M. Shein and M. I. Krasnoselskaya, J. Gen. Chem. USSR, 35, 1944 (1965).

111. S. M. Shein and M. I. Krasnoselskaya, J. Gen. Chem. USSR, 34, 3427 (1964).

112. J. Miller, Aromatic Nucleophilic Substitution, Elsewier Publishing Company, New York, N. Y., 1968.

113. T. Birchall and W. Jolly, J. Am. Chem. Soc., 88, 5439 (1966).

114. J. Miller and V. Williams, J. Chem. Soc., 1475 (1953).

115. J. Miller and V. Williams, J. Am. Chem. Soc., 78, 1975 (1956).

116. J. Bunnett andR. Morath, J. Am. Chem. Soc., 77, 5051 (1955).

117. J. Bunnett, J. Am. Chem. Soc., 79, 5969 (1957).

118. J. Bunnett and J. Reinheimer, J. Am. Chem. Soc., 81, 315 (1959).

119. S. M. Shein and V. Evstifeev, J. Org. Chem. USSR, 5, 906 (1969).

120. S. M. Shein and V. Evstifeev, Org. Reactiv. (USSR), 5, 339 (1968).

121. S. M. Shein and V. Ignatov, J. Gen. Chem. USSR, 32, 3165 (1962); ibid, 33, 2598 (1963).

122. S. M. Shein and V. Ignatov, J. Gen. Chem. USSR, 33, 2620 (1963).

123. J. Bunnett and T. Brotherton, J. Am. Chem. Soc., 78, 155 (1956).

124. K. Brower, J. Am. Chem. Soc., 80, 2105 (1958).

125. H. E. Zimmerman in Molecular Rearrangements, Part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 378.

126. D. J. Gram, Fundamentals of Carbanion Chemistry, Academic Press, New York, N. Y., 1965, p. 223.

127. S. H. Pine, Tetrahedron Letters, 3393 (1967).

128. T. Kaufmann, R. Nurnberg, and K. Udluft, Angew. Chem. Intern. Ed. Engl., 7, 617 (1968).

129. W. E. Truce and W. J. Ray, Jr., J. Am. Chem. Soc., 80, 3625 (1958); ibid., 81, 481 (1959); ibid., 81, 484 (1959).

130. W. E. Truce and M. Guy, J. Org. Chem., 26, 4331 (1961).

131. W. E. Truce and D. Hampton, J. Org. Chem., 28, 2270 (1963).

132. V. N. Drozd and L. Zefirova, J. Org. Chem. USSR, 4, 179 (1968); ibid., 4, 1616 (1968); V. N. Drozd, L. Zefirova, and A. Ustynyuk, 5, 1220 (1969); V. N. Drozd, A. Pak, and A. Ustynyuk, ibid., 5 1409 (1969); V. N. Drozd and A. Nikonova, ibid., 5, 1416 (1969).

133. V. N. Drozd, Dokl. Chem., 169, 657 (1966).

134. V. N. Drozd and L. Nikonova, J. Org. Chem. USSR, 5, 309 (1969); V. N. Drozd, A. Pak, and A. Ustynyuk, ibid., 5, 920 (1969).

135. W. E. Truce and C. Robbins, J. Am. Chem. Soc., 88, 4027 (1966).

136. V. N. Drozd, A. Pak, and A. Ustynyuk, J. Org. Chem. USSR, 5, 1238 (1969).

137. F. Bordwell and B. Lampert, J. Am. Chem. Soc., 71, 1702 (1949).

138. O. Reid, W. Stafford, and J. Ward, J. Chem. Soc., 1100 (1958).

139. K. Hafner, H. Patzelt, and H. Kaiser, Justus Liebig's Ann. Chem., 656, 24 (1962).

140. H. Nozaki and Y. Yamamoto, Tetrahedron Letters, 1123 (1966).

141. P. Argabright, J. Hofmann, and A. Schriesheim, J. Org. Chem., 30, 3233 (1965).

142. H. Nozaki, Y. Yamamoto, and T. Nisimura, Tetrahedron Letters, 4625 (1968).

143. M. A. Wahl and R. Lantz, Bull. Soc. Chim. Fr., 33, 93 (1923).

144. M. Ringeissen, Bull. Soc. Chim. Fr., 333, (1936).

145. P. Todesco and V. Calo, Chem. Commun., 571 (1968).

146. P. Todesco, M. Foa, and A. Ricci, Boll. Sci. Fac. Chim. Ind. Bologna, 23, 233 (1965).

147. P. Gassman and G. Campbell, J. Am. Chem. Soc., 90, 7377 (1968).

148. H. E. Heller, E. D. Hughes, and C. K. Ingold, Nature, 168, 909 (1951).

149. Y. Yukawa, J. Chem. Soc. Japan, Pure Chem. Sect., 71, 547 (1950).

150. P. K. Kadaba and S. P. Massie, J. Org. Chem., 22, 333 (1957).

151. R. R. Dreisbach and S. A. Shrader, Ind. Eng. Chem., 41, 2879 (1949).

152. E. D. Bergmann and M. Benton, J. Org. Chem., 26, 1480 (1961).

153. H. L. Bradlow and C. A. Vander Werf, J. Am. Chem. Soc., 70, 654 (1948).

154. I. Heilbron and H. M. Bunbury, eds., Dictionary of Organic Compounds, Oxford University Press, New York, 1953.

155. M. Scholtz and E. Wassermann, Chem. Ber., 40, 852 (1907).

156. A. H. Sommers and S. E. Aaland, J. Am. Chem. Soc., 75, 5280 (1953).

157. W. W. Groves, British Patent, 472,757, Sept. 4, 1937; Chem. Abstr. 32, 1480 (1938).

158. R. Huisgen, W. Mack, and K. Herbig, Chem. Ber., 93, 412 (1960).

159. E. Lellman and R. Just, Chem. Ber., 24, 2099 (1891).

160. J. Braun, Chem. Ber., 40, 3914 (1907).

161. R. Lukes and M. Forles, Chem. Listy, 50, 1471 (1956).

162. R. Huisgen and J. Sauer, Angew. Chem., 72, 91 (1960+

163. C. Sellers and H. Suschitzky, J. Chem. Soc., 6186 (1965).

164. A. N. Bourns, H. W. Embleton, and M. K. Hansuld, Can. J. Chem., 30, 1 (1952).

165. H. Bock, German Patent, 1,210,871, February 17, 1966; Chem. Abstr. 64, 19484 (1966).

166. R. Huisgen and J. Sauer, Chem. Ber., 91, 1453 (1958).

167. R. Heacock and L. Marion, Can. J. Chem, 34, 1782 (1956).

168. Borge Bak and D. Christensen, J. Chem. Phys., 26, 134 (1957).

169. R. Piccolini and J. D. Roberts, J. Am. Chem. Soc., 77, 4540 (1955).

170. S. W. Benson, The Fundamentals of Chemical Kinetics, McGraw-Hill Book Company, Inc., New York, 1960, p. 18.

171. J. Burdon, C. Patrick, and W. B. Hollyhead, J. Chem. Soc., 6375 (1965).

172. K. C. Ho and J. Miller, Aust. J. Chem., 19, 423 (1966).

173. G. M. Brooke and J. C. Tatlow, J. Chem. Soc., 3253 (1962).

174. E. Nield and J. C. Tatlow, J. Chem. Soc., 166 (1959).

175. M. Stacey, R. Stephens, and J. C. Tatlow, J. Chem. Soc., 4754 (1960).

176. R. De Pasquale and C. Tamborski, J. Org. Chem., 32, 3163 (1967).

177. J. E. Leffler and E. Grunwald, Rates and Equilibria in Organic Reactions, John Wiley and Sons, Inc., New York, 1963, p. 187.

178. P. R. Wells, Chem. Rev., 63, 171 (1963).

179. C. L. Liotta and D. F. Pinholster, Chem. Commun., 1245 (1969).

180. H. H. Jaffe, Chem. Rev., 53, 191 (1953).

181. H. Suhr, Ber. Bunsenges, Phys. Chem., 67, 893 (1963).

182. J. F. Bunnett and R. H. Garst, J. Am. Chem. Soc., 87, 3875 (1965).

183. W. Greizerstein, R. A. Bonelli, and J. A. Brieux, J. Am. Chem. Soc., 84, 1026 (1962).

184. A. M. Porto, A. Castro, and J. A. Brieux, J. Chem. Soc., (B), 963 (1966).

185. R. Heppolette and J. Miller, J. Am. Chem. Soc., 75, 4265 (1953).

186. C. W. L. Bevan, J. Chem. Soc., 655 (1953).

187. E. Berliner and L. C. Monack, J. Am. Chem. Soc., 74, 1574 (1952).

188. A. I. Biggs and R. A. Robinson, J. Chem. Soc., 388 (1961).

189. J. Hine, L. C. Mahone, and C. L. Liotta, J. Am. Chem. Soc., 89, 5911 (1967).

190. A. Streitwieser, Jr., and F. Mares, J. Am. Chem. Soc., 90, 2444 (1968).

191. L. A. Kaplan and H. B. Pickard, Chem. Commun., 1500 (1969).

192. H. G. Adolph and M. J. Kamlet, J. Am. Chem. Soc., 88, 4761 (1966).

193. D. T. Clark, J. N. Murrel, and J. M. Tedder, J. Chem. Soc., 1250, (1963).

194. W. A. Sheppard, J. Am. Chem. Soc., 87, 2410 (1965).

195. D. P. Craig and G. Doggett, Mol. Phys., 8, 485 (1963).

196. J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, J. Am. Chem. Soc., 79, 385 (1957).

197. C. D. Ritchie and R. E. Uschold, J. Am. Chem. Soc., 90, 3415 (1968).

198. D. J. Cram, Fundamentals of Carbanion Chemistry, Academic Press, New York, 1965, p. 19.

199. J. Hine, Physical Organic Chemistry, McGraw-Hill Book Company, Inc. New York, 1962, p. 72.

200. L. Melander, Isotopes Effects on Reaction Rates, The Ronald Press, New York, N. Y., 1960, p. 22.

201. R. B. Bates and C. E. Staples, J. Am. Chem. Soc., 85, 3032 (1963).

202. W. von E. Doering, G. Schroeder, and S. Staley, 144th National Meeting of the American Chemical Society, Los Angeles, California, April, 1963 p. 14M.

203. H. E. Zimmerman, Tetrahedron, 16, 169 (1961).

204. R. B. Woodward and R. Hoffmann, J. Am. Chem. Soc., 87, 395 (1965).

205. R. B. Bates and D. A. McCombs, Tetrahedron Letters, 977 (1969).

206. C. D. Ritchie and R. Uschold, J. Am. Chem. Soc., 86, 4489 (1964).

207. L. B. Clapp, H. Lacey, and G. G. Beckwith, J. Org. Chem., 33, 4262 (1968).

208. B. Achilladelis, P. M. Adams and J. R. Hanson, Chem. Commun., 511 (1970).

VITA

Daniel Farmer Pinholster, Jr., son of Mr. and Mrs. D. F. Pinholster, Sr., was born April 20, 1943 in Gainesville, Florida. He attended Cherokee Elementary and Cartersville High Schools in Cartersville, Georgia, where his high school diploma was received in June, 1961. He attended Emory University where he received an A.B. degree in August, 1965. A year of undergraduate chemistry was taken at Georgia State University, 1965-66. In August, 1966, he began his graduate work at the Georgia Institute of Technology as a teaching assistant. After the first year he was supported by an NDEA Fellowship.